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/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 1198/115	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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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-445/N_000
Name of drug:	Zetia (ezetimibe) 10 mg tablets
Applicant:	MSP Singapore Co., LLC
Indication:	(1) Primary Hypercholesterolemia (*separate reviews for the two other indications, (2) Homozygous Familial Hypercholesterolemia (HoFH) and (3) Homozygous Sitosterolemia, have been prepared*)
Documents reviewed:	Volumes: 1.1, 1.2, 1.512 to 1.695, amendments dated April 2, 2002, April 5, 2002, April 19, 2002, May 9, 2002, August 23, 2002, September 12, 2002
	Location of the NDA in EDR (electronic documents room): \\CDSESUB1\N21445\N_000\
Project manager:	William Koch, R.Ph.
Clinical reviewer:	Jean Temeck, M.D. (HFD-510)
Dates:	Received 12/27/01; user fee deadline: 10/27/02
Statistical reviewer:	Japobrata Choudhury, Ph.D. (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Concurrence by:	Stephen Wilson, Dr.P.H. (HFD-715)
Keywords:	NDA review, clinical studies, analysis of covariance, interaction

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1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSIONS AND RECOMMENDATIONS

The three studies reviewed here for the Primary Hypercholesterolemia indication (one comparing ezetimibe 10 mg with placebo, one comparing ezetimibe 10 mg + simvastatin with simvastatin, and the third comparing the addition of ezetimibe to ongoing statin monotherapy with the statin monotherapy) have provided statistical evidence in favor of the benefit of ezetimibe 10 mg.

The quantitative (not qualitative) interactions found have been noted in Section 2.4. Findings in Special/Subgroup Populations.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

The specific Phase II/III clinical therapy studies performed to support all three indications (1) Primary Hypercholesterolemia, (2) Homozygous Familial Hypercholesterolemia (HoFH), and (3) Homozygous Sitosterolemia, and the total numbers of patients by treatment per study are shown in Table 0.1.1[1].

Note: This document is the review for Indication (1). Separate reviews for the two other indications have been prepared, although an overview of the whole clinical program for all 3 indications as provided by the sponsor has been provided in this document in Section 2.1.

Specific Indication for this document: (1) Primary Hypercholesterolemia

ZETIA, administered alone or with an HMG-CoA reductase inhibitor, is proposed to be indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, [redacted] in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Seven Phase III studies with treatment phases of 8 weeks or 12 weeks are included to support the 3 anticipated paradigms for the clinical use of ezetimibe in the treatment of primary hypercholesterolemia: (1) ezetimibe administered alone (Monotherapy Studies) (**P00474 and**

[1] In the Appendix Table (or Appendix Figure) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section. Both Tables and Figures are under one unique sequence without any distinction between them.

P00475), (2) coadministration of ezetimibe and statins with simultaneous initiation of the 2 therapies (Factorial Coadministration Studies) (**P00679, P00680, P00691, and P00692**), and (3) coadministration of ezetimibe and statins with addition of ezetimibe to ongoing statin therapy (Add-On Study) **(P02173/P02246).**

Note: Per consultation with the reviewing Medical Officer, in-depth statistical review and analyses have been done only with respect to the primary efficacy variable LDL-C and primary analysis (method) in three studies, Study P00474, Study P00680, and Study P02173/P02246 (Section 2.3.3) for this indication:

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 Monotherapy Studies- Primary Hypercholesterolemia								
P00474	Effect of EZ 10 mg monotherapy on LDL-C and other lipids, safety	R, DB, PC, LIPG	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 - 85 397/430 746/81	827 20 - 85 382/320 585/57	Placebo EZ 10	205 622
Phase III Ezetimibe/Statin Coadministration – Factorial Coadministration Studies								
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	868 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
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	6 weeks, QD in AM or PM with statin as per statin label	789 22-85 443/336 693/76	379 25-85 222/157 337/42	Placebo (+ statin) EZ 10 (+ statin)	380 379

1.3 PRINCIPAL FINDINGS

The three studies reviewed here for the Primary Hypercholesterolemia indication (one comparing ezetimibe 10mg with placebo, one comparing ezetimibe 10 mg + simvastatin with simvastatin, and the third comparing the addition of ezetimibe to ongoing statin monotherapy with the statin monotherapy) have provided statistical evidence in favor of the benefit of ezetimibe 10mg in these studies.

Study P00474 showed that ezetimibe 10mg group had a mean percent change of direct LDL-C, from baseline to endpoint, of -17.69% compared with 0.79% for placebo. Only quantitative (opposed to qualitative) interactions of BMI, Triglycerides, Cardiovascular Risk Factors, and Diabetes mellitus with the treatment response were seen.

In Study P00680, mean percent change of approximately 50% was seen in the ezetimibe plus simvastatin pool compared with 36% in the simvastatin alone pool. Quantitative (not qualitative) interactions of the baseline characteristics HDL-C and Race (Caucasian, non-Caucasian) with treatment response were seen.

Study P02173/P02246 showed that 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. Quantitative (not qualitative) interactions of "Race" (Caucasian, non-Caucasian) and "Center" with the treatment response were seen.

When the non-Caucasian group is further divided into subgroups, some qualitative (at least numerically) interaction of race with treatment response was seen toward the end of the study period. See Section 2.4. Findings in Special/Subgroup Populations, for details.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

(An overview of the whole clinical program for all 3 indications as provided by the sponsor is in the following Section 2.1.)

2.1 INTRODUCTION AND BACKGROUND

Note: Except where specifically mentioned otherwise (as notes, reviewer's comments, conclusions, etc.), all other results and statements in this document are the sponsor's. In particular, the material in Sections 2.1 to 2.3.2 is almost verbatim from the sponsor's submission.

In preclinical and clinical pharmacology studies, ezetimibe was demonstrated to be a novel cholesterol absorption inhibitor with significant cholesterol-lowering properties and without significant safety concerns. Thus, ezetimibe was investigated as a possible new therapeutic agent for hypercholesterolemia, particularly elevated plasma concentrations of low-density-lipoprotein cholesterol (LDL-C), a major risk factor for the development and progression of cardiovascular diseases. In view of its novel mechanism of action, ezetimibe was proposed to be complementary to hydroxymethylglutaryl (HMG-) CoA reductase inhibitors or "statins", the most commonly prescribed lipid-lowering agents. Therefore, emphasis was placed on the potential for achieving additional LDL-C reductions by coadministering ezetimibe with statins. Coadministration was considered to be particularly appropriate for use in individuals unable to attain LDL-C therapeutic targets due to either the severity of their hypercholesterolemia, efficacy limitations of current drug therapies (including statins) or risks that limit the use of adequate doses of current drug therapies.

Given the structural similarities between plant sterols and cholesterol, and preclinical evidence that ezetimibe reduced plant sterol absorption in animals, ezetimibe also was investigated as a possible treatment for homozygous sitosterolemia, a condition characterized by increased tissue accumulation of plant sterols, including sitosterol, and premature atherosclerosis.

The Phase II/III ezetimibe clinical development program included 12 double-blind, placebo- or active-controlled studies with investigational treatment phases of 8 or 12 consecutive weeks and an ongoing, open-label, long-term extension study that were designed to demonstrate the efficacy and safety of ezetimibe therapy for the following 3 indications:

1. Primary Hypercholesterolemia

ZETIA, administered alone or with an HMG-CoA reductase inhibitor, is proposed to be indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, [redacted] in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.)

Note: Separate reviews for the following two indications have been prepared.

2. Homozygous Familial Hypercholesterolemia (HoFH)

ZETIA, administered with an HMG-CoA reductase inhibitor approved for HoFH, is proposed to be indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

3. Homozygous Sitosterolemia

ZETIA is proposed to be indicated as adjunctive therapy for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

The specific Phase II/III clinical therapy studies performed to support these indications, (1) Primary Hypercholesterolemia, (2) Homozygous Familial Hypercholesterolemia (HoFH), and (3) Homozygous Sitosterolemia, and the total numbers of patients by treatment per study are shown in Table 0.1.1.

§ There were three Phase II studies (C96- 411/ C96- 345, C98- 010, C98-258) with treatment phases of 8 weeks or 12 weeks to support the selected therapeutic dose (10 mg), the dose interval

(once daily), and the timing of dose administration (AM or PM) for the Phase III studies. Results of these studies are in Section 4 of ISE in the NDA.

§ Seven Phase III studies with treatment phases of 8 weeks or 12 weeks are included to support the 3 anticipated paradigms for the clinical use of ezetimibe in the treatment of primary hypercholesterolemia: (1) ezetimibe administered alone (Monotherapy Studies) **(P00474 and P00475)**, (2) coadministration of ezetimibe and statins with simultaneous initiation of the 2 therapies (Factorial Coadministration Studies) **(P00679, P00680, P00691, and P00692)**, and (3) coadministration of ezetimibe and statins with addition of ezetimibe to ongoing statin therapy (Add-On Study) **(P02173/P02246).**

In the Monotherapy Studies **(P00474 and P00475)**, subjects with primary hypercholesterolemia (LDL-C 130 to 250 mg/dL) received randomized treatment with ezetimibe 10 mg or ezetimibe placebo daily for 12 weeks.

In the Factorial Coadministration Studies **(P00679, P00680, P00691, and P0069)**, subjects with primary hypercholesterolemia received randomized treatment with ezetimibe 10 mg alone, various doses of statins (lovastatin, simvastatin, pravastatin, or atorvastatin) alone, ezetimibe plus various doses of statins, or placebo. In the Add-On Study **(P02173/P02246)**, randomized treatment with either ezetimibe or matching placebo was added to ongoing statin therapy in patients who had primary hypercholesterolemia, known CHD, or multiple cardiovascular (CVD) risk factors and who required further LDL-C lowering.

§ Use of ezetimibe also was evaluated for 2 special dyslipidemic populations with unmet needs for adequate therapy (reviewed in separate documents): (Indication 2) subjects with HoFH, and (Indication 3) subjects with homozygous sitosterolemia.

The HoFH study **(P01030)** evaluated the efficacy of coadministering ezetimibe 10 mg with simvastatin or atorvastatin (40 mg or 80 mg) as well as with regular LDL apheresis in subjects already stabilized on such treatments. The homozygous sitosterolemic study **(P02243/P02257)** tested the efficacy of ezetimibe as an adjunct to current therapeutic regimens, which generally consisted of a low-plant-sterol diet and, in some subjects, the use of bile-acid-binding resins.

§ A total of 2995 subjects with primary hypercholesterolemia were exposed to ezetimibe 10 mg/day for at least 8 weeks; 2598 of these were exposed to ezetimibe 10 mg/day for 12 weeks. Thirty-three patients with HoFH and 30 patients with homozygous sitosterolemia were exposed to ezetimibe 10 mg/day for 12 weeks and 8 weeks, respectively.

§ In addition to results from these core studies, results from an ongoing, open-label, long-term extension study **(P00476)** are included to support the long-term durability of ezetimibe-induced

reductions in plasma LDL-C concentrations. In this study, subjects who completed P00474 or P00475 were continued on ezetimibe for up to 24 months. During this open-label period, investigators had the option of adding lovastatin (10, 20, 40 mg, following a titration procedure) or simvastatin (10, 20, 40, 80 mg, following a titration procedure) to ongoing ezetimibe therapy in order to achieve LDL-C targets established by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) II. Thus far in this study, 1313 subjects have been exposed to ezetimibe for up to 18 months; 530 (40%) of these are also currently on statins.

§ The Phase II/III Ezetimibe Clinical Development Program was multinational, with 8 studies conducted exclusively in the United States (**C96-411/C96-345, C98-010, C98-258, P00474, P00475, P00679, P00680, and P00691**) and 4 studies conducted in both the United States and at international sites (**P00692, P02173, P01030, P02243/P02257**).

2.2 DATA ANALYZED AND SOURCES

Data used by the reviewer are from the electronic document room:
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2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

Note: The sponsor's results and conclusions for Indication (1), Primary Hypercholesterolemia, are following. To re-emphasize, Sections 2.1 to 2.3.2 are almost verbatim from the sponsor's Integrated Summary of Efficacy (ISE). The reviewer has reviewed only three studies for this indication. His findings have been presented at appropriate places. His silence in Sections 2.1 to 2.3.2 does not imply agreement with the sponsor's statements (his comments, if any, are in italic as notes). The sponsor has presented a large number of results and conclusions, all of which may not be based on the primary hypotheses (may not even be mentioned in the Protocol or Data Analysis Plans). The p-values stated and the conclusions drawn by the sponsor are without multiple comparison adjustments (although adjustments are needed for the non-primary variables).

