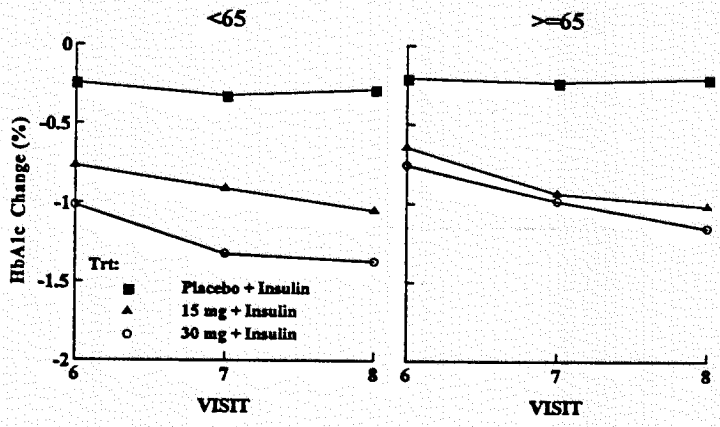
Age

Mean change from baseline in HbA_{1c} for patients age <65 and ≥65 years is displayed in Table 72 and Figure 34. P-value for treatment-by-age group interaction was 0.78.

Table 72 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group – Study 014

Subgroup	Placebo+Insulin	Pio 15 mg + Insulin	Pio 30 mg + Insulin
<65 years old			
n	136	130	129
Baseline Mean	9.93	9.91	10.12
Mean Change	**-0.28**	**-1.05**	**-1.37**
SE	0.10	0.11	0.11
≥65 years old			
n	41	47	56
Baseline Mean	9.31	9.47	9.28
Mean Change	**-0.21**	**-1.01**	**-1.16**
SE	0.15	0.11	0.12

Figure 34 Mean Change from Baseline in HbA_{1c} (%) by Age Group – Study 014



Study PNFP-010 (Sulfonylurea)

The study was conducted in 54 centers in the U.S. to compare the safety and efficacy of two doses of pioglitazone (15 or 30 mg) and placebo as add-on therapy to sulfonylurea in type 2 diabetes patients poorly controlled (HbA_{1c}≥8%) with sulfonylurea, with or without metformin or acarbose. Prior to the 16-week treatment period, there was a 2-week screening period followed by a 1 or 4-week single blind placebo period, during which patients discontinued all antidiabetic drugs other than sulfonylurea. The trial included men and women 30 to 75 years of age with a BMI in the range of 25 to 45 kg/m^2), a stable sulfonylurea therapy regimen at least 30 days before enrollment, HbA_{1c}≥8.0% (Visits 1 & 3), and fasting C-peptide level>1 ng/mL (Visit 1).

Screening 2 Weeks	Single-Blind 4 Weeks	Double-Blind Treatment 16 Weeks	Follow-up 1 Week
		Pioglitazone 30 mg+SU	SU
SU	Placebo+SU	Pioglitazone 15 mg+SU	SU
		Placebo+SU	SU

Week		-2	B	Day 1	4	8	12	16	
Visit	V1		V2	V3	V4	V5	V6	V7	V8	V9

The primary efficacy variable was change from baseline in HbA_{1c}. The secondary variables were fasting glucose, fasting insulin, fasting C-peptide, triglycerides, total cholesterol, fractional cholesterol, and HbA_{1c} responder rate which was defined as normalization of HbA_{1c} or a 0.65% reduction in HbA_{1c} from baseline. Fasting insulin level was not a secondary outcome.

Efficacy Results - Study 010

Of the 998 patients who signed an ICF, 21 were rescreened and 13 of these randomized. A total of 560 patients were randomized in 73 sites 187 to the placebo+SU, 184 to the 15 mg+SU and 189 to the 30 mg+SU treatment group. A total of 478 (85%) patients completed the study. Poor glycemic control was the most common reason for patient withdrawal. The incidence rates were 10% (19/187) for the placebo+SU group, 10% (18/184) for the 15 mg+SU group and 4% (8/189) for the 30 mg+SU group. Table 73 displays patient disposition.

Table 73 Patient Disposition – Study 010

	Placebo	15 mg+SU	30 mg+SU
Randomized	187	184	189
Completed	157	155	166
Withdrawn	30	29	23
Lack of Efficacy	13	12	4
Adverse Event	9	7	7
Withdrew Consent	4	5	7
Lost to Follow-up	2	1	2
Non-Compliance	0	1	1
Protocol Violation	1	0	0
Inclusion/Exclusion	1	0	0
Other	0	3	2

Demographic Characteristics

Most patients were Caucasian (79%) and male (59%). The mean age was 56.7 years. The mean weight was 92.99 kg. The mean BMI was 31.96 kg/m^2. Most patients (86%) had not received other antidiabetic medications beside SU before the enrollment. No statistical significant differences among the treatment groups for any of the demographic or baseline characteristics. Table 74 displays baseline levels of the efficacy variables.

