FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

SEVENTY-THIRD MEETING

OF THE

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

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8:13 a.m.

Thursday, April 22, 1999

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

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ALSO PRESENT:

LARRY SASICH, PHARM.D.

C O N T E N T S

NDA 21-071, AVANDIA (rosiglitazone maleate)
SMITHKLINE BEECHAM PHARMACEUTICALS

P R O C E E D I N G S

(8:13 a.m.)

DR. BONE: Good morning. I'm Dr. Henry Bone. I'm the Chairman of the Endocrinologic and Metabolic Drugs Advisory Committee, and we're declaring the 73rd meeting of this committee in session.

This meeting will discuss the new drug application for rosiglitazone maleate for diabetes mellitus type 2.

The first order of business is the reading of the meeting statement by Kathleen Reedy, the Executive Secretary.

MS. REEDY: The conflict of interest statement for the Endocrinologic and Metabolic Drugs Advisory Committee, April 22nd, 1999.

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 FDA's Freedom of Information Office located in room 12A-30 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.

I'd like to then go around the table and introduce each person who is sitting here at the front from the FDA and from the committee, and we'll start with Dr. Bilstad, please.

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

DR. SOBEL: Sol Sobel, Director of the Division of Metabolic and Endocrine Drug Products.

DR. MISBIN: Robert Misbin, medical officer.

DR. STEIGERWALT: Ron Steigerwalt, pharmacology team leader.

DR. ILLINGWORTH: Good morning. Roger Illingworth, member of the advisory panel, Portland, Oregon.

DR. HAMMES: Richard Hammes, Consumer Representative, pharmacist, University of Wisconsin.

DR. BONE: I'm Dr. Bone, the Chair, from Detroit, Michigan.

MS. REEDY: Kathleen Reedy, FDA.

DR. HIRSCH: Jules Hirsch, New York.

DR. GENUTH: Saul Genuth, Cleveland.

DR. NEW: Maria New, New York.

DR. MOLITCH: Mark Molitch, Chicago.

DR. LEVITSKY: Lynne Levitsky, Boston.

DR. SEEFF: Leonard Seeff, NIDDK and VA.

DR. LEWIS: James Lewis, Georgetown University.

DR. BONE: Thank you very much.

We're going to have a series of presentations by the sponsor and they are outlined in your agenda. The committee members have been requested, unless there's something that is an absolutely crucial point of understanding of what has been presented, to wait till after the presentations are complete to ask questions because the sponsor feels that very likely questions will be answered in a succeeding presentation.

After the sponsor's presentation, we'll have a short intermission and then go to the FDA presentations.

I'd like to introduce Dr. David Wheadon, who will be leading the presentations for the sponsor.

DR. WHEADON: Thank you, Dr. Bone.

It's amazing to see that something in Washington has eclipsed, at least today, the NATO summit.

(Laughter.)

DR. WHEADON: I'm David Wheadon, Vice President of Regulatory Affairs at SmithKline Beecham.

We certainly thank the committee and the agency for this opportunity to present to you this morning data concerning Avandia, rosiglitazone maleate, as a treatment

for type 2 diabetes. We certainly believe that Avandia will represent a significant contribution to the therapeutic armamentarium for the treatment of type 2 diabetes.

To briefly outline our presentation for you, in addition to introducing the day, I will go very quickly through preclinical highlights on Avandia. I will then be followed by Dr. Anthony Rebuck who will discuss the efficacy profile of Avandia. Dr. Elizabeth Rappaport will then follow to discuss the safety evaluations of Avandia in clinical trials. Dr. Douglas Greene of the University of Michigan will discuss a risk/benefit assessment of Avandia as a treatment for type 2 diabetes, and rounding out the day will be Dr. Tadataka Yamada, our head of R&D, who will summarize the SB presentations.

The key messages that we hope to leave with the committee at the end of our presentation are as follows:

Avandia is a potent, antidiabetic agent with activity as an agonist at the PPAR gamma nuclear receptor.

It is indeed effective in monotherapy, as well as in combination with metformin.

Additionally, long-term studies, specifically through 52 weeks, have shown a durability of effect.

The safety profile of Avandia has been well characterized with no signal of hepatotoxicity, a neutral

effect on lipids, particularly on the LDL/HDL ratio, and a minimal cardiovascular/hemodynamic side effect profile.

Additionally, a positive risk/benefit assessment has been seen with Avandia as a treatment for type 2 diabetes.

To highlight the preclinical findings I'll be discussing for a few moments, we have conducted an extensive program of preclinical studies which indicate that Avandia has greater pharmacological potency and a better hepatic safety profile than troglitazone. Our studies have extended and confirmed the observations of others that certain preclinical findings, for example, hemodynamic and cardiovascular effects, are common to the thiazolidinediones as a class. Thus, preclinical studies predicted efficacy and brought to life issues related to safety which permitted appropriate evaluation and monitoring of safety in patients entered into clinical trials.

Our observations in preclinical studies also provided a rational basis for risk assessment.

The PPAR gamma nuclear receptor is a key molecular target for the thiazolidinediones. They, the thiazolidinediones, have high affinity for the ligand binding domain of PPAR gamma, but not PPAR alpha or PPAR delta. These agents as a group activate PPAR gamma to

regulate the expression of genes encoding proteins involved in lipid and glucose metabolism.

How exactly do these events relate to pharmacologic activity and efficacy?

In line with our observations regarding the selectivity and potency of Avandia is the evidence of efficacy in rodent models of obesity, insulin resistance, and type 2 diabetes. It has been shown in these models that Avandia increases insulin sensitivity in liver, skeletal muscle, and adipose tissue. With this increase in insulin sensitivity, an improvement in glycemic control has been seen without incumbent hypoglycemia. Additionally, as would be expected, a lowering of plasma concentrations of free fatty acids and triglycerides has also been seen. And perhaps most interestingly, protection against pancreatic beta-cell insulin depletion has also been observed in animal models.

As indicated previously, it is clear that the thiazolidinediones as a class possess certain activities in common based on similar observations of drug-related effects in animals and humans. Among these are adipocyte hyperplasia and normal fat depots, namely the subcutis, epididymis, and bone marrow, contributing at least in part to increased body weight observed in animals.

Increased plasma volume and decreased

hematocrit were consistently observed in association with cardiac hypertrophy. Our studies have shown that increased plasma volume is related to increased sodium and water retention and occurs in association with lowered mean arterial blood pressure and a marked increase in regional blood flow up to 400 percent in subcutaneous fat. Well-controlled studies in dogs and rats, using echocardiography and integrated telemetry systems, indicated that cardiac hypertrophy is an adaptive response to increased preload.

Also in common with other thiazolidinediones, Avandia has been shown to inhibit ovarian steroidogenesis, primarily progesterone. It has been shown to cause fetal toxicity primarily in mid to late gestation, but no teratogenic effects have been observed. Additionally, benign lipomas seen in lifetime studies of Avandia in rats are recognized to be a class effect of the thiazolidinediones.

This slides shows the chemical structure of Avandia and troglitazone. The thiazolidinedione portion of these two molecules are marked in yellow, and it is the primary determinant of binding to the PPAR gamma receptor, while the side chains, marked in red for Avandia and blue for troglitazone, govern the binding affinity and hence the potency of agonist activity. The binding affinity and agonist potency of the thiazolidinediones at PPAR gamma are

highly correlated with their antidiabetic potency. Hence, the dose of Avandia required to elicit a therapeutic effect in patients with type 2 diabetes is about 100 times less than the generally recommended dose for troglitazone.

Our preclinical studies have also identified differences in the hepatic safety profile of Avandia compared to troglitazone. ALT increases were seen only in one species with Avandia, namely the dog; whereas, increases were seen in multiple species with troglitazone. While only limited conclusions can be drawn from cell culture studies, we found that troglitazone was toxic to culture rat hepatocytes, whereas Avandia was not toxic at the same or higher concentrations up to the limit of solubility for Avandia, which was 100 micromolar. Although the precise mechanism of hepatotoxicity induced by troglitazone is not known, the absence of hepatotoxicity associated with Avandia in rats, either in vivo or in vitro, indicates that hepatic effects are not related to activation of PPAR gamma. Since Avandia is clearly more potent as an antidiabetic agent compared to troglitazone, it does not exhibit the hepatotoxic potential of troglitazone, we believe the side chain of troglitazone is an important determinant of hepatotoxicity. However, other potential mechanisms cannot be ruled out.

Qualitative and quantitative differences in

metabolism and disposition of Avandia and troglitazone may also be important when considering the hepatotoxic potential of these two thiazolidinediones in patients. Noteworthy in this context is the marked difference in volume of distribution. For Avandia, this is slightly greater than plasma volume, approximately .1 to .2 liters per kilogram, whereas for troglitazone, it exceeds plasma volume by 100-fold, indicating a significantly greater distribution of troglitazone throughout body tissues relative to Avandia.

Likewise the half-life of Avandia in man, approximately 4 hours, is considerably shorter than the half-life of troglitazone. The latter may be related to the extensive enterohepatic recirculation of troglitazone which is not a characteristic of Avandia metabolism in elimination.

Finally, a significant difference in the ratio of drug-related material in liver relative to plasma, less than or equal to 1 for Avandia, approximately 15 for troglitazone, a potent and clinically significant induction of cytochrome P450 3A4 for troglitazone, and elimination of drug-related material primarily via the liver for troglitazone and the kidney for Avandia may all predispose animals and humans to the hepatotoxicity manifested by troglitazone.

In summary, our comprehensive preclinical evaluation of Avandia, coupled with an extensive investigation of mechanisms related to toxicities seen in animal studies, highlighted clear potential benefits for Avandia as it went into clinical trials, including an improvement in glycemic control based on improved insulin sensitivity, a decrease in concentration of free fatty acids in plasma, a favorable drug interaction profile, principally looking at the induction of 3A4, and an improved hepatic safety profile.

At the same time these preclinical investigations also raised potential safety issues, including cardiovascular and hemodynamic effects, reduced hematocrit, and increased body weight. Consequently, these were the subject of detailed assessments in our clinical trials and will form the basis of the presentations that you will hear later this morning.

It is my pleasure now to turn over the podium to Dr. Anthony Rebuck who will discuss the efficacy profile of Avandia.

DR. REBUCK: Thank you, David. Good morning.

I'm just going to present two things today: the efficacy of Avandia in monotherapy and the efficacy of Avandia in combination with metformin. I'd like to fill in the background with data concerning the lipids, durability

of effect, and endogenous insulin sparing.

The data I present will support the two indications for which Avandia is filed: monotherapy as an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes, and concomitantly with metformin when diet and metformin alone do not result in adequate glycemic control.

The Avandia phase 2/3 clinical program comprised over 3,400 patients on monotherapy, almost 650 in combination with metformin, and over 1,200 in combination with sulfonylurea.

The 8- to 12-week studies were dose-finding. The 26-week studies, of which there were 7, were double-blind, either active or placebo-controlled. The 52-week study was active-controlled, and the 104-week studies were either cardiac safety or open label extensions.

The focus of my presentation today will be on monotherapy and combination with metformin. The data for efficacy with sulfonylurea is in the final stages of preparation and will be submitted to the agency shortly. The safety from sulfonylurea will be included with the monotherapy and metformin combination and will be presented later by Dr. Rappaport.

I'd now like to present the dose response of Avandia in monotherapy.

This is change from baseline in fasting plasma glucose at week 8. It's pooled monotherapy data and includes patients previously treated on diet only, as well as those who had previously been treated with other oral agents. The lowest effective dose, in terms of fasting plasma glucose, was 2 milligrams a day. However, the most clinically significant glucose lowering effects were at 4 and 8 milligrams a day. 12 milligrams a day gave no further benefit. Therefore, 4 and 8 milligrams were the doses used for the phase 3 clinical trials that I'll be presenting today.

Does Avandia work in monotherapy?

Two principal placebo-controlled, 26-week monotherapy studies: study 11 with 500 patients and study 24 with 900.

