glycemic control, which is really the goal certainly in developing diabetes compounds.

Now, looking at 991-040, this was, as I said, a six month placebo controlled trial. It had an eight week placebo run, and the screening period was back here at week minus nine, minus ten. Patients had their insulin doses stabilized. Both of these studies were insulin requiring Type II diabetics. I didn't make that point earlier, but this is the population.

Their insulin doses were stabilized during this point in time. They were then randomized to one of three treatment groups, treated for six months, and then there is an open label extension going on of this study beyond this which about two-thirds of the patients have chosen to enter.

Now, an important point to make is that the values that were the entrance criteria for this study are those that were obtained at week minus nine, minus ten. The baseline

measurements which are used for determination of change from baseline were the average across this eight week period of time.

The inclusion criteria for 991-040 is obviously that people had to have Type II diabetes as defined by the NDDG. A fasting C-peptide of at least 0.8 was required. This is a very low level, but we felt like the patients should have at least some beta cell function to participate in this study. This in fact turned out to be not a problem at all because the number of people who were excluded on the basis of C-peptide levels was extremely small in this trial.

They had to be on insulin only. They could not be treated with a concomitant oral agent and insulin at the time that they were screened. They had to be on at least 30 units of insulin per day. And as you'll see in a minute, they were actually on very much more insulin than that. And they had to have an elevated glyco-hemoglobin or HbA1c of between 8

and 12 percent at week minus ten or minus nine, that is, their screening values.

You are going to see during the baseline period some of these people did drift down. There were very few of these in which that occurred. But a few did drift down below 8 percent. And glucose also had to be elevated above 140 at week minus 10 or minus 9.

So basically, these were folks that were on the right side, if you will, of the action side of Dr. Olefsky's earlier slide from a glucose and HbA1c standpoint.

This is the characteristics of the patients that were in this trial. There was a fairly good randomization between men and women in terms of gender split. The ethnic breakdown was fairly representative of Type II diabetes in the United States, with around 70 percent Caucasian, 15 to 20 percent African American, 10 to 14 percent Hispanic, and then a few others hidden here in the bottom.

The age of these people was in

general in their mid-50s. We did have a few younger patients, and here there were very few patients that were younger than 40 in this trial, and the means and medians are very close. So the mean values that are here are quite representative of the population as a whole.

These were obese individuals with BMIs that were up in the mid-30s, and weights of approximately 100 kilograms. So these were obese individuals that participated in these studies. Again, we had a few that were on the low end, but this represents a very small minority.

In general, these individuals had diabetes an average of 10 years. Again, a few more short term patients, and obviously some longer term patients that were up around 20 years as well. And they had all been on insulin, or they had been on insulin on an average for approximately five years. There were six patients who had been on for less than

one year. All of those had been on for at least six months.

The total daily insulin dose was high. It was between 71 and 75 on average. We had a few people that were on the low end, and we had some people that were on the very high end, the highest being 280 units of insulin per day. And 25 percent of the patients were on at least 100 units of insulin per day in this population.

Their HbA1cs in spite of these large doses of insulin were not well controlled. The means are between 9.32 and 9.51, so they represent a population that looks fairly similar to the data that Dr. Olefsky showed you earlier this morning. They had elevated fasting glucoses between 214 and 219, again a few on the low end. This is due to that baseline run-in where we had a few people slip their values down below that. And the C-peptides were between 1.6 and 1.7.

Now, this is the disposition of

patients in the study. There was a very high completion rate in this trial of between 88 and 91 percent, so the intention to treat analysis I'm going to be showing you in a few minutes in fact represents people in general who did complete the study, since most of them did.

If you look at the reasons why people withdrew from this trial -- and just starting with adverse events, for an example, there was a 4 percent drop due to AEs in the placebo group, less than 1 percent at 200, and 5 percent at 600, so really no clear pattern here. And the rest of the reasons were scattered amongst various other reasons, including non-compliance, voluntary withdrawal, et cetera. But in general, this study had an extremely high completion rate.

Now, this is the results of the glucose and HbA1c for the study. I just want to start on the top with the fasting serum glucoses. The placebo group had a slight increase across the course of the study, but

really didn't change a whole lot during the 26 weeks. The 200 milligram group had a fall that basically leveled off across through here.

And one thing I want to point out in both of these treatment groups, both the 200 and the 600 milligram dose group here, which is shown in blue, is that you see the glucose falling. Most of the effect is seen within the first four weeks, when you add Rezulin to insulin. So from the clinician's standpoint, this is an important point, that he is going to see --

he or she is going to see what they are looking for in the first month or so of therapy, and then they stay basically flat across there.

The HbA1cs mirror this. There is a nice fall. And I'll show you the mean change from baselines here in just a minute. But the time force is very consistent with the fall in glucose. And they go down here in the 600 milligram group with means that are actually

dropping below 8 percent at 600 milligrams, and getting down to about 8½ percent or so here at 200 milligrams.

When you look at the change from baseline in the placebo group -- let's start with the glucoses here on the right --

there is basically no change. At 200 milligrams, they are down about 35 milligrams per deciliter, and 48 milligrams per deciliter for 600. These are both statistically significant decreases.

In terms of HbA1c, at 200 milligrams there is a fall of .84, and at 600 milligrams there is a fall of 1.41, again these both being highly statistically significant. And we think this group represents a very meaningful clinical reduction in glucose in these patients who were quite refractory to their current therapy at the type of treatment with Rezulin.

DR. BONE: Excuse me. Are those groups, the two treatment groups, significantly different from each other?

DR. WHITCOMB: I don't believe so. No, there is no statistical significant difference between 200 and 600 milligrams based on apparent comparison between those two.

Now, one of the interesting things in this trial is what happened to the insulin doses. And let me just take a step back for a second and tell you what the instructions were that were given to the physicians regarding insulin dose adjustments during the course of this study.

Physicians were instructed to try to hold insulin doses as close to baseline as possible. However, they were instructed if the glucoses were below 100 milligrams per deciliter on two occasions, that they should consider an insulin dose reduction. They could, of course, reduce insulin at any time that they felt was appropriate for safety concerns, or increase it for safety concerns as well.

And what we see in this is that the

placebo group basically stayed rock solid across there, no change at all in the insulin dose of the placebo group. But when you look at the Rezulin group, there is a 15 percent fall here at 200 milligrams and an almost 40 percent reduction in the insulin dose at 600 milligrams. So these people are now getting down to means that are in the mid-40s for their insulin doses.

So the HbA1cs that you saw on the preceding slides occurred in the face of this much less insulin for these patients. And just graphically comparing this, this is a 15 percent reduction at 200 and a 42 percent reduction at 600 milligrams per day compared to placebo, which is 1 percent.

So when you look at the pictures side by side, you see that there was both a significant reduction in glycemic control, which is the very important thing, but also there was a reduction in the insulin requirements for these patients as well.

(Slide)

Now, an important way, we think, of looking at the data is trying to see people who were getting to some target. And for the purposes of this slide I am showing you the 8 percent cut of data. These are people who ended up with an HbA1c that was less than 8 percent. So, remember, on Dr. Olefsky's slide there was -- the action was eight, the goal was seven. We have looked at people that are less than eight basically for the purposes of this slide.

(Slide)

And there are -- the whites are the baseline groups here. So you had, you know, around 9, 10, 14 percent here that were in these groups at baseline. When you look at six months, there is 11 percent in the placebo group. There is 30 percent at 200 and 56 percent at 600. And remember, these people were using less insulin at the end of the study for a number of reasons.

So in terms of summarizing the efficacy data from 991- 040, there were significant decreases at both 200 and 600 milligrams in terms of fasting glucose, HbA1c, and total daily insulin dose. The patients who achieved an HbA1c less than 8 percent are 11 percent in the placebo group, 30 percent at 200, and 57 percent at 600 milligrams.

And just as a matter of speculation, we think that even further reductions of HbA1c may be achievable with less insulin dose reduction. In other words, if the physicians chose to add back the little bit of the insulin that they took away, you might be able to get even more patients down to target in this very, very refractory population. So we think this is very exciting information in terms of the use of Rezulin in these particular patients.

Now, let's move on to look at the companion study. And I want to point out from the outset the design of this trial was very different from that was the 040 study. This

again was a six month placebo controlled study that we designed in discussions with the FDA that had a primary endpoint of combined insulin dose reduction and glycemic control as measured by capillary glucose, the patient's home glucose monitoring.

So for a patient to reach the target level which we set as the response parameter in this study, they had to have both of these occur. And I'll show you in a minute what we meant by these types of reductions. This again was a placebo controlled study. It only had a four week baseline run-in period, three treatment groups, placebo two and four. Again, this has an open label extension beyond the six months, which is going on now.

