One concern would be no change in ApoB, and therefore an increase in the number of LDL particles. If these particles are potentially less atherogenic, that would potentially -- even though the constraints may increase, may -- I think we need to get more information about this -- may actually confer benefit.

I think we just need more data on that.

DR. BONE: Do you think we have enough information now to make a recommendation about approval? Or do you think that that additional information needs to be obtained before?

DR. ILLINGWORTH: I think the lipid changes are small. It isn't like we are looking at a 15 to 20 percent increase in LDL cholesterol. And I think the data I would interpret is consistent with a reduction in hepatic triglyceride production or potentially an enhancement of triglyceride clearance, but

no effect on the number of particles produced by the liver.

DR. BONE: I see. One or two of the committee members also commented on the potential for effects on vascular smooth muscle and so forth. In taking all of these questions into account, Dr. Sherwin, perhaps you would comment on the cardiovascular and other risks here.

DR. SHERWIN: Well, I think that the animal data make one take pause in that I think it is important that the company, given the fact that these patients are at high risk for cardiovascular disease and congestive heart failure, I think it is important that the cardiac data be monitored longer term.

And even though we have data that supports the view that drug is not harmful in the doses we are using in the clinical setting, I think that one has to look longer term to be 100 percent sure of the full impact of the medication.

And so there is concern. I think it is important that the company continue to monitor this and not just end at this point with their cardiac assessment data. Nevertheless, I don't think that the cardiovascular problems that we have come across in the humans at least -- I'm not one to say that this is enough of a concern to say that we would want to disapprove it on that basis.

DR. BONE: And so we have the -- to summarize briefly -- and I invite the sponsor to add something if they wish. The principal concern that was raised in the pre-clinical studies was this very impressive and totally unexplained cardiomegaly in the rodent experiment. And perhaps with that mind, the company has excluded patients with significant heart disease from clinical trials to date.

Is there anything else -- I mean, those are the two pieces of -- Dr. Hirsch, did

you have a comment?

DR. HIRSCH: Yes. I think given the sort of matrix of genes and effects that led to the discovery of this in the first place, the PPAR-gamma-2 and what it does and so on, I think it would be wise somewhere to say that no one should take this drug who has a great likelihood of laying down more adipocytes, for example, during pregnancy or childhood or adolescence or -- I can't think of any -- I mean, one of the nightmares is that this will be a wonderful drug, everyone will be euglycemic, and then 40 years later they will all weigh 75 pounds more with a great big -- you know, we don't understand what this does and how it works so that -- that's a caution, I think.

And it seems to me, just on the basis of what we know of the basic science of where this came from, the drug, and what it does that any circumstance in which there is likely to be adipocyte hyperplasia would be one in which you

would not want to use the drug.

DR. BONE: Do you think you could at this point -- our state of knowledge is such that we could address that in a labeling rather than affect the approval?

DR. HIRSCH: I would think that it shouldn't be used in pregnancy, and it shouldn't be used in children, adolescence.

DR. BONE: Probably it is unlikely to be used in children for this particular indication. But that would implications for the longer term, I suppose.

DR. SHERWIN: Congestive heart failure.

DR. BONE: Dr. Sherwin.

DR. SHERWIN: Since we have excluded patients with serious heart disease, I think it behooves us at this point to exclude that population, too.

DR. BONE: Do you think special studies should be done in that population, or in clinical studies?

DR. SHERWIN: Of course.

DR. BONE: Any other comments from the committee members concerning cardiovascular -- the question of cardiovascular risk? Just for myself, it seems that -- you know, we have got the idea, and Dr. Olefsky mentioned, that growth factors are probably responsible for some of the toxic effects or presumed harmful effects of insulin on vascular disease, although that is not explicitly proven at this point.

And a residual concern remains in my mind, since we -- about whether the promoter mechanism that is involved here could have a role in the pathogenesis of some of those problems. And I don't know if we can explicitly exclude that, although we had an earlier discussion about where these sequences might be found.

And I wonder if the company now has that information.

DR. SALTIEL: Yes. Thank you, Dr.

Bone. Well, just to try to reiterate what I said before, we had really found no oncogenes which have PPAR response elements in their promoters. Now, we have looked at a few. We haven't looked at every oncogene. There are many oncogenes that have been identified.

DR. BONE: But do you have computer matching systems for doing that? Have you not done that yet?

DR. SALTIEL: Well, I think we have run through a number of them. We haven't looked at -- all of the promoters for all of the oncogenes haven't even yet been identified.

DR. BONE: But you have looked at the ones -- have you looked at all the ones that have been?

