DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS

ADVISORY COMMITTEE

VOLUME II

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8:00 a.m.

Holiday Inn Silver Spring
Kennedy Room
8777 Georgia Avenue
Silver Spring, Maryland

PARTICIPANTS

Nelson G. M.D., Chair
LCDR Cathy Groupe, RN, BSN, Executive Secretary

MEMBERS:

Sonia Caprio, M.D.
Dean Follmann, Ph.D.
Steven W. Ryder, M.D., Industry Representative
(non-voting)
Paul D. Woolf, M.D.

CONSULTANTS (VOTING):

Kenneth D. Burman, M.D.
Susan Dianne Lellock, Patient Representative
Lynne L. Levitsky, M.D.
Thomas T. Aoki, M.D.
Susanna L. Cunningham, Consumer Representative

FDA STAFF:

Robert J. Meyer, M.D.
David Orloff, M.D.
Julie Golden, M.D.
Jeri El Hage, Ph.D.

C O N T E N T S

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. WATTS: I would like to call the meeting to order. We will start with announcements from the Executive Secretary, Cathy Groupe.

Conflict of Interest Statement

LCDR GROUPE: The following announcement addresses the issue of conflict of interest and is made part of the record to preclude even the appearance of such at this meeting. Based on the submitted agenda 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 present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance with 18 U.S.C. Section 208(b)(3), full waivers have been granted to the following participants:

Dr. Nelson Watts for consulting on unrelated mattes for a competitor, and for being on

the sponsor's advisory board on unrelated matters, for which he receives less than $10,001 per year, per firm.

Dr. Thomas Aoki for consulting on unrelated matters for a competitor, and for being on speakers' bureaus on unrelated matters for two competitors, for which he receives less than $10,001 per year, per firm.

Dr. Paul Woolf for consulting on unrelated matters for a competitor, for which he receives less than #10,001 per year.

A copy of the wavier statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

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.

We would also like to note that Dr. Steven

Ryder has been invited to participate as a non-voting industry representative, acting on behalf of regulated industry. Dr. Ryder is employed by Pfizer.

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. Thank you.

Introductions

DR. WATTS: I would like to have the committee introduce themselves. I will start. I am Nelson Watts. I am an endocrinologist at the University of Cincinnati. We will move down to Dr. Ryder and go around.

DR. RYDER: Steven Ryder. I am in Pfizer global R&D and I am the non-voting industry representative.

DR. FOLLMANN: I am Dean Follmann, head of biostatistics at NIAID.

DR. WOOLF: Paul Woolf. I am an endocrinologist at Crozer Chester Medical Center.

DR. CAPRIO: Sonia Caprio. pediatric endocrinology, Yale.

MS. LELLOCK: Dianne Lellock, patient representative.

DR. CUNNINGHAM: Susanna Cunningham. I am a professor at the University of Washington School of Nursing, in Seattle and I am here as the consumer representative.

DR. AOKI: Tom Aoki. I am a professor at the University of California at Davis in Sacramento, California.

DR. BURMAN: Ken Burman. I am head of endocrinology at the Washington Hospital Center and a professor at Georgetown.

LCDR: Cathy Groupe, FDA Advisors and Consultants Staff and executive secretary to the committee.

DR. LEVITSKY: Lynne Levitsky. I am a pediatric endocrinologist at Mass General Hospital, in Boston.

DR. EL HAGE: I am Jeri El Hage. I am the pharmacology supervisor in Metabolic and Endocrine

Drugs and will give the preclinical presentation this morning.

DR. GOLDEN: Julie Golden, medical officer in Metabolic and Endocrine Drugs.

DR. ORLOFF: David Orloff, director of Metabolic and Endocrine Drugs.

DR. MEYER: Bob Meyer. I am the director of the Office of Drug Evaluation II.

DR. WATTS: Thank you. We will start with an introduction from Dr. Orloff.

Welcome

DR. ORLOFF: Thank you, Dr. Watts. Let me first welcome Dr. Watts as the official chair of the Metabolic and Endocrine Drugs Advisory Committee to this first meeting as chair. Let me thank the members, the consultants and the FDA participants for being present. We look forward to discussion today.

Let me begin with some background. Muraglitazar is a dual, that is gamma, alpha, non-thiazolidinedione, PPAR agonist proposed for treatment of type 2 diabetes mellitus. It shares

pharmacologic mechanisms with two approved PPAR gamma agonists, rosiglitazone and pioglitazone, and with the fibric acid derivatives, including gemfibrozil and fenofibrate. As such, by design and as demonstrated in clinical studies, it has apparent salutary effects on both glucose and lipid metabolism.

The pharmacology and preclinical, animal, toxicology of muraglitazar and of a large number of gamma and dual PPAR agonists also under development continue under extensive review by Dr. El Hage and by her staff. Dr. El Hage will discuss selected relevant preclinical toxicologic findings with muraglitazar in the context of the overall findings with the class of PPAR agonists.

Additionally, the rodent carcinogenicity of this heterogeneous class of drugs is the subject of obvious intensive study by pharmaceutical sponsors and by the FDA. Dr. El Hage will also present an overview of the state of knowledge in that regard, obviously with specific reference to the findings with muraglitazar.

The clinical safety and efficacy of rosiglitazone and pioglitazone have been extensively evaluated both pre- and post-approval. Most notable from a clinical safety standpoint is that both drugs are associated with dose-related fluid retention, believed to be a form of so-called refeeding edema due to enhanced insulin action, and perhaps significantly compounded by direct PPAR gamma effects to increase sodium reabsorption in the distal renal tubule.

It is furthermore apparent that there is a spectrum of susceptibility to the fluid retaining effects of PPAR gamma agonists. Data from the muraglitazar trials show that this drug shares these presumed PPAR gamma-mediated clinical effects.

Finally, although a subject of great clinical interest and ongoing investigation, the effects of PPAR gamma agonists on modifying cardiovascular risk in patients with type 2 diabetes have not been established. The cardiovascular disease risk modifying effects of

certain fibric acid derivative PPAR alpha agonists, on the other hand, have been demonstrated in patients with mixed dyslipidemia or, more precisely, the low HDL atherogenic triglyceride-rich lipoprotein profile associated with type 2 diabetes and metabolic syndrome. The anti-atherosclerotic effects of muraglitazar have not yet been studied.

Let me offer an extremely brief overview of the Pargluva program. Extensive clinical investigations have characterized the effects of Pargluva in the control of glycemia in patients with type 2 diabetes as monotherapy, as well as in combination with metformin or sulfonylurea. The mean absolute, that is to say not placebo-subtracted, hemoglobin A1c reductions with the proposed doses of 2.5 mg and 5 mg of muraglitazar daily ranged from 0.9 to 1.2 percentage units across the trials.

Additionally, at these doses muraglitazar was associated with consistent average reductions in triglycerides, apoB, and non-HDL cholesterol,

and with mean increases in HDL cholesterol across the submitted trials.

The clinical safety of muraglitazar has, likewise, been addressed in the large Phase 2 and 3 clinical program. The study population appears to be representative of the general population with type 2 diabetes in whom the drug is apt to be used, with regard to duration and severity of the disease, and it clearly included patients at very high risk for cardiovascular events, as is evident from the review of the narrative histories of some of the patients who experienced cardiovascular disease events on treatment.

What are the central issues for discussion today? The glucose lowering effects of the proposed 2.5 mg and 5 mg daily muraglitazar doses are clear, and the FDA defers to the sponsor on the presentation of the clinical efficacy data with Pargluva. That said, as you will have noted in your backgrounders, he clinical and statistical reviews of efficacy raise the issue that the 1.5 mg dose of muraglitazar, not proposed for marketing in

the U.S., also appears effective. The sponsor will address this issue and the committee will be asked to comment on it.

Dr. Golden's presentation will focus entirely on the safety data from the muraglitazar clinical trials. As she will detail further, muraglitazar, like other PPAR gamma agonists as I said a moment ago, was found to cause fluid accumulation and, as such, to precipitate congestive heart failure in susceptible individuals. This is particularly evident with the high doses, 10 mg and 20 mg daily, studied but not proposed for marketing. In addition, though, the 5 mg dose, which appeared marginally more potent for glucose lowering than 30 mg of pioglitazone in head-to-head comparisons, not surprisingly, was also associated with higher rates of fluid-related adverse events.

Additionally, an imbalance in the incidences of cardiovascular death and of serious cardiovascular adverse events, other than congestive heart failure, relative to placebo and

pioglitazone has arisen in the muraglitazar clinical trial experience. These differences are based on very small numbers of events in individual studies and on small numbers overall. The cardiovascular death and serious cardiovascular adverse event imbalances are primarily driven by the outcomes in two of the many trials conducted, that is to say one trial drives the death imbalance and the other trial drives the non-congestive heart failure cardiovascular adverse events imbalance. These two trials were in patients not adequately controlled on metformin or sulfonylurea therapy, respectively, representing groups at higher risk for cardiovascular disease. The extent to which the known and expected effect of this potent PPAR gamma agonist to cause fluid retention might have contributed to the overall observed imbalance must be explore.

Furthermore, in seeking to explain the imbalance, the possibility of some other, unanticipated pharmacologic effect of muraglitazar must be considered. In that regard, the

pharmacology of the drug and the preclinical findings with muraglitazar suggest neither arrhythmogenic nor thrombotic effects, nor a direct cardiac or vascular toxic potential in human.

A careful review of the cases of cardiovascular death and serious cardiovascular adverse events in order to inform discussion and conclusions about likely causation by muraglitazar has been undertaken by Dr. Golden, and she will highlight several of these in her presentation, as I am sure will the sponsor. Here, it is important to emphasize that complicating any case-by-case evaluation of possible causation by drug or, for that matter, comparator, even when we are at the patient's bedside, much less when we are behind a desk, is the fact that cardiovascular, particularly atherosclerotic, events are common in patients with type 2 diabetes. Indeed, vascular disease is assumed to be universal and aggressive in these patients, and in many of the cases clinical and/or pathologic evidence of severe atherosclerosis was documented.

For these and many other reasons, establishing a role of the specific treatment in individual instances of cardiovascular adverse events or death is exceedingly difficult, if not impossible. It must be conceded, however, that so too is eliminating the study drug, case by case, as a potential contributor to the events. We look forward to the discussion of these issues and, more importantly, of the overall findings regarding the efficacy and safety of the trials. Again, I thank everybody in advance and I am going to turn it back over to Dr. Watts.

DR. WATTS: Thank you, Dr. Orloff. We are now ready for the company's presentation and that will be introduced by Dr. Brian Daniels.

Bristol-Myers Squibb Presentation

Introduction

DR. DANIELS: Thank you, Dr. Watts. Members of the committee, good morning. I am Brian Daniel, the senior vice president of global development at Bristol-Myers Squibb. It is a privilege to be with you today and discuss the data

on muraglitazar for the treatment of type 2 diabetes.

Currently, type 2 diabetes affects about 18 million people in the United States. Due to the aging of the U.S. population and the increase in risk factors such as obesity, the incidence of the disease is growing at an alarming rate. Multiple therapeutic regimens are available, including diet and exercise, but the unmet medical need remains high. Only one-third of patients achieve the ADA glycemic goal and less than 1/10 achieve the combined ADA glycemic and lipid goals. This epidemic is taking its toll on our patients in the form of microvascular damage, including blindness and kidney disease, as well as macrovascular damage leading to amputations, cardiovascular events, strokes and death.

Muraglitazar was discovered and developed to address this unmet need. Muraglitazar offers a new choice in diabetes care where presently only two insulin sensitizers are available. It was designed to be both a potent insulin sensitizer and

to address dyslipidemia that is present in patients with type 2 diabetes. We have extensively studied muraglitazar over the last six years. Several aspects of the program, which you will hear about today, are notable.

We engaged in an intensive preclinical investigative toxicology program on the relevance of the rodent carcinogenicity findings to humans. The clinical efficacy and safety was evaluated in a large population of patients with multiple co-morbidities. An active comparator was utilized in one of the Phase 3 clinical trials and a large database was accumulated with exposures of up to two and half years in patients with type 2 diabetes.

From this research we have concluded that muraglitazar has a favorable benefit/risk profile and represents and important therapeutic option for patients with type 2 diabetes and their physicians.

However, we are entering a new era in pharmaceutical development and in drug evaluation. We need to recognize explicitly that with all new

medications assessment of benefit/risk at time of approval can only be an estimate. Therefore, our company is committed to ongoing efforts to continuously define the therapeutic benefits and the potential human risks with muraglitazar. To accomplish this we have submitted to the FDA an pharmacovigilance plan, including a pharmacoepidemiology study, to allow for the continuous benefit/risk assessment once muraglitazar is available.

In addition to these research efforts, we will take steps within the marketplace to assure appropriate use of muraglitazar. In our promotional and educational activities with muraglitazar Bristol-Myers Squibb will address the expected risks of heart failure. We will also educate physicians on the need to closely evaluate their patients and to take appropriate actions as they are needed. We will actively support independent educational programs that will address heart failure in diabetes. Finally, as with all new medications, Bristol-Myers Squibb will not

conduct direct-to-consumer advertising for at least one year. This will allow our physicians to be educated on using muraglitazar correctly and to ensure that these educational efforts are effective.

This is the order of today presentation. Let me begin with Dr. David Kendall. Dr. Kendall is an endocrinologist and chief of the International Diabetes Center, and an associate professor at the University of Minnesota. He will provide us with an overview of the disease burden in type 2 diabetes. Dr. Kendall?

Meeting the Needs for Type 2 DM

DR. KENDALL: Thank you, Brian. Dr. Watts and members of the committee, for any involved in the clinical care of patients with diabetes it is clear that providing optimal care for these individuals remains a significant clinical challenge, and that the unmet medical needs for such patients are substantial.

Reaching or achieving intensive blood glucose targets in patients with diabetes is

clearly a central component of this care. But in addition to targeting hypoglycemia in these individuals, they are commonly affected by a characteristic dyslipidemia, characterized by elevated triglycerides, low concentrations of HDL cholesterol and an increased prevalence of small dense LDL particles. In addition, patients with diabetes are commonly affected by hypertension, and all of these components require our clinical attention. Achieving sustained control of each of these parameters requires vigilance by both patients and their providers as the effectiveness of many current therapeutic regimens may wane over time.

Single agent therapy for type 2 diabetes does not reliably maintain glucose control in many patients and, as such, combination therapy and/or the use of insulin treatment is often required. This need for multi-drug therapies for glucose control, coupled with the need to address other important metabolic abnormalities, often affects patient compliance.

The data that shaped our current recommendations for glycemic targets in diabetes are derived from the landmark DCCT and UKPDS. With the completion of these trials, the unequivocal benefit of intensive glycemic control was established. Targeting lower blood glucose values is known to significantly reduce the risk of the characteristic microvascular complications in both type 1 and type 2 diabetes. These results support the need to pursue even tighter glucose control, justifying the trust that early advocates of intensive glucose control had placed in population epidemiologic data for diabetes.

The role of intensive glucose control for the management of cardiovascular risk remains an active area of investigation. However, it is well known that individuals with type 2 diabetes in particular are at significantly elevated risk for cardiovascular disease and diabetes is now considered a cardiovascular disease equivalent.

But just as for microvascular complications in the past, we currently rely on

epidemiologic data to best define the risks of CVD in those with poor glucose control. We currently apply these data as an article of faith to support the potential benefit of aggressive glucose lowering in those at risk for cardiovascular disease. While there is clear and convincing evidence to support the lowering of LDL cholesterol, lowering of blood pressure to limit cardiovascular risk in diabetes, the impact of improving glycemic control, managing other components of the lipid disorder in diabetes, such as HDL cholesterol and triglycerides, and the management of insulin resistance is currently supported mainly through epidemiologic data.

It is well-known though that added risks for fatal and non-fatal coronary heart disease events, as well as stroke and risk for peripheral arterial disease, are increased in patients with type 2 diabetes. This increase in risk ranges from 13 percent up to 28 percent for each one percent increase in hemoglobin A1c. Similarly, any decrement in HDL cholesterol of 3.9 mg/dL or 0.1

millimolar is associated with a 15 percent increase in cardiovascular risk. Finally, a 1 millimolar, or 88 mg/dL, increase in triglycerides is associated with a between 14-37 percent increase in the risk of a cardiovascular event.

Given the increase in cardiovascular risk in patients with diabetes, current treatment guidelines set forth by the American Diabetes Association focus not just on A1c but also on other key cardiovascular risk factors.

Shown here are the current treatment targets set forth, well-known to most in this audience. A1c targets of less than seven percent; LDL targets of less than 100 mg/dL; as well as triglyceride targets under 150; similarly, targeting HDL cholesterol values in excess of 40 mg/dL for men and 50 mg/dL for women, as well as targeting lower blood pressure values, systolic blood pressure less than 130.

Despite the fact that these goals are generally well-known, effective control of these myriad risk factors remains elusive, with a

significant fraction of diabetes patients not achieving adequate control.

Recent data derived from the NHANES database has shown that the percentage of patients achieving an A1c of less than seven percent is approximately one-third, and this number has declined over the past decade. In addition to these discouraging results, these data also show that only one-third of patients achieve diabetes targets for any of the lipid parameters listed. If one looks at the sum total of each of these risk factors, we see that only two percent of patients receive optimal care or are treated to target for all four components. Without question, new therapies and new approaches to treatment must be sought if we are to improve the clinical care of patients with diabetes.

The activators of two nuclear hormone receptors, the so-called peroxisome proliferator activated receptors, or PPARs, have distinct and now well characterized effects on energy metabolism. Pharmacologic PPAR activators have

been developed to address both the management of type 2 diabetes and the treatment of dyslipidemia. Activation of PPAR gamma receptors, expressed primarily in fat cells, leads to a decrease in circulating free fatty acids and improvement in insulin sensitivity and glucose uptake with a resultant decrease in plasma glucose, this improvement in glucose control occurring in those with diabetes and pre-diabetes.

Activation of PPAR alpha receptors are those expressed predominantly in liver and muscle and leads to an increase in free fatty acid oxidation, a decrease in apo CIII production and an increase in apo A1 concentrations. The effect of PPAR alpha agonists is primarily to reduce plasma triglycerides and increase levels of LDL cholesterol. In addition, these compounds increase the generation of more buoyant LDL particles.

The activation of PPAR alpha and gamma may provide benefits related not just to diabetes but also to atherosclerosis and cardiovascular diseases through complex mechanisms that we are just now

beginning to understand.

With this, I would like to introduce Dr. Fred Fiedorek, from Bristol-Myers Squibb to provide an overview of the muraglitazar development program. Thank you.

Muraglitazar Overview

DR. FIEDOREK: Thank you, David. I am Fred Fiedorek, vice president of global clinical research at Bristol-Myers Squibb. As an endocrinologist who has cared for patients with diabetes while on the faculty at the University of North Carolina Chapel Hill, it is, indeed, a privilege for me to be a part of today's presentation.

David highlighted the continuing needs of patients with type 2 diabetes. Muraglitazar was developed to address these needs. Muraglitazar was conceived actually to be a potent activator of PPAR gamma, the target of thiazolidinediones, rosiglitazone and pioglitazone, as well as being an activator of PPAR alpha, the target of fibrate drugs. The chemistry and pharmacology design

objective was to combine these PPAR activities, addressing insulin resistance and glycemic needs through PPAR gamma activation, and addressing HDL cholesterol and triglyceride needs through PPAR alpha activation. Muraglitazar was designed to achieve these results in a single molecule that also promises to provide favorable impact on the atherosclerotic and inflammatory processes that damage the vasculature in type 2 diabetes over time.

Clinical pharmacology studies provided evidence that muraglitazar possesses the basic properties of a useful medicine, with favorable pharmacokinetic and drug metabolism features allowing once daily dosing and yielding high bioavailability in patients. There were also no clinically important pharmacokinetic interactions by age, gender or race. Hepatic elimination of muraglitazar is into the bile by multiple P450 metabolic pathways. Finally, there are no clinically significant drug-drug interactions and, specifically, no interactions with medications

commonly used by type 2 diabetes patients.

With these properties established, a comprehensive development program was designed and undertaken based on the known benefits and risks of the two available PPAR gamma agonists and the two fibrates currently used by doctors and patients.

Non-clinical safety has been evaluated with a thorough toxicology program, as well as extensive rodent carcinogenicity studies. This includes special mechanistic studies of bladder tumorigenesis, the finding of greatest theoretical concern. These data do not indicate that muraglitazar will pose a carcinogenic risk to humans.

On the clinical side, a robust program of almost 4,000 patients evaluated benefits and risks in type 2 diabetes. A key feature of this clinical program was a large dose-ranging Phase 2 study that helped us define the two doses we took forward into Phase 3. We have now generated extensive clinical data on the efficacy and safety of muraglitazar for these proposed doses and even higher.

The clinical data will show that muraglitazar offers substantial and consistent efficacy for both glycemic and lipid parameters in type 2 diabetes. In addition, the safety of muraglitazar is consistent with its underlying PPAR gamma activity with predictable and manageable dose-related events.

We are seeking the following indication: Muraglitazar should be indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus. It should be indicated for use as monotherapy and also for use as combination with metformin and sulfonylureas. Beyond glycemic control, muraglitazar's efficacy in diabetic dyslipidemia should also be considered as a benefit of treatment.

Our presentation of the muraglitazar development program will not begin with Dr. Mark Dominick. Mark has been responsible for the preclinical safety program and will present its key findings and conclusions. Mark?

Non-Clinical Safety

DR. DOMINICK: Thank you, Fred, and good morning. The non-clinical safety of muraglitazar was evaluated in a comprehensive program of routine toxicity and investigative mechanistic studies. The program included studies to determine the single and repeat dose toxicity; genotoxicity; reproductive toxicity; adverse pharmacologic activity; and carcinogenic potential of muraglitazar in animals. In general, very high systemic drug exposures were achieved in these studies to muraglitazar's excellent oral tolerability. Of note, the chronic toxicity studies were conducted in rats and monkeys because these species are believed to more accurately predict potential PPAR-mediated adverse effects in humans compared to dogs which are uniquely sensitive to PPAR agonists.

In repeat dose toxicity studies the majority of effects in rats and monkeys were pharmacologically mediated and similar to those observed with the marketed PPAR gamma agonists.

Importantly, muraglitazar was not hepatotoxic, myotoxic, nephrotoxic or cardiotoxic, and was not teratogenic or genotoxic at doses and exposures markedly higher than those observed clinically. Moreover, it displayed no significant in vitro off-target receptor or ion challenge activity. In lifetime studies in rodents muraglitazar was associated with some positive tumor findings. This was not unexpected since the marketed PPAR alpha and PPAR gamma agonists all are positive in rodent tumor studies.

Because of the regulatory concern of the cardiovascular safety and carcinogenic potential of these agents, the presentation of non-clinical safety for muraglitazar will overview results of cardiovascular safety, carcinogenicity and relevant mechanistic studies. The non-clinical cardiovascular safety of muraglitazar was evaluated in a standard battery of safety pharmacology and routine safety studies. In the investigator hERG and Purkinje assays muraglitazar demonstrated no potential for repolarization disturbances at

exposures approximating 2,200 times the human plasma free drug concentration at 5 mg.

In addition, there was no evidence of QTc prolongation in telemeterized dogs after a single intravenous dose at exposures equivalent to 120 times the human Cmax, or in monkeys after chronic dosing at exposures up to 68 times the human AUC.

QT prolongation was seen in dogs, but only at overtly toxic doses and clinically non-relevant exposures. Additionally, there were no heart rate changes and only minimal reductions in blood pressure in dogs and monkeys at similarly high multiples of the clinical exposure.

