In addition, we have called in other renowned hepatologists at various times to review the cases. Willis Madre in Dallas has reviewed essentially all of the cases. Additional hepatologists have seen some cases have been Steve Shanker in San Antonio and Neil Kaplowitz in Los Angeles.

Before I show you the results of the actual analysis, I want to make two points that have come up earlier. One is there is an increased background of liver disease in the diabetics due to nonalcoholic steatohepatitis or NASH, an increased in viral Hepatitis C. There's no question these can progress to cirrhosis, hyperbilirubinemia, encephalopathy, and death.

However, as you've heard before, these would not be expected to cause an acute liver failure picture. However, their presence would predispose individuals to develop an acute liver failure picture where they otherwise might not have.

This is another point --I'm sorry if some can't see it in the back -- that was made earlier. This is the most recent review of acute liver failure cases that occurred at 13 academic medical centers between 1994 and 1996, and the point made -- there

were 295 total cases -- actually what they call cryptogenic or non-A, non-B, non-C hepatitis accounted for 43 cases or 15 percent of the total cases.

This is not a category because of lack of a complete work-up. There does appear to be a discrete entity which acute liver failure of unknown cause, and there's been nothing characteristic or even pathomnemonic of troglitazone induced acute liver failure, including histology.

So with any individual case, it's not possible to say with absolute certainty that the drug was the cause.

This makes a point that has not been brought up previously, and that's that we anticipate when looking at spontaneous reports of hepatocellular injury postmarketing to find the number of jaundice cases to outweigh the number of deaths, that is, the number of those jaundice patients who go on to die by about ten to one, that is, a ten percent incidence of death amongst those that are jaundiced, and I've listed several drugs here. I've picked these because they're still on the market.

This trend actually applies to other drugs now off the market, such as tiolinic, and to show you how to read it, I'll just go with the nonsteroidal

diclofenac, where a recent review by several respected liver experts concluded that 90 cases reported to the FDA -- this was over a one and a half year period -- of jaundice was due to the drug. This is hepatocellular jaundice, and seven went on to die, or about a seven percent death rate in those with jaundice.

And there are two points in this. One is we expect in looking at hepatocellular injury to see a jaundice to death rate of about ten to one. That's what's anticipated as generally seen.

The other point is that ten percent of people who are reported to jaundice will go on to die. So although we've heard about 43 cases of acute liver failure, the most conservative approach is really to look at all patients who have become jaundiced.

Now, I'm going to go to the actual analysis here and give you the actual numbers. There were a total of 290 cases where jaundice or an equivalent term, yellow eyes icterus, was present somewhere in the Med Watch report.

Ninety-six in this review process were felt to be unlikely or unrelated to drugs, such things as metastatic cancer to the liver, for instance, leaving 194 cases of jaundice that were considered to

be probably related to drug, possibly related to drug, or to have insufficient data to draw any conclusion.

My charge from the beginning from the company has been to consider all cases to be due to the drug unless an alternate, more likely etiology can be identified. So we'll assume that 194 cases of hepatocellular jaundice were due to the drug.

Now, what that tells us from historical precedent is we would anticipate approximately 20 of those to go on and succumb from the injury.

These are the tally of U.S. deaths and transplants. Within that 194, there were 75 total cases, and I will show you in a subsequent slide all of the numbers. Sixteen were judged to be probably related to the drug, and another 12 were judged to be possibly related to drug, coming up with a total of 28, or close to the ten-to-one ratio anticipated.

Now, within these 28 patients, there were confounding factors, and I've summarized them on the next slide. Seven had clearly documented, significant preexisting liver disease. Three had Hepatitis B surface antigenemia. Two had confirmed cirrhosis. One had biopsy proven NASH, and one patient had cytomegalovirus infection concomitantly, and I'll talk about that case in a minute.

Nine were on drugs known to produce severe hepatocellular injury, and 12 had neither drugs known to produce hepatocellular injury or documented preexisting liver disease, but actually each of these cases is quite complicated, and I urge the Committee members to look at the summaries and the company has binders with the actual Med Watch reports for those who want all of the available information.

This is building on the last slide. We see our 28 probable/possible. There was an additional 12 patients who had insufficient data to arrive at a conclusion, and if you add those 12 to the 28, you would come up with a number of 40 patients who had a liver related death or transplant that could be attributed to the drug.

Thirty-five of these cases, to have them all add up, I think there's been universal agreement that they're unlikely related to the drug. So the FDA number of 35 deaths and transplants in the U.S. reported experience obviously lies between 28 and 40, and in discussions between the company and the FDA, that is the number that is agreed upon, and that is the number that was taken forward.

We heard another number, which is 43, which includes people fitting the definition or

appeared or may have fit the definition of acute liver failure. The bottom line: there are people who almost died but didn't, and of course whenever you have a population of 194 jaundice patients and 35 succumb, some will come very close to dying and pull back from the edge.

So as I see it, there's really no discrepancy in terms of agency and other numbers.

Now, one of the things that is most disturbing and compelling is the fact that there were two acute liver failure culminating in death in the two clinical trials that you heard about. These two cases are within the 16 that have been categorized in this process as probably related to drug.

It is interesting though. In the entire worldwide experience in clinical trials, which now is over 15,000 individuals, there have only been four patients who have apparently developed jaundice. Two were in the preapproval clinical trials when there were no stopping criteria for serum ALT, and the other two are the two cases in the clinical trials that went on to have acute liver failure and died.

Now, this is not following historical precedent. I'd be happy to expound on other ideas, but it does at least raise the possibility that there

might be something unusual about these two patients who died in the clinical trials.

In fact, there were issues with each of these patients. I'm going to give them and allow the Committee to draw their own conclusions.

The patient that was in the NIH trial had a flu-like prodrome prior to elevations of serum ALT greater than three times the upper limit of normal. This was apparently due to an acute CMV infection, as documented by IgM antibodies to the cytomegalovirus. The liver was involved because a viral inclusion body was noted in an hepatocyte in liver biopsy.

The patient went to transplant, at surgery was found to have necrotic colon, which was resected. This is a very unusual complication for acute liver failure.

The NIH got their own team of very distinguished hepatologists listed here. This is their entire concluding paragraph in the letter indicated, stating, "According the Committee concludes that hepatic necrosis in this case was probably caused by troglitazone and believes that an important contributory role in the fatal outcome may have been played by bowel necrosis, a lesion for which the CMV infection is speculatively incriminable."

The second case was admitted, had acute liver failure on admission or shortly thereafter. The relatives gave the history that this patient had a very substantial liver intake or alcohol intake. I'm quoting directly from the Med Watch form when I say 12 beers daily for 20 years.

Could this have been an alcohol related liver injury? The serum AST was higher than the ALT, consistent with alcoholic hepatitis on admission. However, the height of the serum AST and ALT, which was above 1,000 is really not consistent with alcoholic hepatitis alone. No liver histology was obtained in this individual.

So I think troglitazone unquestionably contributed to the liver injury in each patient, and I think it is appropriate that they are part of the 16 probable troglitazone related deaths. However, I think it's reasonable to assume that both patients probably had underlying liver disease that reduced their ability to survive the drug related injury.

This summarizes the nine cases we've heard about that were called rapid risers, and I realize this is a difficult slide to see. The numbers here in parentheses actually refer to the case summaries in your briefing document.

These cases have been reviewed through our process, and the bottom line is that four of them seem to fit the definition as described, that is, an ALT elevation or onset of what has turned out to be a very severe liver injury, possibly acute liver failure with a documented normal serum ALT less than 30 days before.

The remainder -- and I don't have time to go into them -- we either felt had other unlikely etiologies or felt the data didn't support that.

Now, the first patient is actually someone who complete had a very acute event actually and completely recovered. So it's a semantic issue. Is this a failure of monitoring if the person has entirely recovered?

But in any event three or four patients that appeared to have fit that definition of such a rapid rise, monthly monitoring would not have caught it.

By the way, these three death cases are the only three cases in the 35 that fit that criterion.

Now, in my final minute I've been asked to say some comments about the mechanism of hepatotoxicity. It is not known. In part, this

reflects the nature of studies with essentially all idiosyncratic hepatotoxins, which is that there is no animal yet identified that gets the toxicity, and in vitro models, such as cell cultures, develop toxicity only at very high blood concentrations.

In fact, data in a cell culture needs to be cautiously interpreted since the human disease does not develop until two to seven months on drug. It's not an acute event.

However, there have been three specific mechanisms that have been actively pursued. One is the quinone metabolite. One is a comment we heard earlier, the fact that troglitazone appears to induce an enzyme in liver called CYP384, and then possibly PPAR gamma activation itself within the liver, and I'll make quick comments about both.

This is the troglitazone molecule. The three major metabolites are listed here. Two are sulfate and glucuronide conjugates, respectively. The third is the so-called quinone metabolite. This is the moiety here. Troglitazone has a well publicized Vitamin E moiety on it. It's this moiety that produces this quinone metabolite.

Quinones have a track record for causing acute , predictable liver disease, and follow-up

compounds in this class lack this moiety, do not make this quinone metabolite, and are rumored to have lower incidence of ALT elevations, and for all of these reasons there's been intense interest to determine whether the quinone metabolite is, in fact, involved in the toxicity.

In spite of a lot of people trying, the quinone is stable. It's been produced in large quantities, injected into animals, added to cell culture media. I'm unaware of any data that suggests the toxicity is higher than parent troglitazone or others in the class, and I think people from the company are prepared to talk about this later if people are interested.

The other comment though is actually this quinone metabolite is made from Vitamin E itself and is actually detectable in the blood of people who don't even receive exogenous Vitamin E. Vitamin E has not been associated with acute liver failure, to my knowledge, and that should be of some comfort to those of us who take this supplement daily.

The next mechanism is CYP3A4 induction, which is believed to involve an intracellular receptor called PXR. Troglitazone enjoins other drugs that have this property. Some, such as the antibiotic

rifampin, the anti-seizure drugs phenytoin and carbamazepine, have been associated with acute liver failure, but others, such as glucocorticoids have not. So the role this may play is unclear.

Finally, it is possible that PPAR activation itself within the liver could be involved in the toxicity because this activation has caused a change in cell differentiation, apoptosis under certain conditions, but to my knowledge, there's no evidence that supports this.

So to conclude my talk, acute liver failure due to troglitazone is a rare event. I believe it is idiosyncratic, and I can talk about timing, change of risk over time if people are interested.

Assessment of many of the cases is not straightforward. Nonetheless, the agreed upon number of U.S. deaths and transplant due to the drug is now 35.

The mechanisms involved in troglitazone hepatotoxicity are unknown, although this remains a very active investigation.

Thank you.

I think I will now introduce the next speaker, which is Dr. Pierce from Parke-Davis.

DR. PIERCE: Thank you.

In the previous presentation, Dr. Watkins outlined the pathophysiology of the adverse liver events associated with Rezulin therapy. In this presentation, we turn our attention to the incidence of those events in different populations of patients.

