

Table 51 Adjusted\* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 027

	Placebo			Pioglitazone			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
	157	259.9	5.71	165	254.38	5.58	-5.51	7.77	-20.8 9.77	0.48
Week 4	156	-3.84	3.94	164	-26.7	3.86	-22.86	5.52	-33.72 -12	<0.01
Week 8	157	-5.32	4.17	165	-35.11	4.07	-29.79	5.82	-41.26 -18.32	<0.01
Week 12	157	-4.24	4.24	165	-43.51	4.14	-39.28	5.93	-50.95 -27.6	<0.01
Week 16	157	-5.18	4.23	165	-42.83	4.13	-37.65	5.92	-49.31 -26	<0.01

## C-peptide &amp; Insulin

Fasting C-peptide and insulin were significantly different between pioglitazone-treated patients and the placebo-treated patients at endpoint (Tables 52, 53 & Figure 24).

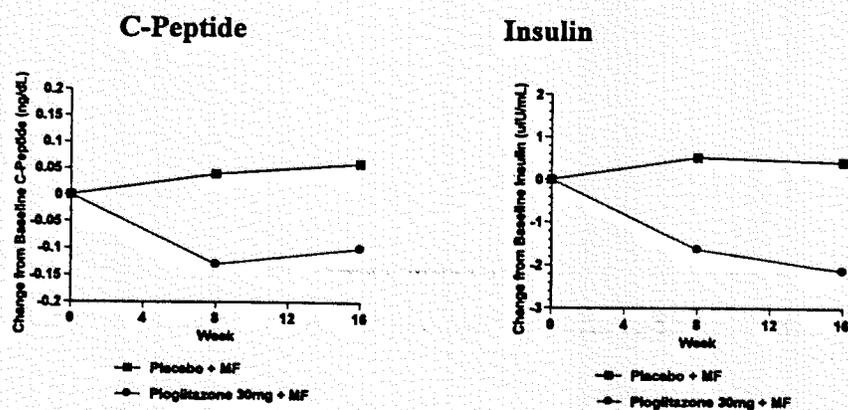
Table 52 LSM Change from Baseline in C-Peptide (ng/mL) by Visit (LOCF) – Study 027

	Placebo+MF			30 mg+MF			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	148	2.18	0.07	159	2.08	0.07	-0.09	0.09	-0.27 0.09	0.31
Week 8	146	0.04	0.04	156	-0.13	0.04	-0.18	0.06	-0.3 -0.05	0.01
Week 16	148	0.06	0.05	159	-0.1	0.05	-0.16	0.07	-0.3 -0.02	0.03

Table 53 LSM Change from Baseline in Fasting Insulin ( $\mu$ IU/mL) by Visit (LOCF) – Study 027

	Plb+MF			Pio 30mg + MF			Difference from Placebo			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline										
Week 8	146	0.52	0.61	155	-1.64	0.59	-2.15	0.86	(-3.84 -0.47)	0.01
Week 16	148	0.42	0.71	157	-2.13	0.68	-2.54	0.98	(-4.48 -0.6)	0.01

Figure 24 LSM Change from baseline in C-Peptide and Insulin – Study 027



## Lipids

At endpoint (Week 16), the LSM change in triglycerides was -20.0 mg/dL for the Plb+MF group and -63.4 mg/dL for the Pioglitazone 30mg + MF group. The treatment difference of -43.4 mg/dL was significant (p=0.03). The LSM change in total cholesterol was -1.2 mg/dL for the Plb+MF and +5.7 mg/dL for the Pioglitazone 30mg + MF group. The p-value for the placebo subtracted difference of 6.9 mg/dL in TC was not significant (0.09). HDL was significantly different (p<0.01) at endpoint with an increase of 3.2 mg/dL in the Pioglitazone 30mg + MF compared to no change in the Plb+MF group. For LDL, it was not significant (p=0.12) when comparing a change of +2.7 mg/dL for the Plb+MF group and 6.9 mg/dL for the Pioglitazone 30mg + MF group (Tables 54-57 & Figure 25).

