I. Title and General Information

1.1. Title/Heading:

MEDICAL OFFICER'S REVIEW OF NDA SUPPLEMENT

1.1.1. NDA : 20-702S003
1.1.2. M.O. Review # 1
1.1.3. Submission Date:08/16/97
Assigned Date: 04/15/98
1.1.4. Review completed date:7/8/98

1.2. Drug
1.2.1. Generic name: Atorvastatin calcium.
1.2.2. Proposed trade name: Lipitor.

1.3. Sponsor: Park-Davis Research and Development.

1.4. Pharmacological Category: Inhibitor of 3-HMG-CoA Reductase.

1.5. Proposed Revisions:

"Hypertriglyceridemia (Fredrickson Types IV and V
"In a dose-response study in patients with isolated hypertriglyceridemia, atorvasatatin 20 mg daily reduced TG and LDL-C by 34% and 31%, and atorvastatin 80 mg daily reduced TG and LDL-C by 42% and 36%."

"Lipitor is indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Types IV and V) who present a risk for pancreatitis."

1.6. Dosage Form and Route of Administration: 20-80 mg/day orally.

1.7. NDA Drug Classification:

1.8. Important Related Drugs: Other 3-HMG-CoA-reductase-inhibitors.

1.9. Other Related Reviews:

2. Materials Reviewed: CANDA submission.
NDA: 20-702/S003.

3. Clinical Background:

3.1. Relevant human experience:

3.1.1.:

Atorvastatin is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, apo-B, and TG in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Types IIa and IIb).

3.1.2:

In the current labelings for clofibrate and niacin, the following statements appear "....may be considered for the treatment of Adult patients with very high serum TG levels (Type IV and V hyperlipidemia) who present a risk of abdominal pain and pancreatitis and who do not respond adequately to a determined dietary effort to control them." However, this indication is not based on clinical data.

3.1.3:

This review will narrowly focus on the responses of total-TG, VLDL-TG, LDL-TG and HDL-TG to atorvastatin therapy in patients with Fredrickson Type IV and Type V. The clinical significance of the these responses will be discussed in the context of possible pancreatitis risk reduction.

4. Clinical Studies:

4.1. Protocol : 981-38

4.1.1. Objectives:

1). To determine the effect of atorvastatin on TG and other lipoprotein fractions in patients with hypertriglyceridemia.
2). To determine if atorvastatin results in a retribution of TG in various lipoprotein fractions in these patients.
3). To assess the safety of atorvastatin.

4.1.2. Design:

A 4-week, double-blind, placebo-controlled, multicenter study of once daily atorvastatin.

4.1.3. Protocol 981-38:

4.1.3.1. Study Population:

a). Inclusion Criteria:

1). Ages

2). Body mass index (BMI) <32 kg/m2.
3). TG >350 mg/dL for 2 measurements at Weeks -2, -1.

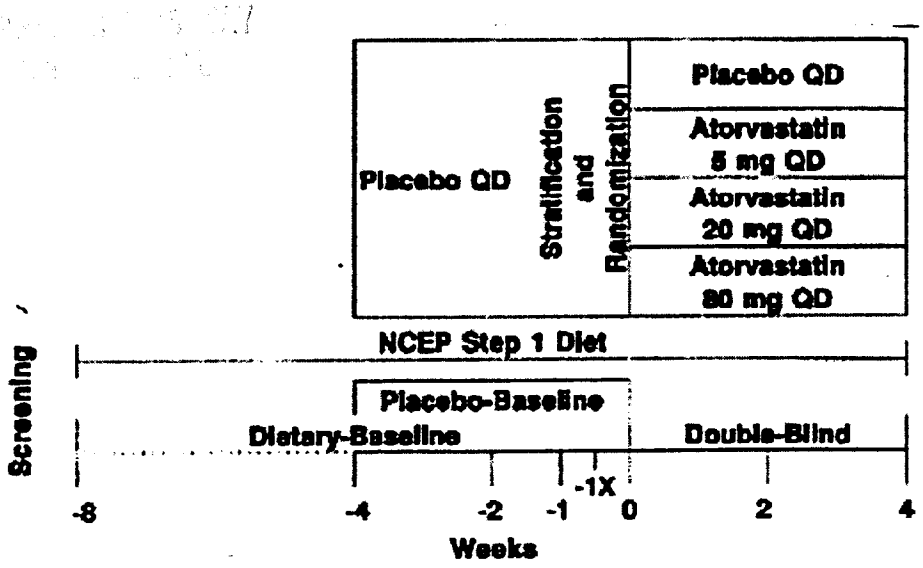
b). Exclusion Criteria:

1). Women of childbearing potential or women who were breast-feeding.
2). Consumed more than 14 alcoholic drinks per week.
3). Were taking insulin or oral hypoglycemic agents.
4). Had renal dysfunction, nephrotic syndrome with dysproteinemia, BUN >30 mg/dL, or creatinine >2.0 mg/dL.
5). Had active liver disease, hepatic dysfunction, AST or ALT >2 times upper limit of normal.
6). Had metabolic or endocrine disease that might influence serum lipids or lipoproteins.
7). Were hypertensive with clinic ,sitting BP >95 mm Hg.
8). Were using any excluded concurrent medications or had taken probucol within 1 year or other lipid-lowering drugs within 4 weeks prior to screening.
9). Were participating in another clinical study concurrently or within 30 days prior to screening.

4.1.3.2. Study Design/Procedures: A 4-week, double-blind, placebo-controlled, multicenter study.

The overall design is shown below:

Figure 4.1 :Schematic Presentation of Study Design:



1). Patients were asked to record their diary food and drink intake in a diary. Food Record Rating (FRR) scoring of patient dietary intake was performed. A patient following the NCEP Step I diet should have a FRR score of <10.

2). Clinical laboratory tests were taken on Screening, Weeks -4, -2, -1, 0, +2 and +4.

3). Lipid profile were taken on Weeks -2, -1, 0, +2. And +4. Patients were required to have fasted for a minimum of 12 hours prior.

4). PE were performed at Screening and at the end of the treatment. Slit lamp exam. Was performed at Week -1.

5). Coagulation factors were done in Weeks 0 and +4.

6). Compliance with the study medication was judged by capsule count at each clinic visit.

4.1.3.2. Endpoints:

Efficacy was evaluated based on mean percent reduction from baseline at the last visit of the double-blind period.

4.1.3.3. Statistical considerations:

Analysis of variance (ANOVA) and analysis of covariance (ANCOVA) were used to calculate the adjusted mean percent changes in TG. The calculated "the adjusted mean percent changes " were based "on the analysis of variance model that included the effects of treatment and center for patients in the <160 mg/dL stratum and treatment, center, stratum, and the treatment-by-stratum interaction for all patients". Assuming the variance model selected is correct, this approach is acceptable .

4.1.4. Results:

4.1.4.1. Patient Disposition, comparability:

Table 4.1: Patients' characteristics at Baseline:

Characteristics Stratum	Placebo N = 14	Atorvastatin Treatment Group (mg) 5 N = 13	20 N = 16	80 N = 13	All[a] N = 56
Gender, N					
Men					
LDL-C ≤160 mg/dL	10	9	10	11	40
LDL-C >160 mg/dL	2	2	2	2	8
Women					
LDL-C ≤160 mg/dL	2	2	3	0	7
LDL-C >160 mg/dL	0	0	1	0	1
Race, N					
White					
LDL-C ≤160 mg/dL	11	11	12	11	45
LDL-C >160 mg/dL	2	2	2	2	8
Other					
LDL-C ≤160 mg/dL	1	0	1	0	2
LDL-C >160 mg/dL	0	0	1	0	1
Age, years					
Median (min,max)					
LDL-C ≤160 mg/dL	49.5 ( )	51.0 ( )	51.0 (	48.0 (	51.0 ( )
LDL-C >160 mg/dL	53.5 ( )	49.0 ( )	54.0 (	49.0 ( )	54.0 ( )
All	49.5 ( )	51.0 ( )	52.0 (	48.0 ( )	51.0 ( )
Distribution by Age, N					
<65 years					
LDL-C ≤160 mg/dL	11	8	12	11	42
LDL-C >160 mg/dL	2	2	3	2	9
≥65 years					
LDL-C ≤160 mg/dL	1	3	1	0	5
LDL-C >160 mg/dL	0	0	0	0	0
BMI, kg/m^2					
Mean (SE)					
LDL-C ≤160 mg/dL	26.8 (0.9)	28.1 (0.8)	28.1 (0.7)	29.3 (1.0)	28.0 (0.4)
LDL-C >160 mg/dL	27.5 (1.5)	30.5 (1.5)	27.3 (1.9)	30.5 (1.5)	28.8 (0.9)
All	26.9 (0.8)	28.5 (0.7)	27.9 (0.7)	29.5 (0.8)	28.2 (0.4)
Baseline[b] LDL-C, mg/dL					
Mean (SE)					
LDL-C ≤160 mg/dL	102.8 (8.6)	111.8 (9.2)	113.5 (6.6)	100.5 (9.6)	107.3 (4.2)
LDL-C >160 mg/dL	190.3 (1.0)	177.0 (3.7)	166.1 (8.9)	184.8 (1.8)	178.1 (4.3)
All	115.3 (11.2)	121.8 (10.3)	123.4 (7.6)	113.5 (11.9)	118.7 (5.0)
Baseline[b] Total TG, mg/dL					
Mean (SE)					
LDL-C ≤160 mg/dL	650.7 (52.7)	573.8 (55.4)	711.1 (88.0)	603.9 (53.6)	638.5 (33.0)
LDL-C >160 mg/dL	459.5 (15.5)	378.3 (10.0)	435.9 (12.3)	397.7 (1.0)	419.9 (11.7)
All	623.4 (48.6)	543.7 (50.8)	659.5 (76.2)	572.2 (49.9)	603.3 (29.8)

1). 56/90 patients who entered the placebo-baseline period qualified to enter the double-blind period and were randomized to study treatments.

2). About 10% of the patients had concurrent medications, most commonly used were musuloskeletal agents.

3). Patients randomly assigned to the four treatment groups were comparable in their baseline characteristics.

4). 1/56 patients, in the LDL-C >160 mg/dL stratum of the 80-mg atorvastatin treatment group withdrew prior to study completion and lost to follow-up.

