

## ABSTRACT

Liver function monitoring is recommended in patients receiving a thiazolidinedione (TZD). Pioglitazone (PIO; up to 45 mg) or placebo (PBO) was administered to 5238 high-risk patients with type 2 diabetes mellitus (T2D) and cardiovascular disease in PROactive (mean duration=34.5 months). We examined the effects of PIO on liver safety in this patient population. Laboratory assessments for liver function (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase [AP]) were performed at every visit during year 1 and every 6 months thereafter. The results show that there was a general shift toward normalization of ALT and AST values in the PIO group from baseline to final visit compared to no change or an increase in the PBO group.

### Patients With at Least one ALT, AST, or AP ≥3xULN at End of the Trial

	PIO N=2605	PBO N=2633	Between-Group P-Value
ALT	20 (0.8%)	33 (1.3%)	0.0791
AST	20 (0.8%)	31 (1.2%)	0.1312
AP	7 (0.3%)	8 (0.3%)	0.8120

At study entry, similar proportions of PIO and PBO patients had ALT (9.7% and 10.7%), AST (6.1% and 6.9%), or AP (6.7% and 5.8%) values above the upper limit of normal (>ULN), respectively. In the PIO group at final visit, the occurrence of elevated ALT decreased to 5.9%, whereas there was a small increase in the PBO group (11.9% at final visit; P<0.0001 between groups). More PBO than PIO patients also had elevated levels of AST (7.3% vs 4.5%; P=0.0001), respectively. There was a small decrease in the proportion of patients with AP values >ULN in the PIO group (to 5.9%) and a small increase in the PBO group (to 6.6%; P=not significant [NS]). In the PIO group, mean ALT decreased from 28.3 IU/L at baseline to 26.2 IU/L at final visit, whereas there was a small increase (2.0 IU/L) in the PBO group (P<0.0001 between groups). Long-term PIO treatment was associated with an improved hepatic laboratory profile compared with PBO in this high-risk T2D patient population. Since ALT is a marker of the amount of liver fat related to liver insulin resistance, these data suggest that treatment with PIO is associated with a lowering of liver fat content.

## INTRODUCTION

Complications of diabetes involving both microvascular and macrovascular systems contribute to increased disability and reduced life expectancy [1]. Risk of macrovascular damage among persons with diabetes is 3-5 times that of a matched nondiabetic population. The underlying pathology appears to involve an acceleration of atherosclerosis, which is especially common among diabetic patients.

Whereas microvascular complications can be controlled through management of glycemia, macrovascular outcomes remain unimproved through treatment with conventional antidiabetes agents. Insulin resistance is common to the genesis of both atherosclerosis and T2D. In diabetes, insulin resistance is coupled to receptor dysfunction. In atherosclerosis, insulin resistance may have both direct effects on the cardiovascular system, as well as indirect effects mediated by imbalances in blood glucose, lipids, clotting factors, endothelial function, and other factors.

Considerable indirect evidence suggests that peroxisome proliferator-activated receptor (PPAR) agonists may favorably influence macrovascular outcome [2]. In contrast to other antidiabetes agents that function by other mechanisms of action, PIO, a TZD that functions as a PPAR $\gamma$  agonist, addresses a core defect of T2D by reducing insulin resistance at the cellular level. This study was designed to evaluate whether PIO (versus PBO) in combination with other antidiabetic agents might reduce the incidence of macrovascular events associated with T2D.

## OBJECTIVES

- 1) To demonstrate that PIO reduces total mortality and macrovascular morbidity in high-risk patients with T2D.
- 2) To further characterize the safety of PIO in this patient population.

The analysis of liver safety is presented here.

## METHODS

• Multicenter, randomized, double-blind, placebo-controlled, parallel-group study design.

