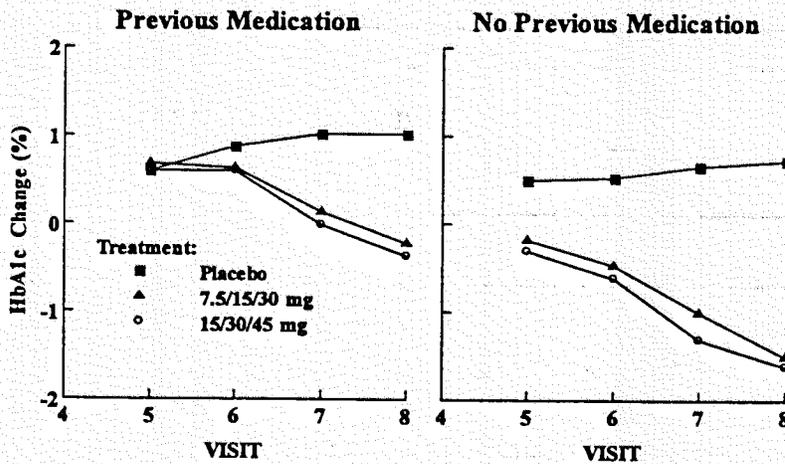


Table 31 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Previous Antidiabetic Medication – Study 012

Subgroup	Placebo	Pioglitazone	
		7.5/15/30 mg	15/30/45 mg
Previous Medication			
n	61	65	65
Baseline Mean	10.90	10.42	10.85
Mean Change	1.01	-0.23	-0.37
SE	0.16	0.19	0.17
No Previous Medication			
n	22	20	20
Baseline Mean	10.22	10.12	10.28
Mean Change	0.73	-1.50	-1.62
SE	0.27	0.21	0.31

Figure 15 Mean Change from Baseline in HbA_{1c} (%) by Previous Medication

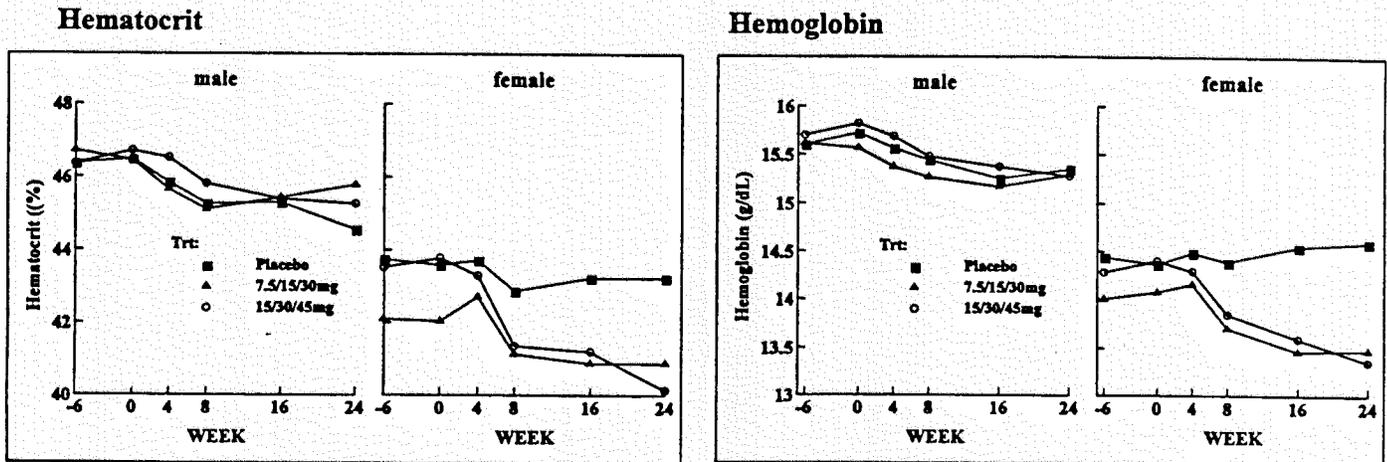


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Hematocrit & Hemoglobin

The observed mean hematocrit and hemoglobin levels by gender and visit are displayed in Figure 16