4.1.4.2. Efficacy endpoint outcomes:

4.1.4.2.1: Primary Efficacy Analyses: Mean Percent Changes From Baseline in Total Triglycerides were computed at Weeks 2 and 4 and shown below:

Table 4.2:. Mean (SE) of Triglycerides (mg/dL)

Time Point Stratum Parameter[a]	Placebo	Atorvastatin Treatment Group (mg)		
		5	20	80
Triglycerides at Week 2				
LDL-C ≤160 mg/dL, N	12	11	13	11
Baseline	650.7 (52.7)	573.8 (55.4)	711.1 (88.0)	603.9 (53.6)
Double Blind	652.3 (97.5)	403.5 (37.4)	498.1 (68.3)	296.8 (32.4)
% Change	0.7 (12.9)	-26.9 (6.5)	-30.5 (4.2)	-48.8 (5.6)
LDL-C >160 mg/dL, N	2	2	3	1
Baseline	459.5 (15.5)	378.3 (10.0)	435.9 (12.3)	396.7 (NA)
Double Blind	413.5 (7.5)	242.0 (10.0)	295.3 (40.9)	169.0 (NA)
% Change	-10.0 (1.4)	-35.9 (4.3)	-32.6 (7.8)	-57.4 (NA)
All, N	14	13	16	12
Baseline	623.4 (48.6)	543.7 (50.8)	659.5 (76.2)	586.7 (51.9)
Double Blind	618.2 (86.2)	378.7 (35.7)	460.1 (59.1)	286.2 (31.4)
% Change	-0.8 (11.1)	-28.3 (5.6)	-30.9 (5.6)	-49.6 (5.1)
Triglycerides at Week 4				
LDL-C ≤160 mg/dL, N	12	11	13	11
Baseline	650.7 (52.7)	573.8 (55.4)	711.1 (88.0)	603.9 (53.6)
Double Blind	640.5 (101.2)	409.5 (28.3)	512.8 (126.0)	330.0 (42.1)
% Change	-3.3 (8.7)	-26.0 (5.2)	-32.4 (7.0)	-40.3 (9.7)
LDL-C >160 mg/dL, N	2	2	3	1
Baseline	459.5 (15.5)	378.3 (10.0)	435.9 (12.3)	396.7 (NA)
Double Blind	346.0 (47.0)	293.0 (27.0)	330.0 (28.4)	96.0 (NA)
% Change	-25.0 (7.7)	-22.3 (9.2)	-24.0 (7.3)	-75.8 (NA)
All, N	14	13	16	12
Baseline	623.4 (48.6)	543.7 (50.8)	659.5 (76.2)	586.7 (51.9)
Double Blind	598.4 (90.9)	391.6 (26.8)	478.6 (103.3)	310.5 (43.1)
% Change	-6.4 (7.7)	-25.4 (4.5)	-30.8 (5.8)	-43.2 (9.3)

1). The reduction in total TG was dose-related, i.e. at Weeks 4, the reductions were 10 (2%) , 164 (28%), 198 (28%), and 274 (45%) mg/dL for the placebo, 5 mg, 20mg, and the 80 mg groups respectively.

2). There was a significant treatment-by-baseline interaction (p=0.02). The Sponsor attributes this to 2 patients who had baseline TG levels >900

mg/dL and experienced an increase of 759 and 443 mg/dL. The percent changes from baseline were reanalyzed after deleting the data of patient 201 who was randomized to 20 mg group. This is shown in Table 4.3.

Table 4.3: Mean (SE) Percent Changes in TG (mg/dL):

Parameter Stratum	Placebo	Atorvastatin Treatment Group 5 mg	20 mg	80 mg
Triglycerides				
LDL-C ≤160 mg/dL	N = 12	N = 11	N = 12	N = 11
Raw Means	-3.3 (8.7)	-26.0 (5.2)	-37.5 (5.2)	-40.3 (9.7)
Adjusted Means	-4.6 (8.2)	-27.6 (8.5)	-39.1* (7.9)	-42.6* (8.6)
All	N = 14	N = 13	N = 15	N = 12
Raw Means	-6.4 (7.7)	-25.4 (4.5)	-34.8 (4.5)	-43.2 (9.3)
Adjusted Means	-14.2 (10.7)	-24.0 (10.7)	-30.5 (8.8)	-61.6*+ (14.4)

SE = Standard Error.
LDL-C = Low-density lipoprotein cholesterol.
* Significantly different from placebo, p <0.05
\+ Significantly different from the 5 mg group, p <0.05

1). The reanalyzed mean percent changes were similar to that in Table 4.2 which included the data of patient 201. For patients with LDL-C< 160 mg/dL, the mean percent changes in TG in the 20 and 80 mg treatment groups were significantly different from the placebo group (P<0.05).

2). The Sponsor's calculated "the adjusted mean percent changes " which were based "on the analysis of variance model that included the effects of treatment and center for patients in the <160 mg/dL stratum and treatment, center, stratum, and the treatment-by-stratum interaction for all patients". are shown below:

Table 4.4: Summary of Adjusted Percent Change from Baseline:

Parameter Stratum	Placebo	Atorvastatin Treatment Group (mg) 5	20	80
Triglycerides				
LDL-C ≤160 mg/dL	N = 12	N = 11	N = 13	N = 11
Mean % Change	-5.3	-27.3	-33.6*	-42.4*
SE	8.9	9.1	8.2	9.2
All Patients	N = 14	N = 13	N = 16	N = 12
Mean % Change	-16.3	-23.3	-28.9	-60.9*
SE	11.3	11.4	9.4	15.4

LDL-C = Low-density lipoprotein cholesterol.
SE = Standard Error.
* Significantly different than placebo, p <0.05

1). According to the Sponsor, "For patients in the <160 mg/dL stratum, there was no significant treatment-by-center interaction. There was also no significant effect of age or treatment-by-age interaction. Due to the small number of female patients and those who were not white, the effects of gender and race were not investigated".

2). The adjusted mean percent changes from baseline for LDL-C <160 mg/dL , the 20 and 80 mg/dL treatment groups were significantly different from the placebo group, (P,0.05) . No actual TG levels are provided along with mean percent changes.

4.1.4.2.2. **Secondary Efficacy Analyses:**

Mean Percent changes from baseline in LDL-TG, VLDL-TG, and HDL-TG are shown below:

Table 4.5: Mean (SE) of LDL-TG, VLDL-TG and HDL-TG at Week 4:

Parameter Stratum	Placebo	Atorvastatin Treatment Group (mg) 5	20	80
LDL-TG (mg/dL)				
LDL-C ≤160 mg/dL, N	12	11	13	11
Baseline	45.1 (2.7)	46.9 (3.1)	47.7 (4.9)	37.9 (4.2)
Week 4	46.1 (1.9)	37.7 (3.6)	32.0 (2.3)	23.6 (3.8)
% Change	4.3 (4.4)	-20.4 (4.9)	-29.9 (3.5)	-38.1 (5.9)
LDL-C >160 mg/dL, N	2	2	3	1
Baseline	55.0 (1.7)	45.0 (4.3)	56.3 (9.9)	30.3 (NA)
Week 4	57.0 (10.0)	36.0 (9.0)	36.0 (6.5)	16.0 (NA)
% Change	4.3 (21.3)	-21.2 (12.4)	-36.2 (0.5)	-47.3 (NA)
VLDL-TG				
LDL-C ≤160 mg/dL, N	12	11	13	11
Baseline	579.2 (51.1)	501.7 (53.5)	639.4 (86.9)	543.7 (50.2)
Week 4	567.2 (98.5)	348.5 (27.5)	457.4 (126.3)	287.3 (38.9)
% Change	-4.3 (9.1)	-27.4 (5.9)	-34.4 (7.5)	-41.4 (10.3)
LDL-C >160 mg/dL, N	2	2	3	1
Baseline	385.2 (19.2)	316.8 (14.8)	358.6 (19.4)	354.0 (NA)
Week 4	268.5 (36.5)	237.5 (13.5)	273.7 (18.7)	75.0 (NA)
% Change	-30.6 (6.0)	-24.7 (7.8)	-22.8 (8.9)	-78.8 (NA)

HDL-TG

LDL-C ≤160 mg/dL, N	**12**		**11**		**13**		**11**	
Baseline	**26.4**	**(2.2)**	**25.2**	**(2.1)**	**24.0**	**(1.5)**	**22.3**	**(1.8)**
Week 4	**26.8**	**(3.1)**	**23.4**	**(1.4)**	**23.5**	**(2.0)**	**19.1**	**(1.7)**
% Change	**2.6**	**(7.8)**	**-4.8**	**(4.3)**	**-1.7**	**(6.3)**	**-11.5**	**(8.1)**
LDL-C >160 mg/dL, N	**2**		**2**		**3**		**1**	
Baseline	**19.3**	**(2.0)**	**16.5**	**(0.5)**	**21.0**	**(2.0)**	**12.3**	**(NA)**
Week 4	**20.5**	**(0.5)**	**19.5**	**(4.5)**	**20.7**	**(3.2)**	**5.0**	**(NA)**
% Change	**7.5**	**13.7)**	**17.5**	**(23.7)**	**-2.5**	**(6.2)**	**-59.5**	**(NA)**

1). The mean percent decrease from baseline in LDL-TG were 20%, 29.9% and 38.1% in the 5, 20, and 80 mg/dL treatment groups for patients with LDL-C <160 mg/dL. The corresponding percentages for patients with LDL-C >160 mg/dL were 21.2%, 36.2% and 47.3% respectively..

2). The mean percent decrease from baseline in the VLDL-TG were 27.4%, 34.4% and 41.4% in the 5, 20 and 80 mg/dL treatment groups for patients with LDL-C <160 mg/dL. The corresponding percentages for patients with LDL-C >160 mg/dL were 24.7%, 22.8% and 78.8% respectively.

3). The mean percent decrease from baseline in HDL-TG were 4.8%, 1.7% and 11.5% in the 5, 20 and 80 mg/dL treatment groups for patients with LDL-C <160 mg/dL. The corresponding percentages for patients with LDL-C >160 mg/dL were increase of 17.5%, decrease of 2.5% and 59.5% respectively.

