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# Liver Safety in Patients with Type 2 Diabetes Treated with Pioglitazone

## Results from a 3-Year, Randomized, Comparator-Controlled Study in the US

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## Abstract

**Background/aims:** Non-alcoholic fatty liver disease (NAFLD), the major hepatic manifestation of type 2 diabetes mellitus, is the most common liver disease in the US. Thiazolidinediones, a commonly used drug class for the treatment of type 2 diabetes, have emerged as a potentially useful treatment for NAFLD. There are, however, lingering concerns about their potential toxicity as well as emerging concerns about how to monitor for and assess hepatotoxicity. We conducted a randomized, long-term, double-blind, hepatic safety study at 171 centres in the US in which 2097 patients with type 2 diabetes received either pioglitazone or glibenclamide (glyburide).

**Methods:** Patients were randomized to receive either pioglitazone (15–45 mg once daily) or glibenclamide (5–15 mg once daily) for 3 years. The primary objective was to evaluate drug-induced liver injury manifested by liver enzyme elevations, measured every 8 weeks for the first year and every 12 weeks thereafter. The primary endpoint was a confirmed ALT greater than three times the upper limit of normal (>3 × ULN) with a secondary endpoint of 8 × ULN.

**Main results:** The intent-to-treat population included 1051 pioglitazone-treated and 1046 glibenclamide-treated patients; of these, 411 pioglitazone patients and 413 glibenclamide patients completed the study. The incidence of hepatocellular injury was 0 with pioglitazone and 4 (0.38%) with glibenclamide ($p = 0.0617$). Analyses of the secondary endpoints revealed no ALT >8 × ULN for pioglitazone versus 1 with glibenclamide ($p = 0.4988$); no ALT >3 × ULN + total bilirubin 2 × ULN with pioglitazone versus 1 with glibenclamide ($p = 0.4988$); and fewer ALT >3 × ULN single elevations with pioglitazone ($n = 3$) than with glibenclamide ($n = 9$; $p = 0.0907$). Significantly ($p \leq 0.05$) fewer cases of ALT >1.5 × ULN, aspartate aminotransferase >1.5 × ULN and γ-glutamyl transpeptidase >1.5 × ULN were seen with pioglitazone compared with glibenclamide. No case of hepatic dysfunction or hepatic failure was

reported in either treatment group; two cases of hepatic cirrhosis with glibenclamide were reported.

**Conclusion:** This study demonstrates an hepatic safety profile of pioglitazone similar to that of glibenclamide in long-term use in patients with poorly controlled type 2 diabetes.

Trial registration number (clinicaltrials.gov): NCT00494312

## Background

Non-alcoholic fatty liver disease (NAFLD), primarily associated with insulin resistance/type 2 diabetes mellitus, is the most common liver disease in the US[1] and the third leading indication for liver transplantation.[2] Patients with NAFLD often progress to non-alcoholic steatohepatitis, with many further progressing to cirrhosis and, in some cases, hepatocellular carcinoma. Thiazolidinediones (TZDs) have emerged as a potential but as yet unproven therapy for NAFLD. There are, however, concerns about their potential hepatotoxicity due to the experience with troglitazone, which was withdrawn from the market because of drug-induced liver injury (DILI).

TZDs are highly selective agonists of the nuclear receptor peroxisome proliferator activated receptor-gamma (PPARγ).[3] They enhance insulin sensitivity, lower insulin levels and improve glucose homeostasis – all of which are beneficial in the treatment of diabetes. Because they do not disrupt the feedback mechanism that regulates glucose metabolism, TZDs are not associated with hypoglycaemia. TZDs have additional effects that may be uniquely therapeutic for NAFLD. There is increasing evidence that insulin resistance is a downstream effect of excess energy that, in the liver, leads to excess free fatty acids.[4] This may in turn lead to up-regulation of apoptotic receptors and induce tumour necrosis factor-gamma (TNFγ), which inhibits PPARγ.[5,6] TZDs increase fatty acid metabolism, lower triglycerides, increase adiponectin, increase fatty acid uptake by adipocytes, and shift visceral fat to subcutaneous fat – all of which should be beneficial in the treatment of NAFLD. Recent studies have, in fact, confirmed the benefits of both pioglitazone and rosiglitazone in NAFLD.[7,8] Interestingly, in the rosiglitazone trial, absence of diabetes was a predictor of response, raising the possibility that insulin resistance and type 2 diabetes are downstream effects of fatty liver disease.

The experience with troglitazone heightened the awareness of potential hepatotoxicity of the newer TZDs (pioglitazone and rosiglitazone) despite the absence of signals of hepatotoxicity during development or at the time of US FDA approval.[9] To date, there are only scattered reports of hepatotoxicity with the TZDs, with an estimate of acute liver failure from the FDA adverse drug reporting of 3–4 per million patient-years of exposure.[10,11] Nor is there evidence that patients with underlying liver disease are at increased risk of DILI.[12] It is increasingly apparent that DILI is not a class characteristic of TZDs, but rather a unique property of troglitazone. Furthermore, numerous studies support the hepatic safety of the TZDs, including a long-term cardiovascular outcome study,[13] a pooled analysis of mostly 1-year studies[14] and a post-marketing cohort surveillance study.[15] Nonetheless, a lingering perception persists that TZDs may be associated with DILI.

In this study,[1] we report the results of a 3-year, randomized, double-blind, multicentre, comparator-controlled study designed to determine whether pioglitazone is associated with DILI in patients with diabetes. The comparator agent was glibenclamide (glyburide),[16] a widely used sulphonylurea that has only rarely been associated with mixed hepatocellular/cholestatic and

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granulomatous reactions in the liver.[17-19] The study was designed and performed in accordance with a phase IV commitment made to the FDA upon regulatory approval of pioglitazone for marketing in the US.