**Table 54 LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 027**

	Placebo+MF			30mg+MF			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	149	300.39	25.86	161	298.86	24.9	-1.53	35.07	-70.56	67.5	0.97
Week 8	148	5.26	20.82	161	-82.94	19.96	-88.2	28.85	-145.02	-31.38	<0.01
Week 12	149	-13.81	12.75	161	-79.96	12.25	-66.15	17.68	-100.98	-31.33	<0.01
Week 16	149	-19.96	14.73	161	-63.37	14.14	-43.41	20.42	-83.62	-3.19	0.03

**Table 55 LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 027**

	Placebo+MF			30mg+MF			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	149	211.93	4.28	161	212.84	4.12	0.91	5.8	-10.51	12.32	0.88
Week 8	148	-0.31	2.9	161	2.37	2.78	2.68	4.02	-5.24	10.6	0.51
Week 12	149	-0.12	3.2	161	1.42	3.07	1.54	4.43	-7.19	10.27	0.73
Week 16	149	-1.21	2.96	161	5.71	2.85	6.92	4.11	-1.18	15.01	0.09

**Table 56 LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 027**

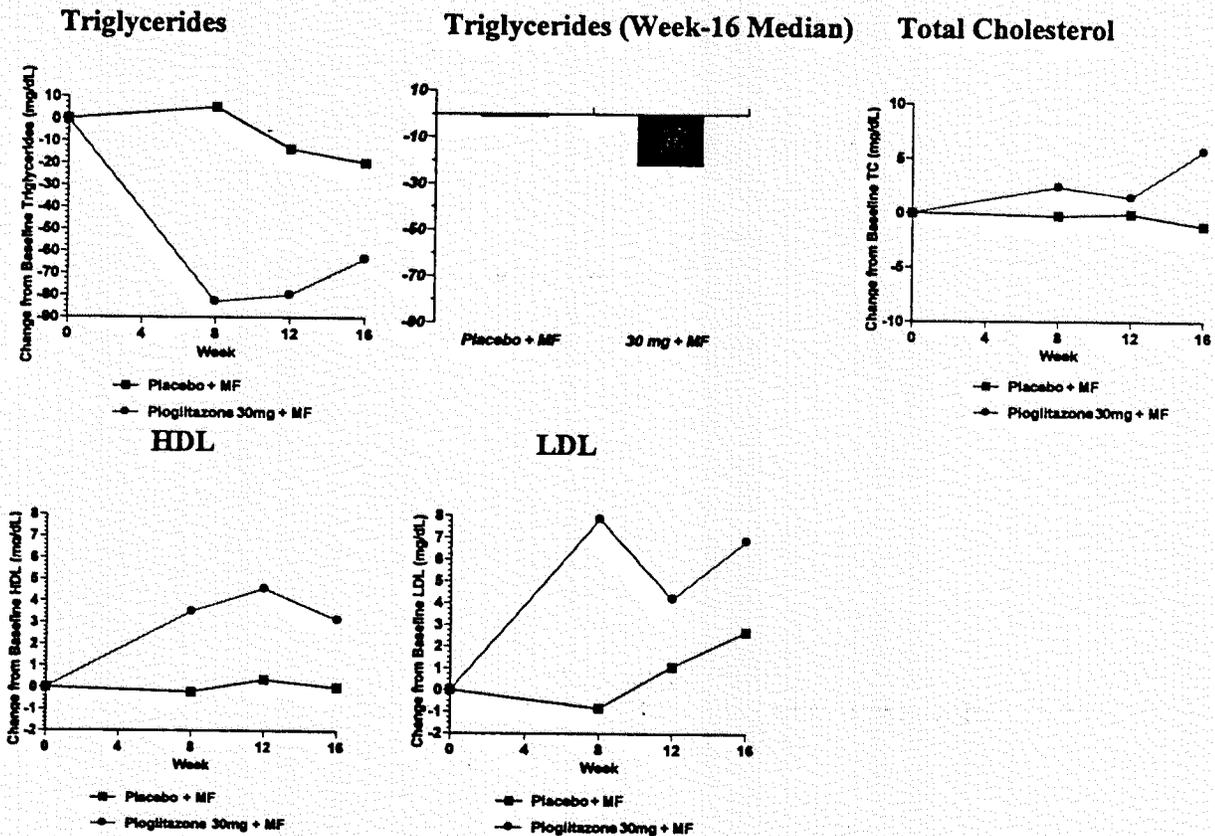
	Placebo+MF			30mg+MF			Difference from Placebo				p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.		
Baseline	143	42.09	1.00	158	42.86	0.95	0.78	1.35	-1.89	3.44	0.57
Week 8	141	-0.21	0.85	158	3.52	0.79	3.73	1.16	1.45	6.02	<0.01
Week 12	142	0.37	0.97	158	4.59	0.91	4.22	1.32	1.61	6.83	<0.01
Week 16	143	0.02	0.67	158	3.16	0.64	3.13	0.93	1.31	4.96	<0.01

**Table 57 LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 027**

	Placebo+MF			30 mg+MF			Difference from Placebo*			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	125	118.00	3.15	129	119.3	3.07				NS
Week 8	117	-0.84	1.94	129	7.85	1.80	8.69	2.59	3.59 13.79	<0.01
Week 12	121	1.08	2.11	127	4.21	2.04	3.13	2.87	-2.53 8.78	0.28
Week 16	121	2.68	1.95	125	6.85	1.87	4.17	2.64	-1.04 9.37	0.12

