the mike, in terms of your first question, looking at those patients with elevated triglycerides and those effects, fortunately that's a subset analysis that we have done, but we've not again had a chance to discuss with the agency. So, we're not able to show that.

But we'll let Dr. Brunzell answer the remainder of your question.

DR. BRUNZELL: Is it okay if I talk about a class effect with a different drug?

DR. BONE: I have no objection.

DR. BRUNZELL: You know, troglitazone, for example, has a variable effect on triglyceride. There are about 20 published papers. In about half of them, it comes down; in the other half, it doesn't. But in the studies where they looked within the subgroups, those that had the high triglycerides actually are the ones whose triglyceride came down. Those who had normal triglycerides did not. And it fits with Dr. Mele's data where those that get the greatest response in glucose lowering are the ones that seem to get the best benefit.

Related to the APO lipoproteins, as I mentioned before, there's a small, but significant increase in LDL APO-B, but a marked, much higher increase in LDL cholesterol. The only way to do that is to get rid of the small, dense LDL, and the only way I know to do that is to

decrease hepatic lipase.

Now, your argument about the LDL/HDL ratio -- the people with cholesterol ester transfer protein deficiency, about 1 in 10,000 individuals in Japan, and nobody here. It's highly unlikely that that's what's going on here.

So, I think that with the changes in LDL composition that suggest hepatic lipase-mediated changes, the changes that are occurring in HDL would, by argument, I think be such that should be done. There is a study going on in New York looking at body composition, insulin sensitivity, hepatic lipase, and these lipoproteins, and APO lipoproteins. It is started and it's about a third of the way initiated.

DR. BONE: Thank you. Any further comment from Dr. Illingworth and then Dr. Misbin? Nothing from Dr. Illingworth. Dr. Misbin, please.

DR. MISBIN: I think one should be very cautious about quoting the troglitazone data. With respect to triglycerides, there was a general fall in triglycerides in patients treated with troglitazone. Now, there was an exception in that some of the patients -- in one of the trials, there was an attempt to take patients off of insulin. So, there was a rise of triglycerides that was associated with that reduction. But in general, I think

the statement is true that the triglyceride levels fell with troglitazone, and that actually we see as a distinction with rosiglitazone.

DR. BONE: Dr. Brunzell returns to the microphone.

DR. BRUNZELL: What I attempted to do in getting prepared for this is to look at all of the troglitazone literature. There are about 21 papers that actually discuss the issue of the response of triglyceride to troglitazone. Two-thirds of the ones between 1991 and 1996 were associated with a decrease in triglyceride. The ones subsequent to that aren't. If you start then doing subgroup analyses, it goes back to the high triglyceride people. The ones who get the best response to glucose lowering are the ones that come down.

DR. MISBIN: With all due respect, we have actually seen the data. We've done more than count the papers. There will also be data presented tomorrow which I think is relevant. So, I would respectfully suggest that we might not make any definite conclusions about class effects. That I do not think is appropriate.

DR. BONE: Thank you, Dr. Misbin. I appreciate your comment.

Well, I think we've had some very good general discussion on most of the safety related topics we are

going to be addressing later in the questions and some additional ones that were brought up. Maybe one of the things to come back to is how the members of the committee would envision using this drug from a standpoint of its efficacy if it were available, how would that fit into practice, and does it appear to be useful. Maybe we would ask the diabetologist, Dr. Genuth, to start the discussion.

DR. GENUTH: I think I would use the drug. I think it will be useful. One of the hard decisions that I think has to be made these days is if you're going to begin monotherapy in someone who has either failed on diet and exercise or is a new onset patient whose glycemic levels are so high that you feel you need to start with a drug and maybe take the drug away later, I think the hard question is whether to begin in an obese patient a thiazolidinedione or metformin, which is one of the reasons for my concern about comparing them. But I think that this drug would be a fair competitor to metformin in that in those two clinical situations, obese patient, newly diagnosed with type 2 diabetes, who has glucose levels so high that you think they need pharmacological therapy to relieve their symptoms, et cetera, maybe later hoping to get them controlled just with diet and exercise, or the patient who has done well for a while with diet and exercise and is now uncontrolled.

What I haven't come to a conclusion about yet in my own mind is how useful this drug will be in treatment of patients who have failed, are no longer controlled, on other drugs. At the moment, I think the weight of the evidence is that it would be useful to add to metformin, just kind of extrapolating from that other thiazolidinedione, whose name I won't mention. It would likely be useful added to a sulfonylurea or added to insulin.

So, I basically think whatever we thought that other thiazolidinedione is good for, this one is equally good for, possibly even slightly better for, at least with no worsened risk and likely a decreased risk. I'm still not sure in my own mind to what extent we should apply the lessons of that other thiazolidinedione --

(Laughter.)

DR. GENUTH: -- to this one as far as the liver is concerned. I'm just kind of mulling over whether we need to have monitoring or --

DR. BONE: We can come back to that. I guess I'm thinking about how we would use this.

DR. GENUTH: I would monitor perhaps for a year. You don't have to monitor forever. If you monitor in a post-marketing phase for a year and nothing happens, that would, I think, be quite reassuring.

DR. BONE: I'm going to ask Dr. Molitch and then Dr. Levitsky to comment and then everybody else kind of discuss about how they would think this might be used and whether they do think it would make a useful addition to the armamentarium.

DR. MOLITCH: I think I would agree with Dr. Genuth. Again, I've also learned, as Dr. Greene, never to argue with Dr. Genuth. He's always right. It would be a useful drug under these same circumstances.

I think some of the side effects that we've heard about today I think bear continued watching. One of the concerns I have is perhaps this amenorrhea issue with monkeys and whether this will be seen in humans when we are able to give it to women who aren't using contraceptives. It's a little bit of a concern to me. I think it's something that could be looked for in a larger population as we go along, when we look for all of these other complications as well.

But it seems like it would be a very useful drug in patients who have some degree of insulin resistance which is really the majority of patients who have got type 2 diabetes.

DR. BONE: When we're asked in a little while to address the question of monotherapy, would you distinguish between its efficacy, a little bit along the

lines that Dr. Genuth did, between initial therapy of a previously untreated patient or a patient not treated pharmacologically, I should say, and as an alternative? Would you make that same distinction?

DR. MOLITCH: I think the distinction to be made under the circumstances that we talked about last time was probably because of risk/benefit ratio differences, and if that risk/benefit ratio for this drug is to be perceived to be considerably less perhaps than trogilitazone, then it could be thought about as a first-line drug as well.

DR. BONE: I see what you mean, but I'm talking about for patients who are already on a drug.

DR. MOLITCH: Yes.

DR. BONE: You would just replace it.

DR. MOLITCH: No. I think if a patient is already on one oral agent, the tendency in general now is to add a second medication.

On the other hand, one of the things that was sort of brought home to us today and maybe we should think about more carefully for all of these drugs is the responder issue. We're seeing that perhaps with this drug there's a 70 percent responder issue which means that 30 percent of patients don't respond and maybe they would respond to a monotherapy with another drug. But we haven't extrapolated that to all of the drugs that we're using and

maybe we should be thinking more carefully about that.

But in general, the idea is if you don't respond to one drug, you add a second drug rather than switching.

DR. BONE: Dr. Levitsky.

DR. LEVITSKY: Well, as a pediatric endocrinologist, we always think that our patients with type 2 diabetes are more difficult than everybody else's patients with type 2 diabetes because they tend to be adolescents.

I would use this as an additional drug, start off with another drug and add it later on. I would not use it as my primary agent because I think of its effect on the adipocyte presently.

DR. BONE: From a patient standpoint, Ms. Killion, do you have a comment at this point?

MS. KILLION: Well, I thought Dr. Genuth was talking about me because I initially started out at a very high glycemic level, went on two drug therapies to bring it down, went to diet and exercise, continued for a while, and then went back on another drug, on metformin actually. So, I've sort of been all around that idea of having many therapies that have worked for a while and then failed. So, the prospect of an addition to the armamentarium is very pleasing to me, and this one seems, at least

initially, to have less dramatic adverse effects as that other agent that we're not talking about today.

DR. BONE: One thing I think we all have to bear in mind when we're talking about trying to compare the safety information that's available about a drug prior to its registration and the safety information we obtain about a drug in about the next month after it's on the market is an order of magnitude difference in the number of exposures. I think one of the things we just have to understand is that with an exposure of 5,000 patients or so, we get certain kinds of information and we can get an estimate about what the rate is of common to uncommon problems.

But if we have an event that occurs in 1 out of 10,000 people who are exposed, we may very well just not see it, and if there's no other signal, if it's truly an idiosyncratic phenomenon, what we can do and what the registration authorities in this country or anyplace else can do is try to make a risk estimate that the risk is relatively small prior to registration. But there's simply no way to estimate very rare or very uncommon things, so I think we all have to bear that in mind.

I know the members of the committee are well aware of this and the sponsor and the agency, but sort of a public awareness issue is you can narrow down what your

risk level is, but you will never have quite the same information before a drug goes on the market as you do after a million or so people have taken it. It's a different kind of information, more intensively studied, but just a smaller exposure level.

Any other comments from other members of the committee about the efficacy or use or how they would see this in clinical practice? Yes, Dr. Hammes.

DR. HAMMES: More a question I guess. If I'm interpreting the data correctly, we've seen studies comparing it to glyburide and sulfonylurea, which seem to indicate that the glyburide was more effective in lowering blood sugar, and in the combination therapy one where they went to monotherapy with metformin, when metformin was withdrawn, we lost glycemic control. So, trying to get my mind together on monotherapy here, it seems that we've been shown data that suggest that it's less effective than either of those two different types of drugs. Am I on the right line here, or where am I?

DR. GENUTH: With regard to glyburide, there was a time difference that was important. Glyburide was more effective early, the first few months, and then if you look at a year, the results are pretty similar between glyburide and rosiglitazone I think. I'd have to go look at the graphs again. So, I don't think that they are much

different, at least up to a year. Now, maybe at 5 years, they'd be very different because we know by then maybe 30 to 50 percent of the patients on sulfonylureas would no longer be very well controlled. That might not be true with this class of drugs, and we'll probably never know that until we approve them and see what happens in 5 years. But I hope somebody tracks it as systematically as possible.

DR. BONE: I think the sponsor actually had extension studies that are out to 2 years now. Is that right?

DR. WHEADON: Yes.

DR. BONE: Good, okay.

Dr. Misbin had a comment.

DR. MISBIN: I wonder if anyone on the committee would like to comment on the gender difference. That perhaps went by too quickly, but Joy Mele presented data which we all thought was rather impressive on the gender difference, particularly relevant to the sulfonylurea. It seemed quite clear to us that rosiglitazone was equivalent to glyburide in women but was clearly inferior in men. I wonder if people would comment on this. This is something that could potentially be in the label.

DR. BONE: Dr. Molitch.

DR. MOLITCH: Maybe I can just ask a question. I think you did this, but I'm not sure. Did you reanalyze it just on a milligram per kilogram basis to factor in either body surface area or body weight and it still holds true that there's a difference in gender? Is that correct?

DR. MISBIN: We could make a presentation, if you wish. The question came up, was this simply a dosing matter? Are the men being under-dosed? I think that's what you're asking.

DR. MOLITCH: Yes.

DR. MISBIN: And we concluded that that was not the case, which was kind of surprising, but that's just not what the data showed. It's actually rather interesting. You do see a very nice dose-response curve in men, but it just doesn't go very far, and in women, it's clearly quite different and quite effective. We could show that if you wish.