DR. SALTIEL: We have looked at all -- a lot of the major ones, but not at every one.

But let me just add that there is really no effect of the drug on transformation of cells, and there is no effect of the drug on

the growth of cell. It doesn't potentiate other growth factors to promote the growth of cells. And it doesn't induce the secretion of growth factors.

So a priori, there is no prediction that we would expect to see increase in oncogene activity or oncogene synthesis.

DR. BONE: And with respect to the vascular disease, your inference is that the lack of growth factor effect -- if insulin is acting by an IGF-like mechanism, you believe that this would not.

DR. SALTIEL: Well, I don't want to get into a long seminar about the signal transduction effects of insulin. I see Dr. Sherwin squirming over there at the thought of it.

(Laughter)

DR. SALTIEL: I think scientifically, in the field of insulin of action, many of us believe that there are distinct mechanisms promoting growth and metabolism. And there is

no evidence to believe that the growth promoting pathways are activated or potentiated by the drug in any way.

DR. BONE: Thank you. That's what I was trying to get at. Dr. Sherwin, would you care to comment? No? All right.

Well, the next topic that we're asked to address is this question of body compartment fluid distribution. Are there members of the committee who wish to add anything from the earlier discussion about this expansion of the plasma volume, which is apparently attributed to a fluid shift?

DR. SHERWIN: Other than we need to understand it.

DR. HIRSCH: To know the degree of it. I mean, the data on extracellular fluid volume or whatever, I gather you are accumulating that. But we have no --

DR. BONE: I think what --

DR. HIRSCH: Today we have plasma volume, but not compartmental analysis of any

kind.

DR. BONE: If I understood correctly, there was an increase in plasma volume of about 250 milliliters or something like that. And it was inferred that this was due to redistribution because body weights didn't change, although the precision of measurements of the body weight might be right around 250 grams, I suppose.

DR. HIRSCH: Plus the body fat that would be --

(Simultaneous discussion)

DR. HIRSCH: We can't tell that, certainly. So it could be --

DR. BONE: And the plasma volume expansion occurred in the first week on treatment. Is that correct? The first month. I think it said eight days.

DR. WHITCOMB: Yeah, the first month. I think that the point that you make is a very good one, which is that body composition studies are warranted to see what is going on,

and those are going on now to try to understand that better.

DR. BONE: I think that body composition issue, in a broader sense, addresses Dr. Hirsch's concern about the fact that these response elements seem to have something to do with adipocytes.

DR. WHITCOMB: That's correct.

DR. BONE: Other comments about this body fluid compartment?

DR. ILLINGWORTH: Do you have any information about the effects on the renin angiotensin system? Since ACE inhibitors seem to correct the problem.

DR. WHITCOMB: We have not done that study directly to add ACE inhibitors to see if it negates the volume expansion, if that is the question. We have assessed the renin angiotensin system to the extent that you can in large clinical trials, and don't see any big changes in the numbers.

But obviously, those studies have not

been perhaps in the careful way you might if you were really looking at that in terms of salt loading and so forth to do that.

DR. BONE: Have you done a CRT type study to just look -- since it is a short term effect, the animals' cardiac enlargement occurred very promptly, and the patients -- and it was at least one of the sponsor's representatives attributed this potentially because of the effect of the ACE inhibitor to that mechanism. And the fluid increase or fluid shift occurs relatively promptly.

It seems to me this is the sort of thing that could be addressed in a fairly small number of subjects in a clinical research center type of setting to look at, in a very tightly controlled way, effects on their renin angiotensin system. And have you done those experiments?

DR. WHITCOMB: The effect on plasma volume is one to two months. But I mean, that isn't to say that we couldn't -- certainly

couldn't do that. I didn't quite get, were you trying to ask if we should also be looking at the heart enlargement at that same time to see if that was happening? You weren't --

DR. BONE: No.

DR. WHITCOMB: -- that together.

DR. BONE: A phenomenon was observed which occurred acutely --

DR. WHITCOMB: Yes.

DR. BONE: -- in the animal experiments, and which was attributed to a renin angiotensin mechanism, at least by implication. Also, you have sub-acute, fairly prompt effect on plasma volume. And it begs the question of investigating that in a very tightly controlled, small-scale mechanistic type of human study.

DR. WHITCOMB: We have a study planned exactly to do that. If that was the question, then yes, we're planning to do that.

DR. BONE: But you haven't done it yet.

DR. WHITCOMB: We have not done it yet, no.

