FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

SEVENTY-THIRD MEETING

OF THE

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

8:10 a.m.

Friday, April 23, 1999

Congressional Ballroom
Bethesda Marriott
5151 Pook's Hill Road
Bethesda, Maryland

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ATTENDEES (Continued)

TAKEDA PHARMACEUTICALS REPRESENTATIVES:

MARTHA CHARNEY, PH.D.
SAMUEL M. COHEN, M.D., PH.D.
JAMES W. FRESTON, M.D., PH.D.
MARIETTA M. HENRY, M.S., M.D.
NEIL KAPLOWITZ, M.D.
DAVID E. KELLEY, M.D.
FREDERICK E. RENO, PH.D.
ROBERTA L. SCHNEIDER, M.D.

ALSO PRESENT:

MARGARET HIMELFARB

C O N T E N T S

NDA 21-073, ACTOS (pioglitazone hydrochloride)
TAKEDA PHARMACEUTICALS

P R O C E E D I N G S

(8:10 a.m.)

DR. BONE: Good morning. I am Dr. Henry Bone. I am chairing the 73rd meeting of the Endocrinologic and Metabolic Drugs Advisory Committee, which is now in session.

Today's meeting will discuss certain aspects of the compound pioglitazone. And I want to explain at the very beginning that this is a little bit different from some of our meetings. We are not being asked to make a specific recommendation regarding approval or otherwise today.

The application for this compound was received somewhat more recently. And please correct me if I make any errors. If I understand it correctly, the application was received somewhat more recently than the compound that was discussed yesterday. So, the agency felt that it was premature to discuss all of the aspects of efficacy with this compound.

However, because there is considerable general interest in safety aspects of the class and each drug individually in this class, it was felt that it was timely to at least have that discussion at the present time. So, the focus on the review up to this point and so forth have all been on making sure that we had as complete information

about safety as possible.

The agency and the committee very much appreciate Takeda's participation on this basis. And I want to emphasize that absolutely no inference should be drawn from this somewhat unusual approacn regarding the efficacy aspects of this compound whatsoever.

Any further comment?

(No response.)

DR. BONE: All right. The first thing I would like to do is have the introductions, and we'll just start at my extreme right, with Dr. Bilstad from the agency.

DR. BILSTAD: Jim Bilstad, Office of Drug Evaluation II.

DR. SOBEL: Sol Sobel, Endocrine/Metabolic Division.

DR. MISBIN: Robert Misbin, Medical Officer.

DR. STEIGERWALT: Ron Steigerwalt, pharmacology team leader.

DR. ILLINGWORTH: Good morning. Roger Illingworth, member, FDA Advisory Panel, Portland, Oregon.

DR. HAMMES: Richard Hammes, consumers' representative, University of Wisconsin.

DR. CRITCHLOW: Cathy Critchlow, Department of Epidemiology, University of Washington.

DR. BONE: Henry Bone, Michigan Bone and

Mineral Clinic, in Detroit.

DR. REEDY: Kathleen Reedy, Food and Drug Administration.

DR. HIRSCH: Jules Hirsch, member of the panel, New York.

DR. GENUTH: Saul Genuth, Cleveland, ad hoc member of the panel.

DR. LEVITSKY: Lynne Levitsky, Mass General, Boston.

DR. MOLITCH: Mark Molitch, Northwestern University, Chicago.

MS. KILLION: Rebecca Killion, patient representative.

DR. BONE: Thank you.

The next item is the meeting statement, which will read by the Executive Secretary, Kathleen Reedy.

DR. REEDY: The following announcement addresses the issue of conflict of interest with regard to this meeting, and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants, the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting, with

the following exceptions.

In accordance with 18 United States Code 208(b), full waivers have been granted to Dr. Mark Molitch, Dr. Henry Bone and Dr. Saul Genuth. Copies of these waiver statements may be obtained by submitting a written request to the FDA's Freedom of Information Office, located in Room 12-A30 of the Parklawn Building.

In addition, we would like to disclose for the record that Dr. Mark Molitch has past interests which do not constitute financial interests within the meaning of 18 United States Code 208(a), but which could create the appearance of a conflict. The agency has determined, notwithstanding these interests, that the interest of the government in Dr. Molitch's participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Molitch may participate in today's session.

In the event that the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants, we ask, in the interest of fairness, that they address any current

or previous financial involvement with any firm whose products they may wish to comment upon.

DR. BONE: Thank you very much.

Dr. Sobel, did you have some remarks to make?

DR. SOBEL: I have nothing really to add. Your statement captured what we wanted to convey. I feel that the complete discussion of various safety issues that pertain to the Takeda compound will be made. And as Dr. Bone said, in regard to efficacy, we just haven't had the time, because this is a more recent application, to reach agency closure on this. But this in no way implies any problems or negativity with the efficacy of this compound. We continue to look with interest at this whole class of compounds and would appreciate your further discussion of safety aspects today.

DR. BONE: Thank you, Dr. Sobel.

We'll go on to the presentation by the sponsor in just one minute.

As we did yesterday, we are asked that unless there is a burning technical, specific factual question, we'd like to take the questions from the committee at the end of the complete presentation. So often the companies feel that their questions may be answered in a subsequent presentation and this helps us to move right along. But if there's a point of fact that has to be clarified after our

talk, please let me know about that.

The first presenter for Takeda will be Dr. Schneider.

DR. SCHNEIDER: Good morning, Mr. Chairman, members of the committee, guests of the committee, and members of the audience. It's a pleasure this morning to be here to discuss the safety aspects of pioglitazone hydrochloride, brand name Actos, on behalf of Takeda Chemicals International, Takeda America Research and Development Center, in Princeton, and the Marketing and Sales Group, Takeda Pharmaceuticals America, just outside of Chicago.

I'm Dr. Roberta Schneider. I'm Vice President of Drug Development in the Princeton facility. And as you've probably already surmised, Actos is another of the thiazolidinedione class. It has been evaluated for the treatment of type 2 diabetes mellitus in monotherapy and also in combination with sulfonylurea, metformin, and insulin. Applications to market have been filed in the United States, in Japan, and in Europe. And today's presentation will focus only on the safety of Actos.

I'm going to provide just a second or two of history about the drug. Then we'll move on to Dr. Frederick Reno, to talk about preclinical pharmacology and toxicology. I'll come back and begin the safety assessment

section.

Takeda thought that it was so important to have a thorough evaluation of the safety, the hepatic safety, of this compound that we created a Hepatology Advisory Board with some of the leading hepatologists and gastroenterologists in the country. Two representatives of the Board will be speaking this morning, and we will have another two eminent colleagues with us to help answer questions. Dr. Jim Freston, Professor of Medicine, University of Connecticut Health Center, is co-chair of the group, and will be presenting, as will Dr. Neil Kaplowitz, from the University of Southern California.

After conclusion of the liver section, we'll move on to a few more aspects of safety that we haven't covered, and then Dr. David Kelley will sum up with a clinical perspective of the utility of this class of compounds and the safety of Actos in particular.

There are a number of representatives here; I'll just kind of mention the ones that are from the Princeton organization who are here to answer questions and help us with the presentation: Dr. Cindy Rubin, Dr. Vince Houser, Alyson Spedding, and Dr. Annette Mathison from statistics and data management.

We also have a number of consultants here with us: Stephanie Rais, for regulatory affairs; Colleen

Johnson and Fred Reno, for preclinical information; Dr. Martha Charney, for questions related to pharmacokinetics. As I mentioned, Dr. Freston, Dr. Kaplowitz, Dr. Kelley. And some additional consultants: Dr. Hy Zimmerman, Dr. Roberto Lang, Dr. Stephen Eck, Dr. Keith Tolman. And some laboratory colleagues: Dr. Henry, Dr. Cohen and Dr. Glant.

You've probably never heard the ancient history of the thiazolidinedione, so here it is. In 1982, Takeda Chemical Industries, in Osaka, Japan, identified the first thiazolidinedione, called ciglitazone, in its search for an agent that had lipid-lowering properties. In 1986, Takeda synthesized pioglitazone. And in 1989, pioglitazone was licensed to the Upjohn Company for U.S. development. Clinical studies were started in Japan. And in 1995, Takeda, in Princeton, took over the obligation for the IND. And in the following year, we began phase 2-3 studies in the U.S., and they were also begun in Europe.

We filed our NDA on January the 15th, about 6 weeks later than the NDA you heard yesterday. And we really are grateful for this prompt review and the ability to share this information with you. In addition, our colleagues in Europe submitted their registration dossier. And, as I mentioned, a dossier has already been filed in Japan.

Today's presentation, as we mentioned, will

talk about preclinical pharmacology and toxicology and clinical trial safety data. So, without further ado, let me turn the program over to Dr. Reno, to talk a little bit about toxicology.

DR. RENO: Thank you, Dr. Schneider. And good morning, everyone.

I would like to describe for you this morning, and very briefly, the extent of the preclinical pharmacology and toxicology studies that have been conducted with pioglitazone. With regard to pharmacology, the data indicates that pioglitazone lowers glucose levels in both obese and diabetic animals, that there is no hypoglycemic effect in normal animals. The primary activity is by the increase of insulin-dependent glucose disposal in peripheral tissues, primarily in skeletal muscle. It decreases hepatic glucose output. It lowers triglyceride levels both in genetically diabetic and normal animals. And as we heard yesterday, although it is not completely understood, there is a growing body of evidence that suggests that one of the mechanisms of action for this class of drugs involves the activation of PPAR gamma receptors. And so, the sum of that would say that it reduces hepatic insulin resistance, and there's also an activity with regard to the differentiation of adipocytes that probably is responsible for the primary activity in

lipid lowering.

With regard to pharmacokinetics, when we scan the data across all of the studied animal species, the drug is rapidly absorbed. Absolute bioavailability across species runs between 81 and 94 percent.

In animal species and in humans, there are six metabolites that are formed. Three of these metabolites are active. The relative potency of those three metabolites for glucose lowering is approximately one-half that of pioglitazone, and is approximately three-quarters that of pioglitazone with regard to the lowering of triglycerides.

There is no microsomal enzyme induction or inhibition associated with this drug.

The fecal elimination biliary excretion predominates in all species except the monkey, where urinary excretion predominates.

And the main cytochrome P450 isoforms are the 2C8 and the 3A4.

As you heard yesterday and as we know is generally characteristic of this class of compounds, there is a characteristic change that occurs in the heart. This has been identified essentially in several animal models. And that the threshold effect with regard to pioglitazone is primarily related to just simply an increase in heart

weight. The threshold dose at which this begins to occur in these animal species varies across the species. But the conclusion from all of the mechanistic studies that have been done with regard to this compound says that although there is a cardiac hypertrophy that is noted, there is no change in cardiac function.

This cardiac effect is most sensitive in the dog. It's interesting to note that in the dog, the ED50 for the pharmacological effect is the lowest in the dog compared to the other animal models. And for the cardiac changes, the ratio of the animal to human area under the plasma concentration time curve at the threshold dose, where these changes are initially seen, runs between 7 and 12 for all species except for the dog, where it's lower.

Also, as we saw yesterday, and it's consistent with this class of drugs, there are changes in hematologic parameters. We've seen this in multiple animal models. The threshold effect, or actually the effect that's seen at any dose, is involved with the decrease in red blood cell parameters, primarily RBC count, hematocrit, and hemoglobin. Again, the threshold dose at which this occurs varies across the species that have been studied.

These changes, this effect of the decreased red cell parameters, occurs early in the study. It reaches a plateau, and generally does not get worse as the study

continues. And these studies have involved studies for up to 1 year in duration. And the assessment would be that basically these animals are physiologically normal.