I will present data on the risk of serious hepatic events from two different sources. First, I will discuss the incidence of such events in clinical trials of Rezulin conducted worldwide. Second, I will turn to incidences from the marketed drug experience. I will present three different estimates.

One, the overall rate since launch;

Two, the rate before and after implementation of labeling changes incorporating liver enzyme monitoring requirements;

And, three, the rate as a function of duration on therapy.

These data will confirm that the rate of adverse events is declining.

Now, let me turn to the clinical trial data. Troglitazone has been simultaneously developed by three different pharmaceutical companies: Parke-Davis in the U.S., Glaxo Wellcome in Europe, and Sankyo in Japan. The three companies collectively

have studied troglitazone in approximately 15,000 patients.

In addition, the NIH sponsored a clinical trial which included troglitazone and studied diabetes prevention.

The first column of this table shows the number of patients taking troglitazone in Parke-Davis, Sankyo, Glaxo Wellcome, and NIH sponsored trials.

The second column shows the number of those patients who developed jaundice.

And the third column shows the number of those patients who died because of liver failure.

Note that the two patients who died also experienced jaundice. These patients appear in both columns. These patients have also been discussed in detail by Dr. Watkins.

Overall, based on the two deaths in 15,591 individuals exposed to Rezulin in clinical trials, the incidence of liver related death or transplant is one in 7,800. Because the incidence is based on only two events, the small numerator leads to a very wide, 95 percent confidence interval, ranging from a high of one in 2,200 to a low of one in 62,900.

Because of the wide confidence interval, the small number of cases, and their complexity, the

incidence rate may have little predictive value for purposes of estimating the true incidence. It is, therefore, not possible to confidently extrapolate this estimate of risk from the clinical trial experience to the setting of marketed drug.

I would also like to comment briefly on the data presented by Dr. Graham to estimate the incidence of liver related death or transplant in clinical trials.

Dr. Graham did not include in his presentation data from several Parke-Davis clinical trials, all of which have been submitted to the FDA. In fact, the total of Dr. Graham's slide was 10,141. Approximately an additional 5,000 patients were in the clinical trials done by Parke-Davis and submitted to the FDA.

Also I'd like to clarify another point. I understood Dr. Graham to say that the Sankyo and Glaxo Wellcome data were not submitted. They were submitted to the FDA.

We believe all data must be considered to have a complete and accurate understanding of what transpired during the clinical trials. Importantly, there were no liver related deaths, no transplants, and no cases of jaundice in the trials that were not

presented by Dr. Graham.

The excluded trial data are poolable, in our opinion with the other data, and the best estimates of risk are derived from looking at all of the data as we have done here.

Now, let me turn to the question of the postmarketing incidence. Overall the incidence of liver related death or transplant during the postmarketing experience is approximately one in 45,000 individuals. For the purposes of this presentation, we will focus on an unambiguous case definition, namely, death due to liver failure and liver transplant.

We will also use the 35 cases of liver related death or transplant considered by the FDA to be possibly or probably associated with Rezulin, although I note that outside expert hepatologists do not agree with some of those attributions.

Our denominator is based on new therapy starts since launch.

May I have Slide 57, please?

The source for our denominator is the NDC source retail pharmacy database. This is a database generated from very detailed tracking of prescriptions at 11,000 U.S. retail pharmacies. These pharmacies

provide detailed new prescription starts and persistency data. These 11,000 pharmacies are distributed throughout the United States. They're very representative of the entire U.S. population.

The next slide, please.

In order also to evaluate the issue of persistency, which is very important in understanding the issue of risk as a function of duration on drug, we have conducted three different studies evaluating persistency.

In May 1997, we commissioned them to follow 5,020 patients, and they do this in a very detailed way. Each patient is given a unique identifier, and that patient's return to the pharmacy every month is followed. That is how the data is generated.

Because of a great deal of publicity, negative publicity, I might add, we were concerned that perhaps the persistencies were changing over time. So we subsequently conducted or commissioned two additional studies looking at a cohort which began therapy in March of 1998, as well as one that began therapy in September of 1998, and you can see the numbers in each of those cohorts.

Next slide, please.

This data shows the persistency of those three cohorts. You can see in red is the cohort begun in May of '97, in blue the cohort begun in March of '98, and in green, the cohort begun in September of '98.

This is actual Rezulin patient persistency, and it's a percent of the patients who began. You can see that there's an issue. The patients are given a 30-day grace period in the calculation, and that's the reason that the first two dates show both the 100 percent.

Then the persistency is followed, and you can see by looking, for example, at month six approximately 60 percent of the patients are still on drug. Since the total new therapy starts amounts to 1.58 million, this amounts to one million people who have been treated with the drug for up to six months. That means that there's half a million people approximately who have been treated with the drug for more than six months.

You can see that despite the negative publicity that the basic curves for these persistencies have not substantially changed.

Next -- leave that. Back one slide, please. Yes.

Based on this data source, we estimate the number of patients to have taken Rezulin since launch at 1.58 million. As the slide shows, this yields a simple rate for liver related death and transplant associated with Rezulin since launch of one in 45,000.

I might also add that from another data source, the Physicians' Drug and Diagnosis Audit, which follows the prescribing of 3,400 physicians monthly, we have a number from that of 57 percent of the patients that are being prescribed Rezulin being female. This differs from the number presented by Dr. Graham.

Of course, this number, one in 45,000, is only an estimate. Dr. Graham noted that there is some degree of under reporting of adverse events for Rezulin, as well as for all other drugs.

However, both theoretical, as well as empirical, data suggest that the level of reporting of liver related deaths and transplants in the Rezulin patients is quite high.

Let me turn to the factors that tend to increase reporting rates. The first such factor is newness of the drug. The rates of reporting for new drugs tend to be significantly higher than reporting rates for older drugs, with the number of reports

typically peaking the second year of market.

Reporting rates for Rezulin, which was first marketed in early 1997, would share in this phenomenon of newness.

The second factor is severity. Simply put, a large proportion of reported events for all drugs is serious events, and that is what we are discussing today.

The clarity of the signal is also an important factor both in the detection and the reporting of adverse events. Events such as jaundice are readily identified as signals of organ damage which may be drug related, making it more likely that a physician would report the occurrence.

Another important factor is the overall trend in adverse event reporting. During the past 20 years, there has been a significant increase in the number of reports filed with the FDA. For example, in 1980, on 10,000 advertise event reports were filed. By 1997, the number of yearly reports for all drugs had increased to 240,000.

Thus, Rezulin was introduced in 1997 into a medical milieu already undergoing rapid growth in adverse event report. Although this has not been discussed in the literature, to our knowledge, I would

suggest that active liver function test monitoring, particularly with the stopping rule, is another factor that would tend to increase reporting. It is very likely that such monitoring would enhance reporting of liver related adverse events because physicians have become intensely attuned to the possible association of the drug to the event being monitored.

Another factor is product marketing efforts. Rezulin is part of the intensely competitive market of oral hypoglycemic agents and is actively detailed. Parke-Davis has several contacts each year with approximately 80 percent of physicians who issue 80 percent of all Rezulin prescriptions. These contacts have increased awareness of Rezulin safety and likely have led to an increase in reporting.

It is also worth noting that sales representatives from other companies do not hesitate to remind physicians of Rezulin safety.

(Laughter.)

DR. PIERCE: Lastly, but perhaps most importantly is the publicity factor. Rezulin has been the subject of extensive publicity in both the lay and medical media, and a substantial proportion of this publicity has focused specifically on adverse liver events.

The stimulating effect of publicity on the reporting of adverse events in the case of Rezulin is demonstrated on the next slide.

This figure shows the number of cases of jaundice, hyperbilirubinemia in the orange bars reported by month since launch. These bars also include all of the deaths and transplants because all of these patients also were jaundiced.

We used jaundice hyperbilirubinemia because the data is more robust than purely looking at deaths and transplants to show the effect of publicity. The labeling changes, "Dear Doctor" letters and attendant media publicity in the fall and winter of 1997 and in the summer of 1998 stimulated two peaks in adverse event reporting. There's one, two.

Also note that the number of reports has declined from these peaks. This is not due to the decline in drug usage, since the number of patients taking Rezulin has continued to increase since launch.

Lastly, as reflected in the blue bars which show the number of reports by date of onset in a given month, note that some events were occurring, especially early, but unreported until the publicity associated with the "Dear Doctor" letters.

Each of these noted factors is well known to increase reporting rates, and each is applicable to Rezulin. However, in order to get a better understanding of the level of reporting, we have tested this conclusion in two ways.

First, we contacted the United Network of Organ Sharing, the National Liver Transplant Registry. Because UNOS records virtually all transplants in the United States and because its records reflect relevant drug usage by the patient, this database provided us with an opportunity to determine whether any transplants associated with Rezulin usage were unreported to Parke-Davis or the FDA.

According to their database, 4,394 liver transplants were performed in the U.S. in 1998. Four of the liver transplants were in patients who had taken Rezulin, and each of these cases had been reported to Parke-Davis and the FDA.

Conclusion: there is no evidence of unreported transplants in 1998.

Next, to further test the level of AE reporting for Rezulin, Parke-Davis commissioned a third party to conduct a survey of physicians in February of 1999. The survey had two goals: one, to determine the physician's likelihood of reporting

adverse events; and, two, to determine actual monitoring practices for patients taking oral hypoglycemic drugs.

To minimize bias, the survey contained an equal number of questions about safety monitoring and reporting practices for metformin, sulfonylureas and Rezulin. It is important to note that the physicians did not know who sponsored the survey, and they were assured that their responses would be kept confidential.

Six hundred physicians were selected at random from a pool meeting the following criteria. First, they had to be in the top nine deciles of Rezulin prescribers, and each specialty matched the specialty mix in a general prescriber population.

The results showed that 92 percent of physicians stated they would report liver related death and transplant associated with Rezulin. Confirming the clarity of signal and severity points mentioned earlier, physicians were much more likely to report serious outcomes, such as liver failure and death, compared to other symptoms.

Note the contrast between the high reporting rates for fatal outcomes either from liver failure of lactic acidosis and the low rate, 17

percent, for hypoglycemia.

Now I'd like to digress for a moment to discuss the additional data derived from the physician survey. In addition to the level of AE reporting, we also inquired as to the level of compliance with monitoring requirements, as set forth in the labeling for Rezulin. The data were encouraging, but point to an area where we can intensify our efforts.

The results showed that 96 percent of physicians were aware of the need for liver enzyme monitoring for Rezulin. The physicians stated that 97 percent of their patients received baseline liver function tests prior to the initiation of Rezulin and 82 percent of patients received monthly monitoring for the first eight months according to the label.

You will notice that these results conflict with the monitoring data presented by Dr. Graham.

(Laughter.)

DR. PIERCE: The next slide.

I'm going to suggest why that might be.