In study 11, if patients were taking antidiabetic medications, these were stopped. 4 weeks later, patients entered a 4-week diet and placebo run-in period. Patients were then randomized to receive either placebo or Avandia, 4 milligrams a day or 8 milligrams a day, given in two divided doses.

Study 24 had a similar design. Patients were randomized to receive either placebo or the same Avandia doses as in study 11, that is to say, 4 or 8 milligrams a day, given as a single daily dose or two divided doses.

The primary efficacy parameter was change from baseline in hemoglobin A1c at week 26. The primary comparisons were between the Avandia groups and placebo.

Patients were on average 60 years of age. Two-thirds of them were males. The baseline body mass index was on average 30 kilograms per meter squared. Three-quarters of the patients were white.

Baseline fasting plasma glucose was between 220 and 230 milligrams per deciliter with baseline hemoglobin A1c of approximately 9 percent.

The duration of diabetes was on average 5 years and fully one-quarter of the monotherapy patients were previously on diet alone.

This analysis includes the diet only and the previously treated patients. At week 26, both Avandia groups showed significant decreases from baseline in fasting plasma glucose. The placebo group showed slight deterioration in glycemic control. Compared with placebo, the treatment effect was 57 milligrams per deciliter for 2 milligrams twice a day of Avandia and 76 milligrams per deciliter for 4 milligrams twice a day, both highly statistically significant.

A similar pattern of response both with respect to baseline and placebo was seen for the primary endpoint. The decrease in hemoglobin A1c at week 26 for Avandia 2

milligrams twice a day was 1.2 percent compared to placebo, and for 4 milligrams twice a day was 1.5 percent compared to placebo.

In study 24, decreases in fasting plasma glucose from baseline were seen for both the 4 milligrams per day and 8 milligrams a day both for once daily and twice daily Avandia dosing. Compared to placebo, the decreases ranged from 31 to 62 milligrams per deciliter in a dose-ordered fashion.

Responders are defined as patients who achieved reductions in fasting plasma glucose of at least 30 milligrams per deciliter from baseline. The percentage of responders in the placebo group was less than 20. For 4 milligrams twice a day of Avandia taken once or twice a day, the percentage of responders was 45 to 54. For 4 milligrams twice a day, 70 percent of patients had reductions in fasting plasma glucose of at least 30 milligrams per deciliter.

As with fasting plasma glucose, the treatment effect for hemoglobin A1c was robust. For 4 milligrams total daily dose, once daily or twice daily dosing were therapeutically equivalent by prespecified equivalence criteria. While both 8 milligrams per day dosing regimens were effective in improving glycemic control, they were not therapeutically equivalent. The best efficacy for Avandia

was seen at 4 milligrams twice a day, the treatment effect with respect to placebo being 1.45 percent.

Within each of the monotherapy trials, we enrolled a variety of patients of varying disease severity as reflected by their prior therapy: diet alone comprising 25 to 30 percent of the monotherapy patients, prior single drug therapy, and prior multiple drug therapy.

For the 225 patients who had never previously received antidiabetic medications, all doses, whether given once or twice a day, resulted in robust improvements in hemoglobin A1c from baseline. The treatment effect being as high as 1.5 percentage points.

For the 542 patients previously treated with a single antidiabetic agent, 8 milligrams was clearly more efficacious than 4 milligrams a day, although both doses showed positive treatment effects compared to placebo.

Even among the 140 patients who had been withdrawn from multiple antidiabetic agents, 4 milligrams twice a day achieved an improvement in glycemic control with respect to baseline.

So, in summary, Avandia used as monotherapy is effective in improving glycemic control at doses of 4 milligrams a day and 8 milligrams a day, either once daily or in divided doses. Based on the overall changes in glycemic control and the responder analysis that I've shown

you, the recommended starting dose of Avandia as monotherapy is 4 milligrams a day.

Is this effect durable?

Evidence for durability was taken from study 20. This study was a double-blind, double-dummy design in which 600 patients were enrolled. If they had been treated previously with antidiabetic agents, these were discontinued. Patients then entered a 4-week diet and placebo run-in period before being randomized to receive one of three regimens for 52 weeks. The regimens were: Avandia 2 milligrams twice a day plus placebo, Avandia 4 milligrams twice a day plus placebo, and placebo plus glyburide. The glyburide was treated to effect during the first 12 weeks, then kept constant for the remainder of the study. By contrast, of course, the Avandia doses were kept constant throughout the 52 weeks.

In the glyburide group, shown here in white, there was a fairly rapid decrease in fasting plasma glucose during the glyburide titration period, reaching a plateau in 6 to 8 weeks. However, over the second half of the study, there was an apparent deterioration of glycemic control. By contrast, in the Avandia treated groups, there was a more gradual decline in fasting plasma glucose, reaching a plateau by 16 weeks. For 4 milligrams twice a day, the glycemic control appeared to be maintained up to

52 weeks.

Similarly for hemoglobin A1c, there was loss of glycemic control with sulfonylurea during the second 6 months of therapy versus durability of effect for Avandia 4 milligrams twice a day.

One might predict reporting of hypoglycemia as adverse events among the sulfonylurea treatment group. Indeed, investigator reports of hypoglycemia occurred at 12 percent of the glyburide treated patients with 3 percent being withdrawn, versus the low number of patients experiencing hypoglycemia in the Avandia treated groups. Less than 2 percent of Avandia treated patients were reported to have hypoglycemia and only 1 patient among the 400 withdrew for this cause.

Here we show the effect of Avandia on fasting insulin and C-peptide in study 20, as well as the insulin precursors, proinsulin and split proinsulin. Treatment with Avandia resulted in improvement in glycemic control, while insulin and C-peptide levels decreased. This observation is consistent with Avandia's mechanism of action as an insulin sensitizer. By contrast, of course, insulin levels increased with glyburide therapy, consistent with its mechanism of action as an insulin secretagogue.

Insulin and insulin precursors have been suggested to be associated with increased cardiovascular

risk. Both insulin and its precursors are significantly reduced by Avandia. The reduction in insulin precursors also suggests a reduced demand on pancreatic beta-cells with restoration of beta-cell function.

Avandia, therefore, has a durable effect. The improvement in glycemic control is maintained on chronic therapy with no evidence to suggest the development of tolerance. Improvements in glycemic control are associated with reductions in endogenous insulin, C-peptide, proinsulin and insulin split products.

It's well recognized that patients with diabetes characteristically have a variety of lipid disorders. We, therefore, examined the effects of Avandia on cholesterol subfractions, triglycerides, and free fatty acids.

These are perhaps best illustrated in the 52-week active-controlled study 20. In the Avandia treated groups, there was an initial increase in LDL cholesterol, reaching a plateau by 3 months. Little further change occurred up to month 12. These findings are, of course, consistent with a class effect.

The increase of LDL may be offset by a gradual, prolonged increase in HDL cholesterol. At 12 months while the LDL cholesterol had increased by 12 percent, the HDL cholesterol had increased more, specifically 19 percent.

Accordingly, in patients treated with Avandia, there was a small initial increase in LDL/HDL ratio, followed by a gradual decline, the mean value at 12 months being at or below baseline.

Based on the preclinical efficacy in rodent models of type 2 diabetes, we would have predicted a lowering of triglyceride levels. In fact, there was great degree of variability in the triglyceride levels, as can been seen by the standard errors. Overall, however, the effect of Avandia on triglycerides appears to be neutral and, indeed, seem to be little different from that seen with glyburide.

Free fatty acids are thought to play a role in the development of insulin resistance and may play a role in the impairment of pancreatic beta-cell function. We were pleased to observe, therefore, a decrease in free fatty acids in both Avandia treatment groups. This decrease in free fatty acids was demonstrated as early as 3 months and appeared to be sustained over 12 months. One notes with interest that while Avandia and glyburide had similar effects on glycemic control at 12 months, Avandia's effect on free fatty acids appeared to be far more robust.

So, there is a small increase in LDL and HDL cholesterol, with preservation of the LDL/HDL cholesterol ratio. There's a neutral effect on triglyceride levels and

a sustained reduction in free fatty acids.

Finally, does Avandia work in combination with metformin?

This I recognize is a rather daunting figure, so please bear with me as we work our way through it.

Patients who were taking acarbose, the acarbose was stopped. Patients who were taking sulfonylureas, sulfonylureas were stopped. These patients plus those who were on diet and exercise alone were started on 1 gram of metformin a day and that was continued for a week. In the second week, the dose was increased to 1.5 grams of metformin a day and that was continued for a week. Then 2 grams a day, and finally the maximum dose of metformin, 2.5 grams a day. Patients who were on sulfonylureas plus metformin combination therapy, the sulfonylureas were stopped, and patients who were just on metformin, these two groups entered this dose cascade at a level that corresponded with their previous metformin dose.

Patients had one more hurdle to overcome. They were only eligible for randomization if, despite maximal doses of metformin, they had still not achieved adequate glycemic control. Inadequate control in this context is defined as a fasting plasma glucose between 140 and 300 during the maintenance period. They were then randomized to metformin plus placebo or metformin plus Avandia 4

milligrams once a day or metformin plus Avandia 8 milligrams once a day.

There are some important differences in the patients in the metformin studies. Specifically the disease duration is now between 7 and 8 years. Less than 5 percent were on diet only, and over 50 percent were previously treated with combination therapy.

At week 26, both of the combination therapy groups showed significant decreases in fasting plasma glucose from baseline. The metformin group deteriorated very slightly. Compared with metformin alone, the treatment effect for the Avandia plus metformin combination therapy groups was between 50 and 53 milligrams per deciliter.

As before, responders were defined as patients who achieved a 30 milligram per deciliter decrease in fasting plasma glucose from baseline. The percentage of responders in the metformin group was 20, while in the Avandia plus metformin combination groups, the percentage of responders was between 45 and 61.

As with fasting plasma glucose, the effect on hemoglobin A1c was both clinically and statistically significant, the level decreasing between 1 and 1.2 percent compared to metformin alone.

In the so-called metformin synergy study, there

was a similar metformin titration and maintenance period. The patients who were still poorly controlled on maximum dose of metformin were randomized to continue metformin, discontinue metformin and begin Avandia 4 milligrams twice a day, or add Avandia while metformin was continued.

In the patients inadequately controlled on maximum dose metformin but who were allowed to continue metformin for a further 6 months, there was little further change in fasting plasma glucose. When metformin was abruptly discontinued and replaced with Avandia alone, fasting plasma glucose increased. By contrast, when Avandia was added to the background metformin, there was a marked decrease in fasting plasma glucose. Clearly, Avandia in combination with metformin achieved a level of glycemic control superior to that observed for either agent alone. Since Avandia and metformin have different mechanisms of action, these results suggest a synergistic effect.

This experiment doesn't permit a comparison between metformin and Avandia efficacy, nor is it reflective of how an inadequately controlled patient is managed in clinical practice.

The responders were defined as before. While the responder rate was low, both in the metformin and Avandia groups, combination therapy resulted in 67 percent

of patients who lowered their fasting plasma glucose by at least 30 milligrams per deciliter.

One might predict, of course, similar changes in hemoglobin A1c lagging behind the changes in fasting plasma glucose. Remember that in this study the duration of the run-in and maintenance period permitted those patients treated with metformin to attain a steady state condition. By contrast, for patients who had their metformin abruptly discontinued and began Avandia, one would predict an initial increase in hemoglobin A1c due to withdrawal of maximum dose metformin, perhaps coupled with a slower onset of action of thiazolidinedione. When patients are poorly controlled on maximum doses of metformin, it would be more appropriate to use combination therapy. The right-hand column on this slide clearly demonstrates the improvement in control when Avandia is added to the regimen in this patient population.

We have summarized the monotherapy data here. This is the no-effect line. Any data falling to the right of that line, would favor placebo. Any data falling to the left of that line would favor Avandia. I've represented here the once-a-day studies in dotted lines and the twice-a-day studies in solid lines, each represented by 95 percent confidence intervals. Clearly all the data fall to the left of that line.