One of the things I'd like to point out here is that, as we heard yesterday, both the cardiac changes and the hematologic changes are felt to be associated with an increase in plasma volume. And one of the mechanistic studies that Takeda has carried out indicated that the initiation of treatment with furosemide, concurrent with the administration of pioglitazone, prevents the manifestation of both the cardiac hypertrophy and the hemodilution that's seen in the hematological data. If treatment with furosemide is initiated after the initiation of treatment with pioglitazone, the effects are maintained and do not get any worse from that point forward.

Because of the emphasis of this class of drugs with regard to the liver, I'd like to share with you the global liver findings that we've seen. We have seen liver changes in a number of the animal models. The threshold effect that begins with this particular finding is an increase in liver weight or the histologic findings of cellular hypertrophy. By and large, this effect can almost be considered an adaptive response to the volume of drug that's moving through the liver. And actually, this particular effect you see with a number of different

classes of drug. And the threshold dose varies according to species, and I want to show you some of the information here.

These are the threshold doses at which liver changes occur in a survey of all 34 repeated dose toxicity studies that have been conducted with pioglitazone. You'll notice that in all cases, the threshold effect -- in other words, the dose at which these findings occur first -- is generally related to either increase in liver weights or a histologic diagnosis of hepatocellular hypertrophy.

A couple of other things worth pointing out are the instances of elevated ALT. Elevated ALT occurs consistently only in the dog. In this particular study here at this particular dose, these ALT increases were seen consistently throughout the 1-year duration of this particular study. But it's important to note that at the conclusion of 1 year of treatment, even though there were consistent ALT increases throughout the duration of that study, there were no histologic changes that would suggest there's a degenerative process going on.

In all of the species, the only species that indicated that there was something other than just hypertrophy is in the dog -- at very high doses, where you begin to see the beginnings of the inflammatory process and eventually winds up in atrophy and necrosis.

A couple of other points I would make as we conclude this presentation. I'm going to share a little bit of information with you with regard to reproduction studies, with the carcinogenicity studies, and we are going to discuss the finding of urinary bladder calculi in the rat carcinogenicity study.

Mutagenicity studies. The mutagenicity studies that were done with the parent drug, both with and without metabolic activation, were completely negative. There were some isolated instances of positive findings when the metabolites alone were tested. But the concentrations at which that effect occurred were significantly higher than any circulating plasma concentration of those metabolites from the clinical studies.

I'm going to talk a little bit about serum lipids, and as I said previously, there is no hepatic microsomal enzyme induction or inhibition.

I wanted to spend just a minute on this slide, because of some of the discussions that we had yesterday. Pioglitazone, in all of these studies, as far as the parental animals, in this particular study, there was no effect on reproductive performance at a dose that's significantly higher than the human clinical dose.

One of the things I would point out in this particular study is that these animals are pre-treated

prior to the time they are mated through three successive cycles in the rat. And there was no effect on the reproductive performance of these animals at that dose.

The drug is not teratogenic. As we saw yesterday, there is some degree of fetal effects that occurred. They are not malformations. They are either changes in body weight or some effects on survival. But the doses at which this occurs are very high. And our conclusion from these studies is that pioglitazone does not represent a reproductive risk to humans.

The carcinogenicity studies were completed in accordance with ICH guidelines. The mouse study is completely negative.

In the rat study, there was the presence of calculi-induced tumors of the urinary bladder only in the male rats. There were no tumors or even pre-neoplastic lesions of the urinary bladder in either the long-term studies in the dog or the monkey.

One of the things I would point out with regard to the calculi is that these type of calculi can only really form when the pH of the urine is 6.5 or higher. And through a number of follow-up studies that were done to that study, that was fairly well confirmed. The safety feature associated with this is that, by and large, the data from all of the clinical studies indicates that the pH

of human urine never reaches the level of 6.5.

The second reason why these tend to occur in rats, and you don't see urinary bladder calculi causing any kind of a problem in a clinical situation, is that rats, of course, are horizontal quadrupeds, and because of that, the calculi can sit on the epithelial surface of the urinary bladder for a prolonged period of time. This results in what we generally refer to as solid-state carcinogenesis. That's a very well-understood phenomenon for close to 40 years. Whereas humans, being a biped, will generally, if there are calculi, will either present to their physician or the emergency room and the situation will be alleviated.

In summary, the preclinical studies would say that pioglitazone is extremely effective in lowering blood glucose levels in diabetic animals, that insulin resistance is decreased. There are minor hepatic changes that are seen that, despite some relatively high doses in these animals species, never result in a degenerative process of the liver tissue. There is some conclusive evidence with regard to plasma volume expansion, with dilutional effects seen in the hematological studies.

A secondary consequence of that is cardiac enlargement in both rodents and dogs. That finding is not seen in monkeys. There are metabolic benefits related to insulin resistance and glucose homeostasis. The effects

that are seen here are generally consistent with other agents in this class of drugs, and that throughout all of these studies, there is no unique toxicity that's of any clinical significance.

I'd like to turn the program now back over to Dr. Schneider.

DR. SCHNEIDER: Thank you, Dr. Reno.

I'm going to show just two slides on pharmacokinetics, even though that wasn't in my list of blurbs, but mostly from the safety perspective.

As Dr. Reno, mentioned, there are a number of metabolites, and some of them are physiologically active. The two major metabolites, M-III and M-IV, are pharmacologically active and have peak concentrations 12 to 16 hours after dosing. The half-life of at least one of these is somewhere in the neighborhood of 24-26 hours -- up to 30 in some studies, and this accounts for the ability to dose pioglitazone, or Actos, once a day. And that's the dose that we used in all the studies.

No interactions with glipizide, metformin, digoxin, or warfarin were seen in strictly designed PK studies. There was no appreciable effect of age. As we saw yesterday, females have slightly higher serum levels. We found exactly the same thing.

And we also evaluated this compound in subjects

with hepatic impairment and renal impairment. In hepatic impairment, the extent of exposure to pioglitazone and the active metabolites, in terms of AUC values, was similar for both normal subjects and subjects with moderate hepatic impairment, and similar kinetics for normal subjects and subjects with renal impairment were seen when that was evaluated.

Let's move on now to the clinical safety assessment. I'm going to present the first several bullets on the slide, and then turn the program over to Dr. Freston and Dr. Kaplowitz, to talk about liver safety. And then I'll come back and talk about four or five additional issues that you heard a little bit about yesterday, or that we've also identified with our compound.

Actos was evaluated as monotherapy and as combination therapy throughout the world. Actos was taken by 4,514 subjects, or patients, with over 1,630 patient years. Most of the subjects and most of the patient years were in the United States, where we accumulated 1,207 patient years in 2,549 subjects or patients. Europe contributed in excess of 270 patient years, and Japan 153 patient years.

In the United States studies, you can see the bars showing the clinical pharmacology, placebo-controlled, long-term open label, and total. For this and all the rest

of the slides that show pioglitazone, or Actos, and placebo, the tan bar is placebo and the purple bar is Actos. And you can again see the 2,540 total subjects or patients and the 1,207 patient years of exposure.

This shows the exposure that was in the NDA in the light green color, and the exposure that will be accumulated after the NDA and the 120-day safety update are combined. You can see a larger number of patients with longer exposure, out to 6 and 12 months, and 12 months and longer is now up to 452. As we mentioned before, this is sort of an unusual situation, where we actually get to present the information to you at the advisory board before the agency gets a chance to get the 120-day safety update. So, that's the numbers that will be in that update.

Actos was studied in six randomized, double-blind, placebo-controlled parallel groups studies in the United States. It was studied in three monotherapy studies. And it was studied in three combination therapy studies: one each with sulfonylurea, metformin, and insulin.

These studies were slightly different than the model that is often used in that patients were permitted to stay on the same drug, the same dose, the same regimen of the companion medication that they had been on when they entered the program. We later did analyses based on the

total daily dose as specified in the package insert, and analyzed those who had a high or a low intake of the drug or the median change in terms of insulin. So, those analyses were done, and there was no difference between the groups.

As I mentioned, Actos was given once daily for all doses in all trials. In the monotherapy trials, we used 7.5 to 45 milligrams. In the combination therapy trials with sulfonylurea and insulin, we used 15 and 30 milligrams. And in combination with metformin, we used 30 milligrams. The duration of all of the studies was 16 to 26 weeks.

This slide shows the monotherapy study design. There was either an 8- or a 6-week screening baseline period, at which point patients were randomized, and then received treatment for 16, 24 or 26 weeks. Study 001 is the largest of the monotherapy studies and had four dose groups of Actos, as shown, and placebo. It was 26 weeks in duration.

Study 12 was a forced dose titration study, where the patients randomized to the Actos treatment arms received 7.5 milligrams for 4 weeks, 15 milligrams for 4 weeks, and 30 milligrams for 16 weeks in one arm. And the other arm was 15 milligrams titrated to 30, titrated to 45, and then 45 was the dose for the remaining 16 weeks. These

were not titrated based on effect. It was a forced titration. And the last follow-up monotherapy study is study 26, in which Actos and placebo were studied, and only one dose of Actos was evaluated.

The three combination therapy studies were identical in design, with the only difference being in the doses that were administered. Again, a 6-week screening stabilization period until baseline, and baseline visit was randomization, followed by 16 weeks of treatment. As I mentioned, in the sulfonylurea and insulin studies, we used 15 milligrams and 30 milligrams of Actos, and in the metformin study, we evaluated 30 milligrams of Actos.

There are two ongoing, long-term, open-label studies. The first is study 11. This is a monotherapy, where patients were allowed to roll over from study 001, the first monotherapy study, with all the different doses, or they were allowed to be enrolled fresh into that trial with what we called new patients. The same doses were used, and doctors were permitted to titrate to effect. In these open-label studies, also doctors were permitted to go up to 60 milligrams per day, if so desired, for a glycemic control.

In study 031, the second of the long-term ongoing studies, there were patients who rolled over from the other two monotherapy studies or rolled over from the

three combination therapy studies. In this case, they were allowed to be dosed up to 45 milligrams in either group. And they still have the same design for the new patients, who go through a screening and a baseline period, and then treatment. As I mentioned, these are both ongoing and open-ended.

The U.S. studies were designed to include a spectrum of patients with type 2 diabetes in a wide range of clinical settings. We did not try to exclude patients whose diabetes was worse or with certain medical conditions. The age in these studies was 30 to 75. The permissible BMI range was 25 to 45. And the HbA1c at baseline had to be greater than or equal to 8 in all studies except monotherapy study 001, in which the entry criteria was an HbA1c of 7.

C-peptide was also used as an entry or inclusion criteria. And in all studies except the insulin combination study, a level of 1 nanogram per ml was needed.

This slide shows the placebo-controlled monotherapy studies all grouped together in terms of their baseline demographic and parameters related to glycemic control and also lipids. The mean age was 54.6 years. You can see the distribution of gender and of race. And BMI, the average, was about 31.12. And you can see a nice matching of the groups throughout.

This shows the four lipid parameters that we evaluated. I'm not going to talk too much about them, but just to show the very comparable nature of the groups.

This shows the LDL/HDL ratio, and you can see the similarity in the ratio of LDL/HDL and total cholesterol LDL, as well as similarities in the HbA1c and fasting blood glucose levels at entry.

This slide shows the placebo-controlled combination therapy study demographic characteristics at baseline. Again you can see the mean age was 56.6, mean BMI was about 33, and you can see very similar characteristics in the drug and placebo groups.

This shows, again, the four primary lipid parameters. Again, you can see no difference between the groups.

And the last slide in this group shows the LDL ratios, total cholesterol to HDL, and LDL to HDL, as well as mean baseline hemoglobin A1c and fasting plasma glucose.

This shows the patient accountability and the disposition of patients in the monotherapy studies. As I mentioned, there was a relatively long washout period of 6 to 8 weeks, during which patients who had prior antidiabetic medications were essentially washed off those medications, then randomized, and started treatment with the double-blind therapeutic agents.

