Note: This reviewer's alternative analyses, performed with the data supplied by the sponsor electronically, did not reveal any concern with respect to the statistical significance of the primary efficacy.

Mean Percent Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Direct LDL-C) Between Baseline and Endpoint: Intent-to-Treat Data Set (Pooled Treatment Groups)

	All Simvastatin n=263	Ezetimibe 10 mg + All Simvastatin n=274	p-value[a]
Baseline	(n=263)	(n=273)[b]	
Mean value in mg/dL [mmol/L]	178.58 [4.62]	176.33 [4.56]	0.20
Endpoint	(n=261)	(n=268)	
Mean value in mg/dL [mmol/L]	113.64 [2.94]	88.18 [2.28]	<0.01
Mean percent change from baseline (SEM)	-36.07 (0.89)	-49.88 (0.88)	<0.01
Difference from All Simvastatin in mean percent change from baseline (95% confidence limits)	N/A	-13.80 (-16.26, -11.35)	<0.01

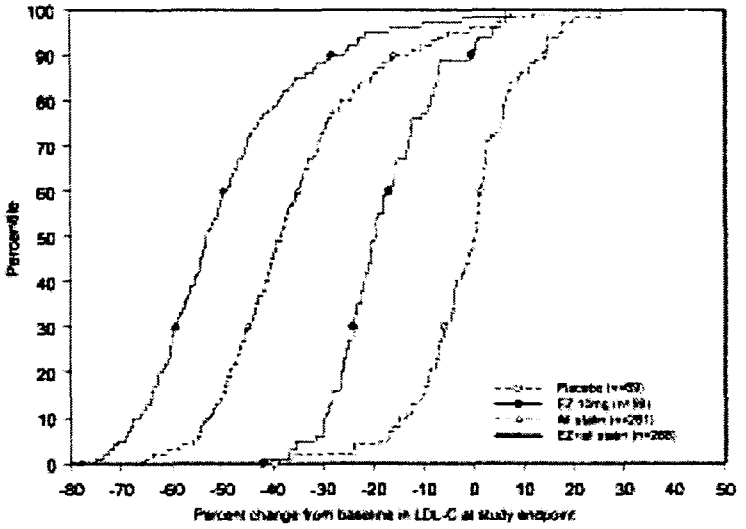
a: Comparison between All Simvastatin and Ezetimibe 10 mg + All Simvastatin
b: Subject 23/000153 (EZ 10+Simva 80) had missing baseline data for direct LDL-C.

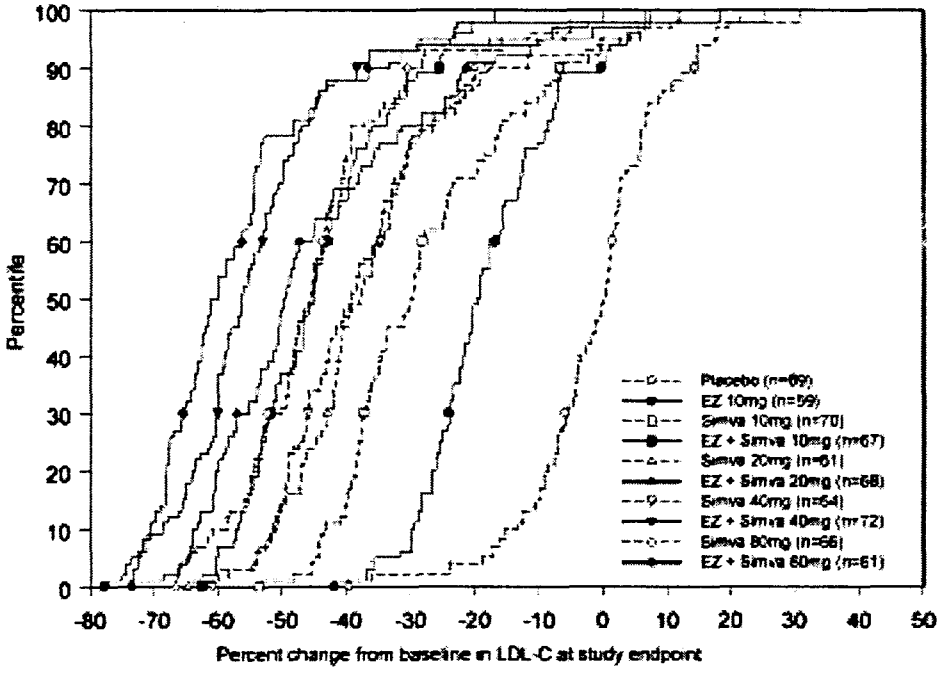
Means and standard errors in this table are least-square means and standard errors based on the ANOVA model that extracts effects due to dose (simvastatin : 0 mg, 10 mg, 20 mg, 40 mg and 80 mg), treatment (ezetimibe 10 mg, ezetimibe placebo), and dose-by-treatment interaction.

All Simvastatin=pool of all doses of simvastatin; EZ 10 mg+All Simvastatin=pool of all doses of simvastatin coadministered with ezetimibe 10 mg; N/A=not applicable

Source Data: Section 14.2.2.1.1.1 of the NDA.

§ Cumulative Distribution Functions of Percent Change from Baseline in LDL-C at Study Endpoint are provided below:





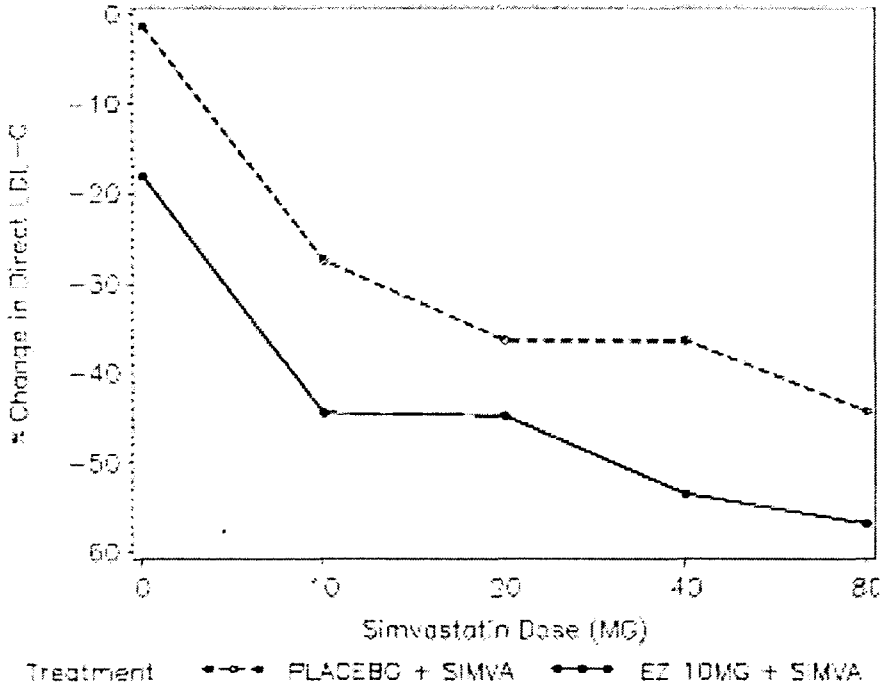
From these, percent of patients (y-axis value) with a value of Percent Change from Baseline in LDL-C at Study Endpoint, smaller than or equal to a value on the x-axis can be read. For

example, 50% of the ezetimibe 10mg patients had a ≤–19.6% change from baseline; whereas, 50% of the placebo patients had a ≤0.0% change from baseline.

Separation of all treatments from placebo was evident. Simvastatin 10mg alone performed better than ezetimibe 10mg alone.

§ Results of the effect of coadministration of ezetimibe 10 mg with each dose of simvastatin are displayed graphically below.

Effect of coadministration of ezetimibe 10 mg with simvastatin on mean percent change from baseline in plasma concentration of direct LDL-C at endpoint: Intent-to-Treat Data Set (Individual Treatment Groups). Source Data: Section 14.2.2.1.1.1.



§ The sponsor stated about the treatment by dose interaction and the best estimate of the added ezetimibe effect:

> Although the test for treatment- by-simvastatin dose interaction for the percent change from baseline in direct LDL-C at study endpoint across the simvastatin doses was statistically significant (p=0.04) (Section 14.2.2.1.1.1.1), it was determined that the best estimate of

added ezetimibe effect would still be the average effect across all doses of statin for the following reasons:

• The effect sizes for all dose comparisons except EZ 10+Simva 20 vs Simva 20 (8.5%) were generally consistent with the overall average effect (EZ 10+Simva 10 vs Simva 10 = 17%, EZ 10+Simva 40 vs Simva 40 = 17%, EZ 10+Simva 80 vs Simva 80 = 13%). Thus, a discrepancy was only noted at the simvastatin 20 mg dose, but not at the higher or lower doses.

• If the effect was not really constant over the range of simvastatin doses, one would expect a monotone dose-response relationship, ie, the differences between ezetimibe + simvastatin and simvastatin alone would be either increasing or decreasing with dose. A statistical test of this hypothesis (Section 16.1.9.2.) was non-significant (p=0.67), indicating that the differences were not increasing/decreasing with dose.

• The test for treatment-by-simvastatin dose interaction was non-significant (p=0.72) if the data for the primary variable at all time points (Week 2 to Week 12) were considered (Section 16.1.9.2.).

• The test for treatment-by-simvastatin dose interaction was non-significant for the protocol-evaluable population at endpoint (p=0.18) (Section 14.2.2.1.1.2.1.).

Note: We can only say that there is inconsistency with respect to the simvastatin doses. In the same way that there seems to be some uncertainty with respect to the real situation with respect to the variability among the doses, the average effect also cannot be ascertained. The sponsor stated in the Data Analysis Plan, "If the interaction is not statistically significant at level alpha=0.05, then the best estimate of added ezetimibe effect is the average effect across all doses." Now, we have a statistically significant interaction (p=0.04).

§ Coadministration of ezetimibe 10 mg plus simvastatin was also more efficacious than ezetimibe 10 mg alone in reducing plasma concentrations of direct LDL-C from baseline to endpoint (Table below). The difference (approximately 32%) in mean percent change from baseline to endpoint between the coadministration pool and ezetimibe 10 mg alone (approximately –50% vs –18%) was statistically significant (p<0.01).

Mean Percent Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Direct LDL-C) Between Baseline and Endpoint: Intent-to-Treat Data Set (Ezetimibe 10 mg and Coadministration Treatment Groups):

	Ezetimibe 10 mg n=61	Ezetimibe 10 mg + All Simvastatin n=274	p-value[a]
Baseline	(n=61)	(n=273)[b]	
Mean value in mg/dL [mmol/L]	181.32 [4.69]	176.33 [4.56]	0.08
Endpoint	(n=59)	(n=268)	
Mean value in mg/dL [mmol/L]	147.86 [3.82]	88.18 [2.28]	<0.01
Mean percent change from baseline (SEM)	-18.06 (1.87)	-49.88 (0.88)	<0.01
Difference from Ezetimibe 10 mg in mean percent change from baseline (95% confidence limits)	N/A	-31.81 (-35.87, -27.76)	<0.01

a: Comparison between Ezetimibe 10 mg and Ezetimibe 10 mg + All Simvastatin
b: Subject 23/000153 (EZ 10+Simva 80) had missing baseline data for direct LDL-C.

Means and standard errors in this table are least-square means and standard errors based on the ANOVA model that extracts effects due to dose (simvastatin : 0 mg, 10 mg, 20 mg, 40 mg and 80 mg), treatment (ezetimibe 10 mg, ezetimibe placebo), and dose-by-treatment interaction.

EZ 10 mg+All Simvastatin=pool of all doses of simvastatin coadministered with ezetimibe 10 mg; N/A=not applicable

Source Data: Section 14.2.2.1.1.1.

§ Among the dropout cohorts considered (April 19, 2002 submission), the results in the ezetimibe (or ezetimibe+all statin) cohorts were almost always better (at least numerically) than those in the placebo (or all stain+placebo) cohorts. The rare exceptions involving very few patients cannot appreciably change the overall differences in results.

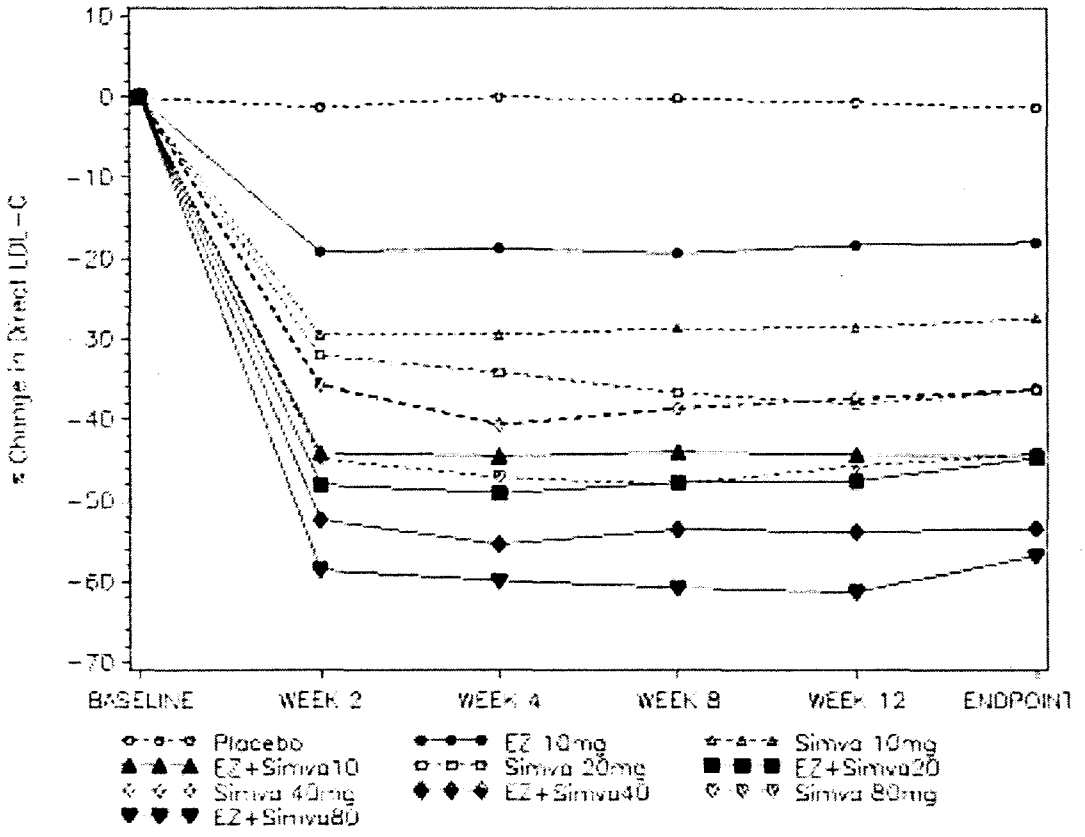
§ Since the overall treatment effect was significant, results between individual treatment groups were compared. These analyses were performed to evaluate the potentially incremental effects of ezetimibe on reducing LDL-C concentrations when coadministered with each dose of simvastatin, and facilitate comparison between each dose of simvastatin to which ezetimibe 10 mg was coadministered and the same or higher doses of simvastatin alone. These results are attached as Appendix Table 2.3.1.

