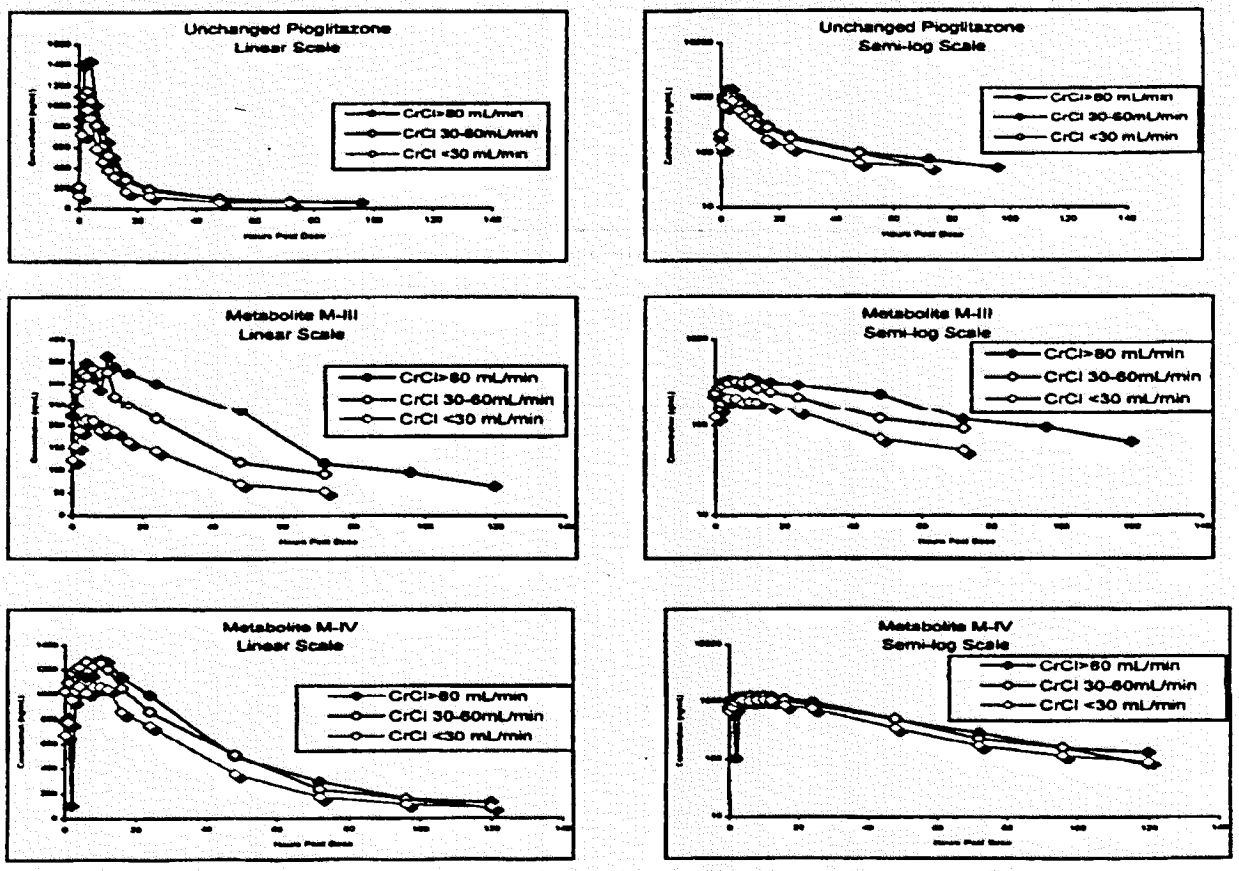
Renal

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, Cmax values for pioglitazone and M-III were statistically significantly lower in subjects with severe renal impairment. There was no change in T1/2.

