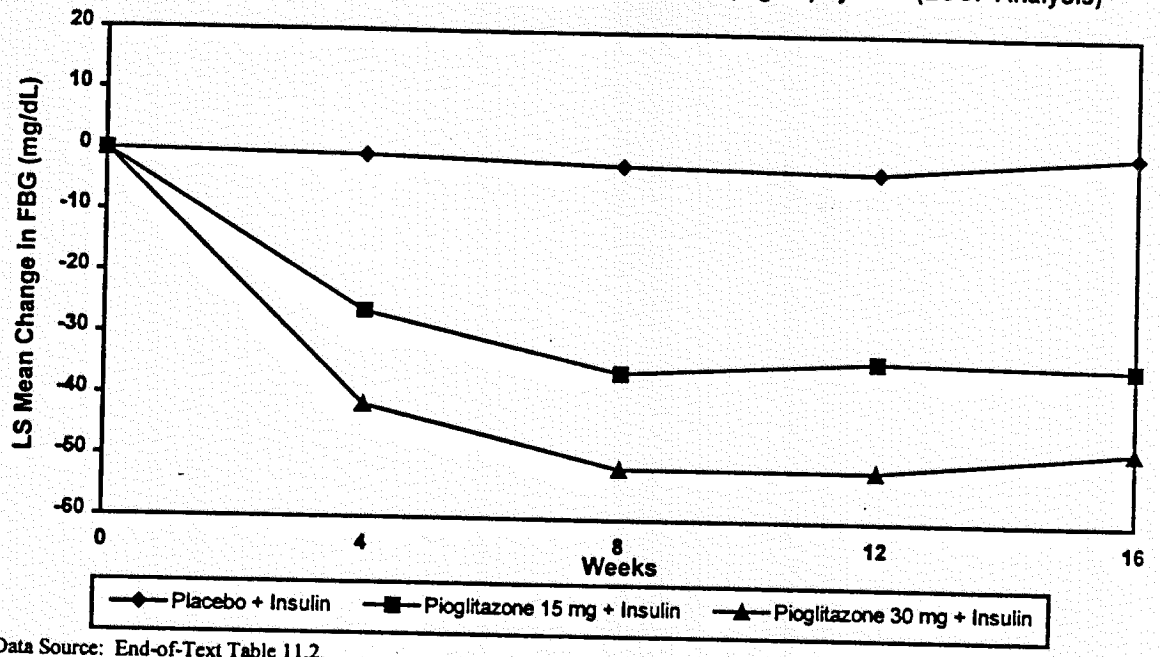
Table 9.4.1.1.1: LS Mean Change From Baseline for HbA_{1c} (%) by Visit (LOCF Analysis)

Visit	Placebo + Insulin (N=187)	Pioglitazone 15 mg + Insulin (N=191)	Pioglitazone 30 mg + Insulin (N=188)
Baseline[a]			
N[b]	177	177	185
LS Mean	9.75	9.75	9.84
SE	0.099	0.099	0.097
Week 8			
N	173	175	184
LS Mean Change	-0.25+	-0.71+*	-0.89+*
SE	0.069	0.068	0.067
Week 12			
N	177	177	185
LS Mean Change	-0.30+	-0.89+*	-1.17+*
SE	0.078	0.077	0.076
Week 16 (Endpoint[c])			
N	177	177	185
LS Mean Change	-0.26+	-0.99+*	-1.26+*
SE	0.084	0.084	0.083
LS Mean Difference[d]		-0.73	-1.00
95% Confidence Interval[e]		(-1.00, -0.47)	(-1.27, -0.74)

[a] Baseline is the last value taken during the baseline period.
[b] N at baseline includes patients who had a value at both baseline and endpoint.
N at each visit includes patients who had values at both baseline and visit.
[c] Endpoint is the last measurement taken during the double-blind treatment period.
[d] Difference between each dose of pioglitazone + insulin and placebo + insulin in mean change from baseline.
[e] For LS mean difference, based on ANCOVA and Dunnett's t-distribution.
Note: Model for baseline based on a 2-way ANOVA with effects for pooled center and treatment. Model for change from baseline based on a 2-way ANCOVA with effects for pooled center, treatment, pooled-center-by-treatment interaction, and baseline as a covariate.
+ Significant change from baseline ($p \leq 0.050$), based on a paired t-test.
* Significantly different from placebo + insulin ($p \leq 0.050$), based on Dunnett's test.
Data Source: End-of-Text Tables 9.2 and 9.3, Listing 8.1, and Statistical Appendix 2.1.

FBG was unchanged in placebo-treated patients but fell 35 mg/dl and 48 mg/dl in patients on 15 and 30mg PIO. Mean baseline FBG was 221-229 in all groups.

Figure 9.4.1.2.1: LS Mean Change From Baseline for FBG (mg/dL) by Visit (LOCF Analysis)



Data Source: End-of-Text Table 11.2.

