ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE #65

Topic: "Troglitazone for Diabetes Mellitus"

AFTERNOON SESSION

Wednesday, December 11, 1996

12:50 p.m. to 3:14 p.m.

Bethesda Holiday Inn

The Versailles Rooms I and II

8120 Wisconsin Avenue

Bethesda, Maryland

approach taken in their design of the responder analysis, within which we participated, does have some merit, and I hope you will agree.

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Let's just say a few words about efficacy. I really believe there is really no issue here. The treatment effect that was observed in the first pivotal study I think is highly clinically significant. This would translate into a very significant reduction in complications given the DCCT relationship between glycemic control and complications. And it appears to be operating in the way that we would like by working closer to the root of the problem in these patients.

Again, we come back to the responder analysis that was use in the second pivotal study. As I made clear, I believe that this is appropriate, and the results I consider clinically significant.

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Now, let's briefly go over the safety issues. Again, we'll come back to them in the afternoon. First of all, the cardiac effects. Just to summarize, we have seen some toxicity in rodents at high doses. We have the reassurance of no findings in monkeys. However, these were necessarily fairly small studies and at fairly low doses.

We have noticed the increase in blood volume in humans, as was found in animals. I think this could be perhaps related to the cardiac finding, or the effect of increasing animal heart weight. But that remains to be seen.

And of course, we have the monitoring study, where echocardiography is being used to follow the cardiac function of patients that are treated with either Glyburide or troglitazone. And thus far, the results -- well, the results are in, and they are negative. But by thus far I mean I don't

believe that this entirely resolves the issue. Clearly this is not a terribly sensitive way of addressing the issue, though I think it is as good as the company could do at this stage in the drug's development.

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Lipids again we'll come back to this afternoon. And we'll be benefiting from the expertise of Dr. Illingworth, of course, who will be able to make a much better statement about the significance of these changes. It's worth just noting that there are some good things that have been noted. That is, HDL seems to increase, and so do triglycerides.

On the other hand, there is a small but significant increase in serum LDL and, of course, total cholesterol since HDL also increases.

There is also the reference -- and we could call this fluff here because that's just what is being talked about, fluffy LDL

particles that may be somewhat less atherogenic than hard, dense LDL particles. Again, we will await Dr. Illingworth's testimony on this particular point.

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I will bring to your attention the issue of -- well, I'll skip over the change in hematocrit that was observed. I think that is readily explained by the increase in blood volume that was demonstrated both in humans and animals.

But I'll go to an issue that was not really highlighted. Certainly it has been mentioned in the briefing book. And that is that there was in my mind a significant decline in the neutrophil count across all studies. And this amounts to about a 7 percent decline compared with a 1 percent decline in controls.

Now, it is possible this could be related to hemodilution, though I am not aware that there is such an effect in terms of the

white cell series, as you would have the red cells. You could say at least that probably the total neutrophil count does not decrease based on these findings of fluid changes. But again, I think we need to keep in mind that there is an effect on the white cell series. This could have, in the population, some kind of significance, though in the individual certainly this is not clinically significant.

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The other issues that we might talk about a little further this afternoon include our limited experience with long-term exposure.

Now, fortunately, I think we have ample experience. We have much better experience than is exemplified in the -- or is reflected in the briefing book table that deals with this issue. The company does have now, I believe, over 500 patients that exceed the one year in duration of treatment.

We do, I think, have need for more

explanation about how the dose was chosen, and perhaps need for more dose response data. We have one dose response study. I'm not sure that this will be entirely all we would like to have in making some kind of intelligent response about optimization of dosage.

And as I mentioned, we have no knowledge about tissue distribution of the drug in primates. This is maybe to put far down on the wish list. I really hate to see monkeys give their all for this kind of question, which is not going to really definitively answer any of the issues, but might give some reassurance about our concerns related to carcinogenicity and other organ effects.

Well, that is my set of comments about the development and the data that have ensued from the development of this drug. I frankly have been encouraged by the efficacy and the mechanism of action that this drug has shown. Certainly in the introduction of a novel therapeutic approach we have to take sort

of a leap before we -- or we do take a leap in making the drug available without definitive resolution of all of the safety issues.

I feel that the company has done a very good job in addressing these potential safety issues. And I think that we will be benefitting from the advice from the committee in regard to further pursuing them.

This will conclude the FDA presentation, Mr. Chairman.

DR. BONE: Thank you, Dr. Fleming.

Perhaps members of the committee will have questions for either Dr. Steigerwalt or for Dr. Fleming at this point. Anyone? I have one or two.

Dr. Steigerwalt, you referred to the fact that a special committee is reviewing the carcinogenicity issue, particularly I think with respect to the vascular tumors.

Can you tell us the status of that?

DR. STEIGERWALT: We had an initial meeting Monday, I believe, and there were some

questions on the rat study, more for clarification than particular concerns, so that there is going to be another meeting next week. And I was provided with some more information by the sponsor this morning. So we will be --

DR. BONE: But that hasn't been reviewed at this point.

DR. STEIGERWALT: It has been reviewed by the pharmacologist. But it has not be through the carcinogenicity assessment committee.

DR. BONE: I see. So the committee then will, I take it, have to sort of deliberate in the absence of any final information about that particular potential risk.

DR. STEIGERWALT: No. I think we have the amount of information necessary. The committee just has not seen what I saw this morning. And they will be provided with that information, and we should be able to clarify any --

DR. BONE: I mean this committee.

DR. STEIGERWALT: Oh, this committee. That's true.

DR. BONE: Okay. So we will not have the benefit of that information. That remains an open question, I think. All right. Then were there other questions? I have one or two more, but I don't want to -- Dr. Fleming raised the question of the duration of the studies. And particularly since this is a novel class of compounds, we do not have other compounds of this general chemical structure in use.

And obviously, this is a chronic, perhaps perpetual -- perpetual administration is foreseen in millions of people. And for many compounds which will be given for chronic indications in large numbers of people, a somewhat longer, a year or even longer, studies are required for initial approval, I guess both from the standpoint of being certain about the duration of efficacy and also about safety and long term administration.

Dr. Fleming, could you talk about how this decision of six months was arrived at? I think that would be helpful to the committee.

DR. FLEMING: Well, six months is a fairly standard duration for controlled studies, particularly when it involves placebo control. We're often not able to go beyond three to six months in the assessment of an anti-diabetic therapy.

Just as a rule of thumb, we like to have at least 1,000 patient years' exposure and a fair percentage of patients who have been treated in excess of one year. And this is the -- I think the sort of main point about duration is not so much expecting to have controlled trials extending for a one year period, but having to some extent a supplementation with extension of controlled studies, as is the case here.

So we are in the ballpark, I think, for the development of the general indication, that is, the use of troglitazone for the

general population. We have virtually all of the data, safety data, in-house now for that purpose so that we can make a risk/benefit assessment based on this much larger experience.

Obviously, you need far few numbers of patients to address efficacy, and that is why we are satisfied with the relatively small number of patients that were studied in the two pivotal studies. They have amply demonstrated efficacy. Safety requires a much larger end. That end is achieved with the additional data from patients studied under the monotherapy indication being sought.

DR. BONE: Are drug interaction studies being performed in the program with other oral hypoglycemic agents?

DR. FLEMING: Yes. There are data, and that is a very good question because obviously there would be some rationale in using this drug in combination therapy with sulfonylurea agent, obviously.

DR. BONE: Probably we'll get into that this afternoon.

DR. FLEMING: We'll get into that.

DR. BONE: Thank you.

Other questions for either Dr. Steigerwalt or the committee or for other FDA members? Thank you.

Well, it is now 11:50, and I think we should -- excuse me just a second.

(Pause)

DR. BONE: I think we'll have adjournment for lunch, and we'll return at 12:45. All right? We'll start at 12:45 sharp. Thank you.

(Whereupon, at 11:50 a.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(12:50 p.m.)

DR. BONE: -- very nearly all present? Yes, I think we are. We are reconvening the meeting of the Metabolic and Endocrine Drugs Advisory Committee for the discussion of a number of topics this afternoon related to the use of troglitazone in Type II diabetics who are insulin requiring.

After the morning's presentations and discussion, we have decided to make a little change in the program for this afternoon. There were so many questions related to the dosing issues, selection of doses, dose response curve and so forth, that we have decided to make that the first topic instead of the third. And I think that will help make sure that those issues are fully addressed, and that will facilitate the flow into the later part of the discussion.

