

Subgroup Analysis

The HbA_{1c} change from baseline were evaluated in gender, age, race, baseline BMI, time of enrollment, and use of previous antidiabetic medication using the LOCF data of the ITT population. The interaction between subgroup and treatment was explored by ANOVA with terms of treatment, center, subgroup and treatment-by-subgroup interaction in the model.

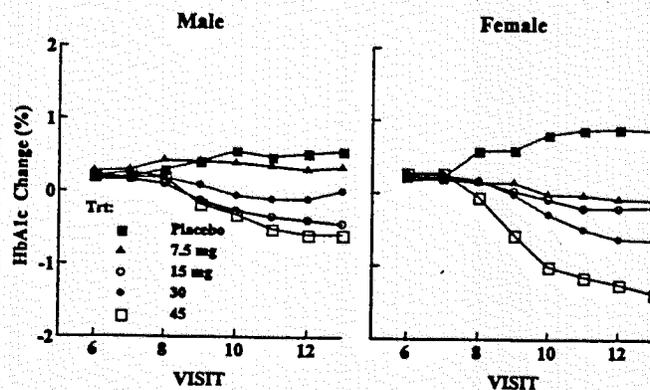
Gender

The descriptive statistics in mean change from baseline in HbA_{1c} at endpoint by gender are displayed in Table 14 and Figure 5. The overall p-value for gender-by-treatment was significant (p=0.02.) When each treatment group was examined, the treatment-by-gender was significant for the 7.5 mg, 30 mg, and 45 mg, groups but not the 15 mg group (p=0.88).

Table 14 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender (LOCF) – Study 001

Subgroup	Placebo	Pioglitazone			
		7.5 mg	15 mg	30 mg	45 mg
Men					
n	36	52	44	50	46
Baseline Mean	10.69	10.06	9.90	10.21	10.02
Mean Change	0.54	0.33	-0.45	0.02	-0.59
SE	0.24	0.17	0.24	0.19	0.22
Women					
n	43	28	35	35	30
Baseline Mean	10.13	9.89	10.53	9.99	10.78
Mean Change	0.87	-0.10	-0.19	-0.60	-1.37
SE	0.17	0.21	0.20	0.20	0.41

Figure 5 Change from Baseline in HbA_{1c} by Gender – Study 001



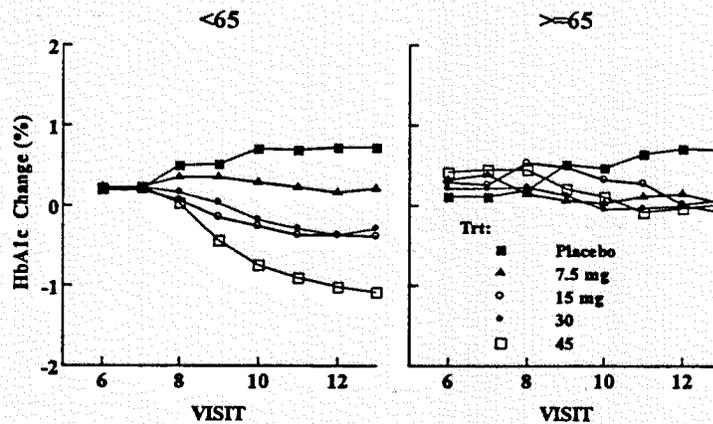
Age

Mean change from baseline in HbA_{1c} at endpoint by age group (<65, ≥65) are displayed in Table 15 and Figure 6. The p-value for the test of interaction between treatment and age group was 0.18.

Table 15 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group (LOCF) – Study 001

Subgroup	Placebo	Pioglitazone			
		7.5 mg	15 mg	30 mg	45 mg
<65 years old					
n	70	68	69	76	63
Baseline Mean	10.58	10.16	10.32	10.18	10.47
Mean Change	0.72	0.20	-0.39	-0.28	-1.09
SE	0.16	0.15	0.17	0.15	0.24
≥65 years old					
n	9	12	10	9	13
Baseline Mean	8.84	9.10	9.21	9.63	9.61
Mean Change	0.69	0.03	0.06	0.13	0.02
SE	0.33	0.37	0.46	0.36	0.46

