CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-702/S025

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA #	20-702 SE8-025
Drug Name:	Lipitor (atorvastatin calcium) tablets
Sponsor:	Parke-Davis Pharmaceutical Research
Indication:	Geriatric Use Labeling Supplement [redacted] Section of the Draft Labeling
Review Documents:	Electronic submission dated August 10, 2000, SAS data sets and its related submissions dated 3/5/01, 3/26/01, and faxes 4/26/01 and 4/30/01 to be formally submitted in late May
Medical Team:	Elton Herman, M.D. and Mary H Parks, M.D. (HFD-510)

The following review has discussed with the medical review team. The sponsor's Tables and Figures referred to in the text can be found in the Appendices after the review text starting on p.11 of this review.

The sponsor's request of geriatric labeling and draft labeling [redacted] section were based on the subset of geriatric patients in the clinical trial ACCESS for the geriatric labeling and for the revised clinical studies section. A letter was issued (internal signed off date March 29, 2001) to the sponsor on the unbundling of the geriatric submission and the [redacted] submission. The electronic data of ACCESS was submitted along with the original supplement NDA submission. This reviewer had performed the necessary evaluation based on the entire ACCESS trial and the requested geriatric subpopulation. It is noted that the geriatric subgroup evaluation would be appropriate only if the complete review of the original ACCESS trial demonstrates a significant treatment effect on atorvastatin. In a recent internal labeling meeting on May 14, 2001, it was acknowledged that this statistical review will be logged into the DFS system and used as a part of the further review should the sponsor use the ACCESS trial to pursue a [redacted] in the future. The review on the geriatric subpopulation still applies to the geriatric labeling.

HIGHLIGHTS OF ISSUES

Results of ACCESS trial raise a potential concern about one of the co-primary safety parameters, i.e., percentage of patients with persistent transaminase elevations measured by ALT or AST elevations. There were 10 patients (0.51%) treated with atorvastatin who reported persistent transaminase elevations defined as 2 consecutive ALT/AST levels >3 x the upper limit of normal. This appeared to be a 3-fold increase with atorvastatin calcium (95% CI 1-fold to 11-fold) than the All Controls statins (0.15%) combined, nominal p-value of 0.052.

The results of ACCESS trial appeared to show that atorvastatin is superior to the All Controls group on the co-primary efficacy endpoints of (1) the percent change from baseline in LDL-C and (2) the percent of patients meeting NCEP LDL-C criteria at initial dose (week-6). For safety, atorvastatin patients appeared to be more likely to have persistent liver function elevations, marginally significantly different, than the All Controls group. There was no report of patients developing myopathy defined as CPK > 10 times the ULN on two consecutive measurements and associated muscle symptoms.

Given that the overall study showed a positive atorvastatin effect, geriatic use labeling and clinical studies section draft labeling are reviewed and evaluated accordingly.

Keywords: Geriatric Use, Cochran-Mantel-Haenszel Test, Clinical Study.

1 BACKGROUND

Lipitor (atorvastatin clacium) Tablets has been approved for treatment of hypercholesterolemia in 1997. It has been marketed in the United States since February 1997. Parke-Davis, on behalf of and as agent for Warner-Lambert Export Limited, submitted an updated text describing new data on **Geriatric Use,** [redacted] section. According to the sponsor's submission dated August 10, 2000, "It was

agreed with the Division that the proposed changes in the **Geriatric Use** [redacted] of the labeling could be revised in a single submission."

Data to Support the Proposed Geriatric Use Labeling are

- Extensive post-marketing surveillance database evaluated with respect to geriatric use.
- Literature search was done to capture any published cases of adverse events that would suggest differences in safety between the elderly population and the general population.
- The ACCESS study

This review focuses on the evaluation of the ACCESS clinical trial and its subgroup by age and by other factors.

2 ACCESS STUDY

"A 54-week open label assessment of the safety and efficacy profile of atorvastatin as compared to fluvastatin, lovastatin, simvastatin, and pravastatin when used to optimally control primary hypercholesterolemia (Type IIA) and mixed dyslipidemia (type IIB), which included a significant number of elderly patients"

Trial Design: This was a 54-week, multi-center (158 centers), open-label, randomized, parallel-arm study in a patient population with or without documented coronary heart disease (CHD) and/or peripheral vascular disease (PVD). A total of 3919 patients were randomized in a 4:1:1:1:1 ratio to receive atorvastatin (n=1958), fluvastatin (n=497), lovastatin (n=498), pravastatin (n=481), and simvastatin (N=482), respectively. The sample size was not based on power consideration, rather it was judged to provide sufficient data to evaluate the safety of atorvastatin relative to the other statins. The study consists of 3 phases, see Figure 1 in p.11. The screening phase ranged from 5 to 12 weeks, followed by a 4-week lead-in phase, and a 54-week, open-label treatment phase. **During the treatment phase, titration in dose was initiated only after lipid determinations assessed at weeks 6, 12, and 18 were shown not to meet the patient's NCEP (National Cholesterol Education Program)* target lipid value. After the NCEP target goal was reached, no further upward titrations were allowed regardless of subsequent lipid values. No back titration was allowed.** The starting dose was 10mg with atorvastatin, pravastatin, and simvastatin and was 20mg with fluvastatin and lovastatin. The maximum dose after titration, however, was 80mg with atorvastatin, fluvastatin, and lovastatin and was 40mg with pravastatin and simvastatin. Study visits took place at screening and at weeks - 4, -2, 0, 6, 12, 18, 24, 30, 42, and 54, as shown in Schedule of Study Evaluation and Procedures of Table 3 (see p.12). Trial was initiated in May 1997 and ended in January 1999.

*NCEP Risk Category	Target LDL-C Level (NCEP)
No CHD/PVD and 1 or no risk factors	<160 mg/dL
No CHD/PVD and 2 or more risk factors	<130 mg/dL
Clinically evident CHD or PVD	≤100 mg/dL

The primary objective of the study was to determine the safety and efficacy profile of atorvastatin as compared to other HMG Co-A reductase inhibitors when used to treat patients as per NCEP LDL-C guidelines. The primary efficacy parameters were the percent change from baseline in LDL-C and the percent of patients meeting NCEP LDL-C criteria at initial dose (week-6). The primary safety parameters was the % of patients with persistent (2 consecutive ALT/AST levels >3 x the upper limit of normal) liver function elevations, and the % of patients developing myopathy in addition to routine safety monitoring. The protocol specified statistical rationale and analysis is summarized. For the primary efficacy parameters, atorvastatin was to be compared to each control treatment separately; for the primary safety parameters, atorvastatin was to be compared to the control treatments combined, called All Control.