## Methods

### Experimental Procedures

The study was conducted at 171 US centres (31 October 2000 through to 15 June 2005). Eligible patients were 18–80 years of age with a diagnosis of type 2 diabetes,[20] had haemoglobin A1c (HbA1c) levels ≥7.0% and were taking the maximum daily dose of either glibenclamide (20 mg) or other second-generation sulphonylureas,[21] metformin monotherapy or metformin in combination with a second-generation sulphonylurea. Patients who discontinued troglitazone treatment during March or April 2000 for reasons other than adverse experiences were eligible; however, patients with other prior TZD exposure, ongoing use of first-generation sulphonylurea medications or taking more than the maximum daily dose of glibenclamide were not eligible for participation.

Patients with type 1 diabetes, a history of ketoacidosis, body mass index <20 or >48 kg/m$^2$, ALT ≥2.5 times the upper limit of normal (≥2.5 × ULN) or a history of hepatobiliary disease were excluded. Patients with New York Heart Association class III or IV heart failure or a recent history (within 6 months) of myocardial infarction (MI), cerebrovascular accident or other acute cardiovascular event were also excluded. The use of antidiabetic agents (other than study drug and companion medications), weight-loss agents, continuous (>2 weeks) corticosteroid therapy or niacin therapy were prohibited during the study.

The study was conducted in accordance with the World Medical Association Declaration of Helsinki (2000).[22] All patients provided written informed consent.

Sulphonylurea use was discontinued at screening (≤2 weeks prior to treatment randomization). Randomization was 1 : 1 (pioglitazone : glibenclamide) stratified by baseline glibenclamide use and factors potentially contributing to hepatotoxicity (e.g. HMG-CoA reductase inhibitor ['statin'] use, ALT level >1.5 × ULN). Treatment assignment was via an interactive voice-response service vendor. All study personnel and patients were blinded to treatment assignment; study drugs were over-encapsulated and provided in a double-dummy design to maintain treatment blinding.

Study drug doses were increased to the maximally tolerated daily dose (up to 45 mg for pioglitazone or 15 mg for glibenclamide) to maintain glycaemic control. Lack of glycaemic control was defined as HbA1c levels ≥7.5% for 3 months. Earlier dose titration was permitted for hyperglycaemia based on clinical findings and laboratory tests. If the maximally tolerated daily dose of study drug failed to achieve glycaemic control, metformin dosing was increased (up to a maximum of 2000 mg daily) or added to the treatment regimen. For patients taking the maximally tolerated daily dose of study drug and metformin, insulin was added.

Downward titration of study drug dose occurred in cases of serious hypoglycaemia or multiple hypoglycaemic events in a single day only after insulin and metformin doses were first reduced and then discontinued.

Assessment visits occurred every 2 months during the first year and every 3 months thereafter. Liver enzyme testing was performed at screening, at each scheduled visit (including the final visit) and when clinically indicated (i.e. when symptoms suggestive of hepatic dysfunction, e.g. nausea, vomiting, abdominal pain, fatigue, anorexia or dark urine, occurred). Dosing compliance, adverse events (AEs), use of concomitant medications, vital signs and changes in medical history were recorded at each visit. HbA1c and urinalysis were determined periodically throughout the study.

### Primary and Secondary Variables

The primary endpoint was the incidence of ALT >3 × ULN, confirmed by an immediate repeat test. The secondary endpoints were incidences of liver abnormalities defined as (i) ALT >8 × ULN; (ii) ALT >3 × ULN, but ≤8 × ULN for four consecutive measurements within a 3-month period; (iii) ALT >3 × ULN plus total bilirubin >2 × ULN; and (iv) an elevation >1.5 × ULN or

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| Case summary: | | |
|---|---|---|
| Assessment: | | |
| type of reaction: | | |
| severity: | | |
| exposure: | | |
| temporal sequence: | | |
| competing cause: | | |
| dechallenge: | | |
| rechallenge: | | |
| Causality attribution: | | |
| **Definitely related**<br>Exposed<br>Temporal sequence<br>No obvious competing cause<br>Dechallenge positive<br>Rechallenge positive | **Possibly related**<br>Exposed<br>Temporal sequence<br>Obvious competing cause<br>Dechallenge positive | **Probably related**<br>Exposed<br>Temporal sequence<br>No obvious competing cause<br>Dechallenge positive<br>Rechallenge negative/ ambiguous/not done |
| **Probably not related**<br>Exposed<br>More likely competing cause<br>Dechallenge negative/ambiguous<br>Rechallenge negative/ambiguous | **Definitely not related**<br>Not exposed/other obvious cause | |
| Confounders present: | | |
| A. Hepatocellular: ALT >3 × ULN, alkaline phosphatase 2 × ULN<br>Cholestatic: ALT <3 × ULN, alkaline phosphatase >1 × ULN<br>Mixed: ALT >3 × ULN, alkaline phosphatase >1.5 × ULN | B. Mild: ALT <3 × ULN, bilirubin normal, asymptomatic<br>Moderate: ALT >3 × ULN, <8 × ULN, bilirubin normal, asymptomatic<br>Severe: ALT >8 × ULN and/or bilirubin >2 × ULN and/or symptomatic/hospitalized | |

**Fig. 1.** Worksheet for assessment of drug-induced liver injury (DILI) based on Roussel Uclaf Causality Assessment Method (RUCAM) scale.[23] (i) Hepatocellular reaction = ALT >3 × upper limit of normal (ULN), alkaline phosphatase <2 × ULN; cholestatic reactions = ALT < 3 × ULN or ALT elevation only, alkaline phosphatase >2 × ULN or alkaline phosphatase elevation only; mixed reactions = those not meeting above criteria. (ii) Temporal sequence = yes if reaction occurred ≤6 months post-exposure. (iii) Case summary included age, height, weight, sex, concomitant medications and medical conditions.

baseline, whichever was greater, in AST, ALT, total or direct bilirubin, alkaline phosphatase (ALP), or γ-glutamyl transpeptidase (γGT). Samples for laboratory tests were collected after an 8-hour fast and analysed at a central laboratory (Clinical Reference Laboratory, Lenexa, KS, USA).

