# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 021073

## MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

/S/ [redacted]

Date: 6/23/99

JUN 30 1999

From: Saul Malozowski
Acting Medical Team Leader

Subject: Pioglitazone-NDA 21,073, Actos® Takeda Pharmaceuticals

To: Solomon Sobel /S/ [redacted] 6/30/99
Division Director, DMEDP

The documentation provided to support the approval of pioglitazone for the treatment of type 2 diabetes clearly establishes the glucose lowering properties of this compound, either as monotherapy or in combination with sulfonylureas, metformin, and insulin. These beneficial effects were also seen when HbA1c was used as the endpoint. Effects are progressive, reaching maximal HbA1c reductions after several months of exposure. These effects seem to be sustained for at least 12 months. Reductions in these parameters have been associated with decrease risks for macro and microvascular complications with other anti-diabetic drugs such as sulfonylureas, metformin and insulin. Whether these benefits can be also be attributed to pioglitazone remains to be clarified.

The main safety concerns with this drug relates to the potential development of acute liver failure, due to the complications associated with the use of troglitazone, a drug in the same class, and of cardiac hypertrophy seen in preclinical studies with troglitazone, rosiglitazone and pioglitazone.
The results of all short and long term studies with this product have dispelled some of these concerns regarding hepatic events, because no cases or indication of liver toxicity were detected during this period. The information submitted and reviewed, suggests that under the conditions experienced during the clinical development pioglitazone did not show any evidence of hepatotoxicity. Similarly, the cardiac safety profile seems to be benign in the patient population exposed. The supporting studies to dispel these concerns, however, were limited in scope and time exposure. It remains to be seen whether these concerns are further clarified once the drug reaches the market and patients with other profiles to those studied in the pivotal studies are exposed and/or the time of exposure increases. It is also important to stress that patients with NYHA stage 3 and 4 have been not yet exposed to this moiety. These two issues (hepatotoxicity and cardiac toxicity) are properly addressed in the label. A decision regarding the need for liver enzyme monitoring and its frequency, as discussed in the AC meeting, has been made and this product will follow the warning listed in the two previously approved glitazones.

Anemia was seen more frequently in patients receiving pioglitazone than placebo. The number of cases seen during the studies and the characterization of this complication does not suffice to assess whether this drug may cause anemia and if so, what mechanism is involved and what patients may be more prone to develop anemia. The magnitude of the changes observed were not clinically significant, but in a few cases. Phase 4 studies should explore these issues in depth. The label fairly conveys the occurrence of this complication.

Weight increments were seen consistently across studies in the patients receiving pioglitazone. In contrast to HbA1c levels that plateau after several weeks, weight tended to continue to increase throughout the studies with no evidence of pause. Weight increments accrued were in excess of 5% of initial body weight in some studies. Currently drugs approved for the treatment of obesity require weight reduction of this magnitude. It is believed that weight reduction of this extent could be beneficial to obese patients in reducing the risk for cardiac complications. Type 2 patients are obese and are at risk for cardiac complications. Pioglitazone increases their weight while reducing their HbA1c. Whether this balance between improvements in glycemic control and worsening in weight would be beneficial remains to be explored. Patients as well physicians should be informed as to this "imbalance." The current label should address this issue appropriately.

It is quite curious that the improvements in glycemic control are seen more clearly in females at equal dosages. Pioglitazone tends to result in weight increments (fat mass) and by this mechanism appears to further improve glycemic control. The sponsor has not yet clarified where the weight accumulates. The improved responses suggest that weight increments are the result of fat accumulation. No studies in humans with this compound have yet elucidated whether the fat is deposited in the abdomen (increasing the cardiac risk) or in some other(s) region(s) of the body. Because males have less fat than females tend to respond better to this drug, these findings tend to point out that fat and not muscle is the main target for this compound. If the PPARγ receptor target were mostly in the muscle, males were to be more responsive to this drug. Again, the evidence seems to point to fat and not to muscle as the main target for this product. We do not have information as to the diet that these patients had during the studies nor assessment of whether appetite increased in subjects receiving pioglitazone. This needs to be further clarified.

Other important finding in the development of this drug used as monotherapy, are its overall beneficial or neutral effects on lipid markers, in contrast to the two previously approved glitazones. Troglitazone was overall neutral while rosiglitazone tended to worsen cholesterol, and LDL. Thus, these potential beneficial findings are unique to pioglitazone monotherapy and suggest that it may have a neutral effect or even reduce the risk for cardiovascular complications. The mechanisms underlying these actions are unknown. When pioglitazone was used in combination with metformin or insulin, however, LDL increased.

Any beneficial effects in lipid profiles of pioglitazone monotherapy should be balanced with the weight increments, a finding that is not welcome in the treatment of type 2 diabetics. Weight decrements tend to result in these lipid improvements and the paradoxical neutral effect of pioglitazone on lipids in patient increasing their weight is a phenomenon not well understood. The clinical significance of these changes, if any, is unknown.

Information regarding the mechanism of fluid retention is also lacking. The sponsor could have answered this question early on during the drug development process. The fact that this was not done hinders the ability to properly address this issue in the label in order to alert subjects that may be more prone to get this complication and to develop a rational treatment for those patients that do.

Due to the pre-clinical and clinical information regarding a role in affecting the action of P-450 enzymes, the potential role on numerous systemic actions (in particular, steroidogenesis and vitamin D metabolism) remains to be clarified.

Recommendations:
I concur with Dr. Robert Misbin's recommending approval of this compound. The label, however, should reflect his and my recommendation to properly reflect the outcomes of the studies as well as the risks involved in the use of pioglitazone. There is an imperative need to perform phase 4 studies to further clarify issues that have not been properly addressed during the previous phases or that because the intrinsic limitations of the drug developing process can not be elucidated until a drug is introduced to the market.

JUN 23 1999

MEDICAL OFFICER"S REVIEW: NDA 21-073

Actos (Pioglitazone) - Sponsor - Takeda



Robert I Misbin MD
Medical Officer – HFD 510
June 23, 1999

Introduction:

Pioglitazone( PIO) is the third thiozolidinedione to be considered for approval. The first of this class, troglitazone, was approved in 1997. The major problem with the use of trogltiazone has been liver failure. Its label now includes a boxed warning and monthly liver enzyme ( ALT) monitoring is suggested. The monotherapy indication was removed in June 1999. Based on a preliminary review of the liver-related events in this application, it appeared that PIO was less likely to cause hepatitis than troglitazone. For this reason PIO was given a priority review. Safety issues related to PIO were discussed at an Advisory Committee meeting April 23 1999, one day after the rosiglitazone application was discussed. The NDA for Rosiglitazone (Avandia), the second drug in this class, was approved May 25 1999. The Avandia label contains language that reflects the Division's belief that it is much less likely to cause hepatitis than troglitazone. As will be discussed later in detail, it appears that PIO is also much less likely to cause hepatitis than trogltiazone. The Advisory Committee also expressed this view.