Table 74 Mean Values at Baseline in Efficacy Variables – Study 010

	Placebo+SU n=187			30 mg+SU n=184			30 mg+SU n=189			p-value*
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
HbA_{1c}	186	**9.90**	1.46	182	**10.01**	1.30	188	**9.88**	1.28	0.65
FBG (mg/dL)	186	**236.8**	61.84	183	**246.8**	61.72	188	**238.4**	54.83	0.26
Fasting C-Peptide (ng/mL)	181	**2.49**	1.002	183	**2.5**	0.992	185	**2.39**	0.890	0.49
Fasting Insulin (μIU/mL)	181	**19.99**	18.34	182	**17.48**	11.94	185	**18.08**	9.80	0.24
Triglycerides (mg/dL)	187	**264.4**	258.04	184	**277.4**	281.98	188	**264.7**	248.95	0.87
Total Cholesterol	187	**212.2**	46.58	184	**212.0**	45.55	188	**215.4**	45.96	0.75
HDL (mg/dL)	184	**42.6**	11.75	179	**41.6**	10.86	186	**41.8**	11.53	0.74
LDL (mg/dL)	160	**123.7**	37.98	156	**124.0**	35.33	161	**127.1**	37.01	0.56

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

Efficacy Results - Study 010

Primary Efficacy Variable - HbA_{1c} Change from baseline to Week 16

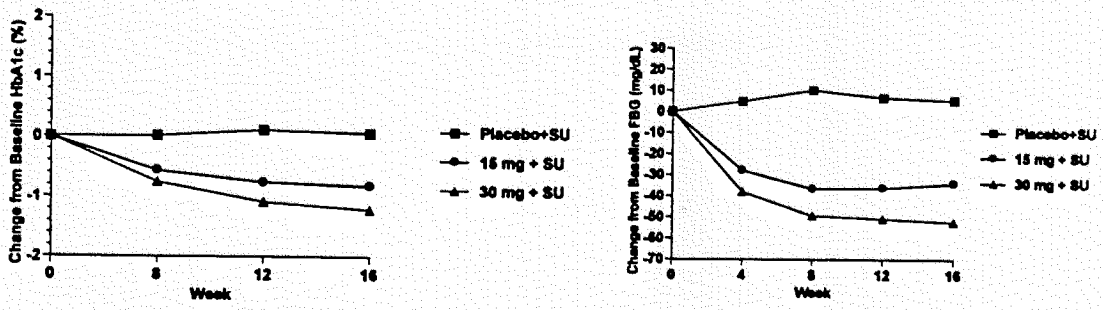
Table 75 Adjusted* LSM Change from Baseline in HbA_{1c} (%) by Visit (LOCF) – Study 010

		Pioglitazone					
Visit	Placebo+SU n=181	15 mg +SU n=176[a]			30 mg+SU n=182[b]		
	LSM	LSM	SE	p	LSM	SE	p
Baseline	**9.86**	**10.01**	0.10	0.45	**9.93**	0.10	0.86
Week 8	**0.01**	**-0.57**	0.07	<0.01	**-0.76**	0.07	<0.01
Week 12	**0.11**	**-0.76**	0.08	<0.01	**-1.09**	0.08	<0.01
Week 16 Endpoint	**0.06**	**-0.82**	0.09	<0.01	**-1.22**	0.09	<0.01
LSM Difference from placebo, SE		**-0.88**	0.13		**-1.28**	0.13	
95% C.I.		(-1.17	-0.58)		(-1.57	-0.99)	

* Adjusted by Dunnett procedure comparing all means with a control

[a]n=175, [b]n=182 at Week 8

Figure 35 LSM Change from Baseline in HbA1c & FBG over Time - Study 010



Secondary Efficacy Variables

Change from baseline FBG was significantly different from placebo+SU for the two pioglitazone+SU groups at endpoint. Table 76 and Figure 35 display the results by time.

