ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTE #65

Topic: "Troglitazone for Diabetes Mellitus"

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P R O C E E D I N G S

DR. BONE: Good morning. I'm Dr. Henry Bone. I'm calling to order Day 2 of the Endocrinologic and Metabolic Drugs Advisory Committee's 65th meeting. The topic for today is troglitazone for diabetes mellitus.

I think we'll start by asking the members of the committee and the FDA members who are at the table here to introduce themselves. Representatives of the sponsor will be introduced or are introducing themselves as they go through their presentation.

If we can start with Dr. Hirsch.

DR. HIRSCH: Jules Hirsch, Rockefeller University in New York.

DR. ZAWADZKI: Joanna Zawadzki. I'm in private practice in endocrinology in this area, and I'm a clinical associate professor at Georgetown University.

DR. CARA: Jose Cara, pediatric endocrinology and diabetes, Henry Ford

Hospital.

DR. CRITCHLOW: Cathy Critchlow, epidemiology, University of Washington.

DR. ILLINGWORTH: Roger Illingworth, Oregon Health Sciences University, Portland, Oregon.

MS. REEDY: Kathleen Reedy, the Food and Drug Administration.

DR. BONE: Henry Bone, Henry Ford Hospital, Detroit, Michigan.

DR. SHERWIN: Bob Sherwin, Department of Medicine, Yale University.

DR. COLLEY: Colleen Colley, VA Medical Center, Portland, Oregon.

DR. STEIGERWALT: Ron Steigerwalt, pharmacologist, FDA.

DR. FLEMING: Alexander Fleming, medical officer.

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

DR. BONE: Thank you. The next item is a statement to be read by Kathleen Reedy,

executive secretary.

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

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting when evaluated against the agenda, with the following exception: Dr. Mark Molitch will be excluded from participating in all matters concerning Rezulin and Prelay.

In addition, we would like to disclose for the record that Dr. Sherwin previously had a limited involvement in a study concerning troglitazone. This study has

clinically ended. Currently, he has no financial interests or involvement related to this product. Since this study is only referenced but not included in the study submitted in the support of Rezulin and Prelay, Dr. Sherwin may participate fully in the discussions and vote relating to these products.

In the event that the discussions involve any other product 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 interests 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, Ms. Reedy. The next point in the meeting is the open public

hearing component of the meeting.

As you know, this is an extraordinary thing in the United States, that we have the opportunity for members of the public to address the advisory committee when drugs are being reviewed.

We have a letter from the American Diabetes Association which is distributed to the committee, and we have one person who will be speaking. We'll ask Margaret Himmelfarb to come up and make a statement and disclose any conflicts of interests or financial involvements, please.

MS. HIMMELFARB: Good morning. Thank you for allowing me to speak to you today. My name is Margaret Himmelfarb, and I am from Baltimore. I am a member of the international board of the Juvenile Diabetes Foundation and its research grant review committee. I have no financial interest in the product under discussion today, and I appear at my own expense.

I am here not as a spokesperson for the Juvenile Diabetes Foundation, nor to endorse this or any specific product. Rather, I speak today from the perspective of a parent of a child with diabetes who is concerned about the well-being of the millions of people who like my son Michael wage a daily battle to beat the odds against this killer disease.

Diabetes, as you know, is one of the deadliest diseases known to man, frequently leading to serious complications: blindness, heart attack, stroke, kidney failure, and amputation. It is estimated that diabetes shortens life expectancy by as much as a third. This year, treating diabetes and its complications will cost our nation $138 billion, 15 percent of the total health care budget.

My son has had diabetes since he was four years old. Today he is a junior at Princeton University. While most kids his age believe that they are invulnerable, Michael is

acutely aware of his mortality. He has known since far too young an age that, in a very real sense, he controls his own destiny. His future depends in large measure on how he manages his diabetes.

The diabetes' complications and control trial prove conclusively that maintaining normal glycemia can reduce the likelihood of diabetic complications by as much as 76 percent. That study made it quite clear that the primary goal of diabetes management must be to maintain optimal blood glucose control.

I welcome troglitazone to our arsenal of therapeutic weapons, as I recently rejoiced at the addition of metformin and humilog (phonetic) to our portfolio of treatment options. As troglitazone is purported to enhance insulin sensitivity, I expect that it will be the treatment of choice for many people who are insulin-resistant.

But a note of caution is in order.

Troglitazone, because it is an oral agent, will attract the interests of primary care physicians who want to avoid prescribing insulin for their Type II diabetes patients. And of course, it will appeal to those people with diabetes who want to avoid taking insulin shots.

But troglitazone should be considered as a substitute for insulin only where it proves equally effective. Its effectiveness must be assessed on a case by case basis with the aid of home blood glucose monitoring and routinely scheduled glycosylated hemoglobin tests.

In cases where troglitazone does not provide normal glycemia, it must not be used as a substitute for insulin. The cost would be too great. Health care professionals must keep in mind that insulin is the most effective agent for reducing blood glucose.

Most people imagine that taking shots is the hardest part of diabetes management.

Ironically, it turns out to be the easiest. Worrying about and, for the less fortunate, coping with complications are the real challenges of diabetes. Insulin shots become as routine as brushing your teeth, even for little children.

In conclusion, if the members of this august advisory committee determine that troglitazone is ready for the marketplace, and I certainly hope that you are able to do so, I urge you to mandate that specific information accompany this product detailing the importance of continually evaluating diabetic control using home blood glucose monitoring and hemoglobin A1cs. This information should be included in package labeling, insertion materials, and advertising copy, and be designed for the edification of the consumer as well as the physician.

Thank you.

DR. BONE: Thank you very much. The next item on our agenda is the introductory

remarks of Dr. Fleming, who is a group leader for the group responsible for this review at the Division of Endocrine and Metabolic Drugs.

DR. FLEMING: Well, ladies and gentlemen, again thank you very much for being here. We welcome you, and on behalf of my colleagues, Dr. Sobel at the FDA, we again want to express our gratitude to the members of the advisory committee for being here and for participating in this key step in the drug evaluation process.

I want to also thank Mrs. Himmelfarb for coming, taking this time and effort to give her testimony. Again, it reminds us that after all it is the patient for which we must place our primary consideration.

Now, the results of the diabetic control and complication trials have with good reason energized the community of patients and health care providers who contend with this disease in striving for better control. Unfortunately, the implications of this trial

for treatment of non-insulin dependent diabetics are limited.

Now, there is no reason to doubt the potential for achieving the relationship between improved glycemic control and reduced complications that were seen in the DCCT. But achieving it is another thing. The reason is, of course, that we are talking here about two entirely different but related disorders.

We can view insulin dependent diabetes, such as suffered by Mrs. Himmelfarb's son, as a classic hormone deficiency state. Now, it is true that we don't have an entirely physiologic replacement therapy for this condition. But we come a lot closer to that than we do for Type II diabetes.

Now, insulin-dependent diabetes -- or, I'm sorry, non-insulin-dependent diabetes -- is clearly a much more complicated disorder, that it involves at least for a time in the natural history of the disease an absolute excess of endogenous insulin.

Now, adding on additional insulin through insulin therapy has a number of established and supposed drawbacks. Insulin therapy itself may therefore be a two edged sword in this sense.

Oral therapy, at least with sulfonylurea agents, has its own drawbacks. They may be in some ways worse compared with insulin in the way that they work and the specific toxicities that this drug class carries.

The point is we do not have effective therapy, drug therapy, for Type II diabetes presently, and we urgently need new therapies for this condition in order to achieve the potential that the DCCT has suggested. And this should explain why we are here earlier than might otherwise be the case.

The agency is making every effort to expedite the evaluation of urgently needed treatments. Does this mean that we lower the bar at the same time? Let's be very clear

about this: absolutely not. We are going through the full evaluation process. We are only attempting to expedite it.

And so we have very important work ahead of us today. The recommendations of the committee will be instrumental in the ultimate decision that is made about the benefit and risk of this drug. And I think you might be interested in knowing the process that has been used to, in part, get us here today because it relates to the format that this meeting itself will be conducted under.

The format, as you can see, involves a session in the afternoon of interactivity under a number of defined issues. This is in contrast to the usual approach that we take, where the sponsor goes first or in some cases last, but nonetheless makes a full presentation followed by a sort of counter presentation from the agency.

