q12h, ezetimibe 10 mg, ezetimibe + cholestyramine 4g q12h, and ezetimibe 10 mg + cholestyramine 4g q12h + simvastatin 20mg. The data demonstrated that cholestyramine significantly decreased the systemic exposure to ezetimibe and total ezetimibe, with a mean reduction of ~55% in total ezetimibe bioavailability (based on AUC).

Protocol P00252 and P00753:
These 2 protocols evaluated the potential interaction between ezetimibe and fibrates.

Protocol No. P00252 was a drug interaction study between Gemfibrozil and Ezetimibe in 12 healthy adult male volunteers. The study was a randomized, open-label, 3-way crossover study. The treatment groups were: ezetimibe 10 mg/day, gemfibrozil 600 mg q12h and ezetimibe 10 mg/day plus gemfibrozil 600 mg q12h. Each treatment was administered to each subject for 7 days followed by a 7-day washout period between treatments. All medications were administered orally. PK analysis indicated that ezetimibe did not alter the pharmacokinetics of gemfibrozil. However, gemfibrozil coadministration caused an ~ 1.7-fold (or ~70%) increase in exposure (AUC 0-24h) to total and conjugated ezetimibe, while exposure to unconjugated ezetimibe was increased ~1.5 fold (~50% increase).

P00753 was a drug interaction study between Fenofibrate and Ezetimibe. 33 adult male and female subjects with hypercholesterolemia participated. The study was a randomized, placebo-controlled, multiple-dose, parallel-group study. Subjects were randomized to one of the following four treatments: fenofibrate 200 mg plus ezetimibe 10 mg or fenofibrate 200 mg or ezetimibe 10 mg or placebo. All doses were administered orally, once-daily in the morning for 14 consecutive days. 32 subjects completed the study (one subject randomized to ezetimibe, received only one dose and then withdrew for personal reasons). PK analysis indicated that ezetimibe did not significantly alter the pharmacokinetics of fenofibrate. However, coadministration of ezetimibe and fenofibrate resulted in an ~50% mean increase in the exposure to total and conjugated ezetimibe (based on log-transformed AUC). Evaluation of the efficacy of coadministration compared to placebo, and to ezetimibe monotherapy and to fenofibrate monotherapy is demonstrated in the following table:

Pharmacodynamics: The mean (SE) Day 14 percent (%) change from Baseline in serum lipids following once-daily oral administration of ezetimibe 10 mg alone, fenofibrate 200 mg alone, the coadministration of fenofibrate 200 mg and ezetimibe 10 mg or placebo for 14 days to healthy hypercholesterolemic subjects is shown in the table below.

Treatment	LDL-C	Total-C	HDL-C	TG
Placebo (n=8)	-10.1 (4.78)	-8.38 (3.97)	-14.1 (2.18)	19.1 (13.9)
Ezetimibe 10 mg (n=8)	-22.3 (5.66)[c]	-19.6 (4.00)[b]	-13.3 (4.40)	-4.57 (12.8)
Fenofibrate 200 mg (n=8)	-13.5 (3.11)	-13.0 (2.43)	-6.09 (3.63)	0.28 (11.4)
Fenofibrate 200 mg + Ezetimibe 10 mg (n=8)	-36.3 (3.48)[a,d,f]	-27.8 (1.69)[a,d]	-1.97 (4.67)[b,f]	-32.4 (4.50)[a,e]

a: p<0.01 vs. placebo.
b: p≤0.03 vs. placebo
c: p=0.06 vs. placebo.
d: p<0.01 vs. fenofibrate 200 mg.
e: p=0.05 vs. fenofibrate 200 mg.
f. p≤0.05 vs. ezetimibe 10 mg.

The coadministration of fenofibrate 200 mg and ezetimibe 10 mg caused a significantly greater ($p < 0.05$) mean percent reduction in LDL-C compared to either drug alone or to placebo, with a mean day 14 reduction of ~23% and 14% more for the combination treatment vs. fenofibrate or ezetimibe alone, respectively. In addition, coadministration resulted in a significantly greater ($p \leq 0.05$) mean % reduction in TC and TG compared to fenofibrate alone or placebo. In this study, mean HDL-C decreased in all treatment groups.

Factorial Coadministration Studies:
In the lovastatin, simvastatin and atorvastatin factorial studies, plasma drug samples were obtained at week 12 to determine if there was a drug interaction between ezetimibe and these respective statins. On June 21, 2002 I asked Dr. Wei Qiu, biopharmaceutics reviewer to also review these data.

In the lovastatin factorial study, plasma samples for total, conjugated and unconjugated ezetimibe were obtained 14-15 hr following the previous evening dose during week 12 of either ezetimibe 10 mg (46 subjects) or ezetimibe 10 mg coadministered with lovastatin 10, 20 or 40 mg (37-39 subjects/treatment group). Coadministration resulted in similar (within ~15%) mean values of total, conjugated and unconjugated ezetimibe compared to ezetimibe alone. Therefore, the pharmacokinetics of ezetimibe were not significantly affected by the coadministration of lovastatin. In addition, it was determined if the pharmacokinetics of lovastatin were affected by the coadministration of ezetimibe. Plasma concentrations of lovastatin and its metabolite,

hydroxylovastatin were obtained at week 12 in 22-27 subjects on lovastatin 10, 20 or 40 mg alone and in 18-22 subjects on lovastatin 10, 20 or 40 mg coadministered with ezetimibe. The mean plasma concentration of lovastatin in the subjects who received lovastatin alone was within 5-13% of that seen with the corresponding dose of lovastatin coadministered with ezetimibe. However, the mean concentration of hydroxylovastatin was ~30% lower in the group who received lova 10 mg alone compared to the eze + lova 10 mg group. At the 20 and 40 mg lovastatin doses, the mean concentration of hydroxylovastatin was ~50% and 75% higher, respectively than the mean concentration with coadministration. The sponsor concluded that the pharmacokinetics of lovastatin were not significantly affected by the coadministration of ezetimibe.

In the simvastatin factorial study, plasma samples for total, conjugated and unconjugated ezetimibe were obtained 13-14 hr following the previous evening dose during week 12 of either ezetimibe 10 mg or ezetimibe 10 mg coadministered with simvastatin. The estimated mean total and conjugated ezetimibe concentrations were each higher by ~11 ng/ml in the pooled ezetimibe plus simvastatin group compared to the ezetimibe alone group. Although statistically significant ($p= 0.025$ and 0.019), the sponsor stated that this increase was within the random fluctuation of concentration data, given an estimated intersubject standard deviation for total and conjugated ezetimibe of 32 ng/ml and 30 ng/ml, respectively. As no statistically significant differences were detected between the individual coadministration treatment groups, the sponsor stated that it appeared that the increases in total and conjugated ezetimibe concentrations due to simvastatin coadministration were independent of the dose of simvastatin. Unconjugated ezetimibe concentrations were not affected by the coadministration of simvastatin.

In the atorvastatin factorial study, plasma samples for total, conjugated and unconjugated ezetimibe were obtained 24 hr following the previous morning dose during week 12 of either ezetimibe 10 mg or ezetimibe 10 mg coadministered with atorvastatin. Total, conjugated and unconjugated ezetimibe concentrations from the subjects who received ezetimibe with atorvastatin were not statistically significantly different from those of the subjects who received ezetimibe alone ($p \geq 0.16$), suggesting that atorvastatin in the dose range of 10 to 80 mg had no significant effect on ezetimibe.

Familial Homozygous Hypercholesterolemia:
Plasma total and conjugated ezetimibe levels were measured during week 12 of treatment. The median elapsed time from the last dose to the time of the plasma sample was 24 hours for the patients dosed with ezetimibe and atorvastatin and 12 hours for those dosed with ezetimibe and simvastatin.

Table 1 Mean (%CV) Plasma Concentrations of Total Ezetimibe, Conjugated Ezetimibe and Ezetimibe During Week 12 Following Once-Daily Oral Administration of Ezetimibe or Placebo in Combination With Placebo, Atorvastatin or Simvastatin to Patients With Homozygous Familial Hypercholesterolemia

Treatment Group	n	Ezetimibe (ng/mL plasma)		
		Total Ezetimibe	Conjugated Ezetimibe	Ezetimibe
Placebo + Atorvastatin 80 mg	12	3.59 (309)	2.85 (300)	0.740 (346)
Ezetimibe 10 mg + Atorvastatin 40 mg	12	31.3 (50)	28.5 (49)	2.82 (67)
Ezetimibe 10 mg + Atorvastatin 80 mg	12	33.6 (57)	28.1 (59)	5.44 (93)
Placebo + Simvastatin 80 mg	4	0 NA	0 NA	0 NA
Ezetimibe 10 mg + Simvastatin 40 mg	4	95.8 (72)	83.9 (76)	11.8 (51)
Ezetimibe 10 mg + Simvastatin 80 mg	4	33.6 (39)	29.2 (40)	4.42 (108)

NA = Not appropriate

There were 2 patients dosed with atorvastatin 80 mg alone who had inexplicable measureable ezetimibe plasma concentrations.
Mean plasma total and conjugated ezetimibe concentrations were similar when ezetimibe was administered with either atorvastatin 40 or 80 mg. Although the mean plasma ezetimibe concentration was higher for atorvastatin 80 mg compared to that with atorvastatin 40 mg, the increase was influenced by two patients.
Mean plasma total and conjugated ezetimibe and ezetimibe concentrations when ezetimibe was administered with simvastatin 80 mg were ~35% compared to that when ezetimibe was administered with simvastatin 40 mg. Analysis of variance based on these limited data (n= 4/treatment group) indicated that the differences were not statistically significant ($p > 0.10$).

IV. Description of Clinical Data and Sources

A. Overall Data

The sources of clinical data used were the clinical trials conducted by the sponsor and, for homozygous sitosterolemia, literature reports as well. Specifically, 12 completed, double-blind, placebo- or active-controlled Phase II/III studies of 8-12 weeks duration and an ongoing, open-label, 24-month extension study were reviewed in detail. These studies are enumerated in the section IV.B.