C peptide levels rose slightly in patients on placebo but fell slightly in patients on PIO Mean triglyceride levels rose from 238 to 250 mg/dl in patients on placebo but fell from 260 to 205 mg/dl at 30 mg PIO. There was a small but statistically significant rise in HDL cholesterol in patients on PIO. Starting from a mean of about 43 mg/dl in all groups, there was a fall of 0.7 mg/dl in placebo patients vs increases of 2.8 and 3.4 mg/dl in patients on 15 and 30 mg PIO. The mean body weight at baseline was about 96 kg. Patients on placebo lost an average of 0.11 kg after 16 weeks, compared to gains of 2.53 and 3.92 kg on 15 and 30 mg of PIO. Seven patients on PIO were withdrawn from the study because of weight gain.

Based on the change in HbA1c PIO appeared to be more effective in women than in men.

Table 9.4.2.8.1.1: Mean Change from Baseline in HbA_{1c} (%) at Endpoint[a] by Gender (LOCF Analysis)

Subgroup	Placebo + Insulin (N=187)	Pioglitazone 15 mg + Insulin (N=191)	Pioglitazone 30 mg + Insulin (N=188)
Men			
N[b]	82	80	94
Baseline Mean[c]	9.72	9.86	9.86
Mean Change	-0.36	-0.87	-1.07
SE	0.117	0.132	0.115
Women			
N[b]	95	97	91
Baseline Mean[c]	9.84	9.74	9.88
Mean Change	-0.19	-1.18	-1.55
SE	0.112	0.113	0.125

[a] Endpoint is the last measurement taken during the double-blind treatment period.
[b] N includes patients who had a value at both baseline and endpoint.
[c] Baseline is the last value taken during the baseline period.
Data Source: End-of-Text Table 21.1 and Listings 4.2 and 8.1.

There were no consistent or meaningful differences with respect to age, race, obesity or insulin dose, although patients with starting HbA1c over 9% at baseline showed a larger reduction in all three arms.

Safety:

Safety issues raised by this study are the same as for other studies. These include CPK elevation ,anemia and edema. CPK elevation > 3x ULN occurred in one patients on placebo, one on 15 mg and seven on 30 mg of PIO. One patient on 30 mg had a CPK over 8000. One patient in this study had a generalized skin rash that was believed to be drug related. ECG changes occurred in 4 patients on placebo, 4 patients on 15 mg and 3 patients on 30 mg PIO Grade 3c urine cytology was reported in two patients on placebo and one on 30 mg PIO.

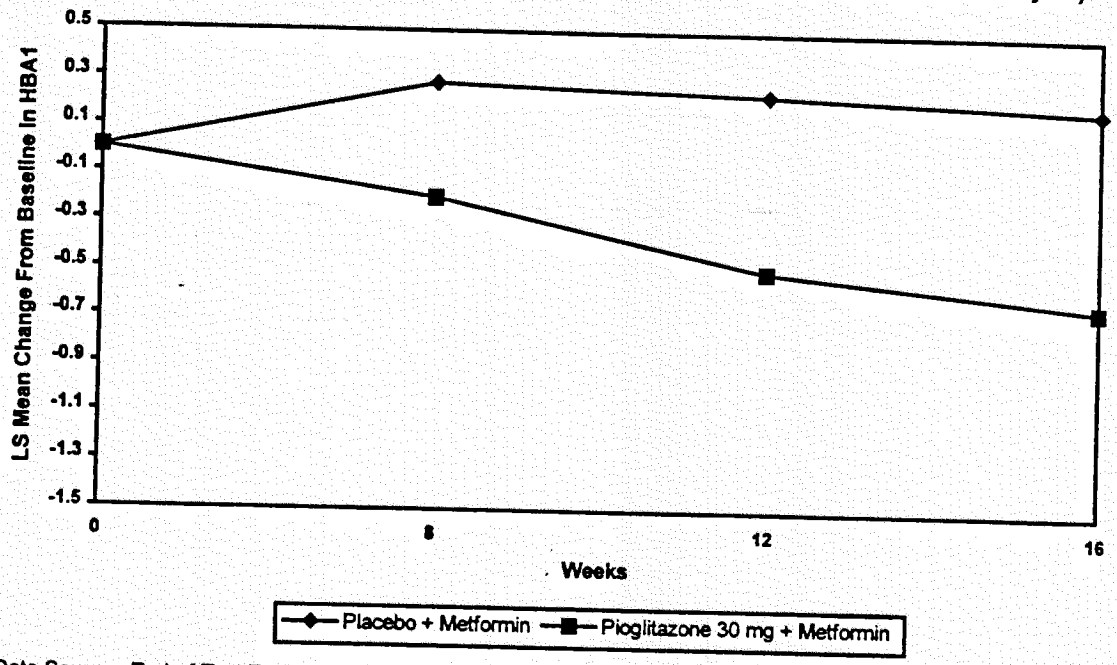
PNFP 027 – Pioglitazone with metformin

This was a 16 week double-blind comparison conducted in the United States of PIO vs placebo in patients inadequately treated with metformin. Patients had to have been on a stable dose of metformin at least 30 days before screening. If patients were on acarbose or a sulfonylurea, these medications had to be discontinued at screening. There was a 6 week run-in before randomization, two weeks on metformin alone and 1 week metformin plus placebo (single blind). Patients in whom a stable metformin dose had not been documented had a four week single blind placebo run-in. Patients were required to have HbA1c of least 8% at screening and before beginning the single-blind placebo run-in two weeks later. Fasting C peptide was greater than 1 ng/ml. Patients were withdrawn from the study of the developed serum creatinine above 1.5 for men and 1.4 for women, LVH by ECG or echo ore FBG> 400 mg/dl on two consecutive visits.