### Safety Assessments

Safety variables included AEs, clinical laboratory tests (haematology, serum chemistry and urinalysis), vital signs and physical examination. Patients were monitored for evidence of drug intolerance and AEs (clinical or laboratory evidence); AEs were collected at each study visit and not adjudicated. The study was monitored by an independent Drug and Safety Monitoring Board (DSMB).

Determination of DILI causality was assessed using a modified Roussel Uclaf Causality Assessment Method RUCAM scale[23] (figure 1). Consensus was reached by a five-member DSMB, who defined the severity as mild, moderate or severe, and causality as definitely related, probably related, possibly related, probably not related or definitely not related.

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### Statistical Analyses

The proposed recruitment of 2000 patients randomized to study drug (1000 patients per treatment group) was determined by agreement with the FDA. Analyses were based on the intent-to-treat population, which included all patients who received at least one dose of medication. The Cochran-Mantel-Haenszel procedure[24] was used for treatment comparison of the primary endpoint. When the number of patients experiencing an event was <5, a Fisher Exact Test was performed and a p-value reported. The Kaplan-Meier method was used to describe the time to first occurrence of the primary endpoint; a log-rank test was used to determine treatment-group differences. The primary endpoint was also analysed for the pre-specified subgroups of age (<65 years, ≥65 years), sex, race (Caucasian, non-Caucasian), randomization stratification (ALT >1.5× ULN: yes or no) and baseline disease status (HbA1c <8.0%: yes or no). Analyses of primary and secondary endpoints were also performed in a subset of patients who took concomitant statins.

Time to withdrawal due to either an AE or lack of therapeutic effect is described using the Kaplan-Meier method; a log-rank test was used to determine treatment-group differences. For HbA1c, changes from baseline were analysed using a two-way analysis of co-variance, with treatment and pooled centre as fixed effects and baseline value as co-variate.

## Results

### Patient Disposition and Baseline Characteristics

A total of 2120 patients were randomized into the study: 1063 pioglitazone and 1057 glibenclamide (figure 2). Overall, 824 (38.9%) patients completed the study; 1290 (649 pioglitazone, 641 glibenclamide) did not complete the study. The most common reasons for this were withdrawal of consent, lost to follow-up, AEs and investigator discretion. There were no apparent treatment-group differences in the reasons for not completing. The intent-to-treat population included

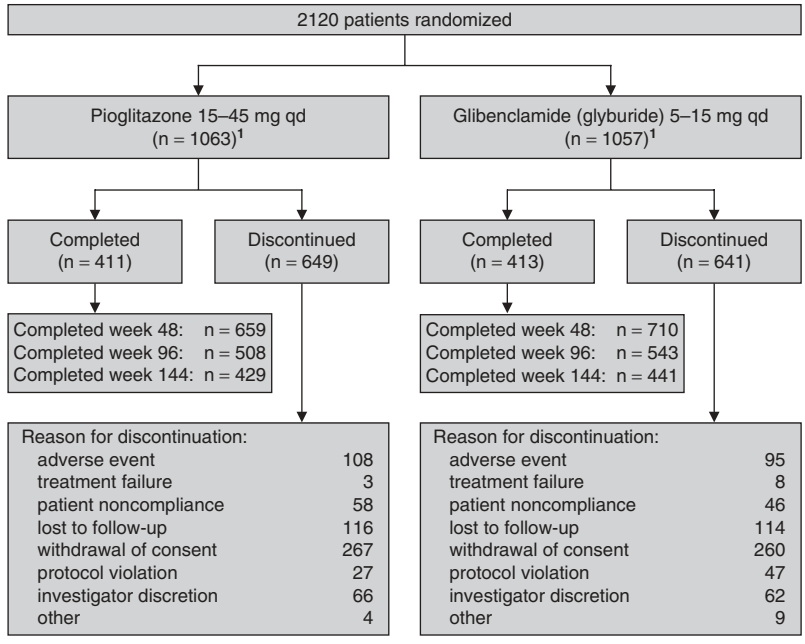


**Fig. 2.** Patient disposition. **qd** = once a day. **1** Information for three patients in each treatment group could not be verified. Therefore, these six patients are counted as randomized but not included in the disposition breakdown.