As confirmed by the Chief Medical Officer of United Health Care, there are several significant issues with the data. In a letter provided to Dr. Bilstad and shared with Dr. Graham so as not surprise

him or blind side him, and we provided this data to the FDA this week, the Chief Medical Officer noted:

One, that claims data from laboratory service providers is missing as much as 40 percent of the time.

And, two, claims data are not submitted at all.

And, three, delays in receipt of claims processed common extend from 120 to 150 days or more. Only this latter problem was addressed by Dr. Graham.

Accordingly, he concluded, and I quote, quote, "Simply put, a retrospective analysis of available UHC claims data cannot be relied upon to assess actual monitoring of patients by physicians."

Those circumstances are not unique to UHC and do not reflect on the quality of services provided by that group, or compliance with LFT monitoring. Because of such problems with lab data capture, however, the claims data should not be interpreted to reflect the absolute level of monitoring. Rather, the data are best interpreted as showing trends only.

In fact, the data suggest a doubling, if not tripling, in the number of patients being monitored during the period covered by the labeling changes.

So where does this leave us? Based on the available data, the rate of monitoring compliance appears to be reasonably high, but as Dr. Zerbe will describe later, we will act on these results to intensify patient and physician awareness in an effort to increase compliance with LFT monitoring.

This would be expected to further increase the incidence -- decrease the incidence of liver related death and transplant.

For the reasons previously described, the level of reporting of adverse events associated with Rezulin is high, although it simply is not possible to conclusively determine what percentage of events are reported. Accordingly, any estimate is speculative at best, and we do not believe that such speculation is appropriate in this context.

Moreover, risk estimates for other drugs rare, if ever, account for possible under reporting. Because the comparative risk discussion that you will hear in a moment is so crucial to an understanding of the Rezulin risk-benefit assessment, and because that discussion is based on data relating to other drugs which is expressed without reference to under reporting, it is important that we compare apples to apples.

In addition to the overall incidence since launch, another important question is this. Has there been a change in the incidence of serious liver adverse events with the labeling changes?

The incidence rates of jaundice hyperbilirubinemia, blue line, and death due to liver failure and transplant, orange line, expressed as reports per 100,000 patient-years are shown in this figure. Shown are all cases of jaundice and hyperbilirubinemia regardless of attribution to troglitazone by date of onset.

Twenty-one cases of jaundice hyperbilirubinemia and one death could not be included in this figure because the onset date for these events was not known.

This slide shows that the reporting rate peaked in late 1997. Thereafter the rates for these events have declined.

This table shows the reporting rate for death due to liver failure and transplant over time expressed another way. In the first column is the time interval. In the second is the number of cases in each period based on their date of therapy start. In the third is the number of new patients taking Rezulin and each time interval.

The data show that in 1997, the incidence rate was one in 36,000. Following the initial labeling changes, including adding a boxed warning, the rate fell to one in 57,000.

So far I've presented data on the incidence of serious liver events as a function of calendar time. An equally important question is the incidence rate as a function of duration on therapy.

This slide shows reports of jaundice hyperbilirubinemia and death and transplant expressed in these terms. The figure shows that 240 jaundice hyperbilirubinemia cases in the blue line and the 34 cases of death due to liver failure and transplant, yellow line, in which the duration of therapy is known.

One patient was excluded from that because we don't know the onset date of the therapy. So we can't use that data in this calculation, in this figure.

The figure shows that for both events, the rate declines after approximately six to eight months of therapy.

Note the curve for jaundice hyperbilirubinemia beyond 16 months represents only three cases, actually one case in 16, 17 and 18

months, one case each at this point. The increase in this curve represents a decline in the denominator. In that case you're getting out to very long periods, and there's a cohort driven effect for people both because of persistency and because these patients actually began very early in the marketing of Rezulin and began in a very small cohort. There's a very rapid drop-off.

Finally, we also note that we have no cases with death due to liver failure or transplant beyond 11 months of therapy.

Based on all of the data that I've presented, three conclusions may be stated regarding incidence. First, the incidence of liver related death and transplant associated with Rezulin is low.

Second, the risk for jaundice and death due to liver failure and transplant substantially declines after six to eight months of therapy, and most importantly, the rate of such events has decreased following labeling changes and increased patient and physician awareness of the issues under discussion.

I now turn over the podium to Dr. Faich.

DR. FAICH: Mr. Chairman, could we have the lights up, please?

You'll be happy to know I don't have slides. What I want to do is just highlight a few of the remarks that Dr. Pierce made and make a few additional remarks from the viewpoint of having used spontaneous reporting systems and data bases for many years related to some of Dr. Graham's comments.

Firstly, I would like to commend Dr. Graham on a very thorough analysis and presentation, but as he and others, as we will emphasize, precision, accuracy, reproducibility are all important, and that's what I'd like to comment on.

Let me first comment on under reporting, then talk a little bit about use of databases, and talk about the trial reports once more.

I'd like to emphasize again that it is my distinct impression that reporting rates for liver failure in this situation are almost certainly inordinately high. You've just seen demonstrated to you when you look at jaundice that after each publicity wave, there was a wave of reports.

We saw that with Suprofen. It's a well recognized phenomenon.

Moreover, this is severe organ damage. All of the literature would suggest that reporting rates for organ damage, particularly when there's a

suspicion of drug induction, is higher than other reporting.

And then lastly, remember the secular trend in reporting. Reporting is much higher today, on the order of over 250,000 reports a year, than it was just five and ten years ago. Some of the literature that Dr. Graham cited related to isoniazid and other drugs is all old literature, in each instance things like aplastic anemia. It was not accompanied by this kind of publicity, and it wasn't particularly related to one drug.

The other thing and maybe the last thing and the most telling thing that might suggest that reporting here is quite high is, as Dr. Graham pointed out, one ratio that one might consider is that about one in ten transplants, actually one in ten acute liver failures actually get transplanted. Seven of these cases have been transplanted. That might suggest that the total pool of cases to date is on the order of 70. We're looking at 45 or 43 that have been reported.

So again, what I'd like to leave you with is that extrapolations based on under reporting by multiplying by five or ten or 20 are probably inappropriate.

In terms of accumulated risk, Dr. Graham showed us using survival table methods a distressing picture of increasing hazard, cumulative hazard, culminating at a rate of one in 15,000. I must say the method is not an unreasonable method, but the numbers are probably not right. The reason I say that is Dr. Graham was using United Health Care persistence data to answer the question how many patients are still on drug at three months and six months. You need those kinds of data to factor into the analysis.

What we've shown you from National Drug Source data, which is actually cohort collected data on a very large and representative sample, is that our estimates of persistence are quite a bit higher than his. As Dr. Pierce just pointed out, we estimate that 60 percent of patients are still on drug at six months; 40 percent are still on drugs at one year. That changes that calculation because the denominator is larger. The numerator remains the same and has some of the same uncertainties we've talked about.

If you recalculated using our numbers, you'd get about a doubling, that is, or halving of the rate on the order of one in 30,000. So there should be some comfort in understanding that because it's important.

In terms of trial data, as you've just heard in both previous presentations, there is some uncertainty about the two cases in the clinical trials. There's no question that they were liver failure. The question is: what's their etiology and could they have been screened out using monitoring?

In addition, there's a question about what's the appropriate denominator. Most of the patients in the trials weren't in the trials for more than three months. It is, indeed, true that many of them were not in trials for more than six months, but it is also true that most of the reported cases have had onset within six months of therapy.

That would suggest that if one wants to use the right numerator, it's probably the usual numerator in clinical trials which alls patients as opposed to person-time. That also makes sense because we're likely talking about an idiosyncratic as opposed to a cumulative toxic reaction. If it was cumulative toxic, then person-time becomes very important.

So in this instance it's like to be two over 15,000, so that the point estimate is one in 7,500.

Dr. Graham has also emphasized that in considering safety one ought to look at the lower

bound and take the lowest number in the 95 percent confidence limits. I, indeed, think that's a real philosophical question. I think what one should take is the best point estimate, which in this case is one in 7,500, and recognize that there are wide confidence limits and recognize that there's uncertainty in the numerator as well.

In terms of database issues, the use of the three cases mentioned for United Health Care at this point in time is certainly inappropriate. Everyone knows when you use an automated linked database you have to go back to the chart and look at the clinical data and validate that what's in the automated database is, indeed, the correct diagnosis and look at the clinical course.

Now, I'm fully aware that Dr. Graham is intending to do that, and I applaud that effort, but I think it's very preliminary to suggest that those three cases, indeed, are drug related at this point in time.

Lastly, where is the epidemic? If we're talking about a rate of one in 1,000 for patients who have been treated for more than six months or on that level, we heard at the beginning of this meeting four clinicians describe their management of over 5,000

patients. I didn't hear one case of hepatic failure mentioned.

If we're talking rates of one in 1,000, you'd expect a case or two or three. I don't believe for a moment that there's an epidemic out there that has gone undetected at the transplant centers. All of this links up to how complete is under reporting.

I'm not suggesting that there may not be an association here. I'm just suggesting that the magnitude of the risk has to be examined with great care.

Thank you.

Let me now introduce Dr. Philip Home, please.

DR. HOME: Hi. It's good to be with you.

I'm Philip Home. I'm a physician from Newcastle upon Tyne in United Kingdom. I've had no previous contacts with Parke-Davis, but I have been Chairman of Glaxo Wellcome's International Advisory Board on troglitazone, and I'm also a lead external advisor to NovoNordisk, to Sanofi Pharma, and to Hoeschst Marion Rousseau on diabetes products.

I'd like to talk to you today about comparative safety of anti-hypoglycemic therapies, and in doing so I'm concerned that I may be accused

perhaps of trying to knock other products, and I'd like to show you first that this is not the case.

This is data taken from our diabetes center in Newcastle, where we see about 4,000 people with Type 2 diabetes under care. I've taken the data from the database, as complete as it is so far, for 1998, and you will see that we treat about 25 percent of our patients, perhaps extrapolated in total around 1,000 people on metformin, rather large numbers on sulfonylureas, and insulin, and many of these people on combination therapy.

I have to say we do this enthusiastically, and you'll realize that in terms of this number of patients managed over 20 years, I have experience of the adverse events with metformin and with sulfonylureas that I'm going to talk about, and that we continue to use these therapies despite those adverse events.

Type 2 diabetes, as we heard earlier from the ADA submission and others, is a serious condition, of course, which treatment is required and we now know is effective. We have a limited number of treatment options, all of which we have to use sometimes in combination, and all these options have potential for adverse effects.

At the end I'm going to return to the question of benefits in relation to risks.

The severe adverse events causing death that I'm going to refer to are, of course, disabling hypoglycemia for the sulfonylureas and for insulin; lactic acidosis for metformin; and acute hepatic injury, of course, for troglitazone.

But I'm going to begin first with metformin, and the reasons for choosing this. though we've been using this in Europe for over 30 years, is that it is, of course, a recently approved and introduced drug here in the U.S., and therefore, there is a comparative postmarketing experience with it.