The inclusion criteria were slightly different. We asked these people to have a higher fasting C-peptide level than in the other trial. This is based upon the information that we had from some of our early pilot work which indicated that people who were

most successful in being able to come completely off of insulin and have good glycemic control had this degree of C- peptide. And so we asked that to be an inclusion criteria for this particular trial.

They had to have an HbA1c that was elevated over 7 percent, a fasting capillary glucose that was 140 milligrams per deciliter baseline. And this was based upon the mean of seven days of fasting readings. So we averaged from the patients' diaries from their home glucose monitors the readings. All of the patients in this trial were given a one touch two monitor. Everybody used the same meter during the course of the study.

They had to be on at least 30 units of insulin per day, but less than 150. And importantly, they had to have had a failure of an adequate trial of sulfonylurea or metformin monotherapy prior to treatment. So that was an inclusion criteria for this study.

We also collected the information on

prior insulin dose and documented that in fact patients had previously been treated with sulfonylureas for this study.

We have gone back and retrospectively gotten that same information for 040, and the same pattern of sulfonylurea prior use and percent of patients on maximal doses is very similar for the two trials. So we think that the two populations were really quite similar. Metformin was just being introduced on the market at the time that 068 was started, just from a chronology standpoint, to put that in perspective.

Now, again, this is the patient population, a reasonable split between men and women. The ethnic breakdown had a slightly higher percentage of Caucasians in the 400 milligram group than it did in the other groups. But again, it had representations from African American and Hispanic patients, again patients that were in their mid-50s, very similar to the 040 population, insulin doses

that were between 75 and 71 units per day.

I want to make an important point here, which is that we did collect injection data, frequency of injection data, in the 068 trial. These patients were on between 2.6 and 2.8 injections per day, so almost three injections per day on these kinds of doses. So it looks like the physicians that were treating these patients were making at least an attempt to try to spread their insulin doses and improve their glucose control.

They had been on insulin for between four and a half and -- or around four and a half years. And again, we had a few people that were on the low end. This represents about 10 or 11 patients that had been on at least six months, but less than one year. And again, the patients had diabetes for around 10 years.

They were once again obese, mean BMIs up in the 35s, waist/hip ratios around one, weights of approximately 100 kilograms, almost

identical to those that we saw in the 991-040 population.

They were again not well controlled, HbA1cs that were between nine and nine and a half as a mean, a few on the low end as well -- this represents only a couple percent of patients that were down here --elevated glucoses between 222 and 230, and higher C-peptides than we had in the other population. But we had a few that obviously snuck in that were on the low end as well.

This trial looks very similar to the other in another way, which is that the disposition -- and that is we again had a very high completion rate, between 87 and 88 percent. And I have to tell you that based upon all of the diabetes trials that we have done with Rezulin, the completion rates in these two trials are the highest that we have ever seen overall. So when you look again at the ITT analyses, this represents people who in general were still in the study at the end.

Now, the adverse events basically are very similar. The withdrawal rates due to AEs, 3 percent placebo, 5 percent 200, 4 percent 400 -- really no differences across there, and they are scattered amongst the other reasons, four withdrawals across the other categories.

Now, this was the primary endpoint of the study. The study was designed to achieve this endpoint, and it was powered to achieve this endpoint, and that was to look at the number of patients who achieved either a decrease in fasting capillary glucose of at least 15 percent compared to baseline, or a fasting capillary glucose of less than 140 -- and this number again is based on the average of seven days prior to their visit -- and at least a 50 percent decrease in total daily insulin dose.

So they had to have both to go into the win column, if you will. We have looked at different parcels of this, and I'll show you that information. But for a patient to be

considered a positive within this study, they had to have both things happen. And I think this again gets to the point that just lowering insulin levels is not what this is about. This is about trying to get glucose control better.

The algorithm that we gave to physicians in this study was different than that that was given in 040 because we were going to try to lower insulin levels a little more aggressively in this trial.

First off, they were obviously double-blind. They looked at the fasting capillary glucose at baseline. And then on the next visit, if the FCG had gone down at least 5 percent, then they were to reduce the total daily insulin dose by 25 percent.

We did not tell them how to do that, whether they were to decrease the number of injections or the spread of the insulin. We left that up to the physician.

If the glucoses had not gone down, then they were to not change the insulin

regimen. And of course, insulin could be increased at any time if clinically necessary within this trial, and it could be decreased if clinically necessary for patient safety.

Now, this is the primary endpoints for this study. This is the number of patients and the percent who achieved this target of the combined glucose and insulin lowering. There were 7 percent in the placebo group, 22 percent at 200, and 27 percent at 400, these two being statistically significant. So the primary endpoint of the study was met, and the trial is considered positive on that basis.

We looked at a number of other parameters, the number of patients -- let me go back up here for one other thing, and this is an important point. The HbA1c decreases within these groups were 0.35 percent in the placebo group, and about a decrease of 1 percent in these two groups here. So not only were their glucoses down by their finger sticks, but their HbA1cs had decreased as well.

If you look at the number of people who were able to stop insulin, it was 15 percent at 400 -- that was statistically significant -- 7 percent at 200, and 1 percent, one patient, on the placebo group basically. The reductions in total daily insulin dose, which was another secondary endpoint, is shown here, 41 percent at 400, 30 percent at 200. These were both statistically significant.

Excuse me, these are units, not percents, 41 units and 30 units. This translates into 58 percent and 41 percent reduction at 400 and 200 milligrams respectively. And when we look at the mean number of injections, the reduction that was seen, it was 0.1 in the placebo group, 0.2 at 200, and 0.8 or almost 1 in the 400 milligram dose group.

Now, there was an interesting bimodal distribution when we looked at how physicians reduced insulin as it were. 55 percent reduced it via decreasing the number of injections.

And when you look at that sub-population, or 55 percent in the 400 group, those patients had an average decrease of two injections per day. So they basically went from three to one. 45 percent just had a reduction in their total daily insulin dose without affecting the number of injections. So it kind of gives you some insight into clinical practice and how people are used to adjusting things.

We also looked at the number of patients who had at least a 50 percent decrease in the mean total daily insulin dose. So these are people that just had the insulin reduction without necessarily a glucose control improvement of the magnitude that hit the target, 70 percent at 400, 51 percent at 200, and 19 percent of placebo group, these two being statistically significant.

We also looked at what we think is another very clinical meaningful cut of the data, which is the number of people who got their capillary glucose is under 160 and had at

least a 40 percent reduction in total daily insulin dose, and that was 40 percent at 400 compared to 16 percent in the placebo group, this being statistically significant.

So in terms of summarizing the primary data from this study, there was a significant number of patients who reached the primary endpoint at both 200 and 400 milligrams per day, and the study is positive from that standpoint.

Now, I want to take a moment here and discuss the dose recommendations that we are coming forward with for Rezulin based upon this information.

DR. BONE: Excuse me. Could I just ask one question?

DR. WHITCOMB: Absolutely.

DR. BONE: Just before you get into this, because I think it is relevant. Were the apparent differences between 200 and 400 milligrams in the last study different -- were those significantly different from each other,

the same question I asked about the previous study.

DR. WHITCOMB: Yeah. Let me -- no.

DR. BONE: They weren't? Thank you.

DR. WHITCOMB: I mean, there clearly is a dose response in some of these parameters, but it is not -- there was not a statistically significant decrease, as it were. The study was not powered to necessarily separate the doses.

Now, while I have not yet reviewed the safety data, which is where we are heading here in just a couple of minutes, there are no dose limiting side effects which are important dose recommendations. Therefore, dose recommendations are based upon the efficacy data that I have just shown you.

The recommended starting dose for troglitazone is 200 or 400 milligrams per day. Since the majority of glucose lowering that we see as demonstrated in the 040 study is seen within the first four weeks, we are

recommending that the doses be increased by 200 milligrams at four week intervals. And the maximum recommended dose based on the current data in this population is 600 milligrams per day.

And again this afternoon I think we are going to have more time to discuss the dose issues, is my understanding.

(Slide)

Okay. Now, since I forgot to put that slide up -- that's helpful.

Now, an issue which came up this morning and which is a very important clinical issue within this drug class is what happens to weights of patients. And every time I make a presentation on Rezulin, this is, if not the first question, in the top three certainly that comes up.

These are the weight changes which were seen in the two clinical trials that we have just reviewed. 991-040 had an increase of approximately 1 kilogram in the placebo group,

3 in the 200, and 3½ in the 600 milligram group.