DR. BONE: Okay. Are there other questions or comments? What about this issue of carcinogenicity? We were told that vascular tumors, hemangiosarcomas were seen in some of the tox studies, in the mouse but not in the rat. And of course, there are no -- all the carcinogenicity studies are done in rodents in this case. We don't have any beagles or anything like that.

It's all rodents, in one of the two species, and this is a subject of review by another committee. And we don't have the results of that review at this point. Okay.

With that exact information available --

(Laughter)

DR. BONE: The committee is asked to comment on the significance of the potential risk of carcinogenicity. Dr. Colley, you have a comment on that?

DR. COLLEY: No, I don't specifically, except that if it were to be approved, I would want to have information of any reports in longer term studies. Those studies so far in humans are too short to determine anything from that.

DR. BONE: Anybody else have anything to say on the subject of -- what about the potential for -- we talked about -- we anticipated a moment ago when we were talking about promoter genes -- and the company did give us information they had on looking at the promoter genes that they had looked at.

Any other comments about the potential for carcinogenicity on theoretical grounds? Does anybody have any particular concerns or comments on that? Okay. Yes.

DR. STEIGERWALT: I might like to add that this was not a genotoxic agent. So if there is any other mechanism, it is not directly a genotoxic mechanism.

DR. BONE: I see. Dr. Fleming.

DR. FLEMING: I don't know if it will help or not, but just to explain how we tried to handle the problem of this sort. This is not by any means unusual, as you well know. And we don't expect our panel here to be expert toxicologists and to come to some kind of informed decision about what this particular finding means for humans.

But probably we can expect that you can have some kind of worry factor and incorporate that into your overall risk/benefit assessment. That is basically how we do it. In other words, you must think that this is either an entirely negligible consideration, a moderate consideration, but given the benefit that has been established one that you might be willing to talk to your patient about taking on.

DR. BONE: Well, speaking for myself, I think I would have great difficulty broaching that subject with a patient, saying well, this might tune up your diabetes and give you -- you

know, there is a small chance of a malignancy of your blood vessels. I think it is extremely difficult for me, and I would be very interested in the others' views.

But it is extremely difficult for me to form any kind of assessment knowing that experts in this exact topic in assessing this kind of data from this kind of study are in the midst of a deliberation, but not having the benefit of their advice. I don't know what to say.

DR. FLEMING: But let me again -- let me address that particular issue. I think that to expect that the experts are going to come up with a decision that is significantly different from the preliminary appraisal of our own toxicology expert within the division is fairly unlikely.

In other words, I don't mean to deprecate the value of our expert panel. But then again, they are not going -- they don't have magic hands that will be able to do much

better with this.

This will turn out to be one of those isolated findings where we really will never know what the significance is until many, many decades have passed. And I don't know that we can provide you much more information or much more informed opinion at this point, quite frankly.

DR. BONE: Well, perhaps Dr. Steigerwalt will reiterate his assessment a little more explicitly because I think at least some of us had the impression that he was largely deferring to the judgment of this committee, not trying to prejudge it.

DR. STEIGERWALT: Well, that is true. Since they come up with what would be an official statement, I didn't want to say something that would be misinterpreted. But the issues before the CAC at this moment are relatively minor issues. And I think that the overall conclusion that this was a finding in a single species of hemangiosarcomas, and then

there was the high dose finding in a single sex of the hepatocellular carcinomas, will not change.

Therefore, this will basically remain a single species which is, in our interpretation, less of concern than if this had been positive in both species. So I think what the sponsor has put in the labeling regarding this is accurate.

DR. BONE: Do you recommend a third species be investigated in situations like this?

DR. STEIGERWALT: No.

DR. BONE: Thank you. Anybody, comment, discussion? No. Okay. Thank you. We go on to the next thing. I don't think we have much to add to that.

One of the things that Dr. Sobel emphasized was the importance of characterizing the population for which treatment with troglitazone would be indicated in the initial approval. And we again are cognizant of the

fact that we are talking about a somewhat narrower initial approval than the sponsor would seek in the long run.

And Dr. Sobel has suggested that we may want to focus on particularly needy patients in terms of additional (indiscernible) for the purpose of this initial approval, if that is what the committee recommends and the agency does. And we kind of talked about that a little bit earlier. Then we have had a considerable discussion which bears on a number of points on that.

Would anyone on the panel want to make further comments about the population for whom they would consider this to be indicated based on the data presented up to now? Dr. Sherwin, perhaps.

DR. SHERWIN: Well, I would, if I was going to select the population, would be those people who have failed on an oral agent, at least one, and in whom insulin therapy has already been instituted, and there has been a

failure with insulin therapy to lower glycohemoglobin below 8 percent. Try to keep it simple.