DR. BONE: Do you want to see that? No, all right. We'll take your word for it, Dr. Misbin. Thank you.

Dr. New.

DR. NEW: I would like to just comment that as the women were taking contraceptive tablets and the men were not, the question is, is this an estrogen effect which could involve protein binding?

DR. MISBIN: The women were, by and large, 60 years old, and I don't think many of them were -- the sponsor I think would have to comment. I don't think there were a large number of patients that were taking contraception.

DR. NEW: I was told everybody was.

DR. BONE: Some were postmenopausal he's saying.

DR. NEW: Postmenopausal women frequently take estrogens.

DR. BONE: Well, I think that's a good question. Was there a difference in the response between women who were either premenopausal or on hormone replacement therapy and those who had low estrogen levels due to postmenopausal status?

DR. MISBIN: No, we didn't analyze that.

DR. LEVITSKY: Didn't you show that there was an effect of weight so that the lean men were the ones who responded least well?

DR. MISBIN: Yes, that's exactly right.

DR. LEVITSKY: I guess I saw that and I assumed that when they finished their body composition studies, they're going to have the answer.

DR. MISBIN: No, no. You're exactly right. The lean men responded the least.

DR. HIRSCH: So, it's a matter of percent fat.

DR. MISBIN: Probably, yes.

DR. HIRSCH: The whole issue is a percent --

DR. MISBIN: Well, it could be. There are many potential issues, but this is exactly right.

DR. BONE: Dr. Rappaport was poised to make undoubtedly an informative remark.

(Laughter.)

DR. RAPPAPORT: Only to say that we know only that a small number of the postmenopausal women were on estrogen replacement therapy and we have not done an analysis to see whether they had a differential response.

DR. BONE: It seems like it's an interesting point, and probably you can do the experiment then with your existing data to a certain extent to find out whether this is an estrogen related phenomenon or a percent body fat related phenomenon from just available data. You know, we'll be having a little break, so --

(Laughter.)

DR. BONE: Ms. Killion.

MS. KILLION: Well, as a woman who is not postmenopausal, considering this drug, the thing that struck me was that there seems to be an additional risk/benefit analysis that has to take place here in that you may have some efficacy in your cardiac effects which

you then have to balance against the reproductive effects. That didn't seem to be as positive in that regard. So, as a woman who would be taking something like this, I would want to have more information on that. I'd want to be carefully weighing that as an option.

DR. BONE: I think it's a fair bet that we will not get a prospective study on what happens if you're taking this medicine and conceive. I don't think the sponsor is going to be asked to do that study.

Dr. Genuth.

DR. GENUTH: Well, I'm not so sure of that. One issue we haven't brought up with regard to gender is the fact that this class of drugs has crept into the treatment of polycystic ovary disease, and if this drug did what the other drugs and metformin are claimed to do, some women might become fertile while taking the drug and conceive and possible we will learn at least early effects.

But I really wanted to bring up the subject not just from that point of view, but from the point of view of the fact that I suspect people, if this drug is released for treatment of diabetes, will be tempted to use it for polycystic ovarian disease maybe even more than the previous drug because of less fear of trying it. I'm not quite sure what implications that should have for our recommendations for labeling, but it's something running

around in the back of my mind that it's going to be used that way, and I don't know whether we should recognize that from the start and think of some way to guide that use.

DR. BONE: I think it would be very difficult for the agency to write labeling about unlabeled usage.

(Laughter.)

DR. BONE: I see shaking of the heads from that side of the table.

Other committee members, any additional comments about the clinical trial data, practical clinical issues, concerns about safety questions, or anything like that?

DR. GENUTH: If I may, I have a wish list. I don't know if this is the place for it, but I really wish that right now somehow somebody organized a comparator trial of thiazolidinedione versus metformin versus a sulfonylurea. I'm not so sure about an alpha-glucosidase inhibitor, but those three head to head in enough patients with enough spread in their body weights and starting hemoglobin A1c levels that we would develop some real guidelines for which patient is best off starting on which drug.

DR. BONE: That may be your answer to question 5.

Let's see. It's just on 3 o'clock. Bear with

me for a moment.

(Pause.)

DR. BONE: Let me ask the sense of the committee. I don't know if there's any other discussion that we need to have before we actually go around the table for last comments and then vote on the topics. We have some people here who are nonvoting members with the panel, but we'll ask them to comment after the votes are taken at the end. Do we want to take a break or just go straight ahead?

DR. NEW: Straight ahead.

DR. BONE: Straight ahead, all right. I think we will.

DR. MISBIN: When were you going to discuss monitoring? Is that part of the questions?

DR. BONE: That's a point. That's one of the questions. Let's see. Actually as the questions are written, we have comments about labeling, phase 4 studies, risk/benefit, safety. Thank you, Dr. Misbin. I think what we will do, because I think it's worth having some discussion about monitoring since it's not directly reflected here in the questions --

DR. MOLITCH: Well, we could do it as part of 2.

DR. BONE: That could be one way we could do

that. Is that the sense of the committee to do? And we'll have another opportunity to discuss some aspects of this as well when we discuss tomorrow if it's something that would be broadly applicable.

What I like to do usually then is just go around the table, ask everybody to make their final comment and then vote.

I want to ask one question, though, before we get to that. In question 1, do we want to distinguish within question 1a -- and I suppose this would apply to 3a as well -- between initial monotherapy and change from one monotherapy to another? Maybe what we'll ask people to do is give their yes or no answer, but would be allowed to append a short comment, very short, about how they feel about that alternative. That would give the agency I think a little additional guidance.

Let's just go around the table for one last comment, if anyone wants to make one, including the guests, and then we'll ask the committee members to vote. Then on the comment questions, the essay questions that aren't vote questions, we'll ask everyone to make their comments as well. I guess we'll just start with Dr. Lewis.

DR. LEWIS: My comments are really going to apply to what we do with the liver, and let me hold it until we get to those questions.

DR. BONE: That will be fine because that's a short answer, essay question.

And Dr. Seeff, nods in agreement.

Dr. Levitsky, do you want to make a general comment?

DR. LEVITSKY: Later.

DR. BONE: Dr. Molitch, Dr. New, Dr. Genuth, any additional general comments? Dr. Hirsch?

DR. HIRSCH: The most compelling thing that I see here is that this is extremely useful or very likely to be very useful when someone on metformin is failing and the addition to this to metformin. Otherwise, it becomes a more difficult decision with increasing difficulty as you go down the line. That seems to be the top of it is the way I'm thinking.

DR. BONE: Thank you.

Dr. Critchlow, Dr. Hammes, Dr. Illingworth, and Ms. Killion? No? Thanks.

Well, let's see. The first vote on the left will come from Dr. Molitch on question 1, and just please answer (a) and (b), and if you wanted to make that distinction in (a) along the lines we discussed, that's up to you.

DR. MOLITCH: I would vote for (a) as monotherapy, yes. I would say that it could be used as

monotherapy in place of another drug if the other drug were shown -- the person was shown to be not responding to it.

DR. BONE: Let me read the question. I'm sorry. I should have done that for anyone who doesn't have it. The first question is, do the data demonstrate that rosiglitazone is effective for the treatment of hyperglycemia in type 2 diabetes mellitus: (a) as monotherapy, and (b) in combination with metformin? We're not talking about other combinations today. Just that one.

Dr. New, it's your turn.

DR. NEW: My answer to the first is yes, and I agree with Dr. Molitch that I would be most comfortable if it were a replacement monotherapy for one that has failed.

DR. BONE: Thank you.

Dr. Genuth?

DR. GENUTH: Question 1, yes and yes. Is that all you want, or do you want the rest?

DR. BONE: Did Dr. New vote on 1(b)?

DR. NEW: I said yes.

DR. MOLITCH: I did not vote on 1(b).

DR. BONE: I'm sorry.

DR. MOLITCH: And I would vote yes.

DR. BONE: So, now we've got yes, yes with comments; yes, yes with comments. And Dr. Genuth, on (a) and (b)?

DR. GENUTH: Question 1, yes and yes.

DR. BONE: Yes and yes. Okay. Thank you.

Dr. Hirsch.

DR. HIRSCH: Yes under monotherapy but I've only seen evidence that this is effective in those who are beginning therapy, not stopping other therapy and starting that. If that's what it means, then no, but if what you mean by monotherapy is beginning the therapy before, yes. And I would say yes to the second as well. But that other no is a very important one for me to not take someone off of another drug.

You all disagree with that I assume. Oh, you don't. That wasn't clear to me.

DR. BONE: I think Dr. Genuth had previously commented to that effect.

DR. HIRSCH: So, they have a partial yes then for (a).

DR. BONE: We're clear about this?

DR. NEW: Agreed with Genuth.

DR. BONE: And Dr. Molitch editorialized to the extent he wanted to already.

DR. MISBIN: Excuse me. I think that should be clarified. You may not intend it, Dr. New, but I think what you voted is that patients who are on metformin and they could be taken off of metformin to be put on

rosiglitazone and we would see the deterioration that we showed you before. I don't think that's what you're voting for.

DR. BONE: The Chair's understanding of Dr. New's vote was the following, and please correct me, Maria, if I misunderstood. Dr. New for question 1(a) felt that this would be a yes for initial monotherapy of a previously untreated patient, but if she were switching a patient from another drug, she would only do that if they had failed on the other drug, similar to Dr. Molitch's comment. Is that a correct understanding?

DR. NEW: That's correct. Which is not identical to Jules' and Saul's --

DR. MOLITCH: I think we're still not clear. Can I further clarify this?

DR. BONE: Please, Dr. Molitch.

DR. MOLITCH: I wanted to say switching drugs, if they're shown to be a nonresponder to the first drug, then I would consider switching them, not that they had not achieved goal with the first drug. That's a very different issue.

DR. BONE: Okay. So, you would only switch a nonresponder.

DR. MOLITCH: That's correct.

DR. BONE: And you would use additive therapy

in a partial responder.

DR. MOLITCH: Correct.

DR. NEW: Agreed.

DR. BONE: Dr. New?

DR. NEW: I agree with Dr. Molitch.

DR. BONE: Any clarification, Dr. Genuth?

DR. GENUTH: Yes. I don't completely agree. I would not switch a person who was not doing well on metformin to this drug. I would add it. Now, if there was an excellent response, really phenomenal response, got down to normal, I might be then tempted to try withdrawing the metformin gradually to see if anything happened. If the patient started getting worse, I'd leave the patient on combination therapy. I know that's not answering your question.

DR. BONE: I think it will be very clear to the agency what your views are on that. I really do.

Dr. Hirsch?

DR. HIRSCH: I agree with Saul.

DR. BONE: Thank you.

We'll start with Dr. Illingworth on the right.

DR. ILLINGWORTH: Yes and yes. I would endorse its use as monotherapy and also as a potential drug to use in a poor responder to other drugs and as additional therapy in a person who needs combination drug therapy.

DR. BONE: Dr. Hammes?

DR. HAMMES: I would vote yes and yes. On the first issue, I think important with this obviously with a bit of confusion here among our own panel members is that there must be adequate precautionary measures in the labeling so that the average practitioner can make these same kinds of judgments and to who and when they are being used.

DR. BONE: Well, we'll have an opportunity to discuss labeling later too.

Dr. Critchlow.

DR. CRITCHLOW: Yes and yes. In terms of the monotherapy, it's clear that in the treatment naive there's a response and there is evidence that switching from a situation where the person is responding, that that's not appropriate.