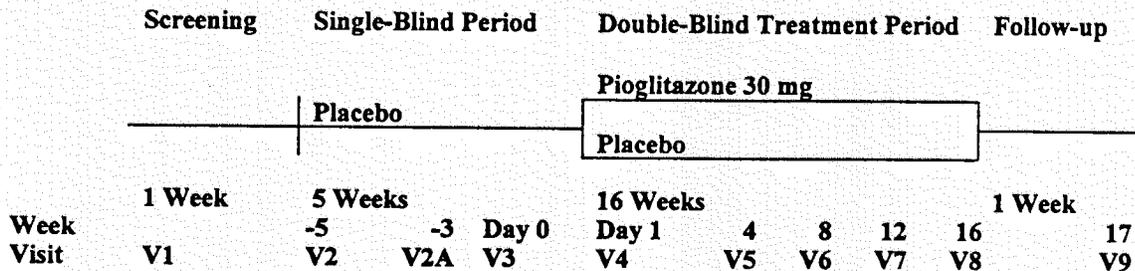
Figure 16 Mean Hematocrit & Hemoglobin Levels by Gender & Visit – Study 012



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Study PNFP-026 (16 Weeks)

This was a double-blind, placebo-controlled, randomized, multicenter, study in 197 patients from 27 centers in the U.S. The study scheme is displayed in the following diagram.



The follow-up visit was for patients who did not enter an open-label extension study, which the sponsor will summarize in a separate report.

The HbA_{1c} inclusion criteria were HbA_{1c} >7.5% at Visit 1 and >8.0% at Visit 3.

Patient Disposition

Of the 447 patients screened, 3 were rescreened. A total of 275 patients entered the single-blind placebo period of which 197 patients were randomized (1 rescreened), 96 to the placebo group and 101 to the pioglitazone 30 mg treatment group. Seventy-three percent of the patient (143) completed the double-blind treatment period, 66% (63/96) of the placebo group and 79% (80/101) of the pioglitazone 30 mg group. Table 32 displays the disposition of patients. Table 33 displays patient discontinuation by time.

Table 32 Patient Disposition – Study 026

	Placebo	Pioglitazone 30 mg
Randomized	96	101
Completed	63 (66%)	80 (79%)
Withdrawn	33 (34%)	21 (21%)
Lack of Efficacy	22 (23%)	15 (15%)
AE: Other Lab	0	1 (1%)
AE: All Other	5 (5%)	2 (2%)
Withdrew Consent (personal)	3 (3%)	2 (2%)
Lost to Follow-up	2 (2%)	0
Non-Compliance	1 (1%)	1 (1%)

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Table 33 Patient Discontinuation by Time – Study 026

	Placebo	30 mg	Total
Randomized	96	101	197
Withdrawn	33 (34%)	21 (21%)	54 (27%)
≤ Week 4	8	3	11 (6%)
> Week 4 & ≤ Week 8	10	10	20 (10%)
> Week 8 & ≤ Week 12	9	7	16 (8%)
> Week 12 & ≤ Week 16	5	1	6 (3%)
> Week 16 & ≤ Week 24	1	0	1 (0.5%)

Baseline characteristics were not significantly different between the treatment groups. The baseline values for the primary and secondary efficacy variables are listed in Table 34.

Table 34 Mean Values at Baseline in Efficacy Variables – Study 026

	Placebo n=96			30 mg n=101			p-value*
	n	Mean	SD	n	Mean	SD	
HbA _{1c}	96	10.42	1.70	101	10.65	1.77	0.310
FBG (mg/dL)	95	272.3	72.74	101	276.1	70.88	0.676
Fasting C-Peptide (ng/mL)	94	2.18	0.97	101	2.14	0.87	0.714
Fasting Insulin (μIU/mL)	94	15.06	12.70	101	15.15	11.38	0.887
Triglycerides (mg/dL)	96	280.2	345.65	101	356.0	531.33	0.185
Total Cholesterol	96	221.3	48.00	101	222.2	67.11	0.869
HDL (mg/dL)	94	39.4	10.83	97	39.9	10.51	0.750
LDL (mg/dL)	76	133.7	36.9	78	128.6	35.35	0.435

* p-values based on treatment and pooled center in ANOVA model

Of the 197 patients who were randomized, 119 (60%) received prior antidiabetic medications. Eleven patients had taken 2 antidiabetic medications concomitantly.