I think this would be just before we start with that, and I believe that probably

the way to start with that is in response to some of the questions that came up this morning, there will be a very short sort of introductory presentation by the sponsor trying to cover some of these things, and then an opportunity for committee members to ask further questions, specifically starting with the dosing and dosing rationale.

Before we start with that, I think it is extremely useful for the committee to have in addition to the questions as they are written out for us for discussion at the end of the day, to have a little more idea of exactly what the agency and the division are looking for from the committee in this discussion. And perhaps Dr. Sobel would comment on that.

DR. SOBEL: First, let me say that we are discussing a drug today that is a truly novel approach to the treatment in a disease entity which requires new drugs to treat effectively. Having been in practice some 20 years ago, I can second the comments made about

the inadequacy of treatment for Type II diabetes, and nothing much really has changed. But this recent activity gives us hope of perhaps invading the realm of Type II diabetes in a more fundamental way.

So what are we looking for? I think the committee made a good start in their questioning, realizing that the molecular approach that the company presented to us also presented to us the potential for many targets in the metabolic cascade which are unknown to us. It's really an unknown area to us.

So the safety considerations which were broached by the fundamental approaches that the committee introduced were certainly welcome, and I would hope that this type of approach is amplified in your discussion as far as safety considerations.

The other issue, the issues that we dealt with in regard to safety as far as the time of exposure -- unfortunately, we have not presented to you the safety update. It just

came in. But that will remain an issue that deserves exploration, the one year exposure.

The efficacy at six months was broached. In looking at the data, one may get the sensation of a slowly drifting upward of both the glycosylated hemoglobin in the blood sugar levels and whether that represents an attack of phylaxis (phonetic), so to speak, or a true lessening of effect or the molecular cunning and wisdom of the body overcoming these genetic effects on the protein is something which I think deserves commentary, whether this promotional activity somehow becomes compensated for by other roots.

But that is speculative, but that is something I think which was inferred by Dr. Bone's and others' commentary.

Then, in a more practical sense, I would like the committee to give us some indication if they deem the risk/benefit is satisfactory here. I think it won't be an entirely generalized recommendation, but will

require a considerable amount of committee input into which sub-populations would they recommend the initial introduction of this potentially very valuable agent, and which may find utility in a much broader field eventually.

But at this point, we would like the cautionary role of the committee in the selection of the best population for the introduction of this drug, if you deem the drug approvable at this time.

So my charge to the committee is to continue on your extremely probing questions that occurred during the presentation this morning, and help us in the more specific applications, possible applications, of this drug.

Thank you.

DR. BONE: Thank you very much, Dr. Sobel. I think that if everyone is in agreement about our plan for the afternoon, we'll invite the sponsor to introduce the topic

of the dosing and rationale.

I anticipate that there will be some information from monotherapy studies as well as from studies in patients using insulin. And just so everyone will understand, there was a discussion about the appropriateness of including this, and I have asked to have this information as well because I gather that it is pertinent.

Okay. Thank you. Please go ahead.

(Slide)

DR. WHITCOMB: One of the comments that I made this morning which I realized after we had made it was a mistake on my part was, based upon this study here in which -- this is the 040 study, this is a slide I showed this morning -- which showed a decrease in glucose and HbA1c in this population. And I made the mistake, or made the mistaken statement, that there was no statistically significant difference between here and here.

There is in fact a .001 difference

for both HbA1c and FSG, so there is a dose separation, if you will, in this particular study. So that was an error on my part. I apologize for that.

In terms of the dose rationale for how we selected the doses for this particular study, during the phase II development of Rezulin, we have looked at -- you can just turn it off now. We have looked at a number of dosing regimens, and we have looked down as low as 100 milligrams and up as high as 800 milligrams during the course of development.

And what we have seen is at 100 milligrams, and this is as monotherapy, which is where this work was done, there was no effect of the drug at 100 milligrams. The first effective dose that we saw in terms of glucose lowering was at 200 milligrams. And this is supported by some mechanistic work that we have also done at 100 milligrams, in which we have basically demonstrated that the improvement in insulin sensitivity as measured

by euglycemic clamp is not improved at 100 milligrams. It looks very different than 200 milligrams.

So that is the rationale for the 200 milligram dose. We think that this data that I just had up there does show a dose response in the insulin requiring population between two and six.

The question as to what is the minimally effective dose in this population I think is -- we can discuss. I think that the HbA1c lowering that we have seen of 0.7 percent at 200 milligrams, some clinicians would say that is minimally efficacious. I mean, if you were going to use a medication for diabetes, you might not want to use one that would lower glucose any less than that does.

So, Dr. Bone, does that get at the --

DR. BONE: Yes. I guess one further question has to do with the glucose clamp experiments. Were those only done in -- were any of those done in insulin-requiring

patients?

DR. WHITCOMB: No. That is all monotherapy information. It would be almost impossible to do that in this population.

(Pause)

DR. WHITCOMB: Dr. Bone, we do have one follow-up comment that I forgot to make, if that is appropriate. Dr. Olefsky.

DR. BONE: Please make it.

DR. OLEFSKY: Just as a specific answer to the question, there are studies ongoing that we are conducting doing glucose clamp studies in insulin treated Type II diabetic patients similar to these kinds of populations. They are not completed, but they are about halfway through. And there is a very clear effect of the drug, the same effect as we see without insulin therapy. There is a very clear effect of the drug to improve insulin-stimulated glucose disposal in the clamp study in the insulin treated diabetic patient.

DR. BONE: My question mainly had to do with whether the same difference between 100 and 200 milligrams was apparent in the studies you are just describing.

DR. OLEFSKY: Right.

DR. BONE: Do you have the answer to that question?

DR. OLEFSKY: No. That we don't have the answer to. We just use the single dose.

DR. BONE: I see. All right. Thank you.

Dr. Zawadzki had a question.

DR. ZAWADZKI: This is just a clarification, but there is a comment in the description for the -- I guess the Physician's Desk Reference, that says Rezulin should not be used as sole therapy in patients with type I diabetes. Is that a misprint, or is that -- or is there something else that we should know?

DR. BONE: I take it your concern is that it implies that it might be used with insulin in type I diabetes.

DR. ZAWADZKI: That's --

DR. SOBEL: I find it amazing how a computer -- that is the one word which we all objected to within the division, sole therapy, with its implications. The labeling would require some fine-tuning, and I think the word "sole" would disappear.

DR. BONE: So neither the -- the company is not at this point seeking an indication --

DR. SOBEL: No.

DR. BONE: -- for use in type I diabetes. Is that correct? And there would be no such implication in whatever labeling was finally --

DR. SOBEL: That's right.

DR. BONE: Okay. Yeah, that could be read as either way.

DR. SOBEL: That's right.

DR. BONE: Okay. Dr. Cara has an additional --

DR. CARA: Is there a limit as to the

maximal dose recommended or that people can use?

DR. WHITCOMB: The maximal dose that we have studied in this population at this time is 600 milligrams. So that would be the maximum dose that we believe we can recommend based on the data that we have.

DR. BONE: Thank you.

Now, there were a number of questions that were asked by members of the committee or raised regarding the dosing this morning. And do I take it that we have resolved the issues as far as everyone is concerned for the moment anyway?

Oh, Dr. Colley.

DR. COLLEY: This is another issue with the labeling as proposed. You mentioned a dosing advancement at intervals of two to four week, although the material presented this morning suggested that four weeks would probably be better for assessing maximal effect.

DR. WHITCOMB: The two to four-week rationale is based upon the glucose lowering curves that I showed you this morning, which is that you see the maximal effect by four weeks. The proposed package insert has a little bit of a range around that. I think we need to have some more discussion about that with the agency as we move closer.

The notion is that most anti-diabetic drugs, the patients are looked at at two week intervals, so we were trying to be somewhat consonant with standard of care, as well not to confuse the issue.

DR. BONE: Dr. Sherwin.

DR. SHERWIN: The AUC in rats, this difference in females and males, have you studied gender effects in humans?

DR. WHITCOMB: We'll have Dr. Koup answer that question for us.

DR. KOUP: I'm Dr. Jeffrey Koup from pharmacokinetics and drug metabolism. Yes, we have done a very extensive population, looking

at the exposure of drugs across 255 patients and volunteers. And there is no indication of any gender specificity to drug metabolism in human.

DR. BONE: One other question that ties into this that came up earlier was the question of employing this drug in conjunction with other oral agents, and what information you have about interaction or co-administration with other oral hypoglycemic agents in general and in this particular population.

DR. KOUP: Before I go into the data, we at this point have done no interaction studies within this population. The drug interaction studies that I'll describe are those looking at globinclomide (phonetic) in combination with troglitazone in non-insulin-requiring patients.