The non-clinical cardiovascular safety assessment also included evaluations of measures of cardiac morphology and contractility. Specific findings included increased heart weights in both rats and monkeys at clinically non-relevant exposures, with correlative microscopic evidence of cardiac hypertrophy in rats at exposures in excess of 300 times the human exposure at 5 mg.

Importantly, heart rates were unaffected

in rats and monkeys at 8 and 17 times respectively human exposure at a 5 mg dose. In monkeys treated for up to one year, there were no echocardiographic changes at up to 14 times human exposure, and no evidence of a negative inotropic effect at up to 44 times human exposure. The only muraglitazar-related echocardiographic finding was slight ventricular wall thickening during both systole and diastole in female monkeys at clinically non-relevant exposures. Lastly, there was no evidence of drug-induced congestive heart failure in non-clinical studies, with the exception of an increased incidence of degenerative cardiomyopathy in male mice treated for up to two years at exposures 141 times the human exposure at 5 mg. Thus, muraglitazar displayed a benign cardiovascular safety profile in non-clinical studies.

The carcinogenicity assessment included two lifetime or two-year studies in mice and one in rats. In mice carcinogenicity findings were limited to a low incidence of gallbladder adenoma

in males at doses at 20 mg/kg and 40 mg/kg. Exposures at these doses were approximately 62 and 141 times the human exposure at 5 mg, whereas exposure at the highest non-tumorigenic dose was 17 times that seen in humans at a 5 mg dose.

In rats the incidences of subcutaneous liposarcoma in males and subcutaneous lipoma in females were increased at a dose of 50 mg/kg where exposures were 48-59 times that seen in humans at 5 mg. Importantly, exposure at the highest non-tumorigenic dose for this effect was at least 37 times than that seen at a 5 mg dose.

The incidence of transition cell carcinoma and combined transition cell papilloma and carcinoma of the urinary bladder were increased in male rats at exposures 8-48 times higher than those seen at a 5 mg dose. At the non-tumorigenic dose for this effect exposure was essentially equivalent to that seen at a 5 mg dose. At the two highest doses tested in male rats, increased amounts of urinary calcium and magnesium containing solids were detected at week nine of the carcinogenicity

study, providing preliminary evidence for urolithiasis as a potential mode of urinary bladder tumor development.

Because of the urinary bladder tumorigenic response in male rats occurred at relatively low exposures, the mode of tumor development was fully investigated. Results of our investigative studies supported an indirect mode of tumor bladder development involving pharmacologically-mediated changes in urine composition that predisposed to urolithiasis.

Specifically, at a tumorigenic dose of 50 mg/kg those changes included maintenance of urine pH at or above 6.5 throughout the day in rats given that dose level. This would facilitate in rats formation of calcium- and magnesium-containing solids. Secondly, there were reductions in urine citrate levels and output which resulted in increased urinary saturation and crystallization of calcium and magnesium salts. Lastly, there was an increase in urinary oxalate, a potential counter-ion for calcium salt formation.

The combination of these pharmacologically-mediated prolifogenic changes, with the predisposition of male rats, to crystalluria resulted in moderate to marked increases in urinary calcium- and magnesium-containing solids. As a consequence of this urolithiasis, there was evidence of focal necrosis and degenerative hyperplasia of the urinary bladder mucosa but primarily in dependent ventral regions of the bladder by three months of treatment. Moreover, the urothelial proliferative changes progressed to transitional cell carcinomas within nine months. Importantly, urinary sedimentations to pH's of less than 6.5 prevented the development of urinary bladder changes by preventing the formation of these urinary solids in the presence of the prolifogenic changes in the urine. This outcome provided strong support for an etiology involving drug-induced composition changes in urine rather than direct drug-related cytotoxicity.

In this table the overall incidence of

urinary bladder proliferative changes through 15 months of dosing at 50 mg/kg is highlighted in blue. Thirty-four of 75 and 22/75 male rats fed a normal diet and given a tumorigenic dose of 50 mg/kg developed urinary bladder hyperplasias and/or tumors respectively. In contrast, none of the 63 rats given the same dose and fed an acidified diet developed either transitional cell hyperplasias or tumors, providing definitive evidence for urolithiasis as a mode of urinary bladder tumor development.

The transitional cell carcinoma diagnosed in one low dose male rat was not clearly drug related since a higher incidence of this same tumor, specifically 5/130, was observed in control male rats in the oral carcinogenicity study.

In assessing the human relevance of crystalluria induced in urinary bladder tumors in the muraglitazar-treated male rats, there are several key factors for consideration. First, the response with muraglitazar was male rat specific, even though drug exposures in the carcinogenicity

studies were higher in female rats and in male and female mice.

Secondly, there were no mucosal cytotoxic, proliferative or inflammatory changes observed in monkeys treated for up to one year at exposures up to 44 times human exposure to the 5 mg dose.

Thirdly, muraglitazar did not induce urolithiasis or increased crystals of any sort in a Phase 3 clinical program. Lastly, crystalluria does not cause urinary bladder mucosal injury, and has not been established as a risk factor for urinary bladder cancer in humans.

Although a carcinogenic hazard was identified in lifetime rodent studies, the weight of evidence from the carcinogenicity and relevant mechanistic studies does not indicate a carcinogenic risk to humans at therapeutic doses and exposures. That is, crystalluria was the mode of urinary bladder tumor development, a mechanism not relevant to humans. Moreover, the high dose rodent tumors were considered of no established clinical relevance since they occurred by

non-genotoxic modes at exposures at least 48 times hither than those seen at a 5 mg dose, and were characterized by safety margins of at least 17-fold at the highest non-tumorigenic dose for each tumor type.

Of note, the rodent tumor profile for muraglitazar was similar to that observed with the marketed PPAR gamma agonists in that urinary bladder tumors have been observed in male rats treated with pioglitazone and adipose tumors have been seen in male and female rats treated with rosiglitazone.

So, in summary, muraglitazar demonstrated excellent oral tolerability and had no hepatotoxic, myotoxic, nephrotoxic or cardiotoxic potential in rats or monkeys at markedly higher exposures than those observed clinically at the 5 mg dose. Muraglitazar had no investigator off-target activity, displayed a benign cardiovascular safety profile and was neither genotoxic nor teratogenic. Finally, results of rodent carcinogenicity studies do not indicate a carcinogenic risk to humans at

therapeutic doses and exposures.

Now I will turn the podium over to Dr. Cindy Rubin who will discuss the clinical efficacy and safety data.

Clinical Efficacy

DR. RUBIN: Thank you, Mark. Good morning. Muraglitazar's Phase 2/3 clinical program is comprehensive, extensive and global, spanning six continents and 23 countries. The clinical program consists of six studies with over 4,600 subjects and more than 3,200 treated with muraglitazar. One study was conducted in 320 non-diabetic subjects with dyslipidemia. Five studies were conducted in subjects with type 2 diabetes. These five studies will be the focus of this presentation.

One of the distinguishing features of the clinical program is a large dose-ranging study in 1,477 subjects. Both the size of the study and the wide range of doses allowed for robust conclusions about dose selection for Phase 3. This study also generated extensive safety data in 745 subjects for

over two years. In addition, the clinical program included three placebo-controlled studies, one in monotherapy and two in combination therapy, and an active comparator study with the marketed TZD pioglitazone.

The studies enrolled subjects with differing degrees of glycemic control. Entry A1c criteria ranged from 7-10 percent. The age for entry was between 18-70 years. Subjects could have a BMI of 41 or below and a triglyceride level of 600 or below. Importantly, subjects with New York Heart Association's class III and IV were excluded in Phase 3, and class II subjects were excluded in Phase 2 only. Statins or fibrates were permitted if they remained stable at baseline until week 12. This was the primary time point for the lipid analyses. Statins or fibrates could be initiated or titrated after week 12 if clinically indicated. However, the co-administration of statins and fibrates was not permitted.

The demographic profile of the subjects in the clinical program is representative of the type

2 diabetes population in the United States. As expected, the monotherapy studies enrolled subjects with a shorter duration of diabetes as these subjects are typically earlier in the course of their disease. The mean ages were 53 and 55 years, and 12 percent and 15 percent of the subjects were age 65 or older. There was a fairly even distribution of males and females. The percent of Black subjects enrolled in the studies from the sites in the U.S. was 11 to 13 percent, which is similar to the percent of Black patients with type 2 diabetes in the U.S.

The study design and methods were similar across the program. All of the studies were randomized, placebo- or active-control, with parallel treatment arms. Each study had a two-week placebo lead-in phase and a 24-week double-blind short-term phase. Four of the studies had long-term, double-blind extensions.

To enable subjects to stay in the long-term phase, several titration steps were built into the study designs. Subjects who did not meet

prespecified glycemic criteria were eligible for titration. The design of the dose-ranging study allowed us to conduct a very thorough and rigorous evaluation of the efficacy and safety of muraglitazar.

The study included five muraglitazar doses, 0.5 mg, 1.5 mg, 5 mg, 10 mg and 20 mg and 15 mg of pioglitazone which is the lowest starting dose. The pioglitazone arm was meant as a benchmark and was not designed as an active comparator. The study did not include a placebo arm. Unique to this study, subjects who failed to meet prespecified glycemic criteria after week six of the short-term phase were allowed to rescue one time to the next higher dose. The primary efficacy analysis was based on the last value prior to rescue or discontinuation carried forward. The long-term extension phase has provided more than two years of data.

Each treatment arm had over 200 subjects which allowed for a robust assessment of both efficacy and safety. In all of the studies the

data set for the primary analysis, change from baseline and A1c, included those subjects who had both a baseline and a post-baseline measurement after at least six weeks of treatment. This allowed for enough time to see a change in A1c levels. What is important to note here is that up to one-third of the subjects on 1.5 mg of muraglitazar and 15 mg of pioglitazone had poor glycemic control and received rescue therapy.

The study enrolled 1,477 subjects with a baseline A1c of 8.1 to 8.3, reflecting a fairly well controlled study population. The results revealed a dose-dependent reduction of A1c levels ranging from 0.25 percent for the 5 mg dose to 1.76 percent for the 20 mg dose. The 5 mg dose had an A1c reduction of 1.18 percent. As there was no placebo arm statistical testing was based on the highest muraglitazar dose and then subsequent doses versus the 0.5 mg dose in a sequential manner. All of the comparisons were significant. The percent of muraglitazar subjects achieving A1c targets followed a similar pattern of dose-dependent

results.

The solid bars represent the threshold of A1c less than 7; the hatched bars are A1c less than 6.5. The 1.5 mg dose of muraglitazar showed modest efficacy, with about 40 percent of subjects able to achieve an A1c goal of less than 7, while with doses of 5 mg or higher more than half of the subjects got below 7.

The safety data from the dose-ranging study demonstrated that there are adverse events that are also dose dependent and reflect the expected profile of PPAR gamma agonists. The increase in weight followed a dose-related pattern similar to the decrease in A1c. However, the events of edema and heart failure followed a different pattern.

The incidence of edema for the 5 mg and under doses of muraglitazar and 15 mg of pioglitazone was similar. There was an increase in the rate of edema at the higher doses of 10 mg and 20 mg. Most of the events of edema were mild or moderate and did not result in discontinuation from

the study. The incidence rates for edema were higher than have previously been reported, which was most likely due to the fact that the investigators were actively looking for edema as part of the safety monitoring plan.

There were seven events of heart failure during the 24-week phase. These events occurred on the two highest doses of muraglitazar, five events on 10 mg and two events on 20 mg. A further discussion of heart failure will be presented later.

Based on the totality of the efficacy and safety results from the dose-ranging study, two doses were selected for Phase 3. The doses of 2.5 mg and 5 mg were selected by balancing safety and efficacy, with 5 mg representing a dose that demonstrated an attractive efficacy profile for glycemic and lipid parameters with minimal safety risks. The 2.5 mg dose was derived from dose modeling with a potential with greater than 0.7 percent reduction in A1c. The 2.5 mg dose also provides a simple dosing multiple for

practitioners.

The 1.5 mg dose was not chosen for further development as one-third of the subjects on this dose had to receive rescue therapy due to poor glycemic control. In addition, the 1.5 mg dose had a minimal effect on lowering triglycerides and apoB and raising HDL cholesterol.

The 10 mg and 20 mg doses both demonstrated a very high degree of efficacy. Currently, the 10 mg dose is being studied as a titration dose for those subjects who need additional glycemic control. The development of 20 mg has been discontinued.

The Phase 3 program consisted of four trials that showed consistent results for A1c lowering, percent of subjects achieving A1c goals and beneficial effects on lipids. The monotherapy study included subjects who were naive to antihyperglycemic therapy. A total of 340 subjects were randomized to muraglitazar of 2.5 mg or 5 mg or placebo. The results for the 2.5 mg dose showed a 1.05 percent reduction in A1c from baseline, and

for the 5 mg dose a 1.23 percent reduction, and both results were statistically significant versus placebo.

In this study only an additional 109 subjects with baseline A1c levels greater than 10 and less than 12 were enrolled into an open-label arm and were treated with 5 mg of muraglitazar. The 5 mg open-label arm had a reduction of 2.62 percent from a mean baseline A1c of 10.7. As this was a non-randomized treatment arm no statistical comparisons were done.

The efficacy of the 2.5 mg and 5 mg doses was also reflected in the percent of subjects at A1c goal by week 24. The 2.5 mg dose achieved 58 percent of subjects to target goal of less than 7. The 5 mg dose achieved 72 percent to a goal less of 7, and 58 percent of subjects less than 6.5.

What was also very impressive was that about 40 percent of the open-label subjects who had a higher mean A1c baseline of 10.7 achieved an A1c goal of less than 7. This is an important result for those patients whose blood glucose can be more

difficult to control.

Importantly, for patients with type 2 diabetes muraglitazar also improves the lipid profile. Subjects treated with 2.5 mg had an 18 percent reduction of triglycerides and a 10 percent increase in HDL cholesterol. Those on 5 mg had a 27 percent reduction of triglycerides and a 16 percent increase in HDL cholesterol. Muraglitazar also had no negative effect on LDL cholesterol levels, and a decrease from baseline of 12 percent for apoB.

In addition to the favorable effects on the lipid profile, we saw clinically meaningful effects on other glucose and insulin-mediated parameters. The homeostasis model assessment, HOMA, was evaluated to determine the impact of muraglitazar on insulin sensitivity and beta cell function, two of the underlying mechanisms involved in the development of type 2 diabetes. A decrease in the HOMA score represents an improvement in insulin sensitivity. Consistent with the pharmacodynamic activity of PPAR gamma agonists as

insulin sensitizers, there was a 24-38 percent reduction in HOMA-IR scores for the 2.5 mg and 5 mg doses of muraglitazar respectively. There were also dose dependent decreases in free fatty acids, further reflecting the mechanism of action of PPAR gamma agonists by which these agents improve insulin sensitivity.

As type 2 diabetes is a chronically progressive disease, many patients will require combination therapy for effective control of their diabetes. Therefore, we performed two placebo-controlled combination studies with two of the most commonly prescribed oral antihyperglycemic agents, sulfonylurea and metformin. The efficacy achieved in the monotherapy studies was also observed in the placebo-controlled combination studies.

A total of 583 subjects inadequately controlled on at least half maximum dose of sulfonylurea participated in the study. The subjects were maintained on 15 mg of glyburide and randomized to muraglitazar 2.5 mg or 5 mg or

placebo. Consistent with the results of the monotherapy study, the primary efficacy endpoint showed a 1.0 percent reduction in A1c for the 2.5 mg dose and a 1.2 percent reduction for the 5 mg dose. Both were statistically significant versus placebo.

Similarly, in the metformin study which had 652 subjects inadequately controlled on at least 1,500 mg of metformin, there was a 0.9 percent reduction with the 2.5 mg dose and a 1.16 percent reduction achieved with the 5 mg dose, and both were statistically significant versus placebo. There was also a consistent response in both studies with the percent of subjects achieving A1c goals.

In these more difficult to treat patient populations the glyburide study had more than 50 percent of subjects achieve the target A1c goal less than 7 on both doses. More than 30 percent achieved levels less than 6.5. As with the sulfonylurea study, a similar percent of subjects in the metformin combination study were able to

achieve goals of less than 7 and less than 6.5.

Lipid parameters followed a pattern consistent with the results seen in monotherapy. In the glyburide use trial, in which subjects had a similar baseline lipid profile as the monotherapy studies, there was a 26 percent decrease in triglycerides with 5 mg, as well as a 14 percent increase in HDL cholesterol, and there was no negative impact on LDL cholesterol and apoB levels were reduced by up to 11 percent. The results for the lipid parameters in the metformin combination were quite similar.

In addition to the standard placebo-controlled studies, muraglitazar was evaluated directly against standard of care pioglitazone. On a background of metformin, subjects were randomized to 5 mg of muraglitazar or 30 mg of pioglitazone. The 30 mg dose of pioglitazone was chosen because at the time the study was designed 30 mg of pioglitazone was the highest dose approved for combination use with metformin.

Upon completion of 24 weeks, subjects continued into a long-term extension for a total of 50 weeks and 1,059 subjects participated in the study. The results showed a 1.14 percent reduction in A1c for 5 mg of muraglitazar and 0.85 percent reduction for 30 mg of pioglitazone. With a 2.9 percent difference between the two treatment arms noninferiority was achieved.

This difference was also reflected in the percent of subjects to A1c goals. Sixty percent of the muraglitazar subjects met the goal of less than 7, whereas 44 percent of the pioglitazone subjects achieved this goal, and 34 percent treated with muraglitazar reached A1c levels less than 6.5 and 23 percent achieved this level with pioglitazone.

The difference between the two treatment groups was also seen with the lipid results. At week 12 muraglitazar 5 mg showed a consistent pattern of triglycerides decrease by 28 percent and HDL increase by 19 percent and apoB levels decrease by 12 percent. Both drugs had no effect on the LDL cholesterol.

Importantly, the glycemic benefits of muraglitazar were maintained over time, as reflected in the 50-week data from the extension phase. After 50 weeks of treatment there was a 1.13 percent reduction in A1c from baseline for muraglitazar and a 0.74 percent reduction for pioglitazone. This difference of 0.39 percent was statistically significant. At 50 weeks the mean A1c level for the muraglitazar-treated subjects remained less than 7. This goal was achieved by 60 percent of subjects and one-third of the subjects reached an A1c of less than 6.5.

Durable glycemic and lipid results were also seen in subjects treated with muraglitazar for up to 104 weeks in the dose-ranging study. In addition to the glycemic efficacy and improvements in lipid parameters seen with muraglitazar, there were also changes seen in other important renal, inflammatory and thrombotic endpoints. Treatment with muraglitazar resulted in up to 33 percent reduction of the albumin to creatinine ratio, a sensitive marker for renal function. Reductions in

biomarkers which have been implicated in cardiovascular disease were also noted. High sensitivity C-reactive protein levels were decreased u to 34 percent in the general study population. In addition, those subjects who had high baseline CRP levels had a reduction up to 50 percent. There were also reductions in the thrombotic markers PAI-1 and fibrinogen. These results suggest the important anti-inflammatory and anti-thrombotic effects of PPAR gamma agonists.

Treatment with muraglitazar in monotherapy and combination therapy at doses of 2.5 mg and 5 mg resulted in consistent dose-dependent, clinically meaningful decreases in A1c levels. Up to 70 percent of subjects treated with 5 mg of muraglitazar were able to achieve A1c goals of less than 7. The glycemic efficacy was also durable up to 104 weeks.

Across all of the studies there were consistent, dose-dependent improvements in lipid parameters with decreases in triglycerides and increases in HDL cholesterol. In addition, apoB

levels were decreased and there was no deleterious effect on LDL cholesterol. The effects on glycemic and lipid parameters were accompanied by favorable changes in renal function and several cardiovascular biomarkers, including CRP, PAI-1 and fibrinogen. Both the 2.5 mg and 5 mg doses demonstrated meaningful clinical results, with the 5 mg dose consistently resulting in greater efficacy for all parameters.

Now I would like to invite Dr. Rene Belder to the podium to present the clinical safety.

Clinical Safety

DR. BELDER: Thank you, Cindy. Good morning. the muraglitazar program was large and contains over 4,000 patients with type 2 diabetes, with the majority of subjects exposed to muraglitazar across a wide range of doses.

The bars represent the time based exposures by dose for the core clinical program. The hatched sections show additional patient exposures from ongoing extension studies that have accrued since the NDA submission. The additional

patient exposure has been combined with the NDA database, collectively called the complete data set.

This database contains data that was available as of June, 2005 for which incidences of events, corrected for patient exposure, have been calculated. The FDA analysis may differ because we are including the more recent data.

Muraglitazar 5 mg is the single dose with the greatest exposure at over 1,500 patient-years of exposure. There are also over 500 patient-years of experience with muraglitazar at 2.5 mg, and a large amount of time on treatment experience with the higher doses of muraglitazar. As is typical for registrational programs, there is a preponderance of exposure to muraglitazar compared to exposure to control agents. Overall, there is over 3,600 patient-years experience with muraglitazar compared to approximately 750 patient-years of exposure to pioglitazone and over 330 patient-years for placebo. This imbalance in exposure among treatments should be kept in mind as

we review the muraglitazar safety profile.

The diabetes population evaluated in the muraglitazar clinical program is representative of the broader diabetes population with patients having considerable co-morbidities in addition to diabetes. Over half of the patients had co-existing hypertension and over 10 percent had a known history of atherosclerotic disease. As would be expected, these patients took a variety of concomitant medications for these coexisting conditions, mostly for underlying cardiovascular disease.

The safety presentation will focus on events of special interest that have been identified as more frequently occurring on PPAR alpha or gamma agonists. For those events that have a known dose-response relationship with PPAR gamma agonists we used 24-week data. These events include edema and weight gain.

For less frequent events and signal detection we used the largest database available, the complete data set. We looked at the

cardiovascular safety of muraglitazar by examining heart failure and atherosclerotic cardiovascular events separately. Furthermore, we evaluated the incidence of cancer, the effects of muraglitazar on liver as well as muscle enzymes.

Edema is a well-recognized side effect of PPAR gamma agonists and is dose related. The short-term data provide a better characterization of the incidence and dose response for edema. There are slightly higher incidences, ranging from 9.8-15.6 for the 5 mg dose as compared to the 2.5 mg dose, placebo or pioglitazone. For all subjects the baseline incidence of peripheral edema ranged from 6-9 percent. In the TAD comparator study in combination with metformin the rate of edema was 2 percent higher on muraglitazar compared to pioglitazone. While it is important to take seriously any event of edema, it is worth noting that most of the cases were considered mild or moderate and very few discontinued due to edema.

One of the typical side effects of drugs used in the treatment of patients with type 2

diabetes, and specifically with PPAR gamma agonists, is an increase in body weight. In the Phase 3 studies a dose-related increase in body weight with the 2.5 mg and 5 mg doses was seen. The largest increase in weight was found in the combination study with glyburide. This was expected since weight gain has been reported with sulfonylurea monotherapy. In the TZD comparator study the increase in weight was 0.8 kg higher for muraglitazar than for pioglitazone, as could be expected based on muraglitazar greater efficacy. The weight gain seen with PPAR agonists is considered to be both from PPAR gamma-mediated fluid retention as well as accumulation of excess calories in peripheral fat.

While the selected safety topics so far focused on the Phase 3 24-week short-term experience, the safety discussion that follows will use the complete data set starting with heart failure, the main safety issue with PPAR gamma agonists.

The literature shows that the hazard ratio

of PPAR gamma agonists for heart failure relative to other oral antihyperglycemic therapies is between 1.2 and 1.8. For insulin the heart failure risk is at least equivalent to that of PPAR gamma agonists. The most likely explanation for the heart failure is the dose-related increase in plasma volume associated with PPAR gamma agonists. Recent evidence suggests that the increase in plasma volume is related to PPAR gamma-mediated increase in renal sodium reabsorption. The heart failure seen with PPAR gamma agonists is considered to be a precipitation of heart failure in patients with preexisting ventricular dysfunction, either systolic or diastolic. Several echocardiographic studies with PPAR gamma agonists have shown that these compounds do not appear to adversely affect myocardial function.

