

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 021073

**Trade Name: ACTOS TABLETS 15 MG, 30 MG, and
45 MG**

Generic Name: PIOGLITAZONE HYDROCHLORIDE

**Sponsor: TAKEDA ARMERICA RESEARCH AND
DEVELOPMENT CENTER, INC.**

Approval Date: 07/15/99

**INDICATION(s): FOR THE IMPROVEMENT OF
GLYCEMIC CONTROL IN PATIENTS WITH TYPE 2
DIABETES MONOTHERAPY OR IN COMBINATION
WITH SULFONYLUREAS, METFORMIN, OR INSULIN
WHEN DIET AND THE SINGLE AGENT DOES NOT
RESULT IN ADEQUATE GLYCEMIC CONTROL.**

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	Included	Pending Completion	Not Prepared	Not Required
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Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 021073

APPROVAL LETTER

NDA 21-073

Takeda America Research & Development Center, Inc.
Attention: Mikihiro Obayashi, Ph.D.
President
101 Carnegie Center, Suite 107
Princeton, New Jersey 08540

JUL 15 1999

Dear Dr. Obayashi:

Please refer to your new drug application (NDA) dated January 15, 1999, received January 15, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACTOS™ (pioglitazone hydrochloride) Tablets 15, 30, and 45 mg.

We acknowledge receipt of your submissions dated March 2, 16, 23 (2), 29, and 31 (2), April 5, 6, 7, 13, 20, and 21, May 21, June 3, 11, and 30 (fax), and July 2 (fax), 5, 6 (fax), 7 (3 fax), 8 (fax), 9 (2 fax), 13 (2 fax), and 15, (5 fax), 1999.

This new drug application provides for the use of ACTOS™ (pioglitazone hydrochloride) Tablets for the improvement of glycemic control in patients with Type 2 diabetes as monotherapy or in combination with a sulfonylurea, metformin, or insulin when diet and the single agent does not result in adequate glycemic control.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft physician labeling submitted July 15, 1999, and the immediate container and carton labels submitted January 15, 1999. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-073." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submissions dated July 7 and 15, 1999:

1. To conduct an evaluation of the pharmacokinetic impact of concomitant administration of Actos and ketoconazole. This will be a 2-way crossover study utilizing a single dose of

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Actos and a single dose of ketoconazole. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999, and the final study report will be submitted to the FDA by September 30, 2000.

2. To conduct a 2-way, cross-over enzyme induction study in patients treated with pioglitazone HCl and Midazolam HCl. This will be a steady-state pharmacokinetic study with 2 weeks of Actos administration, and a single dose of midazolam HCl. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999; and the final study report will be submitted to the FDA by September 30, 2000.
3. To conduct a 6-month study comparing the safety and efficacy of Actos 30 mg versus Actos 45 mg in combination with a sulfonylurea. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999; and the final study report will be provided to the FDA within 24 months after study initiation.
4. To conduct a 6-month study comparing the safety and efficacy of Actos 30 mg versus Actos 45 mg in combination with metformin. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999; and the final study report will be submitted to the FDA within 24 months after study initiation.
5. To conduct a 6-month study comparing the safety and efficacy of Actos 30 mg versus Actos 45 mg in combination with insulin. The protocol will be submitted to the FDA by September 30, 1999; the clinical investigation will begin no later than December 31, 1999; and the final study report will be submitted to the FDA within 24 months after study initiation.
6. To conduct a 3-year outcome study evaluating the occurrence of serious liver disease in 1000 patients treated with Actos compared to an appropriate control group. A draft protocol will be submitted to the Agency by October 31, 1999. The study will be initiated within three months of final protocol agreement, but not later than July 1, 2000.
7. To conduct a randomized, placebo-controlled 6-month clinical study in patients with type 2 diabetes and NYHA Class 2 and early Class 3 congestive heart failure. Evaluation of safety and efficacy parameters will focus on hematologic and cardiac structure and function (echocardiographic or similar evaluation). A draft protocol will be submitted to the Agency by October 31, 1999. The study will be initiated within three months of final protocol agreement, but not later than April 15, 2000.

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Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments should be prominently labeled "PHASE 4 COMMITMENTS."

As you know, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55. However, we acknowledge your letter dated April 13, 1999, requesting a waiver for patients younger than 12 years of age and stating your commitment to file a clinical plan within the next 120 days. The pediatric study requirement for the age range of 0 years to ≤ 11 years of age is waived. We are deferring submission of your pediatric studies for patients ≥ 12 years to 16 years of age until July 31, 2001. We acknowledge your commitment to submit your pediatric study plan for patients ≥ 12 years to ≤ 16 years of age within 120 days after approval of this application.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity, you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity [NOTE: You should still submit a pediatric drug development plan] and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolic and Endocrine Drug Products and two copies of both the promotional materials and the package insert directly to:

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Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ms. Jena Weber, Regulatory Project Manager, at (301) 827-6422.

Sincerely,

/s/

John K. Jenkins, M.D., M.P.H., C.P.

Director

Office of Drug Evaluation II

Center for Drug Evaluation and Research

7/15/99

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

PRINTED LABELING

ACTOS™ (Pioglitazone Hydrochloride) Tablets

NDA No. 21-073

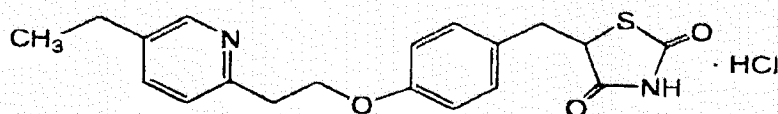
ACTOS™

(Pioglitazone Hydrochloride) Tablets

DESCRIPTION

ACTOS (pioglitazone hydrochloride) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS is used in the management of type 2 diabetes mellitus (also known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes). Pharmacological studies indicate that ACTOS improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis. ACTOS improves glycemic control while reducing circulating insulin levels.

Pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride belongs to a different chemical class and has a different pharmacological action than the sulfonylureas, metformin, or the α -glucosidase inhibitors. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The two enantiomers of pioglitazone interconvert in vivo. No differences were found in the pharmacologic activity between the two enantiomers. The structural formula is as shown:



Pioglitazone hydrochloride is an odorless white crystalline powder that has a molecular formula of $C_{19}H_{20}N_2O_3S \cdot HCl$ and a molecular weight of 392.90 daltons. It is soluble in N,N-dimethylformamide, slightly soluble in anhydrous ethanol, very slightly soluble in acetone and acetonitrile, practically insoluble in water, and insoluble in ether.

ACTOS is available as a tablet for oral administration containing 15 mg, 30 mg, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropylcellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

CLINICAL PHARMACOLOGY**Mechanism of Action**

ACTOS is a thiazolidinedione antidiabetic agent that depends on the presence of insulin for its mechanism of action. ACTOS decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Pioglitazone is a potent and highly selective agonist for peroxisome proliferator-activated receptor-gamma (PPAR γ). PPAR receptors are found in tissues important for insulin action such as adipose tissue, skeletal muscle, and liver. Activation of PPAR γ nuclear receptors modulates the transcription of a number of insulin responsive genes involved in the control of glucose and lipid metabolism.

In animal models of diabetes, pioglitazone reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic of insulin-resistant states such as type 2 diabetes. The metabolic changes produced by pioglitazone result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Since pioglitazone enhances the effects of circulating insulin (by decreasing insulin resistance), it does not lower blood glucose in animal models that lack endogenous insulin.

Pharmacokinetics and Drug Metabolism

Serum concentrations of total pioglitazone (pioglitazone plus active metabolites) remain elevated 24 hours after once daily dosing. Steady-state serum concentrations of both pioglitazone and total pioglitazone are achieved within 7 days. At steady state, two of the pharmacologically active metabolites of pioglitazone, Metabolites III (M-III) and IV (M-IV), reach serum concentrations equal to or greater than pioglitazone. In both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the peak total pioglitazone serum concentrations and 20% to 25% of the total area under the serum concentration-time curve (AUC).

Maximum serum concentration (C_{max}), AUC, and trough serum concentrations (C_{min}) for both pioglitazone and total pioglitazone increase proportionally at doses of 15 mg and

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30 mg per day. There is a slightly less than proportional increase for pioglitazone and total pioglitazone at a dose of 60 mg per day.

Absorption: Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. Food slightly delays the time to peak serum concentration to 3 to 4 hours, but does not alter the extent of absorption.

Distribution: The mean apparent volume of distribution (Vd/F) of pioglitazone following single-dose administration is 0.63 ± 0.41 (mean $\pm$ SD) L/kg of body weight. Pioglitazone is extensively protein bound (>99%) in human serum, principally to serum albumin. Pioglitazone also binds to other serum proteins, but with lower affinity. Metabolites M-III and M-IV also are extensively bound (>98%) to serum albumin.

Metabolism: Pioglitazone is extensively metabolized by hydroxylation and oxidation; the metabolites also partly convert to glucuronide or sulfate conjugates. Metabolites M-II and M-IV (hydroxy derivatives of pioglitazone) and M-III (keto derivative of pioglitazone) are pharmacologically active in animal models of type 2 diabetes. In addition to pioglitazone, M-III and M-IV are the principal drug-related species found in human serum following multiple dosing. At steady state, in both healthy volunteers and in patients with type 2 diabetes, pioglitazone comprises approximately 30% to 50% of the total peak serum concentrations and 20% to 25% of the total AUC.

Pioglitazone incubated with expressed human P450 or human liver microsomes results in the formation of M-IV and to a much lesser degree, M-II. The major cytochrome P450 isoforms involved in the hepatic metabolism of pioglitazone are CYP2C8 and CYP3A4 with contributions from a variety of other isoforms including the mainly extrahepatic CYP1A1. Ketoconazole inhibited up to 85% of hepatic pioglitazone metabolism in vitro at a concentration equal molar to pioglitazone. Pioglitazone did not inhibit P450 activity when incubated with human P450 liver microsomes. In vivo human studies have not been performed to investigate any induction of CYP3A4 by pioglitazone.

Excretion and Elimination: Following oral administration, approximately 15% to 30% of the pioglitazone dose is recovered in the urine. Renal elimination of pioglitazone is

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negligible, and the drug is excreted primarily as metabolites and their conjugates. It is presumed that most of the oral dose is excreted into the bile either unchanged or as metabolites and eliminated in the feces.

The mean serum half-life of pioglitazone and total pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone has an apparent clearance, CL/F , calculated to be 5 to 7 L/hr.

Special Populations

Renal Insufficiency: The serum elimination half-life of pioglitazone, M-III, and M-IV remains unchanged in patients with moderate (creatinine clearance 30 to 60 mL/min) to severe (creatinine clearance < 30 mL/min) renal impairment when compared to normal subjects. No dose adjustment in patients with renal dysfunction is recommended (see DOSAGE AND ADMINISTRATION).

Hepatic Insufficiency: Compared with normal controls, subjects with impaired hepatic function (Child-Pugh Grade B/C) have an approximate 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values.

ACTOS therapy should not be initiated if the patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal (see PRECAUTIONS, Hepatic Effects).

Elderly: In healthy elderly subjects, peak serum concentrations of pioglitazone and total pioglitazone are not significantly different, but AUC values are slightly higher and the terminal half-life values slightly longer than for younger subjects. These changes were not of a magnitude that would be considered clinically relevant.

Pediatrics: Pharmacokinetic data in the pediatric population are not available.

Gender: The mean C_{max} and AUC values were increased 20% to 60% in females. As monotherapy and in combination with sulfonylurea, metformin, or insulin, ACTOS improved glycemic control in both males and females. In controlled clinical trials,

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hemoglobin A_{1c} (HbA_{1c}) decreases from baseline were generally greater for females than for males (average mean difference in HbA_{1c} 0.5%). Since therapy should be individualized for each patient to achieve glycemic control, no dose adjustment is recommended based on gender alone.

Ethnicity: Pharmacokinetic data among various ethnic groups are not available.

Pharmacodynamics and Clinical Effects

Clinical studies demonstrate that ACTOS improves insulin sensitivity in insulin-resistant patients. ACTOS enhances cellular responsiveness to insulin, increases insulin-dependent glucose disposal, improves hepatic sensitivity to insulin, and improves dysfunctional glucose homeostasis. In patients with type 2 diabetes, the decreased insulin resistance produced by ACTOS results in lower blood glucose concentrations, lower plasma insulin levels, and lower HbA_{1c} values. Based on results from an open-label extension study, the glucose lowering effects of ACTOS appear to persist for at least one year. In controlled clinical trials, ACTOS in combination with sulfonylurea, metformin, or insulin had an additive effect on glycemic control.

Patients with lipid abnormalities were included in clinical trials with ACTOS. Overall, patients treated with ACTOS had mean decreases in triglycerides, mean increases in HDL cholesterol, and no consistent mean changes in LDL and total cholesterol.

In a 26-week, placebo-controlled, dose-ranging study, mean triglyceride levels decreased in the 15 mg, 30 mg, and 45 mg ACTOS dose groups compared to a mean increase in the placebo group. Mean HDL levels increased to a greater extent in the ACTOS-treated patients than in the placebo-treated patients. There were no consistent differences for LDL and total cholesterol in ACTOS-treated patients compared to placebo (Table 1).

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Table 1 Lipids in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Triglycerides (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	262.8	283.8	261.1	259.7
Percent change from baseline (mean)	4.8%	-9.0%	-9.6%	-9.3%
HDL Cholesterol (mg/dL)	N=79	N=79	N=83	N=77
Baseline (mean)	41.7	40.4	40.8	40.7
Percent change from baseline (mean)	8.1%	14.1%	12.2%	19.1%
LDL Cholesterol (mg/dL)	N=65	N=63	N=74	N=62
Baseline (mean)	138.8	131.9	135.6	126.8
Percent change from baseline (mean)	4.8%	7.2%	5.2%	6.0%
Total Cholesterol (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	224.6	220.0	222.7	213.7
Percent change from baseline (mean)	4.4%	4.6%	3.3%	6.4%

In the two other monotherapy studies (24 weeks and 16 weeks) and in combination therapy studies with sulfonylurea (16 weeks) and metformin (16 weeks), the results were generally consistent with the data above. For ACTOS-treated patients, the placebo-corrected mean changes from baseline decreased 5% to 26% for triglycerides and increased 6% to 13% for HDL cholesterol.

In the combination therapy study with insulin (16 weeks), the placebo-corrected mean percent change from baseline in triglyceride values for ACTOS-treated patients was also decreased. A placebo-corrected mean change from baseline in LDL cholesterol of 7% was observed for the 15 mg dose group. Similar results to those noted above for HDL and total cholesterol were observed.

In all clinical trials, a reduction in HbA_{1c} was accompanied by increased body weight in ACTOS-treated patients in a dose-related manner. The change in average weight in U.S. placebo-controlled monotherapy trials ranged from 0.5 kg to 2.8 kg for ACTOS-treated patients and -1.3 kg to -1.9 kg for placebo-treated patients. In combination with sulfonylurea, the change in average weight was 1.9 kg and 2.9 kg for 15 mg and 30 mg of ACTOS, respectively, and -0.8 kg for placebo. In combination with insulin, the change

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in average weight was 2.3 kg and 3.7 kg for 15 mg and 30 mg of ACTOS, respectively, and 0 kg for placebo. In combination with metformin, the change in average weight was 1.0 kg for 30 mg of ACTOS and -1.4 kg for placebo.

Clinical Studies

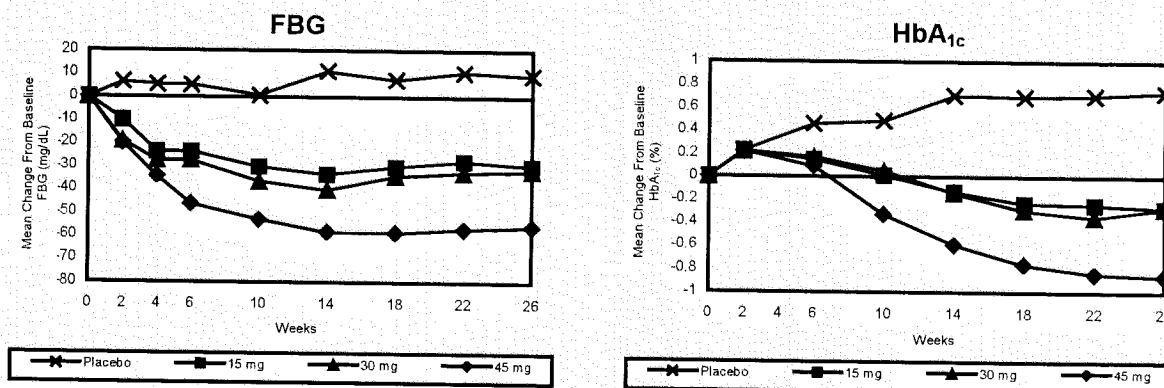
Monotherapy

In the U.S., three randomized, double-blind, placebo-controlled trials with durations from 16 to 26 weeks were conducted to evaluate the use of ACTOS as monotherapy in patients with type 2 diabetes. These studies examined ACTOS at doses up to 45 mg or placebo once daily in 865 patients.

In a 26-week dose-ranging study, 408 patients with type 2 diabetes were randomized to receive 7.5 mg, 15 mg, 30 mg, or 45 mg of ACTOS, or placebo once daily. Therapy with any previous antidiabetic agent was discontinued 8 weeks prior to the double-blind period. Treatment with 15 mg, 30 mg, and 45 mg of ACTOS produced statistically significant improvements in HbA_{1c} and fasting blood glucose (FBG) at endpoint compared to placebo (see Figure 1, Table 2).

Figure 1 shows the time course for changes in FBG and HbA_{1c} for the entire study population in this 26-week study.

Figure 1 Mean Change from Baseline for FBG and HbA_{1c} in a 26-Week Placebo-Controlled Dose-Ranging Study



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Table 2 shows HbA_{1c} and FBG values for the entire study population.

Table 2 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Total Population				
HbA_{1c} (%)	N=79	N=79	N=85	N=76
Baseline (mean)	10.4	10.2	10.2	10.3
Change from baseline (adjusted mean [†])	0.7	-0.3	-0.3	-0.9
Difference from placebo (adjusted mean [†])		-1.0*	-1.0*	-1.6*
FBG (mg/dL)	N=79	N=79	N=84	N=77
Baseline (mean)	268	267	269	276
Change from baseline (adjusted mean [†])	9	-30	-32	-56
Difference from placebo (adjusted mean [†])		-39*	-41*	-65*

[†] Adjusted for baseline, pooled center, and pooled center by treatment interaction

* p ≤ 0.050 vs. placebo

The study population included patients not previously treated with antidiabetic medication (naïve; 31%) and patients who were receiving antidiabetic medication at the time of study enrollment (previously treated; 69%). The data for the naïve and previously treated patient subsets are shown in Table 3. All patients entered an 8 week washout/run-in period prior to double-blind treatment. This run-in period was associated with little change in HbA_{1c} and FBG values from screening to baseline for the naïve patients; however, for the previously-treated group, washout from previous anti-diabetic medication resulted in deterioration of glycemic control and increases in HbA_{1c} and FBG. Although most patients in the previously-treated group had a decrease from baseline in HbA_{1c} and FBG with ACTOS, in many cases the values did not return to screening levels by the end of the study. The study design did not permit the evaluation of patients who switched directly to ACTOS from another antidiabetic agent.

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Table 3 Glycemic Parameters in a 26-Week Placebo-Controlled Dose-Ranging Study

	Placebo	ACTOS 15 mg Once Daily	ACTOS 30 mg Once Daily	ACTOS 45 mg Once Daily
Naïve to Therapy				
HbA_{1c} (%)	N=25	N=26	N=26	N=21
Screening (mean)	9.3	10.0	9.5	9.8
Baseline (mean)	9.0	9.9	9.3	10.0
Change from baseline (adjusted mean*)	0.6	-0.8	-0.6	-1.9
Difference from placebo (adjusted mean*)		-1.4	-1.3	-2.6
FBG (mg/dL)				
	N=25	N=26	N=26	N=21
Screening (mean)	223	245	239	239
Baseline (mean)	229	251	225	235
Change from baseline (adjusted mean*)	16	-37	-41	-64
Difference from placebo (adjusted mean*)		-52	-56	-80
Previously Treated				
HbA_{1c} (%)	N=54	N=53	N=59	N=55
Screening (mean)	9.3	9.0	9.1	9.0
Baseline (mean)	10.9	10.4	10.4	10.6
Change from baseline (adjusted mean*)	0.8	-0.1	-0.0	-0.6
Difference from placebo (adjusted mean*)		-1.0	-0.9	-1.4
FBG (mg/dL)				
	N=54	N=53	N=58	N=56
Screening (mean)	222	209	230	215
Baseline (mean)	285	275	286	292
Change from baseline (adjusted mean*)	4	-32	-27	-55
Difference from placebo (adjusted mean*)		-36	-31	-59

* Adjusted for baseline and pooled center

In a 24-week study, 260 patients with type 2 diabetes were randomized to one of two forced-titration ACTOS treatment groups or a mock titration placebo group. Therapy with any previous antidiabetic agent was discontinued 6 weeks prior to the double-blind period. In one ACTOS treatment group, patients received an initial dose of 7.5 mg once daily. After four weeks, the dose was increased to 15 mg once daily and after another four weeks, the dose was increased to 30 mg once daily for the remainder of the study (16 weeks). In the second ACTOS treatment group, patients received an initial dose of 15 mg once daily and were titrated to 30 mg once daily and 45 mg once daily in a similar

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manner. Treatment with ACTOS, as described, produced statistically significant improvements in HbA_{1c} and FBG at endpoint compared to placebo (see Table 4).

Table 4 Glycemic Parameters in a 24-Week Placebo-Controlled Forced-Titration Study

	Placebo	ACTOS 30 mg ⁺ Once Daily	ACTOS 45 mg ⁺ Once Daily
Total Population			
HbA_{1c} (%)	N=83	N=85	N=85
Baseline (mean)	10.8	10.3	10.8
Change from baseline (adjusted mean ^{**})	0.9	-0.6	-0.6
Difference from placebo (adjusted mean ^{**})		-1.5*	-1.5*
FBG (mg/dL)			
	N=78	N=82	N=85
Baseline (mean)	279	268	281
Change from baseline (adjusted mean ^{**})	18	-44	-50
Difference from placebo (adjusted mean ^{**})		-62*	-68*

⁺ Final dose in forced titration

^{**} Adjusted for baseline, pooled center, and pooled center by treatment interaction

* p ≤ 0.050 vs. placebo

For patients who had not been previously treated with antidiabetic medication (24%), mean values at screening were 10.1% for HbA_{1c} and 238 mg/dL for FBG. At baseline, mean HbA_{1c} was 10.2% and mean FBG was 243 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 2.3% and 2.6% and mean FBG of 63 mg/dL and 95 mg/dL, respectively. For patients who had been previously treated with antidiabetic medication (76%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FBG. At baseline, mean HbA_{1c} was 10.7% and mean FBG was 290 mg/dL. Compared with placebo, treatment with ACTOS titrated to a final dose of 30 mg and 45 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and 1.4% and mean FBG of 55 mg/dL and 60 mg/dL, respectively. For many previously-treated patients, HbA_{1c} and FBG had not returned to screening levels by the end of the study.

In a 16-week study, 197 patients with type 2 diabetes were randomized to treatment with 30 mg of ACTOS or placebo once daily. Therapy with any previous antidiabetic agent

was discontinued 6 weeks prior to the double-blind period. Treatment with 30 mg of ACTOS produced statistically significant improvements in HbA_{1c} and FBG at endpoint compared to placebo (see Table 5).

Table 5 Glycemic Parameters in a 16-Week Placebo-Controlled Study

	Placebo	ACTOS 30 mg Once Daily
Total Population		
HbA_{1c} (%)	N=93	N=100
Baseline (mean)	10.3	10.5
Change from baseline (adjusted mean*)	0.8	-0.6
Difference from placebo (adjusted mean*)		-1.4*
FBG (mg/dL)		
	N=91	N=99
Baseline (mean)	270	273
Change from baseline (adjusted mean*)	8	-50
Difference from placebo (adjusted mean*)		-58*

* Adjusted for baseline, pooled center, and pooled center by treatment interaction

* p ≤ 0.050 vs. placebo

For patients who had not been previously treated with antidiabetic medication (40%), mean values at screening were 10.3% for HbA_{1c} and 240 mg/dL for FBG. At baseline, mean HbA_{1c} was 10.4% and mean FBG was 254 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.0% and mean FBG of 62 mg/dL. For patients who had been previously treated with antidiabetic medication (60%), this medication was discontinued at screening. Mean values at screening were 9.4% for HbA_{1c} and 216 mg/dL for FBG. At baseline, mean HbA_{1c} was 10.6% and mean FBG was 287 mg/dL. Compared with placebo, treatment with ACTOS 30 mg resulted in reductions from baseline in mean HbA_{1c} of 1.3% and mean FBG of 46 mg/dL. For many previously-treated patients, HbA_{1c} and FBG had not returned to screening levels by the end of the study.

Combination Therapy

Three 16-week, randomized, double-blind, placebo-controlled clinical studies were conducted to evaluate the effects of ACTOS on glycemic control in patients with type 2 diabetes who were inadequately controlled (HbA_{1c} ≥ 8%) despite current therapy with a

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sulfonylurea, metformin, or insulin. Previous diabetes treatment may have been monotherapy or combination therapy.

In one combination study, 560 patients with type 2 diabetes on a sulfonylurea, either alone or combined with another antidiabetic agent, were randomized to receive 15 mg or 30 mg of ACTOS or placebo once daily in addition to their current sulfonylurea regimen. Any other antidiabetic agent was withdrawn. Compared with placebo, the addition of ACTOS to the sulfonylurea significantly reduced the mean HbA_{1c} by 0.9% and 1.3% for the 15 mg and 30 mg doses, respectively. Compared with placebo, mean FBG decreased by 39 mg/dL (15 mg dose) and 58 mg/dL (30 mg dose). The therapeutic effect of ACTOS in combination with sulfonylurea was observed in patients regardless of whether the patients were receiving low, medium, or high doses of sulfonylurea (< 50%, 50%, or > 50% of the recommended maximum daily dose).

In a second combination study, 328 patients with type 2 diabetes on metformin either alone or combined with another antidiabetic agent, were randomized to receive either 30 mg of ACTOS or placebo once daily in addition to their metformin. Any other antidiabetic agent was withdrawn. Compared to placebo, the addition of ACTOS to metformin significantly reduced the mean HbA_{1c} by 0.8% and decreased the mean FBG by 38 mg/dL. The therapeutic effect of ACTOS in combination with metformin was observed in patients regardless of whether the patients were receiving lower or higher doses of metformin (< 2000 mg per day or ≥ 2000 mg per day).

In a third combination study, 566 patients with type 2 diabetes receiving a median of 60.5 units per day of insulin, either alone or combined with another antidiabetic agent, were randomized to receive either 15 mg or 30 mg of ACTOS or placebo once daily in addition to their insulin. Any other antidiabetic agent was discontinued. Compared to placebo, treatment with ACTOS in addition to insulin significantly reduced both HbA_{1c} (0.7% for the 15 mg dose and 1.0% for the 30 mg dose) and FBG (35 mg/dL for the 15 mg dose and 49 mg/dL for the 30 mg dose). The therapeutic effect of ACTOS in combination with insulin was observed in patients regardless of whether the patients were receiving lower or higher doses of insulin (< 60.5 units per day or ≥ 60.5 units per day).

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INDICATIONS AND USAGE

ACTOS is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (non-insulin dependent diabetes mellitus, NIDDM). ACTOS is indicated for monotherapy. ACTOS is also indicated for use in combination with a sulfonylurea, metformin, or insulin when diet and exercise plus the single agent does not result in adequate glycemic control.

Management of type 2 diabetes should also include nutritional counseling, weight reduction as needed, and exercise. These efforts are important not only in the primary treatment of type 2 diabetes, but also to maintain the efficacy of drug therapy.

CONTRAINDICATIONS

ACTOS is contraindicated in patients with known hypersensitivity to this product or any of its components.

PRECAUTIONS**General**

ACTOS exerts its antihyperglycemic effect only in the presence of insulin. Therefore, ACTOS should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycemia: Patients receiving ACTOS in combination with insulin or oral hypoglycemic agents may be at risk for hypoglycemia, and a reduction in the dose of the concomitant agent may be necessary.

Ovulation: In premenopausal anovulatory patients with insulin resistance, treatment with thiazolidinediones, including ACTOS, may result in resumption of ovulation. **As a consequence of their improved insulin sensitivity, these patients may be at risk for pregnancy if adequate contraception is not used.**

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in ACTOS-treated patients. These changes primarily occurred within the first 4 to 12 weeks of therapy and remained relatively constant thereafter. These changes may be related to increased

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plasma volume and have not been associated with any significant hematologic clinical effects (see ADVERSE REACTIONS, Laboratory Abnormalities).

Edema: ACTOS should be used with caution in patients with edema. In double-blind clinical trials of patients with type 2 diabetes, mild to moderate edema was reported in patients treated with ACTOS (see ADVERSE REACTIONS).

Cardiac: In preclinical studies, thiazolidinediones, including pioglitazone, cause plasma volume expansion and pre-load-induced cardiac hypertrophy (see PRECAUTIONS, Animal Toxicology). In a six-month placebo-controlled study of 334 patients with type 2 diabetes and a long-term (one year or more) open-label study of more than 350 patients with type 2 diabetes, echocardiographic evaluation revealed no significant increase in mean left ventricular mass index or significant decrease in mean cardiac index in patients treated with ACTOS.

In clinical trials that excluded patients with New York Heart Association (NYHA) Class III and IV cardiac status, no increased incidence of serious cardiac adverse events potentially related to volume expansion (e.g., congestive heart failure) was observed. Patients with NYHA Class III and IV cardiac status were not studied in ACTOS clinical trials. ACTOS is not indicated in patients with NYHA Class III or IV cardiac status.

Hepatic Effects: Another drug of the thiazolidinedione class, troglitazone, has been associated with idiosyncratic hepatotoxicity, and very rare cases of liver failure, liver transplants, and death have been reported during postmarketing clinical use. In pre-approval controlled clinical trials in patients with type 2 diabetes, troglitazone was more frequently associated with clinically significant elevations of hepatic enzymes (ALT > 3 times the upper limit of normal) compared to placebo, and very rare cases of reversible jaundice were reported.

In clinical studies worldwide, over 4500 subjects have been treated with ACTOS. In U.S. clinical studies, over 2500 patients with type 2 diabetes received ACTOS. There was no evidence of drug-induced hepatotoxicity or elevation of ALT levels.

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During placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) ACTOS-treated patients and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥ 3 times the upper limit of normal. The ALT elevations in patients treated with ACTOS were reversible and were not clearly related to therapy with ACTOS.

Although available clinical data show no evidence of ACTOS-induced hepatotoxicity or ALT elevations, pioglitazone is structurally related to troglitazone, which has been associated with idiosyncratic hepatotoxicity and rare cases of liver failure, liver transplants, and death. Pending the availability of additional large, long-term controlled clinical trials and postmarketing safety data following wide clinical use of ACTOS to more fully define its hepatic safety profile, it is recommended that patients treated with ACTOS undergo periodic monitoring of liver enzymes. Serum ALT (alanine transaminase) levels should be evaluated prior to the initiation of therapy with ACTOS in all patients, every two months for the first year of therapy, and periodically thereafter. Liver function tests should also be obtained for patients if symptoms suggestive of hepatic dysfunction occur, e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine. The decision whether to continue the patient on therapy with ACTOS should be guided by clinical judgement pending laboratory evaluations. If jaundice is observed, drug therapy should be discontinued.

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or the ALT levels exceed 2.5 times the upper limit of normal. Patients with mildly elevated liver enzymes (ALT levels at 1 to 2.5 times the upper limit of normal) at baseline or any time during therapy with ACTOS should be evaluated to determine the cause of the liver enzyme elevation. Initiation of, or continuation of, therapy with ACTOS in patients with mildly elevated liver enzymes should proceed with caution and include the appropriate clinical follow-up which may include more frequent liver enzyme monitoring. If serum transaminase levels are increased (ALT > 2.5 times the upper limit of normal), liver function tests should be evaluated more frequently until the levels return to normal or pretreatment values. If ALT levels exceed 3 times the upper limit of normal, the test should be repeated as soon as possible. If ALT levels remain > 3 times the upper limit of normal or if the patient is jaundiced, ACTOS therapy should be discontinued.

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There are no data available to evaluate the safety of ACTOS in patients who experienced liver abnormalities, hepatic dysfunction, or jaundice while on troglitazone. ACTOS should not be used in patients who experienced jaundice while taking troglitazone. For patients with normal hepatic enzymes who are switched from troglitazone to ACTOS, a one-week washout is recommended before starting therapy with ACTOS.

Laboratory Tests

FBG and HbA_{1c} measurements should be performed periodically to monitor glycemic control and the therapeutic response to ACTOS.

Liver enzyme monitoring is recommended prior to initiation of therapy with ACTOS in all patients and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects and ADVERSE REACTIONS, Serum Transaminase Levels).

Information for Patients

It is important to instruct patients to adhere to dietary instructions and to have blood glucose and glycosylated hemoglobin tested regularly. During periods of stress such as fever, trauma, infection, or surgery, medication requirements may change and patients should be reminded to seek medical advice promptly.

Patients should be told that blood tests for liver function will be performed prior to the start of therapy, every two months for the first year, and periodically thereafter. Patients should be told to seek immediate medical advice for unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or dark urine.

Patients should be told to take ACTOS once daily. ACTOS can be taken with or without meals. If a dose is missed on one day, the dose should not be doubled the following day.

When using combination therapy with insulin or oral hypoglycemic agents, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and their family members.

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In anovulatory, premenopausal women with insulin resistance, therapy with ACTOS may cause resumption of ovulation and contraceptive measures may need to be considered.

Drug Interactions

Oral Contraceptives: Administration of another thiazolidinedione with an oral contraceptive containing ethinyl estradiol and norethindrone reduced the plasma concentrations of both hormones by approximately 30%, which could result in loss of contraception. The pharmacokinetics of coadministration of ACTOS and oral contraceptives have not been evaluated in patients receiving ACTOS and an oral contraceptive. Therefore, additional caution regarding contraception should be exercised in patients receiving ACTOS and an oral contraceptive.

Glipizide: In healthy volunteers, coadministration of ACTOS (45 mg once daily) and glipizide (5.0 mg once daily) for seven days did not alter the steady-state pharmacokinetics of glipizide.

Digoxin: In healthy volunteers, coadministration of ACTOS (45 mg once daily) with digoxin (0.25 mg once daily) for seven days did not alter the steady-state pharmacokinetics of digoxin.

Warfarin: In healthy volunteers, coadministration of ACTOS (45 mg once daily) for seven days with warfarin did not alter the steady-state pharmacokinetics of warfarin. In addition, ACTOS has no clinically significant effect on prothrombin time when administered to patients receiving chronic warfarin therapy.

Metformin: In healthy volunteers, coadministration of metformin (1000 mg) and ACTOS (45 mg) after seven days of ACTOS (45 mg once daily) did not alter the pharmacokinetics of the single dose of metformin.

The cytochrome P450 isoform CYP3A4 is partially responsible for the metabolism of pioglitazone. Specific formal pharmacokinetic interaction studies have not been conducted with ACTOS and other drugs metabolized by this enzyme such as: erythromycin, astemizole, calcium channel blockers, cisapride, corticosteroids, cyclosporine, HMG-CoA reductase inhibitors, tacrolimus, triazolam, and trimetrexate, as

well as inhibitory drugs such as ketoconazole and itraconazole. In vitro, ketoconazole appears to significantly inhibit the metabolism of pioglitazone (see CLINICAL PHARMACOLOGY, Metabolism). Pending the availability of additional data, patients receiving ketoconazole concomitantly with ACTOS should be evaluated more frequently with respect to glycemic control.

Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats at oral doses up to 63 mg/kg (approximately 14 times the maximum recommended human oral dose of 45 mg based on mg/m^2). Drug-induced tumors were not observed in any organ except for the urinary bladder. Benign and/or malignant transitional cell neoplasms were observed in male rats at 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m^2). The relationship of these findings in male rats to humans is unclear. A two-year carcinogenicity study was conducted in male and female mice at oral doses up to 100 mg/kg/day (approximately 11 times the maximum recommended human oral dose based on mg/m^2). No drug-induced tumors were observed in any organ.

During prospective evaluation of urinary cytology involving more than 1800 patients receiving ACTOS in clinical trials up to one year in duration, no new cases of bladder tumors were identified. Occasionally, abnormal urinary cytology results indicating possible malignancy were observed in both ACTOS-treated (0.72%) and placebo-treated (0.88%) patients.

Pioglitazone HCl was not mutagenic in a battery of genetic toxicology studies, including the Ames bacterial assay, a mammalian cell forward gene mutation assay (CHO/HPRT and AS52/XPRT), an in vitro cytogenetics assay using CHL cells, an unscheduled DNA synthesis assay, and an in vivo micronucleus assay.

No adverse effects upon fertility were observed in male and female rats at oral doses up to 40 mg/kg pioglitazone HCl daily prior to and throughout mating and gestation (approximately 9 times the maximum recommended human oral dose based on mg/m^2).

Animal Toxicology

Heart enlargement has been observed in mice (100 mg/kg), rats (4 mg/kg and above) and dogs (3 mg/kg) treated orally with pioglitazone HCl (approximately 11, 1, and 2 times the maximum recommended human oral dose for mice, rat, and dogs, respectively, based on mg/m^2). In a one-year rat study, drug-related early death due to apparent heart dysfunction occurred at an oral dose of 160 mg/kg/day (approximately 35 times the maximum recommended human oral dose based on mg/m^2). Heart enlargement was seen in a 13-week study in monkeys at oral doses of 8.9 mg/kg and above (approximately 4 times the maximum recommended human oral dose based on mg/m^2), but not in a 52-week study at oral doses up to 32 mg/kg (approximately 13 times the maximum recommended human oral dose based on mg/m^2).

Pregnancy

Pregnancy Category C. Pioglitazone was not teratogenic in rats at oral doses up to 80 mg/kg or in rabbits given up to 160 mg/kg during organogenesis (approximately 17 and 40 times the maximum recommended human oral dose based on mg/m^2 , respectively). Delayed parturition and embryotoxicity (as evidenced by increased postimplantation losses, delayed development and reduced fetal weights) were observed in rats at oral doses of 40 mg/kg/day and above (approximately 10 times the maximum recommended human oral dose based on mg/m^2). No functional or behavioral toxicity was observed in offspring of rats. In rabbits, embryotoxicity was observed at an oral dose of 160 mg/kg (approximately 40 times the maximum recommended human oral dose based on mg/m^2). Delayed postnatal development, attributed to decreased body weight, was observed in offspring of rats at oral doses of 10 mg/kg and above during late gestation and lactation periods (approximately 2 times the maximum recommended human oral dose based on mg/m^2).

There are no adequate and well-controlled studies in pregnant women. ACTOS should be used during pregnancy only if the potential benefits justifies the potential risk to the fetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies, as well as increased neonatal morbidity and mortality, most experts recommend that insulin

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be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nursing Mothers

Pioglitazone is secreted in the milk of lactating rats. It is not known whether ACTOS is secreted in human milk. Because many drugs are excreted in human milk, ACTOS should not be administered to a breast-feeding woman.

Pediatric Use

Safety and effectiveness of ACTOS in pediatric patients have not been established.

Elderly Use

Approximately 500 patients in placebo-controlled clinical trials of ACTOS were 65 and over. No significant differences in effectiveness and safety were observed between these patients and younger patients.

ADVERSE REACTIONS

In worldwide clinical trials, over 3700 patients with type 2 diabetes have been treated with ACTOS. In U.S. clinical trials, over 2500 patients have received ACTOS, over 1100 patients have been treated for 6 months or longer, and over 450 patients for one year or longer.

The overall incidence and types of adverse events reported in placebo-controlled clinical trials of ACTOS monotherapy at doses of 7.5 mg, 15 mg, 30 mg, or 45 mg once daily are shown in Table 6.

Table 6 Placebo-Controlled Clinical Studies of ACTOS Monotherapy: Adverse Events Reported at a Frequency $\geq$ 5% of ACTOS-Treated Patients

(% of Patients)		
	Placebo N=259	ACTOS N=606
Upper Respiratory Tract Infection	8.5	13.2
Headache	6.9	9.1
Sinusitis	4.6	6.3
Myalgia	2.7	5.4
Tooth Disorder	2.3	5.3
Diabetes Mellitus Aggravated	8.1	5.1
Pharyngitis	0.8	5.1

The types of clinical adverse events reported when ACTOS was used in combination with sulfonylureas (N=373), metformin (N=168), or insulin (N=379) were generally similar to those reported during ACTOS monotherapy with the exception of an increase in the occurrence of edema in the insulin combination study (pioglitazone 15% and placebo 7%). The incidence of withdrawals from clinical trials due to an adverse event other than hyperglycemia was similar for patients treated with placebo (2.8%) or ACTOS (3.3%).

Mild to moderate hypoglycemia was reported during combination therapy with sulfonylurea or insulin. Hypoglycemia was reported for 1% of placebo-treated patients and 2% of patients when ACTOS was used in combination with a sulfonylurea. In combination with insulin, hypoglycemia was reported for 5% of placebo-treated patients, 8% for patients treated with 15 mg of ACTOS, and 15% for patients treated with 30 mg of ACTOS (see PRECAUTIONS, General, Hypoglycemia).

In U.S. double-blind studies, anemia was reported for 1.0% of ACTOS-treated patients and 0.0% of placebo-treated patients in monotherapy studies. Anemia was reported for 1.6% of ACTOS-treated patients and 1.6% of placebo-treated patients in combination with insulin. Anemia was reported for 0.3% of ACTOS-treated patients and 1.6% of placebo-treated patients in combination with sulfonylurea. Anemia was reported for 1.2% of ACTOS-treated patients and 0.0% of placebo-treated patients in combination with metformin.

In all U.S. clinical trials, edema was reported more frequently in ACTOS-treated patients than placebo-treated patients. In monotherapy studies, edema was reported for 4.8% of ACTOS-treated patients versus 1.2% of placebo-treated patients. Edema was reported most frequently in the insulin combination study (15.3% for ACTOS-treated patients versus 7.0% for placebo-treated patients). All events were considered mild or moderate in intensity (see PRECAUTIONS, General, Edema).

Laboratory Abnormalities

Hematologic: ACTOS may cause decreases in hemoglobin and hematocrit. Across all clinical studies, mean hemoglobin values declined by 2% to 4% in ACTOS-treated patients. These changes generally occurred within the first 4 to 12 weeks of therapy and remained relatively stable thereafter. These changes may be related to increased plasma volume associated with ACTOS therapy and have not been associated with any significant hematologic clinical effects.

Serum Transaminase Levels: During placebo-controlled clinical trials in the U.S., a total of 4 of 1526 (0.26%) ACTOS-treated patients and 2 of 793 (0.25%) placebo-treated patients had ALT values ≥ 3 times the upper limit of normal. During all clinical studies in the U.S., 11 of 2561 (0.43%) ACTOS-treated patients had ALT values ≥ 3 times the upper limit of normal. All patients with follow-up values had reversible elevations in ALT. In the population of patients treated with ACTOS, mean values for bilirubin, AST, ALT, alkaline phosphatase, and GGT were decreased at the final visit compared with baseline. Fewer than 0.12% of ACTOS-treated patients were withdrawn from clinical trials in the U.S. due to abnormal liver function tests.

In pre-approval clinical trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure (see PRECAUTIONS, Hepatic Effects).

CPK Levels: During required laboratory testing in clinical trials, sporadic, transient elevations in creatine phosphokinase levels (CPK) were observed. A single, isolated elevation to greater than 10 times the upper limit of normal (values of 2150 to 8610) was noted in 7 patients. Five of these patients continued to receive ACTOS and the other two patients had completed receiving study medication at the time of the elevated value.

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These elevations resolved without any apparent clinical sequelae. The relationship of these events to ACTOS therapy is unknown.

OVERDOSAGE

During controlled clinical trials, one case of overdose with ACTOS was reported. A male patient took 120 mg per day for four days, then 180 mg per day for seven days. The patient denied any clinical symptoms during this period.

In the event of overdose, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

DOSAGE AND ADMINISTRATION

ACTOS should be taken once daily without regard to meals.

The management of antidiabetic therapy should be individualized. Ideally, the response to therapy should be evaluated using HbA_{1c}, which is a better indicator of long-term glycemic control than FBG alone. HbA_{1c} reflects glycemia over the past two to three months. In clinical use, it is recommended that patients be treated with ACTOS for a period of time adequate to evaluate change in HbA_{1c} (three months) unless glycemic control deteriorates.

Monotherapy

ACTOS monotherapy in patients not adequately controlled with diet and exercise may be initiated at 15 mg or 30 mg once daily. For patients who respond inadequately to the initial dose of ACTOS, the dose can be increased in increments up to 45 mg once daily. For patients not responding adequately to monotherapy, combination therapy should be considered.

Combination Therapy

Sulfonylureas: ACTOS in combination with a sulfonylurea may be initiated at 15 mg or 30 mg once daily. The current sulfonylurea dose can be continued upon initiation of ACTOS therapy. If patients report hypoglycemia, the dose of the sulfonylurea should be decreased.

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Metformin: ACTOS in combination with metformin may be initiated at 15 mg or 30 mg once daily. The current metformin dose can be continued upon initiation of ACTOS therapy. It is unlikely that the dose of metformin will require adjustment due to hypoglycemia during combination therapy with ACTOS.

Insulin: ACTOS in combination with insulin may be initiated at 15 mg or 30 mg once daily. The current insulin dose can be continued upon initiation of ACTOS therapy. In patients receiving ACTOS and insulin, the insulin dose can be decreased by 10% to 25% if the patient reports hypoglycemia or if plasma glucose concentrations decrease to less than 100 mg/dL. Further adjustments should be individualized based on glucose-lowering response.

Maximum Recommended Dose:

The dose of ACTOS should not exceed 45 mg once daily since doses higher than 45 mg once daily have not been studied in placebo-controlled clinical studies. No placebo-controlled clinical studies of more than 30 mg once daily have been conducted in combination therapy.

Dose adjustment in patients with renal insufficiency is not recommended (see CLINICAL PHARMACOLOGY, Pharmacokinetics and Drug Metabolism).

Therapy with ACTOS should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT greater than 2.5 times the upper limit of normal) at start of therapy (see PRECAUTIONS, General, Hepatic Effects and CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Liver enzyme monitoring is recommended in all patients prior to initiation of therapy with ACTOS and periodically thereafter (see PRECAUTIONS, General, Hepatic Effects).

There are no data on the use of ACTOS in patients under 18 years of age; therefore, use of ACTOS in pediatric patients is not recommended.

No data are available on the use of ACTOS in combination with another thiazolidinedione.

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HOW SUPPLIED

ACTOS is available in 15 mg, 30 mg, and 45 mg tablets as follows:

15 mg Tablet: white to off-white, round, convex, non-scored tablet with "ACTOS" on one side, and "15" on the other, available in:

NDC 64764-151-04 Bottle of 30

NDC 64764-151-05 Bottle of 90

NDC 64764-151-06 Bottle of 500

30 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side and "30" on the other, available in:

NDC 64764-301-14 Bottle of 30

NDC 64764-301-15 Bottle of 90

NDC 64764-301-16 Bottle of 500

45 mg Tablet: white to off-white, round, flat, non-scored tablet with "ACTOS" on one side, and "45" on the other, available in:

NDC 64764-451-24 Bottle of 30

NDC 64764-451-25 Bottle of 90

NDC 64764-451-26 Bottle of 500

Storage

Store at 25°C (77°F) excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Keep container tightly closed, and protect from moisture and humidity.

Rx only

Manufactured by:

Takeda Chemical Industries, Ltd.

Osaka, Japan

ACTOS™ (Pioglitazone Hydrochloride) Tablets

NDA No. 21-073

Marketed by:

Takeda Pharmaceuticals America, Inc.

475 Half Day Road, Suite 500

Lincolnshire, IL 60069

Eli Lilly and Company

Lilly Corporate Center

Indianapolis, IN 46285

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July 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

MEDICAL REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 6/23/99

From: Saul Malozowski
Acting Medical Team Leader

JUN 30 1999

Subject: Pioglitazone-NDA 21,073, Actos® Takeda Pharmaceuticals

To: Solomon Sobel
Division Director, DMEDP

[Redacted] 6/30/99

The documentation provided to support the approval of pioglitazone for the treatment of type 2 diabetes clearly establishes the glucose lowering properties of this compound, either as monotherapy or in combination with sulfonylureas, metformin, and insulin. These beneficial effects were also seen when HbA1c was used as the endpoint. Effects are progressive, reaching maximal HbA1c reductions after several months of exposure. These effects seem to be sustained for at least 12 months. Reductions in these parameters have been associated with decrease risks for macro and microvascular complications with other anti-diabetic drugs such as sulfonylureas, metformin and insulin. Whether these benefits can be also be attributed to pioglitazone remains to be clarified.

The main safety concerns with this drug relates to the potential development of acute liver failure, due to the complications associated with the use of troglitazone, a drug in the same class, and of cardiac hypertrophy seen in preclinical studies with troglitazone, rosiglitazone and pioglitazone. The results of all short and long term studies with this product have dispelled some of these concerns regarding hepatic events, because no cases or indication of liver toxicity were detected during this period. The information submitted and reviewed, suggests that under the conditions experienced during the clinical development pioglitazone did not show any evidence of hepatotoxicity. Similarly, the cardiac safety profile seems to be benign in the patient population exposed. The supporting studies to dispel these concerns, however, were limited in scope and time exposure. It remains to be seen whether these concerns are further clarified once the drug reaches the market and patients with other profiles to those studied in the pivotal studies are exposed and/or the time of exposure increases. It is also important to stress that patients with NYHA stage 3 and 4 have been not yet exposed to this moiety. These two issues (hepatotoxicity and cardiac toxicity) are properly addressed in the label. A decision regarding the need for liver enzyme monitoring and its frequency, as discussed in the AC meeting, has been made and this product will follow the warning listed in the two previously approved glitazones.

Anemia was seen more frequently in patients receiving pioglitazone than placebo. The number of cases seen during the studies and the characterization of this complication does not suffice to assess whether this drug may cause anemia and if so, what mechanism is involved and what patients may be more prone to develop anemia. The magnitude of the changes observed were not clinically significant, but in a few cases. Phase 4 studies should explore these issues in depth. The label fairly conveys the occurrence of this complication.

Weight increments were seen consistently across studies in the patients receiving pioglitazone. In contrast to HbA1c levels that plateau after several weeks, weight tended to continue to increase throughout the studies with no evidence of pause. Weight increments accrued were in excess of 5% of initial body weight in some studies. Currently drugs approved for the treatment of obesity require weight reduction of this magnitude. It is believed that weight reduction of this extent could be beneficial to obese patients in reducing the risk for cardiac complications. Type 2 patients are obese and are at risk for cardiac complications. Pioglitazone increases their weight while reducing their HbA1c. Whether this balance between improvements in glycemic control and worsening in weight would be beneficial remains to be explored. Patients as well physicians should be informed as to this "imbalance." The current label should address this issue appropriately.

It is quite curious that the improvements in glycemic control are seen more clearly in females at equal dosages. Pioglitazone tends to result in weight increments (fat mass) and by this mechanism appears to further improve glycemic control. The sponsor has not yet clarified where the weight accumulates. The improved responses suggest that weight increments are the result of fat accumulation. No studies in humans with this compound have yet elucidated whether the fat is deposited in the abdomen (increasing the cardiac risk) or in some other(s) region(s) of the body. Because males have less fat than females tend to respond better to this drug, these findings tend to point out that fat and not muscle is the main target for this compound. If the PPAR γ receptor target were mostly in the muscle, males were to be more responsive to this drug. Again, the evidence seems to point to fat and not to muscle as the main target for this product. We do not have information as to the diet that these patients had during the studies nor assessment of whether appetite increased in subjects receiving pioglitazone. This needs to be further clarified.

Other important finding in the development of this drug used as monotherapy, are its overall beneficial or neutral effects on lipid markers, in contrast to the two previously approved glitazones. Troglitazone was overall neutral while rosiglitazone tended to worsen cholesterol, and LDL. Thus, these potential beneficial findings are unique to pioglitazone monotherapy and suggest that it may have a neutral effect or even reduce the risk for cardiovascular complications. The mechanisms underlying these actions are unknown. When pioglitazone was used in combination with metformin or insulin, however, LDL increased.

Any beneficial effects in lipid profiles of pioglitazone monotherapy should be balanced with the weight increments, a finding that is not welcome in the treatment of type 2 diabetics. Weight decrements tend to result in these lipid improvements and the paradoxical neutral effect of pioglitazone on lipids in patient increasing their weight is a phenomenon not well understood. The clinical significance of these changes, if any, is unknown.

Information regarding the mechanism of fluid retention is also lacking. The sponsor could have answered this question early on during the drug development process. The fact that this was not done hinders the ability to properly address this issue in the label in order to alert subjects that may be more prone to get this complication and to develop a rational treatment for those patients that do.

Due to the pre-clinical and clinical information regarding a role in affecting the action of P-450 enzymes, the potential role on numerous systemic actions (in particular, steroidogenesis and vitamin D metabolism) remains to be clarified.

Recommendations:

I concur with Dr. Robert Misbin's recommending approval of this compound. The label, however, should reflect his and my recommendation to properly reflect the outcomes of the studies as well as the risks involved in the use of pioglitazone. There is an imperative need to perform phase 4 studies to further clarify issues that have not been properly addressed during the previous phases or that because the intrinsic limitations of the drug developing process can not be elucidated until a drug is introduced to the market.

JUN 23 1999

MEDICAL OFFICER'S REVIEW: NDA 21-073

Actos (Pioglitazone) - Sponsor - Takeda

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Robert I Misbin MD
Medical Officer – HFD 510
June 23, 1999

Introduction:

Pioglitazone (PIO) is the third thiozolidinedione to be considered for approval. The first of this class, troglitazone, was approved in 1997. The major problem with the use of troglitazone has been liver failure. Its label now includes a boxed warning and monthly liver enzyme (ALT) monitoring is suggested. The monotherapy indication was removed in June 1999. Based on a preliminary review of the liver-related events in this application, it appeared that PIO was less likely to cause hepatitis than troglitazone. For this reason PIO was given a priority review. Safety issues related to PIO were discussed at an Advisory Committee meeting April 23 1999, one day after the rosiglitazone application was discussed. The NDA for Rosiglitazone (Avandia), the second drug in this class, was approved May 25 1999. The Avandia label contains language that reflects the Division's belief that it is much less likely to cause hepatitis than troglitazone. As will be discussed later in detail, it appears that PIO is also much less likely to cause hepatitis than troglitazone. The Advisory Committee also expressed this view.

This application consists of three phase 3 trials of monotherapy and one phase three trial each for combination therapy with sulfonylureas (SFU) metformin, and insulin. All phase 3 trials were placebo controlled. There were no comparative studies. Efficacy data from these trials and data regarding changes in lipids and body weight are discussed in detail. Liver related events and other safety related issues are discussed at the end of this review.

Overview of Phase 3 Studies done in the United States:

There were six double-blind placebo controlled trials completed in the United States. There were three trials of monotherapy and three of combination therapy with sulfonylureas, metformin and insulin. The monotherapy study 001 lasted six months and was followed by an open-label extension. The other trials lasted 16 weeks. Details of patients' exposure and dosages studies are given in the following table.

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Double-Blind Study	Number of Patients					Total Pioglitazone	Total
	Placebo	7.5 mg.	15 mg.	30 mg.	45 mg.		
Completed Monotherapy							
PNFP-001	79	81	81	87	80	329	408
PNFP-012*	84			87	89	176	260
PNFP-026	96			101		101	197
Total	259	81	81	275	169	606	865
Completed Combination Therapy**							
PNFP-010	187		184	189		373	560
PNFP-027	160			168		168	328
PNFP-014	187		191	188		379	566
Total	534		375	545		920	1454
Completed Total							
Total	793	81	456	820	169	1526	2319
Ongoing Monotherapy							
							0
Ongoing Combination Therapy							
							0
Ongoing Total							
							0
Overall Total							
Total	793	81	456	820	169	1526	2319

*Forced titration at Weeks 4 and 8 from 7.5 to 15 to 30 mg, respectively, listed as 30 mg.;
 Forced titration at Weeks 4 and 8 from 15 to 30 to 45 mg, respectively, listed as 45 mg.

**Companion medication was sulfonylurea for PNFP-010, metformin for PNFP-027 and insulin for PNFP-014.

Study PNFP 001

Placebo-controlled trial of PIO monotherapy

This trial was conducted in the USA between Jan 31 1996 and March 13 1998. It was a 26-week double blind comparison of placebo to PIO at doses of 7.5, 15, 30, and 45 mg/d. The double blind comparison was preceded by a six-week single-blind placebo washout from previous antidiabetic medications. Patients who had not been on antidiabetic medications previously could skip the 6-week washout period and enter the two-week baseline period. The requirement for a FBG between 140-240 after the washout was amended to read > 140 mg/dl at screening. The initial protocol stated that patients were to be withdrawn for FBG > 280 mg/dl on two consecutive visits. This was amended to > 400 mg/dl on two consecutive visits. Glucose tolerance testing was performed in patients whose FBG was < 240. Inclusion criteria also included fasting C peptide > 1 ng/ml at screening and HbA1c > 7% before randomization. Patients were excluded for liver chemistries, ALT, AST, alk phosph or bilirubin greater than 2.5 x ULN, creatinine > 1.8 mg/dl or hct < 42 for men and < 36 for women, LVH by voltage criteria, or Ejection Fraction < 40% by echocardiogram.

Each of the five study arms had approximately 80 patients. Approximately 1/3 of these patients were naïve to drug treatment and about 2/3 had been on previous antidiabetic medications. Based on a preliminary view of the data presented at the preNDA meeting, I asked that these two populations be presented separately. The reasons for this are as follows: For naïve patients there was little change in glucose levels from screening to baseline. Glucose levels then fell in patients who received PIO and rose slightly in patients who received placebo. The situation was more complicated in patients who were withdrawn from received previous antidiabetic medication. If one considers only changes from baseline, mean HbA1c levels also fell in these patients on the three highest doses of PIO and rose in patients on placebo. However, if one considers the starting point to be PRIOR to discontinuing previous antidiabetic medication, it is clear that HbA1c levels rose in all groups. This illustrates two important points. The first is that PIO appears to be inferior to patients' previous antidiabetic medication. Since patients' hyperglycemia deteriorates when they are switched to PIO from other medications, it is hard to see how these data can be used to support an indication of initial monotherapy. This is the same problem we faced with troglitazone and led to a statement in the label that patients should not be taken off SFU's and put on troglitazone. A second problem relates that the ethics of how the trial was designed and conducted.

In the initial protocol, inclusion criteria for randomization was a FBG < 240. Patients were to be withdrawn for lack of efficacy if the FBG > 280 on two consecutive visits. The protocol was later amended in August 1996, six months AFTER the patient accrual had begun, which eliminated any upper limit in FBG for entering the trial and stated that patients would be withdrawn for FBG > 400 mg/dl on TWO consecutive visits. Patients could be withdrawn for hyperglycemia "which presented a safety risk to the patient, in the investigator's opinion." But the protocol also states that "the investigator was to make every reasonable effort to keep each patients in the study".

Values over 400 are ordinarily considered high enough to require treatment to prevent development of hyperosmolar syndrome. This degree of hyperglycemia cannot be considered safe remain untreated. Even before the DCCT report showed that control of chronic hyperglycemia was important to prevent diabetes complications, the UKPDS study used a value of 270 mg/dl as the level requiring that placebo patients receive active treatment.

The Sponsor has analyzed their efficacy data based on whether patients had baseline FBG of greater than 280 mg/dl. These patients would not have been eligible according to the criteria of the original protocol. There were 152 patients withdrawn from other antidiabetic medications (primarily sulfonylureas) whose baseline FBG exceeded 280 mg/dl. Data for the 33 placebo and 30 patients on 45 mg PIO are shown in the following table. (Data source tables 9.2.5 and 11.2.5)

	HbA1c	HbA1c	Fasting Glucose	Fasting Glucose
	PLACEBO	PIO 45 mg	PLACEBO	PIO 45 mg
-8 weeks	9.65	9.57	234	241
Baseline	11.62	11.54	325	344
26 weeks	12.58	11.43	316	278

It should be noted that the American Diabetes Association considers a HbA1c of 8 to be too high and should lead to intensification of the treatment regimen. However the patients shown above had HbA1c levels considerably higher and despite that were withdrawn from standard treatment so they could participate in a placebo-controlled trial. I believe that to withdraw patient from active treatment and then allow them to go untreated despite this degree of hyperglycemia is unethical. Although the consent form lists the potential dangers of untreated hyperglycemia, nowhere is it stated that investigators were being paid to recruit their patients into the trial. Given this conflict of interest, it is important that reasonable equipoise be maintained between the risk/benefits of participating in a trial and risks/benefits of not participating. For naïve patients, non-participation is just a continuation of the status and is not very different from receiving a placebo during a trial. But to discontinue standard treatment is really to put a patient in harm's way, particularly when the protocol would allow a degree of hyperglycemia to go untreated which, according to current ADA criteria (persistent fasting glucose over 300 mg/dl), could qualify for hospitalization. The record shows that the change in protocol was submitted in the body of an amendment, and did not receive comment by members DMDEP. Since the cover letter to the submission did not call attention to the substance of the change, it is easy to understand why it was approved as a routine amendment without comment. That the protocol was amended six months after the trial had already begun indicates that the Sponsor was willing to sacrifice patient safety in order to bolster recruitment. For these reasons, I have recommended that efficacy data from patients withdrawn from previous treatment should not be considered in support of this NDA.

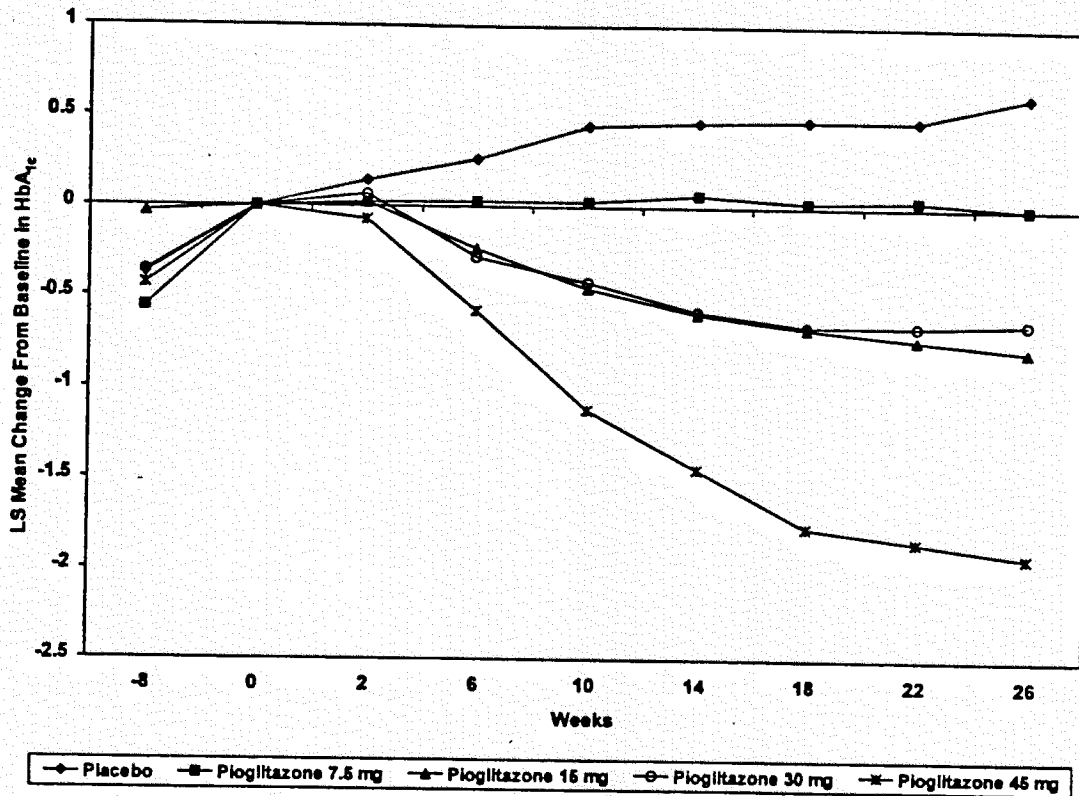
My review is based primarily on the supplemental analysis that I asked for at the preNDA meeting in which naïve patients are separated from patients taken off antidiabetic medications before the trial. The Sponsor also provided an analysis of patients with baseline FBG > 280 mg/dl. These patients would not have been eligible to be studied according to the original protocol. As will be discussed later, the efficacy data on naïve patients is adequate to justify approval. The statistical review provided by Lee Pian is based on an analysis of the entire population as originally planned.

Naïve patients:

There were 127 patients randomized to the six treatment arms, approximately 25 per arm. They had mean age of 52 years, 56% male, 78% Caucasian with mean BMI of 31.3. The M/F ration was reversed in the placebo group. This group had 44% males. Otherwise there were no serious baseline demographic imbalances. Mean baseline HbA1c was about 9.5, FBG 233 mg/dl, C peptide 2.3 ng/ml and insulin 20 uU/ml. As shown in the next figure, there was a reduction from baseline in HbA1c for the three highest doses of PIO, compared to a small but significant rise of 0.62 at 26 weeks in placebo patients. There was little change in HbA1c at the lowest PIO dose which was 7.5 mg. Based on a reduction of at least 0.6, 12% of placebo patients were classified as responders compared to 30%, 62%, 39%, and 71% on 7.5, 15, 30 and 45 mg of PIO, respectively.

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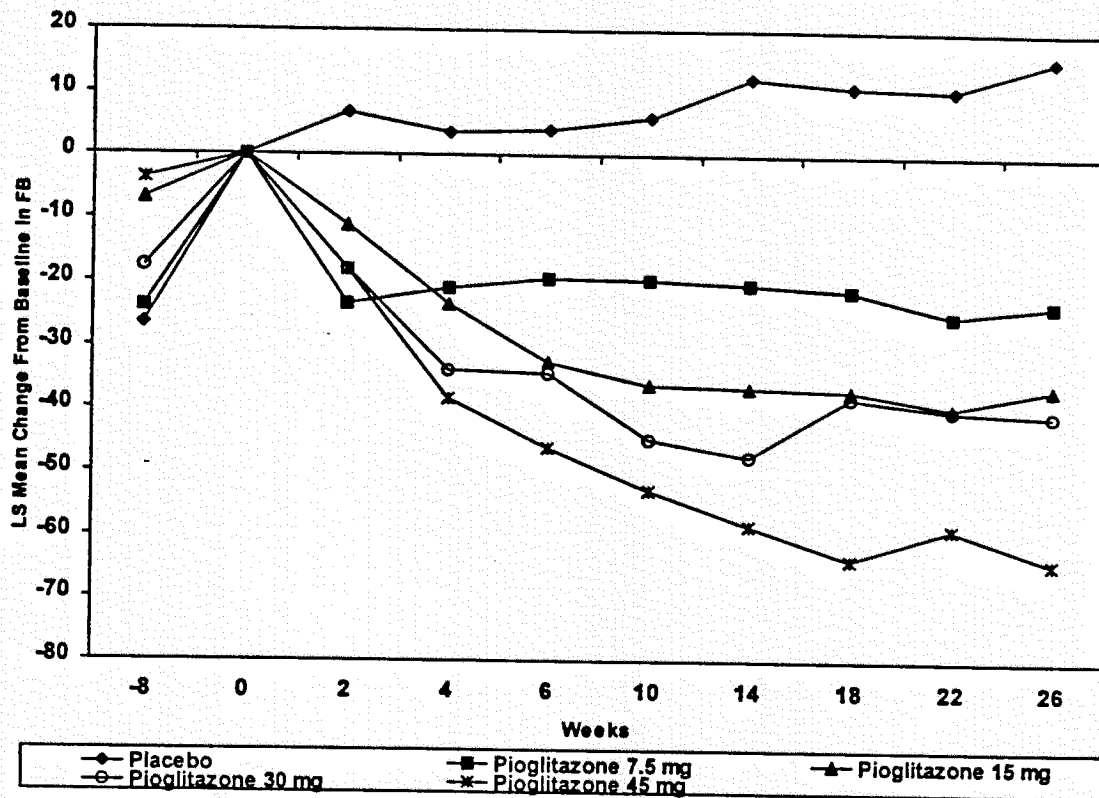
Figure 9.1.1.2.1.1: LS Mean Change from Baseline for HbA_{1c} (LOCF) for Randomized Patients Who Had Received No Previous Antidiabetic Medication



Results of FBG for PIO vs placebo are largely the same as for HbA_{1c}, except that the fall from baseline at 7.5mg is also statistically significant (see figure). It may be worthy of note that the 26 week FBG value for 7.5 mg is virtually the same as the -8 week screening value, which explains why the HbA_{1c} curve at 7.5 mg is essentially flat. One also sees that the time to maximal response for the three highest doses combined as approximately 14 weeks. The response rate based on reduction of at least 30 mg/dl is 12% for placebo patients compared to 41%, 54%, 65%, and 76% for patients on 7.5, 15, 30, and 45 mg PIO respectively.

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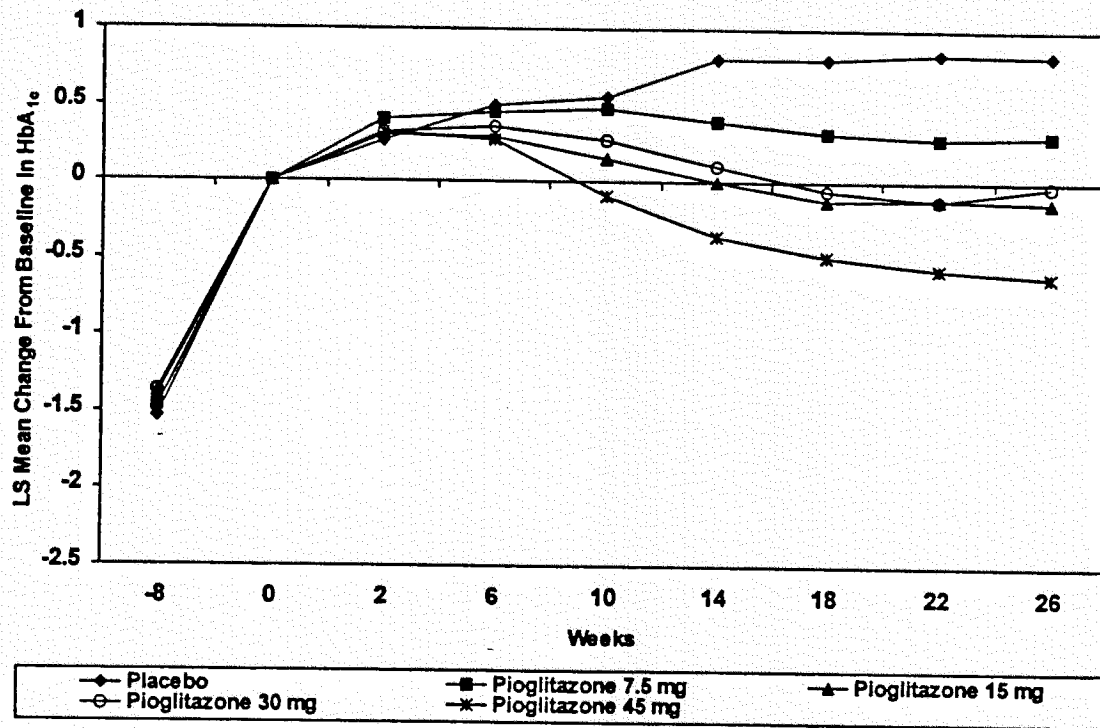
Figure 9.1.1.1.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received No Previous Antidiabetic Medication



Previously treated patients:

There were 281 patients randomized, approximately 55 in each arm. The mean age was 54 years. There were 58% males, 78% Caucasian. The mean BMI was 31. Like with the naïve patients, the male/female ratio was reversed in patients in the placebo group that had 46% males. Mean HbA1c at baseline was 10.51, FBG 280, C peptide 2 ng/ml and insulin 14.7uU/ml. Results of changes in HbA1c and FBG are shown in the following two figures. HbA1c rose 1.53 in placebo patients from screening to baseline and rose 0.83 over the 26 week study (all results are LOCF) for a mean change of +2.33. Among patients on 45 mg PIO the rise from screening to baseline was 1.39 followed by a fall of 0.61 for a mean change of +0.78. The treatment effect of 45 mg PIO is therefore -1.54 (placebo change minus PIO change). Although effective versus placebo, it should be noted that mean HbA1c levels rose in all groups.

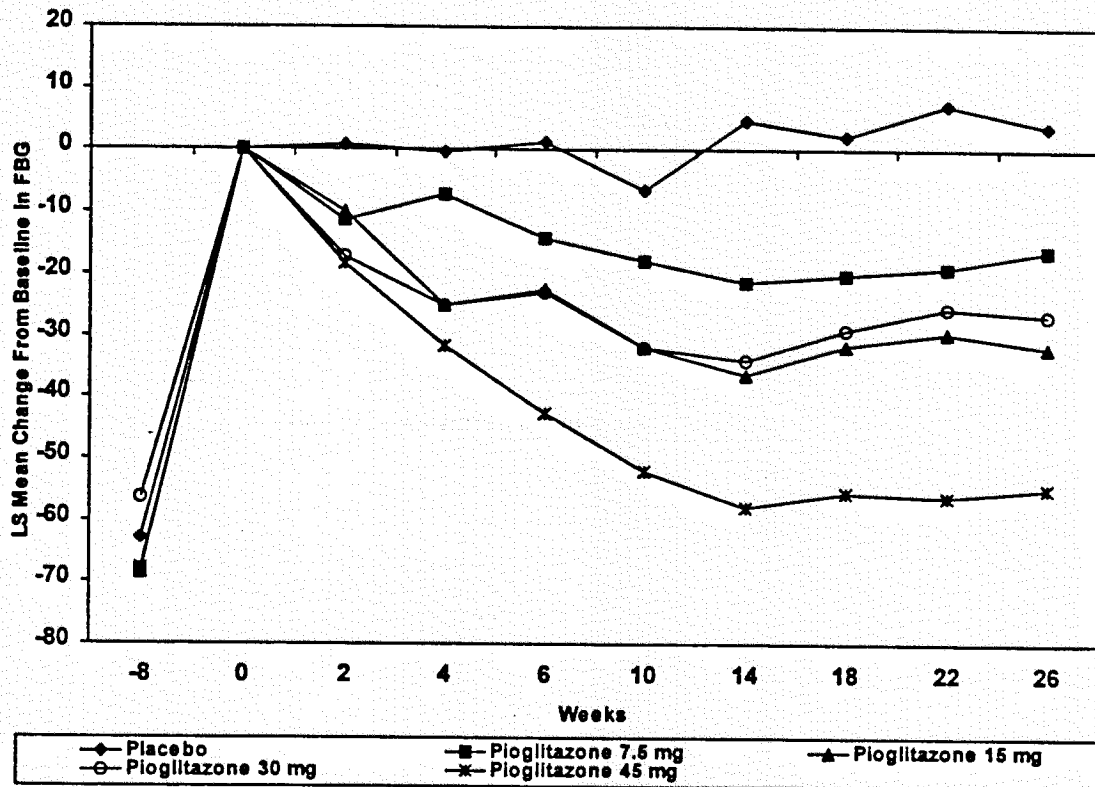
Figure 9.1.1.2.2.1.1 LS Mean Change from Baseline for HbA_{1c} (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



FBG rose 63 mg/dl from screening to baseline for patients on placebo but rose only 4 mg/dl in the subsequent 26 weeks. For patients on 45 mg PIO, the rise from screening to baseline was 68 mg/dl and the fall during 26 weeks of treatment was 55 mg/dl. For all other doses of PIO there was a clear deterioration of FBG levels if one compares screening (previous drug treatment) to 26 weeks of PIO, although the three highest doses of PIO are statistically better than placebo ($p < 0.05$).

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Figure 9.1.1.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



Analyses on Combined Data

Changes in HbA1c for the combined population are shown in the following table. Patients had a mean HbA1c of about 10.4% at baseline, which rose 0.74 in placebo patients and fell 0.86 at 45 mg PIO. There were no differences in C peptide but fasting insulin levels were generally reduced at 30 and 45 mg PIO. Baseline insulin levels were about 15 uU/ml. At 22 weeks there was a mean reduction of 0.97 on placebo compared to a mean reduction of 4.74 on 45 mg PIO. This was statistically different, although at endpoint, the change for placebo was +0.08 compared to -1.55 for 45 mg PIO and -3.30 for 30 mg PIO. The change for 30 mg was statistically significant but the change for 45 mg was not. Changes in insulin levels after glucose ingestion (done only in patients with FBG < 240 mg/dl) were not changed by PIO.

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Visit	Placebo	Pioglitazone			
		7.5 mg	15 mg	30 mg	45 mg
Baseline^a					
N ^b	79	80	79	85	76
LS Mean	10.41	10.04	10.23	10.15	10.34
SE	0.218	0.217	0.218	0.211	0.223
Week 2					
N	78	80	78	84	76
LS Mean Change	0.23 ⁺	0.26 ⁺	0.23 ⁺	0.22 ⁺	0.22 ⁺
SE	0.064	0.063	0.064	0.062	0.066
Week 6					
N	79	80	79	85	76
LS Mean Change	0.46 ⁺	0.33 ⁺	0.15	0.17	0.09
SE	0.106	0.106	0.107	0.104	0.110
Week 10					
N	79	80	79	85	76
LS Mean Change	0.49 ⁺	0.34 ⁺	0.01*	0.05	-0.33 ⁺ *
SE	0.135	0.135	0.136	0.132	0.140
Week 14					
N	79	80	79	85	76
LS Mean Change	0.71 ⁺	0.25 ⁺	-0.13*	-0.14*	-0.59 ⁺ *
SE	0.147	0.147	0.148	0.144	0.152
Week 18					
N	79	80	79	85	76
LS Mean Change	0.70 ⁺	0.21	-0.23*	-0.29 ⁺ *	-0.76 ⁺ *
SE	0.159	0.159	0.160	0.155	0.165
Week 22					
N	79	80	79	85	76
LS Mean Change	0.71 ⁺	0.20	-0.24*	-0.35 ⁺ *	-0.84 ⁺ *
SE	0.165	0.166	0.167	0.162	0.172
Week 26 (Endpoint)^c					
N	79	80	79	85	76
LS Mean Change	0.74 ⁺	0.20	-0.27 ⁺ *	-0.27*	-0.86 ⁺ *
SE	0.169	0.170	0.170	0.165	0.175
LS Mean Difference^d		-0.54	-1.00	-1.00	-1.60
95% Confidence Interval^e		-1.13, 0.05	-1.59, -0.42	-1.58, -0.42	-2.19, -1.00

^a Baseline is the last value taken during the baseline period.

^b N at baseline includes patients who had a value at both baseline and endpoint.

N at each visit includes patients who had values at baseline and visit.

^c Endpoint is the last measurement taken during the double-blind treatment period.

^d Difference between each dose and placebo in mean change from baseline.

^e For LS mean difference, based on ANCOVA and Dunnett's t-distribution.

Note: Model for baseline based on a 2-way ANOVA with effects for pooled center and treatment. Model for change from baseline based on 2-way ANCOVA with effects for pooled center, treatment, pooled-center-by-treatment interaction, and baseline as a covariate.

* Significant change from baseline ($p \leq 0.050$) based on a paired t-test.

* Significantly different from placebo ($p \leq 0.050$) based on Dunnett's test.

Data Source: End-of-Treatment Tables 9.2 and 9.3, Listing 8, and Statistical Appendix 2.1.

There was a consistent increase in body weight in patients treated with PIO. After 26 weeks at 30 mg, and 45 mg PIO the increase in weight was 2.92 kg and 4.66 kg respectively compared to a loss of 0.73 kg in placebo patients. At endpoint the placebo patients had a mean weight loss of 1.28 kg compared to gains of 1.29 and 2.82 kg at 30 and 45 mg PIO respectively. Mean fasting triglyceride levels were about 270 mg/dl and fell in all groups. The mean fall in placebo patients at 26 weeks (endpoint, LOCF) was 21 mg/dl. The reductions at 15, 30 and 45 mg PIO were 54, 39, and 48 mg/dl which were significantly greater than placebo. Total cholesterol, LDL cholesterol and HDL cholesterol rose slightly in all groups but there was no consistent effect of PIO except that HDL cholesterol rose somewhat more at 45 mg PIO. The mean values for HDL cholesterol were about 41 mg/dl at baseline. The mean rise after 26 weeks (LOCF) for placebo patients was 3.0 compared to 7.0 mg/dl for patients on 45 mg PIO. The statistically significant rise

in HDL on 45 mg PIO vs placebo was present at 2 weeks and persisted throughout the 26 week study. Differences at other doses achieved statistical significance at some time points but not others.

Subgroup analysis suggested that PIO might be somewhat more effective in females than in males. Looking only at the 45 mg dose, the reduction of HbA1c (completers) was 1.71 for males and 2.41 for females. 25/46 males (54%) completed the study compared to 19/30 females (63%). Among placebo patients there was a mean rise in HbA1c of 0.43 compared to 0.39 in females. Among placebo patients, those completing the study was 36% for males and 39% for females. Mean change at 26 weeks LOCF for men on placebo was +0.54 and +0.87 for women. At 45 mg PIO the change was -0.59 for men and -1.37 for women . The net effect for men were -1.13 compared to - 2.24 for women. The difference between men and women also appeared to be present at 30 mg PIO (-0.56 compared to - 1.47) but not at 15 mg (-0.99 for men compared to -1.06 for women) source table 9.4.2.8.1.1. PIO seemed less effective in patients over 65 than in younger patients, but the number of patients over 65 was too small to be conclusive. PIO was equally effective in Black and Caucasian patients.

PK:

PK studies showed that the mean trough blood levels after two weeks for PIO were 43,88,124, and 245 ng/ml for 7.5, 15, 30, and 45 mg doses. After 26 weeks, trough blood levels were 49, 84, 104, and 230 ng/ml, respectively. The blood levels of metabolite M-111 and M-1V after 26 weeks at 45 mg/PIO were 328 ng/ml and 807 ng/ml. These values correspond to the 230 ng/ml for unchanged PIO.

Safety:

There were no deaths in the study. More placebo patients than PIO patients dropped out due to poorly controlled hyperglycemia. Otherwise, the dropouts were equally distributed among the treatment groups. AE's of psychiatric disorders occurred in 5% of placebo patients compared to 10% of PIO patients. Peripheral edema was reported in 3% of patients on PIO and none on placebo. There was a dose-dependent reduction in hemoglobin in patients on PIO. At 26 weeks the mean change in hemoglobin for placebo patients was + 0.42 g/dl compared to reductions of 0.13, 0.31, 0.42, and 0.74 g /dl on 7.5, 15, 30, and 45 mg/d of PIO, respectively.

Study PNFP - 011

Long-term open label study with titration to 60 mg

Patients who completed the 26-week placebo-controlled study described above (study 001) were allowed to enter an open label extension study. New patients were allowed to enter De Novo, but treatment with PIO was preceded by an 8-week single blind placebo run-in. All patients had to have HbA1c of at least 7% at day one to enter the study. All patients received an initial dose of 7.5-mg PIO for at least 4 weeks. The dose could then be increased every four weeks in a stepwise fashion to 15, 30, 45, and 60 mg if FBG exceeded 140 mg/dl. Patients on 45 mg received a 30 and 15-mg tablets. Patients on 60 mg received two 30-mg tablets Dosing was with breakfast. The mean age of patients was 54 years. 75% were Caucasian and 62% were male.

A time course of FBG's is shown in the table. In reviewing these data one needs to bear in mind that De Novo patients received PIO starting at "baseline". Rollover placebo patients received PIO starting at "endpoint". Rollover PIO patients had been receiving PIO since "baseline". But at "endpoint" they started a titration from 7.5mg. Most of these rollover PIO patients had been on higher doses previously, hence the rise in FBG that occurred during the first 8 weeks of study. It should also be noted that the duration of PIO treatment is 72 weeks for the De Novo and Rollover Placebo patients but is 98 weeks (26 weeks double blind followed by 72 weeks open label) for the Rollover PIO patients.

Table 9.4.1.2.3: Mean FBG (mg/dL) by Visit (Observed Values)

Visit	De Novo (N=299)	Rollover Placebo (N=56)	Rollover Pioglitazone (N=214)	Total (N=569)
Screen				
N ^b	286	48	193	527
Mean	218.8	231.6	227.1	223.0
SE	3.53	8.91	4.84	2.74
Baseline^a				
N ^b	286	54	207	547
Mean	263.0	272.6	267.4	265.6
SE	4.50	9.31	5.03	3.16
Endpoint of Study AD-4833/PNFP-001				
N ^b	N/A	54	207	261
Mean		279.0	232.7	242.3
SE		9.74	5.60	5.01
Week 4				
N ^b	283	54	205	542
Mean	247.6	269.9	247.4	249.7
SE	4.09	9.91	5.59	3.17
Week 8				
N ^b	268	52	199	519
Mean	233.2	263.7	243.4	240.2
SE	4.13	10.46	5.35	3.16
Week 12				
N ^b	253	50	193	496
Mean	199.1	240.7	226.5	214.0
SE	3.98	11.51	5.25	3.18
Week 24				
N ^b	221	46	172	439
Mean	179.5	220.0	210.1	195.7
SE	3.71	12.00	5.74	3.27
Week 36				
N ^b	197	30	126	353
Mean	178.0	205.1	197.6	187.3
SE	3.68	14.18	6.07	3.26
Week 48				
N ^b	164	23	84	271
Mean	174.7	190.6	188.3	180.3
SE	4.22	15.08	7.65	3.72
Week 60				
N ^b	84	12	51	147
Mean	170.5	173.5	189.9	177.5
SE	5.82	19.74	9.03	4.87
Week 72^c				
N ^b	29	7	24	60
Mean	188.2	160.3	179.1	181.3
SE	11.66	32.05	12.29	8.26

^a For *de novo* patients, baseline is the last value taken during the baseline period. For rollover patients, baseline is defined as the last measurement taken during the baseline period of Study PNFP-001.

^b N at baseline includes patients who had a value at both baseline and at any one visit. N at a visit includes patients who had a value at both baseline and visit.

^c This is the last timepoint that has a total number of patients greater than or equal to 25.

N/A = Not applicable.

Data Source: End-of-Text Table 12.1 and Listing 9.2.

The following table shows a time course for HbA_{1c}, which corresponds, to FBG values shown in the previous table. These results suggest that the efficacy of PIO is maintained long-term. Being an open-label extension study, treatment is on going and only a small number of patients completed week 72 or beyond.

Table 9.4.1.1.2: Mean Change From Baseline for HbA_{1c} (%) by Visit (Observed Values)

Visit	De Novo (N=299)	Rollover Placebo (N=56)	Rollover Pioglitazone (N=214)	Total (N=569)
Screen				
N ^b	254	46	180	480
Mean Change	-0.93	-1.41	-1.03	-1.02
SE	0.089	0.207	0.099	0.063
Baseline^a				
N ^b	255	52	193	500
Mean	9.96	10.62	10.26	10.14
SE	0.115	0.275	0.148	0.087
Endpoint of Study AD-4833/PNFP-001				
N ^b	N/A	52	193	245
Mean Change		0.68	-0.30	-0.09
SE		0.175	0.111	0.098
Week 12				
N ^b	255	51	191	497
Mean Change	-0.33	0.04	-0.21	-0.25
SE	0.080	0.209	0.101	0.061
Week 24				
N ^b	228	46	172	446
Mean Change	-1.20	-0.77	-0.76	-0.98
SE	0.104	0.270	0.110	0.074
Week 36				
N ^b	198	31	123	352
Mean Change	-1.50	-1.23	-1.08	-1.33
SE	0.111	0.333	0.132	0.083
Week 48				
N ^b	164	23	85	272
Mean Change	-1.57	-0.99	-1.03	-1.35
SE	0.120	0.382	0.159	0.095
Week 60				
N ^b	84	14	50	148
Mean Change	-1.45	-1.12	-0.79	-1.19
SE	0.176	0.464	0.229	0.135
Week 72^c				
N ^b	30	8	26	64
Mean Change	-0.74	-0.58	-0.52	-0.63
SE	0.355	0.358	0.296	0.208

^a For *de novo* patients, baseline is the last value taken during the lead-in period. For rollover patients, baseline is defined as the last measurement taken during the baseline period of Study PNFP-001.

^b N at baseline includes patients who had a value at both baseline and at any one visit. N at visit includes patients who had a value at both baseline and the visit.

^c This is the last timepoint that has a total number of patients greater than or equal to 25.

N/A = Not applicable.

Data Source: End-of-Text Table 10.2 and Data Listing 8.

A better way of looking at the results of this trial may be to examine the time course of the cohort that completed week 48 (74 weeks of PIO for the Rollover PIO patients and 48 weeks of PIO for the other patients). HbA_{1c} is shown in the table and FBG is shown in the figure. Of particular importance is that there is no evidence for deterioration of glycemia at the end of the observation period.

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**Table 9.4.1.1: Mean Change From Baseline for HbA_{1c} (%) by Visit
For Patients Who Completed 48 Weeks of Open-Label Treatment (Observed Values)**

Visit	De Novo (N=299)	Rollover Placebo (N=56)	Rollover Pioglitazone (N=214)	Total (N=569)
Screen				
N ^b	164	18	77	259
Mean Change	-0.78	-1.26	-0.80	-0.82
SE	0.100	0.331	0.133	0.078
Baseline^a				
N ^b	165	23	86	274
Mean	9.71	9.86	9.59	9.68
SE	0.133	0.426	0.190	0.106
Endpoint of Study AD-4833/PNFP-001				
N ^b	N/A	23	86	109
Mean Change		0.50	-0.33	-0.16
SE		0.290	0.160	0.143
Week 12				
N ^b	165	23	85	273
Mean Change	-0.46	-0.45	-0.36	-0.43
SE	0.087	0.308	0.146	0.074
Week 24				
N ^b	161	23	86	270
Mean Change	-1.35	-1.01	-0.91	-1.18
SE	0.114	0.376	0.145	0.089
Week 36				
N ^b	163	23	85	271
Mean Change	-1.55	-1.08	-1.05	-1.35
SE	0.122	0.359	0.155	0.094
Week 48				
N ^b	164	23	85	272
Mean Change	-1.57	-0.99	-1.03	-1.35
SE	0.120	0.382	0.159	0.095

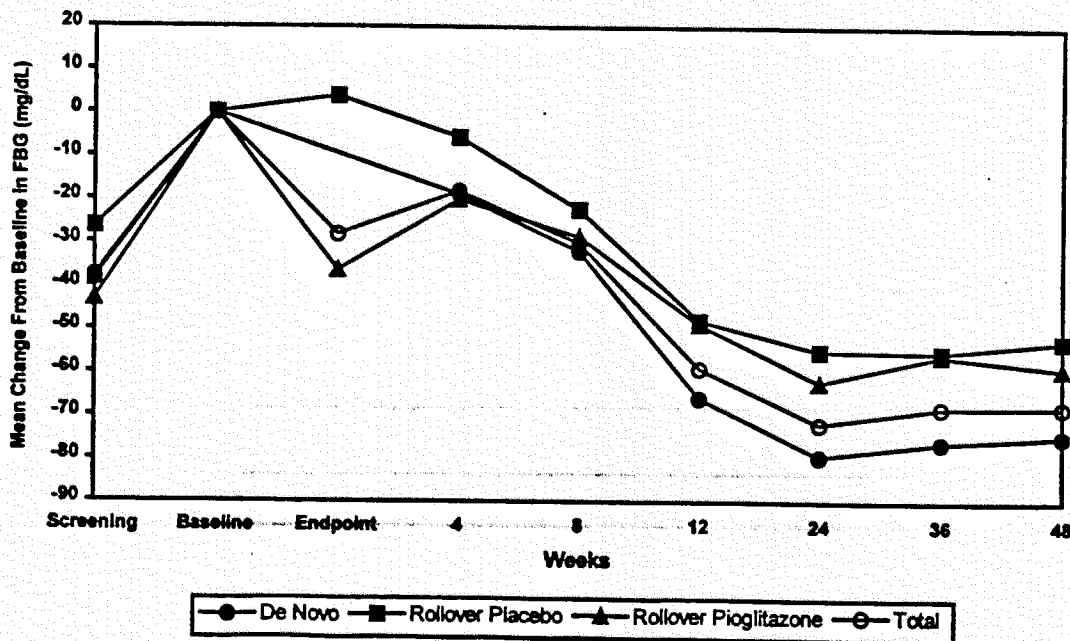
^a For *de novo* patients, baseline is the last value taken during the lead-in period. For rollover patients, baseline is defined as the last measurement taken during the baseline period of Study PNFP-001.

^b N at baseline includes patients who had a value at both baseline and at any one visit. N at visit includes patients who had a value at both baseline and the visit.

N/A = Not applicable.

Data Source: End-of-Text Table 10.2A and Listing 8.

**Figure 9.4.1.2.1: Mean Change From Baseline for FBG (mg/dL) by Visit
For Patients Who Completed 48 Weeks of Open-Label Treatment (Observed Values)**



Data Source: End-of-Text Table 12.2A.

The improvement in hyperglycemia noted in the previous table and figure was associated with a mean weight gain of 5.6 kg. Regrettably there was no evidence that this weight gain had reached a plateau at the end of the observation period. The weight change in the "Rollover PIO" patients is particularly illuminating. The mean weight loss from screening to baseline was 1.38 kg, largely reflecting the hyperglycemia that resulted from the discontinuation of previous drug therapy in most of these patients. The mean weight gain after 26 weeks of PIO was 1.76 kg reflecting improvement in hyperglycemia. However, weight fell slightly during the early part of the open label trial, again reflecting the rise in glucose levels, which occurred due to reduction of the PIO dose to 7.5 mg. However, by week 12 weight was rising again. If one looks at the 12 week intervals, from week 12 - 24, week 24-36 and week 36-48, the mean weight gain was 1.81, 0.95, and 0.79 kg. Thus weight gain was continuing even though improvement of hyperglycemia had plateaued.

Visit	De Novo (N=299)	Rollover Placebo (N=56)	Rollover Pioglitazone (N=214)	Total (N=569)
Screen				
N ^b	175	25	88	288
Mean Change	1.53	1.80	1.38	1.51
SE	0.167	0.363	0.270	0.134
Baseline^a				
N ^b	175	25	88	288
Mean	90.73	90.42	92.74	91.32
SE	1.154	2.295	1.525	0.865
Endpoint of Study AD-4833/PNFP-001				
N ^b	N/A	25	88	113
Mean Change		-0.66	1.76	1.22
SE		0.719	0.364	0.337
Week 4				
N	175	25	88	288
Mean Change	-0.39	-0.45	1.64	0.22
SE	0.134	0.668	0.361	0.158
Week 12				
N	173	23	88	286
Mean Change	0.16	0.13	1.81	0.67
SE	0.189	0.630	0.383	0.178
Week 24				
N	175	22	81	278
Mean Change	2.74	3.22	3.62	3.03
SE	0.286	0.766	0.463	0.233
Week 36				
N	175	25	88	288
Mean Change	4.69	4.93	4.57	4.67
SE	0.365	0.934	0.495	0.280
Week 48				
N	175	25	88	288
Mean Change	5.55	6.34	5.36	5.56
SE	0.402	1.086	0.584	0.316

For *de novo* patients, baseline is the last value taken during the lead-in period. For rollover patients, baseline is defined as the last measurement taken during the baseline period of Study PNFP-001.

^a N at baseline includes patients who had a value at both baseline and at any one visit.

N at visit includes patients who had values at baseline and visit.

N/A = Not Applicable.

Data Source: End-of-Text Table 36.1A and Data Listing 19.

Subgroup analysis showed that PIO was more effective in women than in men. Among de novo patients, men had a mean baseline HbA1c of 9.63 and a reduction of 1.32. Women had a mean baseline of 9.81 and a mean reduction from baseline of 2.00. Differences related to age and race did not appear to be significant. Among the 299 de novo patients, 60 mg was the final dose in 168 (56%) and was the maximal dose used in 172. The 60-mg dose was reduced in four patients because of adverse events, hypoglycemia in one, weight gain in two and light-headedness in one. Among the 56-rollover placebo patients, 60 mg was the final and maximal dose in 37(66%). No new safety issues were uncovered by this long-term open label study.

Study PNFP 026

Placebo-controlled monotherapy study

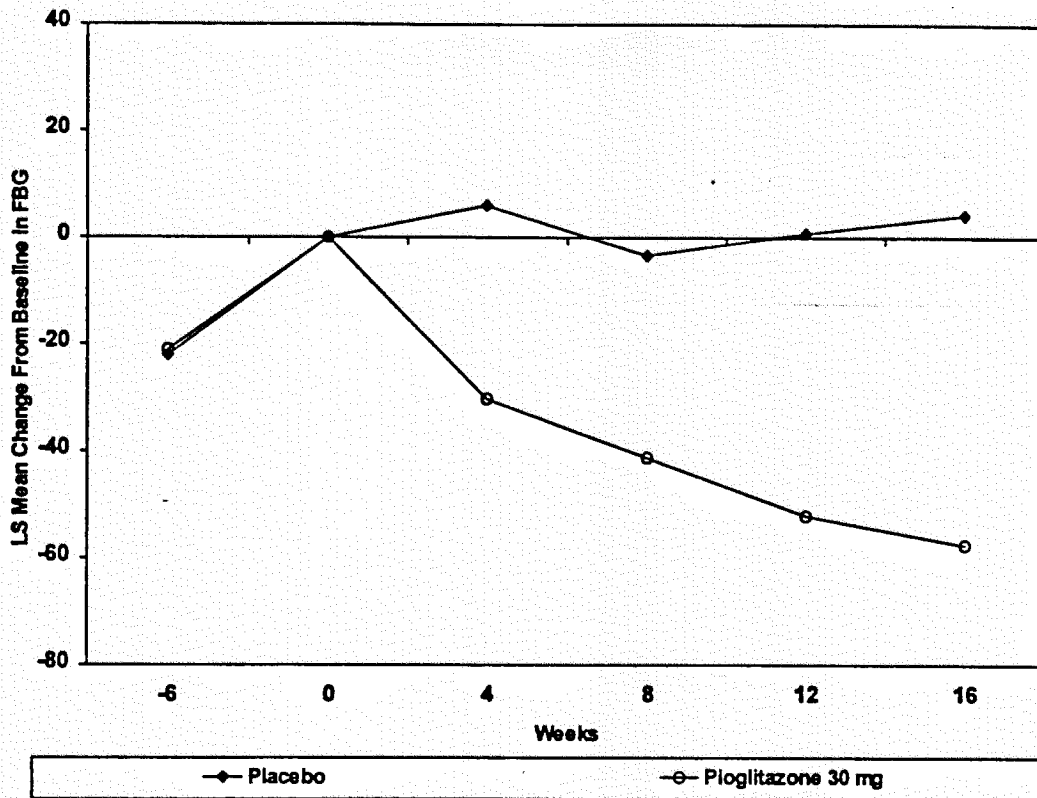
This was a 16 week randomized controlled study which compared PIO 30 mg to placebo. The 16-week double blind placebo portion was preceded by a five-week washout from previous antidiabetic therapy. Inclusion criteria included a HbA1c of at least 7.5 at screening and at least 8 after the washout. Patients were excluded for ALT > 2.5 x ULN. Patients were removed from the study because of insufficient therapeutic effect defined as FBG > 400 mg/dl on two consecutive study visits or hyperglycemia which in the investigator's opinion represented a safety risk to the patient. Reduction in Hb to < 12 for a man and < 10 for a women was also a cause for withdrawal as was development of LVH by EKG. Antihypertensive and lipid lowering drugs were allowed if the dose had been kept constant for 60 days before study. The primary efficacy variable was HbA1c, Secondary variables were FBG, insulin C peptide and lipids. For reason discussed previously, naive and previously treated patients were presented separately.

Naïve patients:

78 patients had not received previous antidiabetic medication. Their mean age was 52 years. Half were male and 62% were Caucasian. The mean BMI was 31.4. For the 37 placebo patients baseline HbA1c was 10.31 The increase from screening to baseline was 0.40 . At the 16 week endpoint (LOCF), HbA1c rose 0.09 (LS mean change) . For patients who received PIO, the mean baseline was 10.13. It had risen 0.25 from screening to baseline. At the 16-week endpoint the mean reduction was 0.89. The reduction in HbA1c with PIO was significantly different from placebo at 12 weeks. The treatment effect at 16 weeks was 0.98. A time course of the change in FBG shown in the figure. The mean baseline was 267 mg/dl in placebo patients and 252 in PIO patients. At 16 weeks the rise in placebo patients was 4.2 mg/dl compared to a fall of 57.6 mg/dl on PIO for a treatment effect of 61.8 mg/dl This figure demonstrates the efficacy of PIO which had not yet plateaued by the end of the 16 week study. The reduction in FBG of about 58 mg/dl in PIO patients should ordinarily have been associated with a reduction in HbA1c of nearly 2.0. That the reduction was only 0.89 is an underestimate of the full effect due to inadequate duration of study.