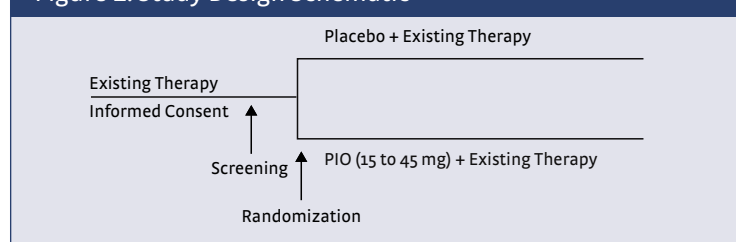
### Subjects were:

- Between the ages of 35 to 75 years.
- Diagnosed with T2D and had an A1C level above the ULN (the local equivalent of 6.5%, as defined by the 1999 International Diabetes Federation Guidelines [3]).
- Required to have had an established history of macrovascular disease, defined as experiencing one or more of the following events at least 6 months prior to study entry: myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass graft, acute coronary syndrome; objective evidence of coronary artery disease; peripheral arterial obstructive disease.

### Main exclusion criteria included:

- Use of insulin as sole therapy for glycemic control for a minimum of 2 weeks during the 3 months prior to study entry.
- Current use of or known hypersensitivity to a TZD.

Figure 1. Study Design Schematic



Treatment with the highest tolerated dose was continued until patients were exposed to PIO (or PBO) for 2.5 to 3.5 years. During the first year, all assessments took place at 1, 2, 4, 6, 8, 10, and 12 months, and then every 3 months thereafter. Liver function tests—including ALT, AST, and AP—were performed at every visit during the first year and every 6 months thereafter.

## RESULTS

### Subject Disposition

A total of 5238 patients received study medication—2605 received PIO and 2633 received PBO. Overall, 5236 patients completed the study (2 patients were lost to follow-up). Of these, 4373 (83.5%) patients completed the study while taking study medication: 2178 (83.6%) in the PIO group and 2195 (83.4%) in the PBO group.

A similar number of patients in each treatment group prematurely discontinued study medication: 427 (16.4%) in the PIO group and 438 (16.6%) in the PBO group. The most common reasons for discontinuation were adverse events (235 and 202 in the PIO and PBO groups, respectively) and withdrawal of consent (171 and 179 in the PIO and PBO groups, respectively).

### Demographic and Baseline Characteristics

There were no differences between treatment groups in any of the demographic or Baseline characteristics, including Baseline laboratory values for liver function.

Table 1. Summary of Demographic and Baseline Characteristics

Characteristic	PIO N=2605	PBO N=2633	Overall N=5238
Gender, n (%)			
Male	1735 (66.6)	1728 (65.6)	3463 (66.1)
Female	870 (33.4)	905 (34.4)	1775 (33.9)
Age (years)	61.9 (7.60)	61.6 (7.75)	61.8 (7.68)
Race, n (%)			
White	2564 (98.4)	2600 (98.7)	5164 (98.6)
Black	10 (0.4)	7 (0.3)	17 (0.3)
Asian/Oriental	29 (1.1)	23 (0.9)	52 (1.0)
Other	2 (0.1)	3 (0.1)	5 (0.1)
BMI (kg/m <sup>2</sup> )	30.7 (4.73)	31.0 (4.79)	30.9 (4.76)
Duration of Diabetes (years)	9.4 (6.94)	9.6 (7.09)	9.5 (7.02)

Data are presented as mean (SD) unless otherwise indicated. SD=standard deviation; BMI=body mass index.

### Extent of Exposure

The mean (±SD) duration of exposure to study medication was 908.2 (±291.43) days for patients in the PIO group and 909.6 (±291.43) days for patients in the PBO group, or approximately 30.3 months for both groups. Approximately 90% of the patients in both treatment groups had their study medication titrated, as scheduled, to the 45 mg dose at Month 2 of the study; from that point onward, over 90% of the patients who remained on study medication received the 45 mg dose. At Month 30, 1943 (94.5%) patients had received 45 mg of PIO and 2040 (97.7%) had received matching PBO.