The incidence of heart failure in the muraglitazar program was calculated per 1000 patient-years of exposure by dose for mono and combination therapy studies separately. The incidence per 1000 patient-years of exposure is

displayed in rows for mono and combination therapy studies and by dose in the columns. Crude incidence rates could not be calculated because of titrations and switches from placebo to active therapy. The results showed that the incidence is lowest in monotherapy and highest with the combination with glyburide. The dose-dependent increase was observed in monotherapy, consistent with the results in the Phase 2 study discussed by Dr. Cindy Rubin. A dose response was also observed with the combination with metformin. Overall, the incidence of heart failure events per 1000 patient-years of exposure is consistent with what would be expected based on epidemiologic data.

Further evidence of the dose-dependent increase in heart failure risk with muraglitazar comes from a Kaplan-Meier time to event analysis. The cumulative incidence of events for heart failure across the entire program shows a higher risk for the 10 mg and the 20 mg doses. Furthermore, the data indicate a relatively constant risk over time.

During the clinical trial program 17 patients experienced heart failure on muraglitazar at doses of 5 mg or less and two patients on pioglitazone. These 19 subjects with heart failure identified by the investigator are ordered in the upper rows by muraglitazar dose and pioglitazone in the bottom rows. The total patient-years of exposure to each treatment is listed to the left side of the table. In the columns are the subject identification number; the therapy the subject was on; the event, if any, the independent heart failure adjudication committee considered to be responsible for the heart failure; echocardiographic findings, if performed; and the time to resolution of the heart failure.

Ten of the 17 muraglitazar-treated subjects had a concurrent event which the adjudication committee considered to be responsible for the heart failure. Echocardiographic findings generally indicated normally to mildly decreased left ventricular systolic function. Resolution of heart failure events occurred in 11 muraglitazar-

and 2 pioglitazone-treated patients, usually within a week. Three events had not resolved at the time of study discontinuation. All but one muraglitazar-patient discontinued muraglitazar therapy. Two subjects died. One subject died of ventricular fibrillation 14 days after a myocardial infarction which caused the heart failure. One subject, with a seven-year history of heart failure, died suddenly a few hours after onset of shortness of breath. One additional patient died nine days after the heart failure had resolved.

An independent adjudication committee was in place to evaluate all possible cases of heart failure. The objective of the adjudication process was to confirm the investigator-reported events and to identify events of heart failure that may not have been diagnosed. The adjudication committee consisted of three independent cardiologists. Possible heart failure events were identified through a predefined list of candidate events that included heart failure and related terms, but also events of edema of moderate or worse severity, as

well as events of dyspnea.

The committee received detailed information on each event. They also received an NT-proBNP value obtained from the stored baseline sample and from a sample obtained at or near the time of the event. The results showed that most investigator-identified heart failure was confirmed. More than half of the heart failure events were attributed to intercurrent events and, in addition, a small number of events of edema or shortness of breath was adjudicated as heart failure. These cases were mild and all events resolved, most while continuing muraglitazar therapy.

Even though cases of heart failure are recognizable and treatable, it is important to be able to identify those patients who may be at higher risk for an event of heart failure. As heart failure was expected to be the main safety issue for muraglitazar, an extensive effort was undertaken to understand risk factors for heart failure. These included pharmacogenetic analysis,

evaluations of NT-proBNP assessments, as well as traditional clinical heart failure risk factor analysis.

The results of our traditional risk factor analysis showed that even in the presence of these risk factors the risk for heart failure is low, from a high of 8 percent in patients who had a previous history of heart failure to 1.2 percent in patients with a history of hypertension. In addition, excluding hypertension, these risk factors taken together identified over 90 percent of the patients who developed heart failure. As expected, in the absence of these risk factors the risk was lower, ranging from 0.6 percent to 0.1 percent.

These analyses indicate that risk factors that recently have been published by the AHA/ADA consensus statement about risk factors for heart failure in patients treated with PPAR gamma agonists also apply to muraglitazar. In particular, a history of heart failure or symptomatic atherosclerotic disease identified

patients at risk for heart failure. As indicated in the AHA/ADA consensus statement, caution should be used when initiating therapy in patients with any of these risk factors.

In summary, consistent with the experience with marketed PPAR gamma agonists, a low incidence of heart failure events is observed with muraglitazar treatment. The incidence of heart failure is dose dependent, and higher in patients with known AHA/ADA risk factors. Diagnosed heart failure resolves with discontinuation of muraglitazar and treatment of heart failure.

Adjudication of a broad range of possible heart failure events indicated that some patients, being described as having dyspnea or moderate or worse edema, have clinically unrecognized heart failure which responds to diuretic therapy without discontinuation of muraglitazar. The safety events of edema, weight gain and heart failure that we have discussed so far are events that are known to occur with a PPAR gamma agonist in greater frequency.

The safety with respect to liver and muscle is discussed as part of signal detection for PPAR gamma and alpha agonists. Cardiovascular events are evaluated as part of the overall cardiovascular safety and because of inconsistent results with respect to cardiovascular events in individual studies.

A numerical imbalance of non-fatal cardiovascular events relative to muraglitazar was noted in one out of the five studies, while another study showed a numerical imbalance in a number of fatal cardiovascular events. Cardiovascular events are, therefore, analyzed in the integrated database. The analyses we performed also take into account the large differences in patient exposure among the treatment groups. However, no intent-to-treat analysis could be performed because no information is available on patients who discontinued due to adverse events or lack of glycemic control.

Cardiovascular events were identified by 52 prespecified terms for atherosclerotic disease

derived from the MedDRA dictionary. These included acute and chronic cardiac and cerebrovascular events. The expected PPAR gamma-mediated events of edema and heart failure associated with fluid retention were analyzed separately.

The events that were included in the analysis broadly included acute atherosclerotic events, including all events related to myocardial infarction and acute coronary syndrome, acute cerebral vascular events such as stoke and TIA, as well as cardiovascular death and sudden or unwitnessed death. Chronic atherosclerotic events were also included, such as angina and myocardial ischemia.

There was a total of 11 patients with cardiovascular events on placebo, 97 on muraglitazar and 15 on pioglitazone. The table also indicates that there was a wide variety of cardiovascular events in this patient population. As can be expected in a patient population with type 2 diabetes, the majority of events were myocardial infarctions and chronic coronary artery

disease.

To understand the number of events in the treatment groups better, it is important to evaluate these relative to the exposure. In addition, the more clinically important acute cardiovascular events were also analyzed. This table consists of two panels. The panel on the left shows the analysis of all cardiovascular events. The panel on the right shows the analyses of the acute cardiovascular events. Each panel has three columns, the total number of patient-years of exposure, the number of patients with an event, and in the last column the number of patients with an event per 1000 patient-years of exposure.

The small differences in the number of patient-years of exposure between the left and the right panel reflect the fact that exposure after an event is not included in the analysis. The results show that the incidence in cardiovascular events, when corrected for duration of exposure, is similar for muraglitazar and placebo.

We also analyzed the number of patients

with an event per 1000 patient-years of exposure by dose. The incidence per 1000 patient-years of exposure is depicted with the 95 percent confidence interval for placebo and muraglitazar and various doses of muraglitazar and pioglitazone. The 95 percent confidence intervals are overlapping. No dose-response relationship is apparent.

We subsequently conducted an analysis of cardiovascular events for muraglitazar by informative dose groupings with a Kaplan-Meier time to event analysis. The results of this analysis, with three times the number of events as for heart failure, are in contrast to the results of the same analysis for the heart failure events. While for heart failure events there was a clear dose-response relationship, the incidence in cardiovascular events does not indicate a higher incidence with increasing dose.

I will now discuss the subset of cardiovascular events that had a fatal outcome. A total of nine patients on muraglitazar and one patient on placebo had a cardiovascular death.

There was no cardiovascular death on pioglitazone. The crude incidence for cardiovascular death is 0.2 percent and 0.3 percent in the placebo and muraglitazar groups respectively.

When a difference in patient exposure is taken into account in the complete data set, the analysis per 1000 patient-years shows an incidence of 3.0 in the placebo and 2.6 in the muraglitazar group. For all three treatment groups the 95 percent confidence intervals are overlapping.

Thus, by taking into account the difference in patient exposure, the apparent imbalance in cardiovascular death is reversed. This illustrates the limitation of analysis on such rare events and uncertainty around the estimates. In the muraglitazar group three patients died of myocardial infarction. Four had a sudden or unwitnessed death, and two patients dies of a stroke.

In summary, despite imbalances in cardiovascular events noted in individual studies, the analyses of the complete data set, taking into

account the differences in exposure, indicate comparable incidences for cardiovascular events and deaths between muraglitazar and placebo. The totality of evidence for muraglitazar also indicates a lack of biologic plausibility for a potential cardiovascular risk. As indicated earlier by Dr. Rubin, surrogate markers for cardiovascular risk all show consistent and clinically important improvements with muraglitazar. A broad diversity of cardiovascular events was noted with both acute and chronic cardiac, as well as cerebral, vascular events. There was no indication of a higher cardiovascular event incidence on the higher muraglitazar doses. And, there is an absence of off-target cardiovascular toxicity in non-clinical and clinical studies.

A small number of subjects were diagnosed with cancer during the muraglitazar clinical program. The incidence of cancer was similar for all three treatment groups and the confidence intervals around the point estimates for the

incidence per 1000 patient-years of exposure were overlapping. There was no pattern found for the types of cancers that occurred during the clinical program.

There were four cases of bladder cancer. Two were on muraglitazar and two were on pioglitazone. Two of the four, one in each treatment group, was a recurrence. Twenty-seven of the 34 muraglitazar patients with a cancer diagnosis had their diagnosis within the first year of treatment.

With respect to overall mortality, the number of deaths per 1000 patient-years of exposure and their corresponding 95 percent confidence intervals are displayed in the graph. The exposure-adjusted incidences were 3.0, 5.2 and 2.6 for placebo, muraglitazar and pioglitazone respectively. Although the point estimate is higher on muraglitazar than placebo and pioglitazone, the small number of events precludes any conclusions with respect to overall mortality, as is also illustrated by the overlapping 95

percent confidence intervals.

As TZD was removed from the market due to liver toxicity, a thorough evaluation of liver function test abnormalities was conducted. Muraglitazar treatment was associated with a reduction from baseline in serum AKT levels. This finding is consistent with the potential benefit that PPAR gamma agonists have on reducing the interhepatic fat that is often present in the liver of patients with type 2 diabetes. In addition, laboratory data from the complete data set was analyzed to look for evidence of hepatotoxicity. This assessment looked at the number of subjects exceeding thresholds of ALT elevations. The analysis showed that fewer subjects on muraglitazar than on placebo or pioglitazone had significant liver function elevations.

Because myopathy is a concern with fibrates, in particular when used in combination with a statin, a careful evaluation of creatinine kinase abnormalities in subjects treated with and without statins was conducted. In the clinical

program, between 19 percent and 24 percent of the subjects were taking a statin. There were two cases of CK elevations greater than 10 times the upper limit of normal in subjects taking a statin and muraglitazar. One of the two cases was on 5 mg. The other cases is not presented in the table as the subject was titrated from 5 mg to 10 mg. Both subjects had no muscle symptoms and the CK returned to normal while remaining on treatment.

Of the muraglitazar-treated subjects with a CK elevation greater than 10 times the upper limit of normal who were not taking a statin, none had associated muscle-related symptoms. The incidence for these events was similar to placebo.

One case of rhabdomyolysis in a 55 year-old male on muraglitazar 5 mg and glyburide, but not taking a statin or a fibrate, was reported. This subject as asymptomatic and had a CK elevation with a peak of 8,513 after yard work. Several days later, while still on muraglitazar, the CK had decreased to 900's. Muraglitazar was discontinued and the CK returned to normal eight days later.

As was expected, the clinical program with muraglitazar established dose-related increases in the incidence of edema, the amount of weight gain, and the risk of heart failure. These are all effects that have been noted with PPAR gamma agonists. They are well understood and are manageable. The 2.5 mg and the 5 mg doses showed effects for these events that were within the range seen with existing PPAR gamma agonists.

In addition, within this clinical program of 3,600 patient-years of exposure our analysis of the most complete data set, which takes into account differences in patient exposure among treatment groups, did not identify increased risk for hepatotoxicity, myotoxicity, cardiovascular events or cancer. However, these potential risks deserve continued monitoring, which is consistent with the understanding that in order to fully evaluate potential risks many more patients will need to be followed for much longer periods of time. Our post-approval pharmacovigilance plan has, therefore, been designed to actively enrich

our understanding of the benefit/risk profile of muraglitazar.

I am introducing Dr. Fred Fiedorek who will discuss the pharmacovigilance plan and provide the overall risk/benefit summary. Thank you.

Clinical Plans, Pharmacovigilance and Benefit/Risk Conclusions

DR. FIEDOREK: Thank you, Rene. Good morning again. We are committed to assuring the appropriate use of muraglitazar post launch and to continuously assessing its benefit and risks. This commitment includes a comprehensive pharmacovigilance plan that goes beyond standard requirements to provide greater insights about benefits and risks, including potential risks that we cannot yet entirely rule out.

Our proposed pharmacovigilance plan has been submitted. Following launch, beyond standard pharmacovigilance requirements, we have also included enhanced monitoring for events of special interest reported by prescribers and patients worldwide. Specific cancers, fatal and non-fatal

cardiovascular events; clinical rhabdomyolysis events and other unanticipated rare events will be tracked. We will also use targeted physician questionnaires to gain additional information regarding events of special interest, and we will periodically assess this accruing safety information.

Additionally, we will undertake a dedicated pharmacoepidemiology cohort study to assess risks and monitor effectiveness of our education efforts regarding appropriate use. This pharmacoepidemiologic cohort study has two objectives: First, it will estimate relative incidences of safety events with muraglitazar compared to other diabetes treatments. Second, it will help us to characterize treatment patterns for patients using muraglitazar.

The sample population will come from a large U.S. managed healthcare database. The study will enroll a total of 15,000 patients, with 5,000 patients on muraglitazar, 5,000 patients on thiazolidinediones, and 5,000 patients on other

diabetes medicines, including sulfonylureas, metformin and insulin. Patients will be accrued into the study at a rate determined by new prescriptions. Safety information based on claims data will be assessed quarterly during the first year.

Because patients may migrate out of the specific healthcare plan, active ongoing follow-up for these three cohorts will include annual questionnaires beginning one year after the start of the study and continuing for the next five years. Dr. Alex Walker is here from Igenics i3 Magnify, the investigative epidemiology division for this managed healthcare firm, and he can help answer any questions you may have about this planned cohort study.

We will take steps to ensure that muraglitazar is used appropriately post launch. It is critical to ensure the appropriate use of any new medicine, especially during this post-approval stage. Several key communication points regarding the risks of muraglitazar will be highlighted in

labeling and in educational materials provided to patients, physicians and other healthcare professionals.

First, muraglitazar should not be used in patients with New York Heart Association Class III or IV heart failure. Furthermore, any patient who develops edema should be evaluated and managed. Patients with severe edema, rapid weight gain or dyspnea should be evaluated specifically for heart failure and treated as necessary.

These recommendations are based on our own data and also on the recommendations arising out of the American Heart Association/American Diabetes consensus statement published last year on the use of thiazolidinediones and the development of heart failure and edema. This information will be included in patient package inserts and in healthcare professional communication materials.

We have plans in place to ensure that product knowledge regarding muraglitazar will continue to grow following launch, allowing for a continuous assessment of benefit and risk.

Overall, we will be following the same general approach regarding the appropriate use of muraglitazar that Bristol-Myers Squibb successfully used when metformin or Glucophage was launched. For metformin, information regarding renal impairment and the risk of lactic acidosis needed to be communicated accurately and appropriately.

Finally, as with all of our new products, Bristol-Myers Squibb will not conduct DTC, or direct-to-consumer, advertising on muraglitazar for at least one year following approval. This policy will ensure that prescribing endocrinologists and other physicians and healthcare professionals first understand its appropriate use.

Every medication offers a balance of benefit and risk. For muraglitazar both have been well characterized with the results of our registrational program you have now heard about. It is important to consider the benefit and risks of muraglitazar in the context of needs for patients with diabetes to achieve their treatment goals. As Dr. Kendall pointed out, treatment needs

in type 2 diabetes remain high. Physicians and their patients are not meeting these treatment goals for both glycemia and lipid control. Muraglitazar may enable patients to reach these diabetes treatment goals through its combined PPAR gamma and PPAR alpha activities.

The improvements in A1c and glycemic parameters, depicted here, provided by muraglitazar are substantial. There were consistent mean drops in A1c of 1.2 percent for the 5 mg dose. In our open-label cohort study in the monotherapy study patients with baseline A1c's above 10 percent had mean reductions of 2.6 percent with this dose. Most importantly, patients reaching and maintaining control a A1c targets of 6 percent, and even those less than 6.5 percent for the American Association of Clinical Endocrinologists--set by that organization, these goals should be met. Additionally, additional benefits should be provided with muraglitazar to improve important CV outcome benefits with time.

Likewise, muraglitazar's improvements in

lipid parameters offer the prospect of long-term benefits as well. Muraglitazar-related rises in HDL cholesterol, decreases in triglycerides and apoB levels, with the maintenance of a stable LDL cholesterol concentration, indicating reduced numbers of atherogenic small, dense LDL particles should all over time contribute to favorable HDL cholesterol and triglyceride benefits that muraglitazar offers; it has the potential to offset some of these hazards. For the 5 mg dose A1c drops of 1.2 percent, HDL cholesterol rises of 6 mg/dL and triglyceride drops of around 40 mg/dL have the potential to counter these hazards of poor control.

Clinical intervention data to support such macrovascular benefits with A1c reductions are now beginning to emerge. The DCCT trial that Dr. Kendall descried earlier is a landmark clinical trial whose impact continues to grow. Ten years ago this trial provided the first definitive evidence for improving microvascular outcomes of any type of diabetes. Now outstanding follow-up of these patients as part of the EDIC extension study

has demonstrated that the 6.5 years of glycemic control now results in large and dramatic improvements in cardiovascular outcomes. In this context, muraglitazar, which is able to bring between 50-70 percent of patients to the goal of an A1c of less than 7 percent, offers the promise of similar benefits over time.

Likewise, as demonstrated in the VA-HIT study, benefits of treatment with PPAR alpha agonist gemfibrozil are clear for cardiovascular outcomes. Major cardiovascular endpoints are impacted positively.

Importantly, we will also conduct a clinical trial in order to assess hard endpoints related to the clinical outcomes you have just heard about. We are committing to this outcome trial to assess the clinical benefits expected from robust A1c and lipid changes seen in our registrational program. This trial will be a large randomized and controlled study with tracking of cardiovascular outcomes as the primary endpoint. It will probably take about five years, depending

on expected size and power. Active monitoring of this trial will include a data safety monitoring board and a steering committee to apply stopping rules for futility or for early benefit.

We expect to start enrollment of this trial in 2006 depending, in part, on ongoing trials of muraglitazar and also on results of important clinical trials for related agents, pioglitazone, the PROactive trial which will be announced next week in Europe, and the FIELD trial on fenofibrate which will be announced later this year at the American Heart Association meetings. Dr. Anthony Keech, a cardiologist and one of the leading investigators for the FIELD trial, is advising us on the design of this planned study. He is here today to answer any questions that the committee may have about our planned study.

Ultimately physicians must balance the proven and expected benefits of muraglitazar with the potential risks of treatment. We have demonstrated that the major risk of muraglitazar is the clinical event of heart failure which occurs in

individuals susceptible to PPAR gamma-mediated fluid retention and vascular volume increases. Heart failure occurring with muraglitazar is not unlike that seen with other drug or dietary precipitants, and its overall incidence appears to be low, presenting in less than 1/250 patients treated during the first six months of our clinical trials. Heart failure occurring with muraglitazar is also symptomatic and recognizable, and often manageable with treatment of diuretic therapy or stopping muraglitazar treatment.

Given our data and these considerations, we believe that the benefits of muraglitazar offset this primary risk of heart failure which occurs on an infrequent basis, primarily in susceptible individuals. Therapy with muraglitazar should be individualized for patients depending on their needs and their clinical status. Muraglitazar 2.5 mg and 5 mg doses are proposed to both be available as initial doses for use in monotherapy and also in combination.

Initial therapy with muraglitazar 2.5 mg

is best for patients with mild degrees of hypoglycemia. This dose is also recommended in patients who are expected to be less tolerant with fluid overload, such as those with New York Heart Association Class II heart failure or the other AHA/ADA risk factors. Active titration should be used outcome meet the treatment target goals for these patients as long as fluid retention side effects do not preclude moving to this higher dose.

Initial therapy with 5 mg muraglitazar is proposed for patients with more severe hypoglycemia. The 5 mg dose is the optimum dose for durably maintaining patients at A1c targets and lipid targets over time.

We will also provide clear warnings and precautions to treating physicians and other healthcare professionals. Muraglitazar will not be indicated for patients with New York Heart Association Class III or IV congestive heart failure or for patients with hepatic insufficiency. Also, muraglitazar will not be indicated for use with insulin or for use in pediatric patients

because these users have not currently been studied. Given its underlying pharmacology, muraglitazar will not be recommended for use with either thiazolidinediones or with fibrates.

Finally, we expect there may be other precautions regarding recognized PPAR gamma side effects, including heart failure and edema, and your deliberations today will be helpful in this regard.

To conclude, muraglitazar is the first dual PPAR alpha, gamma agonist. It achieves and maintains glycemic goals and improves diabetic dyslipidemia. Overall, it possesses an acceptable safety and tolerability profile, with a primary risk for heart failure and events due to fluid retention that are recognizable and well managed. Muraglitazar actually offers a new treatment option for patients with diabetes that goes beyond treatments with TZD and fibrates and can be used usefully and safely.

We would be happy to take any questions now from the committee. Thank you very much. Oh,

one more thing, I am pleased to have with us today multiple consultants, external consultants that will be able to help you with any questions you may have. Dr. Rachel Bijou is a cardiologist in Columbia University, in New York. Dr. Samuel Cohen is from the Department of Pathology and Microbiology at the University of Nebraska. Dr. Ralph DeFronzo is from the University of Texas in San Antonio. Dr. henry Ginsberg is also from Columbia University in New York. Dr. Robert Henry is from the University of California in San Diego. Dr. Anthony Keech, as I mentioned, is from Australia. Dr. David Kendall, who you already heard from, is from the University of Minnesota. Dr. James Neaton is from the University of Minnesota as well. Dr. Brian Strom is from the University of Pennsylvania and Dr. Alex Walker is from Ingenix i3 Magnify in Boston. Thank you again.

Committee Discussion

DR. WATTS: I would like to thank the sponsor for a clear, concise and timely

presentation. We are actually about 15 minutes ahead of schedule. The plan is to have committee questions for the sponsor until 10:30 and then a 15-minute break before the agency presentation. So, are there questions from the committee regarding the sponsor's presentation? Dr. Woolf?

DR. WOOLF: I have a couple of questions. In the 745 patients who were treated for more than two years, can you give us what their doses were?

DR. FIEDOREK: Those were a variety of doses. Those patients primarily rose out of our Phase 2 program and that was a large dose-ranging study. If patients needed rescue they were titrated to higher doses. They ultimately included doses up to 10 mg and for 18 months, in some cases, on 20 mg. But at a certain point we decided only to focus on the 10 mg dose in ongoing studies.

DR. WOOLF: So, is it fair to say that there were no patients on 0.5 and 1.5 who were treated as far as two years?