It has had similar exposure to troglitazone, and its adverse event profile has, of course, been well characterized over the 30 years we've known it.

This information is taken from the letter of Dr. Misbin published in New England Journal of Medicine in 1998, and it relates to the U.S. postmarketing reports within the first 12 months for metformin.

It's estimated that around one million people were exposed to the drug and used it in that time, and that there were 47 cases of confirmed lactic

acidosis, leading certainly to 20 deaths. This gives an estimated event rate of 4.7 per 100,000 patients, or for deaths, of course, 2.0 per 100,000 patients.

Now, Dr. Misbin has more recently published exactly similar parallel data for troglitazone in the Annals of Internal Medicine, although, of course, they relate to a different time period. The exposure in terms of numbers of people with diabetes is broadly similar, with just over a million for troglitazone, and here is the number of fatal events, the 20 we've just seen for metformin and 17 for troglitazone.

Those of you who have read that article will perhaps spot the 17 as slightly lower than the number quoted in the article, and that's because here we're only quoting deaths which occurred within the USA.

The rate then for troglitazone comes to 1.7 per 1,000 patients, comparable to that for metformin in its first year.

There are other data available to us on metformin, and I've chosen here that particularly from the Swedish Adverse Drug Reactions Advisory Committee. This is because I regard this data as more reliable than others. Sweden is a relatively small country,

socially cohesive, and its medical population is well trained and used to reporting. Indeed, from 1975, it's been a legal requirement to report serious adverse events.

This data then is all from the same database. You will see here the death rates that Ian Campbell and Willy Berger calculated using the data from Dr. Wiholm was 2.4 per 100,000 patient-years, and all the rest of the data I'm going to give in this presentation is going to relate to this rate per 100,000 patient-years.

You'll see that broadly comparative rates of lactic acidosis reported over different time periods, and this death rate, I think, is probably the most reliable figure we have, although it may have come down a small amount since that time.

Other data is available from the literature. I think it's less reliable. The Swiss data was based on a postal survey, the U.K. data collected in a less sophisticated fashion. You will see that the data from Canada, from Saskatchewan, gives a rather higher death rate from lactic acidosis in metformin, but I personally have some problems with some of the cases and ascertainment in that study.

In the January Diabetes Care, there is a

paper from the Kaiser Permanente HMO in Northern California by Selby, et al., giving I calculated even a higher rate than that, but again, I have some problems with that because of the small numbers involved. So I'm not going to include it here.

In summary then, in taking those and other papers together, we end up with a death figure of around .9 to nine per 100,000 patients per annum, and I'm going to carry that forward to later in the talk.

Again, from the Swedish Drug Advisory Committee, this is the information that is available in sulfonylureas. Asplund published two papers in Diabetelogia and Diabetic Medicine, one of glyburide and one on gliptizide, although in different time frames.

Ian Campbell has calculated the death rates and case rates from this. Asplund just gave the numbers in the original paper, and the rates here, again expressed per 100,000 patient-years, have been calculated from that.

For the purposes of this talk, I have performed exactly the same calculations on gliptizide, and you will see that the bottom line death rates here are, again, comparable to the figures we've just been talking about, the 3.2 per 100,000 patient-years for

glyburide and 1.6 for gliptizide.

There are data giving higher rates of hypoglycemia as a serious adverse event in the literature. These two come from major databases, this from the Tennessee Medicaid-Medicare database and this from the VAMP database based on U.K. general practice, and you will see that their rates here for the event itself, cases, are very much higher, and this relates partly, I think, to definitions of what is and is not hypoglycemia between studies and also to the nature of the place this information was collected.

The Shorr data calculates that around one percent -- this is percent of the people with hypoglycemia -- around one percent resulted in death. That is a lower figure than much of the historical literature, but higher perhaps than I'm prepared to accept at the moment.

Sulfonylureas then, I think, on that basis will give you a death rate, again, which is not dissimilar to what we've seen before of around 1.4 to 9.8 per 100,000 patient-years.

The U.K. PDS does give rather lower figures for severe hypoglycemia, and this is merely defined as requiring assistance in the same way as the DCCT of 400 and 600 for chlorpropamide and -- sorry --

it's bliperite, respectively, but I put this slide mainly to deal with the question of insulin, and you will notice that they did have one event which was possibly or probably associated with hypoglycemia as a death within the insulin group, but there is a lot more hypoglycemia as a severe event with insulin.

I think for insulin we have to say that while death is perceived uncommon due to hypoglycemia Type 2 diabetes, the U.K. PDS has one death per 1,500 patients. The risk estimates are really rather too uncertain to calculate. Much of the information relates to Type 1 diabetes.

And in the next slide I've actually put my estimates here in brackets to respect its uncertainty.

So these are the figures carried forward for metformin and for sulfonylureas, and now for insulin, and to this I've added the figure for troglitazone. This is based on the last 12 months' data up to March 1999, and the dates are on drug exposure you've just heard about.

And you will see, I think, and all the point I make is that these figures are at least comparable for the four classes of agents involved here.

So what about the question of benefit?

And this is a difficult one to tease out. If we look at U.K. PDS and we try to look at the diabetes related death rate, it comes out as about 1,100 per 100,000 patient-years. So we're talking about figures which are quite different from the two or 1.4 or whatever deaths we were just talking about as a side effect.

If we actually think about what is potentially preventable in terms of the percentage of those deaths, I've chosen here a figure of ten percent, and you should be aware that I've chosen that because it is half, half that prevention that would be expected from the epidemiological data in the U.K. PDS, and it coincides with the point prevalence data in one of the intensive cohorts within U.K. PDS, although it's actually only a quarter of the benefit, statistically significant recorded for death, with metformin in that study.

So this is a conservative figure, and if you relate it to the death rate, then you're saving about 110 people per 100,000 patient-years, which gives you a benefit ratio over that figure of two of about 50 times.

As I've said, this is conservative, however. If we look at Ron Klein's Wisconsin data published in Diabetes Care, the number of deaths is

much higher as a rate than in U.K. PDS, and that's due to the selection and the relative health of the U.K. PDS cohort, which is not typical of Type 2 diabetes as we see it.

And if you apply that ten percent data to the Wisconsin study, then you're ending up with 350 saved people per 100,000 patient-years.

You can, I think, go higher, and if you choose the figures for metformin within U.K. PDS or you allow with troglitazone for its effects on lipids and on matters of endothelial cell function, then I think probably you will be getting up to somewhere around 1,000 here, and on that basis I would say a conservative estimate of the benefit-risk ratio is 50, and a best estimate, somewhere around 500 based on our current data.

So all drugs for treatment of Type 2 diabetes carry some risk. The risk is, I think, low and particularly low by 50 to 500 times compared to the benefit.

The risk from troglitazone is comparable to that with established therapies, and as we've heard just now from Dr. Pierce, the risk with troglitazone appears to be decreasing with time.

Thank you very much.

Sorry. That was going to be the last talk before lunch. So I now have to introduce Dr. Whitcomb.

(Laughter.)

DR. WHITCOMB: You have to introduce me. Okay.

Well, the presentations to this point have focused on the risk portion of the risk-benefit analysis for Rezulin. I would like to shift focus now and look at the benefits of Rezulin.

As with all diabetes therapies, this information is critical to put the risk information in perspective.

This slide overviews the metabolic staging of diabetes. Patients develop insulin resistance as an early event in the course of their disease. This defect is the principal target for troglitazone's action.

Over time, progressive beta cell dysfunction and continued insulin resistance leads to the development of progressive diabetes and its complications.

Our development efforts to this point have focused at patients on all stages of this spectrum. Because of troglitazone's complementary and

differential mechanism of action, the majority of our efforts have focused on demonstrating the efficacy of troglitazone when it is added to patients who have failed other therapies.

We also think, however, that troglitazone is appropriate as initial therapy for many patients.

The data that I will be showing you today is going to focus on several studies that we have completed. We'll be looking initially at insulin combination. We'll we showing you data from the triple therapy, troglitazone, sulfonylurea and metformin studies which have been submitted to the FDA. We'll be showing you data in combination with sulfonylurea, some data as monotherapy, and looking at two emerging areas of interest: first off, the impact on beta cell function and atherosclerotic risk factors, and then I will give a little bit of protected risk reduction using some recent data that we have for impact on microvascular endpoints.

These are data that were shown to this Committee approximately two years ago with the original submission. They were published last year in the New England Journal of Medicine.

This is our combination study with insulin in which these patients were on seven to three units

per day, on average. They'd had insulin requiring diabetes for about five years and diabetes altogether for about ten years. They were obese.

However, in spite of these large doses of insulin, they were poorly controlled with A1c's of 9.4 percent.

These are the fasting serum glucose and HBA1c data from this trial. I'll be referring to HBAC repeatedly during this. This is hemoglobin A1c, for those in the audience unfamiliar with this term. This is a measure of glucose control over approximately 90 to 120-day period.

The fasting serum glucose went down in a dose dependent fashion, down to nearly 50 milligrams per deciliter in combination with troglitazone at 600 milligrams, and the A1c went down as well in a parallel fashion to 1.4 percent after six months of treatment, both of these being statistically significant.

Remember, again, these were people who were on, on average, 74 to 75 units of insulin per day.

What we saw in this trial was a reduction in insulin dose as well. This was not a design or goal of the study, but in response to the lowered

blood sugars which were seen, there was a reduction of 29 units at 600 milligrams per day, which was nearly 40 percent in the insulin doses of these particular patients.

So in combination with insulin, we've been able to demonstrate significant benefits as manifested by an improvement in glucose control and lower insulin requirements in patients uncontrolled on insulin.

Now, I'm going to work my way back up from that curve. We started with late stage diabetes, and now we're going to start to work back up towards the other end of the diabetes continuum.

These are data which were recently submitted to the FDA and which we'll be presenting at the American Diabetes Association in June of this year. This is a study which was done in Canada in which we added troglitazone to people who had failed metformin/sulfonylurea combination up there. The reason we did this study in Canada is sulfonylurea or metformin has been available for many years, and there were a large number of patients that we could draw from for this trial.

This is the baseline characteristics of these patients. They had been diagnosed with diabetes for around 11 years. They had poor glucose control

with an A1c of 9.7 percent in spite of being on two drugs.

They had reasonable beta cell function, and they were obese consistent with most of the other populations that we've studied, and certainly consistent with Type 2 diabetes.

This is the study design. All patients underwent a four-week run-in in which they were maxed on doses of metformin and sulfonylurea. At that point they were randomized to either placebo added to their metformin/sulfonylurea combination or troglitazone at 400 milligrams per day. That's the only dose that was studied in this trial.

They were then followed for 24 weeks. We have an open label extension of this trial, which we are analyzing the data for now.

This is the response. This is in fasting glucose in millimoles. What was seen in the people that were still just on metformin and sulfonylurea was the glucoses continuing to drift up over time compared with a fall when troglitazone was added. Most of the effect was actually seen by about four weeks of therapy, and it was sustained across the six months of this trial. So a very nice fall in glucose.