Here we show combination therapy with metformin. Again, we have the no-effect line. Anything to the right of that line would favor metformin plus placebo. Anything to the left of that line would favor Avandia plus metformin. Once again, we have the once-a-day studies in dotted lines and the twice-a-day study in solid line, again represented by 95 percent confidence intervals. In this display, clearly all the data fall to the left of the no-effect line, and the effectiveness of once and twice-per-day dosing with Avandia is highlighted.

We would conclude by saying that Avandia used as monotherapy in patients previously treated with diet alone or other oral antidiabetic agents or in combination with metformin is effective in improving glycemic control at doses of 4 milligrams a day and 8 milligrams a day. The recommended starting dose of Avandia is 4 milligrams a day. Avandia may be administered as a single daily dose or in divided doses. Avandia in combination with metformin is more effective than either agent alone, consistent with the synergistic effect based on different mechanisms of action. Avandia has a durable effect for up to 12 months. Improvements in glycemic control are associated with reductions in endogenous insulin, C-peptide, proinsulin, and insulin split products. Avandia reduces free fatty acids and preserves the LDL/HDL ratio.

It's now my pleasure to ask Dr. Elizabeth Rappaport to present the clinical safety evaluation.

DR. RAPPAPORT: Good morning. I will describe for you the scope of the safety database, the demographic and clinical characteristics of the patients, and the general adverse event findings. I will then discuss areas that are of interest due to preclinical findings: hemodynamic and cardiovascular effects, hematologic effects, and weight gain. Effects in these areas appear to be common to thiazolidinediones. Finally, I will discuss an area of special interest, the effects of Avandia on the liver.

This is a rather busy slide. The point I would like to make here is that we had a very broad phase 2 and 3 clinical program. We conducted 13 trials to assess the safety and efficacy of Avandia. Patients who completed these trials were permitted to enter open label extension studies. Our trials were conducted in 11 countries in North America and Europe and involved more than 600 clinical investigators. Over 5,000 patients participated in these trials and more than 2,000 of these are currently receiving Avandia in extension studies.

The safety data that I will show you will be based on monotherapy and metformin combination studies that Dr. Rebuck described, as well as studies of Avandia in

combination with sulfonylureas.

Let us now look at the numbers of patients in our trials and the duration of treatment. Nearly 4,600 patients received Avandia alone or in combination with metformin or sulfonylureas. Smaller numbers of patients were treated with placebo, metformin, or sulfonylureas alone.

Of the patients treated with Avandia, more than 3,500 were treated for at least 6 months and over 2,000 were treated for at least 12 months.

Overall our safety database represents 3,600 patient years of observation for patients treated with Avandia, 2,500 patient years for patients treated with Avandia monotherapy, nearly 500 patient years for patients treated with Avandia in combination with metformin, and approximately 800 patient years observation for patients treated with Avandia in combination with sulfonylureas.

The three bars on the right represent patient years of observation for the three comparison groups: placebo, metformin alone, and sulfonylureas alone. Patients in these groups only received study drugs during the double-blind treatment periods, in most cases for 6 months or less. Thus, both the numbers of patients and the duration of observation were less for these groups than for the Avandia treatment groups.

Our safety database represents a broad experience with substantial numbers of patients with type 2 diabetes. This allows us to present a well characterized safety profile for Avandia.

Let us look next at the demographic and clinical characteristics of our patients. The ranges shown here are for patients in the three types of trials: Avandia alone, Avandia in combination with metformin, or Avandia in combination with sulfonylureas. Two-thirds of the patients we studied were male. The mean age of our patients was approximately 59 years. The majority, over 80 percent, were caucasian. In U.S. studies, approximately 75 percent of patients were caucasian and in European studies nearly all patients were caucasian. Most of our patients had a body mass index of more than 27 kilograms per meter squared at baseline. The mean duration of diabetes varied from 5.7 years in patients treated with Avandia alone to 8.7 years in patients treated with Avandia plus sulfonylureas.

The patients whom we studied were not a highly selected group, as we endeavored to make our study population representative of the overall population of patients with type 2 diabetes. At the time of study entry, 40 to 45 percent of patients had hypertension. 18 to 32 percent had hyperlipidemia, with the largest proportions of

patients with hyperlipidemia in the Avandia plus metformin studies. 3 to 9 percent had ischemic heart disease, the largest frequencies in the Avandia plus SU studies, and 7 to 15 percent had peripheral neuropathy. Again, the largest proportions were in the Avandia plus metformin studies.

We did exclude from all of our studies patients with New York Heart Association class III or IV angina or congestive failure and patients with systolic blood pressure greater than 180 or diastolic blood pressure greater than 110 millimeters of mercury. Patients with significant hepatic or renal disease were also excluded.

We did, however, permit patients to enter trials if at screening they had liver enzyme values that were up to 2.5 times the upper limit of the reference range.

Consistent with their underlying medical conditions, a large portion of our patients were taking antihypertensive agents including ACE inhibitors, diuretics, beta blockers, and calcium channel blockers, and varying proportions of patients were taking lipid altering agents when they entered the studies. We observed the largest proportions of patients taking ACE inhibitors and lipid lowering agents in the Avandia plus metformin studies.

The bars on the left side of the figure show that the proportions of patients who had at least one adverse event during the double-blind and open-label therapy were comparable for patients who received Avandia as monotherapy, Avandia in combination with metformin, or Avandia in combination with sulfonylureas.

Although patients who received placebo, metformin, or sulfonylureas were observed for shorter periods of time than patients who received Avandia, the frequency for Avandia treated patients was also comparable to the frequencies in these control groups.

Similarly, the proportions of patients who were withdrawn for adverse events and the proportions of patients who had nonfatal, serious adverse events were comparable for all six treatment groups.

The most common adverse events in our double-blind Avandia monotherapy trials were upper respiratory tract infections and injuries. These occurred with similar frequencies in Avandia treated patients and in patients in the three comparator groups. The injury category includes patients who had cuts and abrasions and patients who had elective surgery during our trials.

Approximately 3.5 percent of Avandia treated patients had adverse events recorded of hypercholesterolemia. This is consistent with the lipid

changes that Dr. Rebuck described.

The pattern of the most frequent adverse events was similar in patients receiving Avandia in combination with sulfonylureas.

When Avandia was given in combination with metformin, upper respiratory tract infections were again the most common events. Diarrhea, a recognized side effect of metformin, did not occur with any greater frequency in patients who received Avandia in combination with metformin than in those who received metformin alone.

We also see here that a higher proportion of patients who received Avandia in combination with metformin had adverse events of anemia reported than did those who received metformin alone. Later on when we review areas of special interest, I will discuss this further.

We examined our data for potential interactions between patient demographic and clinical characteristics and the frequency of adverse events. Avandia was found to be well tolerated across all age, gender, body mass index, and race classifications. It was also well tolerated with medications commonly used in patients with type 2 diabetes, including ACE inhibitors, calcium channel blockers, and beta blockers, and in the presence of common coexisting medical conditions.

Overall, less than 9 percent of patients were

withdrawn from studies due to adverse events and the proportion of patients was similar across all treatment groups.

The three lower rows of this table represent the adverse events that caused withdrawal in more than 1 percent of patients in double-blind trials. Hyperglycemia and aggravated diabetes were the most common adverse events leading to withdrawal in the monotherapy trials. Elevated lactic acid and diarrhea were relevant primarily for trials in which patients received metformin alone or in combination with Avandia.

This slide shows a summary of the serious, nonfatal adverse experiences that we observed in our double-blind and open-label trials. The numbers in this table represent event rates per 100 patient years exposure. The top row has the rates of any serious adverse events. The second has the rates of cardiovascular serious adverse events. The third, injuries, and the last, withdrawals for serious adverse events. Here again, although the period of observation was longer for patients receiving Avandia, we can see that the frequencies were similar across all treatment groups.

As of November 1998, a total of 31 patients who had participated in Avandia clinical trials were reported to have died. 6 of the 28 patients who had received

Avandia were reported to have died of neoplasms more than 30 days after they stopped Avandia treatment. 1 of 600 patients who received placebo died. No patients of the 225 patients who received metformin alone for 6 months were reported to have died during or after clinical trials, and 2 of 845 patients who had received sulfonylureas died.

The event rates are expressed per 100 patient years, and the corresponding 95 percent confidence intervals are shown on the far right. Although these rates are expressed in terms of patient years observation, it is important to keep in mind that we observed nearly 4,600 Avandia treated patients who had a mean duration of therapy of approximately 10 months. Both the numbers of patients and the duration of observation were less for the comparison groups. Mean duration of therapy was about 3.5 months for the placebo patients, 5 months for the metformin patients, and approximately 8 months for the sulfonylurea treated patients.

Our study population included more than 5,000 patients with type 2 diabetes, of whom nearly 4,600 received Avandia. Study patients were relatively unselected. We found Avandia to be safe when administered alone or in combination with metformin or with sulfonylureas. Total daily doses of 4 and 8 milligrams were safe and well tolerated. The overall frequencies of

adverse events, serious adverse events, and withdrawals were similar for Avandia and for comparators. And the overall adverse event profile was similar across all patient subgroups.

We will now move on to the areas that are of interest on the basis of preclinical findings and that appear to be common to thiazolidinediones: hemodynamic and cardiovascular effects, hematology, and weight.

In animals treated with Avandia, we observed hemodilution and plasma volume expansion associated with cardiac hypertrophy. These effects were seen in animals receiving doses that were at least 3 to 6 times the clinical dose expressed in milligrams per kilogram. We, therefore, conducted echocardiography studies in nonhypertensive patients with type 2 diabetes. Further, we evaluated cardiac adverse events in all phase 2 and 3 clinical trials.

The echocardiography study that I will describe here was a 2-year, open-label, glyburide-controlled trial. In order not to confound the assessment of changes in left ventricular mass index, we excluded patients with New York Heart Association class II or III angina or congestive heart failure. We also excluded patients who were being treated with ACE inhibitors, beta blockers, or calcium channel blockers, and patients who had blood pressures

greater than 160 millimeters of mercury systolic or greater than 100 millimeters diastolic.

Despite these entry criteria for blood pressure, approximately 17 percent of patients in this study did have hypertension at baseline as defined by blood pressure greater than 140 millimeters of mercury systolic or 90 millimeters diastolic.

This study is ongoing, and I will present results from the first 52 weeks.

Echocardiograms were done at baseline, week 12, week 28, and week 52. All echocardiograms were read in a blinded fashion by a central reader. We compared changes in left ventricular mass index in the two groups on the basis of a predefined criterion that would permit us to conclude that Avandia was not inferior to glyburide with respect to an effect on left ventricular mass index. We also established a criterion for withdrawal. Any patient with an increase in left ventricular mass of 60 grams was to be withdrawn. No patients have so far met this criterion.

Plotted here are the mean left ventricular mass index values at baseline, week 28, and week 52 for each treatment group. Glyburide is shown on the left of the figure and Avandia is on the right.

On the basis of comparisons between the change

from baseline in the glyburide treated patients and the change from baseline in the Avandia treated patients, we could conclude that Avandia was not inferior to glyburide with respect to effects on left ventricular mass index. So far no patients have met the withdrawal criterion for an increase in left ventricular mass, and no patients shifted from a low or normal left ventricular mass index at baseline to a left ventricular mass index above the reference range at any time during therapy.

Here we have the mean ejection fraction at baseline, week 28, and week 52. Again, glyburide is shown on the left and Avandia on the right side of the graph. In both groups, we can see that there were minimal changes in ejection fraction during the first 52 weeks of the study. Thus, we were able to conclude that Avandia was not inferior to glyburide with respect to changes in ejection fraction.