In this NDA, the sponsor also submitted interim safety reports for the following ongoing studies:
Controlled Studies:
Study P00693: A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Atovastatin in Subjects with Coronary Heart Disease or Multiple Cardiovascular Risk factors and with Primary Hypercholesterolemia Not Controlled by a Starting Dose (10 mg) of Atorvastatin;

Study P00700: A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Simvastatin in Subjects with Coronary Heart

Disease or Multiple Cardiovascular Risk factors and with Primary Hypercholesterolemia Not Controlled by a Starting Dose (20 mg) of Simvastatin;

Study 005 (P02359): A Multicenter, Double-Blind, Randomized, Placebo-Controlled, "Factorial" Design, 12-Week Study to Evaluate the Efficacy of Ezetimibe (SCH 58235) 10 mg/day Coadministered with Multiple Doses of Simvastatin in Patients with Primary Hypercholesterolemia;

Study P02156: Long-Term, Safety and Tolerability Study of Ezetimibe (SCH 58235) or Placebo in Addition to Simvastatin in Subjects with Primary Hypercholesterolemia;

Study P02154: Long-Term, Safety and Tolerability Study of Ezetimibe (SCH 58235) or Placebo in Addition to Atorvastatin in Subjects with Primary Hypercholesterolemia;

Study P02173/P02246: A Multicenter, Double-Blind, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of Ezetimibe (SCH 58235) When Added to Ongoing Statin Therapy with an HMG-CoA Reductase Inhibitor (Statin) in Patients with Primary Hypercholesterolemia, Known CHD or Multiple CV Risk Factors.

Uncontrolled Studies:
Study P02134: Long-Term, Open-Label, Safety and Tolerability Study of Ezetimibe (SCH 58235) in Addition to Simvastatin in Subjects with Primary Hypercholesterolemia who have Previously Completed the 12-Week Double-Blind Study (Protocol Nos. P00679 or P00680);

Study P01416: Long-Term, Open-Label, Safety and Tolerability Study of Ezetimibe (SCH 58235) in Addition to Pravastatin in Patients with Primary Hypercholesterolemia;

Study P01417: Long-Term, Open-Label, Safety and Tolerability Study of Ezetimibe (SCH 58235) in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia;

Study P01418: Long-Term, Open-Label, Safety and Tolerability Study of Ezetimibe (SCH 58235) in Addition to Atorvastatin in Subjects with Coronary Heart Disease or Multiple Cardiovascular Risk factors and with Primary Hypercholesterolemia Not Controlled by a Starting Dose (10 mg) of Atorvastatin.

Other Studies:
Study [redacted]. A Pilot Study to Examine the Efficacy and Safety of Ezetimibe (SCH 58235) [redacted]

B. Tables Listing the Clinical Trials

PHASE II STUDIES: DOSE RESPONSE STUDIES

1. C96-411 and C96-345: Initial Dose-Ranging Study:

Title	Pilot Dose-Ranging Study of the Safety and Efficacy of SCH 58235 Compared to Placebo and Lovastatin in Patients with Primary Hypercholesterolemia
Study design	Randomized, double-blind, fixed-dose, placebo-controlled, parallel group
Objectives	1^0: To evaluate the efficacy and safety of ezetimibe compared to placebo in lowering LDL-C when administered orally in doses of - mg, - mg, 10 mg, - mg and - mg, once a day for 8 weeks in subjects with primary hypercholesterolemia; 2^0: establish the cholesterol-lowering effect dose-response relationship of ezetimibe; compare the cholesterol-lowering effect of lovastatin 40 mg once daily with placebo as an internal reference arm for study design validation
Sample size	124 subjects, 66 men and 58 women, aged 30-71 years with 16-20 subjects in each of 7 treatment groups
Inclusion criteria	Otherwise healthy subjects with primary hypercholesterolemia; calculated LDL-C 160-220 mg/dl and TG ≤250 mg/dl; NCEP Step 1 diet; adequate washout of previous lipid-lowering medication (nicotinic acid, resins and statins: 6 weeks, fibric acid derivatives: 12 weeks and probucol: 1 year)
Exclusion criteria	Among the exclusion criteria were: HoFH; non-type II hypercholesterolemia; CHF NYHA Class III and IV; arrhythmia requiring medication; BP >160/95; MI; coronary artery bypass surgery or angioplasty within 6 months of study entry; history of unstable or severe angina pectoris or peripheral artery disease; diabetes mellitus requiring medication (diet allowed); FBG >140 mg/dl; impairment of renal function (creatinine >1.8 mg/dl, nephrotic syndrome or other renal disease); history of hepatic disease; treatment with psyllium or other fiber-based laxatives unless on a stable regimen for at least 4 weeks; treatment with oral corticosteroids.
Dosing	Placebo: n= 17; Ez - mg: n= 17; Ez - mg: n= 20; Ez 10 mg: n= 18; Ez - mg: n= 16; Ez - mg: n= 18; and lovastatin 40 mg: n= 18; Ez was to be dosed once daily in the morning before breakfast
Duration	Total of 20-28 weeks: 8-16 weeks no-treatment washout (C96-411); 4 weeks single-blind placebo run-in and 8 weeks of double-blind treatment (C96-345)

PK	Determination of plasma total and unconjugated ezetimibe levels at week 8, the day after the last scheduled dose of study medication.
Efficacy endpoints and timepoints	1^0: direct LDL-C: weeks -4, -2, 0, 2, 4 and 8; 2^0: key secondary: calculated LDL-C, TC, TG and HDL-C: weeks -16/-8, -6, -4, -2, 0, 2, 4 and 8; other 2^0: HDL_2-C, HDL_3-C, Apo A_1, Apo B and Lp(a): weeks 0 and 8
Efficacy analyses	1^0: percent change from baseline to endpoint in direct LDL-C for Ez – mg vs. placebo; if the difference was significant, other comparisons between active treatments and placebo could be made. 2^0: % change from baseline for calculated and direct LDL-C, HDL-C, TC, and TG after 2, 4, and 8 weeks of treatment, and for subfractions HDL_2-C, HDL_3-C, Apo A_1, Apo B and Lp(a) at end of treatment. PK analysis: summary statistics (mean, standard deviation and variability) were to be provided for the trough hour. Analysis of variance models were to be used to compare the plasma levels of the treatment groups. Regression techniques were to be used to explore the relationship between dose and plasma concentration.

2. C98-010: "Pivotal" Dose-Response Study:

Title	A Phase II Double-Blind Dose-Response Investigation of the Efficacy and Safety of Four Doses of SCH 58235 Compared With Placebo in Subjects With Primary Hypercholesterolemia
Study design	Randomized, multicenter, double-blind, fixed-dose, balanced-parallel-groups
Objectives	1^0: to confirm the efficacy and safety of a range of doses as determined by a pilot study (C96-411/C96-345) of SCH 58235 compared to placebo in lowering LDL-C when administered orally, once a day for 12 weeks, to subjects with primary hypercholesterolemia; 2^0: to determine the dose-response relationship of the LDL-C lowering effect of SCH 58235
Sample size	243 subjects, 139 men and 104 women, aged 28-75 years with 46-52 subjects in each of 5 treatment groups
Inclusion criteria	Otherwise healthy subjects with primary hypercholesterolemia; calculated LDL-C 130-250 mg/dl (amended after finalization of the protocol from LDL-C lower limit of 130 mg/dl to 160 mg/dl) and TG $\leq$300 mg/dl; NCEP Step 1 diet; adequate washout of previous lipid-lowering medication (nicotinic acid, resins, statins, and other agents such as garlic, fish oils, or other supplements being taken to alter lipid levels: 6 weeks, fibric acid derivatives: 12 weeks and probucol: 1 year)

Exclusion critera	Among the exclusion criteria were: HoFH; non-type II hypercholesterolemia; CHF NYHA Class III and IV; arrhythmia requiring medication; BP >160/95; MI; coronary artery bypass surgery or angioplasty within 6 months of study entry; history of unstable or severe angina pectoris or peripheral artery disease; diabetes mellitus requiring medication (diet allowed); FBG >126 mg/dl; impairment of renal function (creatinine >2.0 mg/dl, nephrotic syndrome or other renal disease); history of hepatic disease including AST or ALT >1.5x ULN; treatment with psyllium or other fiber-based laxatives unless on a stable regimen for at least 4 weeks; treatment with oral corticosteroids; subjects previously randomized to C96-345.
Dosing	Placebo: n= 52; Ez — mg: n= 47; Ez - mg: n= 49; Ez - mg: n= 49 and Ez 10 mg: n= 46
Duration	Total up to 28 weeks: 10 weeks of no-treatment washout, if needed; 6 weeks single-blind placebo run-in; and 12-weeks double-blind treatment
PK	Determination of plasma total and unconjugated ezetimibe levels at week 12, the day after the last scheduled dose of study medication.
Efficacy endpoints and timepoints	1^0: direct LDL-C at weeks -4, -2, 0, 1, 2, 4, 8 and 12; 2^0: key secondary: calculated LDL-C, TC, TG and HDL-C: weeks -16/-8, -6, -4, -2, 0, 1, 2, 4, 8 and 12; other 2^0: HDL_2-C, HDL_3-C, Apo A_1, Apo B and Lp(a): weeks 0 and 12
Efficacy analyses	1^0: percent change from baseline to endpoint in direct LDL-C. The primary efficacy analysis was to be based on a linear trend test of the treatment means, obtained from a two-way analysis of variance modelthat extracted sources of variation due to treatment and center. Because of the small number of subjects enrolled at each center, the treatment by center interaction was not formally tested. If the trend test was significant, pairwise treatment comparisons between the active treatment arms and placebo were to be evaluated using the least-square-means procedure. 95% CI were to be provided for the primary efficacy variable. Analyses at each time point were also to be provided. 2^0: the secondary variables were also to be expressed as percent change from baseline and compared among the treatment groups at each time point and at study endpoint, using the analysis of variance model specified above. PK analysis: summary statistics (mean, standard deviation and variability) were to be provided for the trough hour.