Just doing the math from this, there was

a fall of 2.6 millimoles or 50 milligrams per deciliter or so of fasting plasma glucose compared to a slight increase in the placebo group as being statistically significant.

Again, there was a fall in A1c which mirrored this, a fall of 1.3 percent in combination with metformin, troglitazone, and sulfonylurea, compared to a slight increase of 0.1 percent, again being statistically significant.

Now, one of the important considerations, and I'm going to start to develop this in the next couple of data talks here, is the number of people who reach appropriate targets. We've look at data both at A1c's less than eight or seven percent at the end of the trial. These are the data. There were six percent of the patients on the sulfonylurea-metformin combination, who had an A1c less than eight percent at the end of the study and an A1c less than seven percent was seen in actually one patient in the placebo group.

There were 43 percent of people, less than eight, and 14 percent, less than seven, at the end of the trial, remembering again that these people started out on average at 9.7 percent.

So there was significant glucose lowering

in patients who failed sulfonylurea-metformin combination.

So moving back up the continuum now to people with slightly earlier diabetes perhaps, those are failing on glyburide by itself. So this was a study in which we looked at troglitazone added onto maximal dose glyburide, 12 milligrams per day. This was a 12-month study. It was one of our studies which was used in support of the indication for combination with sulfonylurea. These were people who had failed SU. They had an average FSG that was over 140 milligrams per day, on maximal doses of glyburide.

They were randomized to one of three doses of troglitazone either added to glyburide, switched abruptly to glyburide, or continued on glyburide by itself.

For sake of simplicity, I'm going to show you the time curves here. One monotherapy, the glyburide group, and one of the combination groups. The glyburide group, which is shown here in blue, over the course of the trial had a continued increase in glucose, which is what you'd expect. Obviously these people were uncontrolled at the beginning, the natural course being continued failure. So a rise of about 20 milligrams per deciliter of fasting glucose.

The abrupt switch to monotherapy showed a rise and then a fall at 600 milligrams. This is consistent with what we would expect because troglitazone requires the presence of endogenous insulin. The sudden removal of an insulin secretagogue basically left plasma insulin levels very low, and it takes a lot longer for the drug to work in that situation.

This also has led us to the recommendation that in patients who are either sulfonylurea failures or who are well controlled on sulfonylurea, that troglitazone should be added to, not switched as drug therapy.

Now, the story is very different when you look at the combination. This is the combination of 600 milligrams added, and there's a fall of about 60 milligrams per deciliter in fasting serum glucose by four weeks of therapy, which is then sustained across the course of the trial. I will show you some open label extension data on this particular study in just a minute.

The A1c's basically mirror this. People had started out at about nine and a half, go down and stay down with a mean of 7.8 percent at the end of the trial, A1c's drifting up here for both groups.

Now, these are all of the data groups in terms of combination. This is a comparison of the primary analysis for the study, was the mean difference versus control at 12 months. This is the intention to treat population. There was a fall of 54, 61, and almost 80 milligrams per deciliter of fasting glucose compared to glyburide during the course of the study. This was mirrored by a fall in HBA1c of between 1.6 and 2.7 percent compared to glyburide at the end of the study.

Again looking at the number of patients able to achieve American Diabetes Association goals and targets, the glyburide dose -- remember, again, these were people who were failing the drug. So this is not surprising -- only ten percent were less than eight and one percent less than seven at the end of the study, compared to 33, 33, and 60 percent of patients, less than eight percent at the end of one year; 22, 21, and 41 percent were less than seven percent at the end of the trial.

Weight gain was seen in this particular trial in combination with sulfonylurea. This has been observed in other combination studies. We believe it's a function of the improvement in glycemic control that happens in the study. For example, in the

metformin combination trial I just showed you a few minutes ago, there was a gain of a couple of kilograms in the troglitazone combination group.

Now, what happens to this effect over time? At the end of the 52 weeks of the trial, we allowed patients to enter an open label extension phase, and this is the group who elected to do that.

Remember there were 78 patients originally in this group. All but about five or six patients actually completed the 52 week trial, and 58 of these elected to go into the open label extension. So this is the intention to treat analysis on those 58 people who entered the open label study.

What you see is this fall in HBA1c, which we originally saw is sustained for an additional 72 weeks beyond the 52 weeks of the original study. So 124 weeks of glucose control was evidenced in this trial, and we presented these data at the ADA last year. So very nice, sustained glucose lowering as mirrored by this fall in A1c, which is sustained over time.

Now, in terms of the number of people who get to target levels, this is the A1c group. Less than seven percent who went into the open label extension at 52 weeks; there was 47 percent of people

with an A1c less than seven percent, and 52 percent at 124 weeks of treatment had an A1c less than seven percent.

I'm going to talk in a little bit about why we think that this sustained glucose lowering that we see with this particular drug is occurring or at least one hypothesis.

So in summary, in terms of significant clinical benefits, there is significant and sustained glucose lowering in combination with sulfonylureas, added onto the other findings that we've already seen.

Now, what about troglitazone as initial monotherapy? This has not been as well studied as the prior combinations, but we do have a fair amount of experience with this.

This is a six-month, double blind, placebo controlled study that was one of the trials that was used in support of the application and the approval for monotherapy. The data were published last year in the JCE&M.

There were 402 patients in this particular trial. Eighty-six of these were naive to drug therapy. So about 300 people had previously been treated with SU.

The mean A1c was 8.5 percent, and in this

particular group we studied four different does of troglitazone.

Now, because really the question of interest is really using the product as initial monotherapy in patients, we focused the presentation today really trying to look at that question. So the patient numbers that we'll be showing you are small because they deal with the diet only patients.

This is the fasting serum glucose over time. These again are from the JCE&M publication. This is the placebo group. They basically stay about the same during the course of the study.

There was a fall in all of the treatment groups, and you see really most of the effect here by about a month or so of therapy. There is some drifting down over this period of time. These are the mean data, and there's a fall also at two and 400 milligrams.

Now, one of the aberrancies of this particular trial is this is the only study in which we have not seen a clear dose response at 400 milligrams. As evidenced by the sulfonylurea combination study I've just showed you, that's much more typical.

There was not as much response in the 400 milligram group in this trial even as there was at 200

milligram, both in terms of glucose and in terms of A1c, but focusing on the 600 milligram group here for a second, there was a fall of 42 milligrams per deciliter compared to placebo, which led to a 1.4 percent fall compared to placebo. An absolute fall of one percent was seen in this particular study.

This is the serum insulins from this trial. I've not talked about this to this point. This is the logical place to look at it. These are monotherapy patients. There is a very rapid fall in insulin, which is sustained across the course of all the studies that we've done with troglitazone.

This is about a 25 percent fall in plasma insulin in these patients at 600 milligrams per day, again, consistent with the mechanism of action of reducing insulin resistance.

Now, one of the questions that we've asked is we've seen that the glucose lowering effect of troglitazone in combination with SU is sustained. What do we know about its effects as monotherapy?

This is some data actually that was shown as part of an analysis to the Committee two years ago. These are data actually from a cardiac safety study. So the main purpose of this trial was not to show a lowering of glucose.

The patient numbers are small. We had a lot of dropouts early in this trial. There ended up being 22 patients in the troglitazone arm compared with about 35 in the glyburide arm.

We did instruct physicians during this trial to titrate glyburide for maximal glucose control. The doses of troglitazone were 600 milligrams in the first year and 800 milligrams in the second year.

The point I want to make has nothing to do with absolute fall. It has to do with the pattern. When you look at the intention to treat analysis, which I did not show you here today, you see the same pattern. The absolute magnitude between the two bars is only about a half a percent apart, but the pattern is sustained.

And what we've done is to take the monotherapy trial that I showed you before, the six month study, and we allowed the patients to go into an open label extension. We allowed them to titrate up, and what I've show you here are the patients who were either on four or 600 milligrams at the end of the trial. They were all naive patients. So this is the diet only subset.

Thirty-six patients are indicated here.

This is a completer analysis. There is a difference between the beginning and the end here of about seven patients across the period of time.

There is a sustained and continued fall in HBA1c across time to where the mean at the end is about 7.1 percent. I didn't put a P value on this, but this is highly statistically significant compared to the baseline. Obviously you can't do a placebo analysis on this because the placebo group at six months in this trial was allowed to titrate up, but the same pattern does appear to be emerging in terms of this.

Now, the other question that has been asked is what is the efficacy of troglitazone relative to other agents. This has been a recurring question, and so we wanted to present these data.

This is a head-to-head study which was done in Europe by Glaxo. This is Type 2 patients, again, a mixture of diet only and prior SU treated patients. They were given either one, two or 600 milligrams of troglitazone at a fixed dose. They were titrated up on that form into the maximal tolerated dose. The average dose of metformin at the end of the trial was 1.6 grams as initial monotherapy in these patients.

Now, these are the HBA1c's and fasting serum glucose. This trial was designed to use metformin as the comparator. This is two and 600 milligrams, and basically what you can derive from the conclusion here is that there is not a statistically significant difference in glucose lowering as measured by A1c or glucose compared to the metformin arm of this particular trial.

The other thing that we've looked at is a responder analysis showing the number of people who had at least a one percent fall in HBA1c. This was part of the predetermined analyses for these studies, and what you see is that there is around 39 percent in the troglitazone group and about 35 percent in the metformin group. These were not statistically significantly different from each other. Both of these were greater than 200 milligrams per day.

The insulin levels, there was a difference between these, as you would expect. There was a difference in the lipids, as well. The pattern that we've seen previously of increased LDL, HDL, and total cholesterol compared to metformin was observed in this trial.

There was a fall in free fatty acids, but interestingly enough, in this study there was not a

statistically significant difference in triglycerides, but the patients really were not very hypertriglyceridemic, unlike our U.S. populations.

This is the change in body weight from this trial. There was a fall of 1.6 kilograms, which is what we would expect to see in the metformin only arm. There really wasn't much change at all in the troglitazone arm. This may have been statistically significantly lower than these. Clinical significance I leave up to your judgment.

So it appears that troglitazone is effective as monotherapy, both short and long term.

Now, the other interesting thing about looking at the metabolic staging of diabetes is that this red circle over here on the beta cell defect may have profound effects on the time course of what happens down through here.

One of the interesting hypotheses that has been raised is that the sustained glucose lowering which is observed with troglitazone may be due to the fact that it is either having primary or secondary effects on beta cell function.

So we've started to look at this in a number of model. This is some data from the Zucker diabetic fatty rat in which these animals were

pretreated with troglitazone. This is the only animal slide I'm going to show in this presentation.

Basically what you see is in the lean controls after 18 weeks there's a very normal architecture to this islet, normal appearing beta cells. However, after 18 weeks in the Zucker rat there's hyperplasia, hypertrophy. This is the same magnification here, and disordered array within the beta cell itself.