Patients had a mean age of 56 years. 57% were male. 84% were Caucasian, 7% black and 7% Hispanic. 30% had been on multiple antidiabetic medications previously. The mean weight at baseline was 93 kg, mean BMI was 32 kg/m2. Mean HbA1c at baseline was 9.8%, FBG was 255 mg/dl, C peptide 2.1 ng/ml and insulin 14.7 uU/ml. Mean lipid levels at baseline expressed as mg/dl were triglycerides 297, total cholesterol 213. HDL 43.7 and LDL 119. Patients were taking an average of 61% of the maximal labeled dose of metformin (2550 mg) in both groups. 60% were taking less than 2 g/day, and 40% were taking 2g per day or greater. There were no baseline imbalances for any of these characteristics between the two treatment arms.

After 16 weeks of treatment patients on placebo had a rise in HbA1c of 0.19% compared to a fall of 0.64% for patients on PIO 30 mg/d. The net treatment effect was –0.83% using LOCF. Based on observed values at 16 weeks (excluding 35 placebo dropouts and 17 PIO dropouts) the treatment effect was –1.05%.

Figure 9.4.1.1.1: LS Mean Change From Baseline for HbA_{1c} (%) by Visit (LOCF Analysis)



Data Source: End-of-Text Table 9.2.

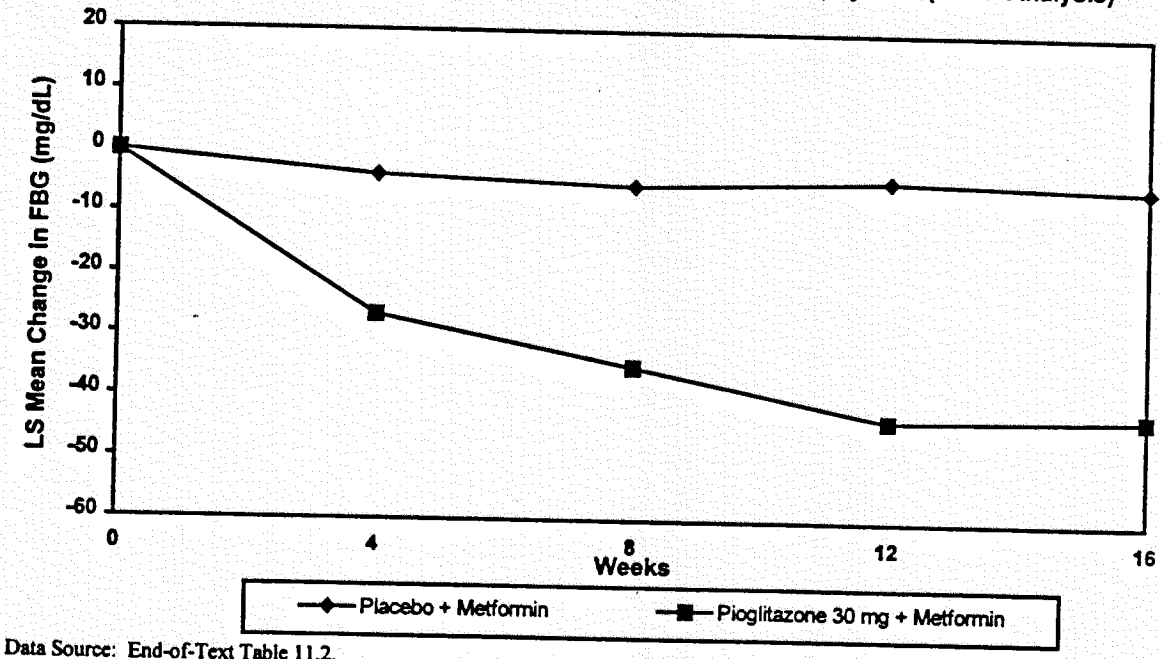
Table 9.4.1.1.2: Mean HbA_{1c} (%) by Visit (LOCF Analysis)

Visit	Placebo + Metformin	Pioglitazone 30 mg + Metformin
Baseline[a]		
N[b]	153	161
Mean	9.74	9.90
SE	0.104	0.113
Week 8		
N	153	160
Mean	10.12	9.69
SE	0.126	0.145
Week 12		
N	153	161
Mean	10.10	9.38
SE	0.131	0.149
Week 16 (Endpoint[c])		
N	153	161
Mean	10.06	9.23
SE	0.130	0.153

[a] Baseline is the last value taken during the baseline period.
[b] N at baseline includes patients who had a value at both baseline and endpoint. N at each visit includes patients who had values at both baseline and visit.
[c] Endpoint is the last measurement taken during the double-blind treatment period.
Data Source: End-of-Text Table 9.1 and Listing 8.

The reduction in HbA1c described above for patients on PIO was mirrored by a reduction in FBG of 43 mg/dl, with a placebo-subtracted treatment effect (LOCF) of – 38 mg/dl.

Figure 9.4.1.2.1: LS Mean Change From Baseline for FBG (mg/dL) by Visit (LOCF Analysis)



Data Source: End-of-Text Table 11.2.