DR. BONE: The Chair would vote yes to question 1(a) with the clarification that it would be a useful drug for monotherapy in a treatment-naive patient. I would probably not want to switch from another drug if I thought that other drug were having any beneficial effect at all. And in combination with metformin, I believe that the evidence is in favor of efficacy as well, that is, certainly.

The next question has to do with the comments.

It says, what comments do you have from the safety standpoint about the effects of rosiglitazone on: (a) liver? B is lipids. C is hemoglobin, and D is the heart.

I think we'll go around the table. We'll include our nonvoting participants after the committee. There are no votes on this. This is going to be all comments. I will ask actually each person to just go right down the list rather than going around four times. So, let's start with Dr. Illingworth, if you will, just go down the list then on number 2.

DR. ILLINGWORTH: I think the question concerning the liver, based on the albeit low frequency of liver abnormalities, there's clearly a need to monitor a baseline liver enzyme test and assess these at to-be-defined treatment intervals on therapy. And I would add to that that in anybody with preexistent liver disease, the drug probably shouldn't be used.

Lipid profile. I think it would be important to get a decent baseline lipid profile and characterize the lipid disorder in the patient and recognize the fact that the drug may change the lipid profile over the course of 2 or 3 months. And so, taking it a month later may not give you where it's going to get to on chronic therapy.

The potential for the drug to raise LDL I view as a potential adverse effect which may require more

aggressive lipid lowering drug therapy. Probably in somebody who has a high level of LDL to start with maybe this would not be the drug to use as initial monotherapy.

With respect to hemoglobin, I think the hemoglobin effects are probably due to dilution and monitor hemoglobin and hematocrit, but I don't think there's any data that suggests there's an adverse effect on erythrocyte, reticulocyte counts or on increased red cell destruction. So, I think the effects on hemoglobin are hemodilution.

Finally, the effects on the heart. I think those are, from my perspective, the effects probably secondary to increased fluid retention and are a compensatory mechanism for fluid retention.

DR. BONE: Thank you, Dr. Illingworth.

Dr. Hammes?

DR. HAMMES: In terms of the liver effects, I would agree that we need to have baseline monitoring and perhaps yearly or some defined interval follow-up given the drug class issues.

In terms of lipids, I think we need adequate precautionary labeling to encourage practitioners to screen out the people that may be at particular risk for increasing LDL in particular.

The hemoglobin and heart issues are I think

relatively minor. Again, particular at-risk patients probably need to be screened out in this regard and adequate precautionary labeling I think would suffice.

DR. BONE: Dr. Critchlow.

DR. CRITCHLOW: This is always difficult, as Dr. Bone said, when you've got an initial population that is just a small fraction of the numbers that will eventually be exposed to the drug.

The other issue is just the representativeness or lack thereof of the study population in comparison to the actual target population or the population with disease, particularly with the gender differential and the relative lack of information in premenopausal women. So, it's difficult to assess. I think that just underlines the importance of a thorough baseline assessment and continued monitoring especially in populations that were not as well represented in the study population as perhaps should or could have been.

DR. BONE: And you would just make those general comments on all those issues?

DR. CRITCHLOW: Yes.

DR. BONE: Thank you.

Dr. Molitch?

DR. MOLITCH: With respect to the liver, it appears that the risk for liver toxicity is probably

considerably less, if there's any at all, compared to troglitazone, but I'm not certain about that based on the small patient population that was so far studied. So, my own thought is that until we know better, I would consider there still to be a hepatic risk and probably to think about monitoring for this drug similar to troglitazone, perhaps monthly for a year or something of that sort, until we are quite sure with the numbers, as they accrue over the next couple of years, that it does not constitute that same kind of safety risk.

With respect to lipids, I am concerned, as is Roger, that the patient with a baseline elevated LDL could be made substantially worse, and I might well use another drug as first line or even second line therapy in the patient who already has baseline elevated LDL levels. Certainly these are something that should be followed every few months for the first year or so just to see where that patient may be going since it does seem to be a change.

The hemoglobin and heart I think are linked together with excessive fluid retention, and there clearly are some patients that are at risk for substantial worsening of congestive heart failure or fluid retention. So, I think this actually should be included in the labeling for this drug, that there may be some people who are at greater risk.

I'm a little bit concerned about the decrease in blood pressure with perhaps increase in sympathetic output that may be occurring which might even potentiate arrhythmias. I think it's an unknown area which I'd like to see studied a little bit more carefully.

Finally, I would add an E to this which is the risk of ovulation disturbance, the risk of amenorrhea occurring in the monkeys. At least I'd like to see some data accrued fairly early on with this drug in ovulating women to make sure that the same thing that occurred in monkeys is not going to occur in humans.

DR. BONE: Thank you.

Dr. New.

DR. NEW: With respect to the liver, I must say that I'm confused because I'm told by liver experts that monitoring with enzymes is not a perfect monitor, that you can have normal to minimally elevated enzymes and still have bad liver disease. So, how do you evaluate liver toxicity if you don't have good remote monitors from blood tests or clinical exam? So, I don't know about the safety of the liver. I'm going to assume that what has been standard practice, which is to measure the enzymes, is the best we have and therefore that's as good as you get.

With respect to lipids, I agree with Dr. Molitch. There's probably no clear adverse effect except

in the patient with increased lipids at the outset.

The anemia is very mild and I think of not great consequence.

And as far as direct evidence that the drug has an effect on the heart, I didn't see this in either the animal models or the humans, that is, no direct effect on cardiomyopathy, cardiac hypertrophy, or any of the things that you would look for.

DR. BONE: Dr. Genuth.

DR. GENUTH: I don't really have much to add. I would second everything Dr. Molitch said about the liver and basically about the lipids. I agree that I don't have any great concern about the heart in humans from the evidence we've seen.

I do have one thing not mentioned yet with regard to hemoglobin, and that's the phenomenon of a sharper drop in the patients who received both metformin and rosiglitazone. I somehow don't feel satisfied with the explanations as to why that particular group behaved that way, and I think that should be further observed in post-marketing surveillance when that particular combination is prescribed.

DR. BONE: Maybe you want to comment on that again at the labeling discussion in a little while.

Dr. Hirsch.

DR. HIRSCH: I agree with what has been said. I think so far as the liver is concerned, I'm a little concerned about very late effects which we'll only know after use of the drug, but I think anyone who has demonstrable liver disease by the usual enzymatic determination shouldn't have the drug.

I think the lipids are a concern. I think everyone who's put on the drug ought to have a lipid analysis done and if they're abnormal, it certainly ought to be repeated within 2 or 3 months to see if other drug treatment is better or an additional drug is needed.

I'm concerned about the hemoglobin. I think it needs more study.

I don't think there's any restrictions that one can impose right now except that anyone who has frank congestive heart failure I think or edema obviously should not be put on the drug.

DR. BONE: With regard to the question of hepatic toxicity, clearly the information that we have at the present time is encouraging in comparison with the marketed drug in this class, troglitazone. But I think we would all be happier -- and certainly I would -- if we understood the mechanism of that toxicity. It's ever conceivable that the transient reversible enzyme elevations that we saw with troglitazone and the occasional

catastrophe actually have different mechanisms. I don't think we can say that for sure. I think that leads us to maintain a note of caution here because those catastrophic episodes were very infrequent.

So, I think we will all be more comfortable when we've treated a few hundred thousand people and hopefully have not seen that problem. But I think we all have to understand that we do the best we can with the information we have and go forward. There's no alternative.

With regard to the lipid situation, I have exactly the same concern here, that we don't completely understand the mechanism of this phenomenon of increasing LDL and what's going on with HDL. I'm guided very much by my colleague, Dr. Illingworth, that this is something that we really need to have sorted out and it sounds like it's something that the company is well along in addressing and just must get that done.

At the moment I think we would have to be cautious and at least check lipids at the beginning and after a period of time to make sure we aren't seeing an unusually bad result in an individual. I think we would particularly keep this in mind in patients who may have other cardiac risk factors, as many diabetics will, even over and above their diabetes.

I think the understanding we have of the hemoglobin and cardiac changes, the anemia and this question that came up about the heart, which doesn't seem to have been a clinical problem, is that the patients actually have an expansion of the extracellular fluid space with no expansion or shrinkage of the red cell volume, as far as we know. But I think this needs to be much better documented in terms of the fact that we only have the one small study on the red cell volume, and we don't, for example, have a red cell volume measurement in patients who achieved criteria for anemia, if I can call it that, whose hemoglobins fell into an anemic range and then were taken off the drug to see if there's an increase in the hemoglobin and hematocrit without a change in red cell volume.

But I think it would also be very important to actually understand what's going on here. We've talked about peripheral vascular resistance and so on without any real solid understanding of the mechanisms involved here. I don't think that the questions that are open on this issue are sufficient to prevent us from using the drug, but I think they are extremely important to our understanding and long-term use of the drug, and I will expect to see those results.

I'd like comments from the nonvoting crew here.

Let's say Dr. Levitsky will start please.

DR. LEVITSKY: Well, I guess I was sitting close enough to Dr. Molitch that he heard my thoughts very clearly. So, I really agree with what he said. I feel very strongly that the initial monitoring for the potential for liver disorder should be exactly as is now recommended for troglitazone because if there is going to be a problem, we should be able to pick it up with that technique and we would be I think really at fault if we didn't suggest that until more information even though it looks like the risk is much less.

DR. BONE: Any further comments on these topics, Dr. Levitsky?

DR. LEVITSKY: No.

DR. BONE: Dr. Seeff?

DR. SEEFF: Well, first of all, let me try to make the waters clearer that I obviously made murky. The transaminases are a very good measure. The only time that I think we've had problems is when people have viral infection in which the lack of enzyme abnormality does not preclude intrinsic liver disease, but I think other than that, I think the transaminases are a good measure.

Jim Lewis suggested to me that had we not had the history that we have and on the basis of the information that we have now, would we even consider

monitoring, and I had to agree that we probably wouldn't because I think that the evidence is that if there is hepatotoxicity thus far, it has not been really fully detected.

Nevertheless, given I think the background that we have, given the fact that there has been shown to be toxicity in one of the animal species, even though I recognize that the two drugs that we are talking about are different in structure and perhaps in the way they function, I would agree that until we know more about this, and particularly in view of the fact that in the first drug that we don't want to mention here, much of the hepatotoxicity appeared and became apparent after the marketing, post-marketing, I would think at least for the next year and perhaps for a couple of years, we should monitor and get information.

I'm particularly concerned about people who have preexisting liver disease. I'm not sure in my mind that I would preclude such people unless they have overt icteric disease, for example, because I'm concerned about the fact that we may preclude treatment of individuals who have steatohepatitis in which I just don't know whether this is going to make things worse. I think we just have to watch those people particularly carefully.

But in any case I would agree that we should

use the same criteria for this drug as we've used for troglitazone.

DR. BONE: Thank you.

Dr. Lewis.

DR. LEWIS: Well, I'm going to respectfully disagree. I think we're suffering from troglitazonian nervosa, to coin a phrase.

(Laughter.)

DR. LEWIS: As Leonard said, if this was the first drug in this class, liver injury wouldn't even be a slide. It would be put up. There was no difference between this drug and any of the other comparators, and we would move on and we would talk about some of the other issues that have been talked about.

I attended at the beginning of this week a two-day seminar put on by the FDA on how do you assess drug toxicity and how do you monitor it. It was apparent from the drugs of recent vintage, which have gotten us into trouble, that there was a signal in terms of an elevation in transaminases that far exceeded that seen with the placebo and with the comparators. You can look at bromfenac and tacrine and tolcapone and a whole bunch of others and including troglitazone. The signal was there, and we now know that those drugs cause serious injury. Monitoring is in place.