This is absolutely prevented by troglitazone after 18 weeks of treatment. You do not see this hyperplasia occur. The natural time course for this is to go on and completely destroy the beta cells. We do not have a -- or the islet -- we do not have troglitazone data at 36 weeks.

So the question is: what does this mean in man? Obviously we're unable to do these kind of pancreatic studies in people. So we've started to look using some other techniques.

These are some data from Dr. Ken Polonsky at the University of Chicago. Ken and his group have conducted a number of studies to determine whether the alterations in insulin secretion and beta cell glucose seen in subjects with impaired glucose tolerance are reversible by treatment with troglitazone. They've

used a couple of techniques. I want to show one of them here just for orientation.

This is a glucose oscillatory curve in which what they're able to do is using intravenous infusions of glucose is to actually raise glucose levels and cause them to fall in a periodic rate.

They are then able to measure the normal entrainment of the pancreas to this, and this, in Ken's opinion and the opinion of many others, signals normal beta cell function that you can entrain normally.

Now, in people with impaired glucose tolerance, the prediabetic condition, you are unable to entrain them normally. The glucose rhythmicity here that you saw before you're able to sustain, but you can't get the beta cell to respond normally. So this is one technique that can be used to measure this response.

Another technique that has been used is using a graded glucose infusion in which you look at the insulin secretory response as a function of fatty or body mass index. In the control population there is the appropriate steep response of the pancreas to this. So very small changes in glucose concentration peripherally cause a very abrupt response in changes

in insulin.

As people develop IGT, this curve flattens, and then as Type 2 diabetes progresses, it gets even worse. So it takes more and more glucose to get the same type of insulin out of the pancreas.

So what does this look like in people with IGT before and after troglitazone? The reason that they've studied IGT patients is these are people without fasting hyperglycemia. We currently have a trial going on in patients with diabetes to see if this same phenomenon holds true.

This was 24 subjects who received either troglitazone or placebo, and these data were published in the JCI in 1997. They looked at a frequently sampled IVGTT to measure insulin sensitivity and the glucose oscillations and the graded IV response I just showed you using those techniques.

This is the subject characteristics. They were obese. They had IGT as evidenced by a two hour glucose of 186. They did not have fasting hyperglycemia.

Insulin sensitivity was doubled following treatment with troglitazone, very consistent with all other patient models that we've looked at. No change in the placebo group.

The graded glucose infusion, remember that the normal has a much steeper curve. This is troglitazone before and after, and notice the way that that curve moves back up to the left. This is statistically significant. There's no change at all in the placebo group.

So it appears looking at this technique that the insulin secretory response is moving much more towards normal.

Now, what about the insulin entrainment. You see here the glucose oscillations going up and down and the complete lack of entrainment here in the IGT, patients treated with placebo before and after. However, using troglitazone after 12 weeks you're able to entrain the pancreas normally to these glucose oscillations and actually lower the total amount of insulin that was required to meet that need.

So troglitazone does appear as well to have positive effects on beta cell function, as I said. How this translates into Type 2 diabetes is something that is currently under investigation.

Now, we don't have time today to go through all of the lipid and atherosclerotic data which has emerged on this drug over the last few years. I've summarized the lipid data on here. I'd

be glad to show any of this later in the discussion if it's of interest.

What's been documented in a lot of publications, including some of our own, is that the drug causes a decrease in free fatty acids, trigercerides, an increase in HDL, an increase in LDL particle size, a decrease in LDL oxidation, and a decrease or no change in ApoB levels.

One of the interesting emerging areas is the effect on vascular function. This was alluded to earlier in the public session. It's becoming clear that based upon data in man and in animals that there is a reduction in PAI-1 activity. This has been demonstrated in man. Platelet activation decreases. This has been demonstrated in vitro. The decrease intimal medial thickening has been shown in man and published last year in the JC&M. Decreases in E-selectin level have been shown in man and decreases in vascular reactivity and flow mediated coronary dilation have also been shown in man.

One of these studies, and I'm just going to show you one piece of data from this, which is very interesting. These are data presented at the American College of Cardiology last year.

They looked at diabetic patients with

angiographically documented coronary vasospasm and residual angina pectoris who were treated for four months with troglitazone. They looked at them at baseline and at four months of treatment, and they also looked at flow mediated vasodilation.

What they demonstrated was a statistically significant decrease in angina pectoris following treatment with the drug, as well as a statistically significant increase in flow mediated dilation, leaving us to think that, in fact, there may be something there that is worth pursuing, and there's a number of studies going on now in larger populations looking at these data.

So troglitazone appears to have positive effects on both beta cell function and atherosclerotic risk factor.

Now, I've shown you data which demonstrate that troglitazone as monotherapy or added onto other treatment failures provides significant and sustained glucose control. An important question to ask is how might this translate into impacting on clinical endpoints.

We have not yet obviously had the time to conduct a long-term endpoint study. Yet based on the results in the U.K. PDS and the DCCT, as well as the

Kumomoto in Japan and the Wester study, which Professor Home made reference to, we would anticipate a positive effect particularly in microvascular disease.

We have used the published model by the group at NIDDK to model and estimate the effect on endpoints using our demonstrated controlled data at 124 weeks from the glyburide comparison. We have assumed conservatively that beyond that 124 weeks where we have surety of data that control worsens at that point in time in a manner seen in the U.K. PDS.

We have no data to suggest that control would worsen at that point in time. So this is a conservative estimate.

The impact on microvascular data falls between the risk reduction between the U.K. PDS and the DCCT. Now, this translates into a reduction of over 7,000 cases of blindness, amputation and renal failure, assuming you followed 100,000 patients over ten years. So the benefits are very substantial.

I'd like to turn this back over now to Dr. Zerbe for the summation.

DR. ZERBE: In this final section of our presentation, it's my intention to summarize the major points and attempt to put the risk-benefit assessment

for Rezulin into perspective.

FDA Commissioner Haney in a recent presentation to the National Health Council summarized our challenge very clearly, which he said, "We need to be very precise when we talk about the whole issue of safety because it is really a judgment made of risk and benefit," end quote.

Precision is key, and all of us must resist the temptation to be influenced by sensationalism and rumor when we assess drug safety. It would be a mistake for this Committee to ignore a significant safety issue, but it would be no less a tragedy for the actions of the Committee to discourage patients with diabetes from seeking appropriate treatment or to seek treatments which provide less overall benefit.

In an attempt to put into perspective the many facts and interpretations that have been presented today, I will frame them as a response to six questions.

First, does troglitazone play a causative role in cases of severe hepatotoxicity?

Two, assuming troglitazone plays some role in such cases, what is the risk of such events?

Three, how does the risk of Rezulin

treatment compare to that of other available agents?

Four, what are the benefits of Rezulin?

Five, is the risk-benefit ratio for Rezulin favorable?

And last, what additional steps can be taken to further improve both the safety and efficacy of Rezulin?

In answer to the first question, does Rezulin play a causative role in cases of severe hepatotoxicity, both Parke-Davis and the FDA agree that the data indicate that Rezulin is associated with rare cases of idiosyncratic liver failure.

That then leads us to the second question. What is the risk of such events? There remains some disagreement between the FDA and Parke-Davis on the role of the drug in some individual cases, but since we are evaluating safety, we've taken a conservative approach, and we've used the larger number of 35 deaths or transplants as determined by the FDA to calculate the rate.

Using this number, the incidence is one in 45,000 patients exposed or approximately one in 34,000 if one considers patient-years of exposure.

Though it has been suggested that this rate may be an under statement of the true rate

because of under reporting, two points are worth emphasizing.

First, published data on the risk of drug therapy is rarely corrected for under reporting since it cannot be accurately quantitated for any agent. So in considering how the risk compares to that of other agents, such unadjusted rate is an appropriate figure to consider.

Second, the data presented by Dr. Pierce support a relatively high rate of reporting for Rezulin. Thus, though no risk should be trivialized, we feel that the rate is low.

Furthermore, the rate estimate of one in 45,000 is based on data from the whole period of Rezulin being on the market. Both Dr. Graham and Dr. Pierce clearly showed that the rate since the label change has decreased significantly. These estimates, based on the second year of marketing were one in 104,000 patients exposed.

So even assuming that all of the cases identified by the FDA were truly related to Rezulin, the risk is low and has decreased since monitoring has been implemented.

These estimates may be low, but if there's a safer alternative with comparative benefits, the

patient is assuming excess risk by using the drug, and that brings us to the third question. How does the risk of Rezulin treatment compare to that of other therapies?

First, we need to agree that the treatment of diabetes is not optional. In the case of impotence, incontinence, acne, or alopecia, for example, patients can elect no treatment and the overall survival is not adversely affected.

No one, however, would argue that pharmacologic treatment of Type 2 diabetes is optional after diet has failed. So when considering the safety of Rezulin, the risk compared to alternative treatments is more relevant than the consideration of absolute risk.

In our presentation we have focused mostly on the risk associated with metformin, and this is not because metformin is an unsafe medication, but because it is used in a way very similar to troglitazone, yet like troglitazone is a relatively recent entry into the U.S. market, and it has clearly identifiable toxicity, that is, lactic acidosis.

Dr. Home showed in his presentation that based on publicly available data, the rate of fatal lactic acidosis associated with metformin was very

similar to that of fatal hepatotoxicity associated with troglitazone. Fortunately changes in labeling and better patient selection have decreased the rate of fatal complications for both drugs.

Likewise the risk of fatal hypoglycemia with insulin or sulfonylureas is reported to be similar to the fatalities with either metformin or troglitazone.

We would conclude from this that though the pathologies differ from drug to drug, all of the available treatments for Type 2 diabetes, including troglitazone, carry a similar, albeit small, risk of death.

A word about future therapies is also appropriate at this time. Much has been speculated about the safety of the newer agents, some of which will be reviewed by this Committee next month. It's worth noting that rare events like lactic acidosis and liver failure are usually not identified until wide exposure in clinical practice.

It would be inappropriate to compare and act upon safety profiles related to serious but rare adverse events between marketed drugs which have exposure in millions of patients and those still in an investigational stage which have exposures in

thousands of patients.

Rare but serious adverse events cannot be reliably excluded by experience in relatively small databases.

Though we conclude that the safety of Rezulin is comparable to alternative pharmacologic treatments available in the Type 2 patient, the benefit must be as good or better if the overall risk-benefit ratio is to be comparable, and thus, we come to the fourth question. What are the benefits of Rezulin?

The unique mechanism of action of Rezulin, that of increasing the sensitivity of cells to circulating insulin, makes it a particularly attractive choice for the treatment of Type 2 patients where a critical defect is insulin resistance. Dr. Whitcomb has shown marked improvements in glucose control when Rezulin is added to the treatment regimen of patients who have failed insulin therapy or failed the combination of sulfonylureas and metformin, shown here. For these patients Rezulin has been critical for the achievement of adequate glycemic control.

Remarkable improvements in glycemic control have also been seen when Rezulin is added to patients who fail sulfonylureas, and this is achieved

with lower circulating insulin levels and appears to provide better control for a longer period of time.