In this study we also measured the mean 24-hour ambulatory blood pressure and heart rate. Plotted here are the changes between baseline and week 52 for the Avandia treated patients in red and the glyburide treated patients in white. The first set of bars represents the changes in heart rate between baseline and week 52. The second and third sets represent changes in systolic and diastolic blood pressure. For patients treated with Avandia, there

was no change in systolic blood pressure compared to a significant mean increase of nearly 4 millimeters of mercury in patients treated with glyburide. For patients treated with Avandia, mean diastolic blood pressure decreased by slightly more than 2 millimeters of mercury, a statistically significant change in diastolic blood pressure. The between-group differences for both systolic and diastolic blood pressure were statistically significant.

We have here the frequencies of serious cardiac adverse events expressed as rates per 100 patient years in all patients treated with Avandia and in patients in our three comparator groups. Here again I would like to call to your attention the numbers of patient years of observation for each treatment group. We have expressed separate rates for serious adverse events of ischemic heart disease, disorders of cardiac rhythm, heart failure, cerebrovascular disorders, and hypertension. The overall rates of these events were low and were comparable among patients treated with Avandia, with placebo, or with comparator drugs.

The majority of patients who participated in our trials and were reported to have died during or after the trials died due to cardiac events. A total of 16 patients died of such events: 14 among the Avandia treated

patients, 1 placebo treated patient, and 1 patient treated with sulfonylureas. In the far right column, deaths attributable to cardiac events are expressed as rates per 100 patient years observation with corresponding 95 percent confidence intervals. The event rate for Avandia treated patients falls within the 95 percent confidence interval for the other treatment groups.

We also compared the rate of cardiac deaths in Avandia treated patients to the rates observed in a similar population of type 2 diabetic patients in another clinical trial and to the rate reported for the United Kingdom Prospective Diabetes Study. Rates are expressed per 100 person years with 95 percent confidence intervals. In the first two lines, we have the event rate for all Avandia treated patients, the same rate that was shown on the previous slide, and for the combined comparator groups. Below that, we have rates observed in patients receiving repaglinide or glyburide in a controlled clinical trial, and finally we have the rate and 95 percent confidence interval for the UKPDS. We can see from this analysis that the rate of cardiac related deaths was comparable for Avandia treated patients and for type 2 diabetic patients in other studies.

Because we observed plasma volume expansion in animals treated with Avandia and because edema had been

reported with another thiazolidinedione, we examined our database for adverse events of edema. We did observe a higher frequency of edema in patients treated with Avandia compared to patients treated with placebo, metformin, or sulfonylureas. However, the majority of these adverse events were mild or moderate and few patients withdrew in our double-blind studies. None of these events were considered to be serious adverse events.

In conclusion, 52-week data from our echocardiography study with Avandia administered at a dose of 4 milligrams twice daily showed no adverse effects on cardiac structure or function and a significant decrease in diastolic blood pressure without a significant change in systolic blood pressure. The frequency of cardiac adverse events with Avandia is similar to the frequencies with comparators. Deaths attributable to cardiac adverse events occurred at a rate that was comparable to rates in other clinical trials of patients with type 2 diabetes. Mild to moderate edema occurred in few patients in a dose-ordered fashion.

We will now look at the hematologic changes observed in patients in our clinical trials.

In preclinical studies, repeated administration of Avandia produced decreases in hemoglobin and hematocrit in rats, mice, and dogs. In healthy volunteers, Avandia

produced no change in red blood cell mass. In patients with type 2 diabetes, Avandia produced small dose-dependent reductions in hemoglobin and hematocrit. In all of our clinical trials, we observed approximately a 1 gram per deciliter mean decrease in hemoglobin at the 8 milligram total daily dose and a corresponding decrease in hematocrit of 3 to 5 percentage points.

These data are from study 20, our 52-week glyburide-controlled trial, which Dr. Rebuck described to you earlier. The changes in hematocrit plotted here are typical of changes we observed in all of our studies. The scale on the y axis goes from 44 percent to 38 percent. Thus, we can see that the patients in this study began with mean hematocrit values of approximately 43 percent. Avandia at a dose of 4 milligrams administered twice daily produced a maximum mean decrease in hematocrit of approximately 3.5 percentage points. The mean hematocrit in the patients at the end of 52 weeks of treatment was approximately 39.5 percent, a value that is within the reference range for both men and women. Most of the change in hematocrit occurred during the first 12 to 18 weeks of treatment with little change thereafter.

In our monotherapy trials, anemia was reported in approximately 2 percent of Avandia treated patients, compared to approximately .7 percent of patients receiving

placebo. And in studies where Avandia was administered in combination with metformin, anemia was reported in 7 percent of patients receiving the combination and in about 2 percent of patients receiving metformin alone. There was little change in other blood cell types.

Since patients treated with Avandia plus metformin had a substantially higher frequency of adverse events of anemia than did other Avandia treated patients, we looked at the objective criteria that we had established to assess hemoglobin and hematocrit in our clinical trials. For all studies, we had defined criteria for hemoglobin and hematocrit values that we would consider to be of potential clinical concern. A hemoglobin value more than 2 grams per deciliter below the lower limit of the age and gender-specific reference range was called a value of potential clinical concern. Similarly, a hematocrit value that was more than 5 percentage points below the lower limit of the age and gender-specific reference range was considered to be of potential clinical concern. Again, among patients treated with Avandia plus metformin, we saw a higher proportion who had these values of potential concern than we did among patients treated with Avandia alone or in combination with sulfonylureas.

We then asked the question: Were patients who enrolled in trials of Avandia plus metformin different from

those who enrolled in trials of Avandia monotherapy or Avandia plus sulfonylureas? In particular, were baseline hemoglobin or hematocrit values different in these groups of patients? We found that they were.

On the basis of baseline hematocrit values, we divided patients into six categories. They fell into one of four quarters of the age and gender-specific reference range or they fell below the reference range or above the reference range. For patients in each type of trial, we then plotted the proportion of patients in each of these six categories at baseline, and what we found was that the frequency distributions of patients who received Avandia monotherapy and of patients who received Avandia in combination with sulfonylureas were comparable.

However, the frequency distribution of baseline hematocrits was shifted to the left among patients who received Avandia plus metformin, indicating that a larger proportion of those patients started our studies with values below the reference range or values in the low part of the reference range.

We then looked to see how these baseline values affected the frequency of low hematocrit values during treatment with Avandia. In all groups, Avandia alone, Avandia in combination with sulfonylureas, or Avandia in combination with metformin, those patients who started at

the low end of the reference range had a higher frequency of these values of clinical concern.

So, in summary, we found dose-dependent reductions in hemoglobin and hematocrit within the first 90 days of clinical trials. Increased duration of exposure produced little additional decrease in hemoglobin or hematocrit. The higher proportion of patients in the Avandia plus metformin groups who had low hemoglobin and hematocrit values appeared to be related to the low baseline values in these patients.

In animal models of type 2 diabetes, treatment with Avandia produced weight gain, as well as amelioration of insulin resistance, glycosuria, and pancreatic beta-cell function. We also observed weight gain in patients treated with Avandia consistent with improvements in glycemic control.

In this figure, we see the dose-dependent increases in weight that occurred following 52 weeks of treatment with glyburide or with Avandia administered at doses of 2 milligrams twice a day or 4 milligrams twice a day in study 20. You will recall from Dr. Rebuck's presentation that patients in all of these groups had significant improvements in fasting plasma glucose and in hemoglobin A1c. Thus, despite increases in weight, glycemic control improved in patients treated with Avandia

for 52 weeks.

In summary, in patients treated with Avandia, we observed mean weight gains of 2 to 3 kilograms during the first 6 to 12 months of treatment, with slight additional increases in patients treated for more than 12 months.

Since we recognize the potential deleterious effects of weight gain, we examined our data to determine the association between weight gain in our Avandia treated patients and the changes in glycemic control, lipid profiles, and blood pressure. We found that even with this weight gain, patients receiving Avandia had significant improvements in glycemic control. The LDL/HDL ratio was preserved and we observed a sustained decrease in free fatty acids.

In study 80, where we employed 24-hour blood pressure monitoring, patients in both the glyburide and the Avandia treatment groups had significant weight gain. Yet, in the Avandia treated patients, we observed a significant decrease in diastolic blood pressure without a change in systolic blood pressure, and in the glyburide treated patients, systolic blood pressure increased significantly.

I would now like to discuss an area of special interest: the effect of Avandia on the liver.

To assess liver safety, we examined liver test

values for all patients in phase 2 and 3 clinical trials and we evaluated the frequency of hepatic adverse events. Liver tests were done during the screening period for each double-blind study. It is important to note that patients with values up to 2.5 times the upper limit of the reference range at screening were permitted to enter the trials. In fact, approximately 5 percent of patients had elevated liver tests at the time of randomization. There was no specific screening to exclude patients with liver disease or with a history of liver disease. Liver tests and adverse events were monitored at each study visit, at baseline, every 4 weeks for 3 months, every 6 weeks for the next two visits, and every 3 months thereafter. There were no specific liver test criteria for withdrawal.

This slide represents the proportion of patients who had an ALT value greater than 3 times the upper limit of the reference range while taking Avandia. This analysis includes patients treated through November 1998 and counts patients who entered the study with baseline values that were already greater than 3 times the upper limit of the reference range. As you can see here, the frequency of these ALT elevations was 0.3 cases per 100 patient years of exposure among patients treated with Avandia, 0.59 cases per 100 patient years of exposure among patients treated with placebo, and 0.78 cases per 100

patient years of observation among patients treated with sulfonylureas or with metformin alone.

This table summarizes the same 13 patients -- or actually the same patients in all the groups that had ALT elevations greater than 3x but less than or equal to 5 times the upper limit of the reference range, greater than 5 times but less than or equal to 8 times the upper limit of the reference range, and greater than 8 times the upper limit of the reference range. As you can see, patients with ALT values greater than 3 times but less than or equal to 8 times the upper limit of the reference range appear in all treatment groups.

The number of patients withdrawn for these liver test elevations are shown here.

The time course of ALT elevations for each of these patients is described in detail in the briefing document that committee members received prior to this meeting. I would like to draw your attention to this individual who had a transient increase in ALT to more than 8 times the upper limit of the reference range during treatment with Avandia and then to this individual who also had a transient increase in ALT during treatment with placebo.

This patient entered our phase 2 study in October 1995. His medical history indicated that he rarely

drank alcohol and that he had had a blood transfusion in 1991. All liver tests were within the reference range at the time he entered the study. 50 days after he started taking study medication, he had a transient elevation of ALT to more than 8 times the upper limit of the reference range. 8 days later, his ALT was 105 international units, less than 2.5 times the upper limit of the reference range. His liver tests were all within the reference range when he completed the study, but AST and ALT rose slightly at a follow-up visit 7 days later.

In March 1996, this patient was screened for participation in another clinical trial. His liver tests were within the reference range, but he was found to have IgG antibodies to hepatitis C.

This patient received placebo during one of our pivotal trials. On treatment day 29, she had an ALT and AST elevations greater than 3 times the upper limit of the reference range. Liver tests were repeated 4 days later and had returned to within the reference range. The patient completed a 6-month study as planned and entered an extension study in which she received Avandia at a dose of 8 milligrams daily for approximately 2 months. She had no further elevations in liver enzymes and was withdrawn from the study due to lack of efficacy.

I would also like to mention 2 patients who

developed jaundice during our clinical trials. The first entered one of our pivotal trials in March of 1997. He had elevated bilirubin, ALT, and AST values on treatment day 30. These values returned to within the normal range 8 days later. 60 days later he presented with complaints consistent with a viral infection and appeared to be jaundiced. He was hospitalized and further evaluation revealed significantly elevated bilirubin and alkaline phosphatase. Biliary obstruction was relieved with endoscopic placement of a biliary stint. A provisional diagnosis of pancreatic cancer with extrahepatic biliary obstruction was made and the patient was withdrawn from the study.

We subsequently learned that 2 months after he had been withdrawn from the study, the patient was reevaluated and found not to have pancreatic cancer. The diagnosis was revised to chronic pancreatitis.