\*ANOVA with treatment, pooled center, and baseline as covariate (no trt-by-center)

**Figure 25 Change from Baseline in Lipids**



**Body Weight**

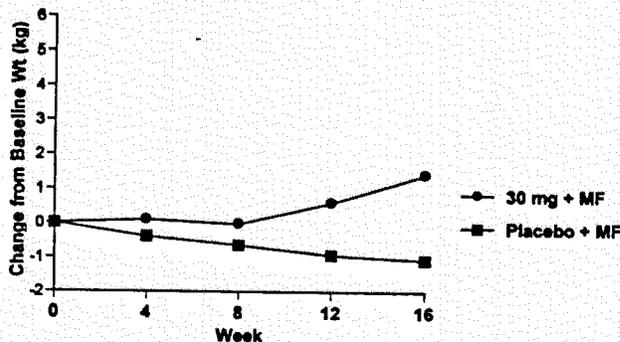
Table 58 displays change from baseline weight (kg) over time for the completers and at endpoint. Pioglitazone+MF-treated patients gained weight compared to placebo significantly during the course of the study. At Week 16 the difference was 2.48 kg. Figure 26 displays the weight change in patients who completed the study.

Table 58 Mean Change from Baseline in Body Weight (kg) (Completers) – Study 027

	Placebo+MF			30 mg+MF			Difference from Placebo*			p
	n	LSM	SE	n	LSM	SE	LSM	SE	95% C.I.	
Baseline	112	93.96	1.60	137	93.24	1.41	-0.71	2.13	-4.90 3.48	0.74
Week 4	112	-0.39	0.14	137	0.09	0.16	0.48	0.22	0.05 0.91	0.03
Week 8	112	-0.64	0.18	137	-0.03	0.40	0.61	0.47	-0.32 1.54	0.20
Week 12	112	-0.93	0.23	137	0.59	0.45	1.51	0.54	0.45 2.58	0.01
Week 16	112	-1.06	0.25	137	1.41	0.27	2.48	0.38	1.72 3.23	<0.01
Endpoint	160	-1.36	0.24	167	0.95	0.24	2.31	0.34	1.64 2.98	<0.01

\*ANOVA with treatment in the model

Figure 26 Changes in Body Weight (kg) – Completers



#### Subgroup Analysis

Changes from baseline in HbA<sub>1c</sub> at endpoint were examined in subgroups of gender, age. The interaction between treatment and subgroup was explored using ANOVA with treatment, subgroup, center, and treatment-by-subgroup terms in the model.

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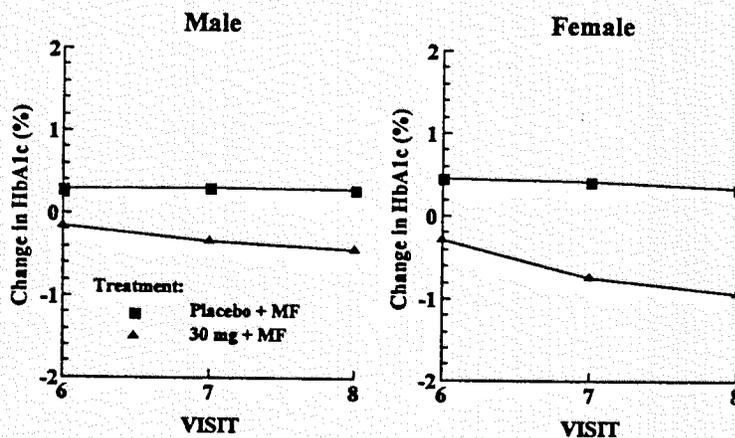
## Gender

Table 59 and Figure 27 display the mean change from baseline in HbA<sub>1c</sub> by gender. The p-value for treatment-by-gender interaction was 0.13.