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**Table I.** Summary of baseline demographics, characteristics and prior use of antidiabetic medications (intent-to-treat population)

| Characteristic | Pioglitazone | | Glibenclamide (glyburide) | |
|---|---|---|---|---|
| | N | 15–45 mg qd | N | 5–15 mg qd |
| Sex [n (%)] | 1051 | | 1046 | |
| male | | 601 (57.2) | | 581 (55.5) |
| female | | 450 (42.8) | | 465 (44.5) |
| Age, y [median (range)] | | 54 (20–82) | | 55 (19–81) |
| Race/ethnicity [n (%)] | 1051 | | 1046 | |
| Caucasian | | 628 (59.8) | | 650 (62.1) |
| African-American | | 152 (14.5) | | 138 (13.2) |
| Hispanic | | 201 (19.1) | | 196 (18.7) |
| Asian | | 36 (3.4) | | 26 (2.5) |
| BMI, kg/m$^2$ [mean (SD)] | 1048 | 32.5 (6.1) | 1045 | 32.5 (6.0) |
| Systolic blood pressure, mmHg [mean (SD)] | 1051 | 130.8 (15.4) | 1046 | 130.3 (15.4) |
| Diastolic blood pressure, mmHg [mean (SD)] | 1051 | 79.4 (9.0) | 1046 | 79.4 (9.0) |
| Duration of diabetes, wks [mean (SD)] | 1046 | 305 (301) | 1043 | 292 (280) |
| HbA1c, % [mean (SD)] | 1048 | 9.5 (2.0) | 1046 | 9.5 (2.0) |
| ALT, U/L [mean (SD)] | 1050 | 28.0 (16.3) | 1046 | 28.3 (16.3) |
| AST, U/L [mean (SD)] | 1050 | 22.1 (10.3) | 1046 | 22.3 (11.2) |
| Alkaline phosphatase, U/L [mean (SD)] | 1050 | 92.3 (27.4) | 1046 | 91.2 (28.0) |
| γGT, U/L [mean (SD)] | 1051 | 37.3 (37.6) | 1046 | 36.5 (30.8) |
| Total bilirubin, mg/dL [mean (SD)] | 1051 | 0.49 (0.23) | 1046 | 0.48 (0.23) |
| Direct bilirubin, mg/dL [mean (SD)] | 1050 | 0.12 (0.05) | 1046 | 0.12 (0.05) |
| Above normal range [n (%)] | 1051 | | 1046 | |
| ALT | | 143 (13.6) | | 163 (15.6) |
| AST | | 73 (6.9) | | 85 (8.1) |
| alkaline phosphatase | | 172 (16.4) | | 163 (15.6) |
| γGT | | 132 (12.6) | | 116 (11.1) |
| total bilirubin | | 29 (2.8) | | 29 (2.8) |
| direct bilirubin | | 3 (0.3) | | 2 (0.2) |
| **Prior medications [n (%)]** | | | | |
| Sulphonylureas | 1034 | 681 (64.8) | 1038 | 677 (64.7) |
| Metformin | 1034 | 722 (68.7) | 1038 | 708 (67.7) |
| Statins | 1034 | 309 (29.4) | 1038 | 296 (28.3) |
| Fibrates | 1034 | 48 (4.6) | 1038 | 59 (5.6) |

**γGT** = γ-glutamyl transpeptidase; **BMI** = body mass index; **HbA1c** = haemoglobin A1c; **qd** = once daily.

1051 pioglitazone-treated and 1046 glibenclamide-treated patients.

Treatment groups were well matched for demographic and baseline characteristics (table I). The study population was 56% male, racially diverse and had a median age of 55 years (range 19–82 years).

Consistent with a population of patients with diabetes, nearly all patients (95%) took at least one concomitant medication. Approximately one-third of patients received statin therapy and fewer than 10% in each group used fibrates. During the study, 39 (0.4%) pioglitazone-treated patients and 58 (0.6%) glibenclamide-treated patients had insulin added to their treatment regimen.

Approximately 40% of patients completed at least 145 weeks of treatment. During the study, 56% of patients reached maximally tolerated daily dose levels (pioglitazone 45 mg and glibenclamide

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15 mg), 25% reached intermediate dosing levels (30 and 10 mg, respectively) and nearly 20% were at the lowest dosing level (15 and 5 mg, respectively). As measured by tablet count, significantly fewer pioglitazone-treated than glibenclamide-treated patients were treatment compliant (82% vs 88%; p = 0.0214).

### Liver Enzyme Effects

The incidence of the primary endpoint (ALT >3 × ULN confirmed by an immediate repeat test) was 0% in the pioglitazone group and 0.38% in the glibenclamide group (p = 0.0617) [table II]. This observation is consistent with the incidence of ALT >1.5 × ULN or 1.5 times baseline (pioglitazone = 26 [2.47%]; glibenclamide = 75 [7.17%]; p < 0.0001) [table II]. Relative to glibenclamide-treated patients, pioglitazone-treated patients also included significantly fewer cases of elevated AST >1.5 × ULN or 1.5 times baseline (p = 0.0040) and γGT >1.5 × ULN or 1.5 times baseline (p < 0.0001).

Pioglitazone-treated patients had reductions in ALT (p = 0.0001), AST (p = 0.0051), bilirubin (p = 0.0657), ALP (p = 0.0002) and γGT (p = 0.0005) from baseline during the study, while glibenclamide-treated patients had slight increases in ALT, AST and γGT, and slight decreases in bilirubin and ALP that were not statistically significant (table III). These reductions were evident at all post-baseline visits out to week 156, with statistically significant between-group differences present at each visit for ALT (p < 0.0001) and AST (p ≤ 0.0051).