There are two studies, the first study of which was a short -- no, that's slide 366. The first study is a rather short-term study, 12 administration, where patients were

administered 200 milligrams of troglitazone, 3.5 milligrams of globinclomide in combination or alone. So it's a three-way crossover study allowing us to evaluate the potential for pharmacokinetic interactions.

We don't need to spend a lot of time on this. Whether you look at maximum concentrations of plasma concentrations for troglitazone or its major metabolite, metabolite-1, or concentrations of globinclomide, there is essentially no pharmacokinetic interaction between these two compounds.

In addition, we also looked at the potential for protein binding displacement, and there appears to be no displacement of protein binding, so that we are comfortable in saying that there is no pharmacokinetic interaction within this study. Because it was relatively short-term and a low dose of troglitazone, there is also no pharmacodynamic interaction.

In other words, the reduction in

glucose that is seen in the globinclomide alone group is very similar to that seen in the combination therapy group. There was a subsequent study conducted by Glaxo that looked at six week therapy, where larger doses of troglitazone, 600 milligrams, were added to patients who had been titrated to effective doses of globinclomide.

In that study, by the end of the six week treatment period, there was an additional reduction in glucose of approximately 20 percent and a reduction in plasma insulin of approximately 23 percent in the combination therapy group. It is also important to note that there was no hypoglycemia seen during the six weeks of concomitant therapy.

So we feel these drugs can easily be co-administered.

DR. BONE: Have you studied any other oral agents, for example, metformin?

DR. KOUP: We have not conducted studies with metformin at this point. From a

pharmacokinetic basis, we could see no rationale for that, in that metformin is eliminated without metabolism and is not protein bound. The dynamic question would still need to be assessed.

DR. BONE: Well, I think clinicians will be obviously concerned with the pharmacodynamic implications of that. I mean, it is an obviously relevant question. Dr. Whitcomb wishes to make an additional comment.

DR. WHITCOMB: We do have one small study going on right now, which is more of a pilot study, combining troglitazone and metformin, which is currently ongoing. The results I can't tell you about at this time, but that study is going on.

DR. BONE: And is that in the insulin requiring or non-insulin?

DR. WHITCOMB: It's in non-insulin requiring patients.

DR. BONE: I see. Are there any ongoing studies at all in the patient

population for which you are seeking the indication today?

DR. WHITCOMB: Specifically looking at the addition of sulfonylurea?

DR. BONE: Or any other --

DR. WHITCOMB: Or any other. Those studies are planned and are soon to begin, but they are not going on at this time, no.

DR. BONE: So you don't have any data whatsoever on that.

DR. WHITCOMB: No.

DR. BONE: At this point. Thank you. Yes, Dr. Sherwin.

DR. SHERWIN: I notice -- I'm sorry. I notice from the slide you put up that the plasma exposure to metabolite-1 is about eightfold higher --

DR. KOUP: That's correct.

DR. SHERWIN: -- than the drug. Is that a biologically active metabolite?

DR. KOUP: No, no, it is not, in vitro. This is a sulfate conjugate of the

parent compound and has no activity in vitro.

DR. BONE: Is it converted to the active conjugate?

DR. KOUP: There is a -- we know that that does occur in the intestine, so there is a likelihood that there would enderopatic circulation, that the conjugate would be deconjugated and reabsorbed, although we really have no direct proof for that in man. That work is being done in rat and dog.

DR. BONE: Thank you. Okay.

And Dr. Cara.

DR. CARA: In looking at the package insert, the dosages in administration, part of it says, "The usual dose of Rezulin is 400 milligrams once daily."

What do you mean by usual dose?

DR. WHITCOMB: The usual dose recommendation is based upon the fact that that is the dose across the entire troglitazone program that we have the most experience with. We have in the 040 study, the patients who were

in the placebo arm were put on 400 milligrams. We have allowed the people who were at 200 that did not have an adequate response in the 068 study to titrate to 400 milligrams.

It was a way of giving the clinicians some guidance in that our first and foremost concern with the compound is that enough is administered to achieve adequate glycemic control. So while we recommended a starting dose of 200 to 400 milligrams, we think that that may be the usual dose, but obviously it can be pushed to 600 milligrams as well.

DR. CARA: I find that statement contradictory to what the following statement says, which is that Rezulin therapy should be initiated at 200 milligrams once daily.

DR. BONE: The response was from the sponsor that this is a work in progress.

(Laughter)

DR. CARA: I suggest that that be amended.

DR. BONE: Thank you. Are there

additional questions from members of the committee relating to the dosing administration or pharmacokinetics questions? Okay. Dr. Illingworth has one.

DR. ILLINGWORTH: Relating to pharmacokinetics. Do you have any data in patients with nephrotic syndrome, since the drug is bound to algorin (phonetic)? Patients with nephrotic syndrome.

DR. KOUP: The simple answer is no, we do not. We have studied the drug in patients with renal impairment, where we believe there are some alterations in plasma protein binding. And the clearance of free drug does not change, so that our anticipation is that there would be minimal effect of alteration in plasma protein binding.

DR. BONE: But there are big differences in the amount of plasma proteins, where they are much lower. So if -- does this mean that you would expect the affinity to be the same, but the fraction of drug that is

unbound would be presumably larger?

DR. KOUP: No. I think what I was trying to imply is the drug is cleared by the liver. It is highly plasma protein bound. And it is the free fraction of the drug or the free concentration which is available for elimination. And whether it is due to displacement or reduction in binding sites, the free clearance of the drug will not change.

What will tend to happen is the total plasma concentration will drop, free concentration will remain the same. So the exposure to active drug would remain the same. That's what we have seen in renal disease, where it is very common to see protein binding displacement.

DR. BONE: Okay. Thank you.

Are there further questions related to dosing, interactions, pharmacokinetics and so on? No. Okay.

Do the committee members feel that the rationale is sufficiently explained? Okay.

Certainly it seems -- just as a comment, it seems to me that -- and I suspect others may agree -- that it would be informative to know that 100 milligrams was not effective in this population. In other words, to have the same kind of dose response information in this population to be assured that the information from the non-insulin-dependent -- non-insulin-requiring group does carry over in the same way -- there is certainly a strong implication that it would, but it isn't established.

And I guess the other question that -- I would be interested in whether the other panel members agree, other committee members agree -- that it would be extremely important to know about interaction with other oral agents in the treatment of Type II diabetes.

Dr. Sherwin, in particular, would you comment on that?

DR. SHERWIN: Well, I would tend to agree that -- I mean, clearly it is important.

On the other hand, my guess is the company is correct, that metformin, given the fact that it is cleared by the kidney, probably won't compete. And Precose, which would be another drug that could be used, I don't see how there would be much interaction there.

So I guess the company focused on sulfonylureas, which really would be the high -- had the highest potential for interaction. So I think it is important to look at them. But I think the yield will be very low.

DR. BONE: Thank you. All right. The next topic that is on the program for discussion -- and I think when we get through these, we'll come back to some of the other topics that the committee raised for general discussion -- has to do with the rationale for defining the pivotal studies' patient populations and the assumption which is implied by that that the patients in these studies would not have responded to reinstitution of sulfonylurea therapy.

I think that the sponsor wanted to make a little introduction to this discussion, and then I suspect that committee members will have their views.

DR. WHITCOMB: Excuse us for one minute while we move some slides around here.

The patient population chosen for the clinical studies that we have presented today were obese. They were poorly controlled with an HbA1c between 9.1 and 9.5, and on an average of 75 units per day of insulin for approximately five years. Over 75 percent of these patients were on over 50 units per day, and over 25 percent were on over 100 units per day.

In the 991-068 study, we documented that a baseline injection frequency was 2.6 to 2.8 per day. This patient population is very similar to the one described by Dr. Olefsky in this morning's presentation and we think represents a real-world Type II insulin requiring population which is inadequately

controlled.

And this gets to point B on the question. Based on data which we were able to collect, between 75 and 80 percent of patients in these two studies were previously on at least half maximal doses of sulfonylurea with over 50 percent on maximal doses.

I should point out that this is based on information we were able to collect. It is probable that the patients, particularly those in the 991-040 study, had in fact been on higher doses in the past.

The data in the literature on adding sulfonylureas to insulin is variable. Amaryl, the sulfonylurea most recently approved, was able to demonstrate some insulin dose reduction, i.e., insulin sparing, but without significant glycemic control.