This is a drug which, from what we know, 5,000 patients, there is no signal. There are a couple of patients who have had elevated enzymes, but in general we have nothing really to base severe hepatotoxicity on.

The notion that patients who have elevated enzymes shouldn't receive this drug I also find troubling because it was studied. There were 250 patients who had elevated enzymes who may have some benign underlying condition, and they would be precluded from this drug and it might be very beneficial to them. This is not troglitazone. From what I can tell from the pharmacology, from the metabolism, it's completely different. The only thing in common is it's a zone.

We can only be wrong I suppose -- and it's easy to say, sure, it's got to be monitored for the next year. What does that buy us? Monitoring, number one, is not easy. It's expensive. We had 4,000 troglitazone patients who were monitored during clinical trials. There was a signal. Now, I wasn't around for when that drug was originally discussed, but 2 percent of the population on troglitazone had elevations in enzymes that were more than threefold elevated. This drug was also monitored for thousands of patients for more than a year. There's no signal.

Now, does that mean it will never cause hepatic

failure? No. You can't ever say that about any drug, but I think we have to be reasonable. We have to be prudent, as people pointed out, and I just don't see the signal here.

And especially among patients who have elevated enzymes to begin with, I agree with Leonard that we ought to know why they're elevated. Do these people have hepatitis C? 2 percent of the population has that. Is that going to prevent them from getting this drug? No. There are many studies that I think should be done post-marketing including studying patients with this non-alcoholic steatohepatitis, find out if this drug helps them, follow people who need anti-lipid drugs, find out if there is any kind of toxicity. There's probably more hepatic injury from the statins than there are from this drug as far as I can tell.

We're assuming it's hepatotoxic. We haven't been shown data that it's really hepatotoxic. I really don't know what to do with dog studies. I don't know that any of us really know what to do with them. We don't have a perfect marker of monitoring, and if we are to believe that this is an idiosyncratic, unpredictable reaction, as we believe it is for troglitazone, which didn't appear during the clinical trials -- all the patients even with very high enzymes, even though they were kept on the drug,

did not progress to liver failure, but there was a signal that something was going on there. We don't have that signal here either.

So, I must say I don't feel the compelling need that the members of the committee seem to have thinking that this is another troglitazone. I hope it is not and I hope that these remarks don't come back to haunt me. But the reality is I think post-marketing we will know what happens. If we do not include monitoring in the labeling, there's a whole bunch of competitors out there who are going to be monitoring this drug for the company and for the FDA, and we will know in fairly short order whether or not the labeling needs to include monitoring if we start seeing idiosyncratic reactions with enzymes, especially the hepatocellular injury. And that is what we are interested in. This is the injury that has a fatality associated with it, not a little bit of a bilirubin rise or an alk phos, but true hepatocellular damage.

As with many drugs, we don't know everything we're going to know about them when they're initially released. The big study, as you've said, is once it's out there and we have hundreds of thousands of people who try it, and if it's going to be useful, we'll know. If it's going to have the toxicity, we will know.

But I don't think we gain very much by giving

this the same class labeling as troglitazone. The labeling is useful to guide physicians on what we know. I think you put it in the label what this did in terms of enzymes relative to the comparators. I think you can certainly point out that it didn't have the same percentage rise that the other drug had although there were no head-to-head studies. These are issues that will come up later and we'll talk about them then.

DR. BONE: Ms. Killion, comments on the safety questions?

MS. KILLION: Well, I think that a healthy dose of troglitazonian nervosa probably is a good thing, but it has to be balanced. I think I agree with Dr. Lewis.

It strikes me that the one thing I remembered from the previous meeting was that even when you did monitor, you recommended monitoring, it was not done anyway for various reasons. One is it's hard to get the patients in. The physicians don't always emphasize it, whatever.

But I think that the safety standards -- I have a level of comfort from what I've heard today not only from the sponsor but from the panel as to the approach and optimism for this particular drug. So, as a patient, I think that I'm very pleased to see that it's going to be added or that it is being considered for being added to the armamentarium.

DR. BONE: Thank you.

The next question will be question 3, and we're just going to go around and vote on this amongst the voting members. We'll start with Dr. Molitch. Question 3 is, based on the available information, do the benefits outweigh the risks for the use of rosiglitazone in the treatment of hyperglycemia in type 2 diabetes: (a) as monotherapy, and (b) in combination with metformin?

DR. MOLITCH: Yes and yes.

DR. BONE: Dr. New?

DR. NEW: Yes and yes.

DR. BONE: Dr. Genuth?

DR. GENUTH: Yes and yes.

DR. BONE: Dr. Hirsch?

DR. HIRSCH: Yes and yes, but we understand (a) now to be not removing another drug and starting this. My vote is monotherapy if this is the beginning drug.

DR. BONE: I think this was understood to be subject to whatever footnotes were added to question 1(a). Is that fair enough?

DR. HIRSCH: Yes.

DR. BONE: Dr. Illingworth.

DR. ILLINGWORTH: Agree. Also yes and yes.

DR. BONE: Dr. Hammes?

DR. HAMMES: Yes and yes.

DR. BONE: Dr. Critchlow?

DR. CRITCHLOW: I would say as a statistician, it would appear so. Yes and yes.

(Laughter.)

DR. BONE: Thank you.

And the Chairman would vote the same way.

Now, we're going to have our recommendations for the labeling of rosiglitazone as question number 4.

I want to clarify something about our plan here. Because of the opportunity -- and we've actually had some remarks pertinent to this already -- to include the views of our hepatologists on questions that may relate to the class, we had originally intended to address these two questions about class labeling regarding hepatic toxicity or monitoring tomorrow. I think we'll allow people to make preliminary comments today, and then any additional comments they want make tomorrow will be made tomorrow. And the FDA will understand that we're doing this a little bit informally but information will be there for you.

So, to be clear, question 4 is going to be, do you have recommendations for the labeling of rosiglitazone? Question 5 will be recommendations about post-marketing studies, and then we will have two additional questions. In fact, I think we should take these before we get to question 5. And they are, should the labeling for other

members of the thiazolidinedione class of drugs -- it means other than troglitazone -- address the subject of hepatotoxicity observed with troglitazone, and if so, how? And the second question, should the labeling for other members of the class specify that liver testing be performed at periodic intervals, and if so, how frequently? Those are going to be questions that will be asked after we talk about rosiglitazone specifically in question 4.

Is everybody clear about this? Okay.

I think we'll just go around the table on question 4 and ask if we have any recommendations for the labeling specifically of rosiglitazone. Many of us have already made comments during the previous discussion and can just refer to those if they like. Let's start with Ms. Killion. And I assume we're talking here about both the product monograph and patient package insert as well.

MS. KILLION: From the patient perspective, I would say I'd want to have the information with respect to the increase in the LDL and also I'd like some information for the effects on women of childbearing age.

DR. BONE: Thank you.

Dr. Illingworth, additional comments on recommendations for labeling for rosiglitazone?

DR. ILLINGWORTH: I think the lipid changes should be in the labeling information underscoring the need

to monitor or get a lipid profile. I would include actually putting the current ADA recommendations for what is the optimal level -- LDL under 100, triglyceride under 200 -- in patients with type 2 diabetes so patients are aware of that and doctors who are using these drugs are aware of those recommendations.

And the need to also potentially look at -- I think this needs to be looked into further -- drug interactions. I was pleased that the drug is metabolized not by the C3A4 system, but I guess taxol and cerevastatin go through the same enzyme metabolism pathway. Perhaps those should be included or something should be included in those. We don't know yet if they're going to have drug interactions with these drugs, hence need for monitoring.

DR. BONE: Dr. Hammes?

DR. HAMMES: I'll just refer back to my comments before and add to that I really think there ought to be something about the gender differences and let the clinician decide if that's significant.

DR. BONE: Thank you.

Perhaps we'll start with Dr. Lewis.

DR. LEWIS: We're not addressing the liver?

DR. BONE: You may include comments on the liver, if you wish, that are specific to this compound. We're going to address the class later.

DR. LEWIS: Every comment I've heard so far should be included in the labeling. Again, what's the labeling for? It's to guide physicians; it's to guide patients on what the drug is all about. Some people read it, some people don't. But I think all you can do is put down what the information is.

As far as the specific liver effects, I would certainly say that with troglitazone there was X amount of elevated enzymes compared to the other groups. I would put down what the figures were with this drug. You might even say there has been post-marketing fatal hepatitis with troglitazone. We don't know if that will happen with this drug. That's a fair statement.

But with no smoke, I would not support definite monitoring other than clinical signs of hepatitis or untoward events now. And even if we did a post-marketing surveillance study, you do another 5,000 patients and if this is a rare event that's 1 in 40,000, so we've got 10,000 patients and we still might not see it. If the enzyme elevations had been more prevalent, that would not have been my recommendation. So, I'm going to stay with basically my explanation from before.

DR. BONE: Thank you.

Dr. Seeff.

DR. SEEFF: Well, with regard to everything but

the liver, I agree with what everybody has said. I'm still uncomfortable about not keeping an eye on the liver enzymes even though I do recognize that the frequency of abnormalities has been very low. I'm particularly concerned that we would have no information in people who have already got preexisting abnormalities, and at the very least I would want to monitor somebody. I would like to get the enzymes done before treatment is started, and if the enzymes are abnormal, I would want to monitor those patients without doubt.

For the rest, there are several options. One is just to do a clinical assessment of the other groups. The other one is to, in fact, monitor at the same rate, which would be easier because it would fit, and the third is to perhaps check out the enzymes at a shorter interval.

I am cognizant of the comment that had been made at the last meeting that we are dealing with people who have diabetes and therefore have to stick their fingers at least on a regular basis. So, it's not that they're going to bleed themselves unnecessarily. They're going to have to do that anyway. I can't remember now whether there is a test for ALT or whether there should be a test for ALT which could be done on a finger stick. If so, there's little doubt in my mind that I would monitor and check and see.

I think that if something went wrong, even though this is quite unlikely, and we didn't keep an eye on this at least for the first year and maybe a couple of years and then reassess -- if nothing has happened and we've seen enough people, we can say that's it. We're comfortable, but I am not comfortable about saying I would just leave this to chance and wait for jaundice to occur because jaundice is too late in my view.

DR. BONE: Well, now that we've had the unanimous opinion of the hepatologists, everything is clear.

(Laughter.)

DR. LEWIS: Let me just comment that I would certainly agree that patients who have baseline abnormalities, just like we would watch them on any other medication, they should be monitored, if that's the term you want. We watch those. How far do we let them go? It's an individual decision based on the drug and the type of toxicity that we're seeing.

But I guess we have a fundamental difference on just basic monitoring of a drug where there's no signal. I harken back to if this was the first drug that we had seen in this class, I don't think we would be making that comment.

DR. BONE: I think we've got this very clear

from the hepatologists. Thank you both very much. You have been remarkably helpful on this.

Dr. Levitsky, comments on the labeling of rosiglitazone.

DR. LEVITSKY: Well, I think pretty much the issues that I agreed with before I'd like to be in the labeling, and I really do feel that although the hepatotoxicity risk is probably very low, we'd better be very, very nervous for a while and monitor frequently.

There are two other things which I think are important for patient labeling if they haven't been mentioned because they'll be of concern to patients, and that is the issue of the development of edema and of weight gain. I think that patients will worry more about those than some of the things we're worried about.

DR. BONE: Well, and what would you say?