Figure 5. Mean Serum Concentrations (ng/ml) After Repeated Dosing Study

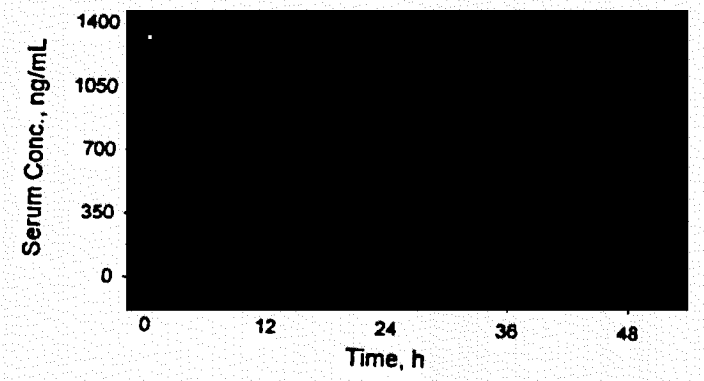


The sponsor explained the phenomenon of lower AUCs for pioglitazone and its metabolites in subjects with severe renal impairment compared to subjects with normal renal function may be consistent with impaired gastrointestinal absorption of pioglitazone in uremic subjects, which has also been reported 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

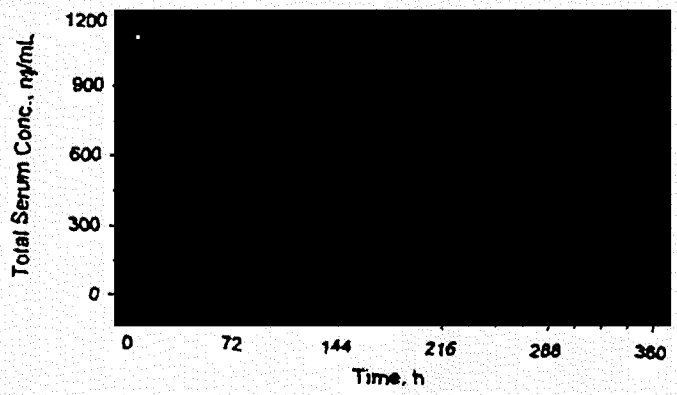


Table 10: PK Parameters in Hepatically Impaired Patients

PK Parameter	Test (Hepatic Patients)	Reference (Normal Subjects)	Test/Reference (x100)	90% Confidence Interval
Pioglitazone				
Cmax (ng/ml)	508 ± 137.3	888 ± 374.6	57.2	43.0, 106
Tmax (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
T1/2 (hrs)	8.77 ± 2.82	5.71 ± 3.25	154	115, 192
M-III				
Cmax (ng/ml)	55.9 ± 20.72	156 ± 25.8	35.8	28.1, 42.0
Tmax (hrs)	24 (16-49)	12 (8-16)	184	147, 221
AUC 0-∞ (ng.hr/ml)	NR	7561 ± 1634.2	-	-
T1/2 (hrs)	NR	25.4 ± 6.79	-	-
M-IV				
Cmax (ng/ml)	365 ± 106.7	377 ± 133.7	96.9	72.6,156
Tmax (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
T1/2 (hrs)	35.9 ± 8.28	32.5 ± 12.16	111	82.3, 139
Total Active Compounds				
Cmax (ng/ml)	641 ± 168.2	1139 ± 454.7	56.3	40.8, 111
Tmax (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
T1/2 (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 Cmax value in the elderly was similar to the mean value in the non-elderly control group, while the median Tmax 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)	Refrerence (non-elderly)	Test/Reference	90% Confidence Interval
Pioglitazone				
Cmax (ng/ml)	959 ± 224.3	956 ± 333.7	102	84.9, 133.5
Tmax (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
T1/2 (hrs)	10.1 ± 6.36	6.89 ± 2.20	145	102.8, 188.0
Total Active Compounds				
Cmax (ng/ml)	1264 ± 294.6	1247 ± 410.1	103	86.2, 132.7
Tmax (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
T1/2 (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 Cmax 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) [redacted]