Now, we have along the way participated in the highly interactive process

with the sponsor in our evaluation of this NDA. For example, we have had on-line communication with the sponsor. This is encrypted to ensure security, but it allows us to answer questions and have immediate answers. And by the same token, the company can communicate with us about their own questions and problems.

So I think this model of interactivity is very useful, not only for the development of drugs in general and their regulation, but for the conduct of this hearing because it will allow us to focus on the issues in an interactive fashion, a way that I think will be very beneficial.

Again I thank you, and I look forward to the proceedings.

DR. BONE: Thank you, Dr. Fleming. The next segment of the committee meeting will consist of the initial presentations by the sponsor. The format that has been arranged for the meeting will have these basic presentations in the morning by the sponsor, a set of

presentations by the agency, and then there are some suggested issues for discussion in the afternoon. And we obviously, as a members of the committee, may have additional points we wish to discuss or address.

The committee are asked to focus their questions in the morning sessions, particularly the sponsors' presentations, on questions and clarifications, and try to put as much of the discussion as possible in the afternoon. But obviously we would want to resolve any questions, ambiguity, or anything like that that we possibly can, or interpretation of what is intended by any of the morning speakers at the time so that we don't have lingering questions.

With that remark, I'll introduce Dr. Martin.

DR. MARTIN: Thank you, Dr. Bone. I'm Irwin Martin from Parke Davis Regulatory Affairs. On behalf of Parke Davis, Warner-Lambert, I'd like to thank the Division

of Metabolism and Endocrine for the opportunity today to present to the committee an overview of our new drug, troglitazone.

Our presentation today will pertain to both Rezulin, the Parke Davis name for troglitazone, and Prelay, the Sankyo USA name for troglitazone. Representatives from Sankyo USA are here should you have any questions specifically for them. However, as noted in your cover letters to your briefing document, Sankyo USA has given Parke Davis permission to speak on their behalf on all data related questions pertaining to their NDA.

We'll spend most of our time this morning providing an overview of troglitazone with a particular emphasis on the issues selected by the division for discussion this afternoon. You will hear shortly of troglitazone's mechanism of action, specifically its ability to improve insulin resistance. There are a number of interesting therapeutic areas all relating to insulin

resistance. These are listed in the slide you see here.

(Slide)

Parke Davis has an interest in troglitazone's utility in all of these areas. We hope to submit an application for each of these if the data support such a filing.

Today, however, we will concentrate our presentation on the subject of this NDA, that is, the effect of troglitazone on Type II diabetic patients on exogenous insulin therapy. In the continuum of diseases related to insulin resistance, these patients are the most severely affected. Our intent was to make this drug available to these patients first. We worked closely with the FDA to assure development of this intent.

Therefore, to put things in perspective, the proposed indication for troglitazone, and again the primary focus of our presentation, is patient with Type II diabetes inadequately controlled on insulin

therapy. In addition, patients controlled with insulin may benefit from Rezulin by reductions in insulin use.

Allow me to provide a brief overview of the history of troglitazone. Early work began in 1979 by Sankyo in Japan. This led to the discovery of troglitazone. The drug was first tested in man in 1987, and the U.S. IND was opened in 1989.

A tripartite development strategy is currently ongoing: Sankyo in Japan, Parke Davis and Sankyo USA in North America, and Glaxo-Wellcome and Sankyo Europe in Europe. The product is approved for marketing in Japan.

There are three separate development programs. All three lead companies are each conducting or have conducted their own pivotal trials for their territories. All companies, however, share information and ideas.

The current NDA contains data by all companies listed here. For this NDA, one of the pivotal studies was conducted by Parke

Davis and the other by Sankyo USA.

Let me give you a brief history of this NDA. The end of phase II meeting for this indication was held during the phase III development of troglitazone for the full Type II diabetes indication. We had conducted a pilot study of patients with Type II diabetes on insulin. All 17 of these patients improved their glucose control while on troglitazone, and all were able to decrease or sometimes eliminate their need for exogenous insulin.

Due to these dramatic results, we and the FDA worked closely together to agree on a program which would allow troglitazone to be made available for these inadequately treated patients as soon as possible. We did this without delaying the development of troglitazone for the full Type II diabetes indication. It was noted that the population in need was far too large for a treatment IND to be practical, so resources were added and put towards an earlier NDA. We

worked with the FDA to agree on the design of the study, 991-068, which you will be hearing about shortly. We also agreed that an ongoing study by Sankyo USA, which is 991-040, could be considered a pivotal study for this NDA.

In January of this year, the pre-NDA meeting was held. And in July, we submitted the NDA. We have therefore come from the pre-NDA -- from the end of phase II meeting to today in approximately 16 months.

As noted earlier, our presentations will be relatively brief and focused primarily on the issues to be discussed this afternoon. Following this introduction, Dr. Olefsky, from the University of California in San Diego, will provide an overview of the proposed indication and the intended patient population.

Dr. Saltiel, from Parke Davis, will then provide an overview of the mechanism of action. Dr. McGuire, from our toxicology department, will summarize the animal toxicology and carcinogenicity data. He will

concentrate on those topics listed under issue four in this afternoon's agenda.

Dr. Whitcomb will then provide an overview of the safety of troglitazone and the efficacy results from the two pivotal studies of patients inadequately controlled on exogenous insulin therapy.

As Dr. Bone has indicated, I understand this afternoon's agenda will allow ample time for questions. Please, however, stop any of the speakers should you have any need to clarify a particular point, and the fuller discussion may be held this afternoon.

Also with us from Parke Davis, should you have additional questions -- we have Dr. Koup from our pharmacokinetics and drug metabolism department, Dr. Venable from biostatistics, and Dr. Vassos from our clinical pharmacology department.

Additionally, we have with us outside experts who may be helpful in answering some of the questions during the afternoon session.

Dr. Finch is professor of medicine emeritus from the University of Washington. Dr. Newbern is professor of pathology at Boston University School of Medicine. Dr. Perez is director of echocardiography at Washington University School of Medicine. And Dr. Swenberg is professor of environmental science and engineering from the University of North Carolina.

I'd now like to introduce Dr. Olefsky, who will provide an overview of troglitazone -- not of troglitazone, sorry -- of the proposed indication and the intended population.

DR. OLEFSKY: Thank you, Irwin, and good morning to the members of the advisory panel and others in the audience here.

I guess my role here is to point out the importance of insulin resistance in the pathophysiology and the etiology of NIDDM, and then to focus in on the importance of insulin resistance in the clinical management of these

patients, particularly those patients who are receiving exogenous insulin.

Now, we now that in order to develop Type II diabetes, one needs at least major metabolic defects. One is insulin resistance, and the other is either an absolute or relative insulin insufficiency. And we also know from a number of studies in pre-diabetic individuals, particularly those done here in the United States, that if one examines pre-diabetic individuals many years before they develop diabetes one finds that these folks are insulin-resistant.

(Slide)

And that leads us to this scheme depicted on this slide here, which actually summarizes the etiology or the natural history of NIDDM. So one starts here with insulin resistance, which could either be acquired or genetic in origin. And if one is insulin-resistant, then the beta cells secrete increased amounts of insulin, creating a

hyperinsulinemic state, and this hyperinsulinemia compensates for the insulin resistance such that you don't have diabetes.

You can have either normal glucose tolerance or perhaps impaired glucose tolerance or IGT. And this is the compensated insulin resistance syndrome, sometimes called the metabolic syndrome, other times called syndrome X.

And based on some analyses done, while the DP, the diabetes prevention program, was being planned we came to the estimate that there was 70 to 80 million Americans who have this compensated insulin-resistant or syndrome X type syndrome here.

We also know that if you have impaired glucose tolerance here, you have a very high risk for the development of NIDDM. And we know that on average in the United States, about 7 percent per year of these patients will convert from the compensated state to Type II diabetes.

And what is the metabolic event that causes this conversion? Well, it is indicated here. It is beta cell failure, either absolute or relative beta cell failure. The beta cells no longer can maintain the hyperinsulinemic state, insulin levels fall. And when insulin levels decline, superimposed on insulin resistance, one develops diabetes with this characteristic set of metabolic abnormalities, and again including insulin resistance is a cardinal feature of established Type II diabetes.

(Slide)

Now, we also know that insulin resistance is a wider problem than simply diabetes, which is the focus of discussion today. And that is indicated here on this slide, which I think is something well known to most of the panel members, and I'll just be very brief about this.