DR. FIEDOREK: I am going to ask Dr. Cindy Rubin to come to the podium to answer the specific

questions about the lower doses.

DR. RUBIN: At the end of the short-term phase all subjects on 0.5 mg were titrated up to the 1.5 mg dose. So, in the long-term phase there were no subjects on 0.5 mg. There were subjects on 1.5 mg, 5 mg and 10 mg, and the 20 mg dose, as Dr. Fiedorek mentioned--those subjects were down-titrated after about a year and a half.

DR. WATTS: Dr. Follmann?

DR. FOLLMANN: I have a couple of questions and I think it would be best if we referred to some of the slides the sponsor presented. First of all, I would like to look at slide number 73 which looks at the risk of cardiovascular events as a function of muraglitazar dose. I would like you to explain a little more about how these groups were formed, muraglitazar less than 2.5 mg, etc.

DR. FIEDOREK: Let me give an initial explanation and then I am going to ask my colleague, Dr. Labriola, to come to the podium. These groups were formed based on accruing time at

the dose. So, the different groupings here may have actually started on a 5 mg, rising from a lower dose, at the time they needed to titrate to that higher dose. Dr. Labriola, would you like to elaborate on this?

DR. LABRIOLA: Dr. Follmann, this particular analysis is not based on randomized treatment assignment because of the titration design that was used in the Phase 2 and Phase 3 studies. The way in which the treatment assignments were enabled was to take the highest dose of muraglitazar that a patient was on prior to or up to the time of the event, and they were assigned that treatment dose and then a Kaplan-Meier analysis was conducted using that as the grouping assignment.

DR. FOLLMANN: Thank you. I would just like to comment on this method of analysis. As you pointed out, this is not based on the original groupings, the randomized groupings, and making groups after the fact can lead to some biases in looking at risk factors.

I would like to give an analogy. Let's suppose I followed a thousand patients for two years and I was interested in whether cigarette smoking increased the risk of death. So, what I do is after everyone has been followed a year I look at those who are surviving and ask them if they smoke cigarettes. If I make a group of smoking at one year versus everyone else and do a Kaplan-Meier analysis, I will find that smoking at one year is probably a good thing because no one in that group will have died during the first year.

We have a similar kind of problem here, where patients who live long enough to get a muraglitazar dose of 10 mg maybe one or two years after randomization are accruing the benefits of having been identified as a two-year survivor. So, I think we should not really pay much attention to this analysis in our consideration of whether there is a dose effect on cardiovascular events. I believe the FDA will be providing some other analyses on this topic.

The second question I have has to do with

page 66 which looks at heart failure risk factors. The first line looks at congestive heart failure, and there are 25 people who had a history of that. Now, when you went over the demographics of the patients who were enrolled you didn't have a column for those who had Class I or Class II heart failure, which I believe was allowed in the study. So, are those 25 individuals there the ones with Class I and Class II heart failure?

DR. FIEDOREK: I can have Dr. Rubin answer this but I think I can answer it myself real quickly. In the Phase 2 study we excluded Class II, III and IV. So, these include patients that were included in Phase 3 that were Class II. That is correct.

DR. FOLLMANN: Your labeling or your recommendations at the end said that you wouldn't recommend this for Class III and Class IV. There has nothing been said about Class I and Class II. So, I am presuming you would like to dose those, if appropriate, and yet very few people with Class I and Class II heart failure have been studied. Is

that fair?

DR. FIEDOREK: Yes, 25 with Class II or Class I heart failure were studied. The recommendation is based on the findings you see here in terms of what we saw, the relative risk for those individuals to get treatment. We do recommend 2.5 mg as the dose to use in those subjects.

DR. FOLLMANN: Thank you.

DR. CUNNINGHAM: I just wanted to ask about the VA-HIT study. You used that as support for the function of your medication, but I would like to know what the all-cause mortality looked like in that study. You gave the cardiovascular mortality but not the all-cause and I never like to hear one without the other.

DR. FIEDOREK: Let me ask one of my experts. Dr. Ginsberg probably knows this better than I do right now.

DR. GINSBERG: Henry Ginsberg, from Columbia University. The VA-HIT total mortality data was a reduction of 11 percent, which was not

statistically significant.

DR. WOOLF: Two questions. The patients who developed edema as an adverse event, how were they treated? How quickly did it resolve? Did it recur? And how many of them subsequently developed congestive failure?

DR. FIEDOREK: We tracked edema very closely in our Phase 2 program and we have a lot of information from that long-term study. I would like to have Dr. Rubin come and answer the question about this and perhaps Dr. Belder would elaborate more on heart failure, but I will start with Dr. Rubin.

DR. RUBIN: We looked at how many subjects were receiving diuretic therapy who had developed edema. Slide 1-42, please.

During the trial those subjects who developed edema on muraglitazar, 24 percent received treatment with a diuretic for the edema, and 24 percent for pioglitazone and 14 percent for placebo. Because the numbers were relatively small we really could not do any further analyses to

fully understand resolution with diuretics or the types of diuretics, but I would say in general subjects were mild to moderate with the types of edema that they developed and diuretic use was not used extensively. In generally we saw loop diuretics being used and for most patients that seemed adequate. But, once again, the numbers were relatively small.

In terms of the development of heart failure, I will ask Dr. Rene Belder to come up.

DR. BELDER: We looked at this three ways. Slide 4-54. We looked at those patients who had a history of edema, and that was based on the case report information of the history page. We also looked at whether or not patients had edema at baseline, and that was on the basis of specific examination of the physician for edema at baseline. Then we looked at the development of edema during the study.

In the left-hand column are patients with that particular history or finding who then developed heart failure. In the right-hand column

are those patients without the history or baseline edema, for instance, who developed heart failure. It is clear from this data that the risk to develop heart failure is highest in those patients who developed edema during the study, whereas the risk of developing heart failure for those subjects who had edema at baseline is not that much different from those patients who do not have edema at baseline. So, the best predictor for heart failure is development of edema, which is consistent with the professional organizations' advice that patients who develop edema should be looked at for the possibility of heart failure.

DR. WATTS: Dr. Burman?

DR. BURMAN: I would like to ask you about the bladder cancer, at least in animals and perhaps in humans. You said a few humans got bladder cancer and one patient had a recurrence. Did you do any studies in humans, like urinalysis or cystoscopy, for anymore information regarding the likelihood or possibility of bladder cancer?

That is one question. The second question

is not directly related to that, which is that the cardiovascular events with beta blockers were higher than expected but you didn't mention putting that as a warning in your labeling.

DR. FIEDOREK: Let me address the first one. In the clinical program we did have a total of four cases of bladder cancer, two on pioglitazone and two on muraglitazar. One in each group was a recurrence. In terms of the measures we put in place to monitor using screening procedures, I would like Dr. Rubin to as the question as to how we handled that in the clinical program.

DR. RUBIN: We did several different analyses to monitor. We wanted to specifically monitor for the evidence of microscopic hematuria. The screening was put into place at baseline and subsequently any subject who developed positive microscopic hematuria on two separate, consecutive occasions was referred to a urologist. If, in fact, there was no clear cause it was readily treatable.

Slide 1-12 shows the results of these

urology referrals. There were 89 subjects referred to a urologist, of which 85 had complete consultation, and 41 of these were normal and for the other 44 the clinical findings are provided in the listing there. Of those, we found two of the new bladder cancer cases that were described. The two previous or the recurrent cases were found for symptomatic reasons or surveillance reasons.

In addition to the microscopic hematuria, we also analyzed routine urine analysis for crystals. Slide 1-9 shows a summary of the crystal data. These are the crystals that have been associated with bladder cancers in rodents, calcium oxalate, triple phosphate and amorphous phosphate. We are presenting the baseline incidence rates and the on-study incidence rates. This was routine urine analysis at baseline and at week 24. What we saw was that there was no increased incidence on study across the treatment arms.

In addition to that, we also looked for the presence of urolithiasis. Slide 1-14. This shows that there was no increased incidence in

urolithiases in muraglitazar-treated subjects as compared to those treated with pioglitazone or placebo.

DR. BURMAN: I might have missed it but what was the incidence of hematuria, microscopic hematuria? Was it higher statistically in the treatment group versus the control group?

DR. RUBIN: We did not do any statistical analyses on microscopic hematuria. There were four bladder cancer cases. Slide 1-17 summarizes these. There were two on muraglitazar and two on pioglitazone. The case on muraglitazar of the recurrence was on 10 mg. This was a patient who had diagnostic of bladder cancer 26 years prior to study entry; was having some obstructive symptoms and went to see his urologist and was diagnosed with a recurrence on day 58.

The pioglitazone patient had a history of bladder cancer two years prior to coming into the study and was picked up on routine surveillance. He went to his urologist and was found to have a recurrence.

The two new cases, for the one on 10 mg the onset day was 573. This patient had microscopic hematuria at baseline which resolved; subsequently returned. He was sent to a urologist; was diagnosed with balanitis; was treated for that; resolved. Subsequently microscopic hematuria returned; was sent for cystoscopy and was diagnosed with bladder cancer. The pioglitazone 30 mg--onset was on day 170. This subject had recurrent UTIs; was sent for an IVP and was found to have a diagnosis of bladder cancer.

They were all four males. They aged from 62 to 71. Two of them had a history of smoking and three of the cases were diagnosed as superficial or noninvasive, and all four have received treatment and are doing well.

DR. FIEDOREK: One other thing I would like to mention, we do, for a lot of our safety findings, look at observed rates in the trial versus expected rates. If I could actually show slide 3-115 as well to give you an understanding of how we put this in context, knowing the expected

rates? Here is listed the observed rate for bladder cancer and the expected rate based on a U.S. database. You had a second question?

DR. BURMAN: On the beta blockers.

DR. FIEDOREK: ON the beta blockers, okay. Yes, we looked at beta blockers and I think I would like to have Dr. Belder describe that in terms of the recommendation for use--what was found in our core slide to describe it as one of the risk factors we looked at. We included looking at it because the New York Heart Association and the American Diabetes Association also comment on that and we wanted to look specifically at that, the use of beta blockers. Dr. Belder, would you like to comment on that?

DR. BELDER: Core slide 66. We looked at the beta blockers and whether or not that confers a risk for heart failure in our program based on the observation in our clinical program that some patients who did develop heart failure were also on beta blockers. I have to mention that this analysis is based on very, very few cases and we

could not perform an adjusted analysis, and many of the patients that are in this analysis had multiple risk factors.

So, at this moment we have a finding that beta blocker use seems to be associated with a higher risk of congestive heart failure but, of course, the reason for treatment by the beta blocker is also related to having coronary artery disease or having an MI. So, we don't know if it is an independent risk or dependent risk. It just identifies a patient who is at risk for heart failure due to other reasons. So, we will continue to look at this, of course, as our database grows over time.

DR. FIEDOREK: That reason is also why we are not including it for sort of what we recommend for patients right now until we learn more about that.

DR. WATTS: I had some questions about weight gain on your core slide 60. It shows that muraglitazar produces weight gain at least double that of pioglitazone, and I am wondering not only

about the magnitude of the weight gain but also the distribution of the weight gain. Is this a shift in the bell-shaped curve or does this seem to be bimodal distribution? And, is there any association between weight gain and edema?

DR. FIEDOREK: Yes, you are referring specifically to the comparative study as well as the other program?

DR. WATTS: Yes.

DR. FIEDOREK: Yes, with muraglitazar 5 mg where we had greater efficacy in glycemic lowering we saw the difference depicted on this slide. I would like Dr. Belder to answer this in terms of the information we have.

DR. BELDER: Yes, the amount of weight gain has been correlated very well with the efficacy of muraglitazar. So, across the entire program the weight gain was very closely correlated with efficacy. Not in that particular study that you mentioned, but we did an analysis by quartiles of weight gain.

Slide 3-5-20 shows the relationship

between efficacy and weight gain. However, it is also remarkable that there is a group of patients who did not have weight gain or, actually, some weight loss and had good efficacy of 1.2 percent reduction. We did not do that particular analysis for the glyburide combination study but across the entire program we have observed weight gains that are consistent with the amount of efficacy that patients achieved.

DR. WATTS: Does the change in weight shift in the bell-shaped curve for the study population, or does it seem to be susceptible individuals? Is there a bimodal distribution?

DR. BELDER: I don't know that data specifically. I think it is a shift in the bell-shaped curve. I see our statistician nodding. Yes, it is a shift in the bell-shaped curve.

DR. FIEDOREK: Yes, we have sort of point estimates, and everything, and I can note that when you look at the population as a whole it is a shift overall in the bell-shape distribution. I would actually like to call Dr. DeFronzo because he has a

lot of experience with assessing weight gain and edema in this particular area. We do think it is a combination of weight gain and edema bud, Dr. DeFronzo, if you could comment?

DR. DEFRONZO: Yes, thank you. It is important to note that this was 30 mg of pioglitazone versus 5 mg muraglitazar, and I probably think that a more appropriate dose to compare would be the 45 of pioglitazone. Of course, that study is now being done. But I think if you extrapolate to what you might expect based on the 30 mg to 45 mg, I don't think the differences in weight really would be significantly different. Moreover, I think it is important in every study that has ever been published, including these data, the more weight that you gain, the better the drop in hemoglobin A1c. We also have extensively studied this in terms of insulin sensitivity. The more weight you gain, the bigger the improvement in insulin sensitivity. We have also looked at beta cell function using insulin secretion measured during the ODT and hyperglycemic

clamps factored by the severity of the insulin resistance, which I think is the best measure of beta cell function. The more weight you gain, the greater the improvement in beta cell function. Similarly, the cardiovascular risk factors, the more weight you gain, the better the improvement in the cardiovascular risk factors.

I know that this seems somewhat paradoxical, but I think you need to look at the distribution of weight gain that occurs with TZDs, and probably will be the same with muraglitazar, versus overeating. When you overeat fat is distributed widely in all tissues in the body, including muscle, liver and visceral fat areas. When you do this you get severe insulin resistance in muscle and liver and we know that visceral fat is associated with increased cardiovascular morbidity and mortality. When you treat with a TZD there is a marked redistribution of fat with a marked decrease in visceral fat, an increase in subcutaneous fat, marked mobilization of fat out of muscle. There is a decrease in the toxic fat

metabolites and there is also a marked decrease in liver fat.

I should also point out that the decrease in liver fat is closely associated with the improvement in insulin sensitivity in the liver and, most recently, Dr. Kruzie[?] showed at the ADA in a study with pioglitazone that the decrease in the fat is strongly associated with an improvement in histologic grade, read blindly by pathologists, and that was both decrease in fibrosis and indices of inflammation.

So, I think that there is a major redistribution of fat that explains why you see these beneficial effects with TZDs and also with muraglitazar, which is quite distinct from what happens when you overeat and gain weight. Although this sounds paradoxical, I think it is a very sound scientific explanation for this.

DR. WATTS: As a follow-up to that, are there recommendations for physicians or patients with regard to weight monitoring and reporting when they start on muraglitazar?

DR. FIEDOREK: Yes, we are recommending that specifically with regard to the primary risk for PPAR gamma-mediated heart failure, that we look for rapid weight gain as a sign potentially of edema. Dr. DeFronzo mentioned weight gain due to glycemic efficacy, and effects in fat take longer to appear. If those appear over time, there are clearly going to be recommendations to have patients watch their diet if a judgment is that it is mainly caloric intake and the fat. But our main focus is on the rapid weight gain that might be due to edema.

DR. WATTS: Dr. Caprio?

DR. CAPRIO: Could you comment about the bone marrow infiltration and suppression that you saw in the dogs? You have not mentioned anything here. Should we not worry about that?

DR. FIEDOREK: Yes, to answer that question I would like Dr. Mark Dominick to come to the podium.

DR. DOMINICK: We did not see infiltration of bone marrow by fat at the clinically relevant

exposures, exposures equivalent to those at the 5 mg dose in mice, rats or monkeys. We did see infiltration of fat at exposure multiples roughly 3, 7 and 9 times human exposure at the 5 mg dose in those species respectively. This was not associated with any decrease in bone marrow cellularity, except in monkeys at exposures approximately 9 times that seen at the 5 mg dose. Nor was it associated with any thinning of bone, other than in mice, at exposures up to 87 times human exposure at the 5 mg dose. Those essentially are the changes that we saw. In the dog we also had evidence of bone marrow hypercellularity, in fact, at relatively lower exposures, therapeutic exposures, again, because they are a particularly sensitive species.

DR. WATTS: Dr. Woolf?

DR. WOOLF: I would like to follow-up on an earlier question. We have heard assertions that the weight gain is partly fluid and partly storing of previously unused calories. Has there been a formal analysis to partition the weight gain

between those two compartments? Then I would like to have a quick question about the proposed outcome study.

DR. FIEDOREK: To answer your first question, we haven't done any formal analyses with any special clinical studies but one is under way where we are looking at that with Dr. DeFronzo. The question about the outcome study?

DR. WOOLF: Yes, are you going to be enrolling noon-diabetics as well as diabetics?

DR. FIEDOREK: We are actually going to need to weight until we get results of the trials in on fenofibrate and pioglitazone, as well as our own trials, using insulin in particular. I am sure we will be enrolling diabetics. Whether we go to earlier forms of pre-diabetes, so to speak, will depend sort of on what we think is necessary to advance the knowledge about muraglitazar related to the other agents.

DR. WATTS: A question for you, Dr. Fiedorek, on your slide 91 that Dr. Kendall also showed earlier that looks at the magnitude of

change in intermediate measures and cardiovascular disease risk. Is there evidence that there is a proportional advantage to go in the other way? What is shown here initially is the increased risk associated with worsening of parameters. So, is there evidence that if you lower those parameters things go back pretty much the same order of magnitude? And what is known about the inter-relationship between these three risk factors? Are they additive, multiplicative?

DR. FIEDOREK: Yes, what is shown here is sort of a meta-analysis of epidemiologic data on the hazards. So, it is as you state, related to the population estimates about what the hazard is to have worse control. The evidence that is emerging from clinical trials, you know, related to macrovascular outcomes, is just now beginning to appear. The DCCT in type 1 diabetes is the one I mentioned that had that impact of A1c long-term with long-term follow-up on cardiovascular outcomes. The VA-HIT is obviously the one that impacts the lipid parameters. We are expecting

results soon on these other trials that I mentioned like pioglitazone and other trials that are being done to look at this in terms of the clinical outcomes. But what I have shown here is just what muraglitazar does related to its registrational program properties on glycemic and lipid parameters, and some reasons to give us a rationale for a clinical outcome study looking at these benefits in an actual intervention study.

DR. WATTS: We will go to Dr. Cunningham and then Dr. Aoki.

DR. CUNNINGHAM: Since there was no change in the LDL, when there is evidence that lowering LDL does have a benefit, you did infer that there was a change in type of LDL. Do you have any data from humans to support that, the LDL subtypes?

DR. FIEDOREK: We have done some initial analyses on particle size as well. You know, as expected from apoB decreases and stable LDL cholesterol concentrations, we see that in monotherapy. In response to the question about how we are assessing that, I would like Dr. Ginsberg to

comment as well about what is expected because we are going to be looking at that in the future as well.

DR. GINSBERG: LDL size has been assessed in several of the studies using NMR, which actually gives you a direct measure of the size of lipoproteins. There was a shift, an increase in larger LDL and reduction in smaller LDL and, as Dr. Fiedorek said, that seems to be the case expected if you look at no change in LDL cholesterol and a fall in apoB, which is a measure of the number of particles. So, I think consistent with other drugs that reduce triglyceride and concomitantly raise HDL, there is almost always in those instances another concomitant, and that is a shift in LDL from small particles to larger, more cholesterol-rich particles.

But I think it is important to note that the drop an apoB means that there are fewer particles. In this case, with the drop in triglyceride there are probably fewer very low density lipoproteins and fewer low density

lipoproteins. That is probably even more important than the size of the LDL.

DR. WATTS: Dr. Aoki?

DR. AOKI? Two questions. Have you looked at the HOMA beta cell function equations to assess whether or not cell preservation is seen to gradually increase and then plateau? Or, is it just those time points in the materials that you supplied? Secondly, have you measured 24-hour urine C-peptide at baseline and at scattered intervals throughout these studies to document whether there is increase in insulin production by these participants' pancreases?

DR. FIEDOREK: The question about pancreatic preservation and effects over time is an important one. We have done HOMA analyses in the clinical studies that Dr. Rubin analyzed. I don't believe we have measured 24-hour urines for C-peptides at all. We have looked, you know, at C-peptide itself. We have also done some preclinical studies that address that question but some of the more detailed analyses will be done in

a mechanistic study with Dr. DeFronzo, and perhaps Dr. DeFronzo could come to the podium and answer that. If you want to see preclinical information on beta cell, I will call my colleague, Dr. Hari Hariharan as well.

DR. DEFRONZO: Two comments. First, the HOMA cell for insulin resistance--and we have published extensively on this--correlates very well with the insulin clamp data. The R value is about 0.7. The beta cell actually correlates very poorly with the hyperglycemic clamp, which would be the gold standard for looking at beta cell function. We have actually a very detailed mechanistic study using hypoglycemic clamps and insulin clamps to look in a fairly sophisticated way at beta cell function. These studies are being done in two centers, one in Pisa, Italy and one in San Antonio. So, I think we will have some very good data on that. But, clearly TZDs, as you know from the tripod/bipod study and also from the DPP do have beneficial effects on beta cell function, and these effects do continue for a long period of time.

Whether similar effects will be seen with muraglitazar I think will come out of these more sophisticated mechanistic studies, but they definitely are under way and close to being completed.

DR. FIEDOREK: Dr. Hariharan, would you want to see the preclinical information we have from this and diabetic animal models?

DR. HARIHARAN: Good morning. I am a discovery biologist with Bristol-Myers Squibb. We have two sets of evidence in diabetic db/db mice which suggest muraglitazar will have a beneficial effect on pancreatic beta cell function, one in severely diabetic db/db mice and a second one in prediabetic db/db mice. Slide 8-27, please.

In this slide the effect of treatment with muraglitazar for two weeks on the oral glucose tolerance test and total pancreatic insulin content is shown. Shown in the left panel, treatment with muraglitazar resulted in reduction of glucose excursion and reduced insulin levels, suggesting thereby improvement in insulin sensitivity. As

shown in the right panel, treatment with muraglitazar increased the total pancreatic insulin content by four-fold as compared to the vehicle-treated animals, suggesting an improvement in beta cell function.

Slide 8-30, please. In this study we have chronically treated for 12 weeks prediabetic db/db mice. These mice, as you may all know, develop age-dependent deterioration of glycemic control and beta cell function. In these mice, as shown in the left panel, treatment with muraglitazar increased total pancreatic insulin content above and beyond levels observed in lean normal mice. The vehicle-treated animals continued to lose pancreatic insulin content from week 4 to week 12.

As shown in the right panel, the insulin content in isolated islet was also increased, and the islets of muraglitazar-treated animals showed improved morphology. So combined, these data suggest, at least in preclinical models, that muraglitazar treatment improves beta cell function.

DR. AOKI: One quick question, the

previous slide suggests that you were increasing first-phase insulin secretion. Is that a common finding, that you reacquire first-phase insulin secretion which would have a profound impact on the postprandial blood glucose levels?

DR. HARIHARAN: We have not systematically followed the whether the phosphate insulin secretion was changed. However, we do have a significant amount of preclinical data that suggests postprandial glucose levels are lowered or actually normalized to the levels found in normal mice.

DR. FIEDOREK: We will have Dr. Kendall add to that.

DR. KENDALL: Two comments. Obviously with improving glycemic control first-phase insulin secretion is restored in a number of patients with type 2 diabetes really independent of the mechanism. But increasing insulin content in the pancreatic islet would obviously further enhance that.