2.1 TRIAL RESULTS

The sponsor defined an intent-to-treat (ITT) population as all patients who were randomized, took at least one dose of study medication, and had valid efficacy evaluations at baseline and post-baseline. Based on this definition, 3.4% (131 patients) of randomized patients (n=3916) were excluded from the ITT patients. That is, 3785 patients were the basis for the ITT efficacy analysis. According to the sponsor, demographic and background data for all randomized patients was similar to the ITT population, see Table 6 of p.13. In the ITT population, all treatment groups were comparable, with mean age of 61.3 years, 89% Caucasian, 61% males, and 12% of patients had <2 risk factors for CHD/PVD, 21% had ≥2 risk factors, and 67% had clinically evident CHD/PVD. Overall, 61% were classified as having Type IIa hyper-cholesterolemia while 39% having mixed dyslipidemia. The mean baseline lipid levels were as follows: LDL-C 178.3 mg/dL, HDL-C 47.6 mg/dL, and LDL-C/HDL-C ratio 3.9, TG 190.0 mg/dL, TC 263.8 mg/dL, and Apo B 169.0 mg/dL.

With respect to cardiovascular history, the most common conditions reported were essential hypertension (56% male, 60% female), angina pectoris (55% male, 40% female), acute myocardial infarction (43% male, 23% female), operations on vessels of the heart (30% male, 19% female), cardiac dysrhythmias (23% male, 19% female), other peripheral vascular disease (12% male, 13% female), and heart failure (8% male, 7% female).

Patient disposition for all randomized patients was summarized in Table 9 (see p.14). The atorvastatin group had the least percentage of patients early discontinued the study (13.6%), these percentages range from 17.4% (simvastatin) to 24.1% (fluvastatin) for the other four statins.

Reviewer's Comments: It is noted that numerically, fluvastatin had the greatest percentage of patients who discontinued the study early due to adverse event (12.9%) and had the least percentage of patients completed the study (75.9%). A closer look of reasons for early discontinuation showed that 0.2% in atorvastatin, 5.0% in fluvastatin, 0.4% in lovastatin, 4.1% in pravastatin, and 1.2% in simvastatin were dropouts due to a lack of efficacy.

EFFICACY

The percent change in LDL-C levels from baseline to Week 6, and the percentage of patients meeting NCEP LDL-C criteria while on their initial dose at Week 6 were the primary measures of efficacy. Secondary efficacy outcomes included the percent change from baseline in other lipid related outcomes at Week 6 and at Week 54, and the percentage of patients achieved their NCEP LDL-C goals at Week 54.

Primary Efficacy Variables:

- **The percent change from baseline in LDL-C (week-6)**

ITT population

Of all randomized patients, 4% to 5% did not have the LDL data at week-6. Baseline LDL-C levels were comparable among the five treatment groups. The percent change in LDL-C from baseline to Week 6 for the ITT population is displayed in Table A under the row labeled "ITT patients". A graphical presentation of mean % reduction is shown in Figure 2 (see p.15).

Table A. Percent change in LDL-C from baseline to Week 6, ITT population and by age subgroups

Patient group	N	Baseline		Percent change		Treatment comparisons
		Mean	(SE)	Mean	(SE)	95%CI for LS mean diff
ITT patients						
Atorvastatin	1888	178.5	0.79	-36.1	0.25	
Fluvastatin	474	178.9	1.59	-18.8	0.54	-18.5, -16.1
Lovastatin	472	178.1	1.46	-26.7	0.58	-10.7, -8.3
Pravastatin	461	179.3	1.57	-19.6	0.58	-17.7, -15.3

Simvastatin	462	175.6	1.45	-29.5	0.54	-7.7, -5.3
<70 years of age						
Atorvastatin	1386	180.4	0.95	-35.2	0.29	
Fluvastatin	340	179.9	1.94	-17.7	0.66	-18.9, -16.1
Lovastatin	350	180.3	1.73	-25.2	0.68	-11.4, -8.7
Pravastatin	348	181.6	1.87	-19.2	0.66	-17.3, -14.7
Simvastatin	345	178.1	1.72	-28.6	0.63	-7.8, -5.1
≥ 70 yrs						
Atorvastatin	502	173.4	1.39	-38.7	0.46	
Fluvastatin	134	176.5	2.76	-21.8	0.92	-19.1, -15.0
Lovastatin	122	171.7	2.63	-30.9	1.00	-9.9, -5.6
Pravastatin	113	172.5	2.68	-20.8	1.24	-20.0, -15.7
Simvastatin	117	168.2	2.56	-32.2	0.96	-8.4, -4.1

Reviewer Comments: The mean percent reduction at week 6 from baseline in LDL-C was statistically significant in all treatment groups, 36% in atorvastatin, 19% in fluvastatin, 27% in lovastatin, 20% in pravastatin, and 30% in simvastatin, respectively. It appeared that the atorvastatin group had the greatest mean percent reduction. The reduction was statistically significantly greater than any of the other four statins, $p \leq 0.001$.

Subgroup Analysis: The sponsor reported that the finding of greater LDL-C reductions in the atorvastatin group compared to the other statins was also seen when stratified by gender (male vs. female), age (< 70 vs. ≥ 70 years), and race (while, black, others), except in the "others" of race showing similar reductions in LDL-C across treatment groups, possibly due to small number of patients in this subgroup. This reviewer requested the sponsor to perform the analysis using the age cutoff of <65 vs ≥ 65 years, generally used for geriatric population. The results of the analysis for each age subgroup (see Ad-Hoc Table 3 in p.16) resembled the findings using the age cutoff of 70 years, as summarized in Table A above.

- **% of patients meeting NCEP LDL-C criteria at initial dose (week-6)**

ITT population

The percentages of patients achieving the NCEP goal at Week 6 are 53% in atorvastatin, 15% in fluvastatin, 28% in lovastatin, 15% in pravastatin, and 38% in simvastatin, respectively. The results can be found in the row labeled "ITT patients" of Table B below. The atorvastatin group had the highest percentage of achieving the goal. The percentage was statistically significantly much higher than any of the other four statins, $p \leq 0.001$.

