CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021073

STATISTICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINSTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUN 17 1999

FROM: Mathematical Statistician (HFD-715)

THRU: Edward Nevius, Ph.D. /S/ 6-17-99
Director, Division of Biometrics II. (HFD-715)

SUBJECT: Revised Package Insert for ACTOS® (Pioglitazone)

APPLICANT: Takeda America Research & Development Center, Inc.

TO: File (NDA 21-073)

Reviewer's Comments:

1. The Monotherapy subsection of the Clinical Studies section of the revised package insert dated May 28, 1999, presents results from a subgroup of randomized patients who were not previously treated with antidiabetic medication (naïve patients).

   The estimators from the 3 monotherapy studies at endpoint in HbA_{1c} are displayed in the following table for all randomized patients and naïve patients.

   Mean Treatment Difference from Placebo in HbA_{1c} for All Randomized Patients and Patients Not Previously Treated with Antidiabetic Medications

HbA_{1c} (%)	ACTOS					
	15 mg		30 mg		45 mg	
Study 01	N	Difference	N	Difference	N	Difference
Randomized	79	**-1.0**	85	**-1.0**	76	**-1.6**
Naïve	26	**-1.4**	26	**-1.3**	21	**-2.6**
Study 12			7.5/15/30 mg		15/30/45 mg	
Randomized			85	**-1.5**	85	**-1.5**
Naïve			20	**-2.3**	20	**-2.6**
Study 26			30 mg			
Randomized			100	**-1.4**		
Naïve			39	**-1.0**		

   Treatment differences for patients who were not previously treated with antidiabetic medications were greater than those for all randomized patients for the 45 mg pioglitazone treatment group (**-2.6%** vs. **–1.6%**) which had only ~20 patients. It seems reasonable to make the label consistent with the Avandia label, which presented monotherapy data for all randomized patients. Presenting only the naive patients in the label gives the sponsor an advantage in the effect size of the HbA_{1c} and FBG reduction.

2. For Monotherapy studies, using the first study as an example, this reviewer proposes to revise the text and to present the efficacy outcome in a table that follows:

> In a 26-week dose ranging study, 408 patients were randomized to receive 7.5, 15, 30, or 45 mg of ACTOS, or placebo of which 125 patients had not been previously treated with antidiabetic medication. The 7.5 mg dose was not statistically significant from placebo. At endpoint, treatment with 15 to 45 mg of ACTOS produced statistically significant improvement in HbA_{1c} and FBG compared with patients who received placebo (see Table 1).

Table 1. Monotherapy: 26-Week Study Mean Change from Baseline

		ACTOS		
	Placebo	15 mg	30 mg	45 mg
N	79	79	85	76
HbA_{1c} (%)				
Mean Baseline	10.4	10.2	10.2	10.3
Mean Change from Baseline	+0.7	-0.3	-0.3	-0.9
Mean Difference from Placebo	-	-1.0	-1.0	-1.6
FBG (mg/dL)				
Mean Baseline	268	267	269	276
Mean Change from Baseline	+9	-30	-32	-56
Mean Difference from Placebo	-	-39	-41	-65

3. This applies to all the sponsor's bar graphs that only presented the treatment differences from placebo for the pioglitazone treatment groups. This reviewer suggests that the change from **baseline** for all treatment groups (**placebo** and the pioglitazone treatment groups) should be presented.

4. On page 9, the sponsor claims all three monotherapy studies indicate that maximal reduction in HbA_{1c} levels may not have been achieved by the end of the study. This statement is a speculation and should be removed.

On page 9, the purpose of the statement "In general, patients who had not been previously treated with antidiabetic medication whose FBG decreased ≥30 mg/dL had an HbA_{1c} decrease of ≥0.5%. Furthermore, approximately one-third of patients whose FBG did not decrease by at least 30 mg/dL also showed a decrease in HbA_{1c} of >0.6%." is unclear.

/S/ [redacted]

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Todd Sahlroot /S/ [redacted] 6/17/99

cc:
Arch NDA 21-073
HFD-510
HFD-510/SSobel, SMalozowski, RMisbin, JWeber
HFD-715/ENevius, TSahlroot, LPian, Division 2 file
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APPEARS THIS WAY ON ORIGINAL

Statistical Review and Evaluation
Clinical Studies

NDA#: 21-073 JUN 17 1999

Applicant: Takeda America Research & Development Center, Inc.

Name of Drug: Actos® (pioglitazone HCl) Tablets

Indication: Type 2 Diabetes

Document Reviewed: 1.001, 1.002, 1.250-1.368
Submission dated January 15, 1999

Medical Reviewer: This review has been discussed with the clinical reviewer, Robert Misbin M.D. (HFD-510)

1. Introduction

Pioglitazone, a thiazolidinedione compound belongs to a class of drugs that act primarily to decrease insulin resistance. In this submission, there were 11 controlled trials (6 monotherapy & 5 add-on therapy) to support the indication of glycemic control in patients with type 2 diabetes. Three U.S. monotherapy and 3 U.S. add-on trials were designated as pivotal. This review discusses the 6 U.S. trials.

2. Monotherapy Trials

General Design

The 6 trials were all double-blind, randomized, placebo-controlled, multicenter studies as summarized in Table 1. The 3 U.S. protocols (& amendments) included patients 30-75 years of age, with a BMI of 25-40 kg/m^2, C-peptide>1 ng/ml at visit 1, a normal thyroid function, weight-maintaining diet, FBG ≥140 mg/dL at Visit 1, HbA_{1c} ≥7.0% at Visit 4 (001), HbA_{1c} ≥7.5% and ≥8.0% at visit 3 (012, 026). Pertinent criteria for removal of patients from study therapy were protocol violation, AEs that, in the opinion if the investigator, required early termination, noncompliance, insufficient therapeutic effect, including FBG>400 mg/dL at 2 consecutive study visits, or which presented a safety risk to the patient, in the investigator's opinion, the development of ketoacidosis, LVH, or anemia.