I would like to return to your question,

Dr. Watts, about the individual impact of improving glycemic control on cardiovascular risk. For those of us involved in DCCT and EDIC, the analysis that has been done and presented by David Nathan for that population with type 1 diabetes, 97 percent of the effect that was shown in this slide, the improvements in cardiovascular risk in DCCT in the adjusted analysis was attributable to improvements in glucose control and not other factors. There are also analyses, again epidemiologic analyses from larger population studies that suggest that the combination of improving triglycerides, HDL and glucose in combination may, in fact, yield greater benefit than any expected response to the individual components, The EDIC database and others have been analyzed in that regard. Again, it is epidemiologic data but supportive.

DR. WATTS: I have a question, if we could show slide 30 that deals with demographics. I didn't see any stratification of response by race or ethnicity. I am wondering if you feel you have adequately studied racial and ethnic groups that

are prone to develop type 2 diabetes, and whether or not you have seen any differences in responses for efficacy or safety.

DR. FIEDOREK: We have studied and looked at these groups, and I would like Dr. Rubin to answer the question.

DR. RUBIN: We had approximately 6-7 percent Black population in the studies which, in the U.S., was between 11-13 percent, consistent with the percent of patients who are Black in the United States. Looking at the efficacy results for that population--slide 1-1--revealed that the efficacy in the Black subjects was slightly better than what we saw in the other populations. Overall, the efficacy results were consistent with the efficacy of the entire study population. So, in the Black subjects, which was about 300 subjects across the program, there was slightly better efficacy.

In terms of ethnicity, we had a fairly large representation of Hispanic Latino subjects, between 19-29 percent. Slide 1-1 shows the

efficacy for this subset of subjects. In the combination studies in particular we saw better efficacy in the Hispanic population as compared to the non-Hispanic. However, once again I want to mention that these small differences are consistent overall with the efficacy that we saw in the program.

When we specifically look at the trials, particularly the combination trials including the Hispanic subjects, their baseline levels were slightly higher. So, we did see somewhat better efficacy in that subject population.

DR. WATTS: What about safety, weight gain, edema, congestive heart failure?

DR. RUBIN: We looked at edema in these subpopulations. In general we saw that Black subjects had a tendency to have more edema but that was true for all treatment groups, including the placebo, muraglitazar and pioglitazone. Also, women tended to have more edema also in all of the treatment groups, including placebo. So, these two groups tended to have more edema across any

treatment arm.

DR. WATTS: And weight gain? Is it different for any racial group or for men versus women?

DR. RUBIN: We looked at men versus women and they have a similar increase of about 1.4 kg, both men and women. In terms of racial differences, the Black population of women had similar edema rates across all treatment groups. So, they are elevated overall. In Black subjects and Black females we found that the edema rates were elevated across all treatment groups as well.

DR. WATTS: Dr. Follmann?

DR. FOLLMANN: I would like to comment on the animal studies for a minute. So, you presented data showing that there is evidence of QT prolongation, bigger hearts and LV thickening in animal models at high doses, and you dismissed that because you said the doses were too high. I have two comments on that.

One is why would you study it if you thought the doses were too high a priori?

Secondly, do you see similar effects, or have you done studies in PPAR alpha or PPAR gamma agonists alone, thinking that, you know, if you saw similar effects in those single agonists you might feel more comfortable about the potential link with cardiovascular events because single agonists have shown a benefit in terms of cardiovascular events? So, have you done other studies? Then, you know, why did you dismiss it with the dose being too high?

DR. FIEDOREK: I am going to ask Dr. Dominick to come to the podium to address your questions.

DR. DOMINICK: First of all, I want to clarify that we had QT prolongation in a one-month study in dogs at doses of 20 mg/kg and 200 mg/kg. In those studies the animals that showed evidence of QT prolongation had up to 92 milliseconds of prolongation but they were at doses inducing up to 42 percent reductions in body weight, 17 percent reductions in food consumption, profound electrolyte disturbances in association with

emesis, CNS depression and hypothermia. So, these were profoundly, overtly toxic doses.

The more important assessment of QT prolongation was in our study in telemeterized dogs after a single intravenous dose where we achieved exposures up to 120 times the human Cmax and saw no evidence of QT prolongation. Moreover, in chronically dosed monkeys even at doses that resulted in profound edema, in assessments at 12 months into that study there was no evidence of QT prolongation at up to 59 times the human exposure. So, in animals that tolerated the drug reasonably well there was no evidence of QT prolongation.

DR. WATTS: Dr. Caprio?

DR. CAPRIO: Do you have any data on hepatic glucose production and postprandial hypoglycemia?

DR. FIEDOREK: Clinical data? No, we haven't done any special studies in that regard. Dr. DeFronzo is doing a study that will be looking at some of that.

DR. DEFRONZO: That study is actually

ongoing on now with tritiated glucose and glutarate water to both look at total hepatic glucose production and gluconeogenesis. But we actually have done this with both rosiglitazone and pioglitazone, and hepatic glucose production falls, albeit slightly significantly. But that is even in the face of about a 30 percent reduction in insulin. So, actually, if you looked at the hepatic insulin resistance index, a fall in hepatic glucose production and fall in insulin means a big improvement in hepatic sensitivity to insulin. With both of the TZDs that are on the market we have also looked at gluconeogenesis and there is a quite significant decline in gluconeogenesis. It correlates very strongly with two factors, a decrease in visceral fat and a decrease in plasma FFA and FFA turnover. I believe this is due to the PPAR gamma effect. I would anticipate that we would see the same things with the muraglitazar mechanism of action when the studies are complete.

DR. WATTS: Dr. Woolf?

DR. WOOLF: I would like to return to the

hematologic arena. On page 158 of the briefing manual and associated table there are indications of slight decreases in hematocrits, hemoglobins and white counts. Returning to our infamous bell-shaped curve, is this a general shift to the left or were there a few people with significant reductions in these parameters?

DR. FIEDOREK: Yes, we have looked at the data for hematocrit and hemoglobin as well as outliers and I would like Dr. Rubin to come to the podium to address your question.

DR. RUBIN: The effects seen on hematologic parameters are consistent with what has been reported with other PPAR gamma agonists. They appear to be related to two phenomena, one of which is related to fluid retention. There is a dilutional effect causing a drop in the hemoglobin and hematocrit. In terms of the white cell blood counts, there appears to be a depression of the bone marrow that does not persist.

To speak to the hematologic hemoglobin parameter, we see dose-dependent decreases,

particularly in the dose-ranging study, that are shown in slide 25. This shows you the dose ranges from 0.5 mg to 20 mg. What is interesting to note is that the decrease in hemoglobin occurs within about the first eight weeks. After that there is a stabilization so there is no further drop. The drop never goes below around 13. What we saw at the 5 mg dose was about a 0.5 g/dL decrease and, once again, it stabilizes after week eight.

There are a few cases of anemia that were reported. Slide 32 shows the adverse events of anemia. There were 15 events of anemia reported in the muraglitazar 5 mg and under dose and the incidence is similar to what is seen in pioglitazone and placebo. Of note, only two of these cases on muraglitazar had a hemoglobin less than 8. One case was related to a GI bleed. The patient had a hemoglobin around 6 which subsequently returned to normal. The second case was an anemia of 7.7 which was associated with an iron deficiency anemia and a B12 deficiency, and the patient was treated for that and the hemoglobin

returned to normal level.

DR. WOOLF: I can assume that in terms of white count no one developed a disastrous white blood count, serious infection and no one has commented on platelets so I am assuming that they remained unaffected.

DR. RUBIN: In terms of white blood count, we also so dose-dependent decreases. Once again, that stabilized after week eight. Slide 5 shows the dose-dependent decreases in absolute neutrophil count. At the 5 mg dose there was a 0.4 mean change from baseline.

There were rare events or very low frequency events of what we defined as neutropenia, which we predetermined to be two ANC counts less than 1,000. We also had one event seen on placebo. That is slide 2. There were three cases on muraglitazar of less than or equal to 5 and one case on placebo. In all of these cases there was no presence of any type of clinical sequelae. No signs of infection that was found on routine lab, and the subjects were discontinued due to protocol.

However, they returned to normal levels within several days. So, it appears to be a very infrequent event that is not associated with any clinical sequelae and subjects do well and return to normal. We did not see a decline in platelets or any other related blood counts.

DR. WATTS: We are almost to our break time. let me ask a final question, if you would bring up slide 35. Dr. Rubin, you may want to stay because this was your presentation. The 1.5 mg dose of muraglitazar brought about 40 percent of subjects to goal. I realize that not only does your drug have a benefit on glucose but has a putative beneficial effect on lipids. That is not part of what you are going for in labeling and approval and since weight gain and edema or heart failure seem to be dose dependent, why would you not consider a 1.5 mg dose for marketing?

DR. FIEDOREK: Let me address that. Dr. Rubin described how we went to Phase 3 and studied the 2.5 mg dose and the 5 mg dose going forward. Besides this reaching target, Dr. Rubin also

described how rescue was required in approximately a third of patients on the 1.5 mg dose of muraglitazar. We considered that as the overall clinical utility the 1.5 mg dose, based on those findings, as well as the lipid information you referred to, which was actually more apparent with 2.5 mg and 5 mg dose, was our rationale for going to the 2.5 mg and 5 mg dose in Phase 3. Also, those considerations on the benefit and clinical utility even in the short-term 24-week study, having a dose that you can be more reliably assured is going to work over time was our thinking.

DR. WATTS: The question may be too strong a term for having to increase the dose if you don't get your initial desired response.

DR. FIEDOREK: Well, no, the rescue was based not on the targets. I wanted to make a distinction between the rescue and the targets. The rescue was making sure that patients had the kind of control we felt they needed to continue in the trial, and that was at a higher range. Targets were what we were looking at ultimately on A1c at

24 weeks and going out further. So, there is a distinction between the rescue criteria which were set to provide adequate control even for the 0.5 mg dose, and that clinical aspect or clinical utility of that dose, knowing that about a third would require rescue within that 24-week period was our thinking around the 1.5 mg dose and the 2.5 mg dose. That, coupled with the fact that safety and tolerability, including over long-term events related to fluid retention were comparable, we didn't see that there was any reason not to try the 2.5 mg dose. We feel overall that 2.5 and 5 represent the optimum net balance of clinical utility and 1.5 is good, but we felt that 2.5 and 5 were better.

DR. WATTS: We will now take a break and reconvene as close to 10:45 as possible.

[Brief recess]

DR. WATTS: Please take your seats. We will go ahead and ask Dr. Golden to begin her prespecified on safety.

FDA Presentation

Clinical Review

DR. GOLDEN: Good morning. Chairman Watts, members of the committee, today I will be presenting the Division's perspective on selected safety issues from this application.

I will be starting with a brief background orienting you to how these data will be presented. Next I will discuss subject disposition and adverse events leading to discontinuation. Then I will present the safety issues for discussion, give you some of our thoughts and raise some questions to consider in your deliberations.

Let me start by highlighting a couple of regulatory issues. First, as you know, troglitazone was the first PPAR gamma agonist approved for the treatment of type 2 diabetes, but was subsequently removed from the market because of hepatotoxicity. Second, as Dr. El Hage will discuss, PPAR compounds are known carcinogens in animals and, therefore, all clinical studies of any new PPAR greater than six months in duration must be supported by submitting two years of preclinical

carcinogenicity data to the agency.

In general, the safety profile of muraglitazar is what one would expect from a compound with PPAR gamma and alpha activity with predominating gamma effects. I will discuss dose-related edema, weight gain and congestive heart failure as context for the discussion of the imbalance of cardiovascular adverse events in the muraglitazar-treated patients.

As you have heard, the safety database included 22 clinical pharmacology studies, five type 2 diabetes studies and one mixed dyslipidemia study. This presentation will be focused on these five type 2 diabetes studies, two of which were monotherapy and three of which were combination therapy studies.

In the six Phase 2 and 3 studies over 3,200 subjects received at least one dose of muraglitazar and almost 3,000 of these were individuals with type 2 diabetes, about half of whom were enrolled in monotherapy studies and half in combination therapy studies. Approximately

2,000 subjects received muraglitazar for at least 24 weeks and 700 for at least 104 weeks.

As short-term data are generally representative of the long-term data, I will be primarily presenting results from the type 2 diabetes trials up to 24 weeks, with the exception of deaths which will be presented in their entirety.

This is to review the study designs with you. I am going to abbreviate the study names for the sake of simplicity so CV168006 will be 006, and so on. Study 006 was a dose-ranging Phase 2b monotherapy study in subjects with type 2 diabetes. Treatment groups included doses of muraglitazar ranging from 0.5 mg to 20 mg and pioglitazone 15 mg. In the short-term phase of the trial subjects on muraglitazar on 0.5 and 1.5 could be titrated to 5 mg, 5010 mg and 10-20 mg one time as needed for glycemic control. Subjects on pioglitazone 15 mg could be titrated to 45 mg. There was a long-term extension phase.

Study 018, 021, 022 and 025 were Phase 3

studies in subjects with type 2 diabetes. Study 018, 021 and 022 were placebo-controlled trials studying the doses planned for marketing, muraglitazar 2.5 mg and 5 mg. Study 018 was a monotherapy study and was completed in 24 weeks. This study also had a muraglitazar 5 mg open-label arm for subjects meeting all other criteria except a higher hemoglobin A1c of 10-12 percent.

Study 021 was a glyburide add-on study with a 24-week short-term phase and a long-term extension phase. Study 022 was a metformin add-on study with a 24-week short-term phase and a long-term extension phase. Study 025 was also a metformin add-on study that compared muraglitazar 5 mg to pioglitazone 30 mg. There was a 24-week short-term phase and a long-term extension phase.

I will review some of the pooling methods to orient you to how these data will be presented. One method was to pool muraglitazar doses up to 5 mg and compare to placebo and pioglitazone doses up to 45 mg. The muraglitazar pooling included doses in the dose-ranging study of 0.5 mg, 1.5 mg and 5

mg in addition to all doses of muraglitazar in the Phase 3 studies. Because this pooling method did not include muraglitazar 10 mg and 20 mg doses I have presented selected results for these doses separately. Pioglitazone pooling included all pioglitazone groups, 15 mg potentially titrated to 45 mg from study 006 and 30 mg from study 025.

I have in some cases presented monotherapy data separately from that of combination studies. Just to remind you, 006 and 018 are monotherapy studies and the rest are combination therapy. All arms of 021 had a background of glyburide and all arms of 022 and 025 had a background of metformin.

There are limitations to combining studies so I will present some data by individual study as well. I will not be presenting any formal statistical analyses. Here is a cumulative summary of the Phase 2 and 3 type 2 diabetes trials. I have presented the data using the pooled treatment groups and have additionally included the muraglitazar 10 mg and 20 mg doses for comparison.

There were approximately three times the

number of subjects in the muraglitazar treatment group as in the pioglitazone treatment group and about four times the number as in the placebo group. The muraglitazar subjects at doses up to 5 mg had a higher rate of completion overall than those on pioglitazone or placebo. A slightly higher percentage of subjects withdrew due to an adverse event in the muraglitazar group as compared to the pioglitazone or placebo groups, and this value is increased to 11 percent at the muraglitazar 10 mg and 20 mg doses. Also, note that a considerably higher percentage of subjects were discontinued due to lack of efficacy in the placebo group than either the muraglitazar or pioglitazone groups.

Here we see adverse events leading to discontinuation at the highest frequency in the muraglitazar-treated subjects. Peripheral edema and weight gain are the most common adverse events leading to discontinuation at the higher muraglitazar doses. Again, these 10 mg and 20 mg muraglitazar doses, represented by the blue bars,

are higher than the doses the sponsor is proposing for marketing. At the doses of muraglitazar up to 5 mg the percentage of edema-related adverse events leading to discontinuation isn't different from placebo. The slightly higher incidence of discontinuations due to adverse events in the muraglitazar treatment group at doses up to 5 mg versus comparator can be attributed to increased events of weight gain, hypoglycemia and heart failure.

Here are the safety issues that I will be discussing. I will start with deaths and then briefly review findings of edema, heart failure and weight gain, some of which you have already heard, primarily to provide a background to the next part of the discussion, which is the numerical imbalance in cardiovascular events between muraglitazar and comparator. I will follow this discussion by providing some background information regarding differences between studies and the patient populations in order to give context for the previous discussion.

The first point for discussion is the incidence of deaths. This figure illustrates the incidence of death in the type 2 diabetes studies. Not presented on this figure is one death in the long-term phase of the mixed dyslipidemia study. It occurred in a subject randomized to muraglitazar 20 mg who was a passenger in a fatal automobile accident.

So just to orient you, the Y axis is the percentage of total subjects and the numbers above the bars are the numbers of subjects with deaths. Also a point about the denominators, I used the sponsor's denominators for the complete NDA data set as presented in their briefing document because of the inclusion of deaths from the short-term and long-term phases of the study. There were 3,125 subjects in the muraglitazar treatment group compared to 823 in the pioglitazone group and 528 in the placebo group. These percentages take into account sample size differences but ignore any differences in exposure between the groups. These incidence rates in include long-term data where

there was somewhat more overall exposure on a per-patient basis for muraglitazar as compared to placebo.

Although there were more deaths and a higher incidence of deaths in the muraglitazar group, it should be noted that the rates in the comparator groups, based on exceedingly small numbers of events, are highly unstable, meaning that even one additional death in either group could impact the result, and note that this would impact both the cardiovascular and cancer death results.

With this caveat, the overall incidence of death in the muraglitazar group is 2.5 to 3 times that of comparators. The percentage of cardiovascular deaths in the muraglitazar-treated subjects was about 1.5 times that of placebo. There were no cardiovascular deaths in the pioglitazone group. The percentage of cancer deaths in the muraglitazar group was about 1.8 times that of pioglitazone-treated subjects. There were no cancer deaths in the placebo group.

As you can see, eight of the cardiovascular deaths were in subjects on doses proposed for marketing, primarily in subjects on muraglitazar 5 mg in combination with metformin. The one monotherapy cardiovascular death was in an individual treated with muraglitazar 20 mg. In the muraglitazar-treated subjects cardiovascular deaths included myocardial infarction, stroke and sudden death. There was one placebo subject who died of a pulmonary embolus.

I have starred three subjects whose course I will detail further and who appeared to have had symptoms of heart failure coincident with the cardiac death. There was one additional subject who initially presented with a myocardial infarction and several days later developed heart failure prior to her death.

This subject was a 54 year-old white male with a six-year history of diabetes and a history of hypertension, obesity and coronary artery disease. On day 115 he presented to the emergency room with abdominal bloating, increasing dyspnea,

orthopnea and lower extremity edema. An electrocardiogram indicated old inferior and extensive anterior infarctions. He was diagnosed with heart failure and was treated with a single dose of furosemide, aspirin, metoprolol and glimepiride. Study medication was permanently discontinued. His heart failure rapidly resolved and he had a normal chest x-ray on day 117 and returned to work.

The next day the subject returned to the investigator site and was noted to have a body weight of 300 lbs, which was an increase of 10 lbs from the previous study visit on day 90. NT-proBNP, a biomarker of congestive heart failure, was elevated at 1,236 pg/mL. His screening value was also elevated at 548. The subject reportedly refused to have a physical exam done and failed to comply with the recommended outpatient cardiac evaluation. On day 125 he was found dead in his home. A coronary examination determined the cause of death to be myocardial infarction.

So, this subject's death was apparently

complicated by right and left heart failure, likely related to extensive old ischemic myocardial damage. The extent to which his final demise was contributed to by muraglitazar is not clear.

This subject was a 66 year-old white female with a four-year history of type 2 diabetes and multiple other medication problems, including congestive heart failure and vascular disease. On day 202 the subject died of sudden death. An event of dyspnea due to heart decompensation was reported to have occurred on the evening before the subject died. An autopsy was not performed and the cause of death was reported as a myocardial infarction. The subject's sudden death was preceded by dyspnea, however, the extent to which this event was heart failure or an anginal equivalent is unclear, as is the contribution of muraglitazar.

This subject was a 59 year-old white male with a two-year history of diabetes and a history of hypertension. On day 43 the subject had a non-serious adverse event of bilateral pitting edema in his ankles.

On day 49 the subject presented to the emergency room with dyspnea and was diagnosed with myocardial infarction and congestive heart failure. He reported that he had some increased exertional dyspnea while mowing his lawn the previous month. He didn't have chest pain but his cardiac enzymes were markedly elevated. The subject rapidly deteriorated and required intubation. On day 50 a cardiac catheterization was performed which revealed a 99 percent stenosis of the left main coronary artery and an 80 percent stenosis of the proximal right coronary artery. An echocardiogram revealed a moderately dilated left ventricle with severe hypokinesis and ejection fraction of 15-20 percent. His condition continued to deteriorate and on day 60 life support was withdrawn and the subject died.

This patient's extensive coronary atherosclerosis, including a 99 percent left main stenosis, was clearly etiologic in his ischemic cardiomyopathy and death. The extent to which muraglitazar may have contributed to decompensation

of his already compromised cardiac status is not, however, clear.

As seen here, the cancer deaths and, indeed, all of the cancers in the muraglitazar program, followed no particular pattern. There were three lung cancer deaths in the muraglitazar-treated subjects. All of these patients had a smoking history. Additionally, there were deaths due to acute myeloid leukemia, breast cancer, hepatocellular carcinoma and pancreatic cancer. One subject in the pioglitazone treatment group died of throat cancer. He also had a smoking history.

One additional point to note with the deaths is that one third of the total deaths and over one half of the cardiovascular deaths in the muraglitazar groups occurred in a single study, 025. This was the active controlled metformin add-on study comparing 5 mg of muraglitazar with 30 mg of pioglitazone. There were about 580 subjects per treatment arm, six deaths in the muraglitazar group versus one death in the pioglitazone group.

Five of these muraglitazar deaths were cardiovascular and one was due to pancreatic cancer. The one pioglitazone death was due to a perforated duodenal ulcer after urolithiasis surgery.

One other noteworthy finding that was not true in any other study was that there were multiple deaths from the same site. In fact, two of the three sites that had cardiovascular deaths contributed two deaths a piece in the study. Site 193 randomized five subjects to muraglitazar and three to pioglitazone. Site 241 randomized 19 subjects to each group.

So, to summarize deaths, there was a higher incidence of overall and cardiovascular deaths among the muraglitazar-treated patients and the cardiovascular deaths are primarily driven by the events in this one study.

I will now address more specific safety issues and start with adverse events of edema, congestive heart failure and weight gain. Fluid retention is a well described PPAR gamma-mediated

effect and correlates with insulin sensitizing efficacy. The sponsor developed a list of predefined terms in order to present a complete picture of edema-related adverse events in the clinical program. This list is not comprehensive but I include it to give you a sense of how edema was defined. For example, fluid retention or overload, generalized and peripheral edema, swelling and hypervolemia.

This figure illustrates the edema-related adverse events in the short-term phase of study 006, the dose-ranging study. In this study investigators were required to assess the presence or absence of bilateral pitting edema at each study visit.

While looking at the next three slides, please note that I have labeled the bars with percentages rather than absolute numbers. The incidence of edema was pretty similar in patients treated with doses of muraglitazar less than or equal to 5 mg. The pioglitazone group was somewhat higher. However, the rates of edema increased

considerably at muraglitazar 10 mg and 20 mg. All events in the lower doses of muraglitazar and pioglitazone were rated as mild or moderate in intensity. Two percent of the subjects on muraglitazar 10 mg and four percent of subjects on 20 mg had events rated as severe or very severe.

This slide combines the findings of edema-related events from the short-term phase of the four Phase 3 studies. In these studies edema-related adverse events were collected by spontaneous reporting. In the studies combined subjects in the muraglitazar groups had a slightly higher percentage of edema-related events than the pioglitazone group and the placebo group had the lowest percentage.