Table 76 Adjusted* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 010

			Pioglitazone					
Visit	Placebo+SU n=182[a]		15 mg +SU n=179[b]			30 mg+SU n=186[c]		
	LSM	SE	**LSM**	SE	p	**LSM**	SE	p
Baseline	**235.99**	4.46	**246.77**	4.49	0.15	**238.93**	4.42	0.85
Week 4	**4.78**	3.32	**-27.79**	3.33	<0.01	**-37.96**	3.26	<0.01
Week 8	**10.24**	3.69	**-36.51**	3.73	<0.01	**-49.40**	3.67	<0.01
Week 12	**6.77**	3.95	**-36.13**	3.99	<0.01	**-50.76**	3.93	<0.01
Week 16 Endpoint	**5.59**	3.81	**-33.84**	3.85	<0.01	**-52.29**	3.80	<0.01
LSM Difference from placebo, SE			**-39.44**	**5.43**	**<0.01**	**-57.88**	**5.38**	**<0.01**
95% C.I.			(-51.49 -27.39)			(-69.82 -45.94)		

* Adjusted by Dunnett procedure comparing all means with a control
[a]n=178, [b]n=177, [c]n=185 at Week 8

At endpoint, C-Peptide and Insulin were significantly better in the 30mg+SU group compared to placebo. The 15mg+SU group was significantly better than placebo+SU in C-peptide (Tables 77, 78 & Fig 36.)

Table 77 Adjusted* LSM Change from Baseline in Fasting C-Peptide (ng/mL) by Visit (LOCF) – Study 010

Visit	Placebo+SU n=174[a]		Pioglitazone 15 mg +SU n=174[b]			Pioglitazone 30 mg+SU n=178[c]		
	LSM	SE	**LSM**	SE	p	**LSM**	SE	p
Baseline	**2.50**	0.07	**2.53**	0.07	0.93	**2.36**	0.07	0.30
Week 8	**0.15**	0.05	**-0.25**	0.05	<0.01	**-0.30**	0.05	<0.01
Week 16 Endpoint	**0.11**	0.05	**-0.20**	0.05	<0.01	**-0.25**	0.05	<0.01
LSM Difference from placebo, SE			**-0.31**	0.07		**-0.35**	0.07	
95% C.I.			(-0.47	-0.16)		(-0.51	-0.20)	

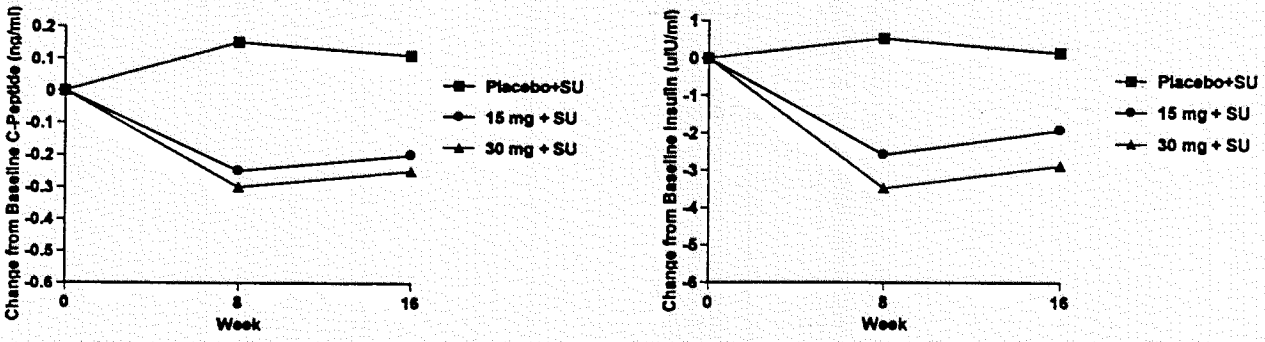
* Adjusted by Dunnett procedure comparing all means with a control
[a]n=173, [b]n=167 [c]n=175 at Week 8

Table 78 Adjusted* LSM Change from Baseline in Fasting Insulin (μIU/mL) by Visit (LOCF) – Study 010

Visit	Placebo+SU n=174[a]		Pioglitazone 15 mg +SU n=173[b]			Pioglitazone 30 mg+SU n=178[c]		
	LSM	SE	**LSM**	SE	p	**LSM**	SE	p
Baseline	**20.28**	1.05	**17.85**	1.05	0.18	**17.68**	1.04	0.14
Week 8	**0.53**	0.61	**-2.58**	0.63	<0.01	**-3.47**	0.62	<0.01
Week 16 Endpoint	**0.15**	0.69	**-1.92**	0.69	0.06	**-2.87**	0.68	<0.01
LSM Difference from placebo, SE			**-2.07**	0.98		**-3.02**	0.97	
95% C.I.			(-4.24	0.10)		(-5.18	-0.86)	