Table B. Percent of patients Meeting NCEP LDL-C criteria at initial dose (Week 6)

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
ITT patients – (# meeting criteria / n)	53% (997/1888)	15% (69/474)	28% (134/472)	15% (71/461)	38% (174/462)
Comparison with Atorvastatin† Difference in %		38%	24%	37%	15%
< 65 years of age † (# meeting criteria / n)	51% (547/1078)	14% (36/262)	25% (69/276)	15% (39/263)	37% (98/265)
≥ 65 years of age † (# meeting criteria / n)	56% (450/810)	16% (33/212)	33% (65/196)	16% (32/198)	39% (76/197)

† $p \leq 0.0001$

Subgroup Analysis: the sponsor reported that atorvastatin maintained a superior percentage of patients achieving NCEP goal at Week 6 in the subgroup analyses. The sponsor also pointed out that patients who did not achieve the NCEP goal at Week 6 were forced to titrate to the next dosage level for that particular treatment group. This reviewer requested the sponsor to perform the same evaluation using 65 years as cutoff. The results are shown in the last two rows of Table B above.

Reviewer Comments: From the description of treatment administration stated in the sponsor submission p.19 of 16162, Item 8 Vol. # 003 "During the treatment phase, titrations in dose were initiated only after lipid determinations assessed at Weeks 6, 12 and 18 were shown not to meet the patient's NCEP target lipid value." This reviewer requested the sponsor to verify the ordering between the timing of dose titration and the counting of patients meeting NCEP LDL-C criteria at initial dose. According to the sponsor's fax communication dated April 26, 2001, "all included patients were still receiving their starting dose at the time of their week 6 assessment". Thus, there was no dose titration at the time of counting the # of patients meeting NCEP LDL-C criteria at initial dose (week-6).

Secondary Efficacy Variables:

The percent change from baseline to Week 6 and to Week 54 in other lipid related variables by treatment groups can be found in Tables 15 (see p.17) and 16 (see p.18).

Table C displays the percentage of patients achieving NCEP goal at Week 54/Endpoint with the ITT patients and by age subgroups defined by less than 65 vs. equal or greater than 65 years of age.

Table C. Percent of patients Meeting NCEP LDL-C criteria at initial dose (Week 54)

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
ITT patients – (# meeting criteria / n)	76% (1452/1902)	37% (178/477)	49% (235/476)	34% (158/462)	58% (271/468)
Comparison with Atorvastatin† Difference in %		39%	27%	42%	18%
< 65 years of age (# meeting criteria / n)	74% (803/1087)	34% (90/265)	44% (123/278)	36% (95/263)	56% (151/270)
≥ 65 years of age (# meeting criteria / n)	80% (649/815)	42% (88/212)	57% (112/198)	32% (63/199)	61% (120/198)

† $p \leq 0.0001$

Reviewer Comments: A consistent atorvastatin effect was observed in percent change from baseline to Week 6 and to Week 54 in other lipid related outcomes of LDL-C, LDL-C/HDL-C ratio, Triglyceride, Total Cholesterol, and Apolipoprotein-B, but not HDL-C. Similar finding was seen in percentage of patients achieving NCEP goal at Week 54/Endpoint across the two age groups of <65 and ≥65 years.

The sponsor also reported percent of patients meeting NCEP goal at both Week 6 and Week 54, as illustrated in Figure 5 (see p.19).

SAFETY

The sponsor used all patients who took at least one dose of study medication in the safety population. There were two pre-specified primary safety parameters. The results are summarized below.

- **% of patients with persistent (2 consecutive ALT/AST levels >3 x the upper limit of normal) transaminase (liver function) elevations**

The sponsor reported 10 patients (0.51%) in atorvastatin group and a total of 3 patients (0.15%) in the other four statin groups and stated that "the rate difference between the atorvastatin group and all control groups (0.36%) was not statistically significant [95% confidence interval (-0.0026, 0.7177)]". The sponsor concluded "The proportion of patients with marked persistent transaminase did not differ significantly between the atorvastatin group and the All Controls group".

Reviewer Comments: The 95% confidence interval in rate difference presented by the sponsor should be (–0.0026%, 0.7177%).

This reviewer performed statistical testing for this primary safety parameter in terms of risk difference and in terms of relative risk and observed a two-sided nominal p-value of 0.052 with risk difference evaluation and with relative risk evaluation. This reviewer used the relative risk measurement to illustrate the findings of a 3-fold increase (95% CI of 1-fold to 11-fold) in % of patients with persistent transaminase elevations with atorvastatin compared to the other four statins may be serious.

Table D. Percent of patients with persistent transaminase elevations – Sensitivity Analyses

	Atorvastatin	All Controls group (All other statins)	RR (95% CI)	Nominal p-value
Data observed % (# with event / n)	0.51% 10/1958	0.15% 3/1958	3 (1, 11)	0.052
Sensitivity analysis – 1	0.51% 10/1958	0.10% 2/1957	5 (1, 20)	0.021
Sensitivity analysis – 2	0.56% 11/1958	0.15% 3/1958	4 (1, 12)	0.032

From Table D, although the observed data showed a borderline nominal p-value of 0.052, one patient difference in reporting persistent transaminase elevation (ALT or AST elevations) could make a difference in terms of statistical significance. This reviewer performed two sensitivity analyses. Sensitivity analysis – 1 removed one patient with event from the all controls group keeping the events in atorvastatin group the same and Sensitivity analysis – 2 added one patient with event in atorvastatin group keeping the events in the All Controls group the same. Both sensitivity analyses indicated a potential signal that atorvastain may cause significantly more patients with persistent transaminase elevations than the All Controls treatment group.

Indeed, the study pre-specified two co-primary efficacy and two co-primary safety variables. All these four endpoints belonged to the primary objective. If one is interested in demonstrating at least one of the four primary variables being statistically significant, the two co-primary efficacy endpoints achieved their statistical significance by this rule. There appeared to be a strong numerical and possibly statistical signal that atorvastain may cause significantly more patients with persistent transaminase elevations than the control treatment.

This reviewer requested the sponsor to further summarize the percent of patients with persistent transaminase elevations by age subgroups. The results of the sponsor's analysis showed that the excess in ALT or AST elevations was primarily seen in the younger age group (age < 65 years). That is, the percentages of patients with elevated ALT or AST were 0.63% (=9/1439) with atorvastatin and 0.07% (=1/1450) with All Control in the <65 years age group, and 0.19% (=1/519) with atorvastatin and 0.39% (=2/508) with all controls in the ≥65 years group. When the event rates were summarized by individual component of transaminase elevation, it appeared that the excess was more prominent in ALT elevation than AST elevation in younger patients. No excess was observed in the older patients.