The second patient was hospitalized for treatment of an exacerbation of myasthenia gravis. Following treatment with Imuran, azathioprine, and plasma pheresis, he developed enterococcal sepsis with suspected ascending cholangitis, accompanied by elevations in bilirubin and alkaline phosphatase, as well as changes in ALT and AST, although the ALT did not reach a level greater than 3 times the upper limit of the laboratory reference

range. The patient remained on Avandia, and bilirubin and other liver test values declined over the next 2 weeks. He was then withdrawn from the study.

So, in summary, we see no signal of Avandia related hepatocellular injury. No patients in our studies had liver failure, and there were no liver related deaths, excluding 1 patient who died of metastatic carcinoma.

We evaluated the safety of Avandia in nearly 4,600 patients representing more than 3,600 patient years of observation. Avandia has a favorable safety profile. There was no signal of hepatotoxicity. Adverse events associated with Avandia therapy included edema, anemia, and weight gain. However, the frequencies of these events were low and they were not dose-limiting. Cardiovascular safety was comparable to placebo and to active comparators.

Thank you.

I'm now very pleased to introduce Dr. Douglas A. Greene, Professor of Internal Medicine and Director of the Michigan Diabetes Research Center at the University of Michigan.

DR. GREENE: Thank you, Elizabeth.

Dr. Bone, members of the panel, representatives of the agency, ladies and gentlemen, it is a pleasure for me to discuss for you today a risk/benefit assessment of the compound that's under discussion, Avandia.

In approaching the risk/benefit assessment, I'd like to make five points: that type 2 diabetes is an unmet therapeutic challenge; that Avandia is a potent PPAR gamma agonist that produces clinically significant, dose-ordered, durable glycemic control alone or with metformin with no evidence of hepatotoxicity and with a good overall cardiovascular risk profile.

We can learn a number of important lessons about type 2 diabetes from the United Kingdom Prospective Diabetes Study, the UKPDS. Type 2 diabetes remains an unmet therapeutic challenge when addressed with the full armamentarium of currently available therapies in the hands of experts in the treatment of type 2 diabetes. The disease continues to progress with increasing metabolic derangement even in the best of hands under the best of therapies. As you can see in the panel here, there is a progressive rise in hemoglobin A1c in both the conventional and intensively treated group in patients under the care of UKPDS investigators.

The UKPDS has also taught us that type 2 diabetes is associated with chronic micro and macrovascular complications and that glucose control improves these outcomes. As you can see in the panel on your right, a 1 percent reduction in hemoglobin A1c based on the UKPDS data is calculated to produce meaningful and significant

reductions in all of the major adverse endpoints associated with chronic type 2 diabetes.

Avandia is an insulin sensitizer in preclinical studies. It shows potent PPAR gamma agonist activity. It modifies gene expression and adipose cell differentiation. It reduces serum insulin, glucose, and free fatty acids in diabetic animals, and it protects against pancreatic beta-cell insulin depletion in insulin-resistant diabetic animals, all consistent with an insulin sensitizing action.

When administered to patients with type 2 diabetes, Avandia produces dose-dependent, clinically significant reductions in plasma glucose and improvement in blood glucose control. As you can see, both at the 4 milligram dose and at the 8 milligram dose, there are reductions in hemoglobin A1c which range between about 1 and 1.5 percentage points decrease compared to placebo.

This effect is durable and clinically significant. Durability was shown in the 52-week study in which Avandia produced a persistent reduction in mean fasting plasma glucose in patients in this study. Moreover, this is a clinically significant reduction, as demonstrated on the right, in which case more than 50 percent of the patients treated with the high dose Avandia therapy achieved fasting plasma glucoses of less than 140 milligrams per dl.

The action of Avandia in man is consistent with its presumed mechanism of action as an insulin sensitizer. There is a reduction in serum insulin, proinsulin, C-peptide, and split products in Avandia treated patients compared to the rise which is seen when insulin secretagogues are given to treat diabetes. Moreover, Avandia therapy reduces the post-prandial excursions of blood glucose with its activity as an insulin sensitizer.

There is no evidence of hepatotoxicity in the clinical exposure of over 3,600 patient years of experience, no cases of drug-related jaundice, liver failure, or death. The rate of elevations in patients treated with Avandia is numerically less than those in patients treated with placebo or active comparators, and there may be structural metabolic profile and potency differences that may explain this distinction from troglitazone.

Finally, there is a good overall cardiovascular risk profile. Avandia produces marked, sustained reductions in free fatty acids, an increase in LDL, HDL, and total cholesterol, with a neutral effect on the LDL/HDL ratio, suggesting minimal long-term risk of increase in cardiovascular events. The triglyceride data are variable with no decrease, despite improved glycemic control and decreased plasma free fatty acids.

There are modest plasma volume increases with a slight corresponding fall in hemoglobin and hematocrit and mild edema. Cardiographic studies show no effect on left ventricular mass index or ejection fraction, and there is a trend toward a decrease in diastolic blood pressure seen in these trials.

In conclusion, type 2 diabetes remains an unmet therapeutic challenge with progressive metabolic deterioration and macrovascular and microvascular complications. Avandia is a potent PPAR gamma agonist with dose-ordered insulin sensitizing hypoglycemic action. It has clinically significant, durable glycemic control alone or in combination with metformin. It produces no evidence of hepatotoxicity and has a good overall cardiovascular risk profile.

And so, it seems to indicate a positive risk/benefit assessment, showing significant reductions in hemoglobin A1c, achieving the 1 percent change that was associated in the UKPDS with significant risk reductions. The safety profile is well characterized in the clinical studies, and Avandia appears to answer an unmet need for treating type 2 diabetes.

It now gives me great pleasure to introduce Dr. Tadataka Yamada, formerly my Chairman of the Department of Internal Medicine at the University of Michigan and now

Chairman of Research and Development at SmithKline Beecham.

DR. YAMADA: I would like to summarize what you have heard about Avandia today.

First, as to its profile, as you have heard, Avandia is a selective and potent agonist at the PPAR gamma receptor. It has a highly favorable pharmacokinetic profile, and there are minimal risks for clinically relevant drug interactions. The drug is effective and safe, and as Dr. Greene just summarized, it has a positive risk/benefit assessment.

In reviewing its efficacy, it is important to remember that approximately 4,100 patients were evaluated, of which 2,900 were placed on Avandia. Efficacy was demonstrated in all monotherapy studies. Here again, included in these monotherapy studies were patients who had been previously treated with diet only, who had been treated previously with monotherapy, and who had been treated previously with multiple drug regimens. Efficacy was demonstrated in combination with metformin. Further improvement in glycemic control was obtained with the addition of Avandia to maximal doses of metformin.

The effect was durable. Improvement in glycemic control was maintained for at least 12 months. Improvement in glycemic control was associated with a reduction in endogenous insulin. A flexible dosing regimen

is possible with once or twice daily administration.

In terms of Avandia's safety, it is important to remember that 5,500 patients were evaluated, of which nearly 4,600 patients were placed on Avandia for a period of over 3,600 patient years. We have a very well-characterized safety profile. There is no signal of hepatotoxicity. There were low incidences of mild to moderate edema, decreased hemoglobin and hematocrit, with few withdrawals. There was a reduction in circulating free fatty acids and otherwise a risk-neutral lipid profile. Cardiovascular safety was comparable to placebo and active comparators.

Accordingly, we propose the following indications for Avandia: as monotherapy as an adjunct to diet and exercise to lower blood glucose in patients with type 2 diabetes mellitus; secondly, to be administered concomitantly with metformin when diet and metformin do not result in adequate glycemic control.

Ladies and gentlemen, on behalf of SmithKline Beecham, it is with the highest possible enthusiasm that we present for your consideration Avandia. As a physician, I must admit to feeling a great sense of satisfaction in being able to present a safe and efficacious treatment for the millions of patients in our country and, indeed, around the world with type 2 diabetes mellitus.

Now Dr. Wheadon will take some questions.

DR. BONE: Thank you very much.

I'd like to note for the record that Ms. Killion and Dr. Critchlow are also here. They weren't introduced at the beginning of the meeting.

I will just mention, as the members of the committee are considering their questions, that in regard to question 4 for this afternoon, contrary to the wording that's on your list, we will be discussing possible labeling issues of all kinds. The original plan was to defer discussion of whether there would be anything to be said about the liver, but since we have Dr. Seeff here and Dr. Lewis today, we're going to take advantage of their availability.

MS. REEDY: Copies of those questions are available on the table outside.

DR. BONE: Yes. So, there won't be any exclusion of topics during that discussion is the main point.

Members of the committee are invited to ask questions about the presentation, and I see an eager look from Dr. Molitch.

DR. MOLITCH: I have a number of questions and many of them I'll ask this afternoon in the more general question and answer session. I think we're just doing

clarification of data now. Is that correct?

DR. BONE: Yes, specific questions related to the presentations.

DR. MOLITCH: One question was with respect to looking at the patients who developed a decrease in hemoglobin and hematocrit in the various subgroups and then looking at the metformin group that seemed to be shifted to the left a little bit and the baseline. Was the assessment of the decrease in hemoglobin and hematocrit of those patients just achieving a threshold value, or was it a delta change in hemoglobin and hematocrit in those patients that was a target? Meaning, of those patients who had a borderline anemia, did they develop a more significant drop in hemoglobin and hematocrit, or were they just closer to a certain threshold level?

DR. WHEADON: We were looking at a threshold value, I think as Dr. Rappaport showed in that slide, but I'll let Dr. Rappaport add more specifically to that.

DR. RAPPAPORT: Dr. Molitch, the deltas were the same regardless of whether the patients were receiving Avandia alone or Avandia in combination. The reason we saw more patients who hit those threshold values in the Avandia/metformin group was that they started out lower.

DR. BONE: Dr. Genuth has a question on this topic and then Dr. New.

DR. GENUTH: Yes. I just wanted to ask, did you adjust either the drop in hematocrit or the final hematocrit for the baseline hematocrit or hemoglobin? And then were there still significant differences among the groups?

DR. RAPPAPORT: We didn't make any adjustment. What we plotted for all our studies was a graph similar to what you saw for study 20; that is, we simply looked at the mean values. And we also counted patients -- and that's also data that I showed -- who actually reached those threshold values, but we made no adjustment. But the deltas were the same regardless of how patients were treated with Avandia alone or in combination.

Does that answer your question?

DR. GENUTH: No, but let's discuss it later.

(Laughter.)

DR. BONE: Dr. New.

DR. NEW: Dr. Wheadon, you made a statement that there was fetal toxicity but no teratogenesis in your preclinical studies. What kind of toxicity did you observe?

DR. WHEADON: I'll allow our preclinical group to specify that. Dr. Patrick Wier can give you specifics on that.

DR. WIER: My name is Patrick Wier. I'm from

Safety Assessment at SmithKline Beecham Pharmaceuticals.

This slide summarizes all of the findings in treatment of pregnant animals with rosiglitazone. We observed in rats and rabbits treated during pregnancy fetal and/or neonatal lethality. You will note also that we observed from treatment of pregnant animals fetal and/or postnatal growth retardation. In none of these studies was there any sign of teratogenicity.

These effects, such as growth retardation, occurred at about 7 times human exposure levels, and in terms of fetal or neonatal lethality, these occurred at about 20 times the human exposure level.

Further studies in rats showed that the sensitive period for induction of these effects was mid or late gestation. There were absolutely no effects in early pregnancy, no teratogenicity. Overall the no-effect doses for these effects in pregnancy were at least 4 times the clinical exposure level.

DR. BONE: Are you making a recommendation about use in pregnancy?

DR. WHEADON: I think that will be something that we will be discussing with the agency, Dr. Bone, but obviously these data will be taken into effect.

DR. BONE: What does that mean?

(Laughter.)

DR. WHEADON: Well, there are some standard recommendations based on studies that you've done preclinically and lack of studies, obviously, in women of childbearing potential in terms of the various pregnancy categories. And that is something we will be discussing with the agency in terms of labeling.