As you can see, in patients who have diabetes, you would expect a dropout. And there was a relatively significant dropout for reasons of glycemic control in the monotherapy studies. A larger percentage of patients dropped out from the placebo group than from the Actos-treated groups. In terms of discontinuation for adverse events, it's an identical percentage, and in terms of discontinuation for administrative reasons, it was relatively small in both groups.

This shows the patient accountability in the combination therapy studies. As I mentioned, you're not required to change doses of medication or change drugs, or go through any kind of a washout period, so we had a much larger percentage of patients who completed the study. And even in this study, though, there was a larger percentage of patients who discontinued because of issues related to glycemic control.

In the long-term, open-label monotherapy study, we still have 277 patients ongoing in the study that we call 011. There have been some that have discontinued for glycemic control. That's still relatively small -- 4, 5, 6 percent in this study -- 5 percent for adverse events, and a larger number for administrative reasons. Some of these include the patient moved out of town, the site closed, those sorts of things, which you would expect in a

longer-term study of this type.

This is a summary of the adverse events in the United States placebo-controlled monotherapy studies. The left-hand bars represent patients who had any adverse experience. The next bar represent those patients who discontinued for an adverse experience not related to glycemic control. The next bar shows any serious adverse experience, and the last bar shows those patients who died.

Again, in this slide, it's the same. This is for the combination therapy studies. You see very similar percentages in each bar.

This is the open-label study. And as you would expect for patients who've now had exposure, the rollover patients have had exposure anywhere from 355 to 990 days, 83 percent have experienced some type of an adverse reaction. The discontinued due to AE is still low, 5 percent, and SAEs is somewhat higher.

Let me just take you through the most frequently reported adverse events, and we're going to talk about some of the specific adverse events after we hear about the liver safety.

Upper respiratory tract infection, headache, myalgia, were all seen in very similar percentages in this study, as well as the combination studies and the long-term study. There were no unique toxicity or adverse

experiences that rose to the top 12 in the open-label study. So, we are just showing this slide, which shows very comparable adverse events, and the next slide, which is the remainder of the top 12: tooth disorder, UTI, influenza, diarrhea, pharyngitis, and arthralgia.

We never did figure out why the people in the Actos-treated group had all their teeth fixed.

(Laughter.)

DR. SCHNEIDER: Let me turn the program over to Dr. Jim Freston, who is going to talk a little bit about what we did with our Actos hepatology expert panel. And then I'll be back to talk about some other safety considerations.

DR. FRESTON: Thank you, and good morning, Mr. Chairman, ladies and gentlemen. I'm James Freston. I'm a gastroenterologist and hepatologist, from the University of Connecticut Health Center. I have a longstanding interest in the effects of drugs on the GI tract and the liver. And this interest is both in research and in clinical care.

As you heard, I've also had the opportunity to serve as co-chair of our unique Actos Hepatology Advisory Board. The other members of this Board are listed on this and the following slide:

Dr. Hyman Zimmerman was our spiritual and

intellectual leader. Hy is our country's foremost authority on the hepatotoxicity of drugs.

Dr. Neil Kaplowitz, in addition to being Chief of the GI and Hepatology Divisions at USC, is the immediate past President of the American Association for the Study of Liver Diseases, our preeminent scientific society in hepatology.

Dr. Keith Tolman, who is Chief of Hepatology and Clinical Pharmacology Programs at the University of Utah, has a longstanding and distinguished record of contributions in hepatotoxicity of drugs.

Rounding out our panel is Dr. A.J. DiMarino, the co-chair. Jay is Chief of Hepatology and Gastroenterology at Jefferson.

Steve Herrine, also from Jefferson, heads their Liver Transplantation Program.

The final member is Dr. Salam Zakko, from the University of Connecticut Health Center.

The activities of this group are summarized here. We spent some time reviewing the preclinical liver profile of Actos, the animal data, much of which was presented to you a few moments ago by Dr. Reno. We also evaluated all of the hepatobiliary data and events that occurred in clinical studies. We examined every case of abnormal LFT's that were reported in the United States and

abroad. We focused not only on the ALT rises, but also on the other LFT's, including the AST, alkaline phosphatase, total bilirubin, and the gamma-glutamyl transpeptidase values. And we compared the behavior of these enzymes in the trials versus what happened in the placebo comparison groups.

We spent a lot of time going over the data that addressed the gold standard in our field of hepatotoxicity, and that is the ALT rises equal to or above 3 times the upper limit of normal. This is a sensitive and highly reliable screen for hepatotoxicity. And so we examined all the patients in detail who had that pattern of LFT abnormality.

We also looked at the overall safety assessment of Actos versus that of Rezulin, using information published in the literature or otherwise on the public record, most of it having been presented to the agency and reviewed by the advisory committee in public meetings.

Finally, we asked the sponsor for additional analyses, and I'm pleased to say they were forthcoming in meeting all of our requests. Then we gave them our opinion about the advisability of monitoring patients who were treated with Actos in the clinic.

We were acutely aware, as is all of our colleagues in the hepatology community, of the

hepatotoxicity issue pertaining to Rezulin. We were therefore concentrating on detecting evidence of a class effect.

By the same token, we were aware that there are significant difference in the chemical structure and the metabolism of the different compounds in the glitazone class. As was mentioned yesterday, these compounds are similar structurally with respect to the right-hand of the molecule, but not the left. Of particular importance possibly is the alpha-tocopherol -- the business end of the alpha-tocopherol moiety, which is stuck on the left side of the Rezulin compound, and that compound is metabolized to quinones. And that's unique with respect to the glitazone class.

We were also quite aware that in the field of hepatotoxicity, class effects occur with predictable hepatoxins in a dose-dependent fashion, or they occur when there's been a sensitivity reaction and there's cross-sensitivity within a class. Idiosyncratic, or so-called unpredictable, reactions are not known to be class effects. Rather, they are unique to a compound.

We concluded in the end that there was no difference between Actos and placebo-treated patients with respect to their hepatic profiles. And in fact, we can find no evidence of hepatotoxicity at all. This and other

considerations led us to recommend to the sponsor that liver test monitoring would be of no value in patients treated with Actos.

In the next few minutes, we'd like to provide you the data that forms the basis for these conclusions. And to do the next portion will be Dr. Neil Kaplowitz, who will present a summary of the U.S. data. I'll come back and describe briefly the European and Japanese data, and finish up with some concluding remarks.

DR. KAPLOWITZ: Thank you very much, Jim. And good morning, everyone.

I am going, as Jim said, to summarize for you the assessment of our hepatology panel that reviewed the liver safety profile of Actos.

I can say at the outset, as Jim indicated, we didn't really find any significant evidence or signal for hepatotoxicity of this agent, and therefore could find no reason to support the concept of a class hepatotoxicity of these glitazones.

So, what I would like to do first is give you an overview of the incidence of abnormal liver tests that occurred with the use of the agent. As Jim indicated and as you've heard probably extensively yesterday, an industry standard in screening for hepatotoxicity is an ALT equal to or greater than 3 times the upper limit of normal. ALT is

a protein enzyme present particularly in the cytoplasm of liver cells, and it is released into the circulation when liver cells die. Therefore it's an index of liver cell injury. I would stress to you that an ALT abnormality that is threefold elevated is a rather mild degree of liver injury. So, ALT elevation is a very, very sensitive means for detecting liver cell death, and therefore is a very reasonable screen for very mild injury.

The data shown on this slide, therefore, is the incidence of this abnormality in the study. The placebo patients are shown in white and the study patients in phase 1, phase 2, and phase 3 are in, I guess this is, purple. And as you can see by the numbers at the top of the bars, the overall incidence of mild ALT abnormality in this study population is quite low, and therefore this is an uncommon event.

Most importantly, as shown on this slide, in the phase 2 study, the comparison of placebo-controlled patients and Actos-treated patients shows that there is absolutely no difference in the incidence of mild ALT abnormality, threefold elevated, in both groups. And this is very comparable to the background placebo data that are seen in other diabetic randomized controlled studies, as Dr. Misbin pointed out to you yesterday. So, again, based on the incidence of ALT abnormality, we could find no

evidence of a significant increase in even mild liver injury.

There were a total of 10 patients who had ALT greater than 10 times the upper limit of normal, and I'd like to describe those for you in some more detail. There is 1 patient who was present in both of these groups who initially was identified in the control study and then carried over into this study. So, in fact, this is 9 patients, plus 1 patient in the phase 1 study, a total of 10 individuals.

This slide summarizes our assessment of these 10 individuals who, again, I'll remind you, had ALT level greater than 3 times the upper limit of normal.

Before I describe how we categorized these patients, I just wanted to point out a very important fact to, which is listed at the bottom of the slide. And that is, in these clinical studies of over 2,500 individuals who received Actos in the U.S. studies, there wasn't a single patient that we could identify in our assessment who had an ALT equal to or greater than 8 times the upper limit of normal.

Now, if you remember Dr. Misbin's presentation yesterday, there were 22 individuals out of a comparable study group -- about 2,500 patients -- who had ALT equal to or greater than 10 times the upper limit of normal in the

troglitazone clinical studies. So, that's 22 versus 0.

We found not a single individual who developed jaundice in these studies; whereas, in the original troglitazone studies, there were two individuals who developed overt liver disease, with jaundice, in the clinical trials.

So, again, this strongly supports the view that there is really no significant propensity to serious liver injury or, if it occurs, it is so extraordinarily rare that we can't identify it.

It also points out that we're not seeing an accelerated or progressive type of worsening liver disease, with progressively rising ALTs to dangerous levels. All we're really seeing are a small number of patients who have mild ALT elevations that occur no more frequently than in placebo, and let me tell you about these 10 individuals, just to further reassure you that we're not dealing with some hidden injury here.

Of the 10 individuals, our panel felt that we could conclusively identify another medical cause for the liver abnormality and, therefore, that five of those individuals could be excluded on the basis of an underlying liver disease, and therefore not having any relationship to Actos.

Four of the individuals had chronic hepatitis.

And this was identified by persistently abnormal ALT tests in the pretreatment interval, throughout treatment, and after treatment. So, these people have chronic hepatitis. One had hepatitis B, one had hepatitis C, and two had chronic hepatitis probably related to non-alcoholic steatohepatitis of diabetes. Another patient had biliary tract disease, with acute cholecystitis and bile duct obstruction from gallstones. And that was the reason for the liver test abnormality. So, 5 of these 10 we excluded.

Another two we felt probably were related to another drug. In both individuals, an agent was taken during the clinical studies. An ALT abnormality occurred temporally associated with this other agent, disappeared with the discontinuation of the other agent, despite the continued use of Actos. Both of the agents implicated are known to be associated with ALT abnormalities. About 1 percent of people who take norfloxacin have been reported to have ALT elevations. And 2 to 4 percent of people who take diclofenac have been noted to have ALT elevations, incidences which are far more frequent than we see with Actos.

Then, finally, there were 3 patients that we considered to be indeterminate, where the situation was sort of atypical. They had low-grade ALT abnormality, but one of them had taken concurrently dicloxacillin, which is

an antibiotic, which is very rarely associated with ALT abnormality. This individual had just a single value that was abnormal. The preceding value and the following value were normal. So, it was kind of a blip of unclear significance.

Then the other two patients were atypical in having unusual temporal association with the drug, but I won't go into that in detail. But suffice it to say we felt this was just background noise.

So, in summary, we didn't feel that any of these 10 cases who had ALT greater than 3 times the upper limit of normal had a clear-cut association with Actos. And in fact, in the majority, we felt that it was pretty clearly not due to Actos.

While they're looking for the slides, let me remind you about a few other facts that came up yesterday. One was a concern regarding perhaps even milder liver injury, and the question of whether ALT values, let's say, between one-and-a-half and threefold abnormal might occur with a different incidence in Actos-treated versus placebo patients.