- **% of patients developing myopathy, defined as CPK > 10 times the ULN on two consecutive measurements and associated muscle symptoms**

The sponsor reported that no persistent elevations of CPK were observed for any treatment groups. According to the sponsor, one patient in fluvastatin group reported an adverse event of rhabdomyolysis which was asymptomatic and had no renal involvement and the diagnosis was based on a CPK value of 5600 mU/mL.

The results broken down by components in the primary safety evaluation are displayed in Table 19 (see p.20) for the safety population.

It is noted that the dosages applied in the five statins vary. Table 22 (see p.21), reported by the sponsor, provides a summary of exposure days by treatment group and the average dose of each study medication.

3 LABELING

Proposed Geriatric Use Labeling

Geriatric Use

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Reviewer Comments: From Review and Evaluation performed in Section 2, this reviewer raised a serious concern on the finding of a 3-fold increase (95% CI of 1-fold to 11-fold) in % of patients with persistent transaminase elevations when treated with atorvastatin compared to the other four statins. Further sensitivity analyses performed by this reviewer indicated that the observed difference (0.51% [10/1958] in atorvastatin and 0.15% [3/1958] in the All Controls group) is very sensitive and could easily reach conventional statistical significance at a two-sided nominal 5% level, by adding or removing one event from either treatment group. This reviewer believes that the observed results of liver function elevations in the overall trial needs to be conveyed. See Reviewer Comments in the Clinical Studies Draft Labeling below.

In addition, ~~_____~~ which has no bearing on age subgroups. The sponsor needs to provide a Table summarized by age with the cutoff of less than 65 years vs. equal or greater than 65 years of age. Comparison on the percentage of patients reaching their NCEP treatment goals would only be comparable at week 6 as the randomization among patients on the treatment dosages were valid before any titration taken place. The last sentence is unrelated to the co-primary efficacy and co-primary safety outcomes evaluated.

A revised labeling is suggested below.

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‡ needs to be presented by age subgroup with appropriate Table number.

Strikethrough are to be deleted. This reviewer's suggestions are in bolded normal fonts.

[

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Strikethrough are to be deleted. This reviewer's suggestions are in bolded normal fonts.

The Labeling under PRECAUTIONS section discussed at the internal meeting dated May 14, 2001. The medical team leader added the following text:

"The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (≥ 65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial 1,958 patients initiated therapy with

atorvastatin 10 mg. Of these, 835 were elderly (≥ 65 years) and 1,123 were non-elderly.

The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was – 38.2% in the elderly patients versus –34.6% in the nonelderly group."

Reviewer's Comments: A comparison of percentage of patients achieving treatment goals is difficult to evaluate when individual patients are variably titrated to achieve the goal.

"The rates of discontinuation due to adverse events were similar between the two age groups.

[redacted]

Reviewer's Comments: The sponsor generated a hypothesis on the relationship between cardiovascular events and extensive disease at baseline in geriatric population. This was not an objective of interest in the ACCESS trial.

SUMMARY

According to the medical review team, statins and other lipid-altering drugs are approved for chronic use. These drugs typically get to market for Types IIa and IIb indication (familial and mixed dyslipidemia). Statins are the standard of practice for the management of the more common dyslipidemias because of their effectiveness, safety, and tolerability. Some lipid disorders may respond better to fibrates, niacin, or a combination of drugs.

ACCESS compares 5 statins. The sponsor seeks labeling addition on the geriatric use of atorvastatin, which was compared with four other statins approved for chronic use. The geriatric labeling request would be valid if the results of ACCESS trial demonstrated a superior effect of atorvastatin for its primary objective. The primary objective of the study was to determine the safety and efficacy profile of atorvastatin as compared to other HMG Co-A reductase inhibitors when used to treat patients to per NCEP LDL-C guidelines.

From this reviewer's review and evaluation, results of ACCESS trial raise a potential concern of one of the co-primary safety parameters. There were 10 patients (0.51%) treated with atorvastatin who reported persistent transaminase elevations defined as 2 consecutive ALT/AST levels >3 x the upper limit of normal. This appeared to be 3-fold increase (95% CI 1-fold to 11-fold) with atorvastatin compared to the All Controls statins (0.15%), nominal p-value of 0.052.

The results of ACCESS trial appeared to show that atorvastatin is superior to the All Controls group on the co-primary efficacy endpoints of (1) the percent change from baseline in LDL-C and (2) the % of patients meeting NCEP LDL-C criteria at initial dose (week-6). For safety, atorvastatin patients appeared to be more likely to have persistent liver function elevations, but not statistically significantly different, than the All Controls group. There was no report of patients developing myopathy defined as CPK > 10 times the ULN on two consecutive measurements and associated muscle symptoms.

CONCLUSION

If the medical division views the results of the ACCESS trial as a positive finding, this reviewer recommends the labeling revisions given in Section 3, p.7-9 of this review.

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Concur: S. Edward Nevius, Ph.D.
Division Director, HFD-715

Todd Sahlroot, Ph.D.
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cc:
Archival NDA 20-702 SE8-025
HFD-510/Div. File
HFD-510/H. Herman, M. Parks
HFD-510/Ms. Simmoneau, CSO
HFD-715/E. Nevius, T. Sahlroot, S. Wang

