

Subgroup analysis showed that PIO was more effective in women than in men. Among de novo patients, men had a mean baseline HbA1c of 9.63 and a reduction of 1.32. Women had a mean baseline of 9.81 and a mean reduction from baseline of 2.00. Differences related to age and race did not appear to be significant. Among the 299 de novo patients, 60 mg was the final dose in 168 (56%) and was the maximal dose used in 172. The 60-mg dose was reduced in four patients because of adverse events, hypoglycemia in one, weight gain in two and light-headedness in one. Among the 56-rollover placebo patients, 60 mg was the final and maximal dose in 37(66%). No new safety issues were uncovered by this long-term open label study.

Study PNFP 026

Placebo-controlled monotherapy study

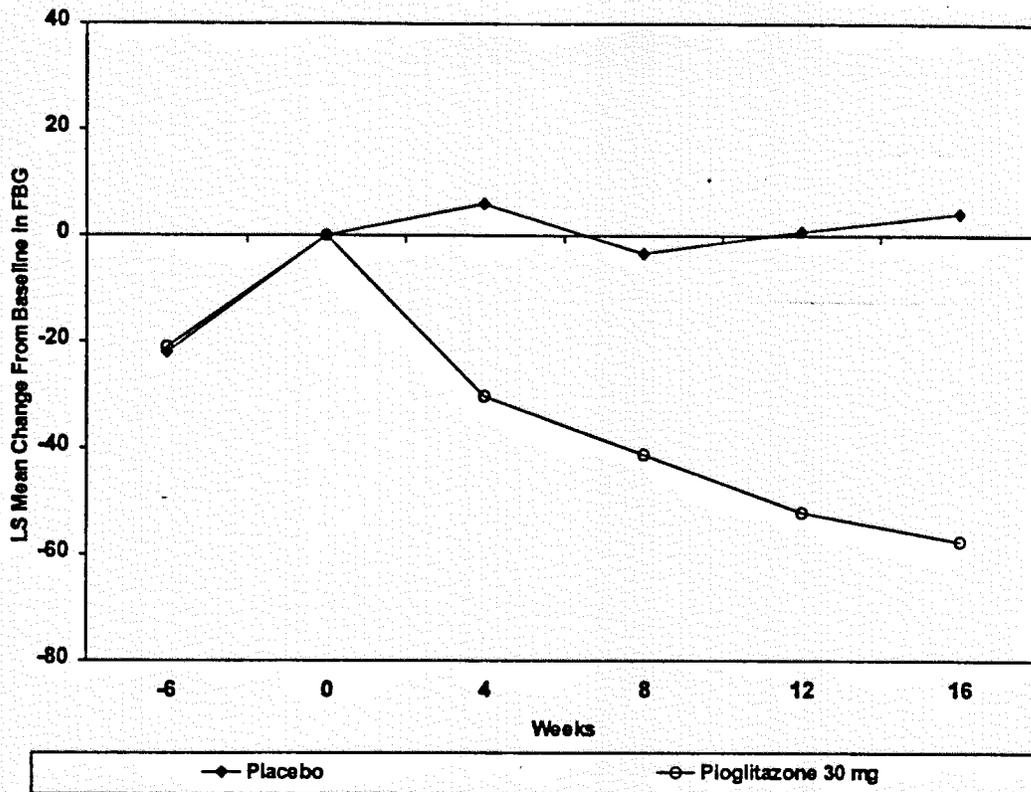
This was a 16 week randomized controlled study which compared PIO 30 mg to placebo. The 16-week double blind placebo portion was preceded by a five-week washout from previous antidiabetic therapy. Inclusion criteria included a HbA1c of at least 7.5 at screening and at least 8 after the washout. Patients were excluded for ALT > 2.5 x ULN. Patients were removed from the study because of insufficient therapeutic effect defined as FBG > 400 mg/dl on two consecutive study visits or hyperglycemia which in the investigator's opinion represented a safety risk to the patient. Reduction in Hb to < 12 for a man and < 10 for a women was also a cause for withdrawal as was development of LVH by EKG. Antihypertensive and lipid lowering drugs were allowed if the dose had been kept constant for 60 days before study. The primary efficacy variable was HbA1c, Secondary variables were FBG, insulin C peptide and lipids. For reason discussed previously, naive and previously treated patients were presented separately.

Naïve patients:

78 patients had not received previous antidiabetic medication. Their mean age was 52 years. Half were male and 62% were Caucasian. The mean BMI was 31.4. For the 37 placebo patients baseline HbA1c was 10.31 The increase from screening to baseline was 0.40 . At the 16 week endpoint (LOCF), HbA1c rose 0.09 (LS mean change) . For patients who received PIO, the mean baseline was 10.13. It had risen 0.25 from screening to baseline. At the 16-week endpoint the mean reduction was 0.89. The reduction in HbA1c with PIO was significantly different from placebo at 12 weeks. The treatment effect at 16 weeks was 0.98. A time course of the change in FBG shown in the figure. The mean baseline was 267 mg/dl in placebo patients and 252 in PIO patients. At 16 weeks the rise in placebo patients was 4.2 mg/dl compared to a fall of 57.6 mg/dl on PIO for a treatment effect of 61.8 mg/dl This figure demonstrates the efficacy of PIO which had not yet plateaued by the end of the 16 week study. The reduction in FBG of about 58 mg/dl in PIO patients should ordinarily have been associated with a reduction in HbA1c of nearly 2.0. That the reduction was only 0.89 is an underestimate of the full effect due to inadequate duration of study.