Indication (1), Primary Hypercholesterolemia [Ezetimibe administered alone or with an HMG-CoA reductase inhibitor as adjunctive therapy to diet, in patients with primary (heterozygous familial and non-familial) hypercholesterolemia]:

Primary Endpoint Analysis: Percent Change from Baseline in LDL-C

Phase III Monotherapy Studies (ISE, Section 7.3.2.1)
The primary efficacy endpoint variable was the percent change in LDL-C from baseline to study endpoint. LDL-C was measured both by [redacted] method (-quantitation), which is the primary one, and from the TC, TG, and HDL-C measurements using

the Friedewald calculation. All laboratory determinations were performed by a central laboratory. Both measures of LDL-C (direct and calculated) are presented side-by-side in the NDA. Primary (direct) results are presented below. Mean percent change from baseline in direct LDL-C in the placebo and ezetimibe 10-mg treatment groups were +0.8 and -18%, respectively, in **P00474** and +0.4 and -17%, respectively, in **P00475.** In the combined analysis, the placebo group had an increase in mean percent change from baseline of +0.3% while the ezetimibe group demonstrated a -17% reduction in LDL-C. The differences between ezetimibe and placebo were significant ($p < 0.01$) in both the studies. Direct LDL-C and calculated LDL-C behaved nearly identically.

Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Direct) Between Baseline and Endpoint: Phase III Monotherapy Studies (Intent-to-Treat Data Set)

	Direct LDL-C		
	Placebo	EZ	EZ - Placebo (CI)
P00474			
Baseline	(n=204)	(n=621)	
Mean value in mg/dL [mmol/L]	164.4 [4.3]	165.2 [4.3]	N/A
Endpoint	(n=199)	(n=606)	
Mean value in mg/dL [mmol/L]	164.9 [4.3]	135.6 [3.5]	N/A
Mean percent change from baseline (SEM)	0.8 (0.9)	-17.7 (0.6)	-18.5** (-20.2, -16.7)
P00475			
Baseline	(n=226)	(n=665)	
Mean value in mg/dL [mmol/L]	168.0 [4.3]	167.8 [4.3]	N/A
Endpoint	(n=210)	(n=628)	
Mean value in mg/dL [mmol/L]	168.9 [4.4]	138.6 [3.6]	N/A
Mean percent change from baseline (SEM)	0.4 (0.8)	-16.9 (0.6)	-17.2** (-18.9, -15.5)
Combined[a]			
Baseline	(n=430)	(n=1286)	
Mean value in mg/dL [mmol/L]	166.3 [4.3]	166.4 [4.3]	N/A
Endpoint	(n=409)	(n=1234)	
Mean value in mg/dL [mmol/L]	166.6 [4.3]	137.0 [3.5]	N/A
Mean percent change from baseline (SEM)	0.3 (0.6)	-17.4 (0.3)	-17.7** (-19.0, -16.5)

EZ = ezetimibe 10 mg.
** $p \leq 0.01$. Least-squares (LS) means and confidence interval (CI) based on the ANOVA model.
a: Combined = Monotherapy Efficacy Pool (P00474 and P00475).
Appendix 6, P00474, P00475

Phase III Monotherapy Arms of the Factorial Coadministration Studies (ISE, Section 7.3.2.2)

Each Factorial Coadministration Study included a monotherapy ezetimibe treatment arm as well as a placebo arm, and (reviewer's clarification: entered) subjects with similar entry criteria in all of these studies. Comparing the data from the 4 monotherapy arms was prespecified since the Factorial Coadministration Studies had the same study design and subjects with similar baseline demographics. One difference to note is that the baseline LDL-C was approximately 180 mg/dL in the monotherapy arms of the Factorial Coadministration Studies versus 166 mg/dL in the 2 Phase III Monotherapy Studies.

Consistent with the findings of the Phase III Monotherapy Studies, the data from the monotherapy arms of the 4 factorial studies showed a mean percent increase from baseline to study endpoint in LDL-C of up to +6% for the placebo subjects and a mean percent change of approximately -18% for the subjects randomized to ezetimibe. The difference between ezetimibe placebo was significant (p 0.01) with a reduction in LDL-C of -17 to -24%. These results are :

Change in Plasma Concentration of Low-Density-Lipoprotein Cholesterol (Direct) Between Baseline and Endpoint: Monotherapy Arm of Factorial Coadministration Studies (Intent-to-Treat Data Set) Direct LDL-C Calculated LDL-C

	Direct LDL-C		
	Placebo	EZ	EZ - Placebo (CI)
Lovastatin P00679			
Baseline	(n=64)	(n=72)	
Mean value in mg/dL [mmol/L	177.8 [4.6]	178.0 [4.6]	N/A
Endpoint	(n=63)	(n=71)	
Mean value in mg/dL [mmol/L]	177.4 [4.6]	144.9 [3.8]	N/A
Mean percent change from baseline (SEM)	-0.03 (1.7)	-18.6 (1.6)	-18.56** (-23.3, -13.9)
Simvastatin P00680			
Baseline	(n=70)	(n=61)	
Mean value in mg/dL [mmol/L]	177.4 [4.6]	181.3 [4.7]	N/A
Endpoint	(n=69)	(n=59)	
Mean value in mg/dL [mmol/L]	175.0 [4.5]	147.9 [3.8]	N/A
Mean percent change from baseline (SEM)	-1.3 (1.7)	-18.1 (1.9)	-16.7** (-21.7, -11.7)
Pravastatin P00691			
Baseline	(n=65)	(n=64)	
Mean value in mg/dL [mmol/L]	177.1 [4.6]	177.4 [4.6]	N/A
Endpoint	(n=62)	(n=63)	
Mean value in mg/dL [mmol/L]	178.9 [4.6]	144.4 [3.7]	N/A
Mean percent change from baseline (SEM)	1.3 (1.6)	-18.7 (1.6)	-20.1** (-24.4, -15.7)
Atorvastatin P00692			
Baseline	(n=60)	(n=65)	
Mean value in mg/dL [mmol/L]	178.1 [4.6]	175.3 [4.5]	N/A
Endpoint	(n=60)	(n=65)	
Mean value in mg/dL [mmol/L]	188.4 [4.9]	142.6 [3.7]	N/A
Mean percent change from baseline (SEM)	5.9 (1.9)	-18.4 (1.9)	-24.3** (-29.6, -19.1)

EZ = ezetimibe 10 mg.
** p≤0.01.
Least-squares (LS) means and confidence interval (CI) based on the ANOVA model.
(P00679 , P00680 , P00691 , P00692)

Pooled Across All Doses For Statins (ISE, Section 8.3.1.2.1)

Primary Efficacy Analysis: Percent Change from Baseline in Direct LDL-C
The primary efficacy analysis for each of the Factorial Coadministration Studies was the percent change from baseline to endpoint by statin, pooled across statin doses, coadministered with ezetimibe 10 mg/day compared to statin-alone (discussion of the results for individual doses is follows below). The mean percent change from baseline in direct LDL-C was -39, -50, -38, and -55% for the coadministration of ezetimibe with the pooled doses of lovastatin, simvastatin, pravastatin, and atorvastatin, respectively, as compared with -25, -36, -24, and -42% for the corresponding pooled statin-alone groups. The difference between the pooled doses of statin

coadministered with ezetimibe versus pooled statin-alone was consistent, approximately -14%, and significant when compared with the pooled statin-alone group (p 0.01). The results for calculated LDL-C **(Appendix Table 0.3.1)** were very similar to those observed for direct LDL-C.

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

	Direct LDL-C		
	All Statin	EZ + All Statin	p-Value[b]
Lovastatin P00679			
Baseline[a]	(n=220)	(n=192)	
Mean value in mg/dL [mmol/L]	177.5 [4.6]	175.8 [4.5]	0.39
Endpoint	(n=218)	(n=190)	
Mean value in mg/dL [mmol/L]	133.4 [3.5]	106.7 [2.8]	<0.01
Mean percent change from baseline (SEM)	-24.7 (0.9)	-39.0 (1.0)	<0.01
Difference from All Statin in mean percent change from baseline (95% confidence limits)	N/A	-14.3 (-17.0, -11.6)	<0.01
Simvastatin P00680			
Baseline	(n=263)	(n=273)	
Mean value in mg/dL [mmol/L]	178.6 [4.6]	176.3 [4.6]	0.20
Endpoint	(n=261)	(n=268)	
Mean value in mg/dL [mmol/L]	113.6 [2.9]	88.2 [2.3]	<0.01
Mean percent change from baseline (SEM)	-36.1 (0.9)	-49.9 (0.9)	<0.01
Difference from All Statin in mean percent change from baseline (95% confidence limits)	NA	-13.8 (-16.3, -11.4)	<0.01
Pravastatin P00691			
Baseline	(n = 205)	(n = 204)	
Mean value in mg/dL [mmol/L]	176.6 [4.6]	176.3 [4.6]	0.87
Endpoint	(n = 203)	(n = 204)	
Mean value in mg/dL [mmol/L]	133.4 [3.5]	109.3 [2.8]	<0.01
Mean percent change from baseline (SEM)	-24.3 (0.9)	-37.7 (0.9)	<0.01
Difference from All Statin in mean percent change from baseline (95% confidence limits)	N/A	-13.4 (-15.8, -11.0)	<0.01

(continued to next page)

	Direct LDL-C		
	All Statin	EZ + All Statin	p-Value[b]
Atorvastatin P00692			
Baseline	(n = 248)	(n = 255)	
Mean value in mg/dL [mmol/L]	179.9 [4.7]	180.0 [4.7]	0.98
Endpoint	(n = 245)	(n = 252)	
Mean value in mg/dL [mmol/L]	103.6 [2.7]	81.3 [2.1]	<0.01
Mean percent change from baseline (SEM)	-42.4 (1.0)	-54.5 (0.9)	<0.01
Difference from All Statin in mean percent change from baseline (95% confidence limits)	N/A	-12.1 (-14.7, -9.5)	<0.01

a: Number of subjects per treatment group for whom a determination was made at both baseline and endpoint.
b: Comparison between All Statin and Ezetimibe 10 mg + All Statin.
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 P00691 P00692)

Individual Doses for Statin (ISE, Section 8.3.1.2.2)
Appendix Table 0.3.2 (Sponsor's Table 41) and **Appendix Table 0.3.3 (Sponsor's Table 42)** provide the incremental observed reductions in direct LDL-C **(Table 41)** and calculated LDL-C **(Table 42)** for ezetimibe coadministered with different individual doses of statin. Significant differences ($p \leq 0.01$) for reducing LDL-C were noted for each dose of statin coadministered with ezetimibe compared to the corresponding statin dose alone for both direct and calculated LDL-C. Additionally, coadministration of ezetimibe with each statin dose resulted in significant differences ($p \leq 0.01$) in lowering LDL-C when compared to the next higher dose of statin-alone, except for 1 of 14 comparisons - that of ezetimibe +atorvastatin 40 versus atorvastatin 80 alone **(P00679, P00680, P00691, and P00692)**.

In all 4 Factorial studies, coadministration of ezetimibe 10 mg with the lowest statin dose (10-mg for each statin) resulted in mean percent reductions in LDL-C concentrations similar to or better than those seen with the highest dose of the corresponding statin-alone tested **(Table 41)**. Of particular note is the comparison of the coadministration of ezetimibe and the 10-mg dose of both simvastatin and atorvastatin with that of the 80-mg dose, the highest recommended dose for these statins. The coadministration of ezetimibe with the 10 mg simvastatin or atorvastatin yielded similar LDL-C reductions as the respective 80 mg statin-alone. Thus, coadministration of ezetimibe 10 mg with 10 mg of either of these statins achieved LDL-C lowering comparable to 3 titrations of statin-alone (i.e., 8-fold increase in dose) for either statin.

The incremental change in LDL-C at different statin doses produced by coadministration of ezetimibe is shown graphically in Appendix **Figure 0.3.4**. The incremental mean percent change gained by the coadministration of ezetimibe and each dose of statin ranged from -8.5 to -17.2%.