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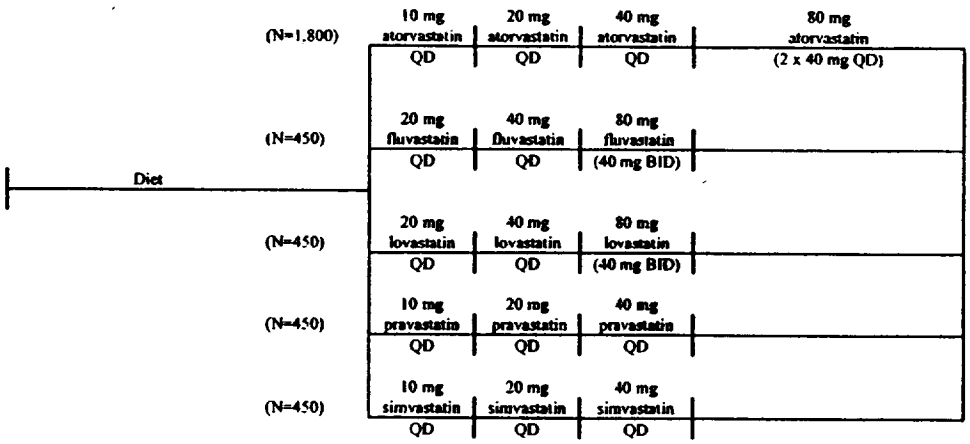
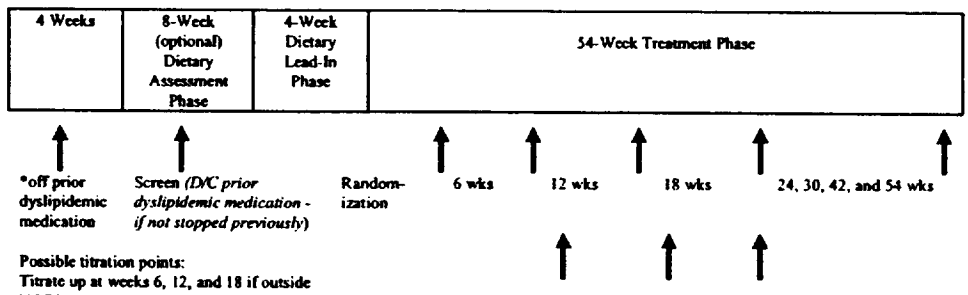
This review consists of 10 pages, which includes 2 Reviewer summary table. The sponsor's Tables and Figures can be found in the Appendices from page 11 to page 21 following the review text.

Figure 1. Study Design Schematic





Possible titration points:
Titrate up at weeks 6, 12, and 18 if outside NCEP targets. No back titration.

*Optional - can discontinue meds at screen.

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APPEARS THIS WAY
ON ORIGINAL

TABLE 3. Schedule of Study Evaluations and Procedures

Study Phase	Screening*	Lead-In Phase		Treatment Phase							
Visit Designation	1	2	3	4	5	6	7	8	9	10	11
Study Week		-4	-2	0	6	12	18	24	30	42	54***
Titration Schedule**											
atorvastatin				10	A	B	C				
simvastatin, pravastatin				10	A	B					
lovastatin, fluvastatin				20	B	C					
Procedures											
Medical Hx	X										
Weight, Blood Pressure	X	X	X	X	X	X	X	X	X	X	X
Physical Exam				X							X[5]
ECG				X[1]							X[5]
Clinical Labs[2]		X									X
Safety Labs[3]				X	X	X	X	X	X	X	
Lipid Profile[4]	X	X	X	X	X	X	X	X	X	X	X
Genotyping											X
Dietary Counseling	X	X	X	X	X	X	X	X	X	X	X
Food Frequency			X								X
Dispense Drug				X	X	X	X	X	X	X	
Adverse Events					X	X	X	X	X	X	X

*Screening: If prior dyslipidemic medications not discontinued, stop medications at Visit 1 (mandatory 4-week washout period for previous medications prior to Visit 2).
Optional additional 4-wk dietary assessment phase prior to 4-wk mandatory dietary lead-in phase (total 12 wks maximum from Visit 1 to Visit 4).

** Titration Schedule
numbers indicate initial mg dosage QD
A, B, C indicate that dose was doubled from prior visit if greater than NCEP target
(A = 10 to 20 mg, B = 20 to 40 mg, C = 40 to 80 mg)

** or at the time of premature discontinuation

1 could be done at any time between Week-2 and randomization

2 Clinical labs are: serum chemistry (ALT, AST, Alk. Phos., CPK and MB fraction if >2 x ULN, BUN, creatinine, bilirubin, glucose, TSH (Week -4 only), HbA1c and βHCG (latter two at Week-4 if necessary) and hematology (RBC, hemoglobin, hematocrit, WBC, platelet count and differential if total WBC is abnormal)

3 Safety labs are: ALT and AST; CPK if clinically indicated

4 Lipid profile is: TC, TG, HDL-C, LDL-C calculated unless TG ≥400, in which case β-quant was used. Apo β was performed at Weeks 0, 6, and 54.

5 Only if clinically indicated

N.B. - All labs were fasting for ≥12 hours

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TABLE 6. Summary of Background Information - ITT Population

Variable	Atorvastatin (N = 1902)		Fluvastatin (N = 477)		Lovastatin (N = 476)		Pravastatin (N = 462)		Simvastatin (N = 468)	
Age (years)										
n	1902		477		476		462		468	
Mean (SE)	61.3	(0.2)	61.4	(0.5)	61.5	(0.5)	61.1	(0.5)	60.9	(0.5)
Age Distribution										
<70 years	1396		343		353		349		351	
≥70 years	506		134		123		113		117	
Race n (%)										
White/Caucasian	1682	(88.4)	425	(89.1)	433	(91.0)	410	(88.7)	417	(89.1)
Black	130	(6.8)	27	(5.7)	25	(5.3)	24	(5.2)	28	(6.0)
Asian	24	(1.3)	8	(1.7)	5	(1.1)	8	(1.7)	8	(1.7)
Other Race	66	(3.5)	17	(3.6)	13	(2.7)	20	(4.3)	15	(3.2)
Gender n (%)										
Male	1172	(61.6)	294	(61.6)	289	(60.7)	289	(62.6)	271	(57.9)
Female	730	(38.4)	183	(38.4)	187	(39.3)	173	(37.4)	197	(42.1)
Body Mass Index (kg/m^2)										
n	1805		449		446		439		440	
Mean (SE)	28.7	(0.1)	28.5	(0.2)	28.8	(0.2)	28.6	(0.2)	28.5	(0.2)
Risk Status n (%)										
<2 risk factors	233	(12.3)	60	(12.6)	49	(10.3)	58	(12.6)	51	(10.9)
≥2 risk factors	383	(20.1)	95	(19.9)	95	(20.0)	104	(22.5)	114	(24.4)
CHD or PVD	1286	(67.6)	322	(67.5)	332	(69.7)	300	(64.9)	303	(64.7)
Type of Hyperlipidemia n (%)										
Type IIa	1153	(60.6)	292	(61.2)	274	(57.6)	280	(60.6)	295	(63.0)
Mixed Dyslipidemia	749	(39.4)	185	(38.8)	202	(42.4)	182	(39.4)	173	(37.0)
LDL-C (mg/dL)										
N	1902		477		476		462		468	
Mean (SE)	178.5	(0.8)	179.0	(1.6)	178.0	(1.5)	179.3	(1.6)	176.0	(1.4)
HDL-C (mg/dL)										
N	1902		477		476		462		468	
Mean (SE)	47.8	(0.3)	46.8	(0.5)	47.2	(0.5)	47.8	(0.5)	48.1	(0.5)
LDL-C/HDL-C Ratio										
N	1902		477		476		462		468	
Mean (SE)	3.9	(0.0)	4.0	(0.0)	4.0	(0.0)	3.9	(0.0)	3.8	(0.1)
Triglycerides (mg/dL)										
N	1902		477		476		462		468	
Mean (SE)	189.6	(1.7)	189.8	(3.2)	195.8	(3.5)	187.8	(3.5)	187.7	(3.5)
Total Cholesterol (mg/dL)										
N	1902		477		476		462		468	
Mean (SE)	264.1	(0.9)	263.7	(1.8)	264.2	(1.7)	264.6	(1.8)	261.5	(1.7)
Apolipoprotein B (mg/dL)										
N	1873		472		468		453		464	
Mean (SE)	169.8	(0.7)	168.2	(1.2)	170.1	(1.2)	168.5	(1.3)	166.2	(1.3)