There are lots of people who have insulin resistance. Not all of them develop

Type II diabetes. But if you have insulin resistance, then you are susceptible to other adverse health events, and insulin resistance can be associated with other things, such as the development of certain forms of hypertension, polycystic ovarian syndrome. It can lead to the exacerbation or perhaps the development of atherosclerosis or cardiovascular disease through the dislipedemias which are associated with insulin resistance, and perhaps even by direct effects of hyperinsulinemia or insulin resistance on the vascular wall leading to cardiovascular disease.

So this is a very wide problem. A certain proportion of patients with insulin resistance go on to develop diabetes.

And let's now return back to this issue right here. And I'd like to show you one piece of data capturing the insulin resistance which exists in patients with Type II diabetes.

(Slide)

These are euglycemic clamp dose response studies which were conducted a number of years ago in which we measured the rate of in vivo overall total body glucose disposal as a function of the steady state plasma insulin concentration in a group of normal subjects, patients with impaired glucose tolerance, and diabetic patients, either obese or non-obese.

Now, the major point I'd like to emphasize with this slide is not just that the diabetic patients here are insulin-resistant compared to controls. That's obvious. The point I would like to make is the magnitude of the insulin resistance.

This is not a subtle defect. These patients have lost anywhere between 60 to 80 percent of their insulin action, so it isn't a mild defect, and these are typical, garden variety, unselected diabetic patients. These are the kind of patients that walk into everybody's clinic. And you can see, these patients have rather substantial insulin

resistance with a 60 to 80 percent decrease in insulin stimulated glucose disposal.

Okay. With that as a kind of background, let me turn to some more clinical management issues. As we heard earlier this morning, the DCCT has clearly demonstrated that control of glycemia will lead to prevention of complications. In fact, what we know from the DCCT is that for every increment of glycemic control we gain an increment of complication prevention.

Now, the DCCT study was done in Type I diabetic patients, but the overwhelming majority of diabetologists, certainly myself included, have made the transition from the DCCT to the treatment of Type II diabetes. And we believe that control of glycemia is important for complication prevention in Type II diabetes as well.

In fact, the ADA has recently suggested some guidelines and some recommendations on this point. And to kind of

paraphrase the ADA's recommendations, it is something like for the -- in terms of with respect to glycemic control, the goal of anti-diabetic treatment should be to reduce the blood glucose levels to as close to normal as possible.

(Slide)

And in recognition of this, they have published and come out with some specific glycemic recommendations. And you can see these recommendations on this slide. And the point here is we are not trying to treat patients to take the edge off the glucose level, but in fact we are trying to treat them to a very specific, very stringent glycemic target.

So you can here what they are recommending, is if the fasting glucose in a treated diabetic patient is above 140 or the hemoglobin A1c above 8 percent, then this should trigger an action. And the action is to intensify your anti-diabetic therapy to drive

those glucose levels down more towards the gold glucose levels, which are depicted here. So we have specific targets that we are trying to shoot for in our attempt to prevent complications in Type II diabetic patients. Well, if these are our targets, how well are we doing? I think intuitively we know that in Type II diabetes we are not doing all that well. Most patients who are on oral hypoglycemic agents, whatever the agent is, do not achieve these kinds of glycemic targets. Even in the small fraction of those that do, this effect is usually temporary.

Over the course of years, we know that this is a progressive disease. Type II diabetes gets worse as the years go by. This has been shown with the UK PDS study, which demonstrated that when even though you can initially control some of these patients on oral agents, as the years go by the disease gets worse. You need increasing doses of drugs, combinations of oral agents. And

eventually, many if not most of these patients will require insulin therapy in order to achieve glycemic control.

The UK PDS study, of course, is done in England. But this is true for the United States, too. And these are some data extracted from a recent review article by Maureen Harris in which she points out that in the United States, 43 percent of all Type II diabetic patients, 2 to 3 million patients, are already on insulin therapy.

But if you look at the degree of control achieved, you can see it is not all that good. The average hemoglobin A1c levels in insulin treated diabetic patients in this country is 9½ percent. That is a far cry from the glycemic targets that I showed you on the previous slide.

These data are actually somewhat old. If one looks at the more recent data, it may be up to 60 percent of all Type II diabetics are on insulin therapy, but still with the same

effect or lack of effect, that is, hemoglobin A1c levels still 9½ percent.

So insulin is being used in large numbers of Type II diabetic patients, but it is not being used effectively, at least with respect to glycemic control. And why is this? Well, certainly we know we could get better glycemic control if we just used more insulin and gave insulin more frequently. But this is difficult to do. And the reason it is difficult to do is that these patients are so insulin-resistant.

So what does it really take with insulin therapy, given this insulin-resistant population? What would you really have to do in order to achieve glycemic targets?

Well, a few years ago we kind of looked at this question by doing a study in which we took a series of garden variety NIDDM patients, brought them into a metabolic ward, and put them on insulin pump therapy, that is, continuous subcutaneous insulin infusions,

brought them under euglycemic control, and then monitored how much insulin on a 24 hour basis, what was the daily insulin does needed to achieve glycemic targets.

Here you can see in the upper panel that we very easily brought the glucose levels within a few days down to this level, which certainly achieves the glycemic targets. And the lower panel shows you the 24 hour insulin dose needed to achieve this degree of glycemic control.

So you can see here that early on we needed 130 or 140 units of insulin a day. This then falls somewhat over the next few days due to improvement in gluco-toxicity. But even out here at the steady state three weeks later, you can see that in order to get glycemic control in your typical, garden variety NIDDM patient, one needs in this case 110 units of insulin a day. And that's a lot of insulin, and this is given continuously by insulin pump.

Now, this study is not done in

isolation. There have been other studies looking at this exact same question, if not using pump therapy then using intensive insulin management with multiple insulin injections a day. And if one surveys these studies, we get the same result. In order to achieve glycemic targets, one needs 110, 120, 130 units of insulin a day in your typical NIDDM patient.

If we are trying to prevent complications, and we are trying to do that by hitting glycemic targets, and many of these people are treated with insulin to accomplish this, you need a lot of insulin. If you are going to give this much exogenous insulin, it is obvious you are going to create a state of hyperinsulinemia. And we examine that in these patients here by measuring the glucose and insulin levels after meal tolerance tests.

Here are the glucose levels after breakfast, and then after lunch. This is in the solid lines here. And you can see that in these insulin pump treated patients, we

actually get very good glycemic control. If we look at the insulin levels here in the dotted lines, you can see that the circulating insulin levels as a result of this exogenous insulin are really very high: two, three, fourfold higher than normal, which is not surprising because we are having to give them 110 units of insulin a day, which is two to fourfold higher than a normal person's pancreas will make in a given day.

So in order to achieve glycemic control, the goal being then to prevent complications, one needs to give a lot of insulin with a complicated insulin regimen and create a state of substantial hyperinsulinemia. So while it is not being done in the overwhelming majority of insulin treated patients, it can be done in a theoretic basis. And this is good for your glucose level, but there are some potential downsides to big dose, multiple insulin injection treatment regimens.

(Slide)

This slide summarizes some of these downsides. First of all, we have the problem of weight gain. We know that when we treat patients with big dose insulin therapy, they gain weight. If one looks at a survey of the studies in which this has been attempted over a period of a couple of months, these patients will typically gain 10 to 15 pounds, and this is not a very satisfactory side effect.

These patients are almost always obese to begin with. They then become more obese. Obesity can make insulin resistance worse. So this is a side effect which neither the patient nor the physician are particularly happy with.

In addition, we have the problem of hypoglycemia. The hypoglycemia is not as big a problem in Type II diabetic patients as it is in type I diabetic patients. But when you are using large dose insulin therapy with multiple injections a day, particularly patients who occasionally skip meals, hypoglycemia can

occur. And it is a problem, and it is a fear in the minds of many practicing physicians when they come to think about large dose insulin therapy.

We also have a problem that in order to administer large doses of insulin, you always need multiple insulin injections per day. And this engenders very complicated insulin treatment regimens which are not well accepted by patients. It requires multiple injections, large doses of insulin, frequent home glucose monitoring, lots of adjustments of diet and exercise. And although this is our goal, this is what should happen, this is not well accepted by patients, and unfortunately, it is also not that well accepted by practicing physicians.