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Figure 9.1.1.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received No Previous Antidiabetic Medication

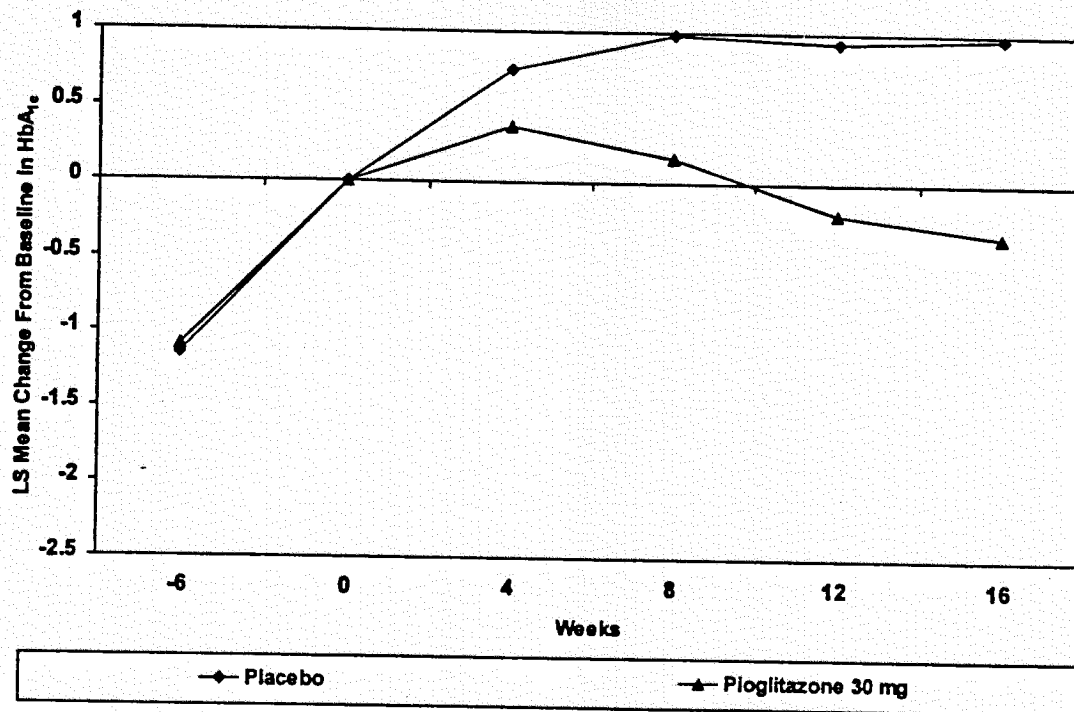


Previously treated patients

The placebo group consisted of 56 patients with mean HbA1c at baseline of 10.25. It had risen 1.14 from screening to baseline and rose an additional 0.97 after 16 weeks. The PIO group consisted of 60 patients with mean baseline HbA1c of 10.72 which had risen 1.09 from screening and which fell a mean of 0.35 after 16 weeks of PIO. The placebo subtracted treatment effect after 16 weeks was 1.32. A time course of the changes in HbA1c and FBG are shown in the figures. In contrast to the previous figures with naïve patients, it appears that a plateau was reached by 12 weeks in these previously treated patients. It is also worth noting that although PIO was superior to placebo, patients never achieved the HbA1c and FBG levels that they had had before previous therapy had been washed out.

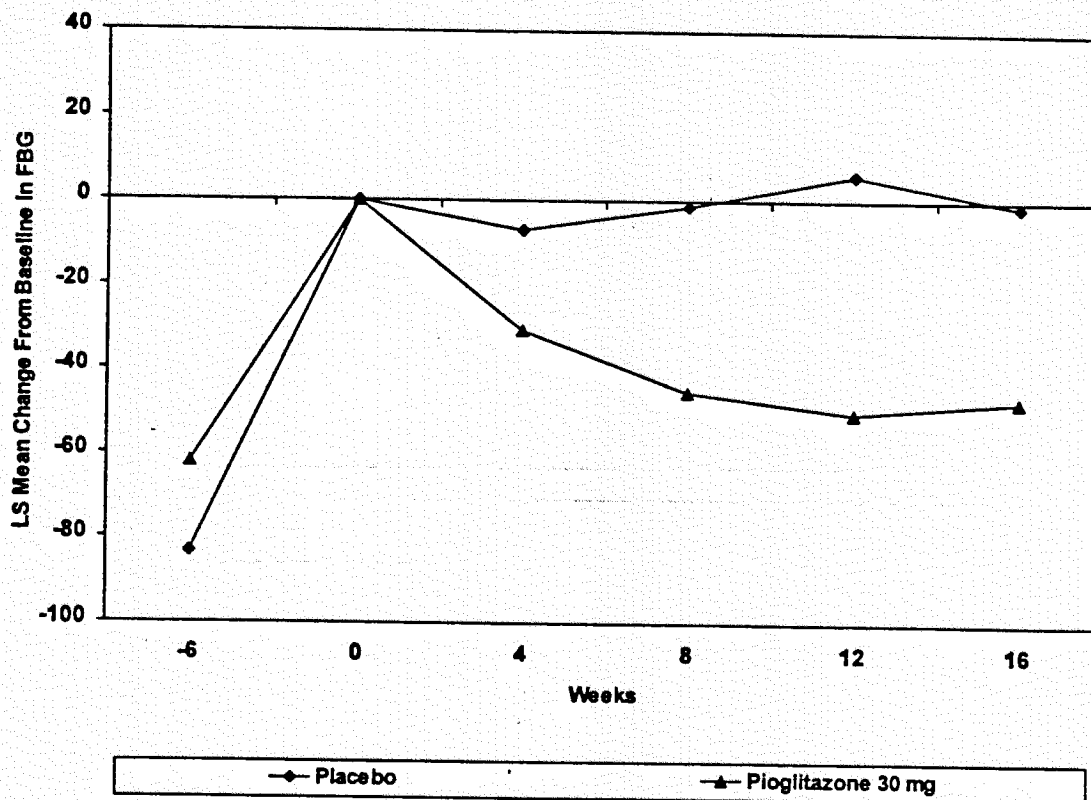
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Figure 9.1.1.2.2.1.1 LS Mean Change from Baseline for HbA_{1c} (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



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Figure 9.1.1.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



There were 28 previously patients whose FBG at baseline was > 280. Their mean FBG at screening was about 227 mg/dl which rose to 333 mg/dl after washout. The final value after placebo treatment was 312 (NDA table 11.1.5). There initial HbA1c was 9.7 at screening. It rose to a mean baseline value of 11.4. After placebo treatment the final mean value was 12.8 (NDA table 9.1.5).

Analyses on combined groups.

C peptide was unchanged in placebo patients but fell 0.23 (baseline 2.21 ng/ml) in PIO- treated patients. There was also a small difference in fasting insulin. Baseline was about 17 uU/ml. This rose about 2 uU/ml in placebo patients and fell about 2uU/ml in PIO patients. The mean difference of 3.84 uU/ml was statistically significant. Plasma triglycerides fell slightly in placebo patients but significantly in PIO patients. The LS mean decrease was 104 mg/dl from a baseline of 400. Both the decrease from baseline and the difference from placebo (85 mg/dl) were statistically significant. There was no difference in total cholesterol but HDL cholesterol rose in PIO patients but were unchanged in placebo patients. The LS mean HDL in PIO patients was 91 at baseline. Both the rise from baseline of 5.3 mg/dl and the difference from placebo of 5.0 mg/dl were significant. Changes in LDL cholesterol were small and not statistically significant. The placebo-subtracted reduction in Hb A1c was 1.07 for man and 1.54 for women. The reduction was 1.22 for patients under 65 and 1.89 for patients over 65 but the total number of patients over 65 was small(19 placebo, 12 PIO). The mean reduction was 1.56 for Caucasians and 2.15 for blacks, but the number of black patients was small(10 on placebo and 9 on PIO). Placebo patients had a mean baseline weight of 87.3 kg. The LS mean change at endpoint was - 1.87 kg. The mean baseline for PIO

patients was 89.9 kg and the LS mean change at endpoint was + 1.35 kg. Using observed values at 16 weeks, placebo patients had a mean loss of 1.98 kg compared to a mean gain of 1.97 kg in PIO patients.

Safety:

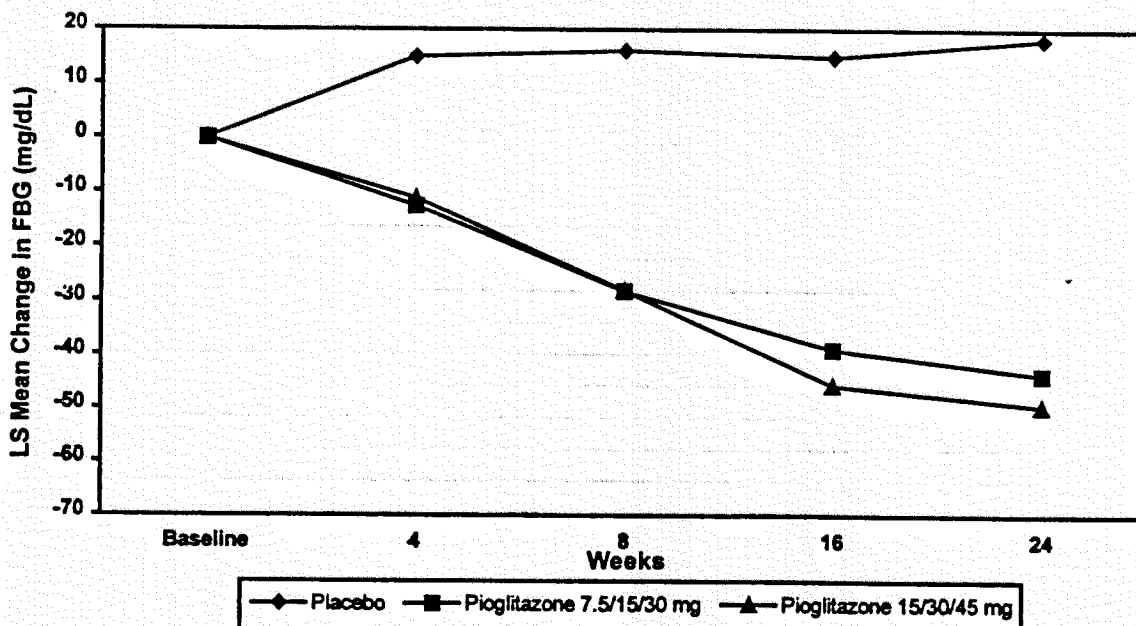
There were no deaths in this study. PIO patients had a mean fall in hemoglobin of 0.52 g/dl compared to a mean rise of 0.03 in placebo patients. There were no additional safety issues.

Study PNFP 012

Placebo-controlled monotherapy study with forced dose titration

This was a three-arm dose-titration study, which began with a six-week placebo washout. One arm received placebo throughout. A second arm began PIO at 7.5 mg. After 4 weeks, the dose was increased to 15 mg and a after 4 more weeks it was increased again to 30 mg. The dose of 30 mg was maintained for the next 16 weeks. In the third arm, patients started at 15 mg, the dose was increased to 30 mg after four weeks and to 45 mg after an additional four weeks. The 45 mg dose was maintained for 16 weeks. Patients were required to have HbA1c > 8% at baseline in order to be randomized. Entry criteria were same as for previous monotherapy studies. Withdrawal due to lack of efficacy was similarly defined as FBG > 400 mg/dl on two occasions or a safety risk in the opinion of the investigator. Lipid lowering and antihypertensive drugs were allowed. Beta blockers, warfarin, and antidepressants were not allowed. The mean age of patients was 56 years. 82% were Caucasian and 56% were male. Mean baseline HbA1c was about 10.6. After 24 weeks, there was a mean increase of 0.75 in placebo patients and decreases of 0.99 and 1.01 in low/high dose PIO respectively. The mean treatment effect was -1.74 for low dose and -1.76 for high dose. The figure shows the time course for reduction of FBG. After 24 weeks the mean placebo-subtracted reduction was 62 mg/dl for low dose and 68 mg/dl for high dose

Figure 9.4.1.2.1: LS Mean Change From Baseline for FBG (mg/dL) by Visit (LOCF Analysis)



Data Source: End-of-Text Table 11.2.

The change in body weight at endpoint was -1.81 kg in placebo patients compared to +0.49 and +1.82 for patients on low and high dose PIO. For completers at 24 weeks the mean change in weight was -1.70 for

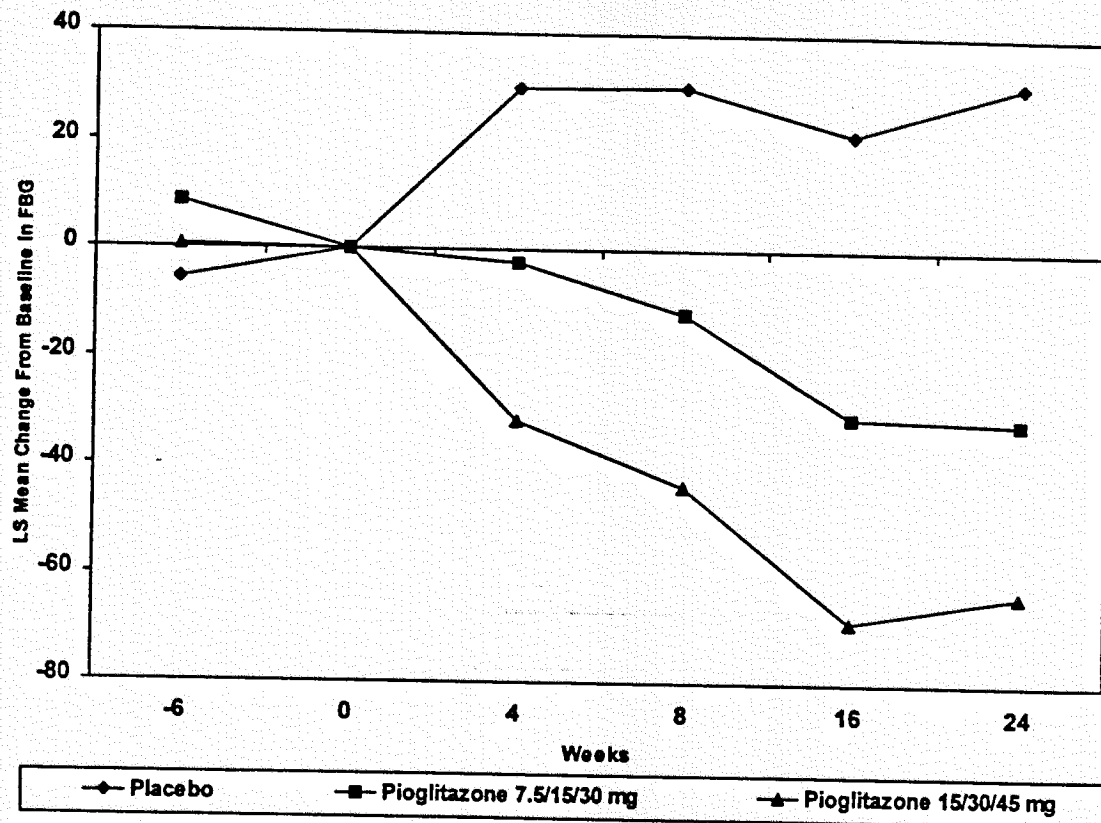
placebo compared to + 1.27 and + 2.58 kg for patients on low and high dose PIO. Mean C peptide fell in all three groups. Mean fasting insulin fell from 15 to 13 uU/ml ($p < 0.05$) in high dose PIO. There were no significant differences between PIO and placebo with respect to insulin and C peptide. Fasting triglyceride levels were about 300 mg/dl at baseline. At endpoint there was a small reduction (NS) of 28 mg/dl in placebo patients but significant reductions of 64 and 102 mg/dl in low and high dose PIO. The placebo-subtracted reduction at high dose PIO of 74 mg/dl was different from placebo. Total cholesterol rose slightly in all groups. Mean HDL was about 41 mg/dl at baseline. The rise of 3.5 and 4.1 in low and high dose PIO at endpoint was significantly different from baseline but not from the small (NS) rise of 1.3 mg/dl on placebo. A small (6% on placebo, 7% and 8% on low and high dose PIO) but significant mean rise in LDL chol was seen in all three groups. PIO tended to be somewhat more effective in women than in men and in patients over 65 than in younger patients. As will be discussed below, the placebo subtracted reduction in HbA1c on high dose PIO was 2.4 in naïve patients and 1.4 in previously treated patients.

Naïve patients:

63 patients (24%) had not previously received antidiabetic medications. Their mean age was 55 years. 85% were Caucasian and 59% were male. Mean BMI was 30.45. There was little change in HbA1c from screening to baseline. Mean baseline values for HbA1c were about 10.3%. From baseline to completion the mean increase in HbA1c among placebo patients was 0.83 compared to mean reductions of 1.45 and 1.76 in patients on low and high dose PIO. All changes from baseline to endpoint were significant. The treatment effect at endpoint was -2.28 and -2.59 for low and high dose PIO respectively. No plateau had been reached in fall of HbA1c by the end of the 24-week treatment (16 weeks at highest dose) period. Mean baseline was about 245 mg/dl. A time course of change in FBG is shown in the figure. One notes little change from screening to baseline. A rise in baseline of about 30 mg/dl occurred over four weeks in placebo patients, which was statistically different from the falls in PIO patients. The mean glucose levels remained largely constant over the remainder of the study but continued to fall in the PIO patients. A maximal reduction of FBG was seen after about 16 weeks. Placebo subtracted change at endpoint was -63 mg/dl for low dose and -95 mg/dl for high dose.

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Figure 9.1.1.1.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received No Previous Antidiabetic Medication

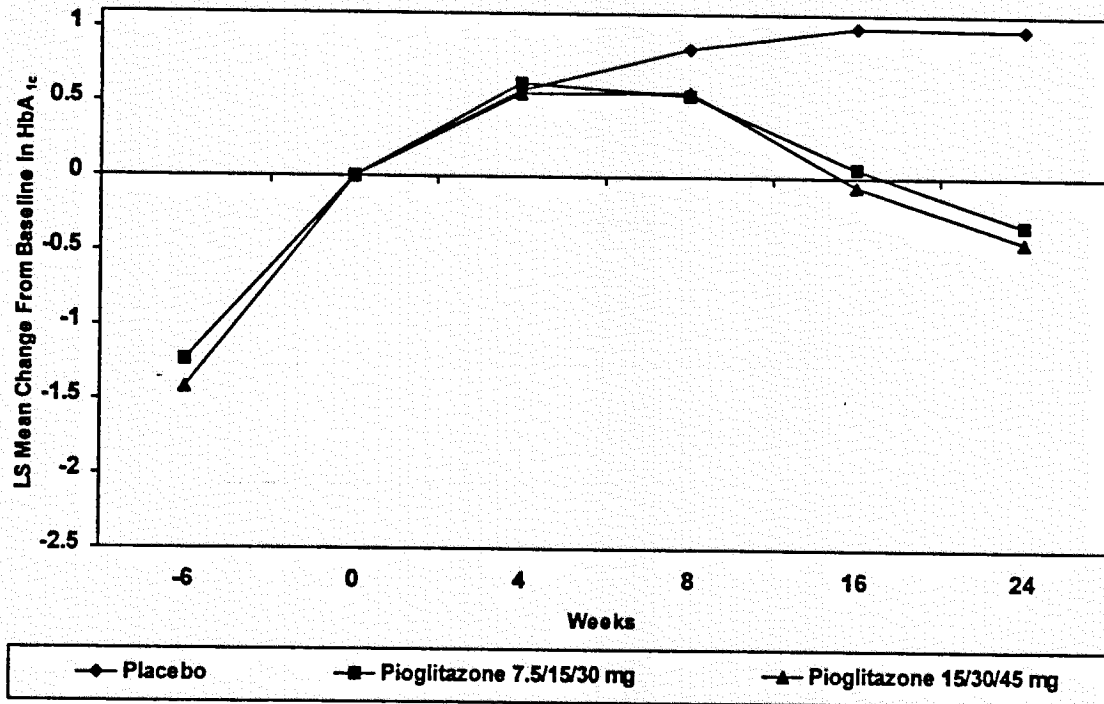


Previously treated patients:

197 patients (76%) had used antidiabetic medications before entering the study. Their mean was 56 years. 83% were Caucasian and 55% were male. Their mean BMI was 31. Time courses of changes in HbA1c and FBG are shown in the figures. FBG rose about 70 mg/dl during the 6-week washout from previous therapy to mean baseline value of about 285 mg/dl. FBG continued to rise slightly in the placebo patients but fell in PIO patients. The change in HbA1c was more gradual. It rose about 1.3 during the washout to a mean baseline of about 10.6. HbA1c continued to rise in placebo patients but fell in PIO patients. Of note is that the deterioration in hyperglycemia during the washout was not completely reversed by PIO. At endpoint placebo subtracted change in HbA1c was -1.31 and -1.42 for low and high dose PIO. For FBG, placebo subtracted change at endpoint was -55 and -60 mg/dl for low and high dose PIO.

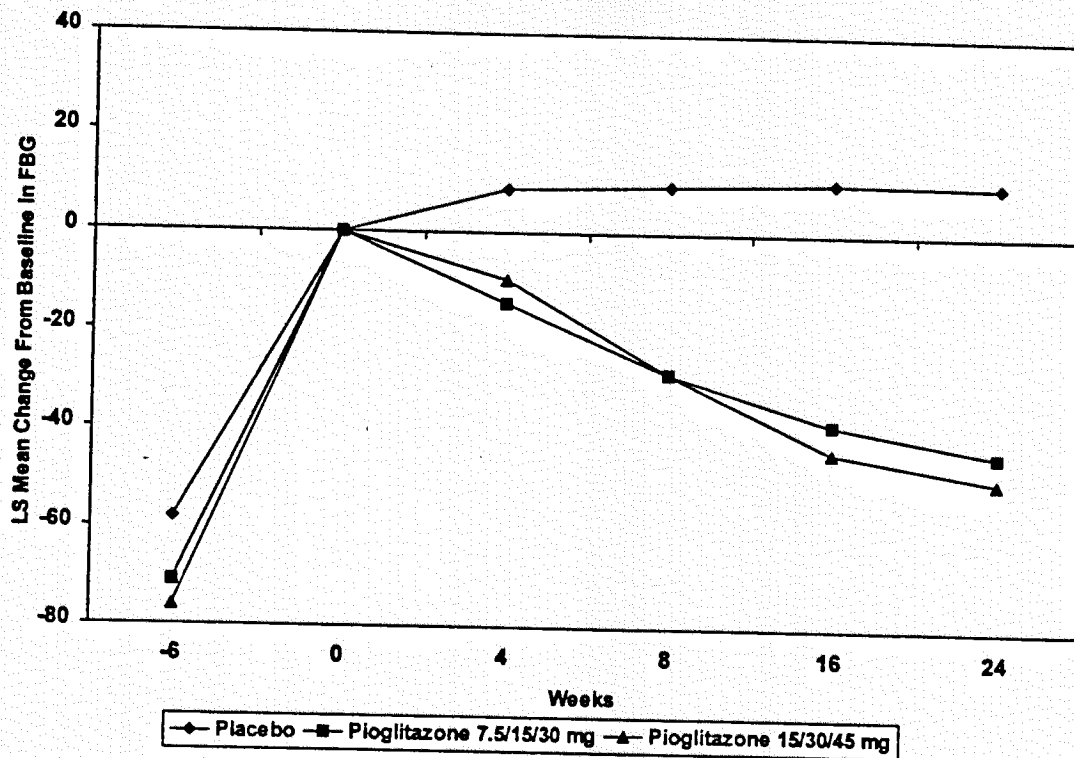
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Figure 9.1.1.2.2.1.1 LS Mean Change from Baseline for HbA_{1c} (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



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Figure 9.1.1.2.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



There were 115 patients taken off of antidiabetic medication whose FBG > 280 at baseline. These patients had a mean age of 56 years. 82% were Caucasian and 52% were male. Mean BMI was 31.3 At baseline mean C peptide was 2 ng/ml and mean fasting insulin was 13 uU/ml. Data for HbA1c and FBG for these patients through end of study (LOCF) are shown in the tables below. Although PIO was effective in lowering FBG and HbA1c levels compared to placebo, it should be noted that even high dose PIO did not restore glucose and HbA1c levels to what they had been before the 6 week washout from previous antidiabetic medication.

	Fasting Blood Glucose, mg/dl		
	Placebo	PIO 7.5/15/30	PIO 15/30/45
- 6 weeks	252	229	227
baseline	329	331	329
24 weeks	330	275	267

	Hemoglobin A1c, %		
	Placebo	PIO 7.5/15/30	PIO 15/30/45
- 6 weeks	10.0	9.8	9.6
Baseline	11.7	11.4	11.4
24 weeks	12.7	11.3	11.0

Safety: There were two deaths, one due to myocardial infarction and one due to leukemia. The deaths occurred among the 84 patients randomized to placebo. There were no deaths in patient treated with PIO. There was a dose-dependent reduction in hemoglobin 0.08 on placebo, 0.45 on low dose and - 0.70 on high dose PIO which was associated with reductions in Hct of 1.2, 1.1, and 2.2 on placebo, low and high dose PIO respectively.

Summary of Efficacy of Monotherapy in Naïve Patients:

As discussed under study 001, I am recommending that approval of the monotherapy indication be based on data from naive patients only. The results of naive patients in the three monotherapy studies summarized in the tables below are consistent with each other and demonstrate the efficacy of PIO in these patients. The reduction of HbA1c in study 026 appears less than expected, but this was a 16-week study and changes in HbA1c lag changes in FBG by 2-3 months. Note that study 012 was a forced titration. The final dose (final 16 weeks) is shown below:

HbA1c

	Placebo	30 mg	45 mg
001			
Baseline	9.04	9.31	9.96
Endpoint 26 weeks	+0.62	-0.64	-1.93
LS mean diff		-1.26	-2.55
012			
Baseline	10.21	10.25	10.36
Endpoint 24 weeks	+0.83	-1.45	-1.76
LS mean diff		-2.28	-2.59
026			
Baseline	10.31	10.13	
Endpoint 16 weeks	+0.09	-0.89	
LS mean diff		-0.98	

Fasting Blood Glucose, mg/dl

	Placebo	30 mg	60mg
001			
Baseline	229	225	235
Endpoint 26 weeks	+15	-41	-64
LS mean diff		-56	-80
012			
Baseline	248	243	236
Endpoint 24 weeks	+31	-32	-64
LS mean diff		-63	-95
026			
Baseline	267	252	
Endpoint 16 weeks	+ 4	-58	
LS mean diff		-62	

Changes in serum lipids in these patients is shown in the tables below. Although only a reduction of triglyceride at high dose PIO is statistically significant vs placebo, there is also a trend for higher HDL levels. LDL and total cholesterol show little change and are certainly not increased by PIO. These results are in contrast to the results of the Rosiglitazone trials that consistently show increases in LDL over placebo

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Fasting Triglyceride, mg/dl

001	Placebo	30 mg	45mg
Baseline	356	235	243
Endpoint 26 weeks	-2	-49	-78
LS mean diff		-47	-76*
012			
Baseline	225	249	275
Endpoint 24 weeks	+14	-26	-78
LS mean diff		-40	-92*
026			
Baseline	371	336	
Endpoint 16 weeks	-48	-81	
LS mean diff		-33	

Total cholesterol mg/dl

	Placebo	PIO 30 mg	PIO 45 mg
001 Baseline	218	236	220
Ednpoint 26 weeks	+12	-3	-3
LS mean diff		-15	-15
012 baseline	222	218	213
Endpoint 24 weeks	+10	-1	-4
LS mean diff		-12	-14
026			
Baseline	222	214	
Endpoint 16 weeks	-8	-2	
LS mean diff		+6	

HDL chol mg/dl

001	Placebo	PIO 30 mg	45 mg
Baseline	37	43	40
Endpoint 26 weeks	+3	+5	+8
LS mean diff		+2	+5
012			
Baseline	43	41	37
Endpoint 24 weeks	+0.1	+1.8	+3.1
LS mean diff		+2	+3
026			
Baseline	38	40	
Endpoint 16 weeks	+1	+4	
LS mean diff		+3	

	LDL chol, mg/dl		
	Placebo	PIO 30 mg	PIO 45mg
001			
Baseline	116	145	140
Endpoint 26 weeks	+6	-6	-5
LS mean diff		-12	-11
012			
Baseline	135	133	123
Endpoint 24 weeks	+8	-6	+4
LS mean diff		-14	-4
026			
Baseline	133	126	
Endpoint 16 weeks	0	-9	
LS mean diff		-9	

Data source for above tables is Takeda briefing document for Advisory Committee

Study PNFP 010

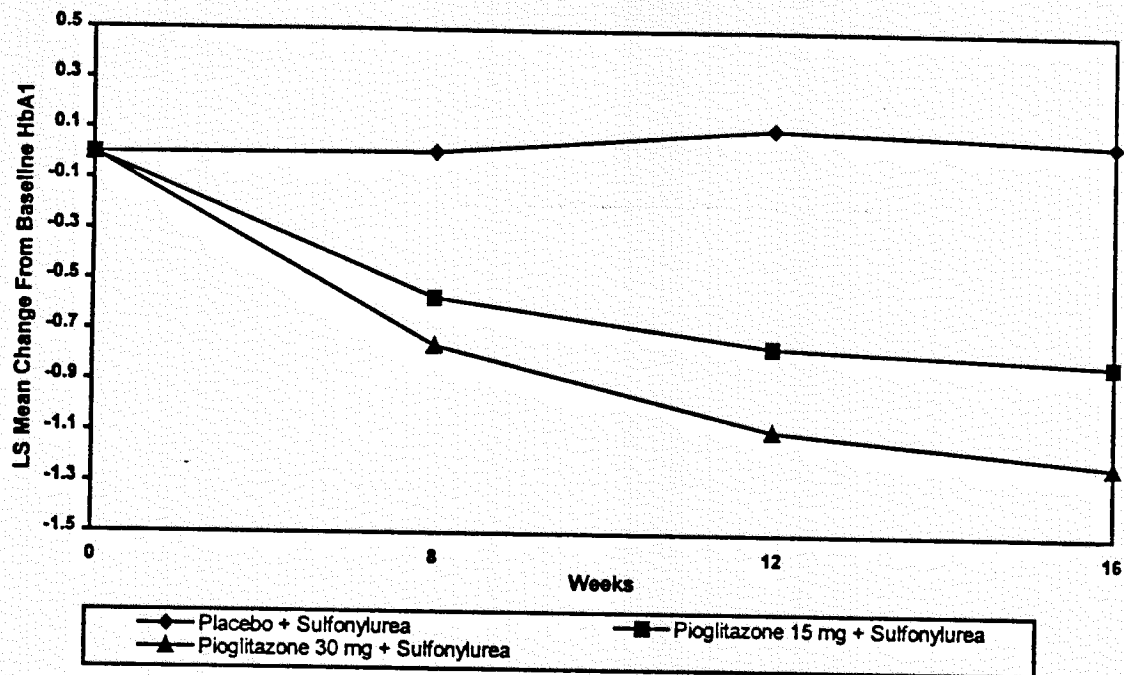
Placebo-controlled study of pioglitazone in Patients on Sulfonylureas.

This study was performed at 54 centers in the United States and compared placebo to 15 mg and 30-mg pioglitazone in patients who had HbA1c levels over 8% despite therapy with sulfonylureas or sulfonylureas plus acarbose or metformin. Following a two-week screening period, patients were treated for four weeks in a single blind manner with their previous dose of SFU plus placebo. Other antidiabetic medications were discontinued at screening. Following the total of 6 weeks of run-in patients were randomized to 15 or 30 mg pioglitazone or placebo. Double-blind comparison lasted 16 weeks. Inclusion criteria were patients with type 2 diabetes between 30 and 75 years of age, on a stable dose of SFU for at least 30 days whose HbA1c was 8.0 or greater at screening and randomization. Fasting C peptide had to exceed 1 ng/dl. Women used contraception where appropriate. Patients were excluded whose liver enzymes exceeded 2.5 x ULN, creatinine over 1.8 ng/dl, anemia of < 12 g/dl for males and < 10 g/dl for females, or class 3 or 4 heart failure or ejection fraction under 40%. In addition to routine safety measures, patients with hematuria on two occasions had urine cytology, and had cystoscopy for three episodes of hematuria or abnormal cells in cytology. Patients were removed from the study for "insufficient therapeutic effect, defined as FBG > 400 mg/dl at two consecutive study visits, or hyperglycemia which presented a safety risk to the patient." The investigator was to make every reasonable effort to keep each patient in the study." Study medication was given as 15 or 30 mg tablets or identical appearing placebo.

The mean age of randomized patients was 56.7 years. 79% were Caucasian and 59% were male. 14% had received other antidiabetic medications (metformin or acarbose) in addition to SFU before starting the study. There were no major demographic or baseline differences. 55% of patients were taking glyburide and 17% were taking glipizide. Approximately 48% were on greater than 50% the maximum labeled dose. At baseline mean HbA1c was about 9.9%, FBG was about 240 mg/dl, mean C peptide was about 2.5 ng/dl and mean serum insulin was 19 uU/ml.

Patients withdrawn for inadequate therapeutic effect were 18/187 placebo patients, 18/184 patients on 15 mg PIO +SFU and 8/189 patients on 30 mg PIO + SFU. Mean changes in HbA1c for ITT patients with LOCF is shown in the table. There was a small rise in HbA1c in placebo patients but reductions in both PIO arms. The treatment effect was -0.88% and -1.28% for 15 and 30 mg respectively. Based on a reduction of 0.6%, the response rate was 34% on placebo, and 57% on 15 mg and 74% on 30 mg PIO. Using observed values the placebo-subtracted treatment effect was -0.94% and -1.30%, using data from 156/177 placebo patients, 154/175 patients on 15 mg and 166/180 patients on 30 mg PIO.

Figure 9.4.1.1.1: LS Mean Change From Baseline for HbA_{1c} (%) by Visit (LOCF Analysis)

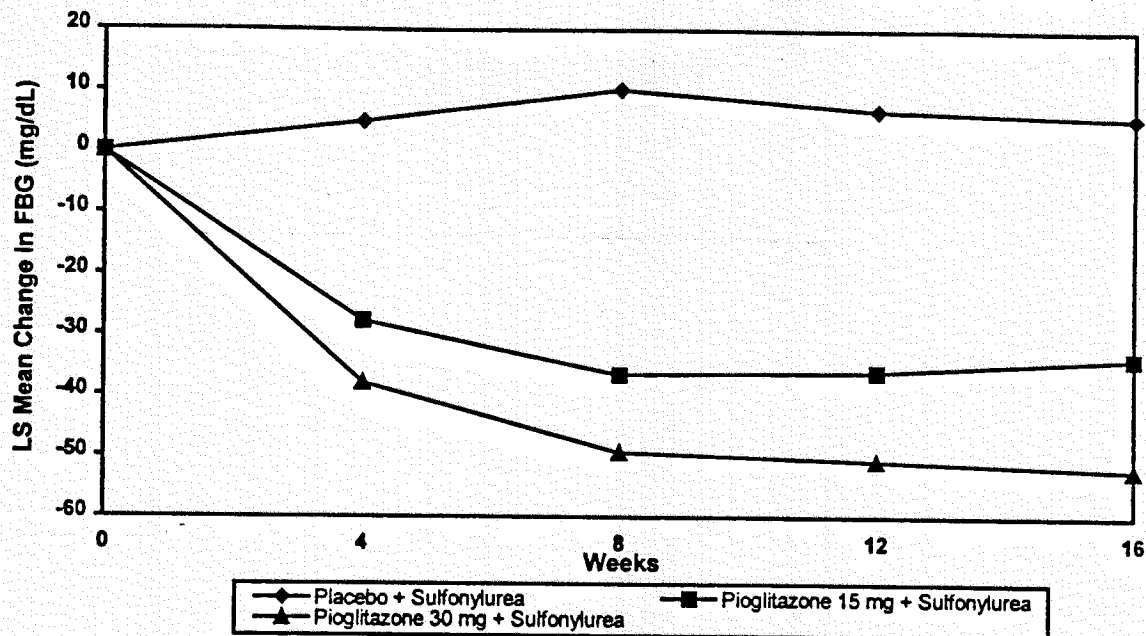


Data Source: End-of-Text Figure 1.2 and End-of-Text Table 9.2.

As shown in the figure, significant reductions in FBG were observed in both PIO arms as early as four weeks with little change in placebo patients. There were small but statistically significant reductions in C peptide and insulin in PIO-treated patients. For instance, the reduction was about 3 uU/ml from a baseline of about 18 uU/ml on 30 mg of PIO.

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Figure 9.4.1.2.1: LS Mean Change From Baseline for FBG (mg/dL) by Visit (LOCF Analysis)



Data Source: End-of-Text Table 11.2.

Serum lipid levels changes were small but would generally be considered clinically beneficial in the PIO-treated patients. Statistically significant changes relative to placebo (which changed little over the course of 16 weeks) for 30 mg PIO were a 26% reduction in triglycerides, and 12% increase in HDL cholesterol with no change in LDL cholesterol. Patients who were treated with PIO gained weight. Starting from a mean of about 93 kg at baseline, the mean weight changes was a reduction of 0.83 kg in patients on placebo compared to a gain of 2.18 and 3.06 kg in patients on 15 and 30 mg PIO respectively.

Subgroup analysis showed that the reduction in HbA1c from baseline was 1.56 for women and 0.96 for men. The change was an increase of 0.03 for both men and women on placebo. FBG change is shown in the table at 16 weeks.

	FBG at 16 weeks		
	Placebo + SFU	PIO 15 mg + SFU	PIO 30 mg + SFU
Men			
Baseline	238	243	242
Mean change	8.5	-30.6	-50.2
Treatment effect		-39.1	-58.7
Women			
Baseline	234	252	233
Mean change	2.8	-45.5	-54.5
Treatment effect		-48.3	-57.2

There were no differences in efficacy with respect to age, race, or body mass index. However, the reduction in HbA1c was greater in patients whose baseline HbA1c was greater than 9% than in patients with lower values. PIO was effective in lowering HbA1c across the range of SFU dose. This is important because previous studies with other add-on drugs (metformin, acarbose, and troglitazone) had been done at the maximum-labeled dose of SFU. Improvement in glycemic control could therefore not have been achieved simply by increasing the dose of SFU. In the PIO study, patients were told to continue whatever SFU dose they had been taking. At the Reviewer's request, subgroup analysis was performed for patients on 50% of

the maximal labeled dose and compared to patients on less than or greater than 50% of the maximal labeled dose. At 30 mg PIO the placebo-subtracted reduction in HbA1c was 1.51% for patients on 50% maximal SFU dose, compared to 1.27% for patients on < 50% max and 1.08% for patients on > 50% max. Regardless of whether these differences are statistically significant, it is clear that PIO works across the range of SFU doses. Hypoglycemic reactions were reported by 7 patients on 30 mg and 1 patient on placebo..

Safety:

Three patients died during this study, 2 on placebo and 1 on 30 mg PIO. All the deaths were cardiac and not believed to be related to treatment. Peripheral edema was reported in 6.3% of 30 mg PIO, 1.1% on 15 mg and 2.1% of patients on placebo. Two patients had markedly abnormal CPK levels. ALT, AST and GGT levels fell in a dose-related manner on PIO. There was also a small reduction in hemoglobin, hematocrit and rbc. All these AE's were seen in other studies and are reported in the general safety section of this review. Severe thrombocytopenia was reported in a patient during the single blind run-in before ever receiving PIO. There were no differences vs placebo in EKG changes or in urine cytology.

014.2 Insulin-treated Patients

This was a placebo-controlled randomized study conducted in the United States of 15mg and 30 mg of pioglitazone vs placebo in patients with type 2 diabetes with HbA1c > 8% on 30 Units or more per day of insulin. The double-blind comparison lasted for 16 weeks. It was preceded by a two week insulin only run-in followed by four week single blind placebo run-in. Patients were then randomized to the three treatment arms, provided that their HbA1c was still at least 8%. Inclusion criteria required that the patient be on insulin continuously for at least four months and be on a stable dose of at least 30 units for 30 days or longer. A fasting C peptide of at least 0.7 ng/ml was also required. The mean age of patients was 57.1 years and 47.3% were male. 73.1% were white and 17% black. The mean BMI was 33.6 kg/m². 12% were on oral antidiabetic agents in addition to insulin which were discontinued at screening. Mean HbA1c at baseline was 9.85%, FBG was 224 mg/dl and C peptide was 1.57 ng/ml. The median insulin dose was 61 units. The mean was 71 units. Patients took an average of 2.5 injections per day. There were no baseline equalities among the three treatment arms.

No attempt was made to change insulin regimen. After 16 weeks, there was a mean decrease in insulin dose of 0.6 unit's in-patients on placebo and reductions of 3 and 8 units respectively in patients on 15 and 30 mg PIO. While not representing an efficacy measure, these reductions in insulin dose are consistent with changes in glycemic control which occurred during the study. Starting from a mean baseline of about 9.8%, there was a statistically significant reduction in all groups. This improvement in control, even in placebo patients, indicated that good practice standards were maintained throughout the study. The placebo-subtracted reduction was 0.73 and 1.00% for 15 and 30 mg PIO respectively for the ITT population. Using observed values (not LOCF) HbA1c reduction was 0.77 and 0.97%.

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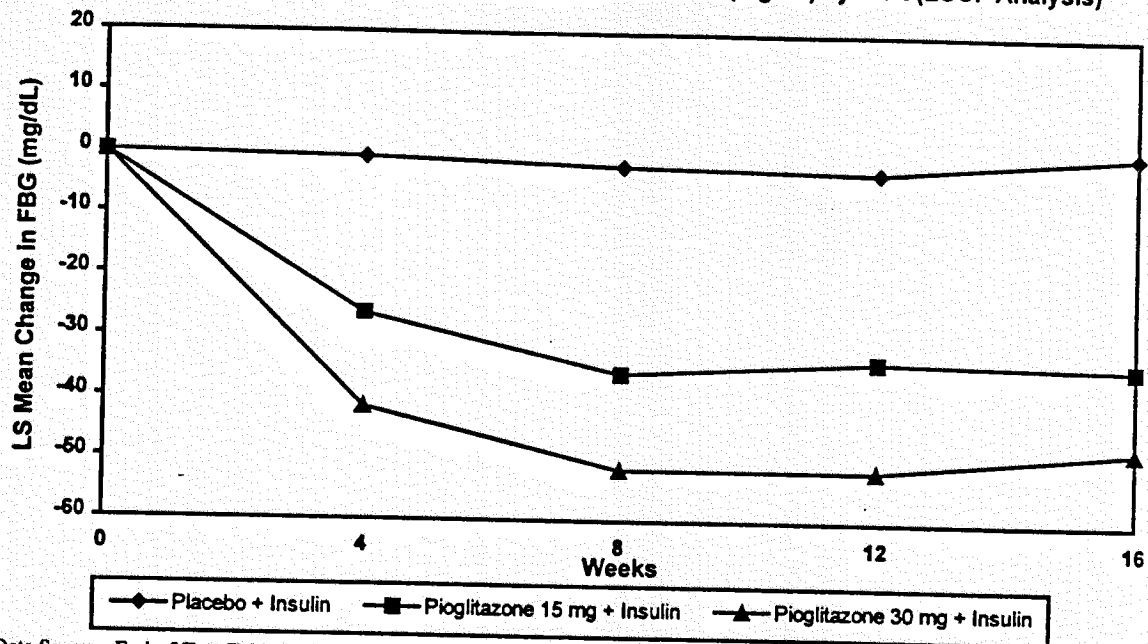
Table 9.4.1.1.1: LS Mean Change From Baseline for HbA _{1c} (%) by Visit (LOCF Analysis)			
Visit	Placebo + Insulin (N=187)	Pioglitazone	
		15 mg + Insulin (N=191)	30 mg + Insulin (N=188)
Baseline^a			
N ^b	177	177	185
LS Mean	9.75	9.75	9.84
SE	0.099	0.099	0.097
Week 8			
N	173	175	184
LS Mean Change	-0.25 ⁺	-0.71 ⁺ *	-0.89 ⁺ *
SE	0.069	0.068	0.067
Week 12			
N	177	177	185
LS Mean Change	-0.30 ⁺	-0.89 ⁺ *	-1.17 ⁺ *
SE	0.078	0.077	0.076
Week 16 (Endpoint^c)			
N	177	177	185
LS Mean Change	-0.26 ⁺	-0.99 ⁺ *	-1.26 ⁺ *
SE	0.084	0.084	0.083
LS Mean Difference ^d		-0.73	-1.00
95% Confidence Interval ^e		(-1.00, -0.47)	(-1.27, -0.74)

- ^a Baseline is the last value taken during the baseline period.
- ^b N at baseline includes patients who had a value at both baseline and endpoint.
- ^c N at each visit includes patients who had values at both baseline and visit.
- ^d Endpoint is the last measurement taken during the double-blind treatment period.
- ^e Difference between each dose of pioglitazone + insulin and placebo + insulin in mean change from baseline.
- ^f For LS mean difference, based on ANCOVA and Dunnett's t-distribution.
- Note: Model for baseline based on a 2-way ANOVA with effects for pooled center and treatment. Model for change from baseline based on a 2-way ANCOVA with effects for pooled center, treatment, pooled-center-by-treatment interaction, and baseline as a covariate.
- + Significant change from baseline ($p \leq 0.050$), based on a paired t-test.
- * Significantly different from placebo + insulin ($p \leq 0.050$), based on Dunnett's test.
- Data Source: End-of-Text Tables 9.2 and 9.3, Listing 8.1, and Statistical Appendix 2.1.

FBG was unchanged in placebo-treated patients but fell 35 mg/dl and 48 mg/dl in patients on 15 and 30mg PIO. Mean baseline FBG was 221-229 in all groups.

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Figure 9.4.1.2.1: LS Mean Change From Baseline for FBG (mg/dL) by Visit (LOCF Analysis)



Data Source: End-of-Text Table 11.2.

C peptide levels rose slightly in patients on placebo but fell slightly in patients on PIO. Mean triglyceride levels rose from 238 to 250 mg/dl in patients on placebo but fell from 260 to 205 mg/dl at 30 mg PIO. There was a small but statistically significant rise in HDL cholesterol in patients on PIO. Starting from a mean of about 43 mg/dl in all groups, there was a fall of 0.7 mg/dl in placebo patients vs increases of 2.8 and 3.4 mg/dl in patients on 15 and 30 mg PIO. The mean body weight at baseline was about 96 kg. Patients on placebo lost an average of 0.11 kg after 16 weeks, compared to gains of 2.53 and 3.92 kg on 15 and 30 mg of PIO. Seven patients on PIO were withdrawn from the study because of weight gain.

Based on the change in HbA1c PIO appeared to be more effective in women than in men.

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Subgroup	Placebo + Insulin (N=187)	Pioglitazone	
		15 mg + Insulin (N=191)	30 mg + Insulin (N=188)
Men			
N ^b	82	80	94
Baseline Mean ^c	9.72	9.86	9.86
Mean Change	-0.36	-0.87	-1.07
SE	0.117	0.132	0.115
Women			
N ^b	95	97	91
Baseline Mean ^c	9.84	9.74	9.88
Mean Change	-0.19	-1.18	-1.55
SE	0.112	0.113	0.125

^a Endpoint is the last measurement taken during the double-blind treatment period.

^b N includes patients who had a value at both baseline and endpoint.

^c Baseline is the last value taken during the baseline period.

Data Source: End-of-Text Table 21.1 and Listings 4.2 and 8.1.

There were no consistent or meaningful differences with respect to age, race, obesity or insulin dose, although patients with starting HbA_{1c} over 9% at baseline showed a larger reduction in all three arms.

Safety:

Safety issues raised by this study are the same as for other studies. These include CPK elevation, anemia and edema. CPK elevation > 3x ULN occurred in one patient on placebo, one on 15 mg and seven on 30 mg of PIO. One patient on 30 mg had a CPK over 8000. One patient in this study had a generalized skin rash that was believed to be drug related. ECG changes occurred in 4 patients on placebo, 4 patients on 15 mg and 3 patients on 30 mg PIO. Grade 3c urine cytology was reported in two patients on placebo and one on 30 mg PIO.

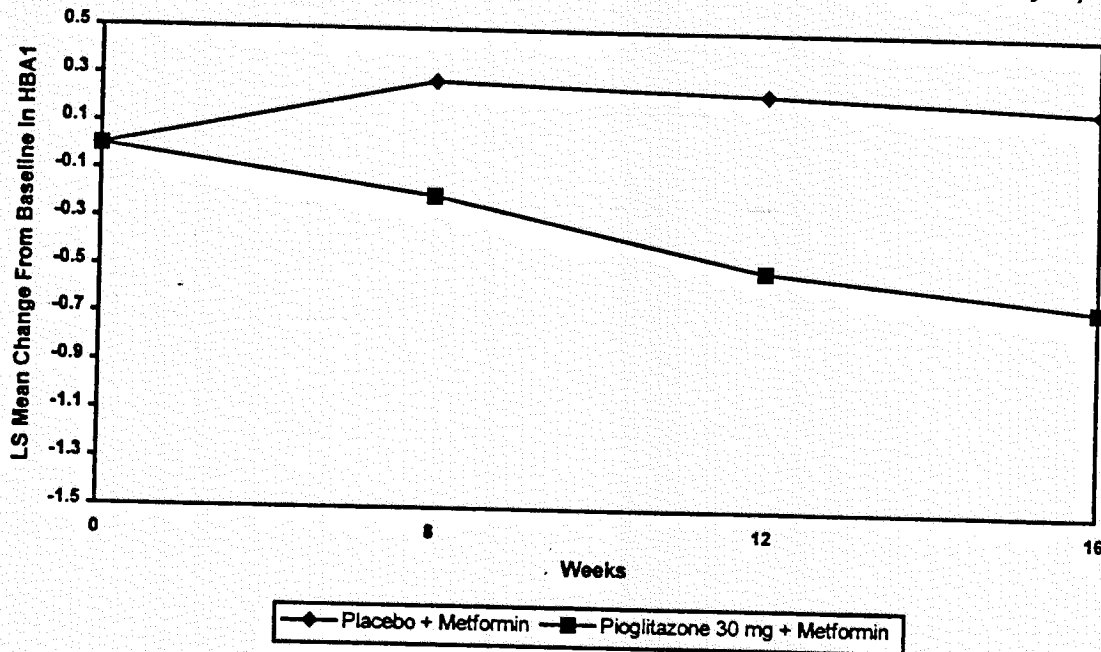
PNFP 027 – Pioglitazone with metformin

This was a 16 week double-blind comparison conducted in the United States of PIO vs placebo in patients inadequately treated with metformin. Patients had to have been on a stable dose of metformin at least 30 days before screening. If patients were on acarbose or a sulfonylurea, these medications had to be discontinued at screening. There was a 6 week run-in before randomization, two weeks on metformin alone and 1 week metformin plus placebo (single blind). Patients in whom a stable metformin dose had not been documented had a four week single blind placebo run-in. Patients were required to have HbA_{1c} of least 8% at screening and before beginning the single-blind placebo run-in two weeks later. Fasting C peptide was greater than 1 ng/ml. Patients were withdrawn from the study if they developed serum creatinine above 1.5 for men and 1.4 for women, LVH by ECG or echo or FBG > 400 mg/dl on two consecutive visits.

Patients had a mean age of 56 years. 57% were male. 84% were Caucasian, 7% black and 7% Hispanic. 30% had been on multiple antidiabetic medications previously. The mean weight at baseline was 93 kg, mean BMI was 32 kg/m². Mean HbA_{1c} at baseline was 9.8%, FBG was 255 mg/dl, C peptide 2.1 ng/ml and insulin 14.7 uU/ml. Mean lipid levels at baseline expressed as mg/dl were triglycerides 297, total cholesterol 213, HDL 43.7 and LDL 119. Patients were taking an average of 61% of the maximal labeled dose of metformin (2550 mg) in both groups. 60% were taking less than 2 g/day, and 40% were taking 2g per day or greater. There were no baseline imbalances for any of these characteristics between the two treatment arms.

After 16 weeks of treatment patients on placebo had a rise in HbA_{1c} of 0.19% compared to a fall of 0.64% for patients on PIO 30 mg/d. The net treatment effect was -0.83% using LOCF. Based on observed values at 16 weeks (excluding 35 placebo dropouts and 17 PIO dropouts) the treatment effect was -1.05%.

Figure 9.4.1.1.1: LS Mean Change From Baseline for HbA_{1c} (%) by Visit (LOCF Analysis)



Data Source: End-of-Text Table 9.2.

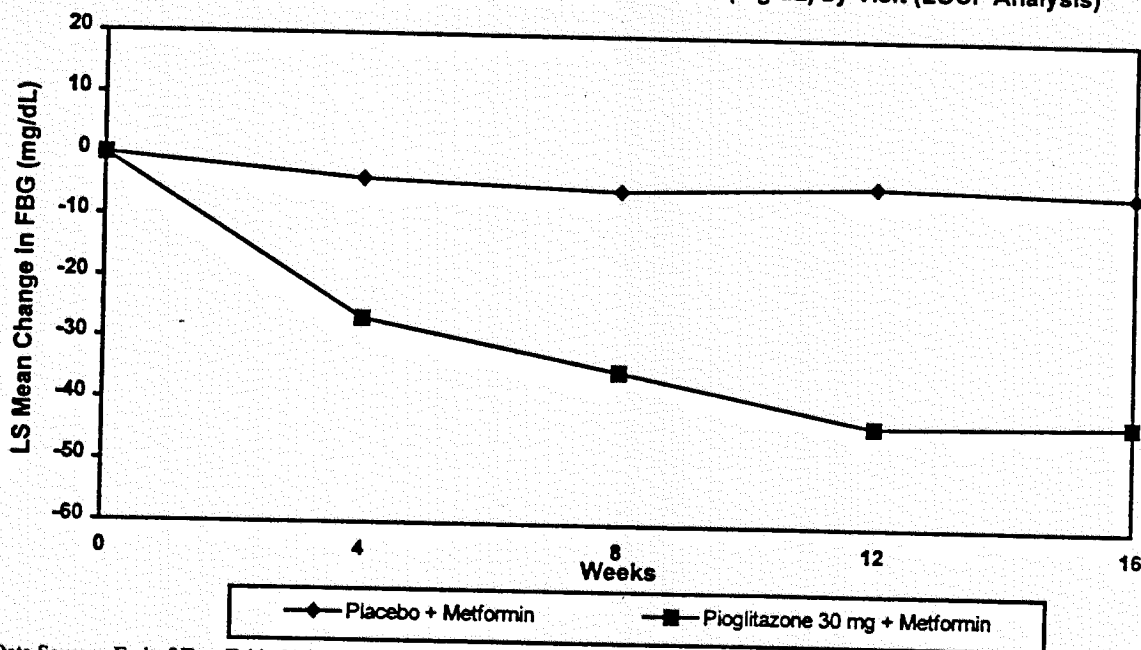
Table 9.4.1.1.2: Mean HbA_{1c} (%) by Visit (LOCF Analysis)

Visit	Placebo + Metformin	Pioglitazone 30 mg + Metformin
Baseline^a		
N ^b	153	161
Mean	9.74	9.90
SE	0.104	0.113
Week 8		
N	153	160
Mean	10.12	9.69
SE	0.126	0.145
Week 12		
N	153	161
Mean	10.10	9.38
SE	0.131	0.149
Week 16 (Endpoint^c)		
N	153	161
Mean	10.06	9.23
SE	0.130	0.153

^a Baseline is the last value taken during the baseline period.
^b N at baseline includes patients who had a value at both baseline and endpoint.
^c N at each visit includes patients who had values at both baseline and visit.
^d Endpoint is the last measurement taken during the double-blind treatment period.
 Data Source: End-of-Text Table 9.1 and Listing 8.

The reduction in HbA1c described above for patients on PIO was mirrored by a reduction in FBG of 43 mg/dl, with a placebo-subtracted treatment effect (LOCF) of -38 mg/dl.

Figure 9.4.1.2.1: LS Mean Change From Baseline for FBG (mg/dL) by Visit (LOCF Analysis)



Data Source: End-of-Text Table 11.2.

As shown in the figure, the maximal glucose lowering-effect of PIO required 12 weeks to achieve. A comparison of the figures showing changes in HbA1c and changes in FBG explains why the reduction in HbA1c at 16 weeks may have underestimated the true efficacy. This is because changes in FBG takes about 12 weeks to be fully reflected in HbA1c. Treatment with PIO was associated with statistically significant placebo-subtracted reductions in C peptide (0.16 ng/dl) and insulin (2.5 uU/ml). The small rise in total cholesterol was not statistically significant. Placebo-subtracted changes in lipids, expressed as mg/dl, which were statistically significant were as follows: triglycerides fell 44, HDL rose 3.19, and LDL rose 4.2. At endpoint placebo patients had a mean weight change of -1.36 compared to a gain of 0.95kg for PIO patients, for a placebo-subtracted gain of 2.31 kg. Using observed values at 16 weeks the net mean gain was 2.47 kg.

Subgroup analysis showed that PIO was more effective in women than in men. The placebo-subtracted fall in HbA1c was 0.72% for men and 1.33% for women. There was no apparent difference for patients over or under 65 years old. The mean placebo-subtracted fall in HbA1c was 0.97% for whites and 0.68% for black, but the number of black patients (13 on PIO 10 on placebo) was too small to draw any definite conclusions. There was no consistent effect of BMI. PIO was effective in patients on less than 2 g of metformin and those on > 2g of metformin. For patients on less than 2g of metformin the placebo-subtracted reduction in HbA1c was 0.91% and in FBG was 38 mg/dl. For patients on 2g or metformin or greater the changes was 1.10% and 45 mg/dl.

Safety:

There were no deaths in this study. 8/160 patients in the placebo arm were withdrawn because of an SAE, two of whom because of hyperglycemia. 5/168 patients in the PIO arm were withdrawn because of an SAE. Liver changes, urine cytology and edema are discussed as part of the ISS. Placebo subtracted reductions in the PIO arm for hemoglobin, hematocrit and rbc count were 0.46 g/dl, 1.4%, and 0.2 x million/uL respectively. A marked abnormal low hemoglobin, hematocrit or rbc count occurred in 4 patients on PIO and 2 patients on placebo. Two additional patients on PIO had reductions in hematocrit of 10% and 7% although the values did not reach the level low enough to be classified as markedly abnormal (this was defined as a 20% reduction in hct or rbc and fall of 3g/dl for hemoglobin). One patient on placebo and three on PIO developed CPK values, which were. 3x ULN. All returned to normal by the end of the study.

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SAFETY

Liver and Biliary system:

SAE's

There were no deaths in the US trials. There was one death in patients on 30 mg PIO in the European trials due to gall bladder carcinoma. In the Japanese studies, one patient on placebo died of cholangiocarcinoma.

12 PIO patients and one placebo patient in US trials had a SAE related to hospitalization for acute cholecystitis. One PIO patient had an ALT > 3 xULN during the acute event which returned to normal two weeks later. In the European trials, there were two patients with biliary system disease on 30 mg PIO. One had carcinoma of the pancreas and was discontinued from the study. The second had acute cholecystitis and was continued on PIO. In the Japanese studies, one patient (2103) on 45 mg PIO was hospitalized for cholecystitis but was continued on the study. There were three patients discontinued because of increased hepatitis enzymes. #4601 had ALT of 67, # 2802 had ALT of 33, and #1301 had ALT of 75.

ALT elevation >3x ULN:

In the US trials, there were 11 patients who had ALT values > 3 xULN. Two on placebo and 9 on PIO. One of the placebo patients had a value of 107 during double blind treatment, which decreased to normal after she was started on PIO in an open-label extension study. A second patients had an ALT of 120 on day 113 on placebo plus SFU.. There is one normal volunteer who had ALT of 268 after 7 days of placebo. Details of the PIO patients are as follows: Cases that are numbered 1-12 were treatment emergent elevations and are presumed to be drug-related.:

USA

- 1 56/2362 - Male Patients has hepatitis C in 1989 and ALT values above normal during placebo run-in, but were less than 3x ULN.. ALT values were 140, 140, and 136 on days 98, 126, and 154 of PIO 7.5 mg. He completed the 181 day study and was entered into open-label extension at 60 mg of PIO. By day 206 his ALT fell to pretreatment levels He continues on 60 mg PIO.
- 2 5/2373 - Male Patient on PIO 30 mg given norflaxacin days 160-180. On day 187, ALT was 343, which returned to normal despite continuation of PIO
- 3 6/2481 - Male Patient developed ALT of 146 on day 15 of PIO 30 mg. This value returned to baseline by day 43
- 4 44/6620 Male Patient had ALT of 130 on day 98 of PIO 30 mg. On day 170, serology showed "chronic active hepatitis B"
- 5 59/4212 Female Patient on PIO 30 mg received dicloxacillin days 72-82 and had ALT of 158 on day 83. By day 96 this had returned to normal
- 6 50/4690 - Male Patient had ALT of 170 on day 468, 14 days after stopping PIO 60 mg. It was "returning toward normal" on day 473. Transaminase levels had previously been normal.
- 7 003/04 - Male patients with ALT of 180 (AST =93) on day 15 of PIO 15 mg .Hospitalized two days earlier with fever and leukocytosis with dx of acute cholecystitis. ALT not measured on admission but AST was 651, bilirubin 2.3. ALT returned to normal two weeks after drug stopped.
- 8 007/06 - Female Patient started taking arthrotec on day 2 and had ALT of 221 on day 29. She stopped arthrotec and ALT was 116 on day 32. By day 31 it had returned to normal of 31 despite continuation of PIO 30 mg

Japan

9 2262 – ALT started at 100 before PIO. After 4 weeks of PIO at 15 mg it reached a high of 196 ALT was 164 when the treatment ended on week 12

10 4801 – Patients with history of hepatitis C received 30 mg PIO for 76 weeks. Prior to treatment the baseline ALT was 101. At week 12 ALT was 191 but at week 60 it was 71. On weeks 72 and 76 when the study ended, ALT were 129 and 225. Bilirubin at week 76 was 0.79 compared to 0.77 at baseline.

11 2801 – Baseline ALT of 99 fell to 55 at week 20, but rose to 136 and 152 on weeks 24 and 28 when the study ended. Bilirubin 1.0 at baseline and 0.7 at week 28. PIO dose was 30 mg

12 2501 – Baseline ALT of 87 rose to 100 and 120 at weeks 20 and 28 when the study ended. PIO dose was 30 mg Bilirubin was 0.7 at baseline and was 0.4 at week 28

In the following cases, the ALT elevation > 3x ULN preceded PIO administration. The one European patient with hepatic duct tumor is also shown here:

Europe – One patient on PIO had elevated ALT with jaundice and obstruction due to cholangioma of the hepatic duct. He died of tumor 80 days after stopping PIO.

USA - 35/4827 Female Patient had ALT of 104 at screening and had periodic elevations as high as 168 during treatment with PIO 60 mg. At day 280 the value was 106, at day 300 it was 107 and was 114 following discontinuation of drug

Japan - 232 – ALT of 165 was the highest value and was at baseline. On PIO 30 mg ALT ranged from 128-145

313 – Baseline was the highest ALT of 117. By 8 weeks of PIO 30 mg ALT had fallen to 58

2122 – Baseline was the highest ALT of 157. By 12 weeks of PIO 30 mg it had fallen to 58.

4802 – Highest ALT was 162 recorded at baseline. While on 30 mg PIO, ALT values fell progressively and was 23 at week 60.

2107 - ALT at baseline was 112 and 132 after 60 weeks of PIO 30 mg/45. Bilirubin 1.1 at baseline and 0.8 at week 60

	ALT elevation during PIO treatment		Total
	Continued on PIO	Withdrawn	
> 3x ULN (102 U/L)	5	7	12 (0.33%)
> 5x ULN (140)	4	5	9 (0.25%)
> 8x ULN (272)	1	0	1 (0.03%)
>30xULN(1020)	0	0	0

N= 2549(USA) + 251(Europe) + 850 (Japan) = 3650

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For comparison, results from the troglitazone and rosiglitazone (RSG) NDA's are shown below:

	ALT elevation during Troglitazone treatment (NDA data base)		
	Continued	Withdrawn	Total
> 3xULN (102 U/L)	25	23	48 (1.9%)
> 5xULN (140)	22	20	42 (1.7%)
> 8xULN (272)	8	14	22(0.9%)
> 30xULN (1020)	0	5	5 (0.2%)

N= 2510

	ALT elevation during Rosiglitazone treatment (NDA data base)		
	Continued	Withdrawn	Total
> 3xULN	6	5	11 (0.25%)
> 5xULN	5	5	10 (0.23%)
>8xULN	2	0	2 (0.05%)

N= 4421 ULN for ALT for calculation was 34 U/L, but threshold for reporting used by SKB was 48 U/L

Both the reporting rate and severity of the ALT elevation were greater with troglitazone than with PIO or RSG. One potential source of this difference is differences in criteria for withdrawal. It was not known during the trials that troglitazone could cause liver failure, hence there were no definite criteria for withdrawal. Delay in withdrawing troglitazone from patients with mild elevations could be potential reason for why some patients developed very high values. However, of the five patients with ALT > 30 x ULN, only one had had an earlier mild elevation (> 5 x ULN) which did not lead to troglitazone withdrawal.

Reporting of ALT elevation over 3xULN in patients on PIO is indistinguishable from placebo in controlled trials (see table below). This was also true for patients on rosiglitazone* but was different for patients on troglitazone: (Reporting for RSG may be lower because 48 U/L was taken as ULN in the NDA as the threshold for reporting values > 3x ULN. Other data bases used 34 U/L)

	ALT elevation > 3 x ULN in controlled trials	
	Active drug	Placebo
PIO		
USA	0.26% (4/1526)	0.25% (2/793)
Japan	0.70% (4/570)	0.70% (2/280)
Troglitazone	1.90% (48/2510)	0.60% (3/475)
Rosiglitazone*	0.25% (11/4421)	0.18% (1/561)
RSG *- Comparators (SFU + Metformin)	0.24% (2/828)	

* normal ALT up to 48

For comparison, reporting of ALT elevations > 3x ULN in other phase 3 trials of antidiabetic agents is shown below:

Acarbose	6-12 months	placebo patients	0.60% (5/865)
Miglitol	6-12 months	placebo patients	0.60% (3/545)
Metformin	29 weeks	metformin, glyburide, placebo	0.40% (4/921)

When one considers that the placebo-controlled comparisons with PIO were 4-6 months, it is clear that the reporting rate of 0.26% for patients on PIO and 0.25% for patients on placebo is very much in line with what has been reported in other phase 3 trials. On the other hand, the relatively small number of patients with long term exposure to PIO is cause for concern. Although total exposure was 1,155 patient years, only 483 patients had exposure beyond 6 months. For patients on troglitazone who developed ALT > 3xULN, the median duration of treatment before recognition of hepatitis was about 4 months. If one assumes that 30 mg of PIO has roughly the same antidiabetic efficacy as 400 mg of troglitazone, but that the two drugs

were equally toxic to the liver based on weight, it follows that the median duration of treatment with PIO until the onset of hepatitis would be 53 months ($400/30 \times 4$ months). Thus, the data in the NDA are not inconsistent with the possibility that long-term exposure to PIO will lead to cases of liver failure like those we have seen with troglitazone.

Hematological Events:

There was dose-related reduction in red cell parameters as follows in the US placebo-controlled monotherapy studies as shown in the table

Dose	Percent changes		
	Hemoglobin	Hematocrit	RBC count
0 placebo	-0.5	-0.2	-0.2
7.5	-0.7	-0.7	-0.2
15	-2.1	-1.5	-2.4
30	-2.6	-1.1	-2.4
45	-3.5	-2.9	-3.6

As mean data, placebo patients had a baseline mean hemoglobin of 14.95 g/dl, which fell by 0.08. PIO patients had a mean of 15.06, which fell by 0.38. These changes are small and not clinically significant in general. Out of 599 PIO patients, there were five patients who had decreases in hct of > 10%. The worst of these were a female whose hct dropped from 35 to 26 but reverted toward normal on follow-up. Similar reductions in hematology measures occurred during the open-label extension.

Combination therapy studies:

PIO used with metformin resulted in a mean drop in hct of 1.2 (SD= 3.02, n=166) from a starting value of 43.6. Reductions with SFU and insulin were 0.7 (SD= 3.20 n=370) and 0.8 (SD = 3.12, n=378) respectively when used with PIO. When used with placebo, metformin was associated with a reduction of 0.1 from 44. No reduction in hematocrit were seen with SFU or insulin. Low hematocrits were reported in 4/163 (2.5%) patients and low rbc in 5/162 (3.1%) on metformin plus PIO compared to 1/152 (0.7%) for metformin plus placebo. 3/166 on metformin plus PIO were reported within markedly abnormal hct at baseline and outside markedly abnormal during the study.

CPK elevation

Three male patients on PIO in the US placebo-controlled studies were reported to have CPK values > 10x ULN. The values were 51 – 195 at baseline (22-198 is normal) and had peak values on drug of 3520 – 4410. One normalized while on drug. The other two normalized after PIO had been discontinued. Four male patients in the combination studies had CPK values over 10 x ULN. One was slightly elevated (250) at baseline. It peaked at 8610 on 30 mg PIO and fell to 357 on last follow-up. Two patients had values of 2150 and 3660, which normalized on drug. One patient had a peak of 5400, which normalized on follow-up. The duration of PIO treatment in these seven patients ranged from 51-189 days. One patient was also taking atorvastatin.

CPK was not measured routinely in either the troglitazone or rosiglitazone NDA's. A review of postmarketing reports of CPK elevation in patients on troglitazone revealed 11 cases reported April – December 1998 which seemed pertinent in that the CPK elevation was not associated with acute MI, "statins", or trauma, or hypothyroidism. Of the 11 cases, 7 had muscle cramps, weakness or increased myoglobin, 2 had malaise, 1 had mildly increased liver tests, and one was asymptomatic. The median CPK elevation was 1122 (750-2513). There were 7 women and 4 men. The median age was 54 years (35 to 75). The dose of troglitazone when listed was 200-400 mg.

Body weight

In US monotherapy studies, baseline body weight was about 90 kg. There was a mean reduction of 1.67 kg (SD 1.88 n=256) in placebo patients compared to a mean gain of 1.21 kg (sd 1.38 n=603) in patients on

PIO. For patients in 48 week open-label study there was a mean weight gain of 5.56 kg. Placebo patients in combination studies lost 0.77, 1.36, and 0.04 kg for SFU, metformin and insulin respectively. Patients on PIO gained 2.42, 0.96 and 3.01 kg respectively. The placebo subtracted weight gain due to PIO was 3.19, 2.31, and 3.05 kg for patients on SFU, metformin and insulin respectively.

Hypoglycemia

Hypoglycemia was reported in 44/379 (11.6%) of patients on PIO plus insulin compared to 9/187 (4.8%) on insulin plus placebo. In two patients on PIO, the study medication was interrupted. The insulin dose was lowered in 7 PIO patients and one placebo patient. One patient on PIO discontinued the study entirely. In monotherapy studies there were reports of 7/606 patients (1.2%) on PIO with hypoglycemia but none were well documented. There were none on placebo.

Edema:

In the monotherapy studies edema was reported in 29/606 (4.8%) patients on PIO compared to 3/259 (1.2%) on placebo. No patient was discontinued because of edema. In combination studies addition of PIO caused increased reporting of edema in all groups. There were two patients in USA trials that were withdrawn because of edema. One patient received SFU. The other patient received insulin. Both received 15 mg PIO. The overall incidence (including non-USA) of edema in controlled studies was 6.6% among PIO patients and 2.3% among placebo patients.

Cardiac:

After 52 days of PIO 30 mg, one patient (PNFP - 026) was noted to have new onset LVH and LBBB. Baseline EKG showed old MI and left axis deviation. LVH was still present at day 87. PIO was withdrawn on day 92. EKG on day 105 showed no LVH and an echocardiogram done on day 105 showed normal LV size. New EKG findings were equally distributed among patients who received PIO and placebo, but five patients on PIO were noted to have cardiomegally on chest x-ray. The ISS does not comment on new onset angina.

The potential for PIO to cause cardiomegally was anticipated from the pre-clinical toxicology. Takeda attempted to address this issue directly by looking for changes in echocardiograms in patients treated with PIO. Results of this study were submitted as an amendment on March 29 1999. The study was a double blind comparison of four doses of PIO (7.5, 15, 30 and 45 mg) vs placebo of myocardial size and function as assessed by echocardiography. The echocardiograms were all read by the same person, Dr Julio Perez. The study consisted of a six week washout, two week single blind run-in and 26 weeks of double blind medication. The entry criteria were similar to previous studies except that patients were excluded if they had valvular abnormalities, ischemic heart disease leading to LV motion abnormalities, or symptomatic heart failure. Each study arm consisted of about 80 patients. The results were summarized as follows: Only negligible changes from baseline were noted for LVMI, CI, and FS for patients in all treatment groups. Similar results were seen for LVM and CO. There were no clinically important differences among the treatment groups for any echo parameter. Shift of > 20% from baseline also revealed no differences.

The results of this study provide little, if any, reassurance that PIO does not damage the heart. The submission does not give an analysis of changes in glycemic control, body weight, lipids etc which can be presumed to have occurred during the study and which could be expected to impact the heart. It is not clear why the Sponsors chose to compare placebo to four doses of PIO. A better design would have been to compare 45 mg of PIO to 20 mg glyburide (or some other SFU at max dose). This study design would have helped to eliminate the confounding variable of changes glycemic control and body weight.

[REDACTED] The PIO study is even less helpful.

Urinary:

Special attention was paid to urine cytology in view of pharm-tox finding of bladder tumors. Category 3c cytology was reported in 4 patients on placebo, 2 patients on PIO 7.5 mg, one patient on 30 mg, one patient on 45 mg four patients on 7.5/15/30 mg and 1 patient on 15/30/45 mg in the US monotherapy studies. In the combination therapy studies five patients had 3c cytology on PIO plus comparator and five patients on placebo plus comparator. No bladder tumors were reported.

Drug interactions:

No significant interactions were found in PK studies of glyburide, glipizide, metformin, digoxin and warfarin. As outlined in the Biopharm review, administration of PIO did not affect the blood steady state blood levels of these other drugs.

APPEARS THIS WAY ON ORIGINAL

Phase 4 studies

The major safety issue relates to the potential for long-term hepatotoxicity. The Sponsor should commit to following patients for three years. If the risk of hepatic toxicity were the same as troglitazone, I would estimate that 1% of patients would develop an ALT > 8x ULN. The study should be powered to be able to detect this kind of abnormality. A second safety issue relates to the potential for PIO to cause or exacerbate heart failure. NDA's for Rosiglitazone and Troglitazone had included echo study comparisons to patients treated with Glyburide. As discussed earlier, the echo study of PIO vs placebo presented earlier is not very convincing. In lieu of doing a study of PIO vs glyburide, I would suggest a study of PIO vs placebo in patients with class 3 and 4 heart failure who have a compelling need for glitazone treatment. Given the fact that metformin is contraindicated in these patients, the therapeutic option for managing hyperglycemia is limited to insulin titration. These patients often have very wide swings in glucose levels and I would think that a trial of PIO would be justified in some cases.

The NDA contains no data on the 45-mg dose used in combination with other antidiabetic medications. A post-marketing study comparing 45 mg to 30 mg will need to be done to make certain that the risk/benefit relationship of 45 mg is acceptable. This study should also be designed to find investigate the gender effect, to determine if the greater efficacy of PIO in women vs men is related to higher blood levels.

Labeling issues (from revised label of May 28, 1999):

The Actos label should conform to those of Rezulin and Avandia where applicable. For instance, the hepatic toxicity section, ALT monitoring every two months, etc should be modeled after the Avandia label.

The lipid section is problematic. It is clear that PIO does not have the adverse effects on lipid levels that Rosiglitazone appears to have. The PIO label should provide enough information to allow one to reach the conclusion that PIO does not adversely affect lipid levels. I would suggest a table of the three monotherapy studies listing differences vs placebo for all the lipid classes for the 30 mg dose. With respect to naïve patients (see page 26-27 of this review), none of these changes were statistically significant in any one study but the trends are in the right direction, particularly the rise in HDL and reduction of triglyceride. There was a statistically significant reduction in triglyceride at 45 mg in two studies. This information could be shown if it were presented together with the weight gain which is also impressive at 45 mg. Reduction of FBG could also be shown for context. In the combination studies, there were statistically significant changes in some lipid classes. These results could be given along with efficacy data for each indication but balance must be provided by including changes in weight.

After consideration of the issues relating to previously treated patients discussed under study 001, the Sponsor had agreed with my suggestion to use only data from naïve patients in its description of the monotherapy trials. However, upon further reflection, this way of presenting the data is not satisfactory. PIO was more effective in naïve patients than in non-naïve patients. Thus presenting data from naïve patients only would appear to make Actos appear more effective than competing products. The label should be revised to show data from naïve and non-naïve patients separately, at least for study 001. The most straight-forward way to present the results would be dose-response curves (0 -45 mg) in study 001 for naïve and non-naïve patients.

The text of the "indications and usage" section is satisfactory except as indicated below. Actos can be used either alone or in combination with SFU's, insulin, or metformin. No comparative claims are made or implied. There is no suggestion that patients be switched from other drugs to ACTOS.

Specific comments:

PD – What is the evidence that Actos improves insulin sensitivity in patients?

The final sentence of the first paragraph: 'Actos in combination with.... etc' is okay as written.

As stated above, I would prefer the lipid data put into later sections regarding individual indications. Also, it is unfair to quote placebo adjusted changes for glucose and lipids but give change from baseline for weight.

Figure 4 does not seem to add much. Data could be given in the text. Fig 5 does not adequately display the time course of treatment. I would include the FBG time course from study 001 (omitting 7.5-mg dose). This figure illustrates that a full effect on FBG reduction takes about three months so any dose adjustment before then would be premature.

Combination therapy: Give information regarding the dose of metformin and SFU that was continued during ACTOS treatment. It is important to show that ACTOS was effective at near-maximal as well as submaximal doses of metformin and SFU. Change in insulin dose can be included in the text.

Changes that occurred in patients in placebo should be stated, not simply subtracted. Data should be expressed as change from baseline for patients on placebo and for patients on PIO.

CPK – give peak levels of transient elevations

The gender effect needs to be discussed, probably along with use in the elderly is best

Dosage and administration : Three months is not adequate time to allow to evaluate efficacy by HbA1c. Three months is adequate for FBG but HbA1c takes longer. It is not clear why starting dose for monotherapy is indicated to be 30 mg but for combination therapy is 15 mg. I think 15 mg should be the starting dose for monotherapy as well.

Summary and Recommendation:

PIO is highly effective in treating hyperglycemia both as monotherapy as well as in combination with SFU's metformin or insulin. Unlike troglitazone, there is no evidence that PIO causes hepatitis. In contrast to rosiglitazone, PIO does not have unfavorable effects on serum lipid levels. As is true for all three drugs in this class, PIO can cause anemia and edema. Its glucose-lowering activity is associated with weight gain. Pending satisfactory label changes and phase 4 commitments, I recommend that this NDA be approved.

ISI [Redacted]

Robert A Misbin MD
Medical Officer
NDA 21073
HFD 510/misbin/sobel/malozowski/weberj
Draft 6/11/99 revised 6/22/1999 finalized 6/23/99

ISI [Redacted]

6/2/99

APPEARS THIS WAY ON ORIGINAL

21073s

JUN 30 1999

Medical Officer's Review

Safety Update (SU) - Pioglitazone (Actos) stamp date June 4, 1999

Deaths:

The SU contains information about two deaths in patients who had been taking placebo in controlled monotherapy studies. There were also three new reports of patients who died in open label monotherapy studies of PIO. Two died of ASCVD, one on day 167 of PIO, the second 20 days post study. The third patient was struck by lightning on day 120. In the placebo-controlled combination studies, three new deaths were reported, all due to coronary artery disease. Two patients had been on placebo plus SFU. One patient had been on PIO plus SFU.

ALT elevations:

One new patient was identified as discontinuing a US study because of ALT elevation > 3 x ULN. This patient had normal enzymes throughout the study but was found to have ALT of 1182 on day 496. A hepatitis screen was positive for hepatitis C. Risk factors were listed as a history of blood transfusions, iv drug abuse and multiple tattoos. PIO was discontinued and he was started on interferon treatment. By 62 days after PIO had been stopped, all his lab tests had returned to normal. In the European studies, one new patient was identified as having ALT > 3xULN but this patient was taking only glibenclamide, not PIO. One Japanese patient on 30 mg PIO was withdrawn because of ALT elevation. He had pretreatment elevation perhaps related to a history of "alcohol abuse" and "fatty liver". His ALT values at weeks -4, baseline, 4, 8, 12, 16, 16 were 95,85,44,78,204,134,201. (Note two values were reported for week 16).

Correction:

The MOR of June 23 states that no bladder tumors were reported. This is incorrect. There was one report of a bladder tumor in a patient on PIO and one in a patient on placebo. Details are as follows: Bladder carcinoma was reported in 1/606 patients on PIO during double-blind treatment of placebo-controlled monotherapy studies compared to 0/259 patients on placebo. In the combination studies, bladder carcinoma was reported during double blind treatment in 1/534 patients on placebo and 0/920 patients on PIO. The placebo patient with bladder carcinoma was also taking metformin.

Summary:

This 120-safety update brings to light no new safety concerns.

ISI [Redacted]

Robert I Misbin MD
June 30, 1999

Green

ISI [Redacted]

ISI [Redacted] 1/32/99

Amman

ISI [Redacted] 6/30/99

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

CHEMISTRY REVIEW(S)

820/Y.../...

JUL - 7 1999

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
 Review of Chemistry, Manufacturing and Controls

NDA 21-073 Chemistry Review # 2 Date Reviewed: 24-JUN-1999

Submission Type	Document Date	CDER Rec. Date	U.F. ID # 3596
Original	15-JAN-1999	15-JAN-1999	
Amendment	07-JUL-1999		(amendment 21)

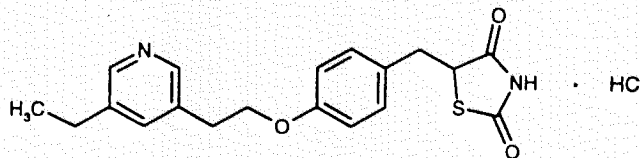
Applicant:	Takeda America Research & Development 101 Carnegie Center, Suite 207 Princeton, NJ 08540	Phone: (609) 452-1113 x-4409 Fax: (609) 452-1218

Drug Product Name	Proprietary:	Actos™
	Nonproprietary/Established/USAN:	Pioglitazone Hydrochloride
	Chem.Type/ Ther.Class:	1 P

Pharmacological Category/indication: Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM whose hyperglycemia cannot be managed by diet alone.

Dosage Form: Tablets	Strength(s): 15-, 30- and 45-mg
Route of Administration: Oral	Dispensed: R

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:



$C_{19}H_{20}N_2O_3S \cdot HCl$
 MW = 356.43 + 36.57 = 392.90
 (±)-5[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride

Comments: All the requested information has been adequately provided. After inspection of the manufacturing facilities, the Division of Quality Control, HFD-322, has given an overall acceptable recommendation (recommendation dated: 07-JUL-1999).

Conclusions & Recommendations: Satisfactory CMC information has been provided for the drug substance, Pioglitazone HCl, and drug product, Actos™ (pioglitazone hydrochloride) Tablets. From the Chemistry viewpoint the application can be approved.

Orig. NDA 21-073
 cc: HFD-510/Division File
 HFD-510/SMalozowski/SMoore/RSteigerwalt/JWeber/XYsern
 HFD-820/JGibbs

/S/ [Redacted]
 Xavier Ysern, PhD

R/D Init by:

filename: /nda/21073_2.doc

AP

/S/ [Redacted]

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21-073 Chemistry Review # 1 Date Reviewed: 24-JUN-1999

Submission Type	Document Date	CDER Rec. Date	Filing Date	U.F. ID #
Original	15-JAN-1999	15-JAN-1999	20-MAR-1999	3596
Amendment	11-JAN-1999			
Amendment	02-MAR-1999	03-MAR-1999		
Amendment	06-APR-1999	07-APR-1999		
Amendment	21-MAY-1999	24-MAY-1999		

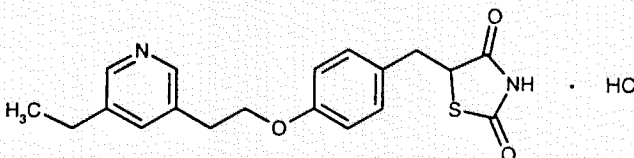
Applicant: Takeda America Research & Development
101 Carnegie Center, Suite 207
Princeton, NJ 08540
Phone: (609) 452-1113 x-4409
Fax: (609) 452-1218

Drug Product Name Proprietary: Actos™
 Nonproprietary/Established/USAN: Pioglitazone Hydrochloride
 Chem.Type/ Ther.Class: 1 S

Pharmacological Category/indication: Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM whose hyperglycemia cannot be managed by diet alone.

Dosage Form: Tablets **Strength(s):** 15-, 30- and 45-mg
Route of Administration: Oral **Dispensed:** R

Chemical Name, Structural Formula, Molecular Formula, Molecular Weight:



C₁₉H₂₀N₂O₃S · HCl
MW = 356.43 + 36.57 = 392.90
(±)-5[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione monohydrochloride

Patent Information: Patent #/ Expiring date/ Type of patent/ Owner/
4,444,779/ 27-JUL-1999/ drug, thiazolidine derivatives/ Takeda Chemical Industries, Ltd./
4,687,777/ 17-JAN-2006/ thiazolidine derivatives, useful as antidiabetic agents/ Takeda Chemical Industries, Ltd./

Conclusions & Recommendations: Satisfactory CMC information has been provided for the drug substance, Pioglitazone HCl, and drug product, Actos™ (pioglitazone hydrochloride) Tablets. From the Chemistry viewpoint the application is approvable pending satisfactory results of the inspection of the manufacturing facilities and an acceptable response to the minor deficiencies listed in the Draft Letter. [REDACTED]

Orig. NDA 21-073
cc: HFD-510/Division File
HFD-510/SMalozowski/SMoore/RSteigerwalt/JWeber/XYsern
HFD-820/JGibbs

/S/ [REDACTED]

Xavier Ysern, PhD

R/D Init by:

AE
/S/ [REDACTED]

filename: /nda/21073_1.doc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

PHARMACOLOGY REVIEW(S)

JUN 30 1999

NDA 20-073

June 30, 1999

DRUG: Pioglitazone (ACTOS™)

INDICATION: NIDDM

**TEAM LEADER MEMO TO FILE REGARDING
PRECLINICAL PHARMACOLOGY/TOXICOLOGY ISSUES
FOR NDA 20-073 (PIOGLITAZONE, ACTOS™)**

The primary toxicity of concern with Pioglitazone is the increase in cardiac weight observed in the animal toxicology studies. This was a consistent finding in all species tested and occurred at low multiples of human exposure. The cardiac/hematological changes have been attributed to adaptive responses to plasma volume expansion and appear to be a class effect for thiazolidinediones. In long term rat and mouse studies (e.g., the 2-year carcinogenicity bioassays) the cause of death at high doses were attributed to cardiac effects.

A finding that is common for thiazolidinediones, increases in liver weights without histological correlates, was also observed in some animal studies (rats, mice, dogs and monkeys), but was not a consistent finding. There were no histological or clinical chemistry findings associated with liver weight increases in rats or mice. There were occasional instances of centrilobular hypertrophy noted in dogs and monkeys. Necrosis and subacute hepatitis was observed in one dog at approximately 50 times the human dose. Thus, although there is an increase in liver weight noted at fairly low multiples of human exposure, changes in histopathology or clinical chemistry are not noted until very high levels of exposure are reached. It is worth noting at this point that dogs appear to be the most sensitive species to the liver effects of thiazolidinediones.

Although this finding in the liver is not consistently found with pioglitazone, it is not possible based on the results of animal studies to say that pioglitazone is "safer" in this respect compared to other thiazolidinediones unless a head-to-head comparison is performed.

There are some points I would like to summarize to support the current labeling recommendations:

1. The mouse lymphoma reference originally included by the sponsor in the label as a negative finding was removed based upon the review of these data by the genetic toxicology committee. It was concluded that the standard assay with parent compound was inconclusive. It was not considered that the assay was adequately performed, therefore, the results should not be included in the label. In additional studies with the mouse lymphoma assay, there was a positive finding in the presence of metabolic activation with the M1 metabolite. This was reproducible and the assay was performed adequately. However, since this metabolite is not found in humans to a significant extent, it was thought that this was irrelevant and should not be included in the label. Findings in other permutations of the MLA were also deemed inconclusive by the committee. Based on the weight of evidence in other genetic toxicology studies which indicate that pioglitazone is not genotoxic, it was considered that the overall findings of the MLA are inconclusive and the MLA

findings should not be included in the label. Other studies indicating no genetic toxicity include the Ames bacterial mutagenesis assay, cytogenetics assays in the CHL, CHO/HPRT and AS52/XPRT models, an unscheduled DNA synthesis assay and an in vivo mouse micronucleus assay.

[REDACTED]

[REDACTED] This metabolite is found in humans and thus could be a possible concern. However, this information was based on an incomplete review. The genetic toxicology committee report indicates that the positive finding was with metabolite M1, which is not present in humans, not MIV.

3. In reference to the bladder tumors, although the proposed mechanism of mechanical irritation by calculi is plausible, there are not sufficient data to conclusively determine that this mechanism is wholly responsible for the bladder tumors observed in male rats [REDACTED]. However, given that the drug appears to be non-genotoxic and the drug itself did not directly induce a proliferative effect in the bladder in a BrdU incorporation experiment, further data may help to support this mechanism. It is of note that statistically significant tumors occurred only in male rats, although there were sporadic findings of benign tumors in female rats and a single occurrence of a bladder tumor in a high dose mouse. These were initially referred to in the label. [REDACTED]

[REDACTED] Currently, the relevance of these tumors in male rats to humans is unclear. The label is modified to reflect this. Note: the committee's summary of tumor findings was as follows:

Mice: no significant tumor findings

Rats: benign/and/or malignant transitional tumors in the urinary bladder in all dose-groups of the males except the lower dose. These were statistically significant by the trend tests.

4. The Pregnancy category was changed from the proposed "B" to "C" based upon the findings of embryotoxicity and delayed development. While there was maternal toxicity in some cases, this was considered to be relatively mild (change in maternal body weight compared to control <10%) and thus the fetal findings are significant. There was no teratogenic response to pioglitazone.

Based on the findings in the animal studies, it is difficult from a strictly Pharm/Tox standpoint to offer an unqualified approval to Pioglitazone. The toxicity of particular concern is the increase in heart weights, which is a consistent finding in all species tested. However, I believe that if clinical safety has been demonstrated in the data submitted to the NDA and such an assessment of safety is made by the reviewing medical officer, that this NDA should be approved. It is my understanding that the sponsor will be performing phase IV studies to examine this effect.

This reviewer recommends that this application is approvable (AE) from a pharm/tox standpoint pending a determination of clinical safety regarding the cardiac effects of pioglitazone.

/S/

6/30/99

Ronald W. Steigerwalt, Ph.D.
Pharmacology Team Leader

cc: NDA Arch
HFD510
HFD510/Steigerwalt/Misbin/HRhee/Weber
Review Code: AE (pending determination of clinical safety and labeling revisions)
Filename: TLmemo.doc

APPEARS THIS WAY ON ORIGINAL

NDA 20-073

June 21, 1999

Takeda America Research and Development Center, Inc.
101 Carnegie Center, Suite 207
Princeton, New Jersey 08540

Submission: 2/23/1999

Received: February 26, 1999

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

Drug: Pioglitazone Hydrochloride(ActosTM), AD-4833

Related: IND
IND
IND

Pharmacological Class: Antidiabetic Agent

Indicated Use: Type II Diabetes

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APPEARS THIS WAY ON ORIGINAL

NDA 20-073

June 21, 1999

Takeda America Research and Development Center, Inc.
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Princeton, New Jersey 08540

Submission: 2/23/1999

Received: February 26, 1999

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

Drug: Pioglitazone Hydrochloride(Actos™), AD-4833

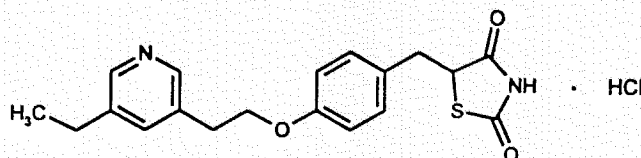
Related: IND
IND
IND

Pharmacological Class: Antidiabetic Agent

Indicated Use: Type II Diabetes

Clinical Dosage: 7.5 - 60 mg

Structure:

 $C_{19}H_{20}N_2O_3S \cdot HCl$

MW = 356.43 + 36.57 = 392.90

(±)-5[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione
monohydrochloride

Foreign Studies: Yes – Please see individual studies.

1. INTRODUCTION (The author would like to acknowledge the fact that this report contains materials directly reproduced from the sponsor's NDA reports. In cases where materials were directly reproduced, the reviewer has evaluated the data and agrees with the sponsor's presentation of the data. Points of disagreement are noted in this review).

One of the characteristic features of non-insulin-dependent (Type II) diabetes is insulin resistance where peripheral tissues have impaired glucose production and its utilization that leads to hyperglycemia. Pioglitazone hydrochloride [AD-4833(HCl) or ██████████] is an insulin sensitizer belonging to the class of thiazolidinediones. The exact mechanism of pioglitazone activity, as well as that of other thiazolidinediones, remains unclear. Pioglitazone decreases hepatic glucose output and increases insulin-dependent glucose disposal in skeletal muscle. Mechanistic studies indicate that thiazolidinediones act at many intracellular sites and can influence several processes to increase cell sensitivity to insulin. These include influence on insulin receptor kinase activity, change in number of insulin receptors, quantity and activity of GLUT-4, modulation of tumor necrosis factor (TNF- α) activity, activation of peroxisome proliferator-activated receptor- γ (PPAR γ), and alteration of hepatic glucose metabolism.

2. PHARMACOLOGY AND PHARMACODYNAMIC STUDIES ██████████

A. Antihyperglycemic Activities

Pioglitazone has been evaluated in a series of studies using normal, genetically obese, and diabetic (KKA^y) mice. Pioglitazone was incorporated into the diet such that the delivered doses were 2.4-24.5 mg/kg/day for four days. Blood glucose was decreased dose-dependently by 25% at a dose of 6 mg/kg/day and by 13% at 2.4 mg/kg/day. The drug also produced a dose-related decrease in plasma triglyceride and non-esterified fatty acids. In addition, the four-day treatment enhanced basal and insulin stimulated glucose oxidation and total lipid synthesis in adipocytes isolated from these mice.

When administered orally by gavage to genetically diabetic mice at doses from 6.25 to 100 mg/kg as a single dose, pioglitazone caused a significant reduction in blood glucose, and was sustained for two days. When administered in the diet in the same study, a dose of 25 mg/kg/day for four days was required to show hypoglycemic activity. Studies have also been conducted in the Wistar fatty rats because they can develop severe insulin resistance in peripheral tissues, such as muscle and adipose tissue, and liver. Pioglitazone administered orally to the rats at doses ranging from 0.3 to 3.0 mg/kg/day for up to one month produced a dose-dependent reduction in plasma glucose, plasma insulin, triglyceride and non-esterified fatty acids, with a dose of 0.5 mg/kg/day producing a 25% reduction in plasma glucose.

The calculated ED₂₅ for pioglitazone base-induced plasma triglyceride lowering was 0.39

mg/kg/day and the ED₂₅ for the HCl salt was 0.47 mg/kg/day. When adjusted for molecular weight, the HCl salt ED₂₅ was 0.43 mg/kg/day. Thus, the pharmacological activities of both formulations were similar.

B. Pioglitazone Effect on Hepatic Tissues

In diabetic KKA^y mouse, treatment with pioglitazone for four days at 20 mg/kg/day decreased blood glucose, but also improved indices of hepatic insulin resistance. However, use of isolated liver cells by clamp techniques indicated that no alterations in phospholipase C activity were seen. In another study, pioglitazone significantly increased liver and brown fat catalase activity at doses ranging from 9 to 70 mg/kg in the KKA^y mouse model. It also increased liver peroxisomal β -oxidation in these mice at doses of 5.6 mg/kg/day and above.

In either genetically obese/diabetic Wistar fatty rats or in streptozotocin-induced diabetic rats, pioglitazone (3 and 10 mg/kg/day for seven days) decreased hepatic glucose production and increased peripheral glucose utilization in response to insulin treatment in the Wistar fatty rat. In streptozotocin-induced diabetic rats, pioglitazone (10 mg/kg for seven days) was also shown to improve hepatic insulin resistance in the presence of a minimal dose of insulin. In this same model, it was shown that the augmentation of insulin was accompanied by increased hepatic glucose-6-phosphate dehydrogenase activity and decreased glucose-6-phosphatase activity.

Using clamp techniques, pioglitazone increased the suppression of hepatic glucose production and peripheral glucose utilization to infused insulin. Pioglitazone also inhibited fatty acid metabolism and gluconeogenesis in isolated hepatocytes from starved Wistar rats. The subcellular mechanism of this effect is not yet clear, but presumably involves an alteration in the expression of those enzymes responsible for gluconeogenesis and possibly fatty acid metabolism.

C. Effects of Pioglitazone on Adipose Tissue

Although numerous studies were performed to identify the effect of the drug on adipose tissue, the outcome of these studies failed to identify a single mechanism of action. In *in vivo* studies, the administration of pioglitazone to diabetic KKA^y mice at doses of 0-71 mg/kg/day for six weeks resulted in a dose related increase in the adipocyte P2 gene (aP2) mRNA in epididymal fat. The aP2 gene is a specific gene implicated in adipocyte metabolism that codes for a protein involved in lipid transport. A similar effect was seen in perirenal fat, and correlated with a decrease in blood glucose. In the Zucker fatty rat, when treated for up to 28 days with pioglitazone at a dose of 10 mg/kg/day, weight gain was increased and glucose, insulin and triglyceride levels were decreased. Pioglitazone has been shown to upregulate the expression of the adipocyte fatty acid binding protein (aFABP) gene. This gene product is a substrate for insulin receptor tyrosine kinase and may be responsible for facilitating insulin signaling in adipocytes.

D. Peroxisome Proliferator-Activated Receptor Gamma

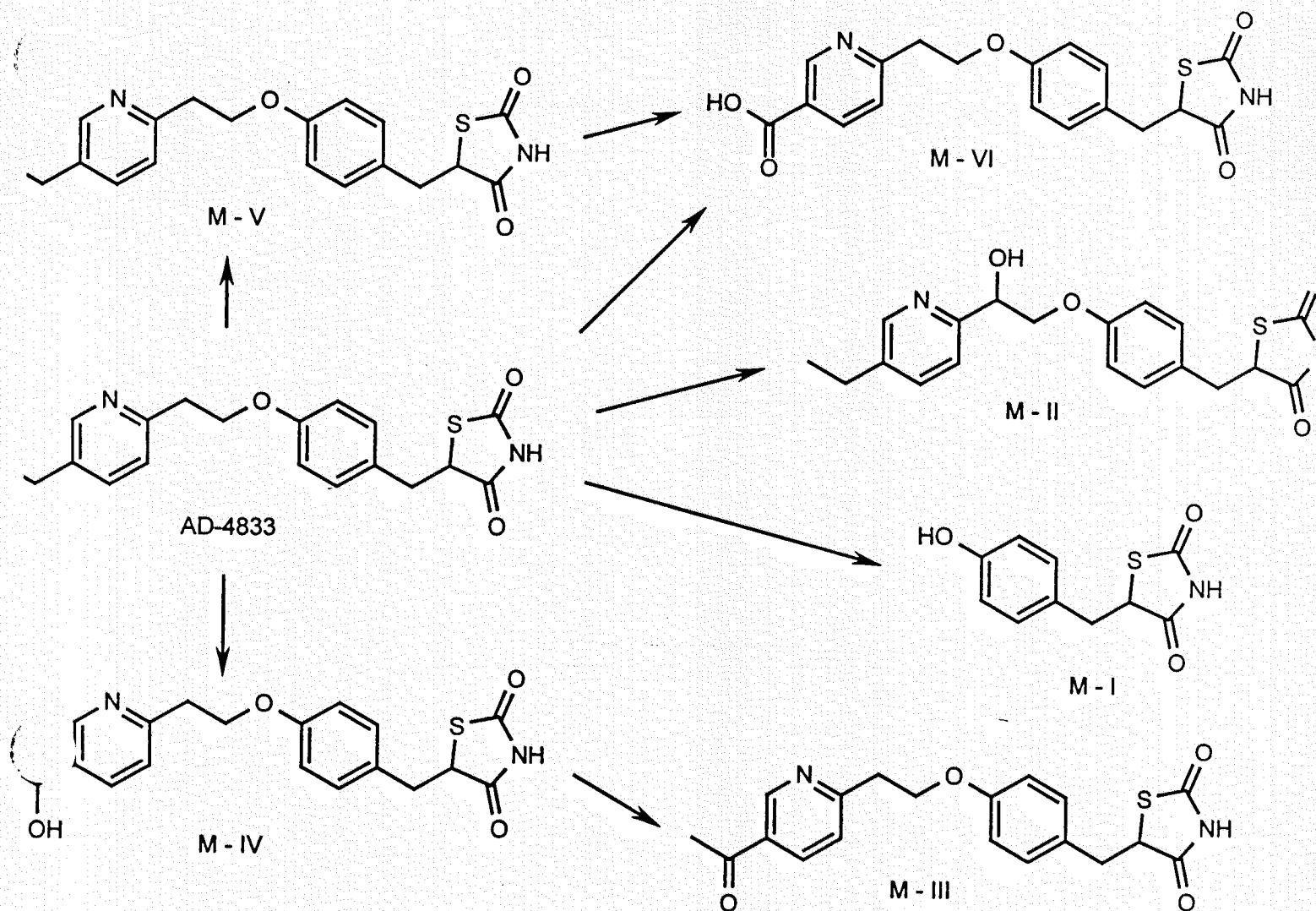
Peroxisome proliferator-activated receptor gamma (PPAR- γ) is part of the PPAR nuclear hormone receptor family. There are three identified subtypes of PPAR: α , δ , and γ , and possibly two subtypes of PPAR- γ . The tissue distribution of the PPARs varies, and PPAR- γ appears mainly in adipose tissue, but may be expressed in other tissues, including skeletal muscle. Initially, PPARs were found to be activated by compounds that caused proliferation of peroxisomes in the liver; subsequently, fatty acids, certain naturally occurring eicosanoids and thiazolidinediones were found to be activators of specific PPAR subtypes.

After binding and activation of PPAR- γ , the activated receptor complex may undergo a conformational change and bind to nuclear elements that regulate transcription of specific DNA sequences. One result of this interaction is differentiation of adipocytes from precursor cells. However, the mechanism of PPAR-induced adipocyte differentiation is not likely to be so simple, as other PPARs have been shown to be stimulated during adipocyte differentiation. Data indicate that specific, high-affinity binding of pioglitazone, to PPAR- γ causes its activation and results in adipocytes differentiation from fibroblasts. The differentiated adipocytes express specific genes coding for enzymes that are involved in lipid metabolism. The finding of increased food intake and increased adipose tissue weight in rats treated with thiazolidinediones provides some evidence of this mechanism *in vivo*.

It has been suggested that the drug induces adipocyte differentiation, and thereby promotes increased fat (triglyceride) uptake by the cells. The lipid lowering effect produced through increased fat uptake by adipose may result in improved glucose utilization by peripheral tissues, such as skeletal muscle. Through stimulation of triglyceride clearance by adipocytes, the skeletal muscle glycolytic pathway may be able to operate more effectively to reduce hyperglycemia. It has been also suggested that activation of PPAR- γ may alter cell production of paracrine or endocrine factor(s). Altered levels of these factors (and perhaps TNF- α) might reduce insulin resistance through yet unexplained mechanisms.

E. Pharmacological Activity of Metabolites of Pioglitazone

Pioglitazone is converted into six main metabolites (see the figure shown below). These metabolites have been evaluated for their hypoglycemic activity. Male Wistar fatty rats received an intraperitoneal injection of pioglitazone or one of its six metabolites (M-I through M-VI) for seven days. Pioglitazone, M-II, M-III and M-IV were injected at doses of 0.3, 1 and 3 mg/kg/day whereas M-I, M-V and M-VI were injected at a dose of 3 mg/kg/day. At the end of the treatment, plasma was collected for glucose and triglyceride determinations.