### Liver Function Results

Incidences of high ALT, AST, or AP values were low in both groups, and very few patients in either group had elevations ≥3xULN in any of these variables. Compared with PBO, PIO patients showed a trend toward normalization of high liver function values from Baseline to the Final Visit.

Figure 2. Effect of PIO Versus PBO on Liver Function Tests at Final Visit



### ALT

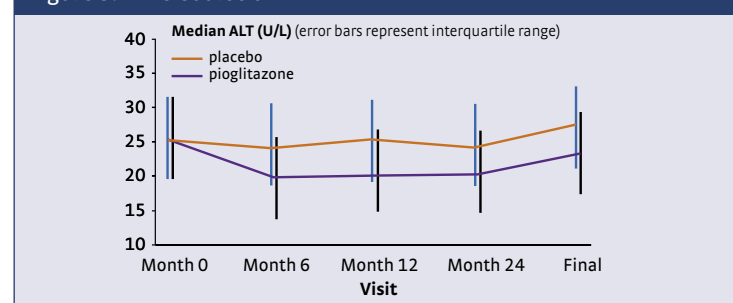
A similar proportion of patients with abnormal ALT results were entered into each treatment group at Baseline. A general shift towards normalization was observed for the PIO group, with a lower percentage of patients having a high ALT value both at Month 30 and the Final Visit compared to Baseline. In the PBO group, a higher percentage of patients had a high ALT value at the Final Visit compared to Baseline. Throughout the study, very few patients had ALT measurements that were ≥3xULN—20 (0.8%) in the PIO group and 33 (1.3%) in the PBO group.

Table 2. ALT Values

ALT (U/L)	N	PIO N=2605	N	PBO N=2633
Baseline				
Mean Value (SD)	2561	28.3 (15.42)	2583	29.2 (19.77)
Number (%) of patients with high ALT*	2561	248 (9.7)	2583	277 (10.7)
Number (%) of patients with ALT ≥3xULN	2561	2 (0.1)	2583	5 (0.2)
Month 30				
Mean Value (SD)	2095	23.8 (11.90)	2104	29.4 (17.77)
Mean change from Baseline (SD)	2066	-4.5 (14.72)	2068	0.0 (18.38)
Percent change from Baseline (SD)	2066	-4.40 (55.070)	2068	12.20 (68.199)
Number (%) of patients with high ALT*	2095	82 (3.9)	2104	211 (10.0)
Number (%) of patients with ALT ≥3xULN	2095	1 (0.0)	2104	2 (0.1)
Final Visit				
Mean Value (SD)	2215	26.2 (15.30)	2217	31.5 (21.14)
Mean change from Baseline (SD)	2179	-2.4 (16.65)	2176	2.0 (21.44)
Percent change from Baseline (SD)	2179	2.58 (51.918)	2176	20.03 (117.576)
Number (%) of patients with high ALT*	2215	130 (5.9)	2217	264 (11.9)
Number (%) of patients with ALT ≥3xULN	2215	4 (0.2)	2217	5 (0.2)

\*Above central laboratory's reference range, 47 U/L. SD=standard deviation.

Figure 3. Time Course of ALT



### AST

A similar proportion of patients with abnormal AST results were entered into each treatment group at Baseline. A general shift towards normalization was observed for the PIO group, with a lower percentage of patients having a high AST value both at Month 30 and the Final Visit compared to Baseline. In the PBO group, a higher percentage of patients had a high AST value both at Month 30 and the Final Visit compared to Baseline. Throughout the study, there were very few patients with AST measurements that were ≥3xULN—20 (0.8%) in the PIO group and 31 (1.2%) in the PBO group.