So we have the physician/patient partnership here really not working in their best interests and not accepting these kinds of complicated insulin treatment regimens. And this is a real hinderance to the institution of

these kinds of therapies or this kind of therapy in the general population.

And finally, as I alluded to earlier, we have the possible effects of hyperinsulinemia and insulin resistance on underlying cardiovascular disease, which after all is a major problem in this target population. Certainly there are lots of epidemiologic and basic science evidence indicating that there is a connection here between insulin resistance, hyperinsulinemia, and heart disease, that many proposed mechanisms -- just as one potential example, if you have very high circulating insulin levels, which I showed you on the previous slide these patients will have when given large doses of insulin, then this insulin can cross over into the IGF-1 receptor and perhaps stimulate perhaps proliferation of either vascular wall cell, smooth muscle cells, et cetera.

There are many possible mechanisms, but certainly there is a lot of thought about

this connection here.

So if our goal is to try to prevent diabetes complications by treating glucose levels to as close to normal as possible, many patients come to insulin therapy. Almost all patients who come to insulin therapy are not on ideal control. One could achieve ideal control, but there are some drawbacks. Some of them are very substantial drawbacks.

What could be done about the problem? Well, if we had a means or a drug that could actually treat insulin resistance, then by improving insulin resistance it should allow physicians to obtain better glycemic control, and at the same time reduce the insulin doses that they have to give to these patients and reduce the number of injections per day that they have to give to these patients, which I think would be a significant advantage for our treatment abilities in this condition.

And as you'll hear later on this morning, troglitazone is a drug which does have

this mechanism of action. It does improve or ameliorate insulin resistance. And as you'll hear later on this morning, in clinical studies it has been shown that when used in combination with insulin troglitazone can allow better control of plasma glucose levels, improvement in glycemia, and at the same time allows a lowering of the insulin injection regimens, both in terms of total dose as well as the number of injections per day.

Let me now turn the rest of -- or not the rest of the proceedings, but the next segment over to Dr. Alan Saltiel from the cell biology department at the Parke Davis Company.

DR. BONE: Excuse me just a moment. Are there members of the committee who have questions? Dr. Cara for starters.

DR. CARA: From a theoretical basis, if you were to design a study in which you are looking at endpoints in terms of drug efficacy for Type II diabetes, what would you look at? I mean, I am now asking you as an expert in

diabetes.

DR. OLEFSKY: Okay. Well, the question is what endpoints would I look at if I was designing a trial. I think that the lessons of the DCCT are so powerful, the connection between glycemia and complications, that the endpoints that I would pick are the usual standard endpoints of glycemic control, which would be hemoglobin A1c levels and various measures of glucose.

In a particular population, like the insulin treated diabetic population, I would add to that, in addition to improved glycemic control, the ability of an agent to simplify the insulin treatment regimens and lower the amounts of insulin that are needed to gain glycemic control.

DR. BONE: Thank you.

DR. SALTIEL: Thank you very much, Jerry. Good morning, everyone.

Well, as you have just heard from Dr. Olefsky, a number of prospective

epidemiological studies across several population groups have indicated that insulin resistance may be the primary defect in the development of Type II diabetes. Indeed, insulin resistance can be detected long before glucose intolerance occurs, at a time when insulin secretion may even be increased.

As this process advances, insulin resistance can be further exacerbated due to a number of factors, including the ensuing disregulation of carbohydrate and lipid metabolism, resulting then in the development of impaired glucose tolerance.

Now, eventually the beta cells can no longer compensate for insulin resistance by secreting increased amounts of insulin. At this stage, insulin secretion falls, usually due to a specific defect in glucose recognition allowing glucose homeostasis to deteriorate and leading then to the development of frank diabetes. Ultimately beta cells fail, as we have just heard, and diabetes worsens.

So this view of the metabolic staging of diabetes indicates that the treatment of insulin resistance has great therapeutic potential for the amelioration of the disease.

Troglitazone is the first drug to advance to late stage clinical trials that was designed specifically to target insulin resistance. And this differentiates troglitazone from other anti-diabetic agents.

Troglitazone is a member of a family of compounds known as the thiazolidinediones. These molecules all share a common structural motif shown here on the right side, the thiazolidine- 2-4-dione, which is the active portion of the molecule.

Additionally, troglitazone was designed to incorporate a vitamin E molality, producing a bi-functional drug that combines the insulin enhancing activity of a thiazolidinedione with a potent inhibitor of lipid peroxidation. And I know many of you know that lipid peroxides have been implicated

in the progression of atherosclerosis, and they also play a role in aggravating insulin resistance.

We have studied this activity of troglitazone in vitro, that is, its antioxidant activity. But its contributions to the clinical effects of the drug are only now just beginning to be explored.

Troglitazone and the other thiazolidinediones are unique in their ability to improve insulin action in almost all animal models of Type II diabetes. And this includes a number of genetic models, such as the OBOB and DBDB mouse, as well as several acquired models, such as the high-fat-diet-adapted rat.

(Slide)

Shown on this slide is the effect of troglitazone on glucose tolerance. And one of these models, the diabetic male Zucker fatty rat -- as you can see, troglitazone lowers fasting hyperglycemia and improves glucose tolerance in these animals. Additionally,

troglitazone can correct the hyperinsulinemia that is associated with insulin resistance in these animals. Now, this is an indirect effect of the drug due to the decreased requirement for insulin.

(Slide)

On this slide, I have tried to summarize some of what we have learned about the effects of troglitazone in various animal models of Type II diabetes. As I have just mentioned, troglitazone can lower fasting hyperglycemia and improve glucose tolerance. Because of the lowered requirement for insulin, the drug can correct the hyperinsulinemia associated with insulin resistance.

In a series of studies that are summarized in your package and described in detail in the NDA, troglitazone has been seen to induce beta cell regranulation indirectly and to increase insulin content in these cells in diabetic rats, suggesting that troglitazone may be able to prevent to some extent the

deterioration in pancreatic function induced by diabetes.

Another component of the diabetic syndrome is the development of dislipedemias. And in certain animal models, troglitazone has been seen to lower VLDL and LDL while raising HTL cholesterol, and can also lower the hypertriglyceridemia associated with diabetes. Additionally, in some animals troglitazone can lower systolic blood pressure, especially in insulin-resistant rats.

Now, in addition to these studies that have been carried out in various animal models, a number of detailed mechanistic experiments have been performed in patients with Type II diabetes in order to learn more about the mechanisms that account for the ability of the drug to improve glucose tolerance.

(Slide)

Shown here are a group of studies done in a group of 11 patients with Type II

diabetes before and after treatment with 400 milligrams per day of troglitazone. This is a meal tolerance test in which meals were administered at zero and four hours. And you can see in this slide that troglitazone lowers fasting blood sugar and accelerates glucose disposal after each meal. Additionally, troglitazone can lower both fasting and postprandial insulin levels.

(Slide)

Now, peripheral insulin resistance is characterized by an attenuation of insulin stimulated glucose disposal. A number of hyperinsulinemic euglycemic clamp studies have been performed, including the one shown on this slide among many, to demonstrate that troglitazone can reverse the insulin resistance of diabetes by increasing insulin stimulated glucose utilization.

And this is a glucose clamp study done in the same 11 patients. And you can see here that troglitazone increases glucose

utilization or glucose disposal rates, assayed here at two different concentrations of insulin in the infusion. Interestingly, in this study, every patient showed this kind of response to the drug.

Elevations in hepatic glucose production are thought to be primarily responsible for the fasting hyperglycemia of diabetes. So hepatic glucose production was evaluated in the same group of 11 patients. And you can see that troglitazone lowers hepatic glucose output to levels approaching those seen in non-diabetic controls. This effect of troglitazone reflects its ability to inhibit glucose synthesis in the liver.

So to summarize from these mechanistic studies, we have learned that troglitazone acts fundamentally as an insulin sensitizing agent, improving insulin resistance and glucose tolerance in patients with Type II diabetes by increasing insulin stimulated glucose disposal primarily in muscle, and by

inhibiting hepatic glucose production.

Now, a number of investigators have tried to get a handle on the molecular mechanisms that underlie these effects of the drug and so have turned to various in vitro tissue culture models in which it is possible to study insulin action.

Now, these studies have revealed that troglitazone can increase insulin stimulated glucose uptake in cultured fat and muscle cell lines, can decrease glucose neogenesis in cultured liver cell lines, and can potentiate the insulin dependent differentiation of adipocytes in tissue culture.