**Table 59 Mean Change from Baseline in HbA<sub>1c</sub> (%) at Endpoint by Gender – Study 027**

Subgroup	Placebo+MF	30 mg +MF
<b>Men</b>		
n	92	88
Baseline Mean	9.74	9.83
Mean Change	0.28	-0.44
SE	0.12	0.16
<b>Women</b>		
n	61	73
Baseline Mean	9.74	10.00
Mean Change	0.39	-0.94
SE	0.19	0.15

**Figure 27 Mean Change from Baseline in HbA<sub>1c</sub> (%) by Gender – Study 027**



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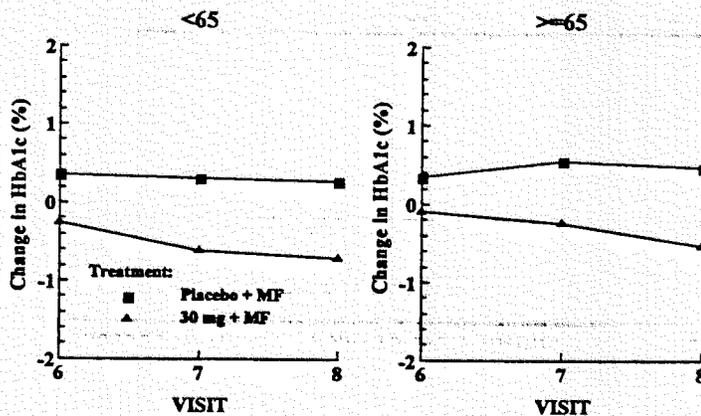
## Age

Mean change from baseline in HbA<sub>1c</sub> for patients <65 and ≥65 years of age is displayed in Table 60 and Figure 28. P-value for treatment-by-age group interaction was 0.97.

**Table 60 Mean Change from Baseline in HbA<sub>1c</sub> (%) at Endpoint by Age Group – Study 027**

Subgroup	Pib+MF	Pio 30mg + MF
<b>&lt;65 years old</b>		
n	125	124
Baseline Mean	9.82	9.95
<b>Mean Change</b>	<b>0.28</b>	<b>-0.71</b>
SE	0.12	0.13
<b>≥65 years old</b>		
n	28	37
Baseline Mean	9.35	9.71
<b>Mean Change</b>	<b>0.48</b>	<b>-0.54</b>
SE	0.23	0.24

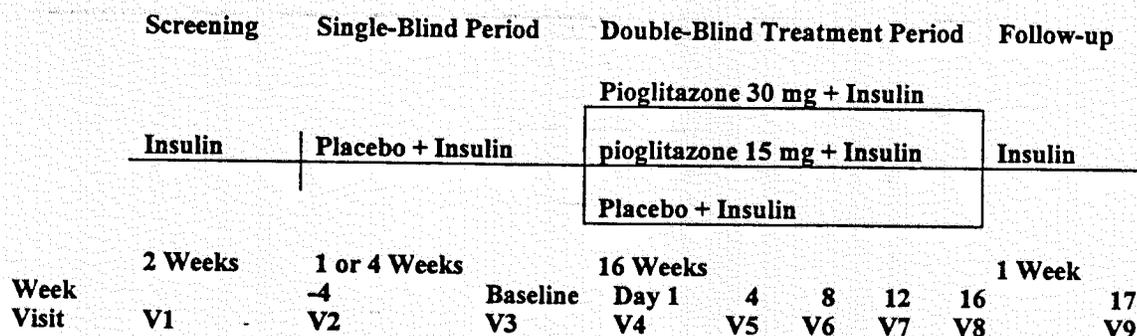
**Figure 28 Mean Change from Baseline in HbA<sub>1c</sub> (%) by Age Group – Study 027**



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### Study PNFP-014 (Insulin)

This was a double-blind, placebo-controlled, randomized, multicenter (84), study of efficacy and safety of 15 mg or 30 mg doses of pioglitazone as add-on to insulin in type 2 diabetic patients. The study scheme is displayed in the following diagram.



#### Patient Disposition

Of the 1157 patients screened (15 rescreened), 674 patients received single-blind medication. A total of 566 patients were randomized (7 rescreened), 187 to the placebo + Insulin group, 191 to the 15 mg pioglitazone + Insulin, and 188 to the 30 mg pioglitazone + Insulin treatment group. Overall completion rate was 88% (497/566.) Table 61 displays the disposition of patients. Table 62 displays patient discontinuation by time.

**Table 61 Patient Disposition – Study 014**

	Plb+Insulin	Pio 15 mg + Insulin	Pio 30mg + Insulin
Randomized	187	191	188
Completed	164	161	172
Withdrawn	23	30	16
Insufficient Therapeutic Effect	3	3	5
AE	3	5	6
Non-Compliance	2	3	1
Lost to Follow-up	4	7	0
Withdrew Consent	8	11	3
Unhappy with Glucose Control	0	3	0
Personal Reasons	8	4	2
Weight Gain	0	4	1
Protocol Violation	3	1	1

Baseline characteristics were not significantly different between the treatment groups. The mean age of randomized patients was 57.1 years. Most patients were Caucasian (73%). Females were slightly more (53%). The mean weight was 96.49 kg. The mean BMI was 33.55 kg/m<sup>2</sup>. Most patients (88%) did not receive antidiabetic medications other than insulin before

enrolling in the study. Baseline values for the primary and secondary efficacy variables are listed in Table 62.