We took a careful look at the randomized clinical study with respect to the whole batter of liver tests, including ALT, AST, gamma-glutamyl transpeptidase, alkaline phosphatase, and total serum bilirubin. And we

found, using just low-grade abnormality of 1.5-fold abnormal or greater, that there was no significant difference in abnormalities of any of those tests -- here we are. I'm glad I remembered what the next slide was, so I'm talking about the correct thing.

(Laughter.)

DR. KAPLOWITZ: This shows exactly what I'm talking about. The placebo is in yellow and the Actos patients are in purple. You will see that there is really no difference in the incidence of mild ALT abnormality, mild AST abnormality, mild GGT, mild alkaline phosphatase, or total serum bilirubin. In most of these cases, in fact, the incidence is lower, numerically lower, in the Actos-treated patients than in the placebo. So this, again, supports the idea that there isn't even a hint of a difference in mild liver injury in this study group.

Another point that came up yesterday was what happens if you have underlying disease. Is the treatment with this type of agents going to make the liver disease worse, or what impact will it have?

So, for that purpose, we identified those patients who, at baseline, before being put on Actos in the randomized studies, had an ALT that was mildly abnormal to begin with, 1.5 to threefold. And ostensibly, anyone with threefold or higher at the baseline would not have been

enrolled in the study, although I think there were one or two that slipped through, overall.

But, anyway, there were 56 patients out of the 1,500 who were treated with Actos who started out with an abnormal ALT, in this low-grade range, before treatment. And there were 31 out of 793 placebo patients -- about the same incidence -- who had low-grade ALT abnormalities before being put in the study.

As you can see, if you first look at those who improved -- and now what I'm showing you is what happened pretreatment, at baseline, compared to the peak ALT abnormality that occurred during treatment, what is the worst ALT that they had during the treatment interval. In 52 percent of those who started out with an abnormal ALT, it actually was lower in the treatment interval. It never reached as high -- or, in other words, it improved during treatment. In the placebo group, this was lower. So, more patients who were treated with Actos improved, had lower ALT during treatment than before treatment, compared to placebo. Very rarely, did an individual have a higher ALT during treatment -- that is, crossing over above the threefold elevated line -- with Actos or placebo. And there was no difference between those.

So, again, this data emphasizes that there is no tendency for Actos to worsen underlying liver

abnormalities that exist in these patients. And, if anything, there's a hint that it may actually improve the liver abnormalities, although this needs to be studied with a large population and more extensively.

So, let me summarize. First of all, the U.S. studies of about 2,500 patients found 10 who had an ALT equal to or greater than 3 times the upper limit of normal, an incidence of .39 percent, which, you will recall, is very comparable to the placebo incidences that have been described in all the different diabetes studies.

There was no difference in these studies between the placebo and Actos-treated patients in terms of the occurrence of ALT abnormalities.

There was no case in which Actos was deemed to be the proximate or likely cause for the ALT elevation by our panel with respect to these 10 patients.

We did see that for those people who started out with a baseline ALT abnormality which was in the 1.5 to threefold abnormal range, Actos treatment was associated with more frequent improvement than placebo and no significant worsening. So, at worst, it didn't do anything adversely to the underlying liver disease.

Finally, most importantly, we saw no signal of serious liver injury. And therefore we saw no patient who had an ALT equal to or greater than 8 or 10 times, for that

matter, the upper limit of normal, and no individuals who developed jaundice. And this is in striking contrast to the clinical studies with troglitazone, where this was seen with sufficiently high frequency in a comparable patient population treated for a comparable amount of time.

So, therefore, in conclusion, the Hepatology Advisory Board found no evidence of hepatotoxicity of Actos.

Thank you.

DR. FRESTON: I'd now like to describe briefly the experience from abroad, specifically Japan and Europe.

In keeping with the format that Dr. Kaplowitz employed, I've plotted here the percent of patients who expressed an ALT rise of equal to or greater than 3 times the upper limit of normal. I'd like to draw your attention to these bars that depict the controlled trial experience in Japan.

Here you can see that the incidence of ALT rises was identical between the Actos-treated and the placebo-treated groups. Over on the right, again in the fashion employed by Dr. Kaplowitz, we show the rises that occurred in the open-label extension studies. We have a higher incidence because the patients were treated for longer periods of time, and therefore had more opportunity to detect an ALT rise that may well have been due to a

coincident condition.

Finally, on the left, we see the European experience. There was just 1 patient in nearly 700 who had a rise equal to or exceeding 3 times the upper limit of normal, quite consistent with the U.S. experience.

We have taken the opportunity to focus on all 11 of those patients who had rises of this magnitude. In all 11 cases, they had other conditions that quite plausibly could be responsible for the ALT increases. For example, in 10 of the 11 patients, the increases were present before treatment began.

Shown down here are the diagnoses that were established in these patients before treatment with Actos. I draw your attention to the fact that half of the patients had NASH, or non-alcoholic steatohepatitis. Also, I'll draw your attention to the case of cholangiocarcinoma. That was the one case that occurred in Europe that did not have a baseline elevation in LAT. This developed during treatment, and obviously the abnormality was found by our panel to be due to the carcinoma and not to the drug.

As I mentioned at the outset, we spent a lot of time trying to give the sponsor an assessment of the hepatic safety of their drug versus that of Rezulin. I would now like to show you the data that we developed. We have tried to compare apples with apples in this analysis,

insofar as that is possible. Actos and Rezulin have obviously never been compared in head-to-head trials. And so we're left with the necessity of utilizing similar trial designs in similar populations. Thus, we have concentrated just on the U.S. experience with Rezulin and Actos.

You can see, when we look at the incidence of ALTs 3x or higher, that there's a striking difference between Rezulin and Actos. If we concentrate on those patients who had rises 10x the upper limit of normal, again we see a dramatic difference. In fact, we didn't find a single case in the Actos experience.

Now, we have all grown wiser over the last 48 hours with respect to this class effect issue. Many of us saw for the first time, the Avandia data yesterday.

I've taken the liberty, on this and the following slide, of plotting the incidence of ALT rises for the three glitazones. In this instance, I have put in a placebo comparator, drawn from the Actos studies, to provide a context, a frame of reference. That's what's happening in the placebo group. You can see that with respect to 3x rises, Actos and Avandia are behaving identically, and quite differently from Rezulin at similar stages in clinical development. And that's important.

On the next slide, we look at the experience with 10x the upper limit of normal. No cases with Actos.

One, as we heard yesterday in some detail, with Avandia, in striking contrast to the experience with Rezulin, again, at a similar stage in clinical development. In one case there was a signal. In two other cases there was no signal.

We spent a lot of time discussing the issue of mandated monitoring. There are, of course, negative consequences to inappropriate monitoring. It's costly. Not only the cost of drawing blood, but in following up the results, relaying the information to the patient, having the patient come back for repeated values in the event that an abnormality is detected.

It's inconvenient. Monthly blood draws, for example, for purposes of monitoring LFTs does not fit into an ordinary care plan in the management of patients with diabetes. This is an extra visit.

As was pointed out by the chairman yesterday, one of the consequences of monitoring could well be to discourage usage of these important drugs by patients who could benefit from them. And it occurred to us that it would be sadly ironic if the same sort of labeling were applied to all three different drugs. And that led, especially primary care physicians, and patients alike, to conclude that the hepatic risk was there for the same -- which it isn't.

Finally, there's a low probability that

monitoring would detect cases. I'd like to just illustrate the point with this slide. Shown on the left is what we call the Zimmerman rule. This was developed on information analyzed and published by Dr. Zimmerman, who is in the audience. This rule tells us that for patients who have ALT rises 10x normal, one can predict that about 1 in 10 will develop jaundice. Moreover, about 1 in 10 of those patients will go on to death or liver transplantation.

The Rezulin experience fits precisely with the Zimmerman rule. About 1 in 200 patients in clinical development expressed ALT rises at 10x level. And about 1 in 2,000 of those developed jaundice. And approximately 1 in 20,000 went on to death or liver transplantation.

I've taken the liberty of adding up the experience with Actos and Avandia in the column to your right. There's just one case in 10,000 that reached that level of 10x. Thus, if the Zimmerman rule applies -- and it has for many years in this field, and did with Rezulin -- we would expect about 1 in 100,000 to develop jaundice, and about 1 in a million to go on to death or liver transplantation.

No one would seriously recommend screening PSAs in 30-year-old men to detect early prostate cancer. And yet the detection rate would be higher than this. Endocrinologists do not routinely recommend screening for

agranulocytosis in their patients being treated with PTU. And that event occurs 1 in a few thousand.

Nevertheless, we're dealing in an environment where there is heightened sensitivity to the Rezulin experience. And we need to react responsibly. Therefore, we have recommended to the sponsor that they do indeed be sensitive to this environment, and to heighten the surveillance mechanisms. There is already sensitization of the spontaneous direct reporting process because of the widespread publicity around Rezulin hepatotoxicity.

More can be done. The companies can be strongly encouraged to, in turn, encourage aggressive efforts on the part of their field force and in their educational programs to heighten awareness of the potential for hepatotoxicity in this class and for the need to report promptly all instances of suspected hepatotoxicity. We can do much more in that regard than has been the case in the past.

Moreover, the sponsors can mandate that their medical departments deal with these reports as a priority. We have reason to believe that that did not occur early in the Rezulin experience.

In contrast, as these reports come funnelling in, as they will inevitably as it was pointed out yesterday, the competition out there will ensure that there

will be a lot of reporting of hepatotoxicity. As they come in, the medical departments can respond promptly to the health provider who has provided the information, but also direct the case to an on-line monitoring process by an independent hepatology board. And after a few years, we can have a few million cases under our belt -- not of hepatotoxicity -- of clinical experience.

(Laughter.)

DR. FRESTON: In conclusion, Mr. Chairman, ladies and gentlemen, 4,514 patients have been treated with Actos in trials worldwide, compared with about 1,200 who received placebo in these comparative trials. In this experience, there was no difference between Actos and placebo-treated patients in terms of their liver function tests. Therefore, there is no evidence of Actos hepatotoxicity. And in fact, in light of what we learned yesterday, it's quite clear that we're dealing not with a class effect, but with the unique idiosyncratic reaction caused by Actos -- or, excuse me -- by Rezulin.

So, we concluded that liver monitoring is not recommended, because there's no signal of hepatotoxicity with this compound or with Avandia. There's no evidence of a class hepatotoxicity therefor, and the hepatic profile is similar -- that is, clean -- similar to other agents that many of us have worked with in drug development. The

profile of this drug is such that it wouldn't even get on an advisory committee if it hadn't been for the previous experience with Rezulin.

Thank you.

I would now like to turn the time back to Dr. Schneider.

DR. SCHNEIDER: Thank you very much, Dr. Freston and Dr. Kaplowitz. Also, for the other members of the Hepatology Board that are here and have contributed to this process, we really appreciate your expertise.

A few other safety considerations that I'll just be going over briefly. I don't think you'll find much variation in the theme from yesterday. One that you'll look at and say, where is that on the list, and it's not there, is weight. We're not going to be discussing weight because of its relationship to efficacy, so it's not on the list.

With respect to hypoglycemia, this slide shows the incidence of hypoglycemia in the U.S. clinical studies. From left to right, the monotherapy, long-term monotherapy, and then the three combination studies, in combination with sulfonylurea, metformin, and in combination with insulin. You can see a larger percentage of patients had hypoglycemia in the insulin study and in the sulfonylurea study than was the case in any of the other studies.

These were all mild to moderate in severity, and we actually asked the doctors to try to keep the insulin dose as close to being the same, so that we could see measurable improvement in HbA1c. They were allowed to lower it if there were reports of hypoglycemia or if they had concerns about hypoglycemia. But this was not a study where we tried to decrease the dose of insulin, but rather to decrease the HbA1c.

So, there was very small occurrence in the metformin study, as would be expected from the mechanism of action. And in the monotherapy study, you'll see that there are seven reports. Doctors were permitted to record hypoglycemia as an adverse event even if there was no blood glucose value to go along with it. So, if the patient described being shaky and sweaty and eating a box of chocolates, it might end up being reported as hypoglycemia. So, there were a number of them that did not have blood glucose measurements with them.