LABELING COMMENTS:

DRAFT LABELING

[redacted]

DRAFT LABELING

[redacted]

APPEARS THIS WAY ON ORIGINAL

/S/ [redacted]

Xiaoxiong (Jim) Wei, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ [redacted]

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

APPEARS THIS WAY ON ORIGINAL

Appendix 1. Study summaries

PROTOCOL INDEX

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 Cmax value was approximately 80% of the mean value of a 45-mg pioglitazone oral suspension, while the median Tmax 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 Cmax 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 Cmax 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

PK Parameter	Test Mean [a] 45 mg Tablet (Treatment B)	Reference Mean [a] 45 mg Suspension (Treatment A)	90% Confidence Interval Test/Reference[b]	
Cmax (ng/mL)	1903 (+785.1)	2448 (i-675.5)	78.7	(64.3, 89.6)[c]
Tmax (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]
T1/2 (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 thc 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.

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 thc 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 I) 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 I and on the mornings of Days 2, 3, 4, and 7 (taken at the same time of day as dose administration on Day I for Periods I and 2).

STUDY VARIABLES:
A. Pharmacokinetic: The following parameters were calculated for unchanged pioglitazone, M-III, M-IV and total pioglitazone: AUC0.t, AUC0.~, Cmax, Tmax, and Ti/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 Cmax, AUC bioequivalence was demonstrated if the 90% confidence interval was between 80% and 120%. For the natural log (In) transformed Cmax, AUC0-t and AUC0-∞, bioequivalence was demonstrated if the 90% confidence interval was between 80% and 125%.

PHARMACOKINETIC RESULTS:

Concentrations of pioglitazone and the two mctabolites in serum were determined by a validated high-performance liquid chromatography method with UV absorbance detection. The lower limit ofquantitation for pioglitazone, M-III, and M-IV was 25.0 ng/mL in serum. The mcan (:i: standard deviation, SD) pharmacokinetic parameters of pioglitazonc, 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.

Pioglitazone

PK Parameter	Test Mean[a] Ix45 mg Tablet (Treatment B}	Reference Mean 3x15 mg Tablet[a] (Treatment A}	Ratio of LS Means Test/Reference[b] (%)	90% Confidence Interval
Cmax (ng/mL)	1482 (+499.7)	1681 (t-496.0)	88.2	(79.7, 96.6)[g]
In (Cmax) (ng/mL)	1404[d]	1612[d]	87.1	(78.8, 96.2)[c]
Tmax	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 (:k4139.1)	91.1	(82.7, 99.5)[c]
ln (AUC(0-t) *(ng*hr/mL)*	12103d	13594[a]	89.0	(80.8, 98.1)c
*AUC(0-∞) (ng*hr/mL)*	*13854 (i-4996.2)*	*15059 (i4506.3)*	*92.0*	*(83.9, 100)[c]*
*In (AUC(0-∞)) (ng*hr/mL)*	*12998[d]*	*14391[d]*	*90.3*	*(82.2, 99.3)[c]*
Ke	0.1081	0.1207	89.6	(77.9, I01)[c]
T1/2 (hours)	9.18 (±7.537)	6.42 (±2.242)	143,	(107, 179)[c]