As shown in the figure, the maximal glucose lowering-effect of PIO required 12 weeks to achieve. A comparison of the figures showing changes in HbA1c and changes in FBG explains why the reduction in HBA1c at 16 weeks may have underestimated the true efficacy. This is because changes in FBG takes about 12 weeks to be fully reflected in HbA1c. Treatment with PIO was associated with statistically significant placebo-subtracted reductions in C peptide (0.16 ng/dl) and insulin (2.5 uU/ml). The small rise in total cholesterol was not statistically significant. Placebo-subtracted changes in lipids, expressed as mg/dl, which were statistically significant were as follows: triglcerides fell 44, HDL rose 3.19, and LDL rose 4.2. At endpoint placebo patients had a mean weight change of -1.36 compared to a gain of 0.95kg for PIO patients, for a placebo-subtracted gain of 2.31 kg. Using observed values at 16 weeks the net mean gain was 2.47 kg.

Subgroup analysis showed that PIO was more effective in women than in men. The placebo-subtracted fall in HbA1c was 0.72% for men and 1.33% for women. There was no apparent difference for patients over or under 65 years old. The mean placebo-subtracted fall in HBA1c was 0.97% for whites and 0.68% for black, but the number of black patients (13 on PIO 10 on placebo) was too small to draw any definite conclusions. There was no consistent effect of BMI. PIO was effective in patients on less than 2 g of metformin and those on > 2g of metformin. For patients on less than 2g of metformin the placebo-subtracted reduction in HbA1c was 0.91% and in FBG was 38 mg/dl. For patients on 2g or metformin or greater the changes was 1.10% and 45 mg/dl.

Safety:

There were no deaths in this study. 8/160 patients in the placebo arm were withdrawn because of an SAE, two of whom because of hyperglycemia. 5/168 patients in the PIO arm were withdrawn because of an SAE. Liver changes, urine cytology and edema are discussed as part of the ISS. Placebo subtracted reductions in the PIO arm for hemoglobin, hematocrit and rbc count were 0.46 g/dl, 1.4%, and 0.2 x million/uL respectively. A marked abnormal low hemoglobin, hematocrit or rbc count occurred in 4 patients on PIO and 2 patients on placebo. Two additional patients on PIO had reductions in hematocrit of 10% and 7% although the values did not reach the level low enough to be classified as markedly abnormal (this was defined as a 20% reduction in hct or rbc and fall of 3g/dl for hemoglobin). One patient on placebo and three on PIO developed CPK values, which were. 3x ULN. All returned to normal by the end of the study.

SAFETY

Liver and Biliary system:

SAE's
There were no deaths in the US trials. There was one death in patients on 30 mg PIO in the European trials due to gall bladder carcinoma. In the Japanese studies, one patient on placebo died of cholangiocarcinoma.

12 PIO patients and one placebo patient in US trials had a SAE related to hospitalization for acute cholecystitis. One PIO patient had an ALT > 3 xULN during the acute event which returned to normal two weeks later. In the European trials, there were two patients with biliary system disease on 30 mg PIO. One had carcinoma of the pancreas and was discontinued from the study. The second had acute cholecystitis and was continued on PIO. In the Japanese studies, one patient (2103) on 45 mg PIO was hospitalized for cholecystitis but was continued on the study. There were three patients discontinued because of increased hepatitis enzymes. #4601 had ALT of 67, # 2802 had ALT of 33, and #1301 had ALT of 75.

ALT elevation >3x ULN:
In the US trials, there were 11 patients who had ALT values > 3 xULN . Two on placebo and 9 on PIO. One of the placebo patients had a value of 107 during double blind treatment, which decreased to normal after she was started on PIO in an open-label extension study. A second patients had an ALT of 120 on day 113 on placebo plus SFU.. There is one normal volunteer who had ALT of 268 after 7 days of placebo Details of the PIO patients are as follows: Cases that are numbered 1-12 were treatment emergent elevations and are presumed to be drug-related.:

USA
1 56/2362 –Male Patients has hepatitis C in 1989 and ALT values above normal during placebo run-in, but were less than 3x ULN.. ALT values were 140, 140, and 136 on days 98, 126, and 154 of PIO 7.5 mg. He completed the 181 day study and was entered into open-label extension at 60 mg of PIO. By day 206 his ALT fell to pretreatment levels He continues on 60 mg PIO.

2 5/2373 – Male Patient on PIO 30 mg given norflaxacin days 160-180. On day 187, ALT was 343, which returned to normal despite continuation of PIO

3 6/2481 – Male Patient developed ALT of 146 on day 15 of PIO 30 mg. This value returned to baseline by day 43

4 44/6620 Male Patient had ALT of 130 on day 98 of PIO 30 mg. On day 170, serology showed "chronic active hepatitis B"

5 59/4212 Female Patient on PIO 30 mg received dicloxacillin days 72-82 and had ALT of 158 on day 83. By day 96 this had returned to normal

6 50/4690 – Male Patient had ALT of 170 on day 468, 14 days after stopping PIO 60 mg. It was "returning toward normal" on day 473. Transaminase levels had previously been normal.

7 003/04 – Male patients with ALT of 180 (AST =93) on day 15 of PIO 15 mg .Hospitalized two days earlier with fever and leukocytosis with dx of acute cholecystitis. ALT not measured on admission but AST was 651, bilirubin 2.3 ALT returned to normal two weeks after drug stopped.