The studies enrolled both naive patients and patients on antidiabetic medication. Before randomization, patients entered a single-blind placebo period (6 weeks) to washout their prior antidiabetic medication (naive patients entered without washout.)

The primary efficacy variable was change from baseline in HbA_{1c}. The secondary efficacy variables in common were FBG, fasting C-peptide, fasting insulin, triglycerides, and cholesterol (total, HDL, and LDL).

Table 1 Brief Summary of Monotherapy Trials

Study ID	# of Centers	Total Sample Size & Treatment Groups	Design	Duration of Treatment
PNFP-001	US 35	408 placebo 7.5, 15, 30, & 40 mg	fixed-dose, dose-ranging phase 2/3	26 weeks 12/15/95 - 3/13/98
PNFP-012	US 32	260 placebo 7.5 → 15 → 30 mg 15 → 30 → 45 mg	forced dose-titration	24 weeks 1/30/97 - 6/01/98
PNFP-026	US 27	197 placebo, 30 mg	fixed-dose	16 weeks 8/14/97 - 7/14/98
EC-201	Germany 59	235 placebo, 15 mg, 30 mg	fixed-dose	26 weeks
CCT-001 (PD-191)	Japan Kaneko	234 placebo, 15, 30, 45 mg	fixed-dose	12 weeks
CCT-011 (PD-193)	Japan Kaneko	134 placebo, 30 mg	fixed-dose	12 weeks

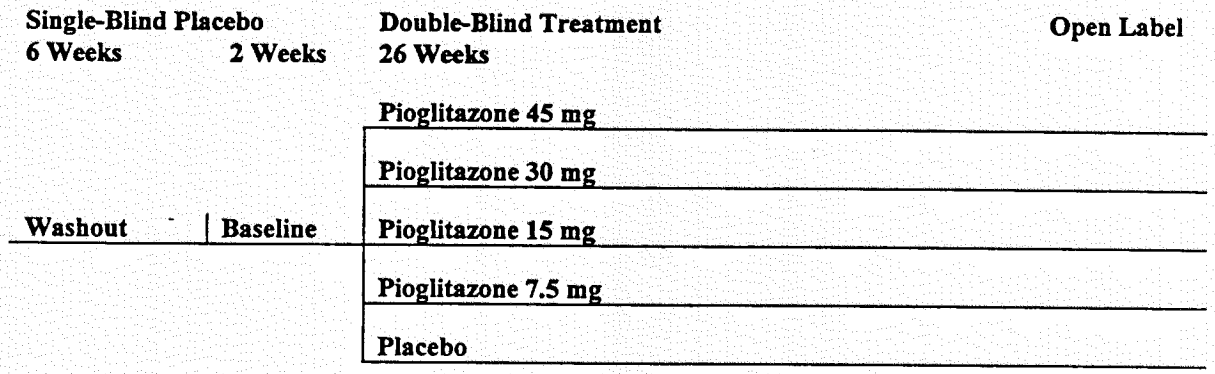
Statistical Plan

Small centers were pooled before unblinding the treatment code. Centers were considered small if the enrollment was < ½ that of the largest center.

The primary analysis for the efficacy variables was on the LOCF dataset of the intent-to-treat population. For a given variable it included patients who were randomized, received at least one dose of the study medication and had a baseline and at least 1 follow-up assessment. Comparison between each pioglitazone treatment group and placebo group was adjusted by Dunnett procedure for multiple pioglitazone dose groups. The analysis of covariance model included terms of treatment, pooled center, and treatment-by-pooled center interaction and baseline value as covariate.

Study PNFP-001 (26 Weeks)

This was a double-blind, randomized, placebo-controlled, multicenter study of 7.5, 15, 30, 45 mg QD of pioglitazone for 26 weeks in type 2 diabetes following a 6-week placebo washout period (previous antidiabetic medications) and 2-week placebo baseline period. Patients had an option to enter a long-term, open-label extension after the double-blind phase. The sponsor will summarize the results from the open-label extension in a separate report.



Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13
Week	-8	-4	-2	Day 0	Day 0	2	4	6	10	14	18	22	26

There were 14 scheduled visits including 4 during placebo washout and baseline period, 9 during double-blind treatment period and a follow-up visit (7-14 days after last dose) for patients who did not enter an open-label extension.

In addition to the above planned model and analysis, the sponsor performed three additional efficacy evaluations on:

1. Proportion of patients with $HbA_{1c} \leq 6.1\%$ at endpoint or a 0.6% decrease in HbA_{1c} from baseline to endpoint and Patients were classified by FBG levels into 3 categories of <140 mg/dL, between 140 and 200 mg/dL and >200 mg/dL at endpoint.
2. A subgroup analysis of the change from baseline in HbA_{1c} in patients enrolled before and after August 7, 1996 (Amendment 4 in effect)
3. A subgroup analysis of changes from baseline in HbA_{1c} and FBG based on prior antidiabetic medication use.

For patients whose triglyceride levels > 400 mg/dL at a given visit, the LDL-cholesterol was not calculated. As a result, the number of patients in the LDL analysis was small and the least square means were not estimable with the full model. Therefore, a reduced model without the interaction term was used in the LDL analysis.