Across the individual treatment groups, mean percent changes from baseline to endpoint in LDL-C ranged from approximately 44% to 57% for coadministration therapy compared with 27% to 44% for simvastatin monotherapy (Appendix Table 2.3.1). The incremental mean percent change observed with the coadministration of ezetimibe with each dose of simvastatin ranged from approximately 8.5% to 17%, and was statistically significant ($p<0.01$) in all cases when compared with each corresponding dose of simvastatin monotherapy. Furthermore, statistically significant differences ($p<0.01$) were noted between each dose of simvastatin coadministered with ezetimibe and the next higher dose of simvastatin monotherapy, and between EZ 10+Simva 10 and Simva 40.

The coadministration of ezetimibe with simvastatin 10 mg resulted in a similar mean percent change in LDL-C as simvastatin 80 mg monotherapy (approximately 44% in both cases). In other words, coadministration of ezetimibe with the lowest dose of simvastatin reduced LDL-C concentrations to a similar extent as increasing the simvastatin dose eight-fold. When ezetimibe was coadministered with simvastatin 80 mg, a further enhancement of the LDL-C-lowering effect was achieved (mean percent change of approximately 57% vs 44% for simvastatin 80 mg alone).

§ The incremental LDL-C-lowering effects resulting from the coadministration of ezetimibe with each dose of simvastatin were seen as early as Week 2 and maintained for the duration of the study (12 weeks). These differences in response between coadministration treatment groups and the corresponding simvastatin alone treatment groups were statistically significant at all time points (Figure below).

Mean percent change from baseline in plasma concentration of direct LDL-C over time and at endpoint, Intent-to-Treat Data Set (Individual Treatment Groups):
(Source Data: Section 14.2.2.1.1.1)

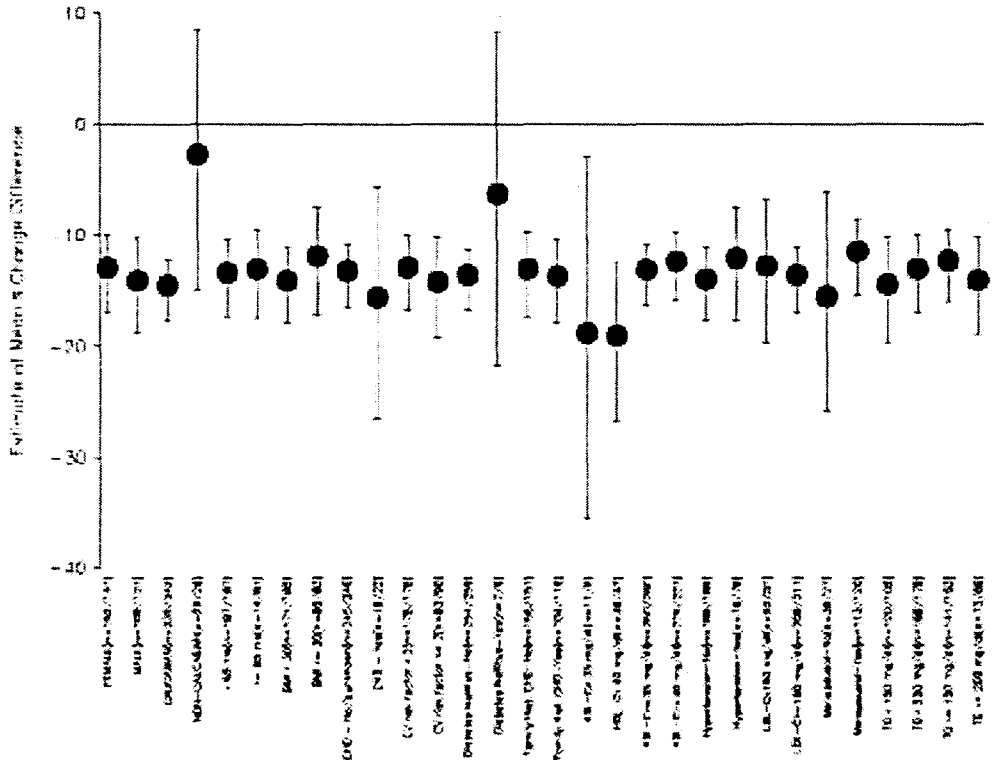


§ Mean percent change from baseline to endpoint in direct LDL-C was examined in subgroups defined by subject baseline characteristics: sex, age, race, LDL-C, HDL-C, TG, hypertension, diabetes mellitus, BMI, menopausal status, known CHD, family history of coronary artery disease, and number of cardiovascular risk factors[3]. Overall, the increase in response resulting from the coadministration of ezetimibe 10 mg with simvastatin observed in each subgroup population was generally consistent with that observed in the total population (Figure below). A smaller treatment effect was noted for non-Caucasians and diabetics, while subjects with lower

[3] The protocol for this study was written while NCEP ATP II guidelines were in effect. Before the data base was locked, new guidelines were established by ATP III. ATP II guidelines were used for most of the data analysis in this report. In addition, ATP III guidelines were used in evaluations of direct LDL-C response in subgroups based on baseline HDL-C and TG concentrations.

baseline HDL-C concentrations tended to respond better than those above the NCEP ATP II or III cutoffs. However, no reliable conclusions can be drawn from these observations because of the small sample sizes in these subgroups. See Section 14.2.2.1.6.and Section 16.1.9.2. of the NDA for more details.

Following are point estimates and 95% confidence intervals of the difference in mean percent change between the two treatment pools in direct LDL-C in various subgroups defined by baseline characteristics, Intent-to-Treat. In subgroup labels, n=X/Y indicates the number of subjects treated with simvastatin alone (X)/number of subjects treated with ezetimibe plus simvastatin (Y).
(Source Data: Section 14.2.2.1.6.2.of NDA.)



The sponsor stated (May 9, 2002), "Conclusion: This exhaustive assessment of the relationship of baseline characteristics to the primary efficacy variable indicates that the conclusions about the treatment group differences are not altered by consideration of these baseline characteristics."

The following is noted about the covariation and interaction effects of baseline characteristics with treatment response. On the one hand, with multiple comparison adjustments, "Race" effect may not be significant. On the other hand, it does not mean that the characteristics not providing smaller p-values have no effects; the non-significance (of the p-value) may be because the study was not powered for these purposes.

Covariation p-values:

Age (continuous)	<0.01
Age (<65, ≥ 65)	<0.01
Race (Caucasian, non-Caucasian)	0.048

That is, the above characteristics influence the treatment response statistically significantly.

The following interaction p-values of baseline characteristics with treatment response were significant at the usual significance level of 0.1 for test of interaction:

HDL-C (continuous) - 0.033
HDL-C (<40, ≥40 mg/dL) - 0.084
Race (Caucasian, non-Caucasian) - 0.011

No multiple comparison adjustments have been employed. However, since the power of the test of interaction is generally poor, we cannot neglect these either. Therefore, the superiority of the (eze + all-statin) over the all-statin group seemed to differ statistically significantly depending on the subgroup based on these characteristics.

However, these interactions were quantitative and not qualitative; i.e. (eze + all-statin) was superior to the all-statin group irrespective of the subgroup in the above characteristics (see Figure above for the amount of superiority).

Since the power of the test of interaction is generally poor and, most of all, since the studies are not powered for tests of interactions in subgroups, we cannot say whether the difference in superiority of the (eze + all-statin) over the all-statin group in the above Figure with respect to other characteristics is real or not.

The treatment by center interaction was non-significant (p=0.502). The most unusual and opposite result was that there was only one simvastatin patient in Center 15, who showed an unusual mean change from baseline of -66.3%. Whereas, the 3 ezetimibe 10mg + simvastatin patients showed a mean change from baseline of -27.3%. One or a few of the 61 centers driving the overall significant results is out of question.

§ Results for calculated plasma concentrations of LDL-C (Friedewald equation) were consistent with those obtained for direct LDL-C. The difference (approximately 15%) in mean percent change for calculated LDL-C from baseline to endpoint between the pools of coadministration

therapy and simvastatin monotherapy (approximately 51% vs 36%) was statistically significant ($p<0.01$), as was the difference (approximately –32%) between coadministration therapy and ezetimibe 10 mg alone (-51% vs -19%; $p<0.01$).

Results for Protocol-Evaluable data set complement the results obtained for the intent-to-treat data set (p.379 of prot. P00680 report).

2.3.3.2g. Reviewer's Comments and Conclusions on Study P00680

The sponsor's results of the primary efficacy analysis demonstrated that coadministration of ezetimibe 10 mg plus simvastatin was more efficacious than (1) simvastatin alone and (2) ezetimibe 10 mg alone, in reducing plasma concentrations of direct LDL-C from baseline to endpoint.

This reviewer's alternative analyses, performed with the data supplied by the sponsor electronically, did not reveal any concern with respect to the statistical significance of the primary efficacy.

Quantitative (not qualitative) interactions of the baseline characteristics HDL-C and Race (Caucasian, non-Caucasian) with treatment response were seen, as noted above.

2.3.3.3 Study P02173/P02246

Title: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Lipid- Altering Efficacy, Safety, and Tolerability of SCH 58235 When Added to Ongoing Therapy With an HMG-CoA Reductase Inhibitor (Statin) in Patients With Primary Hypercholesterolemia, Known Coronary Heart Disease, or Multiple Cardiovascular Risk Factors (Protocol(s) P02173, P02246).

The synopsis of the report:

Study Center(s): 51 centers in the United States; 29 international centers

Clinical Phase: III

Objective(s):

Primary: In patients who have not reached National Cholesterol Education Program Adult Treatment Program II (NCEP ATP II) target low density lipoprotein-cholesterol (LDL-C) levels with ongoing statin monotherapy at study entry:
To evaluate the efficacy of adding SCH 58235 (ezetimibe) 10 mg daily compared with placebo for reducing serum low density lipoprotein cholesterol (LDL-C).

Secondary: In patients who have not reached NCEP ATP II target LDL-C levels on statin alone at study entry: (1) To assess the proportion of patients who achieved NCEP ATP II LDL-C target levels after addition of ezetimibe 10 mg/day versus placebo to ongoing statin monotherapy in this population. (2) To evaluate the safety and tolerability of concomitant treatment with ezetimibe 10 mg/day and statins. (3) To evaluate other lipid, lipoprotein, and apolipoprotein altering effects of adding ezetimibe 10 mg/day to ongoing statin monotherapy.

Methodology: This was a multicenter, double-blind, randomized, placebo-controlled study conducted in conformance with Good Clinical Practices. At randomization (Visit 3) subjects whose LDL-C levels did not meet their treatment goal, were stratified based on whether their screening LDL-C level was 18% above NCEP target or < 18% above target. (NCEP ATP II guideline LDL-C target levels were defined as follows: < 160 mg/dL for subjects without coronary heart disease (CHD) and < 2 risk factors; < 130 mg/dL for subjects without CHD, but having 2 or more cardiovascular risk factors; and 100 mg/dL for subjects with established CHD or diabetes mellitus). Subjects were randomized in a 1:1 ratio to receive either ezetimibe 10 mg daily or matching ezetimibe placebo, to be taken concomitantly with the statin in use at screening. The statin and dose used by the subject at screening was to be maintained for the duration of the 8-week treatment phase of the study. Following the treatment phase, there was a 6-week cholesterol reversibility phase to assess the pharmacodynamics on plasma cholesterol after ezetimibe was discontinued, during which subjects were maintained on their statin monotherapy. Data from the reversibility phase are not included in this report.

Number of Subjects: 769 subjects were in the study: 443 were men and 326 were women. The distribution of subjects receiving treatment assignments was as follows: 379 ezetimibe 10 mg and 390 ezetimibe placebo.

Diagnosis and Criteria for Inclusion: Men and women 18 years of age or older on a stable and approved dose of a statin for at least 6 weeks and having a mean LDL-C level calculated from 2 separate determinations during the screening phase at or above the NCEP-recommended target for the subject's level of risk. Subjects with qualifying LDL-C values below, but close to, the NCEP target levels were entered into the study on a case- by-case basis with prior written approval from the Sponsor. In addition, subject's serum triglycerides at both screening visits were < 350 mg/dL. Subjects were eligible if diagnosed with primary hypercholesterolemia, multiple CHD risk factors (without overt CHD) with associated LDL-C levels above the NCEP ATP II target guidelines, or established CHD or CHD equivalent disease (per NCEP ATP II guidelines), or diabetes mellitus. They must have been previously instructed on an NCEP cholesterol-lowering or similar diet, and be maintaining a stable diet regimen for at least 6 weeks prior to study entry. In addition, subjects were eligible only if their alanine aminotransferase [ALT (SGPT)] and aspartame aminotransferase [AST (SGOT)] concentrations were < 2 times the upper limit of normal (ULN) and creatine phosphokinase (CPK) < 1.5 times the ULN.

Duration of Treatment: The study was approximately 15 weeks in duration, including a 1-week screening period followed by 8 weeks of active double-blind treatment, and a subsequent 6-week follow-up period for safety and lipid reversibility evaluation, the latter phase in which subjects

discontinued blinded ezetimibe or ezetimibe placebo treatment while continuing their statin dosing regimen.

Criteria for Evaluation: The primary efficacy parameter was mean percent change in LDL-C in the group randomized to active ezetimibe 10 mg relative to the group randomized to ezetimibe placebo during ongoing statin monotherapy.