In total, three pioglitazone-treated and nine glibenclamide-treated patients had an ALT value ≥3 × ULN at any time during the study. The reaction was considered severe (i.e. ALT >8 × ULN and bilirubin >2 × ULN) in no pioglitazone-treated patients and in one glibenclamide-treated patient. Among the three pioglitazone-treated patients who discontinued treatment, ALT returned to normal while either on treatment (one patient) or after treatment discontinuation (one patient). The third patient was withdrawn from the study because of a kidney infection and had no follow-up ALT values. Among glibenclamide-treated patients who discontinued treatment, the ALT value returned to normal (one patient) or to <3 × ULN (three patients). For the remaining five glibenclamide patients who continued treatment, ALT levels returned to near-baseline values (within

**Table II.** Summary of liver abnormality incidence (primary and secondary endpoints) at 156 weeks (intent-to-treat population)

| Parameter | Incidence [n (%)] | | Difference in incidence (pioglitazone-glibenclamide) [%] | p-Value[a] |
|---|---|---|---|---|
| | pioglitazone 15–45 mg qd (n = 1051) | glibenclamide (glyburide) 5–15 mg qd (n = 1046) | | |
| **Primary outcome** | | | | |
| ALT >3 × ULN confirmed by immediate repeat test | 0 (0.0) | 4 (0.38) | −0.38 | 0.0617 |
| **Secondary outcomes** | | | | |
| ALT >3 × ULN (%), at least one episode | 3 (0.29) | 9 (0.86) | −0.58 | 0.0907 |
| ALT >8 × ULN | 0 (0.0) | 1 (0.10) | −0.10 | 0.4988 |
| ALT >3 × ULN and total bilirubin >2 × ULN | 0 (0.0) | 1 (0.10) | −0.10 | 0.4988 |
| ALT >1.5 × ULN or baseline, whichever is greater | 26 (2.47) | 75 (7.17) | −4.70 | <0.0001 (95% CI −6.52, −2.87) |
| AST >1.5 × ULN or baseline, whichever is greater | 22 (2.09) | 45 (4.30) | −2.21 | 0.0040 (95% CI −3.71, −0.71) |
| Total bilirubin >1.5 × ULN or baseline, whichever is greater | 7 (0.67) | 4 (0.38) | 0.28 | 0.5478 |
| Direct bilirubin >1.5 × ULN or baseline, whichever is greater | 3 (0.29) | 1 (0.10) | 0.19 | 0.6246 |
| ALP >1.5 × ULN or baseline, whichever is greater | 8 (0.76) | 14 (1.34) | −0.58 | 0.1947 |
| γGT >1.5 × ULN or baseline, whichever is greater | 36 (3.43) | 79 (7.55) | −4.13 | <0.0001 (95% CI −6.07, −2.18) |

a p-Values derived from a Cochran-Mantel-Haenszel procedure when patient numbers were at least five in both treatment groups, otherwise from a Fisher Exact Test. Confidence intervals are only provided for statistically significant differences.

**γGT** = γ-glutamyl transpeptidase; **ALP** = alkaline phosphatase; **qd** = once daily; **ULN** = upper limit of normal range.

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**Table III.** Summary of mean changes from baseline to week 156 for liver function test (intent-to-treat population)[a]

| Analyte | Pioglitazone 15–45 mg qd (n = 1051) | | | Glibenclamide (glyburide) 5–15 mg qd (n = 1046) | | |
|---|---|---|---|---|---|---|
| | baseline | change | p-value | baseline | change | p-value |
| ALT (U/L) | 28.0 | −6.1 | <0.0001 | 28.3 | 2.4 | NS |
| AST (U/L) | 22.1 | −0.6 | 0.0051 | 22.3 | 3.4 | NS |
| Total bilirubin (mg/dL) | 0.49 | −0.06 | 0.0657 | 0.48 | −0.04 | NS |
| ALP (U/L) | 92.3 | −12.6 | 0.0002 | 91.2 | −6.4 | NS |
| γGT (U/L) | 37.3 | −11.9 | 0.0005 | 36.5 | 4.0 | NS |

a Baseline values are expressed as means. Change is mean change from baseline to final visit, and was calculated for 401 patients in the pioglitazone group and 410 patients in the glibenclamide group. p-Values were from analysis of co-variance with terms for treatment, centre and baseline value (as a co-variate).

**γGT** = γ-glutamyl transpeptidase; **ALP** = alkaline phosphatase; **NS** = not significant; **qd** = once daily.

15 U/L). Because of the predetermined criteria, ALT elevations in patients whose ALT returned to normal while on treatment were not designated as drug-induced, leaving two pioglitazone-treated and four glibenclamide-treated patients as having probable or possible DILI. In retrospect, the one pioglitazone-treated and five glibenclamide-treated patients probably did have DILI with so-called adaptation,[25,26] a phenomenon characterized by minor injury to the liver with recovery while still taking the injurious agent and associated with resistance to injury upon subsequent exposure. The mean time to onset for ALT value ≥3 × ULN was 43 (15–67) weeks for pioglitazone and 75 (33–154) weeks for glibenclamide.

#### *Subgroup Analyses*

Analyses of primary and secondary endpoints were performed in a subset of statin-treated patients (table IV). In the presence of statins, patients receiving pioglitazone (n = 397) had fewer incidences of elevated ALT at most thresholds compared with those receiving glibenclamide (n = 390); the difference was statistically significant (p = 0.0005) in the case of ALT >1.5 × ULN or baseline.

There were no differences from the intent-to-treat analysis in subsets of age, sex, race, randomization stratification or baseline disease status for either the primary or secondary endpoints.

### Glycaemic Effects

Consistent with the mechanism of action of the study drugs, early glycaemic control was better with glibenclamide than with pioglitazone treatment through week 16 (mean at week 16 change was −0.29 ± 2.27% with pioglitazone vs −1.12 ± 1.98% with glibenclamide; p < 0.001), similar between treatments until week 48 and better with pioglitazone from week 72 (mean change at week 72 values: −2.07 ± 2.07% vs −1.76 ± 2.10%, respectively; p = 0.0002) through to the end of the study (mean change at week 156 was −2.34 ± 2.08% with pioglitazone vs −1.85 ± 2.07% with glibenclamide; p ≤ 0.0008). However, there was no significant treatment difference in HbA1c at the final visit using the last-observation-carried-forward method (difference of −0.1%; 95% CI −0.3, 0.1).