Figure 6 Change from Baseline in HbA_{1c} by Age Group – Study 001



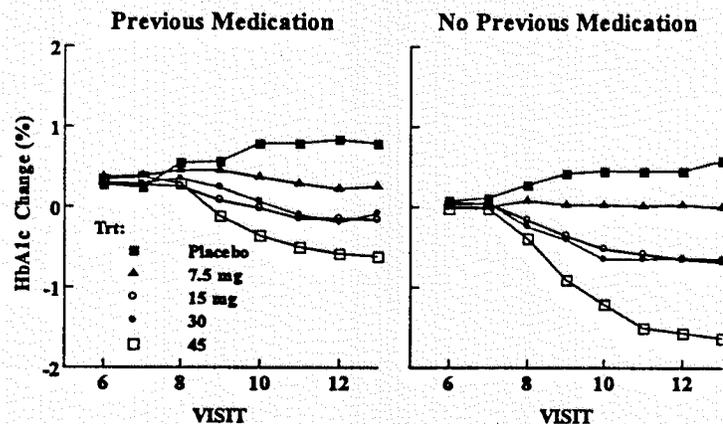
Previous Medication

The descriptive statistics in mean change from baseline in HbA_{1c} at endpoint by previous antidiabetic medication of the LOCF population are displayed in Table 16 and Figure 7. The p-value for treatment-by-previous medication interaction was 0.48.

Table 16 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Previous Antidiabetic Medication – Study 001

Subgroup	Placebo	Pioglitazone			
		7.5 mg	15 mg	30 mg	45 mg
Previous Medication					
n	54	53	53	59	55
Baseline Mean	10.92	10.37	10.32	10.43	10.50
Mean Change	0.79	0.26	-0.16	-0.08	-0.62
SE	0.178	0.164	0.208	0.159	0.265
No Previous Medication					
n	25	27	26	26	21
Baseline Mean	9.22	9.27	9.90	9.42	9.85
Mean Change	0.56	0.01	-0.68	-0.59	-1.63
SE	0.236	0.234	0.219	0.281	0.301

Figure 7 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Previous Antidiabetic Medication – Study 001

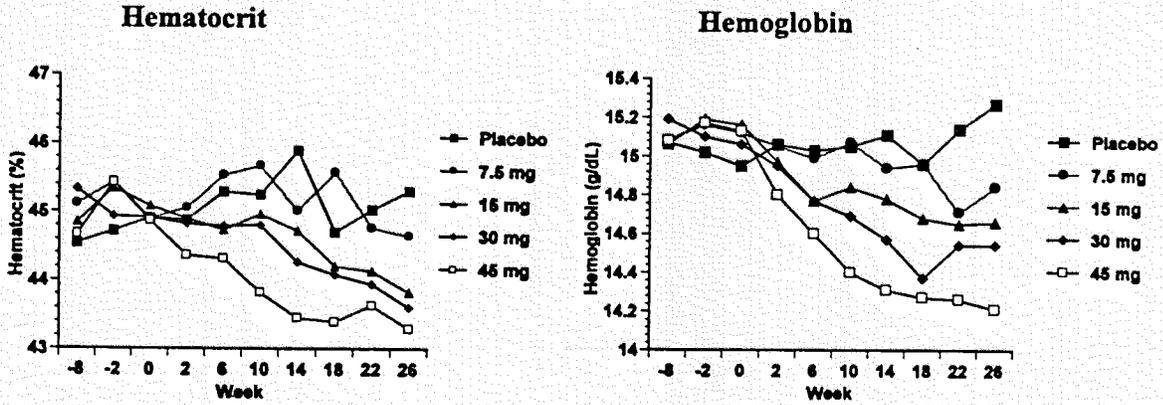


Safety

The sponsor indicated that there were small, dose-related changes from baseline in hematocrit, hemoglobin, and RBCs. At Week 26 of the observed cases, pioglitazone 15, 30, and 45 mg were significantly different from placebo in hematocrit ($p \leq 0.03$). All pioglitazone doses were significantly different from placebo in hemoglobin ($p \leq 0.01$) at Week 26.

The LSMs of the observed cases in hematocrit and hemoglobin are displayed in Figure 8.