Statistical Methods: The data from the domestic study Protocol P02173 was pooled with that of an identical international study Protocol P02246 for analyses. The primary efficacy variable, percent change in LDL-C from baseline was assessed by ANOVA using a model including terms for statin, stratum, region (domestic sites, international sites), and treatment. The key secondary efficacy parameter, percentage of subjects reaching NCEP target for LDL-C was assessed based upon a logistic regression model with terms for statin, stratum, treatment, region, and baseline percent difference from NCEP target. All significance tests were 2-tailed with α=0.05. Assuming that the standard deviation for the percent change in LDL-C is 12, the study has greater than 95% power to detect a 10 percentage point difference between subjects randomized to ezetimibe 10 mg and subjects randomized to ezetimibe placebo.

2.3.3.3a. Objectives

Primary

Addition of SCH 58235 (ezetimibe) 10 mg/ day to ongoing statin monotherapy will result in a further reduction in LDL- C compared with placebo.

2.3.3.3b. Disposition of Patients

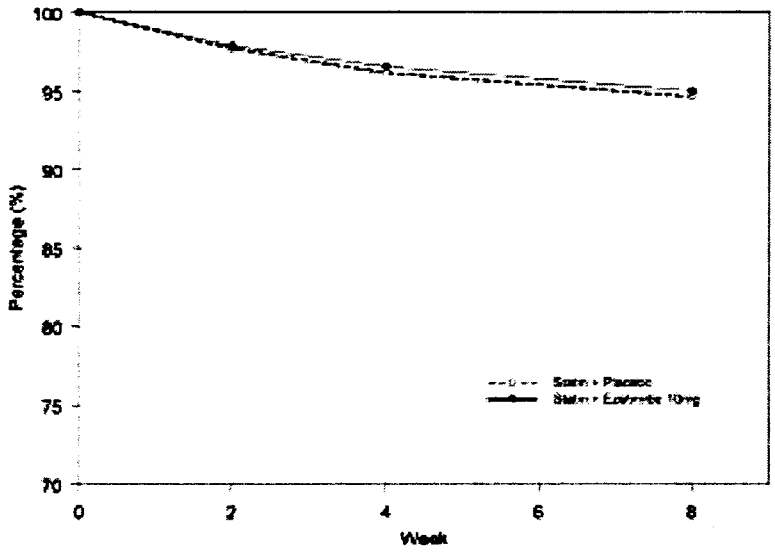
A total of 729 subjects (95%) (see Table below) completed the protocol-specified, double-blind treatment phase, and 40 subjects (5%) discontinued investigational treatment prior to the end of treatment at Visit 6. The primary reason of discontinuation was adverse events, accounting for 27 discontinuations (4% of subjects assigned randomized treatment). There was no pattern or trend across treatment groups in the distribution of subjects who discontinued or in the reasons for discontinuation. A list identifying the individual subjects who discontinued treatment early and the reasons for discontinuation appears in Section 16.2.1 of the NDA Report for Study P02173/P02246.

Disposition of Subjects Following Randomized Treatment Assignment: Number (%) of Subjects:

Disposition of Subjects	Statin + Placebo	Statin + Ezetimibe 10 mg
Received Randomized Treatment Assignment	390 (100)	379 (100)
Completed Treatment	369 (95)	360 (95)
Discontinued Treatment	21 (5)	19 (5)
Adverse event	14 (4)	13 (3)
Treatment failure	0	0
Lost to follow-up	2 (1)	2 (1)
Subject did not wish to continue	4 (1)	3 (1)
Noncompliance with protocol	1 (<1)	0
Administrative	0	1 (<1)
Source Data: **Section 14.4.3.2.**		

Percent of Subjects in Study over Time (P02173/02246) is provided (both in tabular and graphical form) below:

TREATMENT ARM	WEEK 2	WEEK 4	WEEK 8
Statin + Placebo (n=390)	97.7%	96.2%	94.6%
Statin + Ezetimibe 10mg (n=379)	97.9%	96.8%	95.0%



The rate of dropout from the statin+placebo group was only negligibly higher (than the statin + ezetimibe 10 mg group).

The patterns of dropouts due to adverse events were similar for the two treatment groups (The Table and the Figure are in the Sponsor's submission dated April 2, 2002).

Among the dropout cohorts considered (April 19, 2002 submission), the efficacy results in the ezetimibe+statin cohorts were always better (at least numerically) than those in the statin+placebo cohorts.

2.3.3.3c. Protocol Deviations

The following Table provides a rough idea about the protocol violations:

Number(%) of Subjects Who Had Identified Protocol Deviations and Were Excluded From the Protocol-Evaluable Data Set: Subject Who Received Randomized Treatment Assignment

Deviation	Statin + Placebo n=390	Statin + Ezetimibe 10 mg n=379
Any Deviation	25 (6.4)	18 (4.7)
Noncompliance with dosing regimen[a]	8 (2.1)	6 (1.6)
Unacceptable concomitant therapy	3 (0.8)	5 (1.3)
Noncompliance with protocol[b]	14 (3.6)	7 (1.8)

a: Represents subjects who took less than 75% of the total number of doses.

b: Represents subjects who had weight changes of greater than 10 kg over the course of the study, or who changed statin dose during the study, or who discontinued from the study before Day 28.

Source Data: **Section 14.6.**

2.3.3.3d. Demographic and Other Baseline Characteristics

The sponsor stated:

> Summaries of baseline demographic characteristics and habits, any baseline cardiovascular risk categories, and baseline lipid profiles for subjects in the Intention-to-Treat data set are presented in ... " (reviewer addition: on pages 82 to 89 of the report for this study in the NDA)" by pooled treatment group (all statins + placebo versus all statins + ezetimibe 10 mg) and by individual statin treatment group + placebo or ezetimibe 10 mg. Overall, the baseline characteristics of the data set were appropriate to address the objectives of the study, with no

unusual findings reported. The data set consisted of 326 females and 443 male subjects, ages 22 to 85 years old, who had hypercholesterolemia with baseline plasma concentrations of calculated LDL-C ranging from [redacted] mg/dL. Mean baseline plasma concentrations of calculated LDL-C were comparable between the treatment groups and ranged from 138 mg/dL to 139 mg/dL. In general, the treatment groups were also balanced with regard to age, gender, race, diet, weight, and body mass index. Most subjects were Caucasian (90%). Approximately 9.6% of subjects had no CHD with less than 2 cardiovascular risk factors with LDL-C 160 mg/dL; 22.6% of subjects had no CHD with 2 or more cardiovascular risk factors and LDL-C 130 mg/dL; and 67.7% of subjects had CHD, diabetes and/or CHD-equivalent disease with LDL-C 100 mg/dL. Baseline general medical history is summarized in Section 14.1.1.2. ... The mean baseline plasma concentrations of calculated LDL-C were 138.8 mg/dL and 138.1 mg/dL for the statin + placebo and statin + ezetimibe 10-mg groups, respectively.

Percentage of subjects by baseline statin therapy: the percentages of simvastatin subjects at baseline were 30.0% and 32.5% for the placebo and ezetimibe 10-mg groups, respectively. The corresponding proportions of atorvastatin subjects were 41.5% and 38.5%, respectively.

The p-values for baseline comparisons provided by the sponsor on request (dated May 9th, 2002) were only for baseline variables identified in the protocol and none of them were <.05.

Slight numerical imbalances between the two treatment groups of primary interest are noted in a few characteristics, e.g.:

Number (%)

Risk Factor	Stratum	Statin + Placebo (n=390)	Statin + Ezetimibe 10 mg (n=379)
No CHD and <2 RF, LDL-C ≥4.14 mmol/L (160 mg/dL)	I	19 (56)	19 (48)
	II	15 (44)	21 (53)
No CHD and ≥2 RF, LDL-C ≥3.37 mmol/L (130 mg/dL)	I	36 (45)	55 (59)
	II	44 (55)	39 (41)

Stratum I: Subjects with LDL-C values <18% above the NCEP-defined target.
Stratum II: Subjects with LDL-C values ≥18% above the NCEP-defined target.
Source Data: Section 14.1.1.3.

2.3.3.3e. Measurements of Treatment Compliance and Other Factors That Could Affect Response

On the results of treatment compliance and compliance with the visit schedule, compliance with the diet, and changes in body weight, the sponsor stated, "Overall, the results show good compliance with provisions of the protocol, and no obvious difference among groups that might affect the interpretation of the outcome."

The compliance rate for a subject was defined as the total number of doses taken divided by the total number of doses the subject was supposed to have taken during the 8-week double-blind treatment period. Over 90% of subjects had greater than or equal to a 90% compliance rate.

Distribution of subjects by category of percent compliance:

Compliance Category	Statin + Placebo (n=390)	Statin + Ezetimibe 10 mg (n=379)
≥94%	345	327
94% to 90%	17	18
90% to 85%	7	12
85% to 75%	9	12
75% to 60%	4	3
<60%	8	7
Source Data: Section 14.2.1.1.		

The distribution of days of participation in the Randomization Phase is summarized below. There were no consequential differences in participation between the two treatment groups of primary comparison.

Table 35 Extent of Exposure: Number of Days of Participation in the Randomization/Active Treatment Phase: Intent-to-Treat Data Set

(Protocol No. P02173/P02246)

	Statin + Placebo (n=390)	Statin + Ezetimibe 10 mg (n=379)
Days in Randomization/Active Treatment Phase[a]		
Mean (SD)	55.3 (8.0)	55.5 (8.7)
Median	56	56
Min-Max	[redacted]	[redacted]
Frequency by Interval: Number (%) of Subjects with a Maximum Indicated Number of Days in Randomization/Active Treatment Phase		
0 days	0	0
1 - 7 days	1 (0.3)	3 (0.8)
8 - 21 days	8 (2.1)	5 (1.3)
22 - 42 days	7 (1.8)	8 (2.1)
43 - 70 days	371 (95.1)	359 (94.7)
> 70 days	3 (0.8)	6 (1.6)
Missing	0	0

a: n=390 for placebo treatment group and n=379 for ezetimibe treatment group for summary statistics
SD = standard deviation
Source Data: Section 14.3.

From the results provided by the sponsor, the reviewer does not see any major imbalances between the treatment groups.

2.3.3.3f. Efficacy Results (Sponsor's Analyses)

The sponsor stated that the Data Analysis Plan was finalized (Jul. 31, 2001) before the database lock (Aug. 18, 2001). The "Data Analysis Plan" (submitted April2, 2002) stated:

> The primary efficacy variable, percent change from baseline in LDL- C after 8 weeks of treatment, will be assessed by an ANOVA model. Because of the limited number of patients per study site, study site and treatment- by- site interaction will not be included in the primary analysis model. The impact of site(s) on results will be explored in sensitivity analyses (for details, see Section VI. STATISTICAL TECHNICAL ISSUES, F. Subgroup Analysis). The initial ANOVA model will include terms for statin (simvastatin, atorvastatin, other), stratum, region (domestic sites, international sites), treatment, treatment- by- statin interaction, treatment- by- stratum interaction, and treatment- by- region interaction. The interaction terms will be tested and removed from the ANOVA model if found to be not significant ($p > 0.050$) or quantitative in nature [1]. The key secondary efficacy variables (total- C, TG, and HDL- C) and other secondary efficacy variables (Non HDL- C, Apo B, Apo A- I, Apo A- II, LDL- C: HDL- C, total- C: HDL- C, CRP) will also be evaluated using the above ANOVA model. The parametric method will be the primary approach. The underlying assumptions for the analysis of variance will be checked by Shapiro-Wilk test for normality and Levene's test for homogeneity of variances for the primary and secondary lipid variables. If these assumptions are violated, parametric approach will be corroborated with a nonparametric method based upon Tukey's normalized ranks; the interpretation of the results will be based on the nonparametric results. The least- squares mean (LS mean) for each treatment, between- treatment difference, and 95% confidence intervals (95% CI) will be estimated from the above ANOVA model.

The Data Analysis Plan also stated:

> The primary analysis will be an intention- to- treat approach at endpoint after 8 weeks of treatment. The intention- to- treat data include all patients who receive randomized treatment assignment. For percent change (or change where appropriate) analysis from baseline to endpoint, patients who have a baseline measurement and at least one postbaseline value will be included in the intention- to- treat analysis.
>
> The protocol-evaluable analysis will exclude patients and/ or data points with clinically important protocol deviations based on a set of prespecified criteria described in Section VII. GROUND RULES FOR ANALYSIS. G. Description of Protocol- Evaluable Population.
>
> Any substantial differences between conclusions from analyses based on the intention- to-treat and the protocol- evaluable populations will be investigated and explained.

Primary efficacy comparison: (statin + ezetimibe 10mg) vs (statin + placebo)

Least-square (LS) mean percent changes from baseline to endpoint in calculated LDL-C of -3.67% and -25.14% were observed for statin + placebo and statin + ezetimibe 10 mg, respectively. Addition of ezetimibe 10 mg/day to ongoing statin monotherapy further reduced calculated LDL-C by 21.5% with respect to LS mean percent changes from baseline compared with statin alone (p 0.001) (Table below).