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Figure 9.1.1.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received No Previous Antidiabetic Medication

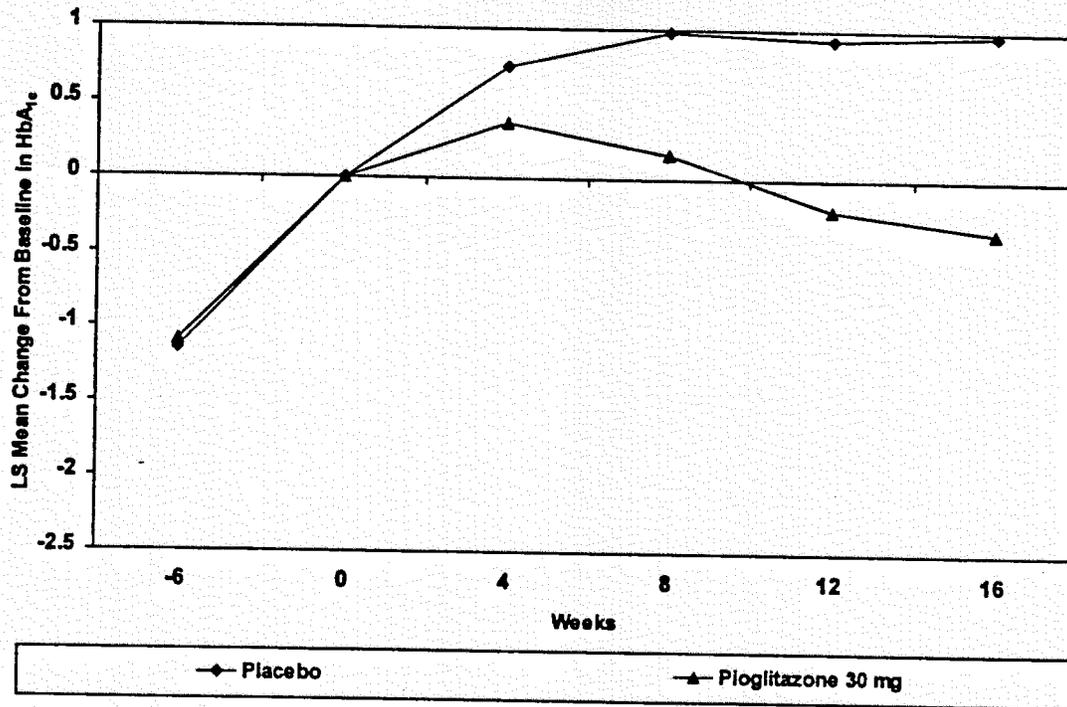


Previously treated patients

The placebo group consisted of 56 patients with mean HbA1c at baseline of 10.25. It had risen 1.14 from screening to baseline and rose an additional 0.97 after 16 weeks. The PIO group consisted of 60 patients with mean baseline HbA1c of 10.72 which had risen 1.09 from screening and which fell a mean of 0.35 after 16 weeks of PIO. The placebo subtracted treatment effect after 16 weeks was 1.32. A time course of the changes in HbA1c and FBG are shown in the figures. In contrast to the previous figures with naïve patients, it appears that a plateau was reached by 12 weeks in these previously treated patients. It is also worth noting that although PIO was superior to placebo, patients never achieved the HbA1c and FBG levels that they had had before previous therapy had been washed out.

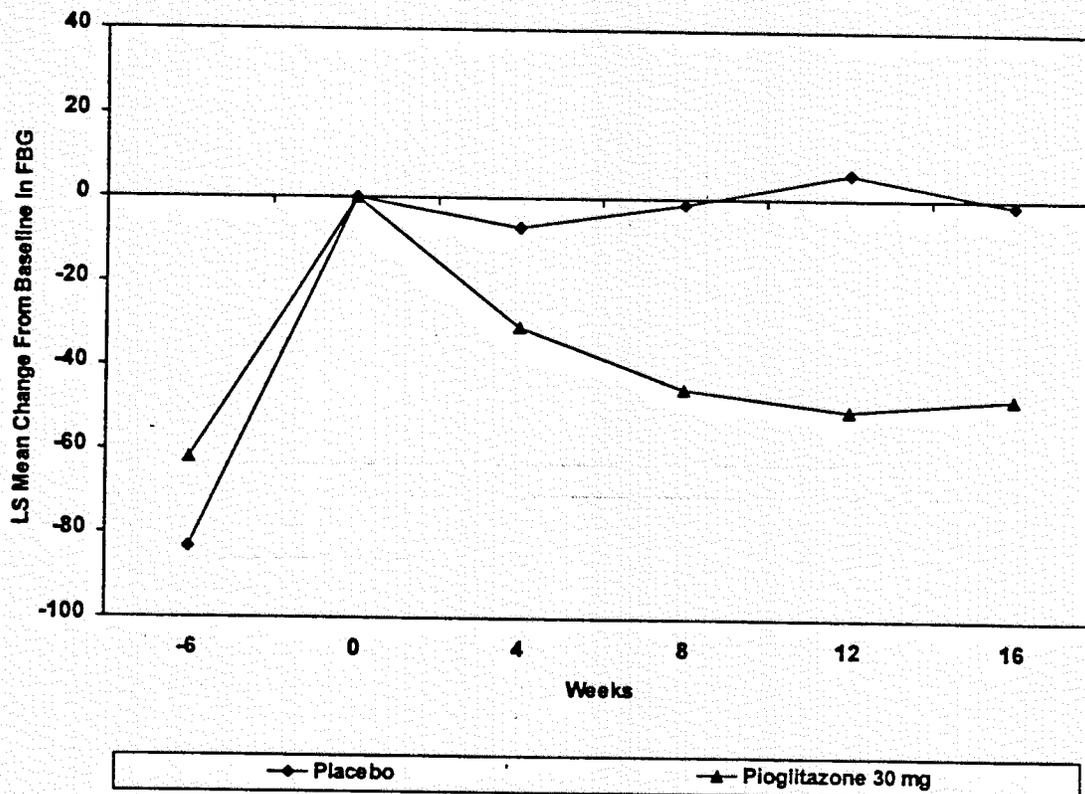
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Figure 9.1.1.2.2.1.1 LS Mean Change from Baseline for HbA_{1c} (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



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Figure 9.1.1.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



There were 28 previously patients whose FBG at baseline was > 280. Their mean FBG at screening was about 227 mg/dl which rose to 333 mg/dl after washout. The final value after placebo treatment was 312 (NDA table 11.1.5). There initial HbA1c was 9.7 at screening. It rose to a mean baseline value of 11.4. After placebo treatment the final mean value was 12.8 (NDA table 9.1.5).