Now, there is a very important point to make about the diet instructions which were given to patients in 040. Because of our concern that we wanted to ensure that any improvement in glycemic control that we saw was due to the drug and not to a weight loss, the patients were specifically instructed in a weight maintenance, non-weight losing diet for the course of this study. So if the patients were seen and their weights were coming down, they were encouraged to try to put some weight back on.

So I think that clouds this a little bit in terms of looking at this information. And when you look at 068, which was again in a very similar patient population, you see that the placebos went down about a kilogram. There is no change at all at 200. And so if you compare these two, they are obviously quite different. And at 400 milligrams, they went up

.6 kilograms. So there is really no significant changes in weights across the 911-068 study.

Now, we have gone and looked at the total population of patients that we have studied in North America at this point in time to try to address this further.

This is the weight change from baseline, which is seen in the composite database that we have at this point in time for Rezulin. When you look at the placebo group, there is a mean change of 1 kilogram with the standard deviation of three. There is a weight increase in the Rezulin group of .75 kilograms with a standard deviation of four. And the 76 Glyburide patients had 0.5.

And I haven't reviewed this for you yet, but there are about 30 or 40 patients in this group that have been on high dose 800 milligram therapy for two years. And I'll come back to that in just a few minutes.

So these are the weight changes that

we have seen. We have looked at the different doses to see if there is any dose effect in the total population. Again, the placebos are down to about a kilogram. At 200 milligrams, there is really no change, 0.3 gain, 0.5 loss at 400 milligrams, 1 kilogram gain at 600, and a .3 loss at 800. And again, this represents some of the long term patients in the clinical trials.

Based upon the data that we have here, we are not seeing weight gain as something which is occurring frequently in the studies. When we look at the overall database, there is no weight change which has been observed.

When we look at the two studies together and the insulin requiring Type II patients, in the 040 study there is a small amount of weight gain which was seen in all groups, including the placebo group. And in the 068 companion study in very similar patients, there is no weight gain that was seen

in that particular group.

Now, obviously, when you are introducing a new class of drug into a market which has got a lot of patients in it, you have a lot of concerns about what does the safety data look like. And so I want to spend some time in detail going through the human safety data that we have accumulated on Rezulin, as this is obviously a very important thing to consider.

(Slide)

Now, this is a subset if you will of the first slide that you showed that was difficult to read. And basically, what it outlines is the overview of the source and the number of participants which were included in the application. This application had a safety cutoff of last April in terms of composite data that was available at that time. And as I said a few minutes ago, that included about 1,261 patients from North America. And I will be coming back to these 1,261 patients more in a

minute because that is the integrated data that we'll be looking at from a side effect profile.

We also have all of the safety data from 629 patients from Europe that are in the Glaxo-Wellcome trials. And we have another 1,000 patients from Japan, including 200 that have been treated for one year, that we have all of the safety data available from that.

Now, this 3,121 number was as of last April with the composite safety that was available. To date there are roughly 6,000 patients that have been treated with Rezulin. And I will show you in a minute of how that safety data is rolling in.

So this is the number which is in the application. But if you look at real-world numbers, if you will, of patients, it is around 6,000. We have access to all of the serious adverse event and death data from both the Glaxo-Wellcome studies and from the studies in Japan, and have compared them very closely with the information that we are accumulating in

North America to make sure that there are no differences.

What I can tell you is that there has been very few differences that have been seen in any of the safety data between the three companies to this point in time. I will try to point out some small differences as I go through the rest of the presentation here.

Now, a very important piece of information is not just the number but how long have they been treated. And this is a cut of the information that is in the application that you have in front of you. And as you can see, it includes about 281 patients that have been treated for at least six months, and 46 that have been treated for at least a year. And in fact, most of these people are close to two years. They were just right under the two year cut, so they didn't make it onto a separate line.

This comes out to approximately 22,000 total patient weeks if you add this all

up, or about 400 patient years. I want to make a very important point. The safety update that we will be providing shortly to the FDA includes a much larger number of patients which much larger exposures.

This is the information that we'll be providing in the safety update. It increases the number of people who have been treated for at least six months to 1,100, the number of people that have been treated for at least a year to 547, and the number of people that have been treated for at least 18 months to 30. And this is a very important group here, the number of one year patients that we'll be submitting shortly.

I can tell you that our preliminary look at that information looks very, very similar to the safety data that I'll be reviewing for you today. But again, the agency will have the opportunity to review all of this data in the safety update shortly.

Now, I want to focus back on the

1,261 patients where we have fully integrated all of the safety data from the clinical trials to this point in time that we are reviewing here today. There are 400 patients in there that are insulin requiring Type IIs that received Rezulin, 189 placebo, 765 that have received Rezulin without insulin compared to 175 placebo patients. Most of these are from a large phase II study that was 12 weeks in duration.

The 77 Glyburide patients out here are all from our long term cardiac safety study that I'll be making reference to in just a few minutes. The IGT patients are around 70, and the PCOS patients are approximately 25. I didn't make this point earlier, but none of the -- when I gave the number about 6,000 patients, I did not include any of the patients who will be enrolling in the diabetes prevention trial in that number. So that's obviously going to continue to go up as well, but I did not include those, just in terms of your mental

math.

Now, this is the breakout of adverse events by age. The placebo group -- this is the less than 65 crowd. This here is about 80 percent. The Rezulin crowd less than 65 is just a little over 75 percent, really quite comparable. When we look at older subjects that are over 65, again actually it is interesting. They have a lower incidence in AEs in both of these than the younger patients, but again very comparable numbers here. And the Glyburide numbers tend to be a little bit higher.

(Slide)

Now, this is an important slide because basically what it tells us is what I mentioned a few minutes ago when we were talking about dose recommendations. And when we look at the total AE profile for the drug, there does not appear to be any increased incidence of adverse events across these doses that we have looked at, and they are all

basically around 80 percent, including the placebo group, very consistent with other diabetes studies that we have done.

This is the number of -- or the adverse events which occurred in at least 5 percent of Rezulin treated patients. The placebo group is on the left, the Rezulin group is on the right. These are expressed as percent. We could have shown the one and three percent tables as well. It would have taken up a lot more slides. The pattern is really very similar, which is that there is very minimal, if any, difference in the adverse event profile of the agent compared to placebo.

I want to point out one very important thing, and that is that if you look at the incidence of peripheral edema, which has been an issue which has been raised on the basis of some of the fluid questions earlier this morning, we're not seeing that in the trials that we have done so far in North America. They are 6 percent in the placebo

group, and there is 5 percent in the Rezulin group in terms of peripheral edema, and really not a lot of other differences in the adverse event rates between these two populations.

Now, an important consideration when you are using insulin, and Dr. Olefsky mentioned this this morning, is hypoglycemia. And so when you add an agent which improves insulin sensitivity, looking at hypoglycemia is really important. And so we have done that in these two insulin taking trials.

One thing I should point out is that in the monotherapy studies that we have done with Rezulin to date, we have not seen one instance of hypoglycemia with the drug given as monotherapy. One would expect that based upon the mechanism of action you just don't see it. But obviously, when you add it to insulin, it is going to be a possibility.

For the purposes of data analysis definitions, we agreed with the FDA to define anything as true hypoglycemia as a glucose less

than 50. And I'll show you how we have done that analysis in just a minute here.

These are the two studies shown side by side, 991-040, which was the more fixed dose insulin study, if you will, and 068, which was the more variable dose insulin study, if you will. And if you look at the percent of any report -- this is any report by the patient of any neural glycopenic symptoms of hypoglycemia, it is 34 percent at placebo, 41 percent at 200, and 61 percent at 600.

When you look at these events which occurred with a glucose of less than 50, the numbers drop quite a bit, as you would imagine, 8 percent in the placebo group, 14 percent here, and 23 percent here. But importantly, if you look at the number of patients who met the DCCT criteria for a severe hypoglycemic reaction, i.e., one which required third party intervention, there is only one example of that. That was in one patient who had 600 milligrams who was taken to an urgent care

center, given intravenous glucose, and returned home without any other sequelae.

Now, remember that in this group, the investigators were specifically instructed not to reduce insulin unless the glucoses were consistently below 100. In the 068 trial, they were reducing them if they got -- as they were going down in their glucose as well as if they were getting below 140.

And so the incidence of hypoglycemia is much lower in this trial, 8 percent for placebo, 19 percent at 200, 14 percent at 400. When you look at those that actually had a low glucose, true hypoglycemia, there is no difference across these groups, 4, 8, and 5 percent. And there were no episodes of DCCT defined serious hypoglycemia.

So an important consideration -- or what instructions do we propose to give physicians about the use of this agent in combination with insulin in terms of insulin dose reduction?