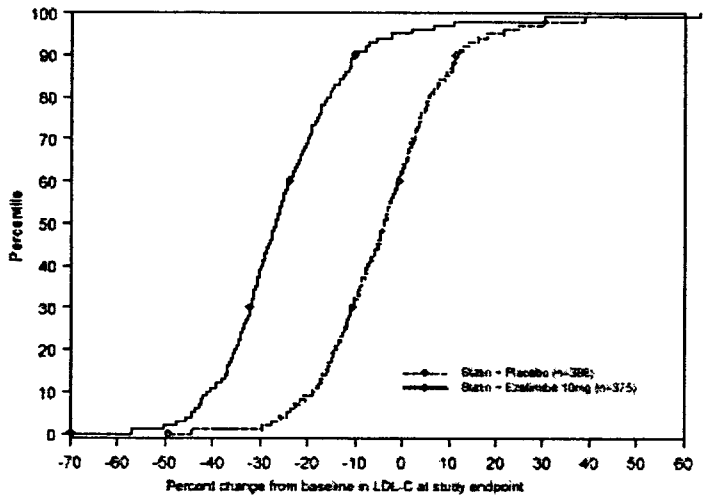
Percent Change in Plasma Concentration of LDL-C Between Baseline and Endpoint: Intent-to-Treat Data Set

	(Protocol P02173/P02246)	
LDL-C	Statin + Placebo	Statin + Ezetimibe 10 mg
Baseline	(n=390)	(n=379)
Raw Mean Value in mg/dL (mmol/L)	138.81(3.60)	138.12(3.58)
Endpoint	(n=388)	(n=375)
Raw Mean Value in mg/dL (mmol/L)	132.83(3.44)	102.47(2.65)
LS Mean percent change from baseline (standard error)[a]	-3.67(0.74)	-25.14(0.74)
Difference from Placebo in LS Mean percent change from baseline (95% confidence limits)[a]	-21.5(-23.5, -19.5)	

a: Least-squared means and standard errors based on the ANOVA model
Source Data: **Section 14.2.2.1.1.1.1.**

§ The Cumulative Distribution Functions of Percent Change from Baseline in LDL-C at Study Endpoint (P02173/02246) is provided below:

Figure

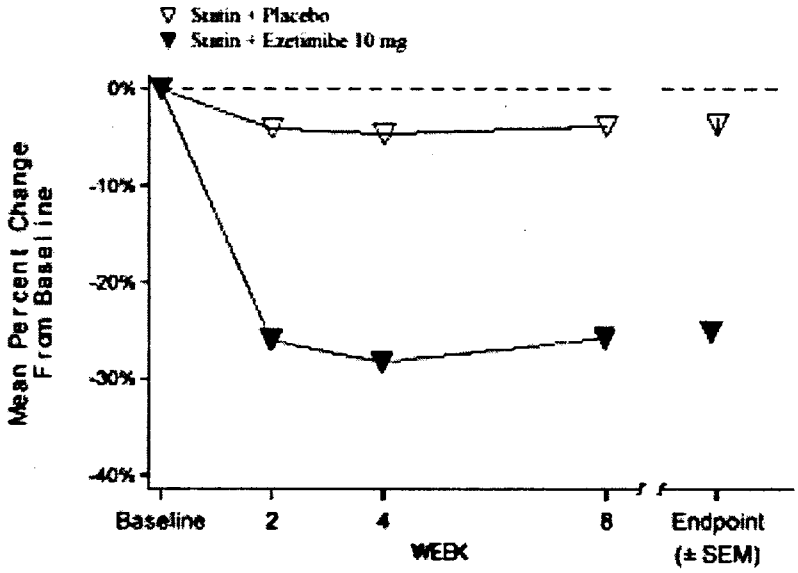


From this, percent of patients (y-axis value) with a value of Percent Change from Baseline in LDL-C at Study Endpoint, smaller than or equal to a value on the x-axis can be read. For example, 50% of the statin+ezetimibe 10mg patients had a ≤–26.8% change from baseline; whereas, 50% of the statin+placebo patients had a ≤-4.0% change from baseline.

§ Among the dropout cohorts considered (April 19, 2002 submission), the results in the ezetimibe+statin cohorts were always better (at least numerically) than those in the statin+placebo cohorts.

§ The ezetimibe-induced additional decrease in calculated LDL-C concentration was observed as early as Week 2 and was maintained to the endpoint (Figure below). [*Note: At least numerically, it was not fully maintained at the Week 4 level.*]

LS Mean Percent Change From Baseline in Plasma Concentration of LDL-C Over Time and at Endpoint in the two Treatment Groups: Intent- to-Treat Data Set



§ Results by individual statin are in Appendix Table 3.3.1. The addition of ezetimibe 10 mg to ongoing simvastatin, atorvastatin, and other statin therapy further reduced the LS mean changes in calculated LDL-C by –23.7%, -21.0%, and –19.7% respectively, compared to simvastatin, atorvastatin, and other statin therapy alone. Within the "other statin" category, the results were generally consistent with those for simvastatin and atorvastatin.

§ Further details, including results by each of the 6 statins, are presented in the NDA Section 14.2.2.1.1.1.2. The protocol-evaluable analysis also showed consistent results, and they are presented in NDA Section 14.2.2.1.1.2. A secondary analysis of the subjects who were above NCEP ATP II target LDL-C levels at baseline was also conducted, and it showed consistent results (NDA Section 14.2.2.1.1.3.).

Results for the primary efficacy endpoint, LDL-C percent change from baseline to endpoint, were examined in subgroups defined by subject baseline characteristics: gender, age (<65 versus ≥ 65; < 75 versus ≥75), race (Caucasian versus Non-Caucasian), NCEP ATP II category, body mass index (<25, 25 to 30, 30 to 40, ≥40 kg/m^2), and waist circumference (≤102 cm for men and ≤ 88 cm for women versus > 102 cm for men and > 88 cm for women). The results indicate that the response to ezetimibe 10 mg added to ongoing statin monotherapy was generally consistent across subgroups (Figure below). A secondary Table 24 Figure 2 analysis of subjects who had not reached NCEP ATP II target LDL-C levels at baseline also showed consistent results (NDA Section 14.2.2.1.4.2.).

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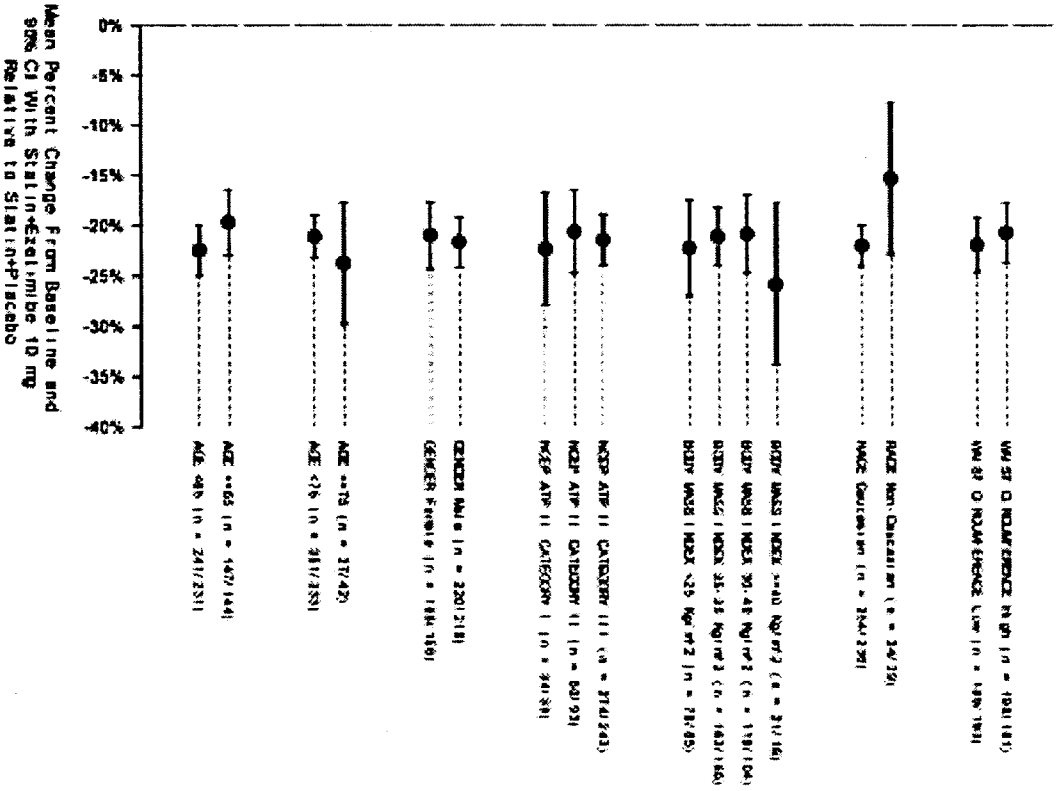
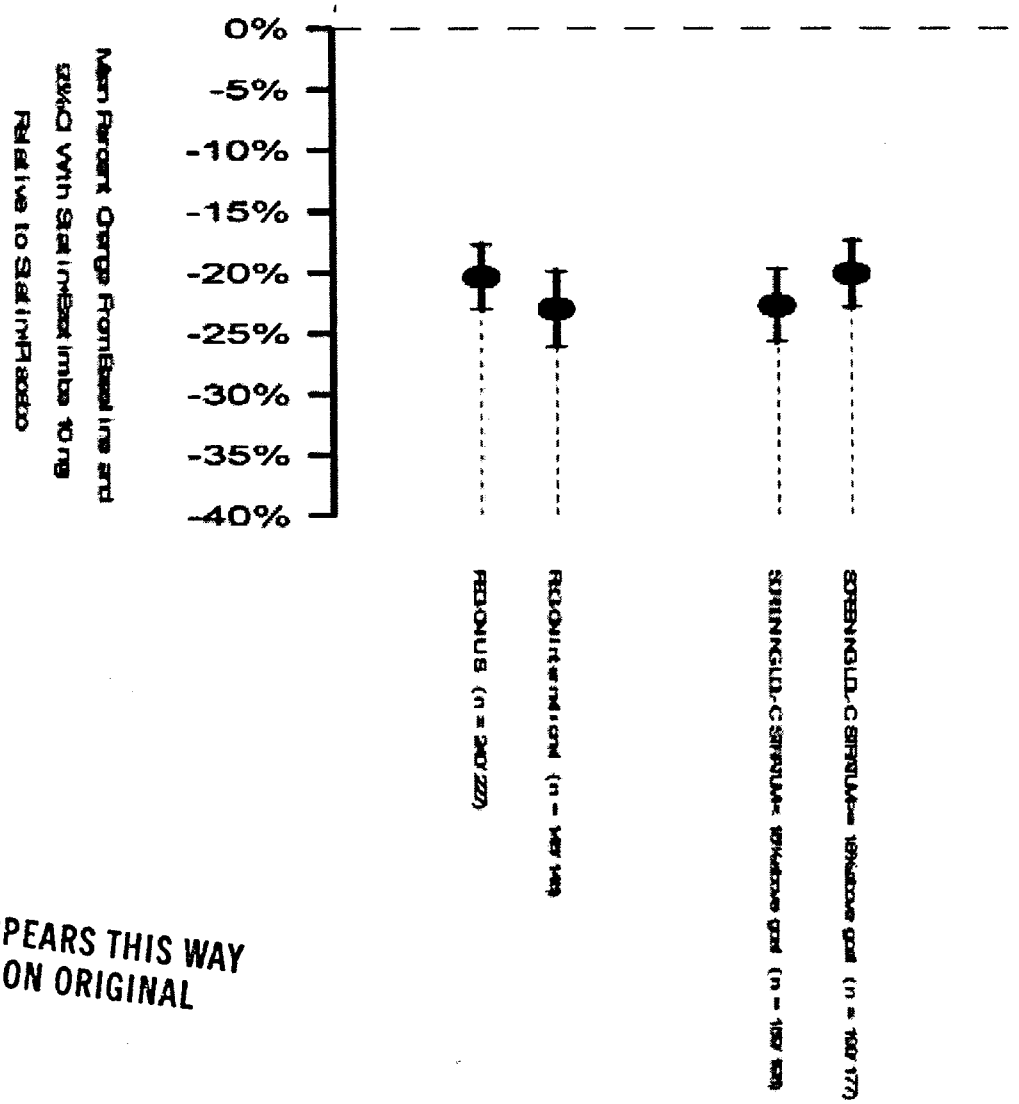
Point estimate and 95% confidence interval of the difference between response (raw mean percent change from baseline) to statin + ezetimibe and statin + placebo in calculated LDL-C, overall and in various subgroups of the population defined by baseline characteristics: Intent-to-Treat Data Set



Source Data: Section 14.2.2.1.4.1.1. and Section 14.2.2.1.4.1.2. In subgroup labels, n = X/Y indicates the number of subjects treated with statin + placebo (X)/number of subjects treated with statin + ezetimibe 10 mg (Y).

The following Figure was provided for two additional subgroups on May 9, 2002:



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The sponsor stated (May 9, 2002), "Conclusion: This exhaustive assessment of the relationship of baseline characteristics to the primary efficacy variable indicates that the conclusions about the treatment group differences are not altered by consideration of these baseline characteristics."

The following interaction p-values of baseline characteristics with treatment response were significant at the usual significance level of 0.1 for test of interaction:

Race (Caucasian, non-Caucasian) –	0.056
Center -	0.003

No multiple comparison adjustments have been employed. However, since the power of the test of interaction is generally poor, we cannot neglect these either. Therefore, the superiority of the addition of ezetimibe to ongoing statin monotherapy over the statin monotherapy group seemed to differ statistically significantly depending on race (Figure above) and center (Region and not Center is presented in the above figure; detailed center results are on pages 39 to 46 of the 5-9-02 submission). Out of nearly 80 centers, in only two U.S. and one international centers results were opposite (treatment group without ezetimibe doing better than the group with ezetimibe).

However, these interactions were quantitative and not qualitative; i.e., the addition of ezetimibe to ongoing statin monotherapy was superior to statin monotherapy irrespective of the race (see Figure above for the amount of superiority) or center (except for 3 out of nearly 80 centers. Detailed results are on pages 39 to 46 of the 5-9-02 submission).

Since the power of the test of interaction is generally poor and, most of all, since the studies were not powered for tests of interactions in subgroups, we cannot say whether the difference in superiority of (Statin + ezetimibe 10 mg) over the (Statin + placebo) in the above Figures with respect to other characteristics is real or not.

2.3.3.3g. <u>Reviewer's Comments and Conclusions on Study P02173/P02246</u>

The sponsor's analyses as well as this reviewer's alternative analyses, performed with the data supplied by the sponsor electronically, provided statistical evidence in favor of the superiority of the addition of ezetimibe 10 mg/day to ongoing statin compared with (addition of placebo to) statin alone, with respect to the primary efficacy variable.

There were statistically significant interactions of "Race" and "Center" with the treatment response. See the previous section for details.