4). The adjusted mean percent decreases at Weeks 4 were analyzed for patients with LDL-C <160 mg/dL. For the LDL-TG, the decreases were 22.2%, 29.9% and 39.2% for the 5, 20 and 80 mg/dL treatment groups. These differences were statistically significantly, (P<0.05) from placebo group. For the VLDL-TG, the corresponding values were 28.7%, 35.7% and 43.6% for the 5, 20 and 80 mg/dL treatment groups. These differences were statistically significantly, (P<0.05) from placebo group. For the HDL-TG, the decreases were 5.9%, 2.1% and 13.0 for the 5, 20 and 80 mg treatment groups. None of these were statistically significantly different from the placebo group.

4.1.4.3. Safety Outcomes:

1). There were no deaths in this study.
2). There were no withdrawals due to adverse events in this study.
3). The was no dose-related adverse event reporting associated with treatment. The adverse events by body system were similar to the previously submitted safety data in the original NDA application.
4). Number of patients with changes in laboratory values are shown below:

Table 4.6: Number of Patients with changes in laboratory values:

APPEARS THIS WAY ON ORIGINAL

Determination[a]	Placebo N = 14	Atorvastatin Treatment Group (mg) 5 N = 13	20 N = 16	80 N = 12
Alk Phosphatase	0	1	0	0
Chloride	1	0	0	0
CPK	0	0	0	1
Glucose	0	0	1	0
Hematocrit	0	0	1	0
Platelets	0	1	0	0
Total Bilirubin	0	1	0	3
Total Protein	1	0	0	0

APPEARS THIS WAY ON ORIGINAL

1). One patient in the 5mg group had an alkaline phosphokinase that was 1 to 2 times upper limits of normal

2). One patient in the 5mg group and 3 patients in the 80mg group had total bilirubin 1 to 2 times the upper limit of normal at Week 2 and/or Week 4 of the double blind period (3 of these patients had these levels prior to randomization).

3). Two most important side-effects of HMG-CoA reductase inhibitors are elevated transaminase levels and the occurrence of myopathy. One patient in the 80mg group had a CPK value that was 3 to 4 times upper limit of normal at Week 2. When the patient abstained from extensive exercise and alcohol prior to Week 4 visit, the CPK value decreased to slightly above the upper limit of normal. No elevations greater than 2 times the upper limit of normal were present in ALT or AST.

4.1.5: Reviewer's Comments/Conclusion of Study Results:

4.1.5.1: Safety:

APPEARS THIS WAY ON ORIGINAL

There were no new/unexpected adverse events reported in this study from the previously submitted safety data and listed in the Labeling.

APPEARS THIS WAY ON ORIGINAL

4.1.5.2: Efficacy:

APPEARS THIS WAY ON ORIGINAL

1). In 47 patients with presumably Fredrickson Type IV (electrophoresis typing was not performed; with LDL - C<160 mg/dL and TG mg/dL), atorvastatin treatment of 5 , 20 and 80 mg/day

resulted in decreases of total TG (-26%, 32%, and -40% respectively). No dose-dependent decreases were demonstrated (only the 80-mg dose was significantly different from the 5 mg-dose group. One type V patient (with chylomicrons) and TG >2400 mg/dL was excluded from the analysis.

2). VLDL-TG, LLDL-TG, and HDL-TG showed decreases also although not to the same extent as total TG. Sponsor statement, "...without causing a redistribution of TG into various lipoprotein fractions" is not supported by the data submitted.

3). 35/47 randomized to atorvastatin treatment at 5, 20 and 80 mg/day achieved statistically significant decreases in total-C, LDL-C, VLDL-C, and total ApoB ($P<0.05$). Statistically significant increase in HDL-C was only seen in the 80 mg dose group.

3). No patient developed panceatitits, therefore the risk of reduced pancreatitis, if any, cannot be assessed.

.4.2. Protocol: 981-42:

4.2.1. Objectives:

1). To assess the efficacy of atorvastatin relative to that of niacin on lipoprotein and apolipoprotein fractions in patients with total cholesterol of >200 mg/dL, TG and apo B>110 mg/dL.

2). To assess the safety of atorvastatin.

4.2.2. Design:

A 12-week, open-label, randomized, parallel-design, active-controlled study..

4.2.3.1. Study Population:

a). Inclusion Criteria:

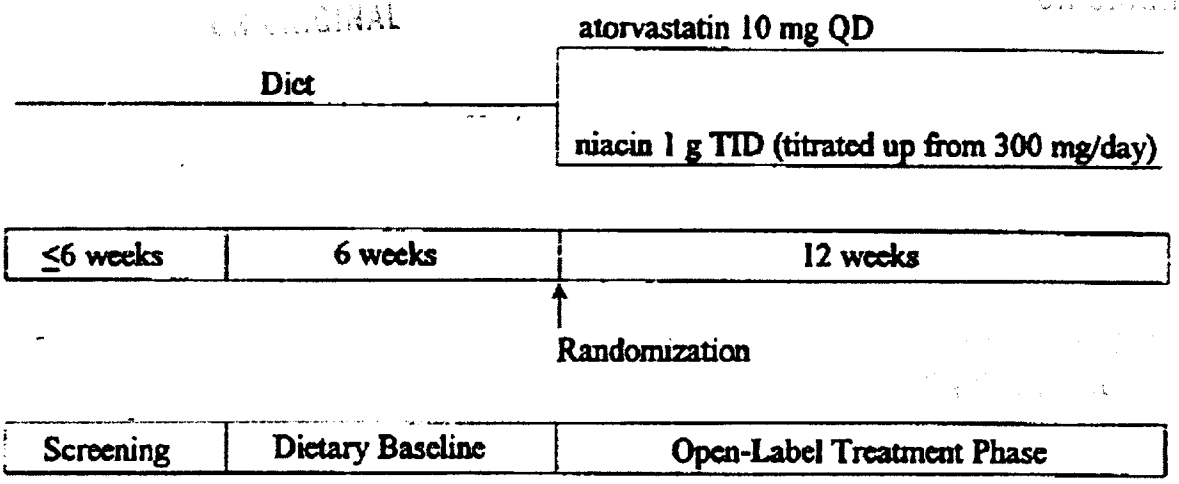
1). Ages
2). Body mass index (BMI) <32 kg/m2.
3). Total cholesterol >200 mg/dL at Weeks -4, and -2.
4). TG value at Weeks -4 and -2.

b). Exclusion Criteria: Same as Protocol 981-38.

4.2.3.2. Study Design/Procedures:

The overall design is shown below:

Figure 4.2.1 : Schematic Presentation of Study Design:



1). Due to the marked vasodilatory reaction many patients experienced while receiving niacin, niacin-treated patients were treated with aspirin ½ hour before each niacin dose.

2). The detailed procedures can be summarized in Figure 4.2.2:

Figure 4.2.2: Schedule of Visits and Procedures: :

Study Phase	Screening	Baseline			Open-Label Treatment				
Study Week		-6	-4	-2	0	2	4	8	12
Physical Examination		X							X
Medical History		X							
Clinic Visit[a]	X	X	X	X	X	X	X	X	X
Clinical Laboratory[b]	X[c]				X				X
Safety Labs[b,d]				X[e]		X	X	X	
Lipid Profile[b,g]	X[f]		X	X	X	X	X	X	X
Special Lipids and Laboratory Data[h]				X	X			X	X
Dietary Counseling	X	X	X	X	X	X	X	X	
Distribute Dietary Diary			X					X	
Dietary FRR Scoring				X					X
Drug Dispensed					X	X	X	X	

1). Lipid profiles were obtained after a minimum of 12-hour fast and between 6 and 18 hours postdose of the study medications.

2). For evaluation of patient's dietary compliance, FRR was calculated from the 3-day diaries completed at Weeks -2 and 12. Patients who were

noncompliant during the treatment phase were counseled but not dropped from the study.

4.2.3.2. Endpoints: Efficacy was evaluated based on mean percent reduction from baseline at the last visit of the double-blind period.

4.2.3.3. Statistical considerations:

The effects of atorvastatin and niacin were compare using analysis of covariance (ANCOVA) "with a model that included the effects of baseline, treatment, center, and type of dyslipidemia". Unadjusted mean percent changes were also used in comparing the treatment groups.

4.2.4. Results:

4.2.4.1. Baseline characteristics of all patients randomized to treatment are showing in Table 4.2.1.:

Table 4.2.1.: Baseline characteristics:

Characteristics	Atorvastatin 10 mg QD N = 55	Niacin 1 g TID N = 53
Gender, N (%)		
Men	35 (64)	35 (66)
Women	20 (36)	18 (34)
Race, N (%)		
White	55 (100)	49 (92)
Black	0 (0)	3 (6)
Other	0 (0)	1 (2)
Age, years		
Median	54	56
Min, Max	28, 77	31, 77
Distribution by Age, N (%)		
<70 years	47 (85)	48 (91)
≥70 years	8 (15)	5 (9)
BMI, kg/m^2		
Median	28	27
Min, Max	23, 32	22, 32

Food Record Rating (FRR) Score[a]				
Mean		9.0		8.2
HDL-C[a], mg/dL				
Mean (SE)	38	(1.3)	36	(1.0)
Total Triglycerides[a], mg/dL				
Mean (SE)	394	(25.7)	358	(14.9)
LDL-TG[a], mg/dL				
Mean (SE)	44	(2.0)	46	(1.7)
VLDL-TG[a], mg/dL				
Mean (SE)	327	(24.7)	291	(14.6)
HDL-TG[a], mg/dL				
Mean (SE)	22	(1.0)	21	(0.9)
Apo B[a], mg/dL				
Mean (SE)	155	(3.7)	159	(4.3)
LDL-apo B[a], mg/dL				
Mean (SE)	134	(3.6)	137	(4.3)
VLDL-apo B[a], mg/dL				
Mean (SE)	21	(1.1)	22	(0.9)
Apo A-I[a], mg/dL				
Mean (SE)	138	(2.9)	132	(2.8)
Lp(a)[a], mg/dL				
Mean (SE)	23	(3.5)	32	(5.3)

SE = Standard error; BMI = Body Mass Index; LDL-C = Low-density lipoprotein cholesterol; VLDL-C = Very low-density lipoprotein cholesterol.