Two published meta-analyses in the literature appear to conclude that some improvement in glucose control may be transiently possible by the addition of

sulfonylurea but without a reduction in insulin dose. Alternatively, insulin doses may be lowered but without an improvement in glycemic control.

The patients who appear to respond best to the sulfonylurea/insulin combination are those on low doses of insulin and with some beta cell function remaining. The C-peptide levels, particularly in the 991-040 study, were low, and they were not on low doses of insulin.

Therefore, we believe that it is unlikely that they would have responded, or whether the response would have mirrored that which was observed with the addition of Rezulin to these same patients.

DR. BONE: Was there any consideration on the agency's part of restricting the indication to sulfonylurea failures?

DR. SOBEL: Let me just say this is part of the risk/benefit. Here we have a new agent with great promise but with areas of

unknowns, as is true with all new agents. Does one move to a new agent, albeit it one with great promise, without trying to utilize to a maximum control with agents whose safety profile is well established?

So it is a philosophic approach, and this is part of the charge to the committee. How much does one wade into new territory before exploring what has been settled? It's an approach which we would like the committee's input as far as risk/benefit. It's really the issue of exploration, I think. Under what conditions does the risk/benefit justify the use of this agent?

DR. BONE: I think that is somewhat clarifying for some of the members of the committee. Let me see if I understand. One of the questions that the committee is being asked to advise about is whether the indication for the initial approval of this compound, which is obviously part of a long program, multiple indications, no doubt -- but that the initial

indication might be a relatively restricted one.

And since the studies were done in a population of patients who had failed in some sense on sulfonylurea with insulin to have any additional benefit from the sulfonylureas, then one question might be whether the committee would recommend restricting the labeled indication to that group.

And the question brought up then about whether these patients were true failures or not is pertinent to whether that has been explicitly tested. Is that kind of what we are getting at?

DR. SOBEL: You've said it right.

DR. BONE: Thank you. Okay. Well, I think that will be helpful to the committee in understanding the meaning of some of the issues that we would like to address.

Dr. Sherwin.

DR. SHERWIN: Would you want to restrict it to sulfonylurea failures or just

oral agent failures in general? Because you are getting a very narrow, you know, definition.

DR. SOBEL: Well, let me -- you know, as the conditions of experimentation were, in the absence of wide distribution of metformin in the month before, I think you should consider this approval in the perspective of the state of the art as it exists today and make your recommendations accordingly.

DR. BONE: So that might be a little broader than --

DR. SOBEL: Pardon?

DR. BONE: That might be slightly broader, along the lines Dr. Sherwin suggested then.

DR. SOBEL: Yes.

DR. BONE: Dr. Cara.

DR. CARA: Well, I think we have to be cautious in really looking at what treatment failure means because there is no evidence that has been presented that indicates that these

patients in fact were treatment failures.

What was suggested was that at some point of their therapy, at some point in the course of their treatment, they had received sulfonylurea therapy, and that treatment had not -- but that could have been done a long time ago or relatively recent.

But it was felt that the patients were still in "poor control" as manifested by glycohemoglobin levels above nine. But that's very different to say it's a treatment failure.

DR. BONE: Well, I think -- go ahead.

DR. SHERWIN: I think the fact that the glucose was so very high suggests these people wouldn't do well with most therapies, surely not sulfonylureas. I mean, patients with fasting glucoses of 220 generally don't respond very well, especially who have had long term diabetes and have been on insulin for a long -- for five years. It is unlikely that they would have much of a response, surely not the kind of response shown in this study.

DR. CARA: But then I think, you know, the issue that you are alluding to -- or I may be mistaken, I don't know. The issue that you might be alluding to is the fact that there may be in fact different severities of diabetes.

DR. SHERWIN: That's for sure.

DR. CARA: And that's a whole different ballgame altogether.

DR. BONE: Well, let me see if we can get a little help here from Dr. Whitcomb or someone else from the sponsor about -- he explained what was meant by a failure this morning. And I think we could just use a refresher on that exact point.

DR. WHITCOMB: Well, I can or I can have Dr. Olefsky also maybe look at it from --

DR. BONE: I think this refers specifically --

DR. WHITCOMB: To the study. Okay.

DR. BONE: -- to the criteria for the studies.

DR. WHITCOMB: In the 991-068 trial, we specifically had as an entrance criteria failure to -- sulfonylurea or metformin. Metformin had just been introduced. It was a late addition into the trial as indicating that. And the investigator was asked as he would to verify -- this is an inclusion criteria along with everything else on there.

We don't routinely go back and have them provide documentation for every little thing on inclusion criteria. But what we did also capture is all prior anti-diabetic medications on these patients, which is information which is submitted as part of the NDA.

We then have gone back through those records to try to understand exactly what went on in these patients. And as I said this morning, many of these patients had been on insulin for at least five years, so the records are somewhat difficult to put everything together with.

But what we were able to document is that many of these patients had been on maximal doses. About 60 percent of them, in fact, had been on maximal doses of sulfonylureas in the past.

Now, it perhaps is a leap, but in general if a patient was doing well on a maximal dose of an oral agent, it is unlikely that they would have been shifted to insulin.

I can't say that definitively. But I think just from a pure clinical standpoint that that's less likely. Maybe Dr. Olefsky would like to comment on the relatively clinical weight of that.

I don't know. Does that get at your question?

DR. BONE: Well, I think then what you are saying is, if we understand correctly, that you had patients who all had received at least 50 percent of the maximal dose, and the majority of whom had received the maximum recommended dose of at least one oral agent.

And the treating physician had regarded this as unsatisfactory from a therapeutic standpoint.

DR. WHITCOMB: That's correct.

DR. BONE: Is that -- but that there were not explicit criteria for what constituted unsatisfactory. In other words, there wasn't a cutoff for glycosylated hemoglobin or something like that. It was a clinical judgment.

DR. WHITCOMB: Right. But the patients obviously that went into the trial were not well controlled where they were now. So that was --

DR. BONE: Right. Were they still on the hypoglycemic agents at the time of screening?

DR. WHITCOMB: No.

DR. BONE: They had just been on at some time in the past. So the fact that their degree of hyperglycemia may have been greater at the time of entry in the study than it was on the other agent, we don't have that information.

DR. WHITCOMB: Well, no.

DR. BONE: Okay. But it was a clinical judgment is what was exercised. Jose, does that --

DR. CARA: Well, I think that is as best as you can get. But it is very different to say these patients were previously treated with sulfonylurea than to say these patients were on sulfonylurea at the time of the entry into the study and were therefore considered treatment failures.

DR. BONE: Right. That is a previous clinical judgment.

DR. CARA: Right.

DR. BONE: Not -- it wasn't a group of patients who were on maximal doses of sulfonylurea exceeding certain parameters and then were entered immediately into the trial. It was a prior history of not doing well on sulfonylurea in the judgment of the clinician and the patient, presumably.

DR. CARA: Right.

DR. BONE: Okay. Dr. Zawadzki.

DR. ZAWADZKI: This is a general comment. Conceptually, I am having a little difficulty dividing the world of Type II diabetes into insulin-requiring or insulin-using and non-insulin-using. I don't think that really separates two distinct populations. In fact, there are many individuals who fail oral sulfonylurea therapy who refuse to go on insulin.

I worry a little bit about the approval of a drug for one distinct population when, in fact, conceptually, it seems it would be really more effective for some of the individuals who fail on diets and oral sulfonylurea therapy currently.

DR. BONE: If I understand correctly -- and maybe this is -- I don't want to be talking too much, but it might help a little bit from the interests of time.

If I understand correctly, that was actually a major thrust of the sponsor's

development program. And the attention was turned to the group taking insulin because of the specific findings about insulin dosage.

Is that correct? And that this is -- well --

DR. WHITCOMB: I think the reason that we went after this population was because in our opinion and the opinion of many expert advisers like Dr. Olefsky, one of the most challenging patient populations to treat is the obese Type II diabetic who is on insulin, that you cannot get their glucoses down.

So we focused our efforts on that, believing that speed in bringing this drug to the market for that particular population was of the essence, while continuing the rest of our development for the rest of Type II diabetes.

And this was something that we had talked with and agreed with the agency was a reasonable strategy based upon the development timelines that we had.

DR. BONE: Anything further?

DR. ZAWADZKI: Yes.

DR. BONE: Dr. Zawadzki.

DR. ZAWADZKI: It seems to me the availability in the marketplace of this drug for the indication that we are discussing today does not really preclude the use of the drug in the larger domain of individuals with Type II diabetes. And I would just like to see some data regarding the use of this drug in other patient -- in the more general patient population with Type II diabetes.