Figure 8 LSM of Hematocrit & Hemoglobin by Week – Study 001



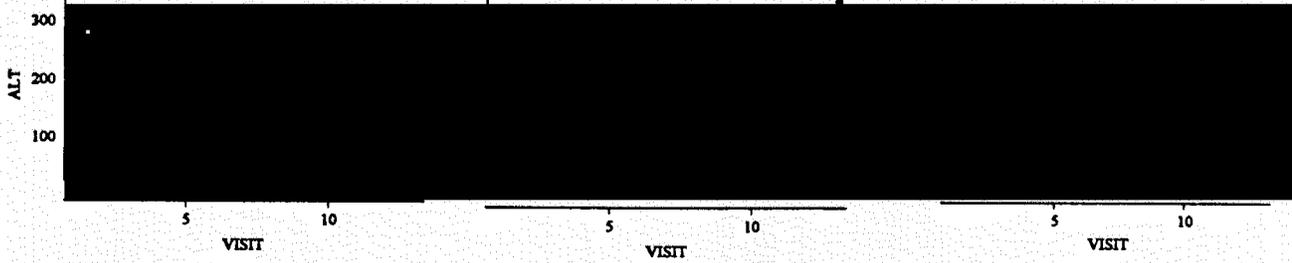
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The reviewing Medical Officer, Dr. Misbin, set 102 U/L as the ULN for ALT. The time course of the 5 patients with ALT>102 U/L is displayed in the following figure.

Patient 2126 (30 mg)

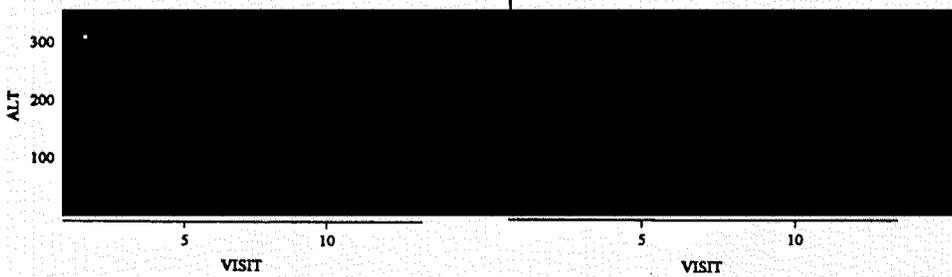
Patient 2373 (30 mg)

Patient 2481 (30 mg)



Patient 2362 (7.5 mg)

Patient 2439 (Placebo)



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Patient Disposition

A total of 560 patients signed an ICF, of those 13 signed twice. Eight of the 13 were randomized. Of the 547 patients who entered the single-blind placebo period, 260 were randomized, 84 to the placebo group, 87 to the 7.5/15/30mg group and 89 to the 15/30/45mg group. The completion rate was 65% (170/260). Table 17 displays the disposition of patients and Table 18 the discontinuation by time.

Table 17 Patient Disposition - Study 012

	Placebo	7.5/15/30 mg	15/30/45 mg
Randomized	84	87	89
Withdrawn	37 (44%)	27 (31%)	26 (29%)
Lack of Efficacy	31 (37%)	20 (23%)	18 (20%)
Adverse Event other than hyperglycemia	4 (5%)	4 (5%)	0
Lost to Follow-up	0	2 (2%)	2 (2%)
Non-Compliance	1 (1%)	0	1 (1%)
Protocol Violation	1 (1%)	0	0
Personal Reasons	0	1 (1%)	5 (6%)
Completed	47 (56%)	60 (69%)	63 (71%)

Table 18 Patient Discontinuation by Time - Study 012

	Placebo	7.5/15/30 mg	15/30/45 mg	Total
Randomized	84	87	89	260
Completed	47	60	63	170
Withdrawn	37	27	26	90
≤ Week 4	13	9	8	30
> Week 4 & ≤ Week 8	9	6	5	20
> Week 8 & ≤ Week 16	11	11	9	31
> Week 16 & ≤ Week 24	4	1	4	9

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Patient Demographic and Baseline Characteristics

Most patients were Caucasians (82%). There were more males (56%) than females. The mean age was 56 years. The mean weight was 90.9 kg with a mean BMI of 30.9 kg/m². The baseline mean values of the primary and secondary variables are presented in Table 19.

Table 19 Mean Values at Baseline in Efficacy Variables – Study 012

	Placebo n=84		7.5/15/30 mg n=87		15/30/45 mg n=89		Overall p-value*
	MEAN	SE	MEAN	SE	MEAN	SE	
HbA _{1c}	10.75	1.659	10.37	1.730	10.60	1.628	0.162
FBG (mg/dL)	282.8	68.23	271.7	69.05	281.5	62.62	0.376
Fasting C-Peptide (ng/mL)	2.11	0.864	2.12	0.815	2.12	0.663	0.989
Fasting Insulin (μIU/mL)	14.19	11.34	14.21	9.36	15.15	11.83	0.785
Triglycerides (mg/dL)	306.0	368.8	296.1	233.1	324.7	312.5	0.710
Total Cholesterol	225.9	57.04	212.0	44.33	219.3	46.07	0.135
HDL (mg/dL)	43.1	11.13	40.7	10.15	39.9	10.31	0.135
LDL (mg/dL)	134.4	39.96	122.0	37.12	124.0	30.13	0.101

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

Of the 260 patients randomized, 197 (76%) patients had received prior antidiabetic medications (52 patients >1 medication.)