Ninety-two percent (182) of the 197 patients were 80% to 120% compliant.

Efficacy Results – Study 026

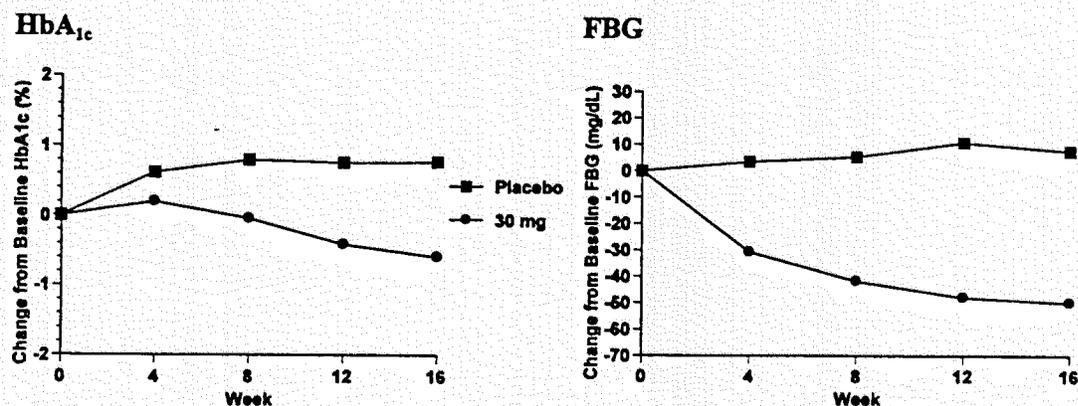
Primary Efficacy Variable – HbA_{1c} Change from Baseline to Week 16

At endpoint (Week 16), the LSM change from baseline in HbA_{1c} in the placebo group was +0.60% compared to -0.76% for the pioglitazone group; the difference of -1.37% was statistically significant (Table 35 & Fig 17.)

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Table 35 Adjusted* LSM Change from Baseline in HbA_{1c} by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	93	10.28	0.19	100	10.54	0.18	0.26	0.25	-0.24	0.75	0.31
Week 4	92	0.61	0.10	98	0.19	0.09	-0.42	0.13	-0.68	-0.15	<0.01
Week 8	92	0.79	0.13	100	-0.05	0.13	-0.85	0.19	-1.21	-0.48	<0.01
Week 12	93	0.75	0.15	100	-0.42	0.15	-1.17	0.21	-1.58	-0.75	<0.01
Week 16	93	0.76	0.17	100	-0.60	0.16	-1.37	0.24	-1.83	-0.9	<0.01

Figure 17 LSM Change from baseline in HbA_{1c} and FBG – Study 026

Secondary Efficacy Variables

At endpoint (Week 16), the LSM change from baseline in FBG was +7.7 mg/dL for the placebo group and -49.8 mg/dL for the pioglitazone group. The between group difference of -57.6 mg/dL was significant (Table 36 & Fig 17).

Table 36 Adjusted* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	91	270.07	7.87	99	272.62	7.63	2.56	10.47	-18.12	23.23	0.81
Week 4	90	3.39	5.24	96	-30.8	5.24	-34.19	7.4	-48.82	-19.56	<0.01
Week 8	91	5.31	5.81	99	-41.75	5.7	-47.06	8.14	-63.13	-30.99	<0.01
Week 12	91	10.79	6.57	99	-47.97	6.45	-58.76	9.21	-76.94	-40.57	<0.01
Week 16	91	7.73	6.94	99	-49.82	6.8	-57.55	9.71	-76.74	-38.36	<0.01

C-peptide & Insulin

Fasting C-peptide and insulin were significantly different between pioglitazone-treated patients and the placebo-treated patients at endpoint (Tables 37, 38 & Fig 18).