DR. BONE: So you are expecting that there will be extensive off label use in other diabetics.

DR. ZAWADZKI: I think there would be.

DR. BONE: Dr. Cara.

Dr. Sherwin, anything to add?

DR. SHERWIN: Well, it makes sense that if you have got a drug that is efficacious in the "patient that is not optimally

controlled," you'd think that you would get more bang for the buck if you used it in patients that could be reasonably well controlled with minimal therapy.

DR. BONE: And if I understand Dr. Zawadzki's concern, it is that there is no data.

DR. ZAWADZKI: Well, we saw some data from (indiscernible) 11, which I think was very impressive data. But I would just like to see a little bit more and longer than 8 to 12 weeks of therapy.

DR. BONE: Yeah. I guess one question we could ask is where does the sponsor's program stand in the non-insulin-using Type II diabetic.

DR. MARTIN: Let me just emphasize that what you saw today was added on to our full-blown indication for Type II diabetes. We did not shift gears to do this. We are still generating data. We will be submitting shortly, frankly, the full indication for Type

II diabetes. We have a lot of data.

This NDA was assembled with the FDA's agreement earlier to make this drug available to the patients who are most in need as soon as possible.

DR. BONE: So you say you are planning very shortly to submit the total program. This presumably means that you have essentially completed your phase III studies, or nearly completed your phase III studies in non-insulin-dependent -- or non-insulin-using Type II diabetics?

DR. MARTIN: That's correct.

DR. BONE: Thank you. Dr. Hirsch.

DR. HIRSCH: The common practical problem would seem to be that someone is on sulfonylurea or something else and they are not well managed, and they are being given insulin at the same time. And now an option comes up.

Either we're saying that maybe this is a drug where you can, with this one drug, now drop that whole thing out of the way, you

will not need the insulin and the sulfonylurea, or if you do need insulin, you'll need a lot less insulin than you had before on the sulfonylurea.

But none of these things have been directly tested. Isn't that right? You don't know that this is true. You know that they have a history of having had difficulty with sulfonylurea and therefore they are on insulin. But there is no direct test of these possibilities right in front of us to see what would be better or not.

But that really is the situation, isn't it? I mean, the situation is someone is -- if they are doing well and they're euglycemic and everything, then forget about it. They don't need the drug. But the notion is here that there is some badness in utilizing insulin alone along with the sulfonylurea, giving more and more insulin to straighten this matter out, which is theoretically arguable, by the way. I don't happen to be a believer in

the evils of insulin as much as the evils of lack of understanding of Type II diabetes.

But is that right? I mean, is that what we are talking about here? That we think that sulfonylurea is fine. It doesn't work well for everybody, so you have got to give some people insulin. You have got to give them a lot more insulin. You keep dicking around with that. And here we have got something where we can -- instead of using the sulfonylurea, we'll stick in the Rezulin and get the insulin down and maybe even make that go away.

But that hasn't been tested.

DR. WHITCOMB: No. Well, let me just make a comment here, and maybe Dr. Sherwin can also address this. The number of people in the United States that are taking concomitant insulin and sulfonylureas is very low. I believe the latest ADA data is around 4 percent.

DR. SHERWIN: It's not a good

combination.

DR. WHITCOMB: I mean, the suggestion here is not that people should first fail sulfonylurea added to insulin and then go to Rezulin. I think most patients that have Type II diabetes in the United States that are on insulin are on it by itself. I mean, they are on insulin as monotherapy.

And what we have been showing here today is that these people are not well controlled with that current regimen. They have got very high glycosylated hemoglobins. And we think that the addition of Rezulin to insulin demonstrates an effect which has not been shown with any other agent to this point in time, and that that is really what we are trying to show.

And the fact that these people got to insulin via sulfonylurea failure, I would put that you're right. We have not directly tested that. But that's pretty well standard of care in the United States for most patients. And

Dr. Sherwin may have an opinion on that as well.

DR. SHERWIN: Well, I think most patients like this who would -- if you would add a sulfonylurea would not do well. So that is, I think, unquestionable, and it is not used very much.

I'm just -- my only concern actually is that our goal should be to lower glucose and to optimize and reach certain target goals. And I suspect to achieve that, you are not going to drop the insulin dose very much at all. In fact, you may even need more insulin to achieve your goals because you haven't achieved it in the majority of people.

And so I think that from a therapy perspective, the goal should be not as much to lower-insulin doses, but to get glucose as close to normal as possible without causing harm. And that study hasn't been done yet to show that aspect of it.

I mean, it doesn't necessarily mean

that you need to do that to get this kind of approval. But I think that the focus should have been how do you optimize treatment to reach target goals and just to get a feeling for how much insulin you need to do that. Surely you need a tremendous amount without the drug. My guess is you'd need a lot less to achieve it with the drug.

DR. BONE: Thank you. Just one further point of clarification that may be helpful to some people is that if I understand correctly, the entry criteria for the studies were not that the patient had to have failed on an oral glycemic agent together with the insulin, but only that they had an unsatisfactory response to an oral hypoglycemic agent prior to starting insulin. So it was sequential rather than in parallel.

And the sponsor is nodding yes, that that's correct. Okay, to make that clear. And I guess the purpose of that was to ensure for the sake of discussion that the patients really

needed to be on insulin. Is that correct, if I can ask this? That was -- they are also nodding, that we know these people needed to be on insulin because they didn't do well on oral agents before.

Okay. Thank you.

Yes, Dr. Cara.

DR. CARA: I think there is an issue that is nagging at me, and I don't know that there is any resolution. But it is really a damned if you do, damned if you don't issue because, I mean, the bottom line is that whether or not we define a specific patient population, the medication is going to be used by everybody.

And I think there is good rationale to suggest its use, although we haven't seen any data. Even though it is clear that the data that we have seen, I think, shows efficacy in patients that are receiving insulin, you can argue that if you can prevent patients from getting on insulin, with its untoward effects

of weight gain and so on and so forth, that patients may actually do better.

So I think there is very good rationale for people to use this medication more freely than we will ever be able to define.

On the other hand, you know, does that mean that the medication should not be approved until that data comes out? I don't know.

DR. SOBEL: Could I just --

DR. BONE: Dr. Sobel, yes you can, please.

DR. SOBEL: I think you raise an important issue about off label use. I think what happens in this type of situation is that we try to keep, if possible, an initial approval a non-trivial approval. However, you can never prevent off label use.

The question is to keep -- to have a solid reason for introduction which is not trivial. And, you know, there is no real

control of off label use. But I think the committee has to decide.

Well, let me just go over the history of how this whole thing evolved. And it was said -- you know, when we first became acquainted with the drug, it was on the basis of a 17 patient study of insulin-using patients, of which, I don't know, seven came off of insulin completely, which is quite impressive. That wasn't replicated in the large clinical studies, but you did get something like 15 percent that were able to come off.

To get back to your question, if you feel from a risk/benefit standpoint and a non-triviality of indication and population that this should be approved, if you believe this, then the concern about off label use is something which is a given to the scene as it exists in drug use in America.

But I think you'll have to confine your view to the requested indication and

whether you feel the population has been well defined and whether the risk/benefit exists, whether one should fully explore -- you know, whether the issue of rigorous insulin management has been chosen before. Is that a requirement, you know, theoretically with rigorous management which may not be acceptable to patients, whether that has been explored, whether other agents, oral agents have been explored. This is the type of questions which I think have to be addressed.

Again, it comes back to our almost ritualistic risk/benefit question. Is it justified to move into this very exciting new drug? But are we justified at this point in accepting known risks and hypothetical risks that I think you have probed into this morning? Are we justified at this point in making a recommendation for approval? That's the question.

DR. BONE: And then presumably we will have the sponsor's -- correct, that they

have a nearly complete application. We would have the remainder of the program before us within the next year presumably.

DR. SOBEL: Yes.

DR. BONE: Dr. Fleming.

DR. FLEMING: And just to add on to Dr. Sobel's comments, we may be fooling ourselves, but we do like to think that physicians and other health care providers read the labeling, and that it does count for something. And we make an effort to be very precise in how the population, the recommended population, is defined. And we will go to some lengths to put cautionary statements about off label use when we feel that it is indicated.

So it is not that we are entirely powerless to address the issue. But I think we all understand that there is certainly limitation in how far we can do that.

DR. BONE: The major impact of the agency really being on the promotion and claims.