3. C98-258: Dose-Regimen Study:

Title	A Double-Blind Investigation of the Efficacy and Safety of Morning Versus Evening Dose of Two Doses of SCH 58235 Compared With Placebo in Subjects With Primary Hypercholesterolemia
Study design	Randomized, multicenter, double-blind, fixed-dose, balanced-parallel-groups

Objectives	1^0: to confirm the efficacy and safety of two doses of SCH 58235 compared to placebo in lowering LDL-C when administered orally, once a day for 12 weeks, to subjects with primary hypercholesterolemia; and to determine whether the effect of SCH 58235 dosed in the evening differs from its effect when dosed in the morning
Sample size	189 subjects, 89 men and 100 women, aged 22-75 years with 36-40 subjects in each of 5 treatment groups
Inclusion criteria	Otherwise healthy subjects with primary hypercholesterolemia; calculated LDL-C 130-250 mg/dl and TG $\leq$300 mg/dl (amended after finalization of the protocol from LDL-C lower limit of 130 mg/dl to 160 mg/dl); NCEP Step 1 diet; adequate washout of previous lipid-lowering medication (nicotinic acid, resins, statins, and other agents such as garlic, fish oils, or other supplements being taken to alter lipid levels: 6 weeks, fibric acid derivatives: 12 weeks and probucol: 1 year)
Exclusion critera	Among the exclusion criteria were: HoFH; non-type II hypercholesterolemia; CHF NYHA Class III and IV; arrhythmia requiring medication; BP >160/95; MI; coronary artery bypass surgery or angioplasty within 6 months of study entry; history of unstable or severe angina pectoris or peripheral artery disease; diabetes mellitus requiring medication (diet allowed); FBG >126 mg/dl; impairment of renal function (creatinine >2.0 mg/dl, nephrotic syndrome or other renal disease); history of hepatic disease including AST or ALT >1.5x ULN; treatment with psyllium or other fiber-based laxatives unless on a stable regimen for at least 4 weeks; treatment with oral corticosteroids; subjects previously randomized to C96-345.
Dosing	Placebo: n= 36; Ez ~ mg AM: n= 35; Ez ~mg PM: n= 40; Ez 10 mg AM: n= 36 and Ez 10 mg PM: n= 36. Ezetimibe ~mg or 10 mg was dosed once daily before a morning meal or at bedtime (placebo taken at alternate times)
Duration	Total up to 28 weeks: 10 weeks of no-treatment washout, if needed; 6 weeks single-blind placebo run-in; and 12-weeks double-blind treatment
PK	Blood samples were collected at the end of treatment (week 12) for analysis of steady-state pharmacokinetics of ezetimibe.
Efficacy endpoints and timepoints	1^0: direct LDL-C at weeks -4, -2, 0, 1, 2, 4, 8 and 12; 2^0: key secondary: calculated LDL-C, TC, TG and HDL-C: weeks -16/-8, -6, -4, -2, 0, 1, 2, 4, 8 and 12; other 2^0: HDL_2-C, HDL_3-C, Apo A_1, Apo B and Lp(a): weeks 0 and 12

Efficacy analyses	1^0: percent change from baseline in direct LDL-C at endpoint. The primary efficacy comparisons were to be Ez 10 mg AM versus placebo and Ez 10 mg PM versus placebo at study endpoint, with the Bonferroni correction for multiplicity applied, adjusted for one interim analysis. If both of these comparisons were significant ($p < 0.025$), Ez 10 mg AM was to be compared with Ez 10 mg PM at the 0.05 significance level, adjusted for the interim analysis. If these comparisons were statistically significant, the same strategy was to be then applied to Ez—mg AM and PM. All analyses were to be performed using an analysis of variance model extracting sources of variation due to treatment and center. Because of the small number of subjects enrolled at each center, the treatment by center interaction was not formally tested. Pairwise comparisons were performed using the least-square-means procedure. 95% CI were to be provided for the primary efficacy variable. Analyses at each time point were also to be provided. 2^0: the secondary variables were also to be expressed as percent change from baseline and compared among the treatment groups at each time point and at study endpoint, using the analysis of variance model specified above. PK analysis: summary statistics (mean, standard deviation and variability) were to be provided for the trough hour

PHASE III STUDIES:

MONOTHERAPY TRIALS: P00474, P00475 and LONG-TERM EXTENSION STUDY: P00476:

	P00474 + P00475	P00476
Title	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 MG Compared With Placebo In Subjects With Primary Hypercholesterolemia	Long-Term, Open-Label, Safety and Tolerability Study of Ezetimibe (SCH 58235) in Subjects With Primary Hypercholesterolemia: Interim Report
Study design	Phase 3, randomized, multicenter (U.S. only), double-blind, fixed-dose, unbalanced-parallel-groups (3:1, ezetimibe to placebo) study in subjects with primary hypercholesterolemia adhering to a NCEP Step I or stricter diet	Ongoing, phase III, multicenter (113 centers in the U.S.), open-label extension study of P00474 and P00475

Primary objective	efficacy (effect on direct LDL-C) and safety of ezetimibe in subjects with primary hypercholesterolemia	Long-term safety and tolerability of ezetimibe 10 mg/day for up to 24 months in subjects with primary hypercholesterolemia; amended: long-term safety of ezetimibe alone or combined with statin
Secondary objectives	Evaluate the change from baseline in other lipid variables: calc. LDL-C, TC, TG, HDL-C, HDL-C subfractions, Apo A-1, Apo B and Lp(a).	Evaluate the proportion of subjects achieving NCEP ATP II target LDL-C levels; Assess the mean percentage reduction of LDL-C levels , while on ezetimibe monotherapy or coadministered with simvastatin or lovastatin; Amended: mean % decrease in LDL-C, TC, HDL-C and TG on ezetimibe $\pm$ statin

Sample size	1,719 subjects (831 men and 888 women) (1,288 subjects on ezetimibe: 431 on placebo)	1582/1719 (92%) of subjects completing the 12-week double-blind treatment phase of P00474 or 475. Of these 1,582 subjects, 1,310 subjects enrolled in P00476. An additional 4 subjects indicated that they did not intend to enroll in P00476 but did. From this total of 1,316 subjects who enrolled into study P00476, 3 did not receive treatment in P00476. Therefore, 1,313 subjects rec'd treatment in P00476. (Note: 1,288 subjects rec'd their first dose of ezetimibe in P00474 or P00475 and 336 rec'd their first dose of ezetimibe in P00476. Therefore, 1,624subjects (795 male and 829 female, aged 18-86 years) rec'd ezetimibe in P00474/475 or 476. Of these 1,624 subjects, 1,094 received only ezetimibe in P00474/475/476 and in the remaining 530 subjects, simvastatin or lovastatin was added to ezetimibe therapy).
Inclusion criteria	Adults aged 18-86 years; calc. LDL-C 130-250 mg/dl; Tg $\leq$ 350 mg/dl; adequate washout of previous lipid-lowering medication[a]	Subjects who completed the 12-week double-blind portion of P00474 or P00475 and were willing to observe the NCEP Step 1 diet for the duration of the study (note: the study did not require maintenance of diet diaries)

Exclusion criteia	Pregnant/lactating women and subjects with certain concomitant illnesses or taking certain prohibited medications[c]	Subjects who discontinued P00474 or P00475 due to adverse events or poor compliance; pregnant/lactating women; prohibited concomitant meds: oral cortocosteroids, cyclosporine, lipid-altering agents other those required by the study; and, for subjects on statins, concomitant use of agents that might interfere with or induce the CYP3A4 isoenzyme of the cytochrome P450

Dosing	Ezetimibe 10 mg/day or placebo	Ezetimibe 10 mg/day. If target LDL-C levels had not been reached after at least 4 weeks, subjects were to receive, in randomized fashion, either simva 10 mg or lova 10 mg. At ≥4 week intervals, the statin dose could be doubled to a maximum of 40 mg. Amendment dated 11/22/00, after study start: -Subjects already receiving ezetimibe + lova or simva were to continue on this regimen with the statin dose titrated to target LDL -The maximum dose of simva was 80 mg rather than 40 mg -Dosing was to proceed as follows for subjects on ezetimibe alone for ≥4 weeks as of the 11/22/00 amendment: *If LDL-C ≤130 mg/dl: continue ezetimibe monotherapy; *If LDL-C >130 to ≤145 mg/dl: add simva 10 mg/day to ezetimibe; *If LDL-C >145 mg/dl: add simva 20 mg/day to ezetimibe -Subjects assigned to receive simva per these criteria but refusing to take it, could continue in the study at the discretion of the investigator
Study duration	2-12 weeks no-treatment washout; 4-8 weeks single-blind placebo run-in; 12 weeks double-blind treatment	24 months

Efficacy endpoints & timepoints for measurement	1^0: % change in direct LDL-C from baseline to endpoint; 2^0: % change from baseline in calc. LDL-C, HDL-C, TC, and TG after 2, 4, 8 and 12 weeks of rx., and for subfractions HDL_2-C and HDL_3-C, Apo A-1, Apo B, and Lp(a) at endpoint	Calculated LDL-C, TC, HDL-C and TG: months 0 (week 12 of P00474/475), 1, 3, 6, 9, 12, 18 and 24; Direct LDL-C: as above but not at months 9 and 18; If statin therapy was added or titrated upward: measure calc. LDL-C, TC, HDL-C and TG at weeks 2, 4 and 12; Amendment: if statin is added, additional visits will be at 6 and 12 months from the start of statin therapy.

Efficacy analyses	Two-way ANOVA model that extracts sources of variation due to treatment and center for the change in direct LDL-C. The 1^0 efficacy analysis will compare the mean % Δ from baseline to endpoint in direct LDL-c between eze and placebo. An estimate of the treatment effect (eze minus placebo) and its 95% CI will be obtained using least square means. 2^0 efficacy variables expressed as mean % Δ from baseline to endpoint will be compared among rx groups at each time point, using ANOVA. Also, the # (%) of subjects achieving an indicated % reduction in direct LDL-c from baseline to endpoint will be computed for the eze and placebo groups (≥15% reduction= responder; other cut-offs: <5%, 5-<15%, 15-<25%; 25-<35% and ≥35%). Proportion of subjects achieving NCEP target LDL-c based on risk factors or presence of CAD at baseline will be computed for eze and placebo treatment groups.	For this interim report (data cut-off: July 15, 2001), 4 lipid variables, calculated LDL-C, TC, HDL-C and TG, were examined using summary statistics. The change and the % change from baseline to endpoint were examined for each variable. The 1^0 timepoints are the study endpoint (each subject's last lab value) and the monotherapy endpoint (last lab value when patient was receiving monotherapy). In addition to these endpoints, the data will be summarized based upon duration of exposure to rx. (e.g. 3, 6, 12 and 24 months). • Descriptive statistics (mean ± S.D.) will be provided for the % Δ from baseline for LDL-c, TC, calc. LDL-c, HDL-c and Tg. • The proportion of subjects achieving target LDL-c stratified by baseline LDL-c and risk factors will be summarized. The above summaries will be provided for all subjects enrolled, for the monorx. chort and for subjects who received ezetimibe + statin.

a= nicotinic acid: 6 weeks; bile-acid binding resins: 6 weeks; statins: 6 weeks; fibric acid derivatives: 12 weeks; probucol: 1 year; and garlic, fish oil, plant stanols and other agents or supplements administered to lower lipid levels: 6 weeks unless PK necessitates a longer washout.
b= total cholesterol
c= see lists below:

CONCOMITANT ILLNESSES

1. Congestive heart failure NYHA Class III or IV.
2. Uncontrolled cardiac arrhythmias.
3. Myocardial infarction, coronary bypass surgery or angioplasty within 6 months of study entry.