With respect to edema, there was an increase in edema in the U.S. clinical trials, in all of the U.S. clinical trials, in all of the Actos-treated groups. You can see the percentages for monotherapy, both the placebo-controlled and the long-term, as well as in combination with the other agents. The largest percent of patients reporting edema was 15.3, in the insulin

combination, and that's in the Actos-treated patients, and 7 percent in those treated with insulin plus placebo.

2 patients were withdrawn from the combination therapy studies as a result of edema, but all the events were considered mild or moderate in intensity.

Next you saw the hematology changes that occur. You saw it in the preclinical model and you saw it yesterday. This is just one slide that shows the four different dose groups of Actos, and the line representing placebo for the placebo-controlled monotherapy study 001. You'll see the top line is the placebo line. The green line is 7.5. The red line is 15. The blue line is 30. And the yellow is 45. You can see that most of the changes occurred during the first 10 to 12 weeks of treatment. And after 14 weeks, essentially the changes had leveled off.

Well, that shows a change from baseline, but let's look at the next slide, which will show us what the actual change in the values were, and these are the means values. The lighter-color bars on the left in each group are those for placebo. The solid bar is baseline. The striped bar is end point. You can see very similar for the placebo groups that did not receive Actos, and you can see the relatively small decreases that, although they were there, were not considered, in most cases, as being clinically significant. The largest magnitude of a mean

decrease was .6 grams per deciliter in the combination with metformin study.

In terms of anemia reported as an adverse experience, you can see the bone-colored bars, again, are the companion agent plus placebo. In this case, these are the three combination therapy studies, because no cases of anemia were reported in the placebo-controlled monotherapy studies or in the long-term open-label studies. So, these show the data of anemia reported as an adverse experience, and a very similar percentage for the placebo and the Actos-treated groups.

Because of the preclinical findings related to the cardiovascular system, a pretty thorough cardiovascular assessment was done. I'm going to talk a little bit on the effects of the serum lipid profile, cardiac adverse experiences, and then echocardiographic evaluation.

Serum lipid levels were not adversely affected during the trials with Actos. Ratios of total cholesterol to HDL, and LDL to HDL, were also not adversely affected. And the effects on lipids that we saw were consistent throughout the entire clinical program.

The next slide shows the four individual parameters that were evaluated. And I'm not going to spend much time on this slide, except to call to your attention that in no case were the Actos-treated groups that are in

the colored lines any worse than the placebo-treated group.

This is the LDL/HDL ratio slide. And a worsening from the baseline ratio would be a line that was above the straight line going across. No worsening occurred in the ratios.

This shows the ratio of total cholesterol to HDL. And again, you can see that there was no worsening in these ratios for any of the doses shown.

This shows the results of similar lipid profiles from one of the combination therapy studies. This is the result from the sulfonylurea therapy study, where we studied two doses, 15 and 30 milligrams, with placebo, in combination with sulfonylurea. And again, just focusing on the concept of not worsening, you can see that in no occasion was there worsening in the individual parameters.

And if we look at the next slide, there was no worsening in the LDL/HDL ratio.

And if we look at the next slide, there is also no worsening in the total-cholesterol-to-HDL ratio.

Let's move on to cardiovascular adverse experiences. This slide includes all patients who are AE term coded to cardiovascular system, general; heart rate and rhythm disorder; or myocardial, endocardial, pericardial, and valve disorder. You can see, going from left to right, again, the same scheme of monotherapy,

long-term monotherapy, and the three combination studies broken out separately, that there are very similar percentages of adverse experiences in the placebo groups as compared to the Actos-treated patients. In no case where placebo was involved was the percentage of adverse cardiovascular adverse experiences higher in the Actos-treated group than in the placebo.

We looked at three common cardiovascular adverse experiences and just kind of broke them out from their classes or categories: ECG abnormal, hypertension, and coronary artery disease. And you can see the numbers and the percents of patients in both the placebo and Actos groups on top for monotherapy. And, again, relatively small percentages and very similar between the placebo and the Actos-treated patients.

And in combination therapy, where the order was a little, tiny bit -- no, it wasn't -- where we also have the same three adverse events listed, and you can again see a great deal of similarity. But in no cases was there a significant elevation in the Actos-treated patients.

There were some cardiovascular adverse events of specific interest. One was cardiomegaly, and another was LVH, and another was cardiac failure. These are of interest because of the animal findings related to left ventricular hypertrophy, as well as edema. We looked at

the occurrence of those three specific adverse events in monotherapy as well as in combination therapy.

The cardiomegaly was always done as a chest x-ray diagnosis. So, if it said cardiomegaly or mild cardiomegaly, that was recorded as an AE by the doctors. They had all been properly sensitized to the possibility that that was something we were looking for.

In one case, the percent of the cardiothoracic ratio went from 51 to 52. In one case it went from 51 to 54. I mean there were very, very small changes. We have the case histories of all of those patients. And one of our cardiologists, Dr. Lang, can discuss those with you if you have any specific questions.

LVH, you can see that was an EKG diagnosis. In most cases, LVH was present at baseline in those patients, but was not recorded, and an adverse event later in the course of the study, when LVH was written on the EKG report, was written down. And Dr. Lang also has all of those cases and can discuss those.

And last but not least, in terms of cardiac failure, there was a very similar percentage and a very low number of patients who had a diagnosis of congestive heart failure, which codes to the term cardiac failure in these studies. And Dr. Lang also has those cases if there's any specific interest.

Again, because of the findings in the preclinical studies, we evaluated the echocardiograms of patients participating in the placebo-controlled double-blind 001 study, as well as patients continuing their participation in study 011, or patients who were new to study 11. As said before, the first study, 001, had doses of 7.5, 15, 30, and 45 milligrams daily. And in the rollover study, they were allowed to go up to 60 milligrams daily.

This is an ongoing study. The first study was 26 weeks in duration and was completed, and echoes were done at baseline, week 14 into the study, or week 26, and echoes have been evaluated for more than 60 patients in each dose group.

The other study is still open-ended and ongoing, study 11. Echoes were done every 6 months for the first year, then annually thereafter. In the NDA, echoes have been read for at least 431 patients: at 6 months for 150; at 12 months, 250; and at 2 years for 200.

The echocardiographic parameters that were included were left ventricular dimension, left ventricular mass, fractional shortening, cardiac output, stroke volume, and the calculated indices of left ventricular mass index and cardiac index.

In addition, there will be more echo data

coming in the 120-day safety update. And these are for additional patients and also for additional time. We now have approximately 270 patients with 1-year echocardiographic data, and 66 patients with 2-year echocardiographic data. And we have patients continuing in those studies -- as I mentioned, 51 rollover patients -- being treated with Actos for 355 to 993 days.

We are also doing additional analyses of the echocardiographic data, adjusted for glycemic control, to make sure that glycemic control issues did not confound any effect on the cardiac dimension.

This colorful but remarkably busy slide shows what happened with interventricular septal thickness, in the upper left; left ventricular internal dimension at end diastole, in the upper right; and left ventricular posterial wall thickness at end diastole. Again, the solid bars in each of the groups represents the baseline measurement, and the striped bar represents the follow-up measurement, or endpoint. And you can see no differences between the groups from baseline to endpoint.

The other three parameters -- left ventricular mass, left ventricular mass index, and fractional shortening -- although you can see some differences between the groups within a group, there were no differences.

And the last two slides show the same

information for patients in the long-term open-label study. And you can see a lot of similarity in the bars from the baseline and the last available. These slides include patients who were new to the 011 study, patients who had rolled over, being treated with Actos in both the 001 and the open-label study, and patients who'd been treated with placebo in the 001 study, who then rolled into treatment with Actos.

In summary, there is no evidence from study 001 or 011, based on the clinical cutoff date for the NDA, of echocardiographic differences between placebo or Actos dose groups. There continues to be no evidence of echocardiographic changes in patients receiving Actos for extended periods of time -- up to 2 years. That data will be included in the 120-day safety update. And preliminary evaluation of the echocardiographic data for patients who received placebo or Actos with similar HbA1c values indicate no impact of Actos on echocardiographic variables. And that data will also be provided in the 120-day safety update.

We're almost at the end. Only two more.

This deals with CPK elevations. We did notice that were several cases -- seven of them altogether out of that 1,880 patients -- of CPK elevations that were 10 times the upper limit of normal. All seven cases represented

isolated values during the study. Three cases were associated with exercise. One case was associated with atorvastatin. None of these patients discontinued because of elevated CPK, and there were no symptoms or adverse events associated with these elevations.

The next two slides will show where these elevations occurred. On the bottom is the days on therapy, and the CPK elevation is shown on the y axis. The blue ones are 30 milligrams. This little red one down here is at 15 milligrams. Some were in monotherapy, some were in combination. And you can see that all the rest of the values around that value are normal.

This shows exactly the same thing in these patients. This was the sum total of all 7 of them. We have asked the central laboratory that we were working with for some additional information about CPK elevations, and they informed us that they do have data that this does occur relatively frequently in clinical trials of agents in diabetes, these sporadic elevations. And we can speak to that. And I'm not sure Dr. Misbin might have some other information about that.

And last but not least, because of the animal finding related to bladder carcinogenicity, we evaluated urinary cytology prospectively in all of our clinical trials. We evaluated patients prior to receiving

double-blind study medication, and then during the studies. Some patients were withdrawn from the study because of benign urinary cytology results.

I'll show you the categorizations on the next slide. The investigators thought they were a little bit scary. Part of the problem is that this is absolutely the first time systematic urinary cytology was done in patients with type 2 diabetes. So, you see things like renal tubular cells and you see other findings. Renal tubular cells, reactive urothelial cells, atypical cells, and they go kind of in a step-wise progression.

We noticed during the trial, and we worked with our colleagues from the laboratory, to understand the relationship. And patients would kind of move from one class to another and back and forth. But what we focused on for the NDA were patients who had 3c and 4 cytology results, as well as any new cases of bladder cancer that were identified. We found no cases of class 4 urinary cytology results.

The next slide shows the class 3 urinary cytology results. The lightest bar, again, is the placebo. And you can see, very small numbers of patients in different studies that had class 3c cytology results. None of the patients with class 3c cytology results, upon follow-up evaluation, had any malignant or pre-malignant

lesion identified.

In addition, no new cases of bladder tumor were identified during prospective evaluation of urinary cytology in any of the patients in the placebo-controlled monotherapy or combination therapy studies in the United States.

Now, I would like to ask Dr. David Kelley to come up and talk to us a little bit about a perspective of the thiazolidinedione class and the safety of Actos in particular.

DR. KELLEY: Dr. Bone, members of the Advisory Committee, their consultants, members of the audience, good morning. My name is David Kelley. I'm an Associate Professor at the University of Pittsburgh, where I'm in the Division of Endocrinology and Metabolism, and I'm a clinical investigator in the areas of type 2 diabetes, obesity and insulin resistance.

Type 2 diabetes is a serious medical problem in the United States today. The prevalence of this disorder continues to increase across the latter half of this century. Diabetes places a substantial burden upon the individuals who carry this diagnosis. In aggregate, it places an enormous burden of cost upon the health care system: $1 in $7 is spent on the care of patients with diabetes.

Yet despite the seriousness of this disorder, undiagnosed and under-treated diabetes continue to be important problems for practitioners and patients. Put simply, not enough patients with diabetes are being diagnosed, treatment is often delayed for these patients, and even when treatment is placed, often the consensus goals for good metabolic control are not being achieved.