DR. BONE: Well, we may have some discussions later too. Thank you.

Other members of the committee had questions. I know there are several. Dr. Lewis I think is next and then Dr. Hirsch. We will make sure everybody here, including the committee members and the guest experts, will have a chance to ask questions.

DR. LEWIS: With respect to the liver enzymes that were measured, there's an interesting group that we heard about. 5 percent of these patients apparently had elevations up to 2.5 times the upper limit of normal. Did you do any breakdown? And I don't know if you have this right now, but for this afternoon. Was there a breakdown of those 200 patients, or whatever the number will be, in terms of what happened to their enzymes that were already elevated? We often never have an opportunity to find out what happens to patients with underlying elevations of one sort or another who go on medications, are they safe, are they not. So, was there any signal in that particular

group?

We seemed to have anointed greater than 3 times the upper limit of normal as the threshold. Do we have an analysis of just elevations of any type with or without bilirubin elevations which were probably all subclinical jaundice? But just to get a better handle on some of these elevations because we really didn't hear about anything below 3 times the upper limit of normal.

DR. WHEADON: We'll start with your first question and that is whether or not we have looked at patients that had the elevations at baseline and what happened with them. Dr. Rappaport, would you like to respond to that?

DR. RAPPAPORT: Of those approximately 260 patients that had elevations at baseline, 4 of them had elevations during the study. In 3 cases, those patients continued on drug. One was later withdrawn with resolution of those transient elevations. Two of them are still on drug in extension studies and one of them was withdrawn for lack of efficacy but not because of liver enzyme elevations.

There was 1 patient of those 4 who completed 6 months of metformin treatment and had several spikes of his ALT values during the metformin study. He was, nevertheless, entered into an extension study where he

received metformin in combination with Avandia, and he had similar patterns of elevations and was eventually withdrawn from treatment.

So, those are the 4 patients of those 260 that had elevations on study.

DR. LEWIS: Does that mean 4 patients who had further elevations?

DR. RAPPAPORT: The rest of them did not go up to 3x at any time during the study.

DR. WHEADON: So, it's 4 of the 5 percent that had continued elevations.

DR. RAPPAPORT: 4 individuals of the 260-some patients that entered the study with elevations.

DR. LEWIS: So, only 4 of 260 who were up to 2.5 times normal at baseline exceeded threefold during the study.

DR. WHEADON: Exactly.

DR. RAPPAPORT: That's correct.

DR. LEWIS: Okay.

DR. WHEADON: Liz, why don't you stay where you are?

In terms of your second question, we chose ALT as sort of the parameter, if you will, of indications of potential hepatocellular injury or hepatotoxicity, but we can comment on the general safety database in terms of

total bilirubin and what have you, and Dr. Rappaport can give a comment to that.

DR. RAPPAPORT: Can I get some clarity on exactly what your second question was?

DR. LEWIS: We have data presented on rises greater than threefold the upper limit of normal for ALT, and I was simply wondering whether there's a greater proportion of patients who may have had elevations above normal, but less than threefold which are not presented, and whether there's any difference in any of those numbers among the comparator groups.

DR. WHEADON: Dr. Misbin is indicating he's going to do some of that presentation, if I'm reading you correctly, Bob, but additionally I think, Elizabeth, you can comment as well.

DR. RAPPAPORT: We didn't do a formal analysis of patients who had elevations that were greater than 2.5 but less than 3 times the upper limit of the reference range.

DR. BONE: I think you're being asked what about patients who were within the normal reference range at the time they started on drug who then rose to between 100 and 300 percent or 1 to 3 times?

DR. RAPPAPORT: I don't have those data.

DR. BONE: Is that correctly stating your

question?

DR. LEWIS: Yes.

DR. BONE: Thank you.

Let's see. Dr. Hirsch had a question. We'll make sure everyone gets to ask.

DR. HIRSCH: I have a few very small ones. It may be just clarification of something or the answers may already have been given.

I was curious about whether all of the anemia and hematocrit changes can be explained by hemodilution. Were there red cell mass studies in man as were done in animals where I gather there is hemodilution? Is that a full explanation for --

DR. WHEADON: Dr. Rappaport?

DR. RAPPAPORT: We did one study in normal volunteers where we actually measured red cell mass using chromium labeling of the red cells, and we found no decrease in red cell mass. Red cell mass remained --

DR. HIRSCH: So, it is hemodilution then.

DR. RAPPAPORT: It appears to be, but that's a single study in a small number of normal volunteers.

DR. BONE: Excuse me. Did you see a decline in hematocrit or increase in body weight in those patients?

DR. RAPPAPORT: This was an 8-week study in normal volunteers: 10 treated with placebo, 10 with 4

milligrams a day, and 10 with 8 milligrams. And in that 8 weeks, we saw a similar decrease in hemoglobin and hematocrit to what we saw in the first 8 weeks in our other studies. We measured red cell mass. It didn't change, and that's the most we can say about that study.

DR. BONE: To what extent does the change in body weight accounted for by this phenomenon?

DR. RAPPAPORT: We think that the fluid retention may be a contributor to body weight increase, but I don't believe it's a major contributor since really very few -- well, I just don't think it's a major contributor.

DR. BONE: Why not?

DR. WHEADON: I think while Dr. Rappaport is conferring, basically we've looked at those patients that have an increase in body weight and the subset of patients that have an increase in body weight are not totally defined by those that may have had the adverse event of edema, for example. So, it's not a clearly distinct population in terms of edema and increased body weight.

But, Elizabeth, do you want to clarify further?

DR. RAPPAPORT: All I can say is that it may be a contributor, but it probably is not the only contributor to increase in body weight.

DR. HIRSCH: But no formal compartmental analysis.

DR. RAPPAPORT: No. Those studies are ongoing. Those are part of our phase 3/4 program, and there are studies that we've initiated to look at changes in body composition related to treatment with Avandia, but we don't have those data yet.

DR. HIRSCH: I have a few other quickies. May I continue?

DR. BONE: Why don't you take one and then we'll come back. Everybody will get their questions asked, but I'd like to move around.

DR. HIRSCH: Yes. I'm just curious about the finding that there's a reduction in steroidogenesis of progesterone in the preclinical studies. I am wondering if there are any progesterone measurements or menstrual alterations in females taking the drug, those who are still in those years of having a meaningful menstrual history.

DR. WHEADON: Let me first call on our preclinical colleagues to comment on that. But I can tell you that in terms of our experience in clinical trials in humans, we only included women who were on birth control. So, we're not able to comment on estrus cyclicity or effect thereof in terms of humans, but I'll ask Dr. Wier if he perhaps can give further explanation from our animal studies.

DR. WIER: Again, I'm Dr. Patrick Wier from

Safety Assessment.

Do you have a question concerning the preclinical finding? Was your question solely restricted to what clinical experience is there?

DR. HIRSCH: I gather the preclinical findings have shown a reduction in progesterone synthesis by some mechanism. I just wonder was any clinical or laboratory bearing on this in any of your studies in man.

DR. WHEADON: Well, as I pointed out, unfortunately, we do not have data in man to augment what you've heard from the preclinical standpoint.

DR. HIRSCH: Humans. Humans.

(Laughter.)

DR. BONE: Homo sapiens, yes.

Let's see. Do we have any questions on the right? No, not at the moment. Dr. Genuth, and we will get everybody.

DR. GENUTH: I want to clarify something that was both stated in, I think, Dr. Rebuck's presentation and stated in the briefing book. If this drug were approved, one of its important uses would be to treat patients who had failed other antihyperglycemic drugs.

In the presentation and the briefing book, it stated that in conclusion in study 093, in which metformin and rosiglitazone were compared singly as monotherapy and

combination therapy, the data looks to me pretty clear that after 7 weeks of metformin, with maximum metformin dosage the last 4 weeks, when those patients were switched to rosiglitazone, they actually got a little worse, let alone show any benefit compared to patients who were just kept on what was ineffective metformin therapy.

Now, I would have thought that the conclusion would be that it doesn't look like giving rosiglitazone to people who are not well controlled on metformin is likely to succeed. And the statement in the briefing book and the statement in the presentation was, well, we can't draw any conclusions from the study because that's not how it would be done in clinical practice. When I tracked that down, the basis for that statement seems to be that about half of the patients were on combination therapy or other monotherapies before they were even switched to metformin.

I don't accept that that's a reason to overlook the fact that rosiglitazone did not improve patients who were failing metformin and in fact blood glucose levels ended up higher. I think it's an important point in terms of labeling indications if the drug gets approved.

DR. WHEADON: Well, I'll ask Dr. Rebuck to respond to that question specifically, but I'll remind you that the study was not designed, in fact, to do a comparison of patients that were responding poorly to

metformin, how they would subsequently do upon being switched to Avandia. But I'll ask Dr. Rebuck to respond further.

DR. REBUCK: I believe that you've stated a very clear argument and have argued in many ways the same as we have in terms of sudden discontinuation of therapy in patients who are in a steady state of maximum dose metformin. All I would add to this discussion is to say that switching from metformin and sulfonylureas was conducted in studies 11 and 24, and the efficacy as monotherapy was apparent in patients who were from the diet only subset, patients previously on a single agent, and patients previously on two agents.

DR. BONE: Perhaps we can spend some more time on that during the later discussion.

Dr. Molitch had a question specific to this morning.

DR. MOLITCH: I'm actually going to perhaps -- I have lots of questions -- but set up some questions for this afternoon that maybe I can give you some advance warning on at this point, which is to address some of the issues that have already been raised, and that is subset analyses. Because as we treat these patients, you mentioned that 20 to 30 percent may have lipid abnormalities, similar numbers may have hypertension. I

would like to have you show us this afternoon or comment this morning, but perhaps this afternoon, looking at the data in those patients who have baseline abnormalities and changes in those abnormalities. So, you showed us that patients have elevated HDL and LDL cholesterol levels. What happens to those patients who have baseline abnormalities of these? What happens in patients who have baseline hypertension to their blood pressures? What happens to patients who have baseline edema or congestive heart failure less than New York Heart Association class III/IV? What happens to their edema over the course of this study?

We're going to be giving this drug, if it's approved, to patients with diabetes with lots of concomitant illness, and we need to know what are the effects of this drug on patients who have those baseline abnormalities. I think we deserve to see the data in those subsets today.

DR. WHEADON: We'll take note of that, and with Dr. Bone's agreement, we'll have that available for you.

DR. BONE: Why don't we plan to take a few minutes for you to make a little short presentation at the very beginning of the afternoon session?

DR. WHEADON: That's fine.

DR. BONE: Thank you.

Other questions? Dr. Illingworth.

DR. ILLINGWORTH: With respect to the increase in transaminases, have you measured creatinine kinase, CPK, as an indicator of muscle abnormalities because often an increase in transaminases is linked to physical activity?

DR. WHEADON: Dr. Rappaport?

DR. RAPPAPORT: We did not measure CPK as a routine safety analysis in our studies.

DR. LEWIS: I might just add that that would be of relevance with AST much more than ALT, which is very liver specific. So, muscle injury, we see AST go up and you might see CPK, but ALT is the best measurement for liver injuries specifically.

DR. BONE: Thank you, Dr. Lewis.

Let's see. We've got Dr. Critchlow.

DR. CRITCHLOW: You presented data that the rate per 100 patient years for adverse events such as the cardiac, for example, adverse events was lower in the Avandia group than in the comparator or the placebo group, but the Avandia patients had more exposure, on average 10 months as compared to something half that for the others. Was there any indication that rate differed, say, in the first half, say, 26 weeks versus the second half?

DR. WHEADON: So, you're asking in terms of time course of the occurrence of events if there is a

difference? I possibly could just answer that. In looking at our NDA database, which basically included our acute studies, and then when the database was extended to the 120-day safety update, which included a lot of the long-term extensions, the relationships that we've discussed with you were the same in those two databases. But I'll see if Dr. Rappaport can augment that answer.

DR. BONE: Dr. Hammes?