Patient Disposition

A total of 965 patients signed an ICF including 29 patients who signed twice (15 were randomized.) Of the 955 patients who entered single-blind period, 408 patients were randomized 79, 81, 81, 87, 80 to the placebo, 7.5 mg, 15 mg, 30, mg and 45 mg treatment group, respectively. Fifty percent (n=202) patients completed the study. The most common reason for withdrawal was insufficient therapeutic effect. Including therapy related withdrawal (hyperglycemia, unhappy with the glucose control), the rates were 49% (39/79), 37% (28/81), 33% (27/81), 33% (29/87), and 29% (23/80) for the groups from placebo to 45 mg pioglitazone. Table 2 displays patient disposition and Table 3 the number of patients discontinued over time.

Table 2 Patient Disposition – Study 001

	Placebo	7.5 mg	15 mg	30 mg	45 mg
Randomized	79	81	81	87	80
Withdrawn	48 (61%)	38 (47%)	45 (56%)	41 (47%)	34 (43%)
Lack of Efficacy	32 (41%)	21 (26%)	23 (28%)	24 (28%)	20 (25%)
Adverse Event	6 (8%)	5 (6%)	4 (5%)	7 (8%)	6 (8%)
Withdrew Consent	7 (9%)	7 (9%)	10 (12%)	6 (7%)	4 (5%)
Lost to Follow-up	0	1 (1%)	4 (5%)	3 (3%)	2 (2%)
Non-Compliance	1 (1%)	0	1 (1%)	0	1 (1%)
Protocol Violation	1 (1%)	3 (4%)	0	1 (1%)	0
Inclusion/Exclusion	0	0	1 (1%)	0	0
Other	1 (1%)	1 (1%)	2 (2%)	0	1 (1%)
Completed	31 (39%)	43 (53%)	36 (44%)	46 (53%)	46 (57%)

Table 3 Patient Discontinuation by Time – Study 001

	Placebo	7.5 mg	15 mg	30 mg	45 mg	Total
Randomized	79	81	81	87	80	408
Completed	31 (39%)	43 (53%)	36 (44%)	46 (53%)	46 (57%)	202 (49%)
Withdrawn	48 (61%)	38 (47%)	45 (56%)	41 (47%)	34 (43%)	206 (51%)
≤Week 4	5	8	11	8	8	40 (10%)
>Week 4 & ≤Week 8	18	11	13	11	8	61 (15%)
>Week 8 & ≤Week 12	12	12	8	9	5	46 (11%)
>Week 12 & ≤Week 16	7	3	3	6	7	26 (6%)
>Week 16 & ≤Week 24	6	3	9	6	5	29 (7%)
>Week 24	0	1	1	1	1	4 (1%)

Patient Demographics and Baseline Characteristics

Most patients were Caucasian (78%). Fifty eight (58%) percent were male patients. The mean age was 54 years. The average weight was 91 kg and the mean body mass index was 31 kg/m^2. At baseline, the mean HbA_{1c} was 10.19% and the mean fasting plasma glucose was 268 mg/dL. The mean values of the primary and secondary variables at baseline are presented in Table 4. The baseline values were not significantly different among the treatment groups except LDL ($p<0.1$).

Table 4 Mean at Baseline in Efficacy Variables – Study 001

	Placebo n=79[a]		7.5 mg n=81[b]		15 mg n=81		30 mg n=87		45 mg n=80		Overall p-value[*]
	MEAN	SE	MEAN	SE	MEAN	SE	MEAN	SE	MEAN	SE	
HbA_{1c}	10.38	1.99	10.03	1.73	10.15	2.08	10.11	2.15	10.31	1.80	0.812
FBG (mg/dL)	267.1	70.49	262.1	69.12	268.2	75.30	267.6	77.67	275.4	69.09	0.872
Fasting C-Peptide(ng/mL)	2.06	0.95	2.17	0.76	2.11	0.74	2.16	0.96	2.02	0.71	0.779
Fasting Insulin (μIU/mL)	15.07	12.32	17.85	14.10	15.37	10.15	18.15	19.196	14.98	10.13	0.393
Triglycerides (mg/dL)	262.0	196.9	313.6	538.7	282.3	231.7	261.9	186.2	287.8	249.2	0.781
Total Cholesterol	224.1	43.18	213.3	61.17	218.7	42.93	222.5	46.69	216.1	45.93	0.608
HDL (mg/dL)	41.6	10.81	40.8	11.01	40.3	10.52	40.8	10.35	40.3	11.82	0.913
LDL (mg/dL)	n=67		n=68		n=66		n=76		n=65		
	139.0	38.26	122.6	27.49	130.2	36.45	135.0	43.09	127.3	35.23	0.071

[*] p-values based on treatment and pooled center in ANOVA model
[a] n=78, C-peptide, Insulin
[b] n=80, HDL
[c] n=86, HDL
[d] n=79, HbA_{1c}, C-peptide, Insulin

Ninety-five percent (95%) of patients were 80% to 120% compliant with the study medication. Of the 408 patients, 281 (69%) patients received prior antidiabetic medications (58>1 medication.)