What are the benefits of agents with the thiazolidinedione class for treatment of patients with type 2 diabetes? This class of drugs targets insulin resistance. And we understand a lot about insulin resistance in the pathophysiology and pathogenesis of this disorder. Insulin resistance is a key underlying physiologic defect of type 2 diabetes. Not only are most patients who have the established disorder characterized by severe insulin resistance, but in the stages leading up to the diagnosis, in those with impaired glucose tolerance, we know that insulin resistance is severe.

We also have a great deal of prospective data, indicating that even years, if not decades, prior to the onset of type 2 diabetes, insulin resistance is a major risk factor for the later development. This is a key aspect that we would like to treat, and treat effectively.

Now, the thiazolidinediones do target this defect. They enhance insulin action, cellular responses to

insulin. They increase insulin-mediated glucose disposal, particularly in the target tissue of skeletal muscle. And this action is somewhat unique and pronounced for this class of agents versus other therapeutic options. And the net result of these effects is to improve insulin sensitivity in a group of individuals, a group of patients, characterized by severe insulin resistance.

We know from clinical experience that thiazolidinediones achieve statistically and more fundamentally clinically important improvements in HbA1c and fasting blood glucose. Now, as Dr. Doug Greene, from the University of Michigan, pointed out yesterday, in reference to the data from the UKPDS, the magnitude of reduction that is generally seen with this class of drugs, if compared to that prospective study, will result in significant decrements in end organ complications of diabetes. That's crucially important.

There's another important finding from the UKPDS study that Dr. Greene brought out. And that is doctors who treat diabetes know that it's a progressive disorder. And if you looked at the time course of HbA1c results in the UKPDS, you saw that despite the active intervention of investigators to control this disorder, there was a progressive deterioration in metabolic control across time, whether treated with insulin, with

sulfonylureas, or with metformin, or combinations therein.

Now, one of the intriguing and striking features of this class of drugs has been a durability of glycemic response. And I think this is a distinguishing characteristic that warrants particular emphasis. The mechanism of action of thiazolidinediones is distinct from other classes. You've heard a discussion of its binding as a ligand to the PPAR gamma system and to enhanced expression of genes and hence enzymes relevant to lipid and glucose metabolism. This is different from other agents within its class.

It is useful both in monotherapy and in combination. And because of its distinctive mechanism of action, it provides a very rational basis for using it in combination. Because it can be used across the range of diabetes and in combination with all other therapies used to treat diabetes, this really provides a very flexible platform for practitioners to use this class of agents in treating their patients.

Let me turn now to summarize briefly the presentation of this morning, which has focused on safety issues of Actos in particular. I remind you that Actos was studied both in monotherapy and combination therapy. Looking at the dozen most common adverse events that patients reported as they were participating in this study,

regardless of whether assigned to placebo or active agent, rates were similar in those treated with Actos as with placebo. This was a very well-tolerated drug, and it was found to be generally safe.

Dr. Kaplowitz and Dr. Freston have taken you through, I think, in great detail, explicitly, that there is no evidence of hepatotoxicity with this agent relative to the rates seen with placebo.

There does not appear to be any risk of increased cardiac risk with this drug. There are some class effects observed with Actos that seemed similar to other thiazolidinediones.

There is a mild anemia that many patients experience. This is quite likely a class effect, because the magnitude was also seen in yesterday's data and previously with troglitazone. Significantly, only a small minority, less than 1 percent, needed to discontinue therapy because of this anemia.

Edema was seen. This, too, appears to be a likely class effect. It was generally mild to moderate.

Today's presentation has focused upon the safety of these agents. When we think about lipids, we know that lipid control is an important goal in the management of patients with type 2 diabetes, to prevent heart disease. When we look at the safety data of lipids

with Actos, I think it is fair to say that the most parsimonious interpretation of that data is that it did not induce adverse effects, if one looks at the LDL-to-HDL ratio, the HDL levels, and the triglyceride levels.

With regard to hypoglycemia, which is always a constraint for practitioners and for patients who are trying to achieve good glycemic control, it is important to reemphasize that with this class of drugs, and with Actos in particular, there is no significant risk of hypoglycemia when used as monotherapy. There was occasional mild to moderate hypoglycemia when used in conjunction with combination therapy in these patients.

And, finally, there were no significant drug-drug interactions identified in the clinical data.

Overall, I think the conclusion is quite firm that the safety profile with Actos is equal to or better than other available diabetes drugs.

I would like to conclude by saying that Actos does have important advantages for clinicians and for patients with type 2 diabetes. This medication can improve the ease of use and therefore compliance. It is once-daily dosing. This is always a compliance issue. It provides flexibility across the spectrum of this disorder, both as monotherapy and in combination therapy. It's a good platform to build upon.

Hypoglycemia does not complicate monotherapy. And this is always an important consideration as we strive to lower the diagnostic criteria and get more patients treated early on in the disorder.

And, second, we have tried to review for you in detail the safety and tolerability of this drug.

Thank you for your attention.

DR. SCHNEIDER: That concludes our presentation, Mr. Chairman.

DR. BONE: Thank you very much.

We will now ask the members of the committee if they have questions specific to the content of the presentations here. We will have our general discussion later. This is really for clarification or information of points covered by the presenters for the sponsor.

Members of the committee?

Dr. Hirsch.

DR. HIRSCH: I didn't notice any presentation of diastolic blood pressure changes. Was that also seen with this drug? It seems to be a class effect with the other drugs.

DR. SCHNEIDER: Although it was seen in some of the Japanese trials and some of the other trials, in the U.S. we didn't focus on that. There was no increase in systolic or diastolic blood pressure, but we didn't really

focus on making sure that blood pressure was taken in a systematically correct fashion. So, we did not identify it in our trials.

DR. HIRSCH: You didn't identify a decline in that.

And the second thing is I didn't get the reason for not presenting the weight data. Could you just tell me again why the weight data were not -- it's not clear to me -- because I would have thought that could be an adverse effect.

DR. SCHNEIDER: It can be an adverse effect, but it is also very tightly linked to efficacy. And so, after discussion with the agency, we concluded that it would be okay, since we're only going to talk about efficacy, to kind of move away from that.

DR. MISBIN: Jules, this was an agency decision. It should be clear, I think, that this was considered to be an efficacy measure, and that we did not want to bring efficacy into this discussion at this moment.

DR. BONE: That was Dr. Misbin, for the record.

DR. HIRSCH: I see. Well, can we conclude, however, that the data showed the same kind of weight increases that are seen with other glitazones? Is that approximately correct?

DR. SCHNEIDER: It's a similar pattern, yes.

DR. HIRSCH: Thank you.

DR. BONE: Thank you.

Others? Dr. Molitch?

DR. MOLITCH: I'm still a little confused from the data as to the metabolism of this drug. It seemed like in the monkeys there was a difference from other species. So, what happens in humans exactly? How is the drug handled?

DR. SCHNEIDER: The drug is metabolized in the liver. There are a total of six metabolites, M-I through M-VI. There are different ratios of the metabolites in the different species. In humans, M-III, M-IV and a small contribution of M-II, the active metabolites do have pharmacologic activity, in terms of glucose lowering, as well as effects on lipids.

DR. MOLITCH: And what happens in patients who have liver damage, significant liver disease? There is no effect on the metabolites, et cetera?

DR. SCHNEIDER: The metabolites themselves, no. The entire area under the curve is very similar. What happens is there's a delay in absorption and a decrease in the total amount of the compound that's absorbed because of factors related to GI absorption of compounds, but there was not an increased amount of any particular metabolite.

Dr. Charney, would you care to comment?

DR. CHARNEY: That's correct.

DR. LEVITSKY: Is there enterohepatic recirculation then?

DR. SCHNEIDER: There is some enterohepatic recirculation. About 30 percent of the drug, is excreted in the urine, and then the rest is thought to be excreted through the feces. And there's a small amount of enterohepatic circulation thought to contribute.

DR. BONE: Dr. Genuth.

DR. GENUTH: I have a couple of questions of fact and a couple of interpretation. The baseline hemoglobin A1C for people entering the monotherapy studies looked to be 10 percent. What's the upper limit of normal in that assay?

DR. SCHNEIDER: In that assay, I believe it was 6.1

DR. GENUTH: And with regard to the liver safety and the comparisons of the three drugs, that was all done on prevalence -- that is, percent of patients who suffered an event, whether it was three times or 10 times upper limit of normal.

Was that analysis also done on the basis of patient years, since I couldn't follow all the numbers to be sure the exposure time was the same?

DR. SCHNEIDER: No, it was not.

DR. GENUTH: I think it should be done that way to be certain that it's a fair comparison.

DR. FRESTON: There wasn't time to precisely adjust for duration of therapy. But we would emphasize that all those data are drawn from clinical trials. These were before approval of Rezulin. We didn't include any of the data about jaundice and death in that analysis. So, we tried to make as much apples and apples as we could. They're all in clinical trials.

DR. GENUTH: Well, to make it apples to apples, it seems to me you do have to correct for whether there are differences in the length of time patients were exposed.

DR. FRESTON: Yes. But we are talking about durations of -- differences of weeks.

DR. GENUTH: Well, that's what I wanted to be sure of. There are no significant differences?

DR. FRESTON: Yes, they could be refined in that regard. But that analysis, precisely, was not done.

The trial designs were quite similar, however.

DR. GENUTH: Yes, I understand that. I just want to be sure the exposure time was approximately the same, and there wasn't some order of magnitude difference.

DR. FRESTON: Yes. Any differences in exposure of time, of course, are dwarfed by the differences in incidence.

DR. GENUTH: Can I ask two questions of interpretation, Dr. Freston, or do you want to turn it over to someone else?

DR. BONE: Well, why don't we turn it over, and we'll be sure to retain those questions.

Further questions?

I think Dr. Illingworth has a question.

DR. ILLINGWORTH: Two questions, actually. One is, the drug is 1 percent soluble in water. Is it absorbed, 99 percent, insoluble? Is the drug therefore dependent on fat absorption for normal absorption? Is it transporting chylomicrons, or does it go from the intestine?

DR. SCHNEIDER: It's my understanding that it is not absorbed by chylomicrons.

Dr. Charney.

DR. CHARNEY: The effect of food study, which would have probably addressed the fat issue, there was very little difference between the two, with and without food. So, it seems to be a very well-absorbed drug.

DR. ILLINGWORTH: But you haven't looked at the absorption in patients with fat malabsorption?

DR. CHARNEY: No.

DR. ILLINGWORTH: Okay. My second question is -- the drug obviously activates PPAR gamma. Given the

one case of myopathy in a patient on atorvastatin and, by analogy, with the myopathy in patients treated with fibrates and atorvastatin, is there any activation of PPAR alpha?

DR. CHARNEY: That's maybe better answered by someone else.

DR. SCHNEIDER: There is a very small degree of PPAR alpha activation. The primary mechanism of action is gamma.

And I'm not sure that I would correctly categorize that one case of the CPK elevation as myopathy. The person had no clinical symptomatology, no adverse experience related to musculoskeletal system was reported for that person at any time during the clinical trial.

DR. BONE: Thank you.

Dr. Levitsky.

DR. LEVITSKY: Is there a scientific basis for the assumption that the small rises in SGOT are caused by whatever it is that causes the idiosyncratic liver damage, which then goes on to cause the disasters that have been seen with the other drug in this class?

DR. FRESTON: No, there isn't. And I'm pleased to have the opportunity to clarify this issue, which came up yesterday. We're dealing here in hepatotoxicity with a pyramid effect. At its base, there are mild reactions

expressed by mild elevations in ALT. And then, as I pointed out, it progresses up, so the development of jaundice just represents a severe extension of underlying liver disease. There aren't two different forms of liver disease -- mild SGOT rises and severe liver disease. It's all the same spectrum.

DR. BONE: How do we know that for sure?

DR. FRESTON: We know that from a vast experience with other drugs and with other diseases that cause hepatic injury. For example, the viral hepatitides.