DR. BONE: Okay. I'm just making a note here.

DR. SHERWIN: Because that is the -- at least according to the ADA assessment is what we should be doing.

DR. BONE: Do other members --

DR. SOBEL: Oral agent -- either a failure on sulfonylurea or metformin?

DR. SHERWIN: I think so. I mean, because I think if you -- nowadays there are enough patients starting on metformin. I mean, the only question that one could ask is whether if metformin failure should be given at trial on sulfonylureas. Generally, it is a futile exercise.

But, you know, my gut feeling is I'm not sure that they need to try it. I don't know what other people think. But my feeling would be if -- once they failed on one and

failed on insulin therapy, that would be the time.

DR. BONE: Dr. Cara.

DR. CARA: Well, I think it is reasonable to say either/or sulfonylurea or metformin therapy failure, currently on insulin, and documented poor control, i.e., glucose, of what we discussed. But I don't think it is appropriate to say failed both.

DR. SHERWIN: I'm confused now. What do you mean by failed both?

DR. CARA: A trial of both sulfonylurea and metformin therapy.

DR. SHERWIN: Oh, you mean as a combined therapy?

DR. CARA: I'm talking about either sequential treatment, the combined therapy, or whatever. I don't --

DR. BONE: So you would agree with Dr. Sherwin's original statement, which was failed on at least one oral agent prior to starting insulin?

DR. CARA: I wouldn't even say that, actually. I mean, I would say currently on insulin therapy and documented poor control based on glycohemoglobin values above 8, 8.5.

DR. BONE: So you would be less restrictive.

DR. CARA: That presumes that in the Type II adult patient, you have already attempted oral therapy, I would imagine.

DR. BONE: So you are saying there is not much of a practical distinction.

DR. CARA: Right.

DR. BONE: In effect.

DR. SHERWIN: Well, that's true. Normally in this country the vast majority of people have started on an oral agent. There is small subgroup of patients who are non-obese who might be started on insulin, who are a little big younger perhaps. But overall, you are right. There is not much of a difference.

But I still think it may be better, given the uncertainty of the drug and the

limited amount of information we have about the overall picture. My gut feeling would be to limit it to those people who fail the two steps.

DR. BONE: Would you quarrel with that, Dr. Cara? Do you think that is --

DR. CARA: I wouldn't quarrel with that. I think for the data that we have seen, though, the important issue is that they are currently on insulin and in poor control. I think that is what we all agree on.

DR. BONE: I see. Any further comment from Dr. Zawadzki or --

DR. ZAWADZKI: No.

DR. HIRSCH: I think it is a clearer statement, sort of easier for me to visualize in the -- what the patient is told or the physician, namely that in this disease the first line of treatment has always been dietary management, weight loss, et cetera. And frequently, this is insufficient, and oral agents are tried. And this particular drug is

useful then after the oral agents and insulin are used and there still is inadequate euglycemia, or something to that effect. But indicate the algorithmic sequence that we are thinking of.

I mean, it is not fair to the physician or anyone else to put some strange sort of thing with an either/or or whatever without indicating what we think the usual algorithm is, and say this is the point at which this drug has value or should be tried.

DR. BONE: I think Dr. Sherwin's original formulation comes pretty close to what you are --

DR. HIRSCH: Yeah. I think a little more emphasis on the weight loss thing, knowing full well how difficult that is to achieve and how rare that occurs. But nonetheless we -- that may not be the case a year or two from now, and we're still working on it.

DR. BONE: So we want to -- you're saying we would like the language to make a

statement about hygienic measures, the prior failure on oral agents, patients on insulin, and then now --

because that gives that certain hierarchy or algorithm, and that this is a supplement in effect to the use of the insulin. Something --

DR. SHERWIN: Well, I think the idea of making the point that they have also failed diet and exercise is important just as a reminder because surely, even in these more advanced patients, many of them, if they had a conversion to Christ and totally change their lifestyles, you know, they might be able to come off everything.

And so it is still the, I think, key element of therapy. And it shouldn't be lost within, you know -- I think we probably should emphasize that point as well.

DR. HIRSCH: Yeah. And the reason for putting that in also is that it gives the reader of this some notion of what we think the

hazards may be because in fact, if we thought this were totally hazard-free, we'd say if you even think you have diabetes just take this stuff, you know.

DR. SHERWIN: Right.

DR. HIRSCH: So, I mean, clearly we have a risk/benefit thing here, and we're lining up all of the things first before you get to this one, and the notion that this is a serious undertaking because this is a drug of a new variety.