DR. HAMMES: I have a question of a little basic pharmacology relative to the pharmacokinetic data presented. The volume of distribution, 4-hour half-life, kidney excretion, greater effect of a b.i.d. versus once-a-day dose, the low liver/plasma ratio all suggest an extracellular fluid distribution with minimal tissue deposition. Given the mechanism of action and the PPAR receptors, how do you explain this? Are there any sites of tissue deposition identified on the preclinicals, and how does this all relate to a perhaps binding half-life and PPAR and what you're seeing in the dose effectiveness?

DR. WHEADON: I'll ask Dr. Richard Chenery to respond to that.

DR. CHENERY: Richard Chenery, Drug Metabolism, SB.

In terms of the distribution of the molecule in our preclinical studies, particularly the rat, we see that

the compound is very rapidly distributed into tissues, but the volume itself is determined by the high degree of protein binding. So, this is a kinetic terminology. But basically the compound does get into tissues very rapidly and effectively and then exits them. The only tissue where there is any retention is melanin tissue where there is some degree of retention which we think to have no great significance.

DR. HAMMES: Do you have data on the binding half-life on the receptor itself?

DR. CHENERY: That's a pharmacology question. I'd have to hand that over to one of my colleagues.

DR. WHEADON: Robin or Steve? Dr. Steve Smith of Pharmacology.

DR. SMITH: Steve Smith, Pharmacology.

We don't have any direct data for half-life of binding to the receptor since it's located with the nucleus the cell and it's hard to do or impossible to do those experiments.

DR. BONE: Thank you.

Dr. Seeff.

DR. SEEFF: I'd like to get back to the ALT for a moment because I'm still a little confused. I wonder if you can give us -- and perhaps this may be discussed this afternoon even in the form of a table -- how many people

actually came into the study with preexisting abnormal enzymes and what proportion were greater than 3 times the upper limit of normal and what proportion were less than 3 times but above normal, and what happened to them in treatment following through? And then how many people developed abnormal enzymes, having come in with normal enzymes, normal ALT, also broken down into greater than 3 times and less than 3 times, and the timing of when that occurred after beginning of treatment? I just need to have that piece of information. It will give me a better understanding of what might have happened.

DR. WHEADON: Again, I think as Dr. Rappaport pointed out, the cutoff for entry was 2.5 times the upper limit of normal, and she discussed those patients. But we can revisit that again and maybe do it in tabular form, if you like. Additionally, I know Dr. Misbin will be looking at a data set that, unlike ourselves, excludes those patients that were elevated at baseline, if I remember correctly, Dr. Misbin, in terms of a table you're doing, that may help answer that question as well.

DR. BONE: I hope you'll have your best effort made to address that whole spectrum of questions, along with the other information, right after lunch.

Let's see. We have several other questions. Dr. Hirsch and then Dr. Illingworth.

DR. HIRSCH: Two brief ones. I notice that there seems to be a statistically significant increase in maybe a trivial matter, upper respiratory tract infections, always with people on the drug as compared with others. I guess that's true, and if it is true, it suggests that maybe any data on IgG levels or leukopenia or anything you might have measured along the way rather than more sophisticated immune studies that would indicate any reason for that.

Lastly, I didn't find it but maybe somewhere in here you can direct me to the actual causes of death of the 28 people who died on the drug. There's probably a listing of it somewhere that I missed.

DR. WHEADON: In answering your second question while Dr. Rappaport is getting up, as we indicated, the majority of those 28 were deaths due to cardiovascular events. If I remember correctly, that was 14 of the 28 deaths were cardiovascular, but we can point you to the right table on that.

Liz, would you like to clarify further?

DR. RAPPAPORT: We also saw the difference in upper respiratory tract infections. The only place where there was a statistical difference was for the patients who received Avandia plus metformin. In the other groups there wasn't a statistical difference. We don't have an answer

for why more of those patients reported upper respiratory tract infections, although it was not a cause for withdrawal, and we don't have any tests of immune function in those patients. So, I can't answer your question except to tell you that, yes, your observation that there were more in that group is correct.

As far as the actual causes of death, of the patients in the Avandia group, 18 were cardiovascular, 6 were neoplasms, and 4 were classified as other. One was an injury. One was a patient who died of intestinal ischemia. Another had a respiratory disorder and another had angioedema. So, those were the patients in the Avandia group.

DR. BONE: Were there any other cases of angioedema?

DR. RAPPAPORT: No.

DR. BONE: Let's see. I think we have Dr. Illingworth and then Dr. Genuth.

DR. ILLINGWORTH: I realize this will come back again this afternoon, but going back to the change in lipoproteins, the increase in LDL of 12 percent and increase in HDL of 19 percent, two brief questions. One is, do you have any information about the mechanisms responsible? And secondly, I disagree with the background statement that says that the rise in HDL will negate the

adverse effects of the rise in LDL. You need to define the mechanism by which the HDL changes. It may not be beneficial at all.

DR. WHEADON: I'll ask Dr. John Brunzell if he could respond to that question for us.

DR. BRUNZELL: Roger, I agree that you can't just across the board say the increase in HDL makes a difference. Some of the background. It looks as if some of these changes may be related to a decrease in hepatic lipase, and the reason I say that is that the LDL cholesterol to APO-B ratio goes up with Avandia therapy. That's one thing suggesting that you no longer are making the small dense LDL. In that case, you'd expect the increase in HDL to be in HDL2. So, if in fact in it's in HDL2, I think it probably is legitimate to say that the LDL cholesterol to HDL ratio staying solid is a good thing.

DR. ILLINGWORTH: But there's no data yet on potential changes with Avandia treatment in hepatic lipase CTV activity, other factors that could affect HDL.

DR. BRUNZELL: Yes. That study is going on as we speak.

Dr. Molitch also asked about preliminary data, baseline data, related to some of the factors. If you're hypertriglyceridemic and you go on Avandia, you then have a significant decrease in triglyceride. If you have a normal

triglyceride level, you don't change. So, overall there wasn't any change in the whole group.

DR. BONE: All right. Thanks.

I believe it was Dr. Genuth next.

DR. GENUTH: Two questions. One really trivial but it puzzled me. Why in the metformin studies did you use 250 milligram tablets so a patient had to take 10 tablets a day versus 1 or 2 tablets of rosiglitazone? The standard tablet of metformin is 500 milligrams or even 850.

DR. WHEADON: I'll let Dr. Rebuck respond to that.

DR. REBUCK: They were 500 milligram tablets.

DR. GENUTH: Then the briefing book misquoted. That's okay then.

A more important question. Several of the presenters and several statements in the briefing book emphasized that insulin, C-peptide, proinsulin, split proinsulin levels all fall with this treatment. That's something emphasized I suspect by all presenters for all drugs in the thiazolidinedione class. An implication is, well, maybe insulin causes cardiovascular disease. So, these drugs would have a unique advantage. First of all, I don't think it's proven that insulin or proinsulin causes cardiovascular disease or events.

That aside, the other statement that's made in

the presentations and in the book is that if insulin levels are lower, then beta-cell function has been restored. I don't think that's quite a correct statement because if beta-cell function had truly been restored, insulin levels would not have fallen until glucose levels were normal. None of the studies seems to ever produce a group of patients whose hemoglobin A1c is 6 percent or less.

So, this class of drugs and this particular member of the class improves glucose levels, which I agree with Doug Greene and everybody else is a very good thing and a real goal. But I don't think it's right to imply that it uniquely improves type 2 diabetes or gets at the real problem in type 2 diabetes when you end up with inadequate insulin secretion for the glucose levels that the patient still has.

DR. WHEADON: Well, I would point out that any conclusions we have drawn, particularly around pancreatic beta-cell function, is really drawn from our findings in animal data, and we obviously will be looking and are looking at whether or not that can then be translated into our clinical trial data in human data. So, we have not at all made that conclusion in terms of our human data.

But I will ask Doug Greene and perhaps he can respond further to that.

DR. GREENE: Well, I always start answering

Saul Genuth's questions with the statement that he's right.

I think that the preservation of beta-cell function was seen primarily in the animal models, and that has led to a speculation that this might occur in man and might be important in terms of long-term effects. There has been discussions to actually do a study like that as a subsequent study, looking at whether or not rosiglitazone in a long-term study might prevent or preserve beta-cell function. But I think that you're correct that the statement about preservation of beta-cell function was based purely on the animal model.

The reason that I, in my summary, called attention to the insulin and insulin split products was not to imply that this had anything to do with cardiovascular risk. Rather, it was to imply that the activity that we see in man is in fact based on an insulin sensitizer mechanism, since we at this point don't have formal clamp studies. So, I didn't mean to imply that that entered the risk/benefit ratio as a cardioprotectant, rather as an implication that the mechanism seen in animal models probably applied to man but with the caveat that insulin clamp studies had not yet been done. So, you're correct.

DR. BONE: Thank you.

Additional questions from the committee regarding the sponsor's presentation at the moment?

DR. WHEADON: Dr. Bone, can I ask for one point of clarification in terms what you would like to have this afternoon? In terms of those patients that had elevations above 3 times the upper limit of normal, there are only 13, and we could very easily discuss all 13 in detail if you would like. We have all of that sort of detail available to the committee. So, we can do that without a problem.

Additionally, if I heard correctly, you also want to know about patients that went from normal to any elevation, not 2.5 or 1.5 or 3, just any elevation at all, if I heard that correctly.

DR. BONE: And how those compare between comparison groups. Obviously the information is in your database. The question is how accessible it will be.

DR. WHEADON: We can do that.

DR. BONE: We don't want to go through them all individually though I'm quite sure.

DR. WHEADON: Just to make the point that there are only 13 that had elevations above 3 times the upper limit just so the committee is clear on that.

DR. BONE: We understand that. I think the concern from the hepatology department here was that we would like to know about milder changes and two things: One, is what was the rate of occurrence of milder changes, and what happened to patients who entered the study with

milder abnormalities that were abnormalities nevertheless?

DR. WHEADON: Okay.

DR. BONE: That was the general concept I believe.

Very well. I have 10:22. If there are no further questions from the committee concerning the earlier presentations, we'll recess for 15 minutes and we'll plan to start again then at 10:37.

(Recess.)

DR. BONE: We are now back in order please. Everyone take your seats immediately.

The next item on the agenda will be the series of presentations by the FDA members, and the first of these will be the pharmacology/toxicology presentation by Dr. Steigerwalt.

DR. STEIGERWALT: Thank you, Dr. Bone.

The FDA presentation is going to consist of three sections. We're going to have a presentation by myself. I'm Ron Steigerwalt, the pharmacology team leader, from the Division of Metabolic and Endocrine Drug Products. My presentation will be followed by a statistical review by Joy Mele, and then after her will be Dr. Robert Misbin for the medical review.

Basically the issues that I have for the preclinical have been discussed pretty well by the sponsor.

I think I'm just going to add some numbers to some of the effects that we've been seeing. So, I would like to discuss two key points for the toxicities that have been identified in the preclinical studies with rosiglitazone. These findings include effects on the heart and liver.

In the first slide, I've summarized the cardiac/hematology findings for rosiglitazone. These were very consistent findings and found in all the species that were examined which includes mice, rats, and dogs. At the upper levels of this finding, you get a 30 percent increase in the cardiac weights in mice and a 45 percent increase in cardiac weights in dogs and rats.

Plasma volume expansion was also observed in all species and hemodilution was manifested as decreases in hematocrit, hemoglobin, and red blood cell counts in all species. This ranged around the level of about 25 percent.

Additionally, there was a decrease in reticulocytes and platelets observed in mice and rats, which is probably also related to this hemodilution effect.

At the high doses, hydrothorax was observed in rats and hydropericardium was observed in dogs. In studies that were dosed high enough where deaths occurred in the animals, the dose-related deaths were generally attributed to cardiac effects.

In summary for the cardiac effects, the cardiac

effects are attributable to effects of increased preload on the heart which is a result of plasma volume expansion. There does not appear to be a direct effect of rosiglitazone on the heart tissue directly or on hematopoiesis.