Efficacy Results - Study 001

Primary Efficacy Variable - HbA_{1c} Change from baseline to Week 26

During the treatment phase, HbA_{1c} was measured at Weeks 2, 6, 10, 14, 18, 22 and 26. Table 5 displays the results of covariance analysis with baseline HbA_{1c} as covariate plus treatment, center and treatment-by-center interaction in the model. From Dunnett adjusted LSM result, it showed that at Week 26 /endpoint, there were statistically significant greater reductions of HbA_{1c} in 15 mg, 30 mg and 45 mg pioglitazone-treated patients than placebo-treated patients. The treatment difference was -1.01%, -1.03%, and -1.60%, for the 15mg, 30 mg and 45 mg pioglitazone-treated

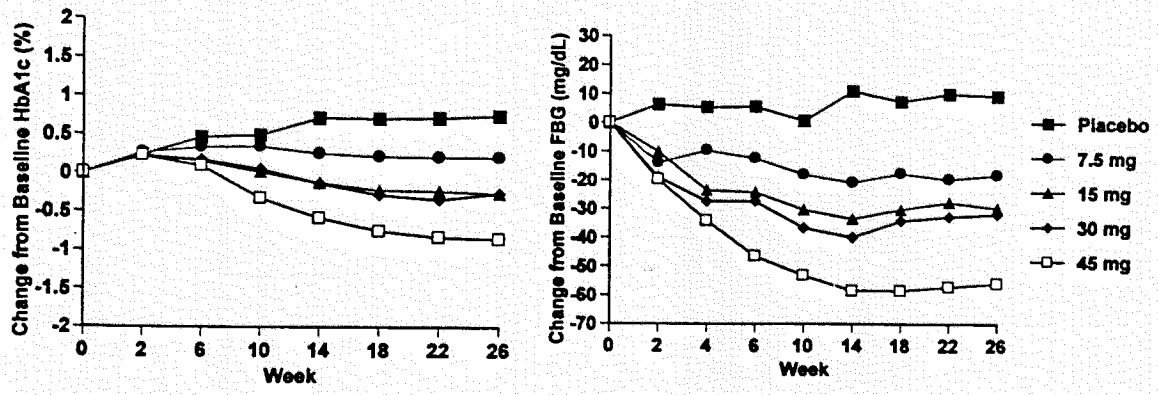
patients, respectively. The LSM change from baseline in HbA_{1c} value by visit week is displayed in Table 5 & Figure 1.

Table 5 Adjusted LSM* Change from Baseline in HbA_{1c} (%) by Visit (LOCF) – Study 001

Visit	Placebo n=79[a]		Pioglitazone 7.5 mg n=80		Pioglitazone 15 mg n=79[a]		Pioglitazone 30 mg n=85[b]		Pioglitazone 45 mg n=76		p-value vs. placebo $P_{7.5}$	P_{15}	P_{30}	P_{45}
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	10.41	0.218	10.04	0.217	10.23	0.218	10.15	0.211	10.34	0.223	0.58	0.94	0.82	1.00
Week 2	0.23	0.064	0.26	0.063	0.23	0.064	0.22	0.062	0.22	0.066	1.00	1.00	1.00	1.00
Week 6	0.46	0.106	0.33	0.106	0.15	0.107	0.17	0.104	0.09	0.110	0.78	0.12	0.16	0.05
Week 10	0.49	0.135	0.34	0.135	0.01	0.136	0.05	0.132	-0.33	0.140	0.86	0.05	0.07	<0.01
Week 14	0.71	0.147	0.25	0.147	-0.13	0.148	-0.14	0.144	-0.59	0.152	0.09	<0.01	<0.01	<0.01
Week 18	0.70	0.159	0.21	0.159	-0.23	0.160	-0.29	0.155	-0.76	0.165	0.10	<0.01	<0.01	<0.01
Week 22	0.71	0.165	0.20	0.166	-0.24	0.167	-0.35	0.162	-0.84	0.172	0.09	<0.01	<0.01	<0.01
Week 26 Endpoint	0.74	0.169	0.20	0.170	-0.27	0.170	-0.27	0.165	-0.86	0.175	0.08	<0.01	<0.01	<0.01
Difference from placebo			-0.54	0.24	-1.00	0.24	-1.00	0.24	-1.60	0.24				
95% C.I.			(-1.13	0.05)	(-1.59	-0.42)	(-1.58	-0.42)	(-2.19	-1.00)				

* Least Squared Means Adjusted by Dunnett procedure comparing all means with a control
[a]n=78, [b]n=84 at Week 2

Figure 1 Change from Baseline in HbA_{1c} and FBG over Time – Study 001



Secondary Efficacy Variables

Fasting Blood Glucose (FBG)

The LSM change from baseline to Week 26 was statistically significantly different from placebo for all pioglitazone groups (Table 4). The treatment effects compared to placebo were -27.5, -39.1, -41.2, and -65.3 mg/dL for the 4 pioglitazone groups (Table 6 & Fig 1.)

Table 6 Adjusted* LSM Change from Baseline in FBG (mg/dL) by Visit (LOCF) – Study 001

Visit	Placebo n=79		Pioglitazone 7.5 mg n=80[a]		15 mg n=79[b]		30 mg n=84[c]		45 mg n=77		p-value vs. placebo $P_{7.5}$	P_{15}	P_{30}	P_{45}
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	268.1	7.93	263.2	7.90	267.0	7.94	269.4	7.72	275.5	8.05	0.98	1.00	1.00	0.86
Week 2	6.43	4.50	-13.95	4.56	-10.01	4.61	-18.99	4.51	-19.78	4.62	0.58	0.94	0.82	1.00
Week 4	5.46	4.83	-9.60	4.86	-23.56	4.91	-27.41	4.78	-34.16	4.96	0.01	0.04	<0.01	<0.01
Week 6	5.66	5.43	-12.32	5.47	-24.18	5.49	-27.37	5.38	-46.36	5.58	0.07	<0.01	<0.01	<0.01
Week 10	0.76	6.02	-17.95	6.06	-30.28	6.08	-36.62	5.97	-53.09	6.19	0.10	<0.01	<0.01	<0.01
Week 14	11.09	6.37	-20.77	6.41	-33.44	6.43	-39.91	6.31	-58.47	6.54	<0.01	<0.01	<0.01	<0.01
Week 18	7.51	6.61	-17.54	6.65	-30.22	6.67	-34.12	6.55	-58.44	6.78	0.02	<0.01	<0.01	<0.01
Week 22	10.16	6.80	-19.60	6.84	-27.68	6.86	-32.67	6.73	-57.16	6.98	0.01	<0.01	<0.01	<0.01
Week 26	9.42	6.72	-18.11	6.77	-29.65	6.78	-31.76	6.66	-55.90	6.90	**0.02**	**<0.01**	**<0.01**	**<0.01**
Difference from placebo			-27.53	9.54	-39.07	9.55	-41.18	9.46	-65.32	9.63				
95% C.I.			-50.96	-4.11	-62.52	-15.62	-64.41	-17.95	-88.97	-41.67				