* Adjusted by Dunnett procedure comparing all means with a control
[a]n=172, [b]n=165 [c]n=172 at Week 8

Figure 36 LSM Change in C-Peptide & Insulin over Time - Study 010



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Lipids

At endpoint, triglycerides levels was significantly reduced in the 30 mg+SU treated patients than the placebo+SU-treated patients, but not significantly in the 15 mg+SU-treated patients. HDL was significantly increased in the 2 pioglitazone+SU groups than the placebo+SU group. LDL was not significantly different to placebo+SU for either of the two pioglitazone+SU groups. The treatment results are displayed in Tables 79-82 & Figure 37.

Table 79 Adjusted* LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 010

Visit	Placebo+SU n=180		Pioglitazone 15 mg +SU n=177			Pioglitazone 30 mg+SU n=181		
	LSM	SE	**LSM**	SE	p	**LSM**	SE	p
Baseline	**258.60**	20.17	**272.05**	20.32	0.85	**259.53**	20.12	1.00
Week 4	**3.89**	13.30	**-45.84**	13.37	0.02	**-68.41**	13.27	<0.01
Week 8	**2.72**	14.42	**-38.93**	14.50	0.08	**-63.06**	14.39	<0.01
Week 16 Endpoint	**-2.64**	13.29	**-38.74**	13.36	0.10	**-71.03**	13.26	<0.01
LSM Difference from placebo, SE			**-36.10**	18.84		**-68.39**	18.77	
95% C.I.			(-77.91	5.72)		(-110.04	-26.73)	

* Adjusted by Dunnett procedure comparing all means with a control

Table 80 Adjusted* LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 010

Visit	Placebo+SU n=180		Pioglitazone 15 mg +SU n=177			Pioglitazone 30 mg+SU n=181		
	LSM	SE	**LSM**	SE	p	**LSM**	SE	p
Baseline	**211.48**	**3.50**	**211.95**	**3.52**	0.99	**214.42**	**3.49**	0.77
Week 4	**2.47**	2.16	**0.4**	2.18	0.72	**1.29**	2.16	0.9
Week 8	**2.94**	2.35	**0.06**	2.36	0.59	**2.2**	2.34	0.96
Week 16 Endpoint	**7.39**	2.75	**0.65**	2.77	0.15	**2.42**	2.75	0.34
LSM Difference from placebo, SE			**-6.74**	3.90		**-4.97**	3.89	
95% C.I.			(-15.40	1.92)		(-13.60	3.66)	

* Adjusted by Dunnett procedure comparing all means with a control

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Table 81 Adjusted* LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 010

Visit	Placebo+SU n=175[a]		Pioglitazone 15 mg +SU n=171			Pioglitazone 30 mg+SU n=179		
	LSM	SE	LSM	SE	p	LSM	SE	p
Baseline	**42.91**	0.87	**41.42**	0.87	0.37	**41.83**	0.86	0.58
Week 4	**-0.30**	0.51	**2.14**	0.50	<0.01	**2.92**	0.50	<0.01
Week 8	**-0.19**	0.54	**1.86**	0.55	0.02	**4.51**	0.54	<0.01
Week 16 Endpoint	**-0.98**	0.55	**1.45**	0.55	<0.01	**3.97**	0.54	<0.01
LSM Difference from placebo, SE			**2.43**	0.78		**4.95**	0.77	
95% C.I.			(0.70	4.15)		(3.23	6.66)	

* Adjusted by Dunnett procedure comparing all means with a control
[a] n=174 at Week 8

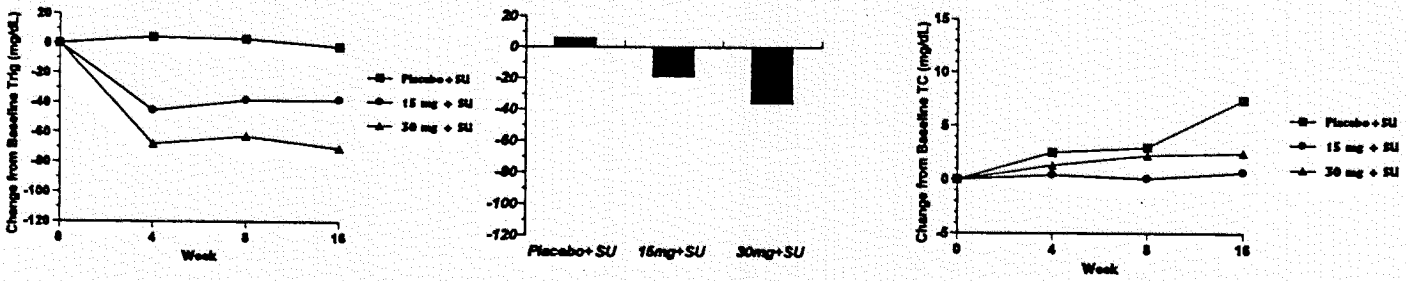
Table 82 Adjusted* LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 010