Pioglitazone(AD-4833) Metabolism and its Potential Metabolites

ED₂₅ values were estimated for decreases in plasma glucose and triglyceride for each administered compound in fatty rats(See table below). Hypoglycemia and hypotriglyceridemia were only observed following dosing with pioglitazone, M-II, M-III and M-IV. Respective ED₂₅ values for decreased glucose were 0.54, 0.99, 1.32 and 0.93 mg/kg and for decreased triglycerides were 0.43, 0.22, 0.47 and 0.53 mg/kg. These data confirm that most of the hypoglycemic and hypotriglyceridemic activity of pioglitazone is due to the parent compound .

Plasma Glucose

	AD-4833	M-I	M-II	M-III	M-IV	M-V
ED₂₅ (mg/kg/day)	0.54	-*	0.99	1.32	0.93	>3.0
Relative Potency (AD-4833=1.0)	1.0	-	0.55	0.41	0.58	<0.18

Plasma triglyceride

	AD-4833	M-I	M-II	M-III	M-IV	M-V
ED₂₅ (mg/kg/day)	0.43	-	0.22	0.47	0.53	>3.0
Relative Potency (AD-4833=1.0)	1.0	-	1.95	0.91	0.81	<0.18

*: Not determined

Since pioglitazone has an asymmetric carbon in its structure and two stereoisomers are known to be present, a study was conducted to evaluate the activity of the two stereoisomers. The potency of each stereoisomer was shown to be equal in potency to the racemate (pioglitazone). In an additional study, the pharmacological activity of ($\pm$), (+), or (-) AD-4833 was studied in male Wistar fatty rats. Rats received oral doses of control material or 1 mg/kg/day of one isomer for seven days. All isomers decreased plasma glucose and triglyceride levels by 30 to 40% and 60 to 70%, respectively. These decreases were statistically significant and were not different between the isomeric formulations.

F. Cardiovascular Effects of Pioglitazone

Pioglitazone was evaluated for cardiovascular and hemodynamic effects in the anesthetized dog. The citric acid vehicle alone or the drug (1 and 3 mg/kg) was given intravenously, and evaluated for effects on mean arterial pressure, heart rate, cardiac output, left ventricular dP/dt/P, right atrial pressure, left ventricular end diastolic pressure, pulmonary artery pressure, and Lead II of the ECG. Cardiac index, stroke volume, and total peripheral resistance were calculated from the above parameters. Some effects were seen with the vehicle alone. The administration of pioglitazone did not produce any effects that were not seen with the vehicle. Therefore, while the data were influenced by the vehicle effects, there were no pronounced effects that could be attributed to the drug. Cardiac hypertrophy was also noted, but furosemide did not completely reverse it.

Cardiac hypertrophy was attributed to the increased plasma volume. In the same study, five day treatment with pioglitazone activated $\text{Na}^+\text{-K}^+\text{-ATPase}$ in the proximal tubules and decreased Na^+ excretion in the urine, suggesting that the drug enhances the reabsorption of sodium and water. Cardiac enlargement was also produced by pioglitazone (10 and 100 mg/kg) in both hypophysectomized and intact rats, indicating that the effect is not dependent upon growth hormone. Thus, these studies indicate that the only major effect on the cardiovascular system is cardiac hypertrophy consequent to increased plasma volume.

3. ADME and PHARMACOKINETICS

AD-4833 was well absorbed from the gastrointestinal tract of mice, rats, dogs and monkeys with bioavailabilities ranging from 81% in mice and monkeys to 94% in dogs. Based on plasma AUC data for AD-4833 and its metabolites. Because AD-4833 is a racemate, possible enantiomer interconversion was studied and was found to occur both *in vitro* and *in vivo* with no changes in elimination. The addition of citric acid to the dose formulation produced a significant increase in bioavailability in both rats and dogs. In addition, slightly, but not statistically significantly higher absorption occurred with the hydrochloride salt of AD-4833 as compared to the acetic acid salt. The salt form did not affect half-life. Food appeared to slow absorption, but the effect was not significant.

A single oral dose resulted in slightly higher C_{max} and AUC values in female rats than in male rats. Repeated dosing appeared to accentuate this response. Dose significantly affected the pharmacokinetics of AD-4833. Dose proportional increases in C_{max} and AUC only occurred at low doses (*i.e.*, 4 mg/kg [repeated dose] or 7 mg/kg [single dose] and below in male rats and 16 mg/kg and below in female rats). Above these doses, increases in C_{max} and AUC values were less than dose proportional. Treatment duration seemed to have no effect on AD-4833 pharmacokinetics in rats and dogs.

AD-4833 was highly bound to human serum albumin (*i.e.*, 97 to 98%). The drug was bound to a lesser extent to other serum proteins. Although AD-4833 could be displaced from its albumin binding site by several compounds, there was little or no displacement. Distribution studies demonstrated that AD-4833 is rapidly distributed to and eliminated from many tissues after single and repeated dosing. However, evidence of accumulation in and/or slow elimination from the fat (brown and epididymal) was observed. Administration to pregnant or lactating rats demonstrated that AD-4833 and its metabolites transfer to the fetus, milk and mammary glands.

Enzyme induction and inhibition studies were performed on AD-4833. AD-4833 was not found to inhibit or induce metabolic enzymes and did not change the microsomal or enzymatic protein content in hepatic microsomes. Although several cytochrome P450 isoforms are involved in the metabolism of AD-4833 to M-IV, CYP1A1 (an extrahepatic cytochrome), CYP2C8, and CYP3A4 are primarily involved. For M-II (a secondary metabolite), isoforms CYP2C9, CYP3A4, and CYP2C8 are involved. AD-4833 undergoes oxidative metabolism to form six metabolites, M-I through M-VI. M-IV is the

primary metabolite in human followed by M-III and M-II; these are pharmacologically active compounds. Although some differences exist between species in the relative amounts of each metabolite produced, metabolism occurs via the same routes.

The excretion of AD-4833 was investigated in mice, rats, dogs and monkeys. Fecal elimination predominated in all species, except monkeys where urinary elimination predominated. Repeated dosing in rats did not alter the elimination pattern. The following table summarizes the pharmacokinetic data. Unless otherwise specified, the route of administration was oral.

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Summary of Pharmacokinetic Data

APK No.	Species	Dose	Tmax (hour)	Cmax ($\mu\text{g}/\text{mL}$)	AUC (0-48 hr) ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	Cumulative Excretion (%)	
						Urine	Feces
1	Mouse	0.5	1	0.51	3.00	23.9	74.9
2	Rat	0.5	4	0.71	7.11	35.5	61.7
	Dog	0.5	0.5	0.32	1.53	16.0	79.9
	Monkey	0.5	4.3	0.48	5.55	73.9	10.7
4*	Rat	5 (IV), 7, 107		--, 12.4, 106	80, 105, 1430	32.4, 41.4, 24.2	64.6, 48.8, 76.8
5**	Rat (pgmnt, albino)	1	4	1.5, 1.7	13.0, 13.6	NR	NR
9	Rat	10	1	13.62	107.47	NR	NR
13	Dog	10	1.4	8.73	26.99	NR	NR
14***	Dog	10	1-1.5	1.01-1.28	3.20-3.43	NR	NR
15	Dog	8	0.88	6.09	17.70 (0-7 hours)	NR	NR
16	Monkey	10, 20		1.23-4.29, 2.23-7.24		NR	NR
17	Dog (fasted)	25	1.12	15.44	53.46	NR	NR
18*	Rat	9.8	1.8	19.9	133	28.5 (f), 15.8 (m)	70.8 (f), 86.9 (m)
20*	Rat	10-300	1-4	3.17-12.68	39.12- 181.47	NR	NR
21*	Rat	100- 3000	4	12.53-13.59	171.78- 230.20	NR	NR
22***	Dog	5-75	1-1.57	6.54-27.72	16.6-128.1	NR	NR
23*	Rat	0.5 (RD, day 7)	4.7	0.96	12.29	35.7	57.5

*AUC 0-24 hours; ** AUC 0-72 hours; *** AUC 0- ∞ hours; IV = intravenous; f = female; m = male; pgmnt = pigmented.

In the mouse repeated dose study, less than dose proportional increases in plasma levels of AD-4833 and its three metabolites occurred. The overall trend in the repeated dose rat studies was for a less than dose proportional increase in Cmax and AUC values for AD-4833 and its three metabolites; some isolated greater than dose proportional findings were noted. In the 90-day and one year dog studies, increases in Cmax and AUC were less than dose proportional. However, in the 26-week dog study, mixed results were reported with greater than dose proportional responses in females and less than dose proportional increases in males. Monkeys exhibited a less than dose proportional increase in Cmax and AUC values following repeated dosing. In the mouse and rat carcinogenicity studies,

the trend was for a less than dose proportional increase in the C_{max} and AUC values for AD-4833, M-II, M-III and M-IV. Isolated instances of greater than dose proportional increases were noted.

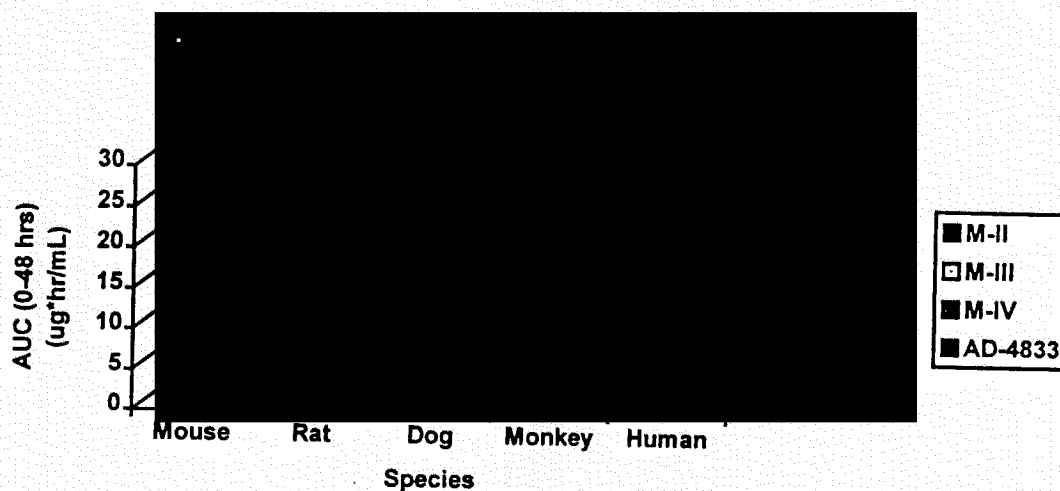
Although the effect of duration could not be assessed in mice, for the rats, increasing dose duration generally produced an increase in C_{max} and AUC values for AD-4833 and/or the metabolites. In general, increasing duration produced increasing C_{max} and AUC values in the dogs, but no consistent duration effect occurred in the monkeys. In all species, the duration effects were expressed at high doses; low doses did not induce this response. Isolated decreases in C_{max} and/or AUC values with increasing dose duration were reported for the high-dose males in the mouse oncogenicity study, but no other duration effect was observed. In the rat oncogenicity study, increasing duration produced decreasing C_{max} and/or AUC values at 63 mg/kg/day for AD-4833, M-II, M-III and M-IV.

No evidence of gender effects was observed in the mouse repeated dose study, but in the rat repeated dose studies females tended to have higher C_{max} and AUC values than males. For dogs, no gender effects were evident overall, and no evidence of a gender effect was observed in monkeys for AD-4833. No gender effects were observed for AD-4833 or M-IV in the mouse oncogenicity study, but for M-II and M-III females had higher C_{max} and AUC values than males. In comparison, in the rat oncogenicity study, females had consistently higher C_{max} and AUC values.

To assess the relationship between animal and human exposures, a comparison was made between AUC values obtained at the NOEL dose in rats, dogs and monkeys with those obtained in a human clinical trial. Animal:human ratios of greater than 1 were obtained for rats and monkeys. A ratio of less than 1 was obtained for dogs as shown in fig. 2.

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Figure 2. AUC Values of AD-4833 and Three Metabolites Following A Single Oral Dose



TOXICOLOGIC STUDIES (Most of all toxicological studies were performed by [redacted] In Japan under GLP standards, unless specified otherwise)

A. Acute Oral Toxicity Study in Mice(T-2)

a. Methods: Crl:CF1[BR] mice (n = 3/sex/group) were given pioglitazone(AD-4833) orally at doses of 0, 337, 674 or 1738 mg/kg; free base equivalents of 0, 300, 600 and 1550 mg/kg, respectively. Clinical observations were performed for 11 to 12 days following the last dosing. A necropsy was performed on every animal. Histological examination was performed only on the organs which appeared abnormal during necropsy.

b. Results: The administration of the citrate-based granulated powder vehicle induced death due to gastric or gastrointestinal bloating. Clinical signs included wheezing, stomach distension and gasping, and occurred in all groups. Because the findings (clinical signs, mortality and pathology) in animals receiving AD-4833(HCl) were the same as those observed in animals receiving the vehicle alone, the acute toxicity of AD-4833(HCl) could not be defined in this study.

B. Acute Intraperitoneal Toxicity in Rat(T-1)

a. Methods: Five Jcl:Wistar rats/sex/group were injected pioglitazone by intraperitoneally at doses of 260, 360, 510, 710 and 1000 mg/kg.

b. Results: Decreased locomotor activity, respiratory depression and hyporeactivity were observed beginning 5 to 10 minutes after dosing in all groups. In addition, hypotonia of

the abdominal muscles and flattened posture were observed in the groups receiving 510 mg/kg and more. Hypotonia of the abdominal muscles was also observed beginning one day after dosing in the 260 and 360 mg/kg groups. Secretion from the Harderian gland was observed beginning one day after dosing in the 1000 mg/kg group and beginning two days after dosing in the 710 mg/kg group. Animals that survived to necropsy were free of these symptoms within six to 12 days.

Respective mortalities in the five dose groups were 0, 1, 1, 4, and 5 for the males, and 0, 0, 1, 4, and 5 for the females. Almost all deaths occurred between two and six days post-dosing. Body weight was decreased or body weight gain suppressed one or two days after dosing in all groups. However, body weight data collected seven and 14 days after dosing indicated normal body weight gain in all groups.

Necropsy of rats that died during the observation period revealed hyperemia of the lung and remnant test article in the peritoneal cavity. In addition, ascites (2-4 mL) and interlobar adhesion of the liver were observed. In rats that survived to necropsy, remnant test article was observed in the peritoneal cavity. Also, enlargement and interlobar adhesion of the liver were observed, and ascites (approx. 3 mL) was noted in a few rats. It was concluded that the intraperitoneal LD₅₀ in rats was 558 mg/kg for males and 587 mg/kg for females.

C. Acute Oral Escalating Dose Toxicity Study (T-7)

a. Methods: Pioglitazone was administered orally to two male and two female Cynomolgus monkeys in escalating doses of 15, 60 and 240 mg/kg of the free base (3 to 5 days between doses). All animals received 240 mg/kg and were observed for 14 days. A similar group received the vehicle only.

b. Results: No treatment related effects on mortality, clinical signs, body weight, food consumption, body temperature, heart rate, hematology, and blood chemistry were seen at any dose. Therefore, the minimum lethal dose of AD-4833(HCl) in Cynomolgus monkeys was >240 mg/kg.

D. 13-Week Oral Toxicity Study in Mice(T-8)

a. Methods: Pioglitazone Lot# was INV.R3095. Ten Crl:CD-1 mice/sex/group were administered pioglitazone orally at doses of 0, 3.2, 10, 32, 100 and 320 mg/kg/day for 13 weeks.

b. Results: Treatment-related clinical signs included excessive salivation after dosing and mortality in the high-dose group mice. Four high-dose males and six high-dose females died as did four high-dose satellite mice (one male and three female). Body weight was slightly (under 5%) increased in the high-dose females, and food consumption was slightly (under 8%) increased in the males (32, 100 and 320 mg/kg/day) and females (10, 32, 100 and 320 mg/kg/day). Both the body weight and food consumption effects were considered pharmacological effects of the drug. Platelet counts, erythrocyte counts and

hematocrit and hemoglobin values were decreased in mice administered 320 mg/kg/day AD-4833(HCl). Mean platelet counts were also decreased in mice administered 100 mg/kg/day.

At necropsy, an increased fat:cell ratio was observed in the femoral bone marrow samples of all treated male groups and in females administered 32 mg/kg/day and above. Increased numbers of megakaryocytes were observed in the splenic red pulp of mice administered 100 and 320 mg/kg/day, as compared to controls.

Mean absolute heart weights were increased in high-dose mice(27%) and in males administered 100 mg/kg/day(13%). The increased heart weight did not have a correlative histopathologic change. Liver weight was increased in the high-dose group(130%); hepatocellular hypertrophy was observed in all AD-4833(HCl) treated groups. This change was primarily centrilobular and increased in both incidence and severity in a dose related manner.

E. 13-Week Oral Toxicity Study in Rats (#89-256)

a. Methods: Lot#R1940. Ten Sprague-Dawley (Jcl:SD) rats were given pioglitazone orally at doses of 0 (distilled water control), 0 (vehicle control), 30 (low), 100 (middle) and 300 (high) mg/kg as free base equivalents for 13 weeks.

b. Results: There were no treatment-related changes in body weight, food consumption, urinalysis and ophthalmology examination. No treatment-related deaths occurred, but one vehicle control female, one low-dose female, one mid-dose male and two high-dose males died due to dosing errors.

Hematology revealed statistically significant decreases in erythrocytes (in both sexes of the mid- and high-dose groups) and hematocrit (in mid- and high-dose females) as shown below. Hemoglobin concentrations (in mid- and high-dose females) was also reduced similarly. And statistically significant increases in mean corpuscular hemoglobin (in both sexes from the high-dose group) were noted. These changes were consistent with anemia. Plasma T₄ levels were decreased in all male treatment groups, but this was determined to be of no toxicological significance because the plasma T₃ level, which has greater physiological activity than T₄, remained unchanged.

Pioglitazone Effect on Hematological Parameters in SD Rat after 13-Week Treatment				
Dose(mg/kg/ Day)	Male Rat		Female Rats	
	Erythrocytes@	Hematocrit(%)	Erythrocytes@	Hematocrit(%)
Control	940	42.6	851	40.9
Placebo	947	43.1	840	40.5
30 mg	938	42.6	820	39.9
100 mg	883*	41.9	770*	38.0*
300 mg	868*	41.0	731*	36.9*

Erythrocyte counts should be multiplied by 10,000. Each value represents mean of 8 to 10 animals.

*P<0.05

Organ weight changes considered to be related to AD-4833(HCl) treatment included a statistically significant increase in heart weight in males and females treated with 100 and 300 mg/kg/day and a statistically significant increase in liver weight in females treated with 100 and 300 mg/kg/day as shown below. Histopathology did not reveal any abnormalities in the liver or hearts.

Pioglitazone Effect on Absolute Organ Weight in SD Rat after 13-Week Treatment				
Dose(mg/kg/ Day)	Male Rat		Female Rats	
	Heart Weight	Liver Weight	Heart Weight	Liver Weight
Control	1.35	13.0	0.76	6.33
Placebo	1.27	13.11	0.73	6.64
30 mg	1.41	12.18	0.83	6.26
100 mg	1.70*	12.38	0.97*	7.22*
300 mg	1.57*	11.82	1.02*	7.94*

*Weights were expressed in mean gram of 8 to 10 animals.

AD-4833(HCl)-related, dose-dependent increases in the amount of adipose tissue in interscapular and mediastinal spaces were found in all AD-4833(HCl)-treated groups. As previously mentioned, the increased subcutaneous adipose tissue in the inguinal-lumbar region was considered a pharmacological effect of AD-4833(HCl). No other gross abnormality was considered to be treatment-related. The only lesion related to AD-4833(HCl) treatment was splenic extramedullary hematopoiesis (SEH). This lesion was present in none of the 20 males or 20 females in both control groups, in 2 males and 1 female of the low-dose group, in 6 males and 3 females of the middle-dose group and in 8 males and 5 females of the high-dose group. The incidence of SEH in the low-dose group was considered by the authors to be well within the range of normal variation based on the historical control data, but because SEH was absent in the control group of this study, a potential effect on hematopoietic function at 30 mg/kg could not be ignored.

c. Conclusion: Anemia with reduced erythrocytes, hematocrit and hemoglobin concentration and splenic extramedullary hematopoiesis were present in rats after 13 weeks of oral administration of AD-4833(HCl) at doses of 100 and 300 mg/kg. The toxicological no-effect dose might be near 30 mg/kg/day.

F. Twenty Six-Week Oral Toxicity Study in Rat(Study#1182)

a. Methods: Lot#R2843. Ten Jcl:SD rats/sex/group were administered pioglitazone orally at doses of 10, 30 and 100 mg/kg/day for 26 weeks. Satellite groups of five rats/sex/dose were also included and treated with the same three AD-4833(HCl) doses as the main study animals. Plasma samples were collected during weeks 13 and 26, and parent compound and M-III and M-IV were measured.

b. Results: No treatment-related changes were seen in mortality, clinical signs, ophthalmoscopy, urinalysis or necropsy. Body weight gain tended to be increased in males in the 10 and 30 mg/kg/day groups from an early stage in the dosing period, but not in the 100 mg/kg group. This increased weight gain was considered to be due to the pharmacological action of the test compound.

Absolute and relative heart weights in both sexes of high-dose rats were increased as shown below. However, there was no change in liver weights and no histopathological changes were noted. Extramedullary hematopoiesis in the spleen and hypocellularity of the femoral and/or sternal bone marrow were observed during histopathological evaluation of the 100 mg/kg/day rats.

Dose(mg/kg/ Day)	Male Rat		Female Rats	
	Heart Weight	Liver Weight	Heart Weight	Liver Weight
Control	1.46	15.80	0.93	7.78
Placebo	1.45	15.22	0.93	8.41
10 mg	1.69*	14.21	1.00	7.55
30 mg	1.71*	13.71	1.05	8.03
100 mg	1.75*	13.68	1.24*	9.10

*P<0.05 and weights were expressed in mean gram of 9 to 10 animals.

Plasma samples collected during weeks 13 and 26 were analyzed for AD-4833, M-III and M-IV. The relative amounts of the parent drug and metabolites in the plasma were: AD-4833 > M-IV > M-III. All analytes produced less than dose proportional increases in Cmax and AUC values. Females attained higher plasma levels of the parent drug and M-IV than males during both collection times. No effect of repeated dosing on Cmax or AUC values was noted for AD-4833 or M-IV. As the dose increased, the AD-4833 Tmax increased, from 0.5 hours at 10 mg/kg/day to 4 to 8 hours at 100 mg/kg/day. Higher plasma levels of M-IV were measured than M-III. M-III exhibited similar pharmacokinetics as AD-4833 and M-IV, with one exception. Repeated dosing resulted in lower Cmax and AUC values in males.

c. Conclusion: Increased heart weight (without accompanying pathology), hypocellularity in the femoral and/or sternal bone marrow and decreased erythrocyte counts (male only) were observed in the 100 mg/kg group. Based on these results, it is concluded that the non-toxic dosage level (or NOAEL) of AD-4833(HCl) was 30 mg/kg/day.

G. One-Year Oral Toxicity Study in Rats (TR#7226-94-007)

a. Methods: Two lots (INVR2728 and INVR2895) were used in the study. Thirty Crl:CD(BR) rats/sex/groups were administered pioglitazone orally via gastric intubation at doses of 4, 16, 63 and 160 mg/kg/day (3.6, 14.5, 57.1 and 145.1 mg/kg/day as AD-4833 free-base equivalents) for a year. 15 rats/sex/group were killed at the completion of the one-year dosing phase. The remaining rats (up to 15/sex/group) were killed after a four-month recovery period. An additional twelve rats/sex/group underwent the same treatment and plasma was collected on days 43, 183 and 363 for toxicokinetic analyses.

b. Results:

Mortality: Three control and 48 AD-4833(HCl) treated rats died prior to the one-year sacrifice. Drug-related early death due to apparent heart dysfunction occurred in the 63 and 160 mg/kg/day males (8 and 18 deaths, respectively) and in the 160 mg/kg/day females (10 deaths) as shown below. In addition, one control and six treated rats were sacrificed during the recovery phase. The cardiac-related deaths were delayed in onset with first mortality on Day 114 for the 160 mg/kg/day males, Day 154 for the 160 mg/kg/day females and Day 255 for the 63 mg/kg/day females.

Death due to	Sex	0 mg	4 mg	16 mg	63 mg	160 mg
Cardiac Failure	Male	0	0	0	8	18
	Female	0	0	0	0	10
Total Death	Male	2	2	3	9	20
	Female	1	0	1	0	13

*The drug dose was in mg/kg/day and each value indicates number of cardiac death.

Cardiovascular Effects: AD-4833(HCl) administered to rats at 63 and 160 mg/kg day caused early increases in body weight followed by delayed decreases (onset around the fourth month of dosing), clinical signs suggestive of cardiopulmonary dysfunction and decreased elasticity of the lumbar skin (females only). Statistically significantly increased absolute and relative (to brain weight) heart weights as well as volume were observed in all treated male groups and in female groups administered 63 and 160 mg/kg/day at the one-year necropsy as shown in a table below. This was considered the primary toxicological effect of the drug, since the changes were not reversed, particularly in male rats after 4-month recovery period. Males were more sensitive to cardiac dysfunction, and cardiomyopathy was present at doses as low as 16 mg/kg/day in males and 64 mg/kg/day in females.

Sex	Males					Females					
	Dose	0	4	16	63	160	0	4	06	63	160
N	15	16	15	15	15	15	15	15	15	15	15
Length	18.93	20.40*	21.62*	22.30*	22.00*	16.68	16.98	17.19	18.44*	18.10*	
DVW	12.15	12.83*	13.27*	13.63*	13.63*	10.96	10.96	11.34	12.16*	12.42*	
Lateral	13.73	14.51*	15.57*	15.83*	16.03*	11.76	11.83	12.27*	13.23*	13.64*	
Volume	3166	3814*	4483*	4839*	4819*	2152	2208	2408*	2976*	3080*	
Weight	1.61	1.91*	2.22*	2.46*	2.55*	1.18	1.19	1.26	1.58*	1.66*	

The unit of dose was in mg/kg/day and N indicates animal numbers. DVW stands for dorso-ventral width in mm and cardiac volume was in mm³. The heart weight was in gm. *P<0.05.

The cardiac enlargement was correlated with histologic multifocal or diffuse myocardial hypertrophy. In addition, myocardial cells had increased cytoplasm and plump oval nuclei. At one year, all external dimensions of the heart had increased by approximately the same amount indicating that the increased weight was directly reflected in an externally measured increase in size. Cross-sectioning revealed increased muscle area in the left and right ventricles and increased size of both ventricles. Recovery animals

showed evenly proportional decreases in both ventricular muscles indicating at least partial recovery from the hypertrophy.

Changes indicating cardiac dysfunction included thoracic cavity fluid, bilateral atrial hypertrophy and increased lung weight. No recovery deaths were attributed to cardiac dysfunction. At the recovery necropsy, evidence of heart dysfunction was nearly reversed but some cardiac hypertrophy and cardiomyopathy (a secondary effect) were present. Recovery was considered complete in all treated females and in the low-dose males.

Hematological Effects: AD-4833(HCl) administered at 16, 63 and 160 mg/kg/day caused statistically significant ($[792, 756 \text{ and } 738] \times 10^4 / \text{mm}^3$, respectively, vs 834 in control) decreases in red blood cell count with a slight, reactive reticulocytosis, slightly decreased platelet counts at all dose levels and other secondary hematologic changes. All hematologic changes were reversed by the end of the four-month recovery phase.

Other Effects: The incidence of early closure of the femoral and/or tibial physal plate was higher in all AD-4833(HCl) treated male groups than in the control. Decreased bone in the sternum was more prevalent in all AD-4833(HCl) treated groups than in the control group. Irreversible broadening of the sternum (osteodysplasia) was evident in all AD-4833(HCl) treated male groups and in female groups administered 63 and 160 mg/kg/day AD-4833(HCl). Pituitary weight and the incidence of pituitary adenoma of the pars distalis were increased in high-dose females at the end of the dosing phase. By the end of the study, the overall incidence of pituitary adenoma was similar for the control and the high-dose females. There was no effect on absolute weight in liver, but the ratio of liver to body weight was reduced by 10 to 20% from the control. Other changes included sporadically decreased in kidney, spleen and testes weight.

Pharmacokinetic Effects: Plasma samples were analyzed for AD-4833, M-II, M-III and M-IV on days 43, 183 and 363. The relative amounts of the parent drug and metabolites in the plasma were: AD-4833 > M-IV $\approx$ M-III > M-II. Less than dose proportional increases in Cmax and AUC values were reported for each of the four analytes. For parent drug, M-III and M-IV, females produced higher Cmax and AUC values than males, but for M-II the opposite effect was observed. Increasing duration resulted in increased Cmax and AUC values for the four analytes in the female rats; this effect was slight for M-II.

c. Summary: AD-4833(HCl) administered orally to rats for one year caused death due to cardiac dysfunction at doses of 63 and 160 mg/kg/day. Evidence of cardiac dysfunction was present at the one-year sacrifice in rats at doses of 16 mg/kg/day or above and cardiac hypertrophy was present in all treated male groups and females treated with 63 and 160 mg/kg/day. Reversible decreases in red blood cell count and adipose tissue changes were also recorded. Because evidence of toxicity occurred at all doses and the drug-related changes were not entirely reversible following a four-month recovery phase, a NOAEL was not determined.

H. 4-Week Oral Toxicity Study in Dog (Study#814/SU)

a. Methods: Three beagle dogs/sex/group received pioglitazone orally in capsules containing 0, 1, 3, or 10 mg AD-4833/kg/day as free base equivalents for 4 weeks.

b. Results: AD-4833(HCl) did not affect body weight, food or water consumption, body temperature, ophthalmoscopy, urine volume, urinalysis, gross pathology, organ weights or histopathology. Some animals in all groups experienced vomiting and soft feces. An increase in heart rate occurred in the low- and high-dose females, however, the values were within normal accepted ranges of variability. Mild extramedullary hematopoiesis was noted in one high-dose female following histopathology, but this effect was considered incidental because concomitant anemia did not occur. A dose-dependent increase in plasma AD-4833 levels was reported. It was concluded that no toxicity occurred in the dogs at doses up to 10 mg/kg/day.

I. 12-Week Oral Toxicity Study (#7220/90/043) in Beagle Dogs

a. Methods: Lot# R1895. Three to 5 beagle dogs/sex/group were administered pioglitazone orally at doses of 0, 1, 3 and 10 mg/kg/day as AD-4833 free base equivalents (1.12, 3.37 and 11.24 mg AD-4833(HCl)/kg/day for 3 months.

b. Results: No effect on body weight, ophthalmic appearance, or water consumption was noted during the dosing period. Food consumption during the dosing period was not statistically analyzed, since the amount of food was limited to 300 grams daily. Ophthalmic examinations and food and water consumption measurements were not performed during the recovery phase, since no treatment-related effects during dosing were observed.

Hematological changes observed in the combined sexes and attributed to AD-4833(HCl) treatment included a statistically significant reduction in hematocrit ($P < 0.05$) and hemoglobin concentration on Days 72 and 90 and in erythrocyte count on Day 90 in Group 4 animals. These parameters returned to normal during the recovery phase. Statistically significant serum chemistry changes which were related to AD-4833(HCl) treatment were observed in Group 4 males or in the sexes combined during the dosing period. These included a decrease in serum albumin on Days 56, 72, 84 and 90, a decrease in total protein on Days 14, 56 and 90, and an increase in alanine aminotransferase on Days 28, 42, 56, 72, 84 and 90 as shown in a table below. There was also an increase in lactate dehydrogenase on Days 42, 72, and 84, and an increase in chloride on Days 28, 42, 56 and 90.

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Sex	Males					Females				
Day@	28	42	56	72	90	28	42	56	72	90
0 mg#	31	27	29	32	31	21	21	21	24	25
1 mg	25	27	27	29	31	30	30	31	31	31
3 mg	29	34	36	37	35	26	24	26	28	30
10 mg	48	50	49	57	60	28	31	34	33	36

ALT unit was in U/L and @ and # indicate days after the drug treatment and pioglitazone dose in mg/kg/day, respectively.

Treatment with AD-4833(HCl) resulted in a small amount of clear fluid observed grossly in the pericardium of one female and one male dog treated with 10 mg/kg/day and sacrificed at dosing termination; this was not observed in any recovery dog. A statistically significant increase in heart weight was noted in Group 4 animals sacrificed at dosing termination. The increase in heart weight was also noted in Group 4 recovery animals; however, no statistical analysis of recovery animals was performed due to the small number of animals. No treatment-related microscopic lesions were noted in any animal, including those in the recovery group.

J. 26-Week Oral Toxicity Study in Beagle Dogs(Study#1183/CH)

a. Methods: Pioglitazone used for this study was citrate-based granulated powder(Lot# R2843), which was provided by Upjohn company. Four beagle dogs (4/sex/group) were administered pioglitazone daily at doses of 0, 1, 3 and 10 mg/kg/day (0, 0.89, 2.67 and 8.90 mg/kg/day as free base equivalents) for 6 months.

b. Results:

Mortality and Clinical Signs: There was no drug-induced death, although a control female dog was sacrificed because of moribund situation. No treatment-related changes were seen in clinical signs, body weight, food consumption, body temperature, heart rate, urine output, water intake, electrocardiography, ophthalmoscopy, urinalysis, plasma T₄ and T₃ levels or the blood coagulation test. No treatment-related changes were observed in any examination in the 1 or 3 mg/kg/day groups.

Slight pale discoloration of the oral mucosa occurred in two high-dose males from weeks 5 to 9. In the 10 mg/kg/day group, one female exhibited decreased erythrocyte count during week 26 (37.8% decrease in comparison to the value during week 14). ALT levels were not affected significantly by the drug, but spleen weights in males were reduced significantly as shown below. A statistically significant increase in platelets and leukocytes was also reported in the high-dose females. Increased heart weight with hydropericardium was observed in one 10 mg/kg/day male; however, no abnormalities were seen in electrocardiography or histopathology. Hydropericardium was also observed in animals receiving more than 10 mg/kg/day in a three-month oral toxicity study.

Parameters	Sex	0 mg	1 mg	3 mg	10 mg
ALT	Male	24	31	24	27
	Female	25	23	26	27
Spleen	Male	31	18*	24	20*
	Female	21	24	23	23

@Drug dose was in mg/kg/day. The units of ALT and spleen weight were in U/L and in gram, respectively.

Interstitial fatty infiltration in the parathyroid gland occurred in one male and three females in the 10 mg/kg/day group; however, the toxicological significance of this change was not clear since no histologic changes occurred in the parenchymal cells.

Plasma samples were collected on days 81 and 179 and were analyzed for AD-4833, M-III and M-IV. The relative amounts of the parent drug and metabolites in the plasma were: AD-4833 > M-IV > M-III. For the females, greater than dose proportional increases in AD-4833 Cmax and AUC values occurred at 3 mg/kg/day and less than dose proportional increases occurred at 10 mg/kg/day. Less than dose proportional increases occurred in the males at all doses. No gender or duration effects were evident for the parent drug. M-IV was formed in greater amounts than M-III. M-III Cmax and AUC values increased in a greater than dose proportional manner for the females and a less than dose proportional manner for the males. Females had higher levels than males and increasing duration produced a slight increase in Cmax and AUC values in both sexes. For M-IV, the increases in Cmax and AUC values followed the same pattern as for M-III, but no gender or duration effects occurred.

Decreased erythrocyte count, increased spleen weight in one female and increased heart weight with hydropericardium in one male were observed in the 10 mg/kg/day group. Based on these results, it is concluded that the non-toxic dosage level of AD-4833 was 3 mg/kg/day.

K. 52-Week Oral Toxicity Study in Dogs (TR#7226-93-002). This study was conducted by [REDACTED] under GLP standards.

a. Methods: Pioglitazone Lot# was R2763-R2874. Six beagle dogs/sex/group were given pioglitazone orally at doses of 0, 1, 3 or 10 mg/kg/day for one year. Following the dosing phase, 2 dogs/sex/group were maintained without drug exposure for a four-month reversibility phase.

b. Results: Clinical Signs: General clinical observations were conducted following the morning dosing and again in late afternoon. Clinical signs related to a toxicological or pharmacological effect were not apparent during this study.

Body Weight and Food Consumption: During the first week of the study, 92% of the study animals exhibited weight loss ranging from 50 to 650 grams. Group mean total body weight changes indicate that the test compound did not have any noticeable effect

on food or water consumption. A consistent body weight decrease was observed in only the mid-dose (3 mg/kg/day) females during the dosing phase (Please see the table below).

Treated Week	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
00	9.0	8.8	8.1	9.2
10	9.0	8.4	7.7	6.7
20	9.2	8.5	8.0	8.7
30	10.0	9.1	8.4*	9.0
36	9.9	9.1	8.2*	8.9
40	9.9	9.1	8.4*	9.0
46	9.9	9.3	8.3*	9.2

Indicate P<0.05 compared to the control.

Hematology and Blood Chemistry: Hematology parameters demonstrated evidence of a regenerative anemia in the mid-dose (3 mg/kg/day) males and high-dose males and females. Serum chemistry assays revealed a biologically significant increase in alanine aminotransferase (ALT) levels in the high-dose males from week 3 to the end of dosing as shown below. By the end of the reversibility phase, all of the hematologic parameters had returned to control values and the ALT levels in the high-dose males had decreased to near normal levels.

Week	Sex	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
3	M	26.8	28.2	31.3	39.1*
	F	27.1	23.5	25.3	28.9
28	M	31.0	29.4	34.1	59.7*
	F	27.0	28.6	25.9	34.0
52	M	32.1	31.8	44.5	80.4*
	F	25.8	31.4	28.8	37.1

Indicate P<0.05 compared to the control.

Plasma bilirubin levels were documented in a table below, which were not altered in all groups. However, the level in females of the high dose group at the week of 55 appeared high. The value was not analyzed statistically by Dunnett's test since there were only two dogs, whose blood level was returned subsequently during the recovery period. Thus, there was no apparent association with other changes such as ALT.

Week@	0	3	7	25	38	46	52	55	59	68
Male	0.3	0.1	0.2	0.2	0.2	0.1	0.3	0.2	0.2	0.1
Female	0.2	0.1	0.1	0.1	0.2	0.3	0.3	0.5	0.2	0.2
N	6	6	6	6	6	6	6	2	2	2

Total bilirubin levels were in mg/dL and @indicates weeks after pioglitazone treatment.

Electrocardiography: There were no meaningful treatment related differences in heart rates, PR, QRS or QT intervals, rhythm or amplitude associated with test article. ST segment depression was noted in all dose groups at a level of 0.1 mv or less, but the ST segment depression above 0.15 mv was seen only in some treated animals in all dose groups. It was not clear whether the ST segment depression was associated with compound administration because there were no pretest electrocardiogram.

Organ Weights: There was a trend towards increased heart weights in the mid- and high-dose males and high-dose females at the one-year necropsy (Please see table below), a trend that was still evident in the high-dose males at the end of the four-month reversibility phase. Electrocardiograms and gross and microscopic tissue evaluations failed to demonstrate any significant myocardial changes. There were not any other morphologic treatment-related tissue changes noted at either the one-year or recovery necropsies.

Tissues	Sex	0 mg/kg/day	1 mg/kg/day	3 mg/kg/day	10 mg/kg/day
Heart	M	92.2	85.2	95.7	107.5*
	F	71.5	72.6	67.0	77.7*
Liver	M	321.9	266.0	274.3	316.5*
	F	254.1	245.6	248.6	253.2*

*Indicate Dunnett's test was not applicable due to limited degrees of freedom and the unit of organ weight is in grams.

Plasma samples collected during months 3, 6, 9 and 12 were analyzed for AD-4833, M-II, M-III and M-IV. The relative amounts of the parent drug and metabolites in the plasma were: M-IV > AD-4833 > M-III > M-II. Virtually none of the dogs produced measurable levels of M-II. For the remaining three analytes (AD-4833, M-III and M-IV), less than dose proportional increases in AUC values were reported, except for a single instance of a greater than dose proportional increase for M-III in both sexes at 6 months. No consistent gender effects were noted, but increasing duration tended to produce increasing AUC values at 9 and 12 months.

c. Conclusion: when beagle dogs were given AD-4833 orally via gelatin capsules daily one year at dose levels of 0, 1, 3, and 10 mg/kg/day, evidence of a regenerative anemia, elevated serum ALT levels, and increased heart weights were observed at the mid- and/or high-doses. By the end of the four-month reversibility phase, the hematologic values had returned to normal and the ALT levels had lowered. However, the myocardial weights were still increased, especially in the high-dose males.

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L. 52-Week Oral Toxicity Study in Monkey(Study#28-05). This study was performed by [REDACTED] under Japanese MHW GLP guidelines.

a. Methods: Pioglitazone Lot# was not specified. Four Cynomolgus monkeys/sex/group were given pioglitazone orally (nasogastric) at doses of 0, 1, 2, 8, and 32 mg/kg/day for 52 weeks. Three animals per sex were added to the control and high-dose groups and allowed to recover from treatment for 16 weeks. Blood samples were collected during weeks 26 and 52 and the plasma drug levels were determined.

b. Results: No mortalities occurred in any group and no treatment-related effects were noted on clinical signs, electrocardiography, ophthalmology, hematology, biochemistry, urinalysis, gross pathology, organ weights, or histopathology (via light or electron microscopy). In the biochemistry screen, a tendency towards a decrease in serum triglycerides was observed in the beginning of the dosing period for each treatment group. A statistically significant increase in food consumption occurred in females at all doses. The increase was noted at various times during weeks 11 through 14. An increase in body weight was measured in males exposed to 8 and 32 mg/kg/day and females exposed to all doses. No abnormalities occurred in any of the recovery animals.

Electron microscopy was performed on heart samples taken from the left ventricular wall of one control male and two high-dose males at the end of the dosing period along with one control male and two high-dose males at the end of the recovery period. Very slight lipofuscin granules were observed in the cardiac muscle cells of both groups of high-dose males as well as in the recovery control male.

Plasma data collected during weeks 1, 26 and 52 were analyzed for AD-4833, M-II, M-III and M-IV. The relative amounts of the parent drug and metabolites in the plasma were: AD-4833 > M-IV > M-III > M-II. Cmax and AUC values for AD-4833 and its three metabolites increased with increasing dose. However, the increase was not proportional to the dose. No sex differences were noted for AD-4833, but females had slightly higher M-II Cmax and AUC values than and males had higher M-III and M-IV AUC values than females. Increasing dose duration decreased Cmax and/or AUC values for the parent drug, M-II, M-III, and M-IV.

It appears that the doses that were selected for the monkey might not be toxicologically meaningful doses since the doses did not produce any toxic effects in male or female monkeys at doses as high as 32 mg/kg/day. The dose represents approximately 20 times of recommended human exposure, based on a body surface area comparison. In addition, Cynomolgus monkeys appear to be resistant species to toxicity induced by thiazolidinediones such as troglitazone or rosiglitazone.

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5. REPRODUCTIVE TOXICITY STUDIES

A. Segment I Reproduction Study I in Rats (TR#7224-98-026)

a. Methods: Pioglitazone Lot#INV.R2728. Forty-two CrI:CD(BR) SD rats/sex/group were given pioglitazone[AD-4833(HCl)] orally by gastric intubation at doses of 0, 10, 20 and 40 mg/kg/day. The drug was administered from 7 and 14 days, respectively, prior to mating until sacrifice, in order to determine the possible adverse effects of this drug on fertility and general reproductive performance, as well as any effects on F₁ offspring development behavior and fertility.

b. Results:

Clinical Observations and Survival: The drug did not result in clinical effects suggestive of marked toxicity and did not affect survivability, estrus, spermatogenesis, copulation, fertility or gestation length in the parental generation. One male in the mid-dose group died prior to mating (the cause of death was most likely a dosing accident); in the high-dose group, one dam died and two were sacrificed in a moribund condition as the result of dystocia. F₀ male and female body weight gains and food consumption prior to mating were increased in all three treatment groups. The increased body weight gain, with increased food consumption, was most likely the result of increased adipose tissue, a pharmacological effect of AD-4833(HCl). Mean relative spleen weight of F₀ males was decreased in the AD-4833(HCl)-treated groups.

Histopathology: The placentas of treated dams sacrificed on gestation day 20 were enlarged. Histopathologic evaluation of the placentas revealed apparent differences in the morphology of the placenta between animals given control article and those given drug, but most were related to the pharmacological properties of the drug and were not considered to be of biologic importance. Necrosis in the cellular component of the basal zone from placentas of dams in the 40 mg/kg/day dose group was the single finding considered to be of toxicological importance and related to AD-4833 (HCl) treatment. Hematology changes included decreased hemoglobin concentrations (males and females) and hematocrits and increased mean cell volume (males only). AD-4833(HCl) treatment also affected serum chemistry parameters as indicated by decreased creatinine kinase and increased alkaline phosphatase, as well as increased cholesterol and decreased total protein (males only).

Fetotoxicity and Teratogenicity: The drug was embryotoxic at 40 mg/kg/day, as evidenced by increased postimplantation losses. Treatment-related fetotoxicity also occurred at doses as low as 10 mg/kg/day, as evidenced by reduced fetal body weights and crown-rump lengths, and increased incidences of visceral and skeletal variations. Gross, visceral or skeletal malformations indicative of teratogenicity in fetuses from dams treated with AD-4833(HCl) were not evident. However, the ability to deliver live newborns was adversely affected in the 40 mg/kg/day dose group, with three dams experiencing dystocia.

F₁ pup survivability was adversely affected in the mid- and high-dose groups during the early postpartum period. Survival rates and clinical observations were comparable in all groups, from weaning to maturation, in animals selected for the F₁ fertility evaluation. Delayed development continued through maturation in the mid- and high-dose groups, as evidenced by continued reductions in mean body weight. The F₁ animals in the high-dose group required three breeding periods to achieve fertility rates comparable to that of the control group. Finally, the means for F₁ gestation length, and the numbers of live, dead and abnormal F₂ pups, as well as mean F₂ pup weights on postpartum day 0, were not adversely affected by AD-4833(HCl) treatment.

c. Conclusion: Segment I fertility and general reproductive performance study with male and female Sprague-Dawley rats given AD-4833(HCl) throughout gametogenesis, mating and gestation as well as during the postpartum period (females only) at doses of 0, 10, 20 and 40 mg/kg/day (AD-4833 free base equivalents), did not determine a no-observed-adverse-effect level (NOAEL) for parental (F₀) toxicity. Other than the dystocia seen in the high-dose group, the parental effects observed in all three groups were consistent with the pharmacological actions of this drug. Teratogenicity was not evident in this study. However, pioglitazone did delay F₁ development as measured in body weight changes and the F₁ fertility was also delayed.

Postpartum Day	0 mg/kg/day	10 mg/kg/day	20 mg/kg/day	40 mg/kg/day
0	6.3	5.8*	5.2*	5.1*
1	7.0	6.6	5.6*	5.7*
4	10.7	10.0	8.3*	7.8*
7	15.5	14.7	12.4*	11.3*
14	31.0	30.1	26.1*	23.1*
21	51.0	46.7*	41.6*	34.8*

*Indicate P<0.05.

B. Range-Finding Segment II Study I in Rats (TR#7224-91-068)

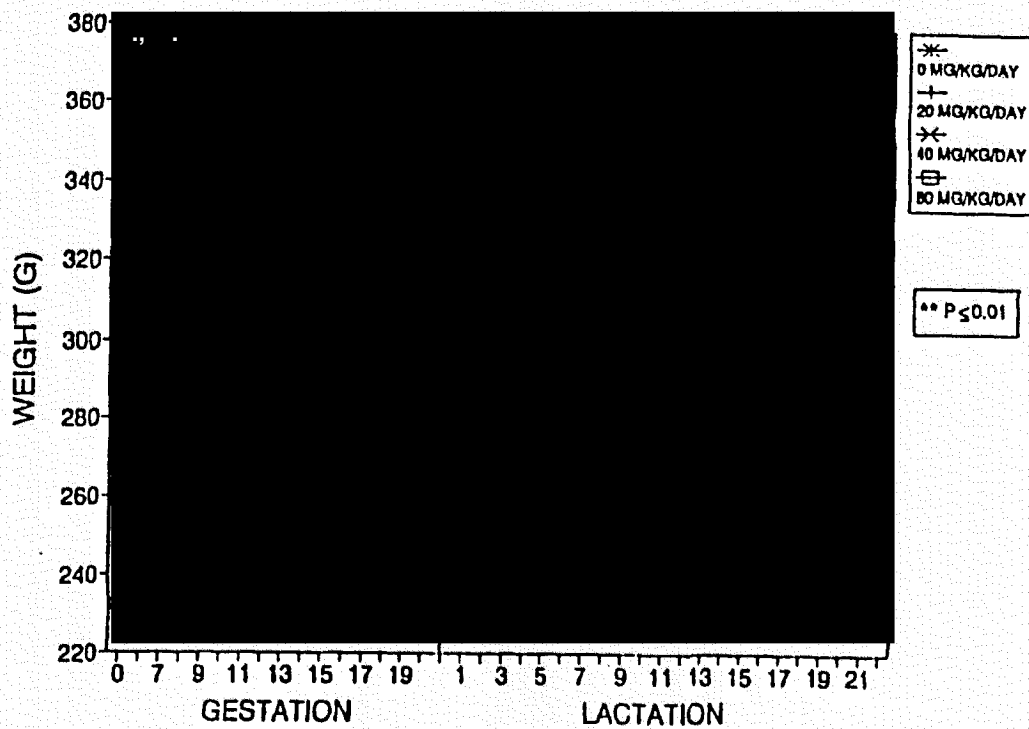
a. Methods: Six pregnant CrI:CD[BR] rats/group received twice daily oral doses of 0, 50, 100, 200 or 400 mg/kg of pioglitazone on gestation days 6 through 20

b. Results: Decreased weight gain occurred in all treatment groups along with red vaginal discharge. The incidence of rales was increased at 400 mg/kg. Several maternal hematology parameters were increased including mean corpuscular volume, platelets, and lymphocytes at 400 mg/kg. AD-4833 was embryotoxic and fetotoxic with resorptions occurring in two and six rats at 200 and 400 mg/kg/day and fetal deaths occurring in one, two and two rats at 50, 100, and 200 mg/kg/day, respectively. In addition, treatment decreased the mean number of live pups per dam, increased the mean number of dead pups per dam, and decreased live pup weight at 50 to 200 mg/kg. Based on these data, a no-observed-adverse-effect-level likely to be below 50 mg/kg.

C. Segment II Teratology Study in Rats (TR7224-93-019)

a. Methods: Lot# (D)25064-MIC-8. Thirty-three to 35 pregnant CrI:SD(BR) VAP/Plus rats were given pioglitazone orally by gastric intubation at doses of 0, 20, 40 and 80 mg/kg/day on days 6 through 17 of presumed gestation. The rats from each dosage group were randomly selected for cesarean section on day 20 of gestation and the fetuses were obtained for morphological evaluation. Other F₀ dams in each group were permitted to deliver naturally. The development and reproductive function of the pups were assessed.

b. Results: No F₀ maternal deaths occurred and no clinical findings that are related to the treatment were observed. Dam body weight gains were significantly reduced on day 18 to 20 of gestation in the high dose group (See the fig. Below). These decreases in weight gain were, at least partly, the result of increased incidences in embryo deaths and reductions in gravid uterine weight in these groups. Biologically and statistically significant delays in the onset of parturition were found in the 40 and 80 mg/kg/day groups. While body weight gains were generally higher among the AD-4833(HCl) dosage groups during lactation, the numbers of pups in the 40 and 80 mg/kg/day groups were reduced.



Pioglitazone Effects on Body Weights in Fo Female Rats During Gestation and Lactation

Gross external, soft tissue and skeletal examinations of the F₁ fetuses did not reveal alterations attributable to AD-4833(HCl). However, the average F₁ fetal body weight was significantly reduced in the 80 mg/kg/day group. Administration of this drug at 40 and 80 mg/kg/day led to significant increases in the incidence of stillbirths and pup

deaths on postpartum day 1 and between postpartum days 2 and 4. Litter size was reduced throughout lactation and pup weight in the 80 mg/kg/day group was significantly reduced on postpartum day 1.

In the F₁ generation, no deaths occurred and clinical observations were not remarkable. Mean body weights in the 80 mg/kg/day F₁ males were significantly reduced from day 1 pre-mating to cohabitation, and mean body weight gain in the 80 mg/kg/day F₁ females was significantly reduced between days 0 and 6 of gestation. Differences between groups in sexual maturation, mating and fertility in the F₁ generation were not apparent. Gross external examination of the F₂ fetuses did not reveal alterations attributable to AD-4833(HCl) administration to the F₀ maternal animals. Cesarean section and litter parameters in the F₁ dams on gestation day 20 were comparable in all groups.

c. Conclusion: The basis of the results from this study, particularly the delays in parturition found in the 40 and 80 mg/kg/day groups, the maternal no-observable-adverse-effect-level in F₀ females for AD-4833(HCl) was 20 mg/kg/day. The NOAEL for developmental toxicity was also judged to be 20 mg/kg/day, based on the reductions in embryo viability, litter size and pup survival in the 40 and 80 mg/kg/day groups; fetal and pup (postpartum day 1) weight in the 80 mg/kg/day group were also reduced. The NOAEL for the F₁ generation rats was 40 mg/kg/day based on reduced body weights (pre-mating period) for males and reduced body weight gains (gestation period) for females in the 80 mg/kg/day group.

D. Range-Finding Segment II Study in Rabbits (TR#7224-92-078)

a. Methods: Lot#INV.R2895. Five Dutch-belted pregnant rabbits/group were given pioglitazone orally at doses of 0, 5, 40, 100 or 400 mg/kg/day on gestation days 6 through 18. All does were sacrificed on gestation day 28. Plasma samples were collected from two does per group on gestation days 6, 12 and 18.

b. Results: Mortalities occurred in the control and two highest dose groups. One control rabbit died on gestation day 15, one 100 mg/kg/day rabbit died on gestation day 8 due to a dosing error, and all high-dose rabbits died within one to three days of dosing. Thus, the sponsor reduced the top dose from 400 to 160 mg/kg/day in subsequent segment II study as presented under item E.

At necropsy, one control animal had pitted kidneys and the control animal that died had tan fluid in the intestines, the 100 mg/kg/day doe that died exhibited fluid in the thoracic cavities and discolored lung lobes, and two high-dose does exhibited reddened stomach mucosa and distended stomachs. Cesarean section revealed no effect on the numbers of resorptions, corpora lutea, implantations, and live or dead fetuses. No malformations occurred.

Plasma concentrations of AD-4833, M-II, M-III and M-IV increased with increasing dose, but in a less than proportional manner. Concentrations of the parent drug decreased from gestation day 6 to day 12, with a further decrease on day 18. An increase in

metabolite levels was not noted during this time. It appears that the NOAEL for maternal and developmental toxicity might be near 40 mg/kg/ day.

E. Segment II Teratology Study in Rabbits (TR7224-93-021)

a. Methods: Lot# INV.R3286. Fifteen to 18 Dutch-belted female rabbit were given pioglitazone orally by gastric intubation on days 6 through 18 of gestation at doses of 0, 40, 80 and 160 mg/kg/day. The does were sacrificed on gestation day 28 for cesarean section examinations.

b. Results: Drug administration resulted in slight maternal toxicity in the mid- and high-dose groups as evidenced by increased incidences of toxicological signs (slight weight loss, scant feces and not eating), which occurred mostly during the treatment period. Some of the findings are documented in a table below. One doe in the high-dose group (doe 73) died on gestation day 26; the cause of death could not be determined for this animal.

The drug was slightly embryotoxic (increased post-implantation loss) at 160 mg/kg/day, a dose that also produced maternal toxicity as shown in a table below. AD-4833 and four of its metabolites were found in circulating sera following oral administration. The levels of AD-4833 increased with dose, as did the four quantitated metabolites and the total quantifiable drug-related material. Although the levels of AD-4833 and three of its metabolites (M-II, M-III, and M-IV) decreased on day 13 of dosing (day 18 of gestation), relative to the first day of dosing, the serum level of the other quantitated metabolite (M-V) increased; thus, the average total steady-state concentration of the analytes was approximately the same on both days.

Observations or Major Findings	Pioglitazone(free base) Dose in mg/kg/day			
	0	40	80	160
Body Weight(g) on Gestation Day 15	3293	3244	3283	3073
Weight Change(%) from Control@	0	-2	0	-6
Not Eating(Mean # of Days)	2.0	1.8	2.9	7.1
Scant Feces(Mean # of Days)	2.7	1.0	4.8	5.8
No. of Does Inseminated	19	19	19	19
No. of Litters	17	17	16	11
Mean No. of Implantations per Doe	7.2	6.8	7.6	6.8
Mean No. of Live Fetuses	6.6	5.9	6.4	4.6
Mean No. of Early Resorptions per Doe	0.4	0.7	1.0	1.5
Mean No. of Early and Late Resorption	0.6	0.9	1.2	2.2*
Postimplantational Loss(%)	8.9	13.1	15.5	32.5*

*Statistically significantly different from the control group, $p < 0.05$. @The data were based on findings on gestation day 15.

c. Conclusion: The segment II teratology study indicates that female Dutch-belted rabbits dosed orally on days 6 to 18 of gestation had mild signs of maternal toxicity at 80

and 160 mg/kg/day. The no-observed-adverse-effect-level for maternal toxicity was 40 mg/kg/day. Slight embryotoxicity was observed at 160 mg/kg/day, a dose that also produced maternal toxicity. Thus, the doses were appropriate and experimental procedures were carried out under valid conditions.

F. Segment III Peri-Postnatal Study I in Rats (TR7224-93-012)

a. Methods: Lot# INV.R2895. Pioglitazone was given orally by gastric intubation at dosage levels of 0, 10, 20 and 40 mg/kg/day to groups of 24 female Crl:CD[BR] (Sprague-Dawley) rats. The rats arrived timed-pregnant (gestation day 0) and were treated on gestation day 15 through postpartum day 21 (weaning); they were killed after F₁ weaning. F₁ rats were evaluated for functional development and reproductive ability.

b. Results: In adult F₀ female Crl:CD[BR] rats the test article did not produce overt clinical toxicity or gross lesions (F₀ dams and F₁ pups). However, F₀ maternal body weight gain during gestation and lactation was increased in all dose groups. The increases in body weight gain occurred, with or without corresponding increases in food consumption. Maternal exposure to AD-4833(HCl) at all dose levels resulted in reduced pup body weight throughout lactation and maturation, which led to delays in anatomical and functional (behavioral) development. Also, there was a slight decrease in pup survival over the first 24 hours postpartum in the high-dose group only. Because administration of AD-4833(HCl) at the three dose levels tested resulted in a general increase in F₀ maternal body weight (gestation and postpartum), increased food consumption during gestation and decreased postpartum food consumption and adversely affected F₁ body weight (decreased) and functional (behavioral) development (delayed), a no-observed adverse effect level in the rat for F₀ maternal and F₁ developmental toxicity could not be established. However, the dose selection was valid since the mid and high doses increased F₀ cardiac weight significantly (P<0.01) from the control by 116% and 115%, respectively.

c. Conclusion: AD-4833 treatment of pregnant Sprague-Dawley rats from gestation day 15 through postpartum day 21 at levels of 0, 10, 20 and 40 mg/kg/day resulted in maternal effects (body weight gain with and without increased food consumption). Pups from dams of all dose groups had reduced body weight and delayed functional (behavioral) development. Pups from dams in the high-dose group had slightly decreased survival for the first 24 hours postpartum. AD-4833(HCl) treatment did not adversely affect F₀ or F₁ reproductive performance. A NOAEL for F₀ maternal and F₁ developmental toxicity could not be established in this study. It is possible that AD-4833(HCl) affected milk production and/or the makeup of the milk.

G. Segment III Peri-Postnatal Study II in Rats (Protocol#520-002)

a. Methods: Lot# INV R4209. Pioglitazone was administered orally to Crl:CDBR VAF/Plus female rats (n = 25/group) at doses of 0, 0.3, 1, 3, and 10 mg/kg/day.

Treatment for the F_0 females began on gestation day 15 and continued through postpartum day 22. Adult males were not treated. On day 4 postpartum, each litter was culled to eight pups. Weaning occurred on day 22 postpartum at which time 25 males and 25 females from each treatment group were selected. On day 90, these F_1 animals were mated. The males were sacrificed immediately following the cohabitation period and the females were sacrificed on gestation day 20.

b. Results: For the F_0 females, no deaths occurred and no treatment effects were reported for clinical signs, body weight, body weight gain, gross lesions, and absolute and relative (to body weight) heart weights. Absolute and relative food consumption was statistically significantly increased on gestation days 15 to 20 in the F_0 females treated with 3 and 10 mg/kg/day. High-dose dams experienced an increased percentage of dams with stillborn pups. An increased average number of stillborn pups per litter and a statistically significant increase in the percentage of still born pups, although these effects were not determined to be treatment-related for several reasons. In the high-dose group, pup weight was decreased throughout lactation reaching statistical significance on days 14 and 22 postpartum. No effects were noted on duration of gestation, gestation index, duration of delivery per pup, or the average number of implantation sites per delivered litter. The live birth index, sex ratio, weaning index, surviving pups per litter, percent male pups and mean live litter size were also not affected.

Clinical and necropsy findings in the pups were not related to AD-4833(HCl) treatment and no effect was noted on reflex or physical development (surface righting, pinna unfolding, eye opening, acoustic startle, air righting, pupil constriction).

In the F_1 offspring, no treatment-related deaths, clinical signs, necropsy findings or changes in sexual maturation were reported. No effects were noted on terminal body weight, absolute individual testes or epididymides weights and the ratio of these organ weights to body weight in the F_1 males. High-dose males and females exhibited a statistically significant reduction in body weight up to postweaning days 50 and 15, respectively. In addition, body weight gain was statistically significantly reduced for the high-dose F_1 males through postweaning day 29. The body weight effect corresponded to a statistically significant reduction in absolute food consumption in the high-dose F_1 males up to postweaning day 22. A related finding was the statistically significant increase in relative food consumption in high-dose F_1 males between 22 and 71 days postweaning and in high-dose F_1 females between 15 and 22 days postweaning.

Behavioral examinations conducted in the F_1 postweaning rats revealed no adverse treatment effect on learning, short-term retention, long-term retention or response inhibition. Additionally, mating and fertility parameters (average number of days of cohabitation, number of rats mated, fertility index, or number of pregnancies per rats that cohabited) in the F_1 offspring were not affected by maternal doses of AD-4833(HCl) as high as 10 mg/kg/day.

Of 25 F_1 females mated per group, the pregnancy incidences were 24, 25, 23, 24 and 25 at respective F_0 maternal doses of 0, 0.3, 1, 3 and 10 mg/kg/day. Cesarean section did not

reveal any treatment-related changes in litter averages for corpora lutea, implantations, live litter sizes, resorptions, fetal body weights, fetal sex ratios or the number of dams with resorptions. No gross external fetal alterations were observed.

c. Conclusion: F₀ maternal NOEL might be 1 mg/kg/day (based on increased food consumption at the higher doses). In the offspring, reduced body weight occurred at 10 mg/kg/day during the lactation and postweaning periods. However, it is not clear whether this effect arose secondary to the therapeutic effects of pioglitazone or whether it was directly related to AD-4833(HCl) toxicological actions. Because of this, a NOEL was not unequivocally identified for the offspring, but the value was at least 3 mg/kg/day. In addition, it appears that the top dose might be too low to evaluate the peri-Postnatal actions of the drug since the dose did not produce any notable toxic signs in F₀.

H. Overall Summary of Pioglitazone Effects on Reproductive System

In rats, pioglitazone had no remarkable effects on parental fertility at the top dose of 40 mg/kg/day, although the dose increased cardiac weight by 15%. The dose represents a multiple of approximately 9 times of the maximum recommended human oral dose of 45 mg based on mg/m². But, the drug was embryotoxic at the dose since it increased postimplantation losses and reduced fetal body weights.

The teratologic effects of pioglitazone were evaluated in rabbits at doses of 40, 80 and 160 mg/kg/day. Two high doses produced some toxic signs such as not eating and weight losses in does. The top dose (9 multiples of the maximum recommended human dose) increased postimplantation loss as the case of rat studies. Pioglitazone effects on peri-postnatal development were studied in rat at doses of 10, 20 and 40 mg/kg/day. There was no overt clinical toxicity in F₀ dams, except a slight increase in body weight. Maternal drug exposure also resulted in reduced pup body weight, which led to delays in physical and behavioral development.

6. GENETIC TOXICITY STUDIES

A. Bacterial Mutagenicity Studies (Study#45/MH)

a. Methods: Pioglitazone was dissolved in DMSO and tested in the plate incorporation assay with a 20-minute liquid preincubation step using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain WP2uvrA at doses of 156, 313, 625, 1250, 2500 and 5000 µg/plate with or without metabolic activation. Pioglitazone was also tested for induction of reverse mutations in the plate incorporation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 at doses of 250, 500, 1000 and 2000 µg/plate.

b. Results: These two tests showed no evidence of bacterial mutagenicity, either in the presence or absence of rat liver S9 metabolic activation system. The positive controls

showed expected levels of mutagenicity. In the bacterial mutagenicity assay using *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 and *E. coli* strain WPuvrA, Metabolites M-I and M-IV showed no mutagenic activity either in the presence or absence of S9 mix. The mutagenicity of Metabolite-V and Metabolite-VI was examined in an Ames test. *S. typhimurium* strains TA98, TA100, TA1535 and TA37 and *E. coli* strain WP2uvrA were used with or without metabolic activation, of which results found that the metabolites were not mutagenic at concentrations of 250, 500, 1000 and 2000 µg/plate.

B. Mammalian Cell Forward Mutation (CHO/HPRT and AS52/XPRT) In this study the sponsor changed pioglitazone lot#(A)1185-TGS-65 to Lot#11885-TGS-65 due to inadvertent error(Document#PN661,T-62)

a. Methods: Dose levels for the definitive mutation assays were chosen on the basis of range-finding experiments using 0.167, 0.500, 1.67, 5.00, 16.7, 50.0, 167, and 5000 µg/mL with and without metabolic (S9) activation. The limit of solubility of pioglitazone was exceeded above 167 µg/mL, and cytotoxicity was noted in both cell lines in the absence of S9. Based on the results of this cytotoxicity prescreen, doses of 25.0, 50.0, 75.0, 100, 200, 300, 400 and 500 µg/mL with S9, and 25.0, 50.0, 75.0, 100, 125, 150, 175 and 200 µg/mL without S9 were evaluated in the mutation assay in each cell line.

b. Results: There were no dose-dependent or statistically significant increases in the average mutant frequencies of either cell line due to treatment with pioglitazone. This conclusion was true whether S9 was used or not. The positive, vehicle and untreated controls performed as expected. Therefore, AD-4833 was judged to be nonmutagenic in both the CHO/HPRT and the AS52/XPRT mammalian cell forward gene mutation assays.

C. Mammalian Forward Mutation (L5178Y/TK) Assays (T-63) This study was conducted by [REDACTED]

a. Methods: Pioglitazone was evaluated for its ability to induce forward mutations at the thymidine kinase (TK) locus in cultured mouse lymphoma L5178Y cells. Based upon the results of cytotoxicity prescreen, two independent assays were performed. In the first experiments concentrations of 25, 50, 100 and 200 µg/mL, and in the second experiment concentrations of 25, 50, 100, 200 and 300 µg/mL were evaluated in the presence and absence of S9.

b. Results: In mouse lymphoma assays, metabolite M-I produced a positive response in the presence of metabolic activation and an equivocal response in the absence of metabolic activation. Metabolite M-IV was considered negative in the assay at the limits of solubility, although an increase in mutant frequencies was seen in the presence of precipitated drug. Metabolite M-V was considered negative in this assay. Some of the positive responses occurred at concentrations that were also highly toxic to the cells and, thus, the positive responses must be viewed with caution. M-VI also produced a positive

response in the presence of metabolic activation and an equivocal response in the absence of metabolic activation.

D. In vitro Cytogenetic Test (T-68, T-69, T-70)

a. Methods: Chinese hamster lung cells (CHL) were exposed in vitro to AD-4833(HCl) for 24 or 48 hours in the absence of a rat liver S9 metabolic activation system and for 6 hours with or without S9. Treated metaphase cells were analyzed for chromosome aberrations at three successive doses set at two-fold intervals: from 0.02 to 0.313 mM in the 24- and 48-hour treatment groups and from 0.313 to 5 mM in the 6-hour treatment groups with or without S9. Dosage levels were determined on the basis of a previously conducted range-finding study.

b. Results: The frequency of cells with chromosomal aberrations did not increase significantly compared to the negative control at any dose tested in any treatment group, which suggests pioglitazone might not be mutagenic in this cytogenetic test. In a cytogenetics assay, however, metabolite M-I produced an increase in mutant frequencies.

E. Unscheduled DNA Synthesis (UDS) Assay (T-71)

a. Methods: Pioglitazone was evaluated in an unscheduled DNA (UDS) assay, which measures DNA repair following chemically-induced DNA damage. Two experiments were conducted, each using rat primary hepatocyte cultures prepared by collagenase perfusion of the liver from a male Fischer-344 rat. For each dose, triplicate cultures were treated in the presence of [³H]-thymidine for 19-20 hours. Treatment conditions were 24- and 48-hour treatment without S9 mix, which were followed by 6-hour pulse treatment with/out S9 mix. The cultures were fixed, washed, mounted on microscope slides and evaluated for UDS by autoradiography. In the preliminary experiment, cultures were treated with 0.01, 0.05, 0.1, 0.5, 1, 5, 10, 25, 50 and 100 µg/mL AD-4833. Slides were evaluated for UDS at 1, 5, 10, 25, 50 and 100 µg/mL. In the replicate experiment, cultures were treated at 1, 5, 10, 25, 50 and 100 µg/mL and the slides were evaluated for UDS.

b. Results: Pioglitazone did not induce a significant increase in UDS over the solvent control. In each experiment, positive, solvent and untreated controls were used and each performed as expected. AD-4833 was not a genotoxic agent under the conditions of this in vitro rat hepatocyte DNA repair assay.

F. Micronucleus Test (T-72)

a. Methods: Pioglitazone was evaluated to determine its ability to induce the formation of micronucleated polychromatic erythrocytes in the bone marrow of treated animals. It was administered via a single intraperitoneal injection to CD-1 mice in a range-finding study involving two males and two females per group at doses of 250, 500, 750, 1000, 1250, 2500 and 5000 mg/kg of body weight. On the basis of the range-finding study, the doses chosen for the definitive micronucleus test were 1250, 2500 and 5000 mg/kg. Five

males and five females were treated for each dose group. Slides were prepared from the bone marrow cells collected at 30, 48 and 72 hours post-dose and scored blind. One thousand polychromatic erythrocytes per animal were scored for the presence of micronuclei.

b. Results: There were no statistically significant increases in the number of micronuclei in polychromatic erythrocytes at any dose due to treatment with AD-4833. The positive and negative controls performed as expected. Therefore, AD-4833 was judged to be nonmutagenic under the conditions of the assay.

7. CARCINOGENICITY STUDIES

A. 104-Week Oral (Gavage) Carcinogenicity Studies of pioglitazone in Mice(Study#295-153). [REDACTED] in Japan under GLP conducted this study.

a. Methods: Male and female Crl:CD-1.VAF/plus mice(60/sex/group) were given either vehicle, placebo(suspension) or pioglitazone(Upjohn preparation) at doses of 3, 10, 30 or 100 mg/kg/day for 104 weeks. An additional satellite group (20/sex/group) was also included for plasma analysis at 6, 12, 18 and 24 months.

The doses were selected in this study based on available data obtained from a 13-week oral gavage study in mice. In the study pioglitazone granulated formulation were administered at doses of 0, 3.2 10, 32, 100 and 320 mg/kg/day. There were increased heart weight in males at 100 mg/kg/day and in females at 320 mg/kg/day. Additionally 4 males out of 10 and 6 females out of 10, in the 320 mg/kg/day group died or were euthanized in extremis. Based on these data, the highest dose was set at 100 mg/kg/day and lower doses were selected using a geometric factor of 3.

b. Results: Mortality:

In males mortality was increased in the high dose group(See the table below), near the end of the study. Losses in the female in the high dose group also exceeded those in other groups, although % mortality in the vehicle group was about the same to the top dose group. It is not clear the reason why the mortality appeared low in the placebo and 10 mg/kg/day groups in males.

Mortality (%) in 2-Year Carcinogenicity Study with Pioglitazone in Mice						
Sex	Vehicle	Placebo	3 mg/kg	10 mg/kg	30 mg/kg	100 mg/kg
Male	56.7	45.0	58.3	45.0	53.3	71.7
Female	68.3	63.3	60.0	48.3	56.7	65.0

Values are % of cumulative mortality at Week 104 and the drug dose was in mg/kg/day.

Clinical Signs: The test article was associated with an increase in the percentage of male animals that had body surface staining from Week 14 in the high dose group. The staining was apparent till the terminal of the study. Females did not develop the incidence

of such body surface staining. The test article had no apparent effect on the incidence, location or total numbers of palpable masses.

Body Weights: The mean body weights of the male group were 26-27 g, while those of the female group were 21-22 g. In the treated male groups, small but significantly decreased mean body weights, compared with vehicle and/or placebo group. However, there were no clear drug dose-dependent changes in the parameter as shown below.

Pioglitazone Dose	Male Group			Female Group		
	Mean*	A	B	Mean*	A	B
Vehicle	36	NA	-2.7	33	NA	0.0
Placebo	37	2.8	NA	33	0	NA
3 mg/kg/day	36	0	-2.7	34	3.0	3.0
10 mg/kg/day	34	-5.6	-8.1	32	-3.0	-3.0
30 mg/kg/day	36	0	-2.7	34	3.0	3.0
100 mg/kg/day	36	0	-2.7	32	-3.0	-3.0

*indicate mean body weight in grams in Week 104. A and B indicate % difference from vehicle and placebo, respectively. NA stands for not applicable.

Food Consumption: Pioglitazone was associated with significantly decreased mean food consumption in the high dose group females. In males, the parameter was not clearly affected by the test article and the effect of the drug on the parameter appeared not significant since there were no drug dose-dependency. In addition, the data are scattered widely due to biological variation as shown below.

Pioglitazone Dose	Male Group			Female Group		
	Mean*	A	B	Mean*	A	B
Vehicle	144.0	NA	1.2	175.7	NA	1.2
Placebo	142.3	0.07	NA	173.6	-1.2	NA
3 mg/kg/day	144.1	0.07	1.3	168.9	-3.9	-2.9
10 mg/kg/day	145.8	1.3	2.5	174.4	-0.7	0.5
30 mg/kg/day	144.3	0.2	1.4	174.8	-0.5	0.7
100 mg/kg/day	143.0	-0.7	0.5	168.2	-4.3	-3.1

*indicate mean food consumption in grams/kg/day in Week 104. A and B indicate % difference from vehicle and placebo, respectively. NA stands for not applicable

Hematology: There were no apparent test article-related alterations in hematological parameters.

Organ Weights: There were significant increases in the mean absolute heart weights in the 30 and 100 mg/kg/day males and females. The mean relative heart/body weight ratios were also increased in these groups, which appeared to be test article-related.

Microscopic Pathology: Test article-related microscopic changes were observed in the brown adipose tissue of all treated groups of male and female mice, which were characterized by cytoplasmic vacuolization and/or fibrosis in both sexes. The brown adipose tissue lesion of vacuolization was diagnosed as steatopathy. The incidence of pertinent brown fat lesions is shown below.

Dose	Vehicle		Placebo		3 mg*		10 mg		30 mg		100 mg	
	M	F	M	F	M	F	M	F	M	F	M	F
Mice	60	60	60	60	60	60	60	60	60	60	60	60
Steatopathy	12	6	21	7	34	30	46	35	50	43	55	58
Fibrosis			2		3	1	3	1	15	9	20	27

*The unit of pioglitazone dose was in mg/kg/day.

Femoral and sternal bone marrows of treated animals were infiltrated with fats, which consisted of varying degrees of vacuolization within the marrow cavity that displaced or compressed the existing marrow. The vacuoles were spherical, clear and were the approximate size of normal fat vacuoles observed in inactive bone marrow. The incidence of fatty infiltration in the marrow is shown below.

Dose	Vehicle		Placebo		3 mg*		10 mg		30 mg		100 mg	
	M	F	M	F	M	F	M	F	M	F	M	F
Mice	60	60	60	60	60	60	60	60	60	60	60	60
Femur	1	5	2	6	12	9	27	17	31	22	43	37
Sternum					1		12	5	21	14	40	32

*The unit of pioglitazone dose was in mg/kg/day.

The incidence of myocardial lesions appeared to be increased by the test article because there was a significant increase in mean heart weights of male and female mice in the mid and high dose groups as shown below. Microscopically, the increased weight was correlated with multifocal inflammatory cell infiltration, multifocal myocardial fibrosis and perivascular inflammatory cell infiltration around the coronary arteries.

Dose	Vehicle		Placebo		3 mg*		10 mg		30 mg		100 mg	
	M	F	M	F	M	F	M	F	M	F	M	F
Mice	60	60	60	60	60	60	60	60	60	60	60	60
Heart	11	6	9	7	25	15	19	18	25	19	20	11

*The unit of pioglitazone dose was in mg/kg/day.

In liver, pigment deposition and hepatocellular hypertrophy were noted, which consisted of a fine, granular, brown pigment located in the cytoplasm of some centrilobular hepatocytes. Brown pigment was observed in both males and females. The

hepatocellular hypertrophy or enlargement of hepatocytes was observed in treated males from the mid and high dose group males and females from the high dose group as documented below.

Dose	Vehicle		Placebo		3 mg*		10 mg		30 mg		100 mg	
	M	F	M	F	M	F	M	F	M	F	M	F
Mice	60	60	60	60	60	60	60	60	60	60	60	60
Pigment*							1		1	2	14	6
Hypertrop*									2		9	2

*The unit of pioglitazone dose was in mg/kg/day. * indicate brown pigmentation and hepatocellular hypertrophy.

In the lungs, an increased incidence of congestion and foreign material was noted in the high dose animals, particularly in the females. In both sexes, congestion was only seen in died on study animals, which might be agonal change or due to gavage injury.

Neoplastic Lesions: Various tissues of control and treated groups had usual types of mouse tumors. Peto analysis of neoplastic lesions present in this study revealed 2 tumor types that were significant ($P < 0.05$). In males, benign pheochromocytoma of the adrenal medulla and in females, leiomyosarcoma of the uterine cervix were statistically significant by both the Peto test and the Cochran Armitage trend test. The incidence of the two tumors is illustrated in a table below.

Dose	Vehicle		Placebo		3 mg*		10 mg		30 mg		100 mg	
	M	F	M	F	M	F	M	F	M	F	M	F
Mice	60	60	60	60	60	60	60	60	60	60	60	60
Pheochro*	0		0		0		0		2		1	
Leiomyos*		0		0		0		0		1		1

*The unit of pioglitazone dose was in mg/kg/day. * indicate pheochromocytoma and leiomyosarcoma, respectively.

Summary and Conclusions: Various toxicological responses to pioglitazone were manifested during the 2-year Carcinogenicity studies in mice. These effects included: increased mortality (100 mg/kg/day); increased mean absolute heart weight and relative (to body weight) heart weight (30 and 100 mg/kg/day); enlarged brown adipose tissue (10 mg/kg/day and higher); increased body staining in males (30 and 100 mg/kg/day); and decreased mean food consumption in females (100 mg/kg/day). Histopathological evaluation revealed brown tissue steatopathy, fatty infiltration of bone marrow, and cardiomyopathy at all doses, and hepatocellular hypertrophy in males at 30 and 100 mg/kg/day. Cardiomyopathy consisted of multifocal inflammatory cell infiltration, multifocal myocardial fibrosis and perivascular inflammatory cell infiltration. For mice, the no-observed-effect level (NOEL) was 3 mg/kg/day. Statistically significant increase in the incidence of two tumors was noted. They were benign pheochromocytoma of the

adrenal medulla in males and, in females, leiomyosarcoma of the uterine cervix. The findings were based on statistical analysis of paired points.

B. 104-Week Oral (Gavage) Carcinogenicity Study of Pioglitazone in Rats(Study#295-152). [REDACTED], in Japan conducted the study under GLP condition.

a. Methods: Male and female Sprague-Dawley (CrI:CD) rats(60/sex/group) were given orally either vehicle, placebo or pioglitazone at doses of 1, 4, 8 (male), 16 or 63 mg/kg/day for 104 weeks. An additional satellite group (20/sex/group) was also included for plasma analysis at 6, 12, 18 and 24 months for analysis of drug metabolite concentrations.

Selection of Dose and Dose Justification in Rats: The dosage levels utilized in this study were selected on the basis of a previous one year oral gavage study in which rats were treated with pioglitazone granulated formulation at 0, 4, 16, 63 and 160 mg/kg/day. There were increased heart weights in males at 4 mg/kg or higher and in females at 63 and 160 mg/kg or higher. In addition, there were findings of thoracic cavity fluid, bilateral atrial hypertrophy and increased lung weights in males at 16 mg/kg or higher and in females at 63 and 160 mg/kg. Mortality was noted in males at 63 and 160 mg/kg and in females at the top dose. On the basis of the data above, the highest dosage level was set at 63 mg/kg/day. Lower doses were selected using a geometric factor of 4.

Results: Mortality: There was a decrease in survival in the high dose group animals of both sexes. But, the percentage of deaths in females in the high dose group did not reach statistical significance and there was no apparent drug dose-response relationship in the parameter as shown below.

Dose	Control	Placebo	1 mg	4 mg	8 mg	16 mg	63 mg
Male	45	60	40	60	62	63	92
Female	45	52	38	45		65	60

*The unit of the drug dose was in mg/kg/day and mortality was expressed in % death out of 60 animals in each cell.

Clinical Signs: The test article was associated with an increase in the percentage of rats that had body surface staining in the 66 through 104 week intervals in 8 and 63 mg/kg/day male groups. The incidence of rales was noted in the high dose group females during week 66 through 104 weeks. An increased incidence of plantar ulcers in all treated females and in the 8, 16 and 63 mg/kg/day males were also noted. All of the other clinical signs found were commonly observed in aging caged rats, which might not be related to the drug treatment.

Body Weights: In almost all animals, pioglitazone increased mean body weights prior to week 70 for both sexes. Toward the end of the studies the parameter was reduced in all

the animals in the high dose group as shown below. However, the reduction in body weight was under 10% of initial body weight for both sexes.

Dose(mg/ kg/day)	Male Rat Body Weight			Female Rat Body Weight		
	Grams	A	B	Grams	A	B
Vehicle	630	NA	-0.2	447	NA	-0.2
Placebo	631	0.2	NA	448	0.2	NA
1	678	7.6	7.4	457	2.2	2.0
4	668	6.0	5.9	455	1.8	1.6
8	640	1.6	1.4	NA	NA	NA
16	658	4.4	4.3	491	9.8	9.6
63	591	-6.2	-6.3	441	-1.3	-1.6

*NA stands for not applicable and A and B indicate % difference from the vehicle and placebo, respectively.

Food Consumption:

Pioglitazone elevated mean weekly food consumption values in the first weeks of study in most of the treated groups except the 1 mg/kg/day group males, which was also observed sporadically in later weeks.

Dose(mg/ kg/day)	Male Rat			Female Rat		
	g/kg/day	A	B	g/kg/day	A	B
Vehicle	47.5	NA	0.8	58.9	NA	1.2
Placebo	47.1	-0.8	NA	58.2	-1.2	NA
1	46.3	-2.5	-1.7	58.3	-1.0	0.2
4	47.0	-1.1	-0.2	58.5	-0.7	0.5
8	46.9	-1.3	-0.4	NA	NA	NA
16	46.8	-1.5	-0.6	59.0	0.2	1.4
63	46.8	-1.5	-0.6	60.4	2.5	3.8

*NA stands for not applicable and A and B indicate % difference from the vehicle and placebo, respectively

Macroscopic Findings: The brown adipose tissue showed enlargement with nodule formation at a dose of 4 mg/kg/day or higher. Cardiac tissues showed enlargement, distention or dilatation in some of mid dose groups and more animals in the high dose group males. In females, the incidence was somewhat lower.

In the urinary bladder there were nodules and occurrence of masses and thickening, which related to the drug treatment. The masses in bladder were more frequently observed in males than the females. Nodules were seen in the urinary bladder of males from the 4 and 16 mg/kg/day groups and in one female at the low dose group. Transitional cell tumors were noted in the mid and high dose group animals as described under microscopic findings.

The lung showed red discoloration in all rats including the control that died during the period of study. But the incidence was increased in the high dose groups. The red discoloration was microscopically found to be due to congestion often secondary to dosing accident. But, it is also possible that the higher incidence of red discoloration of the lung seen in the high dose rats might be either due to a higher mortality rate or secondary to cardiac involvement causing pulmonary congestion. The fluid seen with a slightly increased frequency in the thoracic, abdominal and pericardial cavities of treated rats was considered to be secondary to cardiac edema.

Ulceration of the foot was seen all groups including the control groups, but the incidence was slightly more in all treated groups of females and in the 8, 16 and 63 mg/kg/day males, of which reason was not clear. Other macroscopic changes were all considered to be of spontaneous or agonal origin.

Organ Weights: Organ weights that were recorded at necropsy indicate an elevation in cardiac weights in all treated groups except the low dose group animals. Additionally, the percentage ratio of heart weight over body weight was also increased in the two high doses as shown below. The increase in cardiac weight was attributed to the treatment-related hypertrophy seen microscopically.

Effects of Pioglitazone on Heart Weight in 2-Y Carcinogenicity Studies in Rats							
Group	Vehicle	Placebo	1 mg	4 mg	8 mg	16 mg	63 mg
Body Wt	630	619	683	685	653	660	581
Heart Wt	1.95	1.86	1.98	2.20*	2.38*	2.62*	2.60*
H/B x10	3.15	3.09	2.96	3.29	3.76	4.03*	4.47*

H/B(%) indicates heart weight/body weight x 1000. *P<0.05 compared to vehicle or placebo control. The unit of pioglitazone dose was in mg/kg/day.

Microscopic Findings: The changes involved the brown adipose tissue, femoral and sternal marrow, parotid salivary gland, glandular stomach, femoral and sternal bone, heart, urinary bladder, lung and foot. The fibrosis in the interscapular adipose tissue was pronounced in high dose group females, and was dose-dependent in both sexes. Fatty infiltration in bone marrow of femur and sternum and steatopathy were common in control groups as well as the drug-treated groups, but the incidences were apparently increased in the high dose groups. The changes seen in the bones were closure of the growth plate in the femur and increased width of the sternbrae.

The changes in the heart consisted of hypertrophy of the atrial musculature and thrombosis in the atrium, which were related to cardiac enlargement and distension. The hypertrophy was seen in all drug treated groups of males with increased incidence and severity with increasing dose. In females, the trend was similar, although the incidences were less pronounced in low dose groups. Thrombosis was seen in the control and treated groups of males, but showed a slightly higher incidence in the high dose group.

Test article-related lesions of the urinary bladder were epithelial hyperplasia and benign and malignant transitional cell tumors, which was related to macroscopic masses, nodules

and thickening of the urinary bladder. The nodular type was evident only in males in the 8 and 16 mg/kg/day groups, which were not confirmed in the high dose group as shown below. The combined incidence of all three types of hyperplasia was increased in males in the 8, 16 and 63 mg/kg/day groups. Benign and/or malignant transitional cell tumors were seen in the 4 mg/kg/day group and high dose groups of males.

Rat Urinary Bladder Lesions in 2-Y Carcinogenic Studies with Pioglitazone

Urinary Bladder Lesion	Incidence by Dose (mg/kg/day)						
	0 ^a	0 ^b	1	4	8	16	63
Males							
Hyperplasia, epithelial, papillary	3	0	1	2	1	1	1
Hyperplasia, epithelial, simple	1	3	0	2	7	10	7
Hyperplasia, epithelial, nodular	0	0	0	0	4	1	0
Carcinoma, transitional cell	0	0	0	2	3	5*	4
Transitional cell tumor, benign	0	0	0	0	4	2	2
Females							
Hyperplasia, epithelial, papillary	0	0	1	1	-	0	1
Hyperplasia, epithelial, simple	1	1	2	5	-	3	11
Transitional cell tumor, benign	0	0	1	1	-	1	0

^aVehicle, ^bPlacebo. *Two of the 5 animals also had benign transitional cell tumors, but are not included in the totals for transitional cell tumors.

In order to determine the relevance of the urinary bladder tumors, analyses of the calculi obtained in the rat carcinogenicity study revealed the primary components as calcium, magnesium, phosphate and protein. Pioglitazone and its metabolites were not present in the calculi, which suggests the drug and/or its metabolites are not responsible for the cause of the tumor. However, it has not been documented whether the drug or its metabolites facilitate the formation of the calculi.

A strong correlation was observed between the presence of calculi and proliferative lesions in the urothelium of the rats. Increased urinary pH, high osmolality and protein in rats might be favorable conditions for the formation of calculi. However, there was no clear evidence that the drug or its metabolites increased the pH, osmolality and amyloid deposits in rat bladder in drug dose-related manner. As a matter of fact, correlation between the incidence of the tumor and calculi is rather poor, although there was a positive association between transitional cell carcinoma and all combined parameters such as calculi, dystrophic calcifications, mineralization and corpora Amylacea. It has not been documented that the drug or its metabolites alter all of the parameters in drug dose-related fashion.

Summary and Conclusions of Rat Carcinogenicity Studies

Pioglitazone treatment increased mortality at 16 and 63 mg/kg/day, particularly in male rats. Body weight was slightly increased at all doses. Erythrocyte counts were decreased in males at 16 and 63 mg/kg/day and in females at 63 mg/kg/day. Hemoglobin and hematocrit in females at 63 mg/kg/day were also reduced. Brown fat was enlarged at 4 mg/kg/day and higher. Absolute heart weight was also increased in males at 4 mg/kg/day and above and in females at 16 and 63 mg/kg/day. The urinary bladder was thickened in males at all doses, and increased numbers of masses or nodules in the urinary bladder of males at 4 mg/kg/day and above. Urinary bladder lesions included papillary, nodular and simple epithelial hyperplasias in males at 8 mg/kg/day and above and in females at 63 mg/kg/day, and benign and/or malignant transitional cell tumors in males at 4 mg/kg/day and above.

Histopathological evaluations revealed steatopathy of the brown fat (all doses), fatty infiltration of the bone marrow, the parotid salivary gland and the glandular stomach (males at all doses and females at 16 and 63 mg/kg/day), ossification of the femoral epiphyseal plate (4 mg/kg/day and above), increased width of the sternbrae (males at 4 mg/kg/day and above and females at 63 mg/kg/day), atrial muscle hypertrophy (males at all doses and females at 16 and 63 mg/kg/day), and atrial thrombosis (males at 63 mg/kg/day).

It has been confirmed that the presence of urinary bladder calculi in some of the animals with urinary bladder tumors. The sponsor performed additional evaluations, which suggested that the tumors might be specific to the rat, not in the mouse and dogs. And the tumors might be related to the formation of urinary calculi, which contributed to the formation of epithelial tissue hyperplasia. However, there has been no investigation to test the possibility that pioglitazone or its metabolites influence the formation of urinary calculi in drug dose-related manner. It is also difficult to correlate the calculi quantity and the prevalency of the tumors in each group. Although the drug or its metabolites might not produce transitional urinary bladder tumors directly, they may play a role in the tumorigenesis processes indirectly by facilitating calculi in the bladder.

8. OVERALL SUMMARY AND CONCLUSION

Pharmacology and Toxicology: Pharmacology and pharmacodynamic studies indicate that thiazolidinediones produced antidiabetic effects by activating peroxisomal proliferator activated receptor gamma (PPAR γ). The precise underlying mechanism of the beneficial action of pioglitazone remains to be elucidated. Toxicological data indicate that the drug produced various toxicities such as left atrial thrombosis, hydrothorax, cardiohypertrophy and elevation of hepatic enzymes in different laboratory animals.

The fact that pioglitazone produced multiple toxicities might be related its ability to activate PPAR γ , which alters gene expression that dictates multiple molecular and

cellular processes. Pioglitazone increased cardiac weight in drug-treatment duration as well as dose dependently. Experimental evidence indicates that its effect on cardiac weight might not be due to its direct actions on cardiovascular system, but as an adaptive response to its effects on hemodynamic and water distribution. But, we really do not know its primary active site(s) and how it initiates the chain of reactions, which compel the reviewer to take due precaution. In particular, our currently available information does not permit one to predict the life-long exposure effects to the drug on any organ systems. The reviewer believes that we have to wait until we have some understanding of underlying fundamental mechanism(s) of such multiple toxic actions of the drug.

The target organs of the toxicities of pioglitazone are usually vital organs such as heart, liver and blood cell forming cells, although we have limited knowledge on the actions of the drug in other organs such as brain, bone marrow, and neural tissues. Particularly, the drug has very low margin of safety as the ratio of animal to clinical AUC values at the threshold doses for cardiac changes (Please see the table below) is usually around 10.

Species	Dose(mg/kg/day)	AUC(μ g.hr.ml)	AUC Ratio*
Mouse	30(C)	119.3	11.9
Rat	4(Male)	70.4	7.0
Dog	3(Male)	9.4	0.9
Monkey	8.9(C)	74.7	7.4

*Indicates animal to human AUC ratio. Clinical AUC=10 μ g.hr.ml after 30 mg dose; C and M stand for combined sexes and males, respectively.

Genotoxicity: Genotoxicity potential of pioglitazone appears to be negative in the tests of bacterial mutagenicity, mammalian cell forward mutation, chromosomal aberration, unscheduled DNA, mouse micronucleus tests. But the incidence of forward mutations at the thymidine kinase locus of mouse lymphoma L5178Y cells was increased significantly by pioglitazone metabolite MI in triplicate assays in the presence of S-9 mix. The results of assays with metabolite MVI in the absence of S-9 mix were equivocal but results in the presence of metabolite activation were weakly positive. Since MI is not found in humans and the weight of evidence suggests pioglitazone is not genotoxic, its actions in reference to the mouse lymphoma assay were deleted from the label.

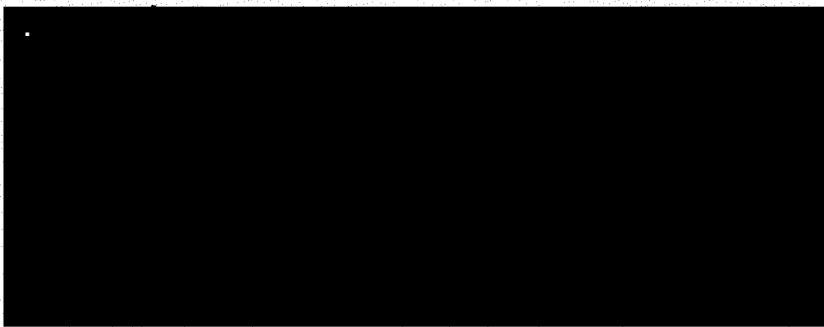
Carcinogenicity: Pioglitazone produced transitional epithelial carcinoma in rat bladder. The sponsor considers that was due to hyperproliferative effect induced by calcium or phosphate calculi which were found in rat bladders. However, there was no evidence that pioglitazone caused a dose-related change in the urine which would have induced differential development of calculi. In addition, it has not been documented that pioglitazone and its metabolites do not play clearly no role in the formation of calculi in the bladder.

Reprotoxicity: The drug was embryotoxic in rats at 40 mg/kg/day, as evidenced by increased postimplantation losses. Treatment-related fetotoxicity occurred at doses as low as 10 mg/kg/day since it reduced fetal body weights and crown-rump lengths.

Pioglitazone did delay F₁ development and delayed F₁ fertility as shown below. These findings should be documented in drug label with Pregnancy Category C.

Postpartum Day	0 mg/kg/day	10 mg/kg/day	20 mg/kg/day	40 mg/kg/day
0	6.3	5.8*	5.2*	5.1*
1	7.0	6.6	5.6*	5.7*
4	10.7	10.0	8.3*	7.8*
7	15.5	14.7	12.4*	11.3*
14	31.0	30.1	26.1*	23.1*
21	51.0	46.7*	41.6*	34.8*

*Indicate P<0.05.



10. RECOMMENDATION:

Pharmacology recommends to approve pioglitazone(NDA21-073) for the proposed indication.

11. Review Code: AP

cc: Original NDA, HFD-510, HFD-345
Ronald Steigerwalt/H. Rhee/J. Weber

/s/

Herman M. Rhee, Ph.D.
Pharmacologist

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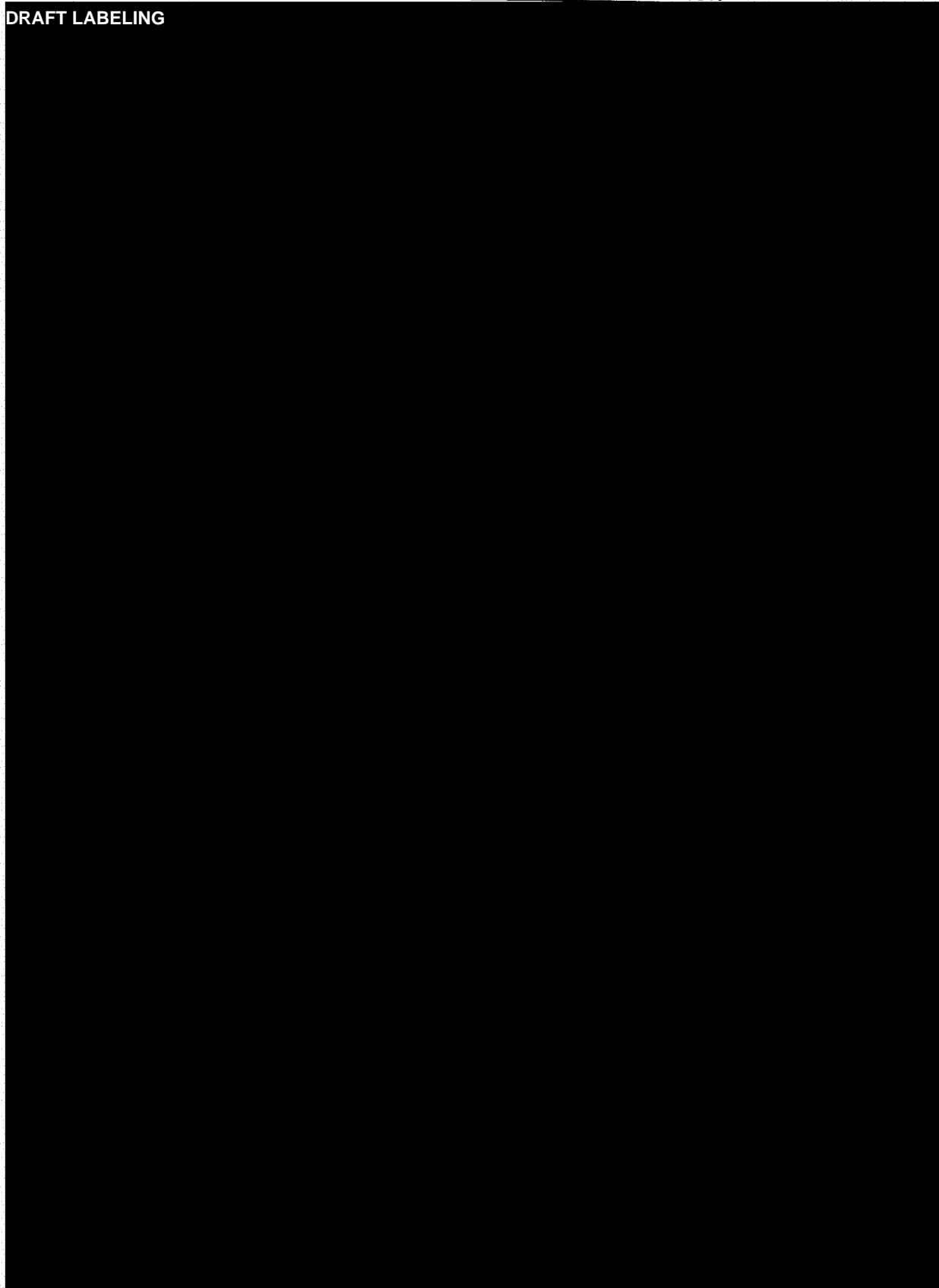
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*See team leader
memo to file*

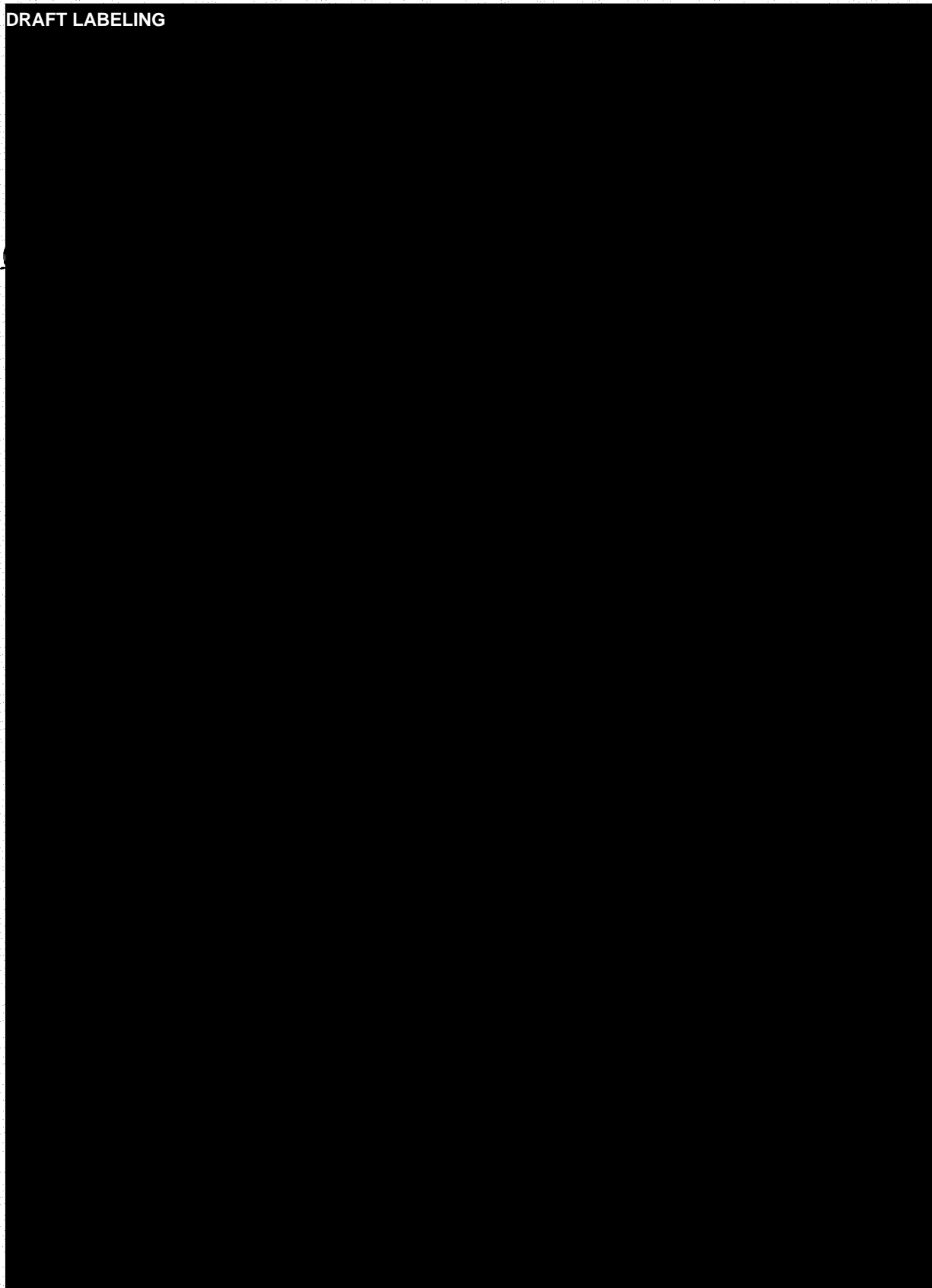
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COMMENTS ON PHARMACOLOGY & TOXICOLOGY LABEL SECTION

DRAFT LABELING



DRAFT LABELING



Left ventricle

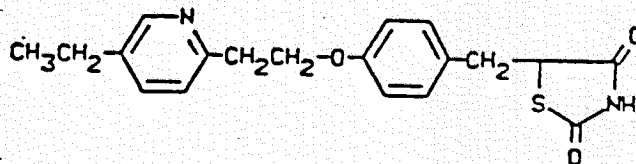
IND [REDACTED]

REVIEW & EVALUATION OF PHARMACOLOGY & TOXICOLOGY DATA
(Original Submission)

I. GENERAL INFORMATION

Date of Submission: 9-20-89Date of Receipt by CDER: 9-25-89Date Assigned to Reviewer: 9-27-89Sponsor: [REDACTED]Drug: Pioglitazone Hydrochloride [REDACTED]Chemical Name and Structure:

5-(4-2-(-ethyl-2-pyridinyl)ethoxy phenyl)-methyl)-2,4-thiazolidinedione HCl



• HCl

Category: Oral-antidiabeticRelated INDs: I [REDACTED]

[REDACTED]

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Proposed Clinical Studies: Initially a single dose tolerance and pharmacokinetic study will be conducted with male volunteers with placebo or pioglitazone hydrochloride [REDACTED] doses of 2, 6, 18, 30, 45, or 60 mg. The duration of the study for each individual volunteer is two weeks but the total study period will be approx. two months. A repeated dose tolerance and pharmacokinetic study will then be initiated with the same treatment regimen along with [REDACTED] 2, 6, 10, 15, or 20 mg TID for seven days. The duration of this study for each individual volunteer is three weeks and the estimated duration of the total study is four months. After completion of this study, a repeated dose efficacy study in otherwise healthy NIDDM (noninsulin dependent diabetes mellitus) volunteers will be undertaken.