* Adjusted by Dunnett procedure comparing all means with a control
[a]n=79, [c]n=82 at Week 2, [b]n=77 at Week 2 & n=78 at Week 4

Fasting C-Peptide & Insulin

Changes from baseline to Week 26 for fasting C-peptide and insulin were not statistically different from placebo in any of the pioglitazone-treated group. Changes of C-peptide and insulin over time are displayed in Tables 7 and 8, respectively and Figure 2.

Table 7 Adjusted LSM* Change from Baseline in C-Peptide (ng/ml) by Visit (LOCF) – Study 001

Visit	Placebo n=78		Pioglitazone 7.5 mg n=80[a]		15 mg n=79[b]		30 mg n=84[c]		45 mg n=76[d]		p-value vs. placebo $P_{7.5}$	P_{15}	P_{30}	P_{45}
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	2.04	0.09	2.15	0.09	2.10	0.09	2.17	0.09	1.99	0.10	0.81	0.98	0.75	0.98
Week 2	0.06	0.07	0.06	0.07	-0.03	0.07	-0.18	0.07	-0.23	0.07	1.00	0.72	0.06	0.01
Week 6	-0.06	0.06	0.02	0.06	-0.12	0.06	-0.13	0.06	-0.27	0.06	0.73	0.82	0.74	0.02
Week 10	-0.08	0.06	0.02	0.06	-0.08	0.06	-0.16	0.06	-0.24	0.06	0.68	1.00	0.77	0.22
Week 14	-0.09	0.06	0.01	0.06	-0.03	0.06	-0.23	0.06	-0.32	0.06	0.61	0.88	0.32	0.04
Week 18	-0.06	0.06	0.01	0.06	-0.05	0.06	-0.14	0.06	-0.23	0.06	0.84	1.00	0.80	0.22
Week 22	-0.06	0.07	0.02	0.07	-0.06	0.07	-0.18	0.06	-0.18	0.07	0.87	1.00	0.51	0.59
Week 26	-0.05	0.07	0.03	0.07	-0.02	0.07	-0.13	0.07	-0.05	0.07	**0.84**	**0.99**	**0.83**	**1.00**
Difference from placebo			0.08	0.10	0.03	0.10	-0.08	0.10	0.00	0.10				
95% C.I.			(-0.17	0.33)	(-0.22	0.28)	(-0.33	0.16)	(-0.25	0.25)				

* Adjusted by Dunnett procedure comparing all means with a control
[a]n=79, [b]n=78, [c]n=83, [d]n=74 at Week 2

Figure 2 Change from Baseline in C-Peptide and Insulin over Time – Study 001

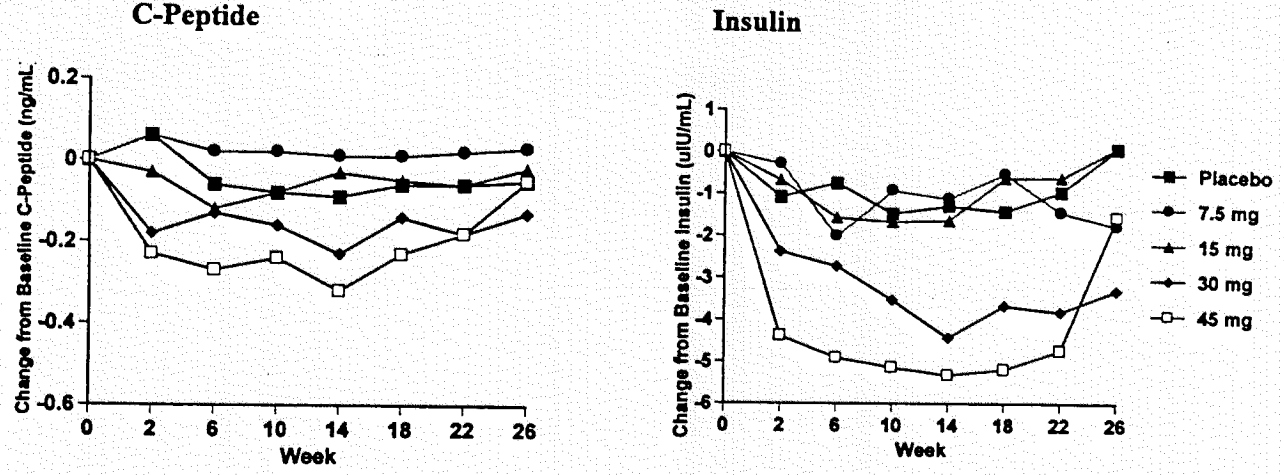


Table 8 Adjusted LSM* Change from Baseline in Fasting Insulin (μIU/ml) by Visit (LOCF) – Study 001