DR. BONE: This is the sort of thing we would expect to evolve over the next period of time. Dr. Zawadzki had a comment or question.

DR. ZAWADZKI: The data we saw today referred to a population with a BMI of about 35. Should there be a comment about obesity in the indication? I just fear some people who might actually have a Type I diabetes mellitus be tried on this in the general population.

DR. BONE: Bob, how would you

incorporate that?

DR. SHERWIN: I mean, it is true that some non-obese type -- that are clinically classified as Type II diabetic patients are really Type I. Theoretically, those patients who are Type I might actually -- and who are insulin failures -- might actually respond. There are patients with Type II diabetes who are non-obese.

My gut feeling would be not to restrict it, but indicate that it should not be used, given our information, on patients who have type I diabetes, maybe highlight that point. But I don't know that I would make weight the criteria. I don't know what other people think, but that would be my view.

DR. BONE: The other point we commented on earlier -- and I think several people felt that since the clinical trials had explicitly excluded patients with a significant cardiac disease, that that should be listed in the labeling as well. Is that the consensus of

the committee? All right.

Are there -- Dr. Illingworth.

DR. ILLINGWORTH: Well, a specific -- specifying cardiac disease as left ventricular dysfunction. I think patients with carotid disease who have diabetes are often not recognized, so they will be probably given this drug and not appreciate that they have that.

DR. BONE: Well, if it isn't diagnosed, I guess that can't be used to restrict its application.

Dr. Whitcomb, what was the actual restriction in the clinical trial? I mean, that's what we're going by.

DR. WHITCOMB: The exclusion was people with class three or four (indiscernible) heart. That was the criteria. We had some that snuck in that were class threes, as it turns out. But as you can see from the safety data, we didn't have a lot of people that got worse. But that was the criteria for the trial.

DR. BONE: So it hasn't been tested in that group.

DR. WHITCOMB: That is correct.

DR. BONE: Okay. I think that -- with Dr. Sobel's earlier comments in mind, we might want to take the scope of testing into account.

Dr. Illingworth again.

DR. ILLINGWORTH: Just one additional comment with respect to my views on the weight issue. Given the fact that BMI probably doesn't -- isn't a good predictor of insulin resistance by (indiscernible) the Japanese, I think to put a good point for you must have a BMI above a certain level would be unduly restrictive also.

DR. BONE: Further comments on this issue about defining the population for purpose of labeling? Well, perhaps we can then proceed to the questions which the agency has asked us to discuss. And some of these are topics that we have discussed earlier. And I think at this

point people can just make, I think, summary remarks for the most part on particularly question one.

Often, we are asked yes or no questions. Some of these are yes or no questions, and a couple of these are essay questions.

(Laughter)

DR. BONE: The first question is in that category. The executive secretary said this could fall in the category of short answer essay questions.

(Laughter)

DR. BONE: What is the clinical significance of the troglitazone treatment effects, that is, reduced hemoglobin A1c levels and total insulin dosage, observed in the two pivotal studies? What is the clinical significance.

Preferably we can just go around and each person in turn make a comment because we have all discussed this at great length

already. Summary comment from Dr. Hirsch.

DR. HIRSCH: I think the reduced HbA1c level is significant and important. I'm not sure about the total insulin dosage, what that -- but I think the fact that some 15 or 17 or whatever percent of people got off of insulin, that is obviously psychosocially or whatever significant. Whether it does matter whether you take a little more or less insulin, I'm not sure about that.

DR. BONE: Thank you. Dr. Zawadzki.

DR. ZAWADZKI: I agree there is probably a clinical significance in Type II diabetes based on data that we have from type I diabetes. But I think the real answer to this question is we don't know long term. And I think that has to be looked at prospectively.

DR. BONE: Dr. Cara.

DR. CARA: Although I agree in principle with Dr. Zawadzki's statement, the data certainly would suggest that a decrease in glycohemoglobin of 1½ percent, as indicated by

the studies, is clinically significant and will most likely impact long term complications related to Type II diabetes.

I think taken together, both studies are clearly indicative of a clinical effect.

DR. BONE: Dr. Critchlow.

DR. CRITCHLOW: I agree with the prior comments. Clearly the results taken together do suggest clinical benefit. And whether that is maintained long term remains to be seen.

DR. BONE: Dr. Illingworth.

DR. ILLINGWORTH: Yeah. I agree with what has been said previously. I think the data in the DCCT trial, you can extrapolate that hypoglycemia is detrimental and if it improves, that is going to be beneficial. And I think the implications of hyperinsulinism and atherosclerosis are so convincing from a number of studies that lowering insulin levels is also going to have clinical benefit, potentially.