DR. LEVITSKY: That there is a possibility of edema, which is not going to be a significant issue, but should be brought to the attention of their physician, and a small possibility of a slight increase weight, which shouldn't interfere with the efficacy of the medication.

DR. BONE: And you wouldn't regard this as something that required precautions in any particular group of patients, for example?

DR. LEVITSKY: Well, perhaps people with

preexisting cardiac disease should be particularly warned about it.

DR. BONE: Thank you.

Dr. Molitch?

DR. MOLITCH: I'm going to side on the side of requiring liver function testing with the idea that it could be a statement saying although nothing has been found with this drug, it has been found with other drugs in this class and monthly monitoring for a year or whatever is deemed appropriate would be worthwhile.

I would put in the precaution about in patients with preexisting heart disease that edema or exacerbation of underlying congestive heart failure can be significant and should be watched for as well.

I'd also have a concern about amenorrhea. It ought to be a potential labeling issue.

DR. BONE: And what would you say?

DR. MOLITCH: I'd say anovulation has been reported in animal species and it's a potential.

DR. BONE: Dr. New?

DR. NEW: I agree with Ms. Killion that it is very important to put in the label that women who are potentially pregnant should not use the drug until safety to the mother and the fetus is demonstrated.

DR. BONE: Thank you.

Dr. Genuth?

DR. GENUTH: Well, first of all, I would put in the labeling that patients who are inadequately controlled with regard to blood glucose on metformin should have this drug added and not substituted.

I also would put something in the labeling to alert the physician to the possibility of anemia in patients receiving a combination of metformin and rosiglitazone.

I found Dr. Lewis' arguments very rational, and if we were working in a vacuum, I would agree with you. But we're not. We are working in a situation where we've had a previous example from a cousin at least of this drug, and probably more like a brother-in-law, and I think that there are issues of public recognition that there is a serious problem with another drug in this class. I think it's just prudent to take cognizance of all those other factors and monitor. I don't know for how long.

I think the most rational way to decide would probably be on a number of patients; that is, statisticians could calculate for us how many patients you would have to treat without any event before you could conclude that the odds for having an event were just too low to worry about. There must be some number like that.

DR. BONE: Dr. Hirsch?

DR. HIRSCH: I agree with Dr. Genuth. I think somehow in the labeling we ought to indicate that the evidence is best for adding this to metformin when metformin is not doing the full job. And I think we have to take into consideration the fact that use otherwise means making a choice of beginning therapy of rosiglitazone or whatever else is available, and I think we can help people by saying that the liver disease should be kept in mind and there should be testing with this. The serum lipids should be kept in mind.

I think also not only the pregnancy, but I would agree with what I thought you were saying earlier, Dr. Levitsky, that if you have a choice, this is not the drug to use in type 2 diabetes in adolescents.

DR. LEVITSKY: I'm not sure. I think we don't know that. That would be my feeling.

DR. HIRSCH: Well, I'm just thinking what one would put down. Say there is concern about its use in adolescents because of the possibility of increasing fat deposition that may not disappear, whatever.

DR. LEVITSKY: I actually have on my list post-marketing studies.

DR. BONE: That may be a point to bring up at that time.

DR. HIRSCH: Well, I think the labeling is what

we're on. I would feel this should be put in the labeling.

DR. BONE: Dr. New.

DR. NEW: We did not discuss whether this drug is advisable in children or not because I don't think it's been tested in children. Therefore, the question is should it be excluded from being used in children. I didn't do that. What I recommended is that it needed a post-marketing study, but I really need guidance as to what the lower age limit should be. If it's going to be used in adolescents, should it be used in a 5-year-old?

DR. BONE: I hate to interrupt a vote, but since this is short answer, essay questions, I'm going to just ask perhaps Dr. Misbin or the sponsor to tell us what the entry age was for the clinical trials that have been performed to date.

DR. MISBIN: Not 5.

DR. BONE: No.

DR. WHEADON: In the trials that you've been looking at, the lower limit was 40.

DR. BONE: Presumably then the label can say that the drug has not been tested in children or adolescents.

DR. MISBIN: It should be pointed out that we don't have data -- the labels don't in general say that. So, do you feel strongly enough to make a specific

exception for this drug? Is this different from all the other drugs that are used? We have labeling for type 2 diabetes --

DR. HIRSCH: I certainly do feel exactly that way.

DR. BONE: Well, I guess I see Dr. Misbin's point, though. If we have the same kind of data in all the other -- I don't know. My view would be to be consistent with policy, but I think there is some concern.

DR. HIRSCH: No. There's an additional item here, and that is the way this drug works. In animals it makes more fat cells and we think this has something to do with obesity, et cetera, et cetera. Until we get data to the contrary, at least the labeling should indicate that when a choice can be made or whatever, the adolescents are sure not the place to fool around with this.

DR. MISBIN: Well, it's one thing to put it in the label as a statement of the facts, the way you just said it. I think it's quite another to have in the indications saying this drug should be used with caution or contraindicated. That's really a different order of magnitude. I don't think anyone would object to putting facts in the label. That certainly should be, but to put it in the indications section, is that actually what you're recommending?

DR. HIRSCH: Caution. I'm not sure it ought to be contraindicated, but certainly caution would be appropriate I think.

DR. BONE: Well, go ahead. Dr. New, further comment?

DR. NEW: You know, this happens in my experience with many drugs where there is no clear evidence of the effect of the drugs in children, particularly on growth and development. Dr. Sobel knows that that's been one of my pleas here is that children shouldn't be orphaned from studies of new drugs. It takes a whole new study because all of you know that the drug clearance rates in children are different from adults and in fact they may need a bigger dose to get the same effect because their metabolic clearances may be bigger. Therefore, scaling it down by weight and all the other things which you'll have to put into this label, if you include children, becomes a big problem because I think to say that children should have their drugs scaled down based on weight or surface area is very flawed logic.

So, my own thing is I don't want to exclude the children, but I think that we should ask for studies in children to be done once they are going to be included in the population treated.

DR. BONE: What would you say about the

labeling for now, though?

DR. MISBIN: I think, though, you have to recognize -- everything you say is completely true, but just recognize, I think, that if there are strong cautionary statements in the label, it will be very difficult to do those studies. So, a strong statement in the label might actually preclude the very data that you wish.

DR. BONE: So, I think the committee has expressed some concern about this. Do we need to further advise the agency about this? Dr. Bilstad, did you have a comment?

DR. BILSTAD: No. We appreciate the comments that the committee has made and we'll take them into consideration.

DR. MOLITCH: I think this issue on the children is not just not having studies done in children. There's a lot of very strong theoretical issues about this that may make it a contraindicated drug in children.

DR. BONE: So, you would make it more of a point than usual.

DR. MOLITCH: I would make it much more of a point than usual until there are clear data, clearly done experimentally, to show that it is safe to do in children. This is a very different drug than the other drugs, and I

think troglitazone falls in the same class.

DR. BONE: Dr. Misbin's point I think is that that will have to be artfully worded if it is to be considered consistent with doing the studies that you want and to have a label, it's going to be an exercise in writing probably to get that just worded.

DR. MISBIN: Well, it's more than that, Mr. Chairman. If people really think it's dangerous in children, we should discuss this. I mean, that's another matter.

DR. BONE: No, no. I don't think that's the implication at all.

DR. MISBIN: Well, I think that's what Dr. Molitch said.

DR. BONE: I think he's saying it's a potential concern.

Dr. Levitsky?

DR. LEVITSKY: I guess that I would feel very bad if you told me, since we've defined childhood as ending at age 18 or in a children's hospital at age 21, that I couldn't use this in a fully grown 14-year-old girl with type 2 diabetes or even a 12 or 13-year-old fully grown. So, I think I'm very worried about this. I think we need to test these drugs in people like that, but it's very hard to define what childhood with type 2 diabetes. I would

hate to think that we had taken this medication away from that population who are often quite poorly controlled.

DR. NEW: I'm very sympathetic with Dr. Levitsky's point of view, but I think we shouldn't exclude adolescents from taking it. Somehow somebody has got to say we need to study children. That's all.

MS. KILLION: I have a question if I can just develop it a little bit. Number one, how common, how prevalent is type 2 diabetes in children?

DR. BONE: The left side of the table are all nodding in unison. It's kind of a wave phenomenon.

MS. KILLION: So, that would be question one.

And two, just as an observation on how studies are conducted, as a woman I have to say that I often find that women are shorted on the study point. So, there's sort of a two-pronged problem here. It occurs to me from what I've read -- and I may be mistaken because I am certainly not as knowledgeable as the rest of the panel -- that the majority of type 2 diabetes patients are women, and yet it seems to me, when I look at these studies, the predominance is overwhelming white male. So, not to inject too much feminism into this, but I have to say that there is a difference.

So, I am worried about what is the prevalence in children and I would ask that the studies be more

balanced to represent the population that is affected.

DR. LEVITSKY: It's the largest increasing group right now just because children are getting more and more overweight.

But in regard to this issue in general, we have a disorder which is more prevalent among Hispanic and African American women and it's been tested in white males.

MS. KILLION: And Native American I guess too as well.

DR. LEVITSKY: And Native American or native peoples in general. So, there are lots of groups that are disenfranchised here.

DR. NEW: I just want to say that in answer to this problem of deciding whether drugs are recommended in children or not, there's a big-scale effort to do drug trials in children. In my unit we've set up a whole thing, an infrastructure, for doing it.

DR. BONE: I guess I am the last one to comment on this. Oh, sorry. Dr. Critchlow.

DR. CRITCHLOW: I just wanted to add one comment to the others and that is just a note about the potential relationship between the lipid increases and decreased hemoglobin A1c response, that that was something that was noted, again just as a caution.

DR. BONE: Thank you.

For my part as far as comments on the labeling, it seems to me that the issue about use in childhood and adolescents is a thorny one in the absence of data. Dr. Molitch has raised the point that this may be more of an issue in this particular case than it might be with some other kinds of drugs. At the same time, both Dr. Levitsky and Dr. New have sort of, in a certain way, stepped firmly on both sides of the fence --

(Laughter.)

DR. BONE: -- by commenting that they really want to be able to use the drug in type 2 diabetics who are adolescents, but are concerned about the fact that we don't have information and need to get more information.

So, I'm getting the feeling here that the sense is that we'd like to see something in the labeling indicating the limit of the information that we have and a cautionary note without making the statement that this is contraindicated. I think that's sort of the drift here. Again, there are sort of nods around the table.

DR. NEW: Yes.

DR. BONE: Yes, okay.

Then further, I would have thought that a comment along the lines previously mentioned about the fluid retention being a potential issue in patients who have basically any other disorder where fluid retention is

an issue. It's not limited to cardiac disease but patients with nephrotic syndrome or whatever, that any condition in which fluid retention is an issue may be potentially aggravated and should be carefully monitored at least clinically.

And I would endorse a number of the other comments that I've heard as well. I don't need to repeat them.

We now are going to discuss a little bit about class labeling questions and we'll have an opportunity to revisit some of these points tomorrow if we think that anything comes up that would alter our view. But we've been given a preview that suggests that the hepatic issues are likely to not be any more of an issue tomorrow. These are two questions. Much of this has already been covered, so we can be concise I think. I'm going to ask each person to take both questions. I think you all have copies of these questions. They're in your packages and it's in the briefing package for tomorrow as well.

Question 1, should the labeling for for other members -- and that would include this drug, other than troglitazone -- of the thiazolidinedione class of drugs address the subject of hepatotoxicity observed with troglitazone, and if so, how? And should the labeling for the other members of the class specify that liver testing

should be performed at periodic intervals, and if so, how frequently?