**Table 62 Mean Values at Baseline in Efficacy Variables – Study 014**

	Placebo+Insulin n=187			15 mg + Insulin n=191			30 mg + Insulin n=188			overall p-value*
	n	Mean	SD	n	Mean	SD	n	Mean	SD	
HbA <sub>1c</sub>	186	9.83	1.36	191	9.84	1.45	188	9.86	1.29	0.97
FBG (mg/dL)	186	220.6	72.48	190	223.7	71.89	188	227.5	68.36	0.62
Fasting C-Peptide (ng/mL)	186	1.54	0.71	188	1.61	0.80	185	1.57	0.80	0.82
Triglycerides (mg/dL)	187	240.0	204.29	191	245.4	192.12	188	256.5	292.41	0.80
Total Cholesterol	187	214.6	44.82	191	212.9	48.68	188	207.8	45.01	0.25
HDL (mg/dL)	185	43.0	11.74	188	42.9	12.56	185	43.2	12.96	0.98
LDL (mg/dL)	162	131.4	38.84	163	124.9	38.65	162	122.5	33.75	0.06

\* p-values based on pooled center (38) and treatment in ANOVA model

Of the 566 patients who were randomized, 68 (12%) received other antidiabetic medications in combination with their insulin (metformin, glibenclamide, glipizide, glimepiride, acarbose, troglitazone, and tolazamide.) Ten of these patients received more than one medication in combination with their insulin.

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

#### Efficacy Results – Study 014

Primary Efficacy Variable – HbA<sub>1c</sub> Change from Baseline to Week 16

At endpoint (Week 16), both pioglitazone treatment groups were statistically significant different from the placebo group in the LSM change from baseline in HbA<sub>1c</sub> (Table 63 & Fig 29) The LSM changes were -0.26%, -0.99%, and -1.26% for the placebo + insulin, 15 mg + insulin, and 30 mg + insulin groups, respectively.

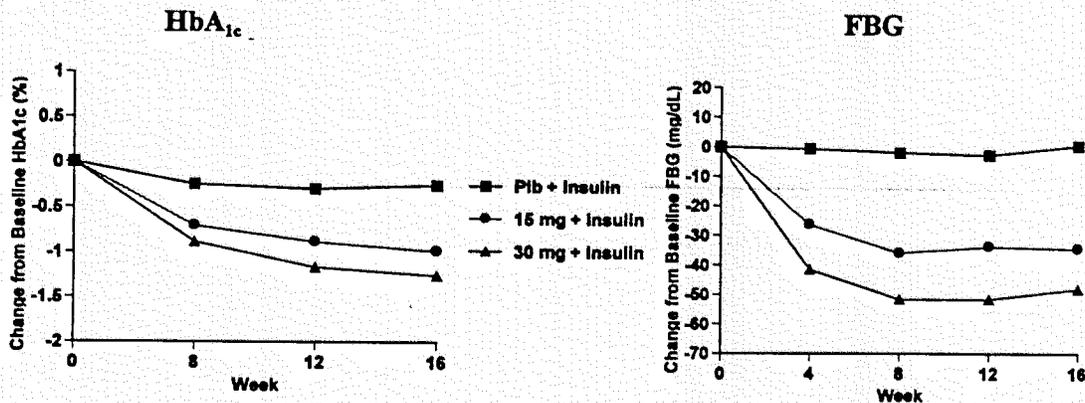
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Table 63 Adjusted\* LSM Change from Baseline in HbA<sub>1c</sub> by Visit (LOCF) – Study 014

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P <sub>15</sub>	P <sub>30</sub>
Baseline	177	9.75	0.10	177	9.75	0.10	185	9.84	0.10	1.00	0.77
Week 8	173	-0.25	0.07	175	-0.71	0.07	184	-0.89	0.07	<0.01	<0.01
Week 12	177	-0.30	0.08	177	-0.89	0.08	185	-1.17	0.08	<0.01	<0.01
Week 16	177	-0.26	0.08	177	-0.99	0.08	185	-1.26	0.08	<0.01	<0.01
Difference from Placebo (SE)				-0.73 0.12			-1.00 0.12				
95% C.I.				(-1.00 -0.47)			(-1.27 -0.74)				

\*Least Squared Means Adjusted by Dunnett procedure

Figure 29 LSM Change from baseline in HbA<sub>1c</sub> and FBG – Study 014



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 30mg + MF group. The between group difference of -37.7 mg/dL was significant (Table 64 & Fig 29).