8 007/06 – Female Patient started taking arthrotec on day 2 and had ALT of 221 on day 29. She stopped arthrotec and ALT was 116 on day 32. By day 31 it had returned to normal of 31 despite continuation of PIO 30 mg

Japan

9 2262 – ALT started at 100 before PIO. After 4 weeks of PIO at 15 mg it reached a high of 196 ALT was 164 when the treatment ended on week 12

10 4801 – Patients with history of hepatitis C received 30 mg PIO for 76 weeks. Prior to treatment the baseline ALT was 101. At week 12 ALT was 191 but at week 60 it was 71.On weeks 72 and 76 when the study ended, ALT were 129 and 225. Bilirubin at week 76 was 0.79 compared to 0.77 at baseline.

11 2801 – Baseline ALT of 99 fell to 55 at week 20, but rose to 136 and 152 on weeks 24 and 28 when the study ended. Bilirubin 1.0 at baseline and 0.7 at week 28. PIO dose was 30 mg

12 2501 – Baseline ALT of 87 rose to 100 and 120 at weeks 20 and 28 when the study ended. PIO dose was 30 mg Bilirubin was 0.7 at baseline and was o.4 at week 28

In the following cases, the ALT elevation > 3x ULN preceded PIO administration. The one European patient with hepatic duct tumor is also shown here:

Europe – One patient on PIO had elevated ALT with jaundice and obstruction due to cholangioma of the hepatic duct . He died of tumor 80 days after stopping PIO.

USA - 35/4827 Female Patient had ALT of 104 at screening and had periodic elevations as high as 168 during treatment with PIO 60 mg. At day 280 the value was 106, at day 300 it was 107 and was 114 following discontinuation of drug

Japan - 232 – ALT of 165 was the highest value and was at baseline. On PIO 30 mg ALT ranged from 128-145

313 – Baseline was the highest ALT of 117. By 8 weeks of PIO 30 mg ALT had fallen to 58

2122 – Baseline was the highest ALT of 157. By 12 weeks of PIO 30 mg it had fallen to 58.

4802 – Highest ALT was 162 recorded at baseline. While on 30 mg PIO, ALT values fell progressively and was 23 at week 60.

2107 - ALT at baseline was 112 and 132 after 60 weeks of PIO 30 mg/45. Bilirubin 1.1 at baseline and 0.8 at week 60

ALT elevation during PIO treatment

	Continued on PIO	Withdrawn	Total
> 3x ULN (102 U/L)	5	7	12 (0.33%)
> 5x ULN (140)	4	5	9 (0.25%)
> 8x ULN (272)	1	0	1 (0.03%)
>30xULN(1020)	0	0	0

N= 2549(USA) + 251(Europe) + 850 (Japan) = 3650

APPEARS THIS WAY ON ORIGINAL

For comparison, results from the troglitazone and rosiglitazone (RSG) NDA's are shown below:

ALT elevation during Troglitazone treatment (NDA data base)

	Continued	Withdrawn	Total
> 3xULN (102 U/L)	25	23	48 (1.9%)
> 5xULN (140)	22	20	42 (1.7%)
> 8xULN (272)	8	14	22(0.9%)
> 30xULN (1020)	0	5	5 (0.2%)

N= 2510

ALT elevation during Rosiglitazone treatment (NDA data base)

	Continued	Withdrawn	Total
> 3xULN	6	5	11 (0.25%)
> 5xULN	5	5	10 (0.23%)
>8xULN	2	0	2 (0.05%)

N= 4421 ULN for ALT for calculation was 34 U/L, but threshold for reporting used by SKB was 48 U/L

Both the reporting rate and severity of the ALT elevation were greater with troglitazone than with PIO or RSG. One potential source of this difference is differences in criteria for withdrawal. It was not known during the trials that troglitazone could cause liver failure, hence there were no definite criteria for withdrawal. Delay in withdrawing troglitazone from patients with mild elevations could be potential reason for why some patients developed very high values. However, of the five patients with ALT > 30 x ULN, only one had had an earlier mild elevation (> 5 x ULN) which did not lead to troglitazone withdrawal.

Reporting of ALT elevation over 3xULN in patients on PIO is indistinguishable from placebo in controlled trials (see table below). This was also true for patients on rosiglitazone* but was different for patients on troglitazone: (Reporting for RSG may be lower because 48 U/L was taken as ULN in the NDA as the threshold for reporting values > 3x ULN. Other data bases used 34 U/L)

	ALT elevation > 3 x ULN in controlled trials	
	Active drug	Placebo
PIO		
USA	0.26% (4/1526)	0.25% (2/793)
Japan	0.70% (4/570)	0.70% (2/280)
Troglitazone	1.90% (48/2510)	0.60% (3/475)
Rosiglitazone*	0.25% (11/4421)	0.18% (1/561)
RSG *– Comparators (SFU + Metformin)	0.24% (2/828)	

* normal ALT up to 48

For comparison, reporting of ALT elevations > 3x ULN in other phase 3 trials of antidiabetic agents is shown below:

Acarbose	6-12 months	placebo patients	0.60% (5/865)
Miglitol	6-12 months	placebo patients	0.60% (3/545)
Metformin	29 weeks	metformin, glyburide, placebo	0.40% (4/921)