II. PHARMACOLOGY

A. Pharmacology Studies Related to the Anti-Diabetic Potential:

1. Hypoglycemic Effects in Models of NIDDM:

Under this heading were reported the studies of dose-dependent hypoglycemic effects of [REDACTED] in laboratory animals (three strains of diabetic mice and Chinese hamsters) and of reducing triglycerides and free fatty acids in all animal species (including dogs) that were tested.

2. Improved Insulin Sensitivity Following Treatment:

Enhanced insulin sensitivity was shown in vivo in Wistar fatty rats in response to insulin injection. In euglycemic clamp studies, pioglitazone produced significant increase in insulin-stimulated glucose clearance and decrease in hepatic glucose production. Similarly there was an enhanced responsiveness of skeletal muscle to insulin in drug-treated KKA_y mice and in Zucker fatty rats. In beagle dogs, however, one week treatment with formulated drug at 0.30 mg/kg/d did not increase the response to a single intravenous injection of insulin (10 or 30 mU/kg).

3. Effects on Thyroid Hormones:

Reduction in plasma thyroid hormone (T₃ & T₄) levels occurred in ob/ob mice on a "cafeteria" diet alone and on drug plus control diet while this effect did not occur in animals given "cafeteria" diet plus drug (42 mg/kg/d) for 7 weeks. KKA_y mice (a crossbred from the obese yellow mouse with the insulin resistant black KK mouse; they are also obese, hyperinsulinemic, and insulin resistant like the ob/ob mouse but are more advantageous for screening since they remain hyperglycemic throughout their lifespan) treated with pioglitazone, however, showed no change or increases in thyroid hormone levels. Thus, the effects of pioglitazone on circulating thyroid hormone levels in mice are inconsistent and substantial variation occurs in the outcomes of different studies.

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B. Cardiovascular and Respiratory Effects:

No cardiovascular or respiratory changes were observed with single doses of pioglitazone intravenously up to 3 mg/kg in dogs or orally up to 10 mg/kg of formulated drug in dogs and cats. No difference of effect was seen between vehicle control and drug on pressor responses to bilateral carotid occlusion, phenylephrine, tyramine, dimethyl-phenyl-piperazinium, or angiotensin II. No difference was seen on depressor responses to acetylcholine, isoproterenol, or histamine.

C. CNS Pharmacology:

50 mg/kg of [REDACTED] given via i.p. to mice had no effect upon amphetamine toxicity, apomorphine cage climbing response, hypoxic stress assay, Bicuculin T.E. protection test, or evoked responses to yohimbine, oxotremorine or apomorphine. Likewise, Pioglitazone 300 mg/kg as a solution in citric acid given orally to rats had no effect upon body temperature, skeletal muscle coordination, or pentobarbital sleeping time. It was also reported that pioglitazone 1 uM applied to rat brain membranes did not affect the equilibrium binding to receptors of etorphine, spiroperidol, flunitrazepam, QNB, dihydroalprenolol, prazosin, clonidine, or LSD. In summary, no CNS activity and no CNS receptor binding were noticed with single doses of drug well above the expected therapeutic level of 0.03 - 0.1 mg/kg.

D. G.I. Physiology:

Pioglitazone was administered orally (in intact rats) or intraduodenally (in pylorus ligated rats). Compared to animals treated with vehicle only, there were no differences in intestinal transit time, volume of gastric juice, or acidity of gastric juice and there was no protection against ethanol-induced gastric injury.

E. Other Screening Data:

The IND contains a number of other studies by Upjohn which seem to be the result from a general screening assays for drug such as platelet aggregation; interleukin-1 and -2; cytotoxicity to T-cells, etc. and the results were all found to be inactive.

III. METABOLISM

The metabolism studies of pioglitazone [REDACTED] were conducted with either the acetate [REDACTED] or the HCl formulation [REDACTED].

I [REDACTED]
A. Absorption:

a. Rat: The bioavailability of [REDACTED] in 5% gum arabic suspension at 10 mg/kg was 53% relative to an oral solution containing citric acid. Plasma levels (AUC) increased linearly with increasing dose at the dosage range from 10 mg/kg to 100 mg/kg, while AUC at 300 mg/kg dose was markedly less than the value expected from the AUC at 100 mg/kg, suggesting that the oral absorption phase was close to saturation at doses higher than 100 mg/kg (Fig. 1). The AUCs of HCl forms [REDACTED] of drug administered at a dose of 10 mg/kg in 5% gum arabic were estimated to be 62% as compared with that of a solution of [REDACTED] in 0.3M citric acid and this analog did not show any apparent difference in availability over the range from 10 to 100 mg/kg. No absorption study was conducted via i.v. route due primarily to a very poor solubility of this drug.

b. Dog: Studies in beagle dog also showed that the addition of citric acid (up to 3 times the amount of the drug) enhanced drug bioavailability (72%; relative bioavail. = 56% compared to an oral solution formula = 39%) from tablets manufactured by either the wet granulation or direct compression methods while micronization of the drug had no or little effect on the bioavailability. The mean AUC, C_{max} (27.0 + 7.3 ug.hr/ml and 8.73 + 2.12 ug/ml, n = 8) for drug with citrate were 77% and 122% greater than the corresponding values of the drug without citrate (15.34 + 10.05 ug.hr/ml and 3.92 + 1.72 ug/ml, n = 8). The T_{max} for the former was, on an average, at one hour after administration while the latter was variable among dogs.

Another dog study where oral solutions of [REDACTED] were administered showed dose proportionality for the drug from 0.6 to 7 mg/kg (dose range from 10 to 100 mg). No apparent effect on T_{max} and $t_{1/2}$ was observed with increasing dose suggesting that the disposition of drug was independent of dose levels of up to 7 mg/kg (linear pharmacokinetics). The dose-normalized C_{max} and AUC values for [REDACTED] were within the range observed for [REDACTED].

Another report from the four-way crossover dose proportionality study in the dog using a [REDACTED] in citrate over the range of 5 to 75 mg/kg, the projected dose range to be used in toxicity studies, showed 1) the AUC values of drug increase proportionally over the dose range tested, 2) C_{max} show a similar trend toward dose proportionality, 3) other disposition profiles (T_{max} , k, $T_{1/2}$) were independent of dose, i.e. linear pharmacokinetics.

The terminal disposition phase of the parent drug was fairly uniform for the various formulations with a rate constant of 0.4-0.5 hr⁻¹ ($T_{1/2}$ = 1.4 to 1.7 hr.). Three metabolites of unknown structure were identified. The parent and M-1 did not appear to accumulate while M-2 and M-3 showed some accumulation. Dosing 1 hr prior to feeding gave an absorption and disposition profile similar to a fasted animal while dosing either with food or 1 hr after feeding caused a reduction (approx. 30%) in absorption and prolonged the absorption phase (T_{max} increase from 0.8-1.2 hr to 2-4 hr).

I [REDACTED]

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- c. Monkey: To determine the bioavailability of drug in monkeys, two female subjects received 10 mg/kg and two other females received 20 mg/kg of four different formulations, one each successive days for a total of 4 days. Assays of the serum levels of [REDACTED] disclosed that the drug in citric acid resulted in the highest serum levels in three of the four monkeys. In addition, a large degree of intersubject variability was present and no dose proportionality was observed when serum levels of low dose group were compared to those from high dose group. It was concluded from the findings that the monkey offers no improvement over the dog as the animal choice.
- B. Tissue Distribution: Distribution in body tissues is wide in the rat with highest concentrations in fat depots followed by other organs, liver and adrenal glands. No tissue distribution studies was made in dog or monkey.
- C. Metabolism: No detectable intact pioglitazone was found in urine or bile of rats and of dogs. The major metabolite in bile in both species was pioglitazone carboxylic acid and its taurine conjugate (rat only) followed by the monohydroxy isomers.
- D. Excretion: Excretion of radioactivity is almost complete via bile and recoveries of radioactive materials were very good both in rats (99%) and in dogs (96%). Almost all drug-related materials is cleared from systemic circulation within 24 hr after a single IV or PO dose.

IV. TOXICOLOGY

Most toxicology studies submitted in this application were conducted by the sponsor in compliance with the GLP requirements (CFR Title 21, Chapter 1, Parts 58, 312, 314) and compliance statements (CFR Title 21, Chapter 1, Subchapter D, Parts 312, 314) were included in the respective study reports. Toxicity studies of 4- and 13-week in rats and 4-week in dogs were conducted by [REDACTED].

As was the case in metabolism studies, the toxicity studies of pioglitazone [REDACTED] were also performed with either the acetate [REDACTED] or the HCl formulation [REDACTED].

A. Acute Toxicity:

Due to an extremely poor solubility of [REDACTED] death occurred from both i.v. (dose range from 18 to 54 mg/kg) and oral dosing (337 to 6596 mg/kg) of the [REDACTED] in citric acid and the vehicle control group alone prior to the presence of any acute toxic signs of drug. Signs of ataxia were however noted in most of the surviving animals from both groups due to acidosis from the excessive citric acid vehicle.

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Gross and histological examination confirmed that the animals died from gastric or gastrointestinal bloat as a result of excessive growth of bacteria which used citrate and produced excessive gas. Pathological evaluation also revealed no differences between animals received citrate alone and those with drug in citrate. Although the acute toxicity of [REDACTED] in rats and mice could not be defined in this study, the estimated LD₅₀ in CF1 mice via i.v. was between 22.5 and 27 mg/kg whereas in SD rats was between 27 and 45 mg/kg.

B. Repeated-Dose Toxicity:

1. Rat(Sprague-Dawley; Jcl:SD)

a. Four-Week Oral Toxicity (conducted [REDACTED])
[REDACTED] suspended in water containing 5% gum arabic, was dosed orally (gastric intubation) to rats (10/s/gp) once daily at doses of 0 (control), 100 (L), 300 (M), 1000 (H) mg/kg. From all parameters observed, there was an increased heart weight in the males from M-, H-dose groups and an increased amount of brown adipose tissue in the interscapular and mediastinal spaces of all dose groups. No other abnormalities were present in this study. It was thus concluded that oral treatment of U-72,107E at a dose as high as 1000 mg/kg/d for 4 consecutive weeks did not cause any adverse toxic effect in rats.

b. Thirteen-Week Oral Toxicity (conducted by [REDACTED])
[REDACTED] in a citrate-based [REDACTED] powder suspended in distilled water, was dosed orally to groups of 10 male and 10 female SD rats once daily at free base equivalent U-72,107 doses of 0 (distilled water), 0 (Vehicle), 30 (L), 100 (M), and 300 (H) mg/kg. The results showed that

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there were no treatment-related changes in BW, food intake, urinalysis and ophthalmological exams. Five animals died from suffocation during the study due to technical dosing errors. Hematological changes of anemia were noted from drug treatment in terms of a decreased RBC in both sexes of M- and H-dose groups, decreased Hct and Hb in female M- and H-dose gps, and an increased MCH in both sexes from H-dose gp.

Organ weight changes were also noted which included an increased heart wt in both sexes and an increased liver wts in females from M- and H-dose gps. There were dose-dependent increases in the amount of adipose tissue in interscapular and mediastinal spaces in all drug treated gps. Histologically, there was no significant lesion. The only lesion possibly related to drug treatment was splenic extramedullary hematopoiesis (SEH) which was considered by the sponsor to be most likely a compensatory response secondary to anemia.

It was concluded that a toxicological NOEL of U-72,107 free base equiv. was 30 mg/kg, although the sponsor did suspect that a potential effect on hematopoiesis of [REDACTED] was present at 30 mg/kg free base equiv. of U-72,107.

c. Thirteen-Week Oral Toxicity [REDACTED]

Two 13-week toxicity studies were conducted to investigate the potential toxicity of [REDACTED] in SD rats. [REDACTED] suspended in water having 5% gum arabic, was dosed orally to groups of 5 male and 5 female rats once daily at doses 0, 30, 100 and 300 mg/kg. No treatment effect was found in BW, food cons, organ wt, and ophthalmoscopic, hematological, serum biochemical, and histological exams. A dose-dependent increase in brown adipose tissue in interscapular and mediastinal spaces and in the subcutis was observed from the drug treated groups. It was concluded that oral treatment with [REDACTED] at dose as high as 300 mg/kg/d for 13 consecutive weeks did not cause any adverse toxic effect in rats.

2. Rabbit (NZW; Preliminary Eye Irritation Study)

[REDACTED] powder was sprinkled in the eyes of 1 male rabbit at a single dose of 100 mg per eye or at a dose of 20 mg per eye per day for 5 days. The right eye was rinsed with sterile water 30 seconds after each dosing while the left eye remained unrinsed. The rabbit was observed for 14 days. Slight conjunctival redness was noted in both eyes at 1 hr after dosing. Both eyes appeared normal for the remainder of the study. It was concluded that [REDACTED] was practically nonirritating to rabbit eyes.

Similarly, a preliminary dermal irritation study where [REDACTED] powder was moistened with sterile water and applied to two skin sites, intact and abraded, of 1 male rabbit at a single dose of 500 mg per site or at a dose of 100 mg per site per day for 5 consecutive days. No irritation occurred at either the intact or the abraded site.

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3. Dog (Beagle)a. Oral Range-Finding Study:

[REDACTED] in gelatin capsules was administered to beagle dogs (1/sex) at escalating doses, starting at 4 mg/kg/d and doubling daily to a maximum of 64 mg/kg/d. This dose was maintained for 10 days for a total of 14 days drug exposure. Observations included daily clinical exams as well as pre- and postdose hematology and serum chemistry determinations. Organ wts and complete gross observations were recorded at necropsy, and tissue specimens were taken for histologic exam. It was concluded from results that the drug was well tolerated at 64 mg/kg. Serum chemistry and histologic findings suggest the heart and liver were the target organs for this compound.

b. Two-Week Oral Toxicity Study:

4/s/dose were orally treated with [REDACTED] formulated in a citrate-based granulation and encapsulated in gelatin capsules for 14 days. The dogs received 75 mg/kg free base equivalents of [REDACTED] twice daily for a total dosage of 150 mg/kg. Clinical signs were unremarkable except for repeated episodes of vomiting after dosing when animals had been fasted prior to dosing. No gross or histological lesion was found to be directly attributed to [REDACTED] treatment, probably because of lack of drug absorption. It was concluded that drug administered a daily total dosage of 150 mg/kg had a potential to cause borderline anemia in dogs after 14 consecutive days of treatment.

c. Four-Week Oral Toxicity

[REDACTED] 3/sex/d at free base equivalent U-72,107 doses of 0, 1, 3, and 10 mg/kg. No treatment-related changes were observed in any parameters measured and it was thus concluded [REDACTED] free base equivalent as high as 10 mg/kg/d did not cause any adverse effect in dogs.

d. One-Month Oral Toxicity:

4/s/gp (4 gps) dosed orally with encapsulated [REDACTED] daily for 30-days at 0, 15, 45, and 150 mg/kg/d. No treatment-related changes were noted except for a signif. changes in serum albumin in 150 mg/kg groups. Since there had been no hepatic enzyme abnormalities or loss of BW, the exact pathogenesis of this observation could not be determined. No histologic lesions were found related to treatments; however, signif. decreases in splenic weight (both absolute and relative to BW) were noted in the females from all 3 treatment groups.

e. 90-Day Oral Toxicity:o Dosage

2/s/dose (2 gps) of 0, 10, 100 mg/kg/d. via oral with encapsulated U-72,107E.

o Results1. Observed signs

All dogs appeared normal throughout the dosing period.

2. Mortality

None

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3. Body Weight/Food Consumption (FC)

No significant dose related BW or FC responses .

4. Hematology /Bone Marrow

Decreased RBC, Hb, and Hct values for 3 of the 4 (one male, two female) in 100 mg/kg dose. This change was evident in days of 30 and 50 samples with RBC values ranging from 14.7 to 28.1% below day 1 levels.

Bone marrow from the right femur at study termination from a female dog in 100 mg/kg showed to be anemic. Microscopically the marrow was normal.

5. Serum Chemistry

At high dose, slight reductions in serum cholesterol noted for 3 of the four dogs; the lowest levels were noted on day 89 (approx. 50 mg/dl below pretest values). Slight elevated serum alanine transaminase (ALT) noted for 2 of the 4 on day 89. These dogs had pretest values of 29 to 36 u/l, the day 89 levels were 79 and 73 u/l.

6. Urinalysis

No dose related changes at termination.

7. Organ Weights

Slight increases noted in liver (both sexes) and heart (females only) weights as % necropsy body wts in both 10 and 100 mg/kg groups.

Testicular wts were low for one of the two 100 mg/kg dosed males.

8. Gross and Histology Observations

Slight to mild subacute hepatitis noted for 3 of the four 100 mg/kg dose group, bile stasis was noted for one of these dogs. Also, bilateral testicular degeneration was noted for one of the two male 100 mg/kg dose recipients.

f. Three-Month Oral Toxicity with 1-month Recovery:

o Drug Dosage

██████████ in a citrate-based ██████████ was administered orally for 90 (male) or 91 (female) days to beagle dogs. In addition to vehicle control (C), a daily dosage of 30 (L), 60 (M), and 150 (H) mg/kg free base of ██████████ was given. C consisted of 4 males and 4 females, and L, M, and H each consisted of 6 males and 6 females. In all groups, one half of the total daily dosage was administered in the a.m. and the other half in the p.m. approx. eight hours later.

o Results

1. Observed signs

Clinical signs associated with drug treatment included vomiting, diarrhea and soft stool, anemia manifested as a pale oral mucosa and abdominal distension. The frequency appeared dose-dependent.

2. Body Weight/Food Consumption (FC)/Water Consumption (WC)

No effect on appearance, BW, or FC was observed. Males in L, M groups, and females in M had a statistically signif. increase ($P < .01$) on some days during the studies in comparison with control. These findings were however considered incidental.

3. Ophthalmic Exams

No treatment effect

4. Laboratory tests

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- o Hematology: A signif. ($P < .01$) reduction of Hct, Hb and RBC in all gps on days 30, 58 and 90 when compared to control and these decrease was dose-dependent. The changes in erythrocyte indicated a severe dose-related anemia and the type of which was normocytic and normochromic.
- o Serum Chemistry
A reduction of serum albumin and total protein in all groups on days 30, 58 and 90; and increased BUN in H on day 30 and in M and H on days 58 and 90; an increased LDH level in M, H on day 30 and in all groups on days 58 and 90; increased serum CPK in L, M, and H on day 30, and in L and H on day 58. Serum cholesterol was lowered in H males and in all females with drug-treated groups on day 30, in all groups of both sexes on day 58, and in all females on day 90 as compared to controls. This cholesterol lowering was regarded as a possible pharmacological effect of drug. A higher Cl in H on days 30, 90, a lower K in M on day 58, and a lower Na in H on day 90 were also noted. These ionic changes were probably due to vomiting and diarrhea.

No treatment-related abnormality was observed in urinalysis.

5. Organ Weights

Increased adrenal and heart (all), kidney(H), liver (M,H) of both sexes and decreased prostate (M,H) and splenic weight (M,H).

6. Pathological Findings

Pathological findings were diverse which included an increased amount of clear abdominal effusion in some of the animals in H, and an enlarged liver which had ruptured in the 2 unscheduled sacrifice males from H, hydropericardium in all drug-treated groups of animals, hepatic congestion, epicardial mesothelial cell proliferation, chronic inflammation and thickening of the epicardium and extramedullary hematopoiesis in the liver and spleen in response to anemia in all gps, hypocellularity with dilated venous sinous in the marrow of the rib and sternum of M, H males and H females, edema in the marrow of femur and serous atrophy of fat in the H males, an excessive number of developing follicles in the ovaries and focal epithelial dysplasia of the mammary gland in all drug-treated female gps, atrophy of prostate in M and H, and excessive involution of the thymus in H animals. It was concluded the [redacted] was poorly tolerated due to multiple toxicities when given orally to dogs at a dosage of 30 mg/kg/d or higher for 3 months.

4. Monkey (Cynomolgus)

a. 4-Day Oral Bioavailability Study:

The objective of this study was to determine the bioavailability of [redacted] in monkeys after administering four different oral formulas, one each successive day, in order to discern if the monkey could be a better animal model. Two females received 10 mg/kg and 2 females had 20 mg/kg of each formulation. Assays of the serum levels of drug disclosed that the solution administered on day 2 resulted in the highest serum levels in three of the four monkeys. The remaining monkey,

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-11-

Monkey #2 (10 mg/kg), vomited shortly after dosing of [REDACTED] soln. In addition, a large degree of intersubject variability was present and no dose proportionality was noted when serum levels from Monkeys 1 and 2 (10 mg/kg) were compared to those from Monkey 3 and 4 (20 mg/kg). Thus, the findings indicated the monkey did not offer any improvement over the dog.

C. Mutagenicity Studies

a. Ames Assay:

[REDACTED] (dissolved in dimethylsulfoxide) was tested for bacterial mutagenicity using Salmonella typhimurium strains TA98, TA100, TA 1535, TA1537, and TA 1538. Doses for the assay were 250, 500, 1000 and 2000 ug/plate. The test results showed no evidence of bacterial mutagenicity at any dose, either in the presence or absence of an in vitro liver homogenate (S-9) metabolic activation system.

b. CHO/HPRT and AS52/XPRT Mammalian Cell Forward Gene Mutation Assays:

[REDACTED] was evaluated concurrently in the CHO/HPRT and AS52/XPRT (a genetically engineered cell line which is more sensitive to chromosome breakage than the CHO cell system). Dose levels, elected based on range-finding studies, were 0.167, 0.50, 1.67, 5.00, 16.7, 50.0, 167, 500, 1670 and 5000 ug/ml. The limit of solubility of U-72,107E was exceeded above 167 ug/ml, and cytotoxicity was noted in both cell lines in the absence of S-9. From this prescreen, doses of 25.0, 50.0, 75.0, 100, 200, 300, 400 and 500 ug/ml with S-9 and 25.0, 50.0, 75.0, 100, 125, 150, 175 and 200 ug/ml without S-9 were evaluated. There were no dose-dependent or three-fold statistically significant increases in the average mutant frequencies of either cell line due to treatment with drug. Thus, [REDACTED] was concluded as nonmutagenic.

c. Unscheduled DNA Synthesis (UDS) Assay:

U-72,107E was assayed in the UDS to see if DNA repair occurs following chemically induced DNA damage. Two assays were made, each using rat primary hepatocyte cultures prepared by collagenase perfusion of the liver from a male F-344 rat. The cultures were fixed, washed, mounted on microscope slides and evaluated for UDS by autoradiography. In each test negative controls (dimethylsulfoxide-solvent- and untreated medium) and a positive control (2-acetylaminofluorene) were used. The results did not induce a significant increase in UDS over the solvent control. Hence it was concluded that drug was not a genotoxic agent.

d. Micronucleus Test:

[REDACTED] was evaluated to determine its ability to induce the formation of micronucleated polychromatic erythrocytes in the bone marrow of treated animals. On the basis of the range-finding study the doses of 1250, 2500 and 5000 mg/kg were administered via i.p. to CD-1 (5/s/gp). Slides were prepared from the bone marrow cells collected at 30, 48 and 72 hrs after a single i.p dose and scored blind. The results were compared with negative (2% dimethylsulfoxide) and positive (0.5 mg/kg triethylenemelamine) controls. There were no significant increases in the number of micronuclei in polychromatic erythrocytes at any dose tested. Thus, the drug was considered as nonmutagenic.

I [REDACTED]

-12-

V. SUMMARY AND EVALUATION:

The current classification of diabetes mellitus divides patients into two major categories, insulin dependent (IDDM, Type I) and non-insulin dependent (NIDDM, Type II). Type I patients have little endogenous insulin whereas Type II patients have normal or even elevated insulin levels. Approximately 90% of the estimated five million diabetes in the United States are Type II.

Type II diabetics are frequently characterized by obesity and insulin resistance. Treatment is by either diet, oral agent, or insulin. Patients often fail to adhere to their prescribed dietary program. The oral agents often fail to provide continued therapeutic response and insulin fails to solve the problem of the diabetics' insulin resistance. Thus, the ideal therapeutic agent for these patients should act directly on the target tissues and alleviate the insulin resistant state. [REDACTED] is a thiazolidinedione and appears to function in several animal models by such a mechanism.

The results of the general pharmacological studies related to efficacy suggested that [REDACTED] lowers blood glucose by increasing glucose uptake and by reducing hepatic glucose production. The data also showed that this drug does not interact with any classical pharmacological systems and does not have any known non-specific actions that would be predicted to adversely affect other physiological systems. Although the underlying mechanism of the effect was not elucidated, it would appear to involve an enhanced responsiveness to insulin. The improved insulin sensitivity following treatment with drug resulted in a lowering glucose and insulin concentrations in non-insulinopenic diabetic animals but did not affect glucose levels in normal animals. As such, this drug appears to offer a novel treatment for diabetes without the potential for hypoglycemia of currently available therapy and with the potential to avoid the adverse consequences of long-term hyperinsulinemia.

Pharmacokinetic evaluations of pioglitazone in the dog indicated a terminal disposition phase half-life of 1.4-1.7 hr, with dose proportionality from 1-10 mg/kg for an oral solution containing citric acid and 5-75 mg/kg for the granulated formulation. Kinetics were linear and food obviously effects absorption. Three drug metabolites (M1, M2, M3) of unknown structure were observed in the serum of dogs and monkeys with M1 having a serum profile similar to the parent drug and M2 and M3 having longer disposition half-lives. Accumulation of drug and M1 was not observed but was present for M2 and M3. In the rat, similar metabolites were observed. Their absorption disposition, however, was not linear which indicates differences between species of animals.

I [REDACTED]

Almost all drug metabolites were cleared from systemic circulation within 24 hr after a single i.v. or p.o. dose. Pioglitazone and metabolites showed potential accumulation in fat depots, liver, and adrenal glands in rats, although this was not confirmed by other species. Elimination of drug metabolites in animal models was primarily by biliary excretion.

The animal toxicity studies of pioglitazone [REDACTED] consists of studies conducted with either the acetate [REDACTED] or the HCl formulation [REDACTED]. All toxicological data generated with [REDACTED] utilized drug dissolved in citric acid, or, as a citrate-based granular powder due to an extremely poor solubility of U-72,107A. Because of such limited solubility of drug and death due to the toxicity of the vehicle occurred, the acute toxicity of [REDACTED] was not determined. In various repeated-dose toxicity studies, no insight into pioglitazone toxicity was gained from shorter-term testings; However, data from the 3-month studies showed some notable toxicity signs. In separate 13-wk oral studies in rats conducted [REDACTED] or [REDACTED], increased deposition of adipose tissue was noted at a dosage level of 30 mg/kg/d or higher. In contrast to an earlier observation from ciglitazone [REDACTED] in which cataracts were produced in Sprague-Dawley rats (not noted in Wistar rats) after 5 weeks of oral administration at 30 mg/kg/d or greater doses, no cataracts were induced in 3-month studies conducted in the same strain rat with U-72,107A or [REDACTED] at doses up to 300 mg/kg/d or in dog studies at doses up to 150 mg/kg/d. Anemia was not noted for [REDACTED]-treated rats at these doses but was noted for [REDACTED]-treated female rats at a dose of 100 mg/kg/d or greater. Other notable signs in rats at high ciglitazone doses (100 to 300 mg/kg/d) were elevated liver enzymes and increased organ weights. Increased heart wts were also noticed for rats treated with [REDACTED] (HCl and acetate) and increased liver wts were noted with [REDACTED] but the level of liver enzymes was not remarkable in either studies.

In dogs, dosages up to 10 mg/kg/d [REDACTED] for 1-month were well tolerated producing no drug-related effects. Preliminary results of the 3-month oral study conducted at lower dosages indicate a low incidence of anemia and hydropericardium at the 10 mg/kg/d dosage level. Increasing the dosage to 30 mg/kg/d or greater for 3 months induced multiple toxicities clinically and in multiple organ systems. The most unusual findings were anemia with hypocellularity of selected bone marrow and hydropericardium. The sponsor argued that since there is no known common cause of these 2 conditions in dogs, the pathogenesis can not be presented. Nevertheless, with exception of organ wt change, all toxic findings were found to be reversible within 1-month of drug withdrawal. It appeared from the data of relative organ wts that these would reverse if given more time.

As is apparent from the foregoing discussion, [REDACTED] produces more toxicity in dogs than in rats; thus, the dog is considered more sensitive species for toxicity testing of this drug. The reason for this is not clear although the metabolism differences known at present would in part be an explanation. Since rats were administered drug once daily, and dogs on

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the 3-month toxicity study were dosed twice daily, the rat would have a greater chance of clearing all the drug and related materials before the next dose as compared to the dog. Faster clearance could decrease toxicity. Studies to date indicate pioglitazone toxicity in rats and dogs consists of reversible anemia and hydropericardium (dogs only), and increased heart and liver wts. The NOEL for [REDACTED] administration over 3 months was set as 3 mg/kg/d in the dog which is approx. 100X the proposed initial clinical single dose (0.03 mg/kg for a 70 kg person).

Mutagenicity studies showed that pioglitazone is negative for genotoxic potential in the in vitro Ames, CHO/HPRT and AS52/XPRT mammalian cell and UDS assays, and in the in vivo micronucleus test in mice.

VI. CONCLUSION AND RECOMMENDATIONS

The preclinical investigations conducted by Upjohn and Taketa with the anti-diabetic drug, pioglitazone, in this IND are adequate to meet the FDA requirement for support of the proposed clinical studies (Phase I). The pharmacological spectrum of this drug in the animal models supports the potential efficacy in man for the therapy of non-insulin dependent Type II diabetes. However, this drug at dosages of 30 mg/kg/d or greater, at least in dog, induced anemia, elevated liver enzymes and increased heart and liver weights. Admittedly the reported toxicology studies were of relatively short duration and therefore appropriate chronic studies will have to be performed by the use of same drug formulation for the clinical studies, [REDACTED] to further determine the extent of toxicity. It is, therefore, recommended that the following preclinical studies be conducted:

letter to sponsor

1. In view of some indication for potential bioaccumulation of drug metabolites in dog over time when administered twice daily, a well-designed pharmacokinetic study is required to further elucidate this possibility along with full characterization of drug metabolites. We also need data on serum levels of the drug and metabolites under steady state conditions to determine the degree of similarity of rats and dogs to humans.
2. From the toxicity data submitted to date, it is clear that U-72,107A produces more toxicity in dogs than in rats, and increasing the dosage in dogs induced multiple toxicities clinically and in organ systems. As such, a careful consideration of long-term toxicity testing is very important and it is critical that ~~the maximum tolerated dose~~ be used as the high dose to demonstrate overt toxicity ³. Please submit the results of the range finding studies and a rationale for the doses to be employed for the ~~chronic toxicity and carcinogenicity~~ studies.

rat & mouse

3. When available,

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Because of potential testis toxicity, Seq I repre studies should be initiated as soon as possible.

3.

*Histology studies
please keep in*

that the high dose should produce some maternal toxicity.

for the

/S/ [Redacted]

Cheong (John) C. Chah, Ph.D.

/S/ [Redacted]

11/16/89

- CC: IND Arch
- HFD-345
- HFD-502/JWeissinger
- HFD-510
- HFD-510/Supv. Pharmacologist
- HFD-510/CChah/11/09/89/Wang 0606p

APPEARS THIS WAY ON ORIGINAL [Redacted]

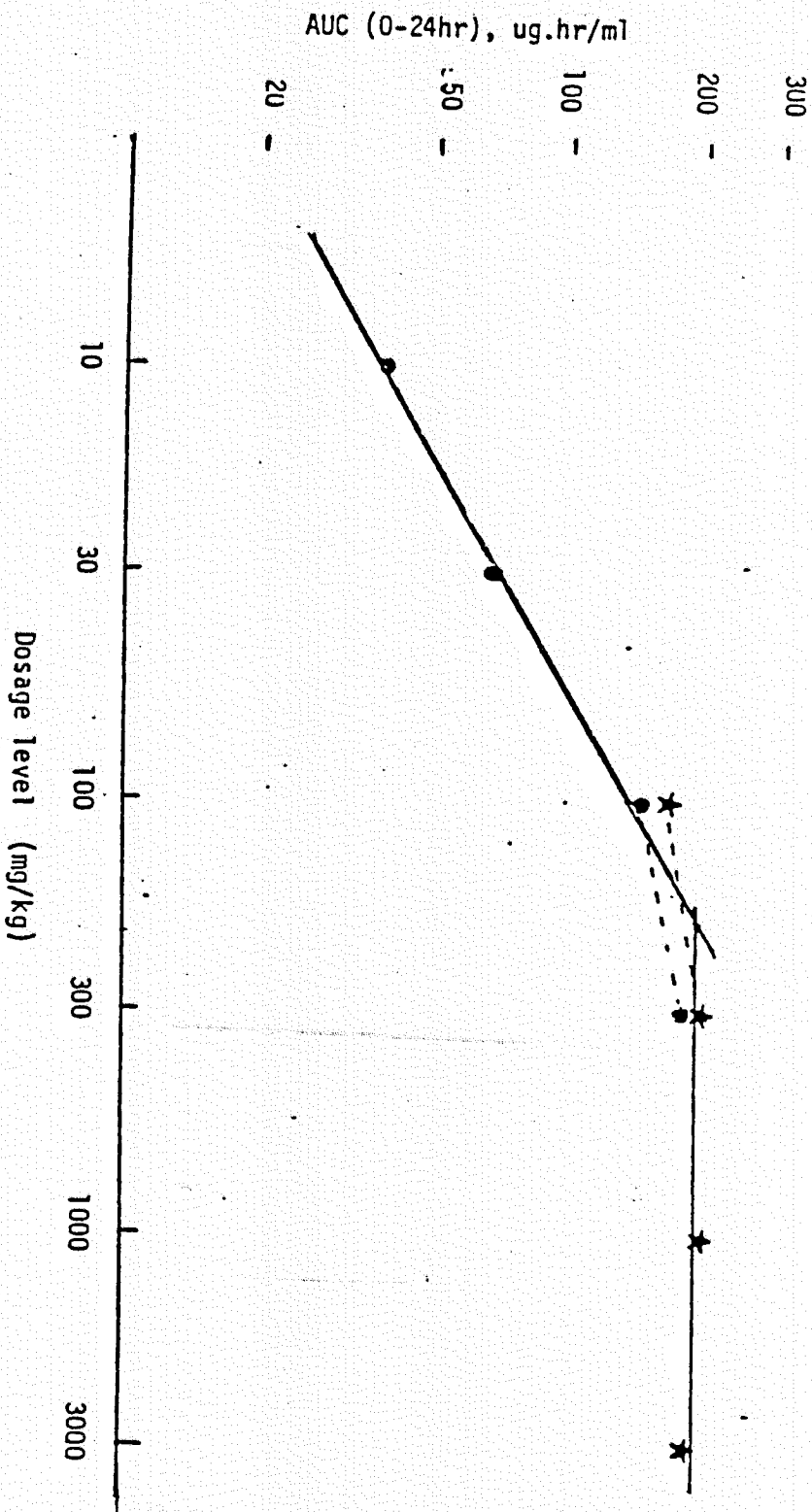
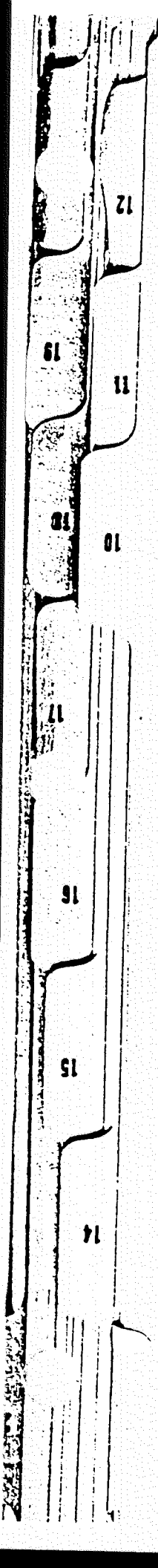


Fig. 1 Relationship between AD-4833 dosage level and AUC(0-24) in rats
Data are expressed as the mean of three rats.
--- : results from the previous study.

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JORDAN

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IND# [REDACTED]

Sponsor: [REDACTED]

Review No. 3

Date of Review: 2/24/1991

AMENDMENT NO. 005

Date of submission: 1/17/1991

Drug: Pioglitazone HCl(U-72,107A)

Class: Oral hypoglycemic agent

Related: IND# [REDACTED]

Date of previous pharmacology reviews: 11/16/1989

This information amendment contains 15 specific technical reports. Among these only selected technical reports, which are relevant to drug safety, pharmacology and toxicology, will be reviewed briefly below.

1. TR No. 7250/90/024, CHARACTERIZATION OF PIOGLITAZONE EFFECTS ON H4-11-E CELLS; AN INSULIN RESPONSIVE CELL LINE

Effects of pioglitazone on H4-11-E cells, an insulin responsive rat hepatoma cell line derived from the Reuber hepatoma H-35, was investigated. Since pioglitazone is known to be an insulin sensitizer, the sponsor predicted that the drug would accelerate H4-11-E cells growth. Pioglitazone which was dissolved in DMSO at a concentration of 25 mM inhibited growth of the cells in a dose-dependent manner (fig 1). The cells exposed to a dose of 25 μ M initially exhibit growth inhibition, however upon removal of the drug and an addition of fresh media, they follow a growth curve parallel to control. Analysis of the cell cycle revealed that pioglitazone causes a non-specific cell cycle arrest.

Comments: Cell growth inhibitory doses of pioglitazone were higher than those needed for in vivo pharmacological effects in diabetic model mice (KKAY). Inhibitory effects of this drug on other cells, particularly in vivo are needed to be established.

2. TR No. 7250/90/061, PIOGLITAZONE INDUCED CHANGES IN GENE EXPRESSION

The sponsor has previously demonstrated that pioglitazone enhances the insulin regulated differentiation of 3T3-L1 cells to adipocytes. In the present study the sponsor showed that the drug does similar effect the differentiation of 3T3-L1 cells induced by insulin-like growth factor-1 (IGF). But, the drug does not elicit such differentiation in the absence of insulin or IGF. When triglyceride accumulation is measured as the end point of differentiation,

activities known to increase during differentiation were increased by pioglitazone over the activities seen with insulin or IGF alone. However, there was a lag period of 18 to 24 hours between the onset of drug treatment and increased activities. For induction of the mRNA it was required to incubate the cells with pioglitazone and insulin or IGF. The sponsor speculates that the induced genes encode regulatory proteins which enhance the response of cells to insulin.

Comments: Pioglitazone enhances either insulin or IGF action on 3T3-L1 cell differentiation, of which action could be extended to other tissues mediated by these hormones.

3. Technical Report No. 7250-90-062 THE ANALYSIS OF THE aP2 PROMOTOR; A POSSIBLE TARGET FOR AN INSULIN SENSITIZING AGENT

In an effort to understand the mechanism that pioglitazone enhances sensitivity of target tissues to insulin, the sponsor studied effects of the drug on production of mRNA of aP2(adipocyte specific fatty acid binding protein). Pioglitazone increased the aP2 mRNA 10-fold of control level within 4 hours of treatment in 3T3-L1 cells, which suggests the aP2 gene is a candidate for direct action of the drug. The sponsor also cloned aP2 promoter sequences by polymerase chain reaction. The promoter sequences(750 bp) and a truncated promoter fragment(250 bp) was placed into chloramphenicol acetyltransferase reporter gene. And the combinant was transfected into staged 3T3-L1 cells. Promoter specific expression and specific regulatory regions within the aP2 promoter sequence(e.g., glucocorticoid responsive element) were confirmed.

4. Technical Report No. 7250-90-063 PIOGLITAZONE INDUCTION OF aP2 mRNA In Vivo

The objective of this study was to investigate pioglitazone action on fat tissue aP2 mRNA in vivo, since the sponsor demonstrated that the drug induced directly the aP2 mRNA in vitro. Administration of pioglitazone(up to 71 mg/kg/day for six weeks) to ob/ob mice resulted in a dose-dependent increase in aP2 mRNA from epididymal fat with a 3-fold increase. In perirenal fat from KKAY mice the drug(20 mg/kg for 4 days) increased the aP2 mRNA by two-fold with proportional changes in blood glucose and insulin, suggesting certain relationships among these parameters(fig. 2).

Comments: Pioglitazone increased the aP2 expression in C57 mice without effecting blood glucose. The drug is not able to increase the aP2 expression in streptozotocin-treated rats, although insulin sensitivity is augmented by pioglitazone in the model. Pioglitazone improves insulin sensitivity in all tissues while aP2 mRNA induction may be an adipose-specific.

5. Technical Report No. 7250-90-032 RECEPTOR-COUPLED HIGH AFFINITY GTPase ACTIVITY IN HUMAN PLATELET MEMBRANES

As part of a study of the effects of pioglitazone on insulin action, the objective of this investigation was to determine the response of GTPase activity of human platelet membranes to insulin. High affinity GTPase activity was not affected by insulin (0.1 to 100 nM) added either simultaneously with GTP or up to 20 min prior to substrate addition. Low affinity GTPase activity was also negligibly affected by insulin. Pioglitazone did not alter high affinity GTPase activity measured in the absence or presence of insulin (30 nM). This study shows that human platelet membranes contain a high affinity GTPase that is unresponsive to insulin under a variety of experimental conditions where stimulation by other agonists is observed. This suggests that agonist-responsive GTPase activity is not be a useful index for insulin receptor-G protein interactions.

6. Technical Report No. 7250-90-039 EFFECT OF PIOGLITAZONE ON GLUCOSE UPTAKE IN L6 MUSCLE CELLS AND RAT CARDIAC MYOCYTES

Both L6 skeletal muscle cell line and rat cardiac myocytes were used to determine the effect of pioglitazone on glucose transport, using radioactive 2-deoxy D-glucose and 3-O methyl D-glucose. Pioglitazone increased glucose transport in a time and dose dependent manner in differentiated L6 cells like insulin does. The insulin and pioglitazone doses for optimal glucose transport were 0.17 μ M and 20 μ M, respectively. The effect of insulin and pioglitazone was additive. Rat cardiac myocytes were also insulin responsive as measured by increased glucose transport with increased time in culture.

7. Technical Report No. 7250-89-051 PIOGLITAZONE TREATMENT LOWERS CIRCULATING CHOLESTEROL IN CHOLESTEROL-FED RATS AND REDUCES INTESTINAL ACAT ACTIVITY IN RATS AND DIABETIC MICE

The major cause of death in diabetes is coronary heart disease as a result of atherosclerosis. The exact cause(s) of premature atherosclerosis in diabetes is unknown, although diabetic patients have many risk factors such as hypertension, altered circulating lipids and increased blood viscosity. Pioglitazone reduces circulating triglycerides in several species. This drug also reduces total and beta-cholesterol in rats fed a moderately hypercholesteremic diet, although it may not reduce circulating cholesterol in animals on a normal diet. The reduction in circulating beta-cholesterol is known to associate with a reduction in both intestinal and hepatic microsomal acyl-CoA:cholesterol acyltransferase (ACAT) activity. Pioglitazone produced a dose-dependent decrease in the intestinal ACAT activity of the diabetic ob/ob mouse without affecting circulating cholesterol. These data suggest that ACAT might be under the control of insulin so that insulin deficiency might contribute to higher intestinal ACAT activity. The objective of this present study was

to re-examine the effect of pioglitazone on circulating cholesterol concentrations.

Pioglitazone reduced circulating triglycerides in most of tested animals (except ob/ob mice), but had little effects on circulating cholesterol in animals on a normal laboratory diet (Table I). Pioglitazone also reduced circulating triglycerides and insulin, which might be related to an improved sensitivity of the peripheral tissues to insulin. Pioglitazone treatment tended to decrease ACAT activity in the gastrointestinal microsomes of rats. The fact that pioglitazone treatment had no effect on cholesterol levels in the animals on a normal rodent diet suggests that an effect of pioglitazone treatment might be to affect cholesterol absorption. Intestinal ACAT, an enzyme thought to be essential for absorption of dietary cholesterol, appears to be under the negative control of insulin.

7. Technical Report No. 7250-89-089 EFFECT OF [REDACTED] ON INSULIN TOLERANCE AND MEAN STIMULATED RESPONSE IN NORMAL DOGS.

The objective of this study was to determine whether a pioglitazone dose selected by extrapolation from mouse data was efficacious in dogs. The effect of pioglitazone on insulin sensitivity was assessed by two methods: (1) insulin tolerance test profiles measuring the response of serum insulin and glucose to an exogenous insulin bolus and (2) pre- and postprandial testing of serum samples for the insulin, glucose, triglycerides, and non-esterified free fatty acids response to endogenous insulin. Two groups of six lean mongrel dogs were studied using a placebo controlled with a crossover design with a 2 week washout period separating the 7-day treatment phases. A placebo or pioglitazone was administered once daily as a citrate formulation in a gelatin capsule. No statistically significant effects were observed for any parameter in response to pioglitazone. Serum drug levels were determined in samples from representative dogs obtained immediately prior to the low dose insulin tolerance tested. These data indicate that pioglitazone is less effective in young, healthy dogs than in their aged, obese counterparts when administered.

8. Technical Report No. 7250-89-062. THE EFFECT OF PIOGLITAZONE HCl ON TOTAL SERUM T4 AND T3 LEVELS IN THE DOG.

Symptoms, such as anemia, pericardial effusion and hepatomegaly, which resemble those occurring in hypothyroidism were observed in dogs treated with pioglitazone. Thus, the purpose of this study was to examine the effects of pioglitazone on serum levels of T4 and T3 in dogs. Six male and 6 female dogs were treated with pioglitazone at doses of 30, 60 and 150 mg/kg/day for 90 days. By one month serum T4 and T3 levels had decreased in all pioglitazone treated dogs to levels about 2/3 control levels. T4 and T3 in treated dogs remained low during the treatment period with one exception. Serum T3 levels in the 30 mg/kg group increased after one month and by 90 days were no longer

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significantly different from control. This study suggests that pioglitazone appears to have a negative effect on thyroid hormone economy and the reduced serum T4 and T3 levels observed in the treated dogs could have contributed to those side effects resembling to symptoms of hypothyroidism.

9. Technical Report No. 7256-90-004 PIOGLITAZONE BIOAVAILABILITY COMPARISON IN THE DOG; ORAL SOLUTION, PATH/TOX FORMULATION, AND CLINICAL FORMULATION(PROTOCOL 89-235).

In animal models pioglitazone-HCl has been shown to have enhanced bioavailability when administered with citric acid. However, the total amount of citric acid and the drug to citric acid ratio necessary to achieve optimal bioavailability have not been completely defined. The objective of this study was to evaluate the potential change in pioglitazone bioavailability for formulation modification in the beagle dogs. Four dogs each received four pioglitazone formulations: an oral solution containing citric acid and 10 mg pioglitazone; the granulated formulation containing 10 mg pioglitazone; two 5-mg clinical formulation capsules(high clinical); and two 2-mg clinical formulation capsules(low clinical). Pharmacokinetic evaluation of the serum concentration-time profiles showed no apparent difference in pioglitazone relative bioavailability for the three solid formulations compared to the oral solution. Statistical evaluation of various pharmacokinetic parameters(AUC, Cmax, Tmax, apparent terminal rate constant and mean residence time) suggested that no significant differences between the four formulations. This result indicates that the bioavailability of the pioglitazone(phase I clinical formulation) is similar to the formulation used in animal safety studies.

RECOMMENDATIONS: None.

cc: IND, HFD-510, HFD-345
A. Jordan/H. Rhee

/S/

Herman M. Rhee, Ph. D.

/S/

/ 3/13/91

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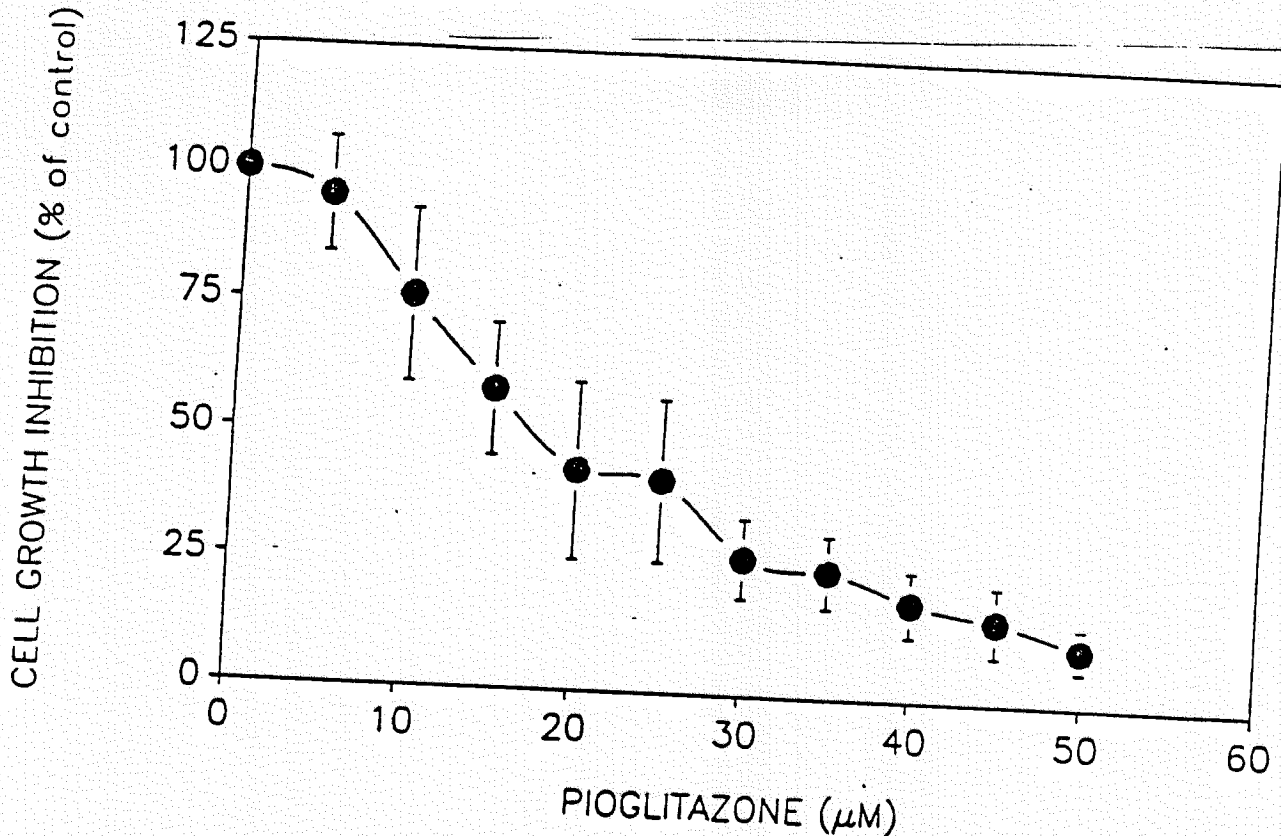
Table I

Summary of Effects of Pioglitazone on Circulating Lipids in Various Animal Models

Animal	Dose mg/kg	Study	Cholesterol (mg/dl)		Triglycerides (mg/dl)	
			Control	Pioglitazone	Control	Pioglitazone
KKAY Mouse	24.5	1	142 ± 12	121 ± 6	817 ± 76	363 ± 16*
ob/ob Mouse	50	2	269 ± 10	290 ± 9	228 ± 23	237 ± 17
db/db Mouse	100	3	164 ± 9	181 ± 5	429 ± 43	220 ± 29*
Chinese Hamster	94	4	147 ± 7	107 ± 4*	808 ± 107	389 ± 51*
Normal Rats	100	5	-	-	200 ± 26	90 ± 8*
Zucker Rat	10	6	-	-	426 ± 55	100 ± 9*

Data are Mean and SEM; * = Statistically significant versus Control group.

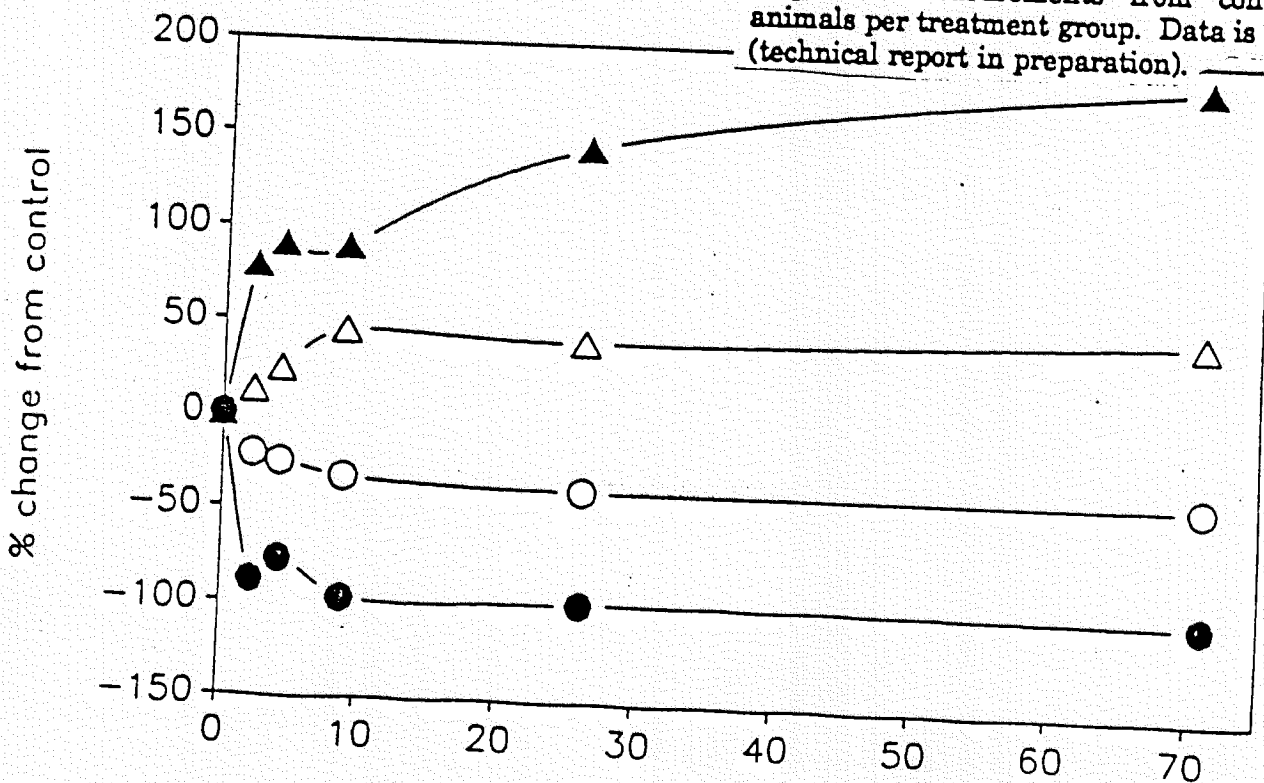
FIGURE 1. Dose Response: H4-II-E cells plated 6-7 hours were treated for 96 hours with pioglitazone. Cells were analyzed by protein or number, and the data plotted as percent of control (control = 100%). The IC₅₀ was 19.5 μ M. Each point represents the mean $\pm$ S.E. of 8 determinants.



ig. 2.

- — ○ blood glucose
- — ● insulin
- △ — △ weight change
- ▲ — ▲ aP2 mRNA

Correlation of aP2 mRNA, blood glucose, plasma insulin, and weight change in ob/ob mice treated with pioglitazone for six weeks. Each point represents the mean percent change of the values of respective measurements from control for six animals per treatment group. Data is from B. Wyse (technical report in preparation).





DEPARTMENT OF HEALTH & HUMAN SERVICES

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H. Rhee

Public Health Service

Food and Drug Administration
Rockville MD 20857

July 3, 1996

Mr. Markus F. Herzig
Takeda America, Inc.
101 Carnegie Center
Princeton, NJ 08540

Dear Mr. Herzig:

Re: IND [REDACTED]/Pioglitazone HCl
Amendment [REDACTED]

On July 19, 1995 our division had a meeting with you for the transfer of IND# [REDACTED] from Upjohn to Takeda America, Inc. During the meeting two ongoing carcinogenicity studies were discussed and Dr. Jordan requested the justification of the dose levels used for the studies.

In response to our request, you indicated that the two carcinogenicity studies [REDACTED] #295-153 and [REDACTED] #295-152) were completed [REDACTED]. Based on your preliminary analysis of the studies, the incidence of focal proliferative lesions in the urinary bladder in rats was reported subsequently on June 20, 1996 [REDACTED].

We have completed our review and have the following requests:

1. Please submit the final results from the two carcinogenicity studies as soon as possible.
2. Since we have not examined your cancer study protocols, please provide justification of dose selection including AUC comparisons in test animals and human exposure.
3. In addition, comparative metabolic profile of pioglitazone in the three species will help in determining the relevance of animal findings to human exposure.

Sincerely,

/s/

[REDACTED]
Herman Rhee, Ph.D.

/s/

[REDACTED]
Ronald W. Steigerwalt, Ph.D.

/s/

[REDACTED] 7/3/96
Solomon Sobel, M.D.
Division Director

APPEARS THIS WAY ON ORIGINAL

cc: OIA/IND
OIA-515/SOBA
OIA-510/HRhee/RSteigerwalt
OIA-511/JORNEC

DEC 3 1996

IND# [REDACTED]

December 2, 1996

Sponsor: Takeda America, Inc., Princeton, NJ. Markus F. Herzig
Tel (609) 452-1113; Fax (609) 452-1218

Amendment Serial No. 071
Submission Date: Nov. 4, 1996

Drug: Pioglitazone HCl (U-72,107A, AD-4833)

Class: Oral hypoglycemic agent

Related: IND [REDACTED]
IND [REDACTED]
IND [REDACTED]
IND [REDACTED]

This amendment contains the sponsor's response to our request of July 3, 1996 on their carcinogenicity studies ([REDACTED] #295-153 and [REDACTED] #295-152). The sponsor performed metabolic studies in rats, mice, and human, using radioactive pioglitazone.

A. Methods: Unspecified number of male Jcl:Sprague Dawley rats and male Crj:ICR mice were administered 0.5 mg/kg of ¹⁴C-Pioglitazone. Pioglitazone-HCl tablet (30 mg) was given to human male volunteers. Blood, urine and feces were collected for the determination of pioglitazone and its metabolites by [REDACTED].

B. Results: Table 1 shows the composition of metabolites in rat and mouse plasma, and human serum. Cumulative excretion of pioglitazone in urine and feces is summarized in table 2. Postulated metabolic pathways of pioglitazone is shown (Fig. 1).

C. Attachment: Two tables and one figure.

D. Recommendations: (Letter to the sponsor)

1. Are the 6 metabolites active? If they are, please indicate the relative activity ratios in three species, mouse, rat and human. Are the two stereoisomers equally active?

2. Please repeat the experiments in Crl:CD BR rats and Crl:CD-1 mice with appropriate sample size since they were used in your two-year carcinogenic studies.

/S/

Herman M. Rhee, Ph. D.

/S/

12/3/96

cc: Original IND, HFD-510
Ronald Steigerwalt/H. Rhee

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Table 1
Composition of metabolites in rat and mouse plasma, and human serum after oral administration of pioglitazone (HCl)

Compound	Rat		Mouse		Human	
	AUC(0-48h)	R(A)	AUC(0-48h)	R(A)	AUC(0-96h)	R(A)
Pioglitazone	7.22 ± 1.11	1.00	3.00	1.00	13.11 ± 3.59	1.00
M-I	0.04 ± 0.02	0.01	0.01	<0.01	0.30 ± 0.92	0.04
M-II	1.30 ± 0.74	0.18	0.31	0.10	0.68 ± 0.27	0.05
M-III	1.97 ± 0.20	0.27	0.25	0.08	11.65 ± 2.98	0.86
M-IV	1.28 ± 0.08	0.18	0.49	0.16	24.81 ± 4.38	1.81
M-V	0.60 ± 0.07	0.08	0.15	0.05	0.92 ± 0.20	0.06
M-VI	0.12 ± 0.05	0.02	0.05	0.02	1.16 ± 0.22	0.08
R(B)	92.6%		86.4%		***	

AUC: Mean ± SD (n= 5 for rats and n= 14 for humans)

AUC for mice was calculated using the mean plasma concentration (n=3) at each time.

Dosing: [¹⁴C]pioglitazone (HCl) 0.5 mg/kg for rats and mice, pioglitazone (HCl) 30 mg/man (as pioglitazone) for humans
AUC: pioglitazone eq $\mu\text{g}\cdot\text{h}/\text{ml}$ for rats and mice, and $\mu\text{g}\cdot\text{h}/\text{ml}$ for humans

R(A): AUC of each metabolite / AUC of pioglitazone

R(A) for humans was calculated using AUC each corrected by the molecular weight of each metabolite to that of pioglitazone

R(B): (total AUC of pioglitazone and M-I to M-VI / AUC of total radioactivity) x 100

***: not calculated

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BEST POSSIBLE

Table 2
Cumulative excretion of pioglitazone and its metabolites in rats, mice and humans
after oral administration of pioglitazone (HCl).

Compound	Rat				Mouse				Human							
	Urine (0-48h)		Feces (0-48h)		Urine (0-48h)		Feces (0-48h)		Urine (0-48h)		Total					
	UC	CON	UC	CON	UC	CON	UC	CON	UC	CON	UC	CON				
Pioglitazone	N.D.	N.D.	1.7	N.D.	1.7	N.D.	N.D.	0.1	0.1	1.0	0.2	1.2	N.D.	N.D.	N.D.	N.D.
M-I	0.1	1.7	N.D.	0.2	0.2	0.1	0.9	0.1	1.0	0.2	0.1	0.3	N.D.	N.D.	0.5	0.5
M-II	N.D.	N.D.	2.7	N.D.	2.7	0.1	3.7	0.1	3.9	0.3	N.D.	0.4	N.D.	N.D.	0.7	0.7
M-III	N.D.	N.D.	0.2	N.D.	0.2	N.D.	0.1	0.1	0.1	0.1	0.1	0.1	N.D.	N.D.	N.D.	N.D.
M-IV	0.1	1.9	1.8	8.9	10.7	N.D.	0.6	0.6	0.6	0.6	1.8	2.3	N.D.	N.D.	7.8	7.8
M-V	9.5	1.4	13.7	2.4	16.1	1.2	0.8	2.0	2.0	2.5	1.6	4.1	11.8	0.8	12.6	12.6
M-VI	2.8	0.1	4.0	0.3	4.3	0.3	0.2	0.5	0.5	7.9	N.D.	7.9	7.8	N.D.	7.8	7.8
Others					25.8			15.7				58.6				
Total		35.5±0.5		61.7±1.9			23.9±5.9		74.9±7.7						29.3±5.9	***

Mean ± SD or Mean (n=3 for rats, n=3 for mice and n=13 for humans)

Dosing: [¹⁴C]pioglitazone (HCl) 0.5 mg/kg for rats and mice
pioglitazone (HCl) 30 mg/man (as pioglitazone) for humans

***: not assayed

N.D.: not detected

UC: unconjugate

CON: conjugated form (glucuronide or sulfate, except for M-V in rats and mice which contains taurine conjugate)

Total: total radioactivity for rats and mice (including "others") and total of pioglitazone and metabolites (M-I to M-VI) for human urine

BEST POSSIBLE

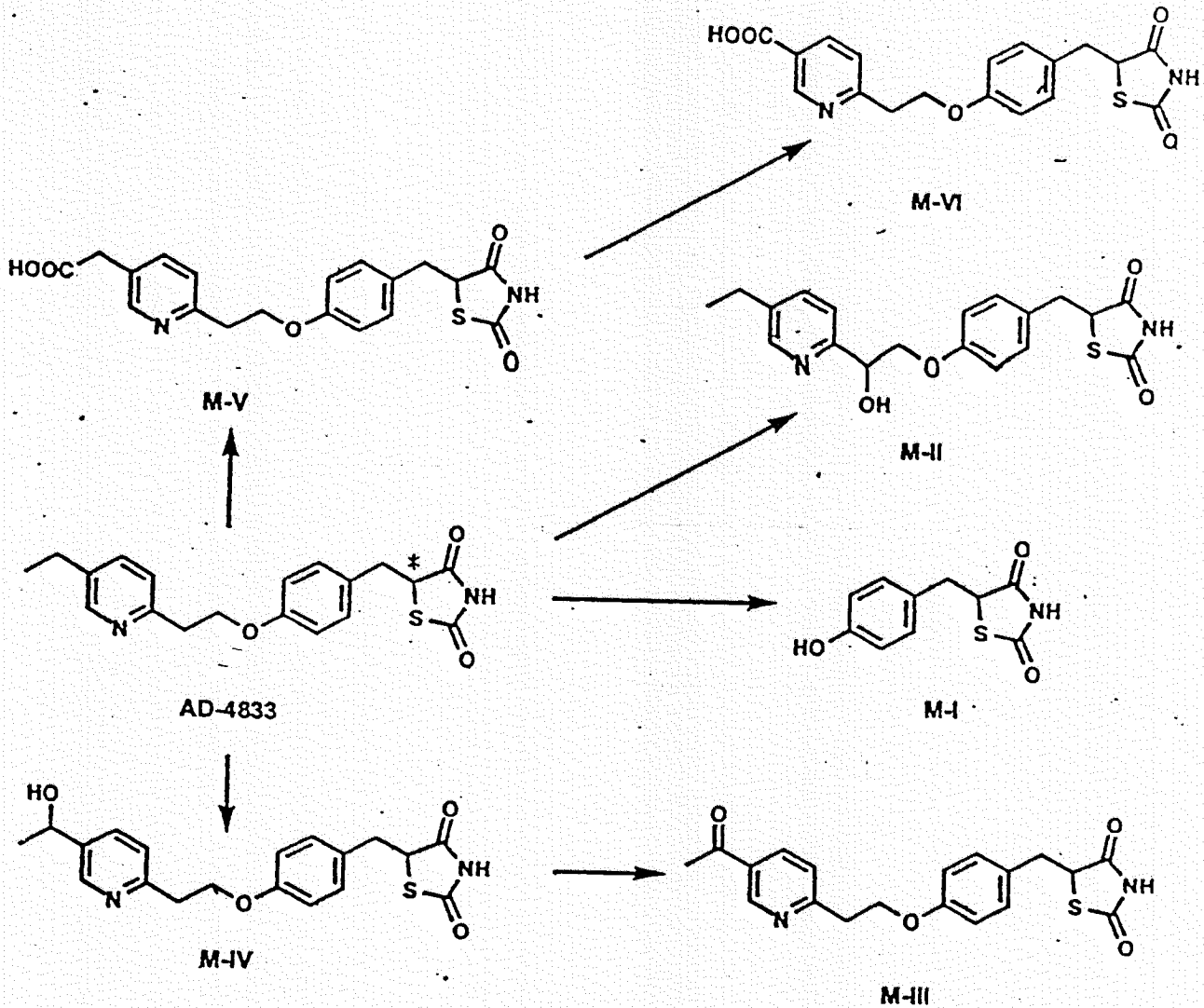


Fig. 1 Postulated metabolic pathways of pioglitazone

*: ^{14}C -labeled position

IND# [REDACTED]

June 23, 1997

Sponsor: Takeda America, Inc., Princeton, NJ. Markus F. Herzig
 Tel(609)452-1113; Fax(609)452-1218

Amendment Serial No. 101
 Submission Date: 6/5/1997

Drug: Pioglitazone HCl(U-72,107A, AD-4833)

Class: Oral hypoglycemic agent

Related: IND# [REDACTED]
 IND# [REDACTED]
 IND# [REDACTED]
 IND# [REDACTED]

In this amendment the sponsor wishes to respond to the points that were raised by the reviewer on September 18, 1996. The main points are summarized below.

1). In order to characterize the metabolites of pioglitazone the sponsor quantitated them in plasma of several species after oral administration, of which results are summarized below.

Met ^e	Mouse		Rat		Dog		Monkey		Human	
	AUC	RA	AUC	RA	AUC	RA	AUC	RA	AUC	RA
Pio ^f	3.00	1.00	7.22	1.00	0.89	1.00	5.55	1.00	13.1	1.00
M-1	0.01	0.01	0.04	0.04	0.12	0.13	0.10	0.02	0.30	0.02
M-2	0.31	0.10	1.30	0.18	0.19	0.21	0.36	0.06	0.68	0.05
M-3	0.25	0.08	1.97	0.27	0.43	0.48	0.40	0.07	11.6	0.29
M-4	0.49	0.16	1.28	0.18	2.41	2.71	2.87	0.52	24.8	1.89
M-5	0.15	0.05	0.60	0.08	0.30	0.34	0.93	0.17	0.92	0.07
M-6	0.05	0.02	0.12	0.02	ND	ND	ND	ND	1.16	0.09
RB	86.4%		92.6%		79.0%		93.1%		NC	

^e Met or M stand for metabolites and ^f indicate parent compound, respectively. AUC represents values from 0 to 24 hrs. RA represents AUC ratio of each metabolite to pioglitazone at dose of 0.5 mg/kg. For human dose was 30 mg. RB shows AUC ratio (total metabolites to total radioactivity) x100. ND and NC stand for not determined and not calculated, respectively.

2). As to the minimum dose of pioglitazone which causes cardiac enlargement, the sponsor provided the followings.

Species	Duration of dose	Sex	Dose level (mg/kg/day)	Mean AUC _{0-24h} (µg.hr/ml)	Dose ratio vs human	Exposure ratio vs human
Rat	1-year	Male	3.6	70.4	7	4.6
		Female	14.5	234	29	15.3
Mouse	2-year	Male	27.0	110	54	7.2
		Female	90.0	287	180	18.8
Dog	1-year	Male	3	9.4	6	0.6
		Female	10	14.5	20	1.0
Monkey	3-month	Male	8	75.3	16	4.9
		Female	8	74.4	16	4.8

*Human dose was 30mg/day (0.5mg/kg/day), which gave an AUC value, 15.3µg.hr/ml.

3). The sponsor noted benign and/or malignant transitional cell tumors in the urinary bladder at dose of 3.6 mg/kg/day in 2-year rat carcinogenicity study. Mean plasma AUC_(0-24 hr) of pioglitazone was 61.2µg.hr/ml. The AUC ratio of rat/human was only 4.

4). The sponsor attached a figure to explain the mode of pioglitazone hypoglycemic action, although the exact mechanism of its action remains to be defined.

5). Finally the sponsor attached an unpublished paper of which title is "Pharmacological activities of pioglitazone.HCl and its metabolites". They compared hypoglycemic action of pioglitazone and its metabolites in Wistar fatty rat. The results are:

Metabolites	Pio ^e	M-1	M-2	M-3	M-4	M-5	M-6
Plasma glucose							
ED ₂₅ (mg/kg/d)	0.54	3.00	0.99	1.32	0.93	3.00	3.00
Relative Pot ^f	1.00	0.18	0.55	0.41	0.58	0.18	0.18
Plasma triglyceride							
ED ₂₅ (mg/kg/d)	0.43	3.00	0.22	0.47	0.53	3.00	3.00
Relative Pot ^f	1.00	0.18	1.95	0.91	0.81	0.18	0.18

Pio^e and relative pot^f indicate pioglitazone and relative potency,

respectively. Potency of pioglitazone was set as 1.00.

6). Summary and Conclusion:

The dog has the closest metabolite profile to human. The rank order for hypoglycemic action was Pioglitazone>M-4>M-2>M-3>M-1=M-5=M-6, while that of its effect on triglyceride was M-2>Pio>M-3>M-4>M-1=M-5=M-6 in Wistar rats. The rank of AUC ratio at the minimum dose that caused cardiac enlargement was mouse>rat>monkey>dog. The AUC ratio in female dog was identical to human, while that in male dog was 0.6. The AUC ratio of rat/human at a dose of 3.6mg/kg/day was 4 when benign and/or malignant transitional cell tumors in the urinary bladder were noted.

7). Attachment: A figure.

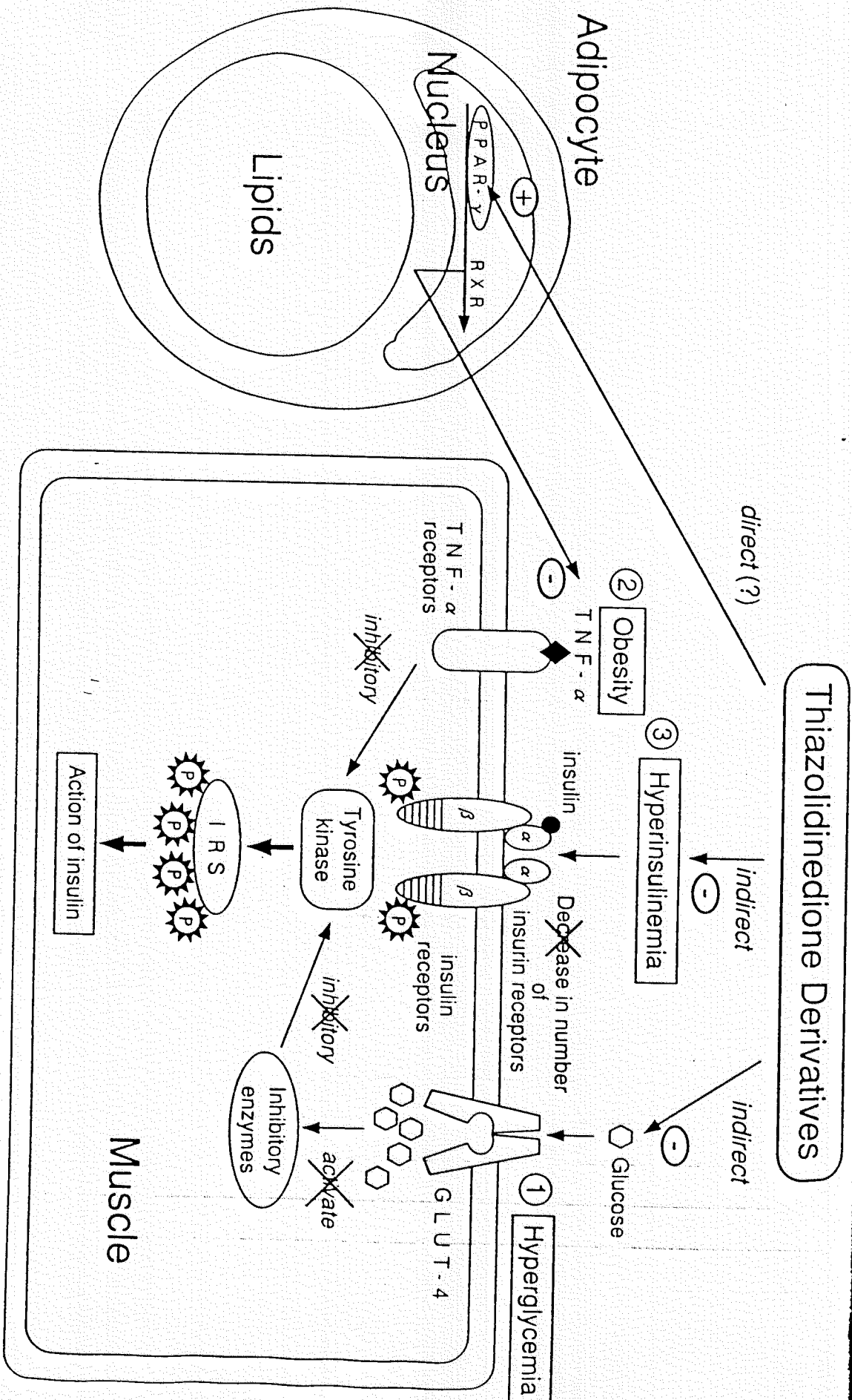
8). Recommendation: None.

/s/

Herman M. Rhee, Ph. D.

cc: Original_IND, HFD-510
Ronald Steigerwalt/H. Rhee

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Possible Mechanisms of Thiazolidinedione Derivatives

IND# [REDACTED]

July 28, 1997

Sponsor: Takeda America, Inc., Princeton, NJ. Markus F. Herzig
Tel (609) 452-1113; Fax (609) 452-1218

Amendment Serial No. 101
Submission Date: 6/5/1997

Drug: Pioglitazone HCl (U-72,107A, AD-4833)

Class: Oral hypoglycemic agent

Related: IND# [REDACTED]
IND# [REDACTED]
IND# [REDACTED]
IND# [REDACTED]

In this amendment the sponsor wishes to respond to the points that were raised by the reviewer on September 18, 1996. The main points are summarized below.

1). In order to characterize the metabolites of pioglitazone the sponsor quantitated them in plasma of several species after oral administration, of which results are summarized below.

Met ^e	Mouse		Rat		Dog		Monkey		Human	
	AUC	RA	AUC	RA	AUC	RA	AUC	RA	AUC	RA
Pio ^f	3.00	1.00	7.22	1.00	0.89	1.00	5.55	1.00	13.1	1.00
M-1	0.01	0.01	0.04	0.04	0.12	0.13	0.10	0.02	0.30	0.02
M-2	0.31	0.10	1.30	0.18	0.19	0.21	0.36	0.06	0.68	0.05
M-3	0.25	0.08	1.97	0.27	0.43	0.48	0.40	0.07	11.6	0.29
M-4	0.49	0.16	1.28	0.18	2.41	2.71	2.87	0.52	24.8	1.89
M-5	0.15	0.05	0.60	0.08	0.30	0.34	0.93	0.17	0.92	0.07
M-6	0.05	0.02	0.12	0.02	ND	ND	ND	ND	1.16	0.09
RB	86.4%		92.6%		79.0%		93.1%		NC	

^e Met or M stand for metabolites and ^f indicate parent compound, respectively. AUC represents values from 0 to 24 hrs. RA represents AUC ratio of each metabolite to pioglitazone at dose of 0.5 mg/kg. Human dose was 30 mg. RB shows AUC ratio (total metabolites to

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		Female	8	74.4	16	4.8

*Human dose was 30mg/day (0.5mg/kg/day), which gave an AUC value, 15.3µg.hr/ml. #Calculated based on AUC of parent compound only.

3). The sponsor noted benign and/or malignant transitional cell tumors in the urinary bladder at dose of 3.6 mg/kg/day in 2-year rat carcinogenicity study. Mean plasma AUC_(0-24 hr) of pioglitazone was 61.2µg.hr/ml. The AUC ratio of rat/human was only 4.

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Plasma glucose							
ED ₂₅ (mg/kg/d)	0.54	3.00	0.99	1.32	0.93	3.00	3.00
Relative Pot [†]	1.00	0.18	0.55	0.41	0.58	0.18	0.18

Plasma triglyceride							
ED ₂₅ (mg/kg/d)	0.43	3.00	0.22	0.47	0.53	3.00	3.00
Relative Pot [#]	1.00	0.18	1.95	0.91	0.81	0.18	0.18

Pio[®] and relative pot[#] indicate pioglitazone and relative potency, respectively. Potency of pioglitazone was set as 1.00.

6). Summary and Conclusion:

The dog has the closest metabolite profile to human. The rank order for hypoglycemic action was Pioglitazone>M-4>M-2>M-3>M-1=M-5=M-6, while that of its effect on triglyceride was M-2>Pio>M-3>M-4>M-1=M-5=M-6 in Wistar rats. The rank of AUC ratio at the minimum dose that caused cardiac enlargement was mouse>rat>monkey>dog. The AUC ratio in female dog was identical to human, while that in male dog was 0.6. The AUC ratio of rat/human at a dose of 3.6mg/kg/day was 4 when benign and/or malignant transitional cell tumors in the urinary bladder were noted.

7). Attachment: A figure.

8). Recommendation: (Letter to the sponsor)

The amendment (Serial No. 101) deals with important pharmacokinetic issues. Animals have different levels of metabolites I through VI and the metabolites have different pharmacological activities. Therefore, it is necessary to calculate animal exposure ratio vs human, based on AUC ratio of parent drug and all relevant active metabolites. Please compare the exposure ratio in this way at the minimum dose of pioglitazone which causes cardiac enlargement and bladder tumors.

/s/

Herman M. Rhee, Ph. D.

cc: Original IND, HFD-510
Ronald Steigerwalt/H. Rhee/M. Johnston

APPEARS THIS WAY ON ORIGINAL

H R H E E

IND # [REDACTED]

September 2, 1998

SEP - 3 1998

Sponsor: Takeda America Research & Development Center, Inc.
Princeton, New Jersey 08540
Scott L. Grossman, Ph. D., Regulatory Director (609)452-1113

Submission Date: 07/22/1998

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
AMENDMENT S#184

Drug: Pioglitazone HCl(AD-4844)

Pharmacological Class: Thiazolidinedione Derivative

Clinical dose: 30 mg per day

1. BACKGROUND: The sponsor wishes to provide additional information in response to this division's request (dated on 2/11/1998) on urine pH in pioglitazone-treated and control animal including human subjects .

2. COMMENTS:

On June 20, 1996 the sponsor submitted to this division the following table as an amendment(Serial Number 061). From their 2-year carcinogenicity studies the male rats had transitional cell tumors. The sponsor attributed the carcinoma in rats was due to high urine pH, which is not relevant to carcinogenic potential of pioglitazone in human because of differential acidic pH.

APPEARS THIS WAY ON ORIGINAL
[REDACTED]

INCIDENCE OF THE FOCAL PROLIFERATIVE LESIONS IN THE URINARY
BLADDER OF MALE RATS IN 2-YEAR CARCINOGENICITY STUDY(S#061)

Dose(mg/kg/d)	0	0	1	4	8	16	63
Sex	M/F	M/F	M/F	M/F	M/F	M/F	M/F
Hyperplasia							
a) Nodular	0/0	0/0	0/0	0/0	3/-	1/0	0/0
b) Papillary	3/0	0/0	1/1	2/1	1/-	1/0	1/1
Transitional cell tumors							
a) Benign	0/0	0/0	0/1	0/1	3/-	2/1	2/1
b) Carcinoma	0/-	0/-	0/-	2/-	4/-	5/-	4/-
Total Lesions	3/0	0/0	1/2	4/2	9/-	9/1	7/1

3. RECOMMENDATIONS (Letter to the sponsor):

Please provide the following information for each rat that had a bladder tumor: urine pH, tumor type, presence or absence of bladder calculi.

cc: Original IND, HFD-510
R. Steigerwalt/H. Rhee/J. Weber

/s/

Norman M. Rhee, Ph.D.

/s/

APPEARS THIS WAY ON ORIGINAL

IND # [REDACTED]

September 2, 1998

Sponsor: Takeda America Research & Development Center, Inc.
 Princeton, New Jersey 08540
 Scott L. Grossman, Ph. D., Regulatory Director (609)452-1113

Submission Date: 07/22/1998

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
AMENDMENT S#184

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Transitional cell tumors							

a) Benign	0/0	0/0	0/1	0/1	3/-	2/1	2/1
b) Carcinoma	0/-	0/-	0/-	2/-	4/-	5/-	4/-
Total Lesions	3/0	0/0	1/2	4/2	9/-	9/1	7/1

3. RECOMMENDATIONS (Letter to the sponsor):

Please provide urine pH values of each control and treated rats including the information as to the presence of calculi in the rats that had bladder carcinoma.

cc: Original IND, HFD-510
R. Steigerwalt/H. Rhee

/s/

Herman M. Rhee, Ph.D.

APPEARS THIS WAY ON ORIGINAL

**STATISTICAL REVIEW AND EVALUATION
CARCINOGENICITY**

Date	APR 2 1999
NDA No.	21-073
IND No.	N/A
Applicant	Takeda America Research and Development Center, Inc.
Name of Drug	Actos™ (pioglitazone HCl)
Document Reviewed	• Rat Study: Vol. 1.048 • Mouse Study: Vol. 1.038
Statistical Reviewer	Ji-Yang (Ted) Guo, Div II/OEB, HFD-715
Pharmacologist	Herman Rhee, Ph.D., ODE 2, HFD-510

Summary

This review evaluates the sponsor's studies of Actos™ [AD-4833 (HCl)] for carcinogenic potential in rats and mice. Based on the survival-data analysis and the tests for dose-tumor positive linear trend, this reviewer informs the reviewing pharmacologist, Dr. Herman Rhee the carcinogenicity findings of Actos™. The following highlights summarize this reviewer's statistical conclusions:

- Actos™ is carcinogenic in **male rats**, causing
 - fibrosarcoma (code: 324) in skin, subcutis (code: 333)
 - carcinoma, transitionalc (code: 798) in urinarybladder (code: 78)
- The Actos™ is carcinogenic in **female rats**, causing
 - lipoma (code: 508) in skin, subcutis (code: 333)
- The Actos™ is not carcinogenic in mice in either sex.

This reviewer concludes: Actos™ is carcinogenic in rats. The probability of erroneously concluding a significant test is 10% or less of the time.

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Introduction

This reviewer evaluates the studies of Actos™ (pioglitazone HCl, coded as AD-4833) for carcinogenic potential in rats and mice, conducted by Takeda America Research and Development Center, Inc. In this report, this reviewer presents to the reviewing pharmacologist, Dr. Herman Rhee his independent carcinogenicity analysis based on the sponsor's data. The computer output of major statistical calculations is included in the appendix.

Sponsor's Studies

The sponsor analyzed the carcinogenic potential of the Actos™ in male and female rats and mice. Table 1 summarizes the sponsor's studies (dated January 15, 1999):

Table 1. Description of Studies

Study Number	295-152	295-153
Species	Rat	Mouse
Strain	CrI: CD® BR	CrI: CD-1® (ICR) VAF/Plus™
Route of Administration	Oral gavage	Oral gavage
Dose Unit	Mg/kg/day	Mg/kg/day
Dose level	0, 0, 1, 4, 8, 16, and 63	0, 0, 3, 10, 30, and 100
Number of Animals/per treatment group	60	60
Length of Study	104 weeks	104 weeks
Study Duration	8/11/93-8/8/95	8/17/93-8/25/95

Please note that the female-rat study does not have the 8 mg/kg/day dose group. The zero-dose groups represent the control. The terminal sacrifice started on and after week 104.

Documents Reviewed

This reviewer did not formally received desk copies of the sponsor's report for review. However, a selected section of the NDA submission was photocopied from pages 17-21, section 5.1.2.3 Oncogenicity, vol. 1.038 & vol. 1.048. This reviewer finds the conclusions on carcinogenicity using these materials.

Data Analyzed

The sponsor submitted the data on a 3.5" diskette labeled FDA FORMAT DATA DISK STUDIES 295-152+153 12/16/98. The data were compressed into a self-extracting file, Mpidata.exe.

The following points list the uncompressed data files:

1. Rat Data (Study 295-152)
 - DATFL152.DAT
 - ORGAN152.DAT
 - TUMOR152.DAT
2. Mouse Data (Study 295-153)
 - DATFL153.DAT

- ORGAN153.DAT
- TUMOR153.DAT

MPI Research created the data files on 12/16/98, indicated in the README file.

Sponsor's Findings

In the rat study, the sponsor appeared to concern the lesions in urinary bladder in rats. In the section of Oncogenicity (section 5.1.2.3, pages 17-21), the sponsor described it's findings for lesions in urinary bladder in rats. This reviewer summarizes the sponsor's findings in Table 2.

Table 2. Number of Lesions in Urinary Bladder in Rats

Sex	Lesion	Incidence By Dose (mg/kg/day)						
		0	0	1	4	8	16	63
Male	Hyperplasia, epithelial, papillary	3	0	1	2	1	1	1
Female		0	0	1	1		0	1
Male	Hyperplasia, epithelial, simple	1	3	0	2	7	10	7
Female		1	1	2	5		3	11
Male	Hyperplasia, epithelial, nodular	0	0	0	0	4	1	0
Female		0	0	0	0		0	0
Male	Transitional cell tumor, benign	0	0	0	0	4	2	2
Female		0	0	1	1		1	0
Male	Carcinoma, transitional cell	0	0	0	2	3	5	4
Female		0	0	0	0		0	0

(Source: Sponsor's table on page 19, section 5.1.2.3)

The sponsor concluded, "These data support the hypothesis that the urinary bladder tumors observed in the male rats were due to the formation of calculi which subsequently induced hyperplasia."

In the mouse study, the sponsor concluded, "No increase in the incidence of tumors and no evidence of an oncogenic effect were observed at any dose."

Reviewer's Comment:

In the Oncogenicity section of the sponsor's report, the sponsor did not directly state whether the lesion in urinary bladder in rats was dose related. In the end, the sponsor concluded, "AD-4833 (HCl) was not considered to represent a carcinogenic risk to humans (page 21, section 5.1.2.3)." This reviewer concludes that the sponsor's viewpoint is equivocal.

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Reviewer's Evaluation

Evaluation of Carcinogenicity Study on Male Rats

To evaluate the sponsor's carcinogenicity study on male rats, this reviewer analyzed the sponsor's data. The reviewer's evaluation comprises the following:

- survival-data analysis
- tumor-data analysis

The reviewer's conclusions are summarized at the end of this section.

Survival-Data Analysis

The survival-data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that the higher the dose level is, the more deaths are likely to occur.

Table 3 shows the number of male rats by treatment by age group. The dose levels labeled "CTRL1," "CTRL2," "LOW," "MED," "MEDHI," "HIGH," and "MAXI" represent 0, 0, 1, 4, 8, 16, and 63 mg/kg/day, respectively. The time interval "104-105" represents the terminal-sacrifice week. Please note that the number of rats died in 78 weeks of study is higher in the MAXI group than in other groups.

Table 3. Number of Male Rats by Treatment and Age Group

Number of Animals
Species: Rat
Sex: Male

	Treatment Group							Total Count
	CTRL1	CTRL2	LOW	MED	MEDHI	HIGH	MAXI	
	Count	Count	Count	Count	Count	Count	Count	
Time Interval								
0-52	4	7	4	3	6	9	13	46
53-78	9	8	2	12	9	14	19	73
79-91	4	8	8	12	13	4	12	61
92-103	10	13	10	10	9	11	11	74
104-105	33	24	36	23	23	22	5	166
Total	60	60	60	60	60	60	60	420

Source: D:\ACTOS\rats.txt

Table 4 describes, for the male rats, the number of deaths, the number at risk, and the cumulative percentages of deaths by treatment and age group.

Table 4. Cumulative Percentages of Deaths in Male Rats

Analysis of Mortality
Species: Rat
Sex: Male

Time(-wks)	Dose														
	CTRL1			CTRL2			LOW			MED			MEDH1		
	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died
0-52	4	60	6.7	7	60	11.7	4	60	6.7	3	60	5.0	6	60	10.0
53-78	9	56	21.7	8	53	25.0	2	56	10.0	12	57	25.0	9	54	25.0
79-91	4	47	28.3	8	45	38.3	8	54	23.3	12	45	45.0	13	45	46.7
92-103	10	43	45.0	13	37	60.0	10	46	40.0	10	33	61.7	9	32	61.7
104-105	33	60	55.0	24	60	40.0	36	60	60.0	23	60	38.3	23	60	38.3

(CONTINUED)

Species: Rat
Sex: Male

Time(-wks)	Dose					
	HIGH			MAXI		
	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died
0-52	9	60	15.0	13	60	21.7
53-78	14	51	38.3	19	47	53.3
79-91	4	37	45.0	12	28	73.3
92-103	11	33	63.3	11	16	91.7
104-105	22	60	36.7	5	60	8.3

Source: d:\actos\rats\m\XAnimalX.txt

Figure 1 helps visualize the cumulative percentages of deaths over time by treatment. The HIGH and MAXI groups clearly shows dose-related mortalities compared with the two control groups.

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Figure 1. Line Graph of Cumulative Percentages of Deaths in Male Rats

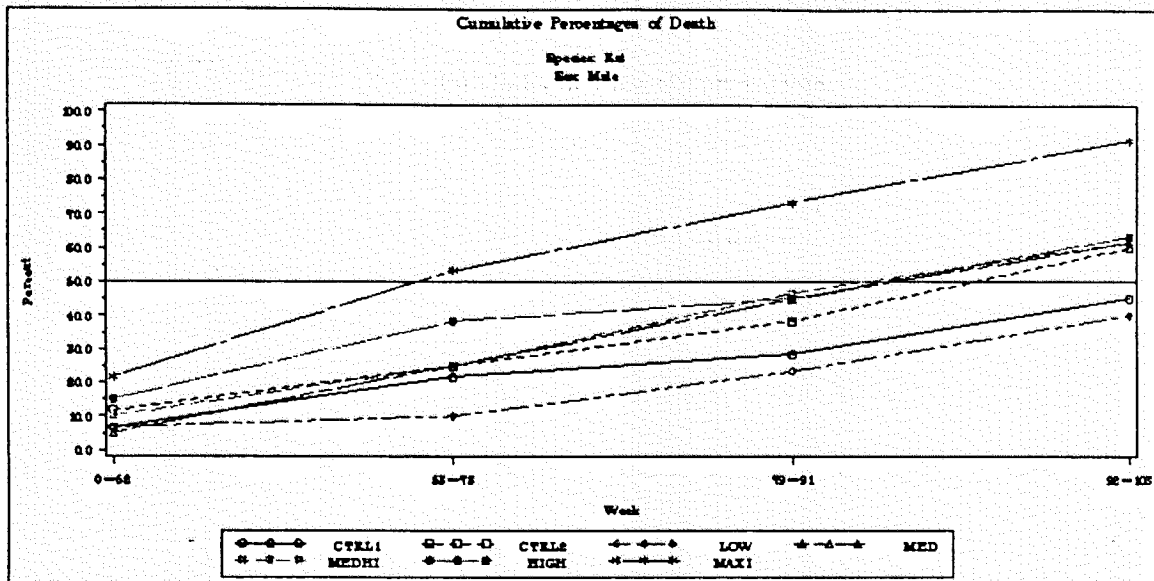
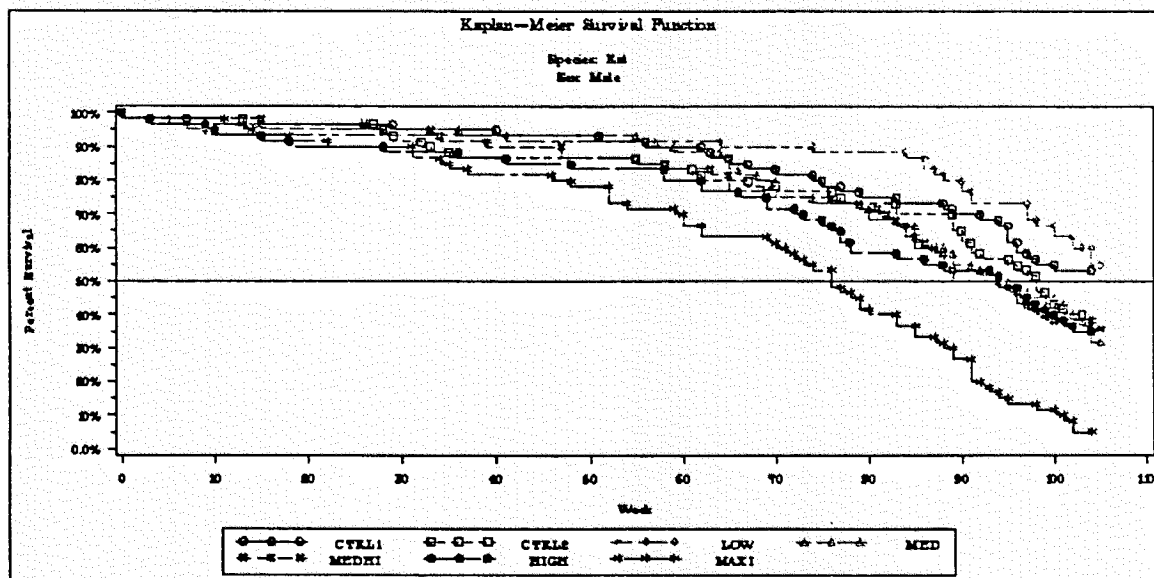


Figure 2 shows the Kaplan-Meier survival functions for male rats. The animals in the MAXI (63 mg/kg/day) group had a markedly lower survival rate than did those in other groups

Figure 2. Kaplan-Meier Survival Functions for Male Rats



The test for dose-mortality trend (Table 5) shows significant results based on the Cox test (p=0) and Kruskal-Wallis test (p=0).

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Table 5. Dose-Mortality Trend in Male Rats

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute			
Species: Rat			
Sex: Male			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	63.88	0.0000
	Depart from Trend	6.24	0.2835
	Homogeneity	70.12	0.0000
Kruskal-Wallis	Dose-Mortality Trend	54.60	0.0000
	Depart from Trend	6.21	0.2868
	Homogeneity	60.80	0.0000

Source: d:\actos\rats\m\XAnimalX.txt

This reviewer's survival-data analysis concludes that the mortality in male rats is positively dose-related. Therefore, the age-adjusted trend test detailed in the following section (Tumor-Data Analysis), is justified.

Tumor-Data Analysis

The tumor-data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tests this trend for every organ and tumor. The resulting p-values are compared against the p-value cutoff points set by the following Agency's procedures. A significant result indicates a dose-tumor positive linear trend.

Statistical Procedure in Evaluation of Tumor-Data Analyses Currently Adopted by CDER Divisions of Biometrics	
•	For tumors found either fatal or non-fatal to all the animals, the statistical interpretation is based on the exact test .
•	For tumors found fatal to some, but not to all animals, the statistical interpretation is based on the asymptotic test , resulting from the combined test. The asymptotic test uses the Z-statistic, which follows a standard normal distribution.
•	To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 0.1, this rule states: • Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level. • Otherwise, the 0.005 significance level may be used.

Table 6 quotes the significant trend-tests for male rats. This reviewer informs the reviewing pharmacologist the statistically significant dose-tumor positive linear trend in the male rats.

Table 6. Significant Trend-Tests for Male Rats

Organ	Tumor	Tumor-Bearing Animals	P-value
Skin, Subcutis (333)	Fibrosarcoma (324)	0 0 0 0 0 2 2	=0.000 (P<0.025)
Urinary Bladder (78)	Carcinoma, transitionalc (798)	0 0 0 2 4 5 4	=0.000 (P<0.025)

Conclusions on Male-Rat Study

This reviewer informs the reviewing pharmacologist that Actos™ is potentially carcinogenic (Table 6). Please note that the test could lead to a false conclusion due to chance alone. However, the probability of erroneously concluding a significant test is about 10% or less.

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Evaluation of Carcinogenicity Study on Female Rats

To evaluate the sponsor's carcinogenicity study on female rats, this reviewer analyzed the sponsor's data. The reviewer's evaluation comprises the following:

- survival-data analysis
- tumor-data analysis

The reviewer's conclusions are summarized at the end of this section.

Survival-Data Analysis

The survival-data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that the higher the dose level is, the more deaths are likely to occur.

Table 7 shows the number of female rats by treatment by age group. The dose levels labeled "CTRL1," "CTRL2," "LOW," "MED," "HIGH," and "MAXI" represent 0, 0, 1, 4, 16, and 63 mg/kg/day, respectively. Unlike the male rats, the study of female rats does not have the 8-mg/kg/day dose. The time interval "104-105" represents the terminal-sacrifice week.

Table 7. Number of Female Rats by Treatment and Age Group

Number of Animals
Species: Rat
Sex: Female

	Treatment Group						Total Count
	CTRL1	CTRL2	LOW	MED	HIGH	MAXI	
	Count	Count	Count	Count	Count	Count	
Time Interval							
0-52	3	1	1	2	4	7	18
53-78	7	7	5	7	14	10	50
79-91	8	4	8	5	14	11	51
92-103	10	19	9	15	7	8	68
104-105	31	29	37	31	21	24	173
Total	60	60	60	60	60	60	360

Source: d:\actos\rats\XAnimalX.txt

Table 8 describes, for the female rats, the number of deaths, the number at risk, and the cumulative percentages of deaths by treatment and age group.