Visit	Placebo n=78		Pioglitazone 7.5 mg n=80[a]		Pioglitazone 15 mg n=79[b]		Pioglitazone 30 mg n=84[c]		Pioglitazone 45 mg n=76[d]		p-value vs. placebo $P_{7.5}$	P_{15}	P_{30}	P_{45}
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	14.83	1.58	17.67	1.56	15.15	1.57	18.38	1.53	15.06	1.60	0.50	1.00	0.30	1.00
Week 2	-1.08	1.16	-0.29	1.16	-0.68	1.16	-2.38	1.13	-4.39	1.24	0.97	1.00	0.84	0.16
Week 6	-0.75	0.89	-2.01	0.88	-1.57	0.88	-2.73	0.87	-4.91	0.90	0.69	0.91	0.30	<0.01
Week 10	-1.47	0.89	-0.92	0.88	-1.67	0.88	-3.53	0.87	-5.14	0.90	0.98	0.98	0.25	0.01
Week 14	-1.29	0.78	-1.11	0.77	-1.63	0.78	-4.43	0.76	-5.32	0.79	1.00	0.99	0.02	<0.01
Week 18	-1.42	0.83	-0.53	0.82	-0.63	0.82	-3.67	0.81	-5.19	0.84	0.86	0.90	0.17	0.01
Week 22	-0.95	0.93	-1.44	0.92	-0.62	0.92	-3.81	0.91	-4.74	0.94	0.99	1.00	0.10	0.02
Week 26	0.08	1.29	-1.76	1.27	0.10	1.28	-3.30	1.26	-1.55	1.30	0.70	1.00	0.19	0.78
Difference from placebo			-1.84	1.81	0.02	1.81	-3.38	1.80	-1.63	1.83				
95% C.I.			(-6.29	2.61)	(-4.43	4.47)	(-7.80	1.05)	(-6.11	2.86)				

* Adjusted by Dunnett procedure comparing all means with a control
[a]n=79, [b]n=78, [c]n=73 at Week 2

Lipids

The lipids of pioglitazone-treated patients were not different from placebo-treated patients in triglycerides, total cholesterol, and LDL at Week 26. Change from baseline in HDL was significant different from placebo in HDL for 45 mg pioglitazone-treated patients at Week 26. Tables 9-12 and Figure 3 display the changes over time in lipids and median values at endpoint for triglycerides.

Table 9 Adjusted LSM* Change from Baseline in Triglycerides (mg/dL) by Visit (LOCF) – Study 001

Visit	Placebo n=79		Pioglitazone 7.5 mg n=80		Pioglitazone 15 mg n=79[a]		Pioglitazone 30 mg n=84		Pioglitazone 45 mg n=77		p-value vs. placebo $P_{7.5}$	P_{15}	P_{30}	P_{45}
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	262.8	34.35	319.0	34.23	283.8	34.40	261.1	33.44	259.7	34.87	0.59	0.98	1.00	1.00
Week 2	6.95	14.45	-34.02	14.57	-18.25	14.70	-17.31	14.32	-35.04	14.81	0.15	0.55	0.58	0.14
Week 6	-19.07	13.81	-44.67	13.91	-71.99	13.93	-49.71	13.68	-77.27	14.15	0.50	0.03	0.33	0.01
Week 10	-21.60	15.03	-63.62	15.14	-54.78	15.17	-49.25	14.89	-74.09	15.40	0.16	0.34	0.49	0.05
Week 14	-30.99	13.58	-52.36	13.68	-59.97	13.70	-45.85	13.45	-69.97	13.91	0.64	0.37	0.85	0.14
Week 18	-28.28	13.58	-45.87	13.68	-58.33	13.70	-40.45	13.45	-65.47	13.91	0.77	0.34	0.92	0.17
Week 22	-25.17	13.74	-44.50	13.84	-54.06	13.86	-40.90	13.61	-53.94	14.07	0.72	0.38	0.83	0.39
Week 26	-20.97	13.70	-30.43	13.80	-53.79	13.82	-39.34	13.57	-48.05	14.03	**0.97**	**0.27**	**0.74**	**0.44**
Difference from placebo			-9.46	19.46	-32.82	19.46	-18.37	19.28	-27.08	19.61				
95% C.I.			(-57.25	38.32)	(-80.62	14.98)	(-65.70	28.97)	(-75.23	21.07)				

* Adjusted by Dunnett procedure comparing all means with a control

[a] n=78 at Week 2

Table 10 Adjusted* LSM Change from Baseline in Total Cholesterol (mg/dL) by Visit (LOCF) – Study 001

Visit	Placebo n=79		Pioglitazone 7.5 mg n=80		Pioglitazone 15 mg n=79[a]		Pioglitazone 30 mg n=84		Pioglitazone 45 mg n=77		p-value vs. placebo $P_{7.5}$	P_{15}	P_{30}	P_{45}
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	224.6	5.44	214.5	5.42	220.0	5.45	222.7	5.29	213.7	5.52	0.47	0.93	1.00	0.42
Week 2	0.73	2.69	-0.10	2.70	8.43	2.72	3.75	2.66	4.75	2.75	1.00	0.14	0.84	0.68
Week 6	3.74	3.12	-2.10	3.13	3.18	3.14	3.22	3.08	4.36	3.19	0.49	1.00	1.00	1.00
Week 10	7.06	3.54	-1.78	3.55	2.72	3.56	4.05	3.50	7.52	3.62	0.24	0.80	0.93	1.00
Week 14	7.60	3.41	-1.14	3.42	2.78	3.43	9.29	3.37	6.38	3.49	0.22	0.71	0.99	1.00
Week 18	4.29	3.31	1.57	3.32	6.19	3.33	5.87	3.27	6.82	3.38	0.94	0.98	0.99	0.96
Week 22	7.98	3.48	-2.06	3.49	4.32	3.50	5.52	3.44	8.68	3.56	0.14	0.87	0.96	1.00
Week 26	8.43	3.40	1.50	3.41	8.11	3.42	6.08	3.36	10.27	3.48	**0.41**	**1.00**	**0.97**	**0.99**
Difference from placebo			-6.93	4.83	-0.32	4.82	-2.35	4.77	1.85	4.88				
95% C.I.			(-18.78	4.92)	(-12.17	11.52)	(-14.07	9.37)	(-10.12	13.82)				

