

## Long-term Pioglitazone Treatment Improves Markers of Liver Function: Results from PROactive

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Liver function monitoring is recommended in patients receiving a thiazolidinedione. Pioglitazone (PIO; up to 45 mg) or placebo (PBO) was administered to 5238 high-risk patients with type 2 diabetes (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 $\geq 3 \times$ ULN 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%;  $p = NS$ ). 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.