Visit	Placebo+SU n=175[a]		Pioglitazone 15 mg +SU n=171			Pioglitazone 30 mg+SU n=179		
	LSM	SE	LSM	SE	p	LSM	SE	p
Baseline	**124.5**	3.07	**124.3**	2.90		**126.5**	**2.96**	
Week 4	**1.46**	1.68	**2.57**	1.64	0.85	**4.61**	**1.69**	0.32
Week 8	**1.66**	1.78	**1.62**	1.78	1.00	**2.10**	**1.80**	0.98
Week 16 Endpoint	**5.98**	1.96	**3.04**	1.92	0.45	**5.12**	**1.95**	0.93
LSM Difference from placebo, SE			**-2.95**	2.74		**-0.87**	**2.76**	
95% C.I.			(-9.03	3.14)		(-7.00	5.26)	

* Adjusted by Dunnett procedure comparing all means with a control
[a] n=174 at Week 8

Figure 37 LSM Change from Baseline in Triglycerides, Total Cholesterol, HDL, & LDL (mg/dL) by Week - Study 010

Triglycerides (Week-16 Median) Total Cholesterol



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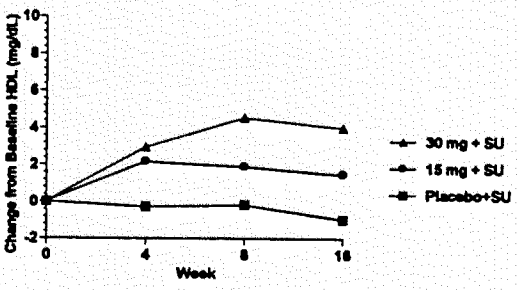
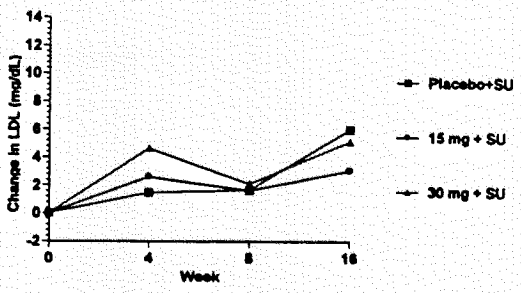
HDL



LDL



Subgroup Analysis

Change from baseline to endpoint in HbA_{1c} was examined in gender, age. The interaction between treatment and subgroup was evaluated by ANOVA with treatment, subgroup, center, and treatment-by-subgroup interaction terms in the model.

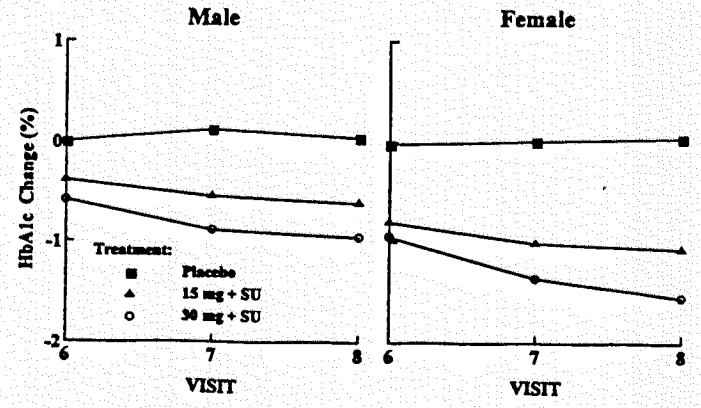
Gender

Table 83 and Figure 38 display the mean changes from baseline in HbA_{1c} by gender. The p-value of treatment-by-gender interaction was 0.038.