The Sponsor's Discussion of Efficacy (ISE, Section 13)

Ezetimibe is a member of a new class of agents that bind to the luminal surface of small intestinal mucosa and selectively inhibit the intestinal absorption of.cholesterol and related plant sterols by preventing their passage across the intestinal wall. Ezetimibe had been shown to be associated with lowering of plasma cholesterol concentrations in several preclinical models, as well as in humans in early clinical pharmacology studies. This was consistent with findings of cholesterol lowering with other agents that inhibit intestinal cholesterol absorption through different mechanisms (e.g., plant sterols/stanols, certain saponins).

Based on the efficacy of ezetimibe for lowering LDL-C in human subjects with hypercholesterolemia in Phase II studies, 10-mg daily dose of ezetimibe was selected as the optimal dose for use in the Phase III Ezetimibe Clinical Development program. This dose was shown to produce a mean inhibition of intestinal cholesterol absorption of 54% in a dual stable-isotope study of 18 hypercholesterolemic human subjects.

Early studies indicated both a moderate LDL-C-lowering effect when ezetimibe was given as monotherapy, as well as incremental reductions in LDL-C concentrations when ezetimibe was coadministered with statins. Therefore, the Phase III program was designed to evaluate the efficacy and safety of ezetimibe 10 mg/day as monotherapy or when coadministered with statins of varying types and doses for the treatment of hypercholesterolemia. For coadministration, 2 treatment scenarios were studied: (1) initiation of ezetimibe and statin therapy simultaneously, and (2) addition of ezetimibe to ongoing statin therapy in subjects who required further LDL-C lowering.

The primary efficacy measurement in all of the pivotal trials was plasma LDL-C concentration. In the majority of studies, both "direct LDL-C" (measured by [redacted] procedure) and "calculated" LDL-C (using the Friedewald equation) were determined. The results for the 2 methodologies were consistent, as expected, since subjects with triglyceride elevations above 350 mg/dL (which can interfere with the accuracy of the calculated measurement) were excluded from these studies. Since calculated LDL-C rather than direct LDL-C is widely used in clinical practice, this measure has been proposed for use in the ezetimibe drug label.

The primary pre-specified efficacy variable in all Phase III studies (except sitosterolemia) was percent change in LDL-C concentrations from baseline to study endpoint, using an intent-to-treat approach. This approach tends to underestimate the true efficacy of the study drug, because subjects who discontinue treatment for any reason but go on to have a lipid measurement at their final visit (as called for by each of the Phase III protocols) are included in the analysis.

Note: This reviewer does not agree with this statement of under-estimation. It cannot be guaranteed that the intent-to-treat approach always under-estimates treatment differences.

Indication (1), Primary Hypercholesterolemia:

Monotherapy

The results of the 2 replicative Phase III Monotherapy Studies which included a total of 1719 hypercholesterolemic subjects demonstrated that ezetimibe 10 mg/d is efficacious in lowering plasma LDL-C concentrations. Demographics of the subjects and baseline lipid values were similar for the active treatment and placebo groups for each of the 2 studies and in the pooled cohort. The mean change in the active ezetimibe group relative to the placebo group was -17.7% for direct LDL-C and -18.2% for calculated LDL-C. These results were consistent with the magnitude of change relative to placebo seen in the earlier pooled Phase II studies (-18.9% for direct LDL-C). Near-maximal LDL-C reduction was evident at 2 weeks and was maintained for the 12 weeks duration of treatment. Approximately 60% of ezetimibe-treated subjects achieved a change in LDL-C from baseline to endpoint of at least -15%.

Measurements of Apo B in subjects treated with ezetimibe monotherapy demonstrated mean percent changes relative to placebo of a magnitude that were in accord with the observed reductions in LDL-C (-14.1%; $p \leq 0.01$). Because Apo B is the major protein constituent of low density lipoproteins, and relatively little of this apolipoprotein is found in non-LDL lipoprotein fractions in the absence of hypertriglyceridemia, this finding suggests that ezetimibe lowers LDL-C concentrations at least in part by decreasing the concentration of circulating LDL particles. Changes in plasma TC concentrations parallel to those for LDL-C were observed, but of a lesser magnitude since TC also includes the cholesterol contained in HDL and TG-rich lipoproteins.

Other lipid variables were also affected by ezetimibe. HDL-C concentrations were significantly increased relative to placebo in the pooled pivotal Phase III monotherapy studies (+2.6%, $p \leq 0.01$) and a significant reduction in TG was observed (-7.8%, $p \leq 0.01$). Thus, ezetimibe produced favorable changes not only in LDL-C but other major lipid parameters associated with atherogenic risk. Similar findings for these lipid variables had been observed in the pooled Phase II studies.

A small increase in Apo A-I with ezetimibe, although not statistically significant, was consistent with the observed increase in HDL-C. Evaluations of HDL subfractions revealed significant mean percent increases in HDL2 relative to placebo (2.9%, $p \leq 0.01$).

Although mean concentrations of Lp(a) decreased significantly in the pooled ezetimibe group relative to the pooled placebo group, assessment of changes in median values, as well, evaluation of changes in Lp(a) across all ezetimibe studies, lead to the conclusion that ezetimibe does not produce clinically meaningful changes in this atherogenic lipoprotein.

Subgroup analysis for change in LDL-C with respect to age, sex, race, baseline LDL-C, and other baseline characteristics of the population in the monotherapy studies showed general consistency of effect.

Factorial Coadministration Studies

In the four Factorial Coadministration Studies, ezetimibe 10 mg/d was coadministered over a range of doses with each of the 4 most widely prescribed statins in the U.S. (lovastatin, simvastatin, pravastatin, or atorvastatin). The primary analysis for each study was the difference in mean percent change in plasma LDL-C concentration for the pooled ezetimibe +statin group versus the statin-alone group.

For these analyses, data from each of the treatment groups receiving coadministration with the same statin at different doses were pooled (e.g., simvastatin 10, 20, 40, or 80 mg each coadministered with ezetimibe) and compared with the corresponding statin-alone pooled groups (e.g., simvastatin 10, 20, 40, or 80 mg). The observed differences represent the incremental LDL-C lowering attributable to ezetimibe, relative to the baseline plasma LDL-C concentrations prior to administration of either statin or ezetimibe.

In each of the 4 studies, the differences between the pooled groups administered ezetimibe plus statin and the corresponding pooled statin-alone groups were highly statistically significant (p 0.01) and were generally consistent in magnitude across studies. The observed incremental reduction of direct LDL-C concentration attributable to ezetimibe ranged from -12.1 to -14.3% and for calculated LDL-C ranged from -12.1 to -15.0%. There was no statistically significant treatment-by-dose interaction in 3 of the 4 studies. A significant interaction was noted in the simvastatin factorial study (p=0.04).

However, as described in detail in Section 8.3.1.2.3., this finding was attributable to anomalous values at endpoint for the low-to-mid dose range, irregularities which were not apparent at early time points, and even at endpoint did not result in a significant interaction in the protocol-evaluable analysis. Thus, the average effect across all doses still provided the best estimate of overall ezetimibe effect when coadministered with different doses of simvastatin. When the mean estimates of ezetimibe incremental LDL-C lowering were pooled across all doses and all of the statins, the extent of LDL-C reduction attributable to ezetimibe was -13.3% for direct LDL-C and -13.8% for calculated LDL-C, relative to the pre-statin/ezetimibe baseline.

Statistically significant ($p< 0.01$) incremental reductions in LDL-C concentrations were seen at every individual statin dose for all 4 statins when coadministered with ezetimibe, relative to the corresponding statin dose administered as monotherapy. The incremental effect was also statistically significant when a given statin dose coadministered with ezetimibe was compared to the next highest (i.e., 2-fold) statin-alone dose. When the lowest coadministration dose (ezetimibe +10 mg statin) was compared with a 4-fold higher dose of the same statin administered as monotherapy, statistically significant incremental LDL-C reductions at endpoint were seen in each case, with the single exception of ezetimibe +lovastatin 10 mg versus lovastatin 40 mg. For the latter comparison, the incremental lowering with coadministered ezetimibe missed statistical significance at endpoint ($p=0.10$), but was significant at Weeks 2 and 8. For the 2 statins (simvastatin and atorvastatin) that were increased in dose up to 8-fold to the approved maximum of 80 mg/d, the mean percent LDL-C reduction achieved by ezetimibe plus 10 mg statin was similar to that achieved by 80 mg of the corresponding statin alone (-44.4%

versus -44.3% for ezetimibe +10 mg simvastatin versus 80 mg simvastatin; -50.4% versus -51.4% for ezetimibe +10 mg atorvastatin versus 80 mg atorvastatin).

Mean percent changes in TC, TG, HDL-C, and Apo B were prespecified as key secondary endpoints. Significant incremental reductions in TC and Apo B were seen with ezetimibe coadministration with all statins at all doses. As noted for ezetimibe monotherapy, the incremental reductions in this apolipoprotein with ezetimibe/statin coadministration suggest that the incremental effect is mediated, at least in part, by incremental decreases in the concentration of circulating LDL particles.

Coadministration of ezetimibe with the 4 statins at all doses yielded incremental reductions in TG. The mean change in TG between the pooled ezetimibe +statin groups versus the pooled statin-alone groups ranged from -7.4% to -10.5% and was statistically significant (p 0.01) for each of the 4 statins. There were no significant treatment-by-dose interactions observed for this variable. Maximal or near-maximal LDL-C lowering was seen at the 2 weeks and was maintained for the 12-week duration of these studies.

Pooling across doses in each factorial study, and comparing ezetimibe +statin versus the corresponding statin-alone group showed incremental mean increases in plasma HDL-C concentrations ranging from +1.4 to +4.5% for the different statins. The increases were statistically significant for all but one of the comparisons (pravastatin). Even for pravastatin, there were statistically significant increases in HDL-C concentrations for the coadministration group versus the pravastatin-alone group at 2, 8, and 12 weeks. As for the other lipid variables, there were no significant treatment-by-dose interactions with any of the 4 statins.

As a consequence of the observed incremental reductions in LDL-C and TC concentrations, in conjunction with incremental increases in HDL-C, ezetimibe/statin coadministration resulted in favorable reductions in the ratios of LDL-C/HDL-C and TC/HDL-C. These ratios are commonly used in clinical practice as a sensitive indicator of CHD risk, since they reflect both the direct relationship of LDL-C or TC with CHD risk, and the inverse relationship of HDL-C and CHD risk.

The HDL subfractions, HDL2-C and HDL3-C, generally moved in the same direction as total HDL-C, in some cases achieving statistical significance and in others not, again without evidence of a treatment-by-dose interaction. The observed incremental increases in Apo A-I with ezetimibe/statin coadministration relative to statins alone, although not statistically significant, were consistent with the more robust increases in HDL-C. For Lp(a), there were no significant differences in mean or median percent changes from baseline for any of the statins when the pooled ezetimibe/statin and statin-alone treatment groups were compared.

Subgroup analyses for change in LDL-C concentration with respect to age, sex, race, baseline LDL-C, and other baseline characteristics of the population demonstrated general consistency of effect for ezetimibe coadministered with statins (Section 9.). However, in pooled analysis across all of the factorial studies, the observed difference for Caucasians was -14.6% versus -6.6% for non-Caucasians.

Among the non-Caucasians (n=120), the mean percent difference was +1.3% for Blacks and -12.0% for other races. Examination of LDL-C concentration changes over time indicated incremental reductions in Blacks at Weeks 2, 4, and 8, but not at Week 12. Anomalous findings at Week 12 were observed particularly in the atorvastatin study, in which a mean increase in LDL-C concentration of approximately +15% was observed in Blacks (n=9) receiving ezetimibe/atorvastatin, despite the fact that at Week 2 there was a change of -10%. There was a particularly large dropout rate (approximately 40%) among blacks in this study.

Moreover, there was no suggestion of diminished efficacy of coadministration therapy in Blacks in either the ezetimibe monotherapy pooled results or the Add-on study. Since consistent ezetimibe efficacy was observed at earlier time points for all statins in Blacks and treatment effects were seen in Blacks in 3 out of the 4 statin factorial studies in which the dropout rates for Blacks were smaller, it is unlikely that the observed race differences in the pooled factorial studies represent a real biological phenomenon.