Because of its mechanism of action, Rezulin is also a logical choice for naive patients. By improving insulin sensitivity, pancreatic responsiveness is maintained, pancreatic entrainment is preserved, and this translates into long-term benefit in monotherapy patients who respond.

This level of improved control provides substantial benefit. Data from the DCCT and U.K. PDS studies would indicate that if we were able to provide this level of control and improvement in hemoglobin A1c to the six million patients in this country who are inadequately controlled by their current treatment and maintain that control for ten years, we would be able to prevent nearly half a million cases of renal failure, amputations, and blindness.

So what are the benefits of Rezulin? Efficacy has been demonstrated in a spectrum of combinations, as well as monotherapy. Its unique mechanism of action is complementary and appears to be preserving endogenous pancreatic function, which translates into better and longer lasting control.

That brings us to the penultimate question. Is the risk-benefit ratio for Rezulin

favorable? The available data show that the risk is low and comparable to alternative therapies. The benefit is complementary and unique, adding significantly to the therapeutic armamentarium in a life threatening disease.

Therefore, the risk-benefit is surely acceptable given the uniqueness of the benefit. Twenty patients every hour die in the United States as a result of diabetes and its complications. Approximately 100 patients with diabetes have died since the beginning of this meeting. These patients desperately need medications that can help them control their disease.

Our final question then is: what additional steps can be taken to further improve the safety and efficacy of Rezulin? Just because we conclude that the risk-benefit ratio is favorable doesn't mean that it cannot be improved further. So what would we propose to do?

In order to further improve safety, we will submit labeling changes to the U.S. that will warn against the use of troglitazone in any patient who has a history of liver disease of any etiology or any patient with a history of alcohol abuse.

We will propose refinement of the trial

period for the assessment of efficacy in naive patients so that only those patients gaining benefit will be continued on the drug.

We will issue a patient package insert, which has already been reviewed by the FDA, so that patients can take a more active role in the management of their disease.

And we will expand patient and physician education programs, such as the Rezulin results program, which provide monthly reminders for liver monitoring.

And last, to enhance the global benefit of the use of Rezulin, we will continue studies to identify those patients most likely to benefit, and we look forward to the opportunity for direct comparative studies with the newer glitizones so that rumor can be replaced by fact.

Some have proposed drastic action, but this morning you heard very compelling anecdotes from physicians dealing with patients who have had dramatic benefits from Rezulin. Denying this drug to those patients would be a serious step, and it must be based on compelling data.

As Dr. Haney said, the evaluation of drug safety must be precise. This Committee would be doing

the patients with Type 2 diabetes a tremendous disservice if it recommended actions which prevented or discouraged physicians or patients from using this drug in a beneficial way as supported by data.

Thank you. We will be glad to entertain your questions.

CHAIRMAN BONE: Thank you, Dr. Zerbe.

We'll take some time now for questions addressed by members of the Committee to the sponsor with respect to their specific presentations, and we will try to keep focused on questions of fact or information here and go into our general discussion and broader discussion of specific points a little later on in the program.

I think Dr. Braunstein had the first question.

DR. BRAUNSTEIN: Actually it's both the sponsor and the FDA. Do you want me to hold off then?

CHAIRMAN BONE: I'm going to suggest that we focus on the questions for the sponsor at the moment so that we can kind of stay organized. Otherwise I think we may lose track, and then I think if you wanted to ask your question of the sponsor now and clarification from the FDA later, that would be fine or we could do that during our general discussion

period.

DR. BRAUNSTEIN: There are a number of discrepancies between what the sponsor has stated and what the FDA has stated, and I'd really like to ask them both the same questions --

CHAIRMAN BONE: All right.

DR. BRAUNSTEIN: -- and have them respond to that. So why don't I wait until the general discussion?

CHAIRMAN BONE: I'm going to ask Dr. Braunstein to make a quick list of those. We'll give a list to each of the people, and we can ask that question, and we'll expect crisp responses on both sides.

Thank you.

DR. BRAUNSTEIN: Fine.

CHAIRMAN BONE: We'll start over here and just work around. Dr. Marcus.

DR. MARCUS: I'm surprised not to have heard anything about tissue concentrations or plasma concentrations of the drug or its metabolite in whether there are people with various polymorphisms in the cytochrome P-450 system or whether there is any attempt to look prospectively at which individuals might be most likely to suffer an adverse consequence.

Surely you have access to tissues or plasma specimens on those people who have become ill, and the question is: are they in any way distinguishable from those who have not?

DR. ZERBE: It's really an excellent question. At the time the first series of events occurred, we initiated as part of the REACH study, which was referred to in the program, a systematic collection of samples to be evaluated for a whole series of drug metabolizing enzymes and to try to identify those patients that were at risk or not.

As you probably recognize, that is a very difficult process, and it takes a very large population. Even the REACH study, which is targeted to be about 5,000 patients, probably will not be large enough to clearly identify it, but we have systematically collected those samples to try to see if there are any genetic predispositions to this problem.

I don't know whether anyone wants to add anything. Al, do you want to say anything or do you have a follow-up question?

DR. MARCUS: Well, what our blood concentrations of troglitazone or its metabolites, do we know that?

DR. ZERBE: Yes. Well, go ahead, Al. Do you want to?

DR. SALTIEL: Maybe I can answer that question. We've actually compared troglitazone and the quinone metabolite levels in patients with elevated ALTs and who do not have elevated ALTs, and they're actually absolutely the same. So there's no prediction there of ALT elevation.

DR. MARCUS: Okay.

DR. SALTIEL: With regard to the other question, I have a list of some of the enzymes that we're looking at in these studies, in the samples which I can show you. It's a list of the usual P-450 related enzymes, and nothing surprising there. So far we haven't really seen anything.

CHAIRMAN BONE: Also, anyone else on the left? Dr. Cara and Dr. Molitch.

DR. CARA: I have a few questions for you if you don't mind, and I'm a little bit confused because of some inconsistencies that I hope you can clarify.

One of them is on page 10 of Dr. Watkins' presentation compared to page 3 of Dr. Pierce's presentation. I'm looking now at the U.S. reports of jaundice in Rezulin treated patients, and then looking

at the worldwide clinical trial data of jaundice.

I mean, on the one hand, of the U.S. reports of jaundice in Rezulin treated patients, that total number is 290, whereas in the trials it's three. What are the actual numbers of patients there? What's the actual denominator there?

DR. ZERBE: The denominator? Well, perhaps I don't have the book in front of me. So perhaps you --

DR. CARA: Part of the problem I'm having is that there's little pieces of data sort of put in, but nothing bringing it all together.

DR. ZERBE: Would it be worthwhile reviewing the set of numbers, this one? And then maybe perhaps we can clarify it based on that series.

DR. CARA: Well, I have a couple of other questions --

DR. ZERBE: Okay.

DR. CARA: -- related to specific numbers that maybe you can put together.

DR. ZERBE: One at a time or --

DR. CARA: However you want to do it. Let me tell you what my questions are.

DR. ZERBE: I'd suggest we do it one at a time because we probably will have to refer to

different tables, if you'd like.

DR. CARA: Okay. So what's the actual number of patients on Rezulin here?

DR. ZERBE: I think Dr. Pierce is behind you ready to address that question.

DR. PIERCE: Well, the denominator in terms of the total number of patients, I suppose, is 1.58 million. This is from the marketed drug experience. Parts of the difference, as I indicated, all of the graphs that I showed with jaundice and bilirubinemia include all patients with jaundice and hyperbilirubinemia without attribution. In other words, it's every case of jaundice and hyperbilirubinemia that we see.

Some of the slides that I showed differed slightly in numbers depending upon the purpose of the slide. If we're looking at the duration of drug therapy, we need to know the onset date of therapy until the event date, and if we don't have both dates, we can't use that patient.

If we're looking at the effect of publicity, we need to know the time of the onset and the time of the report, and if we don't have both of those dates we can't use them. So that's the reason for some of the small differences in numbers.

Does that answer your question?

DR. CARA: Well, no, it doesn't answer my question. It tells me why you can't answer my question.

(Laughter.)

DR. CARA: The other question that I have is related to the data looking at the comparison of the metformin versus the troglitazone treatment, and then looking at patient years per 100,000 patient-years.

My concern is that that may not necessarily reflect true length of treatment per each individual patient., and what I'm concerned about specifically is the issue that was raised earlier this morning regarding patients needing to be on treatment at least six months before you can actually evaluate any sort of clinical data in regards to jaundice and potential liver damage.

Do you have any idea of what the actual incidence is for patients that were on treatment for greater than six months?

DR. ZERBE: I believe that's shown on Dr. Pierce's slide talking about the duration of therapy and the number of cases that occur by duration of therapy. I think you show both hyperbilirubinemia --

DR. CARA: Yeah, but he doesn't include number of patients on that. It's just duration of treatment.

DR. ZERBE: Yeah, you're right, but we can provide that.

DR. CARA: But it could be one patient.

DR. ZERBE: And particularly at the end it is one patient because the reason those numbers go up is because the denominator is falling so quickly, but we could actually calculate, I think the actual number of patients.

You want to know beyond six months?

DR. CARA: Well, I want to know specifically when you're comparing metformin, the incidence of side effects for metformin and insulin and sulfonylureas and whatnot. You made a pretty strong case that troglitazone was not any different, but obviously patients at treated with insulin, metformin, and sulfonylureas for significantly longer than what I've seen treated with troglitazone, which plays a very important role.

I mean, it plays a very important role in potential development of side effects. So if you have any data for patients that have been treated longer than six months in terms of the actual incidence of

things like hyperbilirubinemia, jaundice, and actual acute hepatic failure, that would be very helpful.

DR. ZERBE: Well, I think those data are actually, with the small derivation -- I think we could answer the question fairly quickly.

DR. CARA: Great.

DR. ZERBE: Of those patients, what the rate is, because we know both the denominator and the numerator for all of the months beyond six months; so we could very, very quickly calculate that.

I think there might be some caution in sort of comparing that rate to, say, something with metformin. I think we have to very carefully think through that because there could be other issues related to metformin where a population comparison to metformin may not actually match up or be valid to an after six month comparison with troglitazone, but we would be happy to provide the troglitazone half of that estimate, if that would help.

DR. CARA: Your point is well taken, and I would look forward to seeing the troglitazone data in that regard.

DR. ZERBE: So we can probably do that fairly quickly.

DR. CARA: That would be great.

DR. ZERBE: I'll volunteer my colleagues for that.

CHAIRMAN BONE: Fine. We'll expect to hear that within the questioning period.

DR. ZERBE: Okay.

CHAIRMAN BONE: Let's see. Dr. Colley, I think, has a question.

DR. COLLEY: Regardless of what estimates of numbers of patients might be at risk for toxicity you place confidence in, I think we're all in agreement there is some risk, and one way to reduce that risk is to limit the drug to patients that we know will get an adequate response.