When one considers that the placebo-controlled comparisons with PIO were 4-6 months, it is clear that the reporting rate of 0.26% for patients on PIO and 0.25% for patients on placebo is very much in line with what has been reported in other phase 3 trials. On the other hand, the relatively small number of patients with long term exposure to PIO is cause for concern. Although total exposure was 1,155 patient years, only 483 patients had exposure beyond 6 months. For patients on troglitazone who developed ALT > 3xULN, the median duration of treatment before recognition of hepatitis was about 4 months. If one assumes that 30 mg of PIO has roughly the same antidiabetic efficacy as 400 mg of troglitazone, but that the two drugs

were equally toxic to the liver based on weight, it follows that the median duration of treatment with PIO until the onset of hepatitis would be 53 months (400/30 x 4 months). Thus, the data in the NDA are not inconsistent with the possibility that long-term exposure to PIO will lead to cases of liver failure like those we have seen with troglitazone.

Hematological Events:

There was dose-related reduction in red cell parameters as follows in the US placebo-controlled monotherapy studies as shown in the table

Percent changes

Dose	Hemoglobin	Hematocrit	RBC count
0 placebo	-0.5	-0.2	-0.2
7.5	-0.7	-0.7	-0.2
15	-2.1	-1.5	-2.4
30	-2.6	-1.1	-2.4
45	-3.5	-2.9	-3.6

As mean data, placebo patients had a baseline mean hemoglobin of 14.95 g/dl, which fell by 0.08. PIO patients had a mean of 15.06, which fell by 0.38. These changes are small and not clinically significant in general. Out of 599 PIO patients, there were five patients who had decreases in hct of > 10%. The worst of these were a female whose hct dropped from 35 to 26 but reverted toward normal on follow-up. Similar reductions in hematology measures occurred during the open-label extension.

Combination therapy studies:

PIO used with metformin resulted in a mean drop in hct of 1.2 (SD= 3.02, n=166) from a starting value of 43.6. Reductions with SFU and insulin were 0.7 (SD= 3.20 n=370) and 0.8 (SD = 3.12, n=378) respectively when used with PIO. When used with placebo, metformin was associated with a reduction of 0.1 from 44. No reduction in hematocrit were seen with SFU or insulin. Low hematocrits were reported in 4/163 (2.5%) patients and low rbc in 5/162 (3.1%) on metformin plus PIO compared to 1/152(0.7%) for metformin plus placebo. 3/166 on metformin plus PIO were reported within markedly abnormal hct at baseline and outside markedly abnormal during the study.

CPK elevation

Three male patients on PIO in the US placebo-controlled studies were reported to have CPK values > 10x ULN. The values were 51 – 195 at baseline (22-198 is normal) and had peak values on drug of 3520 –4410. One normalized while on drug. The other two normalized after PIO had been discontinued. Four male patients in the combination studies had CPK values over 10 x ULN. One was slightly elevated (250) at baseline. It peaked at 8610 on 30 mg PIO and fell to 357 on last follow-up. Two patients had values of 2150 and 3660, which normalized on drug. One patient had a peak of 5400, which normalized on follow-up. The duration of PIO treatment in these seven patients ranged form 51-189 days. One patient was also taking atorvastatin.

CPK was not measured routinely in either the troglitiazone or rosiglitazone NDA's. A review of postmarketing reports of CPK elevation in patients on troglitiazone revealed 11 cases reported April – December 1998 which seemed pertinent in that the CPK elevation was not associated with acute MI, "statins", or trauma, or hypothyroidism. Of the 11 cases, 7 had muscle cramps, weakness or increased myoglobin, 2 had malaise, 1 had mildly increased liver tests, and one was asymptomatic. The median CPK elevation was 1122 (750-2513). There were 7 women and 4 men. The median age was 54 years (35 to 75). The dose of troglitazone when listed was 200-400 mg.

Body weight

In US monotherapy studies, baseline body weight was about 90 kg. There was a mean reduction of 1.67 kg (SD 1.88 n=256) in placebo patients compared to a mean gain of 1.21 kg (sd 1.38 n=603) in patients on

PIO. For patients in 48 week open-label study there was a mean weight gain of 5.56 kg. Placebo patients in combination studies lost 0.77, 1.36, and 0.04 kg for SFU, metformin and insulin respectively. Patients on PIO gained 2.42, 0.96 and 3.01 kg respectively. The placebo subtracted weight gain due to PIO was 3.19, 2.31, and 3.05 kg for patients on SFU, metformin and insulin respectively.

Hypoglycemia

Hypoglycemia was reported in 44/379 (11.6%) of patients on PIO plus insulin compared to 9/187 (4.8%) on insulin plus placebo. In two patients on PIO, the study medication was interrupted. The insulin dose was lowered in 7 PIO patients and one placebo patient. One patient on PIO discontinued the study entirely. In monotherapy studies there were reports of 7/606 patients (1.2%) on PIO with hypoglycemia but none were well documented. There were none on placebo.