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Table 8. Cumulative Percentages of Deaths in Female Rats

Analysis of Mortality
Species: Rat
Sex: Female

Time(-wks)	Dose																	
	CTRL1			CTRL2			LOW			MED			HIGH			MAXI		
	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died
0-52	3	60	5.0	1	60	1.7	1	60	1.7	2	60	3.3	4	60	6.7	7	60	11.7
53-78	7	57	16.7	7	59	13.3	5	59	10.0	7	58	15.0	14	56	30.0	10	53	28.3
79-91	9	50	31.7	4	52	20.0	8	54	23.3	5	51	23.3	14	42	53.3	11	43	46.7
92-103	10	41	48.3	19	48	51.7	9	46	38.3	15	46	48.3	7	28	65.0	8	32	60.0
104-105	31	60	51.7	29	60	48.3	37	60	61.7	31	60	51.7	21	60	35.0	24	60	40.0

Source: d:\actos\rate\ANIMALIX.txt

Figure 3 helps visualize the cumulative percentages of deaths over time by treatment. The HIGH and MAXI groups clearly shows dose-related mortalities compared with the two control groups.

Figure 3. Line Graph of Cumulative Percentages of Deaths in Female Rats

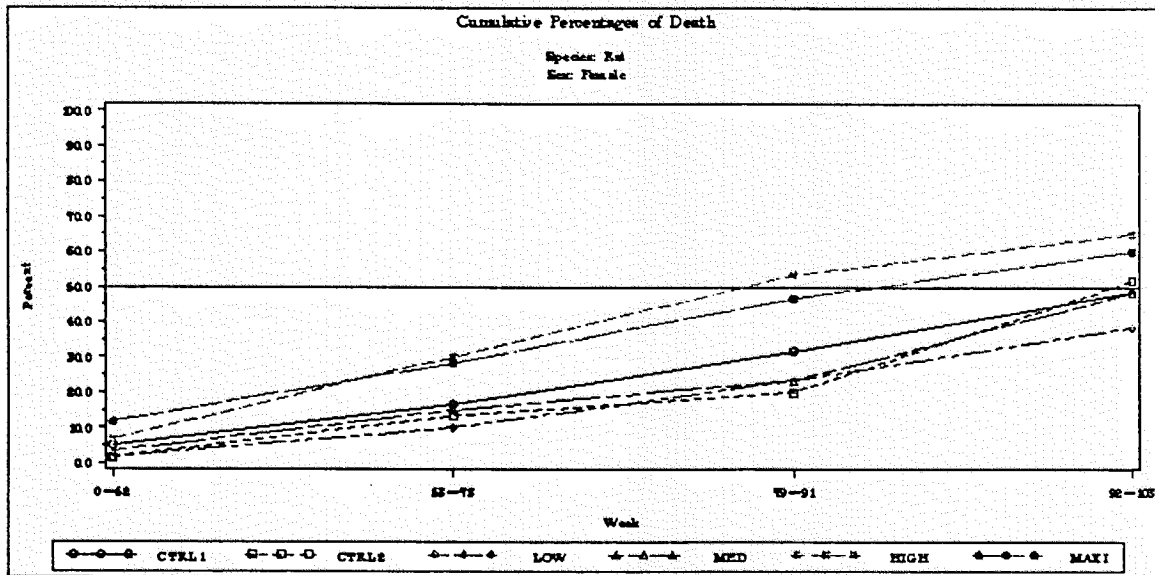
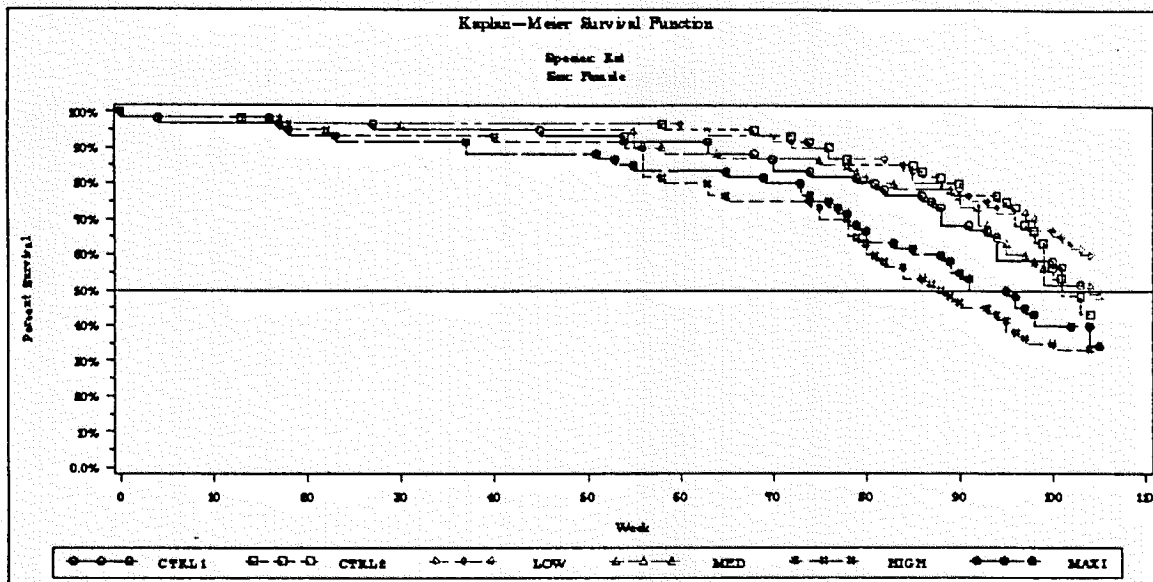


Figure 4 shows the Kaplan-Meier survival functions for female rats. The animals in the HIGH (16 mg/kg/day) and MAXI (63 mg/kg/day) groups died earlier than did those in other groups.

Figure 4. Kaplan-Meier Survival Functions for Female Rats



The test for dose-mortality trend (Table 9) shows significant results based on the Cox test ($p=0.0078$) and Kruskal-Wallis test ($p=0.0022$).

Table 9. Dose-Mortality Trend in Female Rats

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute			
Species: Rat			
Sex: Female			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	7.08	0.0078
	Depart from Trend	10.35	0.0349
	Homogeneity	17.43	0.0038
Kruskal-Wallis	Dose-Mortality Trend	9.36	0.0022
	Depart from Trend	12.46	0.0143
	Homogeneity	21.82	0.0006

Source: d:\actos\rats\1\XANIM1X.txt

This reviewer's survival-data analysis concludes that the mortality in female rats is positively dose-related. Therefore, the age-adjusted trend test detailed in the following section (Tumor-Data Analysis), is justified.

Tumor-Data Analysis

The tumor-data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tests this trend for every organ and tumor. The resulting p-values are

compared against the p-value cutoff points set by the following Agency's procedures. A significant result indicates a dose-tumor positive linear trend.

Statistical Procedure in Evaluation of Tumor-Data Analyses Currently Adopted by CDER Divisions of Biometrics	
•	For tumors found either fatal or non-fatal to all the animals, the statistical interpretation is based on the exact test .
•	For tumors found fatal to some, but not to all animals, the statistical interpretation is based on the asymptotic test , resulting from the combined test. The asymptotic test uses the Z-statistic, which follows a standard normal distribution.
•	To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 0.1, this rule states: • Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level. • Otherwise, the 0.005 significance level may be used.

Table 10 quotes the significant trend-tests for female rats. This reviewer informs the reviewing pharmacologist the statistically significant dose-tumor positive linear trend in the female rats.

Table 10. Significant Trend-Tests for Female Rats

Organ	Tumor	Tumor-Bearing Animals	P-value
Skin, Subcutis (333)	Lipoma (508)	0 0 1 0 1 3	=0.000 (P<0.025)

Conclusions on Female-Rat Study

This reviewer informs the reviewing pharmacologist that the Actos™ is potentially carcinogenic (Table 10). Please note that the test could lead to a false conclusion due to chance alone. However, the probability of erroneously concluding a significant test is about 10% or less.

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Evaluation of Carcinogenicity Study on Male Mice

To evaluate the sponsor's carcinogenicity study on male mice, this reviewer analyzed the sponsor's data. The reviewer's evaluation comprises the following:

- survival-data analysis
- tumor-data analysis

The reviewer's conclusions are summarized at the end of this section.

Survival-Data Analysis

The survival-data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that the higher the dose level is, the more deaths are likely to occur.

Table 11 shows the number of male mice by treatment by age group. The dose levels labeled "CTRL1," "CTRL2," "LOW," "MED," "HIGH," and "MAX1" represent 0, 0, 3, 10, 30, and 100 mg/kg/day, respectively. The time interval "104-106" represents the terminal-sacrifice week.

Table 11. Number of Male Mice by Treatment and Age Group

Number of Animals
Species: Mouse
Sex: Male

	Treatment Group						Total
	CTRL1	CTRL2	LOW	MED	HIGH	MAX1	
	Count	Count	Count	Count	Count	Count	
Time Interval							
0-52	6	7	5	6	9	12	45
53-78	6	5	13	7	7	10	48
79-91	10	5	11	7	8	11	52
92-103	11	10	6	7	8	9	51
104-106	27	33	25	33	28	18	164
Total	60	60	60	60	60	60	360

Source: d:\actos\mice\MAXAnimalX.txt

Table 12 describes, for the male mice, the number of deaths, the number at risk, and the cumulative percentages of deaths by treatment and age group.

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Table 12. Cumulative Percentages of Deaths in Male Mice

Analysis of Mortality
Species: Mouse
Sex: Male

Time (-wks)	Dose																	
	CTRL1			CTRL2			LOW			MED			HIGH			MAXI		
	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died
0-52	6	60	10.0	7	60	11.7	5	60	8.3	6	60	10.0	8	60	15.0	12	60	20.0
53-78	6	54	20.0	5	53	20.0	13	55	30.0	7	54	21.7	7	51	26.7	10	48	36.7
79-91	10	48	36.7	5	48	28.3	11	42	48.3	7	47	33.3	8	44	40.0	11	38	55.0
82-103	11	38	55.0	10	43	45.0	6	31	58.3	7	40	45.0	8	36	53.3	8	27	70.0
104-106	27	60	45.0	33	60	55.0	25	60	41.7	33	60	55.0	28	60	46.7	18	60	30.0

Figure 5 helps visualize the cumulative percentages of deaths over time by treatment. The MAXI (100 mg/kg/day) group had the highest cumulative percentage of death among all groups.

Figure 5. Line Graph of Cumulative Percentages of Deaths in Male Mice

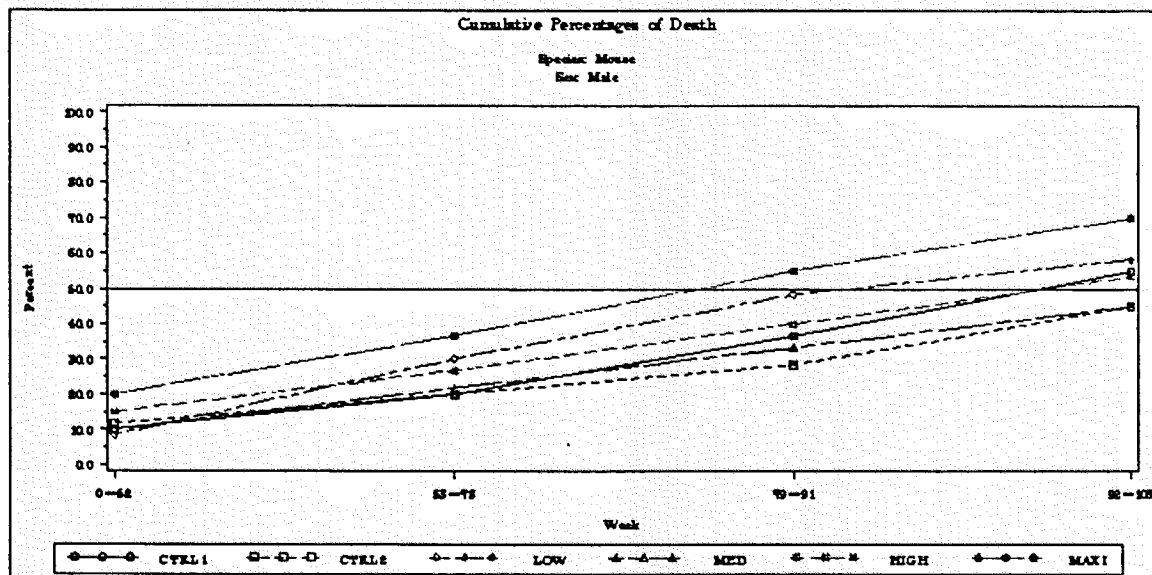
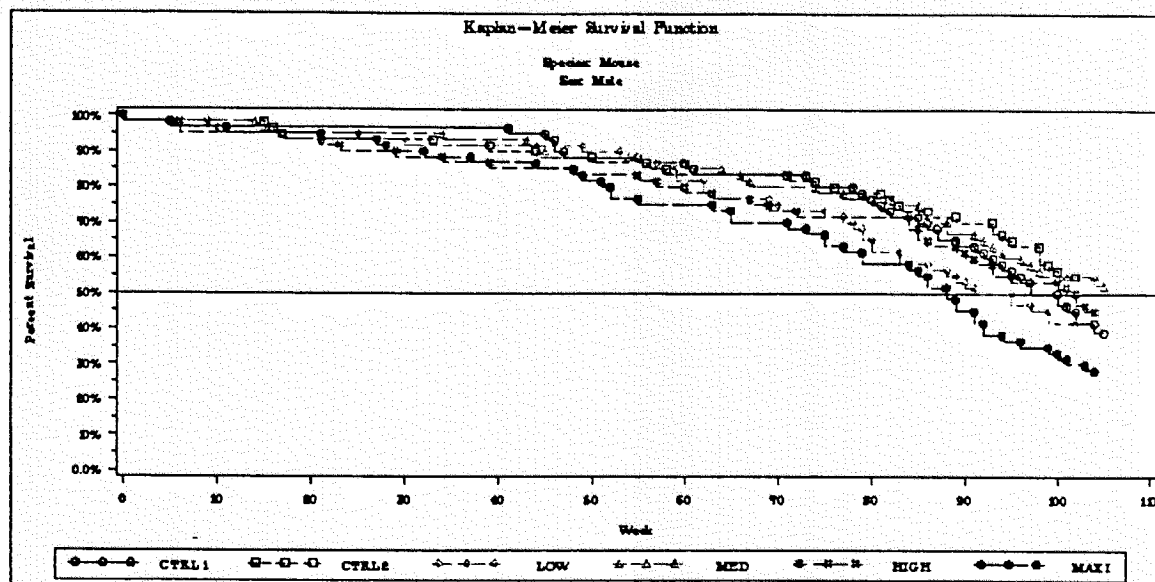


Figure 6 shows the Kaplan-Meier survival functions for male mice. The animals in the MAXI (100 mg/kg/day) group had a slightly lower survival rate than did those in other groups.

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Figure 6. Kaplan-Meier Survival Functions for Male Mice



The test for dose-mortality trend shows significant results based on the Cox test ($p=0.0040$) and Kruskal-Wallis test ($p=0.0044$). (See Table 13.)

Table 13. Dose-Mortality Trend in Male Mice

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute			
Species: Mouse Sex: Male			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	8.31	0.0040
	Depart from Trend	3.77	0.4378
	Homogeneity	12.08	0.0338
Kruskal-Wallis	Dose-Mortality Trend	8.13	0.0044
	Depart from Trend	3.29	0.5112
	Homogeneity	11.42	0.0437

Source: d:\actos\mice\m\XAnimalX.txt

This reviewer's survival-data analysis concludes that the mortality in male mice is positively dose-related. Therefore, the age-adjusted trend test detailed in the following section (Tumor-Data Analysis), is justified.

Tumor-Data Analysis

The tumor-data analysis determines whether the dose-tumor positive linear trend is statistically significant. This reviewer tests this trend for every organ and tumor. The resulting p-values are compared against the

p-value cutoff points set by the following Agency's procedures. A significant result indicates a dose-tumor positive linear trend.

**Statistical Procedure in Evaluation of Tumor-Data Analyses
Currently Adopted by CDER Divisions of Biometrics**

- For tumors found either fatal or non-fatal to all the animals, the statistical interpretation is based on the **exact test**.
- For tumors found fatal to some, but not to all animals, the statistical interpretation is based on the **asymptotic test**, resulting from the combined test. The asymptotic test uses the Z-statistic, which follows a standard normal distribution.
- To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 0.1, this rule states:
 - Tumors with a spontaneous tumor rate of **1% or less** may be tested at the **0.025** significance level.
 - Otherwise, the **0.005** significance level may be used.

This reviewer's analysis does not find any statistically significant dose-tumor positive linear trend in the male mice.

Conclusions on Male-Mouse Study

This reviewer's analysis does not find any statistically significant dose-tumor positive linear trend in the male mice.

APPEARS THIS WAY ON ORIGINAL

Evaluation of Carcinogenicity Study on Female Mice

To evaluate the sponsor's carcinogenicity study on female mice, this reviewer analyzed the sponsor's data. The reviewer's evaluation comprises the following:

- survival-data analysis
- tumor-data analysis

The reviewer's conclusions are summarized at the end of this section.

Survival-Data Analysis

The survival-data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that the higher the dose level is, the more deaths are likely to occur.

Table 14 shows the number of female mice by treatment by age group. The dose levels labeled "CTRL1," "CTRL2," "LOW," "MED," "HIGH," and "MAXI" represent 0, 0, 3, 10, 30, and 100 mg/kg/day, respectively. The time interval "104-106" represents the terminal-sacrifice week.

Table 14. Number of Female Mice by Treatment and Age Group

Number of Animals
Species: Mouse
Sex: Female

	Treatment Group						Total
	CTRL1	CTRL2	LOW	MED	MEDHI	HIGH	
	Count	Count	Count	Count	Count	Count	Count
Time Interval							
0-52	3	3	4	2	3	9	24
53-78	11	7	9	9	9	13	58
79-91	19	12	10	12	7	8	69
92-103	7	16	13	6	15	8	65
104-106	20	22	24	31	26	21	144
Total	60	60	60	60	60	60	360

Source: d:\actos\mice\F\XAnimalX.txt

Table 15 describes, for the female mice, the number of deaths, the number at risk, and the cumulative percentages of deaths by treatment and age group.

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Table 15. Cumulative Percentages of Deaths in Female Mice

Analysis of Mortality
Species: Mouse
Sex: Female

Time(- wks)	Dose																	
	CTRL1			CTRL2			LOW			MED			HIGH			MAXI		
	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died
0-52	3	60	5.0	3	60	5.0	4	60	6.7	2	60	3.3	3	60	5.0	8	60	15.0
53-78	11	57	23.3	7	57	16.7	9	56	21.7	8	58	18.3	9	57	20.0	13	51	36.7
79-91	19	46	55.0	12	50	36.7	10	47	38.3	12	49	38.3	7	48	31.7	8	38	51.7
92-103	7	27	66.7	16	38	63.3	13	37	60.0	6	37	48.3	15	41	56.7	8	29	65.0
104- 106	20	60	33.3	22	60	36.7	24	60	40.0	31	60	51.7	26	60	43.3	21	60	35.0

Figure 7 helps visualize the cumulative percentages of deaths over time by treatment. The doses do not appear to associate the cumulative percentages of deaths.

Figure 7. Line Graph of Cumulative Percentages of Deaths in Female Mice

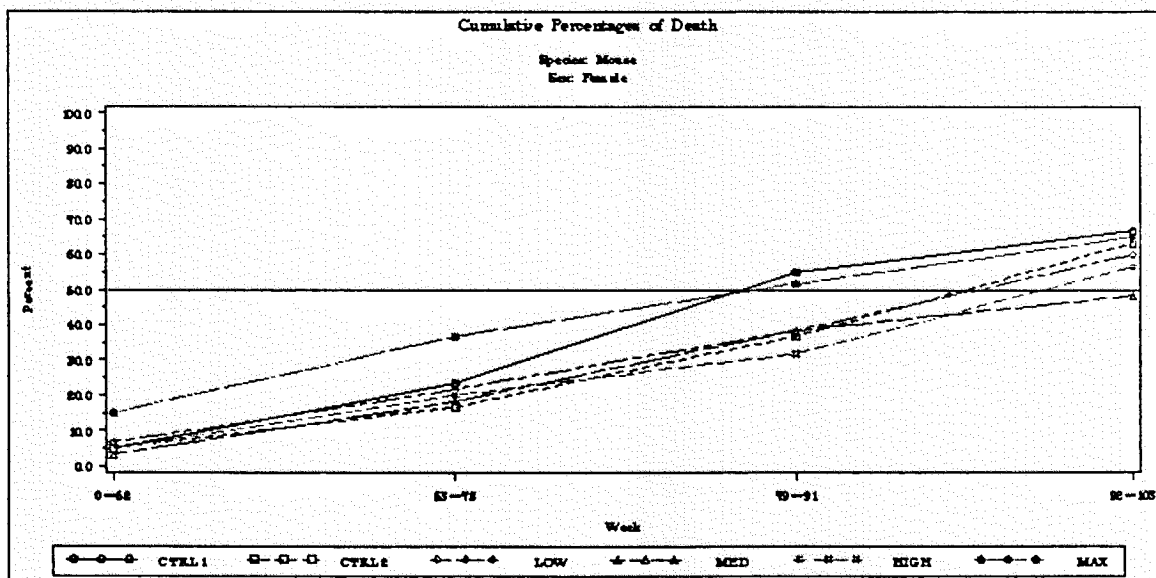
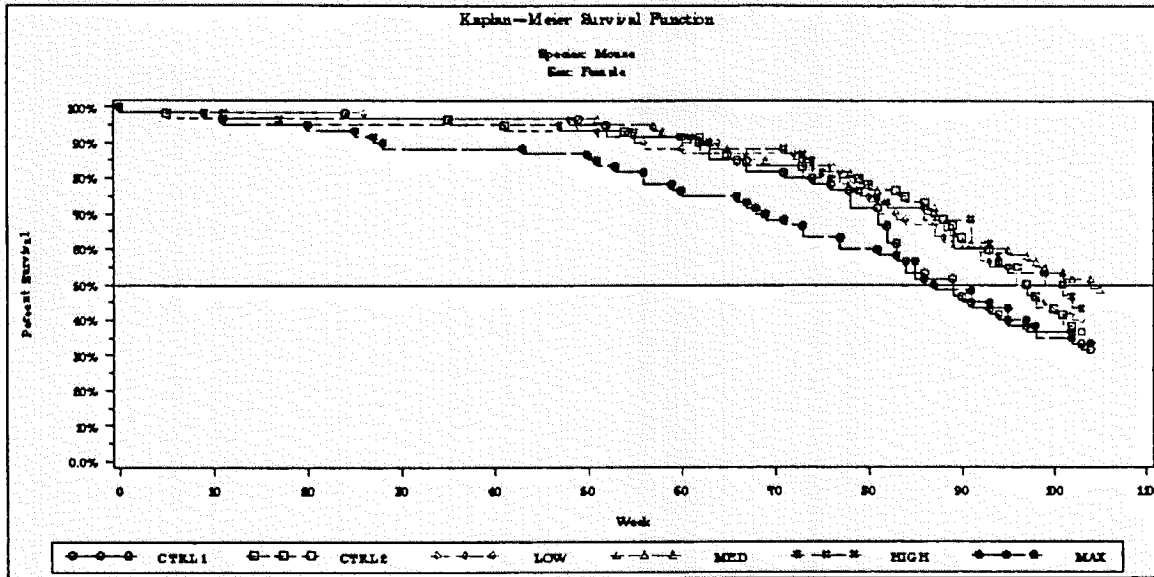


Figure 8 shows the Kaplan-Meier survival functions for female mice. The animals in the MAXI (100 mg/kg/day) group had a lower survival rate than did those in other groups. The MAXI group had more early deaths than did other groups.

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Figure 8. Kaplan-Meier Survival Functions for Female Mice



The dose-mortality-trend test in the following Table 16 does not indicate a significant trend ($p > 0.05$).

Table 16. Dose-Mortality Trend in Female Mice

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute			
Species: Mouse			
Sex: Female			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	1.45	0.2280
	Depart from Trend	5.54	0.2362
	Homogeneity	6.99	0.2212
Kruskal-Wallis	Dose-Mortality Trend	3.27	0.0704
	Depart from Trend	5.38	0.2504
	Homogeneity	8.65	0.1237

Source: d:\actos\mice\fxAnimalX.txt

Tumor-Data Analysis

The tumor-data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tests this trend for every organ and tumor. The resulting p-values are compared against the p-value cutoff points set by the following Agency's procedures. A significant result indicates a dose-tumor positive linear trend.

APPEARS THIS WAY ON ORIGINAL

**Statistical Procedure in Evaluation of Tumor-Data Analyses
Currently Adopted by CDER Divisions of Biometrics**

- For tumors found either fatal or non-fatal to all the animals, the statistical interpretation is based on the **exact test**.
- For tumors found fatal to some, but not to all animals, the statistical interpretation is based on the **asymptotic test**, resulting from the combined test. The asymptotic test uses the Z-statistic, which follows a standard normal distribution.
- To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 0.1, this rule states:
 - Tumors with a spontaneous tumor rate of **1% or less** may be tested at the **0.025** significance level.
 - Otherwise, the **0.005** significance level may be used.

This reviewer's analysis does not find any statistically significant dose-tumor positive linear trend in the female mice.

Conclusions on Female-Mouse Study

This reviewer's analysis does not find any statistically significant dose-tumor positive linear trend in the female mice.

APPEARS THIS WAY ON ORIGINAL

Conclusions

Based on the evaluation of the carcinogenicity studies on rats and mice, this reviewer's concludes that Actos™ is carcinogenic in rats. The probability of erroneously concluding a significant test is about 10% or less.

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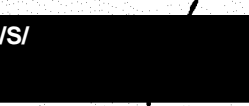
Signoff Page

Statistical Reviewer: Ji-Yang (Ted) Guo

Signature: 

Date: 4/21/99

Concur: Karl K. Lin, Ph.D.

Signature: 

Date: 4/21/99

CC:

Archival NDA 21-073 (Non-Clinical: Carcinogenicity Review)

HFD-510/Division file

HFD-510/HRhee

HFD-510/JWeber

HFD-715/Division file

HFD-715/KLin

HFD-715/Tguo

HFD-715/TSahlroot

HFD-700/CAnello

TG/March 29, 1999/actos.doc

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

STATISTICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUN 17 1999

FROM: Mathematical Statistician (HFD-715)

THRU: Edward Nevius, Ph.D. [redacted] 6-17-99
Director, Division of Biometrics II. (HFD-715)

SUBJECT: Revised Package Insert for ACTOS® (Pioglitazone)

APPLICANT: Takeda America Research & Development Center, Inc.

TO: File (NDA 21-073)

Reviewer's Comments:

1. The Monotherapy subsection of the Clinical Studies section of the revised package insert dated May 28, 1999, presents results from a subgroup of randomized patients who were not previously treated with antidiabetic medication (naïve patients).

The estimators from the 3 monotherapy studies at endpoint in HbA_{1c} are displayed in the following table for all randomized patients and naïve patients.

Mean Treatment Difference from Placebo in HbA_{1c} for All Randomized Patients and Patients Not Previously Treated with Antidiabetic Medications

HbA _{1c} (%)	ACTOS					
	15 mg		30 mg		45 mg	
	N	Difference	N	Difference	N	Difference
Study 01						
Randomized	79	-1.0	85	-1.0	76	-1.6
Naïve	26	-1.4	26	-1.3	21	-2.6
Study 12			7.5/15/30 mg		15/30/45 mg	
Randomized			85	-1.5	85	-1.5
Naïve			20	-2.3	20	-2.6
Study 26			30 mg			
Randomized			100	-1.4		
Naïve			39	-1.0		

Treatment differences for patients who were not previously treated with antidiabetic medications were greater than those for all randomized patients for the 45 mg pioglitazone treatment group (-2.6% vs. -1.6%) which had only ~20 patients. It seems reasonable to make the label consistent with the Avandia label, which presented monotherapy data for all randomized patients. Presenting only the naïve patients in the label gives the sponsor an advantage in the effect size of the HbA_{1c} and FBG reduction.

2. For Monotherapy studies, using the first study as an example, this reviewer proposes to revise the text and to present the efficacy outcome in a table that follows:

In a 26-week dose ranging study, 408 patients were randomized to receive 7.5, 15, 30, or 45 mg of ACTOS, or placebo of which 125 patients had not been previously treated with antidiabetic medication. The 7.5 mg dose was not statistically significant from placebo. At endpoint, treatment with 15 to 45 mg of ACTOS produced statistically significant improvement in HbA_{1c} and FBG compared with patients who received placebo (see Table 1).

Table 1. Monotherapy: 26-Week Study Mean Change from Baseline

	Placebo	15 mg	ACTOS	
			30 mg	45 mg
N	79	79	85	76
HbA_{1c} (%)				
Mean Baseline	10.4	10.2	10.2	10.3
Mean Change from Baseline	+0.7	-0.3	-0.3	-0.9
Mean Difference from Placebo	-	-1.0	-1.0	-1.6
FBG (mg/dL)				
Mean Baseline	268	267	269	276
Mean Change from Baseline	+9	-30	-32	-56
Mean Difference from Placebo	-	-39	-41	-65

3. This applies to all the sponsor's bar graphs that only presented the treatment differences from placebo for the pioglitazone treatment groups. This reviewer suggests that the change from baseline for all treatment groups (placebo and the pioglitazone treatment groups) should be presented.
4. On page 9, the sponsor claims all three monotherapy studies indicate that maximal reduction in HbA_{1c} levels may not have been achieved by the end of the study. This statement is a speculation and should be removed.

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On page 9, the purpose of the statement "In general, patients who had not been previously treated with antidiabetic medication whose FBG decreased ≥ 30 mg/dL had an HbA_{1c} decrease of $\geq 0.5\%$. Furthermore, approximately one-third of patients whose FBG did not decrease by at least 30 mg/dL also showed a decrease in HbA_{1c} of $>0.6\%$." is unclear.

/S/

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Todd Sahlroot

/S/

6/17/99.

cc:

Arch NDA 21-073

HFD-510

HFD-510/SSobel, SMalozowski, RMisbin, JWeber

HFD-715/ENevius, TSahlroot, LPian, Division 2 file

Chron.

APPEARS THIS WAY ON ORIGINAL

Statistical Review and Evaluation
Clinical Studies

NDA#: 21-073

JUN 17 1999

Applicant: Takeda America Research & Development Center, Inc.

Name of Drug: Actos® (pioglitazone HCl) Tablets

Indication: Type 2 Diabetes

Document Reviewed: 1.001, 1.002, 1.250-1.368
Submission dated January 15, 1999

Medical Reviewer: This review has been discussed with the clinical reviewer, Robert Misbin M.D. (HFD-510)

1. Introduction

Pioglitazone, a thiazolidinedione compound belongs to a class of drugs that act primarily to decrease insulin resistance. In this submission, there were 11 controlled trials (6 monotherapy & 5 add-on therapy) to support the indication of glycemic control in patients with type 2 diabetes. Three U.S. monotherapy and 3 U.S. add-on trials were designated as pivotal. This review discusses the 6 U.S. trials.

2. Monotherapy Trials

General Design

The 6 trials were all double-blind, randomized, placebo-controlled, multicenter studies as summarized in Table 1. The 3 U.S. protocols (& amendments) included patients 30-75 years of age, with a BMI of 25-40 kg/m², C-peptide >1 ng/ml at visit 1, a normal thyroid function, weight-maintaining diet, FBG ≥140 mg/dL at Visit 1, HbA_{1c} ≥7.0% at Visit 4 (001), HbA_{1c} ≥7.5% and ≥8.0% at visit 3 (012, 026). Pertinent criteria for removal of patients from study therapy were protocol violation, AEs that, in the opinion of the investigator, required early termination, noncompliance, insufficient therapeutic effect, including FBG >400 mg/dL at 2 consecutive study visits, or which presented a safety risk to the patient, in the investigator's opinion, the development of ketoacidosis, LVH, or anemia.

The studies enrolled both naive patients and patients on antidiabetic medication. Before randomization, patients entered a single-blind placebo period (6 weeks) to washout their prior antidiabetic medication (naive patients entered without washout.)

The primary efficacy variable was change from baseline in HbA_{1c}. The secondary efficacy variables in common were FBG, fasting C-peptide, fasting insulin, triglycerides, and cholesterol (total, HDL, and LDL).

Table 1 Brief Summary of Monotherapy Trials

Study ID	# of Centers	Total Sample Size & Treatment Groups	Design	Duration of Treatment
PNFP-001	US 35	408 placebo 7.5, 15, 30, & 40 mg	fixed-dose, dose-ranging phase 2/3	26 weeks 12/15/95 - 3/13/98
PNFP-012	US 32	260 placebo 7.5 → 15 → 30 mg 15 → 30 → 45 mg	forced dose- titration	24 weeks 1/30/97 - 6/01/98
PNFP-026	US 27	197 placebo, 30 mg	fixed-dose	16 weeks 8/14/97 - 7/14/98
EC-201	Germany 59	235 placebo, 15 mg, 30 mg	fixed-dose	26 weeks
CCT-001 (PD-191)	Japan Kaneko	234 placebo, 15, 30, 45 mg	fixed-dose	12 weeks
CCT-011 (PD-193)	Japan Kaneko	134 placebo, 30 mg	fixed-dose	12 weeks

Statistical Plan

Small centers were pooled before unblinding the treatment code. Centers were considered small if the enrollment was < 1/2 that of the largest center.

The primary analysis for the efficacy variables was on the LOCF dataset of the intent-to-treat population. For a given variable it included patients who were randomized, received at least one dose of the study medication and had a baseline and at least 1 follow-up assessment. Comparison between each pioglitazone treatment group and placebo group was adjusted by Dunnett procedure for multiple pioglitazone dose groups. The analysis of covariance model included terms of treatment, pooled center, and treatment-by-pooled center interaction and baseline value as covariate.

Study PNFP-001 (26 Weeks)

This was a double-blind, randomized, placebo-controlled, multicenter study of 7.5, 15, 30, 45 mg QD of pioglitazone for 26 weeks in type 2 diabetes following a 6-week placebo washout period (previous antidiabetic medications) and 2-week placebo baseline period. Patients had an option to enter a long-term, open-label extension after the double-blind phase. The sponsor will summarize the results from the open-label extension in a separate report.

Single-Blind Placebo					Double-Blind Treatment					Open Label			
6 Weeks			2 Weeks		26 Weeks								
Washout					Baseline					Pioglitazone 45 mg			
										Pioglitazone 30 mg			
Washout					Baseline					Pioglitazone 15 mg			
										Pioglitazone 7.5 mg			
Washout					Baseline					Placebo			
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Week	-8	-4	-2	Day 0	Day 0	2	4	6	10	14	18	22	26

There were 14 scheduled visits including 4 during placebo washout and baseline period, 9 during double-blind treatment period and a follow-up visit (7-14 days after last dose) for patients who did not enter an open-label extension.

In addition to the above planned model and analysis, the sponsor performed three additional efficacy evaluations on:

1. Proportion of patients with $HbA_{1c} < 6.1\%$ at endpoint or a 0.6% decrease in HbA_{1c} from baseline to endpoint and Patients were classified by FBG levels into 3 categories of <140 mg/dL, between 140 and 200 mg/dL and >200 mg/dL at endpoint.
2. A subgroup analysis of the change from baseline in HbA_{1c} in patients enrolled before and after August 7, 1996 (Amendment 4 in effect)
3. A subgroup analysis of changes from baseline in HbA_{1c} and FBG based on prior antidiabetic medication use.

For patients whose triglyceride levels > 400 mg/dL at a given visit, the LDL-cholesterol was not calculated. As a result, the number of patients in the LDL analysis was small and the least square means were not estimable with the full model. Therefore, a reduced model without the interaction term was used in the LDL analysis.

Patient Disposition

A total of 965 patients signed an ICF including 29 patients who signed twice (15 were randomized.) Of the 955 patients who entered single-blind period, 408 patients were randomized 79, 81, 81, 87, 80 to the placebo, 7.5 mg, 15 mg, 30, mg and 45 mg treatment group, respectively. Fifty percent (n=202) patients completed the study. The most common reason for withdrawal was insufficient therapeutic effect. Including therapy related withdrawal (hyperglycemia, unhappy with the glucose control), the rates were 49% (39/79), 37% (28/81), 33% (27/81), 33% (29/87), and 29% (23/80) for the groups from placebo to 45 mg pioglitazone. Table 2 displays patient disposition and Table 3 the number of patients discontinued over time.

Table 2 Patient Disposition – Study 001

	Placebo	7.5 mg	15 mg	30 mg	45 mg
Randomized	79	81	81	87	80
Withdrawn	48 (61%)	38 (47%)	45 (56%)	41 (47%)	34 (43%)
Lack of Efficacy	32 (41%)	21 (26%)	23 (28%)	24 (28%)	20 (25%)
Adverse Event	6 (8%)	5 (6%)	4 (5%)	7 (8%)	6 (8%)
Withdrew Consent	7 (9%)	7 (9%)	10 (12%)	6 (7%)	4 (5%)
Lost to Follow-up	0	1 (1%)	4 (5%)	3 (3%)	2 (2%)
Non-Compliance	1 (1%)	0	1 (1%)	0	1 (1%)
Protocol Violation	1 (1%)	3 (4%)	0	1 (1%)	0
Inclusion/Exclusion	0	0	1 (1%)	0	0
Other	1 (1%)	1 (1%)	2 (2%)	0	1 (1%)
Completed	31 (39%)	43 (53%)	36 (44%)	46 (53%)	46 (57%)

Table 3 Patient Discontinuation by Time – Study 001

	Placebo	7.5 mg	15 mg	30 mg	45 mg	Total
Randomized	79	81	81	87	80	408
Completed	31 (39%)	43 (53%)	36 (44%)	46 (53%)	46 (57%)	202 (49%)
Withdrawn	48 (61%)	38 (47%)	45 (56%)	41 (47%)	34 (43%)	206 (51%)
≤ Week 4	5	8	11	8	8	40 (10%)
> Week 4 & ≤ Week 8	18	11	13	11	8	61 (15%)
> Week 8 & ≤ Week 12	12	12	8	9	5	46 (11%)
> Week 12 & ≤ Week 16	7	3	3	6	7	26 (6%)
> Week 16 & ≤ Week 24	6	3	9	6	5	29 (7%)
> Week 24	0	1	1	1	1	4 (1%)

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Patient Demographics and Baseline Characteristics

Most patients were Caucasian (78%). Fifty eight (58%) percent were male patients. The mean age was 54 years. The average weight was 91 kg and the mean body mass index was 31 kg/m². At baseline, the mean HbA_{1c} was 10.19% and the mean fasting plasma glucose was 268 mg/dL. The mean values of the primary and secondary variables at baseline are presented in Table 4. The baseline values were not significantly different among the treatment groups except LDL (p<0.1).

Table 4 Mean at Baseline in Efficacy Variables – Study 001

	Placebo n=79 ^a		7.5 mg n=81 ^b		15 mg n=81		30 mg n=87		45 mg n=80		Overall p-value ^c
	MEAN	SE	MEAN	SE	MEAN	SE	MEAN	SE	MEAN	SE	
HbA _{1c}	10.38	1.99	10.03	1.73	10.15	2.08	10.11	2.15	10.31	1.80	0.812
FBG (mg/dL)	267.1	70.49	262.1	69.12	268.2	75.30	267.6	77.67	275.4	69.09	0.872
Fasting C-Peptide(ng/mL)	2.06	0.95	2.17	0.76	2.11	0.74	2.16	0.96	2.02	0.71	0.779
Fasting Insulin (μIU/mL)	15.07	12.32	17.85	14.10	15.37	10.15	18.15	19.196	14.98	10.13	0.393
Triglycerides (mg/dL)	262.0	196.9	313.6	538.7	282.3	231.7	261.9	186.2	287.8	249.2	0.781
Total Cholesterol	224.1	43.18	213.3	61.17	218.7	42.93	222.5	46.69	216.1	45.93	0.608
HDL (mg/dL)	41.6	10.81	40.8	11.01	40.3	10.52	40.8	10.35	40.3	11.82	0.913
LDL (mg/dL)	n=67		n=68		n=66		n=76		n=65		
	139.0	38.26	122.6	27.49	130.2	36.45	135.0	43.09	127.3	35.23	0.071

^c p-values based on treatment and pooled center in ANOVA model

^a n=78, C-peptide, Insulin

^b n=80, HDL

^c n=86, HDL

^d n=79, HbA_{1c}, C-peptide, Insulin

Ninety-five percent (95%) of patients were 80% to 120% compliant with the study medication. Of the 408 patients, 281 (69%) patients received prior antidiabetic medications (58>1 medication.)

Efficacy Results – Study 001

Primary Efficacy Variable – HbA_{1c} Change from baseline to Week 26

During the treatment phase, HbA_{1c} was measured at Weeks 2, 6, 10, 14, 18, 22 and 26. Table 5 displays the results of covariance analysis with baseline HbA_{1c} as covariate plus treatment, center and treatment-by-center interaction in the model. From Dunnett adjusted LSM result, it showed that at Week 26 /endpoint, there were statistically significant greater reductions of HbA_{1c} in 15 mg, 30 mg and 45 mg pioglitazone-treated patients than placebo-treated patients. The treatment difference was -1.01%, -1.03%, and -1.60%, for the 15mg, 30 mg and 45 mg pioglitazone-treated

patients, respectively. The LSM change from baseline in HbA_{1c} value by visit week is displayed in Table 5 & Figure 1.

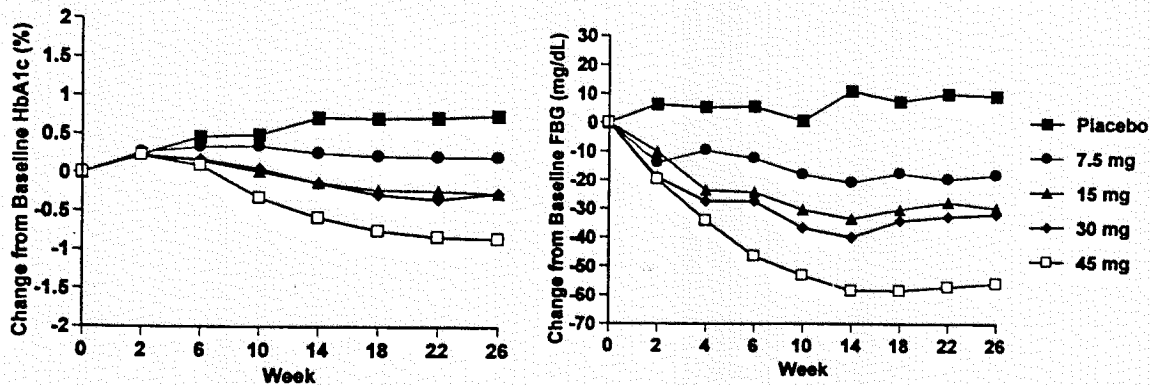
Table 5 Adjusted LSM* Change from Baseline in HbA_{1c} (%) by Visit (LOCF) – Study 001

Visit	Placebo n=79 ^a		Pioglitazone								p-value vs. placebo			
	LSM	SE	7.5 mg n=80	15 mg n=79 ^a	30 mg n=85 ^b	45 mg n=76	P _{7.5}	P ₁₅	P ₃₀	P ₄₅				
Baseline	10.41	0.218	10.04	10.23	10.15	10.34	0.58	0.94	0.82	1.00				
Week 2	0.23	0.064	0.26	0.23	0.22	0.22	1.00	1.00	1.00	1.00				
Week 6	0.46	0.106	0.33	0.15	0.17	0.09	0.78	0.12	0.16	0.05				
Week 10	0.49	0.135	0.34	0.01	0.05	-0.33	0.86	0.05	0.07	<0.01				
Week 14	0.71	0.147	0.25	-0.13	-0.14	-0.59	0.09	<0.01	<0.01	<0.01				
Week 18	0.70	0.159	0.21	-0.23	-0.29	-0.76	0.10	<0.01	<0.01	<0.01				
Week 22	0.71	0.165	0.20	-0.24	-0.35	-0.84	0.09	<0.01	<0.01	<0.01				
Week 26	0.74	0.169	0.20	-0.27	-0.27	-0.86	0.08	<0.01	<0.01	<0.01				
Endpoint														
Difference from placebo			-0.54	-1.00	-1.00	-1.60								
95% C.I.			(-1.13 0.05)	(-1.59 -0.42)	(-1.58 -0.42)	(-2.19 -1.00)								

* Least Squared Means Adjusted by Dunnett procedure comparing all means with a control

^an=78, ^bn=84 at Week 2

Figure 1 Change from Baseline in HbA_{1c} and FBG over Time – Study 001



Secondary Efficacy Variables

Fasting Blood Glucose (FBG)

The LSM change from baseline to Week 26 was statistically significantly different from placebo for all pioglitazone groups (Table 4). The treatment effects compared to placebo were -27.5, -39.1, -41.2, and -65.3 mg/dL for the 4 pioglitazone groups (Table 6 & Fig 1.)

Table 6 Adjusted* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 001

Visit	Placebo n=79		Pioglitazone								p-value vs. placebo			
			7.5 mg n=80 ^a		15 mg n=79 ^b		30 mg n=84 ^c		45 mg n=77		P _{7.5}	P ₁₅	P ₃₀	P ₄₅
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	268.1	7.93	263.2	7.90	267.0	7.94	269.4	7.72	275.5	8.05	0.98	1.00	1.00	0.86
Week 2	6.43	4.50	-13.95	4.56	-10.01	4.61	-18.99	4.51	-19.78	4.62	0.58	0.94	0.82	1.00
Week 4	5.46	4.83	-9.60	4.86	-23.56	4.91	-27.41	4.78	-34.16	4.96	0.01	0.04	<0.01	<0.01
Week 6	5.66	5.43	-12.32	5.47	-24.18	5.49	-27.37	5.38	-46.36	5.58	0.07	<0.01	<0.01	<0.01
Week 10	0.76	6.02	-17.95	6.06	-30.28	6.08	-36.62	5.97	-53.09	6.19	0.10	<0.01	<0.01	<0.01
Week 14	11.09	6.37	-20.77	6.41	-33.44	6.43	-39.91	6.31	-58.47	6.54	<0.01	<0.01	<0.01	<0.01
Week 18	7.51	6.61	-17.54	6.65	-30.22	6.67	-34.12	6.55	-58.44	6.78	0.02	<0.01	<0.01	<0.01
Week 22	10.16	6.80	-19.60	6.84	-27.68	6.86	-32.67	6.73	-57.16	6.98	0.01	<0.01	<0.01	<0.01
Week 26	9.42	6.72	-18.11	6.77	-29.65	6.78	-31.76	6.66	-55.90	6.90	0.02	<0.01	<0.01	<0.01
Difference from placebo			-27.53	9.54	-39.07	9.55	-41.18	9.46	-65.32	9.63				
95% C.I.			-50.96	-4.11	-62.52	-15.62	-64.41	-17.95	-88.97	-41.67				

* Adjusted by Dunnett procedure comparing all means with a control

^an=79, ^cn=82 at Week 2, ^bn=77 at Week 2 & n=78 at Week 4

Fasting C-Peptide & Insulin

Changes from baseline to Week 26 for fasting C-peptide and insulin were not statistically different from placebo in any of the pioglitazone-treated group. Changes of C-peptide and insulin over time are displayed in Tables 7 and 8, respectively and Figure 2.

Table 7 Adjusted LSM* Change from Baseline in C-Peptide (ng/ml) by Visit (LOCF) – Study 001

Visit	Placebo n=78		Pioglitazone								p-value vs. placebo			
			7.5 mg n=80 ^a		15 mg n=79 ^b		30 mg n=84 ^c		45 mg n=76 ^d		P _{7.5}	P ₁₅	P ₃₀	P ₄₅
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	2.04	0.09	2.15	0.09	2.10	0.09	2.17	0.09	1.99	0.10	0.81	0.98	0.75	0.98
Week 2	0.06	0.07	0.06	0.07	-0.03	0.07	-0.18	0.07	-0.23	0.07	1.00	0.72	0.06	0.01
Week 6	-0.06	0.06	0.02	0.06	-0.12	0.06	-0.13	0.06	-0.27	0.06	0.73	0.82	0.74	0.02
Week 10	-0.08	0.06	0.02	0.06	-0.08	0.06	-0.16	0.06	-0.24	0.06	0.68	1.00	0.77	0.22
Week 14	-0.09	0.06	0.01	0.06	-0.03	0.06	-0.23	0.06	-0.32	0.06	0.61	0.88	0.32	0.04
Week 18	-0.06	0.06	0.01	0.06	-0.05	0.06	-0.14	0.06	-0.23	0.06	0.84	1.00	0.80	0.22
Week 22	-0.06	0.07	0.02	0.07	-0.06	0.07	-0.18	0.06	-0.18	0.07	0.87	1.00	0.51	0.59
Week 26	-0.05	0.07	0.03	0.07	-0.02	0.07	-0.13	0.07	-0.05	0.07	0.84	0.99	0.83	1.00
Difference from placebo			0.08	0.10	0.03	0.10	-0.08	0.10	0.00	0.10				
95% C.I.			(-0.17	0.33)	(-0.22	0.28)	(-0.33	0.16)	(-0.25	0.25)				

* Adjusted by Dunnett procedure comparing all means with a control

^an=79, ^bn=78, ^cn=83, ^dn=74 at Week 2

Figure 2 Change from Baseline in C-Peptide and Insulin over Time – Study 001

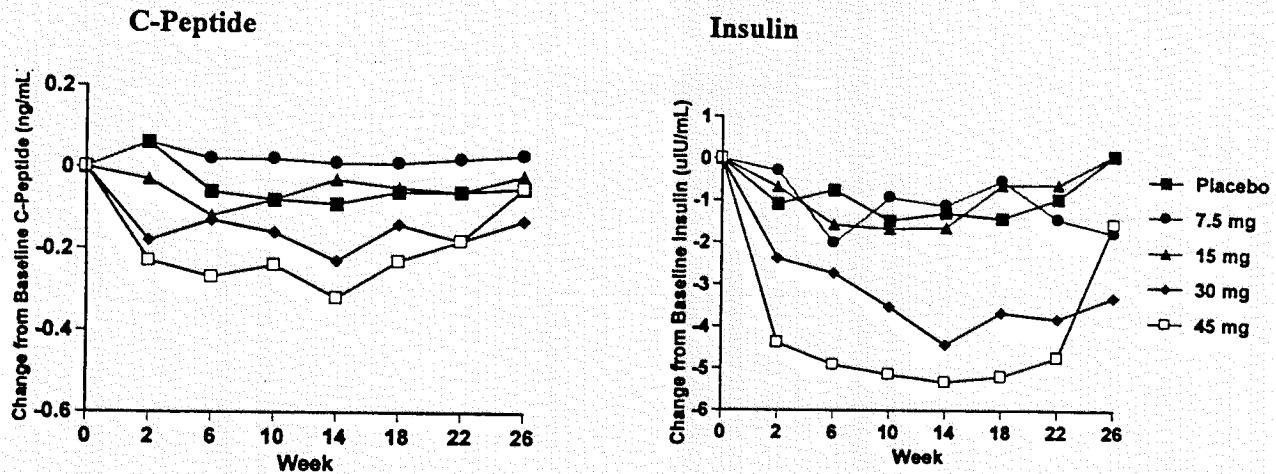


Table 8 Adjusted LSM* Change from Baseline in Fasting Insulin (µIU/ml) by Visit (LOCF) – Study 001

Visit	Pioglitazone										p-value vs. placebo			
	Placebo n=78		7.5 mg n=80 ^a		15 mg n=79 ^b		30 mg n=84 ^c		45 mg n=76 ^d		P _{7.5}	P ₁₅	P ₃₀	P ₄₅
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	14.83	1.58	17.67	1.56	15.15	1.57	18.38	1.53	15.06	1.60	0.50	1.00	0.30	1.00
Week 2	-1.08	1.16	-0.29	1.16	-0.68	1.16	-2.38	1.13	-4.39	1.24	0.97	1.00	0.84	0.16
Week 6	-0.75	0.89	-2.01	0.88	-1.57	0.88	-2.73	0.87	-4.91	0.90	0.69	0.91	0.30	<0.01
Week 10	-1.47	0.89	-0.92	0.88	-1.67	0.88	-3.53	0.87	-5.14	0.90	0.98	0.98	0.25	0.01
Week 14	-1.29	0.78	-1.11	0.77	-1.63	0.78	-4.43	0.76	-5.32	0.79	1.00	0.99	0.02	<0.01
Week 18	-1.42	0.83	-0.53	0.82	-0.63	0.82	-3.67	0.81	-5.19	0.84	0.86	0.90	0.17	0.01
Week 22	-0.95	0.93	-1.44	0.92	-0.62	0.92	-3.81	0.91	-4.74	0.94	0.99	1.00	0.10	0.02
Week 26	0.08	1.29	-1.76	1.27	0.10	1.28	-3.30	1.26	-1.55	1.30	0.70	1.00	0.19	0.78
Difference from placebo			-1.84	1.81	0.02	1.81	-3.38	1.80	-1.63	1.83				
95% C.I.			(-6.29 2.61)		(-4.43 4.47)		(-7.80 1.05)		(-6.11 2.86)					

* Adjusted by Dunnett procedure comparing all means with a control

^an=79, ^bn=78, ^cn=73 at Week 2

Lipids

The lipids of pioglitazone-treated patients were not different from placebo-treated patients in triglycerides, total cholesterol, and LDL at Week 26. Change from baseline in HDL was significant different from placebo in HDL for 45 mg pioglitazone-treated patients at Week 26. Tables 9-12 and Figure 3 display the changes over time in lipids and median values at endpoint for triglycerides.

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Table 9 Adjusted LSM* Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 001

Visit	Placebo n=79		Pioglitazone								p-value vs. placebo			
	LSM	SE	7.5 mg n=80		15 mg n=79 ^a		30 mg n=84		45 mg n=77		P _{7.5}	P ₁₅	P ₃₀	P ₄₅
Baseline	262.8	34.35	319.0	34.23	283.8	34.40	261.1	33.44	259.7	34.87	0.59	0.98	1.00	1.00
Week 2	6.95	14.45	-34.02	14.57	-18.25	14.70	-17.31	14.32	-35.04	14.81	0.15	0.55	0.58	0.14
Week 6	-19.07	13.81	-44.67	13.91	-71.99	13.93	-49.71	13.68	-77.27	14.15	0.50	0.03	0.33	0.01
Week 10	-21.60	15.03	-63.62	15.14	-54.78	15.17	-49.25	14.89	-74.09	15.40	0.16	0.34	0.49	0.05
Week 14	-30.99	13.58	-52.36	13.68	-59.97	13.70	-45.85	13.45	-69.97	13.91	0.64	0.37	0.85	0.14
Week 18	-28.28	13.58	-45.87	13.68	-58.33	13.70	-40.45	13.45	-65.47	13.91	0.77	0.34	0.92	0.17
Week 22	-25.17	13.74	-44.50	13.84	-54.06	13.86	-40.90	13.61	-53.94	14.07	0.72	0.38	0.83	0.39
Week 26	-20.97	13.70	-30.43	13.80	-53.79	13.82	-39.34	13.57	-48.05	14.03	0.97	0.27	0.74	0.44
Difference from placebo			-9.46	19.46	-32.82	19.46	-18.37	19.28	-27.08	19.61				
95% C.I.			(-57.25 38.32)		(-80.62 14.98)		(-65.70 28.97)		(-75.23 21.07)					

* Adjusted by Dunnett procedure comparing all means with a control

^an=78 at Week 2

Table 10 Adjusted* LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 001

Visit	Placebo n=79		Pioglitazone								p-value vs. placebo			
	LSM	SE	7.5 mg n=80		15 mg n=79 ^a		30 mg n=84		45 mg n=77		P _{7.5}	P ₁₅	P ₃₀	P ₄₅
Baseline	224.6	5.44	214.5	5.42	220.0	5.45	222.7	5.29	213.7	5.52	0.47	0.93	1.00	0.42
Week 2	0.73	2.69	-0.10	2.70	8.43	2.72	3.75	2.66	4.75	2.75	1.00	0.14	0.84	0.68
Week 6	3.74	3.12	-2.10	3.13	3.18	3.14	3.22	3.08	4.36	3.19	0.49	1.00	1.00	1.00
Week 10	7.06	3.54	-1.78	3.55	2.72	3.56	4.05	3.50	7.52	3.62	0.24	0.80	0.93	1.00
Week 14	7.60	3.41	-1.14	3.42	2.78	3.43	9.29	3.37	6.38	3.49	0.22	0.71	0.99	1.00
Week 18	4.29	3.31	1.57	3.32	6.19	3.33	5.87	3.27	6.82	3.38	0.94	0.98	0.99	0.96
Week 22	7.98	3.48	-2.06	3.49	4.32	3.50	5.52	3.44	8.68	3.56	0.14	0.87	0.96	1.00
Week 26	8.43	3.40	1.50	3.41	8.11	3.42	6.08	3.36	10.27	3.48	0.41	1.00	0.97	0.99
Difference from placebo			-6.93	4.83	-0.32	4.82	-2.35	4.77	1.85	4.88				
95% C.I.			(-18.78 4.92)		(-12.17 11.52)		(-14.07 9.37)		(-10.12 13.82)					

* Adjusted by Dunnett procedure comparing all means with a control

^an=78 at Week 2

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Table 11 Adjusted* LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 001

Visit	Pioglitazone										p-value vs. placebo			
	Placebo n=79		7.5 mg n=79 ^a		15 mg n=79 ^b		30 mg n=83		45 mg n=77 ^c		P _{7.5}	P ₁₅	P ₃₀	P ₄₅
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	41.70	1.24	40.50	1.24	40.40	1.24	40.80	1.21	40.70	1.25	0.90	0.85	0.96	0.94
Week 2	0.31	0.70	0.81	0.71	3.02	0.73	1.98	0.70	3.16	0.72	0.97	0.03	0.27	0.02
Week 6	1.57	0.74	2.19	0.75	5.13	0.75	4.38	0.75	6.18	0.76	0.94	<0.01	0.03	<0.01
Week 10	1.85	0.78	2.70	0.79	4.49	0.79	4.62	0.78	6.64	0.80	0.86	0.06	0.04	<0.01
Week 14	2.74	0.81	2.50	0.82	4.60	0.82	4.75	0.81	6.35	0.83	1.00	0.31	0.24	0.01
Week 18	2.00	0.79	3.44	0.80	4.85	0.79	4.90	0.79	5.58	0.80	0.50	0.04	0.03	0.01
Week 22	3.13	0.81	2.79	0.82	4.90	0.81	4.57	0.81	5.74	0.82	1.00	0.34	0.53	0.08
Week 26	3.03	0.82	2.79	0.83	5.02	0.82	4.28	0.82	6.96	0.83	1.00	0.26	0.65	<0.01
Difference from placebo			-0.23	1.16	1.99	1.16	1.26	1.16	3.94	1.17				
95% C.I.			(-3.08	2.62)	(-0.86	4.84)	(-1.58	4.09)	(1.07	6.80)				

* Adjusted by Dunnett procedure comparing all means with a control

^an=78, ^bn=76, ^cn=76 at Week 2

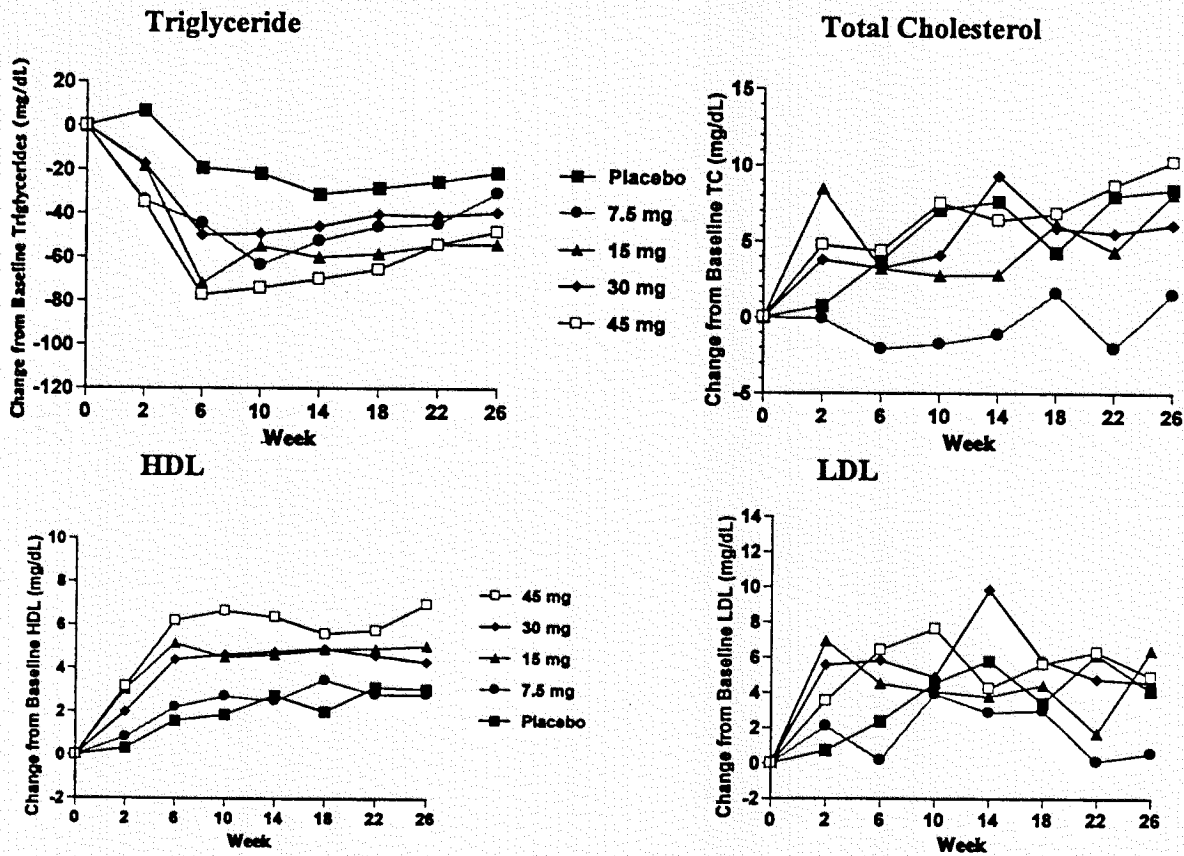
Table 12 Adjusted* LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 001

Visit	Placebo	Pioglitazone												vs. placebo					
		7.5 mg			15 mg			30 mg			45 mg			P _{7.5}	P ₁₅	P ₃₀	P ₄₅		
		n	LSM	SE	n	LSM	SE	n	LSM	SE	n	LSM	SE						
Bl	66	138.8	4.54	67	122.9	4.52	64	131.9	4.64	74	135.6	4.33	65	126.8	4.60				
2	63	0.72	2.33	65	2.09	2.30	63	6.91	2.32	70	5.55	2.21	64	3.53	2.31	0.98	0.18	0.36	0.80
6	64	2.36	2.84	64	0.17	2.86	64	4.50	2.84	73	5.82	2.67	64	6.42	2.84	0.95	0.95	0.78	0.70
10	64	4.53	2.73	65	3.92	2.74	64	4.05	2.74	73	4.88	2.57	64	7.61	2.74	1.00	1.00	1.00	0.84
14	64	5.79	2.88	65	2.87	2.88	63	3.78	2.91	73	9.83	2.71	64	4.25	2.88	0.88	0.97	0.69	0.99
18	63	3.42	2.75	65	2.97	2.73	64	4.42	2.73	73	5.81	2.57	64	5.63	2.73	1.00	1.00	0.92	0.94
22	64	6.15	2.95	65	0.10	2.95	64	1.69	2.95	73	4.75	2.78	62	6.30	3.01	0.40	0.66	0.99	1.00
26	65	4.11	3.06	64	0.56	3.12	63	6.39	3.11	74	4.59	2.89	62	4.91	3.15	0.84	0.96	1.00	1.00
Difference from placebo				-3.54	4.39		2.28	4.35		0.48	4.18		0.80	4.37					
95% C.I.				(-14.31	7.22)		(-8.39	12.95)		(-9.77	10.73)		(-9.93	11.53)					

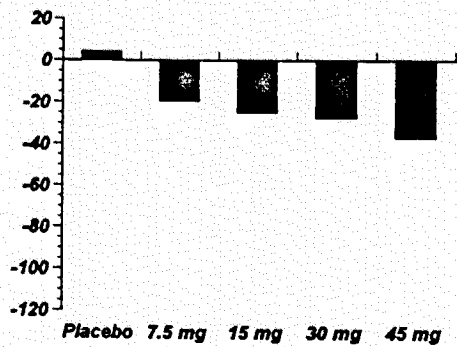
* Adjusted Least Squared Means by Dunnett procedure comparing all means with a control

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Figure 3 LSM Change from Baseline in Triglycerides, Total Cholesterol, HDL, & LDL – Study 001



Endpoint Median Triglycerides



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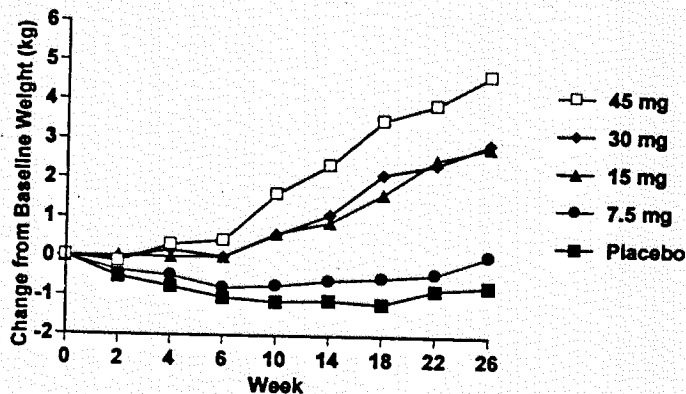
Body Weight

At Week 26, body weight increased in pioglitazone-treated patients compared to placebo-treated patients (Fig 4). The mean changes from baseline of the observed value and endpoint value at Week 26 are displayed in Table 13. At endpoint, it was significantly different from placebo for 15, 30, and 45 mg pioglitazone-treated patients ($p < 0.01$). Figure 4 displays the mean body weight during the course of the study for the completers.

Table 13 Mean Change from Baseline in Body Weight (kg) – Study 001

	Placebo	Pioglitazone			
		7.5 mg	15 mg	30 mg	45 mg
Baseline					
n	79	81	79	87	79
Mean (SE)	90.35 (1.47)	93.54 (1.59)	91.19 (1.78)	90.29 (1.58)	90.77 (1.56)
Endpoint					
Mean Change (SE)	-1.28 (0.36)	-0.59 (0.29)	1.30 (0.33)	1.29 (0.38)	2.82 (0.39)
Week 26 (Observed)					
n	31	42	37	44	47
Mean Change (SE)	-0.73 (0.81)	0.04 (0.41)	2.83 (0.47)	2.92 (0.50)	4.66 (0.41)

**Figure 4 Change from Baseline in Body Weight (kg)
Completers – Study 001**



Seven pioglitazone patients who had a >5% increase from baseline in body weight were withdrawn from the study, although weight gain was not necessarily the reason.

Subgroup Analysis

The HbA_{1c} change from baseline were evaluated in gender, age, race, baseline BMI, time of enrollment, and use of previous antidiabetic medication using the LOCF data of the ITT population. The interaction between subgroup and treatment was explored by ANOVA with terms of treatment, center, subgroup and treatment-by-subgroup interaction in the model.

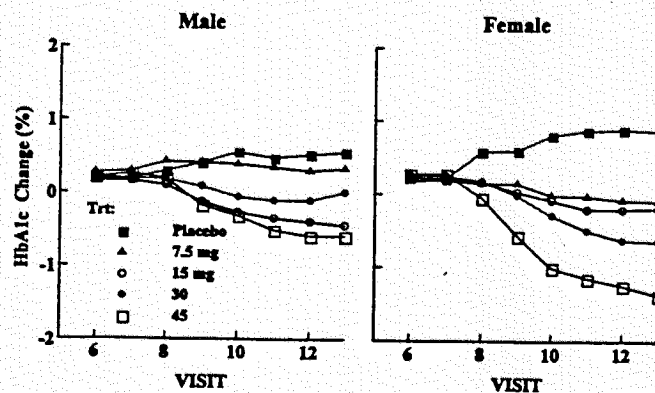
Gender

The descriptive statistics in mean change from baseline in HbA_{1c} at endpoint by gender are displayed in Table 14 and Figure 5. The overall p-value for gender-by-treatment was significant (p=0.02.) When each treatment group was examined, the treatment-by-gender was significant for the 7.5 mg, 30 mg, and 45 mg, groups but not the 15 mg group (p=0.88).

Table 14 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender (LOCF) – Study 001

Subgroup	Placebo	Pioglitazone			
		7.5 mg	15 mg	30 mg	45 mg
Men					
n	36	52	44	50	46
Baseline Mean	10.69	10.06	9.90	10.21	10.02
Mean Change	0.54	0.33	-0.45	0.02	-0.59
SE	0.24	0.17	0.24	0.19	0.22
Women					
n	43	28	35	35	30
Baseline Mean	10.13	9.89	10.53	9.99	10.78
Mean Change	0.87	-0.10	-0.19	-0.60	-1.37
SE	0.17	0.21	0.20	0.20	0.41

Figure 5 Change from Baseline in HbA_{1c} by Gender – Study 001



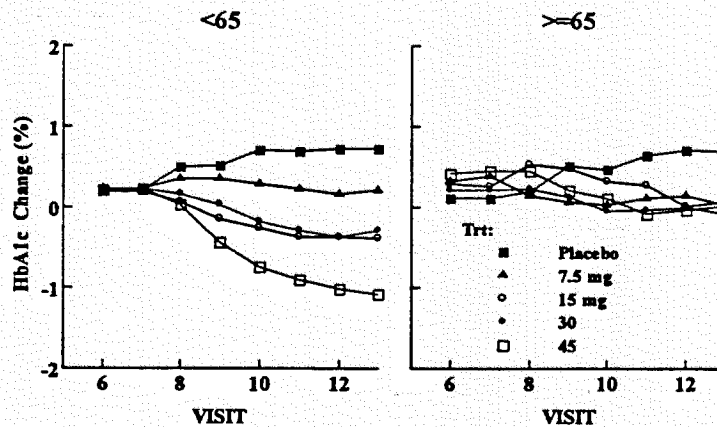
Age

Mean change from baseline in HbA_{1c} at endpoint by age group (<65, ≥65) are displayed in Table 15 and Figure 6. The p-value for the test of interaction between treatment and age group was 0.18.

Table 15 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group (LOCF) – Study 001

Subgroup	Placebo	Pioglitazone			
		7.5 mg	15 mg	30 mg	45 mg
<65 years old					
n	70	68	69	76	63
Baseline Mean	10.58	10.16	10.32	10.18	10.47
Mean Change	0.72	0.20	-0.39	-0.28	-1.09
SE	0.16	0.15	0.17	0.15	0.24
≥65 years old					
n	9	12	10	9	13
Baseline Mean	8.84	9.10	9.21	9.63	9.61
Mean Change	0.69	0.03	0.06	0.13	0.02
SE	0.33	0.37	0.46	0.36	0.46

Figure 6 Change from Baseline in HbA_{1c} by Age Group – Study 001



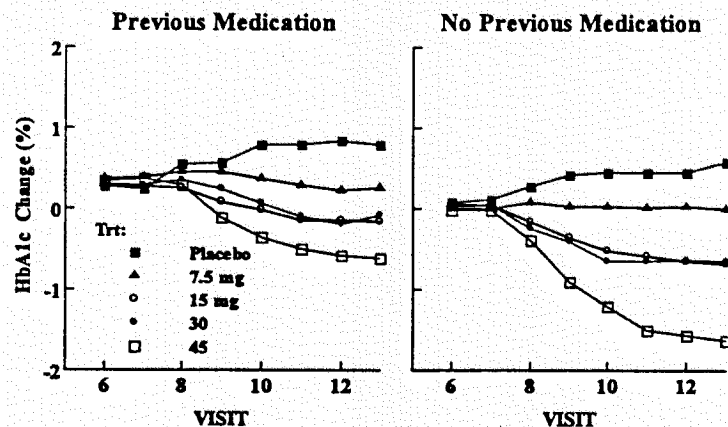
Previous Medication

The descriptive statistics in mean change from baseline in HbA_{1c} at endpoint by previous antidiabetic medication of the LOCF population are displayed in Table 16 and Figure 7. The p-value for treatment-by-previous medication interaction was 0.48.

Table 16 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Previous Antidiabetic Medication – Study 001

Subgroup	Placebo	Pioglitazone			
		7.5 mg	15 mg	30 mg	45 mg
Previous Medication					
n	54	53	53	59	55
Baseline Mean	10.92	10.37	10.32	10.43	10.50
Mean Change	0.79	0.26	-0.16	-0.08	-0.62
SE	0.178	0.164	0.208	0.159	0.265
No Previous Medication					
n	25	27	26	26	21
Baseline Mean	9.22	9.27	9.90	9.42	9.85
Mean Change	0.56	0.01	-0.68	-0.59	-1.63
SE	0.236	0.234	0.219	0.281	0.301

Figure 7 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Previous Antidiabetic Medication – Study 001

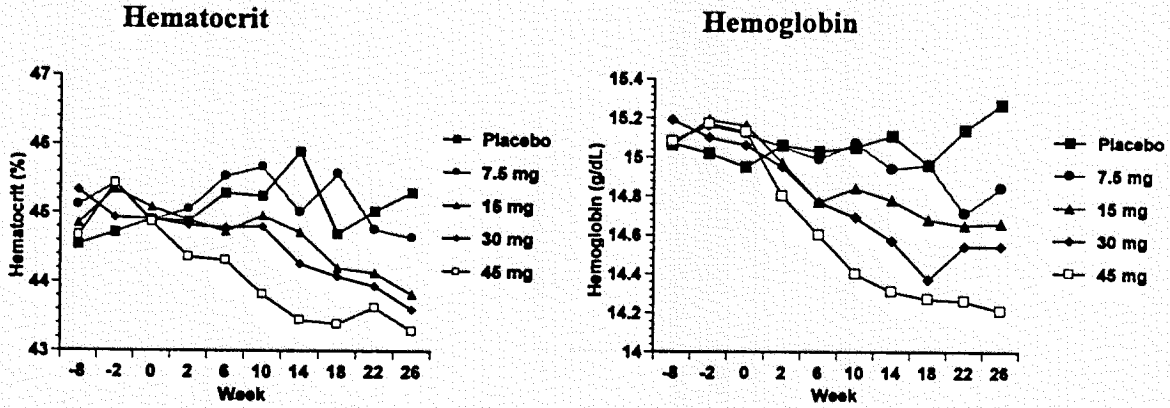


Safety

The sponsor indicated that there were small, dose-related changes from baseline in hematocrit, hemoglobin, and RBCs. At Week 26 of the observed cases, pioglitazone 15, 30, and 45 mg were significantly different from placebo in hematocrit ($p \leq 0.03$). All pioglitazone doses were significantly different from placebo in hemoglobin ($p \leq 0.01$) at Week 26.

The LSMs of the observed cases in hematocrit and hemoglobin are displayed in Figure 8.

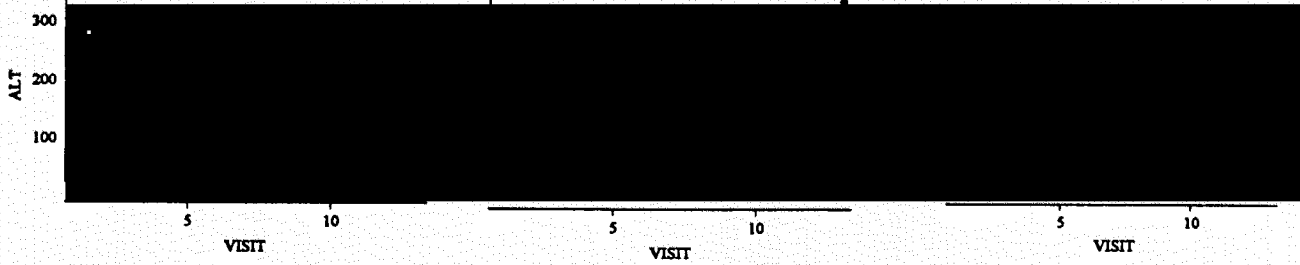
Figure 8 LSM of Hematocrit & Hemoglobin by Week – Study 001



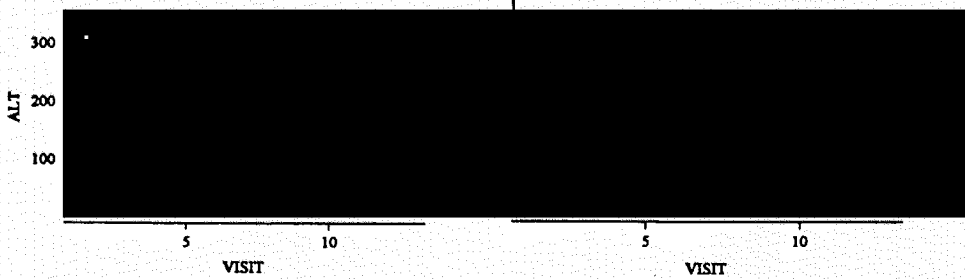
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The reviewing Medical Officer, Dr. Misbin, set 102 U/L as the ULN for ALT. The time course of the 5 patients with ALT>102 U/L is displayed in the following figure.

Patient 2126 (30 mg) Patient 2373 (30 mg) Patient 2481 (30 mg)



Patient 2362 (7.5 mg) Patient 2439 (Placebo)

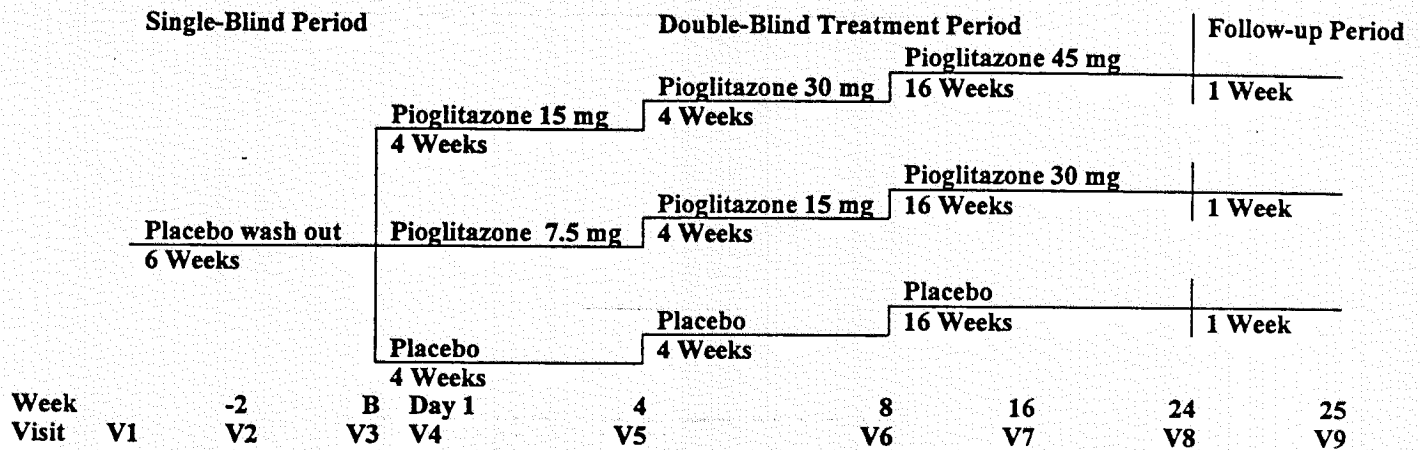


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Study PNFP-012 (24 Weeks)

This was a double-blind, placebo-controlled, randomized, parallel-group, forced dose-titration, multicenter study conducted for a total of 31 weeks in type 2 diabetes from January 30, 1997 to June 1, 1998.

The 6-week, single-blind placebo washout period was followed by a 24-week, double-blind treatment period and a 1-week follow-up period. The study scheme and the forced titration regimen are displayed in the following table:



In Amendment 1 dated February 28, 1997, the overall duration of the study was shortened from 45 weeks to 31 weeks. The washout period was shortened from 8 weeks to 6 weeks and the double-blind treatment period from 36 weeks to 24 weeks. The titration of the first two doses was shortened from 12 weeks to 4 weeks and the duration of the final dose shortened from 12 weeks to 16 weeks.

The number of patients to be enrolled was increased from 192 to 246 patients because concern of a higher than expected discontinuation rate observed in a previous study.

The HbA_{1c} inclusion criterion was increased from >7.0% at visit 4 to HbA_{1c} >8.0% at visit 1 and visit 3.

In Amendment 2 dated July 11, 1997, the HbA_{1c} criterion was changed from HbA_{1c} ≥8.0% at Visit 1 and Visit 3 to HbA_{1c} ≥7.5% at Visit 1 and ≥8.0% at Visit 3.

The primary efficacy variable HbA_{1c} was measured at screening, baseline and weeks 8, 16 and 24 during the treatment period.

Patient Disposition

A total of 560 patients signed an ICF, of those 13 signed twice. Eight of the 13 were randomized. Of the 547 patients who entered the single-blind placebo period, 260 were randomized, 84 to the placebo group, 87 to the 7.5/15/30mg group and 89 to the 15/30/45mg group. The completion rate was 65% (170/260). Table 17 displays the disposition of patients and Table 18 the discontinuation by time.

Table 17 Patient Disposition - Study 012

	Placebo	7.5/15/30 mg	15/30/45 mg
Randomized	84	87	89
Withdrawn	37 (44%)	27 (31%)	26 (29%)
Lack of Efficacy	31 (37%)	20 (23%)	18 (20%)
Adverse Event other than hyperglycemia	4 (5%)	4 (5%)	0
Lost to Follow-up	0	2 (2%)	2 (2%)
Non-Compliance	1 (1%)	0	1 (1%)
Protocol Violation	1 (1%)	0	0
Personal Reasons	0	1 (1%)	5 (6%)
Completed	47 (56%)	60 (69%)	63 (71%)

Table 18 Patient Discontinuation by Time - Study 012

	Placebo	7.5/15/30 mg	15/30/45 mg	Total
Randomized	84	87	89	260
Completed	47	60	63	170
Withdrawn	37	27	26	90
≤ Week 4	13	9	8	30
> Week 4 & ≤ Week 8	9	6	5	20
> Week 8 & ≤ Week 16	11	11	9	31
> Week 16 & ≤ Week 24	4	1	4	9

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Patient Demographic and Baseline Characteristics

Most patients were Caucasians (82%). There were more males (56%) than females. The mean age was 56 years. The mean weight was 90.9 kg with a mean BMI of 30.9 kg/m². The baseline mean values of the primary and secondary variables are presented in Table 19.

Table 19 Mean Values at Baseline in Efficacy Variables – Study 012

	Placebo n=84		7.5/15/30 mg n=87		15/30/45 mg n=89		Overall p-value*
	MEAN	SE	MEAN	SE	MEAN	SE	
HbA _{1c}	10.75	1.659	10.37	1.730	10.60	1.628	0.162
FBG (mg/dL)	282.8	68.23	271.7	69.05	281.5	62.62	0.376
Fasting C-Peptide (ng/mL)	2.11	0.864	2.12	0.815	2.12	0.663	0.989
Fasting Insulin (μIU/mL)	14.19	11.34	14.21	9.36	15.15	11.83	0.785
Triglycerides (mg/dL)	306.0	368.8	296.1	233.1	324.7	312.5	0.710
Total Cholesterol	225.9	57.04	212.0	44.33	219.3	46.07	0.135
HDL (mg/dL)	43.1	11.13	40.7	10.15	39.9	10.31	0.135
LDL (mg/dL)	134.4	39.96	122.0	37.12	124.0	30.13	0.101

* p-values based on treatment and pooled center in ANOVA model

Of the 260 patients randomized, 197 (76%) patients had received prior antidiabetic medications (52 patients >1 medication.)

Efficacy Results – Study 012

Primary Efficacy Variable – HbA_{1c} Change from baseline to Week 24

At endpoint, Week 24, the LSM changes from baseline in HbA_{1c} were statistically significant between the pioglitazone-treated patients and the placebo-treated patients (p<0.01). The HbA_{1c} changes from baseline were -0.55, -0.60 and +0.93 for the treatment group of 7.5/15/30-mg, 15/30/45-mg, and placebo, respectively. The differences from placebo were -1.48% and -1.53% for the 7.5/15/30 mg and 15/30/45 mg groups, respectively.

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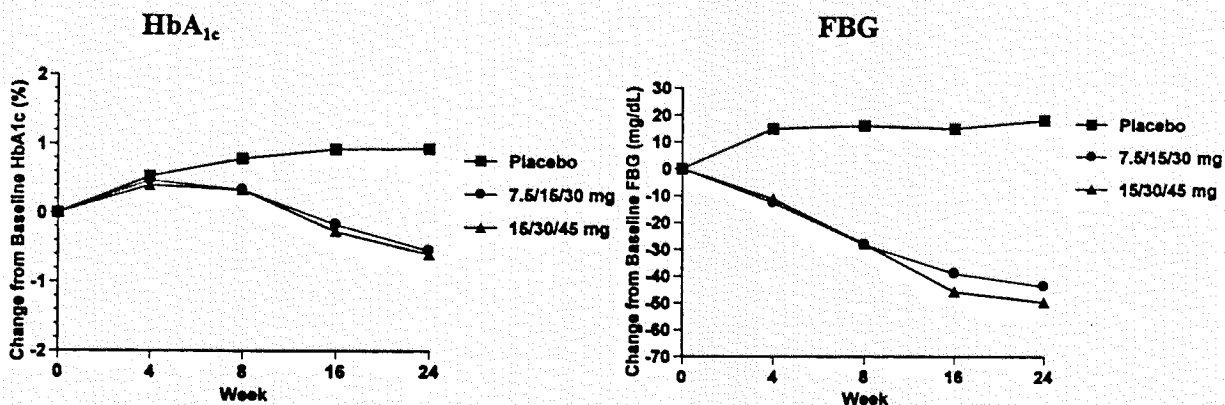
Table 20 Adjusted* LSM Change from Baseline in HbA_{1c} (%) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=83		7.5/15/30 mg n=85 ^a		15/30/45 mg n=85		P ₃₀	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	10.76	0.176	10.34	0.175	10.75	0.175	0.16	1.00
Week 4	0.53	0.100	0.47	0.101	0.40	0.099	0.98	0.69
Week 8	0.78	0.121	0.33	0.121	0.33	0.120	0.04	0.04
Week 16	0.92	0.137	-0.17	0.138	-0.27	0.136	<0.01	<0.01
Week 24, Endpoint	0.93	0.156	-0.55	0.156	-0.60	0.155	<0.01	<0.01
Difference from placebo			-1.48	0.222	-1.53	0.219		
95% C.I.			(-1.97, -0.98)		(-2.02, -1.04)			

*Adjusted Least Squared Means by Dunnett procedure comparing all means with a control

^an=84 at Week 4

Figure 9 Change from Baseline in HbA_{1c} and FBG over Time – Study 012



Secondary Efficacy Variables

Fasting Blood Glucose

The LSM change from baseline to Week 24 in FBG was statistically significant between pioglitazone-treated patients and placebo patients (p<0.01). The reduction in FBG was -61.83 mg/dL for the 7.5/15/30-mg group and -88.14 mg/dL for the 15/30/45-mg group comparing to the increase of 18.16 mg/dL of the placebo group, the difference were -61.83 mg/dL and -67.81 mg/dL for the two pioglitazone treatment groups, respectively (Table 21 & Fig 9.)

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Table 21 Adjusted* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=78		7.5/15/30 mg n=82 ^a		15/30/45 mg n=85 ^b		P ₃₅	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	279.2	7.50	268.0	7.34	281.1	7.21	0.45	0.98
Week 4	14.91	5.00	-12.56	4.95	-11.15	4.87	<0.01	<0.01
Week 8	16.06	5.28	-28.24	5.20	-27.98	5.12	<0.01	<0.01
Week 16	14.94	6.36	-38.97	6.27	-45.73	6.18	<0.01	<0.01
Week 24	18.16	6.55	-43.67	6.46	-49.65	6.36	<0.01	<0.01
Endpoint								
Difference from placebo, SE			-61.83	9.196	-67.81	9.125		
95% C.I.			(-82.32 -41.34)		(-88.14 -47.48)			

* Adjusted by Dunnett procedure comparing all means with a control

^a n=81 at Week 4^b n=84 at Week 4

Fasting C-Peptide & Insulin

At endpoint, fasting C-peptide and insulin were not different between pioglitazone groups and placebo group (Tables 22, 23 & Fig 10)

Table 22 Adjusted* LSM Change from Baseline in Fasting C-peptide (ng/mL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=78		7.5/15/30 mg n=80		15/30/45 mg n=83		P ₃₅	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	2.09	0.091	2.11	0.090	2.12	0.088	0.97	0.99
Week 4	-0.083	0.061	-0.040	0.061	-0.121	0.061	0.84	0.87
Week 8	-0.078	0.067	-0.066	0.067	-0.130	0.066	0.99	0.80
Week 16	-0.076	0.065	-0.159	0.066	-0.279	0.064	0.57	0.05
Week 24 Endpoint	-0.122	0.059	-0.164	0.059	-0.196	0.058	0.83	0.57
LSM Difference from placebo, SE			-0.042	0.083	-0.075	0.083		
95% C.I.			(-0.228 0.144)		(-0.258 0.109)			

* Adjusted by Dunnett procedure comparing all means with a control

^a n=81 at Week 4 & n=83 at Week 8

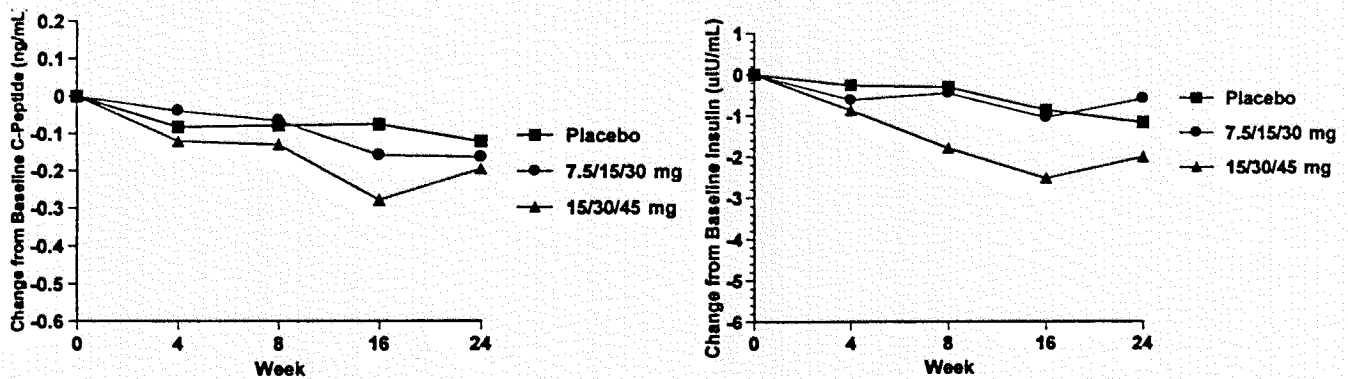
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Table 23 Adjusted* LSM Change from Baseline in Fasting Insulin (μ IU/mL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=78		7.5/15/30 mg n=80		15/30/45 mg n=83 ^a		P ₃₅	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	14.00	1.284	14.26	1.274	15.01	1.255	0.99	0.79
Week 4	-0.27	0.736	-0.63	0.739	-0.88	0.745	0.92	0.79
Week 8	-0.32	1.065	-0.46	1.068	-1.80	1.061	0.99	0.52
Week 16	-0.88	0.912	-1.06	0.914	-2.54	0.908	0.99	0.33
Week 24	-1.18	0.876	-0.60	0.878	-2.02	0.872	0.86	0.72
Difference from placebo			0.57	1.24	-0.85	1.24		
95% C.I.			(-2.19 3.34)		(-3.60 1.91)			

* Adjusted by Dunnett procedure comparing all means with a control
^an=81 at Week 4

Figure 10 Change from Baseline in C-Peptide and Insulin over Time – Study 012



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Lipids

The only statistically significant result in lipid outcome was in the 15/30/45 mg pioglitazone-treated patients in triglycerides at Week 24/endpoint. However, there were outliers in change from baseline triglycerides. When patients with change ≤ -500 mg/dL were deleted the p-value was 0.05 for the 15/30/45 mg group and 0.26 for the 7.5/15/30 mg group. Total cholesterol, HDL, and LDL were not significantly different from placebo. Tables 24-27 and Figure 11 display the results.

Table 24 Adjusted* LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. Placebo	
	n=80		7.5/15/30 mg n=82		15/30/45 mg n=83		P ₃₀	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	303.8	35.50	286.7	25.22	327.1	35.06	0.92	0.85
Week 4	-6.66	21.97	-30.01	21.98	-65.09	22.02	0.67	0.11
Week 8	-22.72	17.88	-52.08	17.89	-77.40	17.92	0.40	0.06
Week 16	-9.04	18.25	-63.75	18.25	-94.42	18.28	0.06	<0.01
Week 24	-27.85	16.31	-63.55	16.31	-102.21	16.34	0.21	<0.01
Difference from placebo			-35.69	23.037	-74.35	23.116		
95% C.I.			(-87.05 15.67)		(-125.89 -22.82)			

* Adjusted by Dunnett procedure comparing all means with a control

Table 25 Adjusted* LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=80		7.5/15/30 mg n=82		15/30/45 mg n=83		P ₃₅	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	227.3	5.69	211.6	5.64	219.3	5.61		
Week 4	3.83	3.51	2.04	3.522	1.28	3.505	0.91	0.83
Week 8	5.40	3.629	5.45	3.642	2.32	3.625	1.00	0.77
Week 16	5.70	3.759	8.12	3.772	2.92	3.754	0.86	0.82
Week 24	7.61	3.823	7.38	3.837	3.02	3.819	1.00	0.60
Difference from placebo			-0.23	5.436	-4.59	5.402		
95% C.I.			(-12.35 11.89)		(-16.63 7.46)			

* Adjusted by Dunnett procedure comparing all means with a control

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**Table 26 Adjusted* LSM Change from Baseline in HDL (mg/dL)
by Visit (LOCF) – Study 012**

Visit	Placebo			Pioglitazone						vs. placebo	
				7.5/15/30 mg			15/30/45 mg			P ₃₀	P ₄₅
	n	LSM	SE	n	LSM	SE	n	LSM	SE		
Baseline	77	43.40	1.22	79	41.20	1.21	81	39.80	1.20		
Week 4	75	0.18	0.83	78	0.79	0.81	79	1.83	0.82	0.91	0.83
Week 8	76	1.47	0.92	78	4.01	0.90	80	4.76	0.91	1.00	0.77
Week 16	76	0.85	0.97	79	3.97	0.95	80	4.52	0.96	0.86	0.82
Week 24	77	1.27	0.92	79	3.46	0.90	81	4.08	0.91	1.00	0.60
Difference from placebo					2.19	1.287		2.81	1.303		
95% C.I.					(-0.68	5.06)		(-0.10	5.71)		

* Adjusted by Dunnett procedure comparing all means with a control

Table 27 Adjusted* LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 012

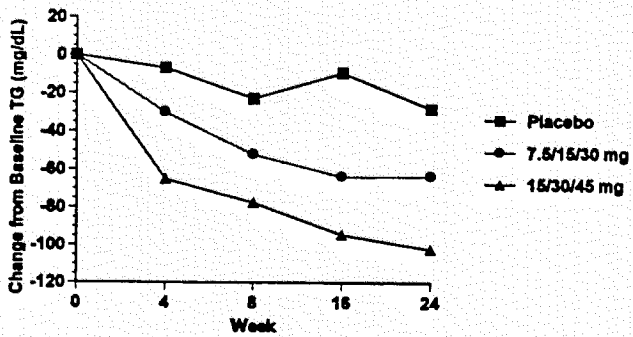
Visit	Placebo			Pioglitazone							
				7.5/15/30 mg				15/30/45 mg			
	n	LSM	SE	n	LSM	SE	p	n	LSM	SE	p
Baseline	65	136.50	4.38	62	121.80	4.53	0.04	65	124.10	4.47	0.09
Week 4	62	4.71	2.88	60	4.25	3.01	0.99	61	8.40	3.14	0.60
Week 8	61	6.32	3.06	59	5.67	3.22	0.99	65	9.89	3.17	0.64
Week 16	61	4.08	3.38	60	8.86	3.36	0.51	65	10.27	3.41	0.34
Week 24	64	8.01	3.14	59	8.51	3.38	0.99	63	10.60	3.48	0.81
LSM Difference from placebo, SE					0.50	4.665			2.59	4.728	
95% C.I.					(-9.95	10.95)			(-8.00	13.18)	

* Adjusted by Dunnett procedure comparing all means with a control

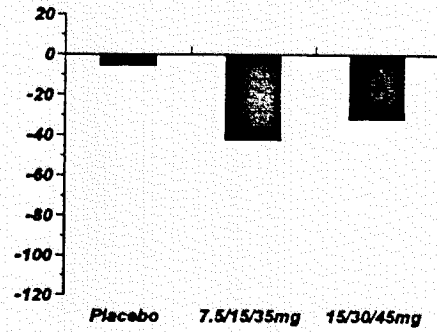
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Figure 11 Change from Baseline in Triglycerides, Total Cholesterol, HDL, & LDL – Study 012

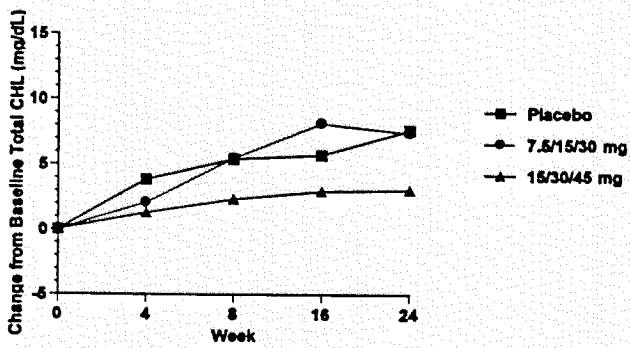
Triglycerides



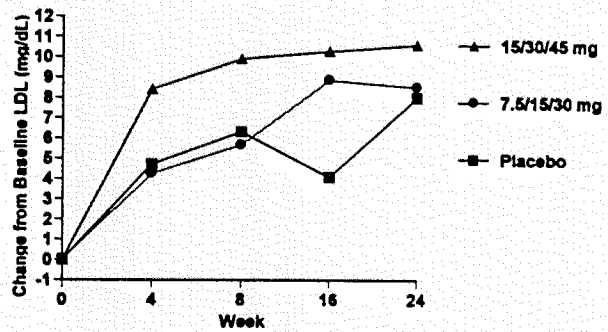
Endpoint Median Triglycerides



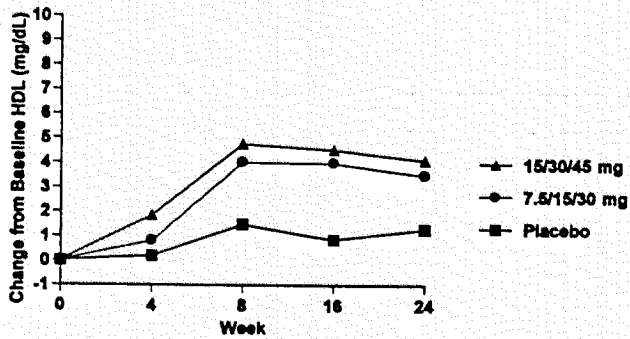
Total Cholesterol



LDL



HDL



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Body Weight

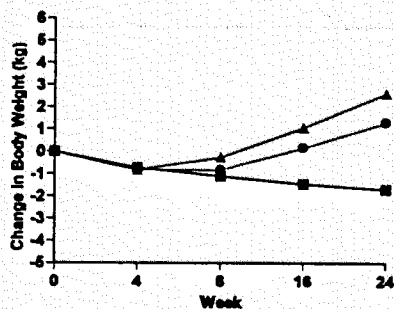
Table 28 displays mean change in body weight for completers over time and at endpoint. At week 24 and endpoint, body weight were significantly increased ($p < 0.01$) in both the pioglitazone treatment groups when compared to placebo group.

Table 28 Mean Change from Baseline in Body Weight (kg) by Visit (Completers) & Endpoint (LOCF) – Study 012

Visit	Placebo		Pioglitazone			
	n=50		7.5/15/30 mg n=62		15/30/45 mg n=65	
	LSM	SE	LSM	SE	LSM	SE
Baseline	91.55	2.46	91.54	2.22	92.53	1.86
Week 4	-0.74	0.23	-0.82	0.20	-0.84	0.21
Week 8	-1.12	0.30	-0.85	0.30	-0.28	0.26
Week 16	-1.46	0.39	0.14	0.43	1.04	0.31
Week 24	-1.70	0.42	1.27	0.48	2.58	0.41
Endpoint*	-1.81	0.37	0.49	0.36	1.82	0.36
Difference from placebo, Wk 24			2.98	0.64	4.28	0.63
95% C.I.			(1.71 4.24)		(3.04 5.53)	

* $n_p=83$, $n_{30}=87$, $n_{45}=89$

Figure 12 Mean Change from Baseline in Body Weight (kg) Completers – Study 012



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Subgroup Analysis

Change from baseline to endpoint in HbA_{1c} was examined in gender, age, and use of previous antidiabetic medications using the LOCF data of the ITT population. The interaction between treatment and subgroup was evaluated by ANOVA with treatment, subgroup, center, and treatment-by-subgroup interaction terms in the model.

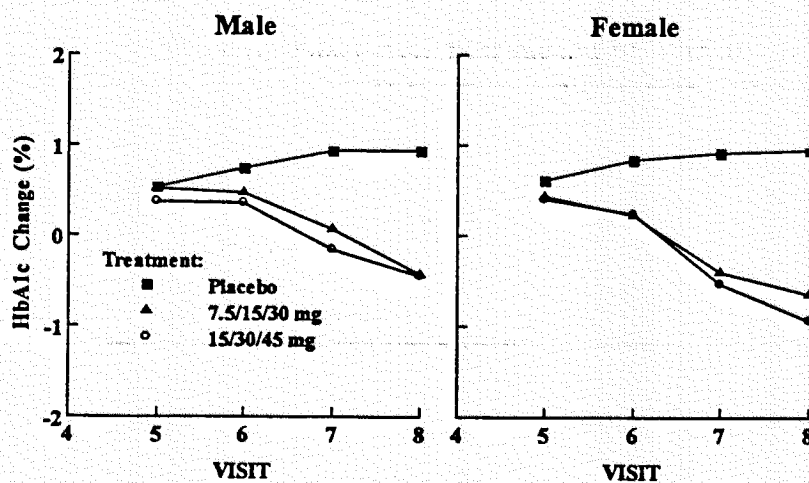
Gender

Table 29 and Figure 13 display the mean changes from baseline in HbA_{1c} at endpoint by gender. The treatment-by-gender interaction was not significant (p=0.72.)