Table 83 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender (LOCF) – Study 010

		Pioglitazone	
Subgroup	Placebo+SU	15mg+SU	30mg+SU
Men			
n	106	103	110
Baseline Mean	9.87	9.81	9.85
Mean Change	**0.03**	**-0.62**	**-0.96**
SE	0.12	0.12	0.13
Women			
n	75	73	72
Baseline Mean	9.83	10.29	10.01
Mean Change	**0.03**	**-1.07**	**-1.56**
SE	0.12	0.14	0.13

Figure 38 Mean Change from Baseline in HbA_{1c} (%) by Gender – Study 010



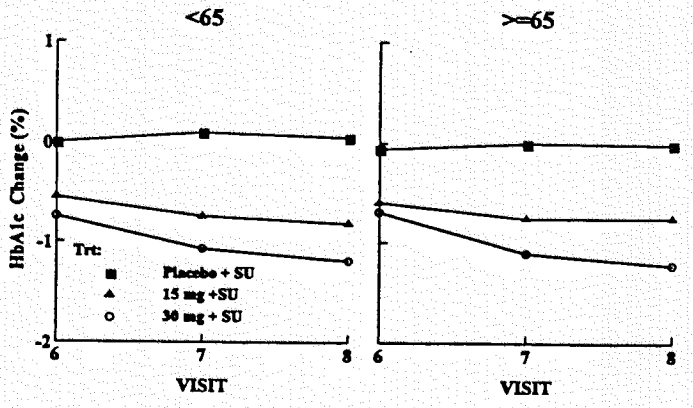
Age

Table 84 and Figure 39 display the mean change from baseline in HbA_{1c} at endpoint for patients <65 and ≥65 years of age. The treatment-by-age interaction was not significant (p=0.99).

Table 84 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group – Study 010

		Pioglitazone	
Subgroup	Placebo+SU	15 mg+SU	30 mg+SU
<65 years old			
n	141	139	141
Baseline Mean	9.98	10.06	10.02
Mean Change	**0.04**	**-0.82**	**-1.19**
SE	0.10	0.10	0.11
≥65 years old			
n	40	37	41
Baseline Mean	9.41	9.79	9.56
Mean Change	**-0.02**	**-0.76**	**-1.23**
SE	0.15	0.19	0.20

Figure 39 Mean Change from Baseline in HbA_{1c} (%) by Age – Study 010



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4. Study Summaries:

Monotherapy

1. The dose ranging trial (001) studied pioglitazone doses of 7.5 mg, 15 mg, 30 mg, and 45 mg for 26 weeks with ~80 patients per group. The overall withdrawal rate was 51%. The drop out rate for the most common reason, insufficient therapeutic effect, was treatment related (25%, 45 mg group to 41%, placebo group.) At Week 26 of the ITT population (LOCF), change from baseline HbA_{1c} was statistically significantly better for the 15 mg (-0.27%), 30 mg (-0.27%) and 45 mg (-0.86%) pioglitazone-treated patients than placebo-treated patients (+0.74%). Treatment differences from placebo were -1.00%, -1.00%, and -1.60% for the 15 mg, 30 mg, and 45 mg pioglitazone dose groups, respectively. The analysis results of 7.5 mg were not consistent in the LOCF (not significant) and OC (significant) analyses. The high and differential withdrawal rates may introduce bias in the study, therefore, the estimates from the study are deemed unreliable and the validity of the study results questionable. As the 7.5 mg dose and the 45 mg dose were studied in only this trial as a fixed dose regimen, the data is not sufficient to determine the efficacy and the safety of the 7.5 mg treatment and the 45 mg treatment.

   Using the criteria set by Dr. Misbin (ALT 3xULN=102 u/L), 5 patients(4 male, pioglitazone & 1 female, placebo) experienced an elevation >102 U/L during the trial. Of the 4 pioglitazone-treated patients, 3 were in the 30 mg group, and 1 in the 7.5 mg group.

2. Study 012 was a 24-week forced titration trial with 3 parallel groups of placebo, 7.5/15/30 mg pioglitazone and 15/30/45 mg pioglitazone (~85 patients per group). Patients were treated with the first 2 doses for 4 weeks each and the last dose for 16 weeks. At endpoint (Week 24), HbA_{1c} change from baseline was statistically significantly different between each pioglitazone group and the placebo group. The HbA_{1c} changes were +0.93%, -0.55%, and -0.60% for the placebo group, the 7.5/15/30 mg group, and the 15/30/45 mg group, respectively. The treatment differences from placebo were -1.48% and -1.53% for the 2 pioglitazone groups, respectively. One placebo patient had an elevation of ALT>102 U/L.

3. Study 026 compared 30 mg pioglitazone treatment (n=100) with placebo treatment (n=93) for 16 weeks. At endpoint, change from baseline in HbA_{1c} was +0.76% for the placebo group and -0.60% for the 30-mg pioglitazone group. The treatment difference was -1.37%.