In summary, the 4 factorial studies demonstrate that coadministration of ezetimibe with statins, irrespective of dose or statin type, produces substantial incremental reductions in plasma LDL-C concentrations in conjunction with reductions in TG and increases in HDL-C, compared with the corresponding statin administered as monotherapy.

Add-On Study

The treatment paradigm for ezetimibe evaluated in the Add-On Study corresponds to that most likely to be encountered in clinical practice, namely patients who are already receiving ongoing statin therapy but are deemed to require further LDL-C lowering. The Add-On Study **(P02173/P02246)** was a large, randomized, placebo-controlled Phase III trial that addressed the efficacy of ezetimibe used in this context.

The study population consisted of 769 individuals who had been taking an approved statin at a stable dose for at least 6 weeks and who had not met their NCEP ATP II LDL-C target. A large percentage of these subjects had established CHD or diabetes mellitus, justifying a target LDL-C of =100 mg/dL. Subjects were randomized to 8 weeks of blinded therapy with ezetimibe 10 mg/day or matching placebo, taken in addition to ongoing treatment with the same open-label statin they were using at baseline.

The addition of ezetimibe to ongoing statin therapy resulted in a mean change from baseline in plasma LDL-C concentration of -25%, compared with -4% for placebo, yielding a mean change in LDL-C for ezetimibe versus placebo of -21.5%. The magnitude of incremental LDL-C reductions in the Add-On Study were consistent across the different statins included: atorvastatin (n=162) -21.0% (95% CI: -24.2, -17.8); simvastatin (n=117) -23.7% (95% CI: -27.3, -20.1), and all other statins pooled (pravastatin, fluvastatin, lovastatin, and cerivastatin [n=111], -19.7% [95% CI: -23.5, -16.0]). This is in agreement with the general consistency of incremental effect observed with ezetimibe across different statins and doses in the factorial studies. The Add-On Study results were also consistent with the Factorial Coadministration Studies in showing

maximal or near-maximal effects on LDL-C concentrations within 2 weeks of initiation of ezetimibe dosing, as well as durability of effect throughout the study (in this case, 8 weeks).

As in the Factorial Coadministration Studies, reductions in TC and Apo B were observed in the ezetimibe group, concordant with the observed reduction in LDL-C. Small but statistically significant increases in HDL-C concentrations were seen with ezetimibe therapy, +2.7% relative to baseline and +1.7% relative to placebo. This was accompanied by a very small numerical increase in Apo A-I, consistent with the more reliably measured (and statistically significant) increase in HDL-C. A small decrease in Apo A-II (-1.8%) was observed with ezetimibe coadministration relative to placebo at endpoint (p=0.02). Unlike HDL-C and Apo A-I, plasma concentrations of Apo A-II have not been clearly associated with CHD risk, therefore the clinical relevance of this finding is uncertain. As in the Factorial Coadministration Studies, the greatest mean percent reductions were seen for the ratio of LDL-C:HDL-C in the context of coadministration, reflecting the favorable effects of ezetimibe on the 2 parameters comprising this ratio.

A key prespecified secondary analysis in the Add-On Study was the percentage of subjects who achieved NCEP ATP II LDL-C targets at study endpoint. The target LDL-C concentrations used for this analysis (and also as criteria for entry into the study) were based on each subject's risk factor profile in relation to the NCEP ATP II guidelines. For the group in which ezetimibe was added to a statin, 76% of subjects achieved target LDL-C at endpoint, versus 27% in the placebo group. Since the study entry criteria and design made it possible for some subjects who were near their LDL-C target to be entered, a number of participants were technically already "at target" at baseline. When the [2]was restricted to those subjects who were not strictly at target at baseline, the percentage of subjects achieving goal at endpoint was 72% for the ezetimibe group versus 19% for the placebo group. An exploratory analysis applying NCEP ATP III criteria, assessed using the baseline demographic data collected for study subjects, produced similar findings. Thus, in this cohort consisting largely of CHD or "CHD-equivalent" subjects who had not reached their NCEP ATP II LDL-C target on their current statin regimen, the addition of ezetimibe 10 mg daily to the ongoing statin therapy brought a large majority of subjects to goal. This result demonstrates that addition of ezetimibe can be a useful alternative to statin dose up-titration, or a valuable adjunct where maximal-tolerated or approved statin doses have already been reached.

The observed mean changes in plasma LDL-C concentrations appear to differ in magnitude for the Factorial Coadministration Studies (approximately -14% across all statins) and the Add-On Study (-21.5%) This apparent disparity results from the fact that the percent changes in the 2 types of studies are calculated in relation to different baseline LDL-C concentrations, one pre-statin (Factorials) and the other post-statin (Add-On). Both perspectives are useful for physicians in clinical practice. They should be made aware of the magnitude of reductions that can be expected in the scenario of adding ezetimibe to ongoing statin therapy (anticipated to be the most

[2] The missing word was supplied by the sponsor orally to be "analysis".

common treatment paradigm), while also being aware of the reductions that can be achieved when statins and ezetimibe are initiated simultaneously.

The Add-On Study population had a substantially higher incidence of established CHD at baseline and was generally a higher CHD risk cohort compared with the populations recruited for the Factorial Coadministration Studies. Consistent with this and with entry criteria that were based on whether or not the subject had achieved NCEP ATP II LDL-C goal on a statin, the mean LDL-C concentration at baseline was lower in the Add-On Study. There was also a higher proportion of males in the Add-On Study. It is noteworthy that despite these differences, the direction and magnitude of the lipid changes observed were consistent with the findings of the Factorial Coadministration Studies. Thus, whether ezetimibe is added to ongoing statin therapy or the 2 are initiated simultaneously, coadministration produces substantial incremental reductions in LDL-C concentrations, in conjunction with reductions in TG and increases in HDL-C concentrations, in a diverse groups of higher- and lower-risk subjects.

The changes produced by ezetimibe on TG and HDL-C concentrations are theoretically favorable with respect to CHD risk. Moreover, all of the coadministration studies indicate that these favorable changes are incremental to favorable changes in the same parameters induced by statins alone. As a result, the mean percent changes in the ratio of LDL-C:HDL-C (viewed by many to be the single best predictor of CHD risk) yielded the largest mean percent reductions among all of the key risk variables in the ezetimibe coadministration and monotherapy studies.

The Sponsor's Efficacy Conclusions

- Ezetimibe 10 mg/d administered as monotherapy was effective in reducing mean plasma concentrations of LDL-C in hypercholesterolemic subjects by approximately 18% relative to placebo.

- Coadministration of ezetimibe 10 mg/d with statins, regardless of statin type or dose, was substantially more effective in reducing mean plasma LDL-C concentrations than the corresponding statin alone. Incremental LDL-C reduction attributable to ezetimibe was similar whether ezetimibe was initiated simultaneously with statins or added to ongoing statin therapy.

Note: The reviewer does not know the criteria the sponsor used for the last conclusion. He has reviewed the add-on study and one of the studies where ezetimibe was initiated simultaneously. He does not see this to be true from the results in Sections 2.3.3.2f and 2.3.3.3f. The difference between All Simvastatin + Ezetimibe 10 mg and All Simvastatin was -13.8; whereas, the difference between Statin + Ezetimibe 10 mg and Statin was -21.5.

- Coadministration of ezetimibe 10 mg/d with statins 10 mg/d yielded LDL-C lowering comparable to or greater than that of the highest dose of the respective statin alone, including 80 mg of simvastatin and atorvastatin.

• Maximal or near-maximal reductions in plasma LDL-C concentrations with ezetimibe monotherapy or coadministration with statins occurred within 2 weeks and were maintained throughout 8 weeks or 12 weeks of double-blind treatment as well as through 12 to 18 months of prolonged open-label ezetimibe monotherapy.

• The effects of ezetimibe on LDL-C concentrations (whether administered as monotherapy or in coadministration with statins) were, in general, consistent among all subgroups analyzed.

Note: The last conclusion is not quite true. See Section 2.4 for this reviewer's findings on subgroup results.

• Relative to placebo, ezetimibe monotherapy produced favorable changes in HDL-C and TG concentrations; when coadministered with statins, ezetimibe produced favorable incremental changes HDL-C and TG that were independent of statin type or dose.

• Based on observed reductions in Apo B concentrations, ezetimibe-induced decreases in plasma LDL-C concentrations were achieved at least in part by reducing the concentrations of circulating LDL particles.

2.3.2 STATISTICAL METHODOLOGIES

THE SPONSOR'S STATISTICAL METHODS FOR EFFICACY ANALYSES (ISE, Section 6)

This section contains a brief description of the approach to the efficacy analyses and details the statistical methodology used in the Phase III clinical efficacy studies that will be discussed in this section of the marketing application. Detailed descriptions of statistical methods employed in each of the individual studies and the pooled studies are provided in the respective Clinical Study Reports and/or the associated Data Analysis Plans (**P00474, P00475, P00679, P00680, P00691, P00692, P02173/P02246, P01030, P02243/P02257**). A Data Analysis Plan for this integrated summary was prepared and approved prior to unblinding of protocols **P00679, P00680, P00691, P00692** .

Approach to Efficacy Analyses
Two approaches to the analysis of efficacy data were used in the Phase III studies: intent-to-treat and protocol-evaluable. These approaches differed in handling of protocol deviations and dropouts. Intent-to-treat was considered primary. Where substantial differences in the conclusions from the 2 approaches were observed, they were investigated and explained in the individual study reports.

Intent-to-Treat Approach
All patients who had a baseline and at least one post-baseline measurement were included in the endpoint analysis according to the group to which they were randomized. For Protocols **P00679, P00680, P00691, P00692, P01030, P02173/P02246, P02243/P02257,** the endpoint value is

defined as the last postbaseline lipid measurement for each particular parameter, regardless of any protocol violations or whether the patient was on or off drug during the period. For Protocols **P00474** and **P00475,** the endpoint value is defined as values taken from the last postbaseline blood draw for a patient, regardless of any protocol violations or whether the patient was on or off drug during the period. For the evaluation of the change from baseline to a particular time point (e.g., Weeks 2, 4, 8, and 12), only those patients who had a baseline value and a postbaseline value at the time point in question were included in the analysis, i.e., in case of missing data, prior postbaseline values were not carried forward.

Protocol-Evaluable Approach
Patients who met key eligibility and evaluability criteria determined before database closure were included in the protocol-evaluable analysis. Criteria for this patient population were prespecified and a list of patients excluded from this analysis and their associated reasons for exclusion was created prior to unblinding each of the studies. For the protocol-evaluable analysis, the endpoint value is defined as the last postbaseline measurement up through 3 days after the patient stops the investigational drug (Protocols **P00679, P00680, P00691, P00692, P01030, P02173/P02246**) or values taken from the last postbaseline blood draw for a patient up through 3 days after the patient stops the investigational drug (Protocols **P00474** and **P00475**). Where substantial differences in the conclusions from the 2 approaches were observed, they were investigated and explained in the individual study reports.

Treatment Comparisons

Monotherapy Studies (P00474 and P00475)
For these studies there were only 2 treatment groups, an ezetimibe 10-mg group and a placebo control group. The primary efficacy comparison was percent change from baseline to endpoint in direct LDL-C. The analysis was done using an analysis of variance (ANOVA) model with terms for treatment group and center. Because of the small numbers of patients enrolled at each center, no formal test of treatment by center interaction was done. Confidence intervals were calculated using the least square means (LSMEANS) from the ANOVA model. The parametric analysis described above was the primary analysis; it was corroborated by a non-parametric analysis.

Factorial Coadministration Studies (P00679, P00680, P00691, and P00692)
For these studies, there were either 8 (**P00679** and **P00691**) or 10 (**P00680** and **P00692**) treatment groups, depending upon the number of dose levels for the statin in each particular study. The treatment groups were ezetimibe 10 mg, ezetimibe placebo, statin (at 3 to 4 doses) and statin (at 3 to 4 doses) plus coadministered ezetimibe 10 mg. The primary efficacy comparison was percent change from baseline to endpoint in direct LDL-C. The analysis was done using an ANOVA model with terms for dose (e.g., 0, 10, 20, 40, and 80 mg, depending upon the study), treatment (i.e., ezetimibe 10 mg, ezetimibe placebo), and dose-by-treatment interaction. The dose effect in the model was treated as a class variable.