Efficacy Results – Study 012

Primary Efficacy Variable – HbA_{1c} Change from baseline to Week 24

At endpoint, Week 24, the LSM changes from baseline in HbA_{1c} were statistically significant between the pioglitazone-treated patients and the placebo-treated patients (p<0.01). The HbA_{1c} changes from baseline were -0.55, -0.60 and +0.93 for the treatment group of 7.5/15/30-mg, 15/30/45-mg, and placebo, respectively. The differences from placebo were -1.48% and -1.53% for the 7.5/15/30 mg and 15/30/45 mg groups, respectively.

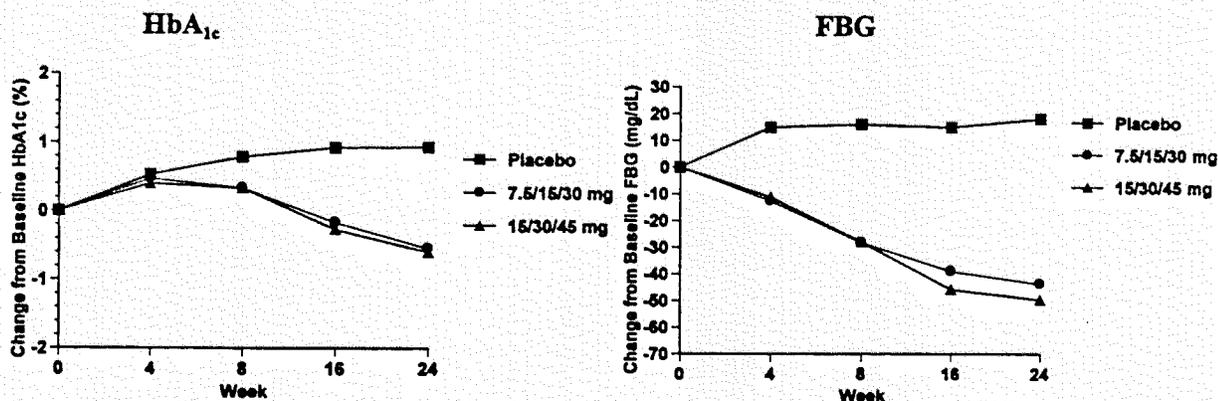
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Table 20 Adjusted* LSM Change from Baseline in HbA_{1c} (%) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=83		7.5/15/30 mg n=85 ^a		15/30/45 mg n=85		P ₃₀	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	10.76	0.176	10.34	0.175	10.75	0.175	0.16	1.00
Week 4	0.53	0.100	0.47	0.101	0.40	0.099	0.98	0.69
Week 8	0.78	0.121	0.33	0.121	0.33	0.120	0.04	0.04
Week 16	0.92	0.137	-0.17	0.138	-0.27	0.136	<0.01	<0.01
Week 24, Endpoint	0.93	0.156	-0.55	0.156	-0.60	0.155	<0.01	<0.01
Difference from placebo			-1.48	0.222	-1.53	0.219		
95% C.I.			(-1.97, -0.98)		(-2.02, -1.04)			

*Adjusted Least Squared Means by Dunnett procedure comparing all means with a control

^an=84 at Week 4

Figure 9 Change from Baseline in HbA_{1c} and FBG over Time – Study 012

Secondary Efficacy Variables

Fasting Blood Glucose

The LSM change from baseline to Week 24 in FBG was statistically significant between pioglitazone-treated patients and placebo patients ($p < 0.01$). The reduction in FBG was -61.83 mg/dL for the 7.5/15/30-mg group and -88.14 mg/dL for the 15/30/45-mg group comparing to the increase of 18.16 mg/dL of the placebo group, the difference were -61.83 mg/dL and -67.81 mg/dL for the two pioglitazone treatment groups, respectively (Table 21 & Fig 9.)