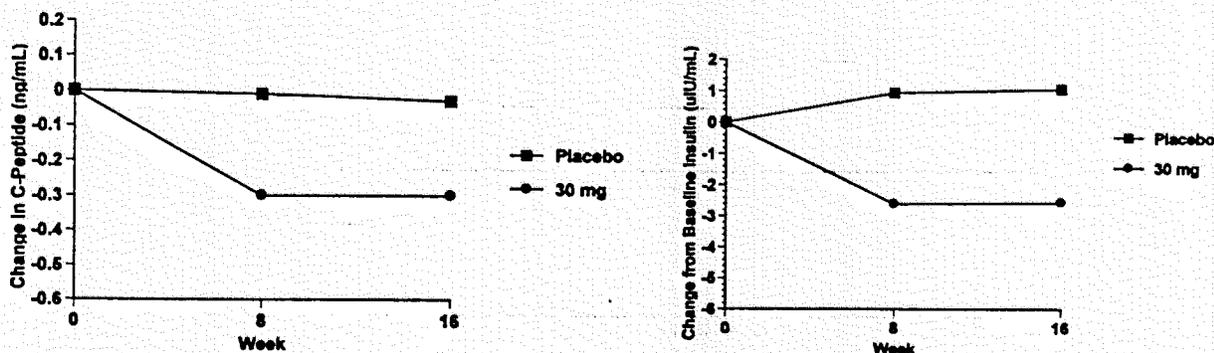
Table 37 LSM Change from Baseline in C-Peptide (ng/mL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	82	2.31	0.11	96	2.21	0.10	-0.10	0.14	-0.38 0.17	0.46
Week 8	82	-0.01	0.06	95	-0.30	0.06	-0.28	0.08	-0.45 -0.12	<0.01
Week 16	82	-0.03	0.06	95	-0.30	0.06	-0.26	0.08	-0.43 -0.10	<0.01

Table 38 LSM Change from Baseline in Fasting Insulin (μ IU/mL) by Visit (LOCF)

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	82	17.18	1.35	96	16.37	1.26	-0.82	1.76	-4.30 2.67	0.64
Week 8	82	0.93	0.88	94	-2.61	0.83	-3.53	1.21	-5.93 -1.14	<0.01
Week 16	82	1.85	0.84	96	-1.98	0.78	-3.84	1.15	-6.10 -1.57	<0.01

Figure 18 LSM Change from Baseline in C-Peptide (ng/mL) & Fasting Insulin (μ IU/mL) by Visit (LOCF) – Study 026



Lipids

At endpoint (Week 16), the LSM change in triglycerides was -18.5 mg/dL for the placebo group and -103.8 mg/dL for the pioglitazone group. The LSM change in total cholesterol was -2.3 mg/dL for the placebo and +2.4 mg/dL for the pioglitazone group. For HDL the LSM change was 0.3 mg/dL for the placebo group and 5.3 mg/dL for the pioglitazone group. For LDL, it was 4.2 mg/dL for the placebo group and 2.7 mg/dL for the pioglitazone group (Tables 39-42 & Fig 19.)

Table 39 LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	85	335.1	47.49	96	400.4	45.26	65.30	62.37	-57.85 188.46	0.30
Week 8	85	-27.05	28.57	96	-92.11	27.69	-65.06	39.74	-143.61 13.49	0.10
Week 16	85	-18.52	19.97	96	-103.77	19.35	-85.25	27.77	-140.14 -30.36	<0.01

Table 40 LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	85	221.81	6.41	96	224.46	6.11	2.65	8.41	-13.97 19.26	0.75
Week 8	85	2.37	4.5	96	0.52	4.34	-1.85	6.26	-14.22 10.52	0.77
Week 16	85	-2.35	3.62	96	2.43	3.5	4.78	5.04	-5.18 14.74	0.34

Table 41 LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	82	39.31	1.3	91	39.74	1.24	0.43	1.68	-2.89 3.75	0.80
Week 8	80	-0.57	1.15	89	4.69	1.05	5.27	1.56	2.19 8.34	<0.01
Week 16	82	0.32	1.13	91	5.33	1.06	5.01	1.55	1.95 8.07	<0.01

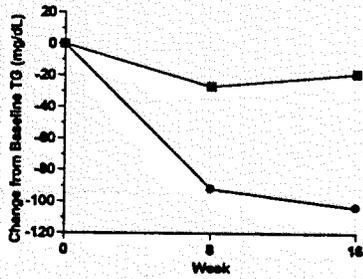
Table 42 LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 026

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	67	130.80	4.76	70	130.91	4.73	0.11	6.38	-12.52 12.75	0.99
Week 8	66	5.54	3.42	71	0.42	3.29	-5.11	4.75	-14.53 4.31	0.28
Week 16	67	4.15	3.46	70	2.70	3.52	-1.46	4.94	-11.25 8.33	0.77