Now, while these effects of troglitazone are consistent with its activity as an insulin sensitizing agent, these actions are relatively slow and do not primarily involve the mobilization of insulin's early signaling pathways.

In addition, troglitazone does not universally enhance the actions of insulin in

vitro. For example, the drug has no impact whatsoever on the growth promoting effects of insulin in tissue culture cells.

Now, taken together, these findings suggested that troglitazone's actions are mediated primarily by a mechanism involving the specific regulation of gene expression. Now, probably the primary progress that has been made in understanding how troglitazone might regulate transcription has emerged from the study of genes that are known to be differentially expressed during adipogenesis.

Now, you'll recall a minute ago I reminded you that troglitazone can enhance adipocyte differentiation in tissue culture cells, leading us and others to study the regulation of genes that are differentiation dependent and tissue culture cell lines of adipocytes such as the 323-L-1 cell.

(Slide)

And shown on this slide is an example of the regulation of one of these genes, a gene

known as AP-2. The AP-2 gene encodes for a fatty acid binding protein, the expression of which is known to be increased in adipocytes. Now, this slide shows an RNA's protection assay. This is a method used to evaluate messenger RNA levels.

We know the AP-2 gene is under the regulation of fatty acids. And you can see here the fatty acid bromopalmitate can increase messenger RNA levels for AP-2. Troglitazone is even more effective than bromopalmitate, markedly increasing the expression of this gene.

Now, let me remind you that gene expression is controlled by a region of the gene known as the promoter. The promoter is under the regulation of transcription factors which can recognize and interact with discreet sequences in the promoter known as upstream activating sequences, or UAS.

Upon activation of the promoter by a transcription factor, RNA polymerase enzymes

are activated, inducing transcription of the gene. Then, of course, the resulting messenger RNA is translated into protein.

Now, the promoter of the AP-2 gene and other thiazolidinedione genes were found to contain sequences that -- or signature sequences or discreet upstream activating sequences that predicted the interaction with and binding to a family of transcription factors known as the nuclear receptors.

Nuclear receptors are regulators of transcription that are themselves activated by small lipophilic molecules or ligands. Examples of this would include the steroid hormones or thyroid hormone.

Now, more specifically, the sequences identified in thiazolidinedione responsive genes were known to interact with a sub-family of these receptors known as the PPARs, or peroxizine proliferator activated receptor. And this finding led to the speculation that thiazolidinediones like troglitazone might

serve as specific ligands for these receptors, inducing them to interact with domains in these genes known as PPAR response elements or PPREs, found in genes that encode for proteins critical to the control of lipid and carbohydrate metabolism.

Now, thus far there are three major members of the PPAR family known, alpha, gamma, and delta. And these receptors all share considerable sequence identity in their activation of DNA binding and ligand binding domain.

Based on these findings, it was hypothesized that thiazolidinediones like troglitazone might serve as ligands for just a subset of these receptors. So to evaluate this hypothesis, a series of binding and transactivation experiments were performed, such as the one shown in this slide.

(Slide)

Now, this slide depicts an experiment, a transactivation experiment, in

which cells were cotransfected with the receptor PPAR-gamma and a reporter gene encoding for the enzyme luciferase that was fused to a promoter containing a thiazolidinedione responsive sequence which is called ARE-7.

(Slide)

Now, in experiments such as this, the expression of the reporter gene depends upon the activity of the promoter, which in turn depends critically on the activity states of the receptor. As you can see on the left hand side of the slide, troglitazone, but not the unrelated compound metformin, increases the expression of luciferase in these cells, reflecting an increased activity of the promoter to which it is fused.

Now, importantly, in the absence of PPAR-gamma, there is no effect at all of the drug. So this experiment and a series of other experiments like this and complementary to this have indicated that there is indeed specificity

among these receptors for different ligands. And I have tried to summarize that on this slide.

(Slide)

While we are still not definitively sure about what natural endogenous ligands may exist for these receptors, we do know that PPAR-alpha appears to be the receptor for a class of compounds known as the fibrates. Activation of this receptor leads to the regulation of expression of genes encoding for different lipoproteins. We're still not completely sure about the precise role of PPAR-delta, but we do know that PPAR-gamma is the receptor for the thiazolidinediones.

Well, we clearly still have much to learn about the physiology and the molecular biology and the molecular interactions of these receptors. But a general picture has now emerged concerning the mechanism by which these drugs can induce cells to become more sensitive to insulin. And I tried to outline this on

this slide.

(Slide)

Again, we know that thiazolidinediones like troglitazone can interact with the nuclear receptor PPAR-gamma, inducing this complex to interact with promoters in genes that encode for proteins critical to the control of carbohydrate and lipid metabolism. In some cases, these genes may themselves be transcriptionally regulated by insulin through mechanisms emanating from the insulin receptor that are really not too well defined but that provide a mechanism for the potentiation of insulin action by thiazolidinediones.

Alternatively, these effects of thiazolidinediones may be insulin independent but insulin mimetic on these genes. And then some of these genes encode for proteins that are post- translationally modified by insulin, proteins that participate in insulin signal transfection or that end up as targets of

insulin action.

So, as you can see, we have made some progress in understanding how thiazolidinediones induce sensitization of cells to insulin. And as I have told you today, we have learned that troglitazone can bind to and activate the nuclear receptor PPAR-gamma. This activated complex can regulate the transcription of genes encoding proteins that are critical to the control of carbohydrate and lipid metabolism by insulin.

Thank you.

Unless there are some questions, I'd like now to introduce Dr. Ted McGuire.

DR. BONE: I believe there are actually a few questions.

DR. SALTIEL: Okay.

DR. BONE: Okay.

Dr. Zawadzki.

DR. ZAWADZKI: Could you please comment a little bit more about the group of 11 individuals who were clamped before and after

troglitazone as to were they on insulin therapy before troglitazone was added, how old they were, and how long they had diabetes, and how long the duration of troglitazone treatment lasted?

DR. SALTIEL: Yeah, thank you. Actually, I'm going to defer this question to Dr. Olefsky since these were his studies.

DR. OLEFSKY: Does this work? Yes, this does work. The patients that were studied were patients who had

Not been treated with insulin. They had either been treated with some oral agent or not on any oral agent therapy. Had they been on oral agent therapy, they were withdrawn for a period of several weeks before they were started on the troglitazone therapy, which was given for a period of 8 to 12 weeks.

Was there some other aspect of it you -- oh, how old they were? Yeah. They -- I couldn't remember the exact age, but they were in the low 50s. They were typical diabetic

patients with BMIs around 30. Their mean, average age was probably 51, 52, 53.

DR. ZAWADZKI: Do we know how long they had had diabetes?

DR. OLEFSKY: We do know. I couldn't give you the exact details. But they would have had diabetes from anywhere between five and ten years. So they were not new onset diabetic patients.

DR. BONE: Dr. Sherwin.

DR. SHERWIN: I'm just curious. Activating the PPAR-gamma receptor, does that itself produce all the effects on carbohydrate on lipid? Because I still have trouble getting the leap. I recognize that the drug binds to the receptor. But are we sure that all of the effects are due to that? That's really what I'm asking.

DR. SALTIEL: Bob, that's a very good question. And you know, there is still a bit of a gap in understanding which are the precise direct and indirect events that occur after

activation of the receptor.

I think we have been able to catalogue a series of genes that we know respond early and respond late. And these responses are all consistent with the up regulation of proteins that are involved in insulin action. I think we don't really know all the molecular details yet about this interaction.

DR. SHERWIN: It seems to me a little more of a growth factor, a differentiation factor. I've always had trouble translating that into glucose transport effects and things like that. So I assume there is still a wide gap in knowledge to take it from a differentiation factor and growth factor in adipocytes to some of the carbohydrate and lipid effects.

DR. SALTIEL: Well, this will take quite a while, I think, to get into this in detail.

DR. SHERWIN: No. I don't want you

to. That's okay.

(Laughter)

DR. SALTIEL: I think there is a fair amount of evidence showing the expression of PPAR-gamma in insulin sensitive tissues, not just in fibroblasts, but also in mature dipocytes and elastin skeletal muscle.

DR. BONE: I guess the question that Dr. Sherwin was asking, though, is how confident are you that that accounts for all of the actions of the drug?