This application consists of three phase 3 trials of monotherapy and one phase three trial each for combination therapy with sulfonylureas ( SFU) metformin, and insulin. All phase 3 trials were placebo controlled. There were no comparative studies. Efficacy data from these trials and data regarding changes in lipids and body weight are discussed in detail. Liver related events and other safety related issues are discussed at the end of this review.

Overview of Phase 3 Studies done in the United States:

There were six double-blind placebo controlled trials completed in the United States. There were three trials of monotherapy and three of combination therapy with sulfonylureas, metformin and insulin. The monotherapy study 001 lasted six months and was followed by an open-label extension. The other trials lasted 16 weeks. Details of patients' exposure and dosages studies are given in the following table.

| Double-Blind Study | Number of Patients | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Pioglitazone | | | | Total | |
| | Placebo | 7.5 mg. | 15 mg. | 30 mg. | 45 mg. | Pioglitazone | Total |
| Completed Monotherapy | | | | | | | |
| PNFP-001 | 79 | 81 | 81 | 87 | 80 | 329 | 408 |
| PNFP-012[+] | 84 | | | 87 | 89 | 176 | 260 |
| PNFP-026 | 96 | | | 101 | | 101 | 197 |
| Total | 259 | 81 | 81 | 275 | 169 | 606 | 865 |
| Completed Combination Therapy[++] | | | | | | | |
| PNFP-010 | 187 | | 184 | 189 | | 373 | 560 |
| PNFP-027 | 160 | | | 168 | | 168 | 328 |
| PNFP-014 | 187 | | 191 | 188 | | 379 | 566 |
| Total | 534 | | 375 | 545 | | 920 | 1454 |
| Completed Total | 793 | 81 | 456 | 820 | 169 | 1526 | 2319 |
| Ongoing Monotherapy | | | | | | | 0 |
| Ongoing Combination Therapy | | | | | | | 0 |
| Ongoing Total | | | | | | | 0 |
| Overall Total | 793 | 81 | 456 | 820 | 169 | 1526 | 2319 |

[+]Forced titration at Weeks 4 and 8 from 7.5 to 15 to 30 mg, respectively, listed as 30 mg.; Forced titration at Weeks 4 and 8 from 15 to 30 to 45 mg, respectively, listed as 45 mg.

[++]Companion medication was sulfonylurea for PNFP-010, metformin for PNFP-027 and insulin for PNFP-014.

Study PNFP 001
Placebo-controlled trial of PIO monotherapy

This trial was conducted in the USA between Jan 31 1996 and March 13 1998. It was a 26-week double blind comparison of placebo to PIO at doses of 7.5, 15, 30, and 45 mg/d. The double blind comparison was proceeded by a six-week single-blind placebo washout from previous antidiabetic medications. Patients who had not been on antidiabetic medications previously could skip the 6-week washout period and enter the two-week baseline period. The requirement for a FBG between 140-240 after the washout was amended to read > 140 mg/dl at screening. The initial protocol stated that patients were to be withdrawn for FBG > 280 mg/dl on two consecutive visits. This was amended to > 400 mg/dl on two consecutive visits. Glucose tolerance testing was performed in patients whose FBG was < 240. Inclusion criteria also included fasting C peptide > 1 ng/ml at screening and HbA1c > 7% before randomization. Patients were excluded for liver chemistries, ALT, AST, alk phosph or bilirubin greater that 2.5 x ULN, creatinine > 1.8 mg/dl or hct < 42 for men and < 36 for women, LVH by voltage criteria, or Ejection Fraction < 40% by echocardiogram.

Each of the five study arms had approximately 80 patients. Approximately 1/3 of these patients were naïve to drug treatment and about 2/3 had been on previous antidiabetic medications. Based on a preliminary view of the data presented at the preNDA meeting, I asked that these two populations be presented separately. The reasons for this are as follows: For naive patients there was little change in glucose levels from screening to baseline. Glucose levels then fell in patients who received PIO and rose slightly in patients who received placebo. The situation was more complicated in patients who were withdrawn from received previous antidiabetic medication, If one considers only changes from baseline, mean HbA1c levels also fell in these patients on the three highest doses of PIO and rose in patients on placebo. However, if one considers the starting point to be PRIOR to discontinuing previous antidiabetic medication, it is clear that HbA1c levels rose in all groups. This illustrates two important points. The first is that PIO appears to be inferior to patients' previous antidiabetic medication. Since patients' hyperglycemia deteriorates when they are switched to PIO from other medications, it is hard to see how these data can be used to support an indication of initial monotherapy. This is the same problem we faced with trogltiazone and led to a statement in the label that patients should not be taken off SFU's and put on troglitazone. A second problems relates that the ethics of how the trial was designed and conducted.

In the initial protocol, inclusion criteria for randomization was a FBG < 240 . Patients were to be withdrawn for lack of efficacy if the FBG> 280 on two consecutive visits. The protocol was later amended in August 1996, six months AFTER the patient accrual had begun, which eliminated any upper limit in FBG for entering the trial and stated that patients would be withdrawn for FBG > 400 mg/dl on TWO consecutive visits. Patients could be withdrawn for hyperglycemia "which presented a safety risk to the patient, in the investigator's opinion." But the protocol also states that " the investigator was to make every reasonable effort to keep each patients in the study".

Values over 400 are ordinarily considered high enough to require treatment to prevent development of hyperosmolar syndrome. This degree of hyperglycemia cannot be considered safe remain untreated. Even before the DCCT report showed that control of chronic hyperglycemia was important to prevent diabetes complications, the UKPDS study used a value of 270 mg/dl as the level requiring that placebo patients receive active treatment.