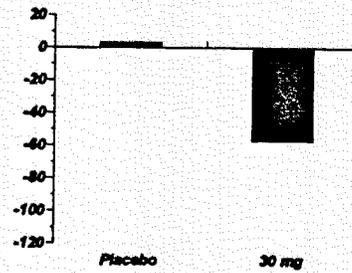
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Figure 19 LSM Change from Baseline in Triglycerides, Total Cholesterol, HDL, & LDL – Study 026

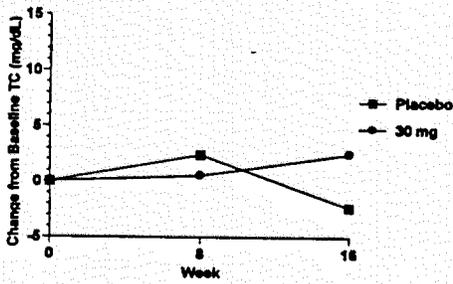
Triglyceride



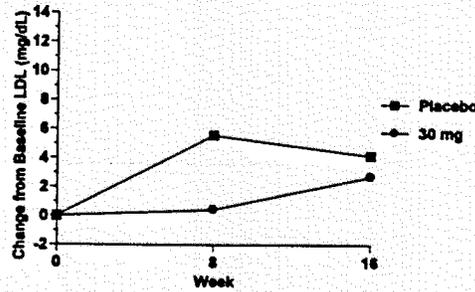
Endpoint Median Triglycerides



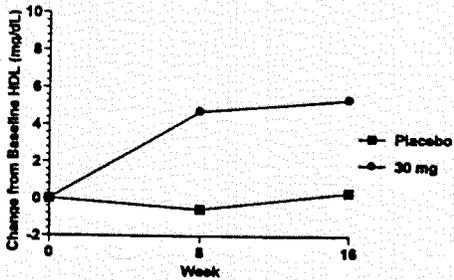
Total Cholesterol



LDL



HDL



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Subgroup Analyses

Changes from baseline in HbA_{1c} at endpoint were examined in subgroups of gender, age, and use of previous antidiabetic medication using the LOCF data of the ITT population. The interaction between treatment and subgroup was explored using ANOVA with treatment, subgroup, center, and treatment-by-subgroup terms in the model.

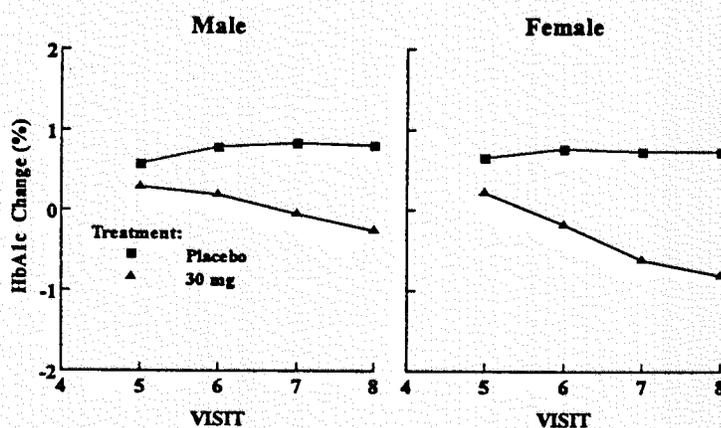
Gender

Table 42 and Figure 20 display the mean change from baseline in HbA_{1c} by gender. The p-value for treatment-by-gender interaction was 0.61.