Analyses on combined groups.

C peptide was unchanged in placebo patients but fell 0.23 (baseline 2.21 ng/ml) in PIO- treated patients. There was also a small difference in fasting insulin. Baseline was about 17 uU/ml. This rose about 2 uU/ml in placebo patients and fell about 2uU/ml in PIO patients. The mean difference of 3.84 uU/ml was statistically significant. Plasma triglycerides fell slightly in placebo patients but significantly in PIO patients. The LS mean decrease was 104 mg/dl from a baseline of 400. Both the decrease from baseline and the difference from placebo (85 mg/dl) were statistically significant. There was no difference in total cholesterol but HDL cholesterol rose in PIO patients but were unchanged in placebo patients. The LS mean HDL in PIO patients was 91 at baseline. Both the rise from baseline of 5.3 mg/dl and the difference from placebo of 5.0 mg/dl were significant. Changes in LDL cholesterol were small and not statistically significant. The placebo-subtracted reduction in Hb A1c was 1.07 for man and 1.54 for women. The reduction was 1.22 for patients under 65 and 1.89 for patients over 65 but the total number of patients over 65 was small(19 placebo, 12 PIO). The mean reduction was 1.56 for Caucasians and 2.15 for blacks, but the number of black patients was small(10 on placebo and 9 on PIO). Placebo patients had a mean baseline weight of 87.3 kg. The LS mean change at endpoint was - 1.87 kg. The mean baseline for PIO

patients was 89.9 kg and the LS mean change at endpoint was + 1.35 kg. Using observed values at 16 weeks, placebo patients had a mean loss of 1.98 kg compared to a mean gain of 1.97 kg in PIO patients.

Safety:

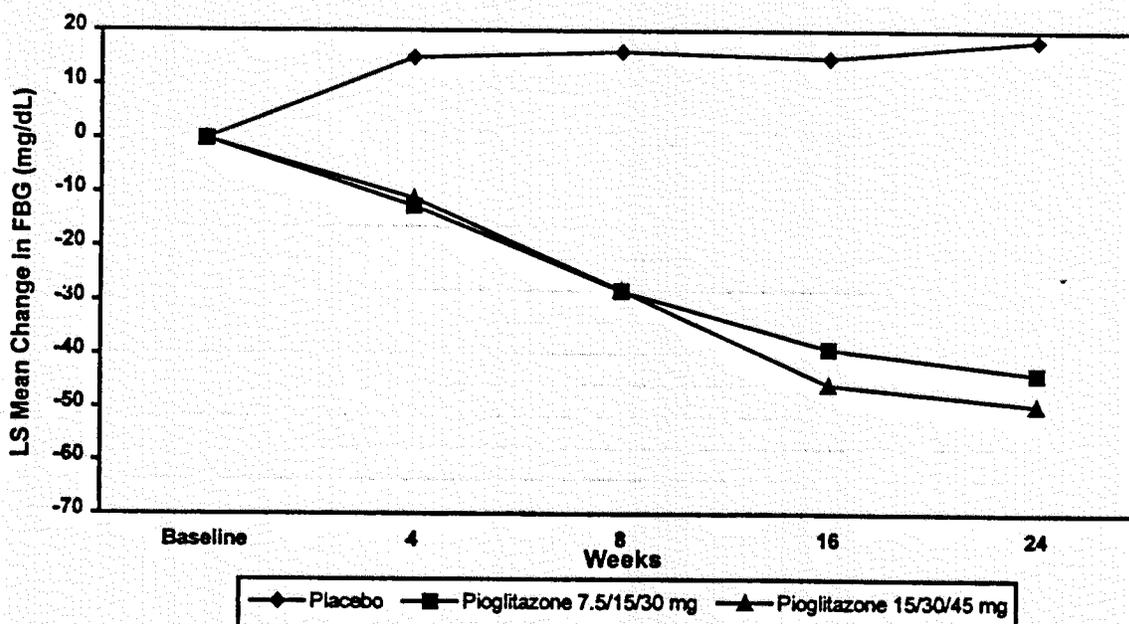
There were no deaths in this study. PIO patients had a mean fall in hemoglobin of 0.52 g/dl compared to a mean rise of 0.03 in placebo patients. There were no additional safety issues.

Study PNFP 012

Placebo-controlled monotherapy study with forced dose titration

This was a three-arm dose-titration study, which began with a six-week placebo washout. One arm received placebo throughout. A second arm began PIO at 7.5 mg. After 4 weeks, the dose was increased to 15 mg and after 4 more weeks it was increased again to 30 mg. The dose of 30 mg was maintained for the next 16 weeks. In the third arm, patients started at 15 mg, the dose was increased to 30 mg after four weeks and to 45 mg after an additional four weeks. The 45 mg dose was maintained for 16 weeks. Patients were required to have HbA1c > 8% at baseline in order to be randomized. Entry criteria were same as for previous monotherapy studies. Withdrawal due to lack of efficacy was similarly defined as FBG > 400 mg/dl on two occasions or a safety risk in the opinion of the investigator. Lipid lowering and antihypertensive drugs were allowed. Beta blockers, warfarin, and antidepressants were not allowed. The mean age of patients was 56 years. 82% were Caucasian and 56% were male. Mean baseline HbA1c was about 10.6. After 24 weeks, there was a mean increase of 0.75 in placebo patients and decreases of 0.99 and 1.01 in low/high dose PIO respectively. The mean treatment effect was -1.74 for low dose and -1.76 for high dose. The figure shows the time course for reduction of FBG. After 24 weeks the mean placebo-subtracted reduction was 62 mg/dl for low dose and 68 mg/dl for high dose

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.