4. Unstable or severe peripheral artery disease within 3 months of study entry.
5. Unstable angina pectoris.
6. Disorders of the hematologic, digestive or central nervous systems including cerebrovascular disease and degenerative disease that would limit study evaluation or participation.
7. Uncontrolled (as determined by HbA1c) or newly diagnosed (within 1 month of study entry) diabetes mellitus.
8. Uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins. Clinically euthyroid subjects on replacement doses of thyroid hormone are eligible for enrollment.
9. Known impairment of renal function (creatinine >2.0 mg/dl), dysproteinemia, nephrotic syndrome or other renal disease (24 hour urinary protein 3+ or 1 gram).
10. Active or chronic hepatobiliary or hepatic disease (Subjects with AST or ALT >2 times the upper limit of the central laboratory reference range will be excluded).
11. Subjects who are known to be HIV positive.
12. Subjects with coagulopathy (PT or PTT at Visit 2 >1.25 times control). a

PROHIBITED CONCOMITANT MEDICATIONS

1. Lipid-altering agents for the whole duration of the study.
2. Oral corticosteroids.
3. Cardiovascular drugs such as: beta blockers, calcium channel blockers, ACE inhibitors, nitrates or α-adrenergic blockers or thiazide diuretics will be allowed, provided the dose remains constant for the duration of the study and the subject has received a stable dose for eight weeks before the initial qualifying LDL-C (Q1) level is drawn. Aspirin up to 325 mg/day is permitted. In addition, aspirin is allowed as a p.r.n. concomitant medication.
4. Treatment with psyllium or other fiber-based laxatives unless treated with a stable regimen for at least four weeks before initial qualifying lipid determination. Dose must remain constant throughout the study period.
5. Treatment with orlistat.
6. Treatment with cyclosporine.
7. Use of any investigational drugs within 30 days of study entry.

a: Protocol specified PT "and" PTT, but "or" was the intended decision mechanism.

FACTORIAL CO-ADMINISTRATION TRIALS: P00679 (LOVASTATIN), P00680 (SIMVASTATIN), P00691 (PRAVASTATIN) and P00692 (ATORVASTATIN):

Title	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Lovastatin, Simvastatin, Pravastatin or Atorvastatin Compared with Placebo in Subjects with Primary Hypercholesterolemia
Study design	Phase 3, randomized, double-blind, placebo-controlled, balanced, parallel-group
1^0 objective	To evaluate the efficacy (effect on direct LDL-C) and safety of ezetimibe co-administered with statin in subjects with primary hypercholesterolemia
2^0 objectives	To evaluate the Δ from baseline in other lipid variables (see 2^0 efficacy endpoints); to determine the proportion of subjects achieving NCEP Adult Treatment Panel (ATP) II target goals for LDL-C; perform subgroup analyses (based on age, race, gender, etc.); and perform exploratory analyses[a].
1^0 Hypothesis	Co-administration of ezetimibe 10 mg/day with a given statin (pooled across all doses) will result in a significantly greater reduction in LDL-C when compared to that given statin administered alone (pooled across all doses) and ez alone.

Total sample size & rx. gps (dosing was once daily in the evening without stipulation to food because the previous bioavailability study did not indicate a food effect)	Lova (L):548 subj Placebo 64 Ez. 72 L 10mg 73 Ez + L 10mg 65 L 20mg 74 Ez + L 20mg 62 L 40mg 73 Ez + L 40mg 65	Simva(S):668 sub Placebo 70 Ez 61 S 10mg 70 Ez + S 10mg 67 S 20mg 61 Ez + S 20mg 69 S 40mg 65 Ez + S 40mg 73 S 80mg 67 Ez + S 80mg 65	Prava (P):538 sub Placebo 65 Ez 64 P 10mg 66 Ez + P 10mg 71 P 20mg 69 Ez + P 20mg 66 P 40mg 70 Ez + P 40mg 67	Atorva(A):628 su Placebo 60 Ez 65 A 10mg 60 Ez + A 10mg 65 A 20mg 60 Ez + A 20mg 62 A 40mg 66 Ez + A 40mg 65 A 80mg 62 Ez + A 80mg 63
Inclusion criteria	Adults aged 18-87 years; calc. LDL-C 145-250 mg/dl; Tg ≤ 350 mg/dl; NCEP adequate washout of previous lipid-lowering medication[b]. (Note: lower cut-off for LDL-C was amended on 4/18/00 from ≥ 160 to ≥145 mg/dl).			
Exclusion criteria	Pregnant/lactating women and subjects with certain concomitant illnesses or taking certain prohibited medications[c]			
Dosing	Ezetimibe 10 mg/day; Statin dose: see above under sample size and rx. groups. All medications were taken orally with the evening meal.			
Duration	2-12 weeks washout of lipid-lowering agents; 4 weeks single-blind placebo run-in; 12 weeks double-blind investigational treatment.			
PK	Ez, lova and OH-lova at week 12	Ez: total and unconjugated at week 12	Not applicable	Ez: total and unconjugated at week 12
Efficacy endpoints and timepoints during the 12-week active rx. period	1^0: % change in direct LDL-C from baseline to endpoint; 2^0: % change from baseline to endpoint in calc. LDL-C, HDL-C, TC, TG, non-HDL-C, HDL_2-C, HDL_3-C, Apo A-1, Apo B, Lp(a), LDL/HDL and TC/HDL. Timepoints for measurement during the 12-week active treatment period: Direct and calculated LDL-C, TC, HDL-C and TG: weeks 0, 2, 4, 8 and 12; Apo A-1, Apo B, Lp(a), HDL_2-C and HDL_3-C: weeks 0 and 12.			
Efficacy analyses	The primary efficacy analysis was performed using a two-way ANOVA model that extracts effects due to dose (statin: 0-80 mg), treatment (ez 10mg, ez placebo), and dose-by-treatment interaction for the % Δ from baseline in direct LDL-C at endpoint (ITT). The comparisons for a given statin were: ez + statin (all doses) vs. statin (all doses) and ez + statin (all doses) vs. ez. Secondary analyses: all with respect to LDL-C ↓: ez vs. placebo; ez+statin vs. statin by a given statin dose and by the next higher statin dose (e.g. ez+lova 10 mg vs. lova 20mg).			

a= the following subgroups were to be evaluated in an exploratory manner based on NCEP ATP III guidelines: Baseline TG (<150, ≥150 mg/dl); baseline HDL-C (<40, ≥40 mg/dl).
b= nicotinic acid: 6 weeks; bile-acid binding resins: 6 weeks; statins: 6 weeks; fibric acid derivatives: 12 weeks; probucol: 1 year; and garlic, fish oil, plant stanols and other agents or supplements administered to lower lipid levels: 6 weeks unless PK necessitates a longer washout.
c= see lists below:

PROHIBITED CONCOMITANT ILLNESSES

1. Congestive heart failure New York Heart Association (NYHA) Class III or IV.
2. Uncontrolled cardiac arrhythmias.
3. Myocardial infarction, coronary bypass surgery or angioplasty within 6 months of study entry.
4. Unstable or severe peripheral artery disease within 3 months of study entry.
5. Unstable angina pectoris.
6. Disorders of the hematologic, digestive or central nervous systems including cerebrovascular disease and degenerative disease that would limit study evaluation or participation.
7. Uncontrolled (as determined by glycosylated hemoglobin HbA_{1c}) or newly diagnosed (within 1 month of study entry) diabetes mellitus.
8. Uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins. Clinically euthyroid subjects on stable replacement doses of thyroid hormone are eligible for enrollment.
9. Known impairment of renal function (plasma creatinine >2.0 mg/dL), dysproteinemia, nephrotic syndrome or other renal disease (24-hour urinary protein 3+ or 1 gram).
10. Active or chronic hepatobiliary or hepatic disease (subjects with AST or ALT >2 times the upper limit of the central laboratory reference range will be excluded).
11. Subjects who are known to be HIV positive.
12. Subjects with known coagulopathy (PT or PTT at Visit 2 >1.25 times control).

PROHIBITED CONCOMITANT MEDICATIONS

1. Lipid-altering agents, other than study drugs for the whole duration of the study.
2. Corticosteroids.
3. Cardiovascular drugs such as: beta blockers, calcium channel blockers, ACE inhibitors, nitrates or α-adrenergic blockers or thiazide diuretics **will be allowed**, provided the dose remains constant for the duration of the study and the subject has received a stable dose for at least 8 weeks before the initial qualifying LDL-C (Q1) level is drawn. Aspirin up to 325 mg/day is permitted. In addition, aspirin is allowed as a prn concomitant medication.
4. Treatment with psyllium or other fiber-based laxatives unless treated with a stable regimen for at least 4 weeks before initial qualifying lipid determination. Dose must remain constant throughout the study period.
5. Treatment with troglitazone (Rezulin) or other thiazolidinedione antidiabetic agents unless treated with a stable regimen for at least six weeks before initial qualifying lipid determinination. Dose must remain constant throughout the study period.
6. Treatment with cyclosporine.
7. Use of any investigational drugs within 30 days of study entry.
8. Treatment with agents with known drug interaction with the given statin. For lovastatin, simvastatin and atorvastatin, examples include antifungal azoles (itraconazole and ketoconazole), macrolide antibiotics (erythromycin and clarithromycin) and nefazodone; for pravastatin, erythromycin. In addition, treatment with other agents that may interfere with or induce the CYP3A4 isoenzyme of the cytochrome P450 system (see **Appendix**) should be avoided when lovastatin, simvastatin or atorvastatin are used.

APPENDIX
DRUGS/AGENTS THAT MAY INTERFERE WITH OR INDUCE THE CYP3A4 ISOENZYME OF THE CYTOCHROME P450 [a]

Generic Name Examples of Trade Names

Acetaminophen Tylenol ®
Alprazolam Xanax ®
Amiodarone Cordarone ®/Pacerone ®
Amitriptyline Elavil ®/Endep ®
Astemizole Hismanal ®
Betamethasone Celestone ®
Carbamazepine Tegretol ®
Cimetidine Tagamet ®
Cisapride Propulcid ®
Clarithromycin Biaxin ®
Clotrimazole Lotrimin ®/Mycelex ®
Codeine Codeine ®
Cyclosporin Neoral ®/Sandimmune ®
Cyclophosphamide Cytoxan ®