Table 43 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender (LOCF) – Study 026

Subgroup	Placebo	30 mg
Men		
n	51	49
Baseline Mean	9.94	10.80
Mean Change	0.81	-0.26
SE	0.20	0.21
Women		
n	41	50
Baseline Mean	11.04	10.51
Mean Change	0.74	-0.80
SE	0.26	0.24

Figure 20 Mean Change from Baseline in HbA_{1c} (%) by Gender – Study 026



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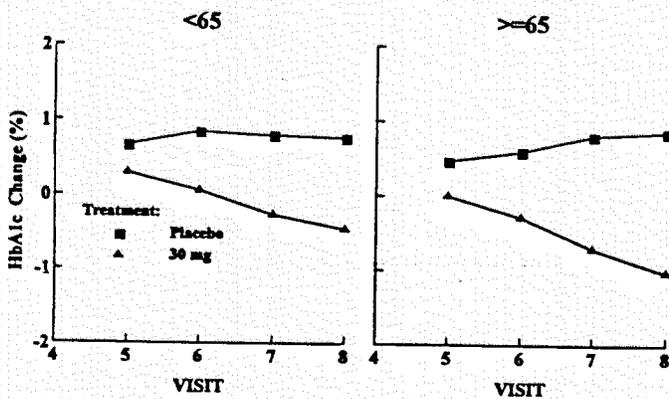
Age

Mean change from baseline in HbA_{1c} for patients <65 and ≥65 years of age is displayed in Table 43 and Figure 21. P-value for the treatment-by-age group interaction was 0.29.

Table 44 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group (LOCF) – Study 026

Subgroup	Placebo	30 mg
<65 years old		
n	74	88
Baseline Mean	10.50	10.73
Mean Change	0.76	-0.46
SE	0.19	0.18
≥65 years old		
n	19	12
Baseline Mean	10.15	10.08
Mean Change	0.86	-1.03
SE	0.20	0.20

Figure 21 Mean Change from Baseline in HbA_{1c} (%) by Age Group – Study 026



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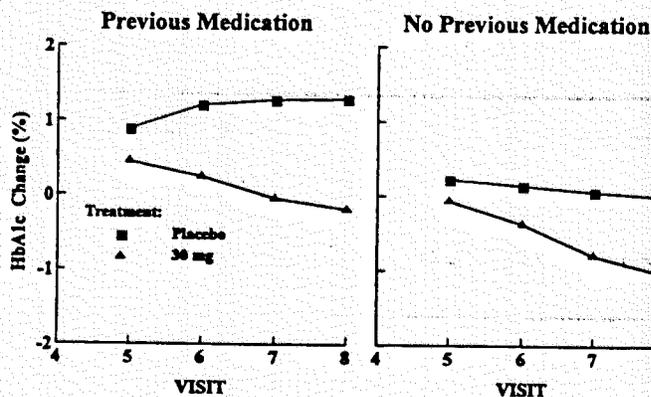
Previous Antidiabetic Medication

Table 44 and Figure 22 display the mean change from baseline in HbA_{1c} by previous antidiabetic medication use. P-value for the treatment-by-previous medication interaction was 0.42.

Table 45 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Previous Antidiabetic Medication (LOCF) – Study 026

Subgroup	Placebo	30 mg
Previous Medication		
n	56	61
Baseline Mean	10.40	10.81
Mean Change	1.29	-0.20
SE	0.18	0.19
No Previous Medication		
n	37	39
Baseline Mean	10.46	10.41
Mean Change	0.01	-1.05
SE	0.24	0.27

Figure 22 Mean Change from Baseline in HbA_{1c} (%) by Previous Medication – Study 026



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3. Add-On Trials

The 5 add-on trials were all double-blind, multicenter, randomized, parallel trials except Study OCT-003 (Japan) which was a single-blind study. The 3 U.S. studies compared the safety and efficacy of pioglitazone and placebo as add-on to either sulfonylurea (010), metformin (027) or insulin (014) in patients with type 2 diabetes not well controlled ($HbA_{1c} > 8\%$) by the current therapy. Patients first entered a 2-week screening period followed by a 1-week or 4-week, single-blind placebo period (4-week for Study 014) to discontinue all antidiabetic drugs other than the companion drug. The double-blind treatment period was 16 weeks. Table 46 summarizes the add-on trials.

The study included patients 30 to 75 years of age, with a BMI 25 to 45 kg/m^2 , a stable background therapy regimen at least 30 days before enrollment, a fasting C-peptide level of $\geq 1ng/mL$ (010, 027) or $\geq 0.7 ng/ml$ (014) at Visit 1, normal thyroid function and $HbA_{1c} > 8\%$.