4. At endpoint, the secondary efficacy outcome change in FBG was significantly greater in the pioglitazone group compared to the placebo group for all 3 studies. The treatment difference from placebo in FBG corresponded to the HbA_{1c} treatment difference; a difference of ~ -40 mg/dL in FBG corresponded to a -1.00% HbA_{1c} difference and a difference ~ -65 mg/dL corresponded to a ~ -1.5% HbA_{1c} difference.

5. For triglycerides, the 30-mg pioglitazone treatment group in Study 026 and the 15/30/45-mg group in Study 012 showed a significant improvement at endpoint. The median change from baseline was -57.5 mg/dL for the 30-mg group and -32 mg/dL for the 15/30/45-mg group.

6. For HDL, the 45 mg group in Study 001 and the 30 mg group in Study 026 showed treatment effects of +7.0 mg/dL and +5.0 mg/dL, respectively.

7. Body weight was significantly increased in the pioglitazone-treated patients. For the observed cases at endpoint, the treatment difference in weight increase was 5.4 kg in the 45 mg group, 4.3 kg in the 15/30/45 mg group, ~ 3.6 kg in the 30 mg and 15 mg group, and 3.0 in the 7.5/15/30 mg group.

8. Treatment differences in HbA_{1c} reduction were greater in women than men. The treatment-by-gender interaction was significant in study 001 (p=0.02), but not in study 012 (p=0.72) and study 026 (p=0.61).

9. The completion rate improved after the 001 trial (50%) with 65% for study 012 and 73% for study 026.

Add-On Therapy

1. Study 010 compared 15 mg and 30 mg pioglitazone and placebo as add-on to sulfonylurea (~ 180 patients per group.) The HbA_{1c} change from baseline to endpoint was -0.82% for the 15mg+SU group, -1.22% for the 30mg+SU group, and +0.06% for the placebo group. The treatment differences of -0.88% and -1.28% were statistically significant. Two placebo+SU patients had an elevation greater than 3XULN of ALT (>102 U/L)

2. The metformin add-on trial studied the 30 mg pioglitazone (n=160) vs. placebo (n=168). The endpoint change in HbA_{1c} was -0.64% for the 30mg+MF group and 0.19% for the placebo group. The treatment difference of -0.83% was statistically significant.

3. The insulin add-on trial (014) compared 15mg and 30mg pioglitazone to placebo (~180 patients per group.) The HbA_{1c} change from baseline to endpoint was statistically significant for both groups. The change was -0.99% for the 15mg+insulin group, -1.26% for the 30mg+insulin group

and -0.26% for the placebo group. Treatment difference from placebo was -0.73% and -1.00% for the 15mg+insulin and 30mg+insulin groups, respectively. Two patients in the 30 mg+insulin group had an elevation of ALT>102 U/L.

4. For FBG at endpoint, the pioglitazone add-on groups were significantly better than the placebo add-on groups for each add-on study. The treatment difference in FBG corresponded to the treatment difference in HbA_{1c}; a difference of -35 mg/dL corresponded to a -0.73% HbA_{1c} difference in the 5mg+insulin group and a difference of -58 mg/dL corresponded to a -1.28% HbA_{1c} difference in the 30mg+SU group.

5. HDL increased in all treatment groups in the 3 add-on trials. It was ~ 2.0 mg/dL in the 15 mg add-on groups (SU or insulin), 3.0 mg/dL for the 30 mg add-on (MF or insulin) and 5.0 mg/dL for the 30 mg add-on to SU.

6. The level of triglycerides in the 30 mg pioglitazone group of each add-on study was significantly reduced compared to the corresponding placebo add-on group. The median change from baseline was -36 mg/dL for the 30mg+SU group, -32 mg/dL for the 30mg+insulin group and -22 mg/dL for the 30mg+MF group.

7. At Week 16 of the observed cases data sets, body weight was significantly increased in the pioglitazone-add-on groups compared to the corresponding placebo add-on group. The treatment difference from placebo was 4.0 kg for the 30mg+insulin group, 3.7 kg for the 30mg+SU group, ~2.7 kg for the 15mg+SU and the 15mg+insulin groups, and 2.5 kg for the 30mg+MF group.

8. Treatment differences measured by HbA_{1c} reduction were greater in women than in men. The treatment-by-gender interaction was significant in study 010 (p=0.04), and study 014 (p=0.03) and borderline for study 027 (p=0.13.)