Danazol Danocrine ®
Dapsone Dapsone ®
Dexamethasone Dalalone ®/Decadron ®/Dexacort ®/Neodecardon ®
Dextromethorphan Robitussin ®/Sucrets ®
Diazepam Valium ®
Digoxin Lanoxin ®
Diltiazem Cardizem ®/Dilacor ®
Disopyramide Norpace ®
Docetaxel Taxotere ®
Doxepin Sinequan ®
Enalapril Vasotec ®
Ergotamine Ergostat ®
Erythromycins E-mycin ®/ERYC ®/Ery-Tab ®/PCE ®/Ilosone ®/EES ®/
Iotycin Gluceptate ®/Erythrocin ®
Estrogen Premarin ®/Estrace ®/Ogen ® Oral Contraceptives
Ethosuximide Zarontin ®
Felodipine Plendil ®
Fexofenadine Allegra ®
Fluoxetine Prozac ®
Flutamide Eulexin ®
Fluvoxamine Luvox ®
Fluconazole Diflucan ®
Glutethimide Cytadren ®
Griseofulvin Fulvicin ®
Hydrocortisone Cortef ®/SoluCortef ®
Imipramine Tofranil ®
Indinavir Crixivan ®
Isoniazid INH ®
Isotretinoin Accutane ®
Itraconazole Sporanox ®
Ketoconazole Nizoral ®
Lidocaine Xylocaine ®
Loratadine Claritin ®
Methyl-Prednisolone Medrol ®
Metronidazole Flagyl ®
Mibefradil Posicor ®
Midazolam Versed ®
Nefazadone Serozone ®
Nelfinavir Viracept ®
Nifedipine Procardia ®/Adalat ®
Omeprazole Prilosec ®
Paclitaxel Paxene ®/Taxol ®
Phenobarbital Phenobarbital ®
Phenylbutazone Phenylbutazone ®
Phenytoin Dilantin
Pimozide Orap ®
Prednisolone Hydeltrasol ®/Pediapred ®/Prelone ®
Prednisone Deltazone ®
Primidone Mysoline ®
Propafenone Rythmol ®
Quinidine Cardioquin ®/Quinaglute ®
Quinine Quinine ®
Rifabutin Mycobutin ®
Rifampicin (Rifampin) Rifadin ®
Ritonavir Norvir ®
Saquinavir Invirase ®/Fortevase ®
Sertraline Zoloft ®
Tacrolimus Prograf ®
Tamoxifen Nolvadex ®
Terfenadine Seldane ®

Theophylline Aminophylline ®/Slo-bid ®/Theo-Dur ®
Tretinoin (retinoic acid) Retin-A ®
Triamcinolone Aristorcort ®/Aristospan ®
Triazolam Halcion ®
Troglitazone Rezulin ®
Verapamil Calan ®/Isoptin ®
Warfarin Coumadin ®
Zafirlukast Accolate ®
Zileuton Zyflo ®
Grapefruit juice (naringenin)
[a] Please note that this list is not exhaustive.

ADD-ON STUDY: Protocol P02173

Title	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study To Evaluate the Lipid-Altering Efficacy, Safety, And Tolerability Of SCH 58235 When Added To Ongoing Therapy With An HMG-CoA Reducatase Inhibitor (Statin) In Patients With Primary Hypercholesterolemia, Known Coronary Heart Disease, Or Multiple Cardiovascular Risk Factors
Study design	Phase 3, multicenter, double-blind, randomized, placebo-controlled. At randomization, subjects whose LDL-C levels did not meet their treatment goal, were stratified based on whether their screening LDL-C was ≥18% or <18% compared to target levels[a]. Efforts were made to achieve a distribution of subjects taking statins of ~1/3 simvastatin, 1/3 atorvastatin and 1/3 all other statins.
1^0 objective	To evaluate the efficacy compared to placebo of adding ezetimibe 10 mg to ongoing statin therapy to reduce LDL-C in patients with primary hypercholesterolemia, known coronary artery disease, or multiple CV risk factors who have not yet reached NCEP ATP II target LDL-C levels[a] to statin alone.
2^0 objective	To assess the proportion of these patients who achieved NCEP ATP II target LDL-C levels after addition of ezetimibe versus placebo to ongoing statin monotherapy; to evaluate other lipid altering effects of adding ezetimibe to ongoing statin monotherapy and to evaluate the safety of coadministration (ezetimibe with statin).
1^0 hypothesis	The addition of ezetimibe 10 mg/day to ongoing statin monotherapy will result in a further reduction in LDL-C compared with placebo.
2^0 hypothesis	Addition of ezetimibe to ongoing statin monotherapy will result in a higher percentage of patients reaching NCEP ATP II target LDL-C compared with the addition of placebo and Coadministration therapy with ezetimibe and statin will have a safety profile similar to therapy with ezetimibe placebo
Sample size and rx. gps.	769 subjects (443 males and 326 females). There were 2 treatment groups: ezetimibe with 379 subjects and 390 ezetimibe placebo

Inclusion criteria	Adults ≥18 years diagnosed with primary hypercholesterolemia, multiple CHD risk factors, or established CHD or CHD equivalent disease (per NCEP ATP II guidelines) or diabetes mellitus. Subjects must have been on a stable and approved dose of statin as well as an NCEP cholesterol-lowering or similar diet for at least 6 weeks[b]. Subjects must have had a mean LDL-C calculated from 2 separate determinations during the screening phase at or above the LDL-C targets listed in the table below for their level of risk. Subjects with LDL-C levels below but close to the NCEP target levels were enrolled on a case-by-case basis with prior approval from the sponsor. Other inclusion criteria were: TG ≤ 350 mg/dl, ALT and AST levels <2x ULN and CPK <1.5x ULN.
Exclusion criteria	Pregnant/lactating women and subjects with certain concomitant illnesses or taking certain concomitant medications[c]
Dosing	Subjects were randomized in a 1:1 ratio to receive either ezetimibe 10 mg daily or matching ezetimibe placebo, to be taken concomitantly with the statin in use at screening. Diet and the statin and dose used by the subject at screening were to be maintained for the 8-week treatment phase of the study. Following the treatment phase, subjects entered a 6-week reversibility phase during which they were maintained on statin alone.
Duration	~15 weeks, which included a 1-week screening period, followed by 8-weeks of active double-blind treatment followed by a 6-week cholesterol reversibility phase. The objective of the reversibility phase was to assess the pharmacodynamics of plasma cholesterol reverting back to baseline after ezetimibe was discontinued, but the statin dose was maintained. (Note: data from the reversibility phase were not included)
PK	Not applicable
Efficacy endpoints & timepoints for measurement during the 8-week active treatment period and the 6-week follow-up period	1^0: mean % change in calculated LDL-C from baseline to endpoint in the group randomized to ezetimibe relative to the group randomized to placebo during ongoing statin therapy. 2^0: percentage of subjects in the ezetimibe + statin group who achieved NCEP ATP II target LDL-C levels at endpoint compared to the placebo + statin group; mean % changes from baseline in TC, TG and HDL-C to endpoint; other secondary efficacy measures were non-HDL-C, apo B, apo A-1, apo A-II, LDL/HDL, TC/HDL and CRP (C-reactive protein) Exploratory: percentage of subjects who achieved NCEP ATP II target LDL-C levels at endpoint. Timepoints for measurement: Calculated LDL-C, TC, HDL-C and TG: weeks 0, 2, 4, 8, 10, 12 and 14; Apo A-1, A-II, Apo B: weeks 0, 2, 4 and 8

Efficacy analysis	The data from the domestic study P02173 was pooled with that of an identical international study P02246 for analyses. The 1^0 efficacy variable, percent change in LDL-C from baseline was assessed by ANOVA using a model including terms for statin, stratum, region (domestic sites, international sites), and treatment. The key 2^0 efficacy parameter, percentage of subjects reaching NCEP target for LDL-C was assessed based upon a logistic regression model with terms for statin, stratum, region, treatment and baseline % difference from NCEP target. All significance tests were 2-tailed with $\alpha = 0.05$. Assuming that the standard deviation for the % change in LDL-C is 12, the study had a > 95% power to detect a 10 percentage point difference between subjects randomized to ezetimibe and those randomized to placebo.

a= NCEP ATP II guidelines recommend initiation of pharmacological therapy to lower LDL-C based on specific LDL-C levels and the presence or absence of clinically overt CHD or multiple CHD risk factors:

	LDL-C target level
Category I: no CHD; <2 CHD risk factors	<160 mg/dl
Category II: no CHD; ≥2 CHD risk factors	<130 mg/dl
Category III: CHD or CHD-equivalent disease (e.g. peripheral artery disease) or diabetes mellitus	≤100 mg/dl

Risk factors:

Positive:

Age (male ≥ 45 years; female ≥ 55 years or premature menopause without estrogen replacement therapy);

Family history of premature CHD (MI or sudden death before 55 years of age in father or other male first degree relative or before 65 years of age in mother or other female first degree relative);

Current cigarette smoking;

Hypertension (BP ≥ 140/90 or taking antihypertensive medication);

Low HDL-c (< 35 mg/dl or < 0.90 mmol/L);

Diabetes mellitus

Negative:

High HDL-c (≥ 60 mg/dl or ≥ 1.55 mmol/L).

18% Cut Points of LDL-C for Stratification:

Risk Category	Target LDL-C	<18% above target assigned to Stratum 1	≥18% above target assigned to Stratum 2
Category 1	<160 mg/dl	<189 mg/dl	≥189 mg/dl
Category 2	<130 mg/dl	<153 mg/dl	≥153 mg/dl
Category 3	≤100 mg/dl	<118 mg/dl	≥118 mg/dl

b= Subjects receiving regular maintenance doses of OTC lipid-lowering medications (e.g. fish oils, omega-3 fatty acid supplements, Cholestin, Benacol, or niacin <200 mg/day) or OTC products (e.g. psyllium, fiber-based preparations and phytosterols) could be enrolled provided they were on a stable dose for as least 6 weeks prior to visit 1 (week –1) and agreed to take the same preparation at an unchanged dose for the study duration (submitted March 26, 2001 as a protocol amendment).
c= for exclusion criteria see below:

Concomitant Medications (Prohibited)

- Lipid-altering agents (other than statins) during the 6 weeks preceding screening.
- Oral corticosteroids (unless the corticosteroids were for replacement therapy to treat pituitary/adrenal disease and patients were treated with a stable regimen for at least the 6 weeks preceding screening).
- Cardiovascular drugs such as beta blockers, calcium channel blockers, ACE inhibitors, nitrates digoxin; or alpha-adrenergic blockers or thiazide diuretics or anticoagulants like warfarin were allowed, provided the dose was expected to remain constant for the duration of the study and the patient has been on a stable dose for at least 6 weeks prior to Visit 1.
- Treatment with psyllium, other fiber-based laxatives, and other over-the-counter (OTC) therapies that affect serum lipids, unless treated with a stable regimen for at least 6 weeks before Visit 1 and the patient agreed to continue this regimen for the duration of the trial.
- Treatment with orlistat.
- Treatment with cyclosporine.
- Use of any investigational drugs within 30 days of study entry.
- Treatment with agents with known interactions with statins including antifungal azoles (itraconazole and ketoconazole), macrolide antibiotics (erythromycin and clarithromycin) and nefazodone. In addition, treatment with other potent agents that could significantly interfere with or induce the CYP 3A4 isoenzyme of the cytochrome P-450 system.