Because the results varied considerably from study to study, I have included the slide to demonstrate the results of edema-related adverse events by study. Again, edema events were dose related and the incidence was generally higher than placebo. Individuals in the muraglitazar 5 mg plus metformin group had moderately higher rates than

those in the pioglitazone plus metformin group, although this would perhaps be expected, given the greater efficacy of the muraglitazar 5 mg dose.

In addition to increased incidence of edema the fluid-retaining effects of PPAR gamma agonists can lead to heart failure in susceptible individuals. Again, I will be presenting the results for the short-term phases of the study. I will start by discussing investigator-reported events and then briefly review the adjudication committee results.

In the monotherapy dose-ranging study 006 the only heart failure events in the short term were in the higher doses.

In the short-term phase of the four Phase 3 studies combined the incidence of heart failure was dose related and greater than placebo. Overall, the numbers were few and the incidence was low.

In considering which studies had subjects with heart failure events, we see that all seven events in the short-term phase of the type 2

diabetes trials occurred in the combination therapy studies. This is consistent with what is known about thiazolidinedione use in heart failure. More edema and heart failure is seen in combination with other antihyperglycemic therapies.

A committee was formed to adjudicate investigator-reported adverse events, as well as other selected events that may be related. These are examples of predefined preferred terms that were used to select events to be sent to the committee.

In the Phase 3 studies the adjudication committee confirmed the six investigator-reported events of heart failure in the muraglitazar-treated subjects but not the one pioglitazone-treated subject. In addition, there were seven additional events of dyspnea or edema that were determined by the committee to be heart failure in the muraglitazar-treated subjects and one in the pioglitazone-treated subjects. Twelve or the muraglitazar-treated subjects were in combination studies and one subject was on muraglitazar 5 mg as

monotherapy.

Finally, before turning our attention to cardiovascular events, I would like to briefly mention weight gain as it also tracks with dose and drug efficacy. I realize that there is a lot to look at on this one slide, but it is to demonstrate the consistent dose relationship to weight change across all studies. These graphs represent weight change over the short-term period of the five type 2 diabetes studies, with weight change in kilograms on the Y axis and time in weeks on the X axis.

I direct your attention to the first graph of study 006 which demonstrates a clear dose relationship to weight gain. The red X's at the bottom represent muraglitazar 0.5 mg and the yellow circles at the top represent muraglitazar 20 mg. Muraglitazar 1.5 mg and pioglitazone 15 mg track very closely together.

The following four graphs demonstrate the Phase 3 studies. In these three graphs are the placebo control studies. The lowest line represents placebo and the upper lines represent

muraglitazar in a dose-related fashion. The last graph is comparing muraglitazar 5 mg plus metformin to pioglitazone 30 mg plus metformin. The muraglitazar had a slightly higher weight increase as compared to the pioglitazone group.

Finally, I will present our perspective on cardiovascular events in this program. The sponsor selected a priori a list of cardiovascular-related adverse events that encompass the following concepts: Myocardial infarction, coronary revascularization, coronary artery disease, angina and myocardial ischemia, cardiac death, stroke and transient ischemic attack. The cardiovascular deaths were only included if the preferred term met the predefined criteria. This list did not include congestive heart failure or related events, although a subject certainly could have had a cardiovascular and heart failure event concurrently. I should not that as this list was predefined there was no post hoc adjudication to determine whether a particular event should be counted, nor was there an adjudication to determine

whether a non-specific concept, such as chest pain, should be counted in an individual case.

This slide presents the sponsor's pooling of events for muraglitazar up to 5 mg, pioglitazone up to 45 mg, and placebo. I have also included results from the subjects treated with the higher muraglitazar doses for comparison. Again, the Y axis is percent and the values above the bars refer to the absolute numbers of subjects with events.

Remember that there were approximately 2,400 subjects in the muraglitazar pooled group versus 823 in the pioglitazone group and 528 in the placebo group. Also, remember that these three groups include subjects in the monotherapy and combination therapy trials, whereas the muraglitazar 10 mg and 20 mg groups were only in the monotherapy dose-ranging study. This figure shows that the percentage of cardiovascular events in the muraglitazar groups was approximately twice that of comparators. However, when presenting pooled events separately by monotherapy and combination therapy the imbalance of cardiovascular

adverse events between muraglitazar and comparator groups occurs in the combination studies.

When we break down the combination studies by individual study you can see how unstable these event rates are. In fact, one study, the glyburide add-on study 021, is really driving this imbalance with 11 events in the mortality arms and none in the placebo arm. When the three studies are combined the events in both groups treated with muraglitazar are higher than comparator although there is no clear dose relationship between 2.5 mg and 5 mg.

Finally, note in study 025, in which the cardiovascular death imbalance was seen, that there does not appear to be a marked difference in overall cardiovascular events between groups. Additionally, the percentage for both treatment groups in study 025 were lower than any of the groups in the other metformin add-on study 022.

These are some descriptions of the 11 cardiovascular events from the short-term phase of the glyburide add-on study 021. Events were

diverse in nature, comprising myocardial infarction, transient ischemic attack, angina and stroke. Let me also bring to your attention a couple of events demonstrating the limitations of the counting rules in capturing events.

This 68 year-old man randomized to muraglitazar 5 mg had electrocardiogram findings consistent with a recent myocardial infarction immediately prior to receiving his first and only dose of study medication. He was hospitalized the next day where diagnostic tests confirmed an MI.

This 54 year-old woman had a stroke on day 26 which was reported to have resolved on day 43, the same day the subject was diagnosed with a 15 mm brain stem tumor. The investigator reported the brain tumor as the cause of the subject's stroke.

Although this seems to be out of order, I will now present some relevant inclusion and exclusion criteria and subject baseline characteristics to provide some context for this presentation. First, all studies state that eligible subjects must have no history of

myocardial infarction, coronary angioplasty or bypass grafts, valvular disease, unstable angina or TIA or stroke within six months prior to study entry.

Because imbalances in cardiovascular deaths and coronary and cerebral vascular adverse events were seen in combination studies 025 and 021 respectively. I am showing you the difference in eligibility criteria between the monotherapy and the combination therapy studies. Subjects enrolled into the monotherapy study must not have received any antihyperglycemic therapy more than three consecutive or a total of seven non-consecutive days four weeks prior to screening. For thiazolidinedione therapy this is six weeks prior to screening. In the combination therapy groups subjects must be receiving treatment with sulfonylurea or metformin, depending on the study, for at least six weeks prior to screening. If a subject was previously on 20 mg of glyburide that requirement was two weeks.

As you can see on this chart of baseline

characteristics, subjects in the monotherapy studies were slightly younger, more likely to be male and have a slightly lower use of statins and diuretics. Mean body mass index, hemoglobin A1c and incidence of metabolic syndrome was similar. The length of time a subject had diabetes was different between the monotherapy and the combination therapy groups. Those in the monotherapy groups had a median duration of diabetes of a little over one and a half years, whereas those in the combination therapy groups had a median duration of five years.

In the Phase 3 studies whether or not a subject had diagnostic coronary artery disease at baseline was also collected. As you can see from this chart, baseline incidence varied widely between and within study, with higher incidence in the muraglitazar 2.5 mg groups than the other arms in study 018 and 021. The study with the fewest cardiovascular adverse events, 025, had the highest rate of baseline coronary artery disease per arm, at over 13 percent. But this was also the study in

which the 5 to 0 imbalance in cardiovascular deaths occurred.

Now let me review the concerns that we have raised, specifically the imbalance of cardiovascular deaths and adverse events, and highlight some points to consider for each issue.

First, to review the issue of deaths in the clinical program, most were due to cardiovascular events or cancer. Among the cardiovascular deaths we have tried to find a unifying cause. In the three deaths I presented to you congestive heart failure either preceded or coincided with the cardiac event that led to death. However, all these individuals had extensive cardiovascular disease and we cannot definitively conclude that the drug was the cause of death in any case. Therefore, despite the imbalance, no clear clinical or pathological pattern in cause of death within the broad cardiovascular category, that is, has emerged.

In addition, it should be restated that the majority of cardiovascular deaths were seen in

one study, 025, which was the metformin add-on pioglitazone controlled study, and that the five deaths only came from three study sites.

As for the issue of cardiovascular events, as with deaths, there was a diverse array of events with no clear unifying pattern selected from a predefined list of coronary and cerebrovascular conditions. When pooling studies the imbalance was observed in the combination therapy studies and was driven by one study, 021, the Phase 3 glyburide add-on study in which there were 11 events in the muraglitazar-treated groups and none in the placebo arm. A review of the events in that study did not alert us to any particular unifying cause and at least two events had questionable drug relationship.

Furthermore, when studies were pooled the events did not follow a dose-related pattern. The occurrence of cardiovascular events in the placebo groups in the combination studies was inconsistent and the lower number of events, particularly in comparator groups, make these incidence rates

unstable.

Finally to conclude, I would like to pose some questions for you to consider during your discussion. First, is it possible that the excess of cardiovascular deaths and events in the muraglitazar-treated subjects are related to fluid retention due to muraglitazar?

If not, is there another plausible pharmacological explanation that might implicate muraglitazar?

Third, are certain patients, such as those with a longer history of type 2 diabetes or other relevant medical history, more vulnerable to the adverse cardiovascular or fluid-related effects of muraglitazar?

Finally, I would just like to acknowledge the various teams that I worked with during my drug review. Thank you.

DR. WATTS: We will go on now to the presentation by Dr. El Hage.

Pharmacology/Toxicology Review

DR. EL HAGE: Good morning, Chairman

Watts, committee members and guests. My presentation will provide an overview of the toxicology profiles of the peroxisome proliferator-activated receptor agonists class in general based on extensive experience with this class at the FDA. So, I ask the patience of the committee and the audience because the majority of this talk will talk about the class in general rather than muraglitazar specifically. In addition, I will discuss the preclinical safety profile for muraglitazar and how it compares to the class in general, as well as how it compares to the approved PPAR gamma drugs.

PPAR receptors are nuclear receptors. They are ligand-activated transcription factors that bind to response elements in target genes to regulate gene expression. There are three PPAR isoforms, alpha, gamma and delta. These receptors are widely distributed and have pleiotropic effects. The alpha receptors are distributed primarily in the liver, heart, kidney, GI tract and skeletal muscle. Gamma receptors are highly

distributed in adipose, vascular endothelium, bladder, epithelium, the immune system, macrophages and the colon. PPAR delta or beta agonists are ubiquitously distributed.

It is clear from our extensive database that PPAR-induced adverse events occur due to receptor-mediated exaggerated pharmacologic effects. As I run through the known sites of PPAR-mediated toxicity it will become clear that the target organs for toxicity are the same sites where the receptors are highly distributed.

As has been discussed, fenofibrate and gemfibrozil are the approved drugs whose action is mediated via PPAR alpha activation. Pioglitazone and rosiglitazone are the approved drugs whose action is mediated via PPAR gamma activation. Muraglitazar represents the first NDA for a PPAR dual agonist. The PPAR alpha potency of muraglitazar is approximately ten times as potent as fenofibrate but the dose of muraglitazar that is given is greater than ten-fold less than fenofibrate. Therefore, the efficacy profile and

safety profile would be expected to be comparable to fenofibrate which, in comparison to the class in general, is a relatively weak PPAR alpha agonist.

The PPAR gamma potency of muraglitazar is comparable to rosiglitazone and muraglitazar is proposed for use in a comparable dose range. Unlike the approved PPAR gamma agonist drugs, muraglitazar has a non-thiazolidinedione structure.

The Division of Metabolic and Endocrine Drugs has reviewed data from more than 40 PPAR compounds. Therefore, our understanding of PPAR-related toxicity is far greater than it was in the late '90's when the first drugs in this class were approved. The toxicity profiles associated with each PPAR subtype are well understood. However, the mechanisms of PPAR-induced toxicity are still not particularly well understood, unfortunately.

There is excellent cross species concordance for PPAR-mediated toxicities, that is, the toxicities are observed in all species, including humans, and the non-toxic exposures in

animals, that is, the exposures with the no adverse effect dose, the non-toxic dose in animals, predict safety clinical exposures. This relates back to the questions of Dr. Dominick on why do you study high doses and why do you think they are not relevant when you see them at high doses. Toxicity studies are designed to push the doses to identify potential targets, but we are only concerned about toxicities that occur at or relatively slightly above therapeutic exposures.

In addition, most PPAR-mediated toxicities are moniterable. Therefore, clinical studies can characterize the safety profile for most PPAR-mediated toxicities. The exception is for the potential to induce cancer. Because the latency period for cancer is quite long--that is, even known human carcinogens take at least ten years for the development of cancer--therefore, the pre-approval safety databases are not adequate to identify the potential in cancer risk. Therefore, companies routinely do two-year rodent carcinogenicity assays to assess the potential of

compounds to produce cancer.

PPAR gamma-mediated adverse events--and I want to specify that this slide is an overview of effects of the class, not muraglitazar--the common PPAR gamma-mediated adverse events are adipose proliferation and deposition in tissues. We had some discussion that PPAR gamma agonists cause fatty infiltration of bone marrow. This is a very common effect with PPAR gamma and dual agonists and it is often seen at exposures in the therapeutic range.

Fluid accumulation, edema, cardiac enlargement and heart failure--we have had an extensive discussion of that already this morning. Notably, this is the dose-limiting toxicity for any agonist with PPAR gamma activity, both in animals and in humans.

Anemia, neutropenia and bone marrow suppression are often seen. Notably, the bone marrow suppressive effects--dogs tend to be much more sensitivity to that. The question earlier addressing bone marrow suppression in dogs is

notable. The relative contribution of hemodilution versus fatty infiltration of the bone marrow to the PPAR gamma-mediated anemia is unclear.

We have had a discussion of neutropenia effects and I will state that neutropenia is observed more commonly with PPAR dual agonists than it is with PPAR gamma only agonists. Lymphoid depletion, that is, splenic atrophy and thymic atrophy, are commonly observed at high doses in animals treated PPAR gamma agonists. Unfortunately, the potential to produce immunotoxicity in animals has not really been well studied.

As we have discussed at length, muraglitazar produced dose- and duration-dependent fluid accumulation, edema and cardiac enlargement in animals and dose-related edema in congestive heart failure in humans.

PPAR alpha-mediated adverse events include peroxisome and hepatocellular proliferation, liver hypertrophy and liver cancer in rodents. This is the finding that led to blaming of the drug class.

Contrary to the published literature, the more potent dual and alpha agonists that are in development do cause two- to five-fold increases of peroxisome proliferation in primates but, notably, no peroxisome proliferation was observed with muraglitazar. And, primates are much less sensitive to these effects than are rodents.

Skeletal and cardiac muscle degeneration is observed with more than 50 percent of alpha compounds, that is, alpha agonists or dual agonists. Skeletal muscle degeneration has also been observed clinically with both dual and alpha agonists. Notably, skeletal muscle degeneration is the dose-limiting toxicity for PPAR delta agonists. Although that is not the topic of our discussion today, but virtually all of the PPAR delta agonists produce skeletal muscle degeneration in animals.

Renal tubular toxicity is observed with about 20 percent of dual and alpha agonists, and it has been observed both preclinically and clinically with proximal renal tubular injury, and it is well-known that PPAR alpha receptors are located in

the proximal tubules.

Gastrointestinal toxicity, including hyperkeratosis, necrosis, ulcers, hemorrhage, have also been commonly observed with PPAR alpha agonists. Rodents are particularly sensitive to this effect but it has also been a dose-limiting toxicity clinically with the PPAR alpha only agonists.

PPAR alpha-mediated toxicities were observed extremely infrequently in animals treated with muraglitazar, and only at very high doses, doses either 30 times higher than the recommended clinical dose or doses associated with severe toxicity. The incidence of these findings was so low that they cannot be clearly associated with muraglitazar treatment.

So, overall, muraglitazar has an excellent preclinical safety profile for most PPAR-related toxicities. There were no findings of liver toxicity, kidney toxicity, skeletal muscle toxicity or GI toxicity. This is consistent with the very weak alpha potency of muraglitazar.

The preclinical safety profile is similar to the approved PPAR gamma products. Notable, there was no premature cardiovascular mortality in two-year studies in mice and rats at very high doses, that is, doses associated with exposures in excess of 50 times the clinical exposures. In addition, there were no premature cardiovascular deaths in monkeys treated for up to one year. BMS conducted two chronic monkey studies with muraglitazar, a nine-month study and a 12-month study. Notably, these findings are different from the class in general for gamma agonists and for dual agonists. In fact, we set doses for study in carcinogenicity studies based on being able to predict premature cardiovascular deaths associated with PPAR gamma activity.

There was no evidence of pericardial or thoracic fluid accumulation. No evidence of atrial dilation or thrombi in animals treated chronically with muraglitazar. Again, these are common findings seen with other PPAR gamma and PPAR dual agonists. So, the overall conclusion here is that

there is nothing in the animal data that predicted an increased cardiovascular risk associated with muraglitazar. In fact, muraglitazar had a cleaner cardiovascular profile than most drugs in the class.

As I alluded to earlier, one of the major safety concerns for this class is PPAR-induced cancer in rodents. The FDA has reviewed the two-year rat and mouse carcinogenicity data for 11 PPAR compounds, five gamma agonists, six dual agonists. The PPAR gamma and dual agonists induce multiple tumor types in mice and rats of both sexes or multiple strains. According to the Environmental Protection Agency and International Agency for Research on Cancer Criteria, for compounds that are multi-species, multi-sex, multi-site, rodent carcinogens are classified as probable human carcinogens.

As Dr. Golden alluded to, the overall findings for the class have led to recommendations that we need the rodent carcinogenicity findings. We need to analyze those findings and establish

safety margins between therapeutic exposures and the exposures associated with tumor formation before allowing long-term clinical trials with this class.

The sites of tumor development with PPARs are consistent with the distribution of the receptors. That is, we see adipose tumors, vascular tumors, bladder epithelial tumors, skin tumors, renal tubular tumors. Since the mode of action for most tumor types is unknown, the human relevance cannot be ruled out at this time.

This slide summarizes the tumor findings observed with the PPAR gamma agonists. You will note that the three previously approved gamma agonists are listed. IN addition, compounds A and B--we have results for those but those compounds have been discontinued for clinical safety issues. For compound C we have findings that resulted from an IND safety report which reported hemangiosarcomas in mice. We do not have the complete results of the two-year rat study or the two-year mouse study and that is why the findings

for the other tumor types are empty.

As you can note, vascular tumors have been observed in mice of both sexes with four gamma agonists. Notably, the approved drugs and marketed drugs, Avandia and Actos, do not produce vascular tumors. Bladder tumors are observed in male rats with pioglitazone. Adipose tumors, lipomas, liposarcomas have been observed with three compounds but, notably, Avandia produced only benign tumors, lipomas, and at high doses, greater than 20-fold clinical exposures. Liver tumors are not commonly seen with the gamma agonists, as would be expected because it is known that rodent liver tumors are induced by PPAR alpha activation. The other tumor types that were seen were muscle tumors, sarcomas in the stomach and cervix and gallbladder adenomas in mice.

The next slide summarizes tumor findings with the PPAR dual agonists. Notably, compound D, E and F have been discontinued due to the rodent tumor findings, and that is because they saw multiple tumor types in rodents of both sexes and

some of the tumors were observed at the lowest dose which provided exposures comparable to the therapeutic exposures.

Again, we can see that 4/6 dual agonists produce vascular tumors. Notably, muraglitazar was not associated with increases in vascular tumors. For one compound we have no data because that drug was discontinued for renal toxicity and the tumor findings and, to my knowledge, the mouse study was never submitted. Bladder tumors were observed with 5/6 dual agonists. Notably, for most compounds it was observed in both sexes.

I apologize, I want to backtrack to one other point regarding the hemangiosarcomas. The hemangiosarcomas, in addition to being observed in both sexes, were observed in multiple strains of mice, B6 mice, CD1 mice. Similarly, the bladder transitional cell carcinomas are observed with 5/6 PPAR dual agonists, and they were observed in multiple strains of rats.

Additional tumor types include fibrosarcomas of the skin in rats, fat tumors,

liposarcomas primarily in rats of both sexes, and multiple other tumor types, liver tumors which would be an expected effect of PPAR gamma agonists, not thought to be relevant clinically. The testicular and thyroid tumors are presumably secondary to the liver effects of PPAR alpha as well. Other tumor types seen, again, were muscle tumors. There were leiomyosarcomas in the uterus and stomach and mammary tumors for several drugs.

The next slide summarizes the overall findings of concern. First, hemangiosarcomas were observed in mice with 8/11 compounds, 4 gamma and 4 dual agonists, observed in both sexes and in multiple strains. The bladder tumors were observed with 5/6 dual agonists and pioglitazone. Notably, the doses of pioglitazone that produced tumors in rats are adequate to fully activate PPAR alpha receptors in rats, which is consistent with this being an effect of dual agonism.

Liposarcomas and lipomas were observed in rats with three gamma and three dual agonists. Sarcomatous tumors at in multiple other sites,

muscles, skin, renal tubules have been observed with three dual agonists. Again three of these dual agonists have been discontinued due to the rodent tumor findings when the tumors were observed with doses in the therapeutic range.

This slide is just a summary slide of the tumors with muraglitazar. The numbers in yellow are the doses studied, which were 1, 5, 30 or 50 mg/kg in rates; 1, 5, 20 or 40 mg/kg in mice. As was previously described, dose-related significant bladder tumors were observed in males. I present my data slightly differently than BMS. I presented the data for lipoma and liposarcoma because I think this is probably the more relevant endpoint. There were statistically significant increases in adipose tumors in males, but only at the highest dose which is, again, greater than 50 times clinical exposures. There were gallbladder adenomas. Although not statistically significant, there was a dose-related trend at the two higher doses and BMS concluded that this was a biologically significant finding because gallbladder hyperplasia was

observed in male and female mice.

I just want to do a brief risk assessment for the bladder tumors. Again, the bladder tumors were induced in male rats at doses greater than 5, which is greater than 8 times the clinical exposures. As Dr. Dominick discussed, BMS did extensive mechanistic studies which, the FDA agrees, provide convincing evidence that muraglitazar-induced changes in urine pH and electrolyte concentrations lead to crystal formation in male rats which produce irritation and hyperplasia which result in bladder cancer. Also as he discussed, this is a mode of action not thought to be relevant to human bladder cancer induction.

There was no evidence of bladder hyperplasia in either the 9-month or the 12-month monkey studies with muraglitazar. However, bladder hyperplasia has been observed in primates treated chronically with other dual and alpha agonists. In addition, muraglitazar differs from most other dual agonists that produce bladder tumors in that they

were only seen in male rats rather than rats of both sexes.

Risk assessment for other muraglitazar-induced tumors--the increased fat tumors in male rats was the only other tumor type that was statistically significantly increased. Again, that was only observed at greater than 50 times the clinical exposure. There was no significant increase in hemangiosarcomas in mice as has been observed with eight other compounds, and the 50-fold safety margin between drug exposures associated with tumors in rodents and therapeutic drug exposures suggests a negligible cancer risk.

I would like to expand on this slightly in stating that muraglitazar, in addition to virtually all the other PPAR agonists that we have carcinogenicity data for, are non-genotoxic compounds. For genotoxic carcinogens threshold doses cannot be defined but for compounds that induce tumors in the epigenetic, non-genotoxic mechanisms, that is, secondary to proliferation or tissue injury which leads to hyperplasia which

progresses to tumors, the thinking is that threshold doses for tumor formation can be defined. As was clearly stated by Dr. Dominick, they saw a slight increase in tumor incidence at 50 times the clinical dose but not increases in tumor incidence at 17 times the clinical dose in mice and actually 40 times the clinical dose in rats.