It is conceivable -- and we've talked about this a bit yesterday among the liver experts who were present -- that a dose-dependent direct hepatotoxin, or one that causes liver reactions through a hypersensitivity reaction, could also be associated, coincidentally, with an idiosyncratic reaction. That's conceivable. But it must be a rare event.

DR. BONE: I thought that was what the hepatologists thought yesterday.

DR. FRESTON: No. We listened to that discussion, as well, and that's why we're pleased to clarify this.

But I'd like to ask Dr. Kaplowitz to amplify on this.

DR. KAPLOWITZ: I think it is an important

question. And I would just echo what Jim has said. The experience with hepatotoxicity that is of an idiosyncratic nature very, very typically is associated with an incidence of ALT abnormalities which is more frequent than the actual incidence of overt liver disease or catastrophic events. This is the whole rationale for surveillance when it is done.

So, if one is going to propose the theory that there are two different mechanisms that are completely unrelated -- a low-grade ALT abnormality, which is inconsequential due to one thing, and then some rare occurrence of overt catastrophic events -- then there would be no rationale for surveillance whatsoever. Because surveillance is going to pick up all these low-grade ALT abnormalities that then in that theory would be of no relevance.

I think our experience -- we can never really be sure about this, but one presumes that amongst those individuals who develop an ALT abnormality, some will have the potential to go on with continued administration of the drug and go on to develop a more severe injury. So that by screening with ALT's in those conditions where ALT abnormalities are frequent, one is identifying a population at risk. Amongst that population, there may be individuals who could have gone on to a more serious liver disease if

the drug were not withdrawn.

So, although in theory one can never really refute your argument that there might be two mechanisms, in actuality, the surveillance process is designed to screen out far more individuals than actually develop overt disease. Our point is that in the case of Actos, we don't see any signal for hepatotoxicity. And so vast numbers of individuals are going to have to be screened to identify the possibility of a rare mild ALT abnormality that would be a signal to a risk.

DR. BONE: I will take the committee members who haven't asked questions yet, and then come back to the others.

Dr. Hammes.

DR. HAMMES: I noticed in the three different slides here on the incidence of adverse effects that there was an approximate doubling of the incidence on your long-term open-label versus the short-term monotherapy. Do you have an explanation for that?

We've looked at three things. We saw the liver incidence of ALT elevations, cardiovascular and edema. All three of those slides showed a doubling between the two studies.

DR. SCHNEIDER: In general, that's related to the duration of exposure. In the placebo-controlled

trials, the monotherapy trials, the maximum duration of exposure was 6 months. And in the open-label trial, the open-label trial, as I said, some patients have been participating for 933 days. We did not see anything very unusual in those rates.

DR. BONE: Other questions?

Let's see, Dr. Molitch and then Dr. Genuth again.

DR. MOLITCH: Yes, a few questions. One, in your liver toxicity studies in dogs, you also found some increase in toxicity, I believe, at high doses, similar to what was reported yesterday for Avandia. Is this, again, related perhaps to this quinone formation from this compound in the dogs, or that theory you don't think holds water?

DR. SCHNEIDER: Let me ask two people to comment, one, Dr. Freston, and then also Dr. Reno.

It's my understanding that most of the significant metabolic effects are happening at really mega, mega doses, 100 grams per kilo per day, and huge doses. And some of this is adaptive changes and then hypertrophy and then this sort of overwhelming growth.

So, let me let Dr. Freston comment, and then, Dr. Reno, if you want to add anything.

DR. FRESTON: The whole purpose of the animal

studies is to identify what toxicities occur at a high dose. And then one scales down the dose and tries to apply that comparable plasma concentration to the human trials. That's the whole purpose. Therefore, we want to identify toxicity in the animals in those studies.

The changes that were described here are typical of the liver reactions that are described when a liver sort of revs up to deal with an increased metabolic burden presented by the drug. Thus, we have swelling of the hepatocytes. There wasn't inflammation. There wasn't the development of fibrosis that might lead on to cirrhosis. And there was certainly no evidence of widespread necrosis.

DR. MOLITCH: Is that different from what was reported yesterday for Avandia, then, with the high doses? Is that a different histologic pattern?

DR. SCHNEIDER: Well, let me ask Dr. Reno to comment about what he perceived about it. He's our preclinical guru, so let him comment about the Avandia in comparison to our data.

DR. RENO: Yes, I can't specifically comment with regard to the liver changes that were seen with troglitazone, because there's no quinone molecule in the pioglitazone molecule. The pattern, however, that we saw in the dog study, of hypertrophy, which eventually leads to

the inflammatory changes and then to degenerative changes, is very classic when you're getting into basically overload levels of a drug going into a very sensitive species.

DR. MOLITCH: A couple of follow-up questions.

DR. BONE: Okay.

DR. MOLITCH: One was, again, yesterda, with Avandia there's a report, with just threefold elevated, or increased doses in monkeys, of anovulation in monkeys. Were studies done in monkeys, looking for this specifically? And were patients in your clinical studies, were the women also all on oral contraceptives? You started out at a lower age range. Were they all precluded from fertility in some way, or do we have any kind of data on ovulation of those women?

DR. SCHNEIDER: In terms of the animal studies, that specific finding of amenorrhea was not looked for, and consequently could not be found, and is not recorded in any of the monkey studies.

In terms of women participating in the clinical trials, women were allowed to participate. We did want them to be on contraceptive therapy during the period of time of the study. And then there were a number of women who were post-menopausal or surgically sterilized who were able to participate in the study. But we did not do a systematic evaluation of ovulation or ovulatory function in

women participating in the clinical trials.

DR. MOLITCH: And my last question will be about, similar to what I had asked for yesterday, with this subgroup analysis. For those patients who started off with elevated LDL levels or those patients who started off with edema or diastolic hypertension, do we have a subgroup analyses for these groups, to show that there were no major clinical worsening in those particular patients?

DR. SCHNEIDER: We did look at those, those three characteristics. We didn't have a slide that shows that, but we can put something together for you, if you'd like to see it, for after lunch.

DR. MOLITCH: Thank you.

DR. SCHNEIDER: Thank you.

DR. BONE: Dr. Genuth had some more questions.

DR. GENUTH: I want to follow up on the dog. That was one of my questions. According to the slide, at 100 milligrams per kilogram, there was some inflammation. You said subacute hepatitis.

DR. SCHNEIDER: Yes.

DR. GENUTH: And at 150 milligrams per kilogram, the word "necrosis" comes up. Now, that's about 300 times the dose that you gave to people; I understand that. Nonetheless, the word "necrosis" came up in liver biopsies of patients who had serious problems from

troglitazone. So, the word has to at least raise slight concern, whether this is totally unrelated to what happened to the people taking troglitazone.

DR. SCHNEIDER: This finding at these really massive doses is very similar to what the folks with Avandia showed yesterday. This finding of hepatitis, inflammation, and significant damage to the liver at these massively high doses is not unknown, especially in the dog as a sensitive species.

Fred, do you want to comment on how many other drugs or other classes of drugs show similar effects in this animal model?

DR. RENO: Let me just say again that because obviously the majority of drugs are metabolized by the liver, when you go into a sensitive species -- and it doesn't necessarily have to be the dog in all cases; in some other cases of other drugs, it might be the monkey or it might be the rat -- but you will eventually reach a dose, if death does not occur first, that these degenerative liver changes will begin to occur.

As Dr. Freston said, the hepatocytes begin to swell. They break. The necrosis -- that's a very typical and well-established pattern when you give massive doses of drugs to animals.

DR. FRESTON: Let me clarify it. It's the

sequence that counts. It's the swelling, the edema, leading to inflammation, and then occasional hepatocellular necrosis. What you see in direct hepatotoxicty is the opposite. You see inflammation, necrosis, and then incidental swelling. So the sequence is all wrong, but it is similar.

DR. GENUTH: And the other question of interpretation I had was for Dr. Freston. The advisory board has more or less said flat-footedly there is no liver toxicity from pioglitazone, and there is no reason to monitor. And we had that opinion from one of our hepatic experts yesterday with regard to rosiglitazone. Nonetheless, if I heard you correctly, you ended up by saying, well, we should have heightened surveillance for the potential of hepatotoxicity in this class. And I want to be sure that I really understand what the final conclusion is.

DR. FRESTON: Yes.

DR. GENUTH: Is it that there is just absolutely nothing to worry about, forget it? Or is the final conclusion that there is a tiny little black cloud that will be difficult to dispel until a million people have been exposed for a year?

DR. FRESTON: Yes. Yes, we concluded that the evidence does not support that there is hepatotoxicity with

Actos. That was our conclusion.

We also concluded, before yesterday's hearings, when the board met, that we could not recommend monitoring for the reasons that I set out.

We live in the real world. We understand that this committee is under pressure, and there's a lot of concern about this issue. One way to deal with an emotional, not a scientific, issue is to take some prudent steps that do not impose an economic or inconvenience or health burden on patients. That's why we came up with some of these alternatives.

DR. GENUTH: Thank you. That's very clear.

DR. BONE: I have a question having to do with the urinary tract stones that were seen. What was the composition of the stones?

DR. SCHNEIDER: Dr. Cohen, could you join us?

DR. COHEN: Six of these were analyzed. And of them, the predominant inorganic components was magnesium and phosphates. So, they're predominantly struvite stones. There was also in a couple of them a fair amount of calcium. And interestingly, in a couple of them, it was only protein and mucopolysaccharide, which is occasionally seen in the rat because of the high background levels that are in the urine.

DR. BONE: Thank you.

DR. COHEN: None of them contained any of the drug or the metabolites at all.

DR. BONE: And the stones that contained calcium were struvite with some calcium oxalate, is that right, or calcium phosphate?

DR. COHEN: They're usually calcium phosphate, not oxalate, in the rat.

DR. BONE: But these were not primarily calcium phosphate or brushite stones?

DR. COHEN: Only the one.

DR. BONE: One. Thank you. That wouldn't, of course, be one that -- well, we don't need to talk about the pH for that. Thank you very much.

Other questions concerning the presentations? Dr. Illingworth.

DR. ILLINGWORTH: The issue of fatty liver came up. And in looking at the background information, some of the patients who had an increase in transaminase were put on the drug. The transaminases improved with treatment. Looking through these, at least three of these in America and some in Japan had fatty liver. It's not mentioned, did these patients also have hypertriglyceridemia as a cause of their fatty liver? And did the treatment reduce triglycerides and hence cause remission of hepatic steatoses?

DR. SCHNEIDER: I'm pretty sure we did not look at those patients specifically for the hypertriglyceridemia or the effect of the drug on those specific patients' triglyceride levels. What we showed was just the mean effect.

Can we get that for those patients, Cindy? Okay. We'll try to get that for you.

DR. BONE: Thank you.

Anything further before we go on to the FDA presentations?

(No response.)

DR. BONE: If not, we will next have a presentation from Dr. Steigerwalt concerning the preclinical safety evaluation.

DR. STEIGERWALT: Thank you very much, Dr. Bone.

The FDA presentation will consist of two separate sections. I will be presenting issues of the preclinical issues, and I will be followed by Dr. Misbin for the medical issues.

Basically, I'm going to take the same approach that I took yesterday, and focus on the preclinical issues for pioglitazone regarding the heart and the liver findings. The characteristics of these findings are very similar to what we've seen with other thiazolidinediones.

We have in the heart an increased heart weight, and this is a very consistent finding in all species. This is rats, mice, monkeys, and dogs that have been tested.

There has also been a finding of the plasma volume expansion and hemodilution, which is characterized by a decrease in hematocrit, hemoglobin and red blood cell counts in mouse, rat and dogs. And you also see changes in reticulocytes and platelets in the rats and mice.

In some cases where you had very severe forms of this hemodilution, you had splenic extramedullary hematopoiesis, which seems to be related to the response to this kind of plasma volume expansion. In addition, in the severe cases, we saw hydrothorax in rats and hydropericardium in dogs, and also atrial thrombosis in rats and mice.