The change in body weight at endpoint was -1.81 kg in placebo patients compared to +0.49 and +1.82 for patients on low and high dose PIO. For completers at 24 weeks the mean change in weight was -1.70 for

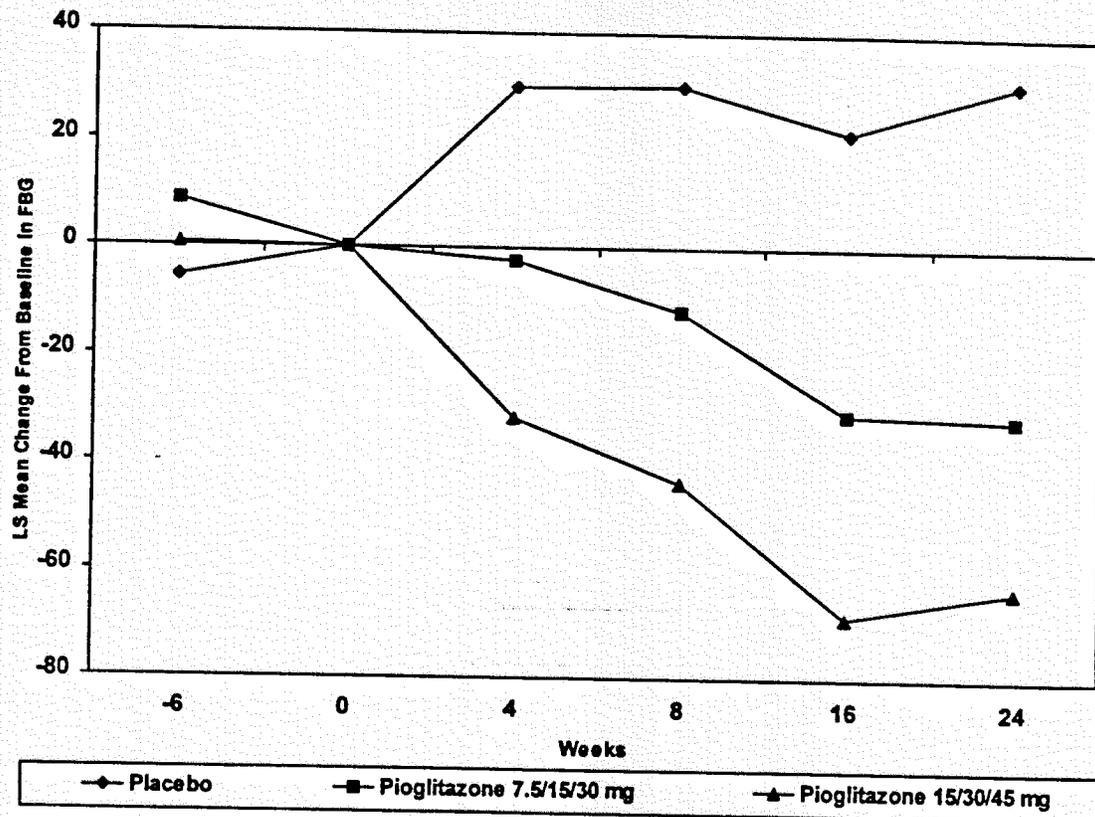
placebo compared to + 1.27 and + 2.58 kg for patients on low and high dose PIO. Mean C peptide fell in all three groups. Mean fasting insulin fell from 15 to 13 uU/ml ($p < 0.05$) in high dose PIO. There were no significant differences between PIO and placebo with respect to insulin and C peptide. Fasting triglyceride levels were about 300 mg/dl at baseline. At endpoint there was a small reduction (NS) of 28 mg/dl in placebo patients but significant reductions of 64 and 102 mg/dl in low and high dose PIO. The placebo-subtracted reduction at high dose PIO of 74 mg/dl was different from placebo. Total cholesterol rose slightly in all groups. Mean HDL was about 41 mg/dl at baseline. The rise of 3.5 and 4.1 in low and high dose PIO at endpoint was significantly different from baseline but not from the small (NS) rise of 1.3 mg/dl on placebo. A small (6% on placebo, 7% and 8% on low and high dose PIO) but significant mean rise in LDL chol was seen in all three groups. PIO tended to be somewhat more effective in women than in men and in patients over 65 than in younger patients. As will be discussed below, the placebo subtracted reduction in HbA1c on high dose PIO was 2.4 in naïve patients and 1.4 in previously treated patients.

Naïve patients:

63 patients (24%) had not previously received antidiabetic medications. Their mean age was 55 years. 85% were Caucasian and 59% were male. Mean BMI was 30.45. There was little change in HbA1c from screening to baseline. Mean baseline values for HbA1c were about 10.3%. From baseline to completion the mean increase in HbA1c among placebo patients was 0.83 compared to mean reductions of 1.45 and 1.76 in patients on low and high dose PIO. All changes from baseline to endpoint were significant. The treatment effect at endpoint was -2.28 and -2.59 for low and high dose PIO respectively. No plateau had been reached in fall of HbA1c by the end of the 24-week treatment (16 weeks at highest dose) period. Mean baseline was about 245 mg/dl. A time course of change in FBG is shown in the figure. One notes little change from screening to baseline. A rise in baseline of about 30 mg/dl occurred over four weeks in placebo patients, which was statistically different from the falls in PIO patients. The mean glucose levels remained largely constant over the remainder of the study but continued to fall in the PIO patients. A maximal reduction of FBG was seen after about 16 weeks. Placebo subtracted change at endpoint was -63 mg/dl for low dose and -95 mg/dl for high dose.