Therefore, our conclusion is that there is really a negligible cancer risk with muraglitazar, despite the signal of concern with the class. And, the carcinogenicity profile of muraglitazar is similar to the approved PPAR gamma agonists and differs significantly from that of the PPAR dual agonist compounds that have been discontinued for tumor findings.

Lastly, the overall preclinical toxicology conclusions are that muraglitazar has an excellent preclinical safety profile, comparable to the approved PPAR gamma agonists. The PPAR gamma-mediated cardiovascular safety profile in animals is similar to the approved drugs in that there are safety margins greater than ten-fold for

compound-induced cardiovascular effects. The rodent carcinogenicity findings with muraglitazar are also similar to the approved drugs. That is, we see bladder tumors in male rats for pioglitazone at high multiples of the human exposure and adipose tumors with rosiglitazone at high doses. None of the compounds produce liver tumors in rodents like the fibrates. The mechanistic data for the bladder tumors and the observation of adipose tumors only at very high drug exposures suggests a negligible risk. Thank you.

Committee Discussion

DR. WATTS: Thank you. We have a few minutes before lunch for questions from the committee to the FDA presenters. In this session and when we reconvene for questions by committee and responses by the agency, if there are any follow-up comments from the sponsor, we would be happy to hear those. Dr. Levitsky?

DR. LEVITSKY: In the study which showed a skewing of rates of cancer, was that well controlled for smoking rates in both groups and

were body weights similar in those two groups and the people who had the malignancies? Can you look at that?

DR. WATTS: From the sponsor's presentation?

DR. LEVITSKY: No, no, no, from Dr. Golden's presentation.

DR. GOLDEN: Can you ask the question again?

DR. LEVITSKY: In the study which showed the skewed rates of cancer occurrence was there good control for smoking incidence?

DR. GOLDEN: There wasn't a specific study that showed the skewing of the cancer death rate. It was across all the studies. I don't have the information. Maybe the sponsor can provide that about smoking distribution across the doses and treatment groups.

DR. LEVITSKY: And the body weight as well or body mass index?

DR. GOLDEN: Body mass index was well matched across groups.

DR. WATTS: Dr. Woolf?

DR. WOOLF: I must confess I am confused. There is a page that appeared on our table, page 13, that is an amended page from the briefing document. Dr. Golden, is this from you or from somebody else?

DR. ORLOFF: This is an errata sheet that relates to the statistical review that was in the background package that was received by the members, and it is actually posted on the web. What it is, it is a replacement page 13 or Dr. Pian's review, a reanalysis or essentially a revised analysis of the deaths and cardiovascular deaths with the inclusion of the pulmonary embolism death in the placebo group.

DR. WOOLF: Who can I address the question to based upon this data?

DR. ORLOFF: Why don't you try addressing it to FDA and we will find someone to answer it?

DR. WOOLF: The sponsor's slide 72 and 74 relating to cardiovascular events and cardiovascular deaths, an incident rate per 1000

years, seemed to show that there was no difference between placebo and any of the doses. I am not a statistician but trying to read the amended page 13 suggests that, using the statistical methods that the statistician used, there might be a difference. But then there are some caveats at the end that said that basically because there were multiple statistical tests that were used the nominal p value may, in fact, be overstated. So, on one hand I have data from the sponsor that seems to show there is no change, and then I have data from the agency that suggests that perhaps there is but perhaps there is not a difference. So, I would like to know.

DR. SAHLROOT: I will try to address that. My name is Todd Sahlroot. I am a statistical team leader with FDA. The analyses that we did on page 13 of the statistical review are based on the combination studies. It does not include any monotherapy data so they are based on the three combination studies. We looked at basically tests for slope across doses of 0, 2.5 and 5 mg based on

a null hypothesis of the zero slope. We did three different tests based on either incidence rate, Kaplan-Meier time to event or a Poisson test based on person years, and that is where we got our p values of 0.04, 0.05 and 0.06. So, it is different data than the sponsor used. We concentrated on the combination studies because that is where, in fact, all the CV events were, except there was one event at 20 mg but that is not a marketed dose.

DR. FOLLMANN: I would just like to add a little bit. The sponsor's analysis that I talked about or mentioned earlier is for cardiovascular events, which would include fatal and non-fatal events. This page 13 is for deaths.

DR. SAHLROOT: Death only.

DR. FOLLMANN: Here we some signal for a trend where higher doses are associated with increased risk of mortality, though we must remember the numbers are small; the studies were not designed to look at these endpoints.

DR. SAHLROOT: Right, So, the comment on the web involving p values is that these are

nominal p values, based on safety endpoints, and not part of a formal hypothesis testing framework that we typically set out to do when we look at efficacy. These are just unadjusted p values.

DR. FOLLMANN: The other point I would like to make I guess related to this is that in the sponsor's package, I think around page 126, they do an analysis of any muraglitazar versus none with their extended or complete data set using cardiovascular events as the outcome. For that analysis they don't report the risk ratio but the p value for that is 0.05, I believe, favoring placebo.

DR. WATTS: Does the sponsor wish to comment?

DR. FIEDOREK: Let me call Dr. Labriola in a minute. I just want to give the context. We were, throughout our program, trying to understand the signals that arose out of individual studies, and trying to do our best to give the broadest interpretation by combining placebo and pioglitazone in the one instance. In the other one

you mentioned we also did some analysis by dose. I would like Dr. Labriola to provide our view on this.

DR. LABRIOLA: Sure. We have done a little bit more exploration on the analysis that was provided in the FDA statistical addendum with respect to cardiovascular mortality, which I hope will be somewhat enlightening to the committee.

Before I begin that, I would like our group to pull up slide SA-39, please. This particular slide demonstrates the contribution to those analyses of the three trials that were included in that analysis. Two of those trials, study 21 and 22, are placebo-controlled studies. Based on those placebo-controlled trials, we calculated the number of cardiovascular deaths per 1000 patient-years of exposure in each of the treatment arms. Study 21, as you can see, had a total of two events, one in the placebo arm and one in the 5 mg arm. In study 22 we also had two events. The two events happened to be one at the lower dose of muraglitazar, 2.5 mg, and an event on

5 mg.

When the two placebo-controlled trials are combined we see that there is an event rate of 3.5 cardiovascular deaths per 1000 patient-years estimated for placebo; 2.1 events per 1000 patient-years for the 2.5 mg dose; and 4.3 events for the 5 mg dose. I do point out, obviously, that those numbers are based on a very small number of events. However, if you were to conduct that trend test--and actually we provided a slightly different trend test, we used the Cox proportional hazards model for the trend--and if you look at the placebo data the p value is 0.739.

The point I am leading to is that it is actually study 25 with the balance of five deaths versus zero which is really highly influential in this analysis. If you look at the three studies combined, the impact of adding study 25 to this analysis shows that the placebo rate when the pioglitazone controls are combined to it changes from 3.5 to 1.4 events per 1000 patient-years. And 2.5 mg was not studied in study 25 and there were

an additional five events on the 5 mg dose. The importance of adding these three studies together is that if you look at the 2.5 mg, when study 25 is added, the actual hazard ratio of 2.5 mg to placebo actually increases from 0.6 to 2.0 due to a study which actually did not study 2.5 mg. The hazard ratio associated with the 5 mg is 5.87. The p value is borderline statistically significant with a value of 0.074. The critical issue we are raising is that it is really focused on and is driven by a single trial in which a small number of events occurred.

DR. FIEDOREK: I would really like to ask in terms of the clinical interpretation of this--we were obviously concerned and the FDA was concerned with this analysis and we were analyzing events related to adverse events and not the adjudicated events. Dr. Keech actually has considerable experience in this realm and is the lead investigator of the field trial, and I would actually like him to comment, if he would, about these analyses and how we can help.

DR. KEECH: Thanks very much. Well, I think the answer is that, unfortunately, there were too few events really to make much out of. Obviously, one can neither rule in nor rule out with so few cardiovascular events the possibility of either a major benefit of this treatment on cardiovascular disease or some harm. That would take several hundred events to do which is why, obviously, the company is committing to a major morbidity and mortality trial.

We see this all the time with very small numbers of events. Even in large-scale trials very small numbers of cancer events, such as breast cancer in the CARE[?] trial occurred raising concerns which were subsequently refuted by other trials with larger numbers of events in them, with the same treatment and the same dose. So, I guess my view would be that whilst there are signals that might raise some concern here, the numbers of events are just too small to draw definitive conclusions about any real concerns or the possibility of benefit. Of course, if a

large-scale morbidity/mortality trial is performed, it is with the intention and expectation of a substantial benefit on cardiovascular events rather than any particular harm.

DR. WATTS: Thank you. Before we break for lunch let me tell those at the horseshoe table that there is space reserved in the back of the restaurant for this group. If there are burning questions we can address them now, otherwise we can reconvene at one o'clock.

[Whereupon, at 12:05 p.m. the proceedings were recessed for lunch, to reconvene at 1:05 p.m.]

A F T E R N O O N P R O C E E D I N G S

Open Public Hearing

DR. WATTS: We will start with an announcement regarding the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your oral or written statement to advise the committee of any financial relationships that you may have with the sponsor, its products and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee

if you do not have any such financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

Now, we have one person who is registered to speak and that is Dr. Peter Lurie. Would you please come forward?

DR. LURIE: Good afternoon. My conflict of interest statement, the declaration is that I have none. Public Citizen takes no money from government or industry.

I am Peter Lurie, deputy director of the Health Research Group and I am here to oppose the approval of muraglitazar because, in our view, the risks are too great with respect to the benefits that have so far been demonstrated.

Let me start with efficacy. It is unquestionable that the sponsor has demonstrated that muraglitazar can modestly reduce hemoglobin A1c and reduce triglycerides and raise HDL by somewhat less impressive degree.

But there are a few things that the committee ought to take in mind. Firstly, as noted by the statistical reviewer, the doses of pioglitazone that were used as comparators in the various studies appear to have been selected to put muraglitazar in a favorable light. Although pioglitazone is approved in doses as high as 45 mg, only the 15 mg and the 30 mg dosage forms were used in the muraglitazar trials. This is one of the oldest tricks in the drug company playbook, comparing your drug to an under-dosed competitor.

Second point, the statistical reviewer notes that the 5 mg dose has only "small incremental" efficacy compared to the 2.5 mg form. Given the safety concerns that I will enumerate and that I am sure you have already discussed and will discuss further, which do seem to be clearly dose related, the risk/benefit ratio for the 5 mg form seems to be particularly adverse.

The possibility of approving a 1.5 mg dosage form has also been raised but, in fact, none of the four Phase 3 trials offered by the sponsor

actually test the 1.5 mg dosage form. There is a Phase 2 trial that does but it doesn't contain a placebo group. In our view, this does not provide a firm enough evidence base to conduct a risk/benefit assessment for the 1.5 mg dose.

Finally with respect to efficacy, and most fundamentally, the studies were not designed to look at hard diabetes outcomes such as micro- or macrovascular disease which, of course, are the real concerns in diabetes management. The randomized portions of the studies were of only 24 weeks duration so we know little about the impact on these outcomes. to the extent that hard outcomes were looked at--I am thinking here of cardiovascular death or overall death--the data seem to show the drug to be associated with an adverse impact.

Let's talk about safety then. The most striking toxicity finding in our view is the apparent increase in deaths, both total deaths and cardiovascular deaths, among patients taking muraglitazar in the clinical trials. The

percentages suffering death for any cause in muraglitazar, pioglitazone an placebo were 0.59 percent, 0.24 percent and 0.17 percent. For cardiovascular disease the percentages were 0.28 percent for muraglitazar, 0 percent for pioglitazone, and 0.17 percent for placebo. According to the sponsor, the relative risks for the 2.5 mg and 5 mg muraglitazar doses respectively were 1.7- and 4.6-fold increase for total death--right?--for all-cause mortality, and 2.0 and 5.9 for cardiovascular mortality.

The company will point out that these are not from randomized trials or the data are drawn from randomized trials but it is not randomized data exactly and will, therefore, claim that there are differences between the study groups. That is something you can't really prove or disprove. Nonetheless, these findings are there and they are consistent and we think they should be taken extremely seriously.

Congestive heart failure--considering only the Phase 3 trials, the rates of congestive heart

failure, the ones confirmed by the adjudication committee, were 0.75 percent for muraglitazar when you look at the 2.5 mg and 5 mg doses, 0.17 percent for pioglitazone, and 0 percent for placebo. This dose-related toxicity and consistent with the toxicities that we see for other compounds with PPAR gamma agonist activity.

Of related concern are the increased rates of, again, dose-related weight gain and edema in muraglitazar-treated patients, which led to many drug discontinuations. The 5 mg dose was associated with weight gains of 2.9 kg to 3.6 kg in the various clinical studies. As the safety reviewer notes, "given the morbidity associated with obesity in the type 2 diabetes diabetic population, significant increases in body weight may limit the use of this drug."

Finally on safety carcinogenicity, muraglitazar does cause tumors in both rats and mice. It does so in both genders and it does so at multiple sites. Therefore, if you use the EPA and IR criteria it is properly classified as a probably

human carcinogen. Moreover, those tumors occurred exactly where you would expect them to happen, where PPAR receptor concentrations are the highest, in the bladder, adipose tissue, gallbladder and uterus.

Of greatest concern are the bladder carcinomas which occurred in male rats in as little as eight times the human exposure, a pretty small multiple considering the differing blood levels that one can get even giving identical doses to different humans. Development of three dual PPAR agonists has been discontinued as a result of similar rodent carcinogenicity findings.

No doubt, the sponsor will try to downplay the bladder carcinogenicity findings with a serious of mechanistic arguments which will include urine pH crystal formation and citrate levels. One can consider those, of course, but many of those arguments apply only to male rodents and the tumors were observed in both genders. And, many of the often negative studies in other animals were either under-powered, of short duration or inadequately

conducted so they provide little assurance.

Finally putting it all together, muraglitazar is a drug with modest ability to reduce hemoglobin A1c but no proven ability to reduce the micro- and macrovascular complications of diabetes. It is a drug that comes into a relatively crowded therapeutic field, where on the order of a dozen other drugs for diabetes are available.

On the other hand, it does appear to be associated with increased risk of total and cardiovascular deaths compared to other drugs on the market, with high rates of congestive heart failure, more weight gain and edema, and it is a proven bladder carcinogen. While excitement about the novel action of a drug is understandable, experience with troglitazone, which came before this committee, which was heralded for its therapeutic effects in part because it had a unique mechanism of action, demonstrates that in the end the wisest course is to pay attention to the clinical data and not to theoretical mechanistic

arguments. On the basis of the data presented, muraglitazar does not merit FDA approval. Thank you.

Committee Discussion and Questions

DR. WATTS: Thank you, Dr. Lurie. Is there anyone else who would like to make comments at this time? Seeing no one, we can go ahead with committee's questions and discussion, questions regarding the FDA presentation from this morning and follow-up with any additional questions. Dr. Aoki?

DR. AOKI: This is directed to Dr. El Hage. Since FDA committee meetings such as this do spend a lot of time looking over the animal data, the question I have is what is the experience of the FDA in looking at cardiovascular events in animals and its relationship to clinical findings? For example, if you find a drug like muraglitazar with a very low probability of problems from a cardiovascular point of view, has this in your experience, or the FDA's experience, manifested itself as low cardiovascular problems in terms of

human scenarios? Granted, that the animals may not have diabetes so that is a variable that we have to take into consideration. But not just looking at muraglitazar but any drug where you look at cardiovascular outcomes in animals, is the concordance 100 percent using the dose ranges that are used in the animal studies, or is it less than 100 percent?

DR. EL HAGE: I will try to answer your question from the last question back to the first. Obviously, I don't work in the cardiovascular drug area. My expertise with those drugs is not as extensive as with this particular class. From hearing statements from the team leaders from the Cardiorenal Division, I don't think they always think there is a good predictor between preclinical data and animal data. However, an exception to this--I have been working with FDA for 18 years; I have never seen a class of drugs where the preclinical toxicity is so predictive of the clinical toxicity for cardiovascular outcomes as well as others.

I can't answer the question whether a good animal outcome will predict a good clinical outcome, but we clearly have extensive evidence to the contrary. That is, for many of these compounds the NOAEL is at the therapeutic exposure but three times the animal NOAEL, five times the animal NOAEL results in death due to CHF in animals--very narrow therapeutic indices--and several of these compounds have been discontinued for clinical cardiovascular events.

So, we know that a bad preclinical outcome predicts a bad clinical outcome. We don't have significant data to know whether a good preclinical outcome predicts a good clinical outcome.

DR. WATTS: Dr. Levitsky?

DR. LEVITSKY: This may be a question for the sponsor. Obviously the 025 trial was concerning to you all. Did you go and look through that trial to look for other confounders that were not well controlled, like smoking for instance?

DR. FIEDOREK: Across the program we looked for those factors. What we focused on was

to look at some of the expected causes like edema. As far as looking across the program for other confounders, we saw, as was answered earlier this morning, that a smoking history also was quite comparable in the various trials. Is there information to show that? You know, I think we are reporting the information accurately.

One of the points that I would like to make is the question about--well, let me show this slide, 311-54. This gives you an idea of the underlying factors, not in the 025 trial per se but for the entire program looking at the underlying cardiovascular risk factors in diabetes, certainly, but also other conditions, that contribute to the risk of having subsequent events. One of the points in interpreting this information is that, clearly, hypertension, the presence or absence, was common without or with a CV events. Those types of events that were more acute in nature, such as unstable angina, such as prior events of interventions, and things like that, did seem to have more of a risk for subsequent cardiovascular

events. Other events where something was completed or a procedure was done didn't seem to have as high a risk, a corrective procedure. I hope this helps you.

DR. LEVITSKY: Well, it would help me if I could see that then divided up into other columns for the different groups. Were there equal amounts of hypertension in each of the different groups, previous MIs, etc? Were those balanced?

DR. FIEDOREK: Let me comment on this and then move on to some other factors that we looked at in terms of baseline characteristics. These factors tended to be most prevalent in the patients who were in the combination studies. As Dr. Rubin mentioned, they had histories of diabetes that were on average five or six years longer. They were on combination therapy and the patients who were on monotherapy had histories of diabetes for one or two years.

Let me actually call up slide 311-55 to give you some of the other baseline characteristics, again, across the program, not

specifically to the 025 study. This does include smoking history and other past histories. Smoking current is the sixth one down. You can see that current smokers had a slightly higher increased risk of a CV events, as you would expect in the general population as well. Other factors that contributed are related to other known cardiovascular risk factors such as cholesterol levels and the other factors here. Does this help?

DR. LEVITSKY: You still haven't address my question though, which is when you look at the groups, are any of those confounders different in the different groups?

DR. FIEDOREK: Dr. Daniels?

DR. DANIELS: In 025 specifically--I think actually this was provided by Dr. Golden at FDA. That study is unique in that in general patients were at a higher baseline risk for a cardiovascular event. If you looked at things like previous history of MI, revascularization, if you look among the treatment groups you don't really see an imbalance in those patient demographics. So, we

have looked to see, obviously, in each one of our studies, both in 021 where we saw an event imbalance in the short term--we didn't really get into it but short-term plus long-term experience in 021 tells a slightly different story because we began to accumulate placebo events in 021 in the long-term part of that. But we have looked in both studies where we had this issue, and carefully interrogated the baseline demographics, including continuous variables and discrete variables, and I can't say there was anything striking that would have predicted the result, other than the fact that we are just talking about five events in the study and, you know, they could have happened in any number of distribution. I think that may answer it.

What Dr. Fiedorek was trying to explain to you is that when we look at who had events across the entire program, not unexpectedly, the people who had events were the people who had not just diabetes, which is a risk factor, but additional cardiovascular risk factors. So, I don't

necessarily think that was an unexpected result.

DR. LEVITSKY: Would you then suggest that that should be a caveat for use of this drug, having all those additional risk factors?

DR. DANIELS: What I would say is that you would want to take that in consideration, particularly as you individualize therapy with respect to dose. I wonder if Dr. DeFronzo has any opinion as to how you would take that part of medical history into picking dose.

DR. DEFRONZO: We have a very large experience at the Texas Diabetes Institute. We treat about 10,000 patients annually. About 30 percent are on pioglitazone. So, amongst our group we have about 18 endocrinologists that discuss this at length. I think that the American Heart/ADA Association has put forward a very nice position paper that says that in Class III/IV congestive heart failure these drugs should not be used and I would put muraglitazar in that category. I think in people with Class II congestive heart failure, these people should be started on the lower dose of

muraglitazar, just as we start on lower dose of pioglitazone or occasionally rosiglitazone but we mostly use pioglitazone. And, these people should be monitored quite carefully. One thing that we find to be very useful is jut to monitor the body weight because that picks out the people early on who are going to gain both fat weight as well as fluid weight.

In fact, if you look at the muraglitazar data, most of the people who had events had multiple components that are in the ADA/AH statement that says that you ought to monitor these people carefully. So, that would be my approach.

A second point is that there is going to be a pharmacovigilance study. As was pointed out, there are going to be 15,000 patients who will be followed up carefully to look for any kind of adverse events and, of course, cardiovascular events are going to be one of the events that they will be looking for.

Then, a third point is that there will be planned an intervention study. I think you need to

recognize that in order to get meaningful data from an intervention study, and in fact intervention studies to prove benefit, you need a minimum of 5,000 people followed for five years with an anticipation of 500 events. So, although there may be this imbalance in these trials, I think it is important to recognize that we are dealing with small numbers of people and that if we really want to come up with more definitive answers we need larger studies. The company is, in fact, planning, in addition to the pharmacovigilance study, a prospective study which, in fact, I believe will decrease cardiovascular events. We are all very excited to find out what PROactive is going to say on September 12 because that may give us some additional insight into the atherosclerotic aspect. Hopefully, we will see that it gives you cardiac protection.

DR. WATTS: Dr. Burman?

DR. BURMAN: I just want to maybe ask Dr. Orloff and his group a question that was brought up by Dr. Lurie and that I have. That is, the

previous PPAR gamma agonists, when they were approved by the FDA, did all of them cardiovascular mortality hard endpoint data?

DR. ORLOFF: None of them did and, to my knowledge, none of them does to this date have any formal morbidity and mortality trial data to address in labeling.

DR. BURMAN: If I could ask a second question related to Dr. Lurie's presentation as well, could you refresh my memory, Dr. Orloff, related to the carcinogenesis, the bladder carcinogenesis in the previous agents you must have evaluated that were withdrawn with regard to dose and duration of causing bladder carcinogenicity compared to muraglitazar. Were they similar dose? Similar frequency of bladder cancer?

DR. EL HAGE: There was similar frequency of bladder cancer. The issue was that for the drugs that were removed from the market the bladder cancer was seen at all doses, with the lowest dose being comparable to therapeutic exposures and in some cases even lower than therapeutic exposures.

So, they felt they had no safety margins for the tumors.

But I will also add an additional comment, that you have to do these specialized mechanistic studies that BMS did to really determine the mechanism for the bladder tumors. It was only once we became aware of this prevalence signal with the dual agonists that we began asking sponsors to monitor clinically, to plan mechanistic studies to try to explain this tumor finding if, indeed, they did test it. So, the data for the earlier drugs did not have the mechanistic data to explain the potential rodent specific mechanism for the cancer. We know that there are a lot of compounds that cause rodent specific bladder tumors. We thought that this was a possibility and that with mechanistic data we would be able to explain it, but we didn't have the data.

A couple of other comments, there were no findings in monkeys of hyperplasia with muraglitazar. Many of the other drugs have tumors in males and females, and they have hyperplastic

findings in monkeys. So, we still have to do extensive mechanistic studies for each drug on a drug-by-drug basis but we still review each individual drug based on the data for that drug.