DR. FLEMING: That's absolutely right. Our division of drug advertising and marketing is extremely active these days in enforcing the marketing approaches of drug manufacturers. And this is also somewhat of an element in the address of this particular issue.

DR. BONE: Dr. Sherwin.

DR. SHERWIN: Is the amount of insulin part of this in terms of indication? I mean --

DR. BONE: Well, the studies were done in patients who were taking at least 30 units, and they averaged about 75. I think recommendations about the labeling would probably be within the purview of the committee to make, but will be in the purview of the division to finally determine.

DR. SOBEL: Well, it was an additional dimension. And apparently there were a number that were analyzable that had multiple doses per day. And the fact that you

are able to demonstrate some protection.

But the real question is not -- I don't think that that parameter is of how much was used. I think the real question is how rigorous should a clinician be in the exploration of conventional therapies before one proceeds to this therapy.

DR. SHERWIN: My own view would be that you should be -- we know about insulin. And surely it makes a lot of sense to use this type of drug in people in whom, in the judgment of the clinician, they cannot manage the patient satisfactorily and reach target goals with insulin. That would be my view.

DR. BONE: All right. Dr. Olefsky wishes to add a word.

DR. OLEFSKY: Just one comment because I'd like to get back to something that Dr. Sherwin said, which I agree completely with. I think in common clinical practice, we know that patients are moved through oral agents before they get on insulin therapy,

including sulfonylureas, and that we do know it is a progressive disease, that even if patients initially respond to an oral agent, eventually they need bigger doses and combinations.

And eventually many of them come to insulin therapy, as Maureen Harris' data show, and as the UK PDS has shown. It is a progressive disease. And in Maureen's data, there are very, very few patients in this country who are in any combination of sulfonylurea and insulin. That is only a couple percent.

So that would not be the common clinical practice. And I think as Dr. Sherwin said, and I think Randy said, the data available on that indicate that that is not a very effective combination anyway. So we do have lots of patients who are on insulin therapy, and that is their sole form of therapy.

Now, we might debate the "evils" of insulin in some way. But I think there is one

-- using this in a tongue-in-cheek way -- evil of insulin which is really not that debatable because it is supported by all the data, and that is that insulin is not used that effectively, that our goal really is to get the lowest glycemic -- I mean, as close to normal as possible within reason. That is our treatment goal.

And as all the data, the demographic data, showed, when physicians in this country use insulin, they do not get glycemic targets. Their patients are running around with hemoglobin A1c levels at 9.5 percent.

And in fact, if you look at the patients recruited into this study, almost the same exact results, people on 70, 80 units of insulin a day, hemoglobin A1cs 9, 9.5 percent. So maybe an evil of insulin is the fact that physicians and patients for a variety of reasons which I think we could all articulate are just not using the insulin effectively enough to get those glycemic targets.

So with a drug that would improve the action of insulin, it really does allow you to get better glycemic control. And I think that what Dr. Sherwin says is the goal, to get glycemic control.

And remember, according to the DCCT study, every increment of improvement in glycemic control gives you an increment in improvement in prevention of complications. So that it is also true for the Type II diabetic population.

You know, we would like to get down to hemoglobin A1cs of seven or maybe even a little bit lower. But to the degree that you can improve it, you're doing something good for the patient. And I think that really should be the focus and the goal.

DR. BONE: Thank you. With regard to this discussion of the target population, are there any additional comments from the committee? Do I take it that the meeting of the minds to a certain extent is that we are

only talking about patients who are currently on insulin therapy, with the implication that control is not satisfactory on the insulin therapy as of the time of starting troglitazone treatment? And there is also the implication these patients have a prior unsatisfactory response to oral agents.

Is that -- is everybody kind of on the same page with that? I'm just asking. I'm not --

DR. SHERWIN: I mean, the only thing I would add is maybe some intent with insulin to try to optimize treatment might be added because obviously, somebody could be -- not have made much of an effort. So I think it is people who -- not with an effort to improve control with insulin, have been unsuccessful.

DR. BONE: That might be hard to write into the labeling. But I see your point, yeah.

DR. SHERWIN: Right.

DR. BONE: Beads of perspiration --

the number of beads of perspiration appearing on the doctor's brow or something like that, you know.

(Laughter)

DR. BONE: Dr. Illingworth.

DR. ILLINGWORTH: The logic that extends to that question -- what about somebody who fails on oral agent or oral agents who is being contemplated for use of insulin, would this substitute for insulin use as the next step in therapy?

DR. BONE: As I understand it, that is not the indication which is being requested. I'm told I'm correct, that that is a separate indication for which the sponsor will be applying in the relatively near future, but not the subject of today's discussion. Okay.

DR. CARA: And maybe the way to get around what Dr. Sherwin suggested is documentation of glycohemoglobin levels above nine while on insulin therapy.

DR. BONE: Well, again that becomes

something that is fairly difficult to enforce, I suspect.

DR. SHERWIN: I would say surely the recommendation of the American Diabetes Association is to institute some change if you're not below 8 percent. So that would be consistent with the ADA recommendation.

DR. BONE: All right. I think now the next topic that we wanted to discuss was this business about estimation of the clinical significance of troglitazone's treatment effects. And in conjunction with this, there were several questions during the morning's discussion about the effects of troglitazone on lipids. And there were some effects of troglitazone on lipids.

And I believe the sponsor is going to summarize those for us. It wasn't part of their presentation this morning. But it seems like a logical place to lead in when we are talking about the clinical significance of a drug's effect.

DR. WHITCOMB: Did we want to do the lipids first, or did you want to do the clinical significance now, or what's your pleasure?

DR. BONE: It seems to me that having the lipid data is almost essential to being able to look at the overall clinical.

DR. WHITCOMB: Okay. What we have asked is for Dr. Don Black, who is the senior director of cardiovascular and clinical research at Parke Davis, to present the lipid information for us.

DR. BONE: And we can look on the menu and see what other information you have.

(Laughter)

DR. BLACK: Thank you. I won't go through full lipid metabolism, but we can talk about that further. I'm sure this committee is very aware of it. Let me just show you some of the effects here on cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides in the two studies that are under discussion

today.

In the total cholesterol level you see here, at the 200 milligram doses in both studies there is a mild increase. This is the adjusted change from baseline in total cholesterol. This is less than 4 percent mean percent change, LDL cholesterol, adjusted change from baseline, again very minor changes in the 200 milligram, 400 milligram, or 600 milligram doses. HDL cholesterol -- again mild changes.

And triglyceride was reduced 25 adjusted change. This was, as you can see here, about 11 percent mean change, and here at 600 milligram dose a bit more than that, about 15 percent mean change, not much change here at this level.

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(Slide)

And just to explain about the triglyceride effect, monotherapy in sulfonylurea combination studies -- these are

other studies than you have been able -- than you have seen yet --

Have shown consistent triglyceride decrease as well. Exogenous insulin, the high dose, decrease, hepatic VLDL production and decreased triglycerides, as we know, in general, about exogenous insulin.

And after starting Rezulin, decreasing exogenous insulin may lead to a transient increase in triglycerides after an initial fall. So some of the background documents you saw in one of the studies, the triglycerides went down then went back up again.

Next slide, please.

(Slide)

But overall in the -- and this is in the 042 study or the long term study of muscular cardiac function. You see there is a reduction in triglycerides here as well for Rezulin and for Glyburide. And this was sustained in the second year as well.

Next slide, please.

(Slide)

Here in the 068 study, mean levels of LDL cholesterol at six months, you see only slight changes in Rezulin at the 200 or 400 milligram doses compared to placebo.

Next slide, please.

(Slide)

And here at HDL again slight increases. So overall, the change in non-HDL to HDL ratio, or the VLDL plus LDL cholesterol compared to HDL did not change. As VLDL cholesterol was reduced and triglyceride was reduced, LDL came up a little bit, but so did HDL. So overall, the risk/benefit, if you will, of lipids didn't change. Next.

DR. BONE: Excuse me. Have you formally calculated that using the prediction equations for risk?

DR. BLACK: Well, since -- I'm sorry. Since the non- HDL to HDL ratio doesn't change, we would assume that it would be zero out on

both sides, yes.

And here the mean change from baseline in ApoB, which is probably, I believe, the strongest predictor of cardiovascular risk -- and you see here no change in placebo at 100 milligrams, 200, 400, or 600 milligrams of Rezulin.

So there is an increased LDL of 3 to 11 percent in diabetic studies, including, as I mentioned, an increase as well in HDL cholesterol, and a slight decrease in VLDL cholesterol. So this is all averaged out.