Because of the small number of subjects enrolled in each center, center effect and treatment-by-center interaction were not included in the model. The comparisons for pooled ezetimibe +statin (10, 20, 40, and 80 mg, depending upon the study) versus pooled statin and versus the ezetimibe

group were performed using contrast statements under the ANOVA model in order to evaluate the primary hypothesis. If the primary statistical hypothesis of no difference between coadministration and statin and between coadministration and ezetimibe was rejected, then the following 4 secondary hypotheses were evaluated:

The incremental effect of ezetimibe across all statin dose groups as evaluated under the model using a test for interaction via a contrast statement.

Ezetimibe alone versus placebo.

Individual doses of statin plus ezetimibe versus the corresponding statin dose group.

Individual doses of statin plus ezetimibe versus the next higher statin dose group (e.g., statin 10 mg plus ezetimibe group versus statin 20 mg group).

Confidence intervals and p-values were provided for all these comparison using the LSMEANS from the ANOVA model. A parametric analysis was the primary analysis; it was corroborated by a non-parametric analysis

Add-On Study (P02173/P02246)
This was a single study with 2 protocol numbers (one U.S., one international) for administrative convenience only. For this study, there were 2 treatment groups, a statin +ezetimibe 10-mg group and a statin +ezetimibe placebo control group. Subjects had to have been on stable statin doses. The primary efficacy comparison was percent change from baseline to endpoint in calculated LDL-C. The analysis was done using an ANOVA model. The initial model included terms for statin (simvastatin, atorvastatin, other), CHD risk stratum, region (U.S. sites, international sites), treatment, treatment-by-statin interaction, treatment-by-stratum interaction, and treatment-by-region interaction. The interaction terms were tested and removed from the ANOVA model if found to be not significant ($p \leq 0.050$) or quantitative in nature. Because of the small number of subjects enrolled in each center, center effect and treatment-by-center interaction were not included in the model. Confidence intervals were calculated using the LSMEANS from the ANOVA model. A parametric analysis was the primary analysis; it was corroborated by a non-parametric analysis.

Note: The reviewer used the conventional 0.1 level consistently for his evaluation of interactions.

The key secondary efficacy parameter of percentage of patients who reach NCEP ATPII target for LDL-C was assessed using logistic regression. The initial logistic model contained terms for statin (simvastatin, atorvastatin, other), region, CHD risk stratum, treatment, baseline percent difference from NCEP target, treatment-by-statin interaction, treatment-by-stratum interaction, and treatment-by-region interaction. The interaction terms were tested and removed from the ANOVA model if found to be not significant (p 0.050) or quantitative in nature.

Pooled Analyses

The 2 replicate Phase III monotherapy studies (**P00474 and P00475**) were pooled to assess changes in the lipid/lipoprotein parameters. This combined population will be referred to as the "Monotherapy Efficacy Pool." The primary variable was percent change from baseline to endpoint in direct LDL-C. An estimate of the treatment effect (ezetimibe minus placebo) and its 95% confidence interval were obtained using LSMEANS from an ANOVA model that contains terms for study and treatment.

Subgroups based on the following were evaluated for direct LDL-C percent change from baseline at endpoint:
Age (< 65, ≥65), (<75, ≥75)
Race (Caucasian, non-Caucasian)
Gender (Male, Female)
Hypertension (Yes, No)
Diabetes Mellitus (Yes, No)
BMI (<30, ≥30 kg/m 2)
Baseline TG (<200, ≥200 mg/dL), (<150, ≥150 mg/dL)
Baseline LDL-C (<160, ≥160 mg/dL)
Baseline HDL-C (<35, ≥35 mg/dL), (< 40, ≥40 mg/dL)
Known CHD (Yes, No)
Family History of Coronary Artery Disease (Yes, No)

The 4 Factorial Coadministration Studies (**P00679, P00680, P00691, P00692**) were pooled to compare the effect of coadministration of ezetimibe 10 mg with the various statins. This will be referred to as the "Factorial Efficacy Pool". Although studies **P02243/P02257 and P01030** also included ezetimibe 10 mg/statin coadministration treatment groups, they were excluded from this analysis because the study designs were different. The primary efficacy variable was percent change from baseline to endpoint in direct LDL-C. The difference between the statin at dose Y plus ezetimibe arm and the statin at dose Y plus placebo arm were calculated for each of the 4 studies for each dose. These differences were plotted to provide a visual assessment of the similarity of ezetimibe effect across statins and dose of statin. In each individual study report an assessment of treatment-by-dose of statin interaction was performed. Since the test for interaction was either not significant (p 0.050) or quantitative (i.e., the treatment effect differed only in magnitude among the statin doses) in nature in each of the 4 studies, an exploratory test was done to assess the similarity of ezetimibe effects across statins using an ANOVA model. The model had terms for statin, treatment (ezetimibe 10 mg or placebo) and statin-by-treatment interaction. The placebo and ezetimibe only arms from these studies were not included in the analysis. The hypothesis of equal treatment effect across statins was tested using the interaction term.

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

The following three studies have been reviewed in depth with a focus on the primary efficacy variable and analysis:

Protocol	Objective(s)	Design	Population	Ezetimibe Treatment Duration and Regimen	No. Subjects Enrolled Age Range (y) Sex (# M/F) Race (# C/N/C) All	Ezetimibe	Treatment Groups Identity	No. Subjects
Phase III Ezetimibe Monotherapy Studies- Primary Hypercholesterolemia								
P00474	Effect of EZ 10 mg monotherapy on LDL-C and other lipids; safety	R, DB, PC, LIPG	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 - 86 382/320 682/57	Placebo EZ 10	205 822
Phase III Ezetimibe/Statin Coadministration – Factorial Coadministration Studies								
P00510	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 ≤250 mg/dL	12 weeks; QD in PM	888 25 - 87 291/377 810/58	335 27 - 84 150/185 309/26	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
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	789 22-85 443/326 683/75	379 25-85 222/157 337/42	Placebo (+ statin) EZ 10 (+ statin)	380 379

The sponsor stated in response (May 9, 2002) to a request for the thorough investigation of covariation and interaction effects, "We have assessed those baseline characteristics that were pre-specified either for the individual protocols or for the ISE. These characteristics were chosen because they were either subgroups that are assessed for all studies (e.g. gender) or those that potentially have a relationship to the primary endpoint (e.g. baseline LDL-C). The baseline."

2.3.3.1 Study P00474

Title: A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg Compared With Placebo in Subjects With Primary Hypercholesterolemia

Summary information of this study follows:

Study Centers: 54 centers in the USA

Studied Period: 10 OCT 1999 to 5 SEP 2000 **Clinical Phase** III

Number of Subjects: 827 subjects, 397 men and 430 women aged 20-86 years, received randomized treatment assignment: 622 ezetimibe 10 mg and 205 placebo.

Diagnosis and Criteria for Inclusion: Otherwise healthy subjects with primary hypercholesterolemia; plasma LDL-C calculated via Friedewald equation (calculated LDL-C) 130-250 mg/dL (≈3.36-6.47 mmol/l) and triglycerides (TG) ≤350 mg/dL (≈ 3.95 mmol/l); NCEP Step I diet or stricter; adequate washout of previous lipid-lowering medication.

Duration of Treatment: 2 to 12 weeks no-treatment washout; 4 weeks single-blind placebo run-in; 12 weeks double-blind investigational treatment.

Criteria for Evaluation: The primary efficacy evaluation was percent change from baseline to endpoint in plasma concentration of direct LDL-C, determined following a ——— ——————— procedure (β-quantification). Percent change from baseline was also determined for calculated LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and TG after 2, 4, 8, and 12 weeks of treatment, and for subfractions HDL_2-C and HDL_3-C, apolipoprotein A-I (Apo A-I), apolipoprotein B (Apo B), and lipoprotein(a) (Lp(a)) at endpoint. Treatment was to be held until after samples were collected on visit days.

2.3.3.1a. Objectives

The primary objective of this trial was to evaluate the efficacy and the safety of SCH 58235 (10 mg/day) in subjects with primary hypercholesterolemia. The primary endpoint will be defined as the percent change from Baseline of the direct LDL-C at treatment endpoint.

2.3.3.1b. Disposition of Patients

A total of 827 subjects received randomized treatment assignment: 205 subjects were to receive placebo and 622 were to receive ezetimibe 10 mg, but two subjects who were to receive ezetimibe had no record of treatment.

The investigators reported that 766 subjects (93%) completed the protocol-specified, double-blind treatment phase without indication of discontinuation and 61 subjects (7%) discontinued investigational treatment early, as shown below.

Twenty-seven discontinuations (3%) were due to adverse events. There was no pattern or trend between the two treatment groups in the distribution of the reasons for discontinuations.

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

	(Protocol No. P00474)	
Disposition of Subjects	Placebo	Ezetimibe 10 mg
Received Randomized Treatment Assignment	205 (100)	622 (100)
Completed Treatment	192 (94)	574 (92)
Discontinued Treatment	13 (6)	48 (8)
Adverse event	5 (2)	22 (4)
Treatment failure	0	0
Lost to follow-up	0	5 (<1)
Subject did not wish to continue	6 (3)	17 (3)
Noncompliance with protocol	2 (<1)	2 (<1)
Did not meet protocol eligibility	0	0
Administrative	0	2 (<1)

The slightly higher adverse event rate in the ezetimibe group is not statistically different from that in the placebo group. However, please note that this does not assure that the rates are really not different. As in all cases of statistical hypothesis testing, it means only that even if they are different, this study (whether powered or not for the detection) failed to detect the difference.

Percent of Subjects in Study over Time:

TREATMENT ARM	WEEK 2	WEEK 4	WEEK 8	WEEK 12
Placebo (n=205)	97.6%	97.1%	94.6%	93.7%
Ezetimibe 10 mg (n=622)	97.8%	96.0%	93.7%	92.3%

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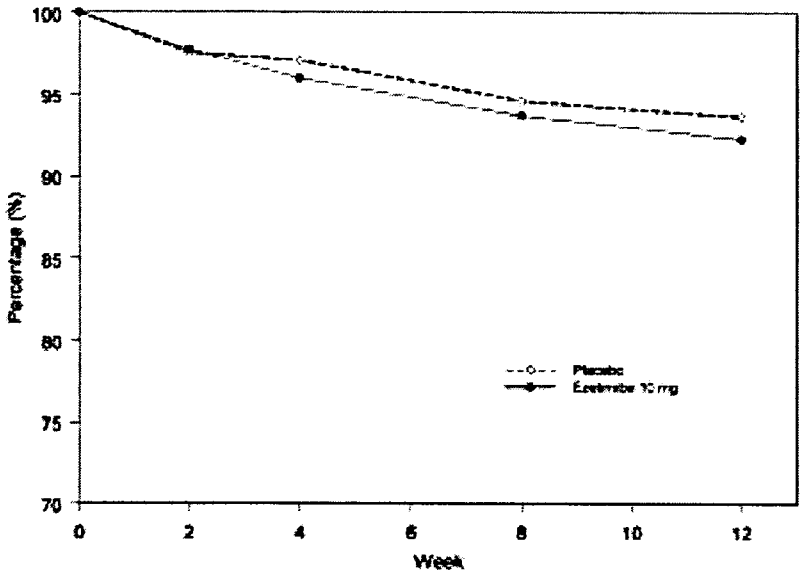
Percent of Subjects in Study over Time (Graph) -- P00474



The rate of dropout from the ezetimibe group was only negligibly higher.

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

2.3.3.1c. Protocol Deviations

Protocol deviations were identified for 173 subjects (21%), as summarized below. These deviations involved noncompliance with the protocol in 132 subjects (16%) and unacceptable concomitant therapy in 61 subjects (7%). However, the deviations were sufficient to result in exclusion from the Protocol-Evaluable Data Set for only 41 (5%) subjects. There was no pattern to suggest that there were more deviations or a difference in the types of deviations in either treatment group. The deviations would not be expected to affect the interpretation of response to treatment.

Apparently, there were more patients with protocol deviations in the ezetimibe group than in the placebo group (one-sided p-value is .07).

Number (%) of Subjects Who Had Identified Protocol Deviations:
Subjects Who Received Randomized Treatment Assignment

	Placebo (n=205)	(Protocol No. P00474) Ezetimibe 10 mg (n=622)
Subjects with Any Deviation[a]	35 (17)	138 (22)
Did Not Meet Entrance Criteria	3 (1)	11 (2)
Insufficient Washout	2 (<1)	5 (<1)
Noncompliance With Protocol	32 (16)	100 (16)
Unacceptable Concomitant Therapy	10 (5)	51 (8)
Administrative	0	1 (<1)

a: Subjects may have had more than one protocol deviation.