DR. SALTIEL: Well, we -- there are a series of studies published correlating the binding affinity and the in vitro activation with anti-diabetic effects of the drug in vivo. So those are correlation studies.

DR. BONE: But the intermediary effects --

DR. SALTIEL: Pardon me?

DR. BONE: But the intermediary steps are what you are asking about, aren't they, Bob?

DR. SHERWIN: Well, no. It is basically the question you asked, can we be sure that that's the only effect of the drug. In other words, is it working with respect to its effects on glucose, particularly and also perhaps lipid, solely on that basis.

DR. SALTIEL: Well, you know, I can't directly answer that until we have a knock-out animal. And even then I'm not sure.

DR. SHERWIN: And we don't have that yet.

DR. SALTIEL: Right, and we don't have that yet.

DR. SHERWIN: Okay.

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

DR. HIRSCH: Well, my question was a similar -- it's the sort of general question, Dr. Saltiel, that relates to what we were just talking about, namely what the evidence is is that thiazolidinedione is the best known of the unnatural ligands that we now have for

PPAR-gamma-2, and that what PPAR-gamma-2 does is open up a whole ensemble of molecular genetic activities that lead to not only differentiation but to what you are differentiating for, namely the storage of triglycerides.

A whole variety of things happen. There are, as you know, a number of papers supporting this, so that I guess this becomes a very key issue then, the degree to which the lessening of insulin resistance, which is in fact a very advantageous thing to have occurred at that moment when you are storing lipid, obviously, is differentiatable or discernible as a separate entity from these other items.

And I guess it also cautions us then to examine all of the animal and human studies in terms of any evidence that anything adverse occurred in terms of there being more adipocytes or smaller ones or more weight change or whatever, it is in relationship to the use of this drugs. So both of the sort of

uppermost level of the clinical observation and the most intense level of how this operates we sort of have to look for this -- the fact that there is kind of a double edged sword here.

Is that fair or is that not?

DR. SALTIEL: No. I think that's a very important point. And Dr. McGuire and Dr. Whitcomb will be addressing these issues in more detail.

What I can tell you is that in the list of in vivo studies that I showed earlier, these were all studies done at a about one week of exposure to the drug, during which time there was no effect at all of the drug on weight gain, adiposity, or food intake. So I think in the in vivo setting, we can differentiate the insulin sensitizing effect of the drug from any increase in fat cell number that is detectable.

There certainly are, in longer term studies with higher doses of drug, increases in fat cell number, prominently in brown fat,

though, in rodents. I think Dr. McGuire will describe this in more detail if you have any more questions.

DR. BONE: Dr. Cara had a question. Is that satisfactory, Dr. Hirsch, for the moment?

DR. HIRSCH: Well, I just wanted to add that there are also some other studies, as you know, of increase in the amount of adipose tissue and increase in appetite, et cetera, in animals under the same circumstances with a repeated -- you know, continued units of the drug.

DR. SALTIEL: Yes.

DR. BONE: Dr. Cara.

DR. CARA: Can you clarify for me whether activation of PPAR-gamma by troglitazone is dependent on the presence of insulin? I mean, I guess I am more confused now than I was before.

DR. SALTIEL: I'm sorry. I'm sorry about that. That's a very good question.

Actually, activation is not dependent on the presence of insulin. But the phenotypic changes that one sees in cells are dependent on the presence of insulin. So --

DR. CARA: How do you explain that?

DR. SALTIEL: Well, I think what thiazolidinediones do is to increase the synthesis of proteins that make cells more responsive to insulin, proteins like the glucose transporters, fatty acid synthetase, and a number of enzymes such as that. So there are more targets of insulin action.

DR. BONE: Are there other questions from other committee members?

I had a question, sort of a follow-on to the earlier questions, and maybe it has two parts. It has to do with the significance of this sequence in other respects.

One is -- one part of this question is the potential role of this sequence in tumor proliferation, oncogenesis. Has that been studied in other model systems? Are there

similar sequences -- this is probably just an ignorant question. Are there similar sequences that might be activated in any of the oncogenes that have been studied, for example?

DR. SALTIEL: You're referring to thiazolidinedione responsive sequences?

DR. BONE: PPAR -- yes.

DR. SALTIEL: Yeah. This is a very good question. I don't know of any examples in which thiazolidinedione action can result in the activation of oncogenes. And in fact, we have looked in a variety of cells and have found that troglitazone does not really potentiate the growth effects of insulin or of serum or of IGF-1.

So I think this is another example of how this is not a universal -- does not have a universal impact on insulin action. And we don't really think that there is any evidence -- again, Ted will discuss this in more detail in a few minutes. But we don't really think there is any evidence at the cellular level to

indicate that troglitazone would sensitize cells in any way to the activation of growth.

DR. BONE: Has the question I asked been explicitly investigated?

DR. SALTIEL: Well, I guess we have never identified or learned about any PPREs in oncogenes, if that is the question.

DR. BONE: Yeah. Have you looked?

DR. SALTIEL: Yes.

DR. BONE: Yeah, okay. Then the other part of that question had to do with exactly a follow-up to Dr. Hirsch's question. The implication behind much of what we have been discussing is that lowering insulin levels would be good because we are concerned about the adverse effect of hyperinsulinemia, for example, on vascular smooth muscle or other cardiovascular implications of long term insulin use.

But from what you've told us, it is conceivable that the response element you were talking about here might actually have just the

same effect as insulin. Is there any -- has that been looked at experimentally?

DR. SALTIEL: Well, again we have looked at fibroblasts and other cell lines that we know respond to thiazolidinediones, looking specifically at whether or not these drugs will by themselves or in combination with growth factors increase thymidine incorporation, for instance. And the drug has no effect at all on the growth of those cells.

So we don't really think that the growth promoting effects of insulin or IGF-1 that you would expect to see in the scenario that you describe would be at all impacted by the drug, from the in vitro data.

DR. BONE: But those are strictly in vitro studies.

DR. SALTIEL: Yes.

DR. BONE: Thank you.

DR. McGUIRE: Thanks, Al. Good morning.

The pre-clinical toxicology program

that has been conducted with troglitazone is very extensive, and it consisted of 139 different studies. And the program very effectively characterized the toxicology profile of the compound.

The main findings that I would like to address before the specific findings, troglitazone was not genotoxic. It did not induce reproductive toxicology, and it poses no significant carcinogenic risk. As Dr. Martin indicated, the issues that I'll address are indicated in your agenda. I'll discuss primarily cardiac enlargement and vascular tumors, but also fluid accumulation.

Cardiac enlargement was observed in rats and mice given high doses of troglitazone in repeated dose studies. And contrary to -- what happened here -- got going in the wrong direction, excuse me. And although there has been fluid accumulation noted with other compounds in this particular class, there was no evidence of abnormal fluid accumulation in

these studies. Troglitazone did not induce pericardial effusion, pulmonary edema, or ascites.

To provide some perspective on the cardiac enlargement, a number of factors were considered: first of all, exposures associated with cardiac enlargement in rodents in comparison with human exposure, an assessment of cardiac function, histopathologic evaluation of cardiac tissue, and species specificity.

The cardiac enlargement was observed at plasma concentrations that were significantly higher than human exposures, 14 to 47 times the AUC at the 400 milligram human dose. In a one year study in monkeys, which included serial echocardiographic evaluations, there was no cardiac enlargement and no evidence of fluid accumulation. The exposures achieved were up to six times the human levels. And in dogs, at exposures that were comparable to humans, there also was no cardiac enlargement.

With respect to an assessment of cardiac function, there were no adverse effects on performance in enlarged hearts of rats that were evaluated using an isolated profusion model. There were no effects on heart rate, left ventricular function, which included a contractility and relaxation performance. And there were no effects on coronary flow or resistance. And in both mice and rats, this cardiac enlargement was non-progressive, and it was reversible following withdrawal of drug treatment.

What I mean by non-progressive is that the majority of the enlargement occurred during the initial 26 weeks of treatment, and the weights essentially stabilized thereafter.

The histopathologic evaluation of heart tissue from mice treated up to two years and rats and monkeys treated up to one year revealed no microscopic changes associated with this cardiac enlargement.

And in terms of species specificity,

the cardiac enlargement was confined to rodents, and it was not seen in monkeys or dogs. And with respect to a potential mechanism of the species specific effect, the renin angiotensin system seems to be involved, since the administration, co-administration, of ACE inhibitor prevented the enlargement.