Table 29 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender (LOCF) – Study 012

Subgroup	Placebo	Pioglitazone	
		7.5/15/30 mg	15/30/45 mg
Men			
n	45	48	48
Baseline Mean	10.38	10.11	10.72
Mean Change	0.93	-0.43	-0.45
SE	0.18	0.21	0.22
Women			
n	38	37	37
Baseline Mean	11.13	10.66	10.71
Mean Change	0.95	-0.65	-0.94
SE	0.21	0.26	0.21

Figure 13 Mean Change from Baseline in HbA_{1c} (%) by Gender



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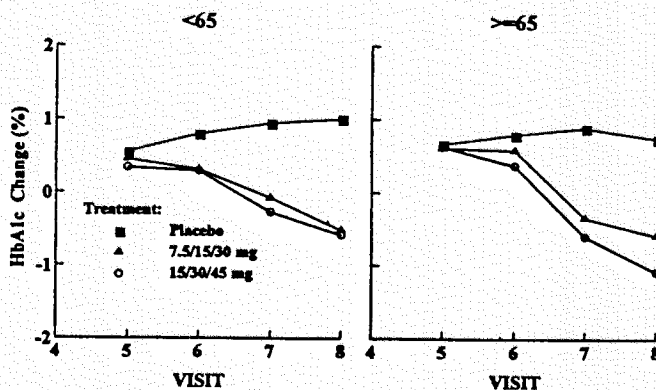
Age

Table 30 and Figure 14 display the mean change from baseline in HbA_{1c} at endpoint for patients <65 and >65 years of age. The treatment-by-age interaction was not significant (p=0.42).

Table 30 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group – Study 012

Subgroup	Placebo	Pioglitazone	
		7.5/15/30 mg	15/30/45 mg
<65 years old			
n	63	66	71
Baseline Mean	10.75	10.37	10.85
Mean Change	1.00	-0.52	-0.58
SE	0.15	0.17	0.18
≥65 years old			
n	20	19	14
Baseline Mean	10.63	10.28	10.04
Mean Change	0.75	-0.57	-1.08
SE	0.32	0.43	0.29

Figure 14 Mean Change from Baseline in HbA_{1c} (%) by Age



Previous Antidiabetic Medication

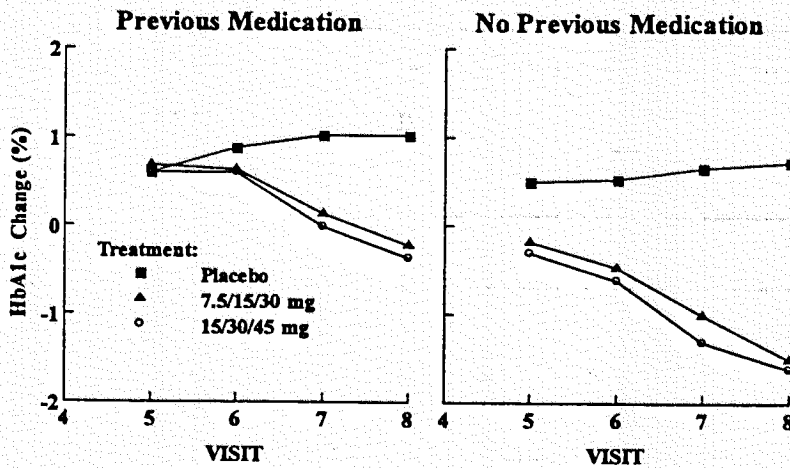
Table 31 and Figure 15 display the mean change in HbA_{1c} by previous antidiabetic medication. The p-value for treatment-by-previous medication interaction was 0.075.

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Table 31 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Previous Antidiabetic Medication – Study 012

Subgroup	Placebo	Pioglitazone	
		7.5/15/30 mg	15/30/45 mg
Previous Medication			
n	61	65	65
Baseline Mean	10.90	10.42	10.85
Mean Change	1.01	-0.23	-0.37
SE	0.16	0.19	0.17
No Previous Medication			
n	22	20	20
Baseline Mean	10.22	10.12	10.28
Mean Change	0.73	-1.50	-1.62
SE	0.27	0.21	0.31

Figure 15 Mean Change from Baseline in HbA_{1c} (%) by Previous Medication

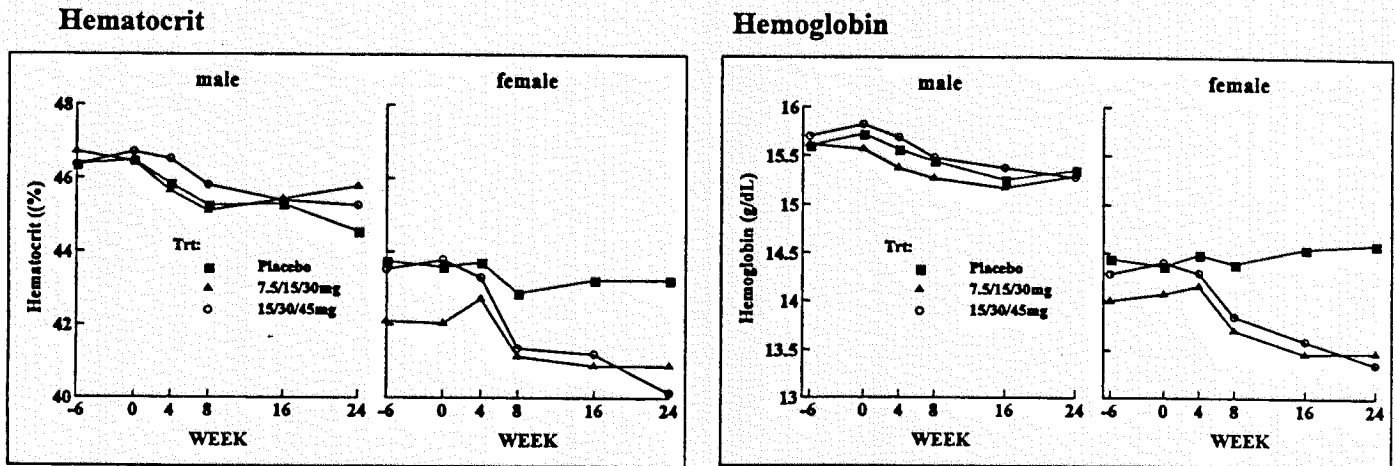


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Hematocrit & Hemoglobin

The observed mean hematocrit and hemoglobin levels by gender and visit are displayed in Figure 16

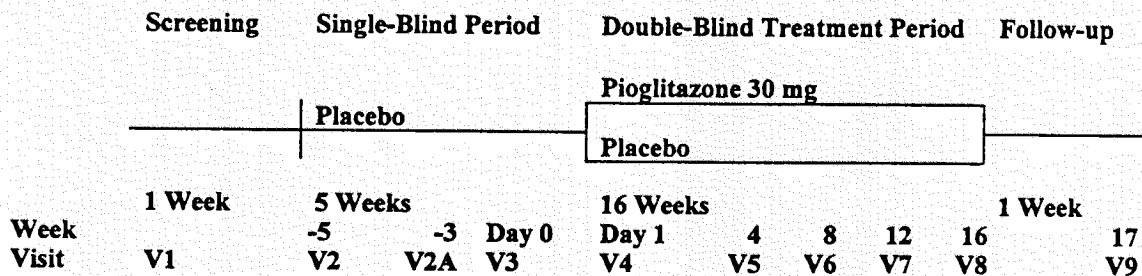
Figure 16 Mean Hematocrit & Hemoglobin Levels by Gender & Visit – Study 012



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Study PNFP-026 (16 Weeks)

This was a double-blind, placebo-controlled, randomized, multicenter, study in 197 patients from 27 centers in the U.S. The study scheme is displayed in the following diagram.



The follow-up visit was for patients who did not enter an open-label extension study, which the sponsor will summarize in a separate report.

The HbA_{1c} inclusion criteria were HbA_{1c} >7.5% at Visit 1 and >8.0% at Visit 3.

Patient Disposition

Of the 447 patients screened, 3 were rescreened. A total of 275 patients entered the single-blind placebo period of which 197 patients were randomized (1 rescreened), 96 to the placebo group and 101 to the pioglitazone 30 mg treatment group. Seventy-three percent of the patient (143) completed the double-blind treatment period, 66% (63/96) of the placebo group and 79% (80/101) of the pioglitazone 30 mg group. Table 32 displays the disposition of patients. Table 33 displays patient discontinuation by time.

Table 32 Patient Disposition – Study 026

	Placebo	Pioglitazone 30 mg
Randomized	96	101
Completed	63 (66%)	80 (79%)
Withdrawn	33 (34%)	21 (21%)
Lack of Efficacy	22 (23%)	15 (15%)
AE: Other Lab	0	1 (1%)
AE: All Other	5 (5%)	2 (2%)
Withdrew Consent (personal)	3 (3%)	2 (2%)
Lost to Follow-up	2 (2%)	0
Non-Compliance	1 (1%)	1 (1%)

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Table 33 Patient Discontinuation by Time – Study 026

	Placebo	30 mg	Total
Randomized	96	101	197
Withdrawn	33 (34%)	21 (21%)	54 (27%)
≤ Week 4	8	3	11 (6%)
> Week 4 & ≤ Week 8	10	10	20 (10%)
> Week 8 & ≤ Week 12	9	7	16 (8%)
> Week 12 & ≤ Week 16	5	1	6 (3%)
> Week 16 & ≤ Week 24	1	0	1 (0.5%)

Baseline characteristics were not significantly different between the treatment groups. The baseline values for the primary and secondary efficacy variables are listed in Table 34.

Table 34 Mean Values at Baseline in Efficacy Variables – Study 026

	Placebo n=96			30 mg n=101			p-value*
	n	Mean	SD	n	Mean	SD	
HbA _{1c}	96	10.42	1.70	101	10.65	1.77	0.310
FBG (mg/dL)	95	272.3	72.74	101	276.1	70.88	0.676
Fasting C-Peptide (ng/mL)	94	2.18	0.97	101	2.14	0.87	0.714
Fasting Insulin (μIU/mL)	94	15.06	12.70	101	15.15	11.38	0.887
Triglycerides (mg/dL)	96	280.2	345.65	101	356.0	531.33	0.185
Total Cholesterol	96	221.3	48.00	101	222.2	67.11	0.869
HDL (mg/dL)	94	39.4	10.83	97	39.9	10.51	0.750
LDL (mg/dL)	76	133.7	36.9	78	128.6	35.35	0.435

* p-values based on treatment and pooled center in ANOVA model

Of the 197 patients who were randomized, 119 (60%) received prior antidiabetic medications. Eleven patients had taken 2 antidiabetic medications concomitantly.

Ninety-two percent (182) of the 197 patients were 80% to 120% compliant.

Efficacy Results – Study 026

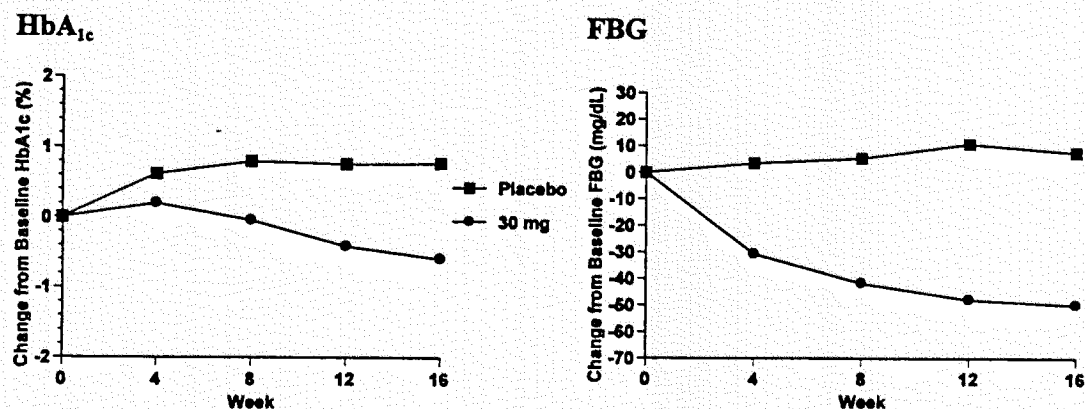
Primary Efficacy Variable – HbA_{1c} Change from Baseline to Week 16

At endpoint (Week 16), the LSM change from baseline in HbA_{1c} in the placebo group was +0.60% compared to -0.76% for the pioglitazone group; the difference of -1.37% was statistically significant (Table 35 & Fig 17.)

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Table 35 Adjusted* LSM Change from Baseline in HbA_{1c} by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	93	10.28	0.19	100	10.54	0.18	0.26	0.25	-0.24	0.75	0.31
Week 4	92	0.61	0.10	98	0.19	0.09	-0.42	0.13	-0.68	-0.15	<0.01
Week 8	92	0.79	0.13	100	-0.05	0.13	-0.85	0.19	-1.21	-0.48	<0.01
Week 12	93	0.75	0.15	100	-0.42	0.15	-1.17	0.21	-1.58	-0.75	<0.01
Week 16	93	0.76	0.17	100	-0.60	0.16	-1.37	0.24	-1.83	-0.9	<0.01

Figure 17 LSM Change from baseline in HbA_{1c} and FBG – Study 026

Secondary Efficacy Variables

At endpoint (Week 16), the LSM change from baseline in FBG was +7.7 mg/dL for the placebo group and -49.8 mg/dL for the pioglitazone group. The between group difference of -57.6 mg/dL was significant (Table 36 & Fig 17).

Table 36 Adjusted* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	91	270.07	7.87	99	272.62	7.63	2.56	10.47	-18.12	23.23	0.81
Week 4	90	3.39	5.24	96	-30.8	5.24	-34.19	7.4	-48.82	-19.56	<0.01
Week 8	91	5.31	5.81	99	-41.75	5.7	-47.06	8.14	-63.13	-30.99	<0.01
Week 12	91	10.79	6.57	99	-47.97	6.45	-58.76	9.21	-76.94	-40.57	<0.01
Week 16	91	7.73	6.94	99	-49.82	6.8	-57.55	9.71	-76.74	-38.36	<0.01

C-peptide & Insulin

Fasting C-peptide and insulin were significantly different between pioglitazone-treated patients and the placebo-treated patients at endpoint (Tables 37, 38 & Fig 18).

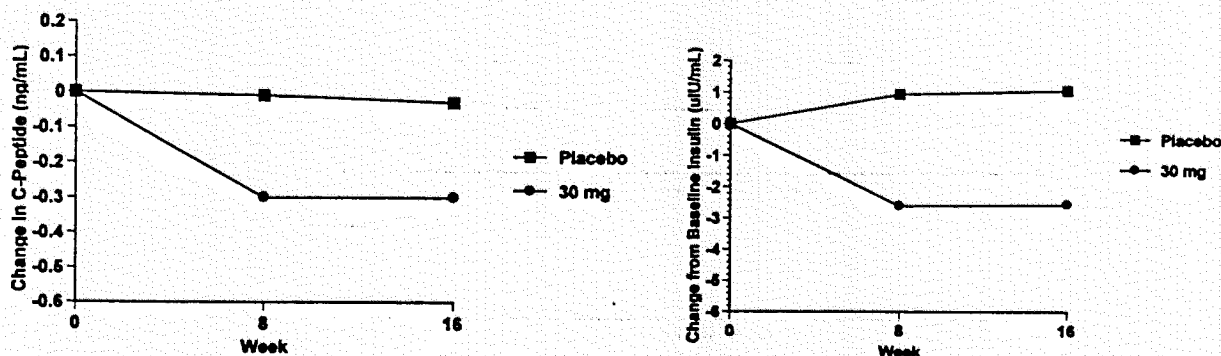
Table 37 LSM Change from Baseline in C-Peptide (ng/mL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	82	2.31	0.11	96	2.21	0.10	-0.10	0.14	-0.38 0.17	0.46
Week 8	82	-0.01	0.06	95	-0.30	0.06	-0.28	0.08	-0.45 -0.12	<0.01
Week 16	82	-0.03	0.06	95	-0.30	0.06	-0.26	0.08	-0.43 -0.10	<0.01

Table 38 LSM Change from Baseline in Fasting Insulin (μ IU/mL) by Visit (LOCF)

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	82	17.18	1.35	96	16.37	1.26	-0.82	1.76	-4.30 2.67	0.64
Week 8	82	0.93	0.88	94	-2.61	0.83	-3.53	1.21	-5.93 -1.14	<0.01
Week 16	82	1.85	0.84	96	-1.98	0.78	-3.84	1.15	-6.10 -1.57	<0.01

Figure 18 LSM Change from Baseline in C-Peptide (ng/mL) & Fasting Insulin (μ IU/mL) by Visit (LOCF) – Study 026



Lipids

At endpoint (Week 16), the LSM change in triglycerides was -18.5 mg/dL for the placebo group and -103.8 mg/dL for the pioglitazone group. The LSM change in total cholesterol was -2.3 mg/dL for the placebo and +2.4 mg/dL for the pioglitazone group. For HDL the LSM change was 0.3 mg/dL for the placebo group and 5.3 mg/dL for the pioglitazone group. For LDL, it was 4.2 mg/dL for the placebo group and 2.7 mg/dL for the pioglitazone group (Tables 39-42 & Fig 19.)

Table 39 LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	85	335.1	47.49	96	400.4	45.26	65.30	62.37	-57.85 188.46	0.30
Week 8	85	-27.05	28.57	96	-92.11	27.69	-65.06	39.74	-143.61 13.49	0.10
Week 16	85	-18.52	19.97	96	-103.77	19.35	-85.25	27.77	-140.14 -30.36	<0.01

Table 40 LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	85	221.81	6.41	96	224.46	6.11	2.65	8.41	-13.97 19.26	0.75
Week 8	85	2.37	4.5	96	0.52	4.34	-1.85	6.26	-14.22 10.52	0.77
Week 16	85	-2.35	3.62	96	2.43	3.5	4.78	5.04	-5.18 14.74	0.34

Table 41 LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	82	39.31	1.3	91	39.74	1.24	0.43	1.68	-2.89 3.75	0.80
Week 8	80	-0.57	1.15	89	4.69	1.05	5.27	1.56	2.19 8.34	<0.01
Week 16	82	0.32	1.13	91	5.33	1.06	5.01	1.55	1.95 8.07	<0.01

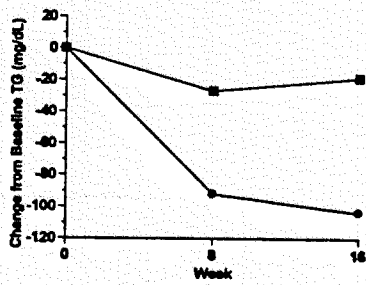
Table 42 LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	67	130.80	4.76	70	130.91	4.73	0.11	6.38	-12.52 12.75	0.99
Week 8	66	5.54	3.42	71	0.42	3.29	-5.11	4.75	-14.53 4.31	0.28
Week 16	67	4.15	3.46	70	2.70	3.52	-1.46	4.94	-11.25 8.33	0.77

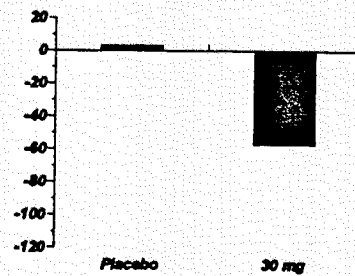
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Figure 19 LSM Change from Baseline in Triglycerides, Total Cholesterol, HDL, & LDL – Study 026

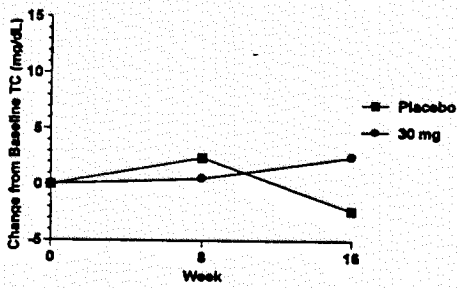
Triglyceride



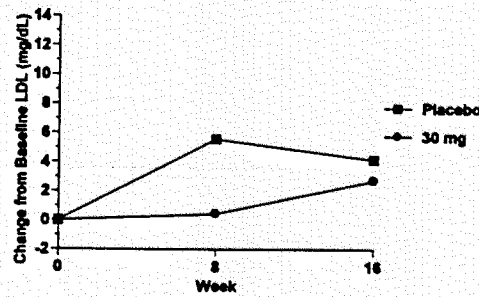
Endpoint Median Triglycerides



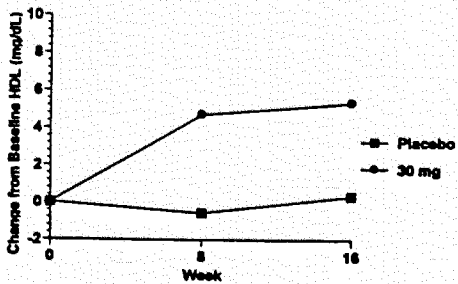
Total Cholesterol



LDL



HDL



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Subgroup Analyses

Changes from baseline in HbA_{1c} at endpoint were examined in subgroups of gender, age, and use of previous antidiabetic medication using the LOCF data of the ITT population. The interaction between treatment and subgroup was explored using ANOVA with treatment, subgroup, center, and treatment-by-subgroup terms in the model.

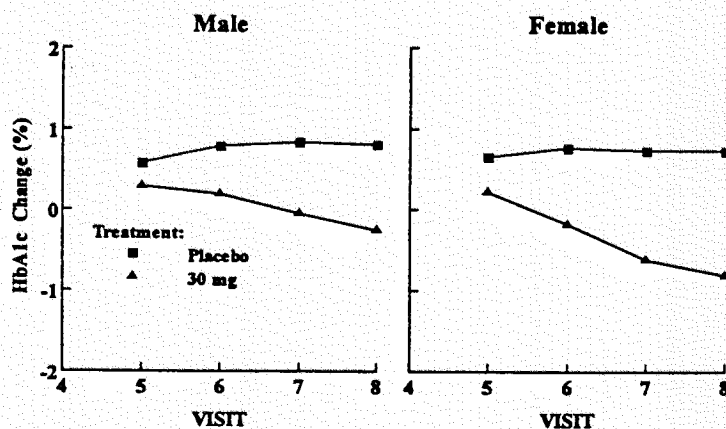
Gender

Table 42 and Figure 20 display the mean change from baseline in HbA_{1c} by gender. The p-value for treatment-by-gender interaction was 0.61.

Table 43 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender (LOCF) – Study 026

Subgroup	Placebo	30 mg
Men		
n	51	49
Baseline Mean	9.94	10.80
Mean Change	0.81	-0.26
SE	0.20	0.21
Women		
n	41	50
Baseline Mean	11.04	10.51
Mean Change	0.74	-0.80
SE	0.26	0.24

Figure 20 Mean Change from Baseline in HbA_{1c} (%) by Gender – Study 026



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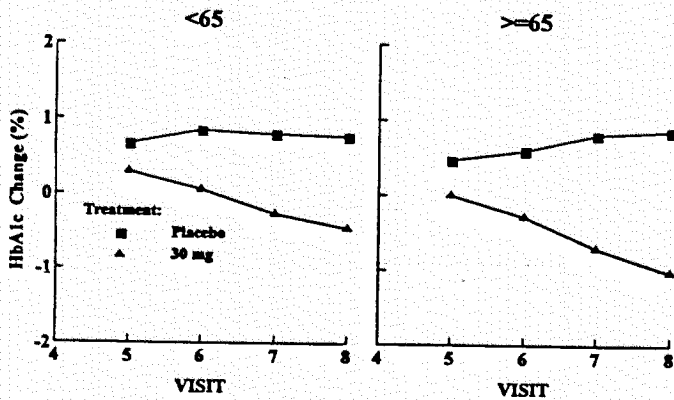
Age

Mean change from baseline in HbA_{1c} for patients <65 and ≥65 years of age is displayed in Table 43 and Figure 21. P-value for the treatment-by-age group interaction was 0.29.

Table 44 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group (LOCF) – Study 026

Subgroup	Placebo	30 mg
<65 years old		
n	74	88
Baseline Mean	10.50	10.73
Mean Change	0.76	-0.46
SE	0.19	0.18
≥65 years old		
n	19	12
Baseline Mean	10.15	10.08
Mean Change	0.86	-1.03
SE	0.20	0.20

Figure 21 Mean Change from Baseline in HbA_{1c} (%) by Age Group – Study 026



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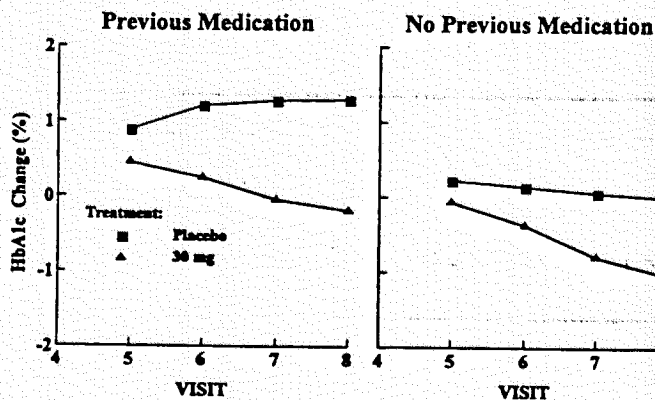
Previous Antidiabetic Medication

Table 44 and Figure 22 display the mean change from baseline in HbA_{1c} by previous antidiabetic medication use. P-value for the treatment-by-previous medication interaction was 0.42.

Table 45 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Previous Antidiabetic Medication (LOCF) – Study 026

Subgroup	Placebo	30 mg
Previous Medication		
n	56	61
Baseline Mean	10.40	10.81
Mean Change	1.29	-0.20
SE	0.18	0.19
No Previous Medication		
n	37	39
Baseline Mean	10.46	10.41
Mean Change	0.01	-1.05
SE	0.24	0.27

Figure 22 Mean Change from Baseline in HbA_{1c} (%) by Previous Medication – Study 026



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3. Add-On Trials

The 5 add-on trials were all double-blind, multicenter, randomized, parallel trials except Study OCT-003 (Japan) which was a single-blind study. The 3 U.S. studies compared the safety and efficacy of pioglitazone and placebo as add-on to either sulfonylurea (010), metformin (027) or insulin (014) in patients with type 2 diabetes not well controlled ($HbA_{1c} > 8\%$) by the current therapy. Patients first entered a 2-week screening period followed by a 1-week or 4-week, single-blind placebo period (4-week for Study 014) to discontinue all antidiabetic drugs other than the companion drug. The double-blind treatment period was 16 weeks. Table 46 summarizes the add-on trials.

The study included patients 30 to 75 years of age, with a BMI 25 to 45 kg/m^2 , a stable background therapy regimen at least 30 days before enrollment, a fasting C-peptide level of $\geq 1ng/mL$ (010, 027) or $\geq 0.7 ng/ml$ (014) at Visit 1, normal thyroid function and $HbA_{1c} > 8\%$.

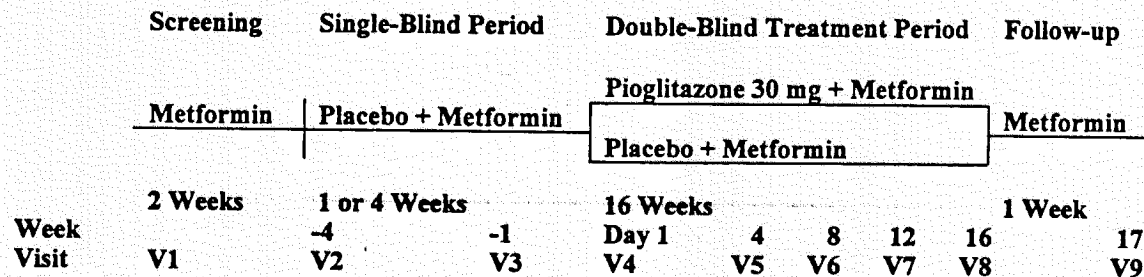
Table 46 Brief Summary of Add-on Trials

Study ID	# of Centers	Total Sample Size & Treatment Group	Design	Duration of Treatment & Study Period
PNFP-010	US 54	560 placebo + SU 15mg + SU 30 mg + SU	Double-blind, multicenter, randomized, fixed-dose	16 weeks 6/2/97 - 8/10/98
PNFP-027	US 43	328 placebo + metformin 30 mg + metformin	Double-blind, multicenter	16 weeks 5/30/97 - 9/14,98
PNFP-014	US 84	566 15 mg + insulin 30 mg + insulin placebo + insulin	Double-blind,	16 weeks 5/30/97 - 9/14,98
OCT-003	Japan Kaneko	237 Placebo + SU 15 mg + SU 30 mg + SU 45 mg + SU	single-blind	12 weeks
OCT-012 (PD-194)	Japan Kaneko	119 placebo + SU 30 mg + SU	double-blind	12 weeks

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Study PNFP-027 (Metformin)

This was a double-blind, placebo-controlled, randomized, multicenter, study in 197 patients from 27 centers in the U.S. The study scheme is displayed in the following diagram.



Patient Disposition

Of the 600 patients screened, 8 were rescreened. Of the 396 patients received single-blind medication, 328 patients were randomized (5 from rescreen), 160 to the placebo + metformin (Plb+MF) group and 168 to the pioglitazone 30mg + metformin (Pio+MF) treatment group. Seventy-six percent of the patients (249/328) completed the double-blind treatment period: 69% (110/160) of the Plb+MF group and 83% of the Pio 30mg + MF group. Lack of efficacy (16%, 52/328) including insufficient therapeutic effect (13%, 43/328), AEs of symptomatic hyperglycemia (0.3%, 1/328) or asymptomatic hyperglycemia (1.2%, 4/328), and unhappy with the glucose control/lack of efficacy (1.2%, 4/328) was the most common reason for withdrawals. Table 47 displays the disposition of patients. Table 48 displays patient discontinuation by time.

Table 47 Patient Disposition – Study 027

	Plb+MF	30mg + MF
Randomized	160	168
Completed	110	139
Withdrawn	50	29
Lack of Efficacy	35	17
AE: All Other	3	5
Withdrew Consent (personal)	3	4
Lost to Follow-up	3	2
Non-compliance	1	0
Protocol Violation	1	0
Other	4	1

Table 48 Patient Discontinuation by Time – Study 027

	Plb+MF	30mg + MF	Total
Randomized	160	168	328
Withdrawn	50	29	79
≤ Week 4	8	10	18
> Week 4 & ≤ Week 8	14	3	17
> Week 8 & ≤ Week 12	23	13	36
> Week 12 & ≤ Week 16	5	3	8

Baseline characteristics were not significantly different between the treatment groups. The mean age of randomized patients was 55.6 years. Most patients were Caucasian (84%), males (57%). The mean weight was 93.3 kg. The mean BMI was 32.1 kg/m². Most patients (70%) did not receive antidiabetic medications other than metformin before enrolling in the study. Baseline values for the primary and secondary efficacy variables are listed in Table 49.

Table 49 Mean Values at Baseline in Efficacy Variables – Study 027

	Plb+MF n=160			30mg + MF n=168			p-value*
	n	Mean	SD	n	Mean	SD	
HbA _{1c}	160	9.75	1.27	168	9.86	1.42	0.51
FBG (mg/dL)	160	258.6	68.55	168	252.3	69.72	0.38
Fasting C-Peptide (ng/mL)	159	2.14	0.80	166	2.06	0.80	0.47
Fasting Insulin (μIU/mL)	159	14.82	10.25	166	14.67	10.63	0.92
Triglycerides (mg/dL)	160	296.9	314.44	168	296.3	289.76	0.99
Total Cholesterol	160	213.1	53.80	168	212.9	47.59	0.92
HDL (mg/dL)	155	42.4	10.39	165	43.0	12.46	0.66
LDL (mg/dL)	138	118.2	37.35	135	120.6	31.23	0.45

* p-values based on treatment and pooled center in ANOVA model

Of the 328 patients who were randomized, 97 (30%) patients had received other antidiabetic medications with metformin. Four patients had taken >1 other antidiabetic medication with metformin.

Treatment compliance (80%-120% compliant) was 94% with the double-blind medication and 85% with the companion (metformin) medication.

Efficacy Results – Study 027

Primary Efficacy Variable – HbA_{1c} Change from Baseline to Week 16

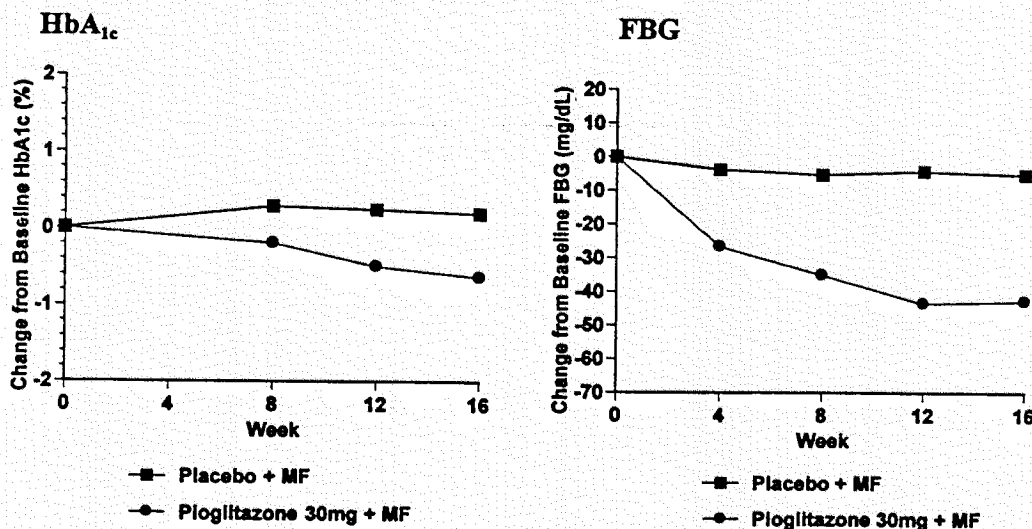
At endpoint (Week 16), the LSM change from baseline in HbA_{1c} in Plb+MF group was +0.19% compared to the -0.64% of the Pio 30mg + MF group the difference of -0.83% was statistically significant (Table 50). Figure 23 displays the

change over time for HbA_{1c} and FBG. The p-values for the treatment-by-baseline and treatment-by-center interactions were 0.09 and 0.54, respectively.

Table 50 Adjusted* LSM Change from Baseline in HbA_{1c} by Visit (LOCF) – Study 027

	Plb+MF			30mg + MF			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	153	9.77	0.11	161	9.92	0.11	0.15	0.15	-0.15 0.45	0.33
Week 8	153	0.28	0.09	160	-0.20	0.09	-0.49	0.13	-0.74 -0.23	<0.01
Week 12	153	0.24	0.11	161	-0.50	0.11	-0.74	0.16	-1.05 -0.43	<0.01
Week 16	153	0.19	0.12	161	-0.64	0.11	-0.83	0.16	-1.15 -0.51	<0.01

Figure 23 LSM Change from baseline in HbA_{1c} and FBG – Study 027



Secondary Efficacy Variables

FBG

At endpoint (Week 16), the LSM change from baseline in FBG was -5.2 mg/dL for the Plb+MF group and -42.8 mg/dL for the Pio 30mg + MF group. The between group difference of -37.7 mg/dL was significant (Table 51).

Table 51 Adjusted* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 027

	Placebo			Pioglitazone			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
	157	259.9	5.71	165	254.38	5.58	-5.51	7.77	-20.8	9.77	0.48
Week 4	156	-3.84	3.94	164	-26.7	3.86	-22.86	5.52	-33.72	-12	<0.01
Week 8	157	-5.32	4.17	165	-35.11	4.07	-29.79	5.82	-41.26	-18.32	<0.01
Week 12	157	-4.24	4.24	165	-43.51	4.14	-39.28	5.93	-50.95	-27.6	<0.01
Week 16	157	-5.18	4.23	165	-42.83	4.13	-37.65	5.92	-49.31	-26	<0.01

C-peptide & Insulin

Fasting C-peptide and insulin were significantly different between pioglitazone-treated patients and the placebo-treated patients at endpoint (Tables 52, 53 & Figure 24).

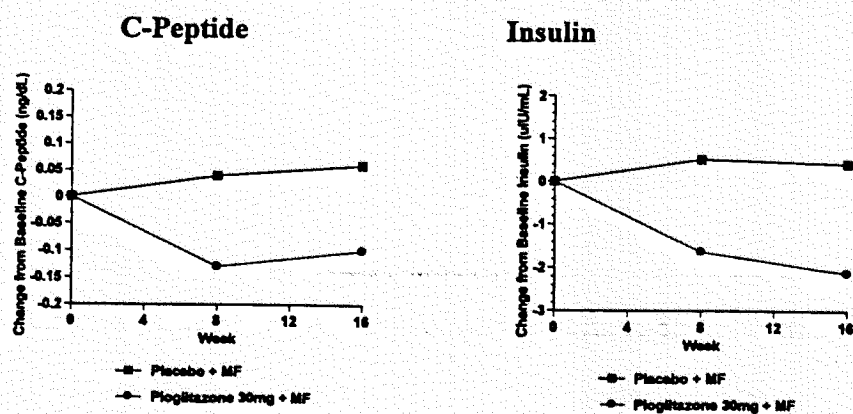
Table 52 LSM Change from Baseline in C-Peptide (ng/mL) by Visit (LOCF) – Study 027

	Placebo+MF			30 mg+MF			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	148	2.18	0.07	159	2.08	0.07	-0.09	0.09	-0.27	0.09	0.31
Week 8	146	0.04	0.04	156	-0.13	0.04	-0.18	0.06	-0.3	-0.05	0.01
Week 16	148	0.06	0.05	159	-0.1	0.05	-0.16	0.07	-0.3	-0.02	0.03

Table 53 LSM Change from Baseline in Fasting Insulin (μIU/mL) by Visit (LOCF) – Study 027

	Plb+MF			Pio 30mg + MF			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline											
Week 8	146	0.52	0.61	155	-1.64	0.59	-2.15	0.86	(-3.84	-0.47)	0.01
Week 16	148	0.42	0.71	157	-2.13	0.68	-2.54	0.98	(-4.48	-0.6)	0.01

Figure 24 LSM Change from baseline in C-Peptide and Insulin – Study 027



Lipids

At endpoint (Week 16), the LSM change in triglycerides was -20.0 mg/dL for the Plb+MF group and -63.4 mg/dL for the Pioglitazone 30mg + MF group. The treatment difference of -43.4 mg/dL was significant (p=0.03). The LSM change in total cholesterol was -1.2 mg/dL for the Plb+MF and +5.7 mg/dL for the Pioglitazone 30mg + MF group. The p-value for the placebo subtracted difference of 6.9 mg/dL in TC was not significant (0.09). HDL was significantly different (p<0.01) at endpoint with an increase of 3.2 mg/dL in the Pioglitazone 30mg + MF compared to no change in the Plb+MF group. For LDL, it was not significant (p=0.12) when comparing a change of +2.7 mg/dL for the Plb+MF group and 6.9 mg/dL for the Pioglitazone 30mg + MF group (Tables 54-57 & Figure 25).

Table 54 LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 027

	Placebo+MF			30mg+MF			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	149	300.39	25.86	161	298.86	24.9	-1.53	35.07	-70.56	67.5	0.97
Week 8	148	5.26	20.82	161	-82.94	19.96	-88.2	28.85	-145.02	-31.38	<0.01
Week 12	149	-13.81	12.75	161	-79.96	12.25	-66.15	17.68	-100.98	-31.33	<0.01
Week 16	149	-19.96	14.73	161	-63.37	14.14	-43.41	20.42	-83.62	-3.19	0.03

Table 55 LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 027

	Placebo+MF			30mg+MF			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	149	211.93	4.28	161	212.84	4.12	0.91	5.8	-10.51	12.32	0.88
Week 8	148	-0.31	2.9	161	2.37	2.78	2.68	4.02	-5.24	10.6	0.51
Week 12	149	-0.12	3.2	161	1.42	3.07	1.54	4.43	-7.19	10.27	0.73
Week 16	149	-1.21	2.96	161	5.71	2.85	6.92	4.11	-1.18	15.01	0.09

Table 56 LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 027

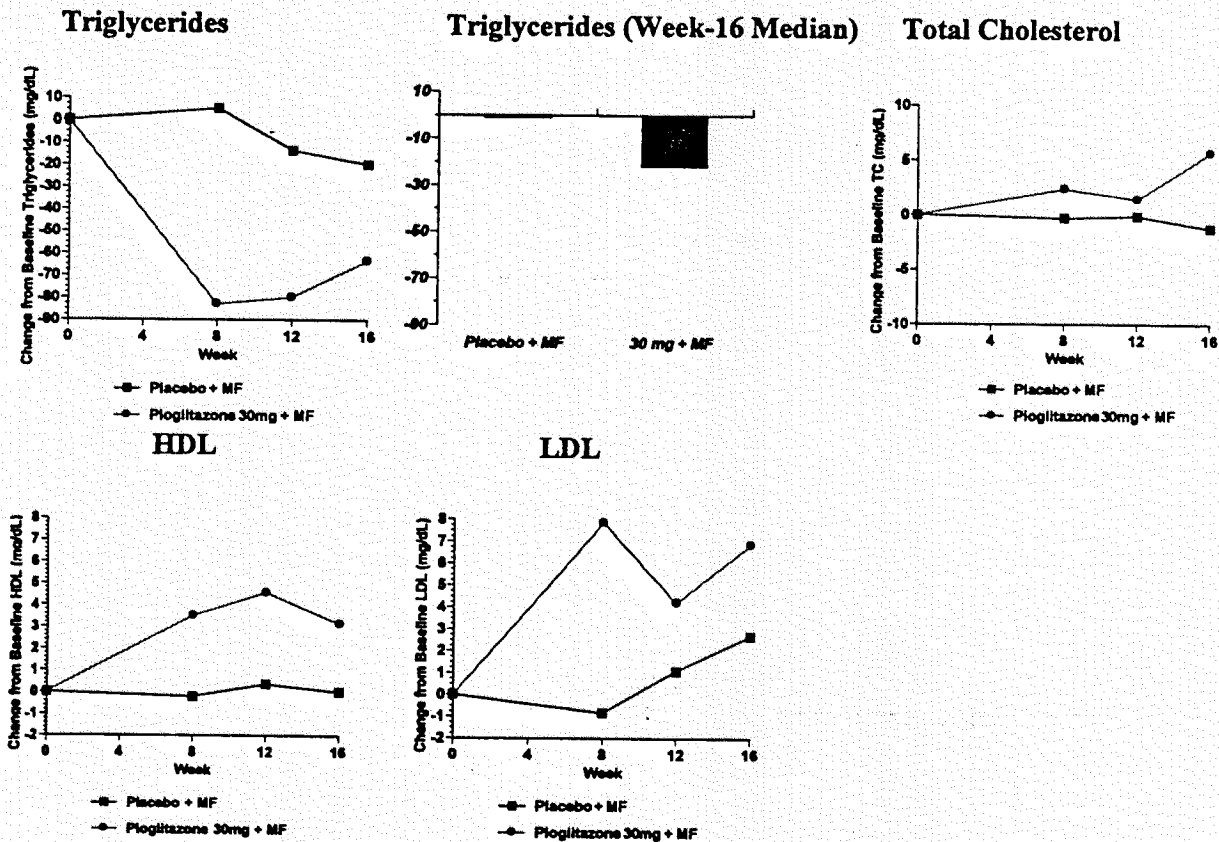
	Placebo+MF			30mg+MF			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	143	42.09	1.00	158	42.86	0.95	0.78	1.35	-1.89	3.44	0.57
Week 8	141	-0.21	0.85	158	3.52	0.79	3.73	1.16	1.45	6.02	<0.01
Week 12	142	0.37	0.97	158	4.59	0.91	4.22	1.32	1.61	6.83	<0.01
Week 16	143	0.02	0.67	158	3.16	0.64	3.13	0.93	1.31	4.96	<0.01

Table 57 LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 027

	Placebo+MF			30 mg+MF			Difference from Placebo*			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	125	118.00	3.15	129	119.3	3.07				NS
Week 8	117	-0.84	1.94	129	7.85	1.80	8.69	2.59	3.59 13.79	<0.01
Week 12	121	1.08	2.11	127	4.21	2.04	3.13	2.87	-2.53 8.78	0.28
Week 16	121	2.68	1.95	125	6.85	1.87	4.17	2.64	-1.04 9.37	0.12

*ANOVA with treatment, pooled center, and baseline as covariate (no trt-by-center)

Figure 25 Change from Baseline in Lipids



Body Weight

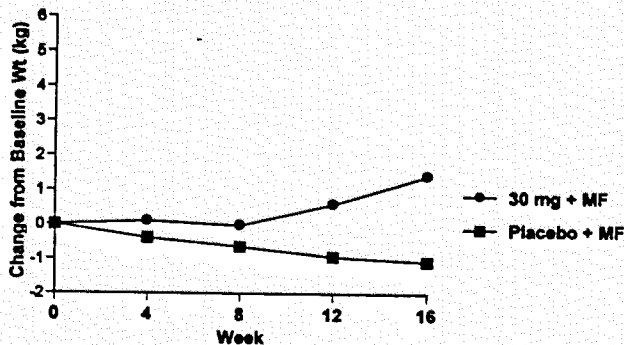
Table 58 displays change from baseline weight (kg) over time for the completers and at endpoint. Pioglitazone+MF-treated patients gained weight compared to placebo significantly during the course of the study. At Week 16 the difference was 2.48 kg. Figure 26 displays the weight change in patients who completed the study.

Table 58 Mean Change from Baseline in Body Weight (kg) (Completers) – Study 027

	Placebo+MF			30 mg+MF			Difference from Placebo*			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	112	93.96	1.60	137	93.24	1.41	-0.71	2.13	-4.90 3.48	0.74
Week 4	112	-0.39	0.14	137	0.09	0.16	0.48	0.22	0.05 0.91	0.03
Week 8	112	-0.64	0.18	137	-0.03	0.40	0.61	0.47	-0.32 1.54	0.20
Week 12	112	-0.93	0.23	137	0.59	0.45	1.51	0.54	0.45 2.58	0.01
Week 16	112	-1.06	0.25	137	1.41	0.27	2.48	0.38	1.72 3.23	<0.01
Endpoint	160	-1.36	0.24	167	0.95	0.24	2.31	0.34	1.64 2.98	<0.01

*ANOVA with treatment in the model

Figure 26 Changes in Body Weight (kg) – Completers



Subgroup Analysis

Changes from baseline in HbA_{1c} at endpoint were examined in subgroups of gender, age. The interaction between treatment and subgroup was explored using ANOVA with treatment, subgroup, center, and treatment-by-subgroup terms in the model.

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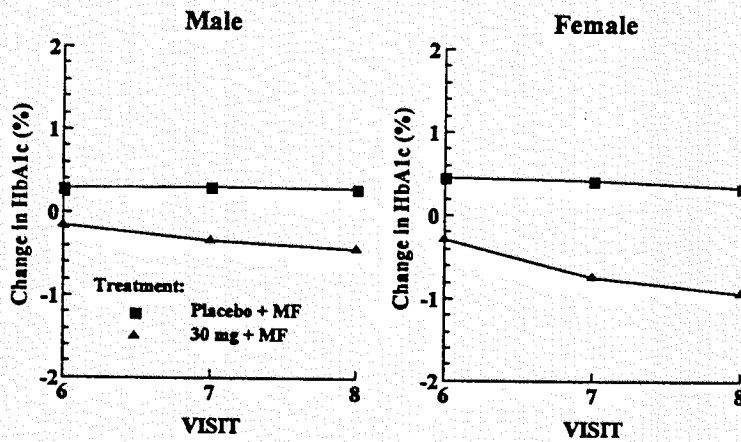
Gender

Table 59 and Figure 27 display the mean change from baseline in HbA_{1c} by gender. The p-value for treatment-by-gender interaction was 0.13.

Table 59 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender – Study 027

Subgroup	Placebo+MF	30 mg +MF
Men		
n	92	88
Baseline Mean	9.74	9.83
Mean Change	0.28	-0.44
SE	0.12	0.16
Women		
n	61	73
Baseline Mean	9.74	10.00
Mean Change	0.39	-0.94
SE	0.19	0.15

Figure 27 Mean Change from Baseline in HbA_{1c} (%) by Gender – Study 027



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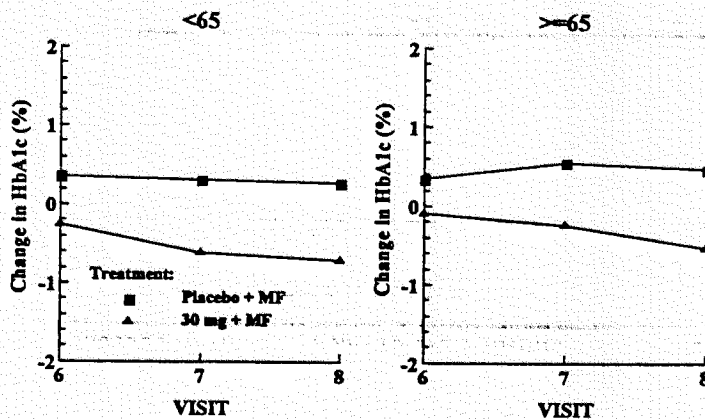
Age

Mean change from baseline in HbA_{1c} for patients <65 and ≥65 years of age is displayed in Table 60 and Figure 28. P-value for treatment-by-age group interaction was 0.97.

Table 60 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group – Study 027

Subgroup	Pib+MF	Pio 30mg + MF
<65 years old		
n	125	124
Baseline Mean	9.82	9.95
Mean Change	0.28	-0.71
SE	0.12	0.13
≥65 years old		
n	28	37
Baseline Mean	9.35	9.71
Mean Change	0.48	-0.54
SE	0.23	0.24

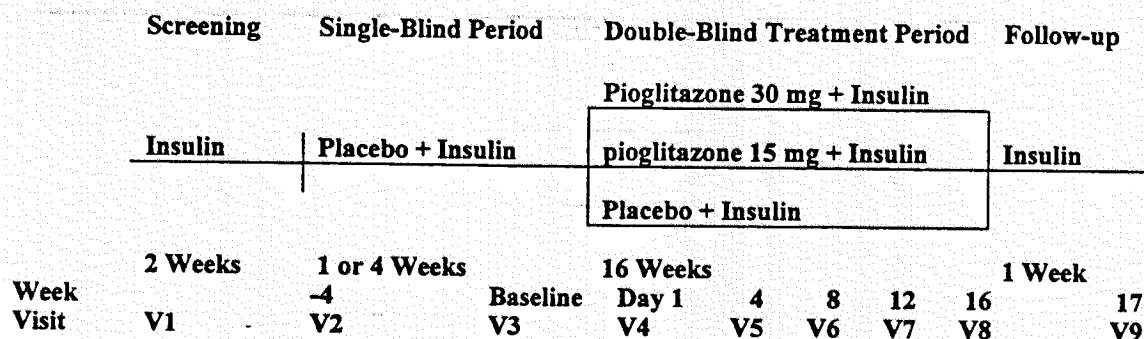
Figure 28 Mean Change from Baseline in HbA_{1c} (%) by Age Group – Study 027



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Study PNFP-014 (Insulin)

This was a double-blind, placebo-controlled, randomized, multicenter (84), study of efficacy and safety of 15 mg or 30 mg doses of pioglitazone as add-on to insulin in type 2 diabetic patients. The study scheme is displayed in the following diagram.



Patient Disposition

Of the 1157 patients screened (15 rescreened), 674 patients received single-blind medication. A total of 566 patients were randomized (7 rescreened), 187 to the placebo + Insulin group, 191 to the 15 mg pioglitazone + Insulin, and 188 to the 30 mg pioglitazone + Insulin treatment group. Overall completion rate was 88% (497/566.) Table 61 displays the disposition of patients. Table 62 displays patient discontinuation by time.

Table 61 Patient Disposition – Study 014

	Plb+Insulin	Pio 15 mg + Insulin	Pio 30mg + Insulin
Randomized	187	191	188
Completed	164	161	172
Withdrawn	23	30	16
Insufficient Therapeutic Effect	3	3	5
AE	3	5	6
Non-Compliance	2	3	1
Lost to Follow-up	4	7	0
Withdrew Consent	8	11	3
Unhappy with Glucose Control	0	3	0
Personal Reasons	8	4	2
Weight Gain	0	4	1
Protocol Violation	3	1	1

Baseline characteristics were not significantly different between the treatment groups. The mean age of randomized patients was 57.1 years. Most patients were Caucasian (73%). Females were slightly more (53%). The mean weight was 96.49 kg. The mean BMI was 33.55 kg/m². Most patients (88%) did not receive antidiabetic medications other than insulin before

enrolling in the study. Baseline values for the primary and secondary efficacy variables are listed in Table 62.

Table 62 Mean Values at Baseline in Efficacy Variables – Study 014

	Placebo+Insulin n=187			15 mg + Insulin n=191			30 mg + Insulin n=188			overall p-value*
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
HbA _{1c}	186	9.83	1.36	191	9.84	1.45	188	9.86	1.29	0.97
FBG (mg/dL)	186	220.6	72.48	190	223.7	71.89	188	227.5	68.36	0.62
Fasting C-Peptide (ng/mL)	186	1.54	0.71	188	1.61	0.80	185	1.57	0.80	0.82
Triglycerides (mg/dL)	187	240.0	204.29	191	245.4	192.12	188	256.5	292.41	0.80
Total Cholesterol	187	214.6	44.82	191	212.9	48.68	188	207.8	45.01	0.25
HDL (mg/dL)	185	43.0	11.74	188	42.9	12.56	185	43.2	12.96	0.98
LDL (mg/dL)	162	131.4	38.84	163	124.9	38.65	162	122.5	33.75	0.06

* p-values based on pooled center (38) and treatment in ANOVA model

Of the 566 patients who were randomized, 68 (12%) received other antidiabetic medications in combination with their insulin (metformin, glibenclamide, glipizide, glimepiride, acarbose, troglitazone, and tolazamide.) Ten of these patients received more than one medication in combination with their insulin.

Treatment compliance (80%-120% compliant) was 94% with the double-blind medication and 85% with the companion (Insulin) medication.

Efficacy Results – Study 014

Primary Efficacy Variable – HbA_{1c} Change from Baseline to Week 16

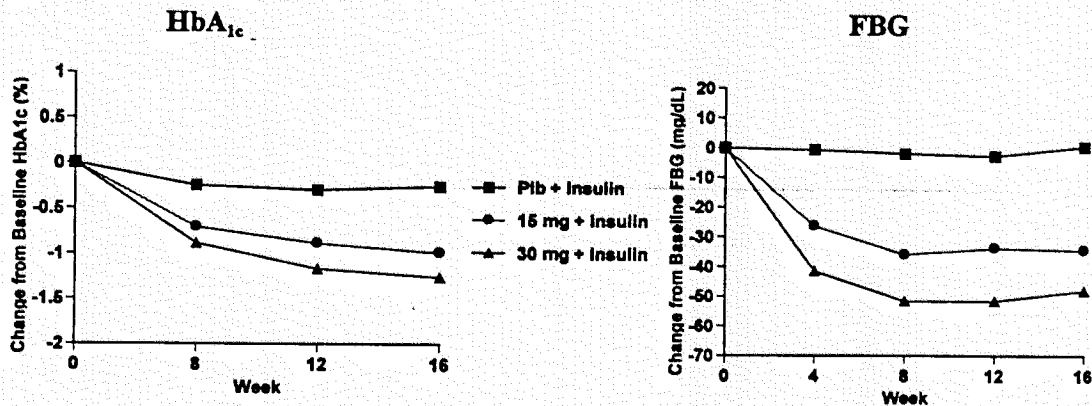
At endpoint (Week 16), both pioglitazone treatment groups were statistically significant different from the placebo group in the LSM change from baseline in HbA_{1c} (Table 63 & Fig 29) The LSM changes were -0.26%, -0.99%, and -1.26% for the placebo + insulin, 15 mg + insulin, and 30 mg + insulin groups, respectively.

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Table 63 Adjusted* LSM Change from Baseline in HbA_{1c} by Visit (LOCF) – Study 014

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P ₁₅	P ₃₀
Baseline	177	9.75	0.10	177	9.75	0.10	185	9.84	0.10	1.00	0.77
Week 8	173	-0.25	0.07	175	-0.71	0.07	184	-0.89	0.07	<0.01	<0.01
Week 12	177	-0.30	0.08	177	-0.89	0.08	185	-1.17	0.08	<0.01	<0.01
Week 16	177	-0.26	0.08	177	-0.99	0.08	185	-1.26	0.08	<0.01	<0.01
Difference from Placebo (SE)				-0.73 0.12			-1.00 0.12				
95% C.I.				(-1.00 -0.47)			(-1.27 -0.74)				

*Least Squared Means Adjusted by Dunnett procedure

Figure 29 LSM Change from baseline in HbA_{1c} and FBG – Study 014

Secondary Efficacy Variables

FBG

At endpoint (Week 16), the LSM change from baseline in FBG was -5.2 mg/dL for the Plb+MF group and -42.8 mg/dL for the 30mg + MF group. The between group difference of -37.7 mg/dL was significant (Table 64 & Fig 29).

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Table 64 Adjusted* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 014

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P ₁₅	P ₃₀
Baseline	179	220.55	5.22	183	221.67	5.15	184	229.28	5.15	0.98	0.38
Week 4	179	-0.67	4.78	182	-26.39	4.69	180	-41.59	4.78	<0.01	<0.01
Week 8	179	-1.91	4.79	182	-35.99	4.70	184	-51.60	4.75	<0.01	<0.01
Week 12	179	-2.67	4.85	183	-33.77	4.75	184	-51.59	4.80	<0.01	<0.01
Week 16	179	0.57	5.09	183	-34.46	4.99	184	-48.04	5.04	<0.01	<0.01
Difference from Placebo (SE)				-35.04 7.12			-48.61 7.16				
95% C.I.				(-50.84 -19.24)			(-64.50 -32.72)				

*Least Squared Means Adjusted by Dunnett procedure

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C-peptide

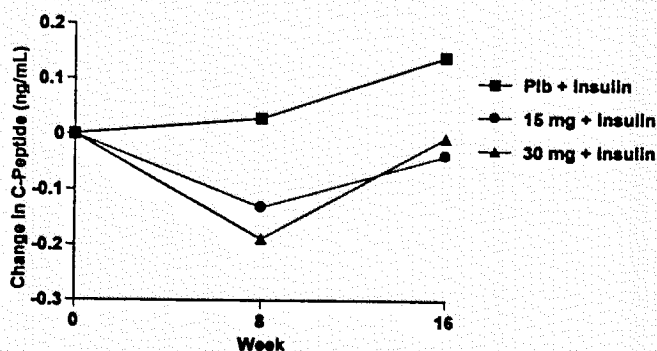
Fasting C-peptide was significantly different between 15 mg + insulin group and placebo group at endpoint. The p-value comparing the 30 mg + insulin group with placebo group was 0.07 (Table 65 & Figure 30).

Table 65 LSM Change from Baseline in C-Peptide (ng/mL) by Visit (LOCF) – Study 014

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P ₁₅	P ₃₀
Baseline	178	1.55	0.06	175	1.59	0.06	179	1.60	0.06	0.87	0.77
Week 8	172	0.03	0.04	169	-0.13	0.04	173	-0.19	0.04	0.02	0.00
Week 16	178	0.14	0.05	175	-0.04	0.05	179	-0.01	0.05	0.02	0.07
Difference from Placebo (SE)					-0.18	0.07		-0.15	0.07		
95% C.I.					(-0.33	-0.02)		(-0.30	0.01)		

*Least Squared Means Adjusted by Dunnett procedure

Figure 30 LSM Change from baseline in C-Peptide – Study 014



Lipids

At endpoint (Week 16), the LSM change in triglycerides was -20.0 mg/dL for the Plb+MF group and -63.4 mg/dL for the Pio 30mg + MF group. The treatment difference of -43.4 mg/dL was significant (p=0.03). The LSM change in total cholesterol was -1.2 mg/dL for the Plb+MF and +5.7 mg/dL for the Pio 30mg + MF group. The p-value for the placebo subtracted difference of 6.9 mg/dL in TC was not significant (0.09). HDL was significantly different (p<0.01) at endpoint with an increase of 3.2 mg/dL in the Pio 30mg + MF compared to no change of the Plb+MF group. For LDL, it was not significant (p=0.12) when comparing a change of +2.7 mg/dL for the Plb+MF group and 6.9 mg/dL for the Pio 30mg + MF group (Tables 66-69 & Fig 31).

Table 66 LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 014

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P ₁₅	P ₃₀
Baseline	176	242.49	17.81	176	230.69	17.75	182	262.32	17.52	0.85	0.64
Week 8	176	-0.29	11.83	175	-25.82	11.72	181	-65.69	11.70	0.22	0.00
Week 12	176	1.22	13.03	176	-18.25	12.90	182	-52.81	12.85	0.46	0.01
Week 16	176	10.95	15.10	176	-11.58	14.95	182	-49.52	14.89	0.46	0.01
Difference from Placebo (SE)				-22.53 21.24			-60.46 21.22				
95% C.I.				(-69.66 24.61)			(-107.55 -13.38)				

*Least Squared Means Adjusted by Dunnett procedure

Table 67 LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 014

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P ₁₅	P ₃₀
Baseline	176	214.03	3.58	176	213.08	3.57	182	207.32	3.53	0.97	0.30
Week 8	176	-0.22	2.18	175	-3.73	2.16	181	-4.89	2.16	0.41	0.22
Week 12	176	-3.14	2.31	176	-2.77	2.29	182	-1.26	2.28	0.99	0.79
Week 16	176	-3.25	2.34	176	-0.15	2.32	182	-1.78	2.31	0.54	0.86
Difference from Placebo (SE)				3.10 3.30			1.48 3.29				
95% C.I.				(-4.21 10.42)			(-5.83 8.78)				

*Least Squared Means Adjusted by Dunnett procedure

Table 68 LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 027

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P ₁₅	P ₃₀
Baseline	173	42.60	0.96	173	43.27	0.95	179	42.70	0.94	0.83	1.00
Week 8	170	-0.44	0.61	172	2.00	0.60	178	3.97	0.59	0.01	0.00
Week 12	173	-1.00	0.60	173	1.92	0.60	179	3.87	0.60	0.00	0.00
Week 16	173	-0.66	0.67	173	2.19	0.66	179	2.75	0.66	0.01	0.00
Difference from Placebo (SE)				2.85 0.94			3.41 0.94				
95% C.I.				(0.76 4.94)			(1.33 5.50)				

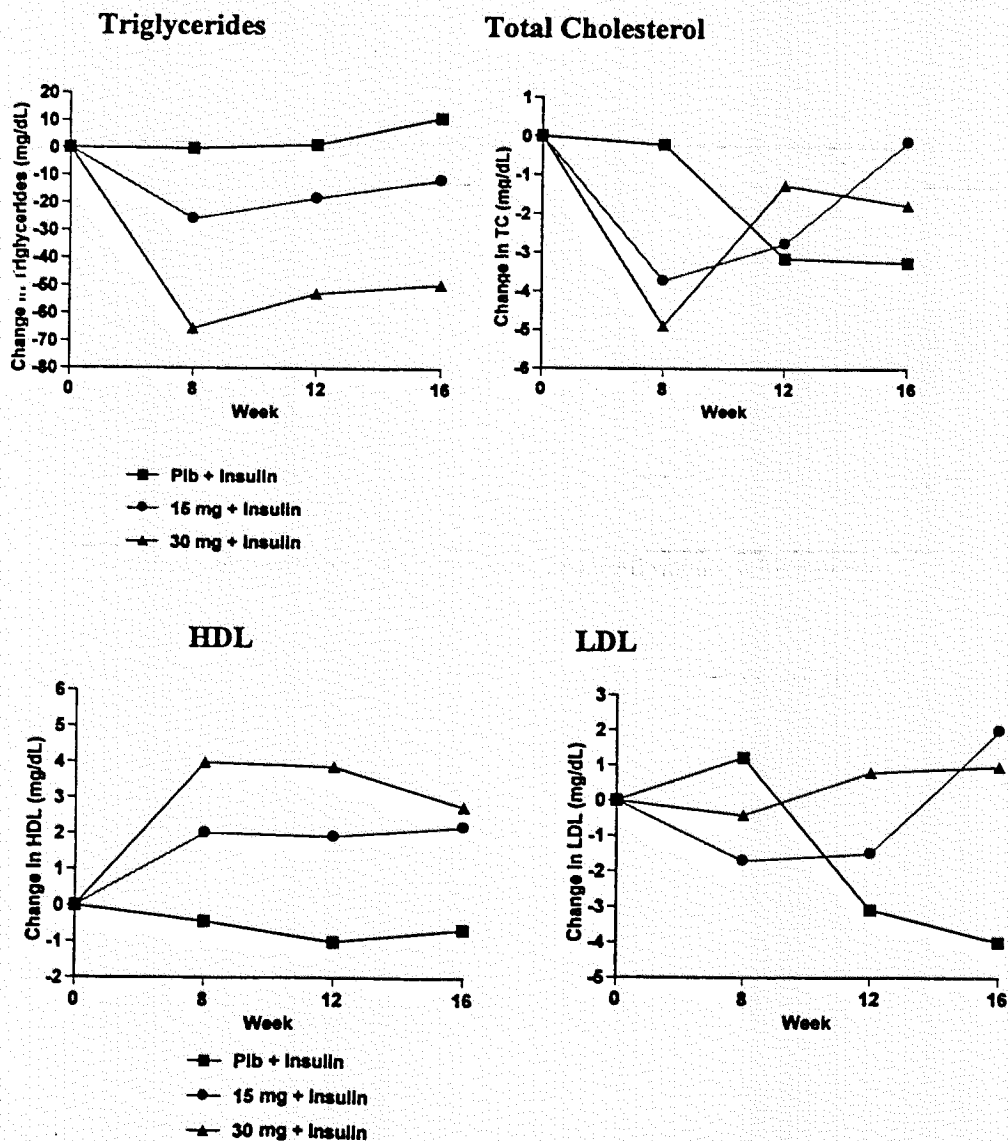
*Least Squared Means Adjusted by Dunnett procedure

Table 69 LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 014

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P ₁₅	P ₃₀
Baseline	173	42.60	0.96	173	43.27	0.95	179	42.70	0.94	0.83	1.00
Week 8	149	1.22	1.95	147	-1.72	1.96	154	-0.43	2.02	0.46	0.78
Week 12	151	-3.10	1.97	149	-1.51	1.96	154	0.79	2.07	0.79	0.30
Week 16	145	-4.00	2.02	147	2.00	1.99	154	0.98	2.08	0.06	0.16
Difference from Placebo (SE)				5.99 2.83			4.98 2.91				
95% C.I.				(-0.28 12.27)			(-1.48 11.44)				

*Least Squared Means Adjusted by Dunnett procedure

Figure 31 Change from Baseline in Lipids



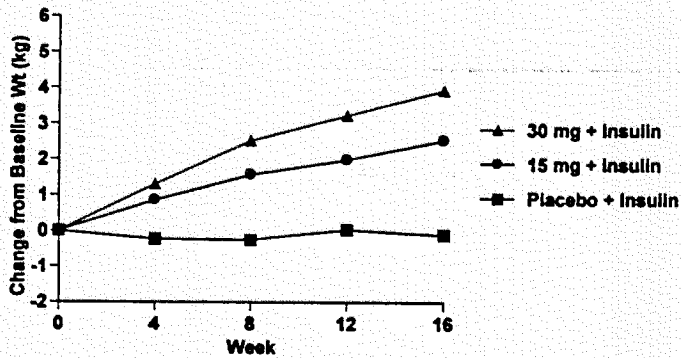
Body Weight

Table 70 displays change from baseline weight (kg) over time for the observed cases and at endpoint. Figure 32 displays mean change in body weight of the completers with constant sample size as at week 16.

Table 70 Mean Change from Baseline in Body Weight (kg) - Study 014

Visit	Placebo + Insulin	15 mg + Insulin	30 mg + Insulin
Week 16			
N	162	165	174
Mean	-0.11	2.53	3.92
SE	0.23	0.25	0.28
Endpoint			
N	182	190	188
Mean	-0.04	2.30	3.73
SE	0.22	0.23	0.27

Figure 32 Mean Changes in Body Weight (kg) – Completers



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Changes from baseline in HbA_{1c} at endpoint were examined in subgroups of gender, and age.

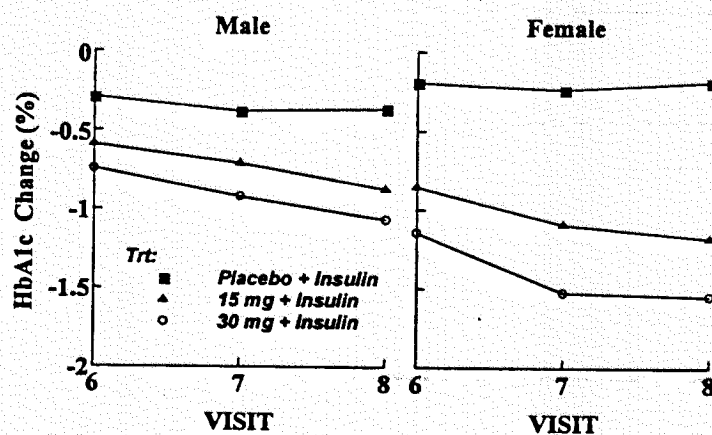
Gender

Table 71 and Figure 33 display the mean change from baseline in HbA_{1c} by gender. The p-value for treatment-by-gender interaction was 0.03.

Table 71 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender – Study 014

Subgroup	Placebo+Insulin	Pio 15 mg + Insulin	Pio 30 mg + Insulin
Men			
n	82	80	94
Baseline Mean	9.72	9.86	9.86
Mean Change	-0.36	-0.87	-1.07
SE	0.12	0.13	0.12
Women			
n	95	97	91
Baseline Mean	9.84	9.74	9.88
Mean Change	-0.19	-1.18	-1.55
SE	0.11	0.11	0.13

Figure 33 Mean Change from Baseline in HbA_{1c} (%) by Gender – Study 014



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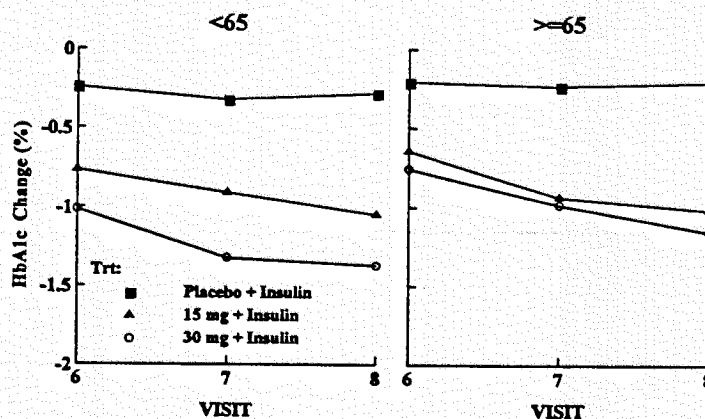
Age

Mean change from baseline in HbA_{1c} for patients age <65 and ≥65 years is displayed in Table 72 and Figure 34. P-value for treatment-by-age group interaction was 0.78.

Table 72 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group – Study 014

Subgroup	Placebo+Insulin	Pio 15 mg + Insulin	Pio 30 mg + Insulin
<65 years old			
n	136	130	129
Baseline Mean	9.93	9.91	10.12
Mean Change	-0.28	-1.05	-1.37
SE	0.10	0.11	0.11
≥65 years old			
n	41	47	56
Baseline Mean	9.31	9.47	9.28
Mean Change	-0.21	-1.01	-1.16
SE	0.15	0.11	0.12

Figure 34 Mean Change from Baseline in HbA_{1c} (%) by Age Group – Study 014



Study PNFP-010 (Sulfonylurea)

The study was conducted in 54 centers in the U.S. to compare the safety and efficacy of two doses of pioglitazone (15 or 30 mg) and placebo as add-on therapy to sulfonylurea in type 2 diabetes patients poorly controlled (HbA_{1c} ≥8%) with sulfonylurea, with or without metformin or acarbose. Prior to the 16-week treatment period, there was a 2-week screening period followed by a 1 or 4-week single blind placebo period, during which patients discontinued all antidiabetic drugs other than sulfonylurea. The trial included men and women 30 to 75 years of age with a BMI in the range of 25 to 45 kg/m², a stable sulfonylurea therapy regimen at least 30 days before enrollment, HbA_{1c} ≥8.0% (Visits 1 & 3), and fasting C-peptide level >1 ng/mL (Visit 1).

Screening 2 Weeks	Single-Blind 4 Weeks	Double-Blind Treatment 16 Weeks				Follow-up 1 Week
		Pioglitazone 30 mg+SU				SU
SU	Placebo+SU	Pioglitazone 15 mg+SU				SU
		Placebo+SU				SU

Week Visit	V1	-2 V2	B V3	Day 1 V4	4 V5	8 V6	12 V7	16 V8	V9

The primary efficacy variable was change from baseline in HbA_{1c}. The secondary variables were fasting glucose, fasting insulin, fasting C-peptide, triglycerides, total cholesterol, fractional cholesterol, and HbA_{1c} responder rate which was defined as normalization of HbA_{1c} or a 0.65% reduction in HbA_{1c} from baseline. Fasting insulin level was not a secondary outcome.

Efficacy Results - Study 010

Of the 998 patients who signed an ICF, 21 were rescreened and 13 of these randomized. A total of 560 patients were randomized in 73 sites 187 to the placebo+SU, 184 to the 15 mg+SU and 189 to the 30 mg+SU treatment group. A total of 478 (85%) patients completed the study. Poor glycemic control was the most common reason for patient withdrawal. The incidence rates were 10% (19/187) for the placebo+SU group, 10% (18/184) for the 15 mg+SU group and 4% (8/189) for the 30 mg+SU group. Table 73 displays patient disposition.

Table 73 Patient Disposition - Study 010

	Placebo	15 mg+SU	30 mg+SU
Randomized	187	184	189
Completed	157	155	166
Withdrawn	30	29	23
Lack of Efficacy	13	12	4
Adverse Event	9	7	7
Withdrew Consent	4	5	7
Lost to Follow-up	2	1	2
Non-Compliance	0	1	1
Protocol Violation	1	0	0
Inclusion/Exclusion	1	0	0
Other	0	3	2

Demographic Characteristics

Most patients were Caucasian (79%) and male (59%). The mean age was 56.7 years. The mean weight was 92.99 kg. The mean BMI was 31.96 kg/m². Most patients (86%) had not received other antidiabetic medications beside SU before the enrollment. No statistical significant differences among the treatment groups for any of the demographic or baseline characteristics. Table 74 displays baseline levels of the efficacy variables.

Table 74 Mean Values at Baseline in Efficacy Variables – Study 010

	Placebo+SU n=187			30 mg+SU n=184			30 mg+SU n=189			p-value*
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
HbA _{1c}	186	9.90	1.46	182	10.01	1.30	188	9.88	1.28	0.65
FBG (mg/dL)	186	236.8	61.84	183	246.8	61.72	188	238.4	54.83	0.26
Fasting C-Peptide (ng/mL)	181	2.49	1.002	183	2.5	0.992	185	2.39	0.890	0.49
Fasting Insulin (μIU/mL)	181	19.99	18.34	182	17.48	11.94	185	18.08	9.80	0.24
Triglycerides (mg/dL)	187	264.4	258.04	184	277.4	281.98	188	264.7	248.95	0.87
Total Cholesterol	187	212.2	46.58	184	212.0	45.55	188	215.4	45.96	0.75
HDL (mg/dL)	184	42.6	11.75	179	41.6	10.86	186	41.8	11.53	0.74
LDL (mg/dL)	160	123.7	37.98	156	124.0	35.33	161	127.1	37.01	0.56

* p-values based on treatment and pooled center in ANOVA model

Efficacy Results – Study 010

Primary Efficacy Variable – HbA_{1c} Change from baseline to Week 16

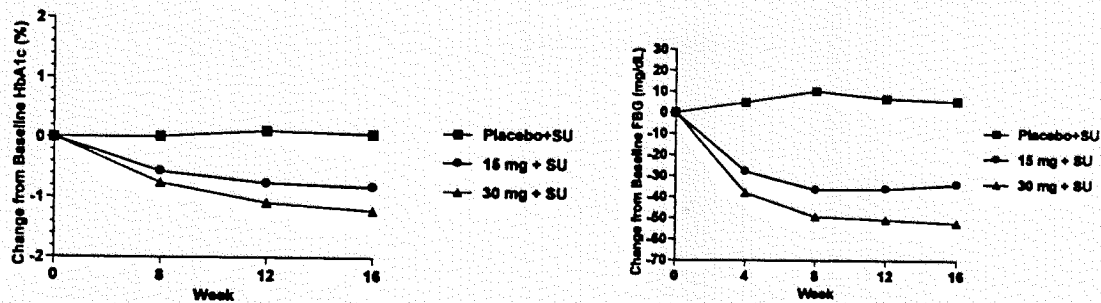
Table 75 Adjusted* LSM Change from Baseline in HbA_{1c} (%) by Visit (LOCF) – Study 010

Visit	Pioglitazone								
	Placebo+SU n=181			15 mg +SU n=176 ^a			30 mg+SU n=182 ^b		
	LSM	SE	LSM	SE	p	LSM	SE	p	
Baseline	9.86	0.10	10.01	0.10	0.45	9.93	0.10	0.86	
Week 8	0.01	0.07	-0.57	0.07	<0.01	-0.76	0.07	<0.01	
Week 12	0.11	0.08	-0.76	0.08	<0.01	-1.09	0.08	<0.01	
Week 16 Endpoint	0.06	0.09	-0.82	0.09	<0.01	-1.22	0.09	<0.01	
LSM Difference from placebo, SE			-0.88	0.13		-1.28	0.13		
95% C.I.			(-1.17 -0.58)			(-1.57 -0.99)			

* Adjusted by Dunnett procedure comparing all means with a control

^an=175, ^bn=182 at Week 8

Figure 35 LSM Change from Baseline in HbA1c & FBG over Time - Study 010



Secondary Efficacy Variables

Change from baseline FBG was significantly different from placebo+SU for the two pioglitazone+SU groups at endpoint. Table 76 and Figure 35 display the results by time.

Table 76 Adjusted^a LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 010

Visit	Placebo+SU		Pioglitazone					
	n=182 ^a		15 mg +SU n=179 ^b			30 mg+SU n=186 ^c		
	LSM	SE	LSM	SE	p	LSM	SE	p
Baseline	235.99	4.46	246.77	4.49	0.15	238.93	4.42	0.85
Week 4	4.78	3.32	-27.79	3.33	<0.01	-37.96	3.26	<0.01
Week 8	10.24	3.69	-36.51	3.73	<0.01	-49.40	3.67	<0.01
Week 12	6.77	3.95	-36.13	3.99	<0.01	-50.76	3.93	<0.01
Week 16 Endpoint	5.59	3.81	-33.84	3.85	<0.01	-52.29	3.80	<0.01
LSM Difference from placebo, SE			-39.44	5.43	<0.01	-57.88	5.38	<0.01
95% C.I.			(-51.49 -27.39)			(-69.82 -45.94)		

^a Adjusted by Dunnett procedure comparing all means with a control

^an=178, ^bn=177, ^cn=185 at Week 8

At endpoint, C-Peptide and Insulin were significantly better in the 30mg+SU group compared to placebo. The 15mg+SU group was significantly better than placebo+SU in C-peptide (Tables 77, 78 & Fig 36.)

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Table 77 Adjusted* LSM Change from Baseline in Fasting C-Peptide (ng/mL) by Visit (LOCF) – Study 010

Visit	Pioglitazone								
	Placebo+SU n=174 ^a			15 mg +SU n=174 ^b			30 mg+SU n=178 ^c		
	LSM	SE	LSM	SE	p	LSM	SE	p	
Baseline	2.50	0.07	2.53	0.07	0.93	2.36	0.07	0.30	
Week 8	0.15	0.05	-0.25	0.05	<0.01	-0.30	0.05	<0.01	
Week 16 Endpoint	0.11	0.05	-0.20	0.05	<0.01	-0.25	0.05	<0.01	
LSM Difference from placebo, SE			-0.31	0.07		-0.35	0.07		
95% C.I.			(-0.47 -0.16)			(-0.51 -0.20)			

* Adjusted by Dunnett procedure comparing all means with a control

^an=173, ^bn=167 ^cn=175 at Week 8

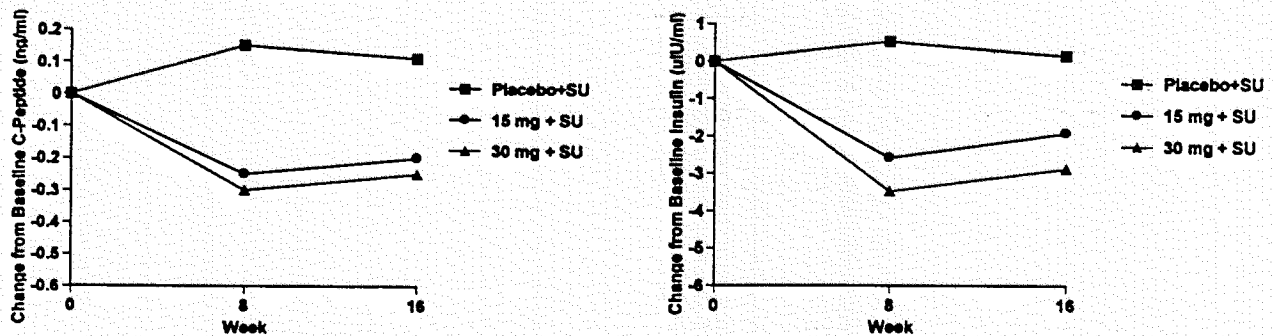
Table 78 Adjusted* LSM Change from Baseline in Fasting Insulin (μIU/mL) by Visit (LOCF) – Study 010

Visit	Pioglitazone								
	Placebo+SU n=174 ^a			15 mg +SU n=173 ^b			30 mg+SU n=178 ^c		
	LSM	SE	LSM	SE	p	LSM	SE	p	
Baseline	20.28	1.05	17.85	1.05	0.18	17.68	1.04	0.14	
Week 8	0.53	0.61	-2.58	0.63	<0.01	-3.47	0.62	<0.01	
Week 16 Endpoint	0.15	0.69	-1.92	0.69	0.06	-2.87	0.68	<0.01	
LSM Difference from placebo, SE			-2.07	0.98		-3.02	0.97		
95% C.I.			(-4.24 0.10)			(-5.18 -0.86)			

* Adjusted by Dunnett procedure comparing all means with a control

^an=172, ^bn=165 ^cn=172 at Week 8

Figure 36 LSM Change in C-Peptide & Insulin over Time - Study 010



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Lipids

At endpoint, triglycerides levels was significantly reduced in the 30 mg+SU treated patients than the placebo+SU-treated patients, but not significantly in the 15 mg+SU-treated patients. HDL was significantly increased in the 2 pioglitazone+SU groups than the placebo+SU group. LDL was not significantly different to placebo+SU for either of the two pioglitazone+SU groups. The treatment results are displayed in Tables 79-82 & Figure 37.

Table 79 Adjusted* LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 010

Visit	Pioglitazone							
	Placebo+SU n=180		15 mg +SU n=177		p	30 mg+SU n=181		p
LSM	SE	LSM	SE	LSM		SE		
Baseline	258.60	20.17	272.05	20.32	0.85	259.53	20.12	1.00
Week 4	3.89	13.30	-45.84	13.37	0.02	-68.41	13.27	<0.01
Week 8	2.72	14.42	-38.93	14.50	0.08	-63.06	14.39	<0.01
Week 16 Endpoint	-2.64	13.29	-38.74	13.36	0.10	-71.03	13.26	<0.01
LSM Difference from placebo, SE			-36.10	18.84		-68.39	18.77	
95% C.I.			(-77.91	5.72)		(-110.04	-26.73)	

* Adjusted by Dunnett procedure comparing all means with a control

Table 80 Adjusted* LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 010

Visit	Pioglitazone							
	Placebo+SU n=180		15 mg +SU n=177		p	30 mg+SU n=181		p
LSM	SE	LSM	SE	LSM		SE		
Baseline	211.48	3.50	211.95	3.52	0.99	214.42	3.49	0.77
Week 4	2.47	2.16	0.4	2.18	0.72	1.29	2.16	0.9
Week 8	2.94	2.35	0.06	2.36	0.59	2.2	2.34	0.96
Week 16 Endpoint	7.39	2.75	0.65	2.77	0.15	2.42	2.75	0.34
LSM Difference from placebo, SE			-6.74	3.90		-4.97	3.89	
95% C.I.			(-15.40	1.92)		(-13.60	3.66)	

* Adjusted by Dunnett procedure comparing all means with a control

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Table 81 Adjusted* LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 010

Visit	Pioglitazone								
	Placebo+SU n=175 ^a		15 mg +SU n=171			30 mg+SU n=179			
	LSM	SE	LSM	SE	p	LSM	SE	p	
Baseline	42.91	0.87	41.42	0.87	0.37	41.83	0.86	0.58	
Week 4	-0.30	0.51	2.14	0.50	<0.01	2.92	0.50	<0.01	
Week 8	-0.19	0.54	1.86	0.55	0.02	4.51	0.54	<0.01	
Week 16 Endpoint	-0.98	0.55	1.45	0.55	<0.01	3.97	0.54	<0.01	
LSM Difference from placebo, SE			2.43	0.78		4.95	0.77		
95% C.I.			(0.70	4.15)		(3.23	6.66)		

* Adjusted by Dunnett procedure comparing all means with a control

^a n=174 at Week 8

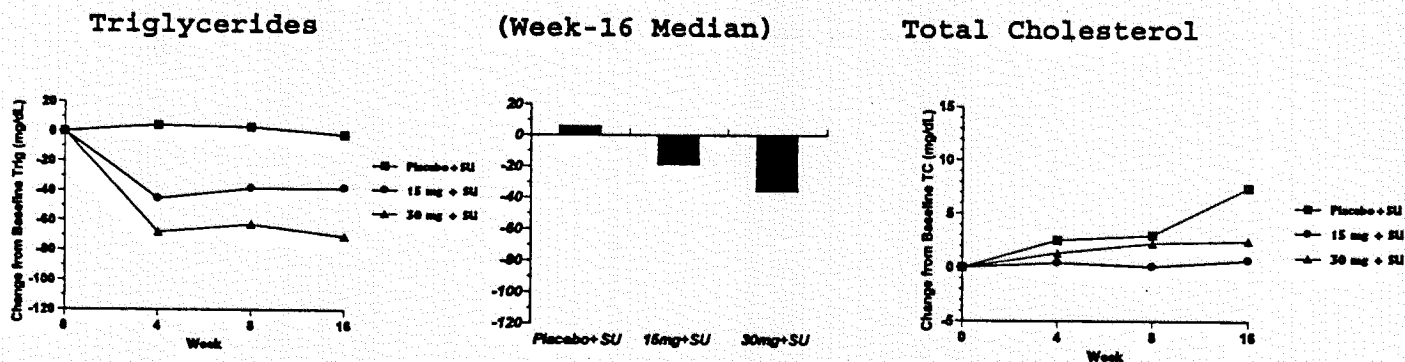
Table 82 Adjusted* LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 010

Visit	Pioglitazone								
	Placebo+SU n=175 ^a		15 mg +SU n=171			30 mg+SU n=179			
	LSM	SE	LSM	SE	p	LSM	SE	p	
Baseline	124.5	3.07	124.3	2.90		126.5	2.96		
Week 4	1.46	1.68	2.57	1.64	0.85	4.61	1.69	0.32	
Week 8	1.66	1.78	1.62	1.78	1.00	2.10	1.80	0.98	
Week 16 Endpoint	5.98	1.96	3.04	1.92	0.45	5.12	1.95	0.93	
LSM Difference from placebo, SE			-2.95	2.74		-0.87	2.76		
95% C.I.			(-9.03	3.14)		(-7.00	5.26)		

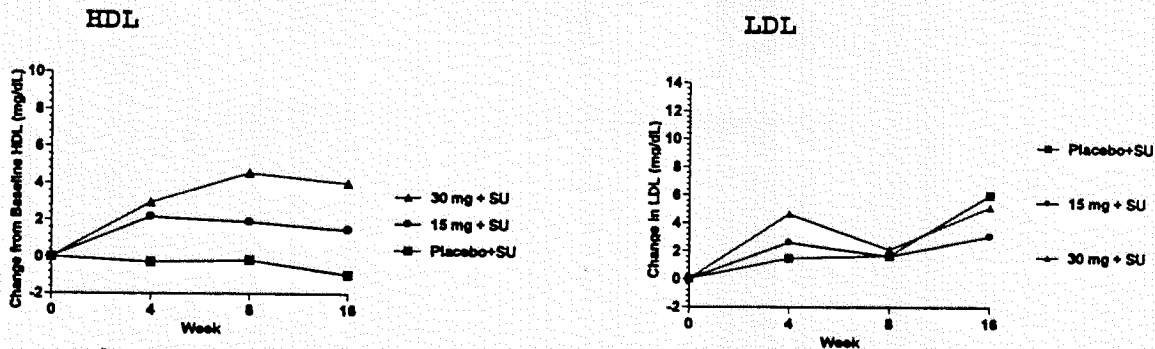
* Adjusted by Dunnett procedure comparing all means with a control

^a n=174 at Week 8

Figure 37 LSM Change from Baseline in Triglycerides, Total Cholesterol, HDL, & LDL (mg/dL) by Week - Study 010



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Subgroup Analysis

Change from baseline to endpoint in HbA_{1c} was examined in gender, age. The interaction between treatment and subgroup was evaluated by ANOVA with treatment, subgroup, center, and treatment-by-subgroup interaction terms in the model.

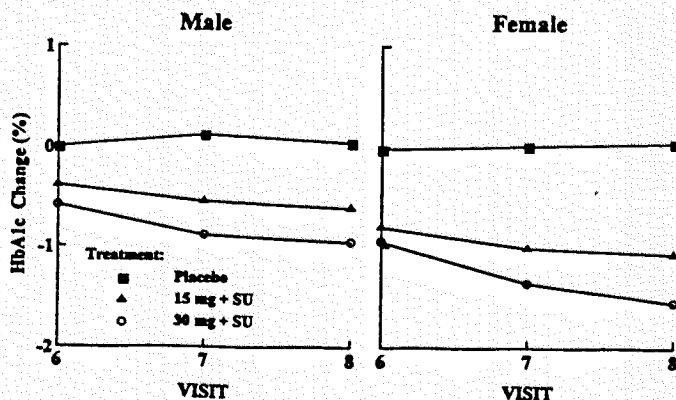
Gender

Table 83 and Figure 38 display the mean changes from baseline in HbA_{1c} by gender. The p-value of treatment-by-gender interaction was 0.038.

Table 83 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender (LOCF) – Study 010

Subgroup	Pioglitazone		
	Placebo+SU	15mg+SU	30mg+SU
Men			
n	106	103	110
Baseline Mean	9.87	9.81	9.85
Mean Change	0.03	-0.62	-0.96
SE	0.12	0.12	0.13
Women			
n	75	73	72
Baseline Mean	9.83	10.29	10.01
Mean Change	0.03	-1.07	-1.56
SE	0.12	0.14	0.13

Figure 38 Mean Change from Baseline in HbA_{1c} (%) by Gender – Study 010



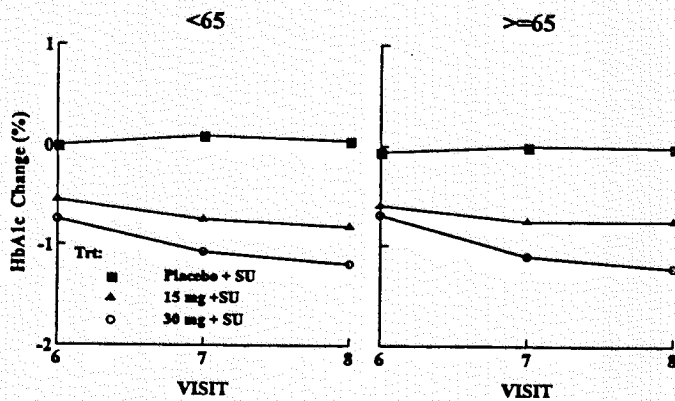
Age

Table 84 and Figure 39 display the mean change from baseline in HbA_{1c} at endpoint for patients <65 and ≥65 years of age. The treatment-by-age interaction was not significant (p=0.99).

Table 84 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group – Study 010

Subgroup	Placebo+SU	Pioglitazone	
		15 mg+SU	30 mg+SU
<65 years old			
n	141	139	141
Baseline Mean	9.98	10.06	10.02
Mean Change	0.04	-0.82	-1.19
SE	0.10	0.10	0.11
≥65 years old			
n	40	37	41
Baseline Mean	9.41	9.79	9.56
Mean Change	-0.02	-0.76	-1.23
SE	0.15	0.19	0.20

Figure 39 Mean Change from Baseline in HbA_{1c} (%) by Age – Study 010



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4. Study Summaries:

Monotherapy

1. The dose ranging trial (001) studied pioglitazone doses of 7.5 mg, 15 mg, 30 mg, and 45 mg for 26 weeks with ~80 patients per group. The overall withdrawal rate was 51%. The drop out rate for the most common reason, insufficient therapeutic effect, was treatment related (25%, 45 mg group to 41%, placebo group.) At Week 26 of the ITT population (LOCF), change from baseline HbA_{1c} was statistically significantly better for the 15 mg (-0.27%), 30 mg (-0.27%) and 45 mg (-0.86%) pioglitazone-treated patients than placebo-treated patients (+0.74%). Treatment differences from placebo were -1.00%, -1.00%, and -1.60% for the 15 mg, 30 mg, and 45 mg pioglitazone dose groups, respectively. The analysis results of 7.5 mg were not consistent in the LOCF (not significant) and OC (significant) analyses. The high and differential withdrawal rates may introduce bias in the study, therefore, the estimates from the study are deemed unreliable and the validity of the study results questionable. As the 7.5 mg dose and the 45 mg dose were studied in only this trial as a fixed dose regimen, the data is not sufficient to determine the efficacy and the safety of the 7.5 mg treatment and the 45 mg treatment.

Using the criteria set by Dr. Misbin (ALT 3xULN=102 u/L), 5 patients (4 male, pioglitazone & 1 female, placebo) experienced an elevation >102 U/L during the trial. Of the 4 pioglitazone-treated patients, 3 were in the 30 mg group, and 1 in the 7.5 mg group.

2. Study 012 was a 24-week forced titration trial with 3 parallel groups of placebo, 7.5/15/30 mg pioglitazone and 15/30/45 mg pioglitazone (~85 patients per group). Patients were treated with the first 2 doses for 4 weeks each and the last dose for 16 weeks. At endpoint (Week 24), HbA_{1c} change from baseline was statistically significantly different between each pioglitazone group and the placebo group. The HbA_{1c} changes were +0.93%, -0.55%, and -0.60% for the placebo group, the 7.5/15/30 mg group, and the 15/30/45 mg group, respectively. The treatment differences from placebo were -1.48% and -1.53% for the 2 pioglitazone groups, respectively. One placebo patient had an elevation of ALT>102 U/L.
3. Study 026 compared 30 mg pioglitazone treatment (n=100) with placebo treatment (n=93) for 16 weeks. At endpoint, change from baseline in HbA_{1c} was +0.76% for the placebo group and -0.60% for the 30-mg pioglitazone group. The treatment difference was -1.37%.

4. At endpoint, the secondary efficacy outcome change in FBG was significantly greater in the pioglitazone group compared to the placebo group for all 3 studies. The treatment difference from placebo in FBG corresponded to the HbA_{1c} treatment difference; a difference of -40 mg/dL in FBG corresponded to a -1.00% HbA_{1c} difference and a difference of -65 mg/dL corresponded to a -1.5% HbA_{1c} difference.
5. For triglycerides, the 30-mg pioglitazone treatment group in Study 026 and the 15/30/45-mg group in Study 012 showed a significant improvement at endpoint. The median change from baseline was -57.5 mg/dL for the 30-mg group and -32 mg/dL for the 15/30/45-mg group.
6. For HDL, the 45 mg group in Study 001 and the 30 mg group in Study 026 showed treatment effects of +7.0 mg/dL and +5.0 mg/dL, respectively.
7. Body weight was significantly increased in the pioglitazone-treated patients. For the observed cases at endpoint, the treatment difference in weight increase was 5.4 kg in the 45 mg group, 4.3 kg in the 15/30/45 mg group, ~ 3.6 kg in the 30 mg and 15 mg group, and 3.0 in the 7.5/15/30 mg group.
8. Treatment differences in HbA_{1c} reduction were greater in women than men. The treatment-by-gender interaction was significant in study 001 (p=0.02), but not in study 012 (p=0.72) and study 026 (p=0.61).
9. The completion rate improved after the 001 trial (50%) with 65% for study 012 and 73% for study 026.

Add-On Therapy

1. Study 010 compared 15 mg and 30 mg pioglitazone and placebo as add-on to sulfonylurea (~ 180 patients per group.) The HbA_{1c} change from baseline to endpoint was -0.82% for the 15mg+SU group, -1.22% for the 30mg+SU group, and +0.06% for the placebo group. The treatment differences of -0.88% and -1.28% were statistically significant. Two placebo+SU patients had an elevation greater than 3XULN of ALT (>102 U/L)
2. The metformin add-on trial studied the 30 mg pioglitazone (n=160) vs. placebo (n=168). The endpoint change in HbA_{1c} was -0.64% for the 30mg+MF group and 0.19% for the placebo group. The treatment difference of -0.83% was statistically significant.
3. The insulin add-on trial (014) compared 15mg and 30mg pioglitazone to placebo (~180 patients per group.) The HbA_{1c} change from baseline to endpoint was statistically significant for both groups. The change was -0.99% for the 15mg+insulin group, -1.26% for the 30mg+insulin group

- and -0.26% for the placebo group. Treatment difference from placebo was -0.73% and -1.00% for the 15mg+insulin and 30mg+insulin groups, respectively. Two patients in the 30 mg+insulin group had an elevation of ALT>102 U/L.
4. For FBG at endpoint, the pioglitazone add-on groups were significantly better than the placebo add-on groups for each add-on study. The treatment difference in FBG corresponded to the treatment difference in HbA_{1c}; a difference of -35 mg/dL corresponded to a -0.73% HbA_{1c} difference in the 5mg+insulin group and a difference of -58 mg/dL corresponded to a -1.28% HbA_{1c} difference in the 30mg+SU group.
 5. HDL increased in all treatment groups in the 3 add-on trials. It was - 2.0 mg/dL in the 15 mg add-on groups (SU or insulin), 3.0 mg/dL for the 30 mg add-on (MF or insulin) and 5.0 mg/dL for the 30 mg add-on to SU.
 6. The level of triglycerides in the 30 mg pioglitazone group of each add-on study was significantly reduced compared to the corresponding placebo add-on group. The median change from baseline was -36 mg/dL for the 30mg+SU group, -32 mg/dL for the 30mg+insulin group and -22 mg/dL for the 30mg+MF group.
 7. At Week 16 of the observed cases data sets, body weight was significantly increased in the pioglitazone-add-on groups compared to the corresponding placebo add-on group. The treatment difference from placebo was 4.0 kg for the 30mg+insulin group, 3.7 kg for the 30mg+SU group, -2.7 kg for the 15mg+SU and the 15mg+insulin groups, and 2.5 kg for the 30mg+MF group.
 8. Treatment differences measured by HbA_{1c} reduction were greater in women than in men. The treatment-by-gender interaction was significant in study 010 (p=0.04), and study 014 (p=0.03) and borderline for study 027 (p=0.13.)
 9. The completion rates in these add-on trials were higher than the monotherapy trials with 85%, 76% and 88% for the sulfonylurea add-on, metformin add-on, and insulin add-on, respectively, compared to 50%, 65% and 73% for the monotherapy trials.

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Figure 40 displays the treatment difference and its confidence interval in HbA_{1c} for each of the pioglitazone treatment group as mono- or add-on therapy.

Figure 40 Treatment Effect (C.I.) in Change from Baseline HbA_{1c} (%)

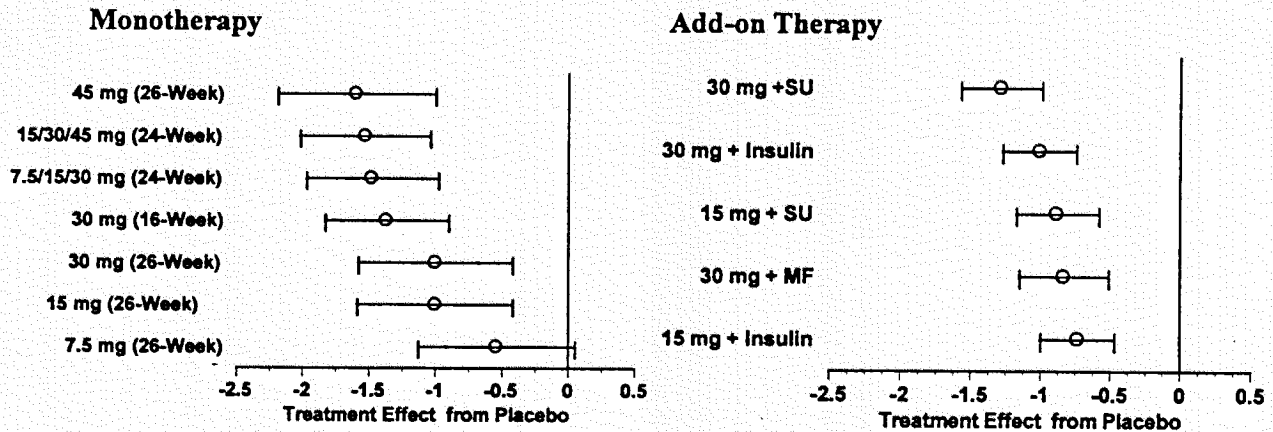


Table 85 summarizes the treatment differences from placebo in secondary variables that were significant.