Maybe we'll vary the order here and ask Dr. Hirsch to comment first.

DR. HIRSCH: Well, I don't think that we should do anything different with any drugs of this class than we've done with the current one, the rosiglitazone. I understand we're addressing the class labeling issue, but I'm just trying to develop my thoughts about it as quickly as I can without having looked at this before.

So, I would agree that the -- because I think the rosiglitazone has very little evidence at this point of hepatic damage or hepatotoxicity, so I would assume that other drugs coming along might be in the same category. Therefore, I would recommend that we do with the other drugs what we've agreed to do with the rosiglitazone. That would seem to be the rational thing to do.

So, the answer to the first one is that we should address the question of hepatotoxicity and indicate that other members of this class have shown this. That's the first thing, and therefore one should be cautious about it. If we're going on, secondly, we should make the same recommendations for testing that we've done with rosiglitazone.

DR. BONE: Well, what recommendation would you

make about testing with rosiglitazone?

DR. HIRSCH: Well, I agree that we should, first of all, have liver profile before starting therapy, and if there's any evidence of aggressive or liver disease of any kind, one shouldn't use the drug. If one does use the drug, that there ought to be monitoring. I guess I'm not in a position to specify how frequently this should be done, but I would imagine this should be done several times within the first year.

DR. BONE: Would you monitor patients who had no evidence of liver disease when they started on therapy?

DR. HIRSCH: Yes. I think that's what we agreed to do with the rosiglitazone.

DR. BONE: I think we're just kind of getting comments. There's no formal agreement on any of this. There's a certain difference of opinion on some of these points.

DR. HIRSCH: I would do it less frequently perhaps, every 3 months or something of that kind, yes, for the first year at least.

DR. BONE: Dr. Genuth.

DR. GENUTH: Without having a lot of time to think about it, right now I would say all members of this drug class should be -- well, labeling, okay. This drug class should indicate in its labeling that one member has

caused serious liver toxicity requiring transplant and death. There can be an individual sentence that follows regarding the data to date on the particular drug that the label is for. So, if the data to date indicates very little risk for rosiglitazone, then the sentence after that could say so. But I think there ought to be an initial sentence that says this drug class has exhibited a really bad adverse effect.

I would monitor on the same schedule that we're doing for troglitazone, but not forever. I think you either pick some reasonable interval of time arbitrarily or, as I said before, try to calculate a volume of patient exposure that would reassure everyone if no serious event occurred.

DR. BONE: Dr. New had made some comments on this topic earlier.

Dr. Molitch?

DR. MOLITCH: I'll reiterate what I said earlier, similar to what Dr. Genuth has said, that there should be some warning that drugs in this class do have toxicity. There's been none noticed for this particular drug. Nonetheless, because of this, we recommend monitoring on a monthly basis for the first year and then less frequently thereafter.

I agree with Saul that there should be some way

of doing a power calculation. We heard last month that even with a rate of 0 in 500, you could get an upper confidence limit, even with no events. So, somehow we should be able to come up with a number to see what the power calculation should be.

DR. GENUTH: It's called the eventless test.

(Laughter.)

DR. SOBEL: I just have one comment that I'd like to make. That sort of calculation would have to look at two variables, the number of patients and the duration of exposure, but that's your idea.

DR. MOLITCH: Yes.

DR. GENUTH: Yes, patient years.

DR. MISBIN: It would also need an estimate. You can't make a power calculation unless you have an estimate. What would you say the estimate is?

DR. MOLITCH: 33 years?

DR. MISBIN: No, no. The estimate for the incidence of the event. Since there are no cases, what estimate would you take?

DR. MOLITCH: It's difficult to know.

DR. GENUTH: Can we answer that tomorrow after we have dinner together tonight?

(Laughter.)

DR. MISBIN: You can answer it tomorrow, but

you won't have any more information.

DR. CRITCHLOW: I think you have to pose a range of possible incidences of 1 in whatever, 1,000, up to 1 in 1 million and just say, given this range, this is what you would expect.

DR. MISBIN: Well, at best 1 in 2,000. Anything other than that would be totally irrational. 1 in 2,000 would be the estimate.

DR. CRITCHLOW: In the absence of any information, all you can do is --

DR. MISBIN: To exclude that with any confidence would be an enormous number of patients.

DR. BONE: Dr. Levitsky, comments on should the labeling of the class address the troglitazone issue, and if so, how? And secondly, what about monitoring?

DR. LEVITSKY: I agree with the two gentlemen who just spoke, and I'll have to let the statisticians work with us to deal with how that plan is going to be carried out so you know when to stop.

DR. HIRSCH: Can I just make a little comment?

DR. BONE: Dr. Hirsch wishes to make a comment.

DR. HIRSCH: This is obviously not going to be an uncommon thing to have a drug which is purposely -- I don't know what this was -- but there will be drugs that are purposely engineered to do the same job that other

drugs do, but don't have an adverse effect, a common adverse effect. With NSAIDs this is a big, big issue.

So, as you think about this, it's not so bad, for me at least, to keep in my mind if some NSAID came along now and it was purposely made to not have GI irritation or something, would I or would I not say something about drugs of this class, et cetera. So, we're getting into that kind of arena here, and there are some recent experiences out there that can help us with whether we should or shouldn't say this.

DR. BONE: It's really show time now for the hepatologists.

(Laughter.)

DR. BONE: We get the final distillation except for comments about post-marketing studies, which will be the final go-round.

DR. SEEFF: This is tougher than it was last time around.

The evidence is that there is little toxicity here, but I am convinced that given the history of what we have faced up until now, that it is mandatory for us to at least monitor this for a particular period of time. Again, I recognize the fact that in the previous drug most of the information came in the post-marketing period, and therefore I think it's appropriate for us at least to keep

an eye on this.

I don't know how to calculate it if you don't have an incidence. It would be wonderful if we could say we needed to follow for a year or 30,000 patients and that will give us the answer. We may just have to choose something that seems reasonable. But I do wish to state that we should revisit at the end of the period of time that we have set, and if there is no evidence whatsoever that there has been toxicity, I think at that point we can stop or we can change our minds.

But for the moment I believe it should be monitored and that the information about troglitazone should be in the label and the information about this particular drug should be in the label, indicating that in comparing the two, this is far lower, but because of the history of the past drug, that we need to do something about it.

I would like to monitor at the same interval that we've decided to monitor individuals who are receiving troglitazone, and if I remember correctly, we were at that point monitoring at monthly intervals for the first 8 months and then at 2 monthly intervals thereafter. I don't know if a change took place after our previous discussion, but if it hasn't, I think at least --

DR. SOBEL: I can comment. After the first

year, it's more discretionary periodically. But everything else is as you said.

DR. SEEFF: So, I would follow the plans that we have for troglitazone.

DR. BONE: Dr. Lewis.

DR. LEWIS: Let me ask the agency whether there's any precedent for removing monitoring from labeling. Once it's in, has it ever been dropped?

DR. BILSTAD: I don't recall any situations right now, but it certainly is possible that we can do that. We constantly look at labeling to see whether it's still relevant, and if, based on new information, we think that it should be changed, we certainly would do that.

DR. SOBEL: A recent example that you probably are aware of is the statins which established a good track record, and we've altered the labeling considerably, monitoring not only about liver. We started with a rather severe position on the lens as far as cataracts. When we gained reassurance that that did not occur, that was dropped. These are just two instances in my division that have occurred within the past several years. So, don't think that once we've established the monitoring, it becomes an ingrained habit.

DR. LEWIS: Well, as far as the class information, it's what I said before. I think the

troglitazone information should be there, what we know about this drug should be there with the statement that there have been no -- we don't know if it's going to cause fulminant hepatitis. That's the only statement you can make. There hasn't been any and there wasn't any signal. So, that's about all you could say. But I think as a class -- there's only one chair in the room at the moment, but there's going to maybe two more added to that. You could certainly do that.

I would stand by what I said before about the monitoring. If you do pretreatment enzymes and they're elevated, those individuals need to be monitored on a clinical basis with whatever frequency the clinician believes is appropriate. I don't know that monthly is going to do it. Tacrine is every 2 weeks. If you're looking for something rare and idiosyncratic, we don't even have a signal that any of the enzymes occurred within a certain monthly period to know what the correct monitoring would be.

There will be individuals and clinicians who may want to monitor at their own discretion knowing about troglitazone even if monitoring is not stated as one of the labeling requirements.

DR. MISBIN: I just wanted to ask a clarification. The troglitazone label currently precludes

the use of the drug in patients that have elevated transaminases of, I think, 1.5. I gather from what you're saying, you would not have that preclusion here. Is that correct?

DR. LEWIS: I would not preclude it. Those individuals should be watched. Even though there was no signal in that group either, they can be monitored as we would monitor anybody with underlying hepatic dysfunction because we don't know.

DR. MISBIN: The rest of the committee feels that as well?

DR. SEEFF: Not only monitored, they should be diagnosed. They've got an abnormal enzyme and you've got to find out what the cause of that is.

DR. MISBIN: It's not something the FDA ordinarily does.

DR. SOBEL: This is not a burning point, but we're speaking of class labeling as of this early part in the evolution of this field. I don't know if this class labeling issue, once we have enough experience to show us that chemical structure and lack of demonstration in the clinical trials has been reassuring, whether this is going to be forever. Every member of the class which may be introduced may not have to go through this initiation. But we're really very young in the field right now, so I think

the class labeling is really quite specific to what's going on in a rapidly evolving field.

DR. BONE: Dr. Hirsch had commented that he would suggest labeling recommend against use in patients with preexisting abnormal liver enzymes. Dr. Lewis has said that he would not take that view necessarily. And Dr. Seeff, I believe, also took the same position but endorsed that we should figure out why their enzymes are elevated, and Dr. Lewis agreed with that.

We have three other people who have already commented here but didn't address the specific issue of whether or not the drug could be used in patients with, let us say, mild abnormalities of their liver enzymes, particularly ALT, prior to starting treatment. I'll just ask each of you to comment on that. Dr. Genuth?

DR. GENUTH: Well, at this point with the relatively little knowledge we have, I would leave that to the discretion of the physician, having given the physician as much information as we can in the PDR.

Can I ask Dr. Sobel about a situation much closer to home than NSAIDs? Is the FDA thinking about any changes in the labeling for sulfonylurea drugs in light of the UKPDS results?

DR. SOBEL: Yes, we are. We feel that the reassurance provided by that should lead to a change in the

labeling, and we have been discussing that internally, that the sulfonylurea class, which got mostly stigmatized by the UGDP, we now have countervailing evidence that is of sufficient magnitude to remove that. But that will take internal discussion.

DR. BONE: With regard to initiation of therapy in patients with preexisting elevation of liver enzymes. Dr. Molitch.

DR. MOLITCH: With less than threefold elevation of liver enzymes I think we're talking about, then I would not preclude its use if there are no obvious cause, other than probable fatty liver. It's also comforting to note that within a 30-year period, we'll be able to get rid of the transaminases for this, if necessary.

DR. BONE: Thank you.

Dr. Levitsky, do you want to comment on the use in patients who have enzyme abnormalities prior to initiation of treatment?

DR. LEVITSKY: My personal small anecdotal experience with that other drug was that the diabetes steatosis -- the enzymes often dropped when you gave them the medication. So, I wouldn't want to deprive people whose enzyme levels were only not more than 3 times normal of the drug.

DR. BONE: All right. Thank you.

Let's see. We're talking about the class labeling. How should we do it and what about monitoring? Ms. Killion?