What factors have you identified that predict that patients will respond to troglitazone therapy, either monotherapy or combination?

DR. ZERBE: Well, first, I think it's important to reemphasize one point that Dr. Bilstad made very early on when we talked about the label change. The restriction of duration of therapy, sort of a test of response, is already in place at two months for monotherapy.

We did that in the final label change. So basically even assessing, you know, the safety risk-benefit in monotherapy to existing data or old data

prior to that label change probably isn't valid because the patients after the label change, if physicians are following the guidelines, would not continue therapy beyond two months if, in fact, they weren't getting benefit.

So the overall risk-benefit has already been improved in that way.

Now, in terms of estimating patients that might benefit preferentially, I think one thing that we are, I guess, looking more carefully at, and Dr. Whitcomb might want to address, and that is patients with particularly high, you know, glucose levels at the time of presentation for monotherapy may not respond as well as patients at the lower levels.

And, frankly, it fits the diabetes model because one of the things that, you know, Rezulin is dependent upon, potentiating the effects of circulating insulin. So if, in fact, it's far advanced and there's less circulating insulin, the benefit may not be as great.

It's difficult to get a clear answer to that question, but that's been one of the possible things that we've talked about as well.

Randy, do you want to add anything to that?

DR. WHITCOMB: The question that you're asking is really a good one. I think the response rates for people with combination therapy, no matter which model you look in, are extremely high, and I think the other point to be made is if you looked at the mean time curves for the response for the population, you see most of the effect by about four weeks or so if you're going to see it.

I think the issue with initial monotherapy is that it's not as clear that the responder time course is as precise. It looks like it's around four weeks by the time you see the response, but again, it depends on where the patient is kind of starting out at, and it looks like people are, say, less than about 250 milligrams per deciliter or so with the fasting glucose initially respond better than those that are higher than that, for example.

We originally thought that maybe something closer to 200 was the right number, but based on analyses I don't think that's the case. I think it's more like 250 or lower as initial monotherapy.

That's not true for combination where the response rate appears to be very high in all models kind of that we've looked at. Again, it depends on how you define responder, which has been one of the

great conundrums out of this.

CHAIRMAN BONE: Thank you.

Drs. Molitch and then Genuth and then New.

DR. MOLITCH: I just have a question of clarification for Dr. Pierce for his second to last slide, which looked at the reports of serious liver events by duration on drug. Is there a way to put that up?

My only question is in looking at the data, it's sort of reassuring that it goes down with duration, but since its rate per 100,000 patient-years, how many patients do you have who are on the drug for more than a year that will allow you to come up with a number out past the year that will give you reasonable confidence that it's close to zero?

DR. PIERCE: Yeah, it's similar to the question that was asked earlier, and I believe I have the answer to that now.

With regard to death and transplants beyond one year, we have none that are attributable.

DR. MOLITCH: What's the denominator?

DR. PIERCE: The denominator beyond one year would be about 400,000, as I've indicated for the persistency. That's for death and transplant.

DR. MOLITCH: But each time point as you

go out further and further, that number gets smaller and smaller?

DR. PIERCE: That's correct.

And the answer to the earlier question about the number of cases of death and transplant beyond six months are seven, and the denominator is 600,000. So that's 1.1 per 100,000.

CHAIRMAN BONE: All right. Thank you very much.

Let's see. Dr. Genuth.

DR. GENUTH: I'd like to ask one question of Dr. Whitcomb and one of Dr. Zerbe.

There's been a lot of emphasis comparing troglitazone and metformin in terms of their safety. So I'd like to understand better the head-to-head comparison between them with regard to efficacy. I'm having a little trouble understanding page 30 and 31 which were slides you showed of the only study I'm aware of anyway where there's direct comparison between the two drugs.

I'm just confused as to what the baseline glucoses and A1c's were and --

DR. WHITCOMB: What page?

DR. GENUTH: Page 30 and 31 in the red Parke-Davis handout.

DR. WHITCOMB: Yeah, that's the slide.

DR. GENUTH: Could you just take me through the numbers?

DR. WHITCOMB: Sure. I'm sorry. I didn't clarify that very much.

Actually if you go to the next slide, I might be able to help you a little bit better. These are the Ns of patients in each of the group. You know, it's a little less than 100 percent treatment group, is the N of patients.

The A1c at baseline for the population was about 8.2 percent. So they were fairly mild, if you will, Type 2 patients.

DR. GENUTH: So looking at that slide, troglitazone at 600 milligrams lowered hemoglobin A1c from 8.2 to 7.3?

DR. WHITCOMB: In this particular trial, yes.

DR. GENUTH: As did metformin?

DR. WHITCOMB: And this, importantly, a dose of metformin -- the instructions to the investigators were to titrate to maximally tolerated dose, which ended up being a mean of 1.6 grams in this particular trial.

DR. GENUTH: Okay.

DR. WHITCOMB: Is that the question?

DR. GENUTH: Yeah. That's the farthest out you have data, is 26 weeks.

DR. WHITCOMB: That is correct. This trial was truncated at the end of six months.

DR. GENUTH: Okay. I'd like to ask Dr. Zerbe. You, I think, suggested in your last summary slide, and I think it's in the new labeling that you're suggesting, that one way to increase the safety of using troglitazone would be to define what a trial period of treatment would be in naive patients previously treated with diet alone.

And I think what it says here is that they get one month at 400 milligrams and another month at 600 milligrams, and then if there's no adequate response, something else should be done for the patient.

Now, first of all, I wonder what the company means by not responding adequately. What's the definition the doctor is supposed to use for an adequate response?

DR. ZERBE: I think there are criteria, are there not, that we actually specify that were agreed to with the FDA? I don't have a package insert in front of me. So we can explain what that was, if

you don't mind, Randy.

DR. WHITCOMB: The definition -- and, again, this was done very arbitrarily -- was a fall of at least 30 milligrams per deciliter of fasting plasma glucose, was the responder definition that was used actually in the monotherapy trials as well as in several other studies.

The data that I showed you for the head to head with metformin was based upon an A1c responder definition, by the way, which is why the numbers are lower than what we've seen generally.

DR. GENUTH: In fact, 30 milligram per deciliter indicator of response irrespective of the starting fasting glucose?

DR. WHITCOMB: That's what we have indicated to this point in time. One of the proposals is that if you have patients that fall at least 30 milligrams per deciliter, but haven't reached ADA goals, is that you add another drug onto it, you know, like a sulfonylurea where there's clearly an added benefit to the patients.

DR. GENUTH: I'm probably not supposed to comment at this point, but I think there's a big difference between dropping from a fasting of 250 to 220 and dropping from a fasting of 150 to 120.

DR. WHITCOMB: Right. I think one of the important things, and you know this better than I do, is that the definition of, quote, response is not standardized, and when you look across drug products, it's very hard to kind of get these data for other drugs to make some comparisons, and you end up with some anecdotal experience. So that's been part of the problem.

DR. GENUTH: If there is no adequate response, is the advice to the physician to try another oral agent as monotherapy or is the advice to the physician to add another drug to troglitazone?

DR. WHITCOMB: Yeah. The current labeling is to seek alternative therapeutic options, I believe is what the labeling says.

DR. GENUTH: Yeah. I'm trying to define that.

DR. WHITCOMB: Well, I'm trying to tell you what was in the labeling. I mean what we think makes sense, quite frankly, is to add something onto it if you've not responded adequately, but I think the question is -- and this gets back into risk-benefit again -- if you respond to the drug as monotherapy but don't reach target, I think it makes sense to add something on.

The question is -- and actually the studies are going on now to define this -- if you don't respond as well and you add on other drugs, what is the response? And those trials are going on right now.

DR. GENUTH: Well, there's a big difference between substituting and adding in the sense that when you add, you continue the risk of liver failure from troglitazone. When you substitute, you get rid of that risk and maybe you --

DR. WHITCOMB: Maybe you pick up another one, right.

DR. GENUTH: -- have a different, competing one.

DR. WHITCOMB: Which is why the notion of adding something on where you've then ratcheted the benefit up another level was the logic in that. Does that make sense, Dr. Genuth?

CHAIRMAN BONE: Thank you.

Dr. New has a question. Dr. Braunstein has kindly written out his two questions, which we'll get to in a few minutes after the FDA and company have had a chance to look at them and formulate the answers so that we can be concise, and from looking at these questions, I think if we can achieve closure on those

questions, it will be very helpful.

Dr. New had the next question.

DR. NEW: I need clarification on the following. What is the evidence that monthly monitoring of liver chemistries is preventive of liver failure, and if there is evidence, I just don't understand entirely what it is, and if there isn't good evidence, why do it?

DR. ZERBE: Well, it's another excellent question, and I think no one knows the true benefit of liver function monitoring. I think we can only approach it sort of in a circumstantial way.

We do know that the label changes that were made called for both monitoring, but at the same time, there was substantial publicity. There was information, professional education about monitoring that increased awareness of the problem.

I think probably you can't totally ascribe the decreased rate in the events to monitoring alone. We believe the monitoring is taking place much more frequently than Dr. Graham suggested. However, I think we would be, you know, insincere if we said that we believe that physicians are monitoring perfectly according to the label.

But I think just the awareness of it,

recognizing the importance of taking the measurements even if they may be at, you know, five and a half weeks instead of exactly at four weeks, probably has contributed to the benefit and also the awareness. That is, if people come in feeling badly, physicians in general are more aware of this as being a potential problem.

So I think it isn't strictly monitoring, but I think the overall awareness is substantial, as we demonstrated in the survey, and I'm sure that has an impact on behavior.

I think we would be reluctant to reach the conclusion that monitoring was playing no role and, therefore, eliminate it.

DR. NEW: Okay.

CHAIRMAN BONE: Dr. Lewis had a question. Oh, Dr. New, did you have --

DR. NEW: No. Just so that you would say that you are convinced that monitoring plays some role in preventing complications of the liver?

DR. ZERBE: I personally would say that, yes, it plays some role. I think the more significant issue is probably that I don't think -- this is a serious enough problem that I don't think we would suggest that it not be done, if that's the question.

CHAIRMAN BONE: Dr. Lewis and then Dr. Kreisberg.

DR. LEWIS: This is sort of a comment on the same point. I don't think there's any question that monitoring when done in a frequent basis like this for a drug that causes unpredictable or what we call idiosyncratic injury, where there's really no markers of who's going to develop that injury; it occurs after several months in moth patients. The only way you can find who's likely to develop more severe injury, not who's going to develop the first instance of injury, but try to prevent them from going on to more severe injury, is with frequent monitoring.

And this is not a drug that's an allergic type reaction, with fever and rash and eosinophils and things like that, which announces itself as an allergic type reaction and you know something's wrong. This doesn't do that until you actually develop the severe liver injury.

And by that time you have hepatitis-like symptoms, which if the patient recognizes them or the physician recognizes them, even if it's in between those monthly periods, additional monitoring should be done according to the new guidelines.

One of my question is I'm not sure if