Table 85 Mean Treatment Difference from Placebo in Secondary Outcome

Study	C-Peptide ng/ml	Insulin µIU/ml	Trigly* mg/dL	TC mg/dL	HDL mg/dL	LDL mg/dL
Mono						
001(45mg)	-	-	-	-	+3.9	-
012(15/30/45mg)	-	-	-32	-	-	-
026 (30mg)	-0.26	-3.8	-57	-	+5.0	-
Add-on						
010(SU)						
15mg	-0.31	-	-	-	+2.4	-
30mg	-0.35	-3.0	-36	-	+5.0	-
027(MF) (30mg)	-0.16	-2.5	-22	-	+3.1	-
014 (Ins)						
15mg	-0.18	NA	-	-	+2.2	-
30mg	-	-	-32	-	+2.8	-

* Median difference from baseline

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5. Conclusions

At endpoint, all the pioglitazone treatment groups, except the 7.5 mg group in the 6 U.S. trials (mono & add-on) showed statistically significant improvement over placebo in the primary efficacy variable, change in HbA_{1c} from baseline. The treatment difference from placebo ranged from -1.0% (15mg, 30mg) to -1.6% (45mg) at Week 26. Pioglitazone-treated patients showed significant reductions in FBG compared to placebo-treated patients. HDL increased in all the treatment groups in the add-on trials. Triglycerides levels decreased significantly in all the 30 mg groups of the add-on trials (sulfonylurea, metformin, and insulin) but not the 15 mg groups. Weight increased in the pioglitazone-treated patients but not in the placebo-treated patients. The treatment difference from placebo for the observed cases was 5.4 kg in 45 mg monotherapy and 3.9 kg in the 30 mg + insulin group.

The maximum recommended dose was 60 mg in the annotated proposed labeling. However, the 60 mg dose was not studied in the controlled clinical trials (only in the open-label trial PNFP-011); therefore, it should not be indicated as the maximum dose. The next highest dose, 45 mg, was studied only in 2 of the 3 monotherapy studies, both of which had very high drop-out rates. The most studied dose was the 30 mg dose, which was effective in all 6 trials.

/s/

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot /s/

Dr. Nevius /s/

cc: Arch NDA 21-073
HFD-510
HFD-510/Ssobel, SMalozowski
HFD-510/RMisbin
HFD-510/EGalliers
HFD-510/JWeber ✓
HFD-715/Division file, LPian, TSahlroot
Chron.

This review contains 73 pages

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW
ADDENDUM**

NDA 21-073	SUBMISSION DATE: July 13, 1999
BRAND NAME:	ACTOS™
GENERIC NAME:	Pioglitazone, 15 mg, 30 mg, 45 mg tablets
REVIEWER:	Xiaoxiong (Jim) Wei, Ph.D.
SPONSOR:	Takeda America, Inc. Princeton, New Jersey
TYPE OF SUBMISSION:	Amendment (Dissolution Specification)

SYNOPSIS:

On July 13, 1999, the sponsor submitted additional data in support of dissolution specification of Q= [REDACTED]. An initial recommendation was that specification be set at [REDACTED] based on the data that the sponsor provided from the bioavailability and scale-up lots. In this submission, the sponsor provided additional dissolution data from several development lots on stability study and 3 commercial lots for launch. Based on the current data, the following dissolution method and specification is recommended to the sponsor:

Apparatus: USP Apparatus 2 (paddle), [REDACTED]
 Medium: HCL-0.3 M KCL buffer, pH 2.0, 900 ml
 Assay: [REDACTED]
 Specification: Q= [REDACTED]

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-073, Amendment (Pioglitazone /ACTOS™) submitted on July 13, 1999. The above recommended dissolution specification should be sent to the sponsor as appropriate,

/S/ [REDACTED]

Xiaoxiong (Jim) Wei, Ph.D.
 Division of Pharmaceutical Evaluation II
 Office of Clinical Pharmacology and Biopharmaceutics

RD/ FT initialed by Hae-Young Ahn, Ph.D., Team Leader [REDACTED]

/S/ [REDACTED]

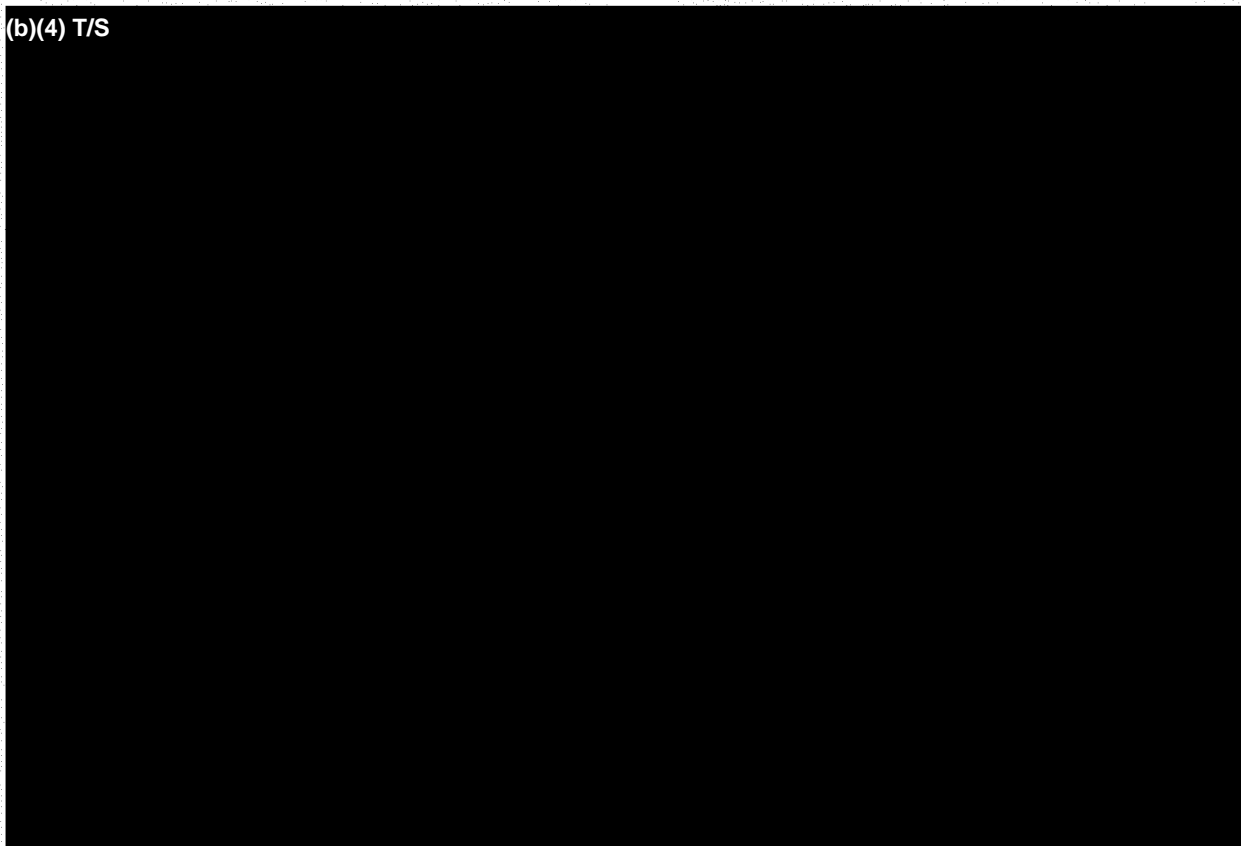
7/14/99

CC: NDA 21-073 (orig., 1 copy), HFD-510(Weber, Ysem), HFD-850 (Lesko, Huang), HFD-870 (Wei, Ahn, M. Chen), CDR (Barbara Murphy).

Code: ~~AE~~ AP

TABLE 4

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JUN 22 1999

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-073	SUBMISSION DATE: 01-15-1999, 03-31-1999, 04-05-1999, 04-06-1999
BRAND NAME:	ACTOS™
GENERIC NAME:	Pioglitazone, 15 mg, 30 mg, 45 mg tablets
REVIEWER:	Xiaoxiong (Jim) Wei, Ph.D.
SPONSOR:	Takeda America, Inc. Princeton, New Jersey
TYPE OF SUBMISSION:	NME, Code: 1P

SYNOPSIS:

Pioglitazone (ACTOS™) has been developed as an oral antidiabetic agent, which belongs to thiazolidinediones. It acts primarily by decreasing insulin resistance. It is proposed to treat type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM).

The sponsor proposes to market three strengths of tablets, 15 mg, 30 mg and 45 mg of pioglitazone. However, the 45-mg tablets have not been used in clinical trial. The **bioequivalent studies** showed that these three strengths are bioequivalent.

The dosage sponsor proposes is an initial dosage of 30 mg once daily as monotherapy and 15 – 30 mg once daily for combination therapy with sulfonylureas, metformin and insulin. The dose can be increased based on therapeutic effect with maximum recommended dose of 45 mg/day.

Pharmacokinetic studies showed that it is rapidly absorbed and metabolized. Based on animal studies, two major metabolites, M-III and M-IV share its pharmacologic activity by 40 – 60% of parent compound (note: M-II is also active but the level is very low in human). At steady state, these two pharmacologically active metabolites reach serum concentrations equal to or greater than parent agent, pioglitazone. The sponsor has defined the parent drug, pioglitazone plus these two active metabolites, M-III and M-IV as the total active pioglitazone. The pioglitazone comprises about 20 – 25% of the total AUC. Pioglitazone and M-III, M-IV are highly bound to serum albumin. Pioglitazone is extensively metabolized by hydroxylation and oxidation mainly through CYP2C8 and 3A4. The drug is mainly excreted as metabolites in the bile and only 15 – 30% of the dose is recovered in the urine. The mean T_{1/2} for pioglitazone and the total pioglitazone ranges from 3-7 hours and 16 to 24 hours, respectively.

Special population studies showed that it may not be necessary to adjust dosage in renally impaired or hepatically impaired patients as well as in elderly patients. The pharmacokinetic parameters were 20 – 60% higher in females than in men, but these studies were not body-weight normalized.

Drug interaction studies between pioglitazone and digoxin, glipizide, warfarin, and metformin indicated that there were no significant changes in pharmacokinetic parameters. The potent CYP3A4 inhibitor, ketoconazole inhibited 85% of pioglitazone metabolism in vitro at the equal molar concentrations. However, the sponsor did not conduct some important drug

equal molar concentrations. However, the sponsor did not conduct some important drug interaction studies involving CYP3A4 such as ketoconazole, erythromycin.

Food may delay the T_{max} but may not affect the value of the total AUC.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-073 (Pioglitazone /ACTOS™) submitted on January 15, 1999. The overall Human Pharmacokinetic Section is acceptable to OCPB. However, OCPB requests Phase IV studies listed under Comments 2 and 3. This recommendation, comments (p. 17), and labeling comments (p. 18) should be sent to the sponsor as appropriate.

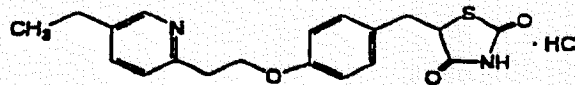
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BACKGROUND:

What is the mechanism of action of the drug?
 What is the previous experience with other drugs in this therapeutic class?

Pioglitazone (ACTOS™) is an oral antidiabetic agent that acts primarily by decreasing insulin resistance. ACTOS™ is used in the management of type 2 diabetes (non-insulin-dependent diabetes mellitus, NIDDM). It improves sensitivity to insulin in muscle and adipose tissue and inhibits hepatic gluconeogenesis.

Pioglitazone belongs to thiazolidinediones. The molecule contains one asymmetric carbon, and the compound is synthesized and used as the racemic mixture. The chemical structure is as shown below:



The pharmacologic activity of ACTOS™ depends on the presence of insulin for its mechanism of action. ACTOS™ decreases insulin resistance in the periphery and in the liver resulting in increased insulin-dependent glucose disposal and decreased hepatic glucose output. Unlike sulfonylureas, pioglitazone is not an insulin secretagogue. Thiazolidinediones act at many intracellular sites and can influence several processes to increase cell sensitivity to insulin. Thiazolidinediones influence insulin receptor kinase activity, control insulin receptor phosphorylation, change the number of insulin receptors, quantity and activity of GLUT-4, modulate tumor necrosis factor (TNF) activity, activate peroxisome proliferator-activated receptor- γ (PPAR- γ) and alter hepatic glucose metabolism.

Troglitazone is a drug in the same category, which has been approved and was recently re-evaluated because of its unpredicted fatal liver toxicity. Rosiglitazone also belongs to this category, which has been approved recently by the Agency.

BIOPHARMACEUTICS**Drug Formulation and Dissolution:**

Are the clinical trial formulations the same as the to-be-marketed (TBM) formulations?
 Has the dosage form equivalence been established among different tablet strengths?
 Has the sponsor developed adequate dissolution method specifications for quality control?

Drug Formulation:

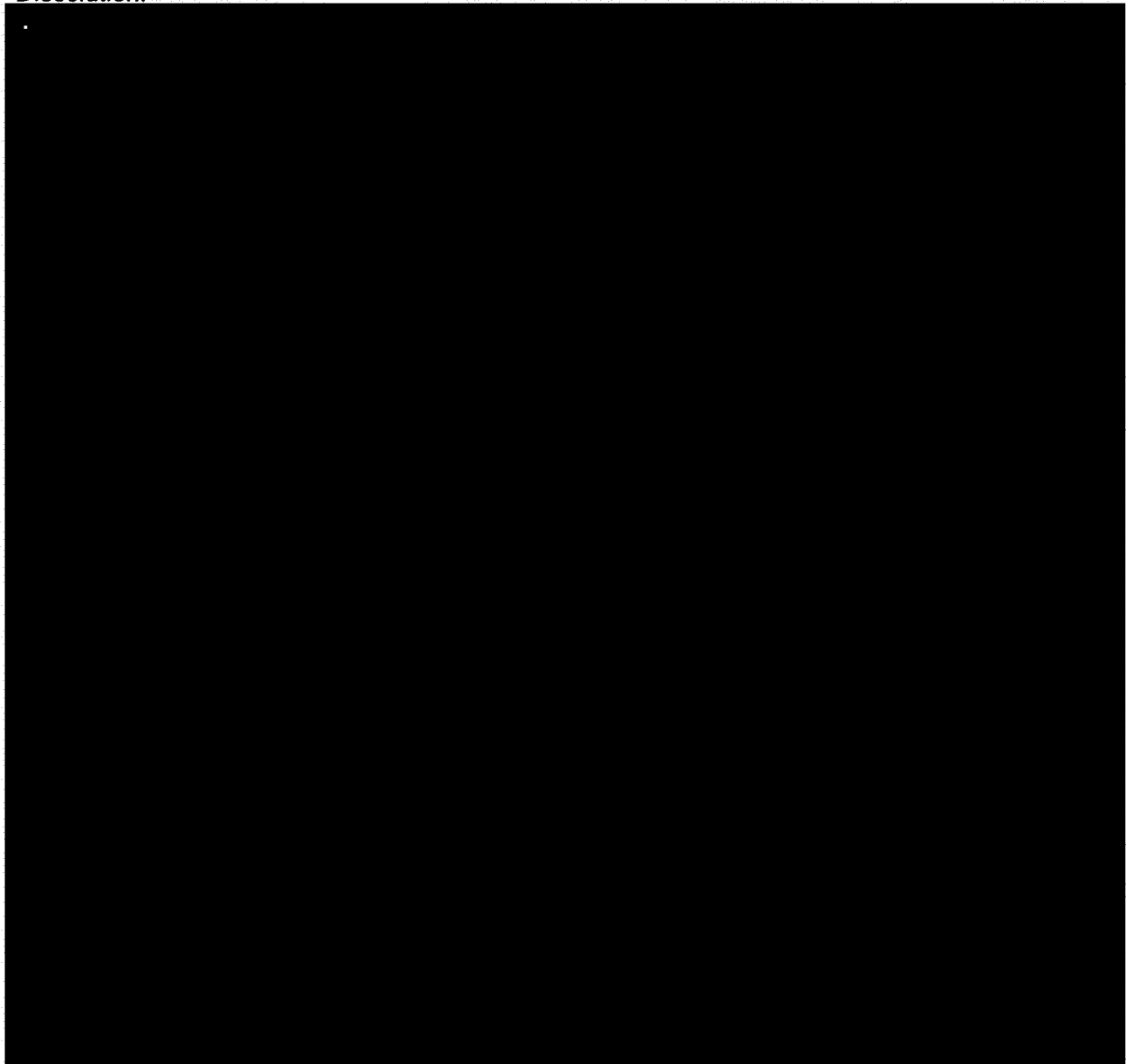
In early developmental stage, Takeda used early stage tablets and capsules. Capsules were used in dose proportionality studies in Phase I trials. However, most of definite Phase I, II, and III trials have been conducted with the late stage tablet formulations. The three tablet strengths used in clinical trials were 7.5, 15, and 30 mg. However, the 15, 30, and 45 mg tablets are proposed to be available in the market. The clinical formulations and to be marketed formulations are the same for 15-mg and 30-mg tablets. The in vivo bioequivalence studies were conducted among these three tablet strengths.

Table 1: Composition of Commercial ACTOS™ Tablets

Ingredient	Function	Composition (mg/tablet)		
		15 mg	30 mg	45 mg
Pioglitazone hydrochloride				
Lactose monohydrate, NF				
Hydroxypropylcellulose calcium, NF				
Carboxymethylcellulose calcium, NF				
Magnesium stearate, NF				
Total				

* Removed during manufacturing process.

Dissolution:



Bioequivalence

Two bioequivalence studies were conducted. The first BE study was performed to compare 1X30-mg tablet with 2 X 15-mg tablets in a single dose, two-period crossover study in 14 Japanese male adult subjects. These two formulations were found to be bioequivalent.

Table 2: PK Parameters of 1X30 mg and 2X15 mg Tablets

PK Parameter	Pioglitazone / Total Active Pioglitazone Compounds			
	Test Mean 1X30 mg Tablet (Treatment B)	Reference Mean 2X15 mg Tablet (Treatment A)	Ratio of LS Means Test/Reference	90% Confidence Interval
C _{max} (ng/ml)	1460±350	1470 ± 450	99	88.5 – 111.9
	1843 ± 381	1823 ± 475	101	90.3 – 114.1
AUC:0-96h (µg.hr/ml)	13.11 ± 3.59	12.78 ± 3.84	103	91.2 – 116.4
	50.26 ± 9.63	49.96 ± 1.07	101	89.4 – 107.6

^aTotal Active Pioglitazone Compounds: unchanged pioglitazone, metabolites II, III, IV.

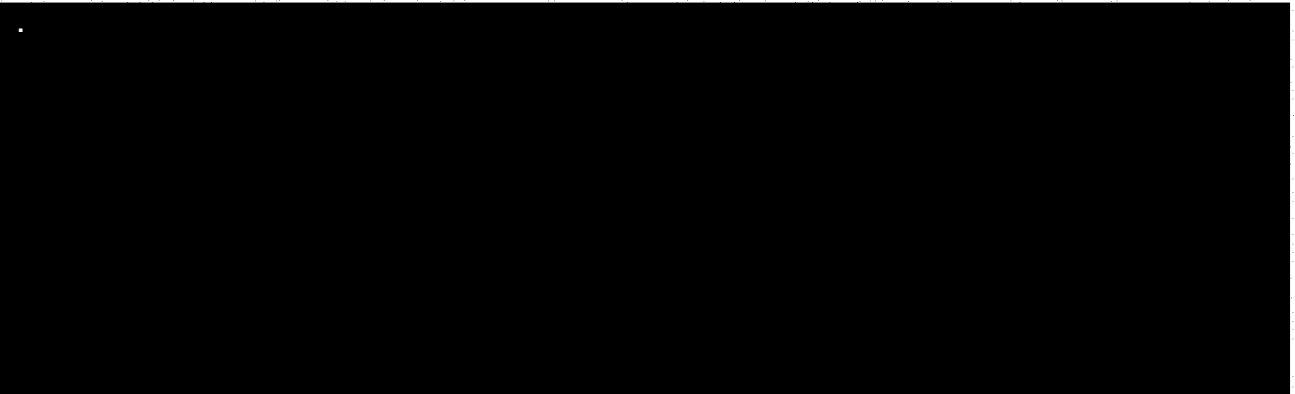
A single dose, open-label, two-treatment, two-period crossover bioequivalence study was conducted in 24 healthy male subjects ranging in age from 18 to 35 years in USA to evaluate whether one 45-mg tablet is bioequivalent to 3 of 15-mg tablets (volume 1.077-78, PNFP-018). These two formulations were found to be bioequivalent.

Table 3: PK Parameters of 1X45 mg and 3X15 mg Tablets

PK Parameter	Pioglitazone / Total Active Pioglitazone Compounds			
	Test Mean 1X45 mg Tablet (Treatment B)	Reference Mean 3X15 mg Tablet (Treatment A)	Ratio of LS Means Test/Reference	90% Confidence Interval
C _{max} (ng/ml)	1482 ± 499.7	1681 ± 496.0	88.2	79.7 - 96.6
	1865 ± 605.3	2108 ± 588.7	88.5	80.1 – 96.9
T _{max} (hour)	3 (2 – 5)	3 (2 – 4)	98.8	90.2 – 107
	4 (3 – 5)	4 (2 – 5)	101	94.4 – 108
AUC:0-∞ (µg.hr/ml)	13.85 ± 5.0	15.06 ± 4.51	92.0	83.9 – 100
	56.90 ± 15.56	62.54 ± 18.56	91.0	84.4 – 97.5

^aTotal Active Pioglitazone Compounds: unchanged pioglitazone, metabolites III, IV.

Analytical Methodology



CLINICAL PHARMACOLOGY

Pharmacokinetics (PK):

What are the basic PK parameters?
 Is the variability in PK in patients similar or different from healthy volunteers?
 What is the effect of food and how dose it influence dosing recommendations?
 Are there active/toxic metabolites, do they accumulate?

Single Dosing versus Multiple Dosing:

Single dose PK studies (P-5232-0001 and CPH-001, 002, 003) were performed during the development of pioglitazone. The single dose study (P-5232-001, USA study) was a double blind, placebo controlled, randomized single dose tolerance trial. It was conducted in 37 healthy male subjects (weight ranging from 60.9 – 93.2 kg); 24 subjects for pioglitazone and 13 subjects for placebo using 2-mg capsules for 2, 18 mg doses and 5-mg capsules for 30, 45, and 60 mg doses. Only unchanged pioglitazone was measured for the determination of PK parameters. The results showed that PK profile is linear in range from 2 to 60 mg (Table 5).

Table 5. PK parameters of unchanged pioglitazone following single doses of pioglitazone

Parameter	2 mg	18 mg	30 mg	45 mg	60 mg
C _{max} (ng/ml)	101 ± 8.08	818 ± 112	1070 ± 184	1577 ± 813	1938 ± 686
T _{max} (hr)	2.13 ± 1.31	1.25 ± 0.645	2.0 ± 1.41	2.63 ± 1.60	2.63 ± 1.11
AUC _{0-∞} (µg.hr/ml)	0.65 ± 0.16	6.40 ± 1.08	7.90 ± 0.87	14.00 ± 6.48	19.00 ± 8.93
T _{1/2} (hr)	3.32	5.13	4.81	5.29	6.93

In study CPH-001-002 conducted in Japan, five different single doses of 5, 15, 30, 45, 60 mg of tablets were administered in 5 subgroups of healthy male subjects (age: 20-50 yr., body weight: 90-120% of standard weight). Both unchanged pioglitazone and total active compounds were determined for PK profiles. The results showed that PK parameters are in Table 6.

Table 6. PK profile of Pioglitazone and Total Active Compounds following single doses of pioglitazone

Parameter/	5 mg	15 mg	30 mg	45 mg	60 mg
Cmax (ng/ml)	300 ± 8.08	900 ± 200	1500 ± 300	1900 ± 400	3000 ± 600
	300 ± 8.08	1100 ± 200	1900 ± 400	2400 ± 400	3700 ± 600
Tmax (hr)	1.5 ± 0.4	1.6 ± 0.5	1.9 ± 0.5	2.4 ± 0.8	1.9 ± 1.0
	2.1 ± 1.0	2.3 ± 0.3	2.3 ± 0.4	2.9 ± 0.9	2.5 ± 1.1
AUC 0-∞ (µg.hr/ml)	2.61 ± 0.70	6.50 ± 1.00	13.90 ± 3.10	18.30 ± 4.90	22.20 ± 2.40
	5.00 ± 0.50	26.20 ± 2.10	57.70 ± 9.30	75.60 ± 16.70	103.00 ± 23.50
T1/2 (hr)	6.0 ± 1.9	5.0 ± 0.6	2.9 ± 0.6	3.5 ± 1.4	5.2 ± 0.2
	N/D	15.4 ± 3.4	20.4 ± 3.1	20.3 ± 1.5	18.3 ± 3.4

In the study CPH-003, the 15-mg tablet was administered in a single dose study. PK parameters were similar to Study CPH-001/002.

In the study CPH-001/002 and 003, multiple doses were also administered to several subgroups in different doses. In CPH001/002, three arms of repeated dosing tests were performed as follows: a repeated once-daily dosing of 30 mg for 8 days, twice-daily dosing of 30 mg for 6 days and once-daily dosing of 60 mg for 8 days. In CPH-003, a repeated once daily dosing of 15 mg for 8 days was conducted.

Table 7. PK of Pioglitazone and Total Active Compounds for Study CPH-001/002

Pioglitazone/ Total Active Compound		Cmax (µg/ml)	Tmax (hr)	^b AUC ₀₋₂₄ (µg.hr/ml)	T1/2 (hr)
30 mg/day, qd, n=6	Day 1	1.7±0.3	2.9±1.2	14.2 ± 4.6	4.9±1.3
		2.1±0.2	3.3±1.0	58.0±11.2	17.4±2.3
	Day 9	1.7±0.3	3.0±0.5	15.3±4.0	4.9±0.9
		3.4±0.5	3.7±1.3	57.5±10.3	20.5±6.0
60 mg/day, bid, n=6	Day 1	1.6±0.3	3.3 ± 0.8	12.8±3.7	4.2±1.1
		2.1±0.2	4.3 ± 1.5	59.1±16.1	17.5±3.1
	Day 9	1.9±0.4	2.4 ± 0.6	14.9±6.1	3.9±1.0
		5.6±1.2	3.0±1.3	93.7±25.1	24.2±5.8
60 mg/day, qd, n=6	Day 1	3.5±0.5	3.3±1.4	20.0±0.4	2.1±0.3
		4.7±0.5	4.2±1.0	113.2±14.5	16.1±2.7
	Day 9	2.8±0.6	3.8±1.3	24.4±4.5	3.8±0.5
		6.6±0.9	5.3±2.1	113.5±14.1	22.6±2.0

^aTotal Active Pioglitazone Compounds: unchanged pioglitazone, M-II, M-III, and M-VI.

^bDay 1: AUC (0 - ∞ h); Day 9: AUC (0-24).

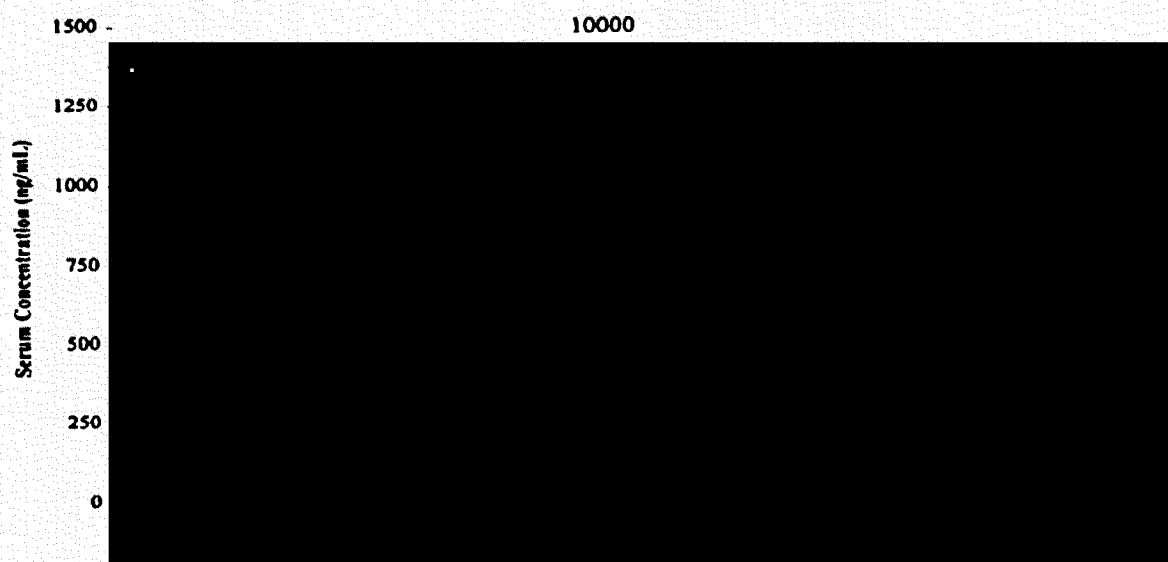
Table 8. PK parameter for Study CPH-003

Pioglitazone/ Total Active Compound		C _{max} (µg/ml)	T _{max} (hr)	AUC ₀₋₂₄ (µg.hr/ml)	T _{1/2} (hr)
15 mg/day, qd, n=6	Day 1	0.7±0.2	2.3±1.1	4.9 ± 0.8	1.8
		0.9±0.2	3.7±1.3	23.5±1.8	18.6±4.1
	Day 9	0.7±0.1	2.5±0.9	4.8±0.4	3.3±0.4
		1.5±0.1	3.1±1.1	22.6±1.4	16.2±2.8

^aTotal Active Pioglitazone Compounds: unchanged pioglitazone, M-II, M-III, and M-VI.

^bDay 1: AUC (0 - ∞ h); Day 9: AUC (0-24).

Figure 2. Pioglitazone and Metabolites Serum Concentration Profiles after a Single 30 mg Dose (Study CPH-050)



Healthy volunteers vs. patients:

A randomized, single blind, multiple-dose study (P-5232-0010) was conducted in three parallel groups of patients with mild-to-moderate NIDDM (N=30). Patients received 15 mg, 30 mg, or 60 mg daily for 14 days. Serum pioglitazone, and M-3, and M-4 concentrations were determined for samples taken following the dose on Day 14. The change in AUC₀₋₂₄ was proportional from 15 mg/day to 30mg/day; however, a less than proportional increase in AUC₀₋₂₄ was observed from 30 mg/day to 60mg/day.

Table 9. Average (± SD) PK parameters for pioglitazone and total active compounds following 14 days of treatment.

Parameter	Treatment		
	15 mg	30 mg	60 mg
Pioglitazone			
C _{max} (ng/ml)	327 ± 106	715 ± 216	972 ± 266
T _{max} (hr)	2.1 ± 1.1	2.5 ± 1.2	2.6 ± 0.97
AUC ₀₋₂₄ (µg.hr/ml)	3.43 ± 1.26	7.65 ± 3.14	10.00 ± 3.40

Total Active Compounds*			
C _{max} (ng/ml)	1052 ± 377	1940 ± 597	2884 ± 536
T _{max} (hr)	5.6 ± 4.0	5.4 ± 2.5	6.3 ± 3.2
AUC ₀₋₂₄ (µg.hr/ml)	18.00 ± 5.91	34.00 ± 9.58	52.00 ± 13.00

*Total Active Pioglitazone Compounds: unchanged pioglitazone, metabolites III, IV.

In this study, there were no Day 1 PK data and no control group (healthy subjects). On Day 14, AUC values in these patients' population were much lower than those from healthy volunteers (study CPH-001/002/003): 52 vs 113.5 for 60 mg/day, which decreased by 54.2%; 34 vs. 57.5 for 30 mg/day, decreased by 42.5% ; and 18 vs. 22.6 for 15 mg/day, decreased by 20.45%, which seems dose-dependent in the extent of decrease. The length of treatment is related to decrease in AUC, Since formulations were different in these studies, this reviewer can not draw any conclusion whether or not it is due to autoinduction or formulation changes. In healthy volunteers' studies, 2-60mg/day is well under linear range however, only patients' PK profiles showed it is less than proportional from 30mg/day to 60 mg/day. These studies were using different formulations and conducted in Japan and USA, respectively. In drug interaction studies, the PK difference in healthy volunteers and patients were minimal, in which the same formulation was used.

Absorption:

Following oral administration, in the fasting state, pioglitazone is first measurable in serum within 30 minutes, with peak concentrations observed within 2 hours. The absolute bioavailability of pioglitazone (Actos™) in humans is not known. However, absolute bioavailability of Actos™ in rats and dogs are 54% and 34%, respectively.

A relative bioavailability of 45 mg tablets of pioglitazone versus 45 mg suspension was investigated in 24 healthy subjects (male: 13, female: 11) in a two period, crossover study. The relative bioavailability of 45-mg tablet over suspension is about 94.5%. Female subjects were found to have 20-50% higher C_{max} and AUC values for pioglitazone. However, this reviewer calculated the mean body weight of female subjects and found that it was about 23% less than the mean body weight of male subjects, which may explain the difference between genders in these PK parameters.

Table 9: Summary of the Mean PK Parameters of Total Active Compounds in the Tablet (Treatment B) and Suspension (Treatment A) Groups.

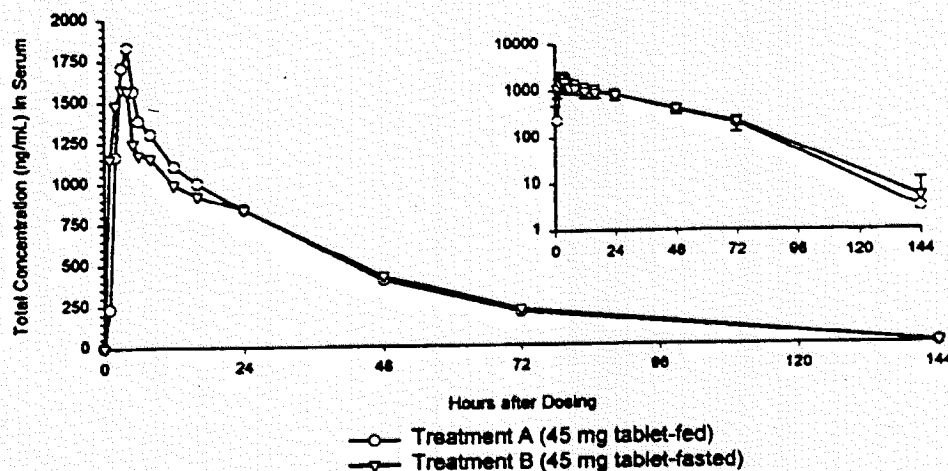
PK Parameter	Test mean 45 mg tablet (Treatment B)	Reference Mean 45 mg suspension (Treatment A)	Test /Reference (%)	90% Confidence Interval
C _{max} (ng/ml)	1903	2448	78.7	64.3 – 89.6
T _{max} (hours)	4.02	5.00	96.9	89.7 – 104.1
AUC _{0-∞} (ng.hr/ml)	56946	60236	94.5	84.1 – 102.0
T _{1/2} (hour)	23.6	20.1	118	106.3 – 129.5

Food slightly delays the time to peak serum concentration to 3-4 hours, but does not alter the extent of absorption, which was examined in Study PNFP-036 in a single-dose, randomized, open-label, single center crossover trial with at least a 5-day washout between

dose administrations. Following oral administration of a 45 mg pioglitazone tablet with food (10 min after an ADA standardized breakfast containing 30% fat), the rate of absorption was slightly modified, with the mean C_{max} increased approximately 18% and the median T_{max} delayed approximately 1 hour compared to that observed in the absence of food. The mean AUC for pioglitazone were comparable between treatments. An examination of the composite serum profile of the parent and metabolites (total active compounds) demonstrated a pharmacokinetic profile similar to that of pioglitazone, with C_{max} increased approximately 18% when administered with food, while mean AUC values were comparable between treatments.

Since clinically pioglitazone will be administered chronically and doses will be selected for individual patients based upon therapeutic effect, this reviewer agrees with the sponsor that the small differences with and without food are not considered clinically relevant and the labeling for administration of pioglitazone with food is not necessary.

Figure 3. Mean Total Concentrations (ng/ml) of Pioglitazone, M-III, and M-IV in Serum, Comparing Treatment A versus Treatment B Subjects.

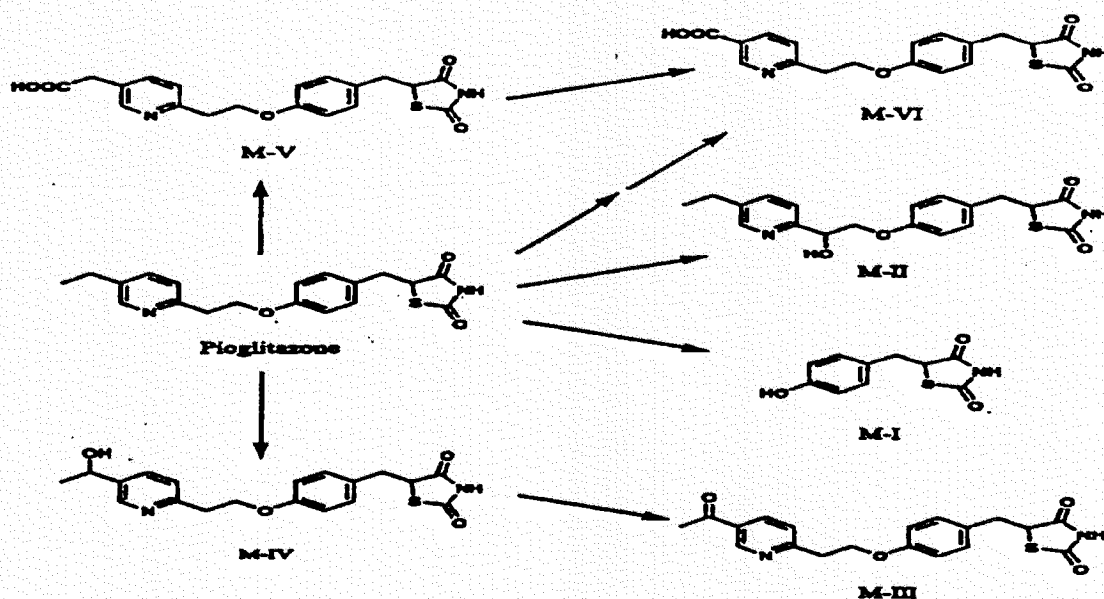


Distribution:

The mean apparent volume of distribution (V_d/F) of pioglitazone following single-dose administration is $0.62 + 0.39$ (mean + SD) L/kg of body weight. Pioglitazone is extensively bound (>99%) in human serum, principally to serum albumin. Pioglitazone was also found to be bound to other proteins, but with lower affinity. Metabolites III (M-III) and IV (M-IV) also are extensively bound (>98%) to serum albumin.

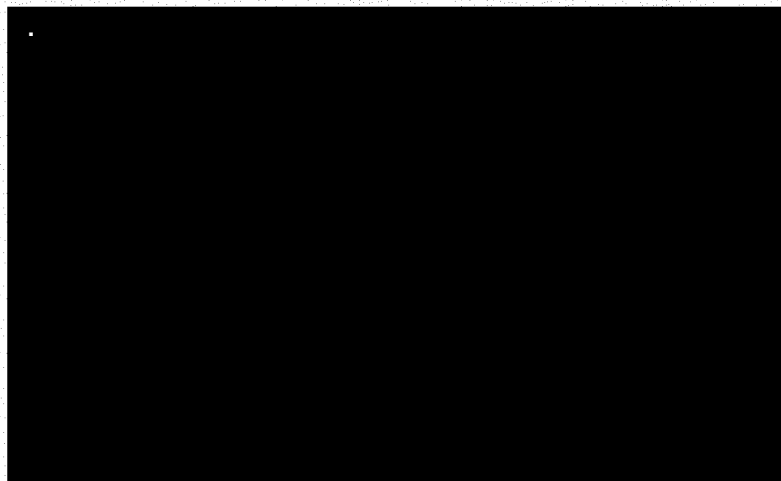
Metabolism:

The metabolic pathways of pioglitazone have been determined as below in humans.



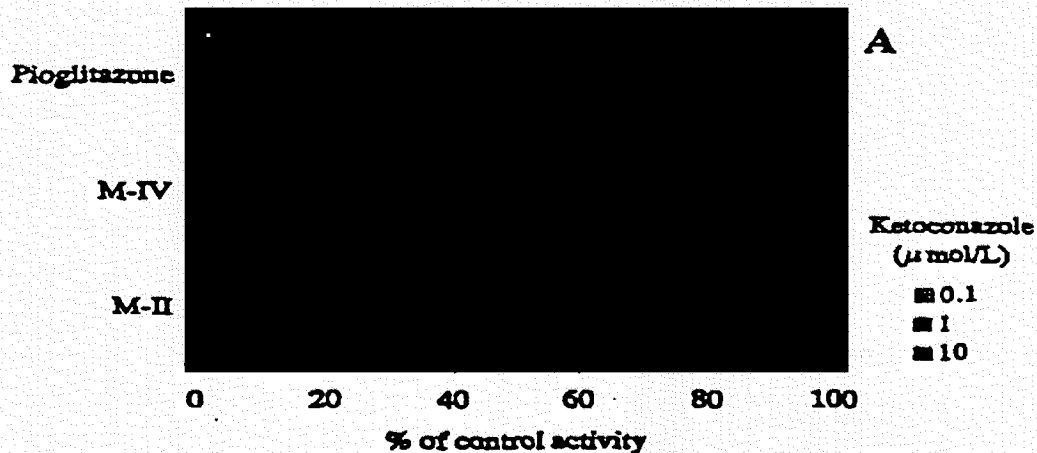
The sponsor conducted some in vitro drug metabolism studies using cDNA expressed CYP cell lines, human liver microsomes with probe substrates as activity index, and some inhibitory drugs such as ketoconazole. Based on cDNA expressed CYP studies, the sponsor concluded CYP1A1 and CYP2C8 are the major isoforms, whereas CYP3A4, CYP2C9, CYP2C19, CYP2D6 are minor enzymes.

Figure 4. In Vitro Metabolism of pioglitazone by Specific CYP Expressed B-Lymphoblastoid Cell Microsomes. Pioglitazone hydroxylation (10 μ M) was incubated with CYP expressing microsomes (2.5 pmol P450/ml) in the presence of NADPH-generating system at 37°C for 120min (mean value, n=2).



Based on the correlation study, the major isoforms were identified to be CYP2C8 and 3A4. However, there are no details in this submission how the correlation studies performed. In addition, the specific CYP3A4 inhibitor, ketoconazole inhibited pioglitazone metabolism by 65 to 85% at the same concentrations to pioglitazone, which is a striking evidence that CYP3A4 may contribute the metabolism of pioglitazone significantly. Since the submission did not have a detailed description on these in vitro studies, this reviewer can't comment on why these studies did not accord to each other in results.

The following figure showed that the effect of ketoconazole on the metabolism of pioglitazone was examined with 10 $\mu\text{mol/L}$ of pioglitazone and 1 mg protein/mL of human liver microsomes. Ketoconazole with the final concentration ranging 0.1 to 10 $\mu\text{mol/L}$ demonstrated a concentration-dependent and potent inhibitory effect on pioglitazone metabolism with both M-II and M-IV formation being inhibited by approximately 65 -85 % at the concentration of 10 $\mu\text{mol/L}$.



Elimination:

Following oral administration, approximately 15 to 30% of the dose was recovered in the urine. Renal elimination of pioglitazone is negligible, and the drug is excreted as metabolites, principally M-V, and their conjugates. The data from animal studies suggests that part of the oral dose may be excreted into the bile either unchanged or as metabolites and possibly then reabsorbed.

The mean serum half-life of pioglitazone and total active pioglitazone ranges from 3 to 7 hours and 16 to 24 hours, respectively. Pioglitazone is a slowly cleared compound with an apparent clearance, CL/F , calculated to be 5-7 L/hr.

V. Special Populations:

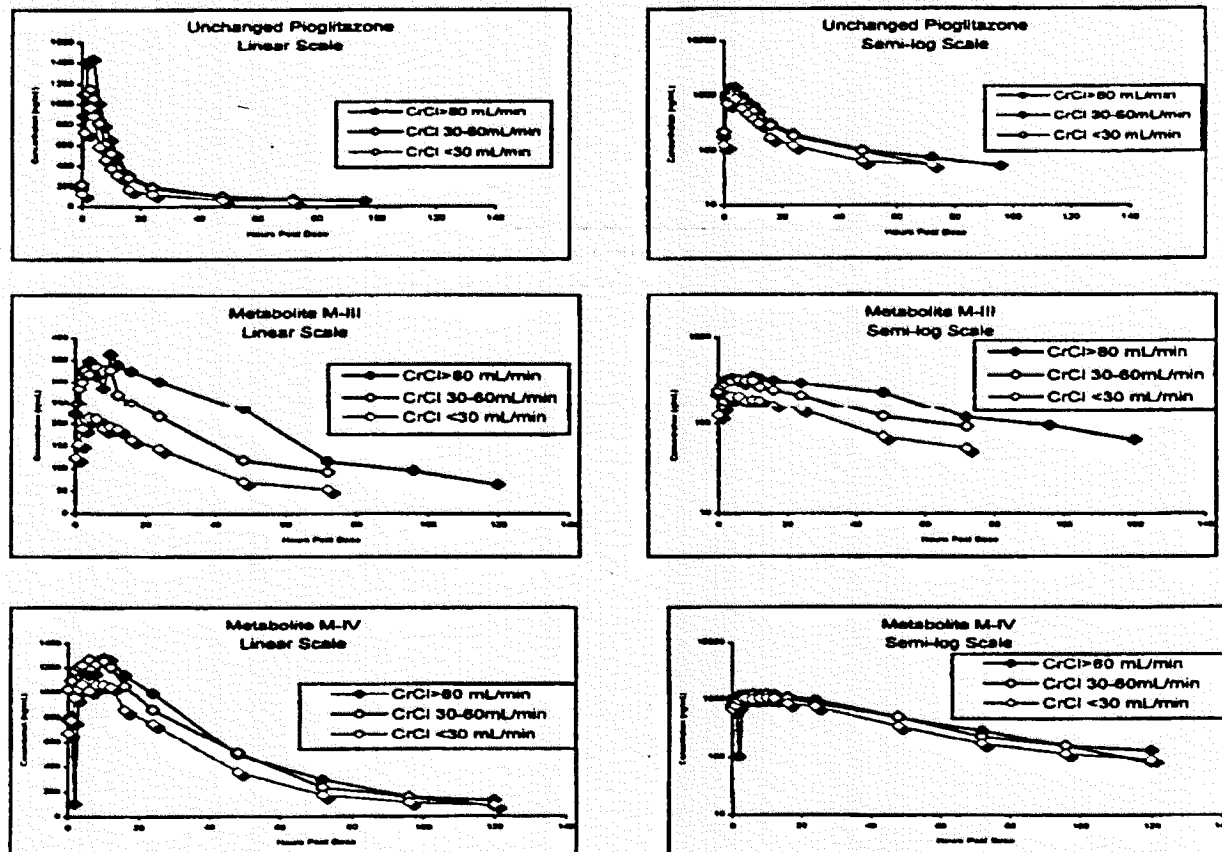
What are the changes in the special populations?
Do special populations and disease state patients (renal, hepatic) require adjustment in their initial dosage regimens?

Renal

One clinical trial was conducted to investigate the pharmacokinetics parameters of pioglitazone and main metabolites M-III and M-IV in serum after single and 10 repeated once daily oral doses of 45-mg pioglitazone in subjects with impaired renal function as compared with subjects with normal renal function. The trial was designed in an open-label fashion with 3 independent groups of subjects (Group 1: subjects with moderate renal impairment, CL_{CR} : 30 – 60 ml/min, n=9; Group 2: subjects with severe renal impairment, CL_{CR} : <30 ml/min, n=12; Group 3: subjects with normal kidney function, CL_{CR} : > 80 ml/min, n=6).

Serum AUCs of pioglitazone and its metabolites M-III and M-IV after single and repeated oral doses of 45-mg pioglitazone were not significantly different in subjects with moderate renal impairment and subjects with normal renal function. Subjects with severe renal impairment had significantly lower AUCs of pioglitazone and M-III and M-IV after single and repeated doses of pioglitazone than healthy subjects (AUC reduction of M-IV after single dose without statistical significance). After repeated doses of pioglitazone, C_{max} values for pioglitazone and M-III were statistically significantly lower in subjects with severe renal impairment. There was no change in $T_{1/2}$.

Figure 5. Mean Serum Concentrations (ng/ml) After Repeated Dosing Study

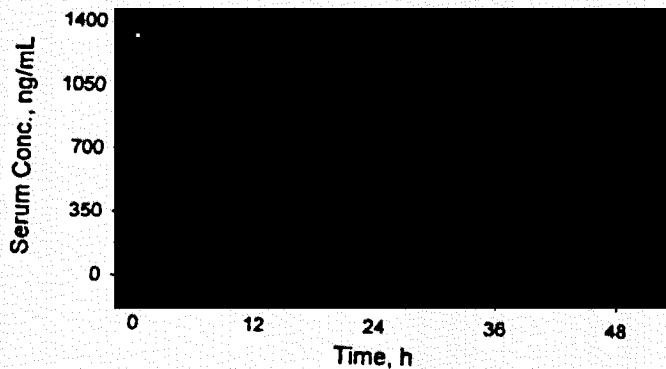


The sponsor explained the phenomenon of lower AUCs for pioglitazone and its metabolites in subjects with severe renal impairment compared to subjects with normal renal function may be consistent with impaired gastrointestinal absorption of pioglitazone in uremic subjects, which has also been reported for cyclosporine, ibuprofen and levobastine. Dose adjustment may not be necessary in patients with impaired renal function.

Hepatic

The effect of impaired hepatic function was investigated in a single dose (30 mg), open label, parallel design, single center, study in the United States (PNFP-007). Twenty-four male subjects, 12 with normal hepatic function and 12 with abnormal hepatic function as classified as Pugh-Child B or C, enrolled in and completed the study. All subjects received a 30-mg pioglitazone tablet 10 minutes after a diet-controlled meal. The following Figure 6 and Table 10 showed that PK profiles in hepatically impaired patients. The dose adjustment may not be necessary.

Pioglitazone Serum Concentration Profiles in Healthy and Hepatically Impaired Patients
US Study PNFP-007



Total Pioglitazone Serum Concentration Profile in Healthy and Hepatically Impaired Patients
US Study PNFP-007

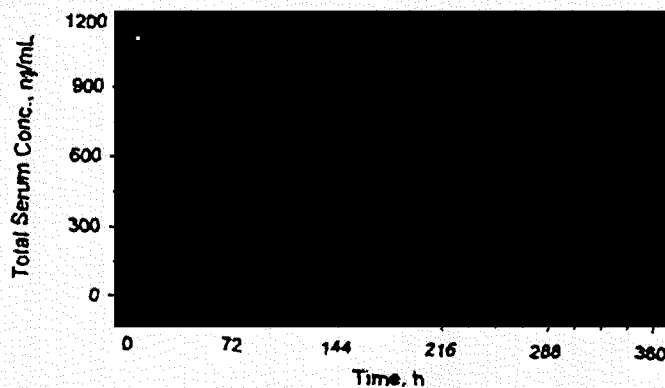


Table 10: PK Parameters in Hepatically Impaired Patients

PK Parameter	Test (Hepatic Patients)	Reference (Normal Subjects)	Test/Reference (x100)	90% Confidence Interval
Pioglitazone				
C _{max} (ng/ml)	508 ± 137.3	888 ± 374.6	57.2	43.0, 106
T _{max} (hrs)	4 (4.0 - 8.02)	4.0 (2.0 - 4.02)	133	111, 156
AUC _{0-∞} (ng.hr/ml)	7333 ± 2509.9	7659 ± 3065.5	95.7	75.8, 125
T _{1/2} (hrs)	8.77 ± 2.82	5.71 ± 3.25	154	115, 192
M-III				
C _{max} (ng/ml)	55.9 ± 20.72	156 ± 25.8	35.8	28.1, 42.0
T _{max} (hrs)	24 (16-49)	12 (8-16)	184	147, 221
AUC _{0-∞} (ng.hr/ml)	NR	7561 ± 1634.2	-	-
T _{1/2} (hrs)	NR	25.4 ± 6.79	-	-
M-IV				
C _{max} (ng/ml)	365 ± 106.7	377 ± 133.7	96.9	72.6, 156
T _{max} (hrs)	24 (11.98-24.03)	12 (8-24)	171	147, 195
AUC _{0-∞} (ng.hr/ml)	27909 ± 6758.7	23838 ± 10417.8	117	93.0, 162
T _{1/2} (hrs)	35.9 ± 8.28	32.5 ± 12.16	111	82.3, 139
Total Active Compounds				
C _{max} (ng/ml)	641 ± 168.2	1139 ± 454.7	56.3	40.8, 111
T _{max} (hrs)	8 (4-12.05)	4 (2.0-8.02)	200	159, 242
AUC _{0-∞} (ng.hr/ml)	35965 ± 7930.7	33357 ± 11135.1	108	88.8, 137
T _{1/2} (hrs)	31.1 ± 8.5	19.7 ± 8.69	158	123, 192

NR: not reported.

Age:

In the US study (PNFP-025), the effect of age was investigated in a single dose (30 mg), open label, parallel design, single center, study trial where 23 (7 elderly and 16 non-elderly) subjects completed the trial. Elderly subjects were between 65 and 85 years of age and non-elderly subjects are between 35 and 50 years of age. The results showed that the mean C_{max} value in the elderly was similar to the mean value in the non-elderly control group, while the median T_{max} value was slightly prolonged in the elderly. In contrast, mean AUC result for pioglitazone was about 20% higher in the elderly (Table 11). Although it is unclear as to the exact mechanism for the observed pharmacokinetic changes, in clinical use pioglitazone will be administered chronically and doses will be selected for individual patients based on therapeutic effect. This reviewer agrees with the sponsor that small changes in the pharmacokinetics of pioglitazone are not considered clinically relevant and a specific adjustment for age does not need to be included in the labeling.

Table 11: PK Parameters in Elderly Subjects from Study PNFP-025

PK Parameter	Test (elderly)	Reference (non-elderly)	Test/Reference	90% Confidence Interval
Pioglitazone				
C _{max} (ng/ml)	959 ± 224.3	956 ± 333.7	102	84.9, 133.5
T _{max} (hrs)	4 (2.0-4.0)	2.0 (1.0 - 4.0)	133	111.9, 153.2
AUC _{0-∞} (ng·hr/ml)	9634 ± 2780.0	7955 ± 2246.2	122	106.4, 144.7
T _{1/2} (hrs)	10.1 ± 6.36	6.89 ± 2.20	145	102.8, 188.0
Total Active Compounds				
C _{max} (ng/ml)	1264 ± 294.6	1247 ± 410.1	103	86.2, 132.7
T _{max} (hrs)	4 (4.0-4.0)	4 (4.0-4.0)	100	-
AUC _{0-∞} (ng·hr/ml)	39600 ± 8660.6	32313 ± 7998.5	117	104.8, 135.7
T _{1/2} (hrs)	23.6 ± 3.68	19.6 ± 4.82	120	102.9, 192

Gender:

Although the sponsor didn't conduct gender-oriented clinical trials, the sponsor did analyze the data available for both genders in studies covering BE, PK, food effect, etc. The PK parameters in women generally are higher from 20 to 60% in comparison with men. However, the results were not bodyweight-normalized. In a BE study, the AUC and C_{max} were 25% higher in women than in men, however, the mean body weight in women group was 23% less than in men. Therefore, this reviewer found that gender difference may be minimized when body-weight taken into account.

Pediatric

No pediatric study was conducted.

Drug Interactions:

Based on the metabolic pathways, what type of drug interactions is expected?
 Is the interacting drug a good choice for the interaction study?
 Is the interaction leading to dose adjustment?

Based on in vitro cDNA expressed CYP microsomes study and correlation study using human liver microsomes, pioglitazone is mainly metabolized through CYP2C8 and 3A4. From chemical inhibition study, ketoconazole inhibited pioglitazone metabolism up to 85% at the equal molar concentration. The sponsor had conducted 5 drug interaction studies including glipizide, phenprocoumon and warfarin, metformin, digoxin, and sulfonylurea drugs. These studies revealed that there are no significant drug interactions after concomitant administration.

Glipizide: double blind, placebo-controlled, two-treatment, two period, multi-dose crossover design: 5 mg glipizide + 45 mg pioglitazone for 7 days. The PK parameters are statistically equivalent between the treatment A (glipizide 5mg + placebo) and treatment B (glipizide 5mg + pioglitazone 45 mg).

Warfarin and phenprocoumon: Either phenprocoumon or warfarin was dosed for a total of 17 days aiming at steady-state concentrations, defined by its effects on prothrombin time on day 8 at the latest. Doses of phenprocoumon or warfarin were adjusted to reach and maintain a Quick's value of 35 ± 5 %. Pioglitazone was co-administered at steady-state anticoagulant treatment with a dose of 45 mg once daily for 7 days. Co-administration of pioglitazone with either phenprocoumon or warfarin did not change the Primary PK or PD parameters of both phenprocoumon and warfarin.

Digoxin: It was a randomized double-blind, two period, crossover trial: digoxin 0.25 mg bid for days 1-3, and 0.25 mg qd on days 4-35, pioglitazone 45 mg or placebo qd on days 10 – 16 or on days 31-37. The 90% confidence interval for AUC₀₋₂₄ after repeated doses of pioglitazone was slightly above the predefined accepted range [103.94 – 127.17]. However, it may not be clinically relevant.

Metformin: Evaluation was performed about the influence of steady-state concentrations of pioglitazone (45 mg qd) on the pharmacokinetic characteristics of single oral dose of 1000 mg metformin in plasma and in urine in the double-blind, placebo-controlled, two-way crossover study in healthy male subjects. It was found there was no difference between two groups.

Sulfonylureas: 8 patients with NIDDM who already took glibenclamide (10 mg/day, 5 patients) or gliclazide (160 mg/day, 3 patients) for one month were co-administered with pioglitazone 30 mg/day for 7 days. In this limited study the co-administration of pioglitazone did not change PK parameters of these two sulfonylurea drugs.

VII. Pharmacokinetic/Pharmacodynamic Relationships

No studies were conducted regarding PK/PD relationship.

COMMENTS TO MEDICAL REVIEWER:

Pharmacokinetic parameters in females are about 20-60% higher than in males across this submission. Since the drug is not prescribed based on body-weight, women may be at potential risk to expose overdose. We suggest that we should propose a labeling requirement on this issue.

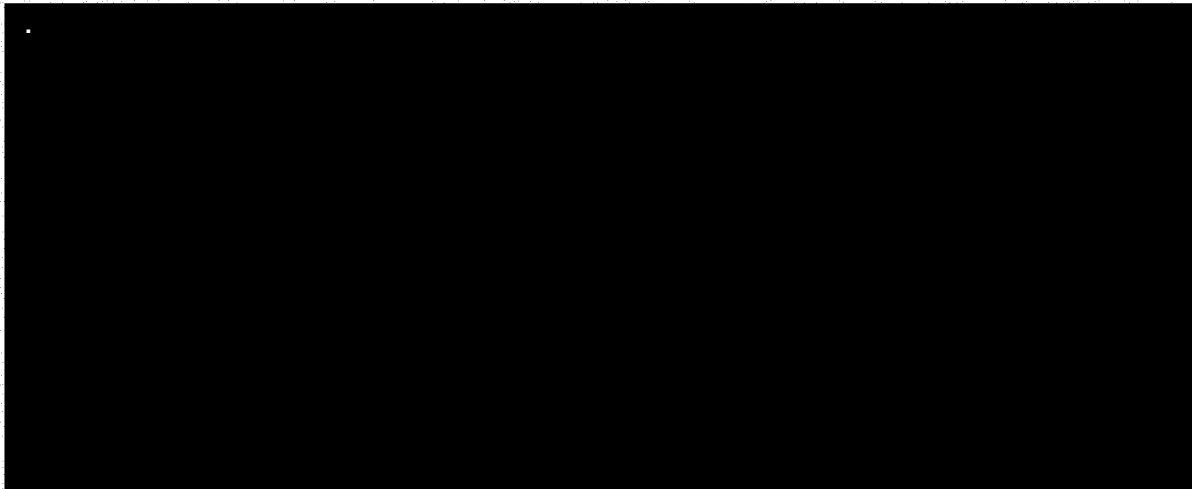
COMMENTS TO BE SENT TO SPONSOR

- 1) There was significant difference in PK parameters between genders. The PK parameters in women were about 20-60% higher than in men. However, these studies were not designed to detect the gender difference in well-controlled studies. And these studies were not body-weight normalized. Obviously, women were exposed to higher doses, which also led to a tendency that pioglitazone is more efficacious in women. Potential toxic reactions are concerned in women taking this drug, particularly when metabolic inhibitory drugs such as ketoconazole are concomitantly administered. Although dose adjustment in women is not required at this point, a close monitoring for potential toxicity should be taken.
- 2) Based on the in vitro drug metabolism studies, pioglitazone is mainly metabolized

through CYP2C8 and 3A4. And ketoconazole, a typical CYP3A4 inhibitor, inhibited 85% of pioglitazone metabolism at the equal molar concentrations. Therefore, there is a great potential for drug interaction involving CYP3A4. The 5 drugs the sponsor picked for drug interaction studies did not include inhibitory metabolic drug interactions involving CYP3A4. As an expert indicated in the recent Advisory Committee Meeting (April 23, 1999), and this reviewer agreed that drug interaction studies between pioglitazone and ketoconazole should be conducted in Phase IV.

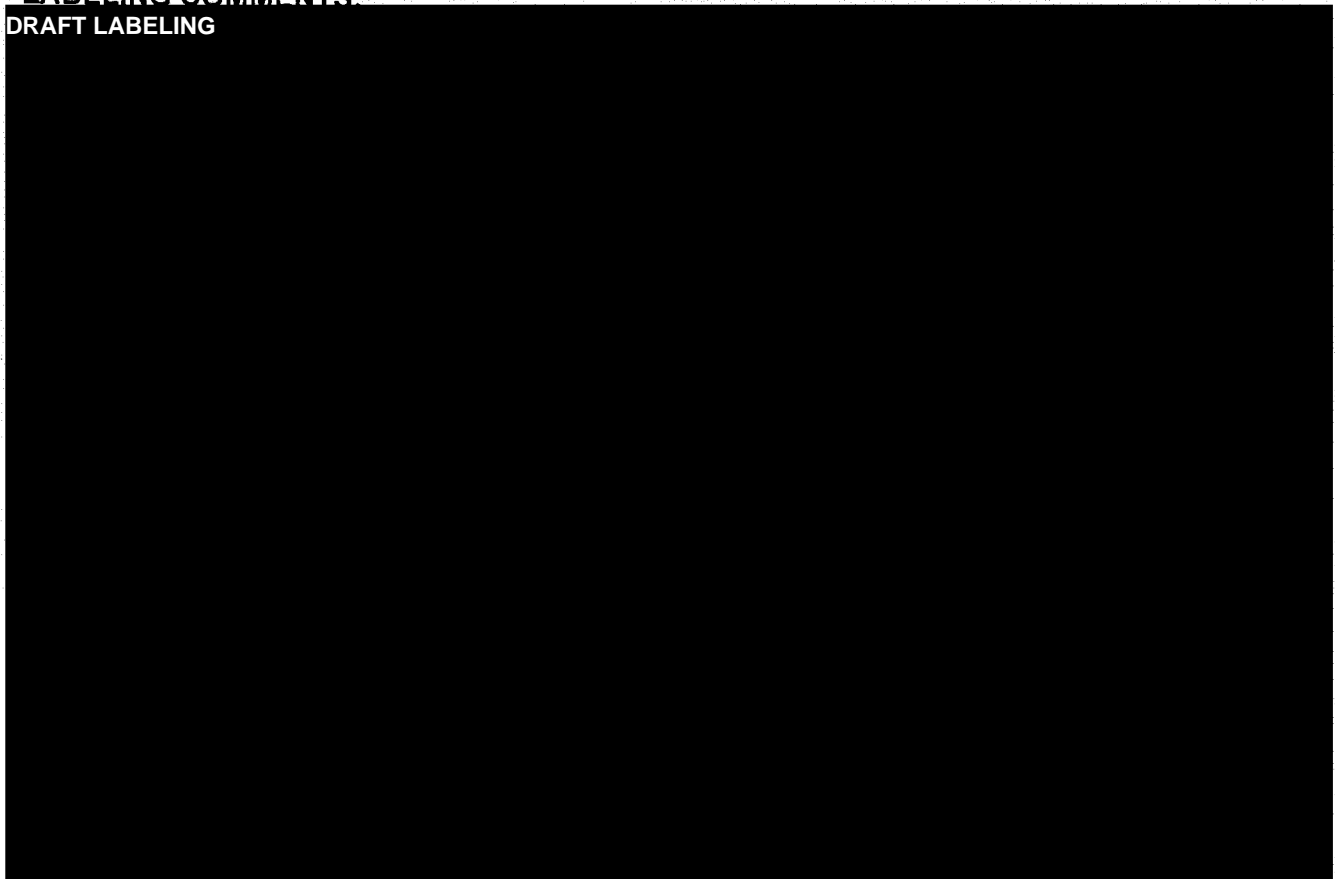
- 3) Since troglitazone is a CYP3A4 inducer and pioglitazone has not been investigated whether or not it is an inducer of CYP3A4 in human, the sponsor should conduct this very important in vivo study in humans as a phase IV commitment.

4)

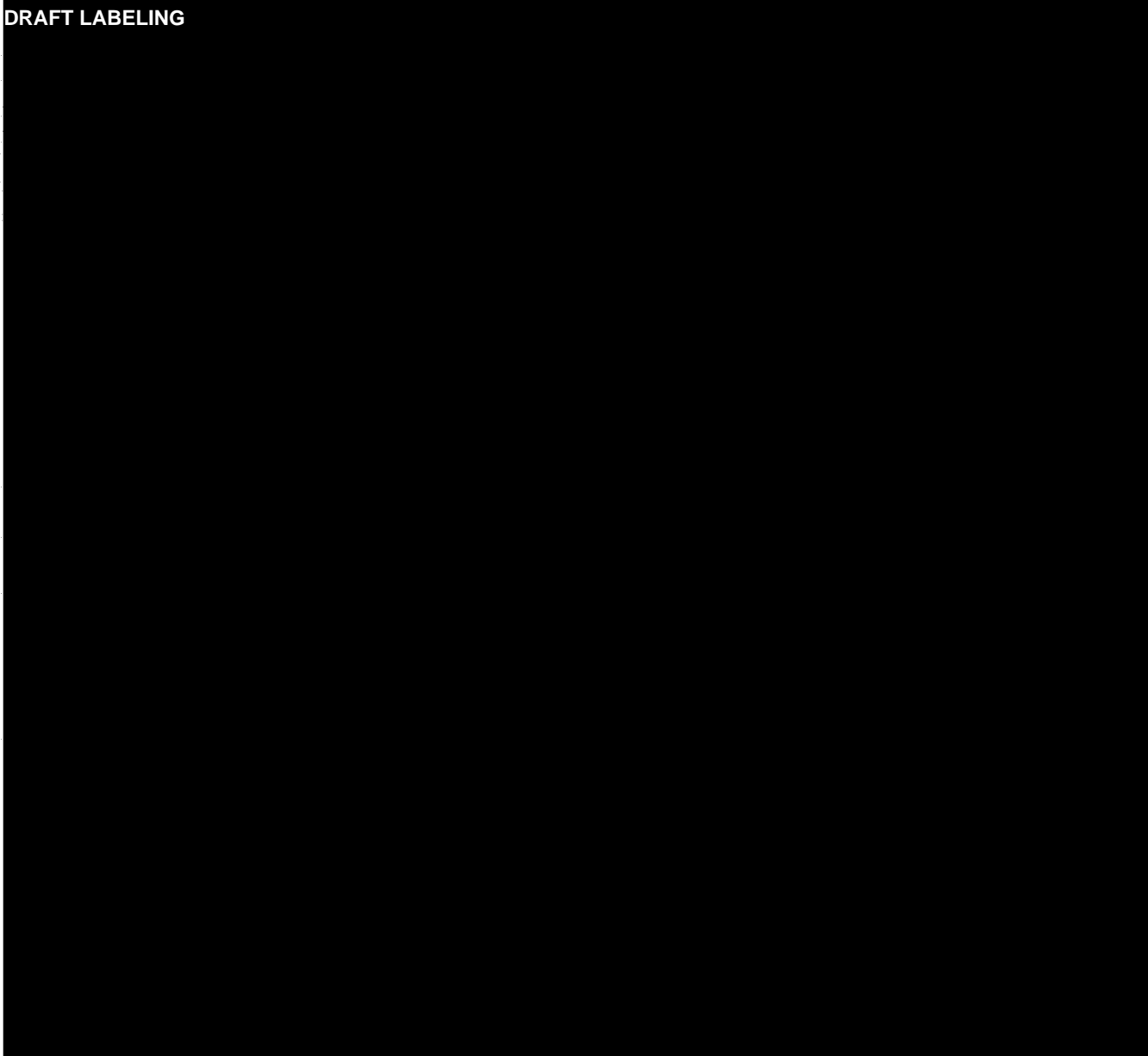


LABELING COMMENTS:

DRAFT LABELING



DRAFT LABELING



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/S/

Xiaoxiong (Jim) Wei, Ph.D.
Division of Pharmaceutical Evaluation II
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/S/

RD initialed by Hae-Young Ahn, Ph.D., Team Leader

CPB Briefing 06-17-1999

Attendees: Lesko, Huang, ChenMe, Hunt, Selen, Ahn, Fossler, Shore, Madani, Uhl, Chatterjee.

FT initialed by Hae-Young Ahn, Ph.D., Team Leader 6/17/99

CC: NDA 21-073 (orig., 1 copy), HFD-510(Weber, Misbin), HFD-850 (Lesko, Huang), HFD-870(Wei, Ahn, M. Chen), CDR (Barbara Murphy).

Code: ~~AE~~ AP

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Appendix 1. Study summaries

PROTOCOL INDEX

Protocol Number	Title	Page
PNFP-035	An open label pharmacokinetic bioavailability study of pioglitazone utilizing a 45 mg suspension and 45 mg tablet in healthy volunteers (volume 1.075-76)	p. 23
PNFP-018	An open label pharmacokinetic bioequivalence study in healthy volunteers comparing 45 mg tablets of pioglitazone with three 15 mg tablets of pioglitazone used in the clinical trials (volume 1077-78)	p.26
P-5232-0001	Single dose tolerance and preliminary single dose pharmacokinetics of pioglitazone hydrochloride in healthy adult male volunteers (volume 1.097-98)	p.30
CPH-001,-002,-003	Clinical Phase I study of AD-4833- single dose and repeated dose studies (volume 1.102-104)	p.31
P-5232-0002	Pioglitazone hydrochloride multiple dose pharmacokinetics in healthy adult male volunteers(volume 1.099-100)	p.32
P-5232-0010	A pharmacokinetic and pharmacodynamic evaluation of the effect of pioglitazone HCL on variations in blood glucose, triglycerides, and insulin levels with meals in patients with non-insulin dependent diabetes mellitus (NIDDM) (volume 1.073-74)	p.33
PNFP-007	An open label evaluation of the effect of impaired hepatic function on the pharmacokinetics of pioglitazone (volume 1.081-82)	p.34
EC-230	Investigation of the pharmacokinetics of pioglitazone (AD-4822) and its main metabolites M-III and M-IV in subjects with impaired renal function (volume 1.083-85)	p.38
PNFP-025	An open-label evaluation of the effect of age on the pharmacokinetics of pioglitazone(volume 1.093)	p.39
PNFP-003	Evaluation of the interaction between pioglitazone and glipizide (volume 1.086-87)	p.43
EC-221	An open-label mono-center study to assess the influence of multiple-dose pioglitazone (AD-4833), 45 mg O.D., on steady-state pharmacodynamics and pharmacokinetics of phenprocoumon and warfarin enantiomers (volume 1.088-89)	p.45
EC-222	Investigation of the effects of a single and repeated once daily doses of 45 mg pioglitazone (AD-4833) on the pharmacokinetics of digoxin at steady-state serum concentrations (volume 1.090-91)	p.46

EC-223	Evaluation of the influence of pioglitazone (AD-4833) HCL 45 mg O.A.D. administration under steady-state concentrations on the pharmacokinetic characteristics of a single oral dose of 1000 mg metformin-HCL in plasma and urine in a double-blind, placebo-controlled, crossover study in healthy male subjects (volume 1.092)	p.47
PNFP-036	An open-label pharmacokinetic food interaction study of pioglitazone utilizing a 45-mg tablet in healthy volunteers (volume 1.095-96)	p.49
7256/92/003	In vitro binding of pioglitazone (U-72, 107): I. Basic studies (volume 1.108)	p.54
7256/92/004	In vitro binding of pioglitazone (U-72, 107): II. Serum protein profile (volume 1.108)	p.55
7256/92/055	In vitro binding of pioglitazone (U-72, 107): III. Competitive binding (volume 1.108)	p.56
A-35-910	Chiral inversion of AD-4833 in rat and human plasma (volume 1.108)	p.57
A-35-797	Identification of human cytochrome P450 involved in the metabolism of AD-4833 and the effect of AD-4833 on the activities of human cytochromes P450 (volume 1.108)	p.58
A-35-972	Contribution of cytochrome P450 isoforms to the metabolism of pioglitazone (volume 1.108)	p.59

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AN OPEN LABEL PHARMACOKINETIC BIOAVAILABILITY STUDY
OF PIOGLITAZONE UTILIZING A 45 mg SUSPENSION AND 45 mg TABLET IN HEALTHY
VOLUNTEERS (PNFP-035)

SUMMARY AND CONCLUSIONS:

Administration of pioglitazone was well tolerated. During this clinical study, based on physical examinations, vital signs, 12-lead ECGs, clinical laboratory evaluations (including blood chemistries, hematology, and routine urinalysis), and adverse events, there were no clinically significant findings that were directly attributed to the drug.

Following oral administration of a 45-mg pioglitazone tablet, the mean C_{max} value was approximately 80% of the mean value of a 45-mg pioglitazone oral suspension, while the median T_{max} values were similar. The pioglitazone tablet formulation was approximately 99% bioavailable relative to the suspension formulation. The mean elimination/disposition rate for pioglitazone was approximately 30% slower following the administration of the tablet than the suspension. Similar results were observed for the two active metabolites, M-III, and M-IV. For both metabolites, the mean C_{max} values following the administration of the tablet were approximately 17% to 20% lower than those following the administration of the suspension while the mean AUC were within 10% of each other. An examination of the composite serum profile of the parent and metabolites or "total" pioglitazone resulted in an approximate 20% reduction in mean peak concentration but no change in the mean AUC values following the administration of the tablet compared to the suspension.

Females, generally, had 20-50% higher mean C_{max} and AUC values for pioglitazone and metabolites compared to males, while the mean elimination/disposition rate constant and oral clearance values for pioglitazone were approximately 15% lower.

Table: Total Active Compounds OF PK Parameters

Test Mean ^a	Reference Mean ^a PK Parameter	90%		Confidence Interval
		45 mg Tablet (Treatment B)	45 mg Suspension (Treatment A)	
	C _{max} (ng/mL)	1903 (+785.1)	2448 (-675.5)	78.7 (64.3, 89.6) ^c
	T _{max} (hour)	4.02 ^d (3.00-5.02) ^a	5.00 ^d (3.00-6.00) ^d	96.9 (89.7, 104.1) ^e
	AUC(0-t) (ng/hr/mL)	51538 (5:19944.0)	55641 (5:16388.0)	92.6 (81.4, 101.4) ^c
	AUC (0-∞) (ng.hr/mL)	56946 (5:19815.2)	60236 (+ 15977.0)	94.6 (84.1, 102.0) ^c
	Ke (hours ⁻¹)	0.0322	0.0371	86.5 (80.8, 92.3) ^f
	T _{1/2} (hour)	23.6 (±8.43)	20.1 (±8.52)	118 (106.3, 129.5) ^f

^a Arithmetic mean and ±SD.

^b Ratio of untransformed parameter means expressed as a percentage.

^c 90% confidence interval for the natural log (ln) transformed parameters.

- d Tmax is expressed as median with the range in parentheses.
- e 90% confidence interval for Tmax calculated using means and standard error from the ANOVA.
- f 90% confidence interval for the untransformed parameter.
- AUC(0-t) Area under the serum concentration time curve from Hour 0 to the last Measurable serum concentration.
- AUC(0-∞) Area under the serum concentration time curve to infinity.
- Cmax Maximum serum concentration.
- Ke Terminal phase elimination/disposition rate constant,
- T1/2 Terminal phase elimination/disposition half-life.
- Tmax Time to maximum serum concentration.

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AN OPEN LABEL PHARMACOKINETIC BIOEQUIVALENCE STUDY IN HEALTHY VOLUNTEERS COMPARING 45 mg TABLETS OF PIOGLITAZONE WITH THREE 15 mg TABLETS OF PIOGLITAZONE USED IN THE CLINICAL TRIALS (PNFP-018)

STUDY OBJECTIVE: To evaluate the bioequivalence of the 45 mg tablet with three 15 mg tablets of pioglitazone used in the clinical trials.

STUDY DESIGN: Two-treatment, two-period cross-over design.

STUDY POPULATION: A total of 24 healthy male subjects, between the ages of 18 to 35 years completed the study.

STUDY DRUG: Twenty-four (24) subjects received a single dose of 45 mg pioglitazone (either three 15mg tablets taken during the clinical trials or the 45 mg tablet) in Period 1. After the seven day washout period (14 days following pioglitazone administration on Day 1) subjects received a single dose of the alternate treatment in Period 2.

CLINICAL PHASE: Phase I

PK SAMPLING SCHEDULE: Serum PK samples were collected at the following times: 0 hour (predose); 1, 2, 3, 4, 5, 6, 8, 12, and 16 hours after administration of the dose on Day 1 and on the mornings of Days 2, 3, 4, and 7 (taken at the same time of day as dose administration on Day 1 for Periods 1 and 2).

STUDY VARIABLES:

A. Pharmacokinetic: The following parameters were calculated for unchanged pioglitazone, M-III, M-IV and total pioglitazone: AUC_{0-t}, AUC_{0-∞}, C_{max}, T_{max}, and T_{1/2}.

STATISTICAL METHODOLOGY: The pharmacokinetic variables were analyzed from serum samples. These analyses were performed on data for pioglitazone, the metabolites M-III and MW, and the total (combined levels of pioglitazone, M-III, and M-IV). For the untransformed C_{max}, AUC bioequivalence was demonstrated if the 90% confidence interval was between 80% and 120%. For the natural log (ln) transformed C_{max}, AUC_{0-t} and AUC_{0-∞}, bioequivalence was demonstrated if the 90% confidence interval was between 80% and 125%.

PHARMACOKINETIC RESULTS:

Concentrations of pioglitazone and the two metabolites in serum were determined by a validated high-performance liquid chromatography method with UV absorbance detection. The lower limit of quantitation for pioglitazone, M-III, and M-IV was 25.0 ng/mL in serum. The mean (± standard deviation, SD) pharmacokinetic parameters of pioglitazone, the two metabolites and the total (combined levels of pioglitazone, M-III, and M-IV) in serum and the 90% confidence intervals for the ratio of test (Treatment B)/reference (Treatment A) are summarized below.

PK Parameter	Pioglitazone			
	Test Mean ^a 1x45 mg Tablet (Treatment B)	Reference Mean 3x15 mg Tablet ^a (Treatment A)	Ratio of LS Means Test/Reference ^b (%)	90% Confidence Interval
C _{max} (ng/mL)	1482 (+499.7)	1681 (±496.0)	88.2	(79.7, 96.6) ^e
ln (C _{max}) (ng/mL)	1404 ^d	1612 ^d	87.1	(78.8, 96.2) ^c
T _{max}	3.00 ^f	3.00 ^f	98.8	(90.2, 107) ^g

(hour)	(2.00-5.00) ^f	(2.00-4.00) ^f		
AUC(0-t) (ng*hr/mL)	12936 (±4800.1)	14198 (±4139.1)	91.1	(82.7, 99.5) ^c
ln (AUC(0-t)) (ng*hr/mL)	12103 ^d	13594 ^a	89.0	(80.8, 98.1) ^c
AUC(0-∞) (ng*hr/mL)	13854 (±4996.2)	15059 (±4506.3)	92.0	(83.9, 100) ^c
ln (AUC(0-∞)) (ng*hr/mL)	12998 ^d	14391 ^d	90.3	(82.2, 99.3) ^c
K _e	0.1081	0.1207	89.6	(77.9, 101) ^c
T1/2 (hours)	9.18 (±7.537)	6.42 (±2.242)	143,	(107, 179) ^c

M-III

PK Parameter	Test Mean ^a 1x45 mg Tablet (Treatment B)	Reference Mean ^a 3x15 mg Tablet (Treatment A)	Ratio of LS Means Test/Reference ^b (%)	90% Confidence Interval
C _{max} (ng/mL)	168 (±50.7)	193 (±63.7)	86.8	(78.4, 95.2) ^c
ln (~ (n-mL)	160 ^d	183 ^d	87.5	(80.3, 95.3) ^e
T _m , (hour)	16.0 ^f (8.00-47.9) ^f	14.0 ^f (6.02-23.9) ^f	107	(83.7, 130) ^g
AUC _{0-t} (ng*hr/mL)	6954 (±2254.3)	7970 (±3039.4)	87.2	(79.1, 95.4) ^c
ln (AUC _{0-t}) (ng*hr/mL)	6584 ^d	7397 ^d	89.0	(81.5, 97.1) ^e
AUC(0-∞) (ng*hr/mL)	9314 (±2827.5)	10164 (±4263.7)	90.6	(82.0, 99.2) ^c
ln AUC(0-∞) (ng*hr/mL)	8924 ^d	9366 ^d	94.5	(86.9, 103) ^e
l _q (hours) ^h	0.0256 (±0.00734)	0.0273 (±0.00649)	93.6	(86.3, 101) ^e
T1/2 (hour)	29.4 (±8.58)	26.8 (±6.67)	109	(100, 119) ^e

M-IV

PK Parameter	Test Mean ^a 1x45 mg Tablet (Treatment B)	Reference Mean ^a 3x15 mg Tablet (Treatment A)	Ratio of LS Means Test/Reference ^b {-}	90% Confidence Interval
C _{max} (ng/mL)	639 (±188.9)	737 (±248.6)	86.8	(78.0, 95.6) ^c
ln (C _{max}) (ng/mL)	613 ^d	702 ^d	87.2	(79.8, 95.4) ^e
T _{max} (hour)	16.0 ^f (6.00-23.9) ^f	16.0 ^f (12.0-23.9) ^f	91.7	(79.2, 104) ^l
AUC _{0-t} (ng*hr/mL)	29977 (±9492.9)	34686 (±12807.7)	86.4	(77.7, 95.2) ^c
ln (AUC _{0-t}) (ng*hr/mL)	285774	32689 ^d	87.4	(79.8, 95.7) ^e
AUC(0-∞) (ng*hr/mL)	35074 (±9011.1)	38044 (±12145.6)	92.2	(85.5, 98.9) ^c
ln (AUC(0-∞)) (ng*hr/mL)	33993 ^d	36369 ^d	93.5	(86.9, 100) ^e
l _q (hours) ^h	0.0269 (±0.00664)	0.0301 (±0.00572)	89.4	(84.8, 93.9) ^e
T1/2 (hour)	27.2 (±6.56)	23.7 (±4.14)	115	(109, 121) ^c

PK Parameter	Test Mean ^a 1x45 mg Tablet (Treatment B)	Reference Mean ^a 5x15 mg Tablet (Treatment A)	Total	
			Ratio of LS Means Test/Reference ^b (%)	90% Confidence Interval
C _{max} (ng/mL)	1865 (±605.3)	2108 (±588.7)	88.5	(80.1, 96.9) ^c
ln (C _{max}) (ng/mL)	1774d	2028 ^d	87.5	(79.3, 96.5) ^e
T _{max} (hour) ^f	4.00 ^f (3.00-5.00) ^f	4.00 ^f (2.00-5.00) ^f	101	(94.4, 108) ^g
AUC _{0-t} (ng*hr/mL)	51441 (±16212.5)	58926 (±19250.8)	87.3	(79.5, 95.1) ^c
ln (AUC _{0-t}) (ng*hr/mL)	49079	56075	87.5	(80.3, 95.4) ^e
AUC _(0-∞) (ng*hr/mL)	56895 (±15560.6)	62542 (±18555.2)	91.0	(84.4, 97.5) ^c
lnAUC _(0-∞) (ng*hr/mL)	54868d	60007d	91.4	(84.9, 98.5) ^e
Ke (hours ⁻¹)	0.0305 (±0.00735)	0.0333 (±0.00641)	91.6	(86.3, 97.0) ^c
T _{1/2} (hour)	24.0 (±5.71)	21.4 (±3.55)	112	(105, 118) ^e

a Arithmetic mean and ±SD.

b Ratio of parameter means for untransformed and natural log transformed parameters expressed as a percent.

c 90% confidence interval for the untransformed parameters.

d Geometric means.

e 90% confidence interval for the natural log (ln) transformed parameters.

f T_{max} is expressed as median with the range in parentheses.

g 90% confidence interval for T_{max} calculated using means and standard errors from ANOVA.

AUC_(0-t) Area under the serum concentration time curve ~ Hour 0 to the last measurable serum concentration.

AUC_(0-∞) Area under the serum concentration time curve to infinity.

Terminal phase elimination/disposition rate constant.

C_{max} Maximum serum concentration.

T_{1/2} Terminal phase elimination/disposition half-life.

T_{max} Time to maximum serum concentration.

SUMMARY AND CONCLUSIONS: Administration of pioglitazone was well-tolerated. During this clinical study, based on physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations (including serum chemistries, hematology, and complete urinalysis), there were no clinically significant findings that could be directly attributed to the drug. Following oral administration of 1x45 mg pioglitazone tablet, the mean C_{max} value for pioglitazone was approximately 88% of the mean value of 3x15 mg tablets, while the median T_{max} values were similar. The mean AUC_{0-t} and the AUC_{0-∞} for pioglitazone 1x45 mg tablet were approximately 92% of the mean value of 3x15 mg tablets. In general, the 90% confidence intervals for the untransformed C_{max}, AUC_{0-t}, and AUC_{0-∞} were contained between 80% and 120% and between 80% to 125% for the natural log transformed parameters, indicating that the 1x45 mg tablet and the 3x15 mg tablets were bioequivalent. The mean elimination/disposition rate constant for pioglitazone was approximately 10⁻⁴ lower following administration of the 1x45 mg tablet as compared to the 3x15 mg tablets. Similar results were

observed for the two active metabolites, M-III and M-IV. For both metabolites, the mean C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ values following the administration of 1x45 mg pioglitazone tablet were approximately 86% to 92% of the values following the administration of the 3x15 mg tablets, and the 90% confidence intervals for the natural log transformed C_{max} , AUC_{0-t} , and $AUC_{0-\infty}$, were generally between 80% and 125%. An examination of the composite serum profile of the parent and metabolites or "total" pioglitazone revealed similar results to those observed with pioglitazone.

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Title: Single Dose Tolerance and Preliminary Single Dose Pharmacokinetics of Pioglitazone Hydrochloride in Healthy Adult Male Volunteers: Report of Protocol P/5232/0001 (BC693)

Author(s): [REDACTED]

Date: December 18, 1990

U-Number(s): U72107A

Keywords: clinical trial, phase I, tolerance, safety, pharmacokinetics

ABSTRACT

Purpose: This initial human exposure to pioglitazone hydrochloride was undertaken to determine the clinical and biochemical tolerance in healthy male volunteers to single doses of pioglitazone hydrochloride over the range of 2-60 mg (free base equivalents).

Methods: Volunteers were informed about the investigational medication and the study, and did provide written consent to participate. Volunteers were observed on an inpatient basis from 24 hours prior to dosing until 24 hours post dose, and were seen in follow-up two days, one week and two weeks post dose. Continuous electrocardiographic monitoring by telemetry, hourly ECG printouts, thrice daily symptoms query, and daily vital signs were obtained. A large battery of laboratory tests were done to seek evidences of any drug related changes. A preliminary pharmacokinetics profile was obtained. Glucose, insulin, and C-peptide responses to a meal were measured.

Results: No changes were found in the clinical observations, laboratory battery, or ECG telemetry that appeared to be drug related. The serum drug levels showed linear kinetics over the dose range studied and a terminal elimination half life of approximately 5 hours. No effect on fasting or meal stimulated glucose was seen. A trend toward decreased insulin response to a meal was seen, consistent with our *in vitro* findings. This was not conclusive for the therapeutic effect hoped for in diseased subjects.

Conclusions: Pioglitazone hydrochloride was well tolerated in single dose in healthy male volunteers over the dose range 2-60 mg; no drug related adverse medical effects were seen; the formulation used showed linear pharmacokinetics over the dose range tested. The safety demonstrated in this single dose trial allowed us to proceed to evaluation of the drug in repeated dose tolerance testing.

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Clinical phase I study of AD-4833- single and repeated dose studies (CPH-001,002, 003)

Summary (CPH-001/002)

Subjects were administered a single oral dose of 5, 15, 30, 45, or 60 mg of AD4833 (HCl) and repeated oral doses of 30 mg/day (given once a day) or 60 mg/day (given once a day or divided into two doses a day) for 8 days. It was found that absorption was good, unchanged drug and active metabolites were found in the blood, and blood levels (AUC and Cmax) for both unchanged drug and active metabolites rose dose-dependently. With a single dose, blood elimination half-life was about 3-5 h for unchanged drug and about 20 h including active metabolites. Fourteen-to-twenty-two percent of the entire dosage was excreted in the urine. Pharmacokinetics with and without eating and with and without citric acid (an absorption promoter) were compared, revealing almost no differences except that Tmax was longer when AD4833 was given after a meal, compared with fasting. In the repeated dosing study, AD-4833 was not observed to accumulate, and almost no difference was seen between the once-a-day and twice-a-day regimens in the one-day AUC for combined unchanged drug and active metabolites in the blood. As for safety, no particularly worrisome adverse events attributable to AD4833 were seen with either repeated doses of 30 or 60 mg, aside from slight increases in GOT and GPT in some AD4833-treated subjects and the placebo group. The incidence rate of side effects attributable to AD4833 amounted to 0% for both subjective symptoms and abnormal changes in laboratory test values (0/57 subjects, including 12 placebo-treated subjects) in the single-dose study. In the repeated-dosing study, it was 0% for subjective symptoms (0/130 subjects, including 12 placebo-treated) and 60% for abnormal changes in laboratory test results. These results demonstrate that a citric acid absorption promoter is not necessary in the AD-4833 preparation, that once a day is an appropriate dosage regimen, and that the drug can be administered before or after breakfast.

the blood concentrations in this trial were found to be dose-dependent, both as regards the unchanged drug and its active metabolites. With dosing regimens of 60 mg per day for 8 days and 30 mg per day for 8 days, some of the trial participants, including those receiving placebo, were found to have mild elevation of GOT and GPT and changes in their blood lipids. With the exception of minor changes in blood lipids, which were similarly observed here, the above changes were not found in any of the patients in the placebo group or the treatment group in this clinical study. Moreover, there were no observed side effects that were thought to be attributable to administration of the study drug. Based on the results reported here and the results that were previously obtained by administering this study drug in single doses of 5-60 mg and in repeated doses of 30 mg per day (arm 1) and 60 mg per day (arm 2), this drug will be administered once daily in the next trial (early phase II). The time of administration may be either before or after breakfast, and the preparation that is employed will not contain citric acid. As far as the drug's safety is concerned, special attention needs to be paid to any abnormalities that may be observed in liver function tests, in addition to the findings concerning anemia and the effects on the heart that were noted in the high-dose group in the pre-clinical toxicity testing.

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Pioglitazone Hydrochloride Multiple Dose Tolerance in Healthy Adult Male Volunteers (P-5232-002)

ABSTRACT

Purpose: This second human study of pioglitazone hydrochloride was undertaken to determine the clinical and biochemical tolerance of healthy male volunteers to daily doses of pioglitazone hydrochloride for seven days over the range of 2 -60 mg/day or 2 - 20 mg TID. Dose level is expressed as mg of free base.

Methods: Volunteers were informed about the study and the investigational medication, and did provide written consent to participate. Volunteers were observed on an inpatient basis from 36 hours prior to the first dose until the morning after the last dose, and were seen in follow-up one and two weeks post discharge. Detailed ophthalmological examination, a large battery of stand-rd laboratory tests, 24 hour ECG monitoring by telemetry, and 2-D echocardiogram were done prior to dosing and repeated three months post exposure; 3, 5, 8, 15, and 22 days after the first dose (laboratory test battery); day 6 (ECG telemetry); day 7 (2-D echocardiogrAm). On day 7 (last day of dosing) frequent blood samples were collected for drug levels, glucose, insulin, and C.-peptide. **Results:** No changes were found in the laboratory test battery, eye examinations, ECG telemetry or echocardiograms that appeared to be drug related. Clinical complaints of abdominal discomfort and headaches were more frequent in drug treated than placebo treated subjects. Pharmacokinetic data are not yet available and will be reported separately. No conclusive drug effects on fasting or meal stimulated glucose, insulin, or C-peptide levels were found.

Conclusions: Pioglitazone hydrochloride was well tolerated in daily and in TH) dosing for seven days in healthy male volunteers over the dose ranges of 2 - 60 mg/day and 2 - 20 mg TID. The adverse medical events possibly drug related seen in this study were headaches and gastrointestinal distress, none of which required interruption of study medication. The safety and tolerance demonstrated in this seven day repeated dose trial is to permit short term efficacy testing in carefully selected patients with non-insulin-dependent diabetes mellitus.

APPEARS THIS WAY ON ORIGINAL

A Pharmacokinetic and Pharmacodynamic Evaluation of the Effect of Pioglitazone HCl on Variations in Blood Glucose, Triglycerides, and Insulin Levels with Meals in Patients with Non-Insulin-Dependent Diabetes Mellitus (NIDDM) (P5232-0010)

ABSTRACT

After dietary and placebo lead-in phases, 30 NIDDM patients received 15, 30 mg or 60 mg of pioglitazone (as Pioglitazone HCl daily for 14 days according to a parallel study design. Subjects were randomized in blocks of three, by Body Mass Index (BMI) into one of the three dose levels. Serum pioglitazone, M-3 and M-4 concentrations for pharmacokinetic analysis were determined for samples taken following the dose on Day 14. Glucose, insulin and triglyceride concentrations were determined for pharmacodynamic analysis for 12 hours after dosing on the day just prior to the start of active medication and on Day 14.

The Day 14 AUC₀₋₂₄ and C_{max} values of pioglitazone, M-4 and M-3 increased with increased doses of pioglitazone HCl. The relationship between AUC₀₋₂₄ and daily dose was linear. The change of AUC₀₋₂₄ was proportional when going from 15 mg/day to 30 mg/day, however, there appeared to be a less than proportional increase in AUC₀₋₂₄ when going from 30 mg/day to 60 mg/day. There were no differences among treatments in the apparent oral clearance of pioglitazone following the different daily dosing levels of pioglitazone HCl. These data suggest that the observed lack of proportionality between AUC₀₋₂₄ and dose was due to differences in absorption rather than change in elimination.

Fasting glucose decreased significantly after two weeks of treatment at doses of 30 mg and 60 mg of pioglitazone. However, there was no significant decrease in serum fructosamine. Subjects with a greater BMI appeared to have a greater decrease in fasting glucose. There was no significant decrease in fasting serum insulin or triglycerides.

After two weeks of pioglitazone treatment, postprandial glucose did not change significantly, but postprandial insulin levels were almost twofold higher in diabetic subjects with a BMI > 34 kg/m².

APPEARS THIS WAY ON ORIGINAL

AN OPEN LABEL EVALUATION OF THE EFFECT OF IMPAIRED HEPATIC FUNCTION ON THE PHARMACOKINETICS OF PIOGLITAZONE (PNFP-007)

STUDY OBJECTIVE: To assess changes in the pharmacokinetics of pioglitazone in subjects With hepatic impairment.

STUDY DESIGN: This was a 14-day, open label, single-center study.

STUDY POPULATION: A total of 24 males (12 with normal hepatic function and 12 with abnormal hepatic function classified by Pugh's Modification of Child's Classification system as Class B or C with numerical Scores >6 [Appendix 16.1]) were enrolled in the study. All 24 subjects (12 with normal hepatic function and 12 with abnormal hepatic function) completed the study.

STUDY DRUG: Twenty-four (24) subjects received a single dose of 30 mg pioglitazone.

CLINICAL PHASE: Phase I

PK SAMPLING SCHEDULE:

Serum PK samples were collected at the following times: 0 hour predose); 15 and 30 min.: 1, 2, 4, 6, 8, 12, and 16 hours after administration of the dose on Day 1; and on the mornings of Days 2, 3, 4, 7, 10, and 14. Urine samples for PK analysis were collected prior to administration of pioglitazone on Day 1 and at 8 hour intervals on Days 1, 2 and 3.

STUDY VARIABLES:

A. Pharmacokinetic

Model independent pharmacokinetic variables (e.g., C_{max} , T_{max} , AUC, apparent elimination rate constant, $T_{1/2}$, Cl_p/F , and V_{darea}/F) were calculated for pioglitazone and its metabolites, M-III (AD-7932) M-IV (AD-7925, and total (defined as sum of pioglitazone, M-III and M-IV).

Statistical Considerations:

All statistical tests were two-sided, Conclusions were based on 90% confidence intervals. Lack of a statistically significant effect of hepatic impairment was assumed if the 90% confidence interval contained 100% or if the ratio of the means for hepatically-impaired/normal was 100%. Only differences of approximately 50% between hepatically-impaired and normal groups were considered pharmacokinetically or clinically meaningful.

PHARMACOKINETIC RESULTS:

Concentrations of pioglitazone and the two metabolites in serum and urine were determined by a validated high-performance liquid chromatography method with UV absorbance detection. The lower limit of quantitation for pioglitazone, M-III, and M-IV was 25.0 ng/mL in serum and 250 ng/mL in urine. Urine data were generally below the limit of quantitation. Very low amounts of M-IV (approximately 1%, on the average, of the administered dose) were recovered in urine of 9 normal subjects and 6 hepatically-impaired subjects. The mean (standard deviation, SD) pharmacokinetic parameters of pioglitazone, the two metabolites and the total (combined levels of pioglitazone, M-III, and M-IV) in serum and the 90% confidence intervals for the ratio of test (hepatically-impaired)/reference (normal) are summarized below.

Test PK Parameter	Pioglitazone		90% Test/Reference ^b Mean Interval	confidence
	Reference Mean ^a (Hepatically-Impaired)	Mean ^a (Normal)		

C _{max} (ng/mL)	508 (± 137.3)	888 (±374.6)	57.2	(43.0, 106) ^c
T _{max} (hour)	4.00 ^a (4.00-8.02) ^d	4.00 ^a (2.00-4.02) ^d	133	(111, 156) ^e
AUC _{0-t} (ng.,hr/mL)	6601 (±2444..2)	6597 (±3452.9)	100	(69.8, 241) ^c
AUC _{0-∞}	7333	7659	95.7	(75.8, 125) ^c
K _e (hours ⁻¹)	0.0867 (±0.02669)	0.1491 (±0.05928)	58.2	(36.4, 79.9) ^f
T _{1/2} (hour)	8.77 (±2.815)	5.71 (±3.250)	154	(115, 192) ^f
V _{darea} /F (L/kg)	0.615 (±0.2234)	0.397 (±.2472)	155	(111, 198) ^f
Cl _p /F (L/hr/kg)	0.052 (±0.0227)	0.048 (±0.0144)	109	(78.9, 138) ^f

M-III

Parameter	(Hepatically-Impaired)	(Normal)	Mean	Interval
C _{max} (ng/mL)	55.9 (±20.72)	156 (±25,8)	35.8	(28,1,42.0) ^c
T _{max} (hour)	24,00d (16.00-49.08) ^d	12.0d (8.02-16,00) ^d	184	(147, 221) ^e
AUC _{0-t} (ng, hr/mL)	1847 (±1269.8)	5678 (±1841.8)	32.5	(16.1, 42.4) ^c
AUC _{0-∞} (ng, hr/mL)	NR	7561 (±1634.2)	-	-
K _e (hours ⁻¹)	NR	0.0290 (±0.00726)	-	-
T _{1/2} (hour)	NR (±6..79)	25.4	-	-

M-IV

PK Parameter	Mean (Hepatically Impaired)	Test Mean ^a (Normal)	Reference Test/Reference ^b Mean	90% confidence Interval
C _{max} (ng/mL)	365 (±106.7)	377 (±133.7)	96.9	(72.6, 156) ^c
T _{max} (hour)	24.004 (11.98-24.03) ⁴	12.004 (8.00-24.00) ^d	171	(147, 195) ^c
AUC _{0-t} (ng*hr/mL)	18967 (±7781.5)	15911 (±11058.9)	119	(83.8, 292) ^c
AUC _{0-∞} (ng*hr/mL)	27909 (5-6758.7)	23838 (+10417.8)	117	(93.0, 162) ^c
K _e (hours ⁻¹)	0.0201 (±0,00394)	0.0234 (±0.00641)	85.8	(65.8, 106) ^f
T _{1/2} (hour)	35.9 (±8.28)	32.5 (±12.16)	111	(82.3, 139) ^f

Total

PK Parameter	Test Mean ^a (Hepatically Impaired)	Reference Mean ^a (Normal)	Test/Reference ^b Mean	90% confidence Interval
C _{max} (ng/mL)	641 (± 168.2)	1139 (±454.7)	56.3	(40.8, 111) ^c

Tmax	8.00d	4.00d	200	(159, 242)e
(hour)	(4.00-12.05) ^d	(2.00-8.02) ^d		
AUC _{0-t}	26260	29615	88.7	(57.8, 216) ^c
(ng-hr/mL)	(±9680.7)	(±14905.2)		
AUC _{0-∞}	35965	33357	108	(88.8, 137) ^c
(ng-hr/mL)	(±7930.7)	(±11135.1)		
Ke	0.0237	0.0411	57.6	(32.4, 82.8) ^f
(hours ⁻¹)	(±0.00578)	(±0.01692)		
T _{1/2}	31.1	19.7	158	(123, 192) ^f
(hour)	(±8.50)	(±8.69)		

a Arithmetic mean and +-SD.

b Ratio of untransformed parameter means expressed as a percentage.

c 90% confidence interval for the natural log (ln) transformed parameters.

d T_m is expressed as median with the range in parentheses.

e 90% confidence interval for T_{max} calculated using means and standard errors from ANOVA.

f 90% confidence interval for the untransformed parameter.

AUC_{0-t} Area under the serum concentration time curve from Hour 0 to the last measurable serum concentration.

AUC_∞ Area under the serum concentration time curve to infinity.

K_e Terminal phase elimination/disposition rate constant.

Maximum serum concentration.

CI-f:

Oral clearance.

T_m Terminal phase elimination/disposition half-life.

V_{d,∞}/F Apparent volume of distribution.

T_{max} Time to maximum serum concentration

SUMMARY AND CONCLUSIONS:

During this clinical study, based on physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations (including serum chemistries, hematology, and urinalysis), there were no clinically significant findings that could be directly attributed to the drug.

Administration pioglitazone was well-tolerated.