MS. KILLION: My thoughts are that because of the way the problems with troglitazone became evident, I think that patients would benefit from a very cautious approach. I think that's desirable, but I think you also have to weigh that with practical considerations and what you're likely to get. I know that previously the liver testing was -- I think the quote was -- abysmal. And I think that's due to a lot of reasons. It's inconvenient for the patients to come and get the test. They don't want to do it. It's whatever. There's a lot of reasons for it.

So, I think we ought to have some kind of information that says that due to the toxicity that was evident in this class of drugs, that you ought to have the initial profile done. If you have elevated enzyme levels, you should have some kind of heightened monitoring. And if you have normal enzyme levels, that you should have probably less frequent monitoring done to ensure that those levels are maintained. So, I think that's a fairly practical approach. It's probably not the most cautious, but I think that it's probably what you'll get.

DR. BONE: Thank you.

Dr. Illingworth.

DR. ILLINGWORTH: I agree that I think the labeling should include mention of what's known about troglitazone.

I think it's fair also to say that this may not be a class effect. The metabolism of troglitazone goes through the C3A4 and rosiglitazone goes through the C28 and 9. So, this may be a different metabolism.

But I think without further data, we still need to endorse liver monitoring. I would probably, given the data I've seen presented in our background and today, be comfortable with a less frequent than a once a month for the first 8 months frequency. Perhaps once a month for 3 months, then once every 2 months for 6 months, and then once every 3 months. That's probably going to be frequent enough. But if the patient went on the drug for a longer time, they'll get more reassured and the doctor will too.

I think also -- and this came up before -- the need for patient education about what are the symptoms of liver toxicity. That needs to be very, very apparent. So, patients are informed these are things to look out for, and perhaps the patient should be given a flow sheet underscoring their need to monitor and then get feedback on what the blood test results are.

I agree with the hepatologists that I don't

think preexistent moderate increase in transaminases should be an exclusion, but I also would strongly endorse find out why the liver enzymes are high. You know, just assume you have hemochromatosis that caused their diabetes he hasn't even recognized. But I would certainly say more frequent monitoring would be appropriate in patients who have mild abnormal liver enzymes at the start. And I would agree if it's more than 3 times normal, they shouldn't be on the drug and find out why.

DR. BONE: Dr. Hammes?

DR. HAMMES: I agree with most of what has been said here.

I want to give one little example, though, about a problem with class labeling of drugs. This was a personal situation we had a few weeks ago where we needed to give a patient a sulfonamide diuretic, acetazolamide, for a brain cerebral reserve study. And there's a class labeling clause in there that gives a precaution of allergies to other sulfonamides. This patient really needed this study and everybody was really nervous about giving him acetazolamide.

So, I spent the best part of an afternoon with the drug information center folks trying to find out what the significance of this reaction was in this case. And all we could find was one single case report many years

ago, and we just wasted a whole afternoon and the patient almost didn't get a study he needed.

So, I think if you do this kind of thing in class action labeling, it's imperative that you give the clinician some idea of what the magnitude of this problem is. And in the case of the drug we're talking about today, there really is no problem, and that needs to be indicated there. In the case of the troglitazone, it was relatively minor, and that should be part of it.

DR. BONE: Dr. Critchlow.

DR. CRITCHLOW: I have nothing to add to the previous two speakers.

DR. BONE: Thank you.

I think that it is inevitable that we will have some reference in the labeling of other drugs of this class to the experience with troglitazone, and I think it is appropriate to distinguish between drugs which have not had this problem and troglitazone in that labeling, along the lines previously discussed by several other members. I think if it turned out that we had two different kinds of problems, as I mentioned earlier with troglitazone, and one was a truly rare, idiosyncratic problem, we are not at the same level of certainty that we would like to be able to say that it couldn't occur with these other drugs.

It seems to me that we have experience with

drugs that have a rate of idiosyncratic, rare, catastrophic reactions at the rate of perhaps 1 in 10,000. Certain drugs come to mind, and the only way we're going to get information of that kind of rare phenomenon is to have good post-marketing data.

I take Dr. Lewis' point that if it weren't for the prior experience, we wouldn't even consider any requirements for monitoring, and I think that one also takes Dr. Seeff's point that in a certain sense we cannot ignore that context until we've got a high level of certainty for a number of reasons.

It seems to me that we're a little bit torn here about what to do about monitoring. To a certain extent, an excessively burdensome monitoring program may actually, as Ms. Killion pointed out, interfere with the use of the drug. We may actually do more harm than good if it turned out we didn't have a problem by making the monitoring so burdensome that people refuse to use a drug that might benefit them. So, we have to recognize that it's not a free lunch, never mind issues of cost and convenience and other practical issues, but we may actually have an adverse effect in a sense for monitoring.

But it strikes me that the issue of potential rare but serious events with this class is only going to be put to bed rapidly if we do have a very intensive post-

marketing surveillance program of some kind. For that reason, I would say that a recommendation for periodic monitoring along the lines several people have previously discussed, with special concern in patients with prior mild abnormalities, is probably what we're going to have to do. I think in a way it may turn out that it will have been a pity if we did that in a situation where the drug simply had no problem, as appears to be the case here, but the greater pity would be probably not to do it if it turns out that there is a less common problem, but one that could have been identified earlier in the clinical course of using the drug.

This is a little bit of being tarred with the other drug's brush, but I think there are so many issues related to this, somewhat reluctantly I will recommend that we do use periodic monitoring along the lines, frequently if there are prior abnormalities, somewhat less frequently -- not as much really -- I mean, there's a mixed purpose to this. One is for the protection of the individual patient, and the other is to accelerate detection of a problem if we have it.

In a way, that's not the best use of patient monitoring in a sense. That's trying to solve one kind of problem with another kind of tool. What we come up with in the way of recommendations for post-marketing surveillance

and studies I think would influence the importance of the individual surveillance. There's an interaction there. In a way, there shouldn't be, but I think it's inevitable that there's an interaction between individual surveillance and how quickly we develop a higher level of confidence about rare events for this drug and perhaps for others in the class.

So, that's a long, complicated answer.

Now we're going to return to question 5 on today's original agenda which is another short essay question, and I'll try to be shorter myself next time. If rosiglitazone were to be approved for marketing, do you have any recommendations for phase 4 (post-marketing) studies?

Dr. Bilstad?

DR. BILSTAD: I just wanted to make a comment. In view of the comments that were made previously about use in the pediatric age group, I would have, of course, encouraged the committee to address that issue here, including the issue of, if you were to recommend studies, down to what age would you recommend that the studies go.

DR. BONE: Thank you. We will address that.

Let's start with Dr. Molitch.

DR. MOLITCH: I think I'll leave the pediatric questions to the pediatricians and perhaps Dr. Hirsch as

well.

But I'm interested in some of the other issues that I think could be addressed in some relatively short-term studies to try to get a better handle on some of the complications so that either they're present and significant or not present and we can do away with them.

I'm interested in the decrease in blood pressure that can occur and what the mechanism may be. Is there increase in circulating catecholamines that may occur secondarily to that that may contribute to arrhythmias? And I think this is an area that can be looked at with a relatively short-term, relatively small numbers of patients.

I've alluded before to this issue of amenorrhea, and I think following women off birth control pills, a certain number of people, looking at ovulatory status I think would be something that would be very helpful to know so that we could either address it as a problem or get rid of that as well.

I think finally the issue of the mechanism of fluid retention, as to whether that's simply all secondary to this decrease in peripheral resistance and activation of renin angiotensin, aldosterone I think is again something that can be addressed with some mechanistic studies, relatively short-term in small numbers of people.

DR. BONE: Thank you.

Dr. Levitsky.

DR. LEVITSKY: Well, I guess I should address the pediatric study that I've been thinking about while I've been listening to everyone else. I think there are a number of issues that should be addressed in a pediatric study, and a beginning age somewhere around 8, 9, or 10 I think is about as early as type 2 diabetes of the classic non-MODY type as has been described. So, that would be fine. Up through 18 would be a fine age range.

I think the issues that I would like to see addressed would be the issue of body composition studies during puberty so that children should be followed to see whether there are different changes in body composition with puberty. These children who may be living on soda pop and Fritos -- potato chips -- we won't use any brand names -- probably will need to be followed to see whether their issues with anemia may be worse. And the issue of puberty becomes important because if they're felt to have a mild 3-beta-HSD block, well, that's something that's seen in young women who are anovulatory and look like they have PCOS. It can be easily monitored by following DHEA and DHEAS. It may also interfere with male puberty as well. So, I think that that will have to be looked at fairly closely.

Yes, I think body composition, puberty, and

anemia were the big issues, aside from diabetic control, obviously, which I thought should be focused on.

DR. BONE: Thank you.

DR. BILSTAD: Henry?

DR. BONE: Dr. Bilstad.

DR. BILSTAD: In the comments that were made earlier on monitoring liver function, there were some comments about size of patient population to get a certain degree of assurance that there was or was not a problem. It implied that there was thinking of some sort of post-marketing surveillance study of a certain number of patients as opposed to simply labeling the drug and waiting for the spontaneous reporting system to produce cases.

So, I guess I would like to urge the committee to address the question of do they really believe that there should be a post-marketing phase 4 study specifically looking at the incidence of adverse liver effects. I think it would be helpful if the committee did specifically address that question.

DR. BONE: I'm sure several of us are planning to.

DR. BILSTAD: Okay.

DR. BONE: Dr. Molitch, did you wish to address that yourself?

DR. MOLITCH: Just to come back to that issue,

I think that we came up with a figure of something like 35 total cases out of somewhere close to a million patients having received the medication. So, it's hard to imagine a post-marketing study that's going to include that number of people for a drug that's going to have, presumably, a smaller incidence of effects as what our hypothesis is. So, I suspect we are going to have to rely upon Medwatch or some spontaneous reporting. There's no way that we can have an accurate surveillance of over a million people getting the drug I would think.

DR. BONE: Would either of our hepatological consultants have a specific recommendation about post-marketing studies as opposed to the surveillance mechanism earlier discussed?

DR. SEEFF: Well, the surveillance program is itself a sort of a post-marketing study, isn't it? If we talk about an endpoint to that and a reassessment at the end of that time, that is almost like a study. So, I sort of see that as a post-marketing study in a way, although I know it's difficult once you write something in the label.

The other thing that is obvious is that all the other populations that were not studied in sufficient quantities, African Americans, Native American Indians, women -- well, women have been studied -- children -- and I can't tell you how far down to go. There is precedence for

a difference in racial response. I'm sure you're aware of the fact that -- I'm sorry to bring this back to hepatitis C, but that's what I do -- there's a difference in efficacy of treatment between African Americans and caucasians. So, here's a response that differs by race. So, I think it's important for us to make sure that all segments of the population are included in the studies and learn more about the effect in other population groups.

DR. BONE: Thank you.

Dr. Lewis, do you have recommendations about post-marketing studies specifically?

DR. LEWIS: I mentioned it would be interesting to use this drug in a situation in the NASH patients, not necessarily diabetics. We've heard about some other off-label uses perhaps for polycystic ovaries and some other uses that will come up.

DR. BONE: Thank you.

Comments about post-marketing studies, Ms. Killion?

MS. KILLION: I don't really have anything to add to that. Thank you.

DR. BONE: Thank you.

Dr. Illingworth?