### Safety Results

The AE profiles were consistent with the known AEs of both study drugs; similar proportions of patients in either group had an AE, a serious AE or treatment-limiting AE (table V).

Hepatobiliary disorders were less frequent with pioglitazone (n = 15 [1.4%]) than with glibenclamide (n = 26 [2.5%]). In particular, cholelithiasis was reported for eight patients (0.8%) in the pioglitazone group and 16 patients (1.5%) in the glibenclamide group. Of the hepatobiliary disorders, five (0.5%) pioglitazone-treated patients and ten (1.0%) glibenclamide-treated patients had events considered serious (table V). Abnormal liver function tests resulted in study discontinuation for two (0.2%) pioglitazone-treated patients and eight (0.8%) glibenclamide-treated patients. There were no cases of hepatitis

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or hepatic failure in either treatment group. There were two reports of hepatic cirrhosis (both in the glibenclamide group). A 36-year-old woman with morbid obesity and minimal aminotransferase elevations was hospitalized for bariatric surgery on study day 475; liver biopsy was performed due to an incidental finding of abnormal hepatic morphology and revealed micronodular cirrhosis. Her liver function values at baseline were ALT 50 U/L, AST 69 U/L and total bilirubin 0.4 mg/dL, and were in the same range prior to surgery. A 62-year-old woman with a history of congestive heart failure (CHF), hypertension, hepatic steatosis and stroke was observed to have grade II–III oesophageal varices, ascites, normal aminotransferase levels and an echogenic liver with lobulated border after hospital admission for diarrhoea and abdominal pain on study day 154. Liver biopsy was performed due to the ascites and ultrasound findings, and revealed prominent fibrosis and cirrhosis without extensive periportal inflammation or bile duct proliferation. Her liver function values at baseline were ALT 30 U/L, AST 57 U/L and total bilirubin 0.4 mg/dL.

Seven deaths were reported during the study. The one death in the pioglitazone group was attributed to acute pulmonary oedema secondary to acute MI, and the six deaths in the glibenclamide group were attributed to cardiac arrest (n = 1), MI (n = 4) and respiratory arrest (n = 1).

Among aggregated cardiovascular AEs, the number of serious CHF events was similar between treatment groups: 12 (1.1%) pioglitazone and 11 (1.1%) glibenclamide. There were fewer events of MI in the pioglitazone group than in the glibenclamide group (n = 7 [0.7%] and n = 12 [1.1%], respectively). Events of stroke were reported in ten (1.0%) pioglitazone patients and nine (0.9%) glibenclamide patients. As mentioned in the Safety Assessments section, these events were not adjudicated by a monitoring committee.

Peripheral oedema was more frequent with pioglitazone; cough and hypoglycaemia were

**Table IV.** Concomitant statin use: summary of liver abnormality incidence (primary and secondary endpoints) at 156 weeks (subgroup of statin-treated patients)

| Parameter | Incidence [n (%)] | | Difference in incidence (pioglitazone-glibenclamide) [%] | p-Value[a] |
|---|---|---|---|---|
| | pioglitazone 15–45 mg qd (n = 397) | glibenclamide (glyburide) 5–15 mg qd (n = 390) | | |
| **Primary outcome** | | | | |
| ALT >3 × ULN confirmed by immediate repeat test | 0 (0.0) | 1 (0.26) | –0.26 | 0.4956 |
| **Secondary outcomes** | | | | |
| ALT >3 × ULN, at least one episode | 0 (0.0) | 2 (0.51) | –0.51 | 0.2453 |
| ALT >8 × ULN | 0 (0.0) | 0 (0.0) | NA | NA |
| ALT >3 to ≤8 × ULN: four consecutive readings within 3 months | 0 (0.0) | 0 (0.0) | NA | NA |
| ALT >3 × ULN and total bilirubin >2 × ULN | 0 (0.0) | 0 (0.0) | NA | NA |
| ALT >1.5 × ULN or baseline, whichever is greater | 8 (2.02) | 28 (7.18) | –5.16 | 0.0005 (95% CI: –8.08, –2.25) |
| AST >1.5 × ULN or baseline, whichever is greater | 8 (2.02) | 16 (4.10) | –2.09 | 0.0888 |
| Total bilirubin >1.5 × ULN or baseline, whichever is greater | 2 (0.50) | 1 (0.26) | 0.2474 | NA |
| Direct bilirubin >1.5 × ULN or baseline, whichever is greater | 0 (0.0) | 0 (0.0) | | |
| ALP >1.5 × ULN or baseline, whichever is greater | 3 (0.76) | 4 (1.03) | –0.27 | 0.7231 |
| γGT >1.5 × ULN or baseline, whichever is greater | 17 (4.28) | 28 (7.18) | –2.90 | 0.0803 |

a p-Values from a Cochran-Mantel-Haenszel procedure when patient numbers were at least five in both treatment groups, otherwise from a Fisher Exact Test. Statin use includes atorvastatin, simvastatin, pravastatin, pravastatin sodium, cerivastatin, cerivastatin sodium, fluvastatin sodium and lovastatin. Confidence intervals are only provided for statistically significant differences.

**γGT** = γ-glutamyl transpeptidase; **ALP** = alkaline phosphatase; **NA** = not applicable; **qd** = once daily; **ULN** = upper limit of normal range.