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Figure 9.1.1.1.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received No Previous Antidiabetic Medication

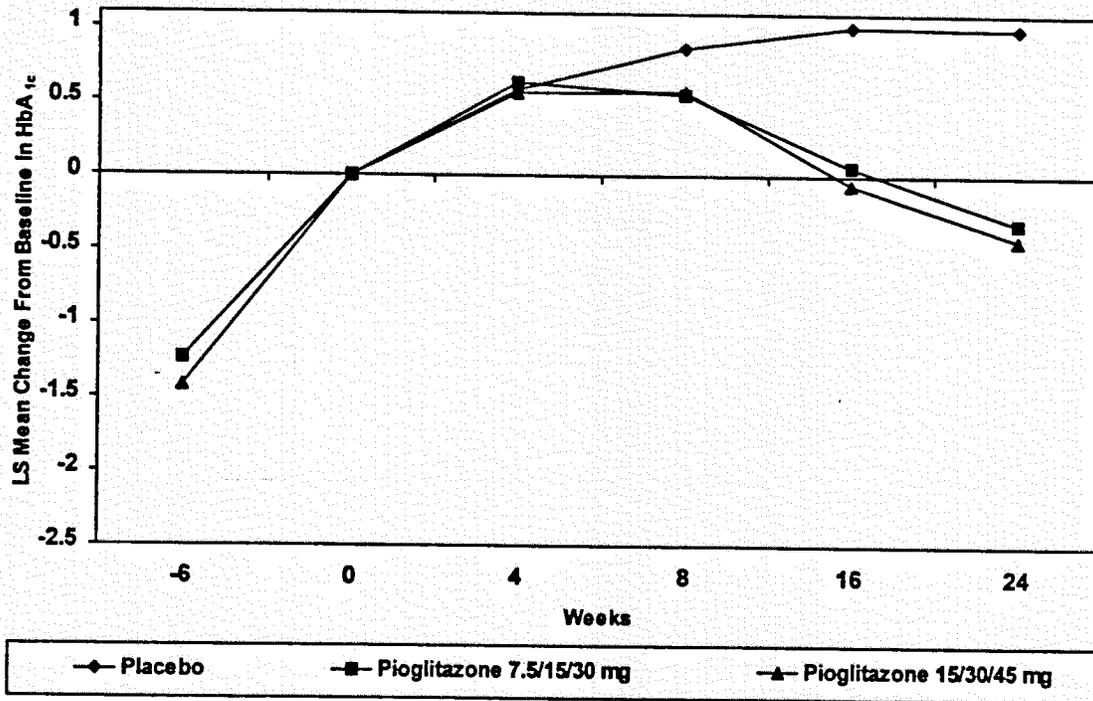


Previously treated patients:

197 patients (76%) had used antidiabetic medications before entering the study. Their mean was 56 years. 83% were Caucasian and 55% were male. Their mean BMI was 31. Time courses of changes in HbA1c and FBG are shown in the figures. FBG rose about 70 mg/dl during the 6-week washout from previous therapy to mean baseline value of about 285 mg/dl FBG continued to rise slightly in the placebo patients but fell in PIO patients. The change in HbA1c was more gradual. It rose about 1.3 during the washout to a mean baseline of about 10.6. HbA1c continued to rise in placebo patients but fell in PIO patients. Of note is that the deterioration in hyperglycemia during the washout was not completely reversed by PIO. At endpoint placebo subtracted change in HbA1c was -1.31 and -1.42 for low and high dose PIO. For FBG, placebo subtracted change at endpoint was -55 and -60 mg/dl for low and high dose PIO.

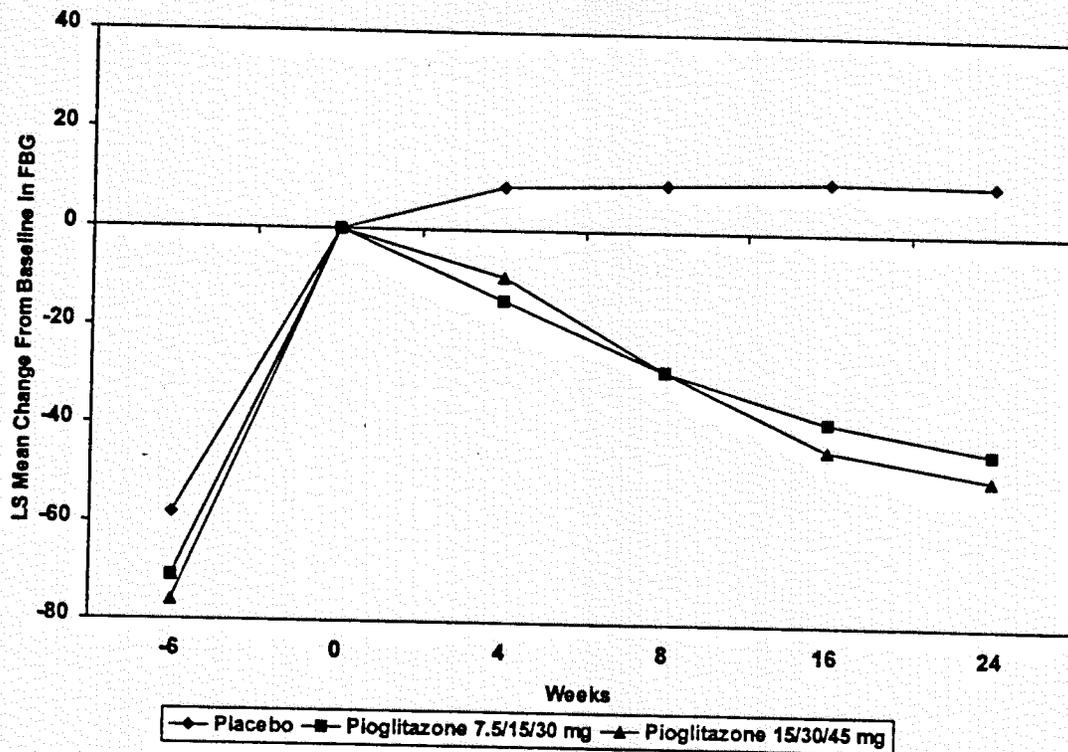
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Figure 9.1.1.2.2.1.1 LS Mean Change from Baseline for HbA_{1c} (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



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Figure 9.1.1.2.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received Previous Antidiabetic Medication



There were 115 patients taken off of antidiabetic medication whose FBG > 280 at baseline. These patients had a mean age of 56 years. 82% were Caucasian and 52% were male. Mean BMI was 31.3 At baseline mean C peptide was 2 ng/ml and mean fasting insulin was 13 uU/ml. Data for HbA1c and FBG for these patients through end of study (LOCF) are shown in the tables below. Although PIO was effective in lowering FBG and HbA1c levels compared to placebo, it should be noted that even high dose PIO did not restore glucose and HbA1c levels to what they had been before the 6 week washout from previous antidiabetic medication.