[a] Mean of measurements at Weeks -2 and 0

[b] Collected from Case Report Forms (CRFs)

1). The 55 patients randomized to atorvastatin and the 53 patients randomized to niacin are comparable in baseline characteristics.

2). 12 (11%) patients did not complete the study; 9 (1 atorvastatin and 8 niacin) due to adverse events, 2 (1 atorvastatin, 1 niacin) were lost to follow-up, and 1 niacin patient did not return for the final visit. Therefore, 96/108 patients completed the study.

3). However, efficacy analyses were based on data from 105 patients who had lipid and special lipid measurements at least once during baseline and study treatment.

4.2.4.2 Efficacy Endpoints Outcomes:

Only the secondary parameters of TG, VLDL-TG. LDL:-TG, and HDL-TG are pertinent to this review. The results are shown below:

Table 4.2.4.2: Mean (SE) values for secondary Efficacy parameters:

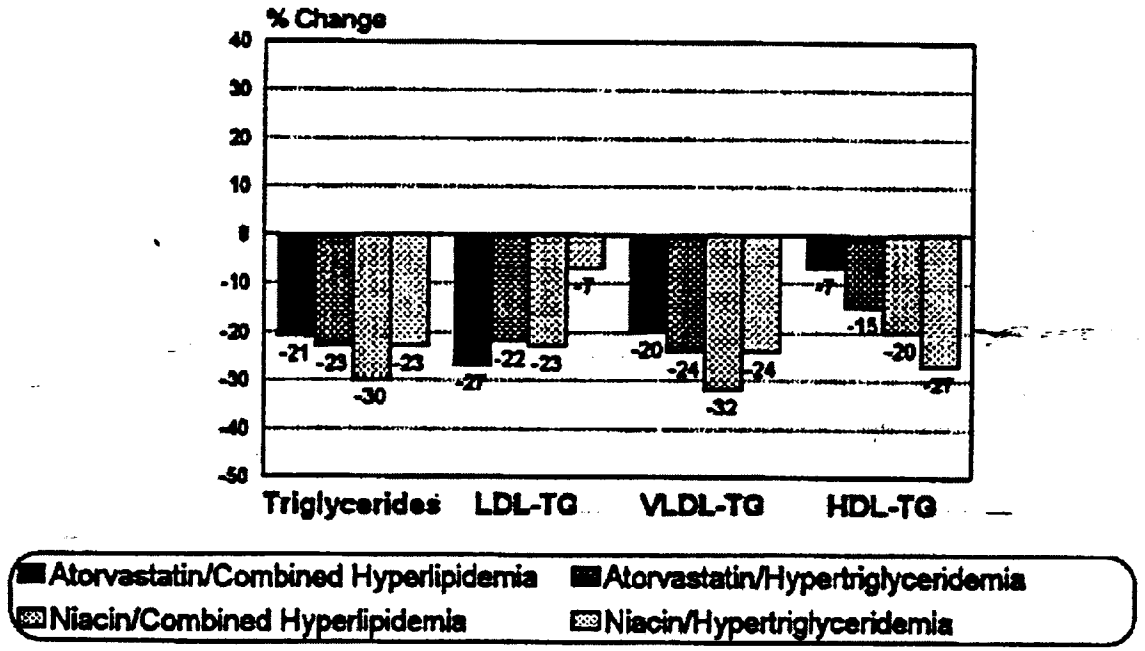
Variable	Atorvastatin 10 mg QD N = 54		Niacin 1 g TID N = 51	
Secondary Parameters				
Triglycerides, mg/dL				
N	54		51	
Baseline	396	(26)	361	(15)
Last Visit	291	(17)	250	(16)
Change	-105	(19)	-111	(16)
% Change[a]	-17*	(4.6)	-29	(4.7)
LDL-TG, mg/dL				
N	54		51	
Baseline	45	(2.0)	47	(1.8)
Last Visit	32	(1.3)	37	(1.6)
Change	-13	(1.4)	-10	(1.3)
% Change[a]	-23	(3.2)	-17	(3.3)
VLDL-TG, mg/dL				
N	54		51	
Baseline	329	(25)	294	(15)
Last Visit	239	(16)	197	(14)
Change	-90	(19)	-97	(15)
% Change[a]	-16*	(5.4)	-30	(5.4)
HDL-TG, mg/dL				
N	54		51	
Baseline	22	(1.0)	21	(0.9)
Last Visit	20	(0.9)	16	(1.0)
Change	-3	(0.8)	-5	(0.8)
% Change[a]	-7*	(4.7)	-24	(4.7)

1). For total TG, VLDL-TG and HDL-TG, niacin at 1 g TID resulted in statistically

significant greater decreases in least square mean values than atorvastatin at 10 mg QD (-17% vs. -29%, -16% vs. -30%, and -7% vs. -24% respectively). The decreases in LDL-TG were similar between niacin and atorvastatin (-23% vs. -17% respectively).

2). Apparently, the responses to niacin was dependent on the type of hyperlipidemia, while that to atorvastatin was type independent. This can be demonstrated by using the "unadjusted mean percentage change from baseline". Since the number of patients with Type IV were only 16 and 11, the statistical significance is unknown. The clinical significance/implication of these differential responses is not obvious. This may simply mean the different mechanisms of action of niacin and atorvastatin by which they decrease TG levels. Whether or not this plays any role in decreasing the probability of pancreatitis is totally unknown.

Figure 4.2.3: Unadjusted Mean Percent Change From Baseline in Lipid Parameters by Type of Dyslipidemia:



Combined hyperlipidemia is Fredrickson Type 11b which had 39(71%) in atorvastatin-treated group and 42 (79%) of the niacin-treated group. Hypertriglyceridemia is Fredrickson Type IV which had 16(29%) in the atorvastatin-treated group and 11(21%) of the niacin-treated group.

4.2.4.3. Safety Outcomes:

1). There were no deaths in this study.

2). 2 atorvastatin-treated patients had a serious adverse events which were not considered to be due to atorvastatin (1 patient had chest pain and 1 patient

had carotid endarterectomy and an attempted atherectomy). There was no serious adverse events for niacin-treated patients.

3). Nine patients (1 atorvastatin and 8 niacin) withdrew from the study due to an adverse events as depicted below:

Table 4.2.4.3: Withdrawals Due to Adverse Events:

Patient Number	Treatment	Adverse Event	Relationship to Drug	Outco
981-42-01-102	Niacin	Dyspepsia	Possibly	Recove
981-42-02-105	Niacin	Vasodilatation Cheilitis Paresthesia Chest Pain	Definitely	Recove
981-42-03-107	Niacin	Asthenia	Unlikely	Recove
981-42-05-103	Niacin	Nervousness	Possibly	Recove
981-42-05-119	Niacin	Rash	Definitely	Recove
981-42-08-203	Atorvastatin	Constipation Pruritus Rash	Probably	Recove
981-42-08-112	Niacin	Insomnia Headache	Unlikely Probably	Recove
981-42-08-202	Niacin	Vasodilatation	Definitely	Recove
981-42-08-207	Niacin	Rash Headache	Definitely Probably	Recove

4). The was no dose-related adverse event reporting associated with treatment. The adverse events by body system were similar to the previously submitted safety data in the original NDA application.

5). Number of patients with changes in laboratory values are shown below:

Table 4.2.4.4.: Summary of Clinical Lab. Abnormalities [Number (%) of Patients]:

Laboratory Parameter	Units	Reason	Atorvastatin 10 mg N = 55		Niacin 1 g N = 53	
ALT	IU/L	>1.5 × ULN	5	(9)	3	(6)
AST	IU/L	>1.5 × ULN	7	(13)	3	(6)
Eosinophils	K/cm^2	>1.5 × ULN	0	(0)	1	(2)
Glucose	mg/dL	>1.25 × ULN	0	(0)	5	(9)
Total Bilirubin	mg/dL	>1.5 × ULN	1	(2)	0	(0)
Any Abnormality			10	(18)	8	(15)

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; ULN = Upper limit of normal.

1). Sponsor's guidelines developed for the atorvastatin program defined clinically important laboratory abnormalities as follows:

AST and /or ALT >3 X ULN at 2 consecutive measurements 1 week apart.
CPK > 10 X ULN at 2 consecutive measurements 1 week apart.

2). No CPK abnormality was reported The AST and ALT abnormalities did not qualify as "clinically important lab. Abnormalities".

4.2.5: Reviewer's Comments/Conclusion of Study Results:

APPEARS THIS WAY
ON ORIGINAL

4.2.5.1: Safety:

There were no new/unexpected adverse events reported in this study from the previously submitted safety data and listed in the Labeling.

APPEARS THIS WAY
ON ORIGINAL

4.2.5.2: Efficacy:

1). In 108 patients with Combined Hyperlipidemia / Fredrickson Type IIb with TC>200 mg/dL and total TG patients treated with niacin 1g TID, experienced statistically significant greater decreases in total TG, VLDL-TG and HDL-TG as compared to 10 mg atorvastatin/day.

2). In the subgroup of patients with "isolated hypertrigly - ceridemia", atorvastatin treated patients showed greater decreases in the "unadjusted mean percentage change from baseline" in total TG, VLDL-TG and LDL-TG. Since the number of patients with Type IV were only 16 and 11, the statistical significance is unknown. The clinical significance/implication of these differential responses is not obvious.

3). No data submitted on pancreatitis.

APPEARS THIS WAY
ON ORIGINAL

4.3: Protocol 981-55:

4.3.1. Objectives:

To compare the effects on lipoprotein fractions and safety of atorvastatin with that of fenofibrate.

APPEARS THIS WAY
ON ORIGINAL

4.3.2. Design:

A 24-week, open-label, randomized, parallel-arm multicenter study.

4.3.3.1. Study Population:

a). Inclusion Criteria:

1). Men or women ages

2). Total cholesterol >200 mg/dL, apoB >110 mg/dL, and TG and <800 mg/dL at Weeks -4 and -2.

3). Women had to be post-menopausal or surgically sterilized practicing a suitable/reliable method of birth control.