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**Table V.** Summary of adverse events (AEs) related to liver function

| AE preferred term | Incidence [n (%)][a] | |
|---|---|---|
| | pioglitazone 15–45 mg qd (n = 1051) | glibenclamide (glyburide) 5–15 mg qd (n = 1046) |
| **Overview of adverse events** | | |
| Patients with at least one AE | 859 (81.7) | 876 (83.7) |
| Patients who discontinued because of an AE | 146 (13.9) | 122 (11.7) |
| Patients with at least 1 SAE | 159 (15.1) | 174 (16.6) |
| Deaths | 1 (0.1) | 6 (0.6) |
| **Most common (>7.5%) AEs** | | |
| Upper respiratory tract infection NOS | 160 (15.2) | 157 (15.0) |
| Arthralgia | 119 (11.3) | 114 (10.9) |
| Sinusitis NOS | 98 (9.3) | 90 (8.6) |
| Diarrhoea NOS | 93 (8.8) | 80 (7.6) |
| Pain in limb | 89 (8.5) | 80 (7.6) |
| Oedema peripheral | 84 (8.0) | 36 (3.4) |
| Bronchitis NOS | 82 (7.8) | 81 (7.7) |
| Back pain | 79 (7.5) | 78 (7.5) |
| Nausea | 77 (7.3) | 84 (8.0) |
| Headache NOS | 70 (6.7) | 80 (7.6) |
| Cough | 67 (6.4) | 108 (10.3) |
| Hypoglycaemia NOS | 40 (3.8) | 119 (11.4) |
| **Hepatobiliary SAEs** | | |
| Hepatobiliary disorders | 5 (0.5) | 10 (1.0)[b] |
| cholecystitis NOS | 4 (0.4) | 3 (0.3) |
| cholelithiasis | 1 (0.1) | 6 (0.6) |
| cholecystitis acute NOS | 0 (0.0) | 1 (0.1) |
| hepatic cirrhosis NOS | 0 (0.0) | 2 (0.2) |

a All incidences represent numbers of patients.

b Ten patients in this treatment group experienced a total of 12 hepatobiliary SAEs, as itemized in the following rows.

**NOS** = not otherwise specified; **qd** = once daily; **SAE** = serious adverse event.

more frequent with glibenclamide. The incidence of bone fracture was similar between the pioglitazone and glibenclamide groups for both men (14 [2.3%] and 14 [2.4%], respectively) and women (16 [3.6%] and 13 [2.8%], respectively). Weight increased by 5.2 kg in the pioglitazone group and 0.9 kg in the glibenclamide group.

## Discussion

Thiazolidinediones are the first of a class of highly effective oral antidiabetic agents that target insulin resistance, an underlying defect in diabetes. They are highly specific PPARγ agonists and are not associated with hypoglycaemia. The first marketed TZD, troglitazone, was withdrawn in early 2000 after approximately 3 years because of reports of DILI (including liver failure with fatalities).

The next TZDs (pioglitazone and rosiglitazone) entered the market in 1999 and were not associated with signals of hepatotoxicity in premarketing trials. For example, a placebo-controlled trial[27] in 1526 patients showed that pioglitazone-treated and placebo-treated patients had the same incidence (0.26% and 0.25%, respectively) of ALT elevations ≥3 × ULN; no patient had an 8-fold elevation of ALT or an ALT elevation with elevated bilirubin – the normal signals of hepatotoxicity as defined by Hy's Law.[28-30] Nevertheless, the troglitazone experience raised concerns about a class effect.

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The FDA recommended not using TZDs in patients with underlying liver disease and also recommended monitoring ALT at 2-month intervals for the first year.[31] These recommendations have since been modified to state that therapy not be initiated if there is evidence of active liver disease or if serum ALT levels exceed 2.5×ULN; periodic monitoring is recommended as clinically indicated.[3,32]

There have been scattered reports of hepatotoxic reactions with both pioglitazone and rosiglitazone.[3,32,33] Recent reviews indicate, however, that the incidence is much lower than that seen with troglitazone and no different from those with other antidiabetic drugs.[34-38] Additionally, in a cardiovascular outcomes trial of 34.5 months' mean duration, 20/2605 pioglitazone patients and 33/2633 placebo patients experienced an ALT elevation >3×ULN at any time; there were no cases of acute liver toxicity.[13] Most patients with diabetes have underlying liver disease, the most common being NAFLD.[1] Ironically, the TZDs are emerging as the preferred pharmacological therapy of NAFLD, with a recently completed 6-month study in patients with non-alcoholic steatohepatitis demonstrating that, relative to placebo, patients treated with pioglitazone had significantly lower ALT and AST levels, decreased hepatic fat content and improved histological findings.[7]

In the current trial, the absolute incidence of ALT elevations was low in both treatment groups. None of the 1051 pioglitazone-treated patients had ALT elevations >3×ULN (confirmed by retest), compared with four glibenclamide patients (0.38%); the difference was not statistically significant. Analyses of the secondary endpoints revealed that the incidences of ALT, AST and γGT >1.5×ULN were significantly higher with glibenclamide than with pioglitazone. There were no significant differences in other secondary endpoints. Combined elevation of ALT >3×ULN plus bilirubin >2×ULN, a more specific signal of hepatocellular injury,[29,30] was not observed in pioglitazone-treated patients and in only one glibenclamide-treated patient.