DR. BONE: Dr. Sherwin.

DR. SHERWIN: I would say that this is a clinically significant effect.

DR. BONE: And I would agree that I think it -- there is an inference involved in the interpretation of the glycosylated hemoglobin levels, but it is a very reasonable and strong inference. And I would also say that I think that the reduction in insulin dosage is perhaps less clearly important, but may well be beneficial also.

I think that brings this to the -- oh, I'm sorry. Dr. Colley. My apologies.

DR. COLLEY: That's all right. I would agree with the previous statements, that the reduction in glycosylated hemoglobin is indeed significant, given that it is comparable to that achieved with metformin, and the effect on insulin is -- we can't make any long term predictions about the meaning of that, although it is theoretically promising.

DR. BONE: The next question is are the study designs and efficacy endpoints

adequate to assess the efficacy and safety of this drug for the proposed patient population. Perhaps Dr. Colley will start first.

DR. COLLEY: We have spent a lot of time going over the proposed population. And if it is defined as those patients who are on insulin therapy Type II diabetics inadequately controlled, and there are adequate warnings in regards to patients who have underlying cardiovascular disorders, that we really don't know about the long term effects, then I would agree it is adequate.

DR. BONE: Dr. Sherwin.

DR. SHERWIN: Well, I think the study designs are adequate to assess efficacy. This is what we said in the first question. The safety issue is a little more problematic because we don't have enough data to fully evaluate that. But I think given the high risk population we are dealing with that the safety issues are not paramount, given what we have.

I mean, in other words, on balance,

the safety issues are of concern, but wouldn't outweigh the benefits that one sees here. But we don't have a full -- obviously, safety requires long term studies. We don't have all of that, those long term studies.

DR. BONE: Okay. Dr. Illingworth.

DR. ILLINGWORTH: Yes. I think the data is sufficient. I think we need more information, though, about potential drug interactions and, for instance, transplant patients on cyclosporine who have Type II diabetes. We need more information about that.

Looking at the list of drugs that are drug interactions, a number that interfere with the cytochrome (indiscernible) system aren't mentioned. And I think we just need more information about those and their ability to potentially interact with this medication.

DR. BONE: Do you think those are necessary prior to making a recommendation about approval?

DR. ILLINGWORTH: No.

DR. BONE: Dr. Critchlow.

DR. CRITCHLOW: I think the study designs are adequate to each assess the individual endpoints that they were designed, and each one -- or together they show or certainly promise some degree of efficacy, that again, you know, we have to make the leap that those results would be confirmed with other studies.

And with regard to the safety, I think, you know, there is probably adequate patient exposure, but certainly not sufficient to rule out the more rare events that might occur.

DR. BONE: Does that mean you think the safety is adequate or not?

DR. CRITCHLOW: I think to the extent that it can be evaluated in pre-approval clinical studies, yes, because with the more rare events, I'm not sure that there are any studies that would identify those.

DR. BONE: Dr. Cara.

DR. CARA: Yes.

DR. ZAWADZKI: I think the study design and efficacy are adequate for an initial presentation. I think there is a lot of concern because this is a new drug, and there is a need for more information to be gathered with time.

DR. BONE: Well, the implications being --

DR. ZAWADZKI: I'm sorry?

DR. BONE: What are the implications of what you just said?

DR. ZAWADZKI: I think this is -- the end, though relatively large for a six month study, is still not adequate enough, as Dr. Critchlow pointed out, to really look at small potential side effects that might occur.

DR. BONE: Would you regard, though, those larger studies as necessary in the pre-approval phase?

DR. ZAWADZKI: I don't think that has been required.

DR. BONE: Okay. Dr. Hirsch.

DR. HIRSCH: Adequate for pre-approval, but will make a comment in three what the patient group is, et cetera.

DR. BONE: I guess I would regard these as the minimum that one could expect for assessment of efficacy and safety for this population. I would certainly have been happier to see this as part of the larger package with complementary data. I think it has come up at several points in the discussion that we are a bit handicapped in that there is a large amount -- this is sort of the tip of the iceberg in a certain way for the development program. And these study designs just do demonstrate the efficacy that we would like to see.

The study designs by themselves are probably not sufficient from a safety standpoint. But I interpret the question to mean -- to incorporate the other safety data we were presented, which represents the safety

updates from the other studies. So I would say the studies themselves are not adequate for safety assessment. But the information presented is just adequate for safety assessment, considering that we have information from lots of other studies. And I would make that distinction.