So, in conclusion, the cardiac enlargement was again confined to rodents. It was non-progressive and reversible. There were no effects on cardiac performance. The enlargement occurred at plasma concentrations that were significantly higher than human exposures. There were no cardiac effects in monkeys treated chronically. And the exposures that were achieved were up to six times the exposure at 400 milligram human dose, and approximately three times at the 600 milligram human dose.

Therefore, troglitazone was not cardiotoxic in the three species that we studied, mice, rats, and monkeys. And as will

be discussed by Dr. Whitcomb, there were no treatment related adverse effects in patients treated chronically.

The other issue that I'd like to address briefly is rodent carcinogenicity. The troglitazone rodent carcinogenicity studies were conducted at maximum tolerated doses, with the compound administered for essentially the entire lifespan of the animal. The experimental designs and the doses that were selected were discussed with the Food and Drug Administration prior to initiation of the studies.

In the mouse carcinogenicity study, troglitazone was administered for 104 weeks, daily by gavage to 60 animals per sex per group at dose levels of 5400 and 800 milligrams per kilogram, the 800 milligrams per kilogram being 100 times the dose at 400 milligrams in humans. There were also two control groups in this study, one receiving the vehicle and the other the formulation exipients.

The findings in the mouse carcinogenicity study included increased incidence of vascular tumors in male mice at 16 times the AUC at the 400 milligram dose, and in female mice at 18 to 23 times the human exposure. Liver tumors were also increased in females, but in females only, and only at the highest dose, an exposure of 23 times the human levels. There was no increase in tumor incidence at 14 times the AUC at the 400 milligram human dose.

To evaluate the relevance of this increased tumor incidence in mice, a number of considerations were addressed, a process that we referred to as weight of evidence analysis.

Considerations included genotoxic potential, extent of exposure in rodents in comparison with human exposures, data from rat carcinogenicity study with troglitazone, and a discussion of biological characteristics of the vascular tumors in mice in comparison with those seen in humans.

With respect to genotoxic potential, information is available from a complete battery of both in vitro and in vivo assays. And in those assays, troglitazone was not mutagenic in either salmonella or E. coli. There was an increase in chromosome aberrations in Chinese hamster lung cells, but that was only seen at cytotoxic doses.

Troglitazone was not clasogenic (phonetic) in V-79 cells. And based on some data that has recently been submitted to the NDA that unfortunately is not part of your background package, the compound has been found to be neither clasogenic nor mutagenic in most lymphoma cells. And based on all of these in vitro mammalian cell assays, troglitazone is not considered to be clasogenic in vitro.

Additional confirmation was provided by the fact that troglitazone was not clasogenic in vivo, in mouse bone marrow micronucleus assays, and did not induce unscheduled DNA synthesis in rat hepatocytes.

Therefore, based on the results of the entire battery of genetic toxicology assays, troglitazone does not pose a genotoxic risk.

The second consideration in the weight of evidence analysis is exposure. The exposures in the mouse carcinogenicity study were significantly higher than the exposures at the 400 milligram human dose represented by this yellow line here, a human AUC of 13.4 microgram hour per mil.

Multiples of the human exposure in male mice were 2 to 16 times, and in female mice 4 to 23 times. Groups where we saw increases in tumor incidence were in the high dose males and the mid and high dose females, at exposures of 16, 18, and 23 times the human level. There were no increases in tumor incidence at 2, 4, and 14 times the human level.

A third consideration in the weight of evidence analysis is data that we have from

a rat carcinogenicity study conducted with troglitazone. And based on that study, there were no increases in tumor incidence in either male or female rats at exposures up to 47 times the human exposure. And as you can see, the exposure here in rats is three times higher than the exposure in mice where we saw an increased incidence in tumors.

A final consideration is the biological characteristics of these mouse vascular tumors. The background incidence of these vascular tumors in mice is highly variable. And also, in the concurrent control groups in our mouse study, there was an unusually high incidence of vascular tumors which may have affected the increased incidence in the troglitazone groups.

An important consideration, the compound induced vascular tumors did not metastasize. This differs from humans in that the vascular tumors noted in humans are quite infrequent, and they also have a tendency to

metastasize.

So, in conclusion, the increased incidence in vascular tumors in mice was observed at exposures significantly higher than the human exposures, and the effects were clearly species specific. There was no increase in tumor incidence at 14 times the AUC at the 400-milligram human dose or nine times at the 600-milligram human dose.

And therefore, based on the entire weight of evidence analysis, troglitazone has no significant genotoxic or carcinogenic risk to humans.

If there are any questions before Dr. Whitcomb reviews the clinical findings, we'll address them here now.

DR. BONE: Dr. Sherwin has a question.

DR. SHERWIN: Yes, a couple. The cardiac effects, do you envision them as being indirect or direct, and are there PPAR-gamma receptors in the heart?

DR. McGUIRE: With respect to the cardiac enlargement that we see, we have no knowledge that that is related to the PPAR receptors. And as to whether PPAR receptors are found in the heart, I'm not sure if Al Saltiel could address that or not.

DR. SALTIEL: There are some, but they are at very low levels expressed.

DR. SHERWIN: I mean, do you think this is volume overload? Or do you have any sense of what is the etiology of -- I mean, it is possible that an ACE inhibitor could reverse some of the effects without it being directly involved in the mechanism.

DR. McGUIRE: Yeah. It seems that the alteration in fluid homeostasis may be involved to some extent. The co-administration of the ACE inhibitor of course reverted the enlargement or prevented the enlargement. But in the case where diuretics were administered concurrently, the enlargement still occurred to a certain extent.

So the actual mechanism is not well understood as to whether it is due solely to volume overload or some other component of the enlargement.

DR. SHERWIN: One other question. Is it possible that a metabolite of the drug could have some of this effect? Because I noticed in the handout that there are metabolites that are generated. Do we know if they are biologically active?

DR. McGUIRE: The actual M3, which is the quinone, is active. And the quinone is at similar concentrations to the actual parent compound. The metabolites are very similar in all of the species that we studied. And the fact that we are not getting cardiac enlargement in non-rodent species would not suggest that one of the metabolites might be involved.

DR. BONE: Other questions? Let's see, Dr. Cara and then Dr. Hirsch.

DR. CARA: I don't know if you feel

comfortable addressing these questions or not. But I am specifically concerned about the pharmacokinetic and pharmacodynamic data concerning troglitazone.

DR. McGUIRE: We have Dr. Koup here from our pharmacokinetics and drug metabolism group who might be able to address those questions more directly.

DR. BONE: Did you plan to make any presentation about that information?

DR. McGUIRE: Not this morning.

DR. BONE: Did you have something planned for this afternoon on that specific topic?

DR. McGUIRE: Not on that specific topic, no.

DR. BONE: Why don't we plan to add a little discussion at that point? Would that suit you, Dr. Cara?

DR. CARA: Well, it might be related to the --

DR. BONE: Oh, go ahead. Why don't

you ask the question now?

DR. CARA: -- some of the clinical studies because --

DR. BONE: I see.

DR. CARA: My concern, and please correct me if I am wrong, is that my understanding is that there isn't a very good dose response relationship between troglitazone dose and observed response in terms of glucose values and other clinical indicators.

How do you explain that? And my concern is that it raises issues regarding not only those related to selection of appropriate dosing, but also regarding some of the data that you have presented in terms of whether or not we are really looking at appropriate dosages.

DR. McGUIRE: The dosages that I showed you are extraordinary doses in comparison to the human doses, ours up to 800 and 1200 milligrams per kilogram. So those are significantly higher doses. Now, in looking at

the exposure in comparison to humans based upon AUC values, the monkey is up to around six, the mouse is up to around 20, and the rat can get up to as much as 47 times the human plasma concentration.

DR. BONE: Perhaps the way to handle that, if sponsor is agreeable, is for the discussion of the rationale for the dose I think would be an appropriate part of the clinical presentation that is upcoming, and that can just be incorporated without necessarily going into all of the pharmacokinetic studies, if that wasn't planned.

But I'm sure we'll have questions about that. I'm not sure that is really appropriate to ask about when we are talking about the toxicology.

Dr. Hirsch had a question about tox.