Because you see this reduction in triglycerides in the VLDL component and the same amount of particles, the ApoB stays the same. There seems to be somewhat of an increase in LDL cholesterol. But this is probably just changing where the cholesterol is as far as particles. And potential impact on atherogenic risk, we believe there is none, that ApoB, there is no change, and no change either negative or positive in the total to HDL

ratio or the non-HDL to HDL ratio.

Thank you much. If you have any questions.

DR. BONE: Perhaps Dr. Illingworth would have a comment or a question, and then Dr. Sherwin.

DR. ILLINGWORTH: Well, Don, thanks for showing that information. I think triglycerides are viewed as a major risk factor in diabetics. But we don't have good data on proof of benefit from lowering triglycerides.

We do have data from two subgroup analyses showing benefit reducing LDL cholesterol, some within 4S and some within the care trial. A small number of patients with Type II diabetes similar to this population got substantial benefit from lowering LDL cholesterol.

So I don't think we know what is the negative impact of a raise in LDL cholesterol. And I think that needs to be an area of exploration.

DR. BLACK: While I don't disagree with what you say, I think the difference in this with the other studies that you mentioned is that also that triglycerides are reduced, HDL was increased, as well as the reduction in LDL cholesterol in those studies. That may have contributed in part to the positive effects that we are seeing.

As you say, in this it is a little bit different. We are not proposing necessarily a positive effect with this. We just feel it is a neutral effect.

DR. ILLINGWORTH: One second question. In the background information, you have done some antitoxin -- studies of LDL oxidation. Is it clear whether troglitazone is carried in LDL? In other words, is this perhaps due to the drug being in LDL itself since it looks quite a lot like vitamin E? Or is it from change in LDL composition that renders it less susceptible to oxidation?

DR. BLACK: Maybe Dr. Whitcomb can

answer that.

DR. WHITCOMB: We've done one small study with Alan Chait up in Seattle where we took C-14 labeled troglitazone. And he was not able to show that it incorporated into the LDL particle.

DR. BONE: Thank you. Anything further? Dr. Sherwin.

DR. SHERWIN: Have you or anybody in the company looked at lipoprotein lipase? And could any of the changes --

DR. BLACK: Not in humans. I think full -- we do intend to look much more at the metabolism of lipoproteins with this compound. The work just hasn't been done yet. Obviously, there are other things as well. Hepatic lipase could be an effect.

DR. BONE: I guess I have a question perhaps I'd like Dr. Sherwin and Dr. Illingworth to comment on, and that is that in spite of the fact that the patients seem to have improved control of their diabetes, there

seems to be sort of a non-effect at best on the LDL level -- I mean, non-effect if you allow for the HDL.

But in other words, we don't see an improvement even though the patient's diabetes is under better control.

DR. ILLINGWORTH: My interpretation of the information -- Don, I welcome your comments -- will be that the effects on -- what you see with fish oils or low dose of fibrase, where the effect is mainly reducing triglyceride production but not affecting ApoB synthesis. So the number of particles produced by the liver probably doesn't change.

DR. BLACK: I absolutely agree. Thank you.

DR. SHERWIN: I think that's correct, too.

DR. BONE: Okay. Did the sponsor have anything else that they wanted to present about clinical significance apart from this morning's presentation? Or should we just

start to discuss it? I know Dr. Hirsch has a question or comment.

DR. WHITCOMB: We have about 60 seconds.

DR. HIRSCH: Well, maybe you can incorporate in whatever you. And I am sort of taken by the fact that a lot of the data have to do with people of body mass indices of about 35.

Do you have any data on whether there is any difference in the efficacy of the drug at different weight levels?

DR. WHITCOMB: That is an excellent question. We have looked at the patient's response with all different BMIs, and there does not appear to be a variability of response. So in other words, if you have a BMI in the high 20s you appear to respond to the drug equally well.

Of course, interestingly enough, a lot of the studies that have been done in Japan are with individuals with BMIs that are in the

low 20s. And they again have seen good response in combination with insulin as well.

DR. SHERWIN: By the way, this just came to mind. Have you looked at leptin levels in these people in view of the fact that it affects fat?

DR. OLEFSKY: I guess I am supposed to comment on the leptin levels. In a study that we did, we did look at leptin levels. This was published a couple of months ago. If you take patients who were treated with troglitazones -- let me make clear, it is people who have a range of BMI treated with troglitazone, and then we repeat the leptin measurements after three months of therapy. And basically, there was no change. The leptin levels were identical before and after therapy.

There was the expected relationship between leptin level and the degree of obesity, both before and after. But there was no change in the mean values before or after.

DR. HIRSCH: There are some animal

studies showing a decline in leptin MRA and adipose tissue after given the drug. There is one that I know of.

DR. OLEFSKY: Yes. There are some animal studies on this. But we wanted to go to humans and see what the result was in humans. And although there may be complicated regulation of leptin, the net result at the end of the study was no change.

DR. HIRSCH: Right.

DR. OLEFSKY: And of course, there was no change in weight either in the studies I am referring to.

DR. BONE: Are there further comments from the committee members concerning a clinical significance beyond the comments that have already been made in the earlier discussion of the treatment effects?

Perhaps Dr. Critchlow would like to start that discussion.

DR. CRITCHLOW: I had a couple of questions. One is, just looking at the two

pivotal studies, one shows at the 200 milligram dose significant effect for decreasing serum glucose. The other did not, although in that study the responder analysis was significant, which incorporated the reduction in insulin as well as the serum glucose.

Also, as far as the glycohemoglobin, one study showed significant decrease there, and the other study did not. And both studies showed that insulin could be reduced at both doses.

Given those constellations of findings, it is difficult to know when you have those two studies can one -- or could you address what percentage of patients in each study you would consider adequately controlled by whatever the relevant criteria would be?

I mean, I understand that both studies were designed to do different things and address different issues. But the -- if really one is considering the management of diabetes with respect to all of these outcomes,

it seems that you have got maybe slightly disparate results. Or you may or may not, I can't tell.

The other question was what specific differences was each study designed to detect, and were those differences in your mind thought to be clinically significant.

DR. WHITCOMB: I think you make a very good point about the differences when you just look at the two studies side by side. And I think one clear difference is the instructions that were given investigators vis-a-vis reductions of insulin dose levels.

In the 040 study, there was only a 15 percent reduction in the insulin dose in that trial, which gave a decrease of glycohemoglobin of about 0.7 percent compared to placebo. In the 040 -- or excuse me, in the 068 study, there was a decrease in insulin dose of about 40 percent. So it was a very large decrease, and in fact to optimize glucose control, it was probably too much.

But what we were trying to ferret out, if you will, in that study is the relative balance between insulin dose reduction and glucose control. And I think what this has shown us is that that balance is really critical in terms of the physician optimizing glucose control, perhaps by not reducing insulin as much as they think that they can get away with. And I think that is going to be a really important point. It gets to some of the comments that Dr. Sherwin made this morning.

But both of the studies were, you know, positive in terms of their primary endpoints as designed and as the studies were set up to do.

DR. CRITCHLOW: No. That's true. But in my mind, we basically have, because of the way the studies were designed -- and I agree that you were working in conjunction with the FDA and whatever. But maybe you could try to show me how we have sort of two studies showing -- or clinical benefit.

I mean, I know -- again, I am trying to wrestle with the issue of two studies that have different endpoints. We basically have no replication of achieving those endpoints.

DR. WHITCOMB: Let me just start with the 200 milligram group in 068. The patients in that group that met the response criteria did have an average glycohemoglobin reduction of 1 percent. So I think the clinical benefit in that sub-population was demonstrated.

I think what that tells us, however, is the 50 percent reduction was totally arbitrary. We started with a 35 percent reduction. And after some negotiations with the agency, ended up at 50 percent. So I think the 50 percent number, which is what we asked the clinicians to drive to, was perhaps over zealous in terms of insulin dose reductions.

And therefore, if you extrapolate back from that insulin dose reduction to something more like you saw in 040, in fact the data is very consistent between the two trials

when you look at them side by side. The difference is the insulin doses.

DR. CRITCHLOW: Could you tell me what specifically each study -- the difference they were powered to detect?

DR. WHITCOMB: Alpha was, you know -- we were looking at --

DR. CRITCHLOW: The difference between placebo and the treatment arms that you were looking to --

DR. WHITCOMB: What was considered an effect?

UNIDENTIFIED SPEAKER: (Inaudible.)

DR. BONE: That has to be restated.