Source: Appendices C.3, C.6, and C.7.

TABLE 9. Summary of Patient Disposition

Category	Atorvastatin n	(%)	Fluvastatin n	(%)	Lovastatin n	(%)	Pravastatin n	(%)	Simvastatin n	(%)
Randomized to Treatment	1958		497		498		481		482	
Did Not Complete Treatment Phase	267	(13.6)	120	(24.1)	91	(18.3)	92	(19.1)	84	(17.4)
Reason Did Not Complete										
Adverse Event	129	(6.6)	64	(12.9)	42	(8.4)	20	(4.2)	39	(8.1)
Other/Administrative Reasons	138	(7.0)	56	(11.3)	49	(9.8)	72	(15.0)	45	(9.3)
Completed Treatment Phase	1691	(86.4)	377	(75.9)	407	(81.7)	389	(80.9)	398	(82.6)
Completed Study Week										
Week 6	1907	(97.4)	481	(96.8)	480	(96.4)	466	(96.9)	468	(97.1)
Week 12	1860	(95.0)	464	(93.4)	461	(92.6)	451	(93.8)	450	(93.4)
Week 18	1826	(93.3)	449	(90.3)	450	(90.4)	436	(90.6)	435	(90.2)
Week 24	1788	(91.3)	421	(84.7)	436	(87.6)	425	(88.4)	424	(88.0)
Week 30	1761	(89.9)	404	(81.3)	426	(85.5)	418	(86.9)	415	(86.1)
Week 42	1740	(88.9)	387	(77.9)	415	(83.3)	401	(83.4)	406	(84.2)
Week 54	1699	(86.8)	378	(76.1)	408	(81.9)	391	(81.3)	399	(82.8)

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Figure 2.
Mean Percent Reduction in LDL Cholesterol
From Baseline to Week 6

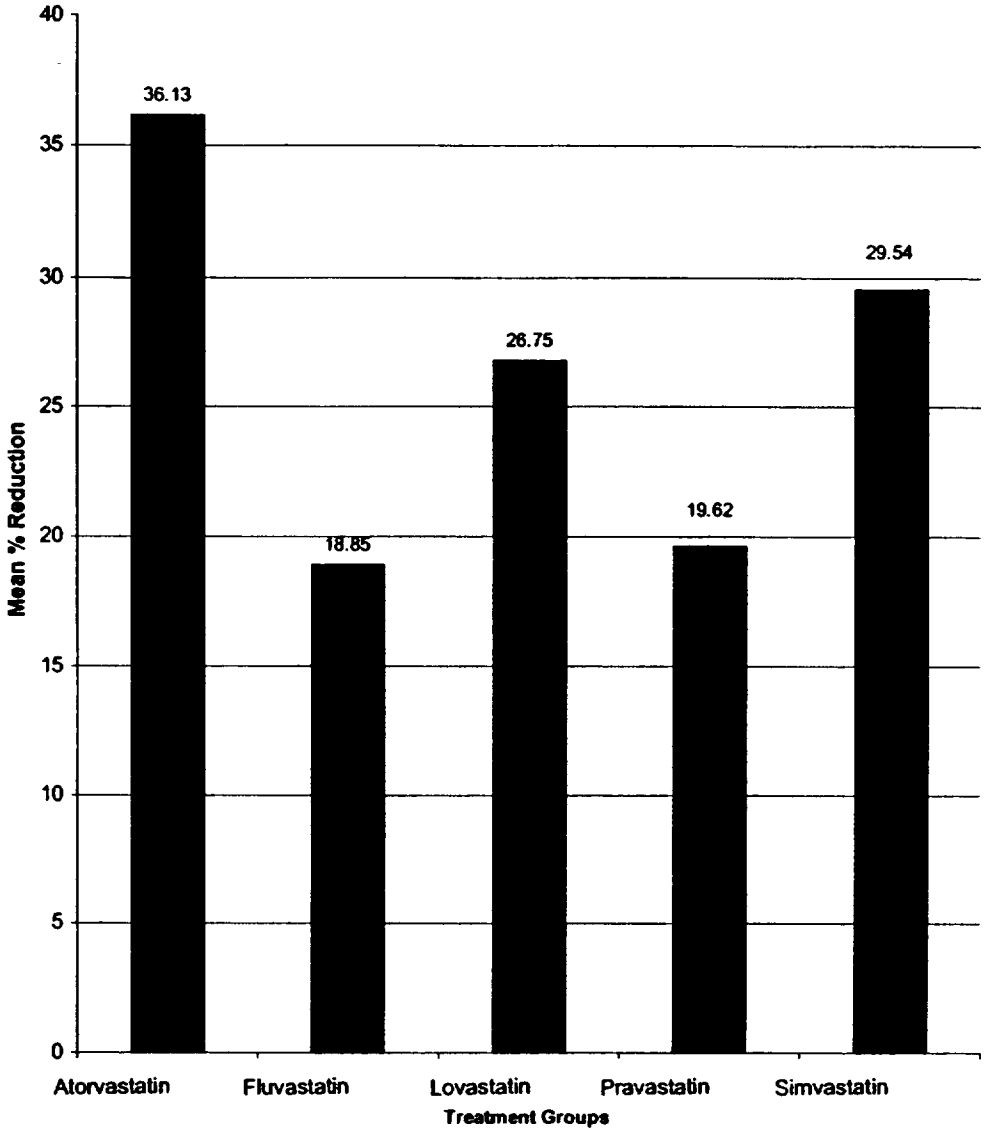

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TABLE 15. Percent Change in Secondary Efficacy Parameters from Baseline to Week 6 - ITT Population