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Table 64 Adjusted\* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 014

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P <sub>15</sub>	P <sub>30</sub>
Baseline	179	220.55	5.22	183	221.67	5.15	184	229.28	5.15	0.98	0.38
Week 4	179	-0.67	4.78	182	-26.39	4.69	180	-41.59	4.78	<0.01	<0.01
Week 8	179	-1.91	4.79	182	-35.99	4.70	184	-51.60	4.75	<0.01	<0.01
Week 12	179	-2.67	4.85	183	-33.77	4.75	184	-51.59	4.80	<0.01	<0.01
Week 16	179	0.57	5.09	183	-34.46	4.99	184	-48.04	5.04	<0.01	<0.01
Difference from Placebo (SE)				-35.04 7.12			-48.61 7.16				
95% C.I.				(-50.84 -19.24)			(-64.50 -32.72)				

\*Least Squared Means Adjusted by Dunnett procedure

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## C-peptide

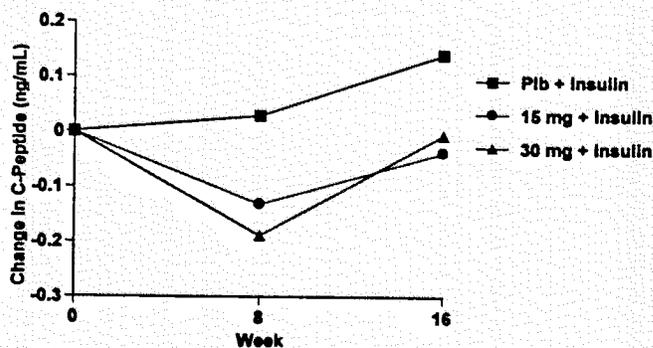
Fasting C-peptide was significantly different between 15 mg + insulin group and placebo group at endpoint. The p-value comparing the 30 mg + insulin group with placebo group was 0.07 (Table 65 & Figure 30).

**Table 65 LSM Change from Baseline in C-Peptide (ng/mL) by Visit (LOCF) – Study 014**

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P <sub>15</sub>	P <sub>30</sub>
Baseline	178	1.55	0.06	175	1.59	0.06	179	1.60	0.06	0.87	0.77
Week 8	172	0.03	0.04	169	-0.13	0.04	173	-0.19	0.04	0.02	0.00
Week 16	178	0.14	0.05	175	-0.04	0.05	179	-0.01	0.05	0.02	0.07
Difference from Placebo (SE)					-0.18	0.07		-0.15	0.07		
95% C.I.					(-0.33	-0.02)		(-0.30	0.01)		

\*Least Squared Means Adjusted by Dunnett procedure

**Figure 30 LSM Change from baseline in C-Peptide – Study 014**



## Lipids

At endpoint (Week 16), the LSM change in triglycerides was -20.0 mg/dL for the Plb+MF group and -63.4 mg/dL for the Pio 30mg + MF group. The treatment difference of -43.4 mg/dL was significant (p=0.03). The LSM change in total cholesterol was -1.2 mg/dL for the Plb+MF and +5.7 mg/dL for the Pio 30mg + MF group. The p-value for the placebo subtracted difference of 6.9 mg/dL in TC was not significant (0.09). HDL was significantly different (p<0.01) at endpoint with an increase of 3.2 mg/dL in the Pio 30mg + MF compared to no change of the Plb+MF group. For LDL, it was not significant (p=0.12) when comparing a change of +2.7 mg/dL for the Plb+MF group and 6.9 mg/dL for the Pio 30mg + MF group (Tables 66-69 & Fig 31).

**Table 66 LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 014**

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P <sub>15</sub>	P <sub>30</sub>
Baseline	176	242.49	17.81	176	230.69	17.75	182	262.32	17.52	0.85	0.64
Week 8	176	-0.29	11.83	175	-25.82	11.72	181	-65.69	11.70	0.22	0.00
Week 12	176	1.22	13.03	176	-18.25	12.90	182	-52.81	12.85	0.46	0.01
Week 16	176	10.95	15.10	176	-11.58	14.95	182	-49.52	14.89	0.46	0.01
Difference from Placebo (SE)				-22.53 21.24			-60.46 21.22				
95% C.I.				( -69.66 24.61)			( -107.55 -13.38)				

\*Least Squared Means Adjusted by Dunnett procedure

**Table 67 LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 014**

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P <sub>15</sub>	P <sub>30</sub>
Baseline	176	214.03	3.58	176	213.08	3.57	182	207.32	3.53	0.97	0.30
Week 8	176	-0.22	2.18	175	-3.73	2.16	181	-4.89	2.16	0.41	0.22
Week 12	176	-3.14	2.31	176	-2.77	2.29	182	-1.26	2.28	0.99	0.79
Week 16	176	-3.25	2.34	176	-0.15	2.32	182	-1.78	2.31	0.54	0.86
Difference from Placebo (SE)				3.10 3.30			1.48 3.29				
95% C.I.				( -4.21 10.42)			( -5.83 8.78)				