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Table 21 Adjusted* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=78		7.5/15/30 mg n=82 ^a		15/30/45 mg n=85 ^b		P ₃₅	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	279.2	7.50	268.0	7.34	281.1	7.21	0.45	0.98
Week 4	14.91	5.00	-12.56	4.95	-11.15	4.87	<0.01	<0.01
Week 8	16.06	5.28	-28.24	5.20	-27.98	5.12	<0.01	<0.01
Week 16	14.94	6.36	-38.97	6.27	-45.73	6.18	<0.01	<0.01
Week 24	18.16	6.55	-43.67	6.46	-49.65	6.36	<0.01	<0.01
Endpoint								
Difference from placebo, SE			-61.83	9.196	-67.81	9.125		
95% C.I.			(-82.32 -41.34)		(-88.14 -47.48)			

* Adjusted by Dunnett procedure comparing all means with a control

^an=81 at Week 4

^bn=84 at Week 4

Fasting C-Peptide & Insulin

At endpoint, fasting C-peptide and insulin were not different between pioglitazone groups and placebo group (Tables 22, 23 & Fig 10)

Table 22 Adjusted* LSM Change from Baseline in Fasting C-peptide (ng/mL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=78		7.5/15/30 mg n=80		15/30/45 mg n=83		P ₃₅	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	2.09	0.091	2.11	0.090	2.12	0.088	0.97	0.99
Week 4	-0.083	0.061	-0.040	0.061	-0.121	0.061	0.84	0.87
Week 8	-0.078	0.067	-0.066	0.067	-0.130	0.066	0.99	0.80
Week 16	-0.076	0.065	-0.159	0.066	-0.279	0.064	0.57	0.05
Week 24 Endpoint	-0.122	0.059	-0.164	0.059	-0.196	0.058	0.83	0.57
LSM Difference from placebo, SE			-0.042	0.083	-0.075	0.083		
95% C.I.			(-0.228 0.144)		(-0.258 0.109)			

* Adjusted by Dunnett procedure comparing all means with a control

^an=81 at Week 4 & n=83 at Week 8

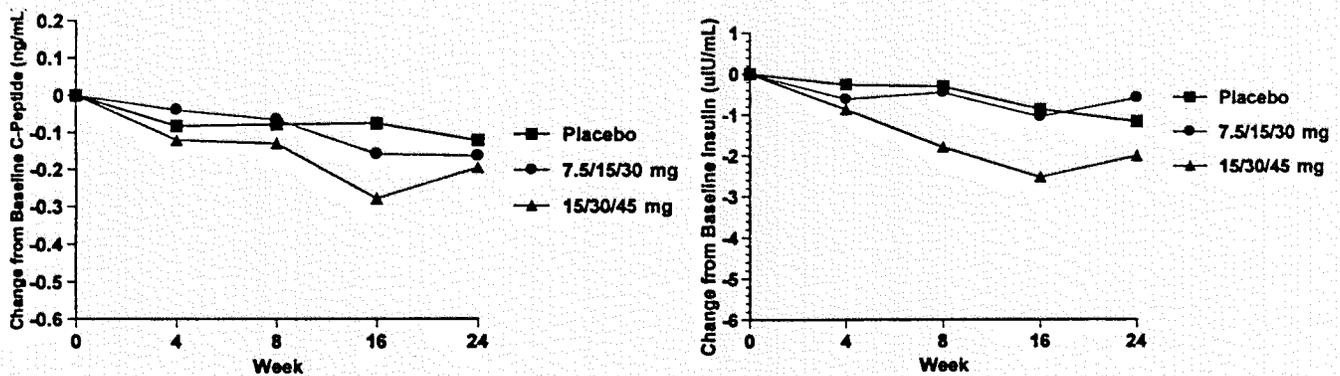
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Table 23 Adjusted* LSM Change from Baseline in Fasting Insulin (μ IU/mL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=78		7.5/15/30 mg n=80		15/30/45 mg n=83 ^a		P ₃₅	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	14.00	1.284	14.26	1.274	15.01	1.255	0.99	0.79
Week 4	-0.27	0.736	-0.63	0.739	-0.88	0.745	0.92	0.79
Week 8	-0.32	1.065	-0.46	1.068	-1.80	1.061	0.99	0.52
Week 16	-0.88	0.912	-1.06	0.914	-2.54	0.908	0.99	0.33
Week 24	-1.18	0.876	-0.60	0.878	-2.02	0.872	0.86	0.72
Difference from placebo			0.57	1.24	-0.85	1.24		
95% C.I.			(-2.19	3.34)	(-3.60	1.91)		

* Adjusted by Dunnett procedure comparing all means with a control
^an=81 at Week 4

Figure 10 Change from Baseline in C-Peptide and Insulin over Time – Study 012



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Lipids

The only statistically significant result in lipid outcome was in the 15/30/45 mg pioglitazone-treated patients in triglycerides at Week 24/endpoint. However, there were outliers in change from baseline triglycerides. When patients with change ≤ -500 mg/dL were deleted the p-value was 0.05 for the 15/30/45 mg group and 0.26 for the 7.5/15/30 mg group. Total cholesterol, HDL, and LDL were not significantly different from placebo. Tables 24-27 and Figure 11 display the results.