From looking at these two together, what we are recommending is something in the middle, which is that when glucoses are consistently getting below 120 that the physician should consider an insulin dose reduction of 10 to 25 percent. We think that this makes medical sense, makes safety sense, and should still be able to achieve the type of glucose control that we would optimally like to see in these patients.

Now, another thing that we have looked at is to look and see if there was any ecoltypal (phonetic) glycemia that happened, glycemia unawareness, if you will. This is based upon looking at all of the capillary blood glucose readings from the 040 study, the fixed dose study. There is about 30 some thousand of these in each of the treatment groups.

The incidence of the number of readings that were actually below 50 is very, very low, .21, .26, and .53 percent. So there

are very, very low incidents of these things happening. If you look at the first morning numbers, they are even lower, .14, .09, and .41. So there does not appear to be a significant amount of hypoglycemia unawareness that we are seeing when Rezulin is added to these patients.

Now, a critical piece of information to look at is the number of serious non-fatal adverse events that you see in any drug development program. For the purposes of this NDA, we had two six month placebo controlled studies, or two six month studies which we are completing at the time of the NDA. We did a rapid assessment and assembling of these serious adverse events and death information from those trials and included them in the application for purposes of summarization.

This brings the number of serious adverse event denominator patients to 1,877 from that 1,261 number that we had before. So we added in approximately 620 patients or so.

This also boosted the placebo group as well.

When you look at the incidence of serious, non-fatal AEs, it is 6 percent in the placebo group and 7 percent in the Rezulin group, so they are nearly identical. When you look at what has been seen in Europe by the Glaxo-Wellcome studies to day, the incidences are almost identical and the patterns very similar. The incidence of serious adverse events in the Japanese studies is approximately 1 percent, so it is lower than what has been seen in either North America or in Europe.

Now, what are these serious adverse events that we are looking at? What is the distribution of these?

These are those events which occurred in greater than or equal to three patients, not 3 percent but three patients. The percentages are shown in parentheses here. And when you look down here, on a percentage basis, you really don't see any difference.

I want to focus in on a couple of key

things, and that is congestive heart failure, because of the questions that have been raised from a cardiac standpoint. We have one patient here in the placebo and three in the Rezulin group. There are three times as many people here, so on a percentage basis, they are really, you know, identical. There is just no clear difference.

Myocardial infarction is very, very similar on a percentage basis between these two. We are not seeing that in the safety data, that there is a significant cardiac risk, remembering that we have a small number of patients who have been out to two years at this point in time.

This is the listing of deaths which have occurred. We have had three of them in the North American studies, one in Europe, and one in Japan. The one in Europe occurred in a Rezulin treated patient who had a stroke. The one in Japan was in a placebo patient who had a myocardial infarction.

In North America we had one stroke in a Rezulin treated patient. This was felt to be unlikely attributable from the investigator. We have had one myelodysplastic syndrome that was felt had insufficient information to assign causality. And we have had one myocardial infarction in a Glyburide treated patient, which was definitely felt not to be due to the drug. So there is no clear pattern that shows up in terms of looking at the overall deaths.

Now, there are several other safety things that we have looked very specifically at based upon the animal data. The first is that in the animal studies a slight decrease in hemoglobin and hematocrit has been seen in animals treated with Rezulin. So we have looked in very much detail with this in the human trials as well.

And what we see -- and this is the combined data from the 040 and the 068, so the insulin requiring patients that we looked at earlier, we see a fall of approximately 0.4 to

0.5 grams per deciliter of hemoglobin within the first four to six weeks, which then levels off and doesn't go down.

We have looked at our data out two years, and this pattern is absolutely rock solid across two years. It goes down by this small amount, and then just continues out. The placebo group goes down a little bit. This is a pooled analysis of all of the patients. There is some dose dependency of this ranging between 0.3 grams at 200 up to 0.6 grams at 600. But the pattern appears to be the same in terms of the time course for the fall.

The number of patients who actually become frankly anemic on Rezulin is the same for placebo as it is for actively treated patients. There was no difference in the number of people who were actually becoming anemic during the course of the studies. Just to look further at this, this obviously raises some questions. Is there some kind of red cell thing that is going on that we need to know

about?

So a study was carried out by Glaxo-Wellcome which enrolled 24 patients for six weeks based upon the time course that we have seen. That seemed like a reasonable point to look at these parameters. We looked at the erythrocyte synthesis parameters, and we looked at erythrocyte destruction parameters. In other words, was there a problem either making or breaking red cells. We also looked at plasma volume and hemacolt (phonetic) to see whether this was a GI blood loss that was occurring.

We looked to normal volunteers instead of diabetics because we wanted to really understand if this was happening independent of what was going on with glucose because glucose shift obviously can cause huge changes in hemoglobin and hematocrits in diabetic patients, depending upon their degree of control.

Well, these are the conclusions from

the data from this study. The small reversible decreases in volume based RBC parameters that we have seen in patients occurred as well here. There was a slight decrease in hemoglobin and hematocrit. The formal studies that we carried out showed no demonstrable effect on RBC production. There was no impact on RBC synthesis in this study, and there was no effect on RBC destruction. So there was not accelerated RBC destruction. Both synthesis and destruction did not occur.

A small 5 to 7 percent increase in plasma volume was observed. And I should point out that what happened in this is the placebo group went down by about 2½ percent to 3 percent, and the treatment groups went up by 2½ to 3 percent. So this is compared to placebo in this particular trial.

Now, as we wind down here, we have also looked carefully at liver function tests in these patients based upon the fact that some hepatocellular hypertrophy was seen in some of

the animal studies. This is looking at AST and ALT levels, people that were anywhere above normal, two times or three times normal.

When you look at the just above upper limits of normal, there are actually more placebo patients than Rezulin treated patients. Two times are basically identical, 2 percent. And when you look on a percentage basis above three times normal, they are very similar on a percentage basis.

But I do want to comment upon these 14 patients that are over here. Seven of these patients were treated through without even knowing that their liver enzymes had gone up, and they went back down again. The other seven did have the drug discontinued with reversibility of the liver function test elevations after the drug was discontinued. We have had one patient who has what looks like was an idiosyncratic reaction to the drug and did develop jaundice, which was reversible with discontinuation of the drug as well.

Now, the final piece of data that I want to show you is from our cardiac safety study. This was a study which was begun about two and a half years ago. The one year data from this trial is in press currently at Diabetes and was presented actually at the ADA as an abstract about 15 months ago.

This was originally a one year study which we extended out to 96 weeks. And what we did was to look at detailed echocardiographic parameters of two populations of patients, one treated with 800 milligrams of Rezulin, and one treated with titrated Glyburide. These were non-insulin-taking Type II patients that entered the study. They had two echocardiograms done at baseline for a baseline measurement, and then they were looked at across the period of time out to 96 weeks.

77 patients were randomized to each of these two groups, and we had dropout rates throughout this to where we had around 45 to 50 patients at a year and less than that out here,

ranging between about a third of the patients in the Rezulin group and about half of the patients in the Glyburide group actually made it all the way out to two years of time. This is the left ventricular mass index measurements of these patients. This is their baseline measurements. This is at week 48, and this is at week 96.

Now, let me just take a minute here and tell you exactly how we did this. Basically, the echocardiograms were done at a number of sites around the United States. They were sent blinded and in a scrambled fashion to a central blinded reading center, who happens to be Dr. Julio Perez from Wash U in St. Louis. He read the data, and the data was then sent back to Parke Davis, where it was integrated with the random code at that point in time. So he was completely independent of what was going on with what the measurements were on the echos.

But what you clearly see here is no

increase in LV mass across 96 weeks with the drug given at a dose of 800 milligrams per day. Glyburide basically is unchanged as well. This measurement has an error rate of between 5 and 10 percent, so you would need to have greater than that really for this to be of any significance at all, and we really didn't even come close to that. And in fact, there is actually a slight decrease in both of the groups in the LV mass.

We also looked at LV function as measured by the cardiac index. In this case, we looked at a number of other parameters which I am not going to show you for sake of time. Basically, what happened is we saw a slight improvement in cardiac index in these patients with Rezulin. It's small and probably not clinically significant, but it certainly did not go down. The Glyburide group basically is unchanged across through here.

So in terms of thinking a little bit more about the cardiovascular aspects of

Rezulin from a hemodynamic and LV mass standpoint, we did not see any evidence of cardiac dysfunction after two years at 800 milligrams per day in terms of either LV mass or cardiac index.