◄

§ §

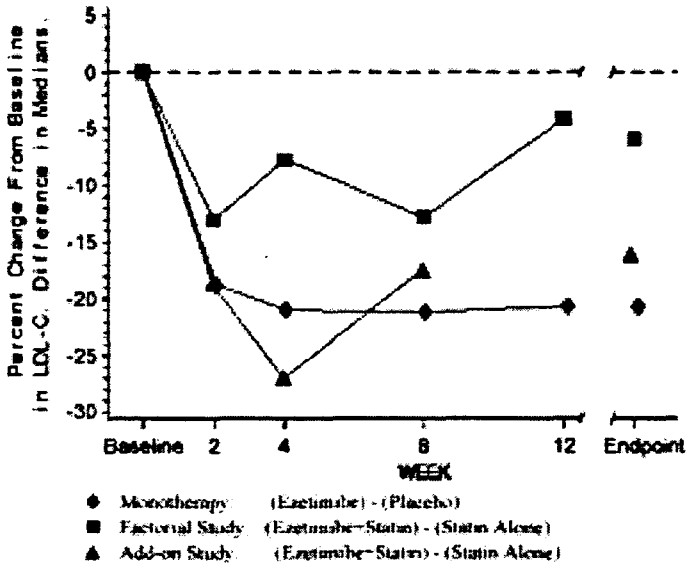
2.4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

(5 studies, 3 indications)

Details along with 95% confidence intervals for subgroups are in Sections 2.3.3.1.f, 2.3.3.2.f, and 2.3.3.1.f for the three studies reviewed in this document. For the other — studies reviewed

—— other indications (separate documents), details are in the corresponding section (f). Statistically significant quantitative (not qualitative) interactions of baseline factors with the treatment response were seen for BMI, Triglycerides, Cardiovascular Risk Factors, and Diabetes mellitus in Study P00474, HDL-C and Race (Caucasian, non-Caucasian) in Study P00680, "Race" and "Center" (many centers with few patients in each) in Study P02173/P02246, both prior and concomitant apheresis in Study P01030, baseline sitosterol and prior surgery in Study P02243/P02257. Non-Caucasian patients did much worse in Study P00680 and Study P02173/P02246 (but at least numerically better in the monotherapy Study P00474) than the Caucasian patients. The reviewing Medical Officer told this reviewer that in the other monotherapy Study P00475 also, Non-Caucasian patients did worse than the Caucasian patients. The following figure on the performance of Black subjects is from the ISE, where studies of similar designs have been pooled (not all of these studies have been reviewed by this reviewer):

Percent Change from Baseline in Calculated LDL-C in Black Subjects over time (difference in medians): in the Factorial Coadministration Studies, the Add-On Study, and the Pooled Phase III Monotherapy (Intent-to-Treat Data Set)

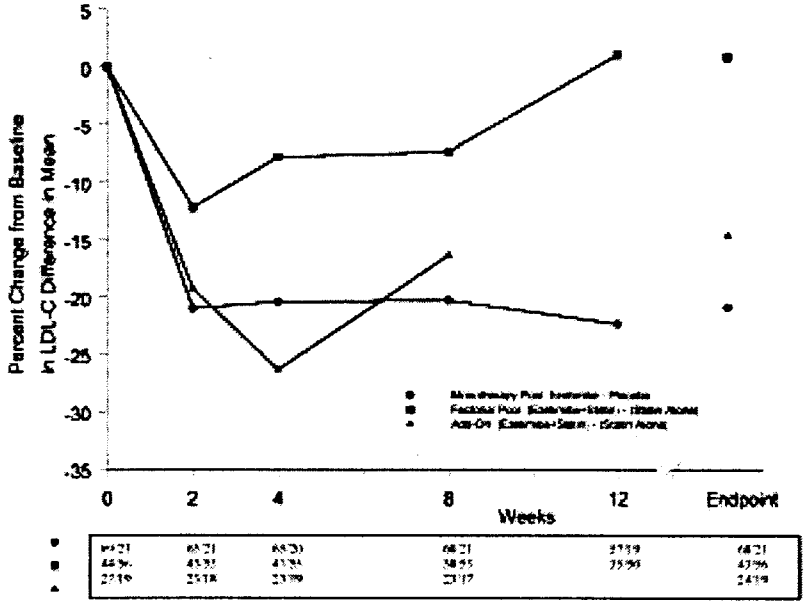


The benefit of coadministration or adding of ezetimibe to statin seems to be decreasing over time. In monotherapy studies pooled (P00474 and P00475), that was not the case.

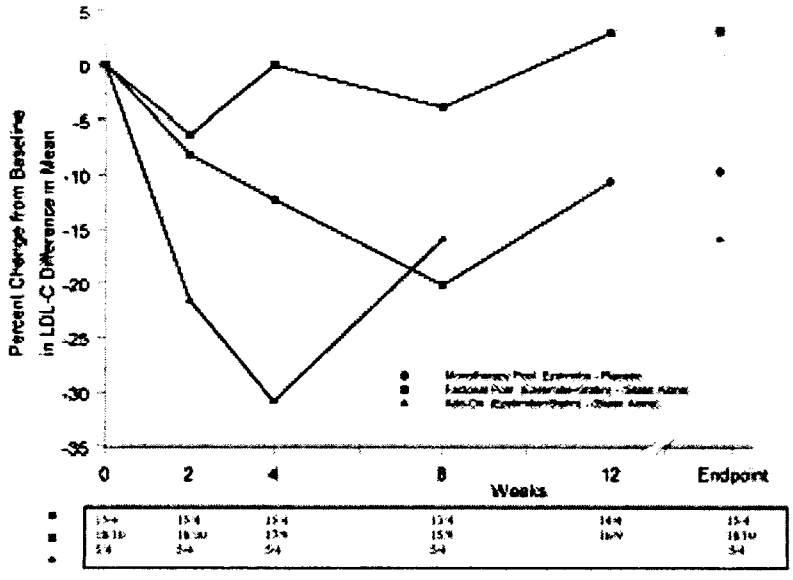
On request the sponsor provided a lot of additional information on the issue of race. Because of small number of patients we are not able to draw a final conclusion but numerically it appears that, in Black and Asian patients, the benefit of (ezetimibe+stain) over statin alone was waning over time. The following figures are given as examples:

Difference in mean versus Time

Race Group: Black



Race Group: Asian



2.5 CONCLUSION

(5 studies, 3 indications)

In spite of the above statistically significant interactions (quantitative only not qualitative, i.e., better response for ezetimibe alone or with another therapy compared with the comparator group in almost all subgroups), all the five studies reviewed provided statistically significant evidence in favor of their respective primary efficacy conclusions. With respect to Black and Asian patients, numerically, (ezetimibe+statin) did not perform better than statin alone at Week 12.

Japobrata Choudhury, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot

Dr. Wilson

CC:
Archival NDA 21-445/N_000

HFD-510/Dr. Parks
HFD-510/Dr. Temeck
HFD-700/ Dr. Anello
HFD-715/Dr. Nevius
HFD-715/Dr. Wilson
HFD-715/Dr. Sahlroot
HFD-715/Dr. Choudhury

J.Choudhury:7-3110: 09/23/02

This review consists of 71 pages of text and 10 pages of appendices.

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APPENDIX

Table 0.1.1

Description of Phase II/III Clinical Therapy Studies

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/NC)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
Phase II Ezetimibe Dose Response Studies								
C96-411/345	Effect of EZ on LDL-C and other lipids (dose ranging); safety; PK	R, DB, PC, PG	Primary hypercholesterolemic (PHC) subjects on a low-fat diet with LDL-C 160 to 220 mg/dL and TG ≤250 mg/dL	8 weeks QD before AM meal	124 30 - 71 66/58 13/11	88 30 - 71 46/43 8/1/8	Placebo EZ 1 EZ 5 EZ 10 EZ 20 EZ 40 lovastatin (L) 40	17 17 20 18 16 18 18
C96-019	Effect of EZ on LDL-C and other lipids (dose response); safety; PK	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG <300 mg/dL	12 weeks QD before AM meal	243 28 - 75 139/104 223/20	191 28 - 75 108/83 176/15	Placebo EZ 0.25 EZ 1 EZ 5 EZ 10	52 47 49 49 48
C96-258	Effect of EZ on LDL-C and other lipids (dose regimen [AM vs PM dosing]); safety; PK	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG <300 mg/dL	12 weeks QD before AM meal or at bedtime (PM)	189 22 - 75 89/100 168/21	153 25 - 75 74/79 135/18	Placebo EZ 5 AM EZ 5 PM EZ 10 AM EZ 10 PM	36 36 40 39 38
Phase III Ezetimibe Monotherapy Studies- Primary Hypercholesterolemia								
P00474	Effect of EZ 10 mg monotherapy on LDL-C and other lipids; safety	R, DB, PC, UPG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL	12 weeks QD in AM	827 20 - 86 397/430 746/81	822 20 - 86 302/320 565/57	Placebo EZ 10	205 622
P00475	Effect of EZ 10 mg monotherapy on LDL-C and other lipids; safety	R, DB, PC, UPG	PHC subjects on a low-fat diet with LDL-C 130 to 250 mg/dL and TG ≤350 mg/dL	12 weeks QD in AM	892 18 - 85 434/458 809/83	888 18 - 85 332/334 668/68	Placebo EZ 10	226 666

(Table 0.1.1 Continued to next page)

Table 0.1.1 Continued

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/N/O)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
Phase III Ezetimibe/Statin Coadministration – Factorial Coadministration Studies								
P00679	Effect of EZ when coadministered with lovastatin (L) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks QD with PM meal	548 28 - 85 229/319 484/64	264 28 - 85 117/147 227/37	Placebo L 10 L 20 L 40 EZ 10 EZ 10+L 10 EZ 10+L 20 EZ 10+L 40	64 73 74 73 72 65 62 65
P00680	Effect of EZ when coadministered with simvastatin (S) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks QD in PM	660 25 - 87 291/377 610/58	335 27 - 84 150/185 306/29	Placebo S 10 S 20 S 40 S 80 EZ 10 EZ 10+S 10 EZ 10+S 20 EZ 10+S 40 EZ 10+S 80	70 70 61 65 67 61 67 69 73 65
P00691	Effect of EZ when coadministered with pravastatin (P) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks QD at bedtime	538 20 - 86 238/300 462/76	268 20 - 86 106/162 236/32	Placebo P 10 P 20 P 40 EZ 10 EZ 10+P 10 EZ 10+P 20 EZ 10+P 40	65 66 69 70 64 71 66 67

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/N/O)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
P00692	Effect of EZ when coadministered with atorvastatin (A) on LDL-C and other lipids; safety	R, DB, PC, PG	PHC subjects on a low-fat diet with LDL-C 145 to 250 mg/dL and TG ≤350 mg/dL	12 weeks QD in AM	628 18 - 86 250/358 533/95	320 26 - 86 136/184 279/41	Placebo A 10 A 20 A 40 A 80 EZ 10 EZ 10+A 10 EZ 10+A 20 EZ 10+A 40 EZ 10+A 80	60 60 60 66 62 65 65 62 65 63
Phase III Ezetimibe/Statin Coadministration– Add-On Study								
P02173	Effect of EZ when added to ongoing therapy with statins on LDL-C and other lipids; safety	R, DB, PC	Subjects with PHC, known CHD, or multiple CVD risk factors who are not at LDL-C targets with a stable regimen of statins and a low-fat diet	8 weeks QD in AM or PM with statin as per statin label	769 22-85 443/326 693/76	379 25-85 222/157 337/42	Placebo (+ statin) EZ 10 (+ statin)	390 379
Phase III Ezetimibe Therapy in Special Dyslipidemic Populations								
P01030	Effect of EZ when coadministered with A or S on LDL-C and other lipids; safety	R, DB, PG	HoFH subjects with LDL-C ≥100 mg/dL on low-fat diet and taking OL A or S 40 mg/day for 6 weeks	12 weeks QD in AM with A, QD in PM with S	50 11 - 74 21/29 45/5	33 11 - 74 16/17 29/4	A/S 80 EZ 10+A/S 40 EZ 10+A/S 80	17 16 17

(Table 0.1.1 Continued to next page)

Table 0.1.1 Continued

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (yr) Sex (# M/F) Race (# C/NC)		Treatment Groups	
					All	Ezetimibe	Identity	No. Subjects
P02243/P02257	Effect of EZ on plasma sterols and lipids/ lipoproteins	R, DB, PG	Homozygous sitosterolemic subjects with baseline plasma sitosterol concentrations >5 mg/dL	8 weeks QD in AM	37 9-72 13/24 33/4	30 9-72 12/18 27/3	Placebo EZ 10	7 30
Ongoing, Uncontrolled, Open-label, Long-term Extension Study								
P00476	Long-term safety and efficacy of EZ as monotherapy or when coadministered with L or S	OL; response-based addition and up-titration of L or S (10-40 mg)	PHC subjects on low-fat diet who completed treatment under Protocols P00474 or P00475	24 months QD in AM as monotherapy or coadministered with statin as per statin label	1313 18-86 655/658 1196/115	1313 18-86 655/658 1198/115	EZ 10 EZ 10 + L/S[a]	783 530

A=atorvastatin; CHD=coronary heart disease; DB=double-blind; EZ=ezetimibe; HoFH=homozygous familial hypercholesterolemia; L=lovastatin; OL=open-label; P=pravastatin; PC=placebo-controlled; PG=parallel group; PHC=primary hypercholesterolemia; QD=once per day by mouth; R=randomized; S=simvastatin; UPG=unbalanced parallel groups.

a: all doses of 10, 20, or 40 mg for L, or 10, 20, 40, or 80 mg for S (following a titration procedure).