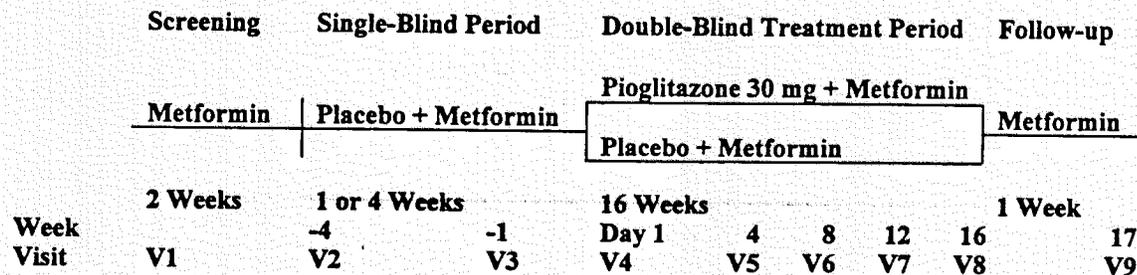
Table 46 Brief Summary of Add-on Trials

Study ID	# of Centers	Total Sample Size & Treatment Group	Design	Duration of Treatment & Study Period
PNFP-010	US 54	560 placebo + SU 15mg + SU 30 mg + SU	Double-blind, multicenter, randomized, fixed-dose	16 weeks 6/2/97 - 8/10/98
PNFP-027	US 43	328 placebo + metformin 30 mg + metformin	Double-blind, multicenter	16 weeks 5/30/97 - 9/14,98
PNFP-014	US 84	566 15 mg + insulin 30 mg + insulin placebo + insulin	Double-blind,	16 weeks 5/30/97 - 9/14,98
OCT-003	Japan Kaneko	237 Placebo + SU 15 mg + SU 30 mg + SU 45 mg + SU	single-blind	12 weeks
OCT-012 (PD-194)	Japan Kaneko	119 placebo + SU 30 mg + SU	double-blind	12 weeks

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Study PNFP-027 (Metformin)

This was a double-blind, placebo-controlled, randomized, multicenter, study in 197 patients from 27 centers in the U.S. The study scheme is displayed in the following diagram.



Patient Disposition

Of the 600 patients screened, 8 were rescreened. Of the 396 patients received single-blind medication, 328 patients were randomized (5 from rescreen), 160 to the placebo + metformin (Plb+MF) group and 168 to the pioglitazone 30mg + metformin (Pio+MF) treatment group. Seventy-six percent of the patients (249/328) completed the double-blind treatment period: 69% (110/160) of the Plb+MF group and 83% of the Pio 30mg + MF group. Lack of efficacy (16%, 52/328) including insufficient therapeutic effect (13%, 43/328), AEs of symptomatic hyperglycemia (0.3%, 1/328) or asymptomatic hyperglycemia (1.2%, 4/328), and unhappy with the glucose control/lack of efficacy (1.2%, 4/328) was the most common reason for withdrawals. Table 47 displays the disposition of patients. Table 48 displays patient discontinuation by time.

Table 47 Patient Disposition – Study 027

	Plb+MF	30mg + MF
Randomized	160	168
Completed	110	139
Withdrawn	50	29
Lack of Efficacy	35	17
AE: All Other	3	5
Withdrew Consent (personal)	3	4
Lost to Follow-up	3	2
Non-compliance	1	0
Protocol Violation	1	0
Other	4	1

Table 48 Patient Discontinuation by Time – Study 027

	Plb+MF	30mg + MF	Total
Randomized	160	168	328
Withdrawn	50	29	79
≤ Week 4	8	10	18
> Week 4 & ≤ Week 8	14	3	17
> Week 8 & ≤ Week 12	23	13	36
> Week 12 & ≤ Week 16	5	3	8

Baseline characteristics were not significantly different between the treatment groups. The mean age of randomized patients was 55.6 years. Most patients were Caucasian (84%), males (57%). The mean weight was 93.3 kg. The mean BMI was 32.1 kg/m². Most patients (70%) did not receive antidiabetic medications other than metformin before enrolling in the study. Baseline values for the primary and secondary efficacy variables are listed in Table 49.