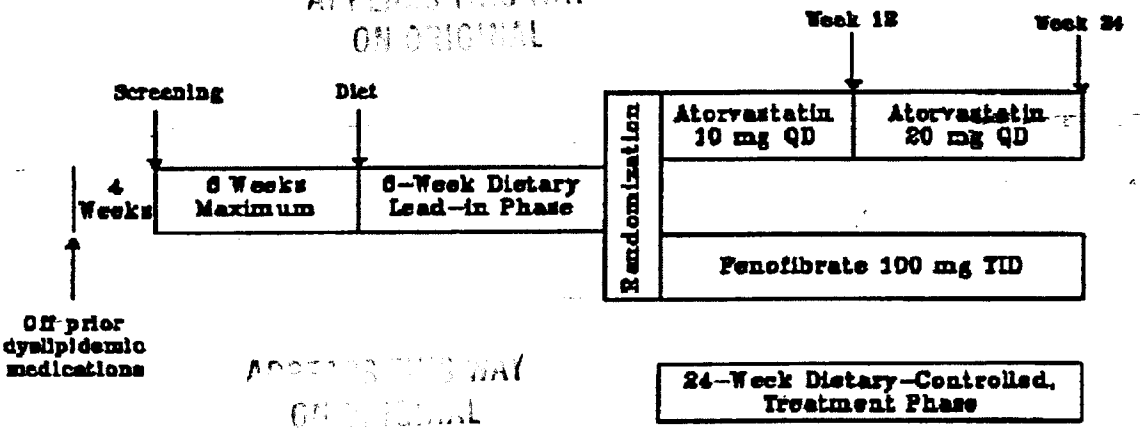
b). Exclusion Criteria:

Same as Protocol 981-38 and Protocol 981 -42.

4.3.3.2. Study Design/Procedures:

The overall design is shown below:

Figure 4.3.1 : Schematic Presentation of Study Design:



1). Amendment 1 extended the treatment period from 12 to 24 weeks at a atorvastatin dose of 20 mg/day.

2). The study was carried out at 7 centers.

Schedule of visits and procedures can be summarized in the table below:

Figure 4.3.2: Schedule of Visits and Procedures:

Study Phase	Screening	Dietary-Baseline			Treatment				
Study Week		-6	-4	-2	0	2	6	12	24
Physical Exam		X							X
Medical History	X								
Clinical Laboratory	X[b]				X	X	X[c]	X[c]	X[c]
Safety Laboratory		X	X	X[c,d]					
Urinalysis by Dipstick		X			X			X	X
Lipid Profile	X[e]		X	X	X	X	X	X	X
Special Lipids				X	X	X	X	X	X
Plasma Storage Sample					X	X	X	X	X
Apo E Phenotyping			X						
Whole Blood Storage Sample					X				
ECG[f]	X				X				X
Dietary Counseling	X[g]	X	X	X	X	X	X		
Distribute Dietary Diary			X				X		
Collect Diary and Determine FRR Score				X				X	X
Dispense Medication					X	X	X		

1). All laboratory tests were performed after a 12-hour fast AT Weeks 0, 2, 6, 12, and 24.

2). Safe lab. Evaluated ALT, AST, alkaline phosphates, total bilirubin, and CPK

3). B-HCG were done on women of child-bearing potential.

4). Lipid profile included total cholesterol, LDL-C, total TG, and ApoB.

4.3.3.2. Endpoints:

Efficacy was evaluated based percent reduction from baseline at Week 12 and Week 24 in total TG, VLDL-TG, LDL-TG (these are the relevant parameters for this NDA Supplement Review)..

4.3.3.3. Statistical considerations:

Analysis of Covariance (ANCOVA) was performed to compare the percent change from baseline (mean of the 2 measurements at Weeks -2 and 0) in all parameters. The primary model used took into account the effects of treatment, center, type of dyslipidemia, and the baseline as a covariate.

4.3.4. Results:

4.3.4.1. Baseline characteristics of all patients randomized to treatment are showing in Table 4.2.1.

Table 4.3.1.: Baseline characteristics:

BEST POSSIBLE COPY

	Atorvastatin			Fenofibrate		
	CHL N = 41	IHTC N = 6	All N = 47	CHL N = 43	IHTC N = 9	All N = 52
Sex, n (%)						
Men	29 (71)	4 (67)	33 (70)	27 (63)	8 (89)	35 (67)
Women	12 (29)	2 (33)	14 (30)	16 (37)	1 (11)	17 (33)
Race, n (%)						
White	38 (93)	6(100)	44 (94)	41 (95)	9(100)	50 (96)
Black	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Asian	2 (5)	0 (0)	2 (4)	2 (5)	0 (0)	2 (4)
Age, yr						
Mean (SE)	49 (2.0)	60 (2.2)	50 (1.9)	53 (1.4)	57 (2.7)	54 (1.2)
Age Distribution, n (%)						
<70 years	39 (95)	6(100)	45 (96)	41 (95)	9(100)	50 (96)
≥70 years	2 (5)	0 (0)	2 (4)	2 (5)	0 (0)	2 (4)
Body Mass Index, kg/m^2						
Mean (SE)	27 (0.4)	27 (1.1)	27 (0.4)	27 (0.4)	28 (1.3)	27 (0.4)
Alcohol Use, Drinks/Week						
Mean (SE)	4 (0.5)	4 (1.7)	4 (0.5)	2 (0.4)	3 (1.2)	3 (0.4)
Mean (SE) Blood Pressure, mm Hg						
Systolic	119 (2.6)	122 (8.3)	120 (2.5)	123 (2.3)	118 (5.3)	122 (2.1)
Diastolic	74 (1.4)	65 (2.0)	73 (1.3)	74 (1.5)	75 (3.8)	74 (1.4)
Fredrickson Type, n (%)						
IIa	2 (5)	0 (0)	2 (4)	1 (2)	0 (0)	1 (2)
IIb	31 (76)	2 (33)	33 (70)	28 (65)	2 (22)	30 (58)
IV	8 (20)	4 (67)	12 (26)	14 (33)	7 (78)	21 (40)
Mean[a] (SE) Lipid Values, mg/dL						
LDL-C	187 (7.6)	109 (7.6)	177 (7.7)	192 (7.6)	107 (4.6)	177 (7.7)
Total Cholesterol	296 (7.7)	234 (8.1)	288 (7.4)	297 (8.6)	246 (6.0)	289 (7.7)
HDL-C	37 (1.5)	31 (1.7)	36 (1.4)	38 (1.3)	30 (1.2)	36 (1.2)
Triglycerides (TG)	384 (18.8)	505 (71.8)	400 (19.4)	338 (12.8)	588 (44.8)	382 (18.4)
HDL-TG	22 (1.2)	28 (3.5)	23 (1.2)	21 (1.0)	31 (3.6)	23 (1.1)
LDL-TG	50 (2.8)	34 (3.4)	48 (2.6)	50 (2.9)	46 (3.6)	49 (2.5)
VLDL-TG	312 (18.7)	443 (70.7)	329 (19.4)	268 (12.6)	511 (46.3)	310 (18.2)
VLDL-C	71 (3.8)	94 (13.9)	74 (3.9)	68 (3.0)	109 (5.6)	75 (3.4)
Apo A-I	133 (3.8)	120 (4.4)	131 (3.4)	133 (2.5)	129 (5.9)	132 (2.9)
Apo B	163 (4.7)	123 (3.0)	158 (4.5)	162 (5.3)	128 (3.3)	156 (4.8)
LDL-Apo B	141 (4.7)	94 (3.6)	135 (4.8)	142 (5.3)	98 (3.3)	134 (5.0)
VLDL-Apo B	21 (0.9)	30 (3.6)	23 (0.9)	20 (0.9)	30 (2.5)	22 (1.0)

1). The patients randomized to atorvastatin and fenofibrate were comparable in terms of race, age , and body mass index.

2). The baseline lipid values were comparable between the two groups although a greater percentage of patients were classified as Type IIb (70%) than in the fenofibrate group (58%) and a greater percentage of patients were classified as Type IV in the fenofibrate group (40) than in the atorvastatin group (26%). Since electrophoresis phenotyping were not performed, no particular significance can be attached to the clinical classification of Fredrickson's Types.

3). It is relevant to note that only 4 patients in the atorvastatin group and only 7 patients in the fenofibrate group had "isolated hypertriglyceridemia" (true Fredrickson's Type IV)..

4.3.4.2 **Efficacy Endpoints Outcomes:** Only the secondary parameters of TG, VLDL-TG. LDL:-TG, and HDL-TG are pertinent to this review. The results are shown below:

Table 4.3.4.2: Mean (SE) values for secondary Efficacy parameters:

Variable	Week 12 Analysis				Week 24 Analysis			
	Atorvastatin 10 mg N = 46		Fenofibrate N = 52		Atorvastatin 20 mg N = 45		Fenofibrate N = 41	
Secondary Parameters								
Total Cholesterol								
Baseline	288	(7.6)	289	(7.7)	288	(7.7)	292	(9.1)
Last Visit	209	(6.3)	247	(6.3)	193	(5.6)	251	(7.3)
Change	-79	(5.5)	-42	(5.5)	-95	(5.1)	-41	(6.6)
Percent Change	-26*	(2.1)	-13	(2.0)	-30*	(2.2)	-11	(2.2)
Total Triglycerides (TG)								
Baseline	402	(20)	382	(18)	402	(20)	369	(19)
Last Visit	292	(18)	196	(12)	276	(20)	215	(17)
Change	-110	(15)	-186	(15)	-126	(19)	-155	(19)
Percent Change	-26*	(4.0)	-48	(3.6)	-29*	(5.7)	-41	(5.6)
VLDL-TG								
Baseline	331	(20)	310	(18)	331	(20)	299	(18)
Last Visit	234	(17)	134	(11)	218	(20)	153	(16)
Change	-97	(14)	-176	(15)	-113	(18)	-146	(18)
Percent Change	-27*	(4.6)	-56	(4.2)	-31*	(6.6)	-47	(6.5)
LDL-TG								
Baseline	49	(2.6)	49	(2.5)	49	(2.7)	48	(1.8)
Last Visit	37	(2.0)	44	(2.1)	36	(2.7)	42	(1.9)
Change	-11	(1.8)	-6	(1.7)	-12	(2.4)	-6	(1.7)
Percent Change	-14*	(4.1)	-2	(3.8)	-23*	(4.9)	-11	(5.1)

a Least squares means provided for percent change based on ANCOVA model with effects due to treatment, center, type of dyslipidemia, and the baseline as a covariate

* Significantly different from fenofibrate ($p \leq 0.05$)

1). Of the relevant secondary parameters, both total TG and VLDL-TG decreased more due to fenofibrate than atorvastatin at both the 12-week and 24-week analysis ($P < 0.05$).