On the next slide I have the liver findings for rosiglitazone. An increase in liver weights was observed in all species. This includes mice, rats, and dogs. And this ranges from 25 to 60 percent. There were no histological or clinical chemistry findings associated with the liver weight increases in rats or mice, or at least no consistent findings with ALT, for example.

In dogs, which appears to be the most sensitive species, there were significant elevations of ALT. In a 6-month dog study at doses of approximately 8 to 80 times the human doses based on surface area comparisons, the elevations of ALT were approximately five to tenfold control levels. At the high dose, this was associated with smaller elevations of AST and LDH which were approximately on the order of twofold control levels.

There was evidence of oxidative stress and hepatic regeneration associated with the high dose finding, but in general there were no histopathological findings of necrosis related with these findings.

In a 1-year dog study, there was an elevation

of ALT, approximately twofold, at a dose that was approximately two times the human dose based on surface area comparisons. These are just general comparisons. I didn't have all the AUC values to make the direct comparisons with AUCs.

I might note at this point that the transaminase findings were not clearly observed with troglitazone because dogs were not extensively evaluated in the preclinical testing with troglitazone.

On the next slide, in summary, the cardiac and hematology findings are generally attributable to adaptive responses to plasma volume expansion and occurs in all species examined.

The findings of elevated ALT, AST, and LDH in the chronic dog toxicology studies provide a signal for potential liver toxicity.

Now, pharmacologists like to make comparisons on no-effect level findings with human exposure to determine a safety margin, and our best estimate of the relative toxicity should be based on chronic animal studies. However, the dose selection for these studies was based upon log increments, which makes the determination of the lowest effect level in the chronic studies a little difficult. Findings are very evident at very high doses, but we don't really have a clear idea of how close to human

exposure that these findings occur.

Based on some estimates from some chronic studies, there are indications that changes in liver and heart weight parameters can be detected at levels close to human exposure on the range of three to six times a human exposure.

In conclusion, while there are limitations to the determination of safety margins based on preclinical findings, data indicate that the cardiac and liver effects did occur in animals at doses close to the human exposure. Therefore, the potential for cardiac and hepatic findings need to be considered in the clinical safety evaluations of rosiglitazone.

Thank you. Now I'd like to introduce Joy Mele, the statistical reviewer.

MS. MELE: First I'd like to mention to the committee members that you should all have copies of my slides.

For my presentation today, I will cover three areas. First I will briefly summarize the primary efficacy results for the five double-blind controlled clinical trials. Then I will discuss the lipid changes. This section will comprise the bulk of my presentation. Lastly I will present results by gender and talk about the treatment-by-gender interaction observed in the monotherapy

trials.

This slides shows the HbA1c levels by week with the last observation carried forward for the placebo-controlled monotherapy trials 11 and 24. The blue line represents the placebo responses, and the red line represents twice-a-day dosing. There was twice-a-day dosing in both trials. Green represents the once-a-day dosing groups. The lower red line -- that's this line and this line -- and the lower green line represent a daily dose of 8 milligrams, and the upper lines represent a 4 milligram daily dose.

Now, on this slide I show the screening and the run-in values in addition to each week on randomized treatment. So, baseline is at the arrow. Note that in all groups, the baseline continues to rise after week 0. Separation of the doses becomes most evident after about 3 months on therapy. At endpoint, each dose group is statistically significantly different from placebo, and results for completers showed a similar relationship among the doses.

This slide shows the results for study 20, the active-controlled study. In this study there were two rosiglitazone treatment arms: 2 milligrams and 4 milligrams twice a day. Here I am only showing the 4 milligram twice a day dose compared to glibenclamide, which

is also known as glyburide in the United States, and that's the name I'll use from here on. Rosiglitazone is red and glyburide is blue.

I have graphed both the last observation carried forward and observed cases results to illustrate the impact of dropouts on the active control comparison. The top red line represents the LOCF data and the lower red line represents the observed cases data for rosiglitazone. Notice that the lines for glyburide are superimposed. For the rosiglitazone arm, the lines are clearly different. The difference between the two sets of estimates is due to exclusion of dropout data from the observed cases analysis. About half the dropouts in the rosiglitazone arm discontinued due to lack of efficacy, so excluding these patients will bias against glyburide. So, the preferred analysis then is the LOCF analysis, and most of the analyses that you saw presented by the sponsor were indeed LOCF analyses.

With the next three slides, I'm going to show you the results of the combination studies 93 and 94. For both of these studies, as the sponsor has mentioned, all patients were titrated to a metformin dose of 2.5 milligrams and maintained on that dose for 4 weeks. The titration and maintenance periods are depicted from minus 6 to 0 on this graph. Again the arrow represents the

baseline. The blue line represents the metformin arm. The top red line on the graph represents rosiglitazone 4 milligrams twice a day given as monotherapy, and the bottom red line shows the results for the combination therapy arm. Treatment effects for the combination therapy arm were all statistically significant, as the sponsor mentioned. Note that essentially no change in HbA1c was seen from screening to baseline during the run-in metformin treatment period and that switching to rosiglitazone monotherapy produced significant increases in HbA1c.

In study 94, the design was similar with regard to the metformin arm. Two doses of rosiglitazone were used in this study: 4 milligrams and 8 milligrams once a day. Both combination arms are significantly different for metformin.

For this slide, I am displaying the two combination studies side by side to show the consistency of response for the combination arms compared to the metformin alone. The treatment effects are both about minus 1 percent.

Now, to sum up the primary a efficacy results, rosiglitazone significantly reduced HbA1c when administered as monotherapy and when added onto metformin at all doses studied. The 4 milligram twice-a-day dose was consistently the most efficacious dose. The magnitude of the responses

were consistent across studies. In a population of patients receiving metformin alone, switching to rosiglitazone monotherapy caused an increase in HbA1c and hyperglycemia in about 6 percent of the patients.

Now, this slide outlines the topics I will cover to examine the lipid response. The focus will be on LDL and the ratio of LDL to HDL. I will also present a few results for the ratio of total cholesterol to HDL and for HDL alone. First I will present the responses over time for all the doses in all the studies. Then I will focus on the 4 milligram twice-a-day dose, showing means and the distribution of the responses. I will make some comments on the lipid responses in subgroups and show the relationship of lipid changes to changes in HbA1c.

The rise in LDL in the three monotherapy studies is very clear, and the dose-response relationship is also obvious in studies 11 and 20 in particular, with larger increases observed for the 4 milligram twice-a-day dose. On these graphs, please notice the baselines. Studies 11 and 24 have comparable baselines -- and I'll point those out -- while in study 20, which is in the middle, the baseline is about 20 milligrams per deciliter higher. And I'll refer to this difference again in a later slide.

HDL also increases over time with the responses

at endpoint for 8 milligram daily doses, being significantly different from comparators.

The results for the ratio of LDL to HDL over time appear to be more variable. At endpoint, the results remain significantly elevated over the comparator. But again, notice the differences among the baselines here.

Now we'll go to the rosiglitazone plus metformin studies, the combination studies. The significant rise in LDL is clear in both studies. The rise in the rosiglitazone monotherapy arm, which is the top red line on the left, is significantly greater than the combination arm and the metformin arm.

Again, the combination therapy shows a significant increase in HDL over metformin.

From this graph, it is quite clear that the rise in LDL to HDL ratio compared to metformin is most strongly seen in the rosiglitazone monotherapy arm. Overall, the results for the combination studies suggest that combination therapy impacts LDL and HDL but the ratio is minimally changed.

I have some overall comments on the lipid responses. Both monotherapy and combination therapy cause a significant rise in LDL and HDL. The ratio of LDL to HDL remains elevated at the end of 26 weeks and 52 weeks monotherapy treatment, but is not increased as a result of

combination therapy. Both LDL and the ratio of LDL to HDL peak after about 2 months of monotherapy and then appear to be decreasing in two studies, studies 11 and 20. That's one monotherapy study and the active-controlled study.

To better understand the lipid responses over time, I looked at the completers for all these studies and found the results to be consistent with the LOCF analyses that I've showed you.

So, I've showed you the comparative data, and next I will be presenting descriptive data to better characterize the lipid responses.

In this table and subsequent slides, I focused on the most efficacious dose, the 4 milligram twice-a-day dose, in the three monotherapy studies. This table summarizes the LDL endpoint results. The first row shows last observation carried forward estimates and the second row the completer results.

At week 26, an increase of 20 percent was seen in the placebo-controlled studies and 12 percent in the active-controlled study. This difference is due to the baseline differences I showed you earlier. I noticed that a larger increase in LDL was associated with smaller baselines, and in fact, if you look at the results broken down by median LDL, what I saw was for the mean value for a subgroup median baseline -- below the median baseline,

which the median baseline was 127, those values were 29 percent and 26 percent, 29 percent for the placebo-controlled studies and 26 percent for study 20. Then if you looked at the subgroups that were above the median, the percent changes were 10 percent and 6 percent. So, the baseline adjusted estimate for studies 11 and 24 is 18 percent, while the baseline adjusted estimate for study 20 is 16 percent. So, they are a little closer than what you see here.

Now, focusing just on study 20, the results for all randomized patients -- that would be this line here. That's the ITT population -- and the results for the completers show essentially no change from week 26 to week 52, suggesting that the response is stable for these time periods.

This table shows the results for the ratio of LDL to HDL. As for LDL, the magnitude of the increase is larger in the placebo-controlled studies than the active-controlled study. Mean increases of 11 percent are seen in the placebo-controlled trial at week 26 compared to an increase of 6 percent in study 20. By week 52, the change is 3.5 percent. Note for both LOCF analyses and the completers, the ratio decreases by about 2 percent.

So, I've showed you the mean responses, and now with this slide I'm showing the distribution of the

endpoint responses. The x axis shows percent change from baseline divided into five intervals. The first interval includes no change and decreases in lipid value. Then the rest of the intervals represent increases of 0 to 10 percent, 10 to 20 percent, 20 to 30 percent, and greater than 30 percent. The x axis is the percent of patients.

About 25 percent of the rosiglitazone patients showed no change or a decrease in LDL. Another 25 percent -- and we're at the other end of the spectrum -- showed an increase greater than 30 percent. For the LDL to HDL ratio, about half the rosiglitazone patients had no change or a decrease. About 22 percent had an increase of greater than 30 percent. Again, that's the last interval.

Some of you may be interested in seeing the distribution of the total cholesterol to HDL ratio. It looks very similar to the LDL to HDL ratio, with half of the patients in the first interval and about 15 percent in the last interval.

This graph is similar in layout to the last ones I showed you. The y axis is again the percentage of patients. But now the x axis shows the endpoint lipid values divided into three intervals. First I'll just focus on the LDL.

The LDL intervals are minus 130, 130 to 160, and greater than 160. 38 percent of the rosiglitazone

treated patients had an LDL greater than 160 at endpoint. At baseline, 19 percent of these rosiglitazone patients had an LDL greater than 160.

The ratio results are less striking. The baseline distributions for these two treatment groups are similar to what you see here for the placebo group. So, the difference between the red and blue bars represents both a comparison to placebo as well as to baseline. The differences are particularly small for the total cholesterol to HDL ratio. That's the far right graph.

Summarizing the magnitude of the lipid response, the mean LDL increase for rosiglitazone 4 milligram twice a day was about 15 to 20 percent. About 25 percent of the patients had a change greater than 30 percent. 38 percent of the patients had an endpoint LDL of 160 or greater. About half of the rosiglitazone 4 milligram twice-a-day dose patients showed no changes in the ratios of LDL to HDL or total cholesterol to HDL. About 25 percent of the patients had an LDL/HDL ratio of greater than 4, and that was about 18 percent at baseline.

Next I will show you the relationship between the LDL response and HbA1c changes.

For this graph, the y axis is now the percent change from baseline of the lipid and the x axis is HbA1c. The first interval includes patients with no change or an