* Adjusted by Dunnett procedure comparing all means with a control

[a] n=78 at Week 2

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Table 11 Adjusted* LSM Change from Baseline in HDL (mg/dL) by Visit (LOCF) – Study 001

Visit	Placebo n=79		Pioglitazone 7.5 mg n=79[a]		15 mg n=79[b]		30 mg n=83		45 mg n=77[c]		p-value vs. placebo $P_{7.5}$	P_{15}	P_{30}	P_{45}
	LSM	SE	LSM	SE	LSM	SE	LSM	SE	LSM	SE				
Baseline	41.70	1.24	40.50	1.24	40.40	1.24	40.80	1.21	40.70	1.25	0.90	0.85	0.96	0.94
Week 2	0.31	0.70	0.81	0.71	3.02	0.73	1.98	0.70	3.16	0.72	0.97	0.03	0.27	0.02
Week 6	1.57	0.74	2.19	0.75	5.13	0.75	4.38	0.75	6.18	0.76	0.94	<0.01	0.03	<0.01
Week 10	1.85	0.78	2.70	0.79	4.49	0.79	4.62	0.78	6.64	0.80	0.86	0.06	0.04	<0.01
Week 14	2.74	0.81	2.50	0.82	4.60	0.82	4.75	0.81	6.35	0.83	1.00	0.31	0.24	0.01
Week 18	2.00	0.79	3.44	0.80	4.85	0.79	4.90	0.79	5.58	0.80	0.50	0.04	0.03	0.01
Week 22	3.13	0.81	2.79	0.82	4.90	0.81	4.57	0.81	5.74	0.82	1.00	0.34	0.53	0.08
Week 26	3.03	0.82	2.79	0.83	5.02	0.82	4.28	0.82	6.96	0.83	1.00	0.26	0.65	<0.01
Difference from placebo			-0.23	1.16	1.99	1.16	1.26	1.16	3.94	1.17				
95% C.I.			(-3.08	2.62)	(-0.86	4.84)	(-1.58	4.09)	(1.07	6.80)				

* Adjusted by Dunnett procedure comparing all means with a control
[a] n=78, [b] n=76, [c] n=76 at Week 2

Table 12 Adjusted* LSM Change from Baseline in LDL (mg/dL) by Visit (LOCF) – Study 001

Visit	Placebo			7.5 mg			15 mg			30 mg			45 mg			vs. placebo $P_{7.5}$	P_{15}	P_{30}	P_{45}
Week	n	LSM	SE	n	LSM	SE	n	LSM	SE	n	LSM	SE	n	LSM	SE				
Bl	66	138.8	4.54	67	122.9	4.52	64	131.9	4.64	74	135.6	4.33	65	126.8	4.60				
2	63	0.72	2.33	65	2.09	2.30	63	6.91	2.32	70	5.55	2.21	64	3.53	2.31	0.98	0.18	0.36	0.80
6	64	2.36	2.84	64	0.17	2.86	64	4.50	2.84	73	5.82	2.67	64	6.42	2.84	0.95	0.95	0.78	0.70
10	64	4.53	2.73	65	3.92	2.74	64	4.05	2.74	73	4.88	2.57	64	7.61	2.74	1.00	1.00	1.00	0.84
14	64	5.79	2.88	65	2.87	2.88	63	3.78	2.91	73	9.83	2.71	64	4.25	2.88	0.88	0.97	0.69	0.99
18	63	3.42	2.75	65	2.97	2.73	64	4.42	2.73	73	5.81	2.57	64	5.63	2.73	1.00	1.00	0.92	0.94
22	64	6.15	2.95	65	0.10	2.95	64	1.69	2.95	73	4.75	2.78	62	6.30	3.01	0.40	0.66	0.99	1.00
26	65	4.11	3.06	64	0.56	3.12	63	6.39	3.11	74	4.59	2.89	62	4.91	3.15	0.84	0.96	1.00	1.00
Difference from placebo					-3.54	4.39		2.28	4.35		0.48	4.18		0.80	4.37				
95% C.I.					(-14.31	7.22)		(-8.39	12.95)		(-9.77	10.73)		(-9.93	11.53)				