The Sponsor has analyzed their efficacy data based on whether patients had baseline FBG of greater than 280 mg/dl. These patients would not have been eligible according to the criteria of the original protocol. There were 152 patients withdrawn from other antidiabetic medications ( primarily sulfonylureas) whose baseline FBG exceeded 280 mg/dl. Data for the 33 placebo and 30 patients on 45 mg PIO are shown in the following table. (Data source tables 9.2.5 and 11.2.5)

| | HbA1c | HbA1c | Fasting Glucose | Fasting Glucose |
|---|---|---|---|---|
| | PLACEBO | PIO 45 mg | PLACEBO | PIO 45 mg |
| -8 weeks | 9.65 | 9.57 | 234 | 241 |
| Baseline | 11.62 | 11.54 | 325 | 344 |
| 26 weeks | 12.58 | 11.43 | 316 | 278 |

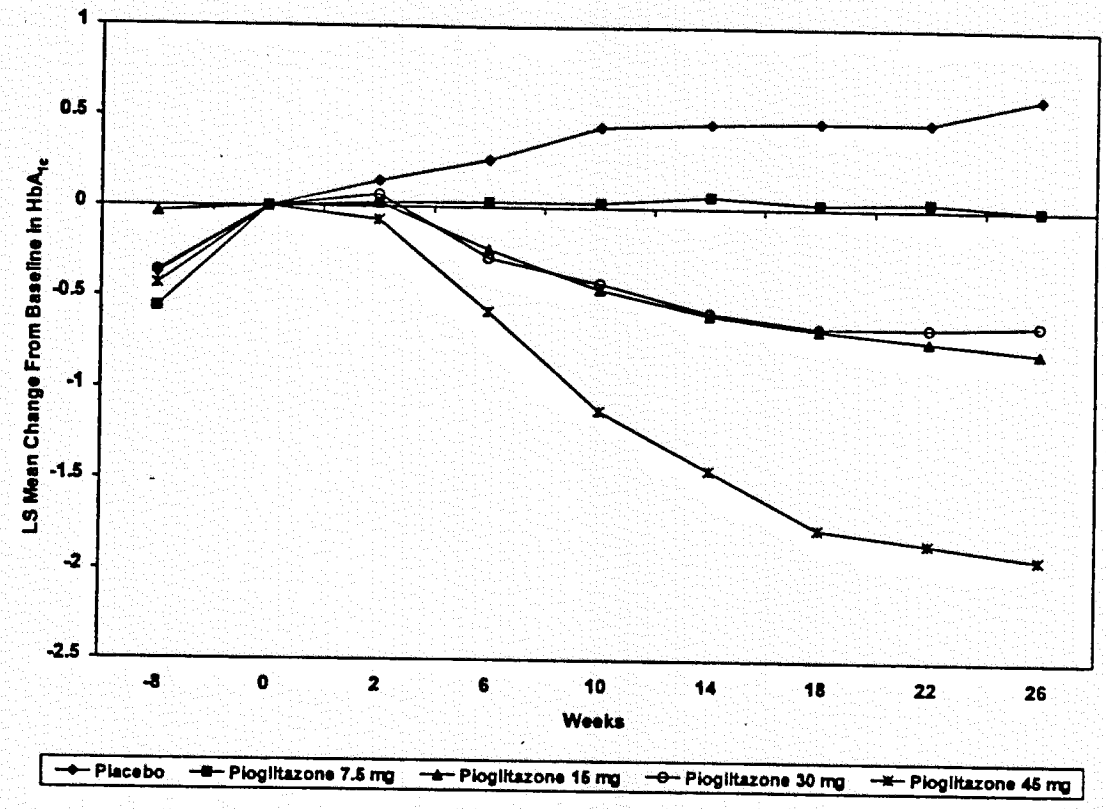
It should be noted that the American Diabetes Association considers a HbA1c of 8 to be too high and should lead to intensification of the treatment regimen. However the patients shown above had HbA1c levels considerably higher and despite that were withdrawn from standard treatment so they could participate in a placebo-controlled trial. I believe that to withdraw patient from active treatment and then allow them to go untreated despite this degree of hyperglycemia is unethical. Although the consent form lists the potential dangers of untreated hyperglycemia, nowhere is it stated that investigators were being paid to recruit their patients into the trial. Given this conflict of interest, it is important that reasonable equipoise be maintained between the risk/benefits or participating in a trial and risks/benefits of not participating. For naïve patients, non-participation is just a continuation of the status and is not very different from receiving a placebo during a trial. But to discontinue standard treatment is really to put a patient in harm's way, particularly when the protocol would allow a degree of hyperglycemia to go untreated which, according to current ADA criteria (persistent fasting glucose over 300 mg/dl), could qualify for hospitalization. The record shows that the change in protocol was submitted in the body of an amendment, and did not receive comment by members DMDEP. Since the cover letter to the submission did not call attention to the substance of the change, it is easy to understand why it was approved as a routine amendment without comment. That the protocol was amended six months after the trial had already begun indicates that the Sponsor was willing to sacrifice patient safety in order to bolster recruitment. For these reasons, I have recommended that efficacy data from patients withdrawn from previous treatment should not be considered in support of this NDA.

My review is based primarily on the supplemental analysis that I asked for at the preNDA meeting in which naive patients are separated from patients taken off antidiabetic medications before the trial. The Sponsor also provided an analysis of patients with baseline FBG> 280 mg/dl . These patients would not have been eligible to be studied according to the original protocol. As will be discussed later, the efficacy data on naïve patients is adequate to justify approval. The statistical review provided by Lee Pian is based on an analysis of the entire population as originally planned.

Naïve patients:

There were 127 patients randomized to the six treatment arms, approximately 25 per arm. They had mean age of 52 years, 56% male, 78% Caucasian with mean BMI of 31.3. The M/F ration was reversed in the placebo group. This group had 44% males. Otherwise there were no serious baseline demographic imbalances. Mean baseline HbA1c was about 9.5, FBG 233 mg/dl, C peptide 2.3 ng/ml and insulin 20 uU/ml. As shown in the next figure, there was a reduction from baseline in HbA1c for the three highest doses of PIO, compared to a small but significant rise of 0.62 at 26 weeks in placebo patients. There was little change in HbA1c at the lowest PIO dose which was 7.5 mg. Based on a reduction of at least 0.6, 12% of placebo patients were classified as responders compared to 30%, 62%, 39%, and 71% on 7.5, 15, 30 and 45 mg of PIO, respectively.

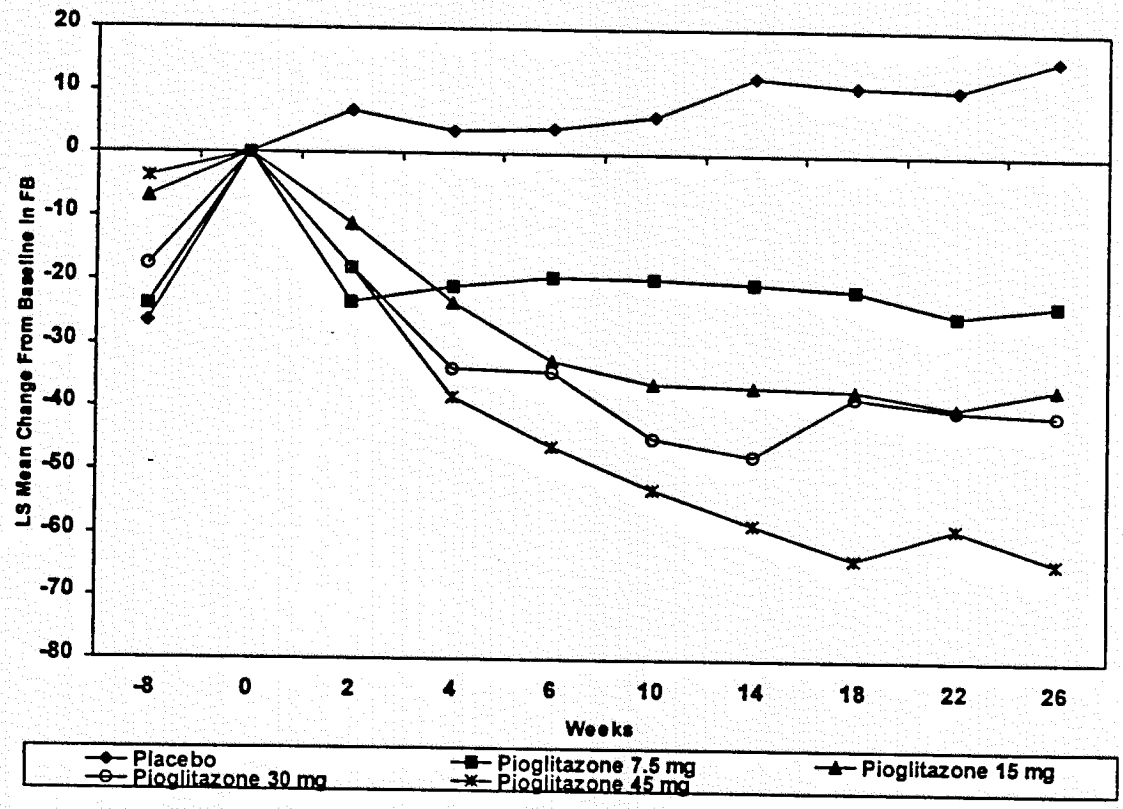
**Figure 9.1.1.1.2.1.1: LS Mean Change from Baseline for $HbA_{1c}$ (LOCF) for Randomized Patients Who Had Received No Previous Antidiabetic Medication**




Results of FBG for PIO vs placebo are largely the same as for HbA1c, except that the fall from baseline at 7.5mg is also statistically significant (see figure). It may be worthy of note that the 26 week FBG value for 7.5 mg is virtually the same as the –8 week screening value, which explains why the Hba1c curve at 7.5 mg is essentially flat. One also sees that the time to maximal response for the three highest doses combined as approximately 14 weeks. The response rate based on reduction of at least 30 mg/dl is 12% for placebo patients compared to 41%, 54%, 65%, and 76% for patients on 7.5, 15, 30, and 45 mg PIO respectively.

APPEARS THIS WAY ON ORIGINAL

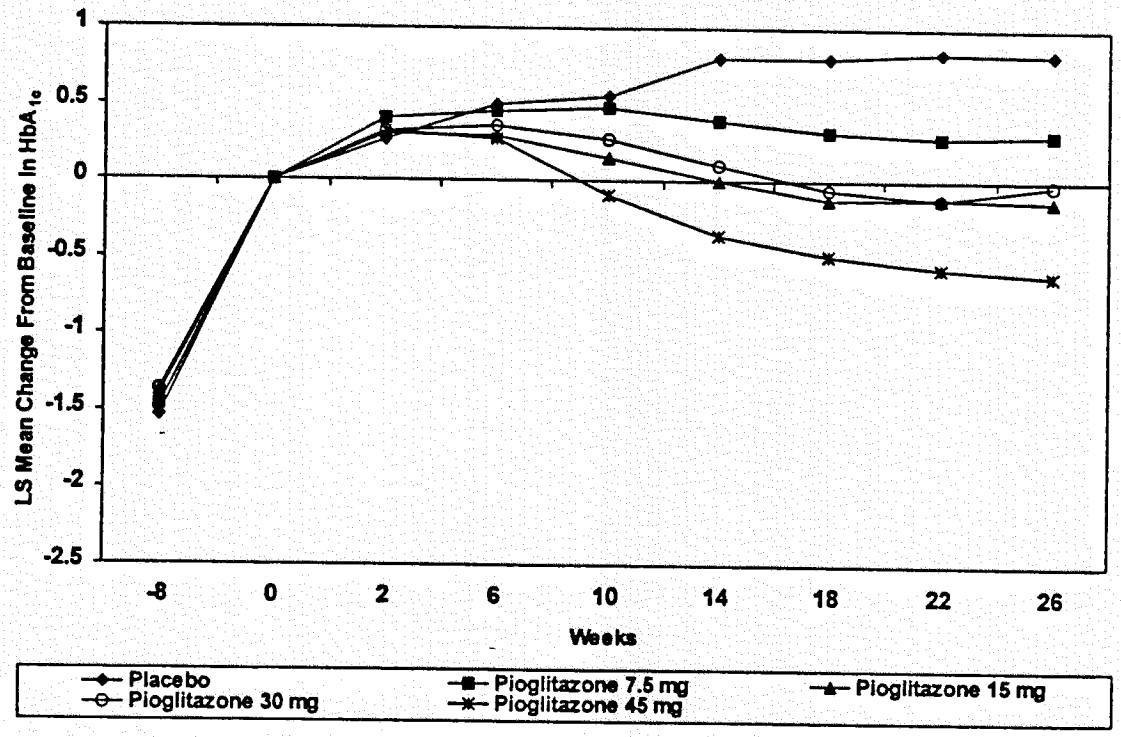
**Figure 9.1.1.1.2.2.1: LS Mean Change from Baseline for FBG (LOCF) for Randomized Patients Who Had Received No Previous Antidiabetic Medication**




Previously treated patients:

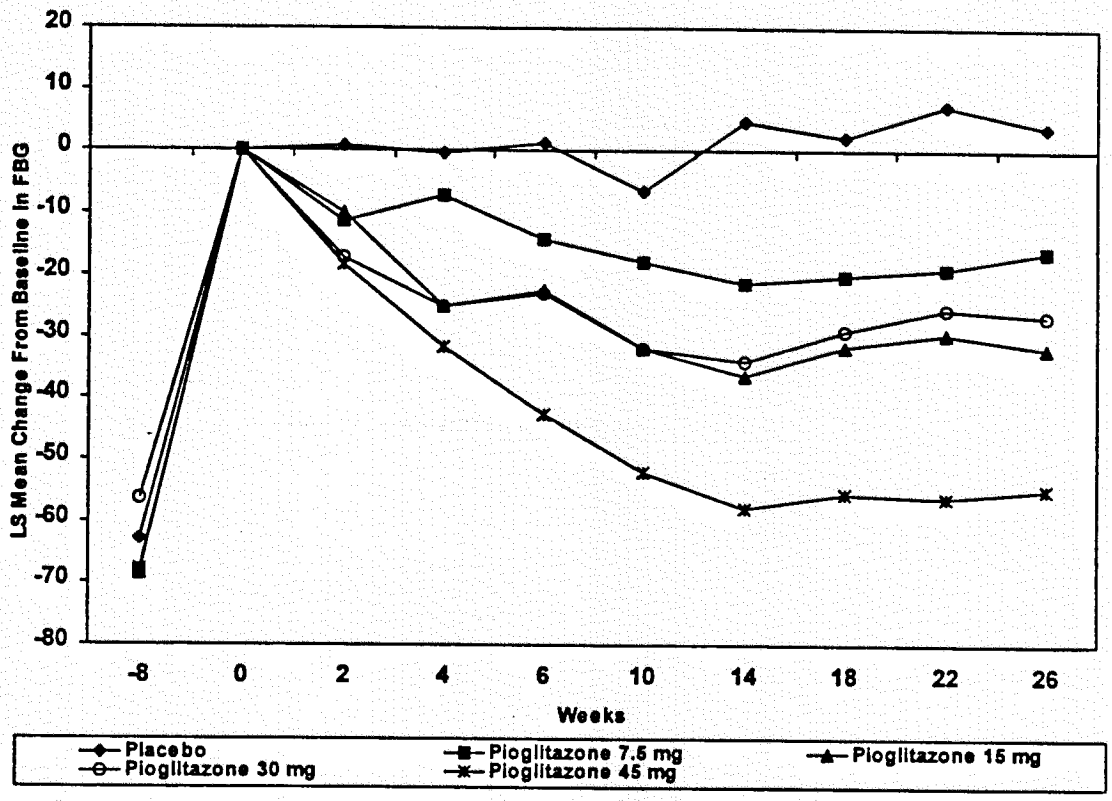
There were 281 patients randomized, approximately 55 in each arm. The mean age was 54 years. There were 58% males, 78% Caucasian. The mean BMI was 31. Like with the naïve patients, the male/female ratio was reversed in patients in the placebo group that had 46% males. Mean HbA1c at baseline was 10.51, FBG 280, C peptide 2 ng/ml and insulin 14.7uU/ml. Results of changes in HbA1c and FBG are shown in the following two figures. HbA1c rose 1.53 in placebo patients from screening to baseline and rose 0.83 over the 26 week study (all results are LOCF) for a mean change of +2.33. Among patients on 45 mg PIO the rise from screening to baseline was 1.39 followed by a fall of 0.61 for a mean change of +0.78. The treatment effect of 45 mg PIO is therefore -1.54 (placebo change minus PIO change). Although effective versus placebo, it should be noted that mean HbA1c levels rose in all groups.

**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**




FBG rose 63 mg/dl from screening to baseline for patients on placebo but rose only 4 mg/dl in the subsequent 26 weeks. For patients on 45 mg PIO, the rise from screening to baseline was 68 mg/dl and the fall during 26 weeks of treatment was 55 mg/dl. For all other doses of PIO there was a clear deterioration of FBG levels if one compares screening (previous drug treatment) to 26 weeks of PIO, although the three highest doses of PIO are statistically better than placebo ( $p<0.05$).

**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**




Analyses on Combined Data

Changes in HbA1c for the combined population are shown in the following table. Patients had a mean HbA1c of about 10.4% at baseline, which rose 0.74 in placebo patients and fell 0.86 at 45 mg PIO. There were no differences in C peptide but fasting insulin levels were generally reduced at 30 and 45 mg PIO. Baseline insulin levels were about 15 uU/ml. At 22 weeks there was a mean reduction of 0.97 on placebo compared to a mean reduction of 4.74 on 45 mg PIO. This was statistically different, although at endpoint, the change for placebo was +0.08 compared to –1.55 for 45 mg PIO and –3.30 for 30 mg PIO. The change for 30 mg was statistically significant but the change for 45 mg was not. Changes in insulin levels after glucose ingestion (done only is patients with FBG < 240 mg/dl) were not changed by PIO.

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

| Visit | Placebo | Pioglitazone 7.5 mg | Pioglitazone 15 mg | Pioglitazone 30 mg | Pioglitazone 45 mg |
|---|---|---|---|---|---|
| Baseline[a] | | | | | |
| N[b] | 79 | 80 | 79 | 85 | 76 |
| LS Mean | 10.41 | 10.04 | 10.23 | 10.15 | 10.34 |
| SE | 0.218 | 0.217 | 0.218 | 0.211 | 0.223 |
| Week 2 | | | | | |
| N | 78 | 80 | 78 | 84 | 76 |
| LS Mean Change | 0.23+ | 0.26+ | 0.23+ | 0.22+ | 0.22+ |
| SE | 0.064 | 0.063 | 0.064 | 0.062 | 0.066 |
| Week 6 | | | | | |
| N | 79 | 80 | 79 | 85 | 76 |
| LS Mean Change | 0.46+ | 0.33+ | 0.15 | 0.17 | 0.09 |
| SE | 0.106 | 0.106 | 0.107 | 0.104 | 0.110 |
| Week 10 | | | | | |
| N | 79 | 80 | 79 | 85 | 76 |
| LS Mean Change | 0.49+ | 0.34+ | 0.01* | 0.05 | -0.33+* |
| SE | 0.135 | 0.135 | 0.136 | 0.132 | 0.140 |
| Week 14 | | | | | |
| N | 79 | 80 | 79 | 85 | 76 |
| LS Mean Change | 0.71+ | 0.25+ | -0.13* | -0.14* | -0.59+* |
| SE | 0.147 | 0.147 | 0.148 | 0.144 | 0.152 |
| Week 18 | | | | | |
| N | 79 | 80 | 79 | 85 | 76 |
| LS Mean Change | 0.70+ | 0.21 | -0.23* | -0.29+* | -0.76+* |
| SE | 0.159 | 0.159 | 0.160 | 0.155 | 0.165 |
| Week 22 | | | | | |
| N | 79 | 80 | 79 | 85 | 76 |
| LS Mean Change | 0.71+ | 0.20 | -0.24* | -0.35+* | -0.84+* |
| SE | 0.165 | 0.166 | 0.167 | 0.162 | 0.172 |
| Week 26 (Endpoint[c]) | | | | | |
| N | 79 | 80 | 79 | 85 | 76 |
| LS Mean Change | 0.74+ | 0.20 | -0.27+* | -0.27* | -0.86+* |
| SE | 0.169 | 0.170 | 0.170 | 0.165 | 0.175 |
| LS Mean Difference[d] | | -0.54 | -1.00 | -1.00 | -1.60 |
| 95% Confidence Interval[e] | | -1.13, 0.05 | -1.59, -0.42 | -1.58, -0.42 | -2.19, -1.00 |

[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 baseline and visit.
[c] Endpoint is the last measurement taken during the double-blind treatment period.
[d] Difference between each dose and placebo 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 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 ($p \leq 0.050$) based on Dunnett's test.
Data Source: End-of-Text Tables 9.2 and 9.3, Listing 8, and Statistical Appendix 2.1.

There was a consistent increase in body weight in patients treated with PIO. After 26 weeks at 30 mg, and 45 mg PIO the increase in weight was 2.92 kg and 4.66 kg respectively compared to a loss of 0.73 kg in placebo patients. At endpoint the placebo patients had a mean weight loss of 1.28 kg compared to gains of 1.29 and 2.82 kg at 30 and 45 mg PIO respectively. Mean fasting triglyceride levels were about 270 mg/dl and fell in all groups. The mean fall in placebo patients at 26 weeks (endpoint, LOCF) was 21 mg/dl, The reductions at 15, 30 and 45 mg PIO were 54, 39, and 48 mg/dl which were significantly greater than placebo. Total cholesterol, LDL cholesterol and HDL cholesterol rose slightly in all groups but there was no consistent effect of PIO except that HDL cholesterol rose somewhat more at 45 mg PIO. The mean values for HDL cholesterol were about 41 mg/dl at baseline. The mean rise after 26 weeks (LOCF) for placebo patients was 3.0 compared to 7.0 mg/dl for patients on 45 mg PIO. The statistically significant rise

in HDL on 45 mg PIO vs placebo was present at 2 weeks and persisted throughout the 26 week study. Differences at other doses achieved statistical significance at some time points but not others.

Subgroup analysis suggested that PIO might be somewhat more effective in females than in males. Looking only at the 45 mg dose, the reduction of HbA1c ( completers) was 1.71 for males and 2.41 for females. 25/46 males( 54%) completed the study compared to 19/30 females ( 63%). Among placebo patients there was a mean rise in HbA1c of 0.43 compared to 0.39 in females. Among placebo patients, those completing the study was 36% for males and 39% for females. Mean change at 26 weeks LOCF for men on placebo was +0.54 and +0.87 for women. At 45 mg PIO the change was –0.59 for men and-1.37 for women . The net effect for men were -1.13 compared to – 2.24 for women. The difference between men and women also appeared to be present at 30 mg PIO ( -0.56 compared to – 1.47) but not at 15 mg ( -0.99 for men compared to -1.06 for women) source table 9.4.2.8.1.1. PIO seemed less effective in patients over 65 than in younger patients, but the number of patients over 65 was too small to be conclusive. PIO was equally effective in Black and Caucasian patients.

PK:

PK studies showed that the mean trough blood levels after two weeks for PIO were 43,88,124, and 245 ng/ml for 7.5, 15, 30, and 45 mg doses. After 26 weeks, trough blood levels were 49, 84, 104, and 230 ng/ml, respectively. The blood levels of metabolite M-111 and M-1V after 26 weeks at 45 mg/PIO were 328 ng/ml and 807 ng/ml. These values correspond to the 230 ng/ml for unchanged PIO.

Safety:

There were no deaths in the study. More placebo patients than PIO patients dropped out due to poorly controlled hyperglycemia. Otherwise, the dropouts were equally distributed among the treatment groups. AE's of psychiatric disorders occurred in 5% of placebo patients compared to 10% of PIO patients. Peripheral edema was reported in 3% of patients on PIO and none on placebo. There was a dose-dependent reduction in hemoglobin in patients on PIO. At 26 weeks the mean change in hemoglobin for placebo patients was + 0.42 g/dl compared to reductions of 0.13, 0.31, 0.42, and 0.74 g /dl on 7.5, 15, 30, and 45 mg/d of PIO, respectively.

Study PNFP – 011
Long-term open label study with titration to 60 mg

Patients who completed the 26-week placebo-controlled study described above (study 001) were allowed to enter an open label extension study. New patients were allowed to enter De Novo, but treatment with PIO was preceded by an 8-week single blind placebo run-in. All patients had to have HbA1c of at least 7% at day one to enter the study. All patients received an initial dose of 7.5-mg PIO for at least 4 weeks. The dose could then be increased every four weeks in a stepwise fashion to 15, 30, 45, and 60 mg if FBG exceeded 140 mg/dl. Patients on 45 mg received a 30 and 15-mg tablets. Patients on 60 mg received two 30-mg tablets Dosing was with breakfast. The mean age of patients was 54 years. 75% were Caucasian and 62% were male.

A time course of FBG's is shown in the table. In reviewing these data one needs to bear in mind that De Novo patients received PIO starting at "baseline". Rollover placebo patients received PIO starting at "endpoint". Rollover PIO patients had been receiving PIO since "baseline". But at "endpoint" they started a titration from 7.5mg. Most of these rollover PIO patients had been on higher doses previously, hence the rise in FBG that occurred during the first 8 weeks of study. It should also be noted that the duration of PIO treatment is 72 weeks for the De Novo and Rollover Placebo patients but is 98 weeks (26 weeks double blind followed by 72 weeks open label) for the Rollover PIO patients.

| Table 9.4.1.2.3: Mean FBG (mg/dL) by Visit (Observed Values) | | | | |
|---|---|---|---|---|
| Visit | *De Novo* (N=299) | Rollover Placebo (N=56) | Rollover Pioglitazone (N=214) | Total (N=569) |
| **Screen** | | | | |
| N[b] | 286 | 48 | 193 | 527 |
| Mean | 218.8 | 231.6 | 227.1 | 223.0 |
| SE | 3.53 | 8.91 | 4.84 | 2.74 |
| **Baseline[a]** | | | | |
| N[b] | 286 | 54 | 207 | 547 |
| Mean | 263.0 | 272.6 | 267.4 | 265.6 |
| SE | 4.50 | 9.31 | 5.03 | 3.16 |
| **Endpoint of Study AD-4833/PNFP-001** | | | | |
| N[b] | N/A | 54 | 207 | 261 |
| Mean | | 279.0 | 232.7 | 242.3 |
| SE | | 9.74 | 5.60 | 5.01 |
| **Week 4** | | | | |
| N[b] | 283 | 54 | 205 | 542 |
| Mean | 247.6 | 269.9 | 247.4 | 249.7 |
| SE | 4.09 | 9.91 | 5.59 | 3.17 |
| **Week 8** | | | | |
| N[b] | 268 | 52 | 199 | 519 |
| Mean | 233.2 | 263.7 | 243.4 | 240.2 |
| SE | 4.13 | 10.46 | 5.35 | 3.16 |
| **Week 12** | | | | |
| N[b] | 253 | 50 | 193 | 496 |
| Mean | 199.1 | 240.7 | 226.5 | 214.0 |
| SE | 3.98 | 11.51 | 5.25 | 3.18 |
| **Week 24** | | | | |
| N[b] | 221 | 46 | 172 | 439 |
| Mean | 179.5 | 220.0 | 210.1 | 195.7 |
| SE | 3.71 | 12.00 | 5.74 | 3.27 |
| **Week 36** | | | | |
| N[b] | 197 | 30 | 126 | 353 |
| Mean | 178.0 | 205.1 | 197.6 | 187.3 |
| SE | 3.68 | 14.18 | 6.07 | 3.26 |
| **Week 48** | | | | |
| N[b] | 164 | 23 | 84 | 271 |
| Mean | 174.7 | 190.6 | 188.3 | 180.3 |
| SE | 4.22 | 15.08 | 7.65 | 3.72 |
| **Week 60** | | | | |
| N[b] | 84 | 12 | 51 | 147 |
| Mean | 170.5 | 173.5 | 189.9 | 177.5 |
| SE | 5.82 | 19.74 | 9.03 | 4.87 |
| **Week 72[c]** | | | | |
| N[b] | 29 | 7 | 24 | 60 |
| Mean | 188.2 | 160.3 | 179.1 | 181.3 |
| SE | 11.66 | 32.05 | 12.29 | 8.26 |

[a] For *de novo* patients, baseline is the last value taken during the baseline period. For rollover patients, baseline is defined as the last measurement taken during the baseline period of Study PNFP-001.

[b] N at baseline includes patients who had a value at both baseline and at any one visit. N at a visit includes patients who had a value at both baseline and visit.

[c] This is the last timepoint that has a total number of patients greater than or equal to 25.

N/A = Not applicable.

Data Source: End-of-Text Table 12.1 and Listing 9.2.

The following table shows a time course for HbA1c, which corresponds, to FBG values shown in the previous table. These results suggest that the efficacy of PIO is maintained long-term. Being an open-label extension study, treatment is on going and only a small number of patients completed week 72 or beyond.

Table 9.4.1.1.2: Mean Change From Baseline for $HbA_{1c}$ (%) by Visit (Observed Values)

| Visit | *De Novo* (N=299) | Rollover Placebo (N=56) | Rollover Pioglitazone (N=214) | Total (N=569) |
|---|---|---|---|---|
| **Screen** | | | | |
| N[b] | 254 | 46 | 180 | 480 |
| Mean Change | -0.93 | -1.41 | -1.03 | -1.02 |
| SE | 0.089 | 0.207 | 0.099 | 0.063 |
| **Baseline[a]** | | | | |
| N[b] | 255 | 52 | 193 | 500 |
| Mean | 9.96 | 10.62 | 10.26 | 10.14 |
| SE | 0.115 | 0.275 | 0.148 | 0.087 |
| **Endpoint of Study AD-4833/PNFP-001** | | | | |
| N[b] | N/A | 52 | 193 | 245 |
| Mean Change | | 0.68 | -0.30 | -0.09 |
| SE | | 0.175 | 0.111 | 0.098 |
| **Week 12** | | | | |
| N[b] | 255 | 51 | 191 | 497 |
| Mean Change | -0.33 | 0.04 | -0.21 | -0.25 |
| SE | 0.080 | 0.209 | 0.101 | 0.061 |
| **Week 24** | | | | |
| N[b] | 228 | 46 | 172 | 446 |
| Mean Change | -1.20 | -0.77 | -0.76 | -0.98 |
| SE | 0.104 | 0.270 | 0.110 | 0.074 |
| **Week 36** | | | | |
| N[b] | 198 | 31 | 123 | 352 |
| Mean Change | -1.50 | -1.23 | -1.08 | -1.33 |
| SE | 0.111 | 0.333 | 0.132 | 0.083 |
| **Week 48** | | | | |
| N[b] | 164 | 23 | 85 | 272 |
| Mean Change | -1.57 | -0.99 | -1.03 | -1.35 |
| SE | 0.120 | 0.382 | 0.159 | 0.095 |
| **Week 60** | | | | |
| N[b] | 84 | 14 | 50 | 148 |
| Mean Change | -1.45 | -1.12 | -0.79 | -1.19 |
| SE | 0.176 | 0.464 | 0.229 | 0.135 |
| **Week 72[c]** | | | | |
| N[b] | 30 | 8 | 26 | 64 |
| Mean Change | -0.74 | -0.58 | -0.52 | -0.63 |
| SE | 0.355 | 0.358 | 0.296 | 0.208 |

[a] For *de novo* patients, baseline is the last value taken during the lead-in period. For rollover patients, baseline is defined as the last measurement taken during the baseline period of Study PNFP-001.
[b] N at baseline includes patients who had a value at both baseline and at any one visit. N at visit includes patients who had a value at both baseline and the visit.
[c] This is the last timepoint that has a total number of patients greater than or equal to 25.
N/A = Not applicable.
Data Source: End-of-Text Table 10.2 and Data Listing 8.

A better way of looking at the results of this trial may be to examine the time course of the cohort that completed week 48 ( 74 weeks of PIO for the Rollover PIO patients and 48 weeks of PIO for the other patients). HbA1c is shown in the table and FBG is shown in the figure. Of particular importance is that there is no evidence for deterioration of glycemia at the end of the observation period.

Table 9.4.1.1.1: Mean Change From Baseline for $HbA_{1c}$ (%) by Visit
For Patients Who Completed 48 Weeks of Open-Label Treatment (Observed Values)

| Visit | *De Novo* (N=299) | Rollover Placebo (N=56) | Rollover Pioglitazone (N=214) | Total (N=569) |
|---|---|---|---|---|
| **Screen** | | | | |
| N[b] | 164 | 18 | 77 | 259 |
| Mean Change | -0.78 | -1.26 | -0.80 | -0.82 |
| SE | 0.100 | 0.331 | 0.133 | 0.078 |
| **Baseline[a]** | | | | |
| N[b] | 165 | 23 | 86 | 274 |
| Mean | 9.71 | 9.86 | 9.59 | 9.68 |
| SE | 0.133 | 0.426 | 0.190 | 0.106 |
| **Endpoint of Study AD-4833/PNFP-001** | | | | |
| N[b] | N/A | 23 | 86 | 109 |
| Mean Change | | 0.50 | -0.33 | -0.16 |
| SE | | 0.290 | 0.160 | 0.143 |
| **Week 12** | | | | |
| N[b] | 165 | 23 | 85 | 273 |
| Mean Change | -0.46 | -0.45 | -0.36 | -0.43 |
| SE | 0.087 | 0.308 | 0.146 | 0.074 |
| **Week 24** | | | | |
| N[b] | 161 | 23 | 86 | 270 |
| Mean Change | -1.35 | -1.01 | -0.91 | -1.18 |
| SE | 0.114 | 0.376 | 0.145 | 0.089 |
| **Week 36** | | | | |
| N[b] | 163 | 23 | 85 | 271 |
| Mean Change | -1.55 | -1.08 | -1.05 | -1.35 |
| SE | 0.122 | 0.359 | 0.155 | 0.094 |
| **Week 48** | | | | |
| N[b] | 164 | 23 | 85 | 272 |
| Mean Change | -1.57 | -0.99 | -1.03 | -1.35 |
| SE | 0.120 | 0.382 | 0.159 | 0.095 |

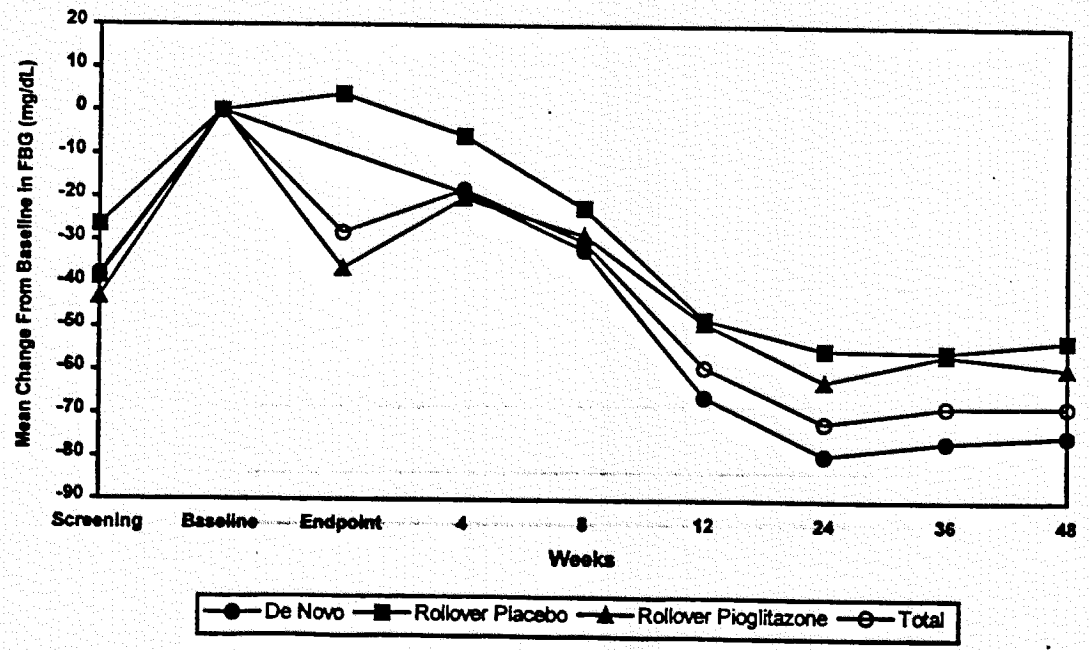
[a] For *de novo* patients, baseline is the last value taken during the lead-in period. For rollover patients, baseline is defined as the last measurement taken during the baseline period of Study PNFP-001.

[b] N at baseline includes patients who had a value at both baseline and at any one visit. N at visit includes patients who had a value at both baseline and the visit.

N/A = Not applicable.

Data Source: End-of-Text Table 10.2A and Listing 8.

**Figure 9.4.1.2.1: Mean Change From Baseline for FBG (mg/dL) by Visit**
**For Patients Who Completed 48 Weeks of Open-Label Treatment (Observed Values)**




Data Source: End-of-Text Table 12.2A.

The improvement in hyperglycemia noted in the previous table and figure was associated with a mean weight gain of 5.6 kg. Regrettably there was no evidence that this weight gain had reached a plateau at the end of the observation period. The weight change in the "Rollover PIO" patients is particularly illuminating. The mean weight loss from screening to baseline was 1.38 kg, largely reflecting the hyperglycemia that resulted from the discontinuation of previous drug therapy in most of these patients. The mean weight gain after 26 weeks of PIO was 1.76 kg reflecting improvement in hyperglycemia. However, weight fell slightly during the early part of the open label trial, again reflecting the rise in glucose levels, which occurred due to reduction of the PIO dose to 7.5 mg. However, by week 12 weight was rising again. If one looks at the 12 week intervals, from week 12 - 24, week 24-36 and week 36-48, the mean weight gain was 1.81, 0.95, and 0.79 kg. Thus weight gain was continuing even though improvement of hyperglycemia had plateaued.

**Table 10.5.3.1: Mean Change from Baseline in Body Weight (kg) For Patients Who Completed 48 Weeks of Open-Label Treatment (Observed Values)**

| Visit | *De Novo* (N=299) | Rollover Placebo (N=56) | Rollover Pioglitazone (N=214) | Total (N=569) |
|---|---|---|---|---|
| **Screen** | | | | |
| N[b] | 175 | 25 | 88 | 288 |
| Mean Change | 1.53 | 1.80 | 1.38 | 1.51 |
| SE | 0.167 | 0.363 | 0.270 | 0.134 |
| **Baseline[a]** | | | | |
| N[b] | 175 | 25 | 88 | 288 |
| Mean | 90.73 | 90.42 | 92.74 | 91.32 |
| SE | 1.154 | 2.295 | 1.525 | 0.865 |
| **Endpoint of Study AD-4833/PNFP-001** | | | | |
| N[b] | N/A | 25 | 88 | 113 |
| Mean Change | | -0.66 | 1.76 | 1.22 |
| SE | | 0.719 | 0.364 | 0.337 |
| **Week 4** | | | | |
| N | 175 | 25 | 88 | 288 |
| Mean Change | -0.39 | -0.45 | 1.64 | 0.22 |
| SE | 0.134 | 0.668 | 0.361 | 0.158 |
| **Week 12** | | | | |
| N | 173 | 23 | 88 | 286 |
| Mean Change | 0.16 | 0.13 | 1.81 | 0.67 |
| SE | 0.189 | 0.630 | 0.383 | 0.178 |
| **Week 24** | | | | |
| N | 175 | 22 | 81 | 278 |
| Mean Change | 2.74 | 3.22 | 3.62 | 3.03 |
| SE | 0.286 | 0.766 | 0.463 | 0.233 |
| **Week 36** | | | | |
| N | 175 | 25 | 88 | 288 |
| Mean Change | 4.69 | 4.93 | 4.57 | 4.67 |
| SE | 0.365 | 0.934 | 0.495 | 0.280 |
| **Week 48** | | | | |
| N | 175 | 25 | 88 | 288 |
| Mean Change | 5.55 | 6.34 | 5.36 | 5.56 |
| SE | 0.402 | 1.086 | 0.584 | 0.316 |

[a] For *de novo* patients, baseline is the last value taken during the lead-in period. For rollover patients, baseline is defined as the last measurement taken during the baseline period of Study PNFP-001.

[b] N at baseline includes patients who had a value at both baseline and at any one visit.
N at visit includes patients who had values at baseline and visit.

N/A = Not Applicable.

Data Source: End-of-Text Table 36.1A and Data Listing 19.