DR. HIRSCH: I just wanted to perhaps highlight if I could two things that were mentioned in the report about histologic

findings that you might want to comment on. One was that the rather odd enlargement of atrial cells specifically in the heart, I wonder whether this was related possibly to atrial natriuretic factor or other issues that could be studied in terms of the --

DR. McGUIRE: Those are interesting possibilities for additional work, but have not been studied yet.

DR. HIRSCH: The second item was of course my perpetual interest in adipose tissue. And I noticed that there were changes noted in the brown fat.

DR. McGUIRE: Yes.

DR. HIRSCH: It seems, though, and it leads -- I'm sorry, if the brown fat changes were in fact of significance physiologically, they would act in the direction of removing brown fat as being active because apparently the fatty droplets were coalescing, indicating --

DR. McGUIRE: That's right, yes.

DR. HIRSCH: -- reduction in brown fat activity, presumably induced by the drug.

DR. McGUIRE: Yeah. What we observed, and it was observed first in rats, although we did see the effect also later in mice, was that as these long term studies progressed there was significant accumulation of the brown fat, hypertrophy and hyperplasia of the brown fat, to the extent that you could actually palpate the interscapular brown fat pad in the rat.

These animals survived very well for two years with no apparent effect associated with that finding.

DR. HIRSCH: I'm sorry. So there was an increase in the amount of brown fat with it.

DR. McGUIRE: Exactly, exactly.

DR. HIRSCH: I thought the histologic findings were in the direction of showing if not atrophy at least an enlargement of the fat droplets and coalescence, making the brown fat turn into white fat, as it were.

DR. McGUIRE: Histologically, with the transition from this multilocular to unilocular occurrence, there actually is -- it actually histologically does tend to look more like white fat. But based upon some immunocytochemistry that we did, this remains brown fat.

DR. BONE: Were any functional studies done on that tissue?

DR. McGUIRE: No functional studies, no.

DR. BONE: Okay. Did other committee members have questions? Dr. Illingworth has a question.

DR. ILLINGWORTH: In the background information, there is mention of hepatic carcinomas in mice.

DR. McGUIRE: That's right.

DR. ILLINGWORTH: Do you assume that this is analogous to the PPAR-alpha situation that is unique to rodents?

DR. McGUIRE: No. We assume that

that's related perhaps to minimal microsomal induction. And this phenomena has been seen with other microsomal inducers over long term studies in mice that eventually form liver tumors. The fact that this occurred only in one dose, one sex -- it was the very highest exposure of 23 times the human levels. We don't consider this to be clinically significant.

And the reference to PPAR and perhaps an effect on liver tumors, we looked at peroxone proliferation in our rat studies, and this compound is definitely not a peroxone proliferator as the term is generally used.

DR. BONE: I think Dr. Fleming had a comment or a question.

DR. FLEMING: Yes. Dr. McGuire, if you could provide a clarification. You are quite correct in stating that the standard chronic toxicity studies did not show any evidence of fluid accumulation, nor were there any histologic changes seen in the heart in

those studies.

However, in the carcinogenicity studies themselves, there were such observations. And I wonder if you could just comment about the significance of those.

DR. McGUIRE: Yes. What we saw in the rat study, the carcinogenicity study which was the two year duration evaluating tumor induction, what we saw late in that study was an increase in mortality. And with that mortality, there also were animals that had fluid accumulation. And the fluid accumulation was largely confined to the thoracic cavity. And that fluid accumulation we associated with the late stage and moribund state of the animal, as the fact that it is occurring very late and the fact that it is associated with an animal that actually dies during the study.

When we looked at animals that survived to termination, there was no indication of any fluid accumulation in those animals.

DR. FLEMING: And the histological changes in the myocardium?

DR. McGUIRE: There is a background incidence in these Wistar rats of myocardial lesion that has ventricular dilatation, atrial thrombosis, and myocardial fibrosis. And in those animals that died, in the rat carcinogenicity study, there was an increased incidence of this background spontaneous lesion.

But the lesion itself, the histopathologic lesion in that case was very, very similar between the one that we ordinarily see in control animals and the ones that were seen in the troglitazone treated animals.

DR. FLEMING: But at least there was a difference between the control group and the high dose group in which it was in.

DR. McGUIRE: Yes, there was.

DR. BONE: Just to pursue this a little further, because I sense there are a number of people that aren't completely --

don't completely feel they understand this yet, the hearts are larger, but they appear to be histologically normal, and there was no evidence of fluid. Or was there ventricular dilatation or was there hypertrophy?

It seems to me that there had to be one or the other to be bigger.

DR. McGUIRE: It is very difficult to see that picture histopathologically. You did see the ventricular dilatation as you got out into the long term studies in these animals. But these hearts of these animals up to one year treatment -- and in fact, mice up to two years and monkeys up to one year histologically look completely normal.

DR. BONE: But the weights were increased? When you say --

DR. McGUIRE: The weights were increased in the rodents only, not in the monkey.

DR. BONE: Yeah, okay. But you couldn't see anything to explain this

histologically, but you in effect you had -- you must have had hypertrophy to have increased weight.

DR. McGUIRE: There is a component of hypertrophy that occurs probably under chronic treatment. In some of our earlier studies, there may have been an increase in heart weight acutely for no reason that we can identify. The actual cardiac enlargement occurs very, very quickly, within five, seven days of treatment in these animals.

DR. BONE: Oh, really? Just to pursue this question about the renin angiotensin axis, did you see any changes in the juxtaglomerular apparatus or other changes to --

DR. McGUIRE: No, we did not.

DR. BONE: And you mention in the report hepatocellular hypertrophy, but you didn't mention it in your presentation. Would you care to comment about that?

DR. McGUIRE: The hepatocellular

hypertrophy to us is not a manifestation of toxicity. What that is is a microsomal induction that occurs with the administration of the compound. And there is no associated histopathology with that hypertrophy.

DR. BONE: Thank you. Dr. Cara had another question.

DR. CARA: Can you tell me if that hypertrophy was dose dependent?

DR. McGUIRE: In the liver?

DR. CARA: In the heart.

DR. McGUIRE: The cardiac enlargement is dose-proportional, yes.

DR. BONE: Are there further questions from the committee concerning Dr. McGuire's presentation? If not, I guess we can proceed.

Thank you, Dr. McGuire.

DR. McGUIRE: Okay. Dr. Randy Whitcomb will now review the safety and efficacy of the compound.

DR. WHITCOMB: Good morning.

As I go through the clinical data here, I will try to draw some correlations between some of the animal information that we have just looked at to perhaps give a slightly different perspective on the information, and perhaps clarify some of the points that have been raised.

The review that I am going to do for you this morning is going to involve looking at efficacy, issues around dose recommendation, questions about weight changes, and then review the safety database as it was submitted within the NDA.

(Slide)

I apologize for this first slide. Anybody that is not sitting beyond about the first row can't see this. But this is just an overview of the program that was included in the NDA. And I will be going in more detail later when I review the safety data as to this overall situation.

As Dr. Martin mentioned, this has

been a tripartite relationship between Parke Davis, Sankyo, and Glaxo-Wellcome. And basically, what we have are 28 studies in the United States that are included in the NDA. Sixteen of those are clin/pharm, 12 clinical studies divided amongst a number of different populations of patients. And again, I'll be going back to this in more detail in a few minutes.

From the Glaxo data, there are 19 studies with approximately 1,000 participants. That's three clinical studies with 629 patients in it. And from Sankyo in Japan, there are 27 studies. A total of 15 of these are clinical, with a few over 1,000 patients. And again, I will go back in more detail in just a few minutes.

I want to come back and focus for the next few minutes on the efficacy data, the primary endpoints from the two pivotal studies which were submitted in support of the application.

We conducted two trials. The first which I will review is 991-40. It was a six month placebo controlled study which included doses at 200 and 600 milligrams of Rezulin. The primary endpoint of this study was HbA1c. This study was conducted by Sankyo US under our IND.

The second complementary study was 991-068. Again this was a six month placebo controlled study. And 200 and 400 milligrams of Rezulin were included in this trial. The primary endpoint was a combined endpoint, which included insulin dose reduction and very importantly, glycemic control. And as I'll go through this in more detail in a few minutes for patients to have been reaching target in this study, they had to have both things.

And one of the points I want to emphasize this morning, because it has been raised earlier, is that in our opinion Rezulin is not a drug that just has people taking less insulin. This is a drug which improves