DR. WATTS: From the committee, other questions or comments either for the FDA or fort he sponsor? It looks like you are ready to proceed with the questions.

DR. ORLOFF: As usual, I need to make a point of clarification. I will not walk you through all the questions but, again, similarly to yesterday for those who were here on the panel, I have asked some yes or no questions in items one and two. Then I have listed some areas for comment and/or discussion in item three. Now, many of those areas for comment and discussion have been the subjects of discussion this morning. I leave it up to the members and the chair as to how much further or what additionally you want to do on these particular subjects and whether you want to raise any new ones.

The major point of clarification I would

like to make is on question two, and this is important because I think the way it is written now is perhaps a little bit confusing. What I would like to ask the committee is that for each of these potential or concerns related to adverse effects of muraglitazar, that is to say fluid and electrolyte metabolism, cardiac effects, hepatic effects and muscle effects--I want you to answer the following question, with an understanding of the sponsor's intent and commitment, as they stated in their presentation, to continue formal investigations of muraglitazar, including an eventual morbidity and mortality trial which, as they mentioned, is still in the planning stage and awaits the results of two important landmark studies, one with pioglitazone and one with fenofibrate, for its final design, at this point, based upon what has been presented and what you have read on the preclinical results and on the clinical trial results, is there sufficient information at this point to assess risk versus benefit? Sufficient information on these topics to integrate it into your assessment of risk and

benefit?

Does anybody have any questions as to what I am asking there or can we move forward?

[No response]

Obviously, question four is the big one. Dr. Watts?

DR. WATTS: Well, we will go through the questions. Cathy, would you go back to number one, please? We will start at my left of the table with Dr. Follmann. We will go through the questions point by point and yes or no is fine. If you have additional comments or explanation, please feel free to ask them.

So, do the efficacy findings with Pargluva 2.5 and 5 mg daily support use for the proposed indications in the treatment of inhaled insulin as monotherapy?

DR. FOLLMANN: Yes.

DR. WOOLF: Yes.

DR. CAPRIO: Yes.

MS. LELLOCK: Yes.

DR. CUNNINGHAM: Yes.

DR. AOKI: Yes.

DR. BURMAN: Yes.

DR. WATTS: Yes.

DR. LEVITSKY: Yes.

DR. WATTS: For combination therapy in patients not adequately controlled on metformin or sulfonylurea alone? We will start with Dr. Levitsky and go the other way.

DR. LEVITSKY: Yes.

DR. WATTS: Yes.

DR. BURMAN: Yes.

DR. AOKI: Yes.

MS. LELLOCK: Yes.

DR. CAPRIO: Yes.

DR. WOOLF: Yes, but I am concerned about the combination of the drug with sulfonylurea and the excess mortality.

DR. WATTS: We will need some people to turn off their microphones so Dr. Cunningham can vote.

DR. CUNNINGHAM: I think I lost my voice. I would say yes but I also have some concerns that

I am going to bring up later.

DR. WATTS: Do you want to bring them up now or is it covered in the later points?

DR. CUNNINGHAM: It is covered later but I just didn't want to sound too enthusiastic.

[Laughter]

DR. WATTS: 1.(b), is there adequate evidence that Pargluva 1.5 mg daily is effective for the proposed indication?

LCDR GROUPE: Dr. Follmann didn't vote.

DR. FOLLMANN: I was going to vote yes.

DR. WATTS: Thank you. We will start with you again this time so we don't miss you. Is there adequate evidence that Pargluva 1.5 mg daily is effective for the proposed indications?

Let me modify that myself. Let me say "is there evidence that," and we can come back if you want and add "adequate."

DR. ORLOFF: I am sorry on this one. This was an oversight on my part or on our part. It was obviously only studied as monotherapy so why don't you just answer it as monotherapy?

DR. WATTS: Monotherapy, and is it okay to say "evidence" rather than "adequate?"

DR. ORLOFF: Sure.

DR. WATTS: Okay. Dr. Follmann?

DR. FOLLMANN: So, this has only been study in the dose-ranging study, and in that study it is important to remember that this was not really a study of 1.5. It was a strategy to start at a dose of 1.5, increasing to a higher dose if necessary. In that study I think about 30 percent of the people ended up on a higher dose. So, for that reason, and also because it is not clear to me what the effect of this drug would be in terms of A1c because it hasn't been studied, in my mind, adequately I would say, no, there is not adequate evidence.

DR. WOOLF: No.

DR. CAPRIO: No.

MS. LELLOCK: No.

DR. CUNNINGHAM: No. It looked to me like only 175 people actually completed on that dose of drug in that short time so no.

DR. AOKI: No.

DR. BURMAN: No.

DR. WATTS: The way I phrased the question was so I could say yes. I think there is evidence that it is effective but it is not adequate evidence.

[Laughter]

DR. LEVITSKY: You took the words out of my mouth, evidence but not adequate.

DR. WATTS: Mine was yes for the way I rephrased the question. So there is, in my view, evidence but it is not adequate evidence.

DR. LEVITSKY: Evidence, not adequate evidence. So, yes to the evidence question.

DR. WATTS: Questions now on safety and we will start with Dr. Levitsky.

LCDR GROUPE: Is he rewording that or changing it?

DR. WATTS: Dr. Orloff, do you want to reword the question or was that just to help us understand question two?

DR. ORLOFF: I will explain one more time.

In answering the question that asks whether, at this time, with an understanding that studies will continue, including a morbidity and mortality trial down the line, do you have enough information on these issues from preclinical and clinical to integrate it into a risk/benefit assessment?

DR. WATTS: We will go through each of these components, and these are for the doses for which approval is being sought, 2.5 mg and 5 mg doses. Do you have enough information, Dr. Levitsky, to integrate the information on fluid and electrolyte metabolism?

DR. LEVITSKY: Yes.

DR. WATTS: Yes.

DR. BURMAN: Yes.

DR. AOKI: Yes.

MS. CUNNINGHAM: Just to change the scene, no, and I can't deal with a promissory note of what the future is going to bring so I have to deal with the here and now and say no.

MS. LELLOCK: Yes.

DR. CAPRIO: yes.

DR. WOOLF: Yes.

DR. FOLLMANN: No.

DR. WATTS: Second is cardiac effects. Dr. Follmann, we will start with you.

DR. FOLLMANN: We discussed this a bit earlier in the day and I am really of two minds about this. Part of me says, you know, there is a small signal here perhaps and the other part of me says that these are really small numbers. If we were doing an events trial where this was a predefined endpoint, cardiovascular events, cardiovascular death, we would be about one-tenth or so through the study and the evidence we see so far would not raise an eyebrow. Nonetheless, I am going to vote no on this.

DR. WATTS: Dr. Woolf?

DR. WOOLF: No.

DR. CAPRIO: Yes.

MS. LELLOCK: Yes.

DR. CUNNINGHAM: No, I think the data are very equivocal and because there is a sing of risk I think we have to vote no.

DR. AOKI: Yes.

DR. BURMAN: No.

DR. WATTS: I say yes. I think the numbers were small. I think the analyses are difficult for me to completely reconcile, partly because they are small numbers and partly because some are based on numbers and some are based on exposure. I think the sponsor has sufficient plan to address this in the future.

DR. LEVITSKY: I am having trouble dealing with the caveat that was added to this question beforehand. Looking at the information we have now, the answer is no. If the question is rephrased as do you think the risks are low enough that we could allow this to go on as long as the sponsor was planning this long-term larger trial, my answer might be yes.

DR. WATTS: I think the intent of all the dancing around the question was to phrase it the way you just did. So, you would vote yes?

DR. LEVITSKY: Are the risks low enough now, although there seem to be risks? Yes.

DR. WATTS: Anyone like to re-vote?

DR. WOOLF: Using Dr. Levitsky's clarification, I will change my vote.

DR. FOLLMANN: I would too if the question is if there is sufficient evidence, not a large events driven study, I would say yes.

DR. BURMAN: Same for me.

DR. WATTS: Let's go around again then. Dr. Ryder, I don't mean to ignore you but if you have questions at any point just wave in my direction. So, revision of question two, which is, is there enough information and plans to gather more in the future to move forward with approval based on the current knowledge? Dr. Follmann?

DR. FOLLMANN: Yes, enough to launch a new trial.

DR. WOOLF: Yes.

DR. CAPRIO: Yes.

MS. LELLOCK: Yes.

DR. CUNNINGHAM: No, I still think it is too equivocal and the signs of risk are too great, and the public that would be exposed to this may be

much sicker. Yes, there would be a trial going on but the entire public would be exposed to the drug while the trial was going on and their risks might be actually higher than for the people who are in the trials here.

DR. AOKI: Yes.

DR. BURMAN: Yes.

DR. WATTS: Yes.

DR. LEVITSKY: Yes, as before.

DR. WATTS: Thank you, Dr. Levitsky, for your clarification. For hepatic effects? Dr. Levitsky, we will start with you.

DR. LEVITSKY: Yes.

DR. WATTS: Yes.

DR. BURMAN: Yes.

DR. AOKI: Yes.

DR. CUNNINGHAM: Yes.

MS. LELLOCK: Yes.

DR. CAPRIO: Yes.

DR. WOOLF: Yes.

DR. FOLLMANN: Yes.

DR. WATTS: And for muscle effects? Dr.

Follmann?

DR. FOLLMANN: Yes.

DR. WOOLF: Yes.

DR. CAPRIO: Yes.

MS. LELLOCK: Yes.

DR. CUNNINGHAM: Yes.

DR. AOKI: Yes.

DR. BURMAN: Yes.

DR. WATTS: Yes.

DR. LEVITSKY: Yes.

DR. WATTS: Question three, are there patients for whom treatment with Pargluva 2.5 and 5 mg daily poses particular safety concerns?

DR. ORLOFF: Dr. Watts, these are issues for discussion.

DR. WATTS: Yes.

DR. ORLOFF: So we don't need a vote.

DR. WATTS: Oh, I see. Okay, no vote. I was going to say that could be a yes or no but that is probably not what we want.

[Laughter]

Why don't we go though in order rather

than free-ranging discussion? So, Dr. Levitsky, are there patients that you see where these doses would pose particular safety concerns?

DR. LEVITSKY: Well, let me tell everyone one of those anecdotes that no one wants to hear. My 92 year-old father, an ex-physician, developed mild hyperglycemia and his general physician put him on one of those other drugs that is approved after he had already developed edema with an alpha blocker. I went and visited him, and my step-mother said, "his legs are so big I can't believe it." He was out of breath and had gained 20 lbs and was full of edema. Those are, unfortunately, the people out there who do start patients on these drugs. I thought that it was a very inappropriate thing even though I am a pediatrician. We stopped the drug and immediately the edema went away.

So, the issue is yes, there are people for whom treatment provides specific safety concerns, and those people, unfortunately, may not be protected because of decision-making which is not

always correct on the outside. Yes, there are.

DR. WATTS: Dr. Burman?

DR. BURMAN: There are certainly multiple concerns that have been brought up in all the presentations--people with known cardiovascular disease, heart disease and not even raising the issue of bladder cancer. Those are issues that might limit the use.

DR. WATTS: Dr. Aoki?

DR. AOKI: I think the primary concern is patients with a history of coronary artery disease with or without a history of congestive heart failure. In my practice I have started the TZDs at a very low level, with very close monitoring, and require that the patient have a scale and if they gain more than five pounds within a two-week period they are to call me for advice in terms of whether I should terminate the medication. I think the same would be true for this group. Whether or not there is a known history of congestive heart failure, I think we should just make a standard--I think a reasonable increase is a five-pound weight

gain in a two-week period--that a red flag is raised and you should really reconsider whether or not that person should be on a TZD or muraglitazar. So, with that caveat--I have many patients in whom I have actually terminated TZDs for that reason because they just retained too much fluid. So, I think there are simple safeguards that one can put in place that allow you to treat patients with CAD and with a history of well compensated CHF.

DR. CUNNINGHAM: I think I would agree that the same patients, all the ones who were excluded from these trials, would be people for whom you might have concerns. I am also worried about the clinicians who don't ever get to these education programs and who don't follow the patients as wonderfully as the people speaking here do.

DR. WATTS: Ms. Lellock?

MS. LELLOCK: I definitely think there are concerns about people who have previous heart disease. My family has heart disease so I would definitely be concerned about starting somebody on

that particular drug. So, I think that there should be safeguards set up.

DR. CAPRIO: I don't have much to add.

DR. WOOLF: I would be concerned. You know, there was a list of patients who developed problems. There were five or six items on that list of previous heart disease, edema, hypertension. I would be concerned about all those folks and, as a corollary, I probably wouldn't start anybody who had those on this drug at any dose and if I was at all unsure, I would certainly start them at the 2.5 mg dose.

DR. FOLLMANN: Virtually no Class I and Class II heart failure patients have been studied so I don't think they should be using this.

DR. WATTS: I think that was the point made earlier. This question raises, to me, what seems like a Catch-22, that this drug is being brought forward as a way of reducing cardiovascular mortality through dual mechanisms of action and the patients who are highest risk for cardiovascular mortality don't seem to do very well with the drug.

So, I think that is going to have to be looked at critically in the ongoing safety studies. I think that may have dealt with the issue of patients for whom a lower starting dose of the drug should be used. So, are there any additional points to be made about that?

DR. AOKI: A quick question, can you use a pill cutter to cut the 1.5 in half without changing its pharmacokinetics or pharmacodynamics?

DR. WATTS: Anyone from the sponsor know what happens with a pill cutter?

DR. AOKI: I mean, if we can't have the 1.5 we can have the 1.25.

DR. FIEDOREK: No, I don't believe that that is going to be a possibility.

DR. AOKI: It is not scored?

DR. FIEDOREK: No.

DR. WATTS: My sense from the discussion is that patients who are at risk but not seriously at risk might be started on a low dose, the low dose being 2.5, given what is being asked for approval.

We will open this just to general comments because there are concerns about cardiovascular effects beyond those based on the expected mechanism of action, that being fluid retention and edema. Is there any reason to think that there might be other negative cardiovascular effects? Dr. Woolf?

DR. WOOLF: As weak as the signal is and as small as the number is, it seems that the excess mortality, cardiovascular mortality, is related to those patients who are in the sulfonylurea trial. That would make me very leery until we have the results of the outcomes trial to use that combination.

DR. WATTS: Other comments?

DR. CUNNINGHAM: I think with metformin too there is a concern. With sulfonylurea one had events; metformin had the deaths I think and the other one had the events. I think events are going to lead to death sooner or later so I think it is a problem.

I also think there is a real problem here

with doing studies and explaining away the results. If you do a study and you get a result that is significant I don't think you should really be allowed to say, yes, but that was because. What is the point of doing the studies if you don't actually attend to the significance of the results that you get? I think it really calls for a need for further study.

DR. WATTS: Just to clarify your comment for me, I am not aware that any of these mortality figures were statistically significant for any of the studies. I mean, what we are looking at is a pooling from a number of different studies.

DR. CUNNINGHAM: Yes, it was three pooled but they were all combination studies. It was page 13 that got handed out.

DR. WATTS: I am not sure I understand your comment about if you are going to do a study explaining away the data because I don't get a sense that any of what we have seen has been explained away. I think we are just trying to understand some post hoc analyses.

Any other comments on cardiovascular issues or any additional concerns about the carcinogenicity data, particularly the bladder cancer? Any concern that that applies to human risk?

DR. BURMAN: I think there is a slight concern, as Dr. Lurie mentioned as well, but it didn't seem to be borne out in the monkey studies.

DR. EL HAGE: If I could comment, the same caveat applies to the monkey studies as applies to clinical studies. You have to do seven-year, ten-year monkey carcinogenicity studies to be able to see tumor findings. The fact that we didn't see hyperplasia is reassuring but it is not an assessment of carcinogenicity.

DR. WATTS: Are there any other issues that panelists of FDA would like us to address before we get to the final question?

DR. AOKI: I have one quick question. I would like to direct it to the sponsor. Is there any data that suggests that either metformin or glyburide increases or decreases glucose oxidation

in the heart?

DR. FIEDOREK: I will let Dr. DeFronzo answer that.

DR. DEFRONZO: There are no data that have looked at that. There are data using PET scanning that shows that insulin resistance that is in peripheral muscle exists in the heart. To the extent that metformin improves insulin sensitivity in muscle through the AMP kinase system, it is possible that you might see an effect in the heart but there are no data that have examined this. I do believe that there are studies that are ongoing looking at TZDs and their effects on the heart. The TZDs work through a mechanism that is quite different from metformin. It drops FFA and up-regulates the insulin signaling system. So, I think there is more reason to believe that you would get more beneficial effects in the myocardium with the TZDs and perhaps pioglitazone. Those studies are currently ongoing and there are not data with metformin.

DR. WATTS: Ms. Lellock?

MS. LELLOCK: I am here as a patient representative and I am a parent of two diabetic young adults. Over the years I have heard all we need to do is lower the A1c; lower the A1c; lower the A1c. That is your goal with diabetes. The trial where the drug has shown that it can do that--I have a sister now who has type 2 diabetes and her A1c is up. If this works for her, then I believe that we can all be happy about that because I think untreated we are heading down the same path as, you know, bad cardiovascular symptoms and so forth. So, I think as long as we can lower the A1c--with the DCCT trials that was the goal.

DR. WATTS: Thank you. Dr. Meyer?

DR. MEYER: Thank you. You asked whether there are other things we might want the committee to discuss. I think between question 1(b) and comment 3(b)--we have sort of danced around this a little bit, but I would just like to hear comments from the committee about the desirability of the sponsor developing more data and then marketing a lower dose, the 1.25 mg dose. I understood that

most folks didn't feel like there was sufficient data existing to allow for that to go forward now, but what is the desirability of the sponsor doing so given their choice not to develop it to date?

DR. AOKI: Well, I really like the idea of studies with the 1.5 mg. In particular, I would be very interested in whether or not the 1.5 mg had pancreatic beta cell preservation activity. I could see this being used in maybe relatively new onset with type 2 diabetic patients. The only question that I would have in that area would be how much of this drug would be needed to accomplish that preservation. Is 1.5 adequate forever or do you have to go up to 5 and 10, or whatever, to preserve pancreatic beta cell function?

A second question would be what impact does it have on intracellular insulin resistance? If 1.5 is sufficient--and this is my gold standard, does it increase glucose oxidation? The reason why I asked that question before is that I am pretty sure that the reason why you have increased cardiovascular morbidity and mortality in these

individuals with muraglitazar or with any drug, and I think that was also demonstrated with metformin and glyburide. There was increased morbidity in the combination as compared to a single drug. I wonder if, in fact, what we are dealing with is a situation, diabetes, which results in decreased glucose oxidation in the myocardium and the net result is that the myocardium has to use free fatty acids. This is much more demanding of oxygen than glucose is. So, if you can decrease insulin resistance, and Schulman at Yale has suggested that if you can decrease free fatty acid metabolites within the cells that the high free fatty acid concentrations or intermediates intracellularly are directly correlated to insulin resistance, then I think 1.5 mg of muraglitazar can reduce that by whatever method, decrease free fatty acid levels, it would be a very strong reason for pursuing that.

DR. WATTS: Dr. Follmann?

DR. FOLLMANN: I guess one thing I have been struggling with when I have been thinking about this drug is the fact that it is a new class

of drugs. So, based on a lot of history, use of A1c and lipid profile as surrogates for outcomes in diabetics, and it is based on a long history, this drug has a very favorable profile in terms of those surrogate endpoints or outcomes. But it is important to remember that a surrogate really needs to be reevaluated within each new class of drugs. If this were not muraglitazar but, say, inhaled insulin or something that we were looking at today and it had the same profile, we would be more inclined I think to discount the signals that we see in terms of adverse events. This is a new class of drugs. So, part of me wonders whether we should re-think or at least examine more carefully the issue of whether these parameters are good surrogates within this class of drugs. For that reason, you know, I look forward to the outcomes trials which should shed light on that issue.

DR. WATTS: Other comments about lower dose, a 1.5 mg dose?

DR. WOOLF: I think having more choices is better than having fewer choices, and having

patients who might be concerned about having some side effects and fluid retention, having a lower dose with presumably a lower incidence of fluid retention and congestive failure would be a good place to go. You are certainly not losing anything. If you don't get the desired improvement in hemoglobin A1c or lipids and the patient is tolerating that dose you can escalate the dose. We do that all the time.

DR. WATTS: I think it would be useful. We had the slide we were shown, that 40 percent of patients on 1.5 mg made it to goal. We don't know what the placebo group would have done but that 40 percent to goal looks pretty good. Dr. Woolf?

DR. WOOLF: From another standpoint, there are 13 doses of Ferrin hormone replacement. We have a wealth of ability to escalate that drug, perhaps even too much. So, having a drug in another disease where we have some options I think would be worthwhile.

DR. WATTS: Ready for the final question? Question 4(a) is should Pargluva be approved for

the proposed indication as monotherapy? Dr. Follmann?

DR. FOLLMANN: No.

DR. WOOLF: Yes.

DR. CAPRIO: Yes.

MS. LELLOCK: Yes.

DR. CUNNINGHAM: Yes.

DR. AOKI: Yes.

DR. BURMAN: Yes.

DR. WATTS: Yes.

DR. LEVITSKY: Yes.

DR. WATTS: Perhaps I should write down (b) into the different combinations just to see if there are specific concern about use in combination with the different agents. So, I will take the prerogative. Should it be approved for combination use with metformin? Dr. Levitsky?

DR. LEVITSKY: I am glad I got that one first. I feel reasonably comfortable with that one in saying yes.

DR. WATTS: Comment on special doses or special populations or any additional information

that is needed.

DR. LEVITSKY: As we have discussed beforehand, I think that the patients who have heart disease who are at risk for edema for other reasons need to be carefully watched, and perhaps should not be considered for this drug combination--with this drug in general.

DR. WATTS: I would say yes, with the same concerns as Dr. Levitsky.

DR. BURMAN: I also have the same concerns. I am very concerned about the cardiovascular death but for this agent I would say yes.

DR. AOKI: Yes.

DR. CUNNINGHAM: No.

MS. LELLOCK: Yes.

DR. CAPRIO: Yes, and I have the same concern.

DR. WOOLF: Yes, but suddenly a light bulb went off. There is a limitation. We don't use metformin in patients with minimal renal sufficiency. I do not believe that this drug

causes renal insufficiency but that is something that is going to need to be monitored I think more than casually. With that caveat, my answer is yes.

DR. FOLLMANN: No.

DR. WATTS: Should this drug be approved for use in combination with sulfonylureas? Again, special populations or concerns, Dr. Follmann?

DR. FOLLMANN: No.

DR. WOOLF: NO.

DR. CAPRIO: No.

MS. LELLOCK: No.

DR. CUNNINGHAM: No.

DR. AOKI: Yes.

DR. BURMAN: No.

DR. WATTS: Yes.

DR. LEVITSKY: Well, this is so difficult because if we say no then this drug will never be adequately tested standard sulfonylureas in large enough numbers to know whether the cardiovascular indication is a problem. Yet, we do put people at risk if we say yes. So, I will say no but I do hope that a larger study will be done, very

carefully controlled.

DR. WATTS: Other questions or issues for the committee? Dr. Woolf?

DR. WOOLF: Picking up on Dr. Levitsky's point, I would hope that when the outcome trial gets launched there will be a combination arm with sulfonylurea.

DR. LEVITSKY: I wasn't clear whether this was a real outcome trial or an observational outcome trial. If it is a true outcome trial, that is great. But if it is simply a registry that is not going to help very much. Is it clear that it is a trial and not a registry?

DR. FIEDOREK: It will be a registry, which is one study, and then there will be another control.

DR. WATTS: I want to thank the presenters and thank the panel. We will adjourn the meeting.

[Whereupon, at 2:00 p.m., the proceedings were adjourned.]

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