Concomitant Illnesses

Congestive heart failure NYHA Class III or IV.
Uncontrolled cardiac arrhythmias.
Myocardial infarction, coronary artery bypass surgery or angioplasty within 3 months of Visit 1.
Unstable or severe peripheral artery disease within 3 months of Visit 1.
Unstable angina pectoris.
Disorders of the hematologic, digestive or central nervous systems including cerebrovascular disease and degenerative disease that would limit study evaluation or participation.
Poorly controlled (HbA1c >9.0%) or newly diagnosed (within 3 months) diabetes mellitus, or change in antidiabetic pharmacotherapy (i.e., change

in dosage [with the exception of ?10 units of insulin] or addition of new medication) within 3 months of screening.
Uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins (i.e., secondary causes of hyperlipidemia). Clinically euthyroid patients on replacement doses of thyroid hormone are eligible for enrollment if TSH was within the normal range at screening by the central laboratory.
Impaired renal function (creatinine =2.0 mg/dL), nephrotic syndrome, or other renal disease.
Active or chronic hepatobiliary or hepatic disease and/or patients with AST/ALT =2 times the ULN.
Patients with screening CPK level =1.5 times the ULN unassociated with a clear history of trauma or severe exertion and documented by repeat measurement.
Patients who were known positive for human immunodeficiency virus
Cancer within the past 5 years (except for basal cell carcinoma).

Note: the protocol was amended on January 3, 2001 to discontinue from the study subjects with LDL-C <50 mg/dl on 2 consecutive occasions, 7 days apart, and they were to be followed until medically stable.

FAMILIAL HOMOZYGOUS HYPERCHOLESTEROLEMIA (FHH) PROTOCOL: P01030 AND THE 1 YEAR EXTENSION STUDY: P01417:

	P01030	P01417
Title	A Phase III Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia (HoFH)	Long-Term, Open-Label, Safety and Tolerability Study of Ezetimibe (SCH 58235) in Addition to Atorvastatin or Simvastatin in the Therapy of Homozygous Familial Hypercholesterolemia: Interim Evaluation
Study design	Phase III, multicenter (4 U.S. and 13 international centers), randomized, double-blind, double-dummy, parallel-group study	Ongoing, phase III, multicenter (4 U.S. and 9 international centers), open-label extension study
1^0 objective	To evaluate the efficacy and safety of ezetimibe 10 mg/day coadministered with atorvastatin or simvastatin in patients with FHH	To evaluate the long-term safety of ezetimibe 10 mg/day coadministered with atorvastatin or simvastatin 40-80 mg/day
2^0 objectives	To evaluate the % Δ from baseline in calculated LDL-C, TC, TG, HDL-C, HDL_2, HDL_3, Apo A-1, Apo B, Lp(a), LDL/HDL and TC/HDL-C	Not stated but inferred to be evaluation of long-term efficacy

1^0 hypothesis	Ezetimibe will produce additive LDL-C lowering when coadministered with statins in patients with FHH compared with statins alone	Long-term treatment of patients with FHH with ezetimibe 10 mg/day in conjunction with atorvastatin or simvastatin is safe and well tolerated
Sample size & Rx. groups	50 subjects (21M and 29F), aged 11-74 years, randomized 2:1 ezetimibe + statin 40/80 mg (n= 33) to statin 80 mg (n= 17). There were 6 treatment groups: atorva 80 mg, ez + atorva 40 mg, ez + atorva 80 mg, simva 80 mg, ez + simva 40 mg and ez + simva 80 mg	41 subjects, 24 women and 17 men, 11-74 years of age; treatment groups: ez 10 mg/day + atorva or simva (10-80 mg/day, titrated as needed)
Inclusion criteria	Subjects with FHH[a]; calc. LDL-C $\geq$ 100 mg/dl while receiving atorva or simva 40 mg; TG $\leq$350 mg/dl; NCEP step 1 diet or stricter, adequate wash-out of fibrates[b]	Only subjects completing P01030 qualified for entry. Subjects were required to adhere to the NCEP Step 1 diet or stricter for the duration of the study.
Exclusion criteria	Pregnant/lactating women and subjects with certain concomitant illnesses or taking certain concomitant medications[c]	Same as for P01030
Dosing	Open-label atorva or simva 40 mg during the lead-in period which was continued into the 12-week double-blind treatment period. See above for the 6 treatment groups during the 12-week treatment period.	The initial dose for all subjects was ezetimibe 10 mg/day + atorvastatin or simvastatin 40 mg. The statin dose was doubled to a maximum dose of 80 mg if an LDL-C target concentration of 100 mg/dl (NCEP ATP II criteria) was not achieved after $\geq$1 month of therapy. Additional study visits were scheduled 4 and 12 weeks after upward dose titration of statin.
Duration	6-14 week lead-in or pre-randomization phase[d] followed by a 12-week double-blind treatment period.	Up to 24 months
PK	The effect of atorva or simva on ezetimibe PK was assessed on plasma ez concentrations (total and unconjugated) obtained at week 12.	Not applicable

Efficacy endpoints and timepoints	1^0: % Δ from baseline in direct LDL-C at treatment endpoint; 2^0: % Δ from baseline to endpoint in calculated LDL-C, TC, TG, HDL-C, HDL_2, HDL_3, Apo A-1, Apo B, Lp(a), LDL/HDL and TC/HDL-C Timepoints for measurement during the 12-week double-blind treatment phase: direct and calc. LDL-C, TC, HDL-C and TG: weeks 0, 2, 4, 8 and 12; Apo A-1, Apo B, Lp(a), HDL_2-C and HDL_3-C: weeks 0 and 12 only.	Direct and calculated LDL-C, TC, TG and HDL-C; Timepoints for measurement: Calculated LDL-C, TC, HDL-C and TG: months 1, 3, 6, 9, 12, 18 and 24 and, also, after 4 and 12 weeks of upward statin dose titration; Direct LDL-C: baseline (week 12 of P01030) and months 12 and 24.
Efficacy analyses	The 1^0 efficacy analysis was the ez + statin 40/80 mg treatment group vs. statin 80 mg treatment group for the 1^0 efficacy endpoint. This analysis was performed using a two-way ANOVA that extracted sources of variation due to treatment (addition of ezetimibe) and statin for the % Δ from baseline in direct LDL-C at endpoint. 95% CI were provided for the 1^0 efficacy variable. Owing to the small number of subjects expected to be enrolled in each center, center effect and treatment by center interaction effect were not included in the model.	Descriptive statistics will be provided for the % change from baseline (week 12 of P01030) for LDL-C, TC, TG and HDL-C. Proportion of patients achieving target LDL-C levels will be summarized. The data will also be summarized based upon duration of exposure to treatment (e.g. 3, 6, 12 and 24 months).

a= FHH: diagnosed by genetic testing or clinically diagnosed by LDL-C ≥220 mg/dl on maximally tolerated lipid-lowering therapy and a <15% response to that therapy in addition to LDL-C >90 percentile in ≥2 first degree relatives and the presence of tendinous xanthomas within the kindred, and/or premature corneal arcus, and/or manifestations of premature CHD;
b= wash-out of fibrates only during the lead-in or prerandomization phase;
c= see lists below:

PROHIBITED CONCOMITANT ILLNESSES

1. Congestive heart failure NYHA Class III or IV.
2. Uncontrolled cardiac arrhythmias.
3. Myocardial infarction, coronary bypass surgery or angioplasty within 3 months of study entry.
4. Unstable or severe peripheral artery disease within 3 months of study entry.
5. Unstable angina pectoris.
6. Disorders of the hematologic, digestive or central nervous system including cerebrovascular disease and degenerative disease that would limit study participation.
7. Uncontrolled (as determined by HbA_1C) or newly diagnosed (within 1 month of study entry) diabetes mellitus.
8. Uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins. Clinically euthyroid subjects on replacement doses of thyroid hormone are eligible for enrollment.
9. Known impairment of renal function (creatinine >2.0 mg/dL), dysproteinemia, nephrotic syndrome or other renal disease (24 hour urinary protein ≥3+ or 1 gram).
10. Active or chronic hepatobiliary or hepatic disease. In addition, subjects with AST or ALT >2 times the upper limit of the central laboratory reference range will be excluded.
11. Subjects who are known to be HIV positive.
12. Subjects with coagulopathy (PT or PTT at Visit 2 >1.25 times control).

PROHIBITED CONCOMITANT MEDICATIONS

1. Fibric acid derivatives.
2. Oral corticosteroids.
3. Cardiovascular drugs such as: β-blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, nitrates, α-adrenergic blockers or thiazide diuretics will be allowed, provided the dose remains constant for the duration of the study and the subject has received a stable dose for eight weeks before the initial qualifying LDL-C (Q_1) level is drawn. Acetylsalicylic acid administered as a platelet aggregation inhibitor or analgesic is permitted.
4. Treatment with psyllium or other fiber-based laxatives unless treated with a stable regimen for at least 4 weeks before initial qualifying lipid determination. Dose must remain constant throughout the study period.
5. Treatment with orlistat.
6. Treatment with cyclosporine.
7. Treatment with troglitazone (Rezulin®) or other thiazolidinedione antidiabetic agents, unless treated with a stable regimen for at least 4 weeks before the initial qualifying lipid determination. Dose must remain constant throughout the study period.
8. Use of any investigational drugs within 30 days of study entry.
9. Treatment with agents with known drug interactions with simvastatin or atorvastatin including antifungal azoles (eg, itraconazole and ketoconazole), macrolide antibiotics (eg, erythromycin and clarithromycin) and nefazodone. In addition, treatment with other agents that may interfere with or induce the CYP3A4 isoenzyme of the cytochrome P450 system should be avoided.
10. Subjects receiving LDL-C apheresis may continue on this therapy provided that they are on a stable regimen (as defined by no alteration in the interval between LDL-C apheresis sessions for the 4 weeks prior to study entry) and lipid levels for study visits are drawn just prior to an apheresis treatment session. Subjects on a regimen of apheresis every two weeks should have a two-week interval between Visit 2 and Visit 3 (at which time Q_1 and Q_2 are drawn, respectively) so that the qualifying lipids can be drawn immediately prior to apheresis sessions. In addition, the interval between Visit 3 and Visit 4 should be 2 weeks so that all three baseline lipid values can be drawn just prior to LDL-C apheresis.
11. Subjects on a stable regimen of resin therapy (as defined by the same dose and regimen for at least 6 weeks prior to Q_1 [Visit 2]) may continue that therapy provided that the daily dose of study drug is taken at least 4 hours prior to administration of the resin or at least 4 hours following any resin dose. In addition, the dose of resin should be taken no less than 4 hours before and no less than 4 hours after administration of study drug.

d= during the pre-randomization phase or lead-in phase, patients must have demonstrated adequate stabilization of their lipid-lowering therapy (same dose and regimen) prior to the first qualifying lipid determination at week –2. For patients on statins, at least 4 weeks of therapy with either atorva or simva 40 mg was required; with at least 6 weeks between the last dose of

another statin or a higher dose of atorva or simva. For bile acid binding resins and nicotinic acid, the stabilization period was at least 6 weeks; probucol, 1 year; LDL-c apheresis, 8 weeks; 6 weeks for other agents that alter lipid levels such as garlic, fish oil and plant stanols; and 4 weeks for psyllium and other fiber-based laxatives. Patients on fibric acid derivatives required at least a 12 week wash-out period. If an approximately equal number of subjects had not been treated with atorva or simva prior to study entry, some subjects could be asked at visit 1 to switch to treatment with the other statin (i.e. either atorva or simva) for the duration of the study.