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Table 0.3.1

Mean Percent Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Calculated) Between Baseline and Endpoint: Factorial Coadministration Studies (Intent-to-Treat Data Set)

Calculated LDL-C		
All Statin	EZ + All Statin	p-Value
(n=220)	(n=192)	
178.9 [4.6]	177.7 [4.6]	0.60
(n=218)	(n=191)	
133.1 [3.5]	105.6 [2.7]	<0.01
-25.4 (0.9)	-40.4 (1.0)	<0.01
N/A	-15.0 (-17.6, -12.3)	<0.01
(n=263)	(n=274)	
180.2 [4.7]	177.6 [4.6]	0.40
(n=261)	(n=269)	
114.0 [3.0]	86.3 [2.2]	<0.01
-36.5 (0.9)	-51.3 (0.9)	<0.01
NA	-14.8 (-17.3, -12.3)	<0.01
(n=205)	(n=204)	
177.6 [4.6]	177.0 [4.6]	0.9
(n=203)	(n=204)	
132.8 [3.4]	106.3 [2.8]	<0.01
-25.2 (0.9)	-38.6 (0.9)	<0.01
N/A	-13.4 (-15.8, -11.1)	<0.01

Calculated LDL-C		
All Statin	EZ + All Statin	p-Value
(n=248)	(n=255)	
181.4 [4.7]	181.8 [4.7]	0.83
(n=246)	(n=253)	
101.1 [2.6]	79.1 [2.1]	<0.01
-44.2 (1.0)	-56.3 (1.0)	<0.01
N/A	-12.1 (-14.7, -9.4)	<0.01

Table 0.3.2

Table 41 Mean Percent Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Direct LDL-C) Between Baseline and Endpoint: Factorial Coadministration Studies Individual Treatment Groups (Intent-to-Treat Data Set)

	Placebo	EZ	Statin 10 mg	EZ + Statin 10	Statin 20 mg	EZ + Statin 20	Statin 40 mg	EZ + Statin 40	Statin 80 mg	EZ + Statin 80
Lovastatin P00679										
Baseline	(n=64)	(n=72)	(n=73)	(n=65)	(n=74)	(n=62)	(n=73)	(n=65)	N/A	N/A
Mean value in mg/dL [mmol/L]	177.8 [4.6]	178.0 [4.6]	177.3 [4.6]	173.5 [4.5]	175.6 [4.5]	175.7 [4.5]	179.7 [4.7]	178.1 [4.6]	N/A	N/A
Endpoint	(n=63)	(n=71)	(n=73)	(n=64)	(n=72)	(n=62)	(n=73)	(n=64)	N/A	N/A
Mean percent change from baseline (SEM)	-0.03 (1.7)	-18.8[a] (1.6)	-19.0 (1.6)	-33.1 (1.7)	-25.0 (1.6)	-39.4 (1.6)	-29.2 (1.6)	-44.5 (1.7)	N/A	N/A
Difference from same dose of statin-alone in mean percent change from baseline (95 % CI)	N/A	N/A	N/A	-14.2** (-18.8, -9.5)	N/A	-13.5** (-18.2, -8.8)	N/A	-15.3** (-20.0, -10.7)	N/A	N/A
Simvastatin P00680										
Baseline	(n=70)	(n=61)	(n=70)	(n=67)	(n=61)	(n=68)	(n=65)	(n=73)	(n=67)	(n=64)
Mean value in mg/dL [mmol/L]	177.4 [4.6]	181.3 [4.7]	175.6 [4.5]	175.3 [4.5]	181.8 [4.7]	177.9 [4.6]	178.7 [4.6]	174.0 [4.5]	180.5 [4.7]	178.1 [4.6]
Endpoint	(n=69)	(n=59)	(n=70)	(n=67)	(n=61)	(n=68)	(n=64)	(n=72)	(n=66)	(n=61)
Mean percent change from baseline (SEM)	-1.3 (1.7)	-18.1[a] (1.8)	-27.4 (1.7)	-44.4 (1.8)	-35.3 (1.8)	-44.8 (1.7)	-36.3 (1.8)	-53.5 (1.7)	-44.3 (1.8)	-56.8 (1.8)
Difference from same dose of statin-alone in mean percent change from baseline (95% CI)	N/A	N/A	N/A	-17.0** (-21.8, -12.2)	N/A	-8.5** (-13.5, -3.5)	N/A	-17.2** (-22.0, -12.3)	N/A	-12.6** (-17.6, -7.6)

Table 41 Mean Percent Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Direct LDL-C) Between Baseline and Endpoint: Factorial Coadministration Studies Individual Treatment Groups (Intent-to-Treat Data Set)

	Placebo	EZ	Statin 10 mg	EZ + Statin 10	Statin 20 mg	EZ + Statin 20	Statin 40 mg	EZ + Statin 40	Statin 80 mg	EZ + Statin 80
Pravastatin P00681										
Baseline	(n=65)	(n=64)	(n = 66)	(n = 71)	(n = 69)	(n = 66)	(n = 70)	(n = 67)	N/A	N/A
Mean value in mg/dL [mmol/L]	177.1 [4.6]	177.4 [4.6]	171.4 [4.4]	176.3 [4.6]	182.6 [4.7]	173.8 [4.5]	175.9 [4.6]	178.7 [4.6]	N/A	N/A
Endpoint	(n=62)	(n=63)	(n = 65)	(n = 71)	(n = 69)	(n = 66)	(n = 69)	(n = 67)	N/A	N/A
Mean percent change from baseline (SEM)	1.3 (1.5)	-18.7[a] (1.6)	-19.7 (1.5)	-34.1 (1.5)	-23.8 (1.5)	-38.0 (1.5)	-29.4 (1.5)	-41.1 (1.5)	N/A	N/A
Difference from same dose of statin-alone in mean percent change from baseline (95% CI)	NA	NA	N/A	-14.4** (-18.6, -10.2)	N/A	-14.2** (-18.4, -10.0)	N/A	-11.7** (-15.9, -7.5)	N/A	N/A
Atorvastatin P00682										
Baseline	(n = 60)	(n = 65)	(n = 60)	(n = 65)	(n = 60)	(n = 62)	(n = 66)	(n = 65)	(n = 62)	(n = 63)
Mean value in mg/dL [mmol/L]	178.1 [4.6]	175.3 [4.5]	183.6 [4.8]	174.8 [4.5]	174.6 [4.5]	182.7 [4.7]	179.3 [4.6]	181.3 [4.7]	182.2 [4.7]	181.1 [4.7]
Endpoint	(n = 60)	(n = 65)	(n = 59)	(n = 65)	(n = 60)	(n = 62)	(n = 64)	(n = 63)	(n = 62)	(n = 62)
Mean percent change from baseline (SEM)	5.9 (1.9)	-18.4[a] (1.9)	-35.5 (1.9)	-50.4 (1.9)	-38.5 (1.9)	-53.7 (1.9)	-43.1 (1.9)	-54.3 (1.9)	-51.4 (1.9)	-59.7 (1.9)
Difference from same dose of simvastatin-alone in mean percent change from baseline (95% CI)	N/A	N/A	N/A	-14.9** (-20.2, -9.7)	N/A	-13.9** (-19.2, -8.6)	N/A	-11.3** (-16.5, -6.1)	N/A	-8.3** (-13.6, -3.1)

*p<0.05 **p<0.01

a Pairwise comparison of ezetimibe 10 mg versus placebo for mean percent change from baseline to endpoint was statistically significant, p<0.01.

Means and standard errors in this table are least-square means and standard errors based on the ANOVA model.

All Statin=pool of all doses of statin; EZ+All Statin=pool of all doses of statin coadministrated with EZ 10 mg; N/A=not applicable

(P00679 P00680 P00681 P00682)

Table 0.3.3

Table 42 Mean Percent Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Calculated LDL-C) Between Baseline and Endpoint: Factorial Coadministration Studies Individual Treatment Groups (Intent-to-Treat Data Set)

	Placebo	EZ	Statin 10 mg	EZ + Statin 10	Statin 20 mg	EZ + Statin 20	Statin 40 mg	EZ + Statin 40	Statin 80 mg	EZ + Statin 80
Lovastatin P00679										
Baseline	(n=64)	(n=72)	(n=73)	(n=66)	(n=74)	(n=62)	(n=73)	(n=66)	N/A	N/A
Mean value in mg/dL [mmol/L]	179.0 [4.6]	179.1 [4.6]	178.3 [4.6]	178.4 [4.6]	177.0 [4.6]	177.1 [4.6]	181.5 [4.7]	179.5 [4.7]	N/A	N/A
Endpoint	(n=63)	(n=71)	(n=73)	(n=64)	(n=72)	(n=62)	(n=73)	(n=65)	N/A	N/A
Mean percent change from baseline (SEM)	0.4 (1.7)	-18.7* (1.6)	-20.2 (1.6)	-34.2 (1.7)	-25.6 (1.6)	-40.8 (1.7)	-30.5 (1.6)	-46.1 (1.7)	N/A	N/A
Difference from same dose of statin-alone in mean percent change from baseline (95% CI)	N/A	N/A	N/A	-14.0** (-18.8, -9.5)	N/A	-15.2** (-19.8, -10.6)	N/A	-15.7** (-20.2, -11.1)	N/A	N/A
Simvastatin P00680										
Baseline	(n=70)	(n=61)	(n=70)	(n=67)	(n=61)	(n=59)	(n=65)	(n=73)	(n=67)	(n=65)
Mean value in mg/dL [mmol/L]	178.1 [4.6]	183.4 [4.8]	176.9 [4.6]	177.4 [4.6]	182.2 [4.7]	178.9 [4.6]	178.1 [4.6]	176.4 [4.6]	182.5 [4.7]	177.8 [4.6]
Endpoint	(n=69)	(n=60)	(n=70)	(n=67)	(n=61)	(n=58)	(n=64)	(n=72)	(n=66)	(n=62)
Mean percent change from baseline (SEM)	-1.5 (1.8)	-19.1* (1.9)	-27.2 (1.8)	-45.5 (1.8)	-36.5 (1.9)	-46.3 (1.8)	-37.5 (1.8)	-55.8 (1.7)	-44.7 (1.8)	-57.6 (1.8)
Difference from same dose of statin-alone in mean percent change from baseline (95% CI)	N/A	N/A	N/A	-18.3** (-23.2, -13.4)	N/A	-9.8** (-14.9, -4.7)	N/A	-18.2** (-23.2, -13.3)	N/A	-13.0** (-18.1, -7.9)

Table 42 Mean Percent Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Calculated LDL-C) Between Baseline and Endpoint: Factorial Coadministration Studies Individual Treatment Groups (Intent-to-Treat Data Set)

	Placebo	EZ	Statin 10 mg	EZ + Statin 10	Statin 20 mg	EZ + Statin 20	Statin 40 mg	EZ + Statin 40	Statin 80 mg	EZ + Statin 80
Pravastatin P00681										
Baseline	(n=65)	(n=64)	(n=66)	(n=73)	(n=68)	(n=66)	(n=70)	(n=67)	N/A	N/A
Mean value in mg/dL [mmol/L]	178.8 [4.6]	179.7 [4.7]	172.4 [4.5]	176.5 [4.6]	182.9 [4.7]	175.4 [4.5]	177.4 [4.6]	179.2 [4.6]	N/A	N/A
Endpoint	(n=63)	(n=63)	(n=65)	(n=73)	(n=69)	(n=66)	(n=69)	(n=67)	N/A	N/A
Mean percent change from baseline (SEM)	-0.6 (1.5)	-19.6* (1.5)	-21.3 (1.5)	-33.8 (1.4)	-23.2 (1.5)	-39.7 (1.5)	-31.1 (1.5)	-42.4 (1.5)	N/A	N/A
Difference from same dose of statin-alone in mean percent change from baseline (95% CI)	N/A	N/A	N/A	-12.5** (-16.5, -8.4)	N/A	-16.5** (-20.6, -12.4)	N/A	-11.4** (-15.4, -7.3)	N/A	N/A
Atorvastatin P00682										
Baseline	(n=60)	(n=65)	(n=60)	(n=65)	(n=60)	(n=62)	(n=65)	(n=65)	(n=62)	(n=63)
Mean value in mg/dL [mmol/L]	180.2 [4.7]	178.7 [4.6]	184.7 [4.8]	178.5 [4.6]	177.0 [4.6]	183.7 [4.8]	179.5 [4.7]	183.5 [4.8]	184.2 [4.8]	183.4 [4.8]
Endpoint	(n=60)	(n=65)	(n=60)	(n=65)	(n=60)	(n=62)	(n=64)	(n=64)	(n=62)	(n=62)
Mean percent change from baseline (SEM)	4.3 (2.0)	-20.0* (1.9)	-36.5 (2.0)	-53.4 (1.9)	-41.8 (2.0)	-54.2 (1.9)	-44.8 (1.9)	-56.4 (1.9)	-53.8 (1.9)	-61.2 (1.8)
Difference from same dose of statin-alone in mean percent change from baseline (95% CI)	N/A	N/A	N/A	-16.9** (-22.2, -11.5)	N/A	-12.4** (-17.8, -7.0)	N/A	-11.7** (-16.9, -6.4)	N/A	-7.3** (-12.7, -2.0)

**p<0.01

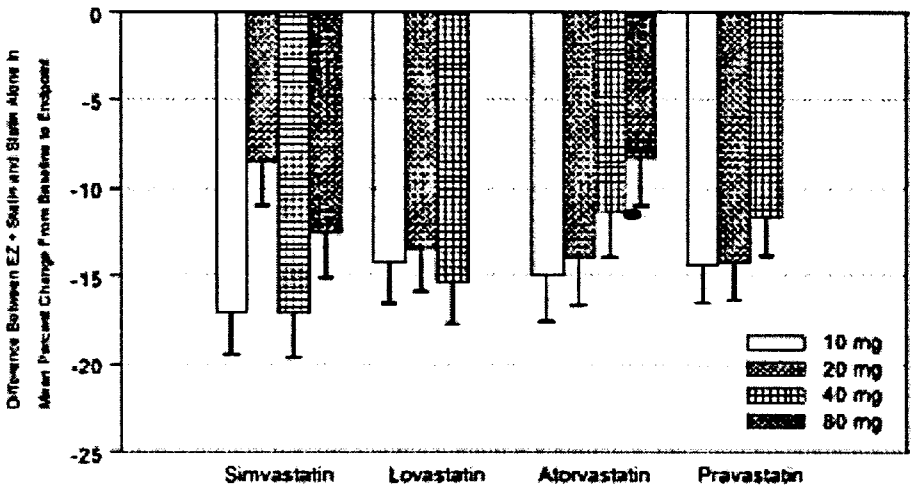
a Pairwise comparison of atorvastatin 10 mg versus placebo for mean percent change from baseline to endpoint was statistically significant: p<0.01

Means and standard errors in this table are least-square means and standard errors based on the ANOVA model.