\*Least Squared Means Adjusted by Dunnett procedure

**Table 68 LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 027**

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P <sub>15</sub>	P <sub>30</sub>
Baseline	173	42.60	0.96	173	43.27	0.95	179	42.70	0.94	0.83	1.00
Week 8	170	-0.44	0.61	172	2.00	0.60	178	3.97	0.59	0.01	0.00
Week 12	173	-1.00	0.60	173	1.92	0.60	179	3.87	0.60	0.00	0.00
Week 16	173	-0.66	0.67	173	2.19	0.66	179	2.75	0.66	0.01	0.00
Difference from Placebo (SE)				2.85 0.94			3.41 0.94				
95% C.I.				( 0.76 4.94)			( 1.33 5.50)				

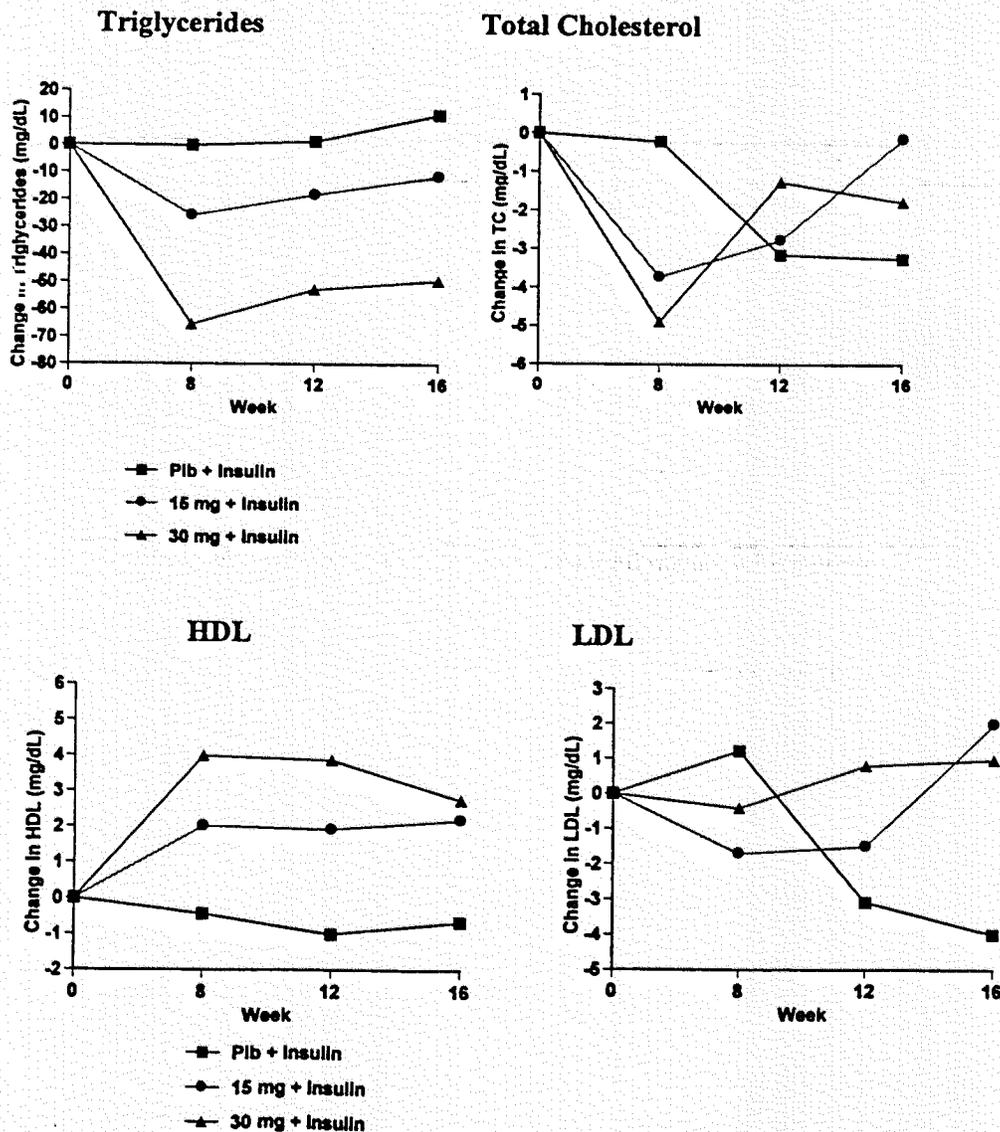
\*Least Squared Means Adjusted by Dunnett procedure