Edema:

In the monotherapy studies edema was reported in 29/606 (4.8%) patients on PIO compared to 3/259 (1.2%) on placebo. No patient was discontinued because of edema. In combination studies addition of PIO caused increased reporting of edema in all groups. There were two patients in USA trials that were withdrawn because of edema. One patient received SFU. The other patient received insulin. Both received 15 mg PIO. The overall incidence (including non-USA) of edema in controlled studies was 6.6% among PIO patients and 2.3% among placebo patients.

Cardiac:

After 52 days of PIO 30 mg, one patient (PNFP – 026) was noted to have new onset LVH and LBBB Baseline EKG showed old MI and left axis deviation. LVH was still present at day 87. PIO was withdrawn on day 92. EKG on day 105 showed no LVH and an echocardiogram done on day 105 showed normal LV size. New EKG findings were equally distributed among patients who received PIO and placebo, but five patients on PIO were noted to have cardiomegally on chest x-ray The ISS does not comment on new onset angina.

The potential for PIO to cause cardiomegally was anticipated from the pre-clinical toxicology. Takeda attempted to address this issue directly by looking for changes in echocardiograms in patients treated with PIO. Results of this study were submitted as an amendment on March 29 1999. The study was a double blind comparison of four doses of PIO (7.5, 15, 30 and 45 mg) vs placebo of myocardial size and function as assessed by echocardiography. The echocardiograms were all read by the same person, Dr Julio Perez. The study consisted of a six week washout, two week single blind run-in and 26 weeks of double blind medication. The entry criteria were similar to previous studies except that patients were excluded if they had valvular abnormalities, ischemic heart disease leading to LV motion abnormalities, or symptomatic heart failure. Each study arm consisted of about 80 patients. The results were summarized as follows: Only negligible changes from baseline were noted for LVMI, CI, and FS for patients in all treatment groups. Similar results were seen for LVM and CO. There were no clinically important differences among the treatment groups for any echo parameter. Shift of > 20% from baseline also revealed no differences.

The results of this study provide little, if any, reassurance that PIO does not damage the heart. The submission does not give an analysis of changes in glycemic control, body weight, lipids etc which can be presumed to have occurred during the study and which could be expected to impact the heart. It is not clear why the Sponsors chose to compare placebo to four doses of PIO. A better design would have been to compare 45 mg of PIO to 20 mg glyburide (or some other SFU at max dose). This study design would have helped to eliminate the confounding variable of changes glycemic control and body weight. [redacted]

[redacted] The PIO study is even less helpful.

Urinary:

Special attention was paid to urine cytology in view of pharm-tox finding of bladder tumors. Category 3c cytology was reported in 4 patients on placebo, 2 patients on PIO 7.5 mg, one patient on 30 mg, one patient on 45 mg four patients on 7.5/15/30 mg and 1 patient on 15/30/45 mg in the US monotherapy studies. In the combination therapy studies five patients had 3c cytology on PIO plus comparator and five patients on placebo plus comparator. No bladder tumors were reported.

Drug interactions:

No significant interactions were found in PK studies of glyburide, glipizide, metformin, digoxin and warfarin. As outlined in the Biopharm review, administration of PIO did not affect the blood steady state blood levels of these other drugs.

[redacted]

Phase 4 studies

The major safety issue relates to the potential for long-term hepatotoxicity. The Sponsor should committ to following patients for three years. If the risk of hepatic toxicity were the same as trogltiazone, I would estimate that 1% of patients would develop an ALT > 8x ULN. The study should be powered to be able to detect this kind of abnormality. A second safety issue relates to the potential for PIO to cause or exacerbate heart failure. NDA's for Rosiglitazone and Troglitazone had included echo study comparisons to patients treated with Glyburide. As discussed earlier, the echo study of PIO vs placebo presented earlier is not very convincing. In lieu of doing a study of PIO vs glyburide, I would suggest a study of PIO vs placebo in patients with class 3 and 4 heart failure who have a compelling need for glitazone treatment. Given the fact that metformin is contraindicated in these patients, the therapeutic option for managing hyperglycemia is limited to insulin titration. These patients often have very wide swings in glucose levels and I would think that a trial of PIO would be justified in some cases.

The NDA contains no data on the 45-mg dose used in combination with other antidiabetic medications. A post-marketing study comparing 45 mg to 30 mg will need to be done to make certain that the risk/benefit relationship of 45 mg is acceptable. This study should also be designed to find investigate the gender effect, to determine if the greater efficacy of PIO in women vs men is related to higher blood levels.

Labeling issues (from revised label of May 28, 1999):

The Actos label should conform to those of Rezulin and Avandia where applicable. For instance, the hepatic toxicity section, ALT monitoring every two months, etc should be modeled after the Avandia label.

The lipid section is problematic. It is clear that PIO does not have the adverse effects on lipid levels that Rosiglitazone appears to have. The PIO label should provide enough information to allow one to reach the conclusion that PIO does not adversely affect lipid levels. I would suggest a table of the three monotherapy studies listing differences vs placebo for all the lipid classes for the 30 mg dose. With respect to naïve patients (see page 26-27 of this review), none of these changes were statistically significant in any one study but the trends are in the right direction, particularly the rise in HDL and reduction of triglyceride. There was a statistically significant reduction in triglyceride at 45 mg in two studies. This information could be shown if it were presented together with the weight gain which is also impressive at 45 mg. Reduction of FBG could also be shown for context. In the combination studies, there were statistically significant changes in some lipid classes. These results could be given along with efficacy data for each indication but balance must be provided by including changes in weight.