The sponsor stated, "There were several occurrences of randomized treatment being assigned out of sequential order or not assigned. These assignments would not be expected to affect interpretation of response to treatment.

At study Site 22:
• Subject Nos. 22/0493, 22/0494, and 22/0495 were assigned after Subject No. 22/0793

At study Site 42:
• Subject No. 42/0364 was assigned Subject No. 0361, but was actually treated as Subject No. 0364; Subject Nos. 42/0365, 42/0366, and 42/0367 were not assigned; and Subject No. 42/0368 was assigned this number not by [redacted] but by a study coordinator (ie, out of sequence)."

Twelve subjects (6%) in the placebo group and 29 subjects (5%) in the ezetimibe group were excluded from the Protocol-Evaluable Data Set, primarily because of insufficient washout of lipid-altering agents before the first qualifying visit (Visit 2).

2.3.3.1d. Demographic and Other Baseline Characteristics

The sponsor stated, "Overall, the characteristics of the data set are appropriate to address the objectives of the study. The data set comprised of male and female subjects, 20 to 86 years of age, who had hypercholesterolemia characterized by plasma concentrations of direct LDL-C approximately [redacted] mg/dl. The mean baseline plasma concentration of direct LDL-C was approximately 165 mg/dl for subjects in both treatment groups. In general, the two treatment groups were well balanced with regard to diet, weight, sex, age, race, physical activity, and smoking history. Most subjects were Caucasian (≈90%)."

Note: The sign '≈' within the quotation above stands for "approximately". From the results provided by the sponsor, the reviewer does not see any major imbalance between the treatment groups.

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. However, there was a statistically significant (without considering multiple comparison adjustments) imbalance (slightly more in the ezetimibe group) with respect to "known coronary heart disease" or "not" with a 2-sided p-value of 0.0252 (done by the reviewer using the Fisher's exact test in SAS PROC FREQ). Since there was no covariation or interaction (submission dated May 9th, 2002) of this factor with treatment in efficacy results, this is of no special concern.

Note: The sponsor reported that there was no washout information for more than 70% of the patients. This may be a potential concern with regards to the quality of the trial.

2.3.3.1e. Measurements of Treatment Compliance and Other Factors That Could Affect Response

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

The distribution of days of participation in the Randomization Phase is summarized below. There was no consequential difference in participation between the treatment groups, and both groups fairly represented 12 weeks of treatment.

Extent of Exposure (Number of Days of Participation in the Randomization Phase, Intent-to-Treat Data Set):

	Placebo (n=205)	Ezetimibe 10 mg (n=622)
Days in Randomization Phase[a]		
Mean (SD)	82.7 (13.9)	82.7 (13.9)
Median	84	84
Min–Max	—	—
Frequency by Interval: Number (%) of Subjects with a Maximum Indicated Number of Days in Randomization Phase		
0 Day	0	2 (0.3)
1–7 Days	2 (1.0)	3 (0.5)
8–21 Days	3 (1.5)	8 (1.3)
22–42 Days	1 (0.5)	10 (1.6)
43–70 Days	5 (2.4)	11 (1.8)
71–98 Days	189 (92.2)	571 (91.8)
>98 Days	5 (2.4)	8 (1.3)
Missing	0	9 (1.5)

a: n=205 for placebo treatment group and n=613 for ezetimibe treatment group for summary statistics.

SD = standard deviation.

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

2.3.3.1f. Efficacy Results (Sponsor's Analyses)

The protocol stated:

> The primary efficacy variable is the percent change from Baseline in direct LDL- C by ——— at study endpoint (last evaluation after randomization for each subject). The primary efficacy comparison is the ezetimibe 10 mg group versus placebo at study endpoint. The analysis will be performed using a two way analysis of variance model that extracts sources of variation due to treatment and center. Due to the small number of subjects expected to be enrolled at each center, the treatment by center interaction will not be formally tested. Ninety- five (95%) confidence intervals will be provided for the primary efficacy parameter. Summary statistics for the primary variable will be provided for the following

subgroups: gender, age (< 65, ≥65) and race (Caucasian and non- Caucasian). In addition to the endpoint analyses, analyses at each time point will also be provided.

The sponsor stated in the report, "All protocol-specified efficacy analyses were performed as described."

Results of the protocol-specified primary efficacy analysis show that ezetimibe 10 mg reduced direct LDL-C from baseline to endpoint relative to placebo, as evidenced by mean percent changes from baseline to endpoint of -17.69% with ezetimibe compared with 0.79% with placebo; the difference between the groups is statistically significant (P<.01). Thus, the study was positive in terms of response to treatment with ezetimibe, as shown below:

Change in Plasma Concentration of Direct LDL-C Between Baseline and Endpoint: Intent-to- Treat Data Set (Protocol No. P00474)

Direct LDL-C	Placebo	Ezetimibe 10 mg
Baseline	(n=204)	(n=621)
Mean value in mg/dl [mmol/l]	164.37 [4.25]	165.15 [4.27]
Endpoint	(n=199)	(n=606)
Mean value in mg/dl [mmol/l]	164.94 [4.27]	135.58 [3.51]
Mean percent change from baseline (standard error)	0.79 (0.87)	-17.69 (0.59)
Difference from placebo in mean percent change from baseline (95% confidence limits)	not applicable	-18.5 (-20.2, -16.7)

Note: all means and standard errors are least-square means and standard errors based on the two-way ANOVA model extracting treatment and center effects.
Source Data: 14.2.2.1.1.1.

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.

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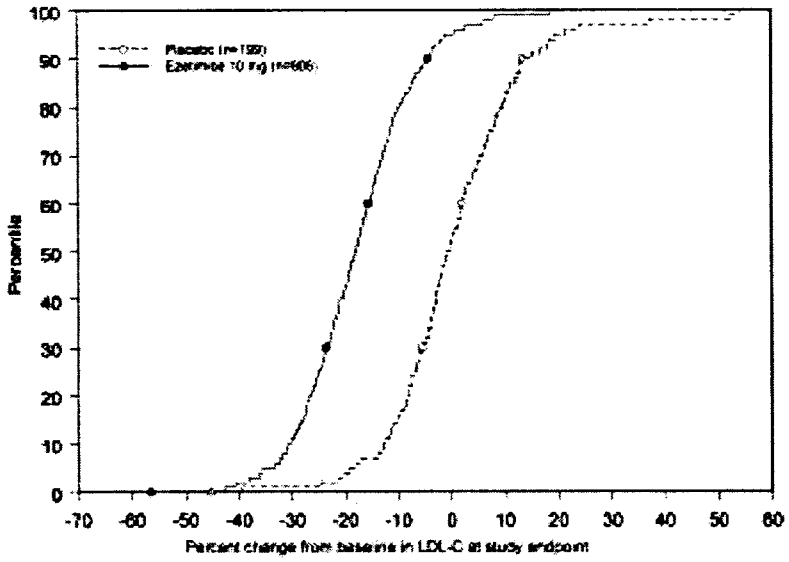
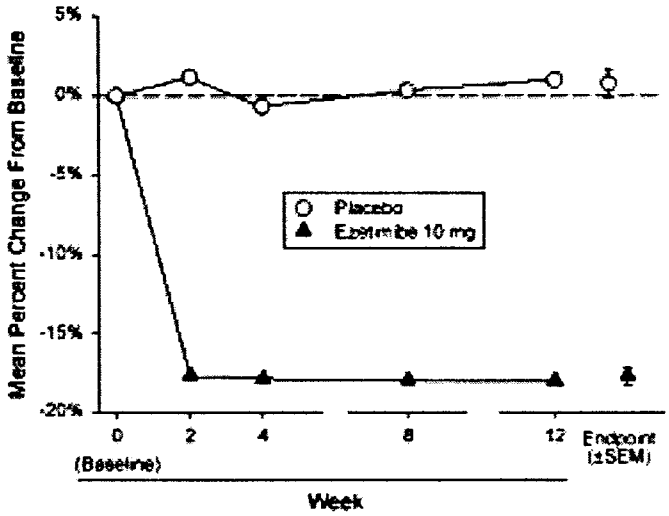
§ Cumulative Distribution Functions of Percent Change from Baseline in LDL-C at Study Endpoint is provided below:



From this, percent of patients (y-axis value) with a value of Percent Change from Baseline, smaller than or equal to a value on the x-axis can be read. For example, about 80% of the ezetimibe patients had a ≤–10% change from baseline compared with only 15% of patients in the placebo group.

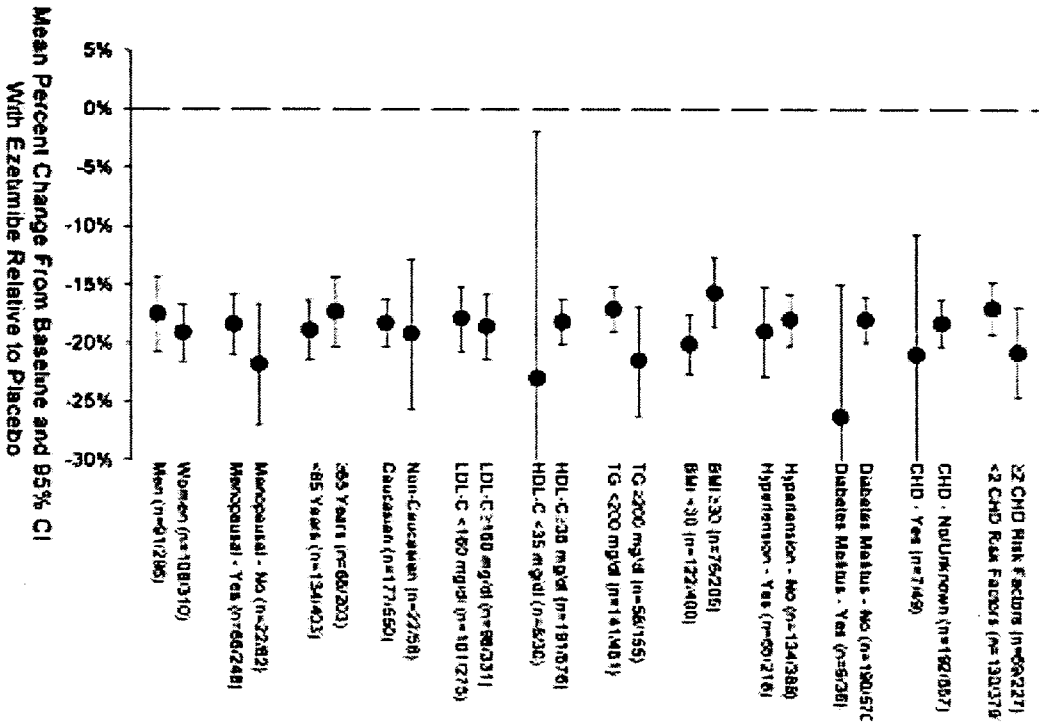
§ Among the dropout cohorts considered (April 19, 2002 submission), the results in the ezetimibe cohorts were almost always better (at least numerically) than those in the placebo cohorts.

§ Significant reduction in direct LDL-C with ezetimibe relative to placebo was observed at Week 2, the first time point when the measure was made, and was maintained throughout the 12-week course of treatment (Figure below).



§ Results for the primary efficacy variable were examined in subgroups defined by subject baseline characteristics: sex, age, race, LDL-C, HDL-C, TG, hypertension, diabetes mellitus, BMI, menopausal status, known CHD, and number of cardiovascular risk factors.

Point estimate and 95% confidence interval of the difference between response (raw mean percent change from baseline) to ezetimibe 10 mg and placebo in direct LDL-C in various subgroups of the population defined by baseline characteristics (Intent-to-Treat Data Set):



In subgroup labels, n=X/Y indicates the number of subjects treated with placebo (X)/number treated with ezetimibe (Y). Means represent raw means, except for the "overall," which is a least-square mean from the statistical model.