We have not seen evidence based upon our composite safety database of an increased incidence of edema or congestive heart failure in the patients that we have studied to this point in time. We have not seen any overall increase in weight of these patients, as you might expect if they were undergoing chronic fluid expansion. And in fact, I should point out in the normal volunteer study that was done over six weeks, where we did see volume expansion, the weights did not change in those patients.

The decreases in hematologic parameters that we have seen suggest that if plasma volume occurs, it occurs very early during the course of treatment with the drug, and then it stabilizes. And there is no

suggestion that this early increase in plasma volume is associated with cardiac symptoms or dysfunction based upon the human data that we have analyzed to date.

So in terms of summarizing the safety profile of the medication -- the drug, I should say -- the adverse events were comparable to placebo. Insulin dose adjustments that we have recommended may be required to prevent hypoglycemia. We don't think this is a significant safety problem, but one which will need to be communicated clearly to physicians and patients.

There is a small decrease in hemoglobin which occurs within the normal range. It appears to stabilize after about six weeks. It does not happen in all patients, but it certainly is something worth noting.

There are transient, reversible increases in liver function tests which are seen in approximately 1 percent of patients. This incidence is comparable to placebo. And

there is no evidence of LV mass increase after two years at high doses of Rezulin, specifically at 1800 milligrams per day.

That should be the last slide in your book, I hope.

DR. BONE: Members of the committee with questions -- I think Dr. Cara and Dr. Zawadzki. Okay, well, several -- everybody has got a question. Okay. Dr. Cara will have the first question.

DR. CARA: Other than the C-peptide concentration, did you look at any other predictors of response or any other predictors of failure to a response?

DR. WHITCOMB: Yeah. That's a very good question. When you add Rezulin to insulin, over 90 percent of the patients have a fall in glucose. That drop that you see within the first month basically happens in almost everybody that you start the drug on when you add it to insulin.

I think that a secondary question is

who has the optimal response to the drug. And I can tell you, we have cut the data every way that we can possibly think of, and there aren't any real good predictors of that. We have people with dramatic responses that had glycohemoglobins up as high as 12½ that went down to 6 on 200 milligrams per day.

You know, the patients were all obese, they were all on high doses of insulin. The people that were on high doses of insulin responded as well as those that were on low doses of insulin.

So we have looked a lot at it because obviously that is a very important question. But in terms of the initial response, the point I want to make is that 90 percent of the people's glucoses in both of the studies go down.

DR. CARA: A couple of follow-up questions. Have you done any dose escalation studies in patients that have not responded favorably?

DR. WHITCOMB: That's a very good question. What we have done is when we went into the open label phase of 068, the patients that had not responded appropriately at 200 were given the opportunity to escalate to 400. I don't have that data summarized yet, but our impression from looking at it is that it does -- you do get an increased response in those patients who didn't respond to two when you go to four.

DR. CARA: How much did you escalate?

DR. WHITCOMB: We went from 200 to 400 milligrams in those patients.

DR. CARA: To 400.

DR. WHITCOMB: Yes.

DR. CARA: Okay. That was the highest dose.

DR. WHITCOMB: In the 068 study, 400 milligrams was the top dose. So that is what they escalated to in the open label phase. What we have done also in -- just to kind of wrap this open label question. The patients

who were on placebo in the 040 study went to 400 milligrams. That was the dose that we chose to put them on. We did not allow them to dose escalate in that particular trial.

DR. CARA: And the last question. When you talk about failure of therapy in your protocol inclusion data, patients that failed to respond to sulfonylurea or metformin therapy, what does that mean?

DR. WHITCOMB: Yeah. That's -- I mean, I think part of what we are going to discuss this afternoon. I can tell you what the data that we collected shows.

What we found was that we were able to get records. Obviously, these people had been on insulin for almost five years, so getting all of their back records was a major challenge. We were able to get data on about 80 percent of the patients, that we could actually get the charts and look at them clearly.

And when you look through that

information, what you see is about 60 percent of the patients had been on clearly maximal doses of sulfonylurea sometime in the past. And all the rest had really been on at least half maximal doses of sulfonylurea some time in the past.

But the entrance criteria basically that we gave the investigator for the entrance into 068 was that they have an understanding based upon the patient's history or other information that they had in fact previously failed an adequate trial of sulfonylurea based upon either maxing out on dose or dose limiting side effects.

DR. CARA: And regarding metformin?

DR. WHITCOMB: Metformin had just been on the market for about a month at the time, so we put metformin in there but we knew there were going to be very few people.

DR. CARA: So it's really not --

DR. WHITCOMB: And for 040 -- excuse me, yes. But for 040 it was -- metformin in

fact was introduced after that trial initiated.

DR. CARA: Right. But it wasn't in fact treatment failure, if you will.

DR. WHITCOMB: No. People did not -- in other words, people did not -- to get on insulin in this trial, people did not have to have had a prior history of failure of both agents, for example, because they weren't there at the time.

DR. CARA: Well, that's misleading.

DR. BONE: Dr. Zawadzki had the next question.

DR. ZAWADZKI: I have a few questions. For the trials 040 and 068, were they double blind?

DR. WHITCOMB: Yes.

DR. ZAWADZKI: And what was the frequency of visits?

DR. WHITCOMB: In both of the studies, they were seen at two week intervals for the first four -- or first eight weeks, and then monthly after that.

DR. ZAWADZKI: You mentioned that they were weight maintenance in the first trial. What was the diet in the second trial?

DR. WHITCOMB: The diet that they were given was a standard diabetic diet trying to -- for these people, 12 to 1800 calorie ADA diet that they were instructed to try to maintain. And I want to say that we did not aggressively try to adjust diets during the course of the 068 trial. It was really more of what they were on kind of diet. But we did try to instruct them in an appropriate diabetic diet.

DR. ZAWADZKI: Did any of the individuals who were tested in these two trials have any evidence of renal impairment, either by serum creatinine or 24 hour urine collections?

DR. WHITCOMB: We had an exclusion criteria above 2 and 2.5 creatinine, so patients were excluded if they were above that. We did not do it in this trial. In another

trial we have going on we're actually looking at protein micro albumin issues to see whether or not there is a change in that.

But that was not -- we did not include any patients who, you know, had frank creatinuria. They were all, you know, urine dipstick at the front end, looked at their creatinines. If they were under 2 to 2.5, then they were included in the trials.

DR. BONE: I think it was Dr. Fleming who had a comment or question, then Dr. Critchlow.

DR. FLEMING: Just for clarification, on the EN in the 96th week cardiac monitoring study, echo monitoring study, there was a switch in the preparation that was actually --

DR. WHITCOMB: That is correct.

DR. FLEMING: -- that was actually used. This is not a big deal, but as I understand it, the first year involved exposure to the equivalent of 580 milligrams to be marketed formulation. You did switch at one

year.

DR. WHITCOMB: At one year, with the new bio -- more bio available formulation to year two, which was more in the mid- 700 range for a dose. Part of it depends on which formulation exactly we were making reference to. But as a general rule, it was in the mid-700 range for between year one and year two is what the patients received.

DR. FLEMING: Just quickly, are there other studies where the nominal dose that you mentioned does not correspond to the equivalent dose?

DR. WHITCOMB: No. All of the phase III studies were conducted with market image drug that has all got the same bio availability.

DR. BONE: Thank you.

Dr. Critchlow and then Dr. Sherwin.

DR. CRITCHLOW: Yes.

Could you please comment on the fact that the glycohemoglobins in 040 decreased in

the face of somewhat moderate reductions in insulin dose, whereas in 068 there did not appear to be a decrease in glycohemoglobin with rather substantial decreases in insulin dose?

DR. WHITCOMB: Well, I think that first off the two study designs were very different. In the 040 trial we were specifically trying to drive the glycohemoglobins down as much as possible. And in the 068 trial we were trying to see what percentage of patients could achieve a balance, if you will, of what was at least a 50 percent reduction in insulin and some improvement in capillary blood glucose.

As it turns out in the 040 study, for example, in the patients who did meet these criteria, their HbA1cs went down about 1 percent. When you look at the total population, however, there were patients who had insulin dose reductions that were perhaps more aggressive than they should have been if they were optimally trying to get the glucose

control down. That's why you really have to look at the two side by side.

There actually was in the 400 milligram group a decrease of HbA1c compared to placebo at the end of the study. It didn't quite meet statistical significance, but it was down. But it wasn't down certainly to the degree that it was in the 068 trial or the 040 trial because the insulin doses were much more aggressively lowered.

One thing that I think that it really points out when you look at these two trials side by side is that the use of Rezulin in combination with insulin is going to put a new paradigm in the field, as it were, about trying to balance agents to optimize glucose control. And I think that is really important point to get across is that for the first time we are going to have potentially another agent which will -- or an agent which will allow us to balance that off and allow the physicians to be able to make those kinds of judgment calls with

their patients.