All Statin=pool of all doses of statin; EZ+All Statin=pool of all doses of statin coadministered with EZ 10 mg; N/A=not applicable

(P00679 , P00680 , P00681 , P00682)

Figure 0.3.4



Incremental Mean Percent Change (SE) in Direct LDL-C when Ezetimibe is Coadministered with Statin Treatment: Factorial Coadministration Studies (Intent-to-Treat Data Set) **(P00679, P00680, P00691, P00692)**

Table 1.3.1

A PHASE III DOUBLE-BLIND EFFICACY AND SAFETY OF ONE DOSE OF SCH 58235 (10 mg) COMPARED TO PLACEBO IN SUBJECTS WITH PRIMARY HYPERCHOLESTEROLEMIA

STUDY P00474 -- INTENT-TO-TREAT POPULATION

PARAMETER: CALCULATED LDL (MG/DL)

	SCH 58235 10 MG		PLACEBO		POOL	PROB		SCH 58235 10 MG - PLACEBO	
	MEAN	S.E.	MEAN	S.E.	STD	TRT	SITE	POINT EST	95% CI
BASELINE									
# OF PTS	422		205						
ACTUAL	164.44	1.03	163.46	1.62	21.69	0.58	0.01	0.98	(-2.46, 4.40)
WEEK 2									
# OF PTS	595		296						
ACTUAL	133.66	1.15	165.43	1.78	23.26	<.01	0.07	-31.8	(-35.5, -28.0)
DIFF	-31.56	0.61	1.24	1.25	16.32	<.01	0.10	-32.8	(-35.4, -30.2)
% CHG	-18.96	0.47	1.00	0.72	9.44	<.01	0.06	-20.0	(-21.5, -18.4)
WEEK 4									
# OF PTS	596		197						
ACTUAL	132.89	1.19	162.78	1.84	23.88	<.01	0.20	-29.9	(-33.7, -26.0)
DIFF	-32.54	0.64	-1.37	1.30	16.95	<.01	0.06	-30.7	(-33.4, -27.9)
% CHG	-19.35	0.49	-0.74	0.76	9.62	<.01	0.13	-18.5	(-20.1, -16.9)
WEEK 8									
# OF PTS	591		196						
ACTUAL	133.26	1.21	164.10	1.84	23.53	<.01	0.33	-30.8	(-34.7, -27.0)
DIFF	-31.77	0.91	-0.36	1.39	17.73	<.01	0.03	-31.5	(-34.3, -28.6)
% CHG	-18.99	0.63	0.00	0.81	10.10	<.01	0.09	-19.0	(-20.7, -17.3)
WEEK 12									
# OF PTS	562		185						
ACTUAL	134.07	1.20	165.89	1.86	23.72	<.01	0.06	-31.8	(-35.8, -27.9)
DIFF	-33.41	0.88	2.02	1.37	17.45	<.01	0.01	-33.4	(-36.3, -30.5)
% CHG	-18.74	0.51	1.43	0.79	10.08	<.01	0.01	-20.4	(-22.1, -18.7)
ENDPOINT									
# OF PTS	605		201						
ACTUAL	134.35	1.25	165.06	1.80	23.77	<.01	0.02	-30.7	(-34.5, -26.9)
DIFF	-30.42	0.85	1.59	1.37	18.03	<.01	0.01	-32.3	(-35.2, -29.4)
% CHG	-18.24	0.51	1.16	0.79	10.44	<.01	<.01	-19.6	(-21.3, -17.9)

MEAN AND S.E. ARE LSMEAN AND LS STD ERROR BASED ON TWO WAY ANOVA MODEL EXTRACTING TREATMENT AND SITE EFFECT

APPEARS THIS WAY
ON ORIGINAL

Table 2.3.1
Mean Percent Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Direct LDL-C) Between Baseline and Endpoint: Intent-to-Treat Data Set (Individual Treatment Groups)

	Placebo n=70	Ezetimibe 10 mg n=61	Simvastatin 10 mg n=70	EZ 10 + Simva 10 n=67	Simvastatin 20 mg n=61	EZ 10 + Simva 20 n=69	Simvastatin 40 mg n=65	EZ 10 + Simva 40 n=73	Simvastatin 80 mg n=67	EZ 10 + Simva 80 n=65
Baseline	(n=70)	(n=61)	(n=70)	(n=67)	(n=61)	(n=69)	(n=65)	(n=73)	(n=67)	(n=64)[a]
Mean value in mg/dL [mmol/L]	177.43 [4.59]	181.32 [4.69]	175.58 [4.54]	175.30 [4.53]	181.60 [4.70]	177.94 [4.60]	176.67 [4.57]	173.97 [4.50]	180.47 [4.67]	178.11 [4.61]
Endpoint	(n=69)	(n=59)	(n=70)	(n=67)	(n=61)	(n=68)	(n=64)	(n=72)	(n=66)	(n=61)
Mean value in mg/dL [mmol/L]	175.01 [4.53]	147.86 [3.82]	127.31 [3.29]	97.21 [2.51]	114.74 [2.97]	98.29 [2.54]	111.66 [2.89]	80.94 [2.09]	100.85 [2.61]	76.28 [1.97]
Mean percent change from baseline (SEM)	-1.33 (1.73)	-18.06[b] (1.87)	-27.42 (1.72)	-44.44 (1.75)	-39.30 (1.84)	-44.78 (1.74)	-38.52 (1.79)	-53.48 (1.69)	-44.25 (1.77)	-56.81 (1.84)
Difference from same dose of simvastatin alone in mean percent change from baseline (95% confidence limits)	N/A	N/A	N/A	-17.01** (-21.83, -12.2) [versus Simva 10]	N/A	-8.49** (-13.46, -3.52) [versus Simva 20]	N/A	-17.16** (-22.01, -12.3) [versus Simva 40]	N/A	-12.55** (-17.56, -7.55) [versus Simva 80]
Difference from next higher dose of simvastatin alone in mean percent change from baseline (95% confidence limits)	N/A	N/A	N/A	-8.14** (-13.13, -3.16) [versus Simva 20]	N/A	-8.46** (-13.37, -3.55) [versus Simva 40]	N/A	-9.23** (-14.03, -4.42) [versus Simva 80]	N/A	N/A
Difference from second higher dose of simvastatin alone in mean percent change from baseline (95% confidence limits)	N/A	N/A	N/A	-8.12** (-13.05, -3.19) [versus Simva 40]	N/A	-0.53 (-5.40, 4.34) [versus Simva 80]	N/A	N/A	N/A	N/A

* p≤0.05, ** p≤0.01

a. Subject 23/000153 (EZ 10+Simva 80) had missing baseline data for direct LDL-C.

b. Pairwise comparison of ezetimibe 10 mg vs placebo for mean percent change from baseline to endpoint was statistically significant, p<0.01.

Means and standard errors in this table are least-square means and standard errors based on the ANOVA model that extracts effects due to dose (simvastatin : 0 mg, 10 mg, 20 mg, 40 mg and 80 mg), treatment (ezetimibe 10 mg, ezetimibe placebo), and dose-by-treatment interaction.

EZ 10=ezetimibe 10 mg; Simva XX=dose of simvastatin in milligrams; N/A=not applicable

Source Data: Section 14.2.2.1.1.1.

Table 3.3.1

Percent Change in Plasma Concentration of LDL-C Between Baseline and Endpoint: Intent-to-Treat Data Set: By Individual Statin

LDL-C		(Protocol P02173/P02246)
	Simvastatin Placebo	Simvastatin Ezetimibe 10 mg
Baseline	(n=117)	(n=123)
Raw Mean Value in mg/dL (mmol/L)	137.55 (3.56)	141.43 (3.66)
Endpoint	(n=117)	(n=123)
Raw Mean Value in mg/dL (mmol/L)	133.21 (3.45)	102.64 (2.66)
LS Mean percent change from baseline (standard error)[a]	-3.11(1.31)	-26.80 (1.28)
Difference from Placebo in LS Mean percent change from baseline (95% confidence limits)[a]	-23.7(-27.3, -20.1)	
	Atorvastatin Placebo	Atorvastatin Ezetimibe 10 mg
Baseline	(n=162)	(n=146)
Raw Mean Value in mg/dL (mmol/L)	140.16(3.63)	141.15(3.66)
Endpoint	(n=161)	(n=144)
Raw Mean Value in mg/dL (mmol/L)	133.75 (3.46)	104.81 (2.71)
LS Mean percent change from baseline (standard error)[a]	-4.01(1.12)	-24.98 (1.18)
Difference from Placebo in LS Mean percent change from baseline (95% confidence limits)[a]	-21.0(-24.2, -17.8)	
	Other Placebo	Other Ezetimibe 10 mg
Baseline	(n=111)	(n=110)
Raw Mean Value in mg/dL (mmol/L)	138.16(3.58)	130.40(3.38)
Endpoint	(n=110)	(n=108)
Raw Mean Value in mg/dL (mmol/L)	131.07 (3.39)	99.14 (2.57)
LS Mean percent change from baseline (standard error)[a]	-3.80(1.36)	-23.54 (1.39)
Difference from Placebo in LS Mean percent change from baseline (95% confidence limits)[a]	-19.7 (-23.5, -16.0)	

a: Least-squared means and standard errors based on the ANOVA model
Source Data: **Section 14.2.2.1.1.1.2.**

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/s/

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9/30/02 05:07:00 PM
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Todd Sahlroot
10/2/02 03:39:39 PM
BIOMETRICS

Steve Wilson
10/7/02 03:06:28 PM
BIOMETRICS

STATISTICAL REVIEW & EVALUATION
(Carcinogenicity Studies)

NDA #:	21,445
Applicant:	Merck & Schering
Drug Name:	Zetia
Alt Drug Name:	Ezetimibe
Molecular formula:	1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone, $C_{24}H_{21}F_2NO_3$.
Drug Class:	Cholesterol/phytoesterol uptake inhibitor
Indication:	Primary hypercholesterolemia
Received Date:	1/17/2002
Documents Reviewed:	EDR, mouse study 96458, rat study 96459, submissions of 12/27/2001 and 7/3/2002
Project Manager:	William Koch
Pharmacology Reviewer:	Indra Antonipillai, Ph.D.
Primary Stat Reviewer:	Ferrin Harrison, Ph.D.

SUMMARY OF REVIEW

There are statistically significant differences in survival in male rats.

There is no statistically significant trend in incidence rate in the tumors tested in both sexes in both rat and mouse studies.

For male rats, the group average food consumption decreased rapidly during the first half year of the study, and continued to decrease slightly up to about week 90. The animals ate less as they became older.

I. COMMON ELEMENTS OF THE DESCRIPTION AND ANALYSES OF RAT AND MOUSE STUDIES

The rodents were 6 weeks old at study initiation.

Each study had 50 toxicity rodents per gender and group, with two placebo groups and three drug groups, low, medium and high dose. There were some additional rodents for plasma analysis, showing drug in plasma.

The schedule of tests included daily viability and weekly clinical observations. Palpable masses were to be examined from weeks 2 to 38 (every 4 weeks in mice and every 2 weeks in rats) and every other week thereafter. Body weight and test article intake were generally measured or estimated weekly to week 13, and every other week thereafter. Opthalmoscopic examinations

were scheduled for once pretest, and once each at weeks 52 and near the end (rat: week 103, mouse: week 104.) Necropsy and histopathology examinations were planned.

The sponsor found no drug-related mortality, clinical observations, palpable masses, food consumption, test article intake, opthalmoscopic examinations, hematology, necropsy, histopathology or survival in either rodent study. The sponsor found differences in body weight only for male rats on medium and high dose drug (less weight), which continued for most of the study but seemed to diminish with age.

II. DESCRIPTION OF RAT STUDY 96459 AND SPONSOR'S ANALYSES AND RESULTS

II.a Description of Rat Study 96459

Design: The animals used were Rat/Crl:CD ® (SD)BR VAF/Plus ®. Administration was oral, 20g male, 15g female offered once daily, with controls receiving the same food without drug. For toxicity, there were two placebo arms, and each treatment and placebo group had 50 rodents per gender.

Table A
Non-placebo Estimated Total Daily Dose Design,
Rat Study 96459

	Male	Female
Low Dose	150	50
Medium Dose	750	250
High Dose	1500	500

The agency agreed to dietary restriction of the rats in this study. Food available was roughly 25% below ad libitum (Sn96459.pdf, animal husbandry pg. 5022.) The details from the sponsor (pg. 20, Sn96459.pdf) are:

> Prior to Day -7, rats were fed ad libitum. Beginning on Day -7, males were offered 20 g of food daily and females were offered 15 g of food daily. The procedure for dispensing the control meal or dietary admixtures of SCH 58235 changed during the study. Initially, daily aliquots were dispensed from polyethylene/polypropylene pouches into standard feeders. At Week 42, carousel feeders were introduced to deliver daily aliquots of meal or dietary admixture.

II.b Sponsor's Analyses and Results of Rat Study 96459

Plasma concentrations were variable (% CV=9-92%). The drug was extensively conjugated in plasma, with unconjugated drug <1.3% of total.

There is no statistically significant trend in incidence rate detected in the tumors tested in both male and female rats.

III. DESCRIPTION OF MOUSE STUDY 96458 AND SPONSOR'S ANALYSES AND RESULTS

III.a Description of Mouse Study 96458

Design: The animals used were Mouse/Crl:CD-1®(ICR)BR VAF/Plus®. Administration was oral, ad libitum for 104-105 weeks, with controls receiving the same diet without drug. For toxicity, there were two control groups of 50 animals each, and three drug groups of 50 mice per gender and group, with estimated daily doses of 25, 100 and 500 mg/kg.

III.b Sponsor's Analyses and Results of Mouse Study 96458

Total and conjugated SCH 58235 concentrations were 2.23 to 3.25-fold greater in female mice as compared to those in male mice (same dose, at least 98% conjugated.)

Sponsor's Conclusion

The drug was not carcinogenic when administered for up to 104 weeks as a dietary admixture to mice at daily doses up to 500 mg/kg.

There is no statistically significant trend in incidence rate detected in the tumors tested in both male and female mice.

IV. REVIEWER'S ANALYSES AND RESULTS

IV.a Analysis of Data of Body Weight, Food Consumption, and Survival

From looking at the graphs (see appendix Figures 1-3) it is clear to this reviewer that the medium and high dose arms differ somewhat in males from low dose and placebo. In Figure 1, body weight, a difference begins around week 44, stabilizes at a substantial level around week 66 and diminishes from week 94 to the end. In Figure 2, food consumption, a difference begins around week 48, stabilizes around week 64 and loses stability and diminishes from week 90 to the end. In Figure 3, survival, a difference from placebo begins around day 322 (week 46) and is sustained to the end, but the three treatment arms do not differ significantly per the following statistical analysis.

We used both Log-Rank and Wilcoxon statistical methodologies without attempting to distinguish the most appropriate, due to similar results. Based on the log survival graph,

exponential mortality cannot be assumed, so the likelihood methodology is not valid, and will not be used. As an aside, based on the log-log mortality graph, a two parameter Weibull distribution cannot be assumed, but a three parameter Weibull distribution might be appropriate.

There is an overall result for difference in mortality between arms at one-tailed $p<.05$, where the left tail would denote the survival curves being unreasonably close together for independently distributed curves. This reviewer used the overall rank statistics for each arm as distance measures to choose which contrasts to examine more closely. First is high versus medium dose (to check the reasonableness of naive pooling of these arms), followed by low dose versus placebo, pooled medium and high doses versus placebo, and last pooled medium and high doses versus low dose.