2). In contrast, LDL-TG decreased more with atorvastatin than with fenofibrate at both the 12-week and 24-week analysis ($P<0.05$). Similarly, both LDL-C and LDL-ApoB showed greater decreases with atorvastatin.

3). These reflect the fact that atorvastatin, a HMG-CoA reductase inhibitor, has potent and direct effect on LDL-lipoprotein synthesis and degradation. On the other hand, HMG-CoA reductase does not play a direct role in either the synthesis or the hydrolysis of TG.

4.3.4.3. Safety Outcomes:

1). No death in the atorvastatin group. There was one death in the fenofibrtate group due to myocardial infarction. One patient each in the fenofibrate group had severe upper G.I. bleed and perforated duodenal ulcer. None of these were considered due to fenofibrate.

2). 11 patients (1 atorvastatin and 10 fenofibrate) withdrew from the study due to an adverse events as depicted below:

Table 4.3.4.3: Adverse Events Resulting in Withdrawal [Number (%) of Patient:

BODY SYSTEM/ Adverse Event[a]	Atorvastatin N = 47		Fenofibrate N = 52	
BODY AS A WHOLE	1	(2)	3[c]	(6)
Allergic Reaction	1	(2)	0	(0)
Asthenia	0	(0)	2	(4)
Headache	0	(0)	1	(2)
Hernia	0	(0)	1	(2)
DIGESTIVE SYSTEM	0	(0)	3	(6)
Anorexia	0	(0)	1	(2)
Gastrointestinal Hemorrhage	0	(0)	1	(2)
Liver Function Tests Abnormal	0	(0)	1	(2)
METABOLIC AND NUTRITIONAL DISORDERS	0	(0)	1[c]	(2)
ALT Increased	0	(0)	1	(2)
AST Increased	0	(0)	1	(2)
MUSCULOSKELETAL SYSTEM	0	(0)	1	(2)
Myalgia	0	(0)	1	(2)
NERVOUS SYSTEM	0	(0)	2	(4)
Libido Decreased	0	(0)	1	(2)
Vertigo	0	(0)	1	(2)
SKIN AND APPENDAGES	0	(0)	1	(2)
Rash	0	(0)	1	(2)

1). One atorvastatin patient withdrew due to allergic reaction.

2). No patient in the atorvastatin group and 2 patients in the fenofibrate group were withdrawn due to liver transaminase levels/abnormal liver function tests.

3). Abnormal laboratory values at ant time during the study are shown below:

Table 4.3.4.4: Abnormal Lab. Values During the Study [Number(%) of Patients]:

Variable	Reference Range (Units)	Reason	Atorvastatin N = 47		Fenofibrate N = 52	
ALT		>ULN	10	(21)	8	(15)
AST		>ULN	6	(13)	10	(19)
Glucose		>1.25 × ULN	3	(6)	4	(8)
WBC		<0.75 × LLN	2	(4)	1	(2)
Any Abnormality			16	(34)	15	(29)

ULN = Upper limit of normal; LLN = Lower limit of normal.

1). No atorvastatin-treated patient and 1 fenofibrate-treated patient had AST/ALT elevations >3X ULN.

2). When patients' maximum baseline values were compared with their highest values during treatment, no significant treatment trend was seen with any elevations in ALT, AST, or CPK.

4.3.5: Reviewer's Comments/Conclusion of Study Results:

APPEARS THIS WAY ON ORIGINAL

4.3.5.1: Safety:

1). No clinically important laboratory abnormalities was observed in the atorvastatin-treated patients, i.e. ALT, AST, and CPK.

APPEARS THIS WAY ON ORIGINAL

2). There were no new/unexpected adverse events reported in this study from the previously submitted safety data and listed in the Labeling.

4.3.5.2: Efficacy:

APPEARS THIS WAY ON ORIGINAL

1). In 99 patients (3 with Fredrickson Type IIa, 63 with Type IIb, and 33 with Type IV) fenofibrate (100 mg TID) treated patients statistically significant greater decreases in both total TG and VLDL-TG than atorvastatin-treated (10 and 20 mg/day) patients at both the 12-week and 24-week analysis ($P< 0.05$).

APPEARS THIS WAY ON ORIGINAL

2). In contrast, LDL-TG decreased more with atorvastatin than with fenofibrate at both the 12-week and 24-week analysis ($P<0.05$). The significance/implication of these findings is not obvious.

3). No data submitted on pancreatitis

5. Overview of Safety:

In this Supplemental NDA submission of 3 clinical studies, no clinically

important abnormal laboratories were observed with the doses used (5, 10, 20, and 80 mg/day). And there were no new/unexpected adverse events reported in these studies from the previously submitted safety data and listed in the Labeling.

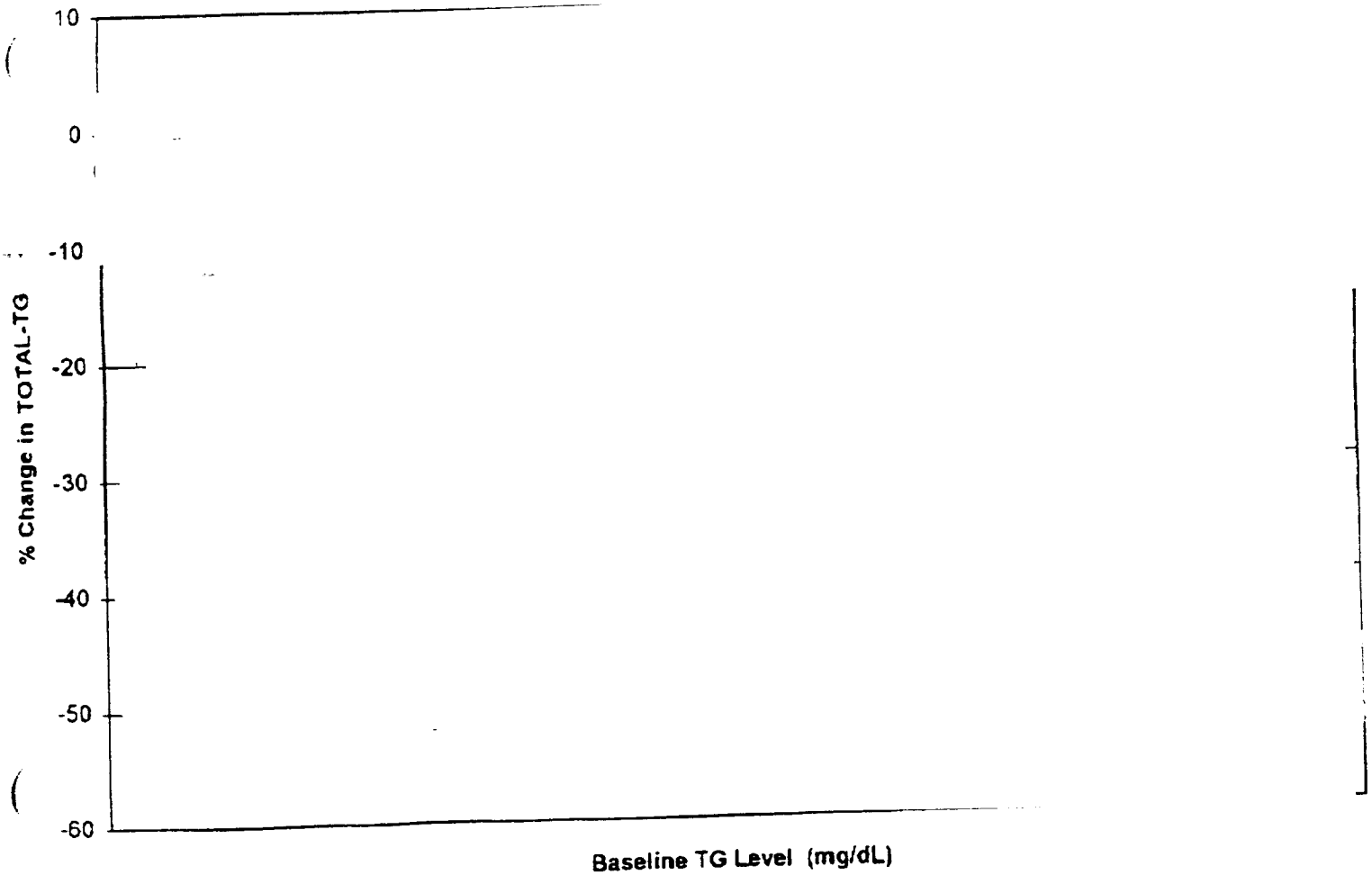
6. **Overview of Efficacy:**

A. Efficacy in decreasing TG:

1). In the three submitted clinical studies, a total of 107 patients with Fredricksons' Type IV were studied. The 47 patients randomized to placebo, 5, 20 and 80 mg of atorvastatin showed statistically significant decreases in total TG. Mean percent decrease were -27.3% , -33.6% and -42,4% respectively for the 5, 20 and 80 mg doses.
Similarly statistically significant decreases were observed in the VLDL-TG, LDL-TG and HDL-TG fractions.