The ALT and AST levels tended to decrease in patients treated with pioglitazone compared with an upward trend with glibenclamide – differences that were statistically significant. The improvement of ALT and other liver function test values in pioglitazone-treated patients may have been due to improvements in NAFLD, as recently reported.[7] The study design precludes differentiating whether this trend may be offsetting a chronic hepatotoxic effect of the drug. Of particular interest in this regard is the ADOPT trial (A Diabetes Outcome Progression Trial) by Kahn et al.,[39] in which newly diagnosed patients with diabetes were followed for 4 years. Both liver test and glycaemic results were nearly the same as in the present study. There were no reports of hepatic failure, hepatitis or cirrhosis in the pioglitazone group, compared with two reports of cirrhosis in the glibenclamide group. Given that these patients had higher AST values than ALT values at baseline and that an AST/ALT ratio higher than 1 almost certainly indicates the presence of cirrhosis, it is highly probable that they had cirrhosis at the time of study entry and thus did not have DILI. Overall, these data suggest that long-term exposure to pioglitazone is not associated with drug-induced abnormalities in liver enzymes, confirm the hepatic safety of pioglitazone with long-term use and suggest a hepatoprotective effect.

Additionally, our results corroborate those of previous studies showing no clinically significant hepatotoxic drug interactions when pioglitazone is administered concomitantly with statins.[3,40,41] Patients on statin co-therapy had a lower incidence of ALT elevations at all thresholds (albeit achieving statistical significance only for ALT >1.5×ULN). Statins have long been considered hepatotoxic, based on preclinical studies of lovastatin.[42]

This study confirms the safety of statin use with TZDs and suggests an element of hepatoprotection associated with statin use. In fact, a recent review has shown that serious DILI occurs less frequently with lovastatin than in patients not treated with statins.[43,44] Other studies have shown that patients with pre-existing liver disease, as manifested by liver enzyme elevations, are not at increased risk of statin hepatotoxicity.[45,46] Specifically, patients with underlying

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hepatitis C are not at increased risk.[47] Ironically, statins are now being used in the treatment of NAFLD[48-51] and showing therapeutic benefits.

The overall safety profile of pioglitazone is consistent with previous experience with the drug. The incidence of AEs, including serious AEs, was generally similar between treatments; however, there were several notable differences. Of the seven deaths in this study, most of which were related to cardiovascular disease, one occurred in the pioglitazone group and six occurred in the glibenclamide group, but none was related to liver toxicity. Consistent with observations in previous trials, the incidences of oedema and weight gain were higher with pioglitazone, while the incidence of hypoglycaemia was higher with glibenclamide. Hepatobiliary disorders (mostly cholelithiasis) were seen less frequently with pioglitazone than with glibenclamide for reasons that are not clear. In alignment with the overall safety and tolerability observed in this study, pioglitazone continues to be recommended as second-line treatment for diabetes in the most recent consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes.[52]

A limitation of this study was the high discontinuation rate (approximately 61% in both groups), perhaps because of patients' resistance to initiating insulin therapy. Despite relatively few patients taking insulin at the end of the study, mean HbA1c levels were relatively high (8.0% with glibenclamide and 7.9% with pioglitazone), suggesting 'psychological insulin resistance', a well-documented phenomenon.[53-55] Withdrawal of consent, which included patients unwilling to initiate insulin therapy, was the most common reason for discontinuation (25% in both groups).

The issue of monitoring for DILI continues to be problematic. The standard has been frequent measurement of liver enzymes in order to detect ALT $>3\times$ ULN,[56] but there is little evidence that this approach is useful and compelling evidence that it is not.[42] The reason for this may be the adaptation phenomenon: while ALT reflects liver injury, the liver's enormous capacity to adapt usually results in repair of the injury with subsequent tolerance and resistance to injury upon rechallenge. This was initially described by Mitchell et al.[25] with isoniazid and recently reviewed by Senior[26] and Mehendale.[57] Thus, the value of the dechallenge (i.e. improvement when a drug is withdrawn) and rechallenge (i.e. recurrence of the event upon rechallenge) is greatly undermined. Later, Dr Hyman Zimmerman introduced the concept of hepatic dysfunction as measured by an elevated bilirubin in the presence of an elevated ALT as a more specific predictor of serious liver injury.[28] This has withstood the test of time and has become known as Hy's Law. There are, however, no data on how frequently monitoring should be undertaken or the sensitivity of given monitoring intervals. There is increasing interest in patient self-monitoring of symptoms, i.e. alerting patients to symptoms such as malaise, anorexia, abdominal discomfort, and dark urine – an approach that has been used successfully with isoniazid. Nevertheless, there is little known about the sequence of symptoms and biochemical evidence of liver injury.

A serious limitation of this and other studies, because of the number of patients, is the ability to detect rare events. In order to detect a rare event with 95% confidence, based on binomial distribution, the number of patients exposed must be at least three times the true incidence – the so-called rule of threes (recently reviewed by Senior[58]). For example, it would require an investigation involving 3000 patients to detect an event with a true incidence of 1 per 1000. In our study, 1290 patients completed the study, thus the detection limit for a serious event was 1 per 430 patients.

## Conclusions

In summary, this 3-year safety study did not detect serious DILI associated with pioglitazone treatment, based on elevation of hepatocellular marker ALT $>3\times$ ULN as the primary endpoint. While there were fewer occurrences of ALT $>3\times$ ULN in the pioglitazone group versus the glibenclamide group, the difference was not statistically significant. Evaluation of secondary endpoints, including profiles of other ALT thresholds and other liver function enzyme

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elevations, confirmed the findings from the primary endpoint and further showed that there was no signal of hepatotoxicity. Additional safety assessments revealed no increased incidence of adverse events or hepatobiliary serious adverse events associated with pioglitazone treatment; however, consistent with previous observations, more weight gain and cases of peripheral oedema were reported with pioglitazone.

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