

Title: Single Dose Tolerance and Preliminary Single Dose Pharmacokinetics of Pioglitazone Hydrochloride in Healthy Adult Male Volunteers: Report of Protocol P/5232/0001 (BC693)

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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. These findings are 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.

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE

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.

APPEARS THIS WAY ON ORIGINAL

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

PKSAMPLING 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., Cmax, Tmax, AUC, apparent elimination rate constant, T1/2, Clp/F, and Vdarea/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) pharrnacokinetic 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 ^m (4.00-8.02) ^d	4.00 ^m (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/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
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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 _{mz_x} (hour)	4.00 ^d (4.00, 4.00) ^d	4.00 ^d (4.00, 4.00) ^e	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.

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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.

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