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

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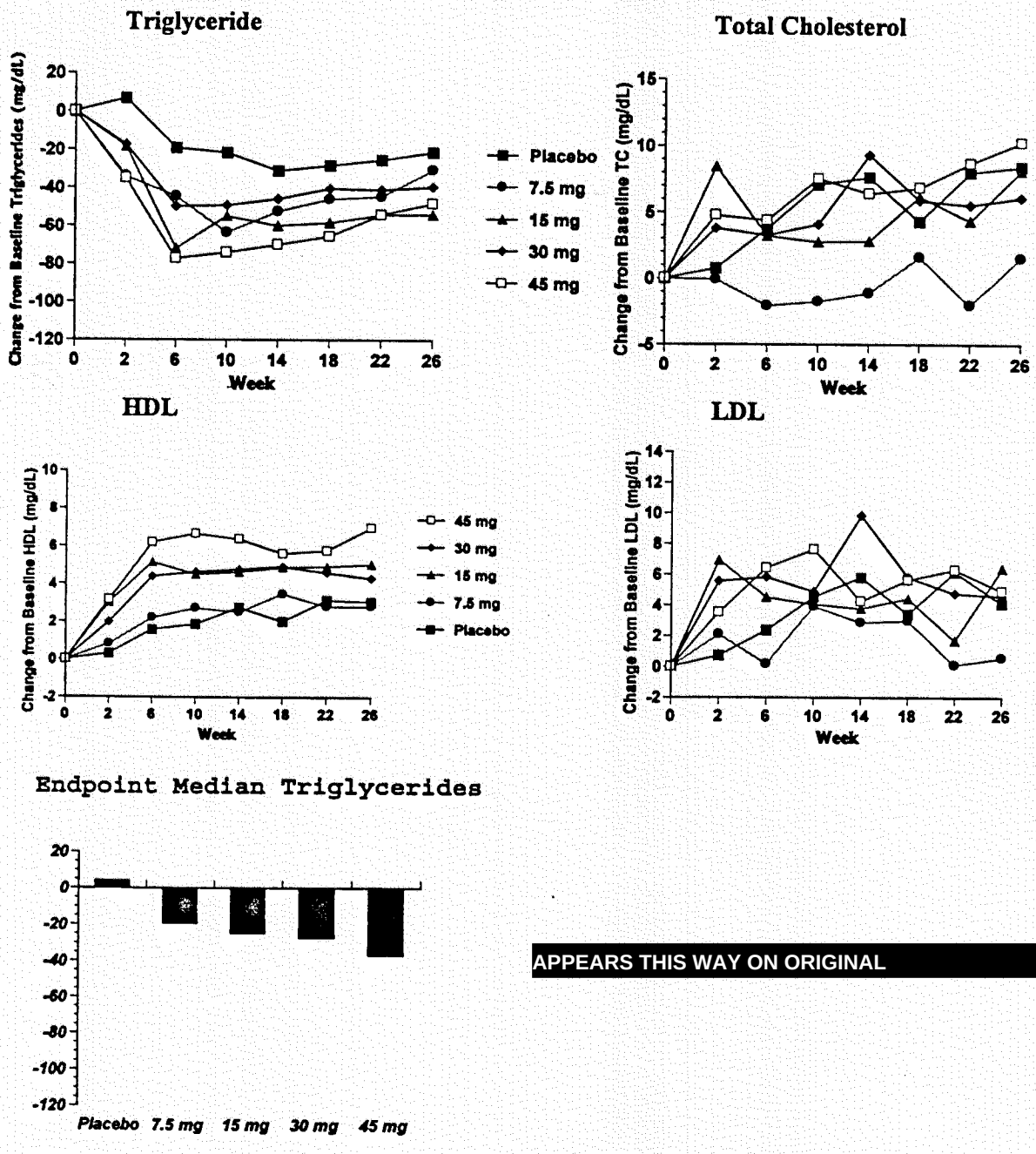
Figure 3 LSM Change from Baseline in Triglycerides, Total Cholesterol, HDL, & LDL – Study 001



Endpoint Median Triglycerides

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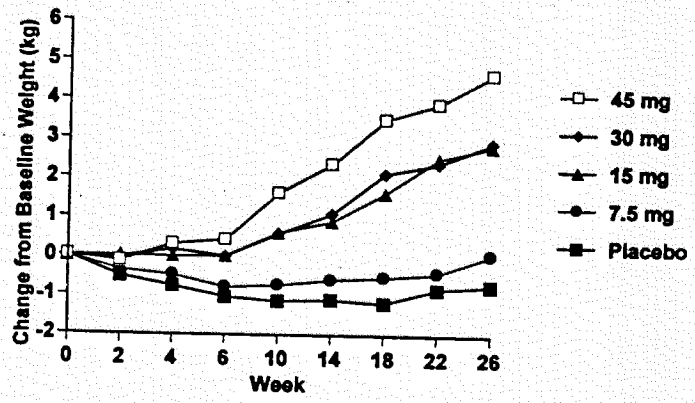
Body Weight

At Week 26, body weight increased in pioglitazone-treated patients compared to placebo-treated patients (Fig 4). The mean changes from baseline of the observed value and endpoint value at Week 26 are displayed in Table 13. At endpoint, it was significantly different from placebo for 15, 30, and 45 mg pioglitazone-treated patients ($p<0.01$). Figure 4 displays the mean body weight during the course of the study for the completers.

Table 13 Mean Change from Baseline in Body Weight (kg) – Study 001

		Pioglitazone			
	Placebo	7.5 mg	15 mg	30 mg	45 mg
Baseline					
n	79	81	79	87	79
Mean (SE)	90.35 (1.47)	93.54 (1.59)	91.19 (1.78)	90.29 (1.58)	90.77 (1.56)
Endpoint					
Mean Change (SE)	-1.28 (0.36)	-0.59 (0.29)	1.30 (0.33)	1.29 (0.38)	2.82 (0.39)
Week 26 (Observed)					
n	31	42	37	44	47
Mean Change (SE)	-0.73 (0.81)	0.04 (0.41)	2.83 (0.47)	2.92 (0.50)	4.66 (0.41)

Figure 4 Change from Baseline in Body Weight (kg) Completers – Study 001



Seven pioglitazone patients who had a >5% increase from baseline in body weight were withdrawn from the study, although weight gain was not necessarily the reason.