Table 24 Adjusted* LSM Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. Placebo	
	n=80		7.5/15/30 mg n=82		15/30/45 mg n=83		P ₃₀	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	303.8	35.50	286.7	25.22	327.1	35.06	0.92	0.85
Week 4	-6.66	21.97	-30.01	21.98	-65.09	22.02	0.67	0.11
Week 8	-22.72	17.88	-52.08	17.89	-77.40	17.92	0.40	0.06
Week 16	-9.04	18.25	-63.75	18.25	-94.42	18.28	0.06	<0.01
Week 24	-27.85	16.31	-63.55	16.31	-102.21	16.34	0.21	<0.01
Difference from placebo			-35.69	23.037	-74.35	23.116		
95% C.I.			(-87.05 15.67)		(-125.89 -22.82)			

* Adjusted by Dunnett procedure comparing all means with a control

Table 25 Adjusted* LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 012

Visit	Placebo		Pioglitazone				vs. placebo	
	n=80		7.5/15/30 mg n=82		15/30/45 mg n=83		P ₃₅	P ₄₅
	LSM	SE	LSM	SE	LSM	SE		
Baseline	227.3	5.69	211.6	5.64	219.3	5.61		
Week 4	3.83	3.51	2.04	3.522	1.28	3.505	0.91	0.83
Week 8	5.40	3.629	5.45	3.642	2.32	3.625	1.00	0.77
Week 16	5.70	3.759	8.12	3.772	2.92	3.754	0.86	0.82
Week 24	7.61	3.823	7.38	3.837	3.02	3.819	1.00	0.60
Difference from placebo			-0.23	5.436	-4.59	5.402		
95% C.I.			(-12.35 11.89)		(-16.63 7.46)			

* Adjusted by Dunnett procedure comparing all means with a control

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**Table 26 Adjusted* LSM Change from Baseline in HDL (mg/dL)
by Visit (LOCF) – Study 012**

Visit	Placebo			Pioglitazone						vs. placebo	
				7.5/15/30 mg			15/30/45 mg			P ₃₀	P ₄₅
	n	LSM	SE	n	LSM	SE	n	LSM	SE		
Baseline	77	43.40	1.22	79	41.20	1.21	81	39.80	1.20		
Week 4	75	0.18	0.83	78	0.79	0.81	79	1.83	0.82	0.91	0.83
Week 8	76	1.47	0.92	78	4.01	0.90	80	4.76	0.91	1.00	0.77
Week 16	76	0.85	0.97	79	3.97	0.95	80	4.52	0.96	0.86	0.82
Week 24	77	1.27	0.92	79	3.46	0.90	81	4.08	0.91	1.00	0.60
Difference from placebo					2.19	1.287		2.81	1.303		
95% C.I.					(-0.68	5.06)		(-0.10	5.71)		

* Adjusted by Dunnett procedure comparing all means with a control

Table 27 Adjusted* LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 012

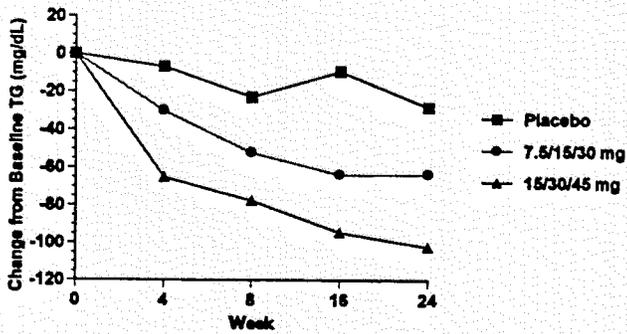
Visit	Placebo			Pioglitazone							
				7.5/15/30 mg				15/30/45 mg			
	n	LSM	SE	n	LSM	SE	p	n	LSM	SE	p
Baseline	65	136.50	4.38	62	121.80	4.53	0.04	65	124.10	4.47	0.09
Week 4	62	4.71	2.88	60	4.25	3.01	0.99	61	8.40	3.14	0.60
Week 8	61	6.32	3.06	59	5.67	3.22	0.99	65	9.89	3.17	0.64
Week 16	61	4.08	3.38	60	8.86	3.36	0.51	65	10.27	3.41	0.34
Week 24	64	8.01	3.14	59	8.51	3.38	0.99	63	10.60	3.48	0.81
LSM Difference from placebo, SE					0.50	4.665			2.59	4.728	
95% C.I.					(-9.95	10.95)			(-8.00	13.18)	