On a request for a thorough investigation of covariation and interaction, the sponsor provided on May 9, 2002, a summary of the investigation along with the corresponding p-values. However, these were done only for the baseline variables identified in the protocol. There were statistically significant covariation (with response) for Baseline LDL-C (continuous, $p < 0.01$) and Baseline Triglycerides (<200, ≥200 mg/dL, p=.002). [*Note: The Figure provided in this submission is not 100% overlapping with the above figure and contains additional subgrouping with respect to TG and HDL-C, while not containing everything in the above figure.*]

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:

BMI (<30, ≥ 30) - 0.019
Triglycerides (<200, ≥200) - 0.027
Triglycerides (<150, ≥150) - 0.089
Cardiovascular Risk Factors - 0.043
Diabetes mellitus - 0.051

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 ezetimibe 10mg over placebo seemed to differ statistically significantly over subgroups in these characteristics (see subgroup figure above).

However, these interactions were quantitative and not qualitative; i.e., ezetimibe 10 mg was superior to placebo irrespective of the subgroup in the above factors.

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 differences in the superiority of the ezetimibe 10 mg over placebo in the above figures with respect to other characteristics is real or not.

The treatment by center interaction was non-significant (p=0.493). There was not a single center, however small the size, that produced opposite results (placebo better than ezetimibe 10 mg). One or a few of the 54 centers driving the overall significant results is out of question.

§ Results for calculated LDL-C concentration (Friedewald equation) complement the results obtained for direct LDL-C. Ezetimibe 10 mg reduced calculated LDL-C from baseline to endpoint relative to placebo, as shown by a mean percent change from baseline to endpoint of -18.24% with ezetimibe compared with 1.36% with placebo; the difference between the groups is statistically significant (P<.01). The ezetimibe-mediated decrease in calculated LDL-C concentration was seen as early as Week 2 and was maintained for the duration of the study. These results are in Appendix Table 1.3.1.

Results for Protocol-Evaluable data set complement the results obtained for the intent-to-treat data set (p.199 and p.211 of prot. P00474 report in the NDA).

2.3.3.1g. Reviewer's Comments and Conclusions on Study P00474

The sponsor's analyses provided statistical evidence in favor of the efficacy of ezetimibe 10 mg.

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 (opposed to qualitative) interactions of BMI, Triglycerides, Cardiovascular Risk Factors, and Diabetes mellitus with the treatment have been noted above.

2.3.3.2 Study P00680

Title: A phase III double-blind efficacy and safety study of ezetimibe (sch 58235) 10 mg in addition to simvastatin compared with placebo in subjects with primary hypercholesterolemia

The synopsis of the report:

Study Center(s): 61 centers in the USA

Studied Period: 20 DEC 1999 to 12 JUN 2001 **Clinical Phase:** 3

Objective(s): The overall objective of this study was to evaluate the efficacy and safety of ezetimibe 10 mg administered daily in conjunction with simvastatin in subjects with primary hypercholesterolemia.

Methodology: Randomized, double-blind, placebo-controlled, balanced-parallel-group comparison conducted in conformance with Good Clinical Practices.

Number of Subjects: 668 subjects, 377 women and 291 men, 25 to 87 years of age, received randomized treatment assignment: 70 placebo, 61 ezetimibe 10 mg (EZ 10), 70 simvastatin 10 mg (Simva 10), 67 EZ 10+Simva 10, 61 Simva 20, 69 EZ 10+Simva 20, 65 Simva 40, 73 EZ 10+Simva 40, 67 Simva 80, and 65 EZ 10+Simva 80.

Diagnosis and Criteria for Inclusion: Subjects with primary hypercholesterolemia; plasma low-density-lipoprotein cholesterol calculated by the Friedewald equation (calculated LDL-C) _145 mg/dL to _250 mg/dL, and triglycerides (TG) _350 mg/dL; NCEP Step I diet or stricter; adequate washout of previous lipid-lowering medication.

Test Product, Dose, Mode of Administration: Ezetimibe 10 mg: white, capsule-shaped, unscored and unbranded tablets; taken orally in the evening.

Duration of Treatment: 2 to 12 weeks of washout of lipid-lowering agents; 4 weeks of single-blind placebo run-in; 12 consecutive weeks of double-blind investigational treatment.

Reference Therapy, Dose, Mode of Administration: All of the following were taken orally in the evening:

- Simvastatin was manufactured by Merck & Co., Inc. and provided to the study administrator as commercial ZOCOR - 10 mg, 20 mg, and 80 mg tablets. The commercial ZOCOR tablets were encapsulated into No. 000 blue, opaque gelatin capsules
- Placebo tablets (identical in appearance to ezetimibe 10 mg tablets)
- Placebo capsules (identical in appearance to simvastatin capsules)

Criteria for Evaluation: The primary efficacy analysis was based on the percent change from baseline of plasma LDL-C determined following a [redacted] (β-quantification) procedure (direct LDL-C) at study endpoint (last available postbaseline direct LDL-C value for each subject) for the Intent-to-Treat population. The primary hypothesis was that the coadministration of ezetimibe 10 mg/day with simvastatin (pooled across all doses: 10 mg, 20 mg, 40 mg, 80 mg) would result in a significantly greater reduction in direct LDL-C when compared with simvastatin alone (pooled across all doses: 10 mg, 20 mg, 40 mg, 80 mg) and ezetimibe 10 mg alone. Secondary efficacy analyses included evaluation of the change from baseline to endpoint for additional lipid variables: calculated LDL-C, total cholesterol (TC), TG, high-density-lipoprotein cholesterol (HDL-C), apolipoprotein B (Apo B), non-HDL-C, HDL2-C, HDL3-C, apolipoprotein A-I (Apo A-I), lipoprotein (a) ($L_p(a)$), and direct LDL-C:HDL-C and TC:HDL-C ratios.

Statistical Methods: The primary efficacy analysis was performed using a two-way analysis of variance 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 for the percent change from baseline in direct LDL-C at endpoint. The comparisons (pooled ezetimibe 10 mg + simvastatin [10 mg, 20 mg, 40 mg, 80 mg] group versus pooled simvastatin [10 mg, 20 mg, 40 mg, 80 mg] group, and pooled ezetimibe 10 mg + simvastatin [10 mg, 20 mg, 40 mg, 80 mg] group versus ezetimibe 10 mg group) were performed using contrast statements under the model in order to evaluate the primary hypothesis.

2.3.3.2a. Objectives

Primary Objective
To evaluate the efficacy and the safety of ezetimibe (10 mg/day) administered daily in conjunction with simvastatin in subjects with primary hypercholesterolemia. The primary endpoint will be defined as the percent change from Baseline of the direct LDL-C at treatment endpoint.

2.3.3.2b. Disposition of Patients

Of the 2645 screened subjects, 668 (25%) continued in the Randomization/Active Treatment Phase and received at least one dose of study medication. A total of 591 subjects (88%) completed the protocol-specified, double-blind treatment phase, while 77 subjects (12%) discontinued investigational treatment early (Table below). The percentage of patients completing the study varied from 80% to 94% in the various treatment groups. The primary reason for discontinuation was due to adverse events, accounting for 42 discontinuations (6% of

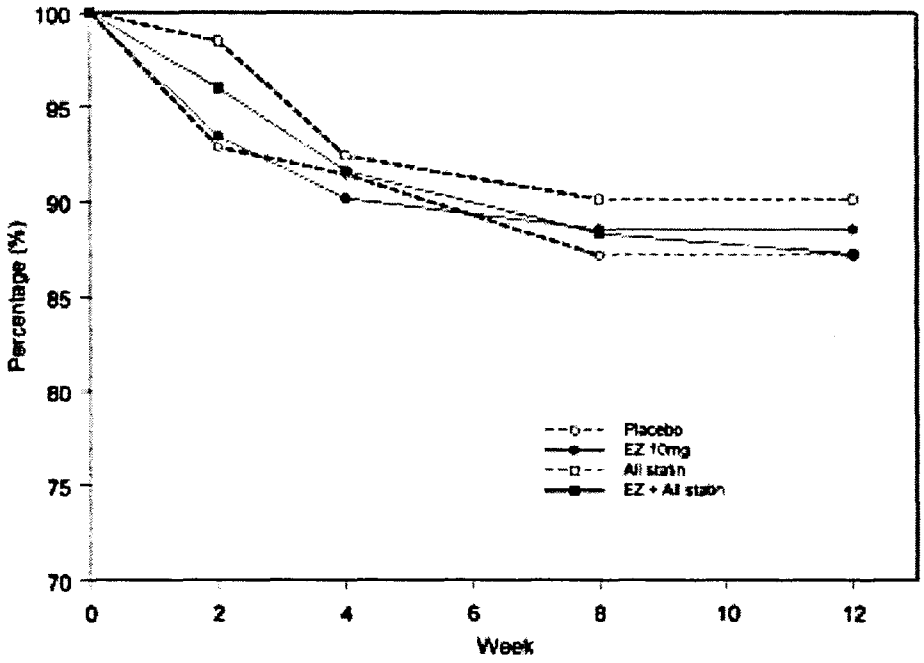
subjects assigned randomized treatment). There was no pattern or trend across treatment groups in the distribution of subjects who discontinued or in the reasons for discontinuation. A list identifying the individual subjects who discontinued treatment early and the reasons for discontinuation appears in Section 16.2.1 of the NDA.

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

Disposition of Subjects	Placebo	EZ 10	All Simva	EZ 10+ All Simva	Simva 10	EZ 10+ Simva 10	Simva 20	EZ 10+ Simva 20	Simva 40	EZ 10+ Simva 40	Simva 80	EZ 10+ Simva 80
Received Randomized Treatment Assignment	70 (100)	61 (100)	283 (100)	274 (100)	70 (100)	67 (100)	61 (100)	69 (100)	65 (100)	73 (100)	67 (100)	66 (100)
Completed Treatment	61 (87)	54 (89)	237 (90)	239 (87)	61 (87)	61 (91)	53 (87)	58 (84)	60 (92)	68 (93)	63 (94)	52 (80)
Discontinued Treatment	9 (13)	7 (11)	26 (10)	35 (13)	9 (13)	6 (9)	8 (13)	11 (16)	5 (8)	5 (7)	4 (6)	13 (20)
Adverse event	3 (4)	5 (8)	14 (5)	20 (7)	4 (6)	2 (3)	6 (10)	7 (10)[a]	2 (3)	3 (4)	2 (3)	8 (12)
Lost to follow-up	0	0	3 (1)	1 (<1)	0	0	0	0	2 (3)	1 (1)	1 (1)	0
Subject did not wish to continue	3 (4)	0	8 (3)	7 (3)	4 (6)	3 (4)	2 (3)	1 (1)	1 (2)	1 (1)	1 (1)	2 (3)
Noncompliance with protocol	3 (4)	2 (3)	1 (<1)	7 (3)	1 (1)	1 (1)	0	3 (4)	0	0	0	3 (5)

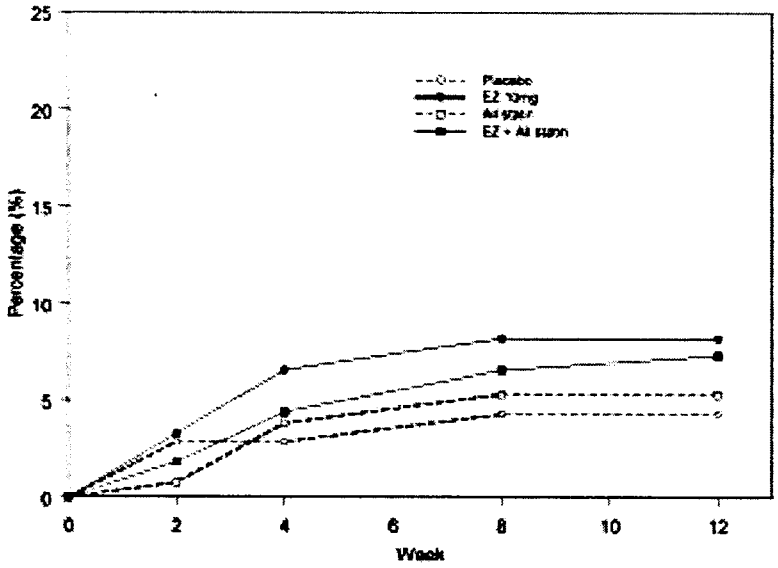
a : Includes Subject 28/000516 (EZ 10+Simva 20), who died during the Randomization/Active Treatment Phase. See **Section 12.3.3.1.** for details.
EZ 10=ezetimibe 10 mg; Simva XX=dose of simvastatin in milligrams; All Simva=pool of all doses of simvastatin; EZ 10+All Simva=pool of all doses of simvastatin
coadministered with ezetimibe 10 mg
Source Data: **Section 14.4.3.3.**