And I hope that that is what the data will continue to support.

DR. BONE: Dr. Sherwin.

DR. SHERWIN: A couple of comments. One, you made a point, the comment about patients being able to stop. And there was a small number, but a statistically higher number of people able to stop insulin. What was the criteria for stopping?

DR. WHITCOMB: For discontinuation?

DR. SHERWIN: Yes.

DR. WHITCOMB: It was basically the same ratchet down algorithm.

DR. SHERWIN: So if their fasting was below 140, they would -- and they sustained that effect once they stopped the insulin?

DR. WHITCOMB: Yes. I mean, that was up to the physician, obviously. If he saw their glucoses going back up, the assumption was that they would, you know, reinstitute insulin. And in fact, that did happen in

patients. Those numbers actually were a little bit lower then came back up.

It's an interesting phenomenon that has been seen in the open label portion of the study, is there are a few patients that were on 200 that when they were titrated up to 400 were actually able to discontinue insulin with improvement in glycemic control as well.

DR. SHERWIN: You commented, and you focused on how many people responded. You didn't talk to us about the negatives and non-responders. And did anybody get worse? In other words, were there people --

DR. WHITCOMB: In terms of people --

DR. SHERWIN: That you were dropping insulin dose, particularly in the 068 study.

DR. WHITCOMB: There were some people whose glucoses did go back up if the insulin levels were too aggressively lowered.

DR. SHERWIN: So there is that potential price.

DR. WHITCOMB: Yes.

DR. SHERWIN: If you are not careful and you are going --

DR. WHITCOMB: Absolutely.

DR. SHERWIN: -- the diabetes worse because that's sort of one of the issues I think that we need to address in terms of further studies, and namely that the improvement is to a level that is still not very acceptable in terms of care, even though it is an improvement, namely that the mean glycohemoglobin is in the eight range.

Now, my question is, how many actually achieved a below seven, which would be the goal of treatment.

DR. WHITCOMB: Yes. At 600 milligrams, 25 percent of people were less than seven.

DR. SHERWIN: Now, in that subgroup of people, was there any difference in terms of hypoglycemic risk within that subgroup?

DR. WHITCOMB: No. Well, I shouldn't -- the percentage of people that had glucoses

less than 50, which the analysis that I showed you did show a dose differential between 600 and 200, that held true as well for people that were in the less than seven ultimate HbA1c crowd.

Am I getting at your -- so it would be lower than it was for a 200 milligram patient that got less than seven, for example.

DR. SHERWIN: Well, now I'm little confused. But I assume it was a slight increase perhaps in --

DR. WHITCOMB: Correct.

DR. SHERWIN: -- hypoglycemic events because I think that one has to be a little bit cautious in terms of the hypoglycemic, which we don't know -- our goal is to optimize care, and we don't know yet whether when you really optimize -- you know, you intensively treat to the point where we reach goals what kinds of problems one might encounter in terms of how it -- and even counter-regulatory defects that might be uncovered.

DR. WHITCOMB: I think the one thing that is important to note is that almost all of the hypoglycemia that was seen occurs in the first six to eight weeks. You rarely see it after that once the drug is instituted. So if you look at the time course of when those things occur, it isn't like someone is going to go along and then four or five months out suddenly have this start happening, that it appears to be an early phenomenon.

DR. SHERWIN: You made a comment that over the course of the phase-in trial, a period of about eight weeks or so, that there was a decline in glucose and glycohemoglobin --

DR. WHITCOMB: A slight shift down.

DR. SHERWIN: -- which is what we see in all of the diabetes related Type II studies. If one focused upon the time zero point, was -- because I don't have a good sense of the drop over that time.

DR. WHITCOMB: Yes.

DR. SHERWIN: What was the magnitude

then of the change in glycosylated hemoglobin?

DR. WHITCOMB: I might just wave at my colleagues from Sankyo US for a minute. I believe it was a 0.1 percent drop in HbA1c across the baseline as a mean. Yeah.

DR. SHERWIN: So it was really a negligible --

DR. WHITCOMB: Yes, yes. It was very small.

DR. BONE: Dr. Colley.

DR. COLLEY: One of the risks of insulin therapy is weight gain in patients. And although you had reductions in insulin dosage, there was no appreciable change in weight. Did you look at the subgroup of patients who were able to stop insulin, and was there any change in weight in that group?

DR. WHITCOMB: That's a good question. It's really variable. We have people who have lost 25 pounds, you know, by stopping insulin or by reducing their doses. We've had people who have gained weight in the

face of insulin going down, which is why the mean data looks, you know, fairly flat.

In this specific subgroup of people who are able to discontinue insulin completely, in general their weights do go down. In the open label pilot study that we did that kind of started all of this a couple of years ago in which five of those patients are now still off of insulin, the average weight loss in that group is about 3½ kilograms. They're about 18 months out now.

DR. SHERWIN: I forgot my question about weight. Although there was not a statistical increase in weight, it appeared to me that there was an increase that probably didn't make -- reach statistical significance. Is that right? Because my recollection was about 1½ kilos difference.

DR. WHITCOMB: From the placebo group, yes. Yeah. I mean, it's an increase of about actually 2½ kilograms.

DR. SHERWIN: Right. And these -- I

mean --

DR. WHITCOMB: About 2½ percent weight change for these people.

DR. SHERWIN: And that's over -- totally over a six-month period, right?

DR. WHITCOMB: Correct. And one of the things I might point out is that in the open label phase of this study, patients -- the weight maintenance diet was abandoned, if you will, and so the follow-up data should be quite interesting to see if these people's weights go back down again once they are told not to try to keep their weight up.

DR. SHERWIN: In your trials without insulin -- because these are people on insulin and have a tendency perhaps to gain weight anyhow, and then you are superimposing perhaps a small increase. What about people who are not on insulin? You must have experience with weight --

DR. WHITCOMB: Yes.

DR. SHERWIN: -- in those

individuals.

DR. WHITCOMB: Well, Rezulin as monotherapy does not cause weight gain in any of the studies that we have done, including this two year cardiac study. When you look at the weights of those patients baseline compared to the end, there is no significant change. So that does not appear to be something which we're seeing as monotherapy, if you will.

DR. SHERWIN: The effect on plasma volume, by the way, do you have a thought about mechanisms?

DR. WHITCOMB: I can give you what we think is one -- there are a couple of hypotheses, I think, one of which we are actually about to start a study to try to investigate. It is possible that the improvement of insulin sensitivity at the level of the kidney may be causing some slight retention of salt and water which we are going to investigate shortly to try to look at that.

The other thing, of course, is that

when you are improving glycemic control, and people -- the fluid shift question is really a very difficult one to address. Now, there is no question that in the normal volunteer study that I showed you, obviously that was not a glucose shift paradigm.

So it -- we think that this is probably a real pharmacologic effect. But the magnitude of it appears to be small. And it certainly appears to stabilize. It isn't like it just keeps continuing on. And it looks like it is a fluid shift, if you will, since the patients -- the normal volunteers didn't gain weight. You are basically moving, you know, water from one compartment into another rather than increasing the total volume of water. We don't see edema. We don't see heart failure.

DR. BONE: Dr. Hirsch and then Dr. Illingworth and then Dr. Cara.

DR. HIRSCH: The fluid shift is very interesting, whatever its mechanism. But it also is a real confound in terms of the weight

situation because what you are interested in with weight is the amount of fat people have, not, you know, what the scale says. And without a compositional study, it is very difficult to know how much change there was in extra cellular fluid volume.

That being case, even small changes in body weight in these individuals can create rather marked improvement of the diabetes. And all of us who treat these people note that a 10 or 15 pound change often makes startling changes in the insulin sensitivity.

So the next question -- well, the first thing is a suggestion that we learn more about the body composition.

DR. WHITCOMB: Can I respond to that first?

I think that is a very good point. A very simplistic bio impedance study was done by Glaxo-Wellcome which did not show any change. But a much more detailed study with MRI scanning and body composition and fat biopsies

and so forth is going on right now to try to further address this issue.

DR. HIRSCH: That's good. The other point that I'd like to make is that the study statistically of the subgroups is very important. That is, the mean weight is very -- given the fact that relatively small changes in weight can create great changes in insulin sensitivity over brief periods of time, it will be very important.

You may -- you obviously have the data and may have already done this, looking at all the corelational possibilities, et cetera, in terms of weight changes during the study and who went what way in these directions.