M-III

PK Parameter	Test Mean' 1x45 mg Tablet (Treatment B)	Reference Mean' 3x15 mg Tablet (Treatment A)	Ratio of LS Means Test/Reference[b] (%)	90% Confidence Interval
Cmax (ng/mL)	168 (.-k50.7)	193 (:L-63.7)	86.8	(78.4, 95.2)c
In (~ (n~mL)	160[d]	183[d]	87.5	(80.3, 95.3)[e]
Tm, (hour)	16.0 f (8.00-47.9) f	14.0 f (6.02-23.9) f	107	(83.7, 130)g
AUC0-t (ng*hr/mL)	6954 (±2254.3)	7970 (±3039.4)	87.2	(79.1, 95.4)c
in (AUC0-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]
In AUC(0-∞) (ng*hr/mL)	8924[d]	9366[d]	94.5	(86.9, 103)[e]
Iq (hours'l)~	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 Pnrnmeter	Tat Mean' lx45 mg Tablet (Treatment B)	Reference Mean" 3x15 mg Tablet (Treatment A)	Ratio of LS Means Test/Reference[b] {.-|	90% Confidence Interval
Cmax (ng/mL)	639 (±188.9)	737 (±248.6)	86.8	*(78.0, 95.6)[c]*
!n (Cmax) (ng/mL)	613[d]	702[d]	87.2	(79.8, 95.4)[e]
Tmax (hour)	16.0[r] (6.00-23.9)[t]	16.0[t] (12.0-23.9)[f]	91.7	(79.2, 104)[l]
AUC0-t (ng*hr/mL)	29977 (±9492.9)	34686 (±12807.7)	86.4	(77.7, 95.2)[c]
in (AUC0-t) (ng*hr/mL)	285774	32689[d]	87.4	(79.8, 95.7)"
AUC(0-∞) (ng*hr/mL)	35074 (±9011.1)	38044 (±12145.6)	92.2	(85.5, 98.9)[c]
In (AUC(0-∞) (ng*hr/mL)	33993[d]	36369[d]	93.5	(86.9, 100)'
Iq (hours'~)	0.0269 (±.00664)	0.0301 (±0.00572)	89.4	(84.8, 93.9)'
T1/2 (hour)	27.2 (±6.56)	23.7 (±i4.14)	115	(109, 121)[c]

Total

PK Parameter	Test Mean[a] lx45 mg Tablet (Treatment B)	Reference Mean[a] 5x15 mg Tablet (Treatment A)	Ratio of LS Means Test/Reference[b] (%)	90% Confidence Interval
Cmax (ng/mL)	1865 (±605.3)	2108 (±588.7)	88.5	(80.1, 96.9)[c]
In (Cmax) (ng/mL)	1774d	2028[d]	87.5	(79.3, 96.5)e
Tmax (hour)'	4.00[f] (3.00-5.00)[f]	4.00[f] (2.00-5.00)[f]	101	(94.4, 108)g
AUC0-t (ng*hr/mL)	51441 (±16212.5)	58926 (±19250.8)	87.3	(79.5, 95. I)[c]
In (AUC0-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]
InAUC(0-∞) (ng*hr/mL)	54868d	60007d	91.4	(84.9, 98.5)e
Ke (hours-I)	0.0305 (±:0.00735)	0.0333 (±0.00641)	91.6	(86.3, 97.0)c
T1/2 (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 (In) transformed parameters.
f Tmax is expressed as median with thc range in parentheses.
g 90% co~. d~ce interval for $Trna_X$ calculated using means and standard errors from ANOVA.

AUC(0-.t) A,rea unoer the sermn concentraUon time curve ~ Hour 0 to the last measurable serum concentration.
AUC(0-∞) Area under the serum cmcemranon tune curve to infinity.
Terminal phase elimination/disposition rate constant.
Cm ax Maximum serum concentration.
T1/2 Terminal phase elimination/disposition half-life.
Tmax 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 £mdings that could be directly attributed to the drug. Following oral administration of lx45 mg pioglitazone tablet, the mean Cmax value for pioglitazone was approximately 88% of the mean value of 3x15 mg tablets, while the median Tmax values were similar. The mean AUC0-t and the AUC0-∞ for pioglitazone lx45 mg tablet were approximately 92% of the mean value of 3x15 mg tablets. In general, the 90% confidence intervals for the untransformed Cmax, AUC0-t, and AUC0-oo were contained between 80% and 120% and between 80% to 125% for the natural log transformed parameters, indicating that the lx45 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 I x45 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 Cmax, AUC0-t and AUC0-∞ values following the administration of lx45 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 Cmax, AUC0-t, and AUC0-∞, 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.