Parameter / Treatment	N	Baseline Mean	Baseline (SE)	Percent Change Mean	Percent Change (SE)	Treatment Comparisons Adjusted Mean Difference^	Treatment Comparisons (SE)
HDL-C (mg/dL)							
Atorvastatin	1888	47.8	(0.27)	5.5	(0.25)		
Fluvastatin	474	46.7	(0.52)	4.2	(0.58)	1.5*	(0.56)
Lovastatin	472	47.2	(0.55)	4.9	(0.48)	0.8	(0.56)
Pravastatin	461	47.8	(0.52)	4.0	(0.51)	1.6*	(0.57)
Simvastatin	462	48.0	(0.52)	5.8	(0.52)	-0.3	(0.57)
LDL-C/HDL-C Ratio							
Atorvastatin	1888	3.9	(0.03)	-39.1	(0.26)		
Fluvastatin	474	4.0	(0.05)	-21.6	(0.56)	-17.6*	(0.60)
Lovastatin	472	4.0	(0.05)	-29.8	(0.57)	-9.4*	(0.60)
Pravastatin	461	3.9	(0.05)	-22.4	(0.57)	-16.7*	(0.61)
Simvastatin	462	3.8	(0.05)	-32.9	(0.58)	-6.1*	(0.61)
Triglycerides (mg/dL)							
Atorvastatin	1889	189.8	(1.68)	-18.0	(0.54)		
Fluvastatin	474	189.9	(3.25)	-5.7	(1.12)	-12.3*	(1.23)
Lovastatin	472	195.9	(3.48)	-10.5	(1.11)	-7.9*	(1.23)
Pravastatin	462	187.8	(3.48)	-3.4	(1.32)	-14.4*	(1.24)
Simvastatin	462	187.1	(3.52)	-10.6	(1.21)	-7.2*	(1.24)
Total Cholesterol (mg/dL)							
Atorvastatin	1889	264.2	(0.91)	-26.3	(0.19)		
Fluvastatin	474	263.6	(1.80)	-13.2	(0.40)	-13.1*	(0.45)
Lovastatin	472	264.4	(1.70)	-19.0	(0.43)	-7.3*	(0.45)
Pravastatin	462	264.6	(1.79)	-13.4	(0.46)	-12.9*	(0.45)
Simvastatin	462	260.9	(1.66)	-20.7	(0.42)	-5.5*	(0.45)
Apolipoprotein-B (mg/dL)							
Atorvastatin	1834	169.8	(0.66)	-27.6	(0.23)		
Fluvastatin	467	168.1	(1.24)	-12.7	(0.50)	-14.8*	(0.53)
Lovastatin	461	170.3	(1.23)	-19.6	(0.52)	-8.1*	(0.54)
Pravastatin	450	168.4	(1.28)	-12.9	(0.54)	-14.7*	(0.54)
Simvastatin	448	166.0	(1.32)	-21.2	(0.51)	-6.1*	(0.54)

^ Adjusted mean difference for percent change based on ANCOVA model with effect due to treatment and the baseline value as a covariate.

* Significantly different from atorvastatin ($p<0.05$).

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TABLE 16. Percent Change in Lipid Parameters from Baseline to Week 54/Endpoint - ITT Population

Parameter / Treatment	N	Baseline Mean	Baseline (SE)	Percent Change Mean	Percent Change (SE)	Treatment Comparisons Adjusted Mean Difference^	Treatment Comparisons (SE)
LDL-C (mg/dL)							
Atorvastatin	1902	178.5	(0.79)	-42.1	(0.29)		
Fluvastatin	477	179.0	(1.59)	-29.0	(0.64)	-13.1*	(0.66)
Lovastatin	476	178.0	(1.45)	-35.5	(0.61)	-6.5*	(0.66)
Pravastatin	462	179.3	(1.57)	-28.0	(0.69)	-14.1*	(0.67)
Simvastatin	468	176.0	(1.45)	-35.7	(0.59)	-6.2*	(0.67)
HDL-C (mg/dL)							
Atorvastatin	1902	47.8	(0.27)	4.7	(0.32)		
Fluvastatin	477	46.8	(0.52)	5.9	(0.77)	-1.0	(0.72)
Lovastatin	476	47.2	(0.54)	5.2	(0.61)	-0.4	(0.72)
Pravastatin	462	47.8	(0.51)	6.0	(0.71)	-1.3	(0.73)
Simvastatin	468	48.1	(0.52)	5.8	(0.60)	-1.2	(0.72)
LDL-C/HDL-C Ratio							
Atorvastatin	1902	3.9	(0.02)	-44.1	(0.31)		
Fluvastatin	477	4.0	(0.05)	-32.0	(0.71)	-12.3*	(0.72)
Lovastatin	476	4.0	(0.05)	-38.1	(0.63)	-6.1*	(0.72)
Pravastatin	462	3.9	(0.05)	-31.1	(0.79)	-13.0*	(0.73)
Simvastatin	468	3.8	(0.05)	-38.4	(0.67)	-5.5*	(0.73)
Triglycerides (mg/dL)							
Atorvastatin	1902	189.6	(1.69)	-19.3	(0.62)		
Fluvastatin	477	189.8	(3.23)	-7.2	(1.66)	-12.1*	(1.44)
Lovastatin	476	195.8	(3.46)	-12.3	(1.45)	-7.5*	(1.44)
Pravastatin	462	187.8	(3.48)	-9.4	(1.32)	-9.7*	(1.46)
Simvastatin	468	187.7	(3.50)	-12.7	(1.26)	-6.3*	(1.45)
Total Cholesterol (mg/dL)							
Atorvastatin	1902	264.1	(0.91)	-30.8	(0.25)		
Fluvastatin	477	263.7	(1.79)	-20.1	(0.51)	-10.6*	(0.53)
Lovastatin	476	264.2	(1.69)	-25.3	(0.49)	-5.4*	(0.53)
Pravastatin	462	264.6	(1.79)	-19.9	(0.51)	-10.9*	(0.53)
Simvastatin	468	261.5	(1.67)	-25.1	(0.46)	-5.4*	(0.53)
Apolipoprotein-B (mg/dL)							
Atorvastatin	1862	169.7	(0.65)	-31.9	(0.27)		
Fluvastatin	471	168.0	(1.24)	-18.8	(0.61)	-12.8*	(0.60)
Lovastatin	468	170.1	(1.22)	-25.4	(0.57)	-6.5*	(0.60)
Pravastatin	452	168.4	(1.28)	-18.7	(0.59)	-13.0*	(0.61)
Simvastatin	458	166.0	(1.30)	-25.1	(0.56)	-6.2*	(0.61)

^ Adjusted mean difference for percent change based on ANCOVA model with effect due to treatment and the baseline value as a covariate.