Table 3. AST Values

AST (U/L)	N	PIO N=2605	N	PBO N=2633
Baseline				
Mean Value (SD)	2561	22.6 (10.42)	2581	22.8 (11.23)
Number (%) of patients with high AST*	2561	155 (6.1)	2581	177 (6.9)
Number (%) of patients with AST ≥3xULN	2561	2 (0.1)	2581	5 (0.2)
Month 30				
Mean Value (SD)	2121	22.8 (8.97)	2120	24.0 (10.23)
Mean change from Baseline (SD)	2094	0.4 (10.15)	2081	1.2 (11.40)
Percent change from Baseline (SD)	2094	9.43 (39.129)	2081	13.51 (46.967)
Number (%) of patients with high AST*	2121	89 (4.2)	2120	161 (7.6)
Number (%) of patients with AST ≥3xULN	2121	3 (0.1)	2120	1 (0.0)
Final Visit				
Mean Value (SD)	2246	22.8 (9.80)	2242	23.7 (11.20)
Mean change from Baseline (SD)	2212	0.1 (11.03)	2200	0.9 (11.87)
Percent change from Baseline (SD)	2212	7.87 (36.749)	2200	11.41 (49.794)
Number (%) of patients with high AST*	2246	102 (4.5)	2242	163 (7.3)
Number (%) of patients with AST ≥3xULN	2246	2 (0.1)	2242	3 (0.1)

\*Above central laboratory's reference range, 37 U/L. SD=standard deviation.

### AP

More patients with AP results that were above the ULN were entered into the PIO group than into the PBO group at Baseline. A general shift towards normalization was observed for the PIO group, with a lower percentage of patients having a high AP value both at Month 30 and the Final Visit compared to Baseline. In the PBO group, a higher percentage of patients had a high AP value at the Final Visit compared to Baseline. Throughout the study, there were very few patients with AP measurements that were ≥3xULN—7 (0.3%) in the PIO group and 8 (0.3%) in the PBO group.

Table 4. AP Values

AP (U/L)	N	PIO N=2605	N	PBO N=2633
Baseline				
Mean Value (SD)	2564	90.5 (32.31)	2585	89.7 (28.69)
Number (%) of patients with high AP*	2564	171 (6.7)	2585	151 (5.8)
Number (%) of patients with AP ≥3xULN	2564	2 (0.1)	2585	0 (0.0)
Month 30				
Mean Value (SD)	2146	74.9 (26.20)	2146	78.7 (28.18)
Mean change from Baseline (SD)	2119	-14.2 (25.56)	2110	-10.7 (23.51)
Percent change from Baseline (SD)	2118	-13.10 (27.058)	2110	-9.74 (26.395)
Number (%) of patients with high AP*	2146	46 (2.1)	2146	73 (3.4)
Number (%) of patients with AP ≥3xULN	2146	1 (0.0)	2146	0 (0.0)
Final Visit				
Mean Value (SD)	2266	87.8 (32.32)	2268	90.8 (33.56)
Mean change from Baseline (SD)	2233	-2.1 (28.79)	2230	1.6 (26.55)
Percent change from Baseline (SD)	2232	0.75 (33.012)	2230	4.5 (33.239)
Number (%) of patients with high AP*	2266	134 (5.9)	2268	149 (6.6)
Number (%) of patients with AP ≥3xULN	2266	2 (0.1)	2268	2 (0.1)

\*Above central laboratory's reference range, 135 U/L. SD=standard deviation.

## CONCLUSION

Long-term PIO treatment was associated with an improved hepatic laboratory profile compared with PBO in this high-risk T2D patient population. Since ALT is a marker of the amount of liver fat related to liver insulin resistance, these data suggest that treatment with PIO may be associated with a lowering of liver fat content.

## REFERENCES

1. International Diabetes Federation. Diabetes Atlas 2000;19.
2. Buchan KW, Hassal DG. PPAR agonists as direct modulators of the vessel wall in cardiovascular disease. Med Res Rev 2000;20(5):350-66.
3. European Diabetes Policy Group. Guidelines for diabetes care. A desktop guide to type 2 diabetes mellitus. International Diabetes Federation European Region. 1998-1999. Diabetic Medicine 1999;16:716-30.