	Fasting Blood Glucose, mg/dl		
	Placebo	PIO 7.5/15/30	PIO 15/30/45
- 6 weeks	252	229	227
baseline	329	331	329
24 weeks	330	275	267

	Hemoglobin A1c, %		
	Placebo	PIO 7.5/15/30	PIO 15/30/45
- 6 weeks	10.0	9.8	9.6
Baseline	11.7	11.4	11.4
24 weeks	12.7	11.3	11.0

Safety: There were two deaths, one due to myocardial infarction and one due to leukemia. The deaths occurred among the 84 patients randomized to placebo. There were no deaths in patient treated with PIO. There was a dose-dependent reduction in hemoglobin 0.08 on placebo, 0.45 on low dose and - 0.70 on high dose PIO which was associated with reductions in Hct of 1.2, 1.1, and 2.2 on placebo, low and high dose PIO respectively.

Summary of Efficacy of Monotherapy in Naïve Patients:

As discussed under study 001, I am recommending that approval of the monotherapy indication be based on data from naive patients only. The results of naive patients in the three monotherapy studies summarized in the tables below are consistent with each other and demonstrate the efficacy of PIO in these patients. The reduction of HbA1c in study 026 appears less than expected, but this was a 16-week study and changes in HbA1c lag changes in FBG by 2-3 months. Note that study 012 was a forced titration. The final dose (final 16 weeks) is shown below:

HbA1c

	Placebo	30 mg	45 mg
001			
Baseline	9.04	9.31	9.96
Endpoint 26 weeks	+0.62	-0.64	-1.93
LS mean diff		-1.26	-2.55
012			
Baseline	10.21	10.25	10.36
Endpoint 24 weeks	+0.83	-1.45	-1.76
LS mean diff		-2.28	-2.59
026			
Baseline	10.31	10.13	
Endpoint 16 weeks	+0.09	-0.89	
LS mean diff		-0.98	

Fasting Blood Glucose, mg/dl

	Placebo	30 mg	60mg
001			
Baseline	229	225	235
Endpoint 26 weeks	+15	-41	-64
LS mean diff		-56	-80
012			
Baseline	248	243	236
Endpoint 24 weeks	+31	-32	-64
LS mean diff		-63	-95
026			
Baseline	267	252	
Endpoint 16 weeks	+ 4	-58	
LS mean diff		-62	

Changes in serum lipids in these patients is shown in the tables below. Although only a reduction of triglyceride at high dose PIO is statistically significant vs placebo, there is also a trend for higher HDL levels. LDL and total cholesterol show little change and are certainly not increased by PIO. These results are in contrast to the results of the Rosiglitazone trials that consistently show increases in LDL over placebo

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Fasting Triglyceride, mg/dl

001	Placebo	30 mg	45mg
Baseline	356	235	243
Endpoint 26 weeks	-2	-49	-78
LS mean diff		-47	-76*
012			
Baseline	225	249	275
Endpoint 24 weeks	+14	-26	-78
LS mean diff		-40	-92*
026			
Baseline	371	336	
Endpoint 16 weeks	-48	-81	
LS mean diff		-33	

Total cholesterol mg/dl

	Placebo	PIO 30 mg	PIO 45 mg
001 Baseline	218	236	220
Ednpoint 26 weeks	+12	-3	-3
LS mean diff		-15	-15
012 baseline	222	218	213
Endpoint 24 weeks	+10	-1	-4
LS mean diff		-12	-14
026			
Baseline	222	214	
Endpoint 16 weeks	-8	-2	
LS mean diff		+6	

HDL chol mg/dl

001	Placebo	PIO 30 mg	45 mg
Baseline	37	43	40
Endpoint 26 weeks	+3	+5	+8
LS mean diff		+2	+5
012			
Baseline	43	41	37
Endpoint 24 weeks	+0.1	+1.8	+3.1
LS mean diff		+2	+3
026			
Baseline	38	40	
Endpoint 16 weeks	+1	+4	
LS mean diff		+3	

	LDL chol, mg/dl		
	Placebo	PIO 30 mg	PIO 45mg
001			
Baseline	116	145	140
Endpoint 26 weeks	+6	-6	-5
LS mean diff		-12	-11
012			
Baseline	135	133	123
Endpoint 24 weeks	+8	-6	+4
LS mean diff		-14	-4
026			
Baseline	133	126	
Endpoint 16 weeks	0	-9	
LS mean diff		-9	

Data source for above tables is Takeda briefing document for Advisory Committee

Study PNFP 010

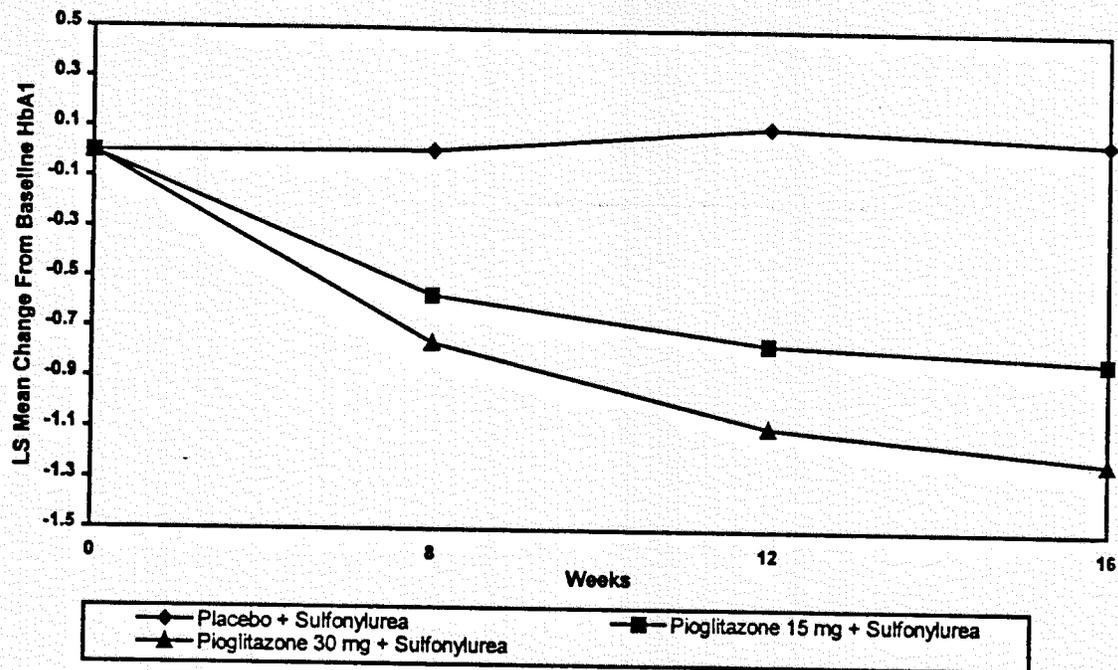
Placebo-controlled study of pioglitazone in Patients on Sulfonylureas.

This study was performed at 54 centers in the United States and compared placebo to 15 mg and 30-mg pioglitazone in patients who had HbA1c levels over 8% despite therapy with sulfonylureas or sulfonylureas plus acarbose or metformin. Following a two-week screening period, patients were treated for four weeks in a single blind manner with their previous dose of SFU plus placebo. Other antidiabetic medications were discontinued at screening. Following the total of 6 weeks of run-in patients were randomized to 15 or 30 mg pioglitazone or placebo. Double-blind comparison lasted 16 weeks. Inclusion criteria were patients with type 2 diabetes between 30 and 75 years of age, on a stable dose of SFU for at least 30 days whose HbA1c was 8.0 or greater at screening and randomization. Fasting C peptide had to exceed 1 ng/dl. Women used contraception where appropriate. Patients were excluded whose liver enzymes exceeded 2.5 x ULN, creatinine over 1.8 ng/dl, anemia of < 12 g/dl for males and < 10 g/dl for females, or class 3 or 4 heart failure or ejection fraction under 40%. In addition to routine safety measures, patients with hematuria on two occasions had urine cytology, and had cystoscopy for three episodes of hematuria or abnormal cells in cytology. Patients were removed from the study for "insufficient therapeutic effect, defined as FBG > 400 mg/dl at two consecutive study visits, or hyperglycemia which presented a safety risk to the patient." The investigator was to make every reasonable effort to keep each patient in the study." Study medication was given as 15 or 30 mg tablets or identical appearing placebo.

The mean age of randomized patients was 56.7 years. 79% were Caucasian and 59% were male. 14% had received other antidiabetic medications (metformin or acarbose) in addition to SFU before starting the study. There were no major demographic or baseline differences. 55% of patients were taking glyburide and 17% were taking glipizide. Approximately 48% were on greater than 50% the maximum labeled dose. At baseline mean HbA1c was about 9.9%, FBG was about 240 mg/dl, mean C peptide was about 2.5 ng/dl and mean serum insulin was 19 uU/ml.

Patients withdrawn for inadequate therapeutic effect were 18/187 placebo patients, 18/184 patients on 15 mg PIO +SFU and 8/189 patients on 30 mg PIO + SFU. Mean changes in HbA1c for ITT patients with LOCF is shown in the table. There was a small rise in HbA1c in placebo patients but reductions in both PIO arms. The treatment effect was -0.88% and -1.28% for 15 and 30 mg respectively. Based on a reduction of 0.6%, the response rate was 34% on placebo, and 57% on 15 mg and 74% on 30 mg PIO. Using observed values the placebo-subtracted treatment effect was -0.94% and -1.30%, using data from 156/177 placebo patients, 154/175 patients on 15 mg and 166/180 patients on 30 mg PIO.

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

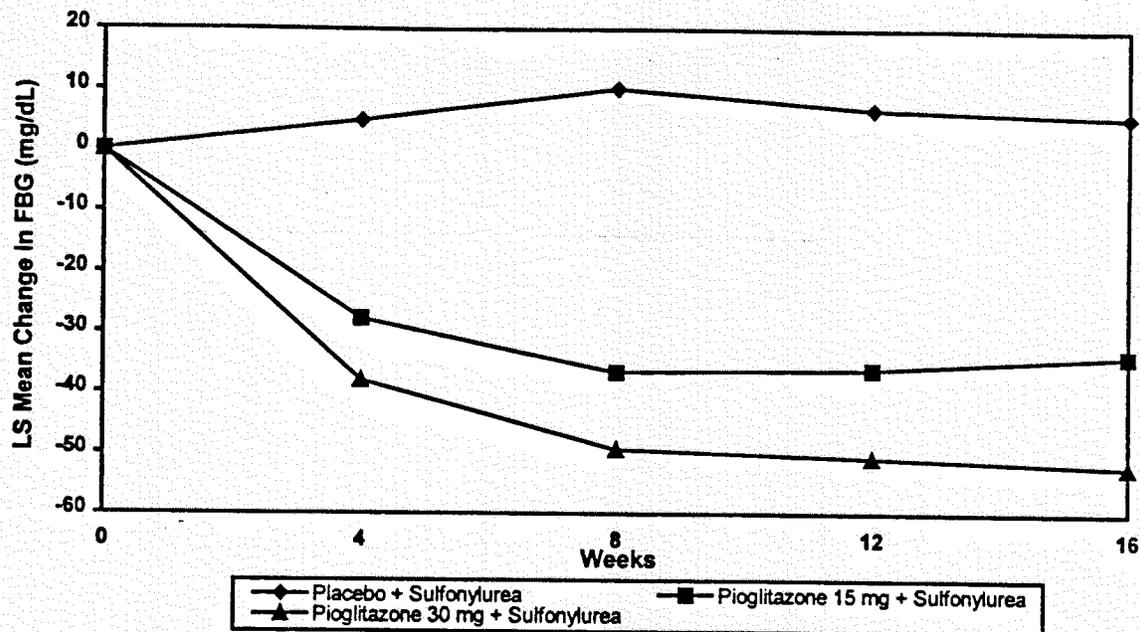


Data Source: End-of-Text Figure 1.2 and End-of-Text Table 9.2.

As shown in the figure, significant reductions in FBG were observed in both PIO arms as early as four weeks with little change in placebo patients. There were small but statistically significant reductions in C peptide and insulin in PIO-treated patients. For instance, the reduction was about 3 uU/ml from a baseline of about 18 uU/ml on 30 mg of PIO.

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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.

Serum lipid levels changes were small but would generally be considered clinically beneficial in the PIO-treated patients. Statistically significant changes relative to placebo (which changed little over the course of 16 weeks) for 30 mg PIO were a 26% reduction in triglycerides, and 12% increase in HDL cholesterol with no change in LDL cholesterol. Patients who were treated with PIO gained weight. Starting from a mean of about 93 kg at baseline, the mean weight changes was a reduction of 0.83 kg in patients on placebo compared to a gain of 2.18 and 3.06 kg in patients on 15 and 30 mg PIO respectively.

Subgroup analysis showed that the reduction in HbA1c from baseline was 1.56 for women and 0.96 for men. The change was an increase of 0.03 for both men and women on placebo. FBG change is shown in the table at 16 weeks.

	FBG at 16 weeks		
	Placebo + SFU	PIO 15 mg + SFU	PIO 30 mg + SFU
Men			
Baseline	238	243	242
Mean change	8.5	-30.6	-50.2
Treatment effect		-39.1	-58.7
Women			
Baseline	234	252	233
Mean change	2.8	-45.5	-54.5
Treatment effect		-48.3	-57.2

There were no differences in efficacy with respect to age, race, or body mass index. However, the reduction in HbA1c was greater in patients whose baseline HbA1c was greater than 9% than in patients with lower values. PIO was effective in lowering HbA1c across the range of SFU dose. This is important because previous studies with other add-on drugs (metformin, acarbose, and troglitazone) had been done at the maximum-labeled dose of SFU. Improvement in glycemic control could therefore not have been achieved simply by increasing the dose of SFU. In the PIO study, patients were told to continue whatever SFU dose they had been taking. At the Reviewer's request, subgroup analysis was performed for patients on 50% of

the maximal labeled dose and compared to patients on less than or greater than 50% of the maximal labeled dose. At 30 mg PIO the placebo-subtracted reduction in HbA1c was 1.51% for patients on 50% maximal SFU dose, compared to 1.27% for patients on < 50% max and 1.08% for patients on > 50% max. Regardless of whether these differences are statistically significant, it is clear that PIO works across the range of SFU doses. Hypoglycemic reactions were reported by 7 patients on 30 mg and 1 patient on placebo..

Safety:

Three patients died during this study, 2 on placebo and 1 on 30 mg PIO. All the deaths were cardiac and not believed to be related to treatment. Peripheral edema was reported in 6.3% of 30 mg PIO, 1.1% on 15 mg and 2.1% of patients on placebo. Two patients had markedly abnormal CPK levels. ALT, AST and GGT levels fell in a dose-related manner on PIO. There was also a small reduction in hemoglobin, hematocrit and rbc. All these AE's were seen in other studies and are reported in the general safety section of this review. Severe thrombocytopenia was reported in a patient during the single blind run-in before ever receiving PIO. There were no differences vs placebo in EKG changes or in urine cytology.

014.2 Insulin-treated Patients

This was a placebo-controlled randomized study conducted in the United States of 15mg and 30 mg of pioglitazone vs placebo in patients with type 2 diabetes with HbA1c > 8% on 30 Units or more per day of insulin. The double-blind comparison lasted for 16 weeks. It was preceded by a two week insulin only run-in followed by four week single blind placebo run-in. Patients were then randomized to the three treatment arms, provided that their HbA1c was still at least 8%. Inclusion criteria required that the patient be on insulin continuously for at least four months and be on a stable dose of at least 30 units for 30 days or longer. A fasting C peptide of at least 0.7 ng/ml was also required. The mean age of patients was 57.1 years and 47.3% were male. 73.1% were white and 17% black. The mean BMI was 33.6 kg/m². 12% were on oral antidiabetic agents in addition to insulin which were discontinued at screening. Mean HbA1c at baseline was 9.85%, FBG was 224 mg/dl and C peptide was 1.57 ng/ml. The median insulin dose was 61 units. The mean was 71 units. Patients took an average of 2.5 injections per day. There were no baseline equalities among the three treatment arms.

No attempt was made to change insulin regimen. After 16 weeks, there was a mean decrease in insulin dose of 0.6 unit's in-patients on placebo and reductions of 3 and 8 units respectively in patients on 15 and 30 mg PIO. While not representing an efficacy measure, these reductions in insulin dose are consistent with changes in glycemic control which occurred during the study. Starting from a mean baseline of about 9.8%, there was a statistically significant reduction in all groups. This improvement in control, even in placebo patients, indicated that good practice standards were maintained throughout the study. The placebo-subtracted reduction was 0.73 and 1.00% for 15 and 30 mg PIO respectively for the ITT population. Using observed values (not LOCF) HbA1c reduction was 0.77 and 0.97%.

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