Item three, based on the efficacy and safety data presented and your assessment of the overall benefits compared to the risks of troglitazone therapy, do you recommend that this drug be approved for use in the proposed, or a modification of the proposed, patient population?

I'm going to ask that we reword this question since we have modified this, and we have a consensus pretty much of who the population is. So we are going to answer this question, if everyone else agrees with me, based on the patient population described and amended by Dr. Sherwin and the rest of us a few minutes ago.

And perhaps we will start with Dr. Critchlow.

DR. CRITCHLOW: Yes.

DR. BONE: Dr. Cara.

DR. CARA: Yes, as proposed.

DR. BONE: Dr. Zawadzki.

DR. ZAWADZKI: Yes.

DR. BONE: Dr. Hirsch.

DR. HIRSCH: Yes. But you include in that statement the pregnancy, adolescence, et cetera, the other things that we made mention of.

DR. BONE: Yes. With the restrictions and exclusions as mentioned.

DR. HIRSCH: Right.

DR. BONE: Right? Okay. Dr. Colley.

DR. COLLEY: Yes.

DR. BONE: Dr. Sherwin.

DR. SHERWIN: Yes.

DR. BONE: Dr. Illingworth.

DR. ILLINGWORTH: Yes.

DR. BONE: And the chair will concur.

All right. If the drug were approved, do you have recommendations for post-marketing studies? And I'm going to start the question to Dr. Illingworth here. I see all the people going out to call their brokers.

(Laughter)

DR. BONE: Dr. Illingworth, I would like you to start the answers to this question 4. If the drug were to be approved, do you have recommendations for post-marketing studies? I'm going to ask you an explicit question.

We talked earlier about the effect on lipids. And I am going to ask you, too, in addition to whatever else you would like to say, please say what kind of studies are necessary to really assess the effect on those risks. Are endpoint studies required?

DR. ILLINGWORTH: Well, given the fact -- I'll answer the second question first. Given the fact that the drug is being approved, or has been approved or recommended for

approval, as a glucose lowering agent, then the lipid effects really are secondary. And so I would not -- my view would be we not propose sort of an endpoint study looking at cardiovascular endpoints based on lipid modification.

I think it would be nice to have some endpoints looking at detailed studies of renal function, detailed studies of echocardiograms, for instance, in patients with left ventricular dysfunction given this class of drugs, or given this drug, potentially studies of vascular reactivity as a means of assessing endothelial function with treatment.

Does hypoglycemia and lowering insulin levels, better control of blood glucose, lead to an improvement in endothelial function, particularly given the fact the drug has some anti-oxidant properties.

I think we also need to better define the potential drug interactions. And as a population who gets -- seems to increase

progressively -- and as one complication of diabetes is renal disease, look at in-patients with mild renal insufficiency. Does this treatment the progression of renal disease -- improve, i.e., favorably improve the deterioration in renal function.

DR. BONE: Dr. Critchlow.

DR. CRITCHLOW: Actually, I have nothing further to add there. I just await some of the data in the other populations that are ongoing.

DR. BONE: Dr. Zawadzki.

DR. ZAWADZKI: We've been discussing the population that is insulin-using. But I would just like to comment that the studies that Dr. Illingworth outlined should be done in those who are also non-insulin-using.

DR. BONE: Dr. Hirsch.

DR. HIRSCH: He touched on most of it. I would just like to add energy metabolism. It would be nice to know something about also some dietary studies, whether any

alterations in what people on the drug eat or don't eat, and adipose tissue studies as well, as we have spoken about.

DR. BONE: Dr. Colley.

DR. COLLEY: I'd like more information on combination therapy in patients who are not on insulin and perhaps on sulfonylurea and/or metformin. The issue on cardiovascular disease was mentioned, patients with preexisting cardiovascular disease also.

It is not clear, the maximum recommended dose is 600 milligrams. But if it is a clear dose response effect, it is not clear if higher doses might be of benefit, and that may be an area for investigation as well.

DR. SHERWIN: Clearly we need to know more about how this drug works. I think that although we have seen a lot of fancy information, we really don't know how this drug really works at a cellular level. And clearly, it is very important that we do understand the mechanism.

Clearly we need to assess the effect of this drug in patients with cardiac disease and look at the impact long term on cardiovascular endpoints. I think that as we begin to optimize therapy, which was not done in these studies, we may run into some problems that we didn't encounter.

For example, if we really try to optimize control with this drug in insulin, in fact we may see a lot of hypoglycemia develop because this is an insulin sensitizing agent. And we have absolutely no information as to whether counter regulation or the response to hypoglycemia might be altered by this drug.