DR. ILLINGWORTH: Well, I think there's a need for some long-term follow-up of patients in a defined

setting. I like the suggestions that Dr. Misbin had comparing, in a well-designed clinical trial, patients given rosiglitazone, metformin, or the combination of both drugs, and looking at basically 3 to 5 years of follow-up, looking at renal function, looking at progression of atherosclerosis, and obviously not ignoring other risk factors. If somebody develops hypercholesterolemia, don't not treat it because they're in a study. So, there needs to be some flexibility in those studies.

As I mentioned before, premenopausal women haven't been adequately studied. That's a population that needs to be further addressed.

PCO was covered. I think that needs to be looked at.

I think there's also a need to look at patients with subtle renal disease such as nephrotic syndrome. The drug is bound to serum albumin. Is it safe to use in patients with nephrotic syndrome? Does it work? It's a common complication of diabetes and that would be a population to look at. A small number of patients well followed could give that information.

I think in a larger study, as well as following microalbuminuria, evidence of renal progression, eye examinations, it would be nice to follow also detailed assessments of body weight, where are the excess calories

being deposited or where is the excess fat being deposited, and compare those, and see do you progressively increase beyond a year, or do you reach stabilization. Those kinds of issues could be well addressed in a well-designed clinical trial.

DR. BONE: Dr. Hammes.

DR. HAMMES: I go along with Dr. Illingworth's statement completely. I'd just like to add to it that I think we have the opportunity here to further elucidate the role of the elevated insulin levels and C-peptides and things like that which is a little controversial, as was mentioned this morning. This drug gives us the opportunity to study that in a little more detail.

DR. BONE: Dr. Critchlow.

DR. CRITCHLOW: I echo previous comments but also want to re-emphasize Dr. Molitch's earlier questions and concerns about looking in more detail at efficacy in patients that might be at higher risk due to presence of other comorbid conditions. That wasn't, I don't think, quite adequately dealt with earlier in the discussion. And that would also bring into play further examination of drug interactions, issues along those lines.

Then in terms of numbers of patients that might be studied in terms of elucidation of rare events, it's hard to know what appropriate flags or red flags would be.

But, say, the incidence of something is 1 in 2,000, it means you still you have to study 20,000 patients to see 10 cases, which at that point you might be where someone starts to pay attention. So, that in and of itself is a large undertaking.

DR. BONE: Thank you.

Let's see. Dr. Genuth, any additional comments regarding post-marketing studies?

DR. GENUTH: Yes. Some things I think are sort of obvious, and the sponsor may already have these on the drawing board. But I think we need relatively short-term -- say, 6 months -- combination therapy studies. We need to study rosiglitazone plus a sulfonylurea drug versus each drug as monotherapy. We need the same thing using repaglinide and rosiglitazone and insulin and rosiglitazone so that we know for sure that we get similar efficacy as has been demonstrated with troglitazone in those instances, except repaglinide I guess I haven't seen in the literature yet. So, I think those should be done quite promptly, and they don't have to be long because I think it's just a question of efficacy of lowering glucose.

As far as the liver is concerned, I'm trying to think of a study that would be better than the Medwatch. It's very difficult. I think maybe it would be better for the committee and the FDA to kind of think about if we're

wrong and if this drug does eventually cause hepatic failure in a small number of patients, how large a signal would you require before sort of reconvening and rediscussing the whole class? Maybe some thought ought to be given to that by the experts. I don't know the number other than to pull one out of the air, but it ought to be less than 40, whatever the number is.

DR. BONE: Dr. Hirsch, comments on post-marketing studies.

DR. HIRSCH: Yes. I can't see any way to do a post-marketing study without the liver damage because of all the problems that have been raised. So, I think even though surveillance is not as a fine a tool for examining this, I think we're going to have to rely on that.

However, I do think post-marketing studies of comparisons of monotherapy has been suggested; that is, studies in children at puberty and adolescence and also in adults comparing the rosiglitazone with other drugs would be a very valuable thing. I think the issue of the obesity should be looked at very carefully in all three groups, that is, in pubertal children, in adolescents, and in adults, and whether in fact fat is laid down, but particularly in the pubertal children and the adolescents.

I do agree that some more cardiovascular studies are needed along the lines that probably the

sponsor is already undertaking to examine the renal effects of this and the pathogenesis of this vascular change or whatever it is that causes the edema.

DR. BONE: Dr. Genuth?

DR. GENUTH: Can I just add one thing to those short-term comparator studies? I agree with Dr. Misbin. They should be designed so that patients, who have not been doing well on some previous form of therapy, are put on a placebo and allowed to be very hyperglycemic for more than a couple days. I think that's both ethically very questionable now, but also it gets in the way of the final evaluations because the more patients you have to drop out for lack of efficacy, the more confounding you have in your final evaluations. So, I think the design of those studies should really be scrutinized very carefully by the FDA before they are allowed to begin.

DR. BONE: Thank you.

I might add that I would be inclined to study adolescents before children. I don't know if the pediatricians would agree, but it sort of seems logical to me to work our way down the chronological ladder rather than start with younger children first.

I certainly would endorse the recommendations for mechanistic studies.

It seems to me that if the sponsor can devise a

way of improving the efficiency of post-marketing surveillance for their particular situation, they would be able to do themselves and the field an awful lot of good. Sort of a rough calculation in my mind is that if we had 100,000 to 200,000 people followed through 6 months and didn't see any apparent drug-related, catastrophic liver problems, I think we'd be pretty comfortable. If we had a rate of 1 in 10,000, that would give us 10 to 20 cases, presumably, if they were all captured.

The issue would be the reporting rate. Now, there was a lot of discussion at the previous meeting about how efficiently cases are reported, and people had different views about whether these very serious cases have a certain reporting rate or a lower reporting rate. But it seems to me that this is -- I don't have the idea right here about exactly how to do this, but it strikes me that with a lot of attention to making that relatively efficient as sort of a proactive surveillance, rather than a passive approach to the surveillance in this situation, the efficiency might be improved quite a bit. If that were the case, then this becomes something where the manufacturer would not be very far into their marketing experience before they could have some very reassuring data.

I see no reason why this kind of surveillance could not be collaborative with the sponsor of the drug

we're discussing tomorrow, if it turns out they're more or less in the same boat, because the issue will very likely turn out to be not either/or, but is troglitazone the outlier.

So, those are some comments on this, and there's a tremendous, I would think, interest on the part of sponsors of the other drugs to really get the best possible information as quickly as possible to confirm this distinction which appears to be legitimate on the basis of the data we have so far.

DR. LEWIS: You're going to have to define your outcomes, though. If you get threefold elevations, what do you do with that?

DR. BONE: I think we're talking about looking for patients with these very severe episodes.

DR. LEWIS: That you pick up on whatever frequency of the monitoring that may be done. It has to be given a lot of thought.

DR. BONE: Yes, I know. The problem is, as was pointed out to us, that the monitoring was not as helpful as we would have liked. It probably caught some of those cases before they went on for much longer, but in many of those cases, there were these fast-developing cases. It's a terrible problem, and I don't think we're going to stay here in session long enough to solve it. But I think

that's the line of thinking I just wanted to commend.

DR. GENUTH: Excuse me. I think that's a very important line to pursue and elaborate on a little bit. It seems to me that, first of all, the event we're really looking for is jaundice, hepatic failure. That's going to be more important to count those accurately than the greater than 3 times the upper limit of normal of ALT. I think we need to know about the hard events as accurately as possible.

I wonder if that can't be done by design through managed care organizations or through HCFA so that some kind of alliance is created between the company, a large enough number of managed care organizations that you can assemble pretty quickly the 100,000, 200,000 patients that Dr. Bone is guessing would be enough for 6 months or a year. If some real thought was given to finally making some health -- I shouldn't say that. If we can use our managed care colleagues to a good purpose --

DR. BONE: It seems to me that an alternative way of looking at it would be to consider using some kind of an incentive process linking the prescribing and the testing. That's an alternative that might be complementary or could be used at the same time.

Well, let me just summarize then, if there are no further comments on post-marketing. Oh, excuse me. Dr.

Illingworth.

DR. ILLINGWORTH: Just one further comment concerning -- I think we've discussed the lipid changes. I would encourage some post-marketing studies to define what the mechanisms responsible for these are and also, as John Brunzell mentioned, look at what happens in patients with different lipid disorders, hypertriglyceridemia of a moderate degree, perhaps some patients with type 3, and see if you can find are there any patients or any lipid disorder that shouldn't be on this drug and define better which patients get a bigger benefit. More likely patients with hypertriglyceridemia are going to get a bigger benefit than somebody with fairly normal triglycerides.

DR. BONE: Thank you.

Further comments on post-marketing studies?

(No response.)

DR. BONE: Well, just to summarize then, we only had a vote count on questions 1 and 3, as you know. The committee unanimously agreed that rosiglitazone was effective as monotherapy for hyperglycemia in type 2 diabetes mellitus, with all of the committee members endorsing its use as effective in initial monotherapy but with several comments to the effect that switching from another drug that was partially effective wasn't what they had in mind as equivalent use.

In question 1(b), all committee members agreed that it was effective in combination with metformin.

In answer to the various sections of question 2, there was an extensive discussion about issues on hepatic safety which I think can be fairly summarized as expressing some pleasure that we did not appear to be seeing the same kind of problem as we did with troglitazone but some caution that there may be less common problems that we can't completely exclude yet.

The comments on the lipids expressed some concern about the rise in LDL cholesterol and discussion about how this would be taken into account in prescribing.

The committee was generally impressed by the information suggesting that there was an effect of retention of fluid to expand the extracellular space, which apparently is the etiology of a decline in hemoglobin and hematocrit.

Additional comments were made about the possible effects, from a safety standpoint, on ovulation, gestation, and body composition in children or adolescents who haven't been studied.

Question 3 was the question of whether benefits outweighed the risk for the use of rosiglitazone in the treatment of hyperglycemia in type 2 diabetes mellitus. Question (a) referred to monotherapy, and there was

unanimous agreement that the benefits did outweigh the risks with similar comments about switching therapy as noted in question 1(a).

Question 3(b) was concerned with the risks versus benefits in combination with metformin and the committee unanimously agreed that the benefits did outweigh the risks in that application.

There were extensive discussions in response to question 4 and two related questions on class labeling. There were extensive discussions about how to handle the issue of the hepatic toxicity that's been recognized in troglitazone, and there were a number of recommendations that that be recognized, but that it not be considered a class effect, but rather a distinction be drawn between the other drugs and troglitazone while it is, nevertheless, incorporated into all of the drug's labeling for the time being.

There were a number of other recommendations generally along the lines of the safety concerns raised in question 2.

In the subsidiary questions, monitoring was the other important point, and there were a number of members who recommended some form of monitoring although there was considerable discussion about exactly how this could be done and what the effectiveness actually would be.

In question 5, if rosiglitazone were to be approved for marketing, do you have recommendations for phase 4 studies, and the number of recommendations were also made which generally related to elucidating the mechanisms of some of the effects that were noted earlier, the physiological effects, and evaluation of groups that had not been adequately studied, especially adolescents and children. And there were some further discussions on the hepatic issue incorporated into that. I'm certainly not going to try to recount all of the comments.

I want to thank the sponsor for their presentation, the agency for their excellent presentation, the guests and the members of the committee for their participation. I want to particularly again, as usual, thank the Advisors and Consultants Staff, and especially Kathleen Reedy, the Executive Secretary, for the very hard and effective work that's done in preparing for these meetings.

If there are no further comments, anything from the agency, I think we're adjourned. Thank you very much.

(Whereupon, at 4:55 p.m., the committee was recessed, to reconvene at 8:30 a.m., Friday, April 23, 1999.)