9. The completion rates in these add-on trials were higher than the monotherapy trials with 85%, 76% and 88% for the sulfonylurea add-on, metformin add-on, and insulin add-on, respectively, compared to 50%, 65% and 73% for the monotherapy trials.

Figure 40 displays the treatment difference and its confidence interval in HbA_{1c} for each of the pioglitazone treatment group as mono- or add-on therapy.

Figure 40 Treatment Effect (C.I.) in Change from Baseline HbA_{1c} (%)

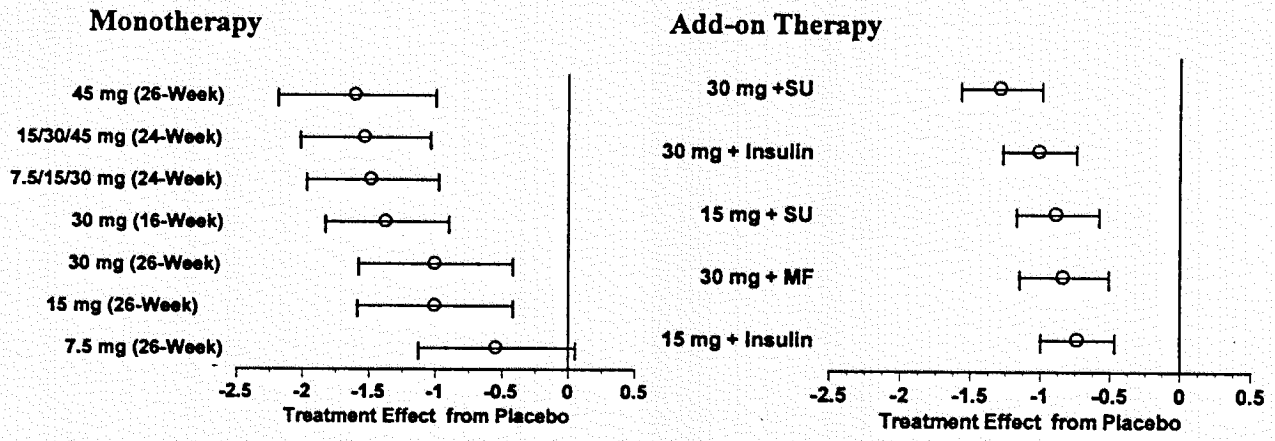

Table 85 summarizes the treatment differences from placebo in secondary variables that were significant.

Table 85 Mean Treatment Difference from Placebo in Secondary Outcome

Study	C-Peptide ng/ml	Insulin μIU/ml	Trigly* mg/dL	TC mg/dL	HDL mg/dL	LDL mg/dL
Mono						
001(45mg)	-	-	-	-	+3.9	-
012(15/30/45mg)	-	-	-32	-	-	-
026 (30mg)	-0.26	-3.8	-57	-	+5.0	-
Add-on						
010(SU)						
15mg	-0.31	-	-	-	+2.4	-
30mg	-0.35	-3.0	-36	-	+5.0	-
027(MF) (30mg)	-0.16	-2.5	-22	-	+3.1	-
014 (Ins)						
15mg	-0.18	NA	-	-	+2.2	-
30mg	-		-32	-	+2.8	-

* Median difference from baseline

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5. Conclusions

At endpoint, all the pioglitazone treatment groups, except the 7.5 mg group in the 6 U.S. trials (mono & add-on) showed statistically significant improvement over placebo in the primary efficacy variable, change in HbA_{1c} from baseline. The treatment difference from placebo ranged from -1.0% (15mg, 30mg) to -1.6% (45mg) at Week 26. Pioglitazone-treated patients showed significant reductions in FBG compared to placebo-treated patients. HDL increased in all the treatment groups in the add-on trials. Triglycerides levels decreased significantly in all the 30 mg groups of the add-on trials (sulfonylurea, metformin, and insulin) but not the 15 mg groups. Weight increased in the pioglitazone-treated patients but not in the placebo-treated patients. The treatment difference from placebo for the observed cases was 5.4 kg in 45 mg monotherapy and 3.9 kg in the 30 mg + insulin group.

The maximum recommended dose was 60 mg in the annotated proposed labeling. However, the 60 mg dose was not studied in the controlled clinical trials (only in the open-label trial PNFP-011); therefore, it should not be indicated as the maximum dose. The next highest dose, 45 mg, was studied only in 2 of the 3 monotherapy studies, both of which had very high drop-out rates. The most studied dose was the 30 mg dose, which was effective in all 6 trials.

/S/ [redacted]

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cc: Arch NDA 21-073
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