* Adjusted by Dunnett procedure comparing all means with a control

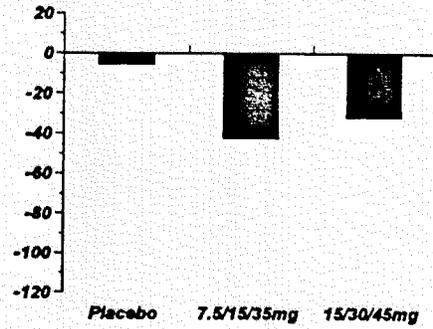
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Figure 11 Change from Baseline in Triglycerides, Total Cholesterol, HDL, & LDL – Study 012

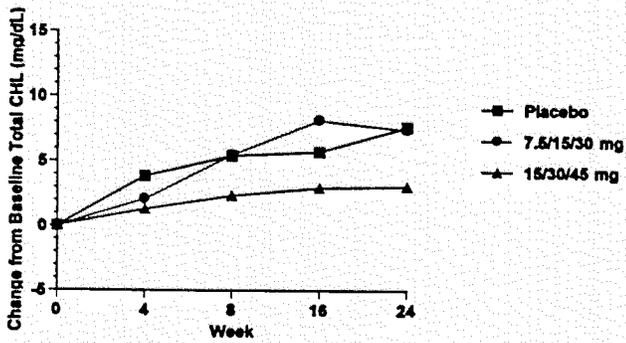
Triglycerides



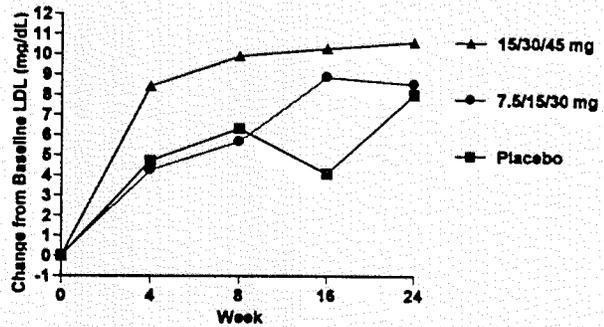
Endpoint Median Triglycerides



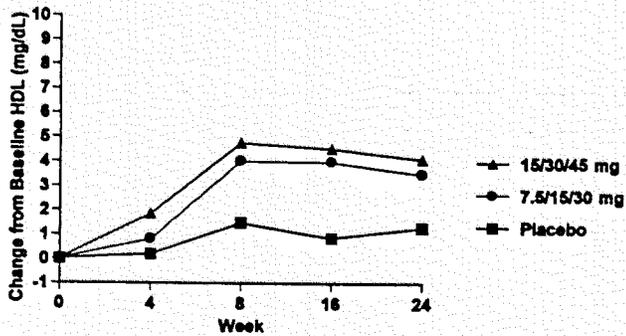
Total Cholesterol



LDL



HDL



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Body Weight

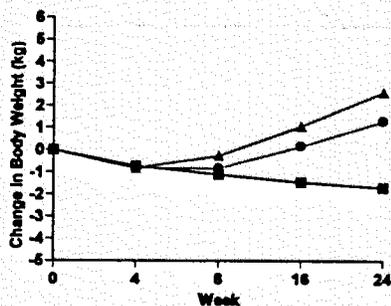
Table 28 displays mean change in body weight for completers over time and at endpoint. At week 24 and endpoint, body weight were significantly increased ($p < 0.01$) in both the pioglitazone treatment groups when compared to placebo group.

Table 28 Mean Change from Baseline in Body Weight (kg) by Visit (Completers) & Endpoint (LOCF) – Study 012

Visit	Placebo		Pioglitazone			
	n=50		7.5/15/30 mg n=62		15/30/45 mg n=65	
	LSM	SE	LSM	SE	LSM	SE
Baseline	91.55	2.46	91.54	2.22	92.53	1.86
Week 4	-0.74	0.23	-0.82	0.20	-0.84	0.21
Week 8	-1.12	0.30	-0.85	0.30	-0.28	0.26
Week 16	-1.46	0.39	0.14	0.43	1.04	0.31
Week 24	-1.70	0.42	1.27	0.48	2.58	0.41
Endpoint*	-1.81	0.37	0.49	0.36	1.82	0.36
Difference from placebo, Wk 24			2.98	0.64	4.28	0.63
95% C.I.			(1.71 4.24)		(3.04 5.53)	