DR. WHITCOMB: It's an excellent question, and we have tried to do that. But the problem is that it doesn't look like it correlates very well, at least in these patients, because obviously we saw the improvements in glycohemoglobins that we saw in 040 in the face of the fact that people as a

total group were gaining some weight. And obviously, that total group is made up of individual patients in subsets. So when we look at the subsets, there is no clear delineators of that.

But, I mean, it is an excellent question and one biologically which I agree with you is a little bit puzzling at this point. But the body composition studies are critical.

DR. BONE: Okay. Thank you. Dr. Illingworth and Dr. Cara, and we'll wrap up this discussion.

DR. ILLINGWORTH: The studies you conducted where you looked at echocardiograms, did any of those patients have evidence of congestive heart failure?

DR. WHITCOMB: No.

DR. ILLINGWORTH: In that subgroup?

DR. WHITCOMB: No. That's a good question. They did not. These were all people with (indiscernible) heart I and II

classification. There were no patients with CHF included.

We originally thought that all of the patients were going to have normal LV masses at baseline. That was our goal because we wanted to -- that wasn't me, was it? As it turns out, about 15 to 16 percent of the patients did have some degree of LV enlargement at baseline. So we actually did pick some patients who were not totally normal from an LV mass standpoint in this study.

DR. ILLINGWORTH: But you don't have a study going on yet in patients with congestive heart failure?

DR. WHITCOMB: No. I think that is a very important point, and one which we have had some very preliminary discussions, that we believe that is an important area to investigate.

DR. BONE: In fact, you have excluded patients with known heart disease from all of your studies to date, if I'm not mistaken.

DR. WHITCOMB: They could not have class three or class four heart-related issues, that is correct.

DR. BONE: Dr. Cara had a --

DR. WHITCOMB: We think that's an important area to look at, I would agree.

DR. BONE: Well, certainly it is not uncommon for diabetics to have a little heart disease. Dr. Cara -- or Dr. Illingworth, were you finished? I'm sorry.

DR. ILLINGWORTH: Just do you have anything on the clotting factors, fibrinogen, factor-7, things like that?

DR. WHITCOMB: Those are being collected in one of the non-insulin-taking studies which is just now completing, and we are summarizing the data. I just don't know what it is right now. But we have looked at all of those things. We have looked -- there is an abstract on PAI-1 floating around from Dr. Fonseca at Arkansas which actually shows a lowering of PAI-1.

We actually -- this was a question that came up earlier about ANF. In one of our phase II studies we looked at ANF in the dose ranging study between 2 and 800 milligrams for 12 weeks, did not see any change in ANF compared to placebo.

DR. ILLINGWORTH: And then finally, you -- the information that the panel got has data on the lipid change. You didn't comment about those. Are you going to come back to that?

DR. WHITCOMB: Well, we -- I did that partly for sake of time, just trying to make sure we got all of the glucose and lipid things first. Was there a specific question? I mean, the lipid discussions are almost a whole --

DR. ILLINGWORTH: Let's leave it for this afternoon.

DR. WHITCOMB: -- thing by itself, you know. I'll do whatever you want. It happens to be a long answer.

DR. BONE: Right. Let's deal with

that later.

Dr. Cara, did you have --

DR. CARA: I have a series of short questions. Do you have any sense of the percent or the actual numbers of patients that were able to use troglitazone as monotherapy?

DR. WHITCOMB: From insulin taking patients we're talking about now?

DR. CARA: Right. How many patients were able to come off insulin?

DR. WHITCOMB: There is a total of 15 percent of patients in the 068 trial came off, and I believe just three or four in the other study.

DR. CARA: Okay. What is the age of the youngest patient that you have treated?

DR. WHITCOMB: Excuse me. What is the what?

DR. CARA: The youngest age treated.

DR. WHITCOMB: In the total program, or in these studies?

DR. CARA: In these.

DR. WHITCOMB: I think we have got a 26-year old that is in there.

DR. CARA: Okay. But nothing less than that?

DR. WHITCOMB: No.

DR. CARA: Okay.

DR. WHITCOMB: We've looked in other studies down to 18, but in this particular study --

DR. CARA: Okay. And in association with the changes in intravascular fluids and the issues regarding hemodilution, did you see any changes in electrolytes, specifically sodium concentrations?

DR. WHITCOMB: No. We have never -- that's a very good question because that kind of gets at the fluid issue. We have never seen hypolytremia or significant changes in sodium in any of the studies we have looked at.

DR. BONE: All right. Other panel questions? Dr. Critchlow, and then I'll have one quick question.

DR. CRITCHLOW: Just one. Of the patients that came off insulin, were they able to stay off?

DR. WHITCOMB: Yes.

DR. BONE: My question --

DR. WHITCOMB: We're continuing to follow them along.

DR. BONE: I thought you told Dr. Sherwin that a few patients went back on.

DR. WHITCOMB: Yeah. I should say, the people at the end of this study that were off -- I think I misunderstood that. During the course of the study, a few more came off and then went back on to optimize their control. But those that were off at the end remained off beyond the six-month period.

DR. BONE: You mentioned a special study looking at red cell production and so on with regard to this drop in the hemoglobin. It was a fairly small study. And I just guess my question, and perhaps you are going to ask Dr. Finch to answer it, is was the study sufficient

in size to pick up a subtle effect.

DR. WHITCOMB: I would -- either Dr. Vassos from clinical pharmacology or --

DR. BONE: Whoever can address that.

DR. WHITCOMB: Tim Vassos.

DR. VASSOS: Yes. You are correct that the study size was small -- patients. What we were primarily interested in in that study was to exclude potentially clinically significant changes in erythrocytes, synthetic perturbation, or hemolysis.

So, therefore, the study could not reasonably be powered to look at these very subtle changes. It would have taken many hundreds of patients looking with formal chromium labeled red cell masses to do that. And so for that reason we were looking for these major clinically significant changes.

DR. BONE: I see. So the finding of no abnormality in that study doesn't really address the small drop at all.

DR. VASSOS: It addresses the small

drop in that the totality of all of the data that was looked at, which not only included the formal red cell mass but also evaluation of reticulocyte count, erythropolitan levels, and also soluble transferrin receptors as a non-invasive means of assessing the developing red cell mass in the marrow, all of those were unaffected.

So whereas we didn't have a power due to patient number, all of the parameters were tending in the same direction.

DR. BONE: Thank you. Well, thank you very much. We are doing fairly well, a little behind where we planned to be on the schedule, but those are always optimistic. I have 10:58. Why don't we take our break until 11:10 and start the FDA presentation at that time.

(Recess)

DR. BONE: The FDA presentation of issues will be introduced by Dr. Fleming. This will be followed by a presentation regarding

pre-clinical toxicology. It looks to me like we have a few people who have not yet re-assembled, but I think all the --

(Pause)

DR. BONE: Apparently we are adjusting the technological marvel.

(Pause)

DR. BONE: It is with great pleasure that I introduce Dr. Alexander Fleming, who will open the discussion from the Food and Drug Administration.

DR. FLEMING: Thank you, Mr. Chairman. And I want to thank Parke Davis for coming to the FDA's rescue. We're having some technical problems, and they are currently putting my presentation into their system, and it ought to be going in just a moment. I hope it won't be altered.

(Laughter)

DR. FLEMING: But that would be fair, perhaps. And while we are getting started --

DR. BONE: The approval letter will

be coming right out of the projection.

(Laughter)

DR. FLEMING: The FDA presentation will be brief and focused more on interpretation than adding any additional information.

Before I get started, though, let me just say that it is necessary and good that we function as a team in the evaluation of this drug within our division.

And I want to acknowledge the work of the primary reviewers on this team: Dr. Mike Fossler, the bio-pharmaceutist, Mike Johnson, our CSO, Bob Misbin, our expert medical officer, Baldeo Tangea, our biostatistician, and very importantly Dr. Herman Rhee, who is our pharmacologist and has spent a great deal of effort and time over the years in evaluating drugs in this particular pharmacologic class. And so the presentation that Dr. Steigerwalt and I will make stands on the shoulders of these team members.

How are we doing? All right. We're here, good. And if we could just go to the next slide.

(Slide)

I want to give you an outline of the talk that Dr. Steigerwalt and I will give. First of all, just a few words about developmental strategy. It is clear that this is not the typical approach to developing the drug for a chronic disorder. We are, after all, beginning with the evaluation of a drug's benefit in a high risk subgroup of the ultimately intended larger population of Type II diabetics.

But there is nothing wrong with this. In fact, I think it shows flexibility on the part of the agency and earnestness in working with industry to get drugs that are desperately needed to those who need them.