DR. WHITCOMB: That's what -- I'm going to try to distill it down. The 040 study at 90 percent power was powered to show a 1 percent difference in HbA1c of placebo to active treatment groups. The 068 study was powered at 90 percent to show a 20 percent difference between active and -- I think it is 20. Actually, I think it was more like 15

percent difference between placebo and active. We'll get the exact numbers for you.

DR. CRITCHLOW: Okay. Then my other question was is there a definition of adequate control that could be applied to each study that some ballpark percent of patients could be classified as reaching that goal?

DR. WHITCOMB: Well, I think in the 040 study it is very clear, which was much more of a fixed dose study. I think we have demonstrated that clearly.

The 068 trial was really designed to see what was that balance between those two endpoints. Part of that is a judgment. I mean, it is a showing that 25 percent of patients were able to achieve a 15 percent reduction in blood -- as it turns out -- let me just drop the glucose -- a 1 percent fall in glycohemoglobin and a 50 percent reduction in insulin dose of clinical significance. I think that is really the question.

DR. BONE: And if I understood Dr.

Sherwin's point earlier and the implication of Dr. Critchlow's comment, it is that the primary endpoint of reduction of the insulin dosage is not one that diabetologists would ordinarily recognize as a primary goal of therapy, but rather blood sugar control.

Is that your point, Dr. Sherwin?

DR. SHERWIN: Yes. I would say that, although I must say that there is circumstantial evidence supporting the view that systemic hyperinsulinemia may be harmful, and it is a concern. We just don't know the downside of that.

Surely, if one could achieve a reduction in insulin dose with no harm, that would be good. But I think that if one had the balance between lowering glycohemoglobin to 1 percent above the normal range or raising insulin, you would choose lowering.

The glucose link is clearly demonstrated. The insulin link is not. And although it is a potential serious problem, it

is not on the hierarchy of things as crucial.

DR. BONE: Well, I think that then -- it sounds to me as though, if I'm pulling this together correctly -- and please, everyone, let me know if I'm not. As Dr. Critchlow has pointed out, we really have two trials testing different hypotheses to a certain extent, the first hypothesis being that you can reduce the glycosylated hemoglobin by a clinically significant amount, and the second being to a large extent that you -- although there is a duality of primary endpoints there, that you can reduce the insulin dose.

And the concern that Dr. Critchlow has expressed is that it is hard to know whether this is a replication or not. There is an implicit -- implicitly, the second trial indicates that if reduction of the glycosylated hemoglobin level had been the primary endpoint and the insulin dosage had not been reduced, then the similar result would have been achieved.

Would the sponsor agree with that summary? Would the agency agree with that summary?

DR. FLEMING: Well, I'd just like to make a comment here that may help a little bit. I think everybody understands very well the agency's well known requirement for confirmation of a clinical observation in order to support an indication. We certainly could ask for an identical trial to be run as the confirmatory study, and that sometimes is done.

But we do think, I believe, in more conceptual terms about confirming perhaps a broader benefit than simply in a biostatistical manner confirming a specific hypothesis.

So this is not an unusual approach by any means. And in fact, I think we were somewhat attracted to the idea that we would do a somewhat different design with a different endpoint that nonetheless would be complementary to the original study performed.

Now, I think Dr. Critchlow's point is

excellent, that we would like to have a unified understanding of the benefit. And we can integrate Dr. Sherwin's comment to say that certainly glycemic control is the first priority.

But we would also, I believe, accept that there is a benefit in itself to reducing insulin, exogenous insulin, dosages. And that relates to the patient's own quality of life, if nothing else.

Now, the way the second pivotal study was designed, I do believe that we have a handle on glycemic control, that certainly we can point to a certain number of responders across both studies in terms of glycemic control. Let's say a 1.0 hemoglobin A1c unit decrement, and probably the company could give us in a moment just how many people across both studies would have responded in that manner.

That I believe addresses, or would allow us to be fairly specific in the address of the question that Dr. Critchlow has rightly

brought up.

DR. BONE: Thank you. Dr. Sobel.

DR. SOBEL: I think that the second study in which flow in the flow sheet algorithm dictated fairly substantial reductions in insulin was trying for an endpoint which had ignited the original interest. It did achieve its goal in 15 percent of the patients.

Again, we are really -- from a hypothetical standpoint, we are testing insulin sensitization. But I agree that what we know is that glucose is the primary consideration, you know, the level of blood glucose.

So on the one hand, the second study was an important study to be done because it tested what our original interest was.

DR. BONE: I think Dr. Critchlow's point, if I can try to just bring it together here, is that it is extremely difficult to estimate the magnitude of benefit from the second study in terms of glycosylated hemoglobin or other things for which we have

good information about the magnitude of the benefit.

Whereas the first study we have some information, the second study, the design of the study was from the point of view of glycosylated hemoglobin reduction self defeating because the insulin was being reduced in a reciprocal way to the drug effect, so that all of our ability to estimate the ability to enhance control of glycosylated hemoglobin depends essentially on the first trial.

However elegant, meritorious, and informative the second trial may be, it doesn't address that particular question which relates to estimating the magnitude of the benefit.

Would the diabetologists here agree with that?

DR. SHERWIN: Yes. I just have one question. Of the 15 percent that came off insulin in that second study, what was their insulin initial dose? Was it the 30 unit type? Or was it more the typical 75 unit level? Do

you know?

DR. WHITCOMB: My recollection is that it was up in the mid-60s, was the mean for that group that came off of insulin.

DR. BONE: So they weren't dramatically different from the group as a whole.

DR. WHITCOMB: No. And again, as I have said on several occasions, our ability to predict who is going to respond in a dramatic fashion to the compound is difficult to do based on insulin dose.

DR. BONE: So insulin secretory capacity wasn't the issue. It has something to do with this sensitization effect, I guess, being somewhat variable.

Dr. Cara.

DR. CARA: Just to play devil's advocate for a bit, let me ask you, maybe Dr. Fleming, if you had a choice, would you prefer to have a second study that largely confirms the first? Or would you rather have the type

of corroborative, complementary study that was done?

DR. BONE: We did have a choice.

(Laughter)

DR. FLEMING: You obviously did, and you made it.

DR. SHERWIN: Based upon the information they had at the time.

DR. FLEMING: Well, I think what we want is both, quite frankly. And how can you really have both with just two studies? You can't, really, unless you accept that in broad terms the second study corroborates the benefit of the first study -- I mean, the general implications of the first study.

Now, if I believe that first study, that is probably enough for me to make some kind of risk/benefit basis. I wouldn't expect a replay of the study to differ a lot from that. And so I'm considering that I have got a study that tells me what the benefit is in terms of improved glycemic control, though

strictly speaking, biostatistically we have not confirmed it.

DR. BONE: I think one thing here is that we are obviously seeing an element of the program well in advance of the bulk of the program, which we understand is coming any day.

Are there others who wish to comment on our ability to estimate the clinical significance, or to comment on the clinical significance itself?

Dr. Zawadzki, how would you compare this with, let's say, the magnitude -- it seems to me this is about the same magnitude of improvement as we saw in glycosylated hemoglobin levels in the metformin studies.

DR. ZAWADZKI: I think that's true. I think most studies show about the same amount of improvement. I think the important thing that this drug may have is that it may have a separate niche in the way it is metabolized.

I wish we had more data about its effects on renal status in patients. But

metformin is not an option in those situations, and this drug may well be.

DR. BONE: Thank you. Other comments about the clinical significance?

We have one more planned issue, which is the significance of the potential risks. And then after we get into that and before we start addressing the questions for the committee specifically, maybe we want to come back to this question.

Now, it will have had a considerable discussion about what population we would recommend this for because while that is an important question, as Dr. Sobel as mentioned in the charge to the committee, it is implied but not explicitly the subject of one other question. So maybe we should deal with that as sort of question A. Okay?

The next item on our agenda, and we will move along here, is the significance of the potential risks. And there are three we have been asked to comment about, but certainly

the committee I think may appropriately wish to raise other questions about potential risks of treatment with this drug if they are not covered in these three topics.

And the first has to do with cardiovascular risk. Perhaps -- the second is body compartment fluid distribution, and the third is carcinogenicity.

Dr. Illingworth, would you care to comment on the cardiovascular implications here?

DR. ILLINGWORTH: Well, from the lipid point of view and lipoprotein point of view, I think we just need more information. As studies have suggested that lowering triglycerides change reciprocally HDL cholesterol and also change the LDL particle size from a small, dense LDL to a more fluffier LDL, it is unclear which of those is "beneficial." But in some studies, if you allow for triglycerides, the association with the small, dense LDL is lost.