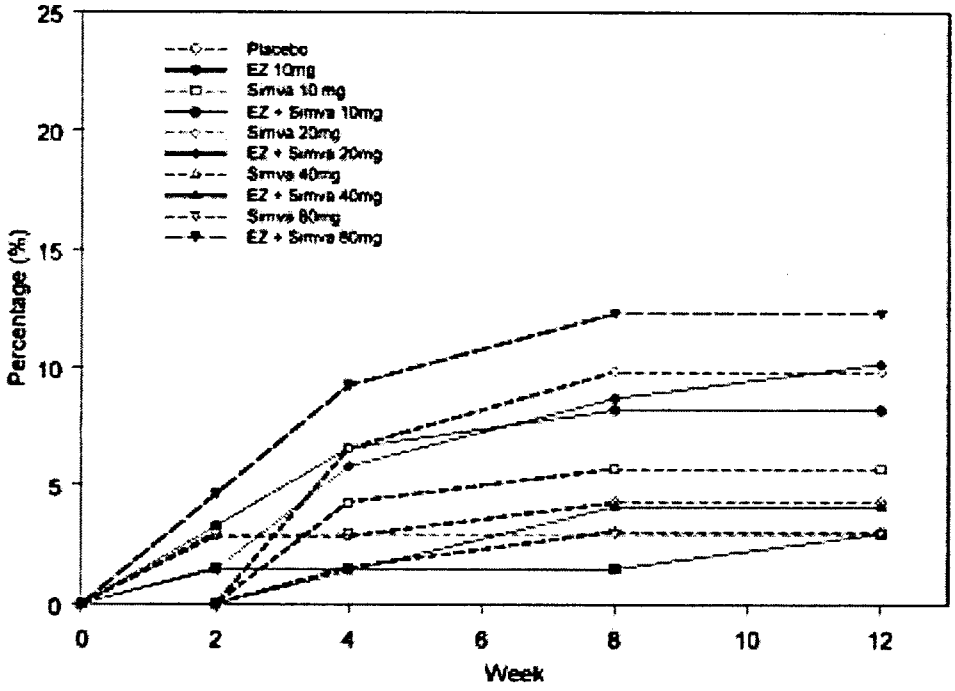
Percent of Subjects in Study over Time (P00680) is provided below:



(The corresponding figure for individual statins is Figure 1.4 of the April 2, 2002 submission. The Ezetimibe+Simva 80mg treatment group showed the highest dropout rate.)

Percent of Subjects Discontinued due to AE is provided below:





The rate of dropout due to adverse events was again the highest in the EZ + Simva 80mg group.

2.3.3.2c. Data Sets Analyzed

Before the data base was locked (7/12/01) and treatment identities were unblinded, the study administrator approved a Data Analysis Plan (Section 16.1.9.1. of NDA) that prespecified (finalization date – 7/6/01) the definition and analysis of efficacy results for two data sets:

Intent-to-Treat Data Set: all subjects who received randomized treatment assignment

Protocol-Evaluable Data Set: all subjects in the Intent-to-Treat Data Set who had at least one lipid determination after randomization with certain exclusions (details in Section 11.1 of the NDA report).

2.3.3.2d. Demographic and Other Baseline Characteristics

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.

Summaries of baseline demographic characteristics and habits, baseline lipid profiles, and baseline cardiovascular risk factors/family history or medical history/physical findings for subjects in the Intent-to-Treat data set are presented in Table 9, Table 10 and Table 11 (pages 96 to 102 of the report in the NDA) by treatment group and by pooled treatment groups (all doses of simvastatin alone or coadministered with ezetimibe 10 mg). The distribution of individual cardiovascular risk factors/family history at baseline is displayed in Table 12 (pages 103 to 106). 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 377 female and 291 male subjects, 25 to 87 years of age, who had hypercholesterolemia with baseline plasma concentrations of direct LDL-C ranging from [redacted] mg/dL. Mean baseline plasma concentrations of direct LDL-C were balanced across treatment groups and ranged from 174 mg/dL to 181.6 mg/dL. Between 30% and 39% of subjects required washout from lipid-lowering agents. In general, the treatment groups were also balanced with regard to age, sex, race, diet, weight, body mass index, physical activity, and smoking history. Most subjects were Caucasian (91%). Slightly more than half of the subjects (55%) had risk factors or a family history of cardiovascular disease. Overall, approximately 43% had a known family history of coronary artery disease, 29% had hypertension, 7% had known coronary heart disease, and 4% had diabetes. Most women were post-menopausal (81%). Approximately 15% of subjects had cardiovascular findings in their medical history or physical examination.

There were slight numerical imbalances in:

Triglycerides													
Mean	(mg/dL)	170.9	180.3	168.7	178.8	164.7	183.6	173.9	177.1	169.8	178.5	167	173.8
SD	(mg/dL)	88.5	84.7	59.8	65.1	61.9	64.1	61	70.1	61	62.6	56.1	64.3
Median	(mg/dL)	158.8	162.7	157	169	147.2	170.7	160.3	165.3	164	171.7	161	169

and status of females (post-menopausal or not, number (%)):

Yes	37 (93)	33 (89)	114 (75)	121 (82)	29 (67)	29 (81)	29 (78)	34 (97)	25 (69)	28 (74)	31 (84)	30 (77)
No	3 (8)	4 (11)	38 (25)	27 (18)	14 (33)	7 (19)	8 (22)	1 (3)	11 (31)	10 (26)	6 (16)	9 (23)

2.3.3.2e. Measurements of Treatment Compliance and Other Factors That Could Affect Response

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

Compliance data (mean percentages of total doses taken) ranged from approximately 90% to 97% (Sections 14.2.1.1. and 16.2.5.1. of NDA).

Summary statistics of the percentages of total doses of study treatment taken for the Intent-to-Treat Data Set follow.

Summary Statistics of Dose Compliance

		Placebo	EE 10mg	Sinvs 10mg	EE 10mg + Sinvs 10mg	Sinvs 20mg	EE 10mg + Sinvs 20mg
		n=72	n=61	n=70	n=67	n=63	n=69
Treatment Unit							
CAPSULE	N	68	61	70	67	61	68
	MEAN	97	97.4	96	96.7	96.6	94.4
	MEDIAN	98.9	98.9	98.5	98.8	98.8	98.8
	MIN						
	MAX						
	STD	4.99	4.69	5.63	4.98	5.69	36
TABLET	N	69	61	70	67	61	69
	MEAN	96.7	97.4	98.9	96.7	96.7	95.2
	MEDIAN	98.8	98.8	98.7	98.8	98.8	98.8
	MIN						
	MAX						
	STD	5.08	4.7	5.67	4.87	5.64	36

APPEARS THIS WAY
ON ORIGINAL

		Simva 40mg	EZ 10mg + Simva 40mg	Simva 80mg	EZ 10mg + Simva 80mg
		n=65	n=73	n=67	n=65
Treatment Unit					
CAPSULE	N	63	72	67	64
	MEAN	97.1	96.3	96.1	91.6
	MEDIAN	97.8	97.7	97.9	97.6
	MIN				
	MAX				
	STD	4.01	4.22	5.34	37.4
TABLET	N	63	72	67	64
	MEAN	97.2	96.4	95.6	90.1
	MEDIAN	98.8	97.7	98.8	97.6
	MIN				
	MAX				
	STD	3.81	4.18	7.32	45.7

		Placebo	EZ 10mg	All Simva groups	All *EZ+Simva * groups
		n=70	n=61	n=263	n=274
Treatment Unit					
CAPSULE	N	69	61	261	272
	MEAN	97	97.4	96.4	94.5
	MEDIAN	98.8	98.8	96.8	98.8
	MIN				
	MAX				
	STD	4.93	4.69	5.15	25.8
TABLET	N	69	61	261	272
	MEAN	96.7	97.4	96.3	94.2
	MEDIAN	98.8	98.8	98.8	98.8
	MIN				
	MAX				
	STD	5.08	4.7	5.75	29.1

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. The percentage of patients with duration 71-98 days varied from 80% (Ez10 +Simva 80) to 93% (Ez10 +Simva 40).

Frequency by Interval: Number (%) of Subjects with the Indicated Range of Days in Randomization/Active Treatment Phase												
0 Day	0	0	0	1 (<1)	0	0	0	0	0	0	0	1 (2)
1–7 Days	1 (1)	3 (5)	0	3 (1)	0	0	0	1 (1)	0	0	0	2 (3)
8–21 Days	3 (4)	1 (2)	4 (2)	6 (2)	0	2 (3)	6	1 (1)	1 (2)	0	3 (4)	3 (5)
22–42 Days	1 (1)	2 (3)	14 (5)	12 (4)	7 (10)	2 (3)	5 (8)	6 (9)	1 (2)	1 (1)	1 (1)	3 (5)
43–70 Days	3 (4)	1 (2)	6 (2)	9 (3)	2 (3)	1 (1)	3 (5)	2 (3)	1 (2)	3 (4)	0	3 (5)
71–98 Days	59 (84)	64 (89)	234 (89)	239 (87)	61 (87)	61 (91)	53 (87)	58 (84)	59 (91)	68 (93)	61 (91)	52 (80)
>98 Days	2 (3)	0	3 (1)	3 (1)	0	1 (1)	0	1 (1)	1 (2)	0	2 (3)	1 (2)
Missing	1 (1)	0	2 (<1)	1 (<1)	0	0	0	0	2 (3)	1 (1)	0	0

EZ 10=ezetimibe 10 mg; Simva XX=dose of simvastatin in milligrams; All Simva=pool of all doses of simvastatin; EZ 10+All Simva=pool of all doses of simvastatin coadministered with ezetimibe 10 mg

Source Data: Section 14.5.

2.3.3.2.f. Efficacy Results (Sponsor's Analyses)

The sponsor stated that the Data Analysis Plan was finalized (Jul. 6, 2001) before database lock (Jul. 12, 2001).

The "Data Analysis Plan" stated:

> The primary efficacy analysis will be based on the percent change from baseline in direct LDL-C at study endpoint (last available postbaseline LDL-C value for each subject) based on the intention-to-treat population. The primary hypothesis is that coadministration of ezetimibe and simvastatin will be more efficacious than simvastatin alone and ezetimibe alone in terms of direct LDL-C reduction. The primary analysis will be performed using an analysis of variance (ANOVA) model that extracts effects due to dose (simvastatin: 0 mg, 10 mg, 20 mg, 40 mg, and 80 mg), treatment (ezetimibe10 mg, ezetimibe placebo), and dose by treatment interaction. Dose effect in the model is treated as a class variable. The comparisons: pooled ezetimibe+simvastatin group versus pooled simvastatin group, and pooled ezetimibe+simvastatin groups versus ezetimibe group will be performed using contrast statements under the model in order to evaluate the primary hypothesis.
>
> The additive effect of ezetimibe across all simvastatin dose groups (10 mg, 20 mg, 40 mg, and 80 mg) will be evaluated under the model using a test of interaction via contrast statement. 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.
>
> The primary hypothesis involves two comparisons: pooled ezetimibe+simvastatin group versus pooled simvastatin group, and pooled ezetimibe+simvastatin groups versus ezetimibe group. Both comparisons must be statistically significant in order for the study to be declared positive.

Results of the primary efficacy analysis demonstrated that coadministration of ezetimibe 10 mg plus simvastatin was more efficacious than simvastatin alone in reducing plasma concentrations of direct LDL-C from baseline to endpoint (Table below). For this primary analysis, data from the four treatment groups involving coadministration therapy (simvastatin 10 mg plus ezetimibe 10 mg, simvastatin 20 mg plus ezetimibe 10 mg, simvastatin 40 mg plus ezetimibe 10 mg, and simvastatin 80 mg plus ezetimibe 10 mg) were pooled and compared with the pooled data from the four treatment groups involving simvastatin monotherapy (simvastatin 10, 20, 40 and 80 mg). Mean percent change of approximately 50% was seen in the ezetimibe plus simvastatin pool compared with 36% in the simvastatin alone pool. The difference between these pools of coadministration therapy and simvastatin monotherapy (approximately 14%) was statistically significant ($p<0.01$).