And so I think that that, as we begin to move into the next era, which is to actually improve control to the extent that we would like to see, I think that it would be important to know whether hypoglycemic risk is going to be a problem in the next stage of therapy.

DR. BONE: Do you think that that should have been done already?

DR. SHERWIN: Well, I think it should be done as an ancillary study. I mean, I'm not sure that that -- I have enough concerns. I don't have any information on that. I have never seen any information on that in the packet or any information at all on that area.

There may be some pre-clinical information. But I think it would be useful as we begin to potentially get into that problem down the road. But I wouldn't think it would mean that, you know -- I think it is follow-up studies that need to be done.

DR. BONE: As I recall, the sponsor did present some information about the rate of hypoglycemia. And could Dr. Whitcomb very concisely summarize what was presented today?

DR. WHITCOMB: The best data probably is looking at all of the blood glucoses that we looked at in the 040 study. And there are 35,000 per treatment group there. The incidence of blood glucose below 50 in the 600 milligram group was 0.49 percent, I believe.

So it appears to be fairly uncommon.

But the point about the counter regulatory hormones, though, I could not tell you. We do not know that information.

DR. SHERWIN: Well, it's just that if our goal, let's say, is to lower the hemoglobin A1c to 6.5 percent instead of mid of 8 percent, you may see a whole new pattern and a whole new ballgame in terms of problems with hypoglycemia that you didn't encounter at the endpoints you set because your goal was in part to reduce insulin dose.

But if you don't do that, you may get into some difficulties. That is all I am saying.

DR. BONE: So you're concerned with that aggressive clinical approach.

DR. SHERWIN: Well, it is not -- if that's the goal of therapy as set by the ADA, to get people as close to normal as possible, and it means lowering glycohemoglobin to below 7, and as you begin to do that, which was not

done in this study, you may begin to see more problems.

DR. BONE: Fair enough. Thank you. The executive secretary, Ms. Reedy, will read Dr. Cara's comment.

MS. REEDY: Dr. Cara is interested in the results of the continuing studies that are not completed, and suggests that they be evaluated by this advisory committee for the broader indication.

DR. BONE: Perhaps one of the sponsor's representatives would just remind us, what is the longest study -- what is the length of the longest of the studies that you expect to submit in your major program? Are you going to a year?

DR. WHITCOMB: Oh, yes. We have a large control trial that is 12 months. And there are open label extensions of all of the studies that I have shown here today, which are -- the safety data on those is 18 months, many of the patients --

DR. BONE: In addition to the year?

DR. WHITCOMB: Yes.

DR. BONE: So it would be two and a half year total?

DR. WHITCOMB: Well, no. I would say the longest duration that any patient has been treated so far is two years.

DR. BONE: All right. But your safety data include patients out to two years?

DR. WHITCOMB: Yes.

DR. BONE: Right. Thank you. Speaking for myself, I think that the -- if the drug were to be approved, I would have the greatest concern about the issue of drug interaction. I think while the phrasing of question was such that I felt the answer was just yes, I think that in terms of the adequacy of the sponsor's program for a population that is basically prone to be sick and take many medications, that this is a glaring deficiency in the program, the fact that relatively few drug interaction studies have been done. And

we're going to run into this all of the time.

So I really think that this is something that needs to be addressed, energetically and promptly. And I would really like to see that because we're going to have sick patients with strange results and wondering whether drug interactions are the problem.

If they are not the problem, it would be very helpful to know that in many clinical settings. So I really would ask the sponsor to get out on this in a hurry and make a big effort on that.

Does anyone have anything to add with regard to the labeling? We have focused on the labeling with regard to the patient population. There was some discussion back and forth about what the starting dosage ought to be. Or the sponsor is recommending 200 milligrams as a starting dosage. Is there any difference of opinion about that? No.

Anything else in the labeling that

needs to be covered? Any additional comments from the committee members? No. Okay.

If I have the numbers -- well, that's right. To summarize then, with regard to the indication of troglitazone for the treatment of Type II diabetes in conjunction with insulin, the committee has voted eight to nothing, right, that the study designs and efficacy endpoints and other information presented, taken together, are adequate to assess the efficacy and safety of this drug for the proposed patient population, which we have described several times now.

And based on the data presented, the committee has unanimously recommended approval of the drug for the indication. And we look forward to seeing the larger package in the relatively near future.

If there is any other comment or final -- no. Then the 65th meeting of the Endocrinologic and Metabolic Drugs Advisory Committee is adjourned.

(Whereupon, at 3:14 p.m., the meeting was adjourned.)

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