After consideration of the issues relating to previously treated patients discussed under study 001, the Sponsor had agreed with my suggestion to use only data from naïve patients in its description of the monotherapy trials. However, upon further reflection, this way of presenting the data is not satisfactory. PIO was more effective in naïve patients than in non-naïve patients. Thus presenting data from naïve patients only would appear to make Actos appear more effective than competing products. The label should be revised to show data from naïve and non-naïve patients separately, at least for study 001. The most straight-forward way to present the results would be dose-response curves (0 –45 mg) in study 001 for naïve and non-naïve patients.

The text of the "indications and usage" section is satisfactory except as indicated below. Actos can be used either alone or in combination with SFU's, insulin, or metformin. No comparative claims are made or implied. There is no suggestion that patients be switched from other drugs to ACTOS.

Specific comments:

PD – What is the evidence that Actos improves insulin sensitivity in patients?
The final sentence of the first paragraph: 'Actos in combination with.... etc' is okay as written.

As stated above, I would prefer the lipid data put into later sections regarding individual indications. Also, it is unfair to quote placebo adjusted changes for glucose and lipids but give change from baseline for weight.

Figure 4 does not seem to add much. Data could be given in the text. Fig 5 does not adequately display the time course of treatment. I would include the FBG time course from study 001 (omitting 7.5-mg dose). This figure illustrates that a full effect on FBG reduction takes about three months so any dose adjustment before then would be premature.

Combination therapy: Give information regarding the dose of metformin and SFU that was continued during ACTOS treatment It is important to show that ACTOS was effective at near-maximal as well as submaximal doses of metformin and SFU. Change in insulin dose can be included in the text.

Changes that occurred in patients in placebo should be stated, not simply subtracted. Data should be expressed as change from baseline for patients on placebo and for patients on PIO.

CPK – give peak levels of transient elevations

The gender effect needs to be discussed, probably along with use in the elderly is best

Dosage and administration : Three months is not adequate time to allow to evaluate efficacy by HbA1c. Three months is adequate for FBG but HbA1c takes longer. It is not clear why starting dose for monotherapy is indicated to be 30 mg but for combination therapy is 15 mg. I think 15 mg should be the starting dose for monotherapy as well.

Summary and Recommendation:

PIO is highly effective in treating hyperglycemia both as monotherapy as well as in combination with SFU's metformin or insulin. Unlike troglitazone, there is no evidence that PIO causes hepatitis. In contrast to rosiglitazone, PIO does not have unfavorable effects on serum lipid levels. As is true for all three drugs in this class, PIO can cause anemia and edema. Its glucose-lowering activity is associated with weight gain. Pending satisfactory label changes and phase 4 commitments, I recommend that this NDA be approved.

/S/ [redacted]

Robert I Misbin MD
Medical Officer
NDA 21073
HFD 510/misbin/sobel/malozowski/weberj
Draft 6/11/99 revised 6/22/1999 finalized 6/23/99

/S/ [redacted]

6/23/99

21073s

JUN 30 1999

Medical Officer's Review
Safety Update (SU) – Pioglitazone (Actos) stamp date June 4, 1999

Deaths:
The SU contains information about two deaths in patients who had been taking placebo in controlled monotherapy studies. There were also three new reports of patients who died in open label monotherapy studies of PIO. Two died of ASCVD, one on day 167 of PIO, the second 20 days post study. The third patient was struck by lightening on day 120. In the placebo-controlled combination studies, three new deaths were reported, all due to coronary artery disease. Two patients had been on placebo plus SFU. One patient had been on PIO plus SFU.

ALT elevations:
One new patient was identified as discontinuing a US study because of ALT elevation > 3 x ULN. This patient had normal enzymes throughout the study but was found to have ALT of 1182 on day 496. A hepatitis screen was positive for hepatitis C. Risk factors were listed as a history of blood transfusions, iv drug abuse and multiple tattoos. PIO was discontinued and he was started on interferon treatment. By 62 days after PIO had been stopped, all his lab tests had returned to normal. In the European studies, one new patient was identified as having ALT> 3xULN but this patient was taking only glibenclamide, not PIO. One Japanese patient on 30 mg PIO was withdrawn because of ALT elevation. He had pretreatment elevation perhaps related to a history of "alcohol abuse" and "fatty liver". His ALT values at weeks –4, baseline, 4, 8, 12, 16, 16 were 95,85,44,78,204,134,201. (Note two values were reported for week 16).

Correction:
The MOR of June 23 states that no bladder tumors were reported. This is incorrect. There was one report of a bladder tumor in a patient on PIO and one in a patient on placebo. Details are as follows: Bladder carcinoma was reported in 1/606 patients on PIO during double-blind treatment of placebo-controlled monotherapy studies compared to 0/259 patients on placebo. In the combination studies, bladder carcinoma was reported during double blind treatment in 1/534 patients on placebo and 0/920 patients on PIO. The placebo patient with bladder carcinoma was also taking metformin.

Summary:
This 120-safety update brings to light no new safety concerns.

/S/ [redacted]

Robert I Misbin MD
June 30, 1999

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/S/ [redacted]
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