And these cardiac changes have been associated with plasma volume expansion, and they don't seem to be associated with functional changes in the animals. Again, this does not appear to be a direct effect on the heart tissue by the drug. The cardiac effects appear to be a response to this plasma volume expansion.

Regarding the liver effects, we again have the increase in liver weights. This was in rats, mice, dogs, and monkeys. And it wasn't always found in all the experiments, but it seems to be a similar finding to the

other thiazolidinediones. Again, there were no histological or clinical chemical correlates in the rats or mice. We have just seen liver effects; we are not seeing elevations of ALT.

But there were occasional findings of centrilobular hypertrophy in dogs and monkeys. I don't know exactly how the correlation goes there. I just noticed those in some of the studies.

This is an error here. This should be a 1-dog study, not just one dog.

As pointed out previously, there was necrosis and subacute hepatitis noticed at very high multiples in this dog study.

Again, as has been pointed out before, the dog is a sensitive species. We had an increase in ALT at about 11-fold the human multiple, based on surface area comparisons. We had about a 2.5-fold increase over control of ALT in the dogs. And then, in another dose group about three times the clinical exposure, we had a very mild increase, about 1.4-fold, compared to controls, in the dog.

And there were some sporadic elevations in ALT noted in some rats and monkey studies, as well, but these were not a consistent finding across the study. So, it's hard to say that this is a -- the dog is obviously still the most sensitive species, and you do see some of these

sporadic findings in other findings in other species.

Also, at very high doses in some of the studies, there were decreases in albumin and total protein in dogs -- again, probably related to the liver effects, and indicating that, at high doses, you might be getting into some functional effects.

Basically, again, we have that the cardiac findings are generally attributed to responses in the plasma volume expansion, and they occur at relatively low multiples of the human exposure. The increases in the liver weight were not as consistently seen as with some other thiazolidinediones, but the finding of ALT in the chronic dog study is similar to what we've seen with rosiglitazone. And that provides a signal that there might be some liver toxicity concern there.

What I've done here is a comparison based on minimum effect levels that were reported in the package from the sponsor to the committee. I've made comparisons of the animal/human ratio, based on surface area comparisons for each of the toxicity endpoints.

For cardiac hypertrophy, we have fairly similar sensitivity between the species, for the mouse, rat, and dog. The minimum effect level is six-fold or less for all species. And it's fairly similar for these.

The hemodilution effect, again, in the rat and

the dog, it's very similar as to the effect on cardiac hypertrophy. We're getting fairly low multiples here. I'm not sure what this means. The monkey and the mouse seem to be very resistant to this effect. We have very high levels here for this.

Again, for the ALT, the dog is fairly sensitive, and we're getting elevations of ALT starting at levels about threefold the human exposure. The issue of the necrosis and the histological findings in the dogs occur at considerably higher multiples here.

The hepatic hypertrophy, again, here, there's a little bit of variability in the sensitivity in the species again. But we do have, particularly for the mouse and the monkey, multiples that are fairly close to the human exposure for the hepatic hypertrophy.

Therefore, I'm basically making the same conclusions that I did yesterday, on the next slide, that the liver and the cardiac effects need to be considered in the clinical evaluation to determine the safety of pioglitazone.

Thank you.

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

The next presentation will be by Dr. Misbin.

DR. MISBIN: Thank you.

I think everyone knows that there are three drugs that we are discussing over these 2 days. And the sponsors of these three drugs are all in this room. And Henry Kissinger was not available, and so it's up to me really to make sure that bloodshed does not follow this meeting.

(Laughter.)

DR. MISBIN: I do feel compelled to make a few statements that may be interpreted, or misinterpreted, to the detriment of one. There are some statements which have been made which could be misinterpreted. And I really feel it necessary to set the record straight.

This morning, there was a statement made which could be interpreted to mean that Parke Davis was not totally attentive to the problem of liver failure in their post-marketing surveillance. This is totally untrue. I can remember exactly -- and if I had my diary, I could tell you date and hour -- that I was called about the first case of liver failure. It was on a Friday afternoon. And within 2 weeks, with the complete cooperation of Parke Davis, we actually had joint public statements by the FDA and Parke Davis in an attempt to correct this problem. This could not have been done without the complete cooperation of Parke Davis. And so any speculation that there was foot dragging here is totally without foundation.

I'd also like to make a statement about the lipids that were discussed yesterday. There was a statement which was made with respect to the lipid changes in Avandia, to imply that those changes may be a class effect. Now, this may or may not be true. It's not absolutely clear. But to allay any possibility of misconception, I felt that it was necessary for Takeda to present their lipid data today so that one would not assume that all the changes seen yesterday with Avandia also applied to Actos. This was an exception, really, to our decision not to have efficacy data today presented by Takeda, but it just seemed impossible to allow the statement to go yesterday without showing you the lipid data that's relevant to a consideration of Actos.

With that, I'd now like to begin.

DR. BONE: Thank you.

DR. MISBIN: There are really only two safety issues that have to be addressed today with respect to pioglitazone. The first is related to the heart, and the second of course is related to the liver.

Now, as we've heard several times, the increase in heart size is really a class effect with respect to all compounds of this class, as found in animal studies. And we really have known all of this all along. And, really, the cardiac problem was really the major issue related to

the review of troglitazone.

The way the problem was dealt with at that time was to do an echocardiographic study. And in that study, troglitazone at maximal dose was compared to glynase, also at maximal dose, and this was done for 96 weeks.

The purpose of doing the study in that way was to eliminate the confounding effect that changes in glycemic control would have. Obviously patients are being treated with drugs and their glycemic control would change, and that would be another variable.

These were largely patients who were already taking sulfonylureas already, although not necessarily at maximal dose. When they were put on a maximal dose of glynase, many of them developed hypoglycemia, and they were withdrawn from the trial on that basis. Many of the patients who were put on 600 milligrams of troglitazone monotherapy did not have an adequate clinical response, and they were also withdrawn because of lack of efficacy. And this is data we've discussed at one forum or another previously.

But the point is that the cohort going forward were really well matched with respect to their glycemic control. And so at the end of 96 weeks, the fact that there was no difference, certainly no detrimental difference, between troglitazone and glynase told us, at a

very minimum, that the change in cardiac function in patients taking troglitazone was no worse than had they been taking a reasonable comparator -- both cardiac function and size.

Now, a similar study design was employed, again, with rosiglitazone, and we heard this discussed yesterday. This is part of an ongoing study. We've already received data on 52 weeks, and you heard that yesterday. But the study design is really the same, and it was to compare a maximal dose of rosiglitazone against a maximal dose of glyburide in an attempt to count and remove changes in glycemic control as a major variable.

Now, the data with pioglitazone, the study design is really quite different. As we heard today, the pioglitazone study is a comparison of pioglitazone, from low to high doses, versus placebo. And it's a 26-week study. I should say we have data on 26 weeks. It's a study going on, as you have already heard.

But I myself have some difficulty about this study design. It seems to me that untreated diabetes cannot be good for the heart. And the only thing I think one could say from the results of this study is that the change in cardiac function in patients on pioglitazone is no worse than the change in cardiac function in patients with untreated diabetes. And to me that's not a very

reassuring statement, and I would appreciate comments from the panel.

Now, this slide has been shown. I showed this slide yesterday. We are going to be revisiting the same issues today as we did yesterday.

Again, this is the results of various phase 3 trials, with the incidence of ALT elevation greater than 3 times normal. Now, I think Dr. Genuth asked the question about duration of treatment. And that's actually, I think, absolutely correct. This study was a little bit shorter than these, and perhaps that accounts for the somewhat fewer number of cases. Although you could see you would have to add up all of these cases -- there are really very, very few. So, a statistical analysis is really not possible.

It's also not a trivial issue to answer the question of duration and express it as patient years. Because one has to account for dropouts, particularly since most of these are placebo patients. So, I don't put this up as a rigorous epidemiologic demonstration of the data of nearly the same quality as Dr. Graham presented to you last month. This is just pretty much an approximation of the situation.

But I think it is relevant, and particularly with respect to monitoring, to look at the data, because I

think if we go forward with monitoring on these drugs, I think this is what we're going to have. We're going to have .6 percent of patients, over 6 or 12 months, will have ALT elevations of 3 times normal. And this is just the background. And really, the challenge is to distinguish toxicity from background.

Now, this again is the data with troglitazone. And I won't go through the same thing I did yesterday. It's the same audience. But I think, when considering monitoring, it might be important to consider what actually would be the effect of monitoring, given this database. If you just applied this database to the general population, what kind of results would one find?

And I think, from an epidemiologic point of view -- this is not an area I have any competence in -- but, generally, people say, well, if you look at a large population, looking for an unlikely but serious event, one has to take into account both the positives, the negatives, the false positives, false negatives, and really ask the question, in any individual case, did this monitoring lead to a correct decision or a decision that was incorrect or unnecessary?

Now, I think it's important to recognize as I've just pointed out, that approximately .6 percent have a baseline elevation here. This is from the studies that I

just showed in the troglitazone/placebo. And I think some of these cases have just nothing to do with the drug whatsoever.

Now, it's also, I think, important to point out that there were a substantial number of cases -- indeed, almost half of the cases -- that had elevations. They would have been identified by monitoring. But, in fact, that didn't make any difference, because they were continued on the drug and the elevation went away. So, I think kind of an approximate way of looking at this is if you were to screen 100 patients taking troglitazone, you would find 2 patients that had this type of abnormality.

In one of those cases, by stopping the drug, you could indeed potentially prevent liver failure or death. In the other case, in the other patient, you would stop the drug unnecessarily. And that's just the price one has to pay for this kind of procedure. But I think to save the liver in one case, it's worth inconveniencing 98 patients than perhaps having a false call on 1 additional patient. But I think this is the type of reasoning that I think we should go forward and try to apply this type of reasoning to the cases of the drugs, pioglitazone and rosiglitazone.

Now, this is the database with pioglitazone. And, again, the same rules here apply as yesterday. I have

recalculated. This data is not exactly the same as what you saw earlier. I believe there were two cases -- one or two; I don't remember -- that I eliminated because the ALT elevation clearly preceded the patient even taking pioglitazone. And so, to be consistent among all these databases, I eliminated those cases.

I would also point out -- and this is in my write-up; the cases are actually there for anyone to read -- that there were several cases of patients that had elevations at the beginning that actually got better when treated with pioglitazone. And this is consistent. This is not just here. We saw that with rosi. We saw that with troglitazone. And I suppose there are various explanations. But the simplest explanation is that these patients have NASH, and the NASH gets better when they're treated with this drug.

And, indeed, we've actually received experimental protocols, looking specifically at patients with NASH, treated with one or the other glitazones, in the hope of correcting this condition. So, it is a complicated question. It's not one that I think a knee-jerk reaction is really likely to be the correct reaction in trying to sort out this matter.

Now, there was one case, according to my way of looking at it, that in fact was over 8 times normal. And I

don't know why we disagree on this. This was a patient that had a value, according to my records, of 340, which is over 8 times normal, or perhaps it was slightly upper limit. And so by the rules that I've tried to impose on all these databases, this case has to be counted as a case.

I would point out, though, this was the patient taking norfloxacin. The temporal relationship to the norfloxacin was very convincing. The patient was on norfloxacin for 10 days. Two days later had a spike in ALT. The norfloxacin had already been stopped. And within a few days, the ALT went down. And the patient continued on pioglitazone without any further sequelae.

So I think, looking at this as an individual case, that would be my interpretation. But there are a lot of individual cases. And I think one has to just have a certain yardstick, and apply that to all the databases. And that's why I'm including this as a case of treatment-emergent ALT elevation on pioglitazone. But I think it should be clear that monitoring in this situation, even in this case, would not have provided much information.

Now, I would also like to take issue with the calculation that we heard this morning. And I think something said, based on the one case in rosiglitazone, that there was one case of jaundice per million, or