Note regarding P01030:
As noted above under "b", subjects on a stable regimen of resin therapy for at least 6 weeks were allowed to continue provided that the **daily dose of study drug was taken at least 4 hours before or after administration of the resin. This provision was included because of evidence that an interaction between ezetimibe and resins resulted in reduced uptake and efficacy of ezetimibe.**
Also, as noted above under "b", subjects on regular LDL apheresis prior to study entry were allowed to continue on that regimen during the study, provided that the interval between apheresis sessions was kept stable throughout the study. In these subjects, blood samples were collected for lipid/lipoprotein analyses immediately prior to their weekly/bi-monthly apheresis session, when LDL-C values were at their highest.

Note regarding P01417:
For P01417, an interim safety report was submitted to the NDA; efficacy was not evaluated (OR analyzed) in this interim report.

HOMOZYGOUS SITOSTEROLEMIA P02243 (centers within the U.S.) and P02257 (centers outside the U.S.):

Title	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 58235 (Ezetimibe) When Added to Current Regimen in Patients With Homozygous Sitosterolemia
Study design	Randomized, multicenter, double-blind, unbalanced-parallel-groups (4:1, ezetimibe 10 mg to placebo) comparison. Subjects were assigned to a stratum based on whether or not they were on treatment with bile salt binding resins.
1^0 objective	to assess the % Δ between baseline (defined as average of the values obtained on study day 1 and the one obtained 3-7 days prior to day 1) and endpoint (endpoint was defined as the average of values at weeks 6 and 8) in plasma sitosterol after double-blind treatment with ezetimibe
2^0 objective	to assess the % Δ relative to baseline in LDL-C and campesterol after double-blind treatment with ezetimibe; to compare changes in the efficacy endpoints between the two treatment groups; to evaluate the safety of ezetimibe in this patient population; Exploratory: to assess the % reduction in size of tendon xanthomas relative to baseline after double-blind treatment with ezetimibe

1^0 hypothesis	Treatment with ezetimibe in homozygous sitosterolemia patients with continued elevations of plasma sitosterol on their current regimens will provide reductions in plasma sitosterol, campesterol and LDL-C
Sample size and treatment groups	37 subjects, 24 women and 13 men, aged 9-72 years. 30 subjects received ezetimibe 10 mg/day and 7 received placebo
Inclusion criteria	Patients with homozygous sitosterolemia, who were ≥10 years of age, with an elevated plasma sitosterol level (>5 mg/dl) on their current regimen. Patients had to be on a stable regimen of treatment (e.g. statins, niacin, probucol, fibrates or psyllium) for this condition for at least 4 weeks prior to placebo run-in.
Exclusion criteria	Pregnant/lactating women; subjects with certain concomitant illnesses[a], and subjects on statins were excluded if they used or were deemed likely to use drugs known to interact with statins- e.g. antifungal azoles: itraconazole and ketoconazole, macrolide antibiotics, nefazodone and protease inhibitors
Dosing	ezetimibe 10 mg/day or placebo. Due to *in vivo* interaction between ezetimibe and cholestyramine [study P00776 which demonstrated a mean reduction of ~55% in total ezetimibe bioavailability (based on AUC) when these two drugs were administered one hour apart], the protocol, which was finalized on 11/28/00, was amended on 2/9/01. Subjects were either discontinued from resin therapy or their dose was reduced to once-daily (administered with the evening meal), if clinically appropriate. If these changes were not considered appropriate, ezetimibe was dosed at least 2 hours before or 4 hours after resins were administered (also see footnote "b")
Duration	Study duration was 12-16 weeks: 1-5 weeks screening period, 3-week single-blind placebo run-in period, 8-week double-blind treatment period
Efficacy endpoints and timepoints during the 8-week double-blind treatment period	1^0: plasma sitosterol; 2^0: LDL-C, campesterol; exploratory: xanthoma size; 3^0: LDL-sterols, HDL-sterols, total sterols, TG, Apo A-1 and Apo B; exploratory: size of xanthomas; Timepoints for measurement during the 8-week double-blind rx. period: Plant sterols and lipids: weeks 0, 2, 4, 6 and 8; Xanthoma measurements: weeks 0 and 8

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Efficacy Analyses	1^0: to assess the % Δ between baseline and endpoint in plasma sitosterol after double-blind treatment with ezetimibe. This was assessed using summary statistics and 95% CI (note: the one subject treated with apheresis therapy was excluded); if the strata (concomitant usage or not of a bile salt binding resin) was found to be significant ($p < 0.10$), least-squares were to be computed from the ANOVA model that included a term for the stratification variable; 2^0: within-group comparisons for the secondary parameters and differences between treatments were to be estimated using least-squares means from the ANOVA model with terms for treatment and strata; The assumption of normality was to be assessed by the Shapiro-Wilk statistic. If the assumptions were found not to hold, a non-parametric analysis using Turkey's normalized ranks was to be used to corroborate or supersede the parametric analysis. The standard error for the median was estimated as 1.075 times the interquartile range

a= see list below:

Illnesses
Congestive heart failure NYHA class III or IV.
Uncontrolled cardiac arrhythmias.
Myocardial infarction, coronary bypass surgery or angioplasty within 6 months of the screening visit (Visit 1).
Unstable angina pectoris or unstable or severe peripheral vascular disease.
Uncontrolled diabetes mellitus (Hb_{A1c}>1 0%). Patients with diabetes mellitus should be on a stable antihyperglycemic regimen for at least 4 weeks prior to the screening visit (Visit 1).
Uncontrolled endocrine or metabolic disease known to influence serum lipids or lipoproteins. Clinically euthyroid patients on stable replacement doses of thyroid hormone (on the same dose for at least 4 weeks prior to study entry and with TSH =1 0 IU/mL) are eligible for enrollment.
Uncontrolled hypertension (systolic BP >200 mm Hg and/or diastolic BP >11 0 mm Hg).
Creatinine >2.0 mg/dL at the screening visit (Visit 1), or active renal disease with significant proteinuria (1 mg albumin/mg creatinine).
Active acute or chronic hepatobiliary disease; AST or ALT >5 times the upper limit of normal of the reference laboratory at the screening visit (Visit 1).
Disorders of the hematologic, digestive (including malabsorptive disorders), or central nervous system including cerebrovascular disease and degenerative diseases that would limit study evaluation or participation.
Patients who are known to be HIV positive.

b= In an *in vitro* study, incubation of the labeled glucuronide metabolite with cholestyramine for 1 hour led to 92% binding. With increasing concentrations of bile salt (taurocholic acid) added to the test tube, as would be present in the GI tract, this binding decreased, reaching only about 10% with higher bile salt concentrations.

Note:

[ ]

C. Postmarketing Experience

Not applicable because the product has not been approved in any country.

D. Literature Review

The published literature was reviewed pertaining to therapeutic options for patients with homozygous sitosterolemia.

V. Clinical Review Methods

A. How the Review was Conducted

The review was conducted using both the paper and electronic copies of the NDA submitted by the sponsor.

B. Overview of Materials Consulted in Review

The individual study reports, the ISE and the Summmary of Efficacy were the primary materials consulted in review. Minutes from previous teleconferences and meetings with the sponsor were also consulted in review.

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Per section 8K of the NDA submission, steps taken by the sponsor to ensure collection of accurate and reliable data included selection of knowledgeable and experienced investigators and study centers; review of protocol procedures with the principal investigators and associated personnel assisting with the study; regular monitoring of study centers to confirm that the study was being conducted in accordance with the protocol and with adherence to the sponsor's standard operating procedures and applicable regulatory requirements; and the use of central laboratories for processing of laboratory test samples, where possible.

In addition, Schering-Plough Quality Assurance auditors conducted a quality assurance audit of selected study centers. The Division of Scientific Investigations (DSI) at FDA is also conducting a similar audit.

Quality control of the electronic database was accomplished by identification and correction of discrepancies prior to loading the data into the database and double-key entry of data using different operators. The resulting database was subjected to a standard checking program, which included range checks and checks for inconsistencies and logical errors. This standard checking program may have been supplemented by an additional set of study-specific checks. Random samples of adverse events, final status, and selected efficacy data from the database were verified against supporting documentation in the case report form. Detected errors were corrected and rechecked prior to finalizing the database.

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Per section 8K of the NDA submission, all clinical studies were conducted in compliance with good clinical practices. US clinical studies were conducted in compliance with the institutional review board regulations under 21 CFR 56 and the informed consent regulations under 21 CFR 50. International clinical studies were conducted in accordance with the principles of the Declaration of Helsinki concerning written informed consent and the rights of human subjects and with all applicable laws as required by the countries in which the studies were conducted.

E. Evaluation of Financial Disclosure

Both Merck & Co., Inc. and Schering Plough submitted finanacial disclosure information since the NDA represented a joint venture.