Following oral administration, the mean C_{max} value in hepatically-impaired subjects was approximately one-half the mean value in the normal group, while the median T_{max} value was prolonged in the hepatic group. In contrast, mean AUC results for pioglitazone were similar in the two groups. The mean elimination/disposition rate constant for pioglitazone was approximately 42% slower and V_d/F 55% higher in those with hepatic impairment than in the control group. Of the two active metabolites, M-III and M-IV, differing effects of hepatic disease were observed. M-III, a minor metabolite, had approximately one-third decrease in mean C_{max}, and AUC in hepatically-impaired subjects compared to that found in healthy subjects. The major metabolite, M-IV, had no change in C_{max} while mean AUC was approximately 20% greater in the hepatically-impaired subjects than in the controls. An examination of the composite serum profile of the parent and metabolites or "total" pioglitazone, resulted in a 50% reduction in the mean peak concentration but no change in the mean AUC values in the hepatically-impaired subjects compared to controls.

Due to the complexity of the underlying hepatic disease, there are a number of mechanisms which could account for these findings, including changes in the protein binding, a decreased intrinsic clearance, and a decrease in the rate of absorption of pioglitazone from the gastrointestinal tract. Although it is unclear as to the exact mechanism for these pharmacokinetic and/or metabolic changes, in clinical use pioglitazone will be administered chronically and doses will be selected for individual patients based on therapeutic effect. Overall, the observed changes are not considered clinically relevant and no specific adjustment for patients with hepatic dysfunction need to be included in the labeling.

APPEARS THIS WAY ON ORIGINAL

Investigation of the pharmacokinetics of pioglitazone (AD-4833) and its main metabolites M-III and M-IV in subjects with impaired renal function

Objectives: To investigate the pharmacokinetics (AUC, C_{max}, T_{max} of pioglitazone and main metabolites in serum, M-III and M-IV, after a single and 10 repeated once daily oral doses of 45 mg pioglitazone in subjects with impaired renal function as compared with subjects with normal renal function.

Methodology: The trial was conducted in an open-label fashion with 3 independent groups of subjects (Group 1: subjects with moderate renal impairment; Group 2: subjects with severe renal impairment; Group 3: subjects with normal kidney function). It was planned to investigate the pharmacokinetics of 45 mg pioglitazone in all three groups of subjects. Group 1 patients were investigated first in order to determine the safe dose (30 or 45 mg) for use in group 2 (severe renal impairment) and 3 (control group).

Number of patients (planned and analyzed): Twenty-eight subjects were planned to be included into the trial. Twenty-seven subjects were included and analyzed.

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS: Serum AUCs of pioglitazone and its metabolites M-III and M-IV after single and repeated oral doses of 45 mg pioglitazone were not significantly different in subjects with moderate renal impairment and subjects with normal renal function. Subjects with severe renal impairment had significantly lower AUCs of pioglitazone and M-III and M-IV after single and repeated doses of pioglitazone than healthy subjects (AUC reduction of M-IV after a single dose without statistical significance). After single dose of pioglitazone, C_w values were not significantly different between groups, but after repeated doses C_w values for pioglitazone and M-III were *statistically* significantly lower in subjects with severe renal impairment compared to healthy subjects. There was no effect of renal impairment on t_{1/2} for pioglitazone, M-III or M-IV after single and repeated doses of pioglitazone. There was also no effect of renal impairment on t_u for pioglitazone and M-III or M-IV after single dose of pioglitazone, but there was a reduction of approximately 50% for pioglitazone, M-III and M-IV after repeated doses of pioglitazone on urinary excretion of metabolites M-IV, M-V and M-VI. Mean urinary excretion of determined metabolites after single and repeated once daily doses of 45 mg pioglitazone was in line with the different levels of total pioglitazone in serum of the different patient populations.

CONCLUSION: The administration of 45 mg pioglitazone in subjects with moderate and severe renal impairment did not show any effects to suggest that dose adjustment in subjects with renal failure is necessary.

APPEARS THIS WAY ON ORIGINAL

AN OPEN LABEL EVALUATION OF THE EFFECT OF AGE
ON THE PHARMACOKINETICS OF PIOGLITAZONE (PNFP-025)

STUDY OBJECTIVE: To evaluate the safety and the effect of age on the pharmacokinetics of pioglitazone.

STUDY DESIGN: This was a 7-day, open label, single-center study.

STUDY POPULATION: A total of 23 subjects, 16 males (8 non-elderly and 8 elderly) and 7 females (4 non-elderly and 3 elderly), were enrolled in the study. All 23 subjects (12 non-elderly and 11 elderly) completed the study.

STUDY DRUG: Twenty-three (23) subjects received a single dose of 30 mg pioglitazone.

CLINICAL PHASE: Phase I

PK SAMPLING SCHEDULE: Serum PK samples were collected at the following times: 0 hour (predose); 15 and 30 min.; 1, 2, 4, 6, 8, 12, and 16 hours after the administration of dosing on Day 1; and on the mornings of Days 2, 3, 4, and 7.

STUDY VARIABLES:

A. Pharmacokinetic: Model independent pharmacokinetic variables (e.g., C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, K_e , Cl_v/F , and V_d area/F) were calculated for pioglitazone (AD-4833), its metabolites M-III (AD-7932) and M-IV (AD-7925), and total (defined as sum of pioglitazone, M-III, and M-IV).

STATISTICAL METHODOLOGY:

General: Data listings were provided for pharmacokinetics and safety data. Summary statistics were provided, if applicable. Data analysis was to be performed using SAS for UNIX, version 6.12. The study population consisted of 23 subjects, 16 males (8 non-elderly and 8 elderly) and 7 females (4 non-elderly and 3 elderly). All available clinical data from the 23 subjects were analyzed.

Pharmacokinetic: The pharmacokinetic variables were analyzed from serum samples. Two-way ANOVA statistical models with age and gender effects were used to calculate confidence intervals for the comparison of the elderly subjects versus non-elderly subjects.

PHARMACOKINETIC RESULTS:

Concentrations in serum of pioglitazone and the two metabolites, M-III (AD-7932) and M-IV (AD-7925), were determined by a validated high-performance liquid chromatography method with UV absorbance detection. The lower limit of quantitation was 25.0 ng/mL for pioglitazone, M-III, and M-IV. Serum levels for each subject at each time point were added for the three compounds to calculate the total (combined levels of pioglitazone, M-III, and M-IV). The mean ($\pm$ standard deviation, SD) pharmacokinetic parameters of pioglitazone, the two metabolites and the total and the 90% confidence intervals for the ratio of test (elderly)/reference (non-elderly) are summarized below.

PIOGLITAZONE

PK Parameter	Test Mean ^a (Elderly)	Reference Mean ^a (Non-Elderly)	Test/Reference ^b	90% Confidence Interval
C _{max} (ng/mL)	959 (±224.3)	956 (±333.7)	102	(84.9, 133.5) ^c
T _{max} (hour)	4.00 ^a (2.00-4.00) ^a	2.00 ^a (1.00,4.00) ^a	133	(111.9,153.2) ^c
AUC _{0-t} (ng*hr/mL)	8561 (±2195.7)	7216 (±2044.3)	120	(105.3, 142.4) ^c
AUC ₀₋₁₆ (ng-hr/mL)	6864 (±1561.1)	6557 (±1863.8)	106	(91.9,128.5) ^c
AUC _{0-∞} (ng.hr/mL)	9634 (±2780.0)	7955 (±2246.2)	122	(106.4, 144.7) ^c
K _e (hour ⁻¹)	0.0955 (±0.05394)	0.1110 (±0.03755)	82.5	(51.9, 113.1) ^f
T _{1/2} (hour)	10.1 (±6.36)	6.89 (±2.197)	145	(102.8, 188.0) ^f
V _d /F (L/kg)	0.581 (±0.3377)	0.511 (±0.1968)	115	(76.1,153.0) ^f
CL _p /F (L/hr/kg)	0.043 (±0.0125)	0.051 (±0.0118)	82.3	(65.6, 99.1) ^f

M-III

PK Parameter	Test Mean ^a (Elderly)	Reference Mean ^a (Non-Elderly)	Test/Reference ^b	90% Confidence Interval
C _{max} (ng/mL)	117 (±42.6)	126 (±38.7)	95.5	(75.9, 117.2) ^c
T _{max} (hour)	16.0 ^a (8.00-24.0) ^a	10.0 ^a (8.00,24.0) ^a	136	(100.6, 170.7) ^c
AUC _{0-t} (ng.hr/mL)	4985 (±2236.4)	4330 (±2091.0)	117	(88.2,174.8) ^c
AUC ₀₋₂₄ (ng.hr/mL)	2113 (±847.5)	2240 (±710.7)	96.6	(74.1,121.5) ^c
AUC _{0-∞} (ng*hr/mL)	7432 (±9215.4)	7176 (±2022.5)	103	(78.4, 136.1) ^c
K _e (hour ⁻¹)	0.0213 (±0.00493)	0.0276 (±0.00468)	77.7	(61.7, 93.6) ^f
T _{1/2} (hour)	34.4 (±9.58)	25.8 (±5.11)	134	(103.0, 165.7) ^c

M-IV

PK Parameter	Test Mean ^a (Elderly)	Reference Mean ^a (Non-Elderly)	Test/Reference ^b	90% Confidence Interval

C _{max} (ng/mL)	439 (±79.5)	421 (±102.8)	105	(90.3, 127.5) ^e
T _{max} (hour)	12.0 ^d (12.0-24.0) ^d	16.0 ^d (8.00-24.0) ^a	105	(80.8, 128.5) ^c
AUC _{0-t} (ng.hr/mL)	20415 (±4191.5)	16940 (±3473.6)	121	(107.1, 140.1) ^f
AUC ₀₋₇₂ (ng.hr/mL)	19762 (±3284.7)	16940 (±3473.6)	117	(104.4, 135.7) ^c
AUC _{0-∞} (ng*hr/mL)	24648 (±4820.7)	19478 ^e (±4067.4)	127	(111.4, 148.3) ^c
K _e (hour ⁻¹)	0.0263 (±0.00511)	0.0312 (±0.00429)	84.7	(73.3, 92.6) ^f
T _{1/2} (hour)	27.2 (±5.28)	22.7 (±3.69)	120	(104.6, 135.3) ^f

TOTAL

PK Parameter	Test Mean ^a (Elderly)	Reference Mean ^a (Non-Elderly)	Test/Reference ^b	90% Confidence Interval
C _{max} (ng/mL)	1264 (±294.6)	1247 (±410.1)	103	(86.2, 132.7) ^c
T _{max} (hour)	4.00 ^d (4.00-4.00) ^d	4.00 ^d (4.00-4.00) ^d	100	
AUC _{0-t} (ng.hr/mL)	35134 (±7620.6)	29609 (±6899.3)	120	(107.0, 138.3) ^c
AUC ₀₋₇₂ (ng.hr/mL)	34357 (±6760.4)	29609 (±6899.3)	117	(104.8, 135.7) ^c
AUC _{0-∞} (ng*hr/mL)	39600 (±8660.6)	32313 (±7998.5)	123	(108.5, 145.7) ^c
K _e (hour ⁻¹)	0.0301 (±0.00509)	0.0368 (±0.00681)	82.1	(69.6, 94.7) ^c
T _{1/2} (hour)	23.6 (±3.68)	19.6 (±4.82)	120	(102.9, 136.9) ^c

a Arithmetic mean ± SD.

b Ratio of untransformed parameter means expressed as a percentage.

c 90% confidence interval for the natural log (ln) transformed parameters, gender adjusted analysis.

d T_{max} is expressed as a median with the range in parentheses.

e 90% confidence interval for T_{max} calculated using means and standard error from the ANOVA.

f 90% confidence interval for the untransformed parameter, gender adjusted analysis.

AUC_{0-t} Area under the serum concentration time curve from Hour 0 to the last measurable serum concentration.

AUC_{0-∞} Area under the serum concentration time curve to infinity.

C_{max} Maximum serum concentration.

Cl_p/F Oral clearance.

K_e Terminal phase elimination/disposition rate constant.

T_{1/2} Terminal phase elimination/disposition half-life.

T_{max} Time to maximum serum concentration.

V_d arca/F Apparent volume of distribution.

SUMMARY AND CONCLUSIONS:

Administration of pioglitazone was well-tolerated. During this clinical Study, based on physical examinations, vital signs, clinical laboratory evaluations (including blood chemistries, hematology, and routine urinalysis), and adverse events, there were no clinically significant findings that were directly attributed to the drug.

Following oral administration, the mean C_{max} value in the elderly was similar to the mean value in the non-elderly control group, while the median T_{max} value was slightly prolonged in the elderly. In contrast, mean AUC result for pioglitazone was about 20% higher in the elderly, probably due to a decrease in oral clearance (18%) observed in the elderly. The mean elimination/disposition rate constant for pioglitazone was approximately 45% slower and V_d/F 15% higher in the elderly than in the control group. Of the two active metabolites, M-III and M-IV, differing effects of age were observed. M-III, a minor metabolite, had nearly superimposable serum concentration-time profiles between the two groups, with only a 22% slower elimination/disposition rate constant. The major metabolite, M-IV, had no change in mean C_{max} while mean AUC was approximately 25% greater in the elderly group. There was a 15% slower elimination/disposition rate constant for M-IV observed in the elderly. An examination of the composite serum profile of the parent and metabolites or "total" pioglitazone resulted in no change in the mean peak concentration and a 20% increase in the mean AUC values in the elderly subjects compared to the non-elderly controls. There were significant gender differences in the absorption and disposition of pioglitazone and its metabolites. Females had 20-60% higher mean C_{max} and AUC values for pioglitazone and metabolites compared to controls, while the mean elimination/disposition rate constant and oral clearance values were 25-40% lower.

Although it is unclear as to the exact mechanism for the observed pharmacokinetic and/or metabolic changes due to age and gender, in clinical use pioglitazone will be administered chronically and doses will be selected for individual patients based on therapeutic effect. Overall, the small changes in the pharmacokinetics of pioglitazone are not considered clinically relevant and a specific adjustment for age does not need to be included in the labeling.

APPEARS THIS WAY ON ORIGINAL

Evaluation of the Interaction Between Pioglitazone and Glipizide

Objectives: To evaluate the pharmacokinetic interaction between pioglitazone and glipizide at steady state and to evaluate the safety of pioglitazone when administered concomitantly with glipizide.

Design: Double-blind, placebo-controlled, two-treatment, two-period, multi-dose crossover design.

Methodology: Blood samples used to determine concentration results were obtained immediately prior to and at scheduled intervals following the oral delivery of pioglitazone and glipizide. Glipizide concentrations were determined for assessment of a drug-drug interaction between pioglitazone and glipizide.

Number of Subjects (planned and analyzed): Sixteen (16) subjects were enrolled in the study. A total of 14 subjects completed the study. Sixteen (16) subjects were included in safety analyses and 14 in pharmacokinetic analyses.

Pharmacokinetics: The effect of pioglitazone on the pharmacokinetics of glipizide was assessed by determining serial plasma concentrations of glipizide following the administration of placebo and glipizide (Treatment A) and following the administration of pioglitazone and glipizide (Treatment B).

Statistical Methods: Pharmacokinetics: The pharmacokinetics of glipizide were assessed by measuring serial plasma concentrations after oral administration. Comparisons were made between the two oral treatments (Treatment A = 5 mg glipizide + placebo; Treatment B = 5 mg glipizide + 45 mg pioglitazone) in order to evaluate the influence of pioglitazone on the pharmacokinetics of glipizide. Bioequivalence was concluded if the 90 % confidence intervals of the ratio of the treatment means for LN(C_{max}), LN[AUC(0-t)], and LN[AUC(0-24)] were within the range of 80 % to 125 %. The parameter values of K_{el}, T_{1/2el}, and T_{max} were also compared between treatments.

CONCLUSIONS

The results of the pharmacokinetic and statistical analyses are summarized in the following tables. The pharmacokinetic and statistical analyses of the data indicated that the administration of 5 mg glipizide + 45 mg pioglitazone (Treatment B) was equivalent to the administration of 5 mg glipizide + placebo (Treatment A). The 90 % confidence intervals of the ratios of the product means for LN(C_{max}), LN[AUC(0-t)] and LN[AUC(0-24)] were all within the range of 80 % to 125 % for the comparison of Treatment B to Treatment A.

Day 7 Plasma Glipizide Pharmacokinetic Parameters		
Pharmacokinetic Parameters	Treatment A Arithmetic Mean (SD)	Treatment B Arithmetic Mean (SD)
C _{max} (n~/mL)	367 (68.4)	332 (42.0)
AUC(0-t) (ng*hr/mL)	1834 (692)	1784 (691)
AUC(0-24) (ng*hr/mL)	1884 (685)	1833 (684)

Tmax (hr)	2.3 (1.2)	2.7 (1.2)
Kel (1/hr)	0.214 (0.0524)	0.214 (0.0516)
T1/2el (hr)	3.51 (1.33)	3.39 (1.31)
Cl/F (L/hr)	2.85 (0.624)	2.94 (0.679)
Vd/F (L)	13.5 (1.60)	13.4 (1.55)

Statistical Comparisons of Day 7 Plasma Glipizide Pharmacokinetic Parameters

Pharmacokinetic Parameter	Treatment B versus A Ratio	90% Confidence Interval
LN(Cmax) ng/mL	91.5%	80.7 - 103.7
LN[AUC(0-t)] (ng*hr/mL)	97.3%	94.5-100.3
LN[AUC(0-24)] (ng*hr/mL)	97.3%	94.4 - 100.2

CONCLUSION:

The coadministration of pioglitazone did not alter the disposition or steady-state pharmacokinetic characteristics of glipizide.

Glipizide in combination with pioglitazone was well tolerated. Adverse events were transient, mild or moderate in severity and equally distributed between both treatment groups. No clinically significant trends in vital signs, physical examinations, or clinical laboratory tests were observed regarding subject safety in respect to the two treatment regimens.

APPEARS THIS WAY ON ORIGINAL

An Open MonoCentre Study to Assess the Influence of Multiple-Dose Pioglitazone (AD-4833), 45 mg o.d., on Steady-State Pharmacodynamics and Pharmacokinetics of Phenprocoumon and Warfarin Enantiomers

Primary Objective: To evaluate the influence of a treatment with pioglitazone, 45 mg once daily at steady-state on the steady-state pharmacodynamics and pharmacokinetics of phenprocoumon and warfarin enantiomers.

Secondary Objective: To evaluate the tolerability and safety of pioglitazone 45 mg in co-administration with phenprocoumon or warfarin.

Methodology: Open label, mono-centre study. Either phenprocoumon or warfarin was dosed for a total of 17 days aiming at steady-state concentrations, defined by its effects on prothrombin time on day 8 at the latest. Doses of phenprocoumon or warfarin were adjusted to reach and maintain a Quick's value of 35 ± 5 %. Pioglitazone was co-administered at steady-state anticoagulant treatment with a dose of 45 mg once daily for 7 days.

Number of Subjects: In total, 24 subjects planned and analyzed of whom 12 subjects each for phenprocoumon and warfarin, respectively.

Duration of Treatment: 7 days continuous treatment with pioglitazone, at least 24 days either phenprocoumon or warfarin (up to 28 days for 2 subjects).

Criteria for Evaluation: Pharmacodynamics: Prothrombin time (PT, Quick's value) and its corresponding international normalized ratio (INR).

Pharmacokinetics: AUC_{0-h}, C_{max} (primary parameters derived from plasma concentrations of phenprocoumon and warfarin following multiple-dose phenprocoumon and warfarin treatment).

CONCLUSIONS

PHARMACODYNAMIC RESULTS:

There was no indication that pioglitazone 45 mg o.d. may change the pharmacodynamic effects of phenprocoumon or warfarin. Estimates for PT and INR ratios test/reference, i.e. with/without pioglitazone treatment, and their 90 %-confidence intervals were within the predefined range of equivalence [0.7, 1.43] during both phenprocoumon and warfarin steady state.

PHARMACOKINETIC RESULTS:

There was also no evidence for a relevant change in the pharmacokinetics of both enantiomers of phenprocoumon and warfarin, respectively. Estimates and their 90 %-confidence intervals were within the predefined range of equivalence [0.8, 1.25] for ratios with/without pioglitazone treatment when AUC_{0-24h} of both enantiomers of phenprocoumon and warfarin are considered.

Co-administration of pioglitazone with either phenprocoumon or warfarin did not change the primary pharmacodynamic or pharmacokinetic parameters of both phenprocoumon and warfarin.

Investigation of the effects of a single and repeated once daily doses of 45 mg pioglitazone (AD-4833) on the pharmacokinetics of digoxin at steady state serum concentrations. A randomized double blind two period cross-over trial

Primary objectives: To investigate the effect of a single and repeated doses of 45 mg pioglitazone once daily on the pharmacokinetics of digoxin (0.25 mg o.d. maintenance dose) at steady state serum concentration.

Methodology: The trial was a randomized double-blind (with respect to pioglitazone and placebo), two period cross-over trial with a wash-out period of 14 days between the two periods, Healthy male Caucasian subjects, range of age 20-40 years, body mass index (BMI) of ≥ 18 kg/m² and ≤ 25 kg/m², written informed consent of the subject.

Number of subjects (planned and analyzed): 12 planned, 14 enrolled and randomized, 2 subjects discontinued due to personal reasons and 12 subjects completed the trial and were analyzed.

Duration of treatment: Digoxin: 0.25 mg b.i.d. on days 1 - 3, 0.25 mg o.d. on days 4 - 37
Pioglitazone: 45 mg o.d. (or placebo) on days 10 - 16 (period 1)
or on days 31 - 37 (period 2).

CONCLUSIONS

The 90% confidence intervals were within the predetermined range for digoxin AUC₀₋₂₄ at single dose pioglitazone coadministration [92.14 - 112.94] and for digoxin C_{max} for both, single dose and repeated doses pioglitazone coadministration [84.94 - 134.03 and 101.43 - 133.98, respectively], Due to slight decrease of the digoxin AUC_{0-24h} in the placebo group (12.18 pg·h/l to 11.24 pg·h/l), the 90% confidence interval for AUC_{0-24h} after repeated doses of pioglitazone was slightly but clinically not relevantly above the predefined accepted range [103.94 - 127.17].

There is no clinically relevant interaction between single dose and repeated doses of 45 mg AD-4833 and repeated doses of 0.25 mg digoxin. The combination was safe and well tolerated in healthy subjects.

APPEARS THIS WAY ON ORIGINAL

Evaluation of the influence of pioglitazone (AD-4833)-HCl 45 mg o.a.d, administration under steady state concentrations on the pharmacokinetic characteristics of a single oral dose of 1000 mg metformin-HCl in plasma and urine in a double-blind, placebo-controlled, cross-over study in healthy male subjects

Objectivns: Investigation on the influence of pioglitazone under steady state conditions after 8 days of treatment with 45 mg qd on the pharmacokinetic characteristics of single oral dose of metformin (1000 mg) in plasma and urine.

Determination of the pharmacokinetic characteristics of pioglitazone and its two main active metabolites (M-HI, M-IV) in serum under steady state conditions and under coadministration of a single dose of metformin 1000 mg. To assess the safety of monotherapy with pioglitazone 45 mg o.d. and the concomitant administration of 1000 mg metformin by laboratory examinations, vital signs, subjective findings/adverse events.

Methodology: A two-way cross-over study with repeated measurements of pharmacokinetic and safety parameters during two consecutive treatment periods. The study procedure was double-blind for pioglitazone/placebo and open (not blinded) for metformin treatment. There was no wash-out phase. Number of subjects.

Test product, dose and mode of administration: Pioglitazone, 3 tablets of 15 mg, oral administration on study days 1-8 (period 1) or 9-16 (period 2) o.a.d. Oral administration (o.a.d.) of pioglitazone or placebo on study days 1-8 (period 1) or 9-16 (period 2) placebo, oral administration of three tablets on study days 1-8.

Statistical Methods:

Pharmacokinetics Listings of individual data (concentration-time data and pharmacokinetic characteristics of metformin and pioglitazone and its main metabolites) and descriptive statistics (arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, dispersion factor and coefficient of variation for the concentrations; and arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, dispersion factor, lower and upper confidence limits for the pharmacokinetic characteristics). Lack of interaction could be considered as an equivalence problem. Therefore, lack of interaction could be concluded if the 90% confidence interval calculated from the error-term of the three-factorial ANOVA after log-transformation for the ratio metformin with and without coadministration of pioglitazone was within the ranges of 0.8-1.25 for AUC and 0.70-1.43 for C_{max}.

Criteria for Evaluation:

Primary Parameters: AUC₀₋₂₄, C_{max} for metformin in plasma and AUC₀₋₂₄, C_{max} for metformin in urine on study days 8 and 16 with and without pioglitazone coadministration

CONCLUSIONS

There were no relevant differences in the single dose pharmacokinetic characteristics of metformin between pioglitazone under steady state conditions and placebo. All statistically tested parameters met the predetermined bioequivalence criteria. No relevant differences in the metformin amounts excreted in urine were found between the groups. These findings supported the results of metformin from plasma pharmacokinetics. The steady state pharmacokinetics of

pioglitazone were comparable to those reported in the literature.

APPEARS THIS WAY ON ORIGINAL

AN OPEN LABEL PHARMACOKINETIC FOOD INTERACTION STUDY OF PIOGLITAZONE
UTILIZING A 45 mg TABLET IN HEALTHY VOLUNTEERS (PNFP-036)

STUDY OBJECTIVE: To evaluate the safety and determine the effect of food on the absorption of a 45 mg tablet of pioglitazone.

STUDY DESIGN: This was an open-label, two-treatment, two-period cross-over design study.

STUDY POPULATION: A total of 23 subjects, 12 males and 11 females were enrolled in the study. Twenty-two subjects (11 males and 11 females) completed the study (Subject No. 10 was discontinued by PI due to a pre-study laboratory abnormality; his Period 1 dose was the only dose taken).

STUDY DRUG: Completed subjects received a single dose of 45 mg pioglitazone in each of two treatment periods in either a fasted or fed state.

CLINICAL PHASE: Phase I

PK SAMPLING SCHEDULE: Serum PK samples were collected at the following times: 0 hour (predose); 1, 2, 3, 4, 5, 6, 8, 12, and 16 hours after the administration of dosing on Day 1; and on the mornings of Days 2, 3, 4, and 7 at the same time of day as the 0 hour samples on Day 1.

SAFETY DATA SAMPLING SCHEDULE: Clinical laboratory tests (including blood chemistry, hematology, and urinalysis) were performed at screening and on Days 0 (i.e., evening prior to dose), 3, and 7. Physical examinations were performed at screening and on Days 0, 4, and 7. Vital signs were recorded at screening and on Days 0, 2, 3, 4, and 7; 12-lead ECGs were performed at screening and on Day 0. Adverse events were recorded throughout the entire study. Subjects with adverse events were followed until the event resolved or the condition stabilized.

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2. SYNOPSIS

(Page 2 of 6)

STUDY VARIABLES:

A. Pharmacokinetic

Model independent pharmacokinetic variables (e.g., $C_{m,-}$, T_{ruax} , $AUC_{0,t}$, $AUC_{0,-}$, terminal phase elimination/disposition rate constant, T_{1a} , Cl_p/F , and V_d-JF) were calculated for pioglitazone (AD-4833), its metabolites M-III (AD-7932) and M-IV (AD-7925), and total (defined as sum of pioglitazone, M-III, and M-IV).

B. Efficacy

No efficacy variables were measured/calculated.

C. Safety

Vital signs, 12-lead ECGs, clinical laboratory tests (hematology, blood chemistry, and routine urinalysis), adverse events, and physical examinations were performed.

STATISTICAL METHODOLOGY:

General:

Data listings were provided for pharmacokinetic and safety data. Summary statistics were provided, if applicable. Data analysis was to be performed using SAS for UNIX, version 6.12. The study population consisted of 23 subjects, 12 males and 11 females. All evaluable pharmacokinetic and clinical data from the 23 subjects were analyzed.

Pharmacokinetic:

The pharmacokinetic variables were analyzed from serum samples. ANOVA statistical models, with gender, sequence, subject within sequence by gender, period, and treatment effects, were used to calculate confidence intervals for the comparison of the test (fed) and reference (fasted) groups and for the comparison of females (test) with respect to males (reference).

Efficacy:

No efficacy analysis was performed.

Safety:

Safety variables were summarized by descriptive statistics where applicable. Adverse events were summarized on the basis of treatment emergent adverse events. Adverse events and serious adverse events were presented by Sponsor-modified WHOART term and body system, by frequency, by relationship, and by maximum intensity.

Statistical Considerations:

All statistical tests were two-sided; 90% confidence intervals for gender were calculated across treatments and the 90% confidence intervals for treatment were calculated across genders. In order to identify changes in pharmacokinetic parameters of pioglitazone that might require a change in dosing, the Sponsor identified a 50% change as being clinically meaningful.

Sample Size Justification:

The sample size chosen for this study was based upon precedent set by other pharmacokinetic studies of a similar nature, not on statistical considerations.

PHARMACOKINETIC RESULTS:

Concentrations in serum of pioglitazone and the two metabolites, M-III (AD-7932) and M-IV (AD-7925), were determined by a validated high-performance liquid chromatography method with UV absorbance detection. The lower limit of quantitation was 25.0 ng/mL for pioglitazone, M-III, and M-IV. Serum levels for each subject at each time point were added for the three compounds to calculate the total (combined levels of pioglitazone, M-III, and M-IV). The mean (+ standard deviation, SD) pharmacokinetic parameters of pioglitazone, the two metabolites and the total and the 90% confidence intervals for the ratio of test (fed)/reference (fasted) are summarized below.

PIOGLITAZONE: SUMMARY OF PK PARAMETERS

PK	Test Mean' 45 mg tablet-fed	Reference Mean" 45 mg tablet-fasted	90% Confidence

Parameter	(Treatment A)	(Treatment B)	Test/Reference ^b	Interval
C _{max} (ng/mL)	1552 (+708.0)	1313 (:1484.9)	118	(100, 130) ^c
T _{m,~} (hou0)	3.00 ^a (2.00-5.00) ^a	2.00 ^d (1.00-4.00) ^a	143	(124, 163) ^e
AUC _{0,t} (ng*hr/mL)	13116 (+5630.5)	13484 (+5034.7)	97.3	(84.9, 107) ^c
AUC _{0,∞} (ng*hr/mL)	14071 (+5727.3)	15100 (4-5544.5)	93.5	(82.0, 103) ^c
K _t (hours ⁻¹)	0.0924 (-0.04757)	0.0654 (:1-.03040)	141	(123, 160) ^f
T _{1/2} (hour)	9.51 (+4.490)	13.8 (+8.47)	69A	(52.0, 86.7) ^f
Vd area/F (L/kg)	0.681 (-0.3189)	0.874 (i-0.4181)	77.6	(63.9, 91.3) ^f
Cl/F (l/hr/kg)	0.0530 (:L-O.O 1953)	0.0478 (i-O.O 1490)	110	(97.5, 122) ^f

- a Arithmetic mean ± SD.
- b Ratio of untransformed parameter means expressed as a percentage.
- c 90% confidence interval for the natural log (ln) transformed parameters.
- d T_{m,x} is expressed as median with the range in parentheses.
- e 90% confidence interval for T_u calculated using means and standard error from the ANOVA.
- f 90% confidence interval for the untransformed parameter.
- AUC_{0,t} Area under the serum concentration time curve from Hour 0 to the last measurable serum concentration.
- AUC_{0,∞} Area under the serum concentration time curve to infinity.
- C_{max} Maximum serum concentration.
- Cl/F Oral clearance.
- Ke Terminal phase elimination/disposition rate constant.
- T_{1/2} Terminal phase elimination/disposition half-life.
- T_{m,x} Time to maximum serum concentration.
- Vd area/F Apparent volume of distribution.

M-III: SUMMARY OF PK PARAMETERS

PK Parameter	Test Mean ^a	Reference Mean ^a	Test/Reference ^b	90% Confidence Interval
	45 mg tablet-fed (Treatment A)	45 mg tablet-fasted (Treatment B)		
C _{mu} (ng/mL)	181 (+39.8)	175 (+49.4)	104	(96.0, 117) ^c
T _{mu} (hour)	20.0 ^d (8.00-24.0) ^d	20.0 ^a (8.00-24.1) ^d	100	(85.5, 115) ^e
AUC _{0,t} (ng*hr/mL)	7976 (5:1901.7)	7760 (±2148.4)	103	(95.4, 116) ^c
AUC _{0,∞} (ng*hr/mL)	10581 (+3041.5)	10404 (+7858.9)	102	(92.5, 111) ^c
I _~ (hours ⁴)	0.0264 (5:0.00717)	0.0239 (+0.00748)	108	(96.6, 119) ^f
T _m (hour)	28.8 (±10.84)	32.1 (+11.34)	92.5	(76.4, 109) ^f

- a Arithmetic mean ± SD.
- b Ratio of untransformed parameter means expressed as a percentage.
- c 90% confidence interval for the natural log (ln) transformed parameters.
- d T_{max} is expressed as median with the range in parentheses.
- e 90% confidence interval for T_{mu} calculated using means and standard error from the ANOVA.
- f 90% confidence interval for the untransformed parameter.
- AUC_{0,t} Area under the serum concentration time curve from Hour 0 to the last measurable serum concentration.
- AUC_{0,∞} Area under the serum concentration time curve to infinity.
- C_{max} Maximum serum concentration.
- Ke Terminal phase elimination/disposition rate constant.
- T_{1/2} Terminal phase elimination/disposition half-life.
- T_{max} Time to maximum serum concentration.

M-IV: SUMMARY OF PK PARAMETERS

PK Parameter	Test Mean ^a 45 mg tablet-fed (Treatment A)	Reference Mean ^a 45 mg tablet-fasted (Treatment B)	Test/Reference ^b	90% Confidence Interval
C _∞ ,u (ng/mL)	614 (-4-192.4)	571 (:1:166.4)	108	(96.7, 119) ^c
T _m (hour)	14.04 (5.00-24.0) ^d	16.04 (8.00-24.0) ^d	85.5	(73.1, 97.9) ^e
AUC _{0-t} (ng*hr/mL)	27130 (±7957.0)	27545 (:1:7973.1)	99.0	(91.3, 107) ^c
AUC _{0-∞} (ng*hr/mL)	32971 (5:9049.4)	33177 (5:8654.1)	99.8	(91.5, 108) ^c
I _∞ (hours ⁴)	0.0270 (t0.00748)	0.0259 (10.00623)	104	(97.0, 111) ^f
T _m (hour)	27.8 (+8.64)	28.2 (:k6.59)	98.6	(88.5, 109) ^f

- a Arithmetic mean ± SD.
- b Ratio of untransformed parameter means expressed as a percentage.
- c 90% confidence interval for the natural log (ln) transformed parameters.
- d T_{∞,x} is expressed as median with the range in parentheses.
- e 90% confidence interval for Tau calculated using means and standard error from the ANOVA.
- f 90% confidence interval for the untransformed parameter.
- AUC_{0-t} Area under the serum concentration time curve from Hour 0 to the last measurable serum concentration.
- AUC_{0-∞} Area under the serum concentration time curve to infinity.
- C_{∞,u} Maximum serum concentration.
- K_e Terminal phase elimination/disposition rate constant.
- T_m Terminal phase elimination/disposition half-life.
- T_{∞,u} Time to maximum serum concentration.

TOTAL: SUMMARY OF PK PARAMETERS

PK Parameter	Test Mean ^a 45 mg tablet-fed (Treatment A)	Reference Mean ^a 45 mg tablet-fasted (Treatment B)	Test/Reference ^b	90% Confidence Interval
C _{∞,x} (ng/mL)	1928 (+846.0)	1625 (+576.9)	118	(101,131) ^c
T _{∞,u} (hour)	4-00 ^d (2.00-5.00) ^e	3-03 ^a (1.00-4.00) ^d	114	(100, 128) ^c
AUC _{0-t} (ng* hr/mL)	49324 (+ 14368.8)	50350 (+ 14108.0)	98.5	(90.5, 107) ^c
AUC _{0-∞} (ng*hr/mL)	56022 (+1 5651.0)	56810 (5:14606.6)	99.0	(90.6, 107) ^c
K _e (hours ⁻¹)	0.0306 (x~0.00705)	0.0298 (+0.00624)	103	(96.2, 109) ^f
T _{∞,u} (hour)	23.8 (-5.74)	24.2 (+4.79)	98.8	(91.1,106) ^f

- a Arithmetic mean ± SD.
- b Ratio of untransformed parameter means expressed as a percentage.
- c 90% confidence interval for the natural log (ln) transformed parameters.
- d T_{∞,u} is expressed as median with the range in parentheses.
- e 90% confidence interval for T_{∞,u} calculated using means and standard error from the ANOVA.
- f 90% confidence interval for the untransformed parameter.
- AUC_{0-t} Area under the serum concentration time curve from Hour 0 to the last measurable serum concentration.
- AUC_{0-∞} Area under the serum concentration time curve to infinity.
- C_{∞,x} Maximum serum concentration.
- K_e Terminal phase elimination/disposition rate constant.
- T_m Terminal phase elimination/disposition half-life.
- T_{∞,u} Time to maximum serum concentration.

SAFETY RESULTS:

During this clinical study, based on physical examinations, vital signs, 12-lead ECGs, and clinical laboratory evaluations (including hematology, blood chemistry, and urinalysis), there were no clinically significant findings that could be directly attributed to study medication. Of the 42 treatment-emergent adverse events (AEs) reported in this study, 40 were mild in severity and 2 were moderate in severity. Of the 42 treatment-emergent AEs reported during this study, the Principal Investigator judged that 30 AEs were not related to test material and the remaining 12 AEs were possibly related to test material.

APPEARS THIS WAY ON ORIGINAL

In Vitro Protein Binding of Pioglitazone: Basic Studies
ABSTRACT

The protein binding of pioglitazone has been studied *in vitro* in normal human serum and human serum albumin. The protein binding was determined by equilibrium dialysis at 37°C. Equilibrium was achieved in thirty minutes, and nonspecific binding to the cell and the membrane was negligible. Protein binding in normal human serum displayed a very small but significant dependence on pioglitazone concentration over the range of 0.034 to 2 ug/ml, and yielded a mean free fraction of $0.78 \pm 0.009\%$. Protein binding to human serum albumin was not dependent on pioglitazone concentration and had a mean free fraction of $2.54 \pm 0.089\%$.

The coefficient of binding for human serum was calculated to be 118.5 ± 1.2 and for human serum albumin 37.95 ± 0.83 .

APPEARS THIS WAY ON ORIGINAL

In Vitro Protein Binding of Pioglitazone : II. Serum protein profile

ABSTRACT

The set-to protein binding profile of pioglitazone was studied by measuring time *relative binding*, *concentration* dependence, and coefficients of binding for three preparations of increasingly pure albumin, three glycoprotein fractions, and two lipoprotein. The three albumin fractions displayed the highest degree of binding to pioglitazone (>97%) and were concentration independent. The glycoproteins exhibited binding from 27-61% and displayed both saturable and nonsaturable binding. Lipoprotein showed binding of about 75% and also displayed both saturable and nonsaturable binding characteristics.

APPEARS THIS WAY ON ORIGINAL

In Vitro Protein Binding of Pioglitazone : III. Competitive Binding

ABSTRACT

The displacement of pioglitazone from human serum albumin by Coumarin, diazepam, U-90760, U-91322, and U-91324 was studied by equilibrium dialysis. All five compounds caused statistically significant displacement of pioglitazone from human serum albumin, but at varying degrees. In the presence of Coumarin at 200 μ M, the coefficient of binding for pioglitazone decreased by 25.4%, and in the presence of 200 μ M diazepam, the coefficient of binding for pioglitazone decreased by about 18.6%. In the presence of U-90760, U-91324, and U-91322 the coefficient of binding for pioglitazone decreased by 3.6%, 3.9%, and 4.8%, respectively. These data and previously generated data suggest that pioglitazone is bound somewhat selectively to site I on human serum albumin at the ethyl-pyridinyl end of the pioglitazone molecule.

APPEARS THIS WAY ON ORIGINAL

Chiral Inversion of AD-4833 in Rat and Human Plasma



Summary

The chiral inversion of AD-4833 in rat and human plasma was investigated *in vitro* and *in vivo*. The *in vitro* chiral inversions between (+)- and (-)-enantiomers of AD-4833 occurred in plasma of rats and humans. At the equilibrium of the conversions, the enantiomer compositions ((+)/(-)) were about 4/6 and 1/1 for rat and human plasma, respectively. The inter-conversions of the enantiomers were also observed after the intravenous and oral administrations of AD-4833 to rats. The chiral inversion was expected to reach equilibrium before the completion of elimination from plasma. There were no obvious differences in the absorption and elimination between enantiomers. Because an *in vitro* chiral inversion was observed in human plasma, an *in vivo* chiral inversion was expected to occur at least in plasma when AD-4833 was administered to humans.

APPEARS THIS WAY ON ORIGINAL

Identification of Human Cytochromes P450 Involved in the Metabolism of AD-4833 and the Effect of AD-4833 on the Activities of Human Cytochromes P450

APPEARS THIS WAY ON ORIGINAL

Summary

In vitro study using microsomes from human B-lymphoblastoid cells expressing human cytochrome P450 (CYP) isoforms was undertaken to investigate the isoforms involved in the metabolism of AD4833 in humans. Microsomes expressing CYP1A1, CYP1A2, CYP2C8, CYP2C9 (Arg and Cys), CYP2C19, CYP2D6 and CYP3A4 were shown to metabolize AD-4833. The other CYP isoforms including CYP2A6, CYP2B6, and CYP2E1 were inactive for the metabolism of AD4833. AD-4833 was metabolized to M-IV, which was a major metabolite in human serum, by CYP1A1-, CYP1A2-, CYP2C8-, CYP2C9 (Arg and Cys)-, CYP2C19-, CYP2D6- and CYP3A4-expressed microsomes, and also to M-II by CYP2C8- and CYP2C9(Cys)-expressed microsomes. These results suggest the contribution of the multiple CYP isoforms to the major metabolic pathway of AD4833 in humans. AD-4833 had no effect on the reactions mediated by microsomes expressing CYP isoforms at higher concentration than the therapeutic concentration. The results of this study indicate the little possibility for clinical drug interactions of AD4833 and co-administered drugs.

APPEARS THIS WAY ON ORIGINAL

Contribution of Cytochrome P450 Isoforms to the Metabolism of Pioglitazone

APPEARS THIS WAY ON ORIGINAL

Summary

The contribution ratios of the major cytochrome P450 (CYP) isoforms to the metabolism of pioglitazone using individual human liver microsomes were determined by a multivariate regression analysis method. After seeking out the major metabolic pathway and the CYP isoforms which were involved in the metabolism of pioglitazone in human hepatic microsomes, multivariate analyses incorporating the activities of the isoforms and the metabolizing rates were carried out.

As a result, CYP2C8 and CYP3A4 were found to be major CYP isoforms, whose contributions to pioglitazone metabolism were sufficient but were comparable with the residual activity caused by the other isoforms. For the elimination of pioglitazone, the contributory ratios of CYP2C8 and CYP3A4 were 39.0 % and 17.0 %, respectively. Thus, the total activities of the other CYP isoforms were also considered to have enough potentials to metabolize pioglitazone while each of them alone did not show any evident involvement. Because an adequate compensatory metabolism could be expected, the effect of concomitant drugs on the metabolism of pioglitazone was considered to be small, even if concomitant drugs occupied or inactivated one of the major CYP isoforms.

APPEARS THIS WAY ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Item 13. Patent Information

**21 CFR 314.50 (h) PATENT INFORMATION
ACTOS (PIOGLITAZONE HCl – AD-4833) TABLETS**

The following two patents were issued for AD-4833. The drug product name for this chemical entity will be ACTOS (pioglitazone HCl) tablets.

21 CFR 314.53 (c)(i); (ii); (iii); (iv)

US Patent Number	Expiration Date	Type of Patent	Patent Owner	US Representative
4,444,779	July, 27, 1999	drug, drug product	Takeda Chemical Industries, Ltd.	Takeda America Research and Development Center, Inc.
4,687,777	January 17, 2006	drug, drug product	Takeda Chemical Industries, Ltd.	Takeda America Research and Development Center, Inc.

Attached are copies of the front and claim pages of US Patent Numbers 4,444,779 and 4,687,777.

14.0 Patent Certification

Reference is made to the subject NDA for Actos™ (pioglitazone hydrochloride) tablets for the management of type 2 diabetes and the requirements of 505(b)(1) of the Federal Food, Drug and Cosmetic Act as amended and 21 CFR 314.50(c)(2).

Declaration under 21 CFR 314.53(c)(2)

The applicant declares that Patent No. US 4,444,779 and Patent No. US 4,687,777 cover the drug pioglitazone hydrochloride, the drug product pioglitazone hydrochloride tablets, 15 mg, 30 mg, and 45 mg and its method of use.

This product is the subject of this application for which approval is sought.

As provided for under the Patent Term Restoration Act, Takeda America Research & Development Center, Inc. will be requesting patent term restoration upon receipt of approval of pioglitazone hydrochloride.

Exclusivity Checklist

NDA: <u>21-073</u>
Trade Name: <u>ACTOS</u>
Generic Name: <u>PIOGGLITAZONE HYDROCHLORIDE</u>
Applicant Name: <u>Takeda</u>
Division: <u>IND-SID (DMEDP)</u>
Project Manager: <u>JENA WEBER (76422)</u>
Approval Date: <u>JULY, 1999</u>

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a. Is it an original NDA? <u>1P</u>	☒ Yes	☐ No
b. Is it an effectiveness supplement?	☐ Yes	☒ No
c. If yes, what type? (SE1, SE2, etc.)		

Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	☒ Yes	☐ No

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Explanation:

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Explanation:

d. Did the applicant request exclusivity?	☐ Yes	☒ No

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	☐ Yes	☒ No

If yes, NDA #

Drug Name:

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade?	☐ Yes	☒ No

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE

SIGNATURE BLOCKS (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.	☒ Yes		☐ No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		☒ No	

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product	
NDA #	
Drug Product	
NDA #	
Drug Product	
NDA #	

2. Combination product.	☐ Yes	☒ No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes	No	

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product	
NDA #	
Drug Product	
NDA #	
Drug Product	
NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of

new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes		No	

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes		No	

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	

1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	

If yes, explain:

2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	

If yes, explain:

c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:	
Investigation #2, Study #:	
Investigation #3, Study #:	

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	Yes		No	
Investigation #2	Yes		No	
Investigation #3	Yes		No	

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

Investigation #1 -- NDA Number	
Investigation #2 -- NDA Number	
Investigation #3 -- NDA Number	

If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1	
Investigation #2	
Investigation #3	

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial

support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Yes		No	
IND#:				

Explain:

Investigation #2	Yes		No	
IND#:				

Explain:

Investigation #3	Yes		No	
IND#:				

Explain:

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				

Explain:

Investigation #2	Yes		No	
IND#:				

Explain:

Investigation #3	Yes		No	
IND#:				

Explain:

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

Yes		No	

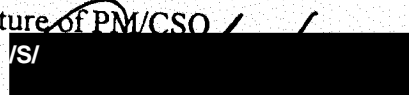
If yes, explain:

exclusivity checklist Section 3 G

Page 6 of 6

Signature of PM/CSO

Date: /S/


6/22/99

Signature of Division Director

Date: /S/


6/30/99

cc:

Original NDA

Division File

HFD-93 Mary Ann Holovac



BACK TO TOP

APPEARS THIS WAY ON ORIGINAL

Edit Pediatric Information for this Submission

User Information

Preparer	JENA WEBER
Title	PROJECT MANAGER/CONSUMER SAFETY OFFICER
Division	HFD-510

Application Information

Application Number	21073
Application Clock Date	Jan 15, 1999
Application Type	N
Applicant Sponsor	TAKEDA AMERICA
Drug Trade Name	ACTOS (PIOGLITAZO TABS
Drug Generic Name	PIOGLITAZONE HCL
<i>(leave supplement number, date and type blank, if original a)</i>	
Supplement Number	0
Regulatory Action	PN Pending
Proposed Indication	Developed to improve the glycem Type 2 diabetes.
Has Proposed Indication been Approved?	☐ Check if YES
Adequacy of Proposed label for Pediatric Dosing	
Is there a Pediatric Phase 4 Commitment in the Action Letter for the Original Submission?	☒ Check if YES
Comments & Recommendations (please date)	□□□□
Is there <u>Pediatric Content</u>?	☐ Yes ☒ No
Save && Continue Clear	

APPEARS THIS WAY ON ORIGINAL

Takeda America Research and Development Center, Inc.
Princeton, NJ

NDA 21-073
Actos™
(Pioglitazone HCl) Tablets

16.0 Debarment Certification

A Debarment Certification as specified by the Generic Drug Enforcement Act of 1992 is provided.

APPEARS THIS WAY ON ORIGINAL

Takeda America Research and Development Center, Inc.
Princeton, NJ

BEST POSSIBLE COPY

NDA 21-073
Actos™
(Pioglitazone HCl) Tablets

Certification of Compliance with the Generic Drug Enforcement Act

In compliance with the Generic Drug enforcement Act of 1992, Takeda America Research and Development Center, Inc. certifies that we did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)] in connection with this application.

M. Obayashi

Mikihiko Obayashi, Ph.D.
President,

Takeda America Research and Development Center, Inc.

Dec. 31, 1998

Date

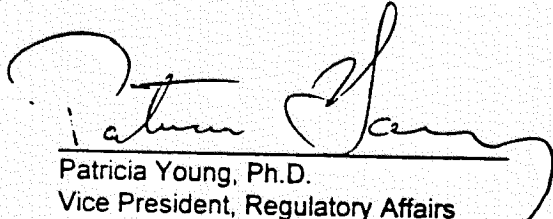
APPEARS THIS WAY ON ORIGINAL

Takeda America Research and Development Center, Inc.
Princeton, NJ

NDA 21-073
Actos™
(Pioglitazone HCl) Tablets

Certification Statement
as requested by the
Generic Drug Enforcement Act of 1992

In compliance with the Generic Drug Enforcement Act of 1992, Covance certifies that we did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) of Section 306 of the Food, Drug and Cosmetic Act in connection with this application.


Patricia Young, Ph.D.
Vice President, Regulatory Affairs
Vice President, Corporate Compliance

12th December 1998
Date

APPEARS THIS WAY ON ORIGINAL

TAKEDA AMERICA RESEARCH AND DEVELOPMENT CENTER, INC. Princeton, NJ	ACTOS® (pioglitazone HCl tablets)

CERTIFICATION OF COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT

In compliance with the Generic Drug Enforcement Act of 1992, [REDACTED]
 [REDACTED] certifies that we did not use in any capacity the services of any person debarred under
 subsection (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act, in connection with this application.

/s/ [REDACTED]

15 Jul 98
DATE

FOR [REDACTED]

/s/ [REDACTED]
 PRINT NAME

APPEARS THIS WAY ON ORIGINAL [REDACTED]

TAKEDA AMERICA RESEARCH AND DEVELOPMENT CENTER, INC. Princeton, NJ	ACTOS® (pioglitazone HCl tablets)

CERTIFICATION OF COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT

In compliance with the Generic Drug Enforcement Act of 1992, [REDACTED] certifies that we did not use in any capacity the services of any person debarred under subsection (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act, in connection with this application.

/s/ [REDACTED]

FOR [REDACTED]

/s/ [REDACTED]

PRINT NAME

July 17, 1998
DATE

TAKEDA AMERICA RESEARCH AND DEVELOPMENT CENTER, INC. Princeton, NJ	ACTOS® (pioglitazone HCl tablets)

CERTIFICATION OF COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT

In compliance with the Generic Drug Enforcement Act of 1992, [REDACTED] certifies that we did not use in any capacity the services of any person debarred under subsection (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act, in connection with this application.

/s/ [REDACTED]

FOR [REDACTED]

7/15/98
DATE

/s/ [REDACTED]

PRINT NAME →

APPEARS THIS WAY ON ORIGINAL

JUL 15 1998

TAKEDA AMERICA RESEARCH AND DEVELOPMENT CENTER, INC. Princeton, NJ	ACTOS® (pioglitazone HCl tablets)

CERTIFICATION OF COMPLIANCE WITH THE GENERIC DRUG ENFORCEMENT ACT

In compliance with the Generic Drug Enforcement Act of 1992, [REDACTED] certifies that we did not use in any capacity the services of any person debarred under subsection (a) or (b) of Section 306 of the Food, Drug, and Cosmetic Act, in connection with this application.

[REDACTED]

FOR

[REDACTED]

[REDACTED]

PRINT NAME

6 AUGUST 1998
DATE

Memorandum

June 30, 1999

JUN 30 1999

To: the NDA file 21-073 Actos (pioglitazone)

From: Solomon Sobel M.D., Director, Division of Metabolic and
Endocrine Drug Products

Subject: Approval of NDA

pioglitazone is the third member of this class to be considered for marketing. The others are troglitazone (Rezulin) and Rosiglitazone (Avandia) which have been approved. Pioglitazone was reviewed at a recent Advisory Committee in conjunction with rosiglitazone. Both safety and efficacy data for rosiglitazone were presented at that meeting but only safety data were presented in respect to pioglitazone. The reason for this was that pioglitazone had been submitted for review somewhat later than rosiglitazone and the efficacy evaluation had not been completed. However, it was decided to present both drugs because the safety considerations were considered paramount. Both rosiglitazone and pioglitazone were found to have less effect on the liver as judged by hepatic enzyme elevation as compared to troglitazone. In fact, there was no clearly demonstrable adverse effect on the liver by either drug.

Rosiglitazone was approved shortly after the Advisory Committee meeting with a recommendation for hepatic enzyme monitoring at the beginning of therapy and every 2 months for the first year and periodically thereafter.

We are now considering pioglitazone for marketing approval. The main issues are:

1. What is the safety profile of pioglitazone in respect to hepatic effects and what should be our degree of hepatic enzyme monitoring?
2. What effect does pioglitazone have in respect to serum lipid alterations?
3. What is the safety profile of pioglitazone in respect to cardiac effects?
4. What indications in respect to monotherapy and combined therapy have been established in the clinical trials?
5. Are there any problems in respect to pharmacotoxicology, chemistry, or pharmacokinetics?
6. Are there any comments from DDMAC in respect to the labeling?
7. What are we asking in respect to phase 4 commitments?

Discussion of above issues.

1. Pioglitazone was given to a total of 3650 patients. Of these, 0.33% had an elevation of ALT hepatic enzyme of greater than 3 times the upper limit of normal. (comparatively the incidence was 1.9% for troglitazone and 0.25% for rosiglitazone. For greater elevations (>8xULN) the incidences were 0.03%, 0.9% and 0.05% for pioglitazone, troglitazone, and rosiglitazone, respectively.

The Division had previously recommended for rosiglitazone that liver enzymes be measured at the initiation of therapy and then

monitored every 2 months for the first 12 months and then periodically thereafter.

We are making the identical recommendation for pioglitazone.

2. In the three monotherapy studies, there was a trend to a beneficial effect in respect to triglycerides (statistically significant), HDL cholesterol, and LDL cholesterol.

In the study in which pioglitazone was combined with insulin the beneficial effect on triglyceride remained. Also, there was a slight increase in HDL. However there was a slight increase in LDL (non significant).

In the study in which pioglitazone was combined with sulfonylurea the lipid effects were all in a favorable direction.

In the study in which pioglitazone was combined with metformin, favorable effects were observed on triglycerides and HDL but the LDL was slightly elevated.

All in all, the effects on lipids with pioglitazone are either favorable as seen in the monotherapy and of mixed effect in the combination studies with metformin and insulin.

3. The clinical studies did not give a signal for an adverse cardiac effect.

A six-month placebo controlled echocardiographic study also did not show a deleterious effect.

We have previously commented that a positively controlled echo study would have been a superior design.

We will further address the possibility of adverse effects on the heart through phase 4 studies.

4. We have granted indications for use in patients with type 2 diabetes as monotherapy and also for use in combination with a sulfonylurea, metformin or insulin.

5. The Pharmacology reviewer recommended approval.

We have discussed ongoing efforts through human hepatic tissue culture studies to help define the possible mode of toxicity of at least one member of the thiazolidinedione class of drugs. From a chemistry standpoint the application may be approved pending satisfactory results of the inspection of manufacturing facilities.

From a pharmacokinetic standpoint there were requests for additional pharmacokinetic studies as outlined in the approval letter.

6. DDMAC has reviewed the labeling and we will incorporate their recommendations.

7. the phase 4 commitments will include additional pharmacokinetic studies and 2 clinical studies which are outlined in the approval letter.

Conclusions:

The Division recommends approval of pioglitazone.

The draft label of June 30, 1999 has been reviewed and it is found to be acceptable

-Solomon Sobel [redacted] 6/30/99

ADA-21-073

HFD-SID

ITFD-SID/Sobol/S Malozowski/R Misbin/XYSERW/S MOORE

HRhee/R STEIGERWALT/L PIAN/TSA/HROUT/J WEIX/HYAHN

ITFD-SII/SWEBER

APPEARS THIS WAY ON ORIGINAL

JUN 28 1999

Labeling T-con with Takeda
Thursday, June 24, 1999

Solomon Sobel, M.D.
Saul Malozowski, M.D.
Robert Misbin, M.D.
Todd Sahlroot, Ph.D.
Jena Weber, BS

Roberta Schnieder, M.D.
Annette Mathison, Ph.D.

The Division went through the package insert page by page (1-21) of the ACTOS labeling from May 28, 1999. Additions and deletions were specified.

These revisions that we requested should be completed by Monday, June 28, 1999. The company will send this updated version to us and provide a working copy on a disk. We need to insert the comments suggested by our Pharmacology team reviewers.

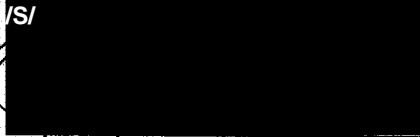
Phase 4 comments to Takeda from FDA:

- JW
1. 2 additional PK studies should be performed, including ketaconazole studies.
 2. 3 additional combination studies should be done including formal PK changes shown in males and females.
 3. Long-term observation of ACTOS utilizing liver function tests in 1000 patients for 3 years (this is in addition to what the company currently has).
 4. The cardiac problem (from Columbia University, class 2, 3, and 4):
 - Cardiac issue must be addressed in some way.
 - Patients with existing heart failure – ethical problems in enrolling this class of patients require a compelling need.
 - Possibility of using ~1000 patients, design an arm to use as a comparator in a managed healthcare system.

/SI


Jena Weber, RHPM

/SI


Robert Misbin, M.D.

APR - 2 1999

T-CON

Note to NDA file: 21-073

Takeda
Attention: Stephanie Rais
Wednesday, March 31, 1999 @ 2pm

Fax: 609-452-1218

Topic: 120-day Safety Update for NDA now under review, and efficacy content of the briefing document that will be submitted to the Agency and subsequently to the Advisory Committee.

Participants: <u>Takeda</u>	<u>FDA</u>
Stephanie Rais	Robert Misbin, M.D.
Roberta Schneider, M.D.	Jena Weber, RHPM

Company was informed that Dr. Misbin will not have his final draft completed for this application until June 1999, so a completed version will not be available by the time the AC convenes.

The format for the 120-day safety update is as follows: for study 11, old information from NDA will appear in regular type; the new information will appear in bold/italic type. Original and updated versions will be ready to compare/contrast. Dr. Misbin requested that a table of new patients that were not included in the original NDA be submitted.

Desk copies will follow, but will not include patient case report forms. These would be too numerous and would add up to extra volumes for our storage and review.

If any new cases of liver abnormalities or increase of CPK levels are reported, these should be highlighted for our attention.

The content of the briefing document for the Advisory Committee for monotherapy will include a presentation by Takeda on naive patients only. The document should arrive to us by April 6, 1999.

We will have a T-con with the company before the advisory meeting to discuss the topics that will be presented, agenda order and to make sure that we are all on the same page.

/s/ [Redacted Signature]

Jena M. Weber, RHPM

/s/ [Redacted Signature]

Robert Misbin, M.D.

Weber

NDA 21-073

MAR 30 1999

Takeda
Attention: Ms. Stephanie Rais
Regulatory Consultant
101 Carnegie Center, Suite 207
Princeton, NJ 08540

Dear Ms. Rais:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Actos™ (pioglitazone maleate) Tablets
Therapeutic Classification: Priority (P)
Date of Application: January 15, 1999
Date of Receipt: January 15, 1999
Our Reference Number: 21-073

This application was filed under section 505(b) of the Act on March 15, 1999, in accordance with 21 CFR 314.101(a). The user fee goal date will be July 15, 1999.

As of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 10 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Page 2

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please contact Ms. Jena Weber, Project Manager, at (301) 827-6422.

Sincerely,

/s/



3.30.99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

15 July, 1999
Ref: 071501SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 026

Dear Dr. Sobel:

The purpose of this Amendment is to provide Addendum 2 to our Phase IV study commitments. Phase IV commitments were provided to the Agency on July 6, 1999 (Amendment 019) and additional commitments were filed as Addendum 1 on July 7, 1999 (Amendment 022). During our meeting with representative of the Division and Dr. Jenkins on July 14, we were asked to provide additional details and a time line for completion of the studies. This information is contained herein.

We have agreed to the following studies as Phase 4 commitments.

Two pharmacokinetic studies:

- 1) An evaluation of the pharmacokinetic impact of concomitant administration of ketaconazole and ACTOS. This will be a 2-way crossover study utilizing a single dose ACTOS and a single dose of ketaconazole, and
- 2) An evaluation of the effect of administration of ACTOS on hepatic enzyme induction, This will be a steady state PK study with 2 weeks of ACTOS administration and single dose midazolam HCl.

Schedule: The protocols will be submitted to the FDA during the 3rd quarter of 1999 and the clinical conduct will begin no later than the 4th quarter of 1999. The final study reports will be provided to the agency by 3rd quarter of 2000.



Dr. Solomon Sobel

15 July, 1999

Page -2-

Three randomized, controlled clinical trials comparing the safety and efficacy of 6 months of treatment with ACTOS 30 mg versus ACTOS 45 mg in combination with:

- 1) sulfonylurea,
- 2) metformin, and
- 3) insulin.

Schedule: The protocols will be submitted to the FDA during the 3rd quarter of 1999, clinical conduct will begin no later than the 4th quarter of 1999. The final study report should be available to be filed to the agency within 18 to 24 months after study initiation.

Two additional studies with special clinical features:

- 1) a randomized, comparative clinical study in patients with type 2 diabetes mellitus and NYHA Class II and early Class III congestive heart failure. This will be an evaluation of efficacy and safety including hematologic and cardiac safety assessments, and.
- 2) a study evaluating the occurrence of serious liver disease in patients treated with ACTOS versus an appropriate control group.

Schedule: The designs for these two studies have not been finalized and will be discussed with the division prior to finalization of the protocols. The clinical phase of each study is anticipated to be somewhat protracted; study 1 will have a long recruitment period and study 2 will have a duration of treatment for 3 years. Therefore, we cannot provide study completion dates, however, we will pursue these studies with all due diligence.

If you have any questions concerning this submission, please do not hesitate to contact me at (609) 734-4404 or Ms. Stephanie Rais at (609) 734-4403.

Sincerely yours,



Roberta L. Schneider, M.D.
Vice President Drug Development



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

13 July, 1999
Ref: 071301SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Re: NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 025

Dear Dr. Sobel:

The purpose of this amendment is to provide official copies of information sent earlier today via facsimile to Dr. Wei, Biopharmaceutics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics. At the time this information was sent to Dr. Wei, a copy was also sent via facsimile to Ms. Jena Weber.

This amendment responds to telephone calls received yesterday from Dr. Wei and Dr. Ahn stating that the dissolution specification of [redacted] could not be accepted without supporting data. We had previously amended the NDA (see Amendment 18) with this specification. The Office of Clinical Pharmacology and Biopharmaceutics believes that the dissolution specification should be [redacted] unless data is submitted to show otherwise.

We are providing data to support our proposed dissolution specification of [redacted]. We were informed by Dr. Ahn that if data could be available by this morning, it would be reviewed and, if found acceptable, an addendum to the review package could be issued to allow the dissolution specification that we have proposed. (The attached data was faxed to Dr. Wei at 8:00 AM this morning.)

This official submission is also being sent via facsimile so that it is available to the Division today. The original signature copy will be sent via Federal Express, Priority Overnight Delivery to arrive tomorrow morning.

Please do not hesitate to contact me if you require any additional information. Furthermore, we will contact you on Wednesday regarding the outcome of this issue.

Sincerely yours,

Stephanie D. Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.



[REDACTED]

We are providing additional data in support of the dissolution specification of not less than [REDACTED] pioglitazone hydrochloride dissolved in [REDACTED] that was recently proposed in response to Dr. Wei's comments.

[REDACTED]

Tables 1 through 4, attached, provide profiles at 10, 20 and 30 minutes for lots in ongoing stability studies and for 3 of the commercial 45 mg batches recently produced for product launch.

[REDACTED]

000001



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PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

July 8, 1999

Robert Misbin, M.D.
Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, MD 20857-1706

Dear Dr. Misbin,

As we discussed, I am forwarding a copy of the narratives for the two patients who had bladder cancer identified during the ACTOS clinical program.

As I mentioned the ACTOS patient had been receiving ACTOS for 16 days when hematuria prompted a repeat urinalysis. At that time the patient revealed a history of bladder cancer treated 2 years earlier with regular follow-ups by the urologist. Additional information from the site, not included in the narrative, was that at the time of the repeat urinalysis, the patient indicated that her urologist had recently found a "spot" on her bladder that he was going to fix.

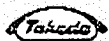
The other patient was in the metformin combination therapy study and had been receiving placebo for 51 days when, during an evaluation by a urologist for frequent urinary tract infections, he was noted to have bladder lesions requiring biopsy and fulgeration. The pathology report from the second surgery (not part of the narrative) indicated a high grade transitional cell lesion (carcinoma-in-situ).

Please call me if you need any additional information.

Sincerely,

Roberta L. Schneider, M.D.
Vice President, Drug Development

Enclosures





TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

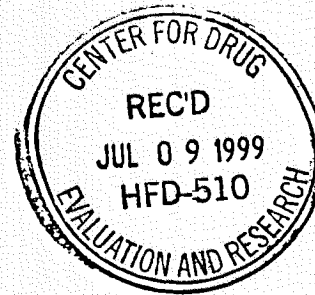
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PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

July 7, 1999

NEW CORRERS

NC

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment 22

Dear Dr. Sobel:

This Amendment is an addendum to the Phase IV commitments filed to the Division in NDA Amendment 19. The additional Phase IV comments are listed below.

An enzyme induction study will be conducted. This will be a 2-way cross-over study in patients treated with pioglitazone HCl for 14 days and the administration of midazolam HCl (Versed®).

After discussions with representatives of the Division earlier today, we commit to a comparative clinical study in patients with type 2 diabetes mellitus and NYHA Class 2 and early Class 3 congestive heart failure. This study will evaluate efficacy and safety parameters focusing on hematologic and cardiac structure and function (echocardiographic or similar evaluation).

We trust these additional Phase IV commitments address all concerns discussed with representatives of the Division during today's teleconferences.

Sincerely,

Robert L. Schenck, M.D. V.P. Drug Development for
Mikihiko Obayashi, Ph.D.
President

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS



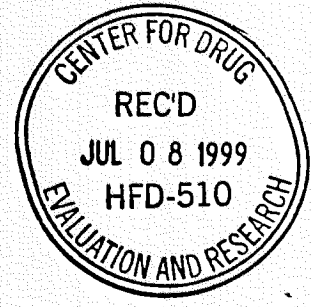
EDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

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PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

July 7, 1999

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
DL



NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment 21

Dear Dr. Sobel:

The purpose of this Amendment is to provide official responses to questions received from the Chemistry Reviewer, Dr. Ysern. On June 30, 1999, a facsimile communication was sent to us containing three requests to finalize the CMC section of the NDA. A copy of the fax is included in Attachment 1 of this submission.

Additionally, on July 1, teleconference took place between Dr. Ysern and Ms. Stephanie Rais, Regulatory Affairs Consultant for Takeda. During that telephone conversation, Dr. Ysern made some additional requests and these are listed in Attachment 1 following the Agency's June 30 facsimile.

At this time we wish to officially inform the Division that a specification has been set for particle size and a revised drug substance specification is provided in Attachment 2.

A request was made by Dr. Ysern that the description test in the drug product specifications be changed to clearly state how the different strengths will be distinguished. Additionally, concerning the drug product specifications, we have been asked by the Biopharmaceutics Reviewer to modify the dissolution specification. Agreement was reached on [redacted]. Both of these changes have been made to the drug product specifications and revised specifications are included in Attachment 3.

Regarding labeling, we accept the use of the ICH full storage statement. As of the writing of this letter, labels were printed at risk and contain the storage temperature included in the labeling in the NDA. It is our intention to discuss this matter further with Dr. Ysern and members of the Division. If we are allowed to use existing labels with the old statement, we will use the ICH statement for all future printings. If we are not allowed to use the printed materials, they will be destroyed and the reprinted labels will contain the revised storage statement.

Attachment 1

Attachment 2

Attachment 3

Dr. Sobel
Amendment 21, Page 2

The following issues were discussed between Dr. Ysern and Ms. Stephanie Rais on July 1, 1999.

Regarding the testing for related substances, the Agency did not make this a regulatory requirement; however, Dr. Ysern strongly recommended that the test be conducted. Testing for related substances will be done but not as a regulatory requirement.

Dr. Ysern noted that a drug substance retest date was not included in the NDA. He stated a retest date of one year seemed appropriate. Takeda Chemical Industries, Ltd. agrees to a one-year retest date.

We trust that this Amendment fully responds to all issues for Item 3 of the NDA. If there are any additional issues or, if clarification is needed for any items, please contact Ms. Rais at (609) 734-4403.

Sincerely yours,

Mikihiko Obayashi, Ph.D.
President



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July 7, 1999

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP

NC



NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment 19

Dear Dr. Sobel:

The purpose of this Amendment is to provide our official Phase IV commitments

Five formal pharmacokinetic studies including ketaconazole, atorvastatin, nifedipine, fexofenadine and ranitidine will be conducted. Two of these studies are scheduled to commence September 1999.

We also agree to conduct a total of three studies comparing the efficacy and safety of ACTOS 30 mg. versus ACTOS 45 mg in combination with sulfonylurea, metformin and insulin.

In addition, we agree to conduct a study, which will collect information from 1,000 patients treated with ACTOS for 3 years regarding the occurrence of serious liver disease.

We wish to have additional discussion with the Division regarding the issue of conducting a second study in patients with NYHA Class 3 and 4 congestive heart failure in view of our recently proposed labeling revision, (page 18, version July 6, 1999).

We trust this covers the Phase IV commitments discussed with representatives of the Division during recent teleconferences.

Sincerely,

Mikihiko Obayashi, Ph.D.
President



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

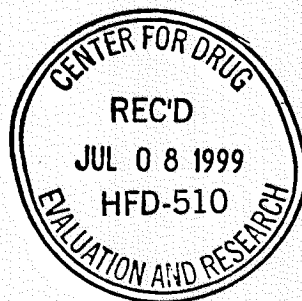
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PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

NDA SUPP AMEND

BS

July 6, 1999
Ref: 070301SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment 20

Dear Dr. Sobel:

The purpose of this Amendment is to provide official copies of information previously sent to Dr. Pian, NDA Biostatistics Reviewer. On two separate occasions, Dr. Pian was provided with data sent via e-mail from Dr. Annette Mathisen, Director of Biostatistics and Data Management. The data provided to Dr. Pian are contained in this submission in Attachments 1 and 2.

On March 17, 1999, after receiving a request to clarify some data in the submission, Dr. Mathisen provided corrected information to Dr. Pian. The data provided is included in Attachment 1.

In response to a request for additional analyses for lipid variables, additional data tables were provided on April 14, 1999. These tables are contained in Attachment 2.

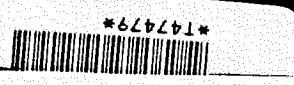
Please do not hesitate to contact me if you have any questions or if you require clarification of any information.

Sincerely yours,

Stephanie D. Rais
Regulatory Affairs Consultant for
Takeda America

Attachment 1

Attachment 2


Takeda**TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.**101 CARNEGIE CENTER • SUITE 207
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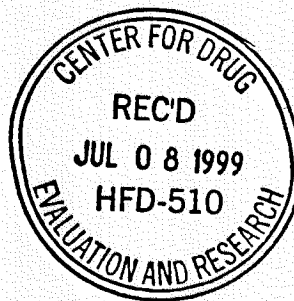
July 2, 1999

NDA SUPP AMEND

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

BB

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment 18



Dear Dr. Sobel:

The purpose of this Amendment is to provide official copies of information previously sent to Dr. Wei, NDA Reviewer for the Office of Clinical Pharmacology and Biopharmaceutics. On two separate occasions, Dr. Wei was provided with data sent via facsimile. The data provided to Dr. Wei are contained in this submission in Attachments 1 and 2. Furthermore, a change in the dissolution specification for the final product is covered in Attachment 3. This information amends Item 6 of the NDA.

In Attachment 1, data are provided explaining the differences in AUC values noted for some studies in Item 6. Attachment 2 contains an additional analysis and tables in response to Dr. Wei's request for PK/PD modeling.

Furthermore, the dissolution specification for the final product was discussed with Dr. Wei and the specification will be revised to 80% in 30 minutes. Further details are included in Attachment 3. The specification documentation for the tablets is being revised by Takeda Chemical Industries, Ltd., the manufacturer, and will be submitted separately as an Amendment to Item 3 of the NDA.

Please do not hesitate to contact me if you have any questions or if require clarification of any information.

Sincerely yours,

Stephanie D. Rais
Regulatory Affairs Consultant for
Takeda America Research and Development Center, Inc.



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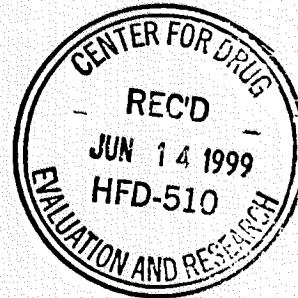
ORIGINAL

11 June, 1999
Ref: 061101SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

ORIG AMENDMENT
BM

Re: NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment # 017



Dear Dr. Sobel:

Pursuant to 21 CFR 314.50, we are hereby amending the above - referenced NDA. At this time we are amending Section 11 (Case Report Tabulations) and Section 12 (Case Report Forms).

On June 3, 1999, we filed Amendment 016, 120 Day Safety Update. As noted in the cover letter for Amendment 016 in order to prepare this safety update, data listings were revised for two ongoing studies. At this time we are providing the Case Report Forms and the revised data listings, which we consider to be raw data supporting the 120-Day Safety Update.

If you have any comments or questions concerning this submission, please do not hesitate to contact me at (609) 734-4403.

Sincerely yours,

Stephanie Rais

Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I. ☐ MEMO
CSO INITIALS	DATE





ORIGINAL

ORIG AMENDMENT

BEST POSSIBLE COPY

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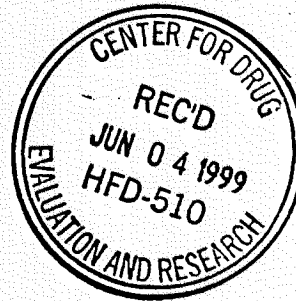
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PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

03 June, 1999
Ref: 060301SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS _____ DATE _____

Re: NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
120-Day Safety Report
NDA Amendment: # 016



Dear Dr. Sobel:

Pursuant to 21 CFR 314.50, we are hereby submitting our 120-Day Safety Update Report. By agreement (telephone call of March 19, 1999) with members of the Division, a three-week extension was granted for the filing of this report. The need for the extension was based on the Division's request that Takeda America Research and Development Corp. (TARDC) present ACTOS at the April 22 and 23, 1999 Metabolic and Endocrine Drugs Advisory Committee Meeting.

The 120-Day Safety Update is included in the attached 9 volumes.

Volumes 1 and 2 contain the revised ISS with the updated information. Volume 2 also contains updated information regarding the echocardiography report. The original echocardiography report was file on March 29, 1999 – amendment 005.

Volumes 3 through 9 contain the appendices and tables that support the data provided in Volumes 1 and 2. Volume 9 also contains the narratives of adverse events (i.e. deaths, serious adverse events and adverse events resulting in discontinuation).



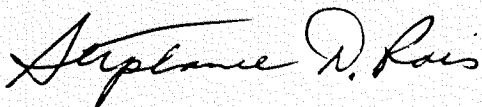
TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

Page 2
120 Day Safety Report

In order to prepare this safety update, data listings were revised for two ongoing studies. These data listings will be filed as an Amendment to the NDA. Case Report Forms (CRFs) are available for the patients covered in this safety update and these will also be filed as an Amendment to the NDA. The data listings and CRFs will be filed the week of June 7, 1999.

If you have any comments or questions regarding this safety update, please do not hesitate to contact me at (609) 734-4403.

Sincerely yours,



Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

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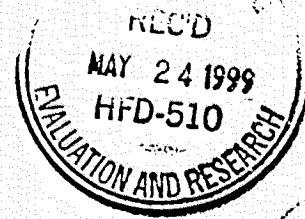
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ORIGINAL

21 May, 1999
Ref: 052101SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 015

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

On March 2, 1999, we filed Amendment 001 containing stability data. As noted in the cover letter for Amendment 001, a commitment to provide stability data for three (3) commercial lots of each strength of tablets was included in the original NDA filed on January 15, 1999 - see NDA Section 4.A.3.8.1 (Volume 1.006, page 001). On March 2, we supplied 3-month stability data. At this time, we are providing the 6-month data for the accelerated storage condition.

The results are summarized in the attached Tables 1 through 3, see Attachment 1. Data is included in three reports from Takeda Chemical Industries, Ltd. as follows:

Report # A-35-1082	15 mg tablets	Attachment 2,
Report # A-35-1083	30 mg tablets	Attachment 3,
Report # A-35-1084	45 mg tablets	Attachment 4.

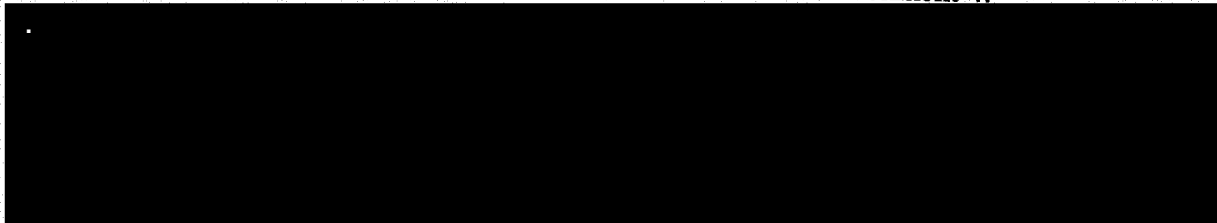
Attachment 1

Attachment 2

Attachment 3

Attachment 4

SI
17-JUN-99



900801



Attachment 1

Dr. Solomon Sobel
21 May, 1999
Page -2-



Attachment 2

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4403.

Sincerely,

Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Attachment 3



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
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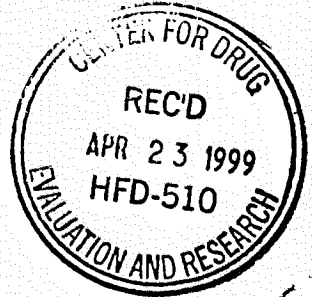
DUPLICATE

April 21, 1999
Ref: 042101SR

~~DRUG AMENDMENT~~

Bm

Solomon Sobel, M.D., Director
Division of Metabolic & endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 21-073
Pioglitazone HCL (AD-4833) Tablets
Amendment: 014

Dear Dr. Sobel:

Reference is made to telephone conversations that took place on April 7 between representatives of Takeda America Research & Development Center, Inc. and Dr. Misbin. Dr. Misbin requested case summaries for patients with selective cardiovascular effects.

On April 19, 1999, the information was faxed to Dr. Misbin. The purpose of this communication is to provide the information as a formal amendment to the pending New Drug Application.

If you have any questions or require any additional information, please do not hesitate to contact the undersigned or Dr. Roberta Schneider at (609) 452-1113.

Sincerely yours,

Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Takeda

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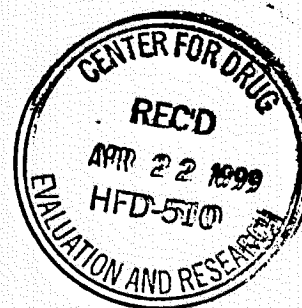
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DUPLICATE

BP
April 20, 1999
Ref: 042001SR

Solomon Sobel, M.D., Director
Division of Metabolic & endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA CRIB AMENDMENT



**RE: NDA 21-073
Pioglitazone HCL (AD-4833) Tablets
Amendment: 013**

Dear Dr. Sobel:

Reference is made to telephone conversations that took place on various occasions between representatives of Takeda America Research & Development Center, Inc. and Dr. Herman Rhee. Dr. Rhee requested data tabulations including the lot numbers of drug used in the toxicology studies, dose levels with AUC data for various effects seen in animals, literature and other information on the effect of the glitazone class of drugs on PPAR gamma.

The information listed above has been provided to Dr. Rhee via three separate facsimile communications. The purpose of this submission is to provide the information (previously sent to Dr. Rhee) as a formal amendment to the pending New Drug Application. In addition to the data that was provided to Dr. Rhee, the fax cover pages are also included in this submission. The submission is organized by date of fax transmission.

If you have any questions or require any additional information, please do not hesitate to contact the undersigned at (609) 452-1113.

Sincerely yours,

A handwritten signature in cursive script that reads "Stephanie Rais".

Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

April 13, 1999

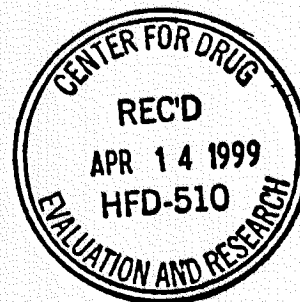
ORIGINAL

BMI

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room 14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

~~ORIGINAL~~

Re: NDA 21-073
Pioglitazone HCl Tablets
Amendment 12



Dear Dr. Sobel:

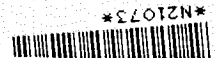
Reference is made to your letter dated March 30, 1999 and received on April 5, 1999. Your letter, copy attached, states that we must request a waiver or file a plan for the assessment of pediatric safety and effectiveness.

In accordance with 21 CFR 314.55, we request a partial waiver of the pediatric study requirement.

ACTOS™ (pioglitazone HCL) is indicated for the treatment of Type 2 or noninsulin-dependent diabetes mellitus (NIDDM). Typically, Type 2 diabetes develops gradually in adults and usually after age 40. Thus, it was frequently referred to as adult-onset or maturity-onset diabetes.

Children usually develop Type 1 or insulin dependent diabetes mellitus and oral agents would not be effective in this setting. Previously, pediatric patients were not thought to develop Type 2 diabetes. However, several authorities in the field of endocrinology have indicated that there is a subpopulation of pediatric patients who metabolically resemble Type 2 diabetes patients and might benefit from oral antidiabetic therapy. In particular, obese adolescents (approximately 12 to 17 years of age) may develop diabetes associated with insulin resistance. Dr. Jaime Davidson presented information about this condition at the March 1998 Metabolic & Endocrine Advisory Committee Meeting.

Takeda America is considering clinical trials for this patient population and will file a clinical plan within 120 days of the receipt of your letter.



FDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

NDA 21-073
Amendment 12

Based upon the information presented above, we request that a waiver be granted under 21 CFR 314.55 c for pediatric patients up to approximately 12 years of age. Again, a clinical plan will be forwarded to cover pediatric patients approximately 12 to 17 years of age.

If you have any comments or questions concerning this amendment, please do not hesitate to contact Dr. Roberta Schneider or me at (609)452-1113.

Sincerely yours,

Stephanie D. Rais
Regulatory Affairs Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: FDA Form 356h

CC: Dr. Diane Murphy
Assoc. Director for Pediatrics

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I. ☐ MEMO
CSO INITIALS	DATE



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

07 April, 1999
Ref.: 040701SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 010

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

In response to Dr. Herman Rhee's request that the toxicology reports (text, figures and summary tables) be provided electronically, Takeda America Research and Development Center, Inc. has had the third set of toxicology reports converted to electronic PDF files which are contained on the enclosed CR-ROM. The enclosed CD-ROM contains the acute and sub-chronic study reports, figures and summary tables. All of the reports contained on the enclosed CD-ROM were originally submitted in Takeda's New Drug Application (NDA #21-073), submitted on January 15, 1999 (#000).

This third and final CD-ROM containing preclinical reports fulfills Dr. Rhee's request for electronic documents.

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4403.

Sincerely,

Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h

Cc: Dr. Herman Rhee (DESK COPY, Letter Only)
Ms. Jena Weber (DESK COPY, Letter Only)





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TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

 101 CARNEGIE CENTER • SUITE 207
 PRINCETON, NEW JERSEY 08540
 TEL: (609) 452-1113 • FAX: (609) 452-1218

 06 April, 1999
 Ref: 040601SR

Solomon Sobel, M.D., Director
 Division of Metabolic & Endocrine Drug Products (HFD-510)
 Office of Drug Evaluation II
 Center for Drug Evaluation & Research
 Document Control Room #14B-19
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, Maryland 20857

NDA No. 21-073
 Pioglitazone HCl (AD-4833) Tablets
 NDA Amendment: # 009

Dear Dr. Sobel:

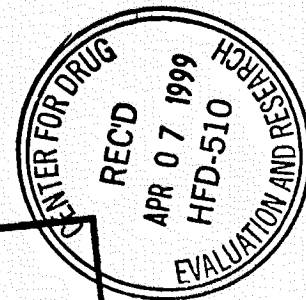
Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

At the request of Dr. Jim Wei (Biopharmaceutics Reviewer), the dissolution studies submitted in the original NDA (15 January, 1999; #000) were repeated in accordance with the Biopharmaceutics guideline on dissolution of immediate release dosage forms. Item 6 of the NDA was amended on March 31, 1999 (#007) with the new dissolution reports.

At this time, we are amending Item 4, Chemistry, Manufacturing and Controls with the repeated dissolution study reports for your review.

Furthermore, around mid-March, Ms. Jena Weber was informed that an FDA inspection had been scheduled for two Takeda Chemical Industry manufacturing facilities in Japan. One of the facilities was to undergo a PAI as a result of the review of a New Drug Application submitted by TAP (Takeda Abbott Pharmaceuticals). The facility scheduled for the PAI is also the facility that manufactures pioglitazone drug substance. Ms. Weber was contacted because we believed this was important information for the Division.

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I. ☐ MEMO
DATE	

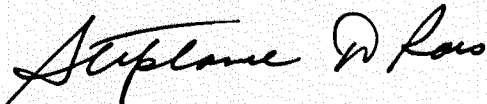


Dr. Solomon Sobel
Ref.: 040601SR
Page -2-

Unfortunately, the scheduled inspection has been postponed because it was to take place during the first week of May and that week is a National holiday in Japan. We believe the PAI will be rescheduled, but we do not know when it will take place.

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4403.

Sincerely,



Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h

Cc: Dr. Xavier Ysem, Chemistry Reviewer (DESK COPY, Submission)
Ms. Jena Weber, Project Manager (DESK COPY, Letter Only)



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-121805 April, 1999
Ref: 040501SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

DESK COPY

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 008

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

In our submission to the Division on 31 March, 1999 (NDA Amendment #007), we submitted several documents including Attachment 5 which contained the tables of precision and accuracy values of the analytical assay used to measure pioglitazone and metabolites. [REDACTED]

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4403.

Sincerely,

Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h

Cc: Dr. James Wei, Biopharmaceutics Reviewer (DESK COPY, Submission)
Ms. Jena Weber, Project Manager (DESK COPY, Letter Only)





TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

31 March, 1999
Ref: 033101SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

DESK COPY

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 006

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

In response to a request from Dr. James Wei, Biopharmaceutics Reviewer (Facsimile dated 12 March, 1999), Takeda America Research and Development Center, Inc. has converted the information listed below into electronic PDF files, which are contained in the enclosed CD-ROM.

This amendment represents the formal submission of the following electronic documents; 1) the ACTOS Package Insert, 2) the annotated Package Insert; 3) the Section 6 summary (Human Pharmacokinetics and Bioavailability), and 4) the individual study summaries in Section 6. These documents were originally submitted in Takeda America Research and Development Center, Inc.'s original New Drug Application (NDA No. 21-073) on 15 January, 1999 (#000).

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4409.

Sincerely,

Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h

Cc: Dr. James Wei, Biopharmaceutics Reviewer (DESK COPY, Letter Only)
Ms. Jena Weber, Project Manager (DESK COPY, Letter Only)





TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

31 March, 1999
Ref: 033102SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 007

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above. (Please Note: This is Amendment number 7. Amendment number 6 is an electronic submission of biopharmaceutics data. Amendment 6 has been sent to Central Document Room, 12229 Wilkins Ave.)

In response to a request from Dr. Jim Wei (facsimile dated 12 March 1999), Takeda America Research and Development Center, Inc. is submitting the below-listed information as requested.

Included in this amendment are the following:

- repeated dissolution studies,
- pH profile,
- a cross-reference table listing the lots of drug product used in the clinical trials,
- tables of precision and accuracy values of the analytical assay used to measure pioglitazone and metabolites.

Further details about the submission appear in an introductory document that follows FDA Form 356H. If you have any questions concerning this submission, please contact the undersigned at (609) 452-1113, extension 4403.

Sincerely,

Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h

Cc: Dr. James Wei, Biopharmaceutics Reviewer (DESK COPY, Submission)
Ms. Jena Weber, Project Manager (DESK COPY, Letter Only)





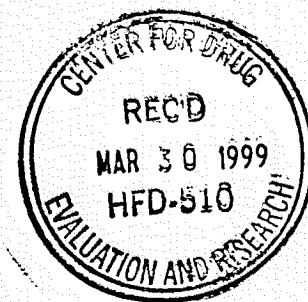
TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

DESK COPY

29 March, 1999
Ref: 032901SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 005

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

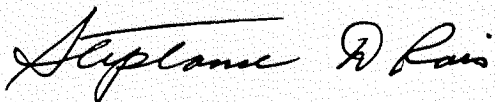
We are submitting the enclosed echocardiographic data based on an agreement reached with the Division during a teleconference between Takeda America Research and Development Center, Inc. and Dr. Misbin, Medical Reviewer, on November 6, 1998 which was also noted in the cover letter for Takeda's original NDA (#21-073) submitted on January 15, 1999 (#000).

Volume 1 contains Addendum A to Report No. AD-4833/PNFP-001.6. Volume 2 and 3 contain Addendum A to Report No. AD-4833/PNFP-011.2. These addenda contain echocardiographic findings. (The appendices contained in these reports are numbered 13, which is a direct continuation from the full clinical reports submitted in the original NDA, which ended with Appendix 12.)

If there are any additional questions, or if any FDA staff would like to discuss the matter further, please do not hesitate to contact either Dr. Schneider or the undersigned at (609) 452-1113, extension 4403.

Dr. Solomon Sobel
032901SR
Page -2-

Sincerely yours,



Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in duplicate)

Cc: Dr. Misbin (DESK COPY)
Ms. Jena Weber (DESK COPY)

APPEARS THIS WAY ON ORIGINAL



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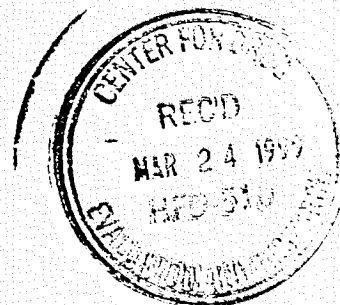
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TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

23 March, 1999
Ref: 032302SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 004

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above. (Please Note: This is Amendment number 4. Amendment number 3 is an electronic submission of preclinical data. Amendment 3 has been sent to Central Document Room, 12229 Wilkins Ave.)

As a result of the teleconference that took place on Friday, March 19, 1999 between Dr. Malozowski, Dr. Misbin and Ms. Weber of FDA and Dr. Schneider and Ms. Rais for Takeda America Research & Development Corp. (TAR&DC), we are enclosing color graphs showing the results from Monotherapy Study 001 and Monotherapy Study 026.

The attachments contain figures showing the results for HbA1c and fasting blood glucose obtained during screening, at baseline, and throughout the double-blind portion of each study. The first figure in each group presents data for all patients combined. The remainder of the figures represents the different subgroups e.g., naïve, previously treated FBG < 280 mg/dl at baseline, etc. Legends are listed at the bottom of each figure and are in color for easy visual identification. For some patient subgroups, the difference from placebo is marked to the right of the figure. Attachments 1 and 2 contain the figures showing the results from Study 001 for HbA1c and fasting blood glucose, respectively



Dr. Solomon Sobel
Ref.: 032302SR
Page -2-

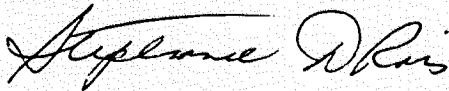
for the 45 mg dose group. Attachments 3 and 4 contain results from Study 026 for HbA1c and fasting blood glucose, respectively for the 30 mg dose group.

These results indicate that in previously treated patients with blood glucose values <280 mg/dl at baseline, pioglitazone HCl at doses of 30 mg (Study 026) or 45 mg (Study 001) is effective and these patients return to baseline values during the treatment period. These figures are provided for purposes of clarification because the data, while contained in the NDA supplemental reports, were not graphically displayed.

Per our agreements made during the teleconference, the previously treated patient subgroup data presented in this submission will not be presented at the Advisory Committee Meeting. As you requested, TAR&DC will present data on naïve patients only. As we agreed, there is adequate data from naïve patients to support NDA approval. As we also discussed, safety data from all patients will be presented at the meeting.

If there are any additional questions, or if any FDA staff would like to discuss the matter further, please do not hesitate to contact either Dr. Schneider or the undersigned at (609) 452-1113, extension 4403.

Sincerely yours,



Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in duplicate)

Cc: Dr. Misbin (DESK COPY)



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218



23 March, 1999
Ref: 032301SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 003

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

In response to Dr. Herman Rhee's request that the toxicology reports (text, figures and summary tables) be provided electronically, Takeda America Research and Development Center, Inc. has had the second set of toxicology reports converted to electronic PDF files which are contained on the enclosed CR-ROM. The enclosed CD-ROM contains the reproductive toxicology studies and the mutagenicity and genotoxicity studies. All of the reports contained on the enclosed CD-ROM were originally submitted in Takeda's New Drug Application (NDA #21-073), submitted on January 15, 1999 (#000).

This is the second CD-ROM to be submitted with preclinical reports. The third CD in the preclinical series will contain the remainder of the toxicology studies (i.e., the acute and sub-chronic study reports, figures and summary tables).



Dr. Solomon Sobel
Ref.: 032301SR
Page -2-

Takeda America Research and Development Center, Inc. has been informed by Dr. Randy Levin that these electronic documents, originally submitted in NDA #21-073, must be forwarded, as an NDA amendment in order to have the enclosed CD-ROM uploaded to Dr. Herman Rhee.

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4409.

Sincerely,



Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in triplicate)

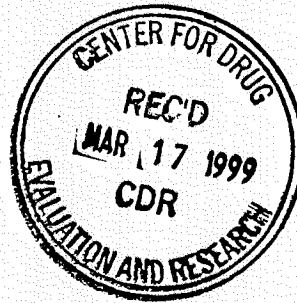
Cc: Dr. Herman Rhee (DESK COPY - cover letter only)
Ms. Jena Weber (DESK COPY cover letter only)



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

DESK COPY

16 March, 1999
Ref: 031601SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 002

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

In response to Dr. Herman Rhee's request that the toxicology reports (text, figures and summary tables) be provided electronically, Takeda America Research and Development Center, Inc. has converted several toxicology reports to electronic PDF files which are contained on the enclosed CR-ROM. The enclosed CD-ROM is one of potentially three CDs that will be submitted. This CD contains the one-year chronic toxicology studies (in rats, dogs, and monkeys), the carcinogenicity studies (in mice and rats), and special studies. All of the reports contained on the enclosed CD_ROM were originally submitted in Takeda's New Drug Application (NDA #21-073), submitted on January 15, 1999 (#000).

As agreed with Dr. Rhee, we have begun processing electronic documents with the most important studies. The next CD will provide electronic versions of the reproductive toxicology studies and the mutagenicity and genotoxicity studies. The third CD in the preclinical series will contain the remainder of the toxicology studies.

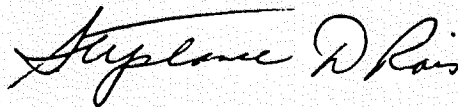


Dr. Solomon Sobel
Ref.: 031601SR
Page -2-

Takeda America Research and Development Center, Inc. has been informed by Dr. Randy Levin that these electronic documents, originally submitted in NDA #21-073, must be forwarded, as an NDA amendment in order to have the enclosed CD-ROM uploaded to Dr. Herman Rhee.

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4409.

Sincerely,



Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in triplicate)

Cc: Dr. Herman Rhee
Ms. Jena Weber

ORIGINAL BC

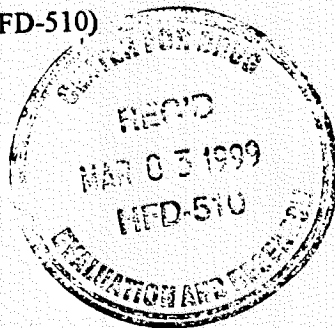
ERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

ORIG AMENDMENT

02 March, 1999
Ref: 030201SR

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
NDA Amendment: # 001

Dear Dr. Sobel:

Pursuant to 21 CFR 314.60, we are amending the New Drug Application (NDA) referenced above.

As noted in the NDA (submitted on 1/15/99, Original Submission #000) Section 4.A.3.8.1 (Volume 1.006, page 001), we are submitting stability results for ACTOS™ tablets made according to commercial conditions. Data is provided for three (3) commercial lots of each strength.

Included in this submission you will find: 1) A summary of the stability of Drug Product; 2) A-35-1071; 3) A-35-1072; 4) A-35-1073; and 5) Tables 1 through 3, which supplement the final reports.

If you have any questions concerning this submission, please contact me at (609) 452-1113, extension 4409.

Sincerely,

Stephanie Rais
Regulatory Consultant for
Takeda America Research and Development Center, Inc.

Enclosure: Form FDA 356h (submitted in triplicate)

REVIEWS COMPLETED	
CSO ACTION:	
☐ LETTER	☐ N.A.I. ☐ MEMO
CSO INITIALS	DATE

Attachment 1

Attachment 2

Attachment 3

Attachment 4

Attachment 5



TAKEDA AMERICA RESEARCH & DEVELOPMENT CENTER, INC.

101 CARNEGIE CENTER • SUITE 207
PRINCETON, NEW JERSEY 08540
TEL: (609) 452-1113 • FAX: (609) 452-1218

15 January, 1999
Ref: 011501MO

Solomon Sobel, M.D., Director
Division of Metabolic & Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Document Control Room #14B-19
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA No. 21-073
Pioglitazone HCl (AD-4833) Tablets
Original Submission: # 000

Dear Dr. Sobel:

Pursuant to section 505 (b) of the Federal Food and Cosmetic Act and 21 CFR 314.50, Takeda America Research and Development Center, Inc. herewith submits our original New Drug Application for ACTOS™ (pioglitazone hydrochloride) Tablets. Takeda America would like to request a priority review of this application based on the discussions at a meeting with the Division's medical reviewers on July 13, 1998 at which the Division indicated that it would consider a priority review designation based on the efficacy and safety information.

ACTOS™ Tablets is a solid oral dosage form developed to improve glycemic control in patients with Type 2 diabetes (Non-Insulin Dependent Diabetes Mellitus, NIDDM). An extensive clinical development program has been conducted in the United States, Japan and Europe. The clinical studies in the US have been conducted under Takeda America Research and Development Center, Inc.'s Investigational New Drug Application, # 33,729.

The clinical program for this NDA is comprised of twenty-four (24) completed clinical pharmacology studies, eleven (11) completed controlled clinical studies including three (3) US pivotal studies of ACTOS™ as monotherapy and three (3) US pivotal studies of ACTOS™ in combination with another therapeutic agent, five (5) completed uncontrolled clinical studies, and thirteen (13) ongoing studies.

JAN 20 1999



Dr. Solomon Sobel
NDA No. 21-073

Page 2
15 January, 1999

A total of 4,989 individuals (4,501 patients and 488 subjects) were enrolled in the completed studies in this clinical program. Of the 4,989 subjects, 3,752 received pioglitazone as either monotherapy or combination therapy. As of the data cut-off date, approximately 2,000 patients were enrolled in the ongoing clinical studies.

The safety and efficacy data from the six (6) US pivotal studies is robust and compelling. It is concluded that pioglitazone hydrochloride is safe and effective for the treatment of Type 2 diabetes (NIDDM) as described in the proposed Package Circular.



This NDA consists of 704 volumes numbered 1.1 through 1.704 and represents the chemistry, manufacturing and controls, preclinical and clinical experience with the product. For your convenience, the locations of the various sections of the NDA are listed in Attachment I to this letter. This NDA also contains CD-ROMs containing the electronic data sets for the two carcinogenicity studies, as well as CD-ROMs containing electronic data sets for the pivotal US clinical studies and human pharmacokinetics studies the locations of the CD-ROMs are also included in Appendix I.

We consider that the application is complete, and will be filed by the Division's 45-day meeting as described in 21.CFR 314.101. Based on an agreement reached with the Division during a conference call November 6, 1998 between representatives from Takeda and Dr. Misbin, Medical Reviewer, Takeda will submit echocardiographic data as an amendment to the NDA within 60 days of the initial filing (21.CFR 314.60(a)). Takeda also references 21 CFR 314.102(c), which provides for an informal meeting with the reviewers of this NDA, and our interest in such a meeting if it is considered to be mutually beneficial.

We are cognizant of our obligations regarding submission of a 4-month Safety Update according to 21 CFR 314.50(d)(5)(vi). Takeda plans to submit this data at the 4-month time point unless the medical reviewers feel that this is not the optimal/most appropriate time to review such a submission. We would like to discuss with representatives of the Division the timing they would prefer for this submission.

In accordance with the Prescription Drug User Fee Act of 1992, a check in the amount of [REDACTED] was sent to the Mellon Bank LockBox, Mellon Bank, Three Melon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 152590001 on [REDACTED].

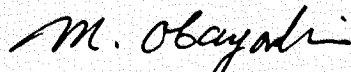
Please note that Takeda America Research and Development Center, Inc. considers this application and all correspondence related thereto as confidential, proprietary, trade secret information and hereby claims protection from disclosure under the applicable sections of 18 USC and Title 21 of the Code of Federal Regulations.

Dr. Solomon Sobel
NDA No. 21-073

Page 3
15 January, 1999

Please contact Dr. Scott Grossman of this office, (609) 452-1113, extension 4409, if you have any questions or comments regarding the application.

Sincerely,



Mikihiko Obayashi, Ph.D.
President

Enclosure: Form FDA 356h