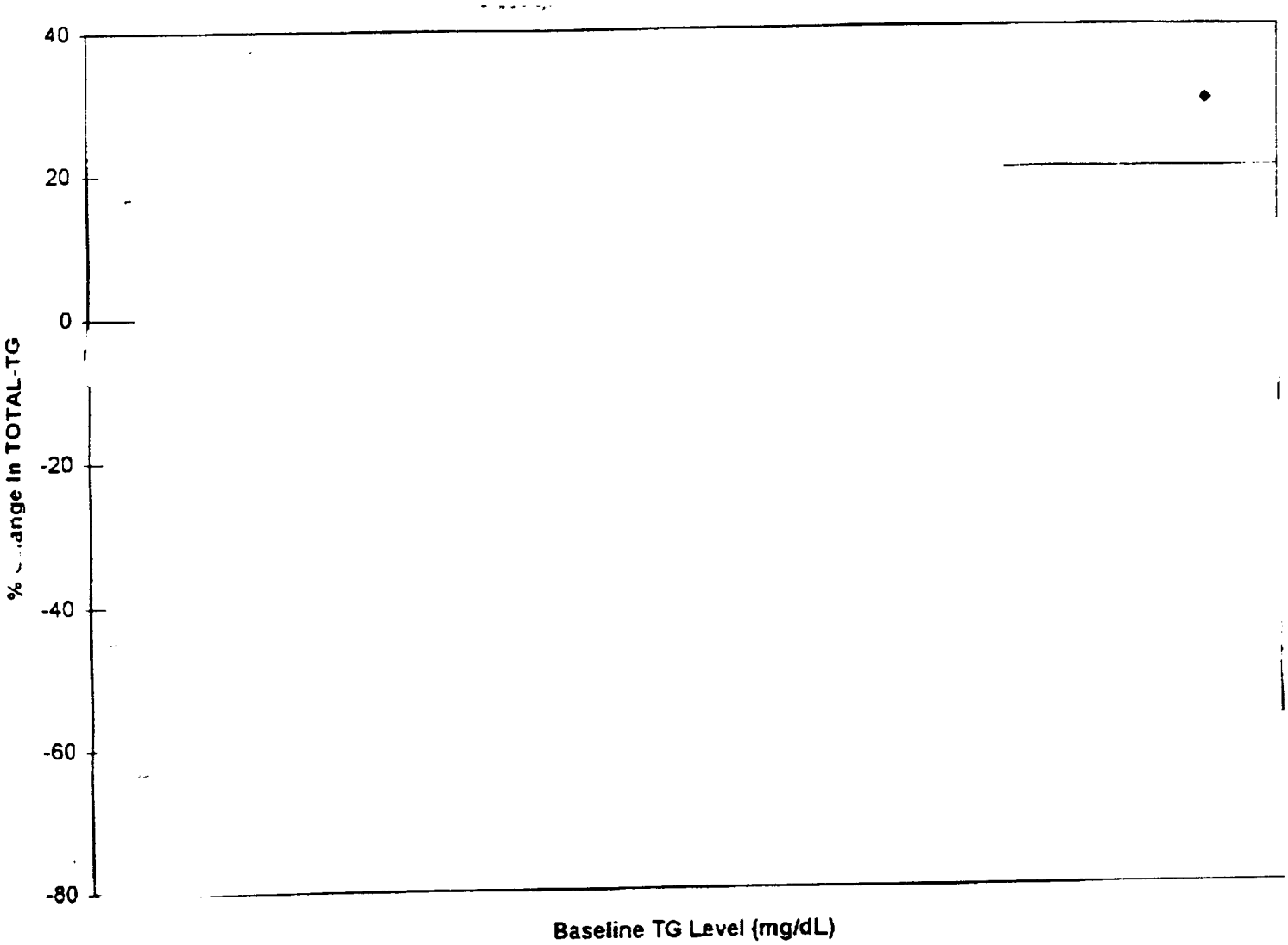
2). To further define the responses, upon request, the Sponsor submitted additional data of the baseline TG levels of individual patients. Since the TG responses were very variable, the median responses were calculated The responses by baseline TG levels can be seen in Figures 6.1-6.3:

Figure 6.1: Scatter Plot of Percent Change from Baseline in Total-TG by Baseline TG for 5 mg Atorvastatin:



1/13 had an increase of total-TG ~ 5%.
The median decrease was -28 vs. Mean % change of -23%.
Correlation Coefficient was not significant at -0.5097%..

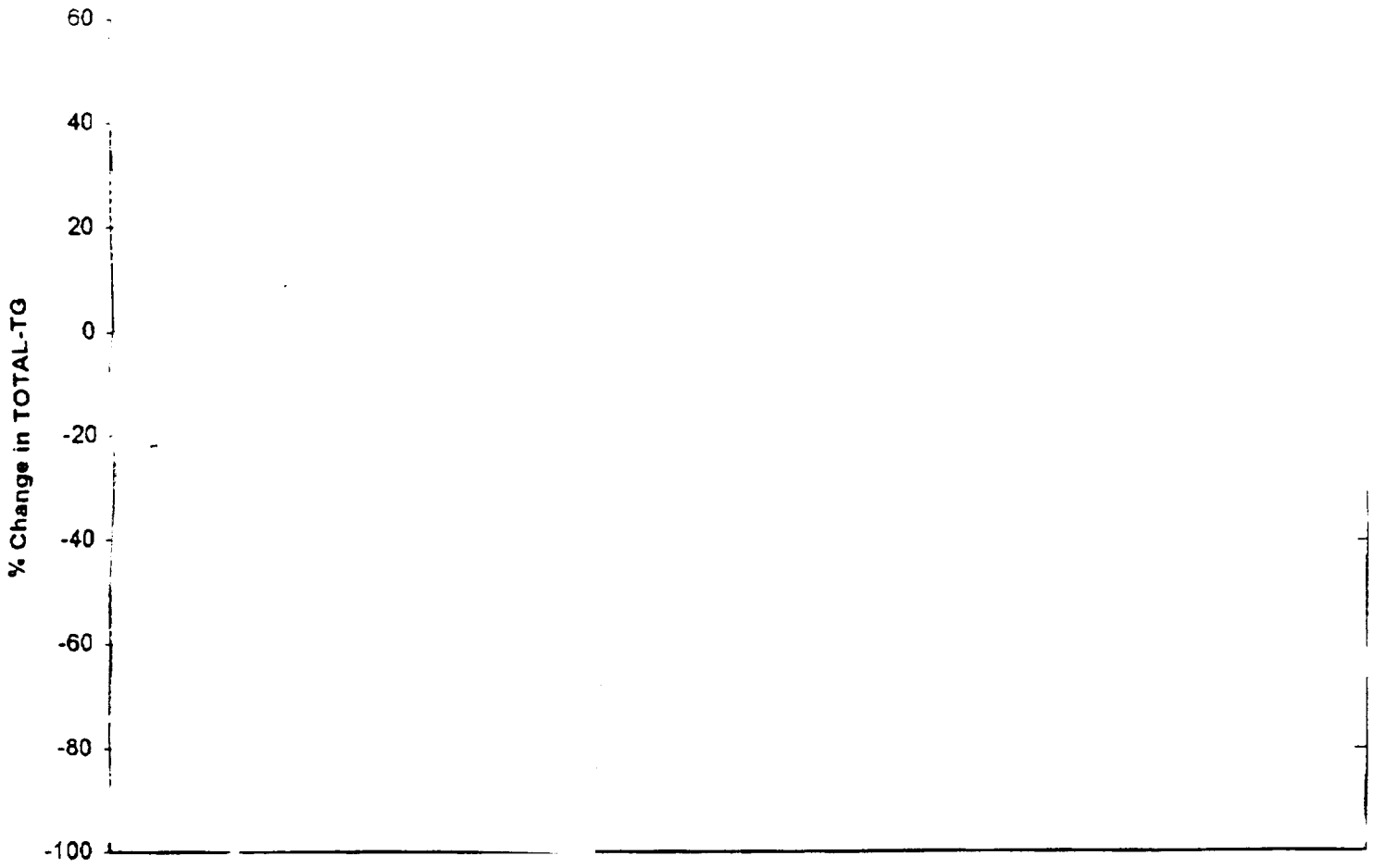
Figure 6.2: Scatter Plot of Percent Change from Baseline in Total-TG by Baseline TG for Atorvastatin 20 mg/day:



APPEARS THIS WAY
ON ORIGINAL

2/16 had increases of total-TG
The median decrease was -33% vs. Mean % change of -33.6%.
Correlation Coefficient was not significant at +0.3349.

Figure 6.3: Scatter Plot of Percent Change from Baseline in Total-TG by Baseline TG for Atorvastatin 80 mg/day:



1/12 had increases of total-TG > 40%.
The median decrease was -47% vs. Mean % change of -42.4%.
Correlation Coefficient was not significant at -0.4215.

3). As can be seen from the above scatter plots, there was no significant correlation between the baseline TG and the response to atorvastatin treatments. This is dramatically depicted in the scatter plot for the 80 mg dose group in which one patient with a baseline TG ~400 mg/dL and the other patient with baseline TG of ~1000 mg/dL had almost the same response,(~80% decrease). One possible reason is the large spontaneous fluctuation of TG due to activity, energy balance, emotional/ psychological state.....etc.

4). The other factor maybe the small number of patients studied (N=47). Therefore, data from other studies (from Data Base 3) were included

Table 6.1: Median (Minimum-Maximum) Percent Change of total TG from Baseline: Sub-group TG>500 mg/dL vs. Total cohorts:

	Parameter.	Placebo	10 mg	20 mg	80 mg
SUB-GROUP TG> 500 mg /dL		n=9	n=28	n=9	n=10
	Baseline	680	546	795	612
	Treated	553	367	436	246
	Change	-128	-173	-359	-367
	% change	-19	-42	-45	-60
TOTAL COHO-RTS N=76	% change	-12	-41	-39	-52
	Change	-63	-231	-192	-296
	Treated	514	329	350	257
	Baseline	617	568	579	537
		n=12	n=37	n=13	n=14

Table 6.2: Median (Minimum-Maximum) Percent Change of non-HDL-C from Baseline: Sub-group TG>500 mg/dL vs. Total cohorts:

	Parameter	Placebo	10 mg	20 mg	80 mg
SUB-GROUP TG> 500 MG /Dl		n=9	n=28	n=9	n=10
	Baseline	229	260	272	241
	Treated	234	176	172	103
	Change	+5	-80	-105	-130
	% change	-13	-32	-45	-58
TOTAL COHO-RTS	% change	-2.8	-33	-43	-52
	Change	-6	-77	-98	-107
	Treated	219	160	128	102
	Baseline	226	239	230	217
		n=12	n=37	n=13	n=14

Table 6.3: Median (Minimum-Maximum) Percent Change of total TG and non-HDL-C from Baseline: Sub-group LDL>160 mg/dL vs. Total cohorts:

	TG		non-HDL-C	
	LDL>160,N=11	COHORTS,N=64	LDL>160,N=11	COH0RTS.N=64
Baseline	623	565	276	235
Treated	341	318	161	147
Change	-262	-231	-116	-80
% change	-46	-41	-38	-37

Table 6.4: Median (Minimum-Maximum) Percent Change of total TG and non-HDL-C from Baseline for TG>1000/1500 mg/dL:

	Parameter	Atorvas. 10 mg	Atorvas. 20 mg	Atorvas. 80 mg
TOTAL TG	Baseline	1067	1020	1502
	Change	-407	-490	+443
	% change	-38	-48	+29
NON-HDL C	Parameter	304	473	348
	Change	-101	-254	-61
	% change	-33	-54	-17

Conclusions:

1. **There was no significant correlation between the baseline TG and TG-lowering to Atorvastatin treatment.**
2. **For total TG, HDL-C and VLDL-C lowering , the linear trend tests across the doses of 10, 20 and 80 mg were not significant.**
3. **For the subgroup of patients with baseline TG>500 mg/dL, the TG and non-HDL-C decreases were similar to the entire cohorts with TGs ranging from 267 to 1502 mg/dL.**
4. **For the subgroup of patients with baseline LDL>160 mg/dL, the TG and non-HDL-C decreases were similar to the entire cohorts with LDL-Cs**

B. Efficacy in reducing the risk of pancreatitis:

1). Fortson et al (Fortson MR; Freedman SN; Webster PD; Clinical assessment of hyperlipidemic pancreatitis, Am. Jour. Gastro.90(12), 1995, 2134-2139) studied the clinical presentation of pancreatitis secondary to hyperlipidemia, the role of alcohol, diabetes, or known causes of hypertriglyceridemia. In 70 cases of documented pancreatitis, hypertriglyceridemia was the etiology in of patients discharged with that diagnosis. Lipemic serum was described in 45%, mean TG levels were 4587+3616 mg/dL. The most common presentation was a poorly controlled diabetic with a history of hypertriglyceridemia. The second presentation was the alcoholic with lactescent serum on admission.

2). This and other studies confirm the view that nondiabetic, nonalcoholic, nonobese patient with hypertriglyceridemia is not a common cause of pancreatitis. Furthermore, the TG levels are usually in excess of There are evidence to suggest that plasma TG removal mechanisms are saturable in man. Brunzell et al (Brunzell JD; Hazzard WR; Porte D; and Bierman EJ: Evidence for a Common, Saturable, TG Removal Mechanism for Chylomicrons and VDLD Lipoproteins in Man,

JCI, 52:1973, 1578-1585), showed that in subjects with fasting chylomicronemia (Type V) on a normal diet, restricting carbohydrate intake led to disappearance of chylomicronemia (Type V to Type IV). Conversely, in those subjects without chylomicronemia, chylomicronemia appeared in response to increased carbohydrate intake (Type IV to Type V). The authors state, "Thus chylomicron concentrations in plasma were altered even though fat intake and presumably chylomicron input into plasma was kept constant. These findings provide evidence for saturation of chylomicron removal mechanisms by alteration of endogenous TG-rich lipoprotein concentrations." They suggest that chylomicrons compete with VLDL lipoproteins for similar removal mechanisms. This accounts for the fact that pancreatitis is common in Type 1 lipoproteinemia with fasting chylomicronemia and it is present in Type IV only when the TG levels are in excess

3). The majority of patients included in this submission had baseline TG levels of <800 mg/dL and a few The risk of pancreatitis was extremely small and the reduction of such risk by decreasing TG cannot be reliably assessed.

APPEARS THIS WAY ON ORIGINAL

7. Labeling Review:

A. Clinical Pharmacology:

Proposed revision:

"Lipitor reduces total-C, LDL-C, VLDL-C, apo-B, and TG and increases HDL-C in patients with isolated hypertriglyceridemia."

Change to:

"Lipitor reduces total-C, VLDL-C, apo-B, and TG and increases HDL-C (only in the 80 mg dose) in patients with isolated hypertriglyceridemia. The clinical benefits of these changes are yet to be determined.

B. Text:

APPEARS THIS WAY ON ORIGINAL

Proposed revision:

Hypertriglyceridemia (Fredrickson Types IV and V)

In a dose-response study in patients with isolated hypertriglyceridemia, atorvastatin 20 mg daily reduced TG and LDL-C by 24% and 31%, and atorvastatin 80 mg daily reduced TG and LDL-C by 42% and 36%."

Change to:

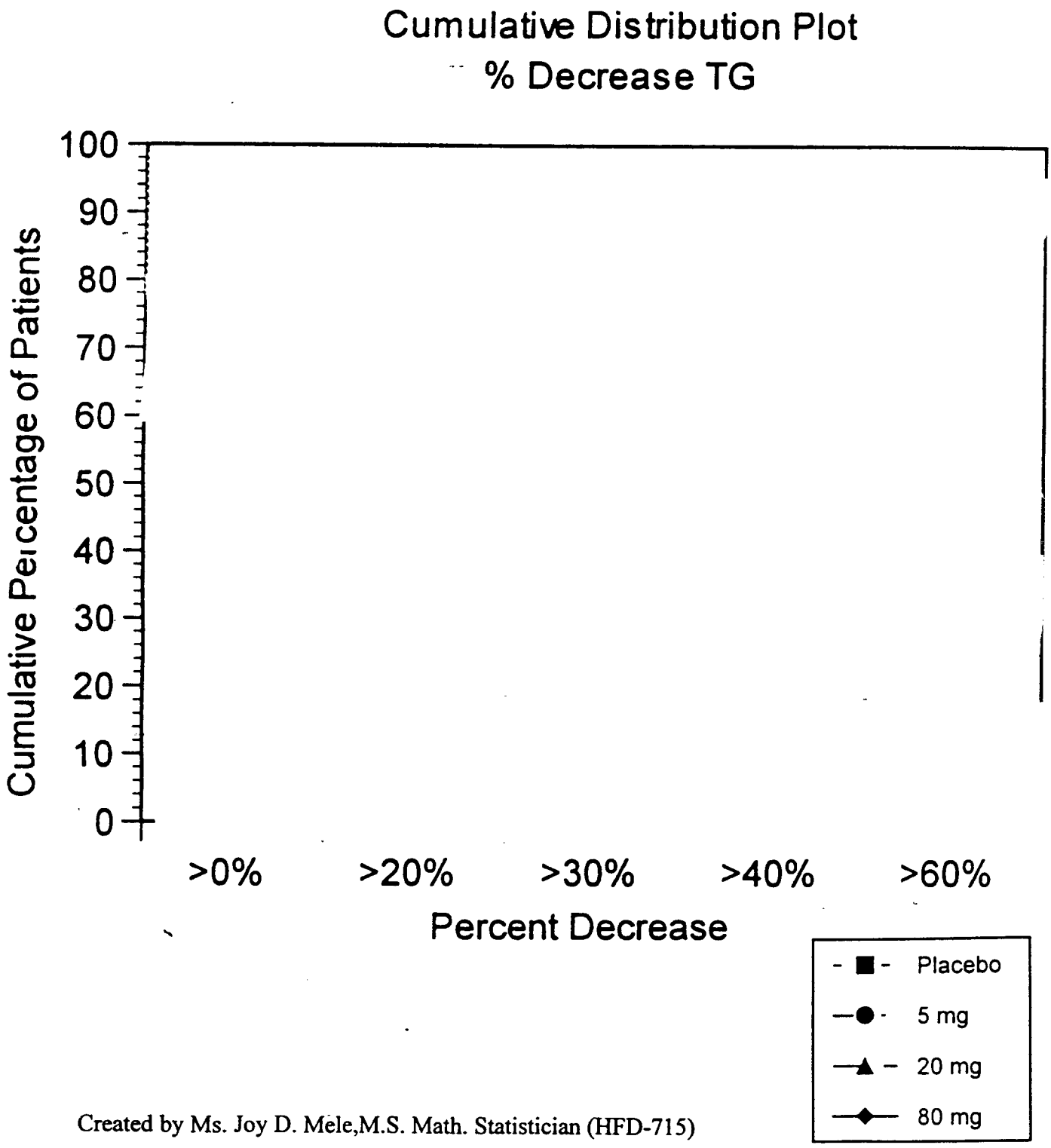
Hypertriglyceridemia (Fredrickson Type IV)

In patients with isolated hypertriglycedemia, treatment with atorvastatin showed:

1. **There was no significant correlation between the baseline TG and TG-lowering to Atorvastatin treatment.**
2. **For total TG, HDL-C and VLDL-C lowering , the linear trend tests across the doses of 10, 20 and 80 mg were not significant.**

3. **For the subgroup of patients with baseline TG>500 mg/dL, the TG and non-HDL-C decreases were similar to the entire cohorts with TGs**

In a dose-response study, the following data are obtained:



Created by Ms. Joy D. Mele,M.S. Math. Statistician (HFD-715)

C. **Indications and Usage:**
Proposed revision:
"Lipitor is indicated as adjunctive therapy to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Types IV and V) who present a risk for pancreatitis."
Change to:
No Type V patient was studied. The majority of Type IV patients included in this submission had baseline TG levels of <800 mg/dL and a few
The risk of pancreatitis was extremely small and the reduction of such risk by decreasing TG cannot be reliably assessed.

APPEARS THIS WAY
ON ORIGINAL

D. **Dosage and Administration:**
Proposed revision:
"Hypertriglyceridemia (Fredrickson Types IV and V) and Dysbetalipoproteinemia (Fredrickson Type III)."
Change to:
"Hypertriglyceridemia (Fredrickson Type IV) and Dysbeyalipoproteinemia (Fredrickson Type III)."

APPEARS THIS WAY
ON ORIGINAL

8. Recommended Regulatory Action:

This NDA Supplement is approvable provided the draft labeling is revised as shown above. This review completed after Team Leader's review. See the Team Leader's review for background and for labeling recommendations.

/S/

7-8-98 S.W.Shen, M.D.

APPEARS THIS WAY
ON ORIGINAL

/S/

Medical Officer, ~~HFD-510~~

CC:
Original NDA Supplement
HFD-510-File
HFD-510-SWSHEN
HFD-510-MSIMONEAU

APPEARS THIS WAY
ON ORIGINAL