Financial information submitted by Merck pertained to the following studies:

1. A Multicenter, Double-Blind, andomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of SCH 58235 When Added to Ongoing Therapy with an HMG-CoA Reducatase Inhibitor (Statin) in Patients with Primary Hypercholesterolemia, Known Coronary Heart Disease, or Multiple Cardiovascular Risk Factors (Protocol 001);

2. A Multicenter, Double-Blind, andomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety and Tolerability of SCH 58235 When Added to Ongoing Therapy with an HMG-CoA Reducatase Inhibitor (Statin) in Patients with Primary Hypercholesterolemia, Known Coronary Heart Disease, or Multiple Cardiovascular Risk Factors (Protocol 002);

3. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 58235 When Added to Current Regimen in Patients with Homozygous Sitosterolemia (Protocol 003);

4. A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of SCH 58235 When Added to Current Regimen in Patients with Homozygous Sitosterolemia (Protocol 004);

5. A Phase III Double-Blind Efficacy and Safety Study of One Dose of SCH 58235 (10 mg) Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol 006);

6. A Phase III Double-Blind Efficacy and Safety Study of One Dose of SCH 58235 (10 mg) Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol 007);

7. Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Subjects with Primary Hypercholesterolemia (Protocol 008);

8. A Randomized, Double-Blind, Placebo-Controlled, Two-Period, Cross-Over Study to Evaluate Ezetimibe (SCH 58235) as an Inhibitor of Intestinal Cholesterol Absorption (Protocol 009);

9. A Phase III Double-Blind Efficacy and Safety Study of SCH 58235 (10 mg) in Addition to Lovastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol 010);

10. A Phase III Double-Blind Efficacy and Safety Study of SCH 58235 (10 mg) in Addition to Simvastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol 011);

11. A Phase III Double-Blind Efficacy and Safety Study of SCH 58235 (10 mg) in Addition to Pravastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol 012);

12. A Phase III Double-Blind Efficacy and Safety Study of SCH 58235 (10 mg) in Addition to Atorvastatin Compared to Placebo in Subjects with Primary Hypercholesterolemia (Protocol 013);

13. Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Addition to Simvastatin in Subjects with Primary Hypercholesterolemia who have Previously Completed the 12-Week Double-Blind Study (Protocol 014);

14. Long-Term Safety and Tolerability Study of SCH 58235 or Placebo in Addition to Simvastatin in Subjects with Primary Hypercholesterolemia (Protocol 015);

15. Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Addition to Pravastatin in Patients with Primary Hypercholesterolemia (Protocol 016); and

16. Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 (10 mg) or Placebo in Addition to Atorvastatin in Subjects with Primary Hypercholesterolemia (Protocol 017).

The following table summarizes the financial disclosure information submitted by Merck for the investigators of the above studies:

Summary of Investigators that Met the Definition of Clinical Investigator		
Investigator Category	Total Number	Comments
Grand Total Number of Investigators/Subinvestigators per Protocol and Site	3,854	1/3854 investigators was listed as a Merck & Co. employee
Total Number of Investigators/Subinvestigators Who Are Certified Regarding an Absence of Financial Arrangements per Protocol and Site	3,004 (78%)	
Total Number of Investigators/Subinvestigators Not Providing Information and Not Certified Per Protocol and Site	762 (20%)	Investigators no longer at site, unable to obtain information (n= 317 or 8%). Investigators not returning reqestred information (n= 445 or 12%)
Total Number of Investigators/Subinvestigators Not Certified Due to "Significant Payments of Other Sorts" or or Equity Interest per Protocol and Site	68 (2%)	Merck stated that they did not enter into any financial arrangement with their clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study. Also, bias was minimized by study design, e.g. double-blind, placebo-control, and multiple study sites.
Total Number of Investigators/Subinvestigators Receiving Payments Based on the Outcome of the Study per Protocol and Site	0	Merck stated that they did not enter into any financial arrangement with their clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the study.
Total Number of Investigators/Subinvestigators with Proprietary Interest in the Test Product or Company Per Protocol and Site	0	

The following table summarizes the financial disclosure information submitted by Schering Plough for the investigators of the following studies: P00474, P00475, P00679, P00680, P00691, P00692, P01030, P02173 (USA)/P02246 (International) and P02243 (USA)/P00257 (International):

Protocol	Number of Investigators for which Financial Cetification Was Not Received but sponsor's review of internal records, for domestic sites, showed no significant payments of any sort	Number of Investigators that have Certified that they have Not Entered into any Financial Arrangements with Schering Plough	Total
P00474	26	270	296
P00475	46	290	336
P00679	57	231	288
P00680	70	282	352
P00691	39	218	257
P00692	5	341	346
P01030	3[a]	47	50
P02173	90	373	463
P02243	13	46	59
Total	349 (14%)	2,098 (86%)	2,447 (100%)
a= sponsor's internal record review for domestic and international sites			

In these studies bias was minimized by study design, e.g. double-blind, placebo-control, and multiple study sites and by objective efficacy endpoints, i.e. plasma lipid levels.

Financial disclosure information was requested of Schering Plough for the non-U.S. sites participating in studies P00692, P02173 and P02243. In addition, financial disclosure information was requested for the following pivotal phase II studies: C96-411/C96-345, C98-010 and C98-258.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

In patients with primary hypercholesterolemia, Zetia monotherapy statistically significantly lowered LDL-C, TC and Apo B relative to baseline and to placebo. When coadministered with any of four HMG-CoA reductase inhibitors (lovastatin, simvastatin, pravastatin or atorvastatin) in patients with primary hypercholesterolemia, Zetia significantly reduced LDL-C, TC, TG and Apo B compared to the statin administered alone. On the other hand, Zetia signifcantly increased HDL-C relative to statin alone only when coadministered with lovastatin, simvastatin, pravastatin or atorvastatin. In addition, coadministration of Zetia with the lowest dose of statin tested, 10 mg, was as effective in reducing LDL-C as the highest dose of statin tested (40 mg for lovastatin and pravastatin and 80 mg for simvastatin and atorvastatin). When added to ongoing statin therapy in patients with primary hypercholesterolemia, CHD or multiple CV risk factors who had not met their target LDL-C goal, Zetia significantly reduced

LDL-C, TC, TG and Apo B and elevated HDL-C relative to statin alone. Maximal or near-maximal reductions in plasma LDL-C concentrations with ezetimibe monotherapy or coadministered with statins occurred within 2 weeks and were maintained throughout 8-12 weeks of double-blind treatment as well as through 8-12 months of open-label treatment.

With the exception of a race difference, reduction in LDL-C was consistent across all subgroups analyzed. The limited efficacy data available suggest decreased LDL-C lowering over time in some racial/ethnic groups but the small sample size confounds interpretation of this finding.

In patients with homozygous familial hypercholesterolemia, the addition of Zetia to ongoing statin therapy significantly reduced LDL-C and TC compared to increasing the dose of statin administered alone.

In patients with homozygous sitosterolemia with elevated plasma sitosterol levels on their current regimen, Zetia significantly reduced plasma sitosterol and campesterol levels relative to placebo.

In summary, the above data support the approval of Zetia administered as monotherapy or in combination with statin and as an adjunct to diet in patients with primary hypercholesterolemia. The data also suppport the approval of Zetia as an adjunct to statin and other lipid-lowering therapy in patients with homozygous familial hypercholesterolemia. Finally, the data support the approval of Zetia as adjunctive therapy in patients with homozygous sitosterolemia.

B. General Approach to Review of the Efficacy of the Drug

The review was conducted using both the paper and electronic copies of the NDA. Efficacy data obtained from the 12 Phase II/III completed double-blind, randomized, placebo- or active-control studies and the long-term, open-label extension study, P00476, were reviewed in detail using the individual study reports, the ISE and the Summary of Efficacy. Efficacy data were not provided for other ongoing studies.

C. Detailed Review of Trials by Indication

PHASE II STUDIES: EFFICACY ANALYSES- LIPID PARAMETERS

Dose Response of Plasma LDL-C Concentrations to Ezetimibe Monotherapy:

Summary of Mean Percent Changes (±SEM) in Plasma LDL-C Concentrations in Response to Monotherapy With Different Daily Doses of Ezetimibe for 8 to 12 Weeks (C96-411/345, C98-010 and C98-258)

Dose Group (mg)	Initial Dose-Ranging Study (C96-411/345) N= 16-20/group[a]	"Pivotal" Dose-Response Study (C98-010) N= 46-51/group[a]	Dose-Regimen Study (C98-258) N= 35-40/group[a]	
			AM	PM
Placebo	+3.8 ± 2.5	+4.3 ± 1.4	-4.9 ± 2.0[b]	
Ez —		-9.9 ± 1.5**		
Ez —	-14.6 ± 2.4**	-12.6 ± 1.5**		
Ez —	-15.7 ± 1.6**	-16.4 ± 1.4**	-16.7 ± 1.9**	-13.8 ± 1.9**
Ez 10	-16.4 ± 2.2**	-18.7 ± 1.5**	-17.5 ± 1.9**	-18.2 ± 1.9**
Ez —	-17.9 ± 2.0**			
Ez —	-20.0 ± 2.0**			
Lova 40 mg[c]	-31.8 ± 2.8**			

**p≤0.01 versus placebo;
a= values shown are least-squares (LS) means and standard errors of LS means (SEM);
b= combined results for AM and PM dosing;
c= the mean percent change from baseline on lovastatin 40 mg was as expected, based on product labeling, thus validating the study design

Comments on the above table:
Collectively, the results show that ezetimibe doses ranging from ——— mg daily for periods of 8 weeks or 12 weeks were significantly more effective than placebo in reducing plasma LDL-C concentrations ($p < 0.01$). The magnitude of LDL-C was directly related to the dose of ezetimibe. Daily doses — mg produced mean reductions in direct LDL-C of <15% from baseline to endpoint. At ~ mg/day, ezetimibe produced mean changes ranging from -13.8% to -16.7% across the 3 studies. At 10 mg/day, the mean changes ranged from –16.4% to –18.7%. Doses — mg resulted in an increase in response that was small relative to the increase in dose. At — mg/day, the highest dose tested, mean changes in plasma LDL-C concentrations were –20%. Similar efficacy was observed whether ezetimibe was taken in the morning or the evening.

Pairwise comparisons between ezetimibe doses, revealed significant differences between the — mg dose versus either of the two lowest doses (- mg and — mg) ($p < 0.05$). In C98-010, mean % changes in LDL-C were significantly greater for both the – mg and the 10 mg doses than for either of the two lowest doses — mg and ¬ mg) ($p < 0.05$). The significance of the differences between the — mg and 10 mg doses were evaluated using results pooled from the two 12-week studies, C98-010 and C98-258. As shown in the following table, mean % changes in plasma LDL-C concentrations were significantly greater with the 10 mg than the — mg dose ($p = 0.03$).

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Comparison of Mean Percent Changes (±SEM) from Baseline to Endpoint in Direct LDL-C Concentrations for Ezetimibe – mg and 10 mg Doses: Pooled Analysis of C98-010 and C98-258			
	Placebo (n= 87)	Ez – mg (n= 124)	Ez 10mg (n= 118)
Direct LDL concentration (mg/dl)[a]	-0.4 ± 1.1	-15.7 ± 0.9	-18.5 ± 0.9
p-value vs. placebo	–	<0.01	<0.01
p-value vs. Ez – mg	<0.1	–	0.03
p-value vs. Ez 10 mg	<0.1	0.03	–
a: values shown are least-squares (LS) means and standard errors of LS means (SEM)			

The greater efficacy of the 10 mg dose versus the – mg dose is further illustrated in the following table which summarizes the numbers and percentages of subjects that achieved at least a 15% reduction in direct LDL-C concentrations by ezetimibe dose. Results represent an analysis of data pooled from C96-411/C96-345, C98-010 and C98-258:

Summary of Subjects With Direct LDL-C Reduction at Endpoint ≥15% by Ezetimibe Dose: Pooