increase in HbA1c. It's important that you understand this axis. The second interval includes decreases up to 1.5 and the last interval, decreases greater than 1.5. So, as we go from left to right in each of these graphs, benefit increases on the HbA1c scale. The relationship between lipids and HbA1c changes is very clear here. Smaller increases in lipids are associated with larger decreases in HbA1c.

The linear correlation between these measures, however, is not strong. So, one is not necessarily predictive of the other. Nevertheless, this relationship is evident irrespective of how the HbA1c intervals were defined and it was seen for all rosiglitazone dose groups.

The lipid changes were consistent for subgroups based on age, baseline weight, body mass index, and percent of ideal body weight. There was a small difference between males and females, where males showed a greater increase than females by a percent change from baseline of about 5 percent. Also for patients with a duration of diabetes greater than 4 years, the mean percent change from baseline was again about 5 percent above the others.

Also, changes were baseline related, as we saw when we were comparing study 20 to the placebo-controlled studies. Larger baseline values were associated with smaller changes in the lipids.

The last area I will cover will be the differential effects observed for males and females. Significant treatment-by-gender interaction for the primary efficacy variable, HbA1c, was seen in all the monotherapy trials. HbA1c was lower for both men and women with a larger response seen for women. This interaction was not significant in the combination studies.

I've chosen one of the placebo-controlled monotherapy trials, study 24, to illustrate the interaction. The graph on the left is for females and on the right for males. The gender differences in the magnitude of response is evident at each dose.

This graph depicts the treatment effects at 95 percent confidence intervals for the three monotherapy trials by gender. Males are in green and females are in purple. The reference line is at 0. That's right here. This is similar to a graph that the sponsor showed. Points to the left of that line favor rosiglitazone and points to the right favor placebo. The blue shaded area contains the estimates from the glyburide-controlled trial, study 20, and estimates in the white area are from the placebo-controlled trials, so you don't get confused about where these estimates should be.

Starting at the top with study 20, the results for males favor glyburide while the results for females

favor rosiglitazone. The next four confidence intervals, as we go down the slide, show the comparisons of rosiglitazone to placebo. In both studies, the results for females show a larger treatment effect than the males. The results are particularly interesting considering that only one-third of the patients in these studies are female.

Now, adjusting for weight comes to mind when considering gender differences, and I found that adjusting for weight and body mass index had little impact on the estimates, but that adjusting for the percent of ideal body weight did. So, let me explain these four graphs.

Both of the graphs on the left are for females, and both of these graphs are for males. The top row shows the subgroup of patients who had an ideal body weight of 100 percent or less. So, these would be your leaner patients. And the graphs on the bottom are for patients who had an ideal body weight above 100 percent. So, these would be your heavier patients generally.

The gender responses look comparable for the heavier patients. That's the bottom row. For leaner patients, the top row, the female response is clearly larger than the male response. So, leaner males appear to gain less benefit even from the most efficacious dose.

On this slide, I've summarized my presentation with a few comments. This is my last slide.

Rosiglitazone was shown to be efficacious for lowering HbA1c as monotherapy and as add-on to metformin.

Statistically significant increases in LDL, HDL, and LDL to HDL were seen at endpoint.

The lipid responses appear to peak after about 2 months of therapy.

And lastly, women show a larger response than men.

Thank you, and now Bob Misbin will give the medical review.

DR. MISBIN: I don't think there is any question that rosiglitazone is a highly effective medication when it comes to lowering glucose levels in patients with diabetes, both as monotherapy and also when used in combination with metformin.

The issue, however, that I would like to put forward is that lowering glucose levels of itself is not the only issue to be considered in treating patients with diabetes, and the division has considerable concerns about some of the other issues that were raised in the statistical report, particularly the increase in body weight and also the changes in serum lipids, which we interpret as being potentially harmful.

Now, I think it's necessary to define various terms and see how different people can look at data in

different ways. This comes from study 24, which is one of the placebo-controlled trials that the sponsor presented. I'm only going to be showing the maximum dose of rosiglitazone, just for the sake of not adding information that really doesn't change the concepts that I want to get across.

Now, when we evaluate data like this, we always consider, in a placebo-controlled trial of this nature, a treatment effect to be the effect seen with the drug minus the effect seen with the placebo. In this case with respect to hemoglobin A1c, which is our primary efficacy variable, hemoglobin A1c increased in patients on placebo. This was because most of them were being withdrawn from other antidiabetic treatments. There was a fall in patients taking rosiglitazone, and then this was the final treatment effect, a treatment effect of a reduction of 1.45, which the sponsor described as being robust and with which I would certainly agree.

Now, this was associated with a change in body weight. There was a fall of .9 kilograms on placebo, a rise of 3.3 kilograms on rosiglitazone, and a net rise of 4.2 kilograms for the treatment effect which was associated with the reduction in hemoglobin A1c.

Now, let's look at the situation with respect to lipid changes. There's one exception, but by and large

I'm showing LDL over HDL. Again, Joy Mele has gone through all the lipid classes, as well as the sponsor, and this is really the variable that I'm going to illustrate my point.

Now, the sponsor I believe has made the statement that this variable is preserved in patients taking rosiglitazone. By that, I think they mean that there is no change from baseline in patients who were treated. I'm not certain I see this exactly, but I think the baseline value for rosiglitazone was 3.02. It rose to 3.12, which was not significantly different. This value is actually a median change, so these don't add up because this is a median of the change rather than the mean. So, this is what I believe is meant by saying that the LDL/HDL ratio is preserved.

However, if one compares that to the placebo group, one finds that the LDL/HDL ratio fell in the placebo group, and if one makes the appropriate comparison, what we believe to be the appropriate comparison, the LDL/HDL ratio was not preserved, but in fact went up. And this is invariably found in all of the data sets that we examined.

Now, the data that I've shown is for a placebo-controlled trial. We don't ordinarily treat diabetic patients with placebos. That's something which is done in a trial but is not ordinarily done in practice. And I think it's, therefore, important to make a comparison to

the active-controlled trials.

Here I think I would like to congratulate and to thank the sponsors for having done these trials. The FDA does not require comparative trials for approval of a new drug. One can have a new drug approved just on the basis of placebo-controlled trials.

Nevertheless, the trials that the sponsor did I think provide a tremendous amount of information about how these drugs actually will be used in practice, and I think they should be congratulated for having the courage to do those trials, particularly since the results, as Dr. Genuth has already pointed out, are not always complimentary and sometimes are somewhat ambiguous.

Now, I'll discuss these in some detail. This is trial number 20 I believe which was a glyburide titration versus rosiglitazone. Again, I'm only going to show the maximal dose of rosiglitazone.

The way this trial was done was a glyburide titration versus a fixed dose of rosiglitazone. Now, this is the only way this trial could be done, and I'm not criticizing at all. You can only give glyburide by a titration because some patients will be very sensitive and will develop hypoglycemia.

But I think it is important to remember in making the comparison that the glyburide titration,

according to the protocol, had to end at 12 weeks of a 52-week trial, and the median dose achieved by patients on glyburide was only 7.5 milligrams, which is not a maximal dose of glyburide. One could go up to 20 milligrams. And so, any comparability statements that could be made at best would be saying that a maximal dose of rosiglitazone is comparable to a submaximal dose of glyburide.

Having said that, I think it's interesting to look at the results. The reduction with glyburide in hemoglobin A1c was .72. The reduction with rosiglitazone was .53. The 95 percent confidence intervals of these two numbers overlap. They barely overlap, but they do in fact overlap. So, one would be able to support a claim of comparability based on these data.

With respect to weight gain, there was a weight gain in both groups not unexpectedly. The glyburide patients gained weight. This I think is something every clinician knows, but the rosiglitazone patients gained even more weight and this was a statistically significant difference. Again, I think this is a reproducible problem that one has to face when using rosiglitazone.

Now, there is another problem I think which deals with statistics. In an ordinary treatment with a drug like glyburide, if a patient developed hypoglycemia, one would not necessarily stop treatment. One would just

decrease the dose of the drug. In the trial, however, patients who developed significant hypoglycemia were withdrawn from treatment. Now, again, I'm not really criticizing this. That may be perfectly acceptable to do in a trial and certainly is medically important to recognize for patient safety. But it does, I think, lead to certain doubts about the basis of the statistical analysis.

The hypoglycemia on glyburide occurred by and large early in the trial. Hemoglobin A1c is the major efficacy variable and that takes months to change, and so taking patients off of glyburide early in the trial because of hypoglycemia does, in my judgment, bias the results because really you're taking out patients who are very sensitive to glyburide. And there was 1 patient in high dose rosiglitazone who was lost to the trial as well, but this is a 6 to 1 ratio here, patients who were being dropped out because of hypoglycemia on glyburide.

With respect to lack of efficacy, the situation is the opposite. There were twice as many patients on high dose rosiglitazone who had to be withdrawn than that on glyburide.

So, this does kind of set up a heads I win, tails you lose kind of situation, and I think that any claim of comparability based on data really is somewhat

suspect unless these data are completely taken into account. And I'm not sure of any valid statistical analysis that really has taken this into account.

Now, if the situation with glyburide was ambiguous, I think the situation with metformin is not ambiguous but is also not very good, as Dr. Genuth had pointed out. Now, I think I have to sympathize with the sponsor.

This trial was done in a certain way. Patients were given an increasing dose of metformin. They were brought up to a maximal dose of metformin, which is 2.5 grams, and then they were divided into three arms. Metformin was continued. Metformin was switched to rosiglitazone or the combination of the two. And the purpose here was to show that the combination of the two is better than either drug alone. And we completely agree with that, and I'm not going to discuss that because it's really not an issue, the synergy between these two drugs.

But what is an issue is really to me the monotherapy comparison because we do have two monotherapy arms here. Now, I say I sympathize with the sponsor because I think this is the right way to do the trial, but it is a problem because if you compare monotherapy, there is a selection bias in favor of metformin and against rosiglitazone. In order to be randomized, patients had to

be able to do reasonably well on a maximal dose of metformin. Those patients that did not have adequate efficacy would be dropped. Those patients who could not tolerate this dose of metformin would be dropped also, and that is a considerable number of patients. So, I think if the trial had been done differently as a head-on comparison, I think the effects would also be different as well. Nevertheless, these are the data we are presented with, and we can't really ignore them.

Now, these are the data for patients, just monotherapy. Again, I'm not discussing the combination because that really is not an issue which is open to much disagreement.

The monotherapy on metformin, as one would expect. They were already on metformin, so these changes are not very large. Hemoglobin A1c continued -- I think that's a slight rise. Yes, thank you very much. That's a slight rise of HbA1c on metformin. I believe that's a decrease of weight. That is an important point to make. And then there are small changes in the LDL/HDL ratio as well as VLDL.

With respect to rosiglitazone, however, there was a rise of 1.3, and even if one subtracts one to the other, this would be a treatment effect compared to these two of 1.2 percent. Now, this is not very different really

from the effects of rosiglitazone versus placebo, and the sponsor described that effect as being robust and I agree. I think that is also a comparison which is robust. But, unfortunately, in this setting it favors metformin as opposed to rosiglitazone.

There's also I think the point made that the improvement in hemoglobin A1c with rosiglitazone is a consequence -- I'm sorry -- the weight gain is a consequence of the improvement in hemoglobin A1c. Well, that's not the case here. Here we had a deterioration of hemoglobin A1c and a weight gain as well. So, clearly this is a point which I think clinicians really do have to take into account.

The changes in LDL/HDL ratio was also a rise, which is worthy of note.

And for the first time we see a rise in VLDL, which is a rise in the rosiglitazone patients versus metformin. This has not been a consistent finding. This is really the only trial where this has become an issue.

It is worthy of note that one would have expected -- at least I would have expected -- that VLDL and triglycerides in general would go down on patients treated with rosiglitazone under various conditions, and it's surprising really that that's not been observed in the trials. The people on the committee know a lot more about

lipids than I do and I really would like their input as to why the finding that I had expected really did not occur.

Now, I'd like to move on to the major issue we have to wrestle with today and that is the problem of liver toxicity. It may not be exactly clear to people who can't read everything what's being shown. This is not a comparison of liver toxicity of these various drugs. Most of the patients that are being shown here were taking placebo. So, please don't get the misapprehension. This is not a comparison of these drugs. These patients were on placebo by and large.

What I'm trying to show, though, is that there is an underlying rate of ALT elevation that occurs in diabetics regardless of their treatment, and to illustrate this point, I've gone over the various databases that I myself have reviewed. This is from the acarbose NDA, the placebo patients in the acarbose NDA, the placebo patients in the miglitol NDA, the placebo patients in the troglitazone NDA. The metformin NDA did not have many placebo patients because most of these trials were comparative. But I pooled all of these just so we don't have to get too many numbers, and there was really no appreciable difference.

Now, there are several points that I want to make. I think there are 15 patients that had ALT values of

greater than 3 times normal in a combined data set of nearly 3,000 or so. Now, 2 of these patients actually had ALT values of 8 times normal. The rest of the patients had much lower values. I'm presenting this really as an illustration of the spontaneous elevations in ALT levels that occur in diabetic patients regardless of the treatments that they are receiving, and I think it is important to differentiate this spontaneous elevation from real evidence of liver toxicity that occurs in clinical trials.

These are the data with troglitazone. This is from the troglitazone NDA and this data is the same as what I discussed in the briefing document that I provided to this committee prior to the meeting last month. The data set was 2,510 patients, and 1.9 percent of these patients had an ALT value of greater than 3 times normal.

Now, I'll just go ahead for the sake of the record and read these actual numbers so we have it in the file. There was a total of 48 patients that had a value of greater than 3 times normal. Of those 48, 42 patients had a value greater than 5 times normal. 22 patients had a value greater than 8 times normal, and 5 patients had a value greater than 30 times normal. Of these 5 patients, 2 patients were jaundiced.

Now, none of these patients had any long-term

effects to the best of my knowledge. When the drug was continued, everybody got better. There was no permanent damage as far as I know. So, that needs to be said.

Now, there are some other points I think about this data set which are very interesting and quite important. The first thing is that I've divided them between those who were withdrawn from troglitazone and those that had troglitazone continued despite the ALT elevation. Now, this is quite an important point because we recognize that there were patients that could have fairly impressive ALT values and have troglitazone continued and the values would go down. The highest value that I'm aware of was a value of 12 times normal in a patient taking troglitazone. The troglitazone was continued and the value normalized by the end of the trial.

Now, this then leads to a potential speculation for differences that you have seen with respect to rosiglitazone and differences with troglitazone. One possibility for the very high values that were seen with troglitazone but not with rosiglitazone is that there might have been a difference in the criteria used to withdraw patients from therapy. In neither trial, to the best of my knowledge, were there any fixed criteria that were used to withdraw the drug. This was done basically at the judgment of the individual physician. But one could make the

argument that if in the troglitazone trial, which was done earlier, if patients were left on the drug longer, it's possible that you would see these very high values as a result of their having been exposed to the drug for a longer period of time than, say, in a different trial in which the patients were withdrawn earlier.

Now, this is a reasonable hypothesis and it's a testable hypothesis. I have looked at it and I believe that it's incorrect. There were 5 patients that had very high values, unequivocally elevated values, greater than 1,000 in every case. Of these 5 patients, there was one case that 2 months prior to the maximal elevation was identified as having an ALT elevation. Troglitazone was not withdrawn. It was continued, and then 2 months later the patient was found to have a value of greater than 30 times normal and the drug was withdrawn.

In the other four cases, however, this situation did not occur. 3 of the patients came in initially, as their initial manifestation of troglitazone toxicity, with very high values. So, a withdrawal based on a previous minimal elevation was not relevant.

In the final case, this patient did in fact have an elevation of ALT. It was elevated to greater than 5 times normal. The troglitazone was discontinued, and despite discontinuing troglitazone, the patient went on to

have an ALT value of 1,000.

So, I think that the argument based on differences between these two data sets based on early withdrawal of treatment in my opinion is not a valid argument. At best one could say that there would only be four cases in the troglitazone data set versus five, and this is in comparison to no cases in the rosiglitazone data set.

Now, this then brings us to rosiglitazone. All of the numbers on this slide are very much lower than the numbers that I've just shown you for troglitazone. The only number which is higher is the total number of patients exposed. The data set of exposure on rosiglitazone was almost twice as many as the number of patients exposed to troglitazone. Yet, the number of patients that had any manifestations of ALT elevation was considerably less.

Now, there were two cases that had values of 8 times normal on rosiglitazone. Both of these normalized despite continuation of the drug. In my evaluation of these two cases, I was rather curious about that. These are two cases that, as I read them, are very similar to cases that I had seen with troglitazone. And this is really the only cause of concern that I have about this data set.

I would point out, however, just as I pointed

out before, that one does occasionally see this as a spontaneous elevation in patients on placebo, and so it is really not possible to say, with any degree of certainty, particularly since there are only two cases, whether this is really just a manifestation of a spontaneous elevation or if it is in fact a troglitazone-like hepatitis in patients on rosiglitazone. One cannot really make that distinction at the present time.

Before I end this, I would like to point out two differences between my presentation and the presentation from the sponsor that you heard a little while ago.

In going over these data, we do not have the head-on-head comparison of rosiglitazone to troglitazone. We don't have it. We will never have it. I think the best thing that we can do is to try to look at the data sets using the same yardsticks, and that's really what I went out of my way to try to do.

Now, for the sake of being consistent, the sponsor told you about 13 cases, and I've only counted 11. I've eliminated two cases because, as I review them, the ALT elevation occurred before the patient got rosiglitazone and did not get worse, in fact, seemed to get better. So, there really is no reason to consider this as a treatment-emergent elevation in ALT. That's really the same way I

looked at the troglitazone data set.

I would add, since the question has come up, that there were many patients that had minimal elevations in ALT, and in general, these elevations went down on either troglitazone or rosiglitazone.

I've asked the sponsor to get out their data and we can discuss this later because it is I think an important point that people don't always understand. But for the sake of this discussion, I'm only counting 11 patients as being treatment-emergent elevations.

Now, there is one other kind of technical point. In the troglitazone NDA, Parke Davis used a value of 34 as the upper limit of normal for ALT. In the rosiglitazone NDA, the upper limit of normal was 48. Now, it's not clear to me whether there's a real difference in the method and the analysis or it's a difference in the populations that were used to establish normative data. This is not an easy question to answer after the fact once the studies are already done.

But in order to eliminate any possibility that anyone could say that we reviewed these data using an inappropriate normal value, I actually used the lower value for the upper limit of normal. I used the troglitazone upper limit of normal on the rosiglitazone data. Now, I'm not saying this is analytically correct, but I'm doing it

so that there will be no speculation that we did not apply the same standards in considering both data sets.

Now, there's only one difference. One of these patients that I'm counting as greater than 8 times normal, the sponsor would have had in this category here. But I just want to make the statement for the record that one cannot say that there was some artifact in the way we compared the data because my intention here was to present a worst case scenario and that's really the way I see it.

Now, let's move on. The next slide, which is the extra slide.

The question came up -- and I think it's a good question -- what happens if you were to drop the upper limit of normal to 2.5 times normal versus 3 times normal? This is also relevant to this question of what the upper limit of normal is.

Now, I've asked the sponsor to do this actually just a few weeks ago, and that's probably why it was not in their presentation. When you drop the upper limit of normal, you do, not unexpectedly, pick up a few more cases. You pick up one more placebo case and you pick up six more rosiglitazone cases. Three times the upper limit of normal is the values that I've shown, .2 percent in placebo, .25 percent with rosiglitazone.

If you drop it to 2.5 times the upper limit of

normal, you get .4 percent with placebo, .4 percent with rosiglitazone, the exact same numbers, and I would point out that .4 percent is virtually the same as what we've seen in every trial that I've ever reviewed in a data set of well over 3,000 patients.

So, the bottom line to all this is that it's my belief that the elevation in ALT values seen in the rosiglitazone NDAs are nothing more than the spontaneous elevations that one will see in diabetic patients regardless of treatment.

Now, just to summarize, I've told you all about the disadvantages of rosiglitazone. There is an increased weight. There is an increase in the LDL/HDL ratio. Anemia I think we have discussed. This is a class effect. I think it's very mild and I'm not especially concerned about it. And edema also. These occurred, but it's not anything which I think is of great concern.

On the other hand, there are clear advantages to rosiglitazone. We've not discussed the durability issue. The sponsor has presented some data about this, and I believe the data they've presented are correct. In my view of all drugs of this class, the longer patients are on it, the better they are. The blood sugar continues to go down which is really quite different from what we see with other oral hypoglycemic agents. Now, admittedly we do not

have a 20-year follow-up, but to the extent that we have any long-term data at all, there's no evidence whatsoever with any of these drugs that the antidiabetic activity wanes.

Lower insulin levels. As Dr. Genuth pointed out, this is very speculative. And it's already been adequately discussed so I won't go into it again. But I think when you're coming up with a ledger and saying pluses and minuses, I think that this is speculative and I think that some of these are fairly speculative as well. I think that it's really up to the committee to make a determination, are the lower insulin levels that you see with rosiglitazone -- does that reasonably offset in your clinical judgment what I think are negative effects on the patients' serum lipids?

Then finally, there's clearly less hypoglycemia in patients taking rosiglitazone than in patients taking sulfonylureas, and that is obviously another major advantage.

Thank you.

DR. BONE: Thank you, Dr. Misbin and the other FDA speakers.

We'll now have an opportunity for the committee members to ask questions directly pertinent to these presentations. Remember we're going to have our general

discussion this afternoon. I guess the lights are coming up and Dr. Molitch has raised his hand. And then the lights were turned out again. I'm not going to speculate about the causal relationship there.

(Laughter.)

DR. MOLITCH: I'm going to ask the FDA the similar question that I asked the sponsor about subgroup analysis. Are these normally distributed lipid data and body weight data? Are they dichotomous data to begin with? Is it appropriate to look at parametric measures of looking at changes in LDL and HDL and body weight, or should we be looking at subgroup analyses of the patients for whom there's not going to be any adverse effect versus some subgroup for whom there is an adverse effect? And have you looked at the data in that fashion?

DR. MISBIN: I don't think it has been looked at in that fashion, but I would defer to the statistician.

MS. MELE: I mentioned in my talk that I did break down the lipids by medians and then I looked at the changes by the median at baseline. And we saw a larger change for patients who had smaller baselines. But I did not break it down further into smaller subgroups, but I did look at it in a more gross fashion.

DR. MOLITCH: I'm not sure that's the right way to do things. If patients have abnormal lipid values to

begin with, would this drug be an inappropriate drug to use in that kind of a patient, and should it be restricted to those patients who have normal LDL and HDL values?

MS. MELE: I did not actually break it down into enough subgroups to look at the highest level, the patients that you're describing, separate from -- I just looked at by median.

DR. MOLITCH: The same thing with body weight. How about in people who had normal versus abnormal body weight? Did one group show a difference in change in body weight over the course of the study compared to the other?

MS. MELE: I did look at that again by the medians to see if there was any signal there and I didn't see any difference.

DR. MISBIN: I think, Dr. Molitch, if you wish to make a recommendation that we do that type of analysis, I think the sponsor could do it. That would be, I think, a reasonable thing that the committee might discuss and I'm sure the data is available. That could potentially be a labeling issue if one's cholesterol is over a particular level, or whatever.

DR. BONE: I believe Dr. Lewis had a question.

DR. LEWIS: Two questions regarding the ALT values. The duration of therapy for many of these patients was just 6 months. There was a large number that went

between 6 and 12 months. What was the distribution where the ALTs greater than 3 times normal occurred? Were they within the first several months of therapy, and how did that compare to the placebo recipients? Is this a random type of response that we're seeing, or was there any aggregate to suggest that it all occurs on treatment within the first 3- to 6-month interval, something like that?

DR. MISBIN: Well, as you pointed out, most of the patients were in 6-month trials. There was the one comparator trial that went to 12 months. The numbers are very small. There are only 11 patients, and there was no obvious pattern. But I don't think one would be able to detect it even if it was there. There were no patients that had a value within a week or 2 after. I really can't answer that any better.

I'm sure the sponsor has that information, and it's actually in the briefing documents. It tells you what dates the maximal elevation occurred. So, I think we could all just look at that. We can always go over the cases individually. But I didn't see any pattern, and if the sponsor saw any pattern, I think they might comment.

DR. BONE: Let's see. Dr. Hirsch had a question.

DR. HIRSCH: I think this is a continuation of the same point. I believe it was in your write-up or

someone's write-up from the agency in which the rather unusual speculation was made that perhaps the liver toxicity is a function of the mass of drug given, as well as time, different from its efficacy. And, therefore, since a very much smaller mass than troglitazone is given here, you or someone hypothesized that one really should be looking at what? 4 or 5 years or something for the onset of liver -- could you comment on that?

DR. MISBIN: You're quite right. This is just a speculation, and that's all there is to it. I don't think we have any data certainly one way or the other. Rosiglitazone is almost 100 times more potent than troglitazone. So, I think if one wanted to make a comparison, it would be 4 to 8 milligrams of rosiglitazone versus, say, 400 milligrams of troglitazone.

On troglitazone, the median time to a maximal ALT elevation was 4 months.

Now, I did have a slide showing, just calculating, what it would take, how long a trial it would take to pick that up. I was admonished not to show it because no one would be willing to make that long of a phase 4 commitment. It actually was 33 years.

(Laughter.)

DR. MISBIN: To my knowledge, that's exceeded only by the time that the ancient Hebrews looked for the

promised land.

(Laughter.)

DR. MISBIN: I was admonished that the agency really was in no position to make that kind of recommendation, so at least in this case, I did do what I was told and removed that slide.

(Laughter.)

DR. BONE: Are there other questions? Yes, Dr. Seeff.

DR. SEEFF: I think that your presentation was very compelling, that the frequency of abnormal enzymes as a reflection of liver disease is extremely low and clearly is consistent with what one might anticipate for diabetics who are not receiving any drug at all because of the steatohepatitis, which, by the way, is not necessarily a benign condition. That's another issue we're facing. Is this something that may progress ultimately to chronic liver disease, but that's a separate issue.

But when we're looking at toxicity, what are the things we're concerned about? We're concerned about acute disease and we're concerned about that because people may progress to fulminant hepatitis, as we've heard from some other drugs, and die acutely.

The other possibility is the development of chronic liver disease, and that may occur with very low

grade enzymes. We see in chronic viral hepatitis C regularly that patients don't have to exceed 100 or 2.5 times the upper limit of normal to have an intrinsic disease that ultimately leads to cirrhosis and perhaps even hepatocellular carcinoma.

The numbers are small and I'm very taken with the data here, that this is not the same as troglitazone with respect to toxicity. But I think we have to be careful about the serum enzymes.

I'm also particularly concerned and why I want to know more about it is what about people who have underlying chronic liver disease who are treated with a drug, what may occur?

Now, I don't have the frequency of abnormal enzymes in this country as a whole, but we know that 2 percent of the country is infected with hepatitis C. It's probably even higher than that. Alcohol is a problem and there are a lot of reasons. I would not be surprised if 5 to 8 percent of people in the United States have got abnormal enzymes to begin with. They're going to be put on a drug that is long-term, presumably for life, drug.

Dialose Plus, which was the first drug that was associated with autoimmune hepatitis, was used for a long time before cirrhosis occurred. Dialose Plus caused autoimmune hepatitis, but very low grade enzymes.

So, the only thing that I'm trying to get to is that I think that we have to think very carefully about serum enzymes. In this case there appear to be other reasons for this, but I think that low grade enzymes should not be ignored.

DR. MISBIN: I think you're completely right, and again the numbers are so infrequent that it's hard to really say anything. Looking at the troglitazone database, I was impressed that patients could have reasonably high enzymes, 400 ALT, and come down to normal. But one never knows. That may not have been drug related.

DR. SEEFF: This happens with hepatitis C. They can go up spontaneously, come down, go up, go down, and in that instance, that is not a benign effect of the disease itself. Here the drug could be considered in that light.

I think long-term follow-up is necessary to see exactly what happens with a drug that has the potential for toxicity, particularly given the history of where we are with this particular class of drugs.

DR. MISBIN: Well, this is an issue which I think we really have to wrestle with this afternoon with respect to the phase 4 commitments because your point is very well taken. The advantage of rosiglitazone is that it's durable, which to me means that once a patient takes

it, they should take it forever. Now, if one considers this to be first-line treatment, that could easily be 20 or 30 years of duration. It would not surprise me whatsoever, based on experience with other drugs, that once rosiglitazone is approved, if it is approved, that a million patients will be taking it within a year or 2. That would mean a million Americans. So, this is a very large number and I think we should all take note of that and deal with it.

DR. BONE: Thank you.

Other questions concerning the presentations? Dr. Genuth.

DR. GENUTH: In your critique of the comparison between rosiglitazone and glyburide, you pointed out that the group getting glyburide reached a median or mean dose of 7.5 milligrams and that that wasn't the maximum that could be given. I don't quite understand that critique.

The figure of 20 milligrams that the PDR points to I've always understood to be the maximum dose the FDA thinks anybody could possibly benefit from, but that's not what we're talking about here. We're talking about the maximum dose that could be given to a particular group of patients who are responding in a particular way. And if the dose titration was stopped because of hypoglycemia, that's as you said, a perfectly good reason not to continue

increasing and, in fact, we would all decrease the dose. So, as far as I'm concerned glyburide was used at its maximum dose, the maximum that could be taken by this group of patients.

DR. MISBIN: I'm not criticizing the trial, and your point is certainly well taken. It's just that they tend to be kind of blanket comparisons and I think that if one were to say glyburide has an equal hypoglycemic effect to rosiglitazone, I would think it's just wise to point out that that was a particular dose. For instance, you could take a lower dose of rosiglitazone -- I didn't show that data, but there was not that comparison.

In ordinary clinical practice, though -- I don't wish to be misunderstood. I think the trial was very well done, as I have already said. In ordinary clinical practice, I think these are essentially equivalent because, very well, of the problem of hypoglycemia with glyburide.

DR. GENUTH: Well, maybe the right way to look at it is the two drugs should be compared each at its clinically optimal dose in the subjects that are being compared. In that case, the glyburide dose is fine. I presume they did it well and it was optimized.

DR. MISBIN: Except it should be pointed out that one would not arbitrarily say 12 weeks. When you treat patients with glyburide, you wouldn't say 12 weeks I

stop, and this was a 52-week trial. If they had gone longer, then I think the glyburide group probably would have been superior based on their reduction in A1c.

DR. GENUTH: Well, it might have been superior.

DR. MISBIN: It might have been.

DR. GENUTH: That's a good critique. I don't think we know what target was being sought. Was normal fasting glucose being sought or normal hemoglobin A1c?

DR. MISBIN: I don't remember that specifically, but I think you should recognize that what I'm saying is really a critique. That is my job, to critique it, and you heard what the sponsor had. And there are whole lot of them. There aren't that many of us. So, things do --

(Laughter.)

DR. MISBIN: Things do tend to come across as a critique.

But the bottom line is that I think that the trial was very, very well done. I think we know quite a lot about how these two drugs are used or should be used, and I think that glyburide is more effective at lowering blood sugar early in treatment, but that that is made up for later on when you see a loss of effect. So, it's what you get at the beginning versus what you get at the end. And I don't mean to come across as being critical. That's

just the way things have to be presented.

DR. GENUTH: Bob, if you and I had been wandering in that desert for 40 years with the rest of the Israelites and I had brought down the Ten Commandments, I think you might have had a critique.

(Laughter.)

DR. MISBIN: The only point I would make is that the Ten Commandments are written on two tablets, which is consistent with the b.i.d. dosing we've been discussing.

(Laughter.)

DR. BONE: Let the record show that everyone in the room is speechless at this point.

(Laughter.)

DR. BONE: I have one or two questions for the statistician if there are no other questions at the moment.

You mentioned that you saw a significant gender difference in the effect on glycemia, but you didn't comment about a gender difference in the effect on lipids. Was this looked at?

MS. MELE: Yes, I think I did mention that actually.

DR. BONE: I missed it.

MS. MELE: Right.

(Laughter.)

MS. MELE: What I said was that the percent

change for males was slightly higher than the mean percent change for females of about 5 percent.

DR. BONE: So, we had greater reduction of glycemia --

MS. MELE: It fits.

DR. BONE: Sorry?

MS. MELE: I said it fits. When we discuss the relationship between the change in HbA1c and lipids, this result for the males and females for the lipids fits with those results because we had a higher response in females, and remember a higher response was associated with as not a big a response in the lipids.

DR. BONE: I guess what I'm trying to ask you is was there an interaction by gender or was this --

MS. MELE: There was not a significant --

DR. BONE: Just a second. Apart from that predictable based on the hypoglycemic effect, was there an independent effect of gender?

MS. MELE: No, not in the --

DR. BONE: I'm sorry. I didn't ask my question --

MS. MELE: Right. It was not a significant gender --

DR. BONE: All right.

And the other question that arose here is a

knotty one, and we may want to discuss this a little further in the afternoon. There was a question of how do you decide when there's an equivalent effect. Would you comment on the power calculation for detection of a difference in the trial where we were discussing equivalence?

MS. MELE: In the active-controlled trial? Okay. That trial was powered to show no bigger than a difference of .5 percent between the active control and rosiglitazone. So, in other words, when you do the confidence interval, the upper bound of the confidence interval -- it was powered so that the upper bound would be no bigger than .5. That was their goal. It was adequately powered for that.

DR. BONE: Okay.

MS. MELE: And so, when you combine the males and females, they achieve that goal.

DR. BONE: Thank you.

Are there other questions from members of the committee? Are there other questions concerning the presentations by FDA? Dr. Lewis.

DR. LEWIS: I just want to ask the division what they thought of the pharm/tox data. We were presented with a conclusion slide that said there's a signal from the animal data, and we sometimes don't know what to do with

animal toxicity studies. Assuming that troglitazone is an unpredictable hepatotoxin, rosiglitazone in humans at least, which far outnumbered the dogs in the trial, didn't show a signal of any kind. How did the division interpret those data?

DR. STEIGERWALT: That's a good point that you've made there. What I did was refer to that as a finding rather than a specific toxicity. We saw a very high effect at a very high dose in the dogs, which got our attention. The effect, of course, is much lower when you're getting to levels that approximate human exposure. So, what we take that as is a signal to look into the clinical studies as to whether we're going to get some kind of finding in the clinical results. In the development of the drug, we would then probably make recommendations in study design so that those issues are addressed. I don't necessarily mean that the animal findings are indicative of the findings that were seen with troglitazone clinically.

DR. BONE: Thank you.

Any other questions for FDA? Yes, Dr. Hammes.

DR. HAMMES: Somewhere either today or tomorrow we're apparently going to look at class labeling largely in terms of liver toxicity. Recalling our discussions of troglitazone last week, it seemed that one of the big issues was the wide error bars in some of the estimates.

Given that, would it not be appropriate to combine the data from the troglitazone, rosiglitazone, and tomorrow's discussion in terms of class action? And will that be forthcoming or what's your feeling on that?

DR. BONE: Well, I guess what we're going to be asked to discuss is whether we're dealing with an effect of individual drugs or whether the drugs should be treated as a class. So, maybe that's an issue for this afternoon.

Dr. New.

DR. NEW: This is a very brief question. As a clinician who would deal with these patients and let's say that you decide to give this drug in combination to lower the blood glucose and the hemoglobin A1c and then you observe that the lipids are rising, the clinician would probably add a lipid lowering drug. Is there any experience that can be given as to what the combination of lipid lowering drugs with the troglitazones or any of this class of drugs to know whether there is a drug-drug interaction?

DR. BONE: Any comment from FDA on actual experience with this? Any comment from the sponsor? Do they have direct experience using --

DR. MISBIN: There were cases that were taking lipid lowering drugs in the data set, but we don't have any specific experience. That would be something the sponsor

would have to address.

DR. SOBEL: The cause for concern is there because the same cytochrome metabolizes the drug, and actually in our troglitazone labeling, mention is made of the same cytochrome being involved. But we haven't seen any empiric data that gives us any alarm yet.

DR. BONE: Anything specific from the sponsor in response to that question?

DR. WHEADON: Roughly 20 percent of the patients in our database were on lipid lowering agents at entry into study. One of the requirements around that was that the dose could not be altered once they came into the study, nor could it be stopped. So, they were on lipid lowering agents. We did not see any differential adverse effect in those patients versus those that were not on.

Additionally, in terms of the P450 issue, as Dr. Sobel has indicated, rosiglitazone goes through 2C8 which is a very distinctive pathway as opposed to 3A4.

DR. BONE: Thank you.

I guess I'll ask a somewhat parallel question. Was there any experience with treatment-emergent edema using diuretics?

DR. RAPPAPORT: Yes. About 30 percent of the patients who developed edema did get put on diuretics. We can only assume that it was effective because very few

patients withdrew due to that adverse event of edema.

DR. BONE: So, we really don't know for sure.

DR. RAPPAPORT: We don't know for sure.

DR. BONE: All right. Thank you very much.

I think if there are no further questions for the FDA, Dr. Hirsch wanted to give the sponsor one more thing to do during lunch.

(Laughter.)

DR. HIRSCH: Sorry. I'm still very curious about the hemodynamic effects, even though they're small, about what the pathogenesis of these is. I wonder if you have any data whatsoever on microalbuminuria, for example, in these patients over the course of the study or plasma albumin levels. If you might look to that or anything related to those issues, I'd be very pleased.

DR. BONE: Thank you.

If there are no further questions pertinent to the FDA presentation, I think we can go to the open public hearing section. I believe we have a presentation by a Dr. Larry Sasich. Will you please give your organization affiliations and list any potential conflicts of interest? Please.

DR. SASICH: Thank you very much. Larry Sasich, Public Citizens Health Research Group, Washington, D.C. And no potential conflicts of interest. I'm standing

in today for Dr. Sidney Wolfe who couldn't be here.

The public is at a distinct disadvantage at FDA advisory committee meetings because we don't have access to summary safety and efficacy information prior to or even at the time that the committee is deliberating a topic. We hope that at some point in the future that this will, in fact, be remedied.

Since we're not able to have the opportunity to look at the data in depth, the things that I would like to say are going to be very brief and very general. I want to make my comments in light of the troglitazone post-marketing safety meeting that occurred last month and the fact that it appears that there's going to be discussion of class labeling or class effects of these drugs this afternoon and tomorrow. I would like to quickly or briefly just sum up by mentioning patient labeling, which is a topic that was discussed at the troglitazone safety meeting.

The things that I remember distinctly or that stand out in my mind most from the troglitazone meeting were that we don't understand the mechanism of hepatotoxicity of troglitazone.

Also, one thing that was very striking was that compliance with liver testing requirements is abysmal. The word "abysmal" was used by one of the committee members

during that meeting. At least post-marketing and post-marketing experience with troglitazone, liver testing may not detect what Dr. David Graham described as rapid risers and the withdrawal of the drug may not prevent progression of liver disease.

In regard to class labeling for these drugs, until shown otherwise, I think it's only prudent to assume that this drug and other drugs in its class are not safer than troglitazone. I chose the word "prudent" very carefully because the word "prudent" is used in the University Group Diabetes Study warning that is included in the labeling for all of the sulfonylurea drugs, that even though we had data in the UGDPS study on one sulfonylurea, that it may be prudent from a safety standpoint to include a class warning or class labeling for all of these drugs.

Just to close, regarding patient labeling, as I mentioned, it was a topic that was raised at the troglitazone post-marketing safety surveillance meeting. There is only one way to ensure that patients do, in fact, receive the labeling that the agency and sponsors intend for them to have. There are approximately 50 drugs right now that do have FDA approved patient labeling. At least the drugs that we've looked at, patients don't receive that labeling. What they receive are computer printouts from pharmacists' computer systems that are completely

unregulated.

There will be a rule that will be final on June 1st this year, a rule that was first proposed by the FDA in 1995, called the Medication Guide Rule. In these circumstances, if the agency deems that a drug requires a medication guide, then the requirement is the mandatory distribution of medication guides to patients. This can only be accomplished if the drug is dispensed in unit of use packaging.

Thank you very much. I hope you would consider medication guides for these drugs and the fact that it is very, very important for patients to have this type of information. Thank you for your attention.

DR. BONE: Thank you very much.

We're going to have a break for lunch now. We're going to plan to be back here at 10 minutes after 1:00.

(Whereupon, at 12:03 p.m., the committee was recessed, to reconvene at 1:10 p.m., this same day.)

AFTERNOON SESSION

(1:15 p.m.)

DR. BONE: The committee is back in session.

The first item of business is an item that's not on the agenda. This will be a brief presentation by Dr. Sobel concerning some of the valuable members of the committee who are now achieving emeritus status.

DR. SOBEL: We at FDA are very dependent on the advisory committee and on its individual members to advise us in making decisions. Recommendations are extremely important to us.

Today we want to express our gratitude to two members who are leaving the committee: Dr. Maria New who has provided a great deal of help in various endocrinologic matters, has provided bridges to the pediatric issues that we sorely need, and also to Cathy Critchlow for her expert advice in issues of epidemiology.

I have here two letters each, one from our center Director, Dr. Woodcock, and one from our Commissioner, Dr. Henney, two letters each which will elaborate more on our extreme gratitude. So, I'll present these.

(Applause.)

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

If I rightly read the intentions of our

Executive Secretary and the Advisors and Consultants Staff, this is not the last we'll see of these emeritus members. They will be valuable consultants, I'm sure, in the future.

The next item will be a mini or micro-presentation, depending on whether we fall under or over 10 minutes, by the company to respond to some of the questions that they were asked to address. They've had the opportunity to see whether the hypoglycemia induced by missing lunch will be offset by the epinephrine level that they will have achieved while preparing the answers to these questions.

(Laughter.)

DR. WHEADON: Thank you, Dr. Bone.

Just to briefly outline our planned micro-presentation, and it will be micro, we'll have Dr. Brunzell lead off with additional comments around the lipid issues which the committee was asking.

That will be followed by the adverse experiences database at baseline looking at patients with preexisting hypertension, preexisting edema, and cardiac heart failure, NYHA class I and II, as was asked.

We'll then go into the efficacy in terms of the metformin issue that was driven by the 093 data and the questions of patients switched from metformin onto Avandia.

And then we'll end with some of the additional

analyses that were asked for in terms of the liver enzyme elevations.

So, Dr. Brunzell?

DR. BRUNZELL: Yes. I'm John Brunzell, Professor of Medicine at the University of Washington, and I'd like to address in the next 2 or 3 minutes the issue of the LDL/HDL cholesterol.

Dr. Mele presented data from studies 11 and 24 which were studies that covered a period of 26 weeks, and what I'd like to do is re-present the data that Dr. Rebuck presented of the 52 weeks, showing at 26 weeks the results are the same as what Dr. Mele said, but if you follow further, you get a different answer.

I'm going to show three slides. One is these are the effects of Avandia on LDL cholesterol at 8 milligrams a day and 4 milligrams a day. You can see that LDL goes up, and it stays up presumably forever.

The thing that's quite different is the slow response of HDL cholesterol. Now, she talked about the effect at 26 weeks here, and you can see that with the oral sulfonylurea, with 4 milligrams a day and with 8 milligrams a day, that in fact HDL continues to go up. So, if the LDL cholesterol stays constant and the HDL cholesterol is going up, you'd expect to see a decrease in the LDL to HDL cholesterol which would be the preferred way for it to go.

In fact, that's exactly what you see. Here's 26 weeks where the LDL/HDL cholesterol ratio is actually higher than it was at baseline, but because of the continued increase in HDL cholesterol, this actually comes back down to baseline or perhaps below. I think that this is a very important observation, that over time both the oral sulfonylureas and the rosiglitazone do this. I think most of the lipid effects, if all of the lipid effects, are probably class effects of this class of drugs.

Are there any questions?

DR. BONE: Dr. Molitch.

DR. MOLITCH: John, what about the people who have baseline lipid abnormalities? Do they follow this same trend or do they act differently?

DR. BRUNZELL: I was very interested in the triglyceride and that's how I got involved in this originally. The only data that I know of that had been done on that basis is the initial baseline triglyceride. The people that have the highest triglycerides actually have a decrease in triglyceride with therapy with Avandia. The other people don't. So, overall you don't see much of an effect.

I think it's a class effect. You see the same thing with troglitazone presented. It was published in Diabetes Care in 1996.

DR. MOLITCH: But if you have somebody who's starting off with an elevated LDL of 160, a low HDL, do they follow the same trend? Do they have a worsening of their LDL to 190 or 200, or what happens?

DR. BRUNZELL: I think the HDL part you can answer because of the known effect that change in triglyceride and HDL with that. The data have not been analyzed to actually answer the LDL. Informally, they said there was no effect, but I haven't actually seen the data myself.

DR. BONE: Dr. Illingworth.

DR. ILLINGWORTH: John, is there any data on changes in APO-B, APO-A1, and potentially Lp-a in response to this drug?

And the second question is, any information about the mechanisms of response for the changes?

DR. BRUNZELL: Yes. There are data on APO-B and LDL. As I mentioned earlier, the LDL cholesterol to LDL APO-B ratio goes up, suggesting they're getting rid of the small, dense atherogenic LDL.

APO-A1, there are some data and I can't tell you what they are. I don't remember. I've seen the data over the last several months.

Lp-a, I don't think there are any data.

I think the mechanism related to the change in

LDL, as I mentioned -- our hypothesis is because of a decrease in free fatty acid, decreasing hepatic lipase. So, we hope to be able to show this, then getting a bigger moiety LDL and more HDL too.

It just occurred to me today and this is pure speculation, but if in fact these people get edema and they're putting on hydrochlorothiazide for that, that raises LDL. That's something that can actually be addressed.

DR. BONE: Further questions for Dr. Brunzell?

This appears to be Dr. Rappaport headed for the podium. You notice I've been associating with statisticians a lot and I said, appears to be Dr. Rappaport.

(Laughter.)

DR. RAPPAPORT: I'm really not sure what to make of that.

I'm going to try to answer some of Dr. Seeff's questions regarding what happens to patients who have elevations in their liver enzymes at baseline, and I think we have a slide for that. This is a look at what happened to patients who began -- actually this answers an earlier question. Dr. Seeff wanted to know how many patients had so-called low grade elevations in their liver enzymes. Is that right? And that's what this slide is.

This is the percentage of patients who received Avandia monotherapy, placebo, Avandia plus metformin, metformin alone, Avandia plus sulfonylurea, or sulfonylurea alone who had elevations in their ALTs in the first row here, elevations in ALT that were greater than 1 time, but less than 3 times the upper limit of the reference range at any time during the study. This is the proportion, the percent of patients. These are percents.

So, here we have for Avandia alone, 4.6 percent; with placebo, 3.4; Avandia plus metformin, 3.3; metformin, 3.9; Avandia plus SU, 6.3; and SU alone, 8.

The other percentages are for alkaline phosphatase and bilirubin, and here quite consistently the Avandia percentages are lower than the corresponding comparator groups.

Now, I think we have another slide which shows you what happened to the patients who had baseline values that were within the reference range. There were approximately 4,000 such patients who were treated with Avandia alone or in combinations, and about 550 patients on placebo. This shows the percentage that remained within the reference range throughout the study. They were about the same. Patients who went to greater than 1, but less than 3 times the upper limit, and that's similar to what you saw earlier, but this is for all Avandia patients

combined. And this is the patients we know about, the ones who went to greater than 3x.

I think we have one more slide where we will tell you something about what happened to the 5 or 6 percent of patients who started our studies with elevations in ALT at baseline. So, this is the last on-therapy ALT in patients whose baseline values were greater than the upper limit of the reference range. This is for all the Avandia patients. There were 249. All the metformin patients, all the SU patients, and all the placebo patients. So, there really was a small proportion of patients in the studies overall that started above the upper limit of the reference range for ALT.

At the end of therapy, the last time we knew about these people, 66 percent were within the reference range. Another 16 percent had had a decrease from their baseline, but they were still a little bit outside the reference range. 6 percent had no change, and 11 percent were above their baseline value but they were still not above 3x because we -- well, that's not true. The few that we know about who were above 3x we've told you about, and the proportions are actually higher for these groups of patients here, although the numbers are very small.

Does that address most of your --

DR. SEEFF: Let me ask you another question

about it. It doesn't compel that the data thus far do not show much with respect to acute hepatotoxicity. We also I think with the previous drug troglitazone also didn't have much at that point and much of the acute problems occurred afterwards in the post-marketing period. So, I just make that point. But I'm compelled that this does not cause acute hepatotoxicity.

The question is about chronic disease and particularly if you start with chronic disease. I don't know if it's possible. There's one case here of a patient who had hepatitis C, and I know that one case doesn't give us everything. But one patient with hepatitis C is started on the drug, has I guess normal transaminases, and within a short time suddenly the ALT rises to 600 and then comes down. Of course, that is not inconsistent with chronic hepatitis C anyway.

Do we have any information? Did people do viral loads, for example? Is it conceivable that in somebody who already has intrinsic liver disease, in this case chronic hepatitis C, and you add this -- could it conceivably lead to problems further on? I say this one case was at least an example to ask the question about.

DR. RAPPAPORT: I can't exclude that possibility. We did not screen patients when they came into our studies or before they came into our studies to

see whether they had evidence of preexisting hepatitis. We didn't do hepatitis C serology or any other hepatitis serology on those patients.

This particular patient, the one who had that very high ALT, actually we don't know when he got hepatitis C. We do know he had a transfusion in 1991. We do know he was hep C positive 60 days after he completed our trial. We really don't know his status at the time he entered the trial, and we were not able to get any saved serum to see whether he actually had hepatitis C at the time he was put on Avandia.

DR. SEEFF: We are struggling with the issue, and this extends beyond this particular discussion. How do you monitor a patient who has intrinsic liver disease, who is put on a drug, and you wonder whether an abnormality occurs as a result of the underlying disease, or is it the result of a drug, for example? We don't really have an answer to that. I know that at the NIDDK we are now trying to look at this issue to see if we can come up with more sensitive measures to make that distinction. So, I understand the problem, but I just mention it for the record.

DR. WHEADON: I might mention just one other thing in addition to what Dr. Rappaport said. As she pointed out in her presentation, the database that you're

looking at is an ongoing database and it includes patients that are in extensions, ongoing extensions of clinical trials. We're constantly repopulating that database. So, it goes beyond the 26 or even 52-week cutoff of the number of studies that you've seen. So, to sort of get at your question of long-term use, do you see a change in pattern, we have not seen that yet.

Dr. Yamada?

DR. YAMADA: I wonder if I might comment, Dr. Seeff. I think the question you ask is a very important and a relevant one.

The closest we can come to an answer is that we did include in our study a large number, 250 more patients with elevated liver enzymes to begin the study. The vast majority of them, in fact, improved, and only 4 of that group went on to have elevated liver enzymes above 3 times normal. So, if you're worried about basic underlying liver disease or undetected hepatitis C or other conditions such as NASH that may be present, the fact is that our study would have included many of them, and most of them, in fact, did very well.

DR. BONE: Thank you.

Are there any other questions at this point? Dr. Rappaport, did you have anything further to show?

DR. RAPPAPORT: There were actually three other

issues that I wanted to answer that came from questions before lunch.

One was a question about what we saw in patients who had a baseline condition of edema. There were relatively few patients in our trials that entered the study with a history or a current condition of edema. Among the patients treated with Avandia alone, there were 76 patients who entered with edema and 2,450 who did not have edema listed. And in the placebo group, there were 22 who entered with edema in their medical history and 579 who did not.

So, looking at those groups -- I think we do have a slide for that. This was part of our evaluation. I apologize for this being small. This is Avandia monotherapy which was the preponderance of our patients. These are 76 patients who had edema at baseline and 2,450 that did not. 22 placebo patients and 579 that did not. These are the overall adverse event profiles for those patients. Although we do see that a slightly higher proportion of those patients who had edema at baseline had edema listed as an adverse event here and then we have edema legs and edema peripheral, although we don't know whether those aren't in some cases the same patients. We haven't collapsed those adverse events. We also see a slightly higher proportion out of these very few patients

who have edema on study in placebo.

There was also some question about aggravated hypertension. Here we have 3 out of these 76 patients had an adverse event of aggravated hypertension on study, and there was also 2 placebo patients who had aggravated hypertension who had had edema at baseline, compared to a smaller proportion who did not.

DR. BONE: Dr. Rappaport, wouldn't the patients with prior edema have had that listed as a background condition rather than an adverse event during the study?

DR. RAPPAPORT: Well, if it worsened, they would have it listed as an adverse event during the study.

DR. BONE: But if it worsened enough for the clinician to say that it was clinically worse.

DR. RAPPAPORT: Yes, correct. Correct.

And then to try to address the question of what happened to patients with hypertension, I think we also have a slide for that. This is again part of our drug disease interaction analysis. Here, of course, we have a much larger proportion of patients. About 40 percent of the patients that enrolled in our studies had hypertension at baseline and similar proportions for the placebo patients. Here again, the overall adverse event profiles are not different for patients with and without hypertension.

And to address the question of aggravated hypertension, about 3 percent of the patients who started out with hypertension had that listed as an adverse event, and 3.3 percent of the placebo patients who started out with hypertension had that listed as an adverse event during the trials.

Finally, there was a question about whether we had any patients with class I or II congestive failure who entered our studies. There were 28 such patients who received Avandia either alone or in combination who entered our trials. Of those, 5 developed edema that was reported as an adverse event during the trials. None of those patients were withdrawn from the studies, and as far as we know, none of the patients on trials had -- well, none of the patients had adverse events that indicated progression of their congestive failure during their time on the trials, but obviously again, the number is quite small.

DR. SEEFF: Can I just make one last comment? I'm sorry to get back to this enzyme this business. If I was a surgeon, I'd be cutting. I'm a hepatologist, so an ALT is meaningful to me. If we went around this room over here and tested everybody, we're going to find ALTs in the middle to lower range. Once you get up to, in my lab, 40, if you get up to 41 or 42, this has meaning. There is something going on.

So, therefore, I note that I guess 4 percent at least in one group and 3.3 percent in another group had abnormal enzymes to begin with and yet we're dealing with a drug that has potential hepatotoxicity. Why were these people not worked up? How could we just accept the fact that they have an abnormal ALT?

Another look-back is beginning in about two weeks time. It's going to be launched and everyone who has got an abnormal ALT, it's going to be suggested they go back and test themselves for hepatitis C.

So, I think that we should know what the underlying problem was with these people because it may have relevance to what happens subsequently. I think I wouldn't just accept an ALT and say, well, it's 46, it's okay, we can give any drug. It doesn't have to be this, any drug. I would like to know what's the matter with that patient before I even started treatment.

DR. WHEADON: Well, Dr. Seeff, I would also remind you the time period during which these studies were done. They were carried out at a time, if you will, that the issue per se with troglitazone or the question of thiazolidinedione was not prevalent. So, you have to keep that in mind in terms of how we allow patients into the study, the rigor with which we may have done serologies, and what have you.

But that notwithstanding, we have to always come back to, as we're fond of saying, the fact that we see no smoke. We have to keep coming back to that.

DR. SEEFF: I accept that.

DR. BONE: There's always a balance to be drawn between trying to have the purest possible study group and having a group that resembles the group of people that would be treated in clinical practice as well. So, it's a continuing balancing act.

DR. WHEADON: One last micro-topic, if you will.

DR. REBUCK: First, I'd like to thank Dr. Misbin for his comments concerning the appropriateness of the experimental design of study 93, which was designed in collaboration with the agency.

(Laughter.)

DR. REBUCK: I'd also like to thank him for confirming that in his evaluation, he felt there was a selection bias which favored metformin, and we certainly agree with that as well.

Can I just show an efficacy evaluable plot and remind ourselves of the difference between the experimental design and the clinical lessons that the practitioner might learn? These patients at this point here had had many weeks of maximum dose metformin and had not achieved

glycemic control.

The clinician would then be faced with two options. Let's run the metformin for another 26 weeks and see if things gradually improve, and they didn't. They didn't deteriorate, but they didn't improve. Clinical logic would say, let's add another agent. Avandia was added and glycemic control improved.

The one option hopefully the clinician would not take is to abruptly stop the metformin and say if this monotherapy maximum dose didn't work, maybe another one will. And clearly it doesn't.

During the initial period, there will be patient dropouts and there were several during this study, but one never catches up.

So, to address the more real-life situation, over lunch we looked at some other numbers to examine the question more directly. This is from study 20. These are changes from screening in hemoglobin A1c in patients who had previously taken monotherapy with metformin. This is the ITT population and there are approximately 22 patients who fell into this group. So, what we have here is screening, then baseline, and then week 52, and clearly at week 52, they're better than they were at screening when they were on metformin.

Thank you very much.

DR. BONE: Would you just clarify? These are patients who were on rosiglitazone monotherapy?

DR. REBUCK: Yes, that's exactly right. That was from study 20.

DR. BONE: And that was the rosiglitazone monotherapy group that you were showing only.

DR. REBUCK: That's correct.

DR. BONE: Thank you.

Dr. Genuth.

DR. GENUTH: I agree that as a clinician I wouldn't stop metformin and start rosiglitazone if it's approved. I wouldn't do it because I saw that data.

DR. BONE: That's all the prepared slides that the company has put together over the interval. Are there any other items pertinent to these questions and answers from the morning?

DR. HIRSCH: Just one more micro-topic. You have no measurements of plasma protein or urinalyses with albumin in diabetics who were edematous.

DR. BONE: They do have that.

DR. WHEADON: The answer to your question concerning microalbuminuria is those analyses are relatively new. We've not had a chance to share those with the agency. In agreement with the agency, we're not able to show those today.

However, we do have I think data concerning albumin. Can we summarize that?

DR. RAPPAPORT: This slide shows you the mean baseline albumin measured in grams per liter for patients who received Avandia monotherapy, for patients who were receiving placebo, SU, and metformin alone. This was the mean value for this group of patients. It's actually a slightly smaller group because some people left the study at between 91 and 196 days. So, the change during the first 6 months of treatment was approximately 1.5 for the Avandia monotherapy patients, 1.1 for placebo, 1 and .7 grams per liter for the corresponding comparator groups, and the percentage changes are given here.

DR. BONE: Let's see. I think that then wraps up the carryover from the morning. Is that right? No. Dr. Genuth has another carryover point.

DR. GENUTH: Is it still open season on the liver for questions?

DR. BONE: I'm trying to just deal with have we covered the topics that we asked the company to prepare answers for.

DR. GENUTH: Oh.

DR. BONE: And have we done that? Other questions or comments about that?

Now, since Dr. Genuth is about the lead us into

a discussion of the liver. Obviously today's presentation concerns itself with rosiglitazone and we are not planning to discuss the other drug in this class that's under review, pioglitazone, until tomorrow, however it's been brought to my attention it may be helpful for today's discussion to just ask a very general question of Dr. Misbin about whether it appears that there are any problems with liver safety that arise with pioglitazone beyond the level that we've seen with rosiglitazone.

DR. MISBIN: No.

DR. BONE: Thank you.

Just if we start branching out a little bit beyond the specific drug, we've got a little background. Obviously, we'll have the opportunity to go into detail tomorrow. We can't do two drugs at the same time. So, we're just doing it this way. And we have the opportunity to have our hepatologists here with us.

What I think we will do is have some general discussion, make sure everybody has covered all the important points that they want to bring up, and then we'll work toward the specific questions that we've been asked to address a little later this afternoon.

Dr. Genuth, you can lead off.

DR. GENUTH: I'd like to ask the sponsor a pharmacology question. If you look at page 36 in the

sponsor's blue book, you have the structures of rosiglitazone and troglitazone, and I think that the person presenting for the sponsor implied at least as a speculation, but I thought implied pretty strongly, that the liver toxicity associated with troglitazone was due to the left side of the molecule looking at the sheet of paper, and that either the process of it's being oxidized to a quinone or a quinone structure itself was causing the toxicity. And by inference, we shouldn't worry so much about rosiglitazone because it doesn't have that same left side of the molecule.

What I'd like to ask the sponsor is, did you synthesize any compounds which just have the left side of the molecule attached to something other than a thiazolidinedione, and when you gave that to dogs, rats, et cetera, did you in fact get liver toxicity?

DR. WHEADON: I can give you the brief answer, but Dr. Gwyn Morgan can probably the more specific. But the answer is no, we've not done that.

DR. GENUTH: You haven't made any compounds like that. It might not be a bad thing to do if you want to prove your thesis then.

DR. BONE: Anything further from the sponsor on that topic? No. Thank you.

Other questions, comments from the committee

members concerning the efficacy or safety? Maybe we'll just for a little while focus on efficacy topics and then we'll come back to the safety issues in a little while. Maybe that will help us structure a discussion a little bit.

Dr. Genuth has an efficacy comment or question.

DR. GENUTH: No. A liver question actually I'd like to ask one of my fellow committee members.

DR. BONE: All right.

DR. GENUTH: I think, Dr. Seeff, you said that in your laboratory 40 or 41 ALT would be abnormal. I'm just curious, how do you set the upper limit of normal in your laboratory?

DR. SEEFF: Well, let me answer that in two parts. We take a mean and two standard deviations and anything outside of that is considered abnormal.

My point is -- and actually they have some data to show this -- we take the upper limit of abnormality as, let's assume, about 40. In many labs this seems to be the case. I don't know what the meaning is of 38 as compared, for example, to 25. My understanding is that if we measured everybody here, we're going to have an AST higher than an ALT even within the normal range, and there are instances in which you have an ALT higher than an AST even within the normal range, but a high abnormality.

There is a paper that has actually looked at this in patients with hepatitis C because there's been a whole issue about what about individuals with hepatitis C who are viremic but have normal enzymes. Is this a problem?

Well, there is a paper that was presented at the liver meetings in Chicago at the end of last year where they looked at people who have transaminases above -- I can't remember exactly the cutoff -- maybe it was above 30, between 30 and 40, therefore normal, and compared it to people who had values below that but who were viremic. And they biopsied them. It's not what we all do, but they did. And, indeed, they found that people with high normal transaminases had much more in the way of inflammation in the liver than those people who had low ALTs.

The only thing I'm trying to get across is that this doesn't make a terrible disease, but hepatitis C, which is now what we're all so caught up with has these fluctuating enzymes and the height of the enzymes really doesn't have much relevance to the severity of the disease or the severity of outcome. You can have patients with transaminases in the 40s and 50s, taking 40 as the upper limit of normal, and the disease will still progress to go on to develop cirrhosis and perhaps to liver cancer.

So, I'm just very wary of the ALT. I think a

low normal ALT, when there's a ratio reversal with the ALT higher than the AST, has some meaning. Now, I don't know that I know enough about what that meaning is, but it's a caution to me to be very careful about what this person may have and to follow up on that.

DR. GENUTH: I asked the question. I appreciate the answer. I asked the question because if you set, as most laboratories do, two standard deviations above normal as your upper limit of normal, then 2.5 percent of the population is going to exceed that upper normal limit.

DR. SEEFF: Yes, I understand.

DR. GENUTH: So, that's kind of a blank which has to be subtracted from the numbers we looked at.

DR. SEEFF: Absolutely. I agree.

DR. GENUTH: Now, maybe to enlarge this slightly, are you suggesting that we're defining normal the wrong way, that we should define normal ALT like we're now defining cholesterol, et cetera on the basis of patient outcomes long term rather than on the basis of two standard deviations in a supposedly healthy population?

DR. SEEFF: If we had the opportunity to do a study of that nature, which would probably take 30 to 40 years to come up with an answer for because even in those who have chronic hepatitis C, for example, we have to follow these people for 30 years before we see really an

outcome that we are concerned about.

We can't change what we do. We set an upper limit of normal and that's what we stick with. I think, though, we need some better measurements of toxicity and of liver damage. The ALT has served us extremely well, but I'm not sure that we don't need better things. And it's something that I know I would like to try to stimulate -- well, I have already got some thoughts going at the NIH to begin to look at this in some detail.

I accept the fact that a normal ALT is the best we can do, but I tell you that as a clinician, if a patient comes in and they have an ALT of 38 and an AST of 25, I worry a little bit about that patient. I keep a close eye on that patient and make sure that I check the patient fairly regularly to see what happens. If it stays below that point, that's fine, but sometimes it goes up. And this may happen. This fluctuates quite regularly.

I'm not sure that I'm confusing everybody here. I probably am.

DR. GENUTH: No. You're not confusing me. You're enlightening me, but it's making me wonder, if we have any concerns still about this drug, whether we should make some recommendation about restricting its use to people whose ALT is less than some value if you're concerned that those people are more vulnerable to

toxicity.

DR. SEEFF: Well, I don't know that. I mean, I don't know that. My assumption is that once you have intrinsic liver disease, if you add something else, it's conceivable certainly to add another viral infection on chronic hepatitis C, you're causing a lot of problems. Now, this is not a virus we're talking about. This is a particular drug.

You see, the mechanism of troglitazone I don't understand. I don't know exactly why it causes the hepatotoxicity. Maybe it's the left side of the molecule and not the right side.

DR. BONE: But, Dr. Seeff, have we had any evidence of serious hepatotoxicity with troglitazone in the absence of substantial ALT elevations?

DR. SEEFF: Well, obviously patients who die of fulminant hepatitis have abnormal enzymes.

DR. BONE: Yes.

DR. SEEFF: I don't know the long-term outcome over many years. That would take a long time.

I think that this drug is far safer with respect to the liver than troglitazone is. I see no evidence at this point that it's associated with acute disease.

My only concern is, what about people with

chronic liver disease? Is there a way of monitoring that? Because I'm assuming that maybe 10 percent of the population who will be treated ultimately with this will have abnormal enzymes. Now, that may be benign, if we call steatohepatitis benign, or it may be something else. And the question always is when you have patients with abnormal enzymes, how do you approach treatment because we struggle with this.

DR. BONE: Well, I guess we're not in a position to develop a new test today. Do you have a specific recommendation?

DR. SEEFF: Are we moving to recommendations?

DR. BONE: No. I mean, are you going to make one later? I think we're either going to have to make a specific suggestion or let that be a topic for another day, aren't we? I'm not sure what else we can do.

DR. SEEFF: Yes.

DR. BONE: We can worry but I don't think it's going to be --

DR. SEEFF: You've asked us to come here as presumably the experts in this area, maybe not. And Dr. Lewis and I will have to draft our -- I'd like to discuss this with him about what I would do about following these people, if at all, if we even do measurements, if we require enzyme abnormalities, or are we simply going to

monitor them for manifest and overt liver disease.

DR. BONE: We'll be talking about specific recommendations like that I think a little later today.

Dr. Lewis I think has a comment or question.

DR. LEWIS: Yes. It's hard to ignore the data we just saw. We have 5 percent of the patients who had chronic liver enzyme elevations of some etiology. We can presume that some of them are NASH. Some of them got better. 4 out of 250 getting worse without any serious clinical development is pretty reassuring. So, in most studies we never even get to see enzyme elevations in patients at baseline where they're kept in a study. Here we have that. So, they've helped us at least determine that for these 250 patients, nothing bad happened. Some of them actually improved.

There are patients on troglitazone who have NASH and whose enzymes have improved. They have not gotten worse. We're dealing there with idiosyncratic, unpredictable injury. All the monitoring in the world may not have predicted all of the things that we saw there.

DR. BONE: Could you just take a second to explain for members of the audience about NASH?

DR. LEWIS: NASH is the acronym for non-alcoholic steatohepatitis, which is a condition we see. It's not unique to diabetics. It happens in thin people,

in obese people, sometimes diabetics, people on steroids, a number of things where there's more than just fat deposition in the liver. There's actually inflammation. I call it fatty hepatitis for my patients as opposed to just fatty liver.

The etiology of that is unknown. It may another virus that's found one day because it seems to behave in 20 percent like chronic viral hepatitis where they can go on to develop severe scarring in the liver and even cirrhosis. So, we don't have a good handle on it.

There is no treatment for it. Right now we tell patients who are overweight to lose weight. We tell hypertriglyceridemic patients to go on a low fat diet or put them on anti-lipid lowering drugs. But for those who are diabetic, we tell them to keep their glucose under control and lose weight and whatever. So, it's very nonspecific therapy that we offer.

Here we have information that some of them got better. Most of them didn't change, and these were individuals who already had these elevations up to two-and-a-half-fold normal. So, we're not dealing with just a little bit of elevation. It was almost the cutoff of the three times normal. So, for me that's pretty reassuring for that group. We've actually got the information at hand to look at.

DR. BONE: Thank you.

To continue this topic, Dr. Molitch looks like he has a comment on this topic.

DR. MOLITCH: Not about liver.

DR. BONE: Dr. Hirsch has a liver point.

DR. HIRSCH: I've got a question to ask the experts. Is there any reason to believe that effects might occur in 2 or 3 or whatever years? Is there any other similar drug situation that you know of that takes many years to accumulate before there's such a hepatic effect?

DR. LEWIS: There's methotrexate which can lead to fibrosis in people. It generally takes years. There are certain other medications that can cause chronic injury very slowly, insidiously over time. Nitrofurantoin is one of those drugs used chronically.

We have no indication that any of these individuals has developed chronic injury. All of the enzyme elevations that occurred became normal, and we wouldn't expect necessarily that injury is occurring when the enzymes return to normal. Now, that's not always the case with things like methotrexate, which is why we do biopsies in some patients, because you can't necessarily correlate enzymes with fibrosis. But we don't see the acute fulminant hepatitis in those individuals, and the treatment for the methotrexate patient is stop the

methotrexate and hope that they don't get any worse.

So, we don't have a lot of drugs that cause the chronic injury to begin with, and we don't predict that necessarily from acute injury.

DR. BONE: Further questions or comments on the liver issue?

Maybe we'll come back to the question of recommendations a little bit later. Let's talk about some of the physiological issues, if we will. And Dr. Molitch is about to lead off the next phase.

DR. MOLITCH: I have three questions under the topic of sort of reproduction if you will that are unrelated to each other.

The first is the incidence in rats. There's a mention in the animal toxicity data of lactotroph hyperplasia that was seen. I was wondering if prolactin levels were measured in those rats, and have prolactin levels been measured in the humans?

The second question has to do with these so-called abnormality in steroidogenesis. That was sort of a very nonspecific term, and I'd like to hear more about what that specifically is. Was there a dose-response effect? Was there changes just in ovarian steroid production or how about adrenal steroid production, testicular steroid production? What do we know about this and have such been

looked for in humans?

And the third issue deals with the increase in fetal loss that occurs. Do we have any known mechanism that might be occurring for that? Is this somehow related to activation of the PPAR receptor, long-term cytokine activation that might occur? Is this something that, for example, if we were to approve this drug, should the drug be stopped months ahead of preparing for pregnancy or is it something where the person could just switch a day before deciding they wanted to get pregnant?

DR. BONE: Thank you.

Somebody is approaching the microphone for the sponsor who has the answers to all those questions.

(Laughter.)

DR. WIER: My name is Dr. Patrick Wier. I'm in safety assessment with SmithKline Beecham Pharmaceuticals.

I think I've captured all your questions and I'll try to go through them in the same order you've presented them.

First of all, you asked a question about the observation of lactotroph hyperplasia in rats. Now, let me start by showing you what happens in the rat when we measure hormone levels. We see on this figure, the dose is shown going from 0 to 80 milligram per kilogram. We're treating rats and we're measuring estradiol and

progesterone levels, in this case on the day of diestrus. You'll see a nice dose-response for reduction in progesterone levels. The progesterone levels fall up to about 60 percent.

Now, you also see it at higher doses and, to a lesser degree, a reduction in estradiol levels.

What you'll see here is that this occurs without a deficiency of gonadotrophin and if anything, there's a slight elevation in FSH, probably in response to the lowering of steroid levels. We also measured prolactin levels in these rats and there was no effect on prolactin. But this experiment is a short-term experiment. These rats were treated for about 2 weeks.

Now, let's talk about the lactotroph hyperplasia. Now, as I've just indicated, in rats we have this phenomenon of a greater reduction in progesterone levels than estradiol. Specifically in the rat then it's important to focus on the ratio of these two because the ratio of estradiol to progesterone in the rat is what is most important to consider the pituitary response. So, in this case you actually have lower estradiol levels and lower progesterone levels, but you have then this increased ratio which is sufficient to stimulate lactotroph hyperplasia.

At the time that this is newly induced in the

animals, at the induction phase, we don't see any effect on prolactin, but of course, it's reasonable to speculate, as I think you are, that if you would get lactotroph hyperplasia in the rats and subsequently look, when there's a large number of lactotrophs, it's reasonable to expect prolactin might go up.

But it's important to recognize that lactotroph hyperplasia was a species-specific phenomenon for this compound. It's not seen in any other species, and it's probably related to this unique aspect of the rat endocrinology in responding to this ratio.

Now, you asked about exactly what is the basis for this so-called abnormality in steroidogenesis. What I've taken you through so far is that it affects both estradiol and progesterone levels.

I'd like to draw your attention to some work that was published in December in Endocrinology, and this work was done in Randy Urbin's laboratory with porcine ovary granulosa cells in culture. Dr. Urbin and colleagues showed that this was a class effect for the thiazolidinediones, that all of these compounds, and most potently troglitazone in his experiment, were capable of reducing progesterone synthesis in this ovarian cell culture.

He also went on to study this a bit at the

mechanistic level. It was shown to be actually independent of FSH stimulation. The effect is still evident, for example, when the cells are stimulated with forskolin.

His suggestion is that this class effect relates to a competitive inhibition of the enzyme 3-beta-hydroxysteroid dehydrogenase, which is the enzyme, of course, that among the reactions converts pregnenolone to progesterone. In fact, in his cell cultures as the progesterone levels go down, the pregnenolone levels go up.

So, I think at this point I'm sort of taking inventory.

DR. MOLITCH: Can you go back also to the prior slide that you had up just a moment before this one?

DR. WIER: Yes, sure.

DR. MOLITCH: Maybe you could comment about the bottom of that slide also.

DR. WIER: Yes.

Having observed this phenomenon in rats, which of course have an estrus cycle, we decided to conduct a study in nonhuman primates, in this case synomologous monkeys. In this experiment, monkeys were treated with either 0.6 mg per kg or 4.6 mg per kg. Now, this lower dose, 0.6 mg per kg, I'd like to point out is about 3 times the clinical dose on a mg per kg basis, also about 3 times the actual exposure level seen in patients given 8 mg per

day.

In this experiment, we followed the monkeys initially for a baseline period of evaluation. So, it was a longitudinal study.

And these animals were selected for having perfect 28-day cycles essentially. They showed the classical cyclical changes in their hormone levels. We observed the normal follicular phase rise in estradiol, a sharp LH surge, followed by the broad luteal phase progesterone rise.

Now, some of the animals showed a reduction in the follicular phase rise of estradiol, and this was then associated with reduced or absent LH surge, followed by a lower or, in fact in some cases, absent luteal phase progesterone rise. It was absent specifically in the animals who then subsequently failed to show menses.

So, in this case what we've done is make an association between specifically the lowering of steroid levels, which is apparently a direct effect within the ovary -- and I want to speak specifically to follicles in the ovary, and that this has an impact on reproductive cycling in rats and monkeys at these exposure levels.

Now, you asked a question about dose response -- I hope I've addressed that aspect of it -- and then said, well, what about other organs and what about

steroidogenesis in other aspects?

Let me take you back to the fact that the way these types of findings are typically investigated is we're conducting toxicological studies, and we start with apical endpoints, for example, estrus cyclicity or organ weights or histopathology. And then if we pick up a signal there, then we first seek, well, is there a clinical biomarker such as a hormone level, and then what's the mechanistic basis to explain this?

Now, in contrast to what we had in the female where we had a clear physiological change that should have been studied, in male animals we didn't have much of a signal.

Now, this summarizes the findings of looking at the male reproductive organs. We did in one case find some effect. It was a very slight reduction in these organ weights. But recognize that this is more than 100-fold the human exposure level in terms of AUC. At 10 milligram per kilogram in male animals -- and by the way, I want to emphasize that those changes in organ weights were not correlated with histopathological changes in the organs.

At also a very high dose, 10 milligrams per kilogram -- here now we're talking a 30-fold or more the clinical exposure -- we had absolutely no effects. Of course, we recognize that the male dogs are sensitive to a

number of endpoints to this compound, but there was absolutely no signal in dogs. So, on this basis we felt that there was not a sufficient physiological signal to warrant looking at the hormone profiles in male animals. So, that work wasn't done.

And similarly, there has not been specifically an investigation of adrenal steroidogenesis because, again, we didn't have the physiological signal to suggest such a finding.

At this point, I think it's best to summarize the steroidogenesis as a finding that is so far restricted to developing ovarian follicle cells, their steroidogenesis, and appears to be a class effect.

Now, moving on from steroidogenesis, you asked a question about the fetal loss. Again, when we conduct animal toxicology studies and we're starting with treating animals through broad periods of time and we're just looking for a signal, in the case of rosiglitazone, treatment of rats with a pretty high dose resulted in fetal deaths. Then we went back to specifically ask the question, well, what part of pregnancy might be sensitive to this phenomenon?

We went back and looked especially during early pregnancy, recognizing that many drug exposures are inadvertent, and this is the time that drug exposure in

pregnancy is most likely to occur. Even at this extremely high dose -- now, recognize the clinical exposure is about 3 microgram hour per ml, so we're about 200-fold now human exposure levels -- we've got no effect on pre-implantation development or implantation or even early organogenesis. In two species, when we've looked exhaustively at fetal development, we've not found any morphogenetic defect to explain the fetal deaths that were observed.

So, then what do we know about these fetal or neonatal deaths? First of all, it's a finding that's seen in rats and rabbits at these exposure levels. Again, the clinical exposure is about 3, so you're about 20-fold times human exposure levels in the rats and about 70-fold higher in rabbits.

Again, rat is where we did our most sophisticated evaluation, and we found that treatment at this point in pregnancy -- and for reference, a rat has about a 21-day gestation -- treatment at this period of time, which is mid to middle/late pregnancy in the rat caused fetal death. And this fetal death was not evident when we looked just at that treatment time, but only a couple of days later. Again, we did careful evaluation of these fetuses, including some histology, no malformation to explain this fetal death. As you would expect then in these kinds of studies, there would be a reduced number of

live-born.

Now, this is still I suppose phenomenology. It helps us really understand what is the hazard, what are the conditions in which it can occur both in terms of timing and in exposure. You asked the question about mechanism. The mechanism for these effects on fetal development is not known. We do know that PPAR gamma can be found in fetal rat tissue in later aspects of gestation. That's where information is available to date, but whether or not this reflects any relationship to this finding would be pure speculation. We only know that we have a compound with this activity and we have this phenomenology occurring in late pregnancy.

The last thing I'd like to point out is that, once again, there's reason to believe that this effect is not unique to rosiglitazone. For example, it's been published in the Japanese literature with treatment of rats in pregnancy with troglitazone, there's significant decreases in fetal weight. In one of these studies, in fact, if you look at the offspring, newly born, the rate of neonatal deaths is higher in the troglitazone group than the control group, 10.5 versus 2.9 percent. So, there's reason to believe that these compounds share some properties both in terms of their effects on ovarian steroidogenesis specifically and their effects on fetal

development.

I think I've covered the inventory, but let me know if I've missed something.

DR. BONE: That's pretty thorough, isn't it, Dr. Molitch?

DR. MOLITCH: Thank you very much for your very complete answer.

I guess one concern I have is that the effects on blocking ovulation occurred at just a threefold increase in dosing compared to humans, so that somehow to me fits within the overall, relatively close to what we might find in some humans compared to others with the dose variability, et cetera, so that it's a little bit of a concern. I think this is something we're going to need to follow along over the course of time to see if fertility is impaired or whether amenorrhea occurs.

I'd be curious to ask Dr. New, do you have any comments about the steroidogenesis?

DR. NEW: I guess that you're going to have to say that the inhibition of 3-beta-HSD is mild or you wouldn't have gotten implantation at all.

And the second is I think we were told that all the women were on contraception, so you couldn't test fertility in the women. But what about the men who were getting rosiglitazone? Were they fertile?

DR. RAPPAPORT: Maria, there is no good answer to that question. We did not ask specifically about fertility in the men who participated in our studies. I suppose we could have had a questionnaire, but we didn't. And I didn't see any adverse event reports of altered libido or decreased sexual function, but we did not ask them about their fertility.

DR. NEW: I think it might be interesting to those who don't work with steroids every day that there's a bit of a paradox in the rodent because the rodent doesn't express the enzyme that is able to convert the 17-desoxysteroids to 17-hydroxylated steroids. And that's necessary to make estrogen. So, the question comes up, how do they make estrogen, how do they make testosterone which require this enzyme? The fact is that it eventually gets expressed in the gonads but doesn't get expressed in the adrenals.

But you need that enzyme that was found to be deficient in order to get implantation. So, I suspect that whatever this drug does to that enzyme, it must be very little.

DR. WIER: I would support that evaluation. I think you make an excellent point reminding us that the fact that we did not see an effect on implantation points to a very specific effect because again, as far as we know,

it seems to be fairly unique to developing follicular cell steroidogenesis.

DR. BONE: Any further comments or questions from the committee on steroid metabolism?

Does Dr. Illingworth or anyone else want to discuss the lipid questions any further?

DR. ILLINGWORTH: I think we've had the data presented to us.

DR. BONE: But what does it mean, Roger?

(Laughter.)

DR. ILLINGWORTH: It depends who you talk to. I personally take the view that without knowing -- an increase in LDL is clearly bad news. In the NCP guidelines, LDL is the main lipoprotein for treatment, diet and drug therapy, with secondary measures being lowering triglycerides and raising HDL.

The consistency of the association between increased levels of LDL and heart disease is very, very consistent. There's inconsistency, though, with situations affecting HDL. Using patients, there are some families with a disorder called cholesterol ester transfer protein deficiency. These shuttle cholesterol esters between HDL and other lipoproteins. So, they have a delayed clearance in HDL. They have very high levels of HDL. This does not protect them against heart disease in the setting of a high

LDL.

So, I would urge the sponsors to look into the mechanism or mechanisms responsible for the change in lipoproteins, particularly the rise in HDL. If this is due to increase in HDL production, then this may be beneficial, but I'm not personally convinced that using the ratio, total cholesterol to HDL, or LDL to HDL ratio, is viable means of doing it. We don't treat the ratio. We treat the level of LDL cholesterol. And something that raises LDL I would view as potentially a detrimental effect.

DR. BONE: Any further comments or discussions from within the committee concerning this point? Dr. Molitch?

DR. MOLITCH: I have another question about the decrease in blood pressure that was seen. This was a relatively mild effect. I think I understood the sponsor to say this was due to decrease in peripheral vascular resistance. Is that correct? Or is that what that's thought to be? What is the mechanism of the mild decrease in blood pressure?

DR. WHEADON: I don't think we speculated as to the mechanism of the reason for the decrease in diastolic blood pressure. At least in that study 80, we showed the ambulatory 24-hour measurements. You do see a significant drop. In terms of the mechanism, we haven't studied it

sufficiently to give a full answer to that.

DR. MOLITCH: Was this associated with any change in heart rate? You should have that data.

DR. WHEADON: Actually that slide also shows heart rate, if I remember correctly. You see a minimal change in heart rate. The most dramatic change is on diastolic. If anything, the heart rate is comparable to baseline if I remember correctly.

DR. MOLITCH: And that is a generalized phenomenon that everybody has a little bit of decrease in diastolic blood pressure or was this restricted to a select few people that brought down the mean?

DR. WHEADON: Again, in study 80, which was the cardiographic study, we looked specifically at 24-hour values. If you look at the overall database, if we look at mean changes, there is a trend for a drop in diastolic, but we did not have the same sort of intensive measurement as we had in study 80.

DR. BONE: Dr. Hirsch.

DR. HIRSCH: This brings up the broader question of the vascular or potential vascular effects of this drug. It seems to me at least that one reasonable hypothesis is that something is opening up the whole after-load; that is, there's an increase in the size of the post-cardiac vascular bed, which accounts for what you're

finding, which is a dilution and even a little bit of dilution of albumin or a little loss of it perhaps, whatever.

But it does bring up the issue of what's the vascular situation of this because with diabetes, we're dealing with a disease, the major complications of which are both microvascular as well as the macrovascular ones that we deal with so much. That's why I would sort of direct everyone's attention to look much more closely at the progression of nephropathy and retinopathy in these individuals and all of the associated surrogate indices of these like microscopic albuminuria, which I gather is under investigation already. But this concerns me deeply, as well as the obesity thing which I'll wait for a moment to get into that.

DR. WHEADON: I think we can comment certainly from a preclinical standpoint in terms of looking at some of the issues that you've raised. So, Dr. Morgan?

DR. MORGAN: If that is appropriate, I can follow up on some of the very interesting observations that you made because we've seen them occurring in parallel in our preclinical studies.

We've conducted integrated telemetry studies which allows us to monitor for 24 hours the effects on most of the cardiovascular indices that you mentioned at very

high doses in rats and dogs. We have made a number of observations, but we are not yet certain of all the mechanisms involved. But we do observe both an acute and a chronic effect on lowering blood pressure. The early effect may be related to the drug's calcium channel blocking activity at very high dose.

But most importantly and particularly interesting in light of your comment about effects on peripheral vasculature, peripheral vasculature resistance is lowered we believe as a consequence of quite a significant increase in regional plasma flow, which may be related to local metabolic events, autocrine, paracrine factors, possibly related to the drug's pharmacological mechanism of action. I must emphasize none of which we have studied in great detail, but this is a very interesting observation.

It may be as a result of opening up collateral channels which causes a generalized reduction in peripheral vascular resistance, a fall in diastolic pressure, and then we believe as a consequence, a physiological response by the kidney, sodium and water retention, and increased plasma volume. That, in turn, results in increased preload, which we have measured, and all the attendant effects on the heart. There is no effect on after-load. There is no increase in systemic pressure.

If I may comment a little about our observations in toxicology studies where the pathology has been studied at length, we have no evidence of peripheral edema, no tissue edema, no ascites. And the drug is very well tolerated in that respect, up to levels 50 times the human therapeutic dose.

However, we have observed cardiac hypertrophy and at very, very high doses, 100 or 200 times a therapeutic dose, we have seen evidence of hydropericardium and hydrothorax, but in all of those animals, there has been an increase in relative heart weight up to 38 to 40 percent. So, it's not surprising.

There is no evidence of impaired venous lymphatic drainage either.

From the pathology standpoint, there is no evidence of microvascular disease and no evidence of macrovascular disease, no basement membrane changes in the microvasculature that one would associated with an effect of the drug, and no toxicity on endothelial cells.

Interestingly -- and I say this with some reservation because the effects of aging and chronic nephropathy in rats is not representative of the human disease -- we have seen a remarkable decrease in the incidence of chronic nephropathy and the associated microvascular pathologies in the kidney in rats and mice in

our lifetime studies.

DR. HIRSCH: I noticed also there were marked regional differences in blood flow changes in some of the animal studies. So, I guess this could be very good or it could be bad. We simply don't know, do we, what these microvascular changes, if they're occurring, might mean?

DR. MORGAN: There is no pathology to reflect any increase in perfusion pressure in the microvasculature of the tissues that experience the increase in regional blood flow. That in the main is fat and subcutaneous tissue and the GI tract, which we assume, but without proof, are rich in PPAR gamma receptors. So, indeed, this might be a beneficial effect in terms of lowering of systemic pressure and a reduction of peripheral vascular resistance overall. If those make a contribution to microvascular disease, then I think there's a prospect of long-term benefit.

DR. MOLITCH: With the reduction in pressure like that, was there any change in catecholamines? Was there a secondary rise in catecholamines?

DR. MORGAN: We have not measured catecholamine levels and there are a variety of other neurohormonal factors that we would like to measure, but we have not done that so far.

DR. BONE: What about the regulatory system for

salt and water balance, for example, renin angiotensin effects in animals or humans? Aldosterone obviously.

DR. MORGAN: We have not assessed aldosterone. We have not assessed renin angiotensin levels either.

DR. BONE: Do you still have some frozen sera from your clinical studies? This would be something that would be potentially doable.

DR. MORGAN: Indeed, we're very interested in that. All I might say in mitigation is that these telemetry systems are so very, very carefully controlled, and take quite a long time to complete. We felt it was wiser not to burden those studies with critical measurements of hormonal levels which, as you well know, need to be done under very tightly controlled conditions. So, separate experiments might be considered for that purpose.

DR. BONE: Anything further on this dilution or extracellular fluid expansion issue from anyone?

Just a further question of my own. I'm not seeing anyone's hands raised. I asked earlier about the extent to which the weight gain could be attributed to this, and I think Dr. Rappaport was not enthusiastic about the ability to analyze this. But it seems to me that the sulfonylurea study actually gives some indication about this because there was a gain of about 2 kilograms in the

rosiglitazone patients and about 1 kilogram in the sulfonylurea patients. So, there was a difference of about 1 kilogram which one might conceivably attribute to the fluid rather than increased insulin effect. I'm just asking for you to comment on that.

Dr. Greene is approaching the microphone.

DR. GREENE: I think you're exactly right, that it's the 52-week study that provides the best answer. If I remember correctly in the 52-week study, the weight gain with glyburide was similar to the weight gain with the lower dose of rosiglitazone, that the high dose of rosiglitazone was about a kilogram or so more. So, it would seem that some of this is just due to the fact that glucose control has been affected.

In fact, although it's not engraved on stone tablets, I carry with me my UKPDS reprints, and if you look at the end of a year, almost all of the intensive therapies in the UKPDS were associated with about a 2.5 kilogram increase in weight. So, I think that probably 50 percent of what we see is in fact related to the changes in glycemic control. The other kilogram or so is probably related to rosiglitazone. And I think in that range, it could very well be due to the changes in fluid.

DR. BONE: That would be just about the same percentage as increase in ECF as you saw decrease in

hematocrit.

DR. GREENE: Yes. The numbers would potentially be in the same range.

DR. BONE: Dr. Hirsch.

DR. HIRSCH: One of the interesting things about PPAR gamma and what thiazolidinedione does to it and we know how this came about altogether is that adipocyte differentiation is enhanced. So, it's very important to find out whether people did become fatter or didn't become fatter to any degree because you'd really like to know that. I'm sort of mildly surprised because the techniques are very available to do that. So, representing the obesity community and my colleagues therein, let me urge that someone find out whether this is adipose tissue or not. This is very possible to do with considerable accuracy.

DR. WHEADON: In fact, we do have an ongoing study where we are looking into that issue.

DR. BONE: Further comments on the topics of salt, water, or fat? Any questions? The three essential substances.

(No response.)

DR. BONE: All right. Let's talk a little bit, if we can, about this question of cardiac effects. Do we really think there's an effect on the heart, and what do we

think it is?

I guess I'm going to ask the sponsor to comment on whether they think they're seeing a direct cardiac effect or are they seeing indirect effects related to this fluid balance issue.

DR. WHEADON: Well, we're deliberating.

DR. BONE: They're voting. The sponsor is voting.

(Laughter.)

DR. WHEADON: We'll let our preclinical folks at least take the initial pass at answering that since that's where we have the wealth of information.

DR. BONE: I'm bringing this up because we're going to be asked to talk about this later, so we want to get everything on the table.

DR. MORGAN: By all the indications in our studies in animals --

DR. BONE: Identify please.

DR. MORGAN: Dr. Gwyn Morgan, Safety Assessment.

By all the indications in our studies in animals at doses within the pharmacological range and therefore somewhat comparable to those in humans, we have seen no adverse effect whatsoever resulting from increased plasma volume nor evidence of cardiac hypertrophy. When

such has occurred, we consider it, as I said a moment ago, related to physiologic reflexes, if you will, and an adaptive response on the part of the heart. So, if I may make that clear in the context of human safety.

So, therefore, the schematic that I'm now presenting is, in effect, an illustration of the hypothesis that I was constructing in my previous remarks. We do believe that as a consequence of all the observations we've made in our telemetry studies and also by echocardiography in rats and mice at very high doses, nevertheless sufficient to evoke responses that we can measure, we have I believe, on the weight of evidence, sufficient indication to say that this is entirely the result of increased preload and increased volume with attendant hemodilution and a fall in hematocrit, as seen in man. Nevertheless, the fall in hematocrit in itself is not a hazard as such; it is not a biomarker of cardiac hypertrophy.

There are several benefits to cardiac function which I will not enlist here, but it is worth pointing out that there is an increase in stroke volume, an increase in ejection fraction, so therefore an improvement in heart function, albeit in normal animals, and certainly adequate cardiac reserve in dobutamine challenge studies that we did.

My point in drawing attention to the fact that

the evidence seems to be overwhelmingly in favor of increased preload is to say that on the other hand, we don't believe that the cardiac hypertrophy that we observe at very high doses in animals is related to a direct trophic effect of the drug, if you will. I distinguish the word trophic from hypertrophic by reference to growth-like factor effects which perhaps you have in mind, those that you might see with T-3 and other growth factors.

In our gene expression studies, in which we've taken mRNA from hypertrophied hearts, the evidence again points to the results of hypertrophy, a workload generated hypertrophy, and not an effect elicited by growth factor-like influences.

So, I hope that I have addressed the mechanism from the standpoint of your question, that it is largely an indirect response of the heart, an adaptive response. There is not an equivalent effect in human patients at pharmacologically active doses and that we do not believe these effects to be related to a growth factor-like effect of the drug in the main, but we cannot exclude it completely at very high doses.

DR. BONE: Any comment from FDA on this topic? No comment I guess from the FDA. Okay.

Any further discussion related to cardiovascular effects? Dr. Molitch.

DR. MOLITCH: I would just make one comment that maybe some people who haven't used troglitazone, at least in clinical practice, haven't realized is that in occasional patients who already have quite significant heart failure, the troglitazone can certainly make a very significant worsening of congestive heart failure with edema that's quite refractory to other types of therapies, requiring very large dose of diuretics and other agents, so that this is not a totally clinically insignificant problem. Based upon the mechanism we've heard here, I would guess we may well see the same kind of a problem that might occur with rosiglitazone again in patients who are otherwise susceptible to this kind of a problem.

DR. BONE: Was this sufficient that you just had to discontinue the drug as opposed to trying to treat them with diuretics?

DR. MOLITCH: Actually to the point where you had to discontinue the drug to get a satisfactory response. Patients were unresponsive to conventional therapy.

DR. BONE: Including loop diuretics and so on. Dr. Molitch nods.

Do we have further discussion on any of the safety related issues that we are going to be asked to address in a little while? We talked about liver. We talked about lipids.

Dr. Illingworth expressed his concern about the implication of the LDL question in the absence of certain knowledge as to the mechanism of change in HDL. Can we get into that a little further? People here know a lot about this, particularly Dr. Illingworth. Do we have an idea what the likely mechanism of this is and how that would influence your thinking?

DR. ILLINGWORTH: The thing that surprises me most is that in the population looked at, there wasn't a decrease in triglycerides, although Dr. Brunzell mentioned that in patients with higher triglyceride levels, you did see a reduction in triglycerides. It would be interesting to see that data presented if you have this, if you look at patients, say, with triglycerides of over 400 or 500, how do they respond? Because the most common lipid abnormality in diabetic patients is hypertriglyceridemia.

With respect to the LDL effects, again if the cholesterol to APO-B ratio changes, that indicates you're changing the composition of LDL, but I'd be interested to know, does the number of LDL particles increase measured by APO-B? Does the APO-B concentration itself increase indicating an increase in number of particles? The same is true for A1.

DR. BONE: Comments from the sponsor?

DR. WHEADON: As Dr. Brunzell is approaching