Table 69 LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 014

	Placebo+Insulin n=187			Pio 15 mg + Insulin n=191			Pio 30 mg + Insulin n=186			vs. Placebo	
	n	LSM	SE	n	LSM	SE	n	LSM	SE	P <sub>15</sub>	P <sub>30</sub>
Baseline	173	42.60	0.96	173	43.27	0.95	179	42.70	0.94	0.83	1.00
Week 8	149	1.22	1.95	147	-1.72	1.96	154	-0.43	2.02	0.46	0.78
Week 12	151	-3.10	1.97	149	-1.51	1.96	154	0.79	2.07	0.79	0.30
Week 16	145	-4.00	2.02	147	2.00	1.99	154	0.98	2.08	0.06	0.16
Difference from Placebo (SE)				5.99 2.83			4.98 2.91				
95% C.I.				(-0.28 12.27)			(-1.48 11.44)				

\*Least Squared Means Adjusted by Dunnett procedure

Figure 31 Change from Baseline in Lipids



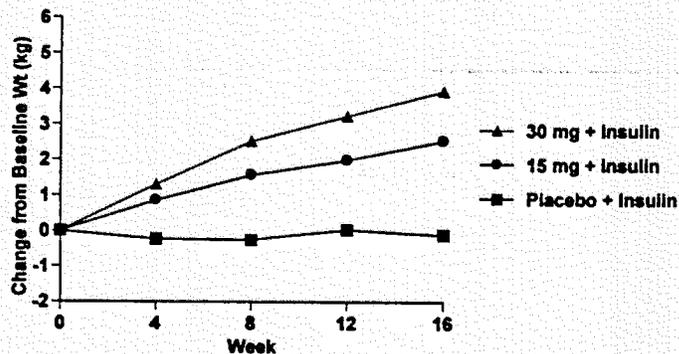
## Body Weight

Table 70 displays change from baseline weight (kg) over time for the observed cases and at endpoint. Figure 32 displays mean change in body weight of the completers with constant sample size as at week 16.

**Table 70 Mean Change from Baseline in Body Weight (kg) - Study 014**

Visit	Placebo + Insulin	15 mg + Insulin	30 mg + Insulin
<b>Week 16</b>			
N	162	165	174
Mean	-0.11	2.53	3.92
SE	0.23	0.25	0.28
<b>Endpoint</b>			
N	182	190	188
Mean	-0.04	2.30	3.73
SE	0.22	0.23	0.27

**Figure 32 Mean Changes in Body Weight (kg) – Completers**



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Changes from baseline in HbA<sub>1c</sub> at endpoint were examined in subgroups of gender, and age.

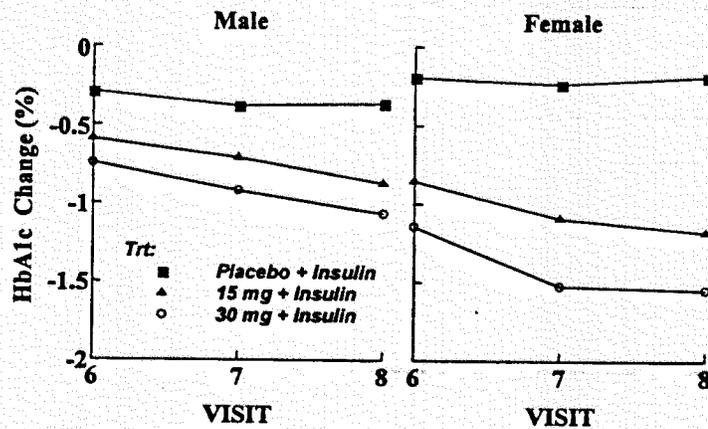
### Gender

Table 71 and Figure 33 display the mean change from baseline in HbA<sub>1c</sub> by gender. The p-value for treatment-by-gender interaction was 0.03.

**Table 71 Mean Change from Baseline in HbA<sub>1c</sub> (%) at Endpoint by Gender – Study 014**

Subgroup	Placebo+Insulin	Pio 15 mg + Insulin	Pio 30 mg + Insulin
<b>Men</b>			
n	82	80	94
Baseline Mean	9.72	9.86	9.86
Mean Change	-0.36	-0.87	-1.07
SE	0.12	0.13	0.12
<b>Women</b>			
n	95	97	91
Baseline Mean	9.84	9.74	9.88
Mean Change	-0.19	-1.18	-1.55
SE	0.11	0.11	0.13

**Figure 33 Mean Change from Baseline in HbA<sub>1c</sub> (%) by Gender – Study 014**



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