* Significantly different from atorvastatin ($p<0.05$).

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Figure 5. Number and Percentage of Patients Achieving NCEP Goal at Week 6 and Week 54
ITT Population

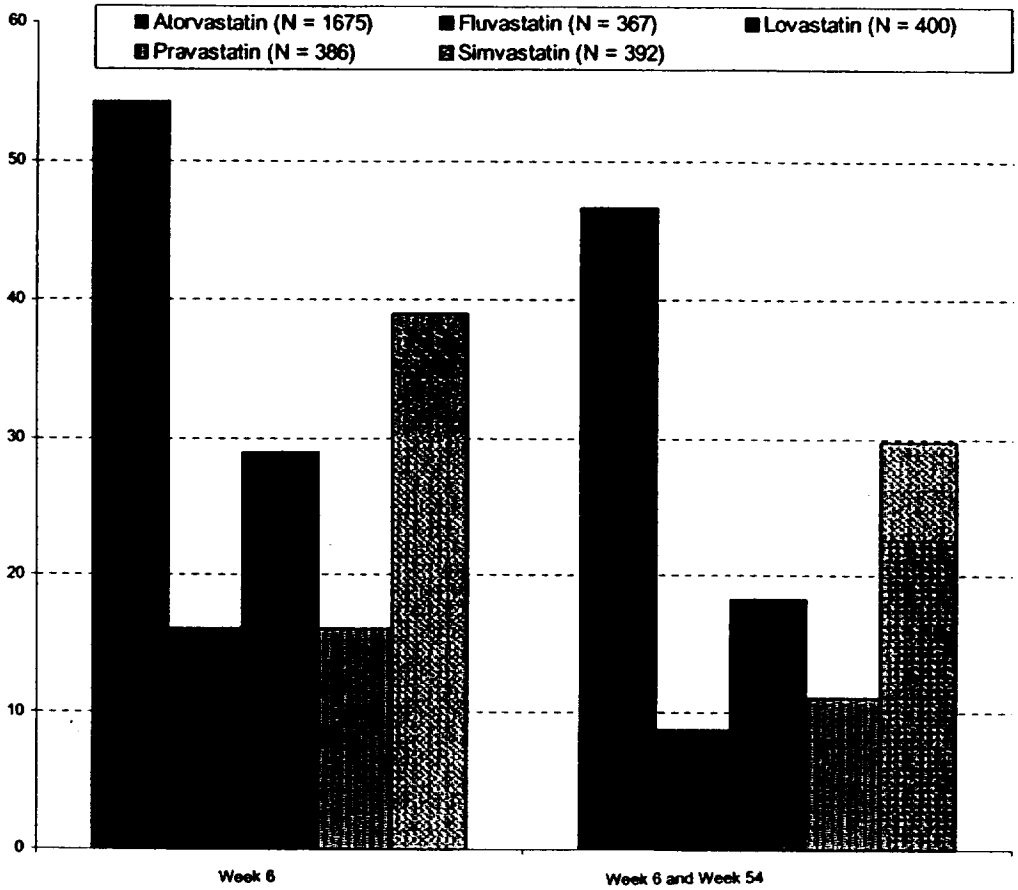

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TABLE 19. Number and Percentage of Patients with Persistent Transaminase Elevations or CPK Elevations - Safety Population

	Atorvastatin (N = 1958)		All Controls (N = 1958)		Fluvastatin (N = 497)		Lovastatin (N = 498)		Pravastatin (N = 481)		Simvastatin (N = 482)		
Parameter	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	Rate Difference*
ALT or AST	10	0.51	3	0.15	1	0.20	0	0.00	1	0.21	1	0.21	0.36
ALT	10	0.51	3	0.15	1	0.20	0	0.00	1	0.21	1	0.21	0.36
AST	3	0.15	1	0.05	0	0.00	0	0.00	1	0.21	0	0.00	0.10
CPK	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0.00

* Atorvastatin % - All Controls %

Persistent transaminase elevations are defined as ALT or AST >3 times the upper limit of normal on 2 consecutive draws. A persistent CPK elevation is defined as CPK >10 times the upper limit of normal on two consecutive draws. If there was no observation following the notable value, the elevation is considered persistent.

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TABLE 22. Summary of Exposure Days by Treatment Group and Course of Titration

Safety Population

Treatment/ Course of Titration	N	%	Mean Days	Average Dose
Atorvastatin				20.7
10 mg	1958	100.0	208.9	
20 mg	886	45.3	160.7	
40 mg	474	24.2	168.4	
80 mg	215	11.0	228.6	
Fluvastatin				54.2
20 mg	497	100.0	88.8	
40 mg	405	81.5	91.2	
80 mg	319	64.2	247.7	
Lovastatin				46.8
20 mg	498	100.0	131.2	
40 mg	339	68.1	119.1	
80 mg	232	46.6	262.5	
Pravastatin				27.6
10 mg	481	100.0	91.6	
20 mg	387	80.5	85.3	
40 mg	320	66.5	260.0	
Simvastatin				20.8
10 mg	482	100.0	158.3	
20 mg	290	60.2	142.7	
40 mg	168	34.9	263.9	

N = number of patients that were to take the given dose.
Exposure Days = date of last dose - date of first dose.
All calculations use assigned doses. Compliance to medication is not used.
Average dose is calculated as the sum of the doses times the number of days on the dose divided by the total number of days.

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/s/

Sue Jane Wang
6/1/01 02:11:04 PM
BIOMETRICS

Todd Sahlroot
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BIOMETRICS

S. Edward Nevius
6/2/01 08:41:12 PM
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Concur with review.

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