We'll be covering a few aspects of animal toxicology or toxicity, actually. We will not really add any new information, but we

will have some comments to add to those that have already been made.

I'll talk a bit about study design and the population for which the drug is intended, and will then talk about efficacy and some selected safety concerns.

Next slide, please. Well, in fact, let's turn it off for a moment. I'd like to have Dr. Ron Steigerwalt come up and make some remarks about toxicology.

DR. STEIGERWALT: Thank you, Dr. Fleming. I'd also like to thank the members of the review team, and particularly Dr. Rhee who went through a lot of data submitted by the company to provide me with this information for this presentation.

Basically, the three major pre-clinical findings have already been discussed by the sponsor, and they include cardiac enlargement, changes in fluid distribution, and the carcinogenicity issue.

Regarding the cardiac enlargement,

this was characterized by an increase in heart weight in the toxicology studies in both mice and rats and was explained as being primarily due to fluid accumulation in the heart muscle.

There was relatively little if any histopathology observed, even when the heart weights increased up to 60 percent greater than control animals, in the mice and the rats. This also tended to occur at the high dose, as the sponsor explained earlier. And as I said, the cardiac enlargement was detected in both mice and rats, and it was a very consistent finding in these studies.

An interesting fact is that there was a two week mouse study performed, and it was found to be a reversible effect, although we did not get any data on longer term studies to determine the reversibility in longer term studies. And I would like to add to that in that a one year study in monkeys, there was no change in blood pressure, electrocardiogram or echocardiograms at three to five times the dose

of the expected human exposure at 400 milligrams -- at the 400 milligram dose.

I would like to add that doses higher than this were not tested. So this provides a safety margin of three to five times the human exposure, but we don't know what happens at higher doses in monkeys. There was also a slight decrease in hematocrit hemoglobin and RBC counts in the monkey study.

Regarding the changes in fluid distribution, in addition to the fluid accumulation in the heart muscle, there was a rat study that demonstrated that there was an increase in plasma volume with consequent hemodilution. This was also shown in a human study, as was just explained by the sponsor. It is not clear if the heart effect and the plasma volume effect are related by the same type of mechanism.

Changes in fluid distribution as a general term is a very consistent characteristic of members of this class of

drug. They may not have all of the same exact effects, but they all have some kind of fluid distribution changes.

And regarding the carcinogenicity studies, as standard operating procedure of the FDA, all carcinogenicity studies are taken to the carcinogenicity assessment committee of Cedar. And this is currently under evaluation by the committee, so I can't make a definite FDA statement on the carcinogenicity findings. But I can say personally as a reviewer that the findings that the sponsor has reported appear to be accurate representation, and these are in the draft labeling providing with their handout.

So therefore, we apparently agree on the same types of toxicity issues, and the sponsor has been working on these in the clinical studies as well.

Thank you.

DR. FLEMING: Thank you, Ron. Now, I would like to just follow with a few remarks

about the animal toxicity that has been reported. And obviously, I go out on a limb to do this because this is not my area of expertise. But I will do what we are asking the committee members to do, and that is to evaluate the results of these toxicity studies and to make some kind of calculation about their significance to use of the drug in humans.

First of all, the issue about the increased heart weight. Now, that was seen in mice and female rats. I think the finding that -- or the observation that it occurs in female rats perhaps gives some insight here, that is, that female rats are more sensitive probably because of metabolic differences, or rather how the drug is metabolized.

Apparently, or for some reason, rats have a much greater AUC exposure than males, and therefore this could explain the observation of the gender difference.

Again, I call to your attention that

this effect has -- this kind of effect on heart weight has been observed in related compounds in the chemical class. We don't want to make too much of a big deal about this because after all, these are data that are not available to you to evaluate. And we feel that the company has gone to every effort to properly evaluate the drug in their own right.

I think it is also interesting that we do, as was said, have the observation that ACE inhibition actually was used to prevent the development of this finding, though it was resistant to furosemide diuresis. And so the inference might be that there is a more specific mechanism involved here. But we really can't say much more.

Now, to go back to, I think, a question that came up from one of our members, could this be a cause or a consequence of another problem that is, to my way of thinking, the fluid distribution issue. Let's go on to the next slide.

(Slide)

Now, we know that fluid balance is altered across body compartments to some extent. We have evidence going all the way from our animal models to humans themselves. As was I think made clear early in the discussion, there was no fluid noted in the standard long term toxicology studies in rats. But in the carcinogenicity studies, it was observed that fluid accumulated in the thoracic cavity and subcutaneous tissues.

Now, I would concur that a very plausible explanation is that these rats were moribund for other reasons and therefore accumulated fluid as a consequence of that process. So we can't make too much about the findings in the carcinogenicity study. But we should not completely dismiss them.

Again, similar findings have been found in related compounds in this category, that is, accumulation of fluid in various body cavities as well as sub-cutaneous tissue. I

think it is very interesting that we have evidence for the increase in blood volume in both rats and humans. And I do believe that this probably explains the small but significant decline in hematocrit that was discussed earlier.

But again, the question is raised, what is the significance of this alteration in fluid balance. I come back again to the cardiac findings. And there were findings besides just the effect on heart weight, as you know. Again, these were changes that were observed in the carcinogenicity studies. However, we can't entirely dismiss them as being explained by the moribund process that was adduced earlier.

I do think that if there is some kind of fundamental alteration in the metabolism or the transport of fluids, that this could be significant over the long term. We have no clinical signals as of yet, but simply we need to keep in mind the potential that ultimately

you could explain the cardiac findings in animals by some kind of fundamental effect in the control of fluid distribution across tissues.

Next slide.

(Slide)

We come back again to the tumor issue. I think it is interesting that females seem to be more sensitive here, though I am not sure that it is explained by drug metabolic differences in mice, which don't seem to be as pronounced as they are in rats. It was mentioned that the female mice also showed hepatocellular carcinoma. This appears to be a fairly insignificant finding peculiar to the species itself.

I think we should also consider this fact, that the drug is concentrated in the liver to a very large extent, far exceeding any other tissue, that is, 30 times the concentration in plasma in rats. We do not have, as far as I know, data from distribution

studies in animals, particularly primates, which would be obviously much more relevant to humans.

But at least in rats we have reason to be concerned about what might happen ultimately in liver, a target tissue. And perhaps we would be somewhat reassured if we had data in primates that showed a much lower concentration.

Next slide.

(Slide)

Here we just point a few miscellaneous and possibly relevant findings. Female rats do appear to be more sensitive to effects on the heart and liver weights, which also increase with high dose exposure, and with respect to fluid changes. I think this again may be explained by drug metabolism differences between male and female rats. Female rats do appear to be more sensitive to the tumorigenic effect, and that may or may not be related to metabolic differences.

But clearly the human drug metabolism is much different from rodents, and that may be of some reassurance.

Next slide.

(Slide)

Now, I'd like to just briefly go over some of the pivotal study design issues which we'll perhaps go into more detail later this afternoon, but just to set the stage for that.

First of all, I think the definition of the patient population is critical, particularly for purposes of labeling. I do believe that the company has taken a reasonable approach in defining the patient population as they have. And I will not go any further now on this particular issue, but I hope we'll come back to it in the afternoon.

Now, you could have said why didn't you, instead of just documenting failure of patients on sulfonylurea therapy, actually put them through a pre-treatment period on sulfonylurea treatment to see if they might,

even though after failing previously, might respond again to sulfonylurea therapy. In fact, they might have even added an arm of sulfonylurea therapy just to see what the incremental benefit of the troglitazone is compared with that of conventional oral therapy.

Well, I think perhaps we would like to have some kind of reassurance that these patients would not have responded pretty well to sulfonylurea therapy. As a clinician, I am very doubtful that there would have been a significant response. I do think it is probably adequate that we have documentation that these patients had at one time previously responded -- had failed to respond to sulfonylurea therapy.

Now, metformin is another issue, or course. As was mentioned, the drug was approved about the time these studies were being developed. But we, of course, do not have any comparative data, nor are we required

to. Let's be plain about that. The company is not obligated to make comparisons with other therapies.

Now, the final issue -- or first of all, the basis of dose selection is something that we will definitely be speaking in more detail about this afternoon, and is of course very important.

The final issue is the question of the clinical significance of reducing exogenous insulin therapy and using that as part of the primary efficacy endpoint. In my way of thinking, the approach of the company in their second pivotal study was actually right on. It pretty much mimics sort of the real world approach of clinicians. They are not going to be in a pure sense treating just hemoglobin A1c levels or aiming to improve glycemic control, but they will at the same time be hoping to reduce the amount of exogenous insulin therapy required.

So I think that the categorical