* $n_p=83$, $n_{30}=87$, $n_{45}=89$

Figure 12 Mean Change from Baseline in Body Weight (kg) Completers – Study 012



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Subgroup Analysis

Change from baseline to endpoint in HbA_{1c} was examined in gender, age, and use of previous antidiabetic medications using the LOCF data of the ITT population. The interaction between treatment and subgroup was evaluated by ANOVA with treatment, subgroup, center, and treatment-by-subgroup interaction terms in the model.

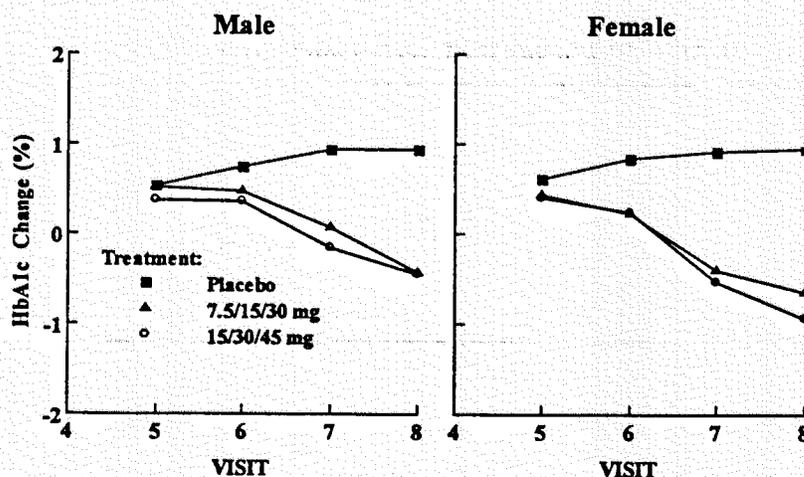
Gender

Table 29 and Figure 13 display the mean changes from baseline in HbA_{1c} at endpoint by gender. The treatment-by-gender interaction was not significant (p=0.72.)

Table 29 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Gender (LOCF) – Study 012

Subgroup	Placebo	Pioglitazone	
		7.5/15/30 mg	15/30/45 mg
Men			
n	45	48	48
Baseline Mean	10.38	10.11	10.72
Mean Change	0.93	-0.43	-0.45
SE	0.18	0.21	0.22
Women			
n	38	37	37
Baseline Mean	11.13	10.66	10.71
Mean Change	0.95	-0.65	-0.94
SE	0.21	0.26	0.21

Figure 13 Mean Change from Baseline in HbA_{1c} (%) by Gender



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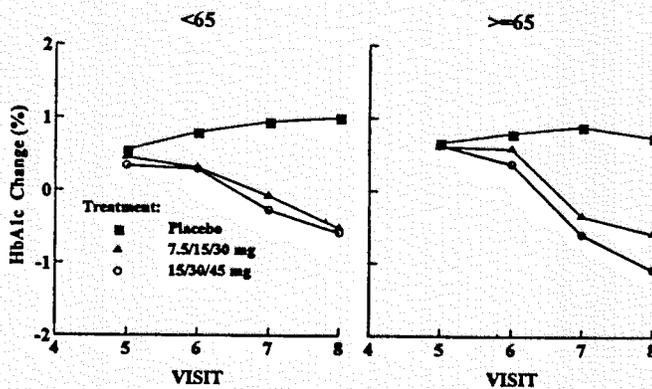
Age

Table 30 and Figure 14 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=0.42).

Table 30 Mean Change from Baseline in HbA_{1c} (%) at Endpoint by Age Group – Study 012

Subgroup	Placebo	Pioglitazone	
		7.5/15/30 mg	15/30/45 mg
<65 years old			
n	63	66	71
Baseline Mean	10.75	10.37	10.85
Mean Change	1.00	-0.52	-0.58
SE	0.15	0.17	0.18
≥65 years old			
n	20	19	14
Baseline Mean	10.63	10.28	10.04
Mean Change	0.75	-0.57	-1.08
SE	0.32	0.43	0.29

Figure 14 Mean Change from Baseline in HbA_{1c} (%) by Age



Previous Antidiabetic Medication

Table 31 and Figure 15 display the mean change in HbA_{1c} by previous antidiabetic medication. The p-value for treatment-by-previous medication interaction was 0.075.

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