Table B
Survival Statistics Per Male Rat Arm

Rank Statistics- Uncensored

DOSEGP	Log-Rank	Wilcoxon	Mortality
Placebo	12.684	2751.0	43%
Low	-6.633	-1321.0	22%
Medium	-3.320	-720.0	28%
High	-2.732	-710.0	30%

Table C
Male Rat Survival Statistics for Inference

	---Log-Rank---		---Wilcoxon---	
	Chi^2	p-value	Chi^2	p-value
Overall (DF=3)	8.8811	p=.0309	9.2204	p=.0265
High vs Medium	0.0140	p=.9057	0.0009	p=.9760
Low vs Placebo	6.1516	p=.0131	5.9054	p=.0151
HighMed vs Placebo	5.1618	p=.0231	5.8177	p=.0159
HighMed vs Low	0.6230	p=.4299	0.4370	p=.5086

Based on the pairwise contrasts in Table C, we can reasonably conclude that animals in low dose survived longer than those in placebo, and that animals in pooled high and medium dose survived longer than those in placebo. These rats on placebo seemed to have periods of weighing more and eating less than those in high and medium dose arms.

The significance of these results is that there are significant differences in survival in male rats. Therefore, it is necessary to use survival-adjusted statistical methodologies in

the analysis of tumor data.

IV.a Analysis of Tumor Data

The statistical methods described in the Agent's draft Guidance for Industry: Statistical Aspects for the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May 2001) were used in this reviewer's tumor data analysis.

The results of the analysis show that there is no statistically significant trend in incidence rate detected in the tumors tested in the mouse study.

In the rat study, there is also no statistically significant trend in incidence rate detected in the tumors tested. but one is close in females. Although the p-value (0.0436) of the trend test of hepatocellular adenoma indicated below is less than 0.5, it is less than 0.025, the significance level used by the Agency for a rare tumor. The trend is considered as not statistically significant.

Organ Code	Organ Name	Tumor Code	Tumor Name	Trend Test P-Value
14	Liver	52	Hepato. Adenoma[B]	0436 >.025

VI. OVERALL CONCLUSION

There are statistically significant differences in survival in male rats.

There is no statistically significant trend in incidence rate in the tumors tested in both sexes in both rat and mouse studies.

For male rats, the group average food consumption decreased rapidly during the first half year of the study, and continued to decrease slightly up to about week 90. The animals ate less as they became older. (Note by the secondary reviewer: The first reviewer checked only the group average food consumption data of male rats.)

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Concur: Dr. Karl K. Lin

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HFD-715/ Dr. Nevius
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Figure 1

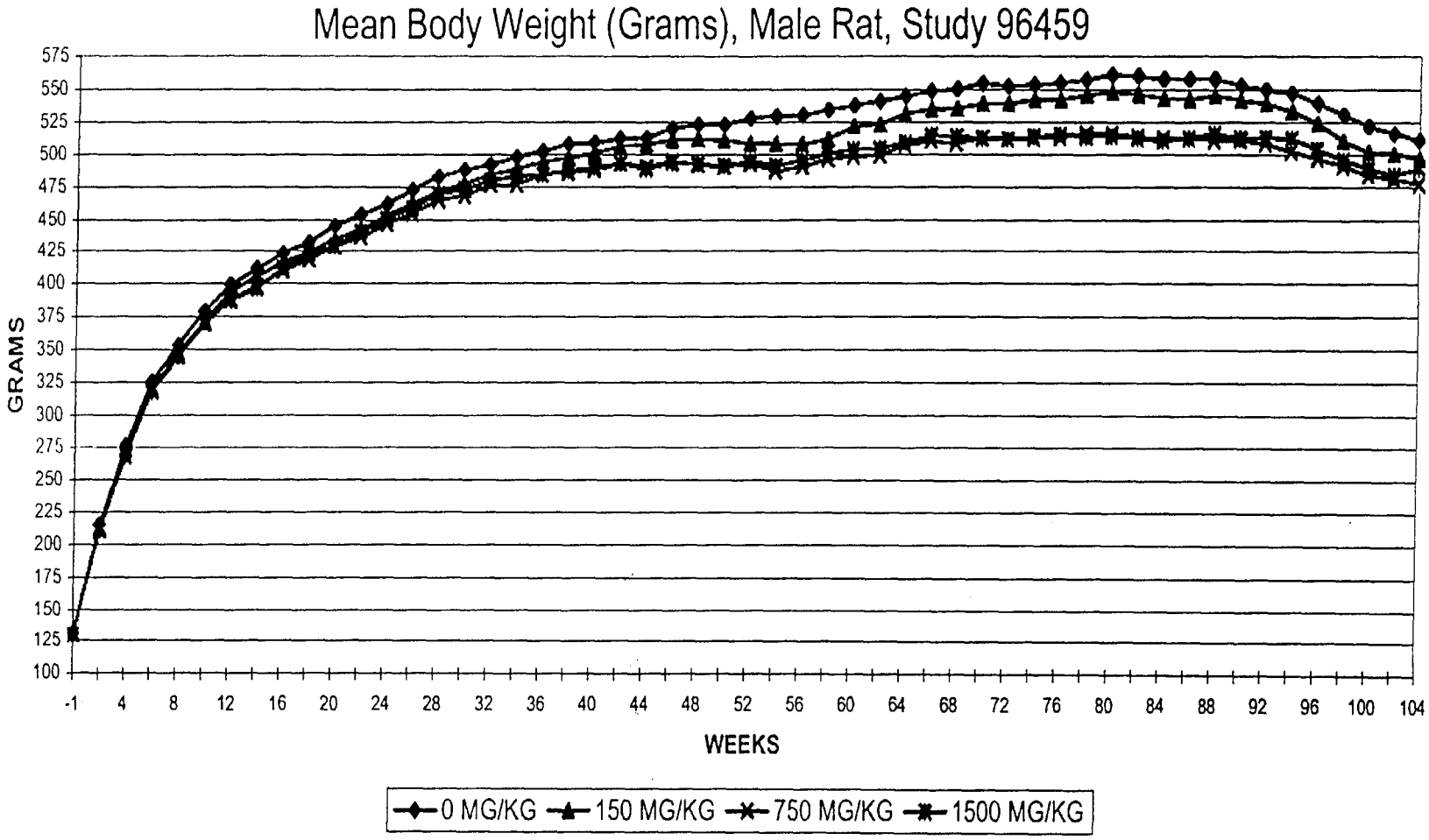

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Figure 2

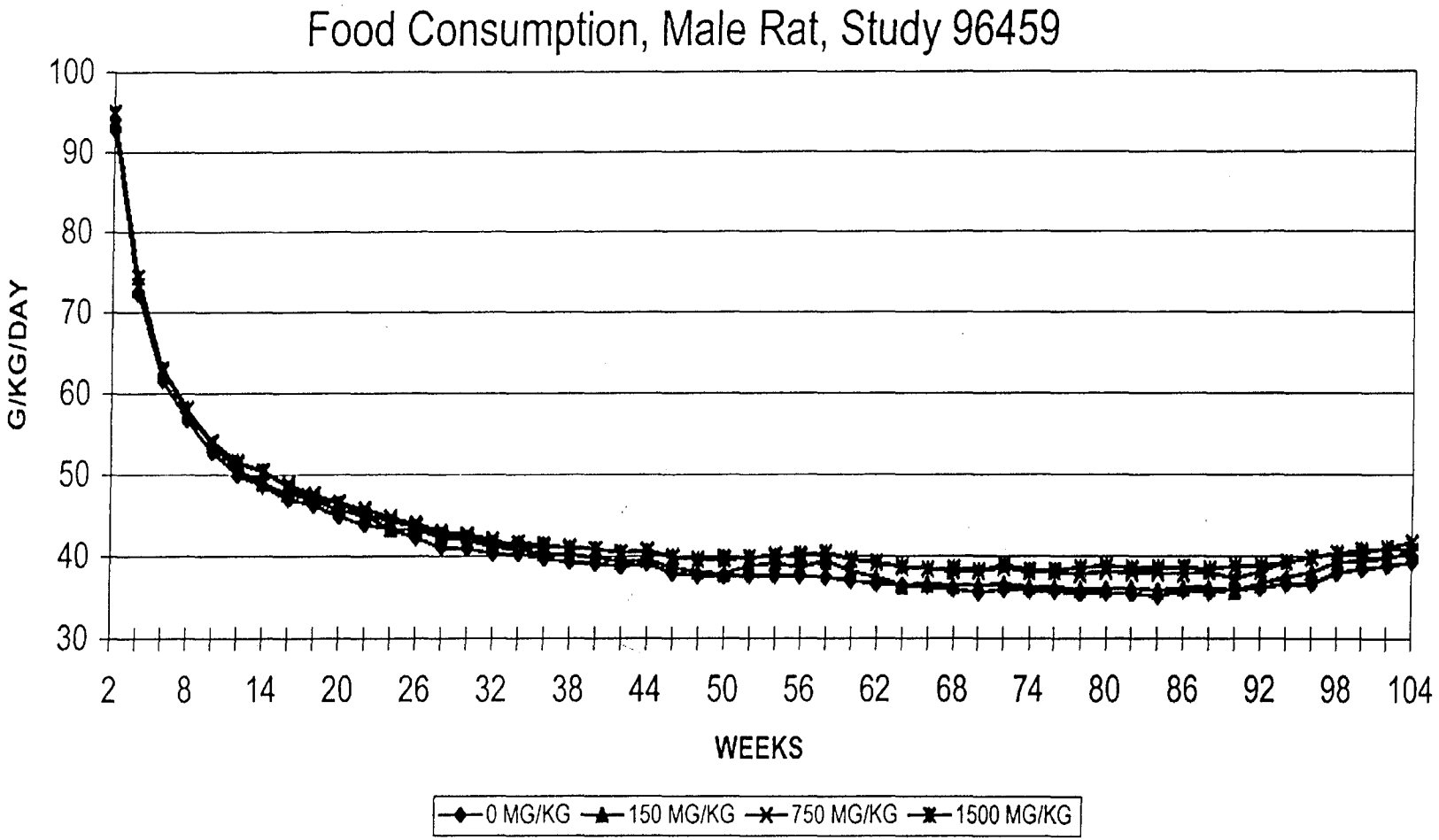

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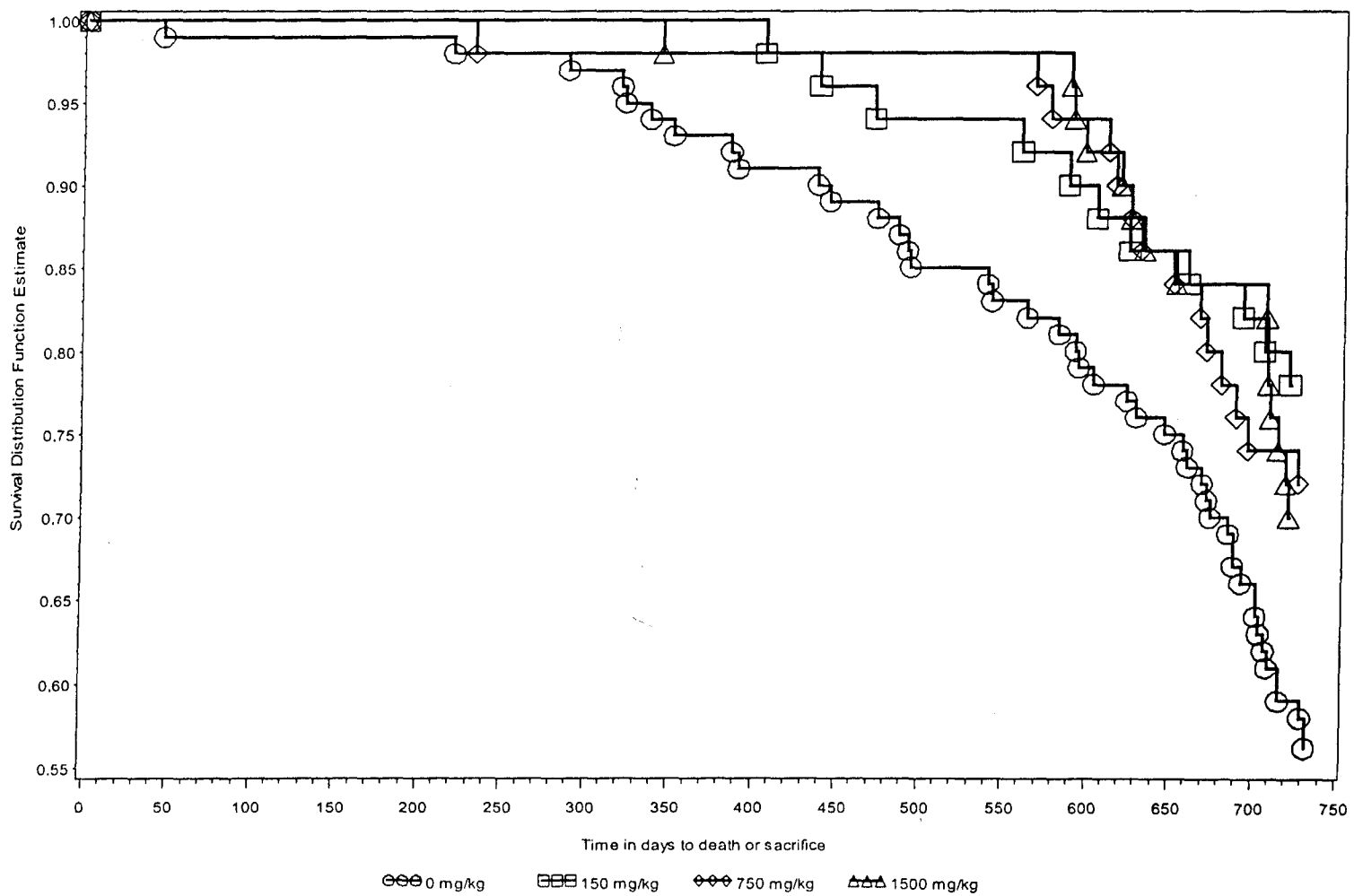
Figure 3

Kaplan-Meier Survival Plot for Male Rats, Study 96459



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/s/

Karl Lin
9/18/02 10:53:01 AM
BIOMETRICS
This statistical review and evaluation report was revised by me. However, its contents were based on a draft report prepared by Dr. Ferrin Harrison earlier.

Karl Lin
9/18/02 10:54:13 AM
BIOMETRICS
Concur with review