Table 49 Mean Values at Baseline in Efficacy Variables – Study 027

	Plb+MF n=160			30mg + MF n=168			p-value*
	n	Mean	SD	n	Mean	SD	
HbA _{1c}	160	9.75	1.27	168	9.86	1.42	0.51
FBG (mg/dL)	160	258.6	68.55	168	252.3	69.72	0.38
Fasting C-Peptide (ng/mL)	159	2.14	0.80	166	2.06	0.80	0.47
Fasting Insulin (μIU/mL)	159	14.82	10.25	166	14.67	10.63	0.92
Triglycerides (mg/dL)	160	296.9	314.44	168	296.3	289.76	0.99
Total Cholesterol	160	213.1	53.80	168	212.9	47.59	0.92
HDL (mg/dL)	155	42.4	10.39	165	43.0	12.46	0.66
LDL (mg/dL)	138	118.2	37.35	135	120.6	31.23	0.45

* p-values based on treatment and pooled center in ANOVA model

Of the 328 patients who were randomized, 97 (30%) patients had received other antidiabetic medications with metformin. Four patients had taken >1 other antidiabetic medication with metformin.

Treatment compliance (80%-120% compliant) was 94% with the double-blind medication and 85% with the companion (metformin) medication.

Efficacy Results – Study 027

Primary Efficacy Variable – HbA_{1c} Change from Baseline to Week 16

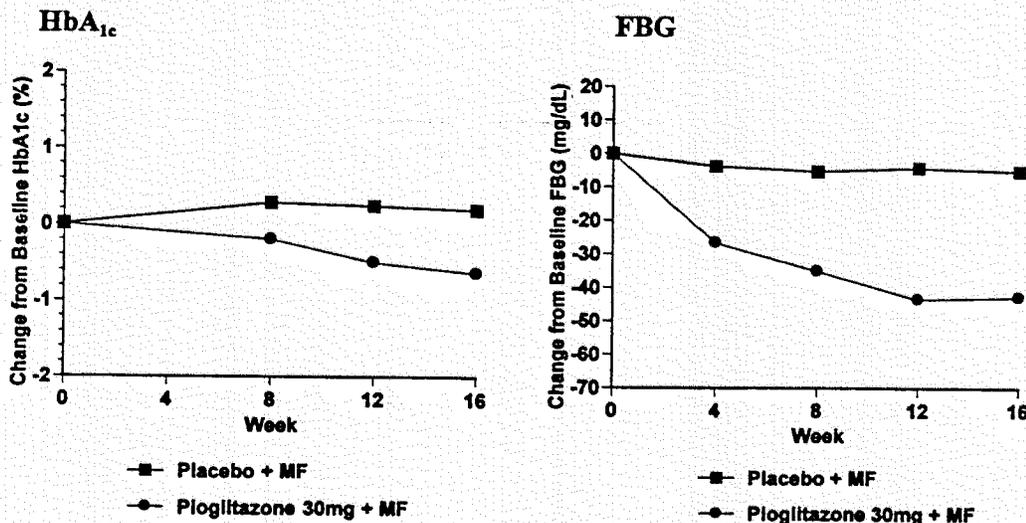
At endpoint (Week 16), the LSM change from baseline in HbA_{1c} in Plb+MF group was +0.19% compared to the -0.64% of the Pio 30mg + MF group the difference of -0.83% was statistically significant (Table 50). Figure 23 displays the

change over time for HbA_{1c} and FBG. The p-values for the treatment-by-baseline and treatment-by-center interactions were 0.09 and 0.54, respectively.

Table 50 Adjusted* LSM Change from Baseline in HbA_{1c} by Visit (LOCF) – Study 027

	Plb+MF			30mg + MF			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	153	9.77	0.11	161	9.92	0.11	0.15	0.15	-0.15 0.45	0.33
Week 8	153	0.28	0.09	160	-0.20	0.09	-0.49	0.13	-0.74 -0.23	<0.01
Week 12	153	0.24	0.11	161	-0.50	0.11	-0.74	0.16	-1.05 -0.43	<0.01
Week 16	153	0.19	0.12	161	-0.64	0.11	-0.83	0.16	-1.15 -0.51	<0.01

Figure 23 LSM Change from baseline in HbA_{1c} and FBG – Study 027



Secondary Efficacy Variables

FBG

At endpoint (Week 16), the LSM change from baseline in FBG was -5.2 mg/dL for the Plb+MF group and -42.8 mg/dL for the Pio 30mg + MF group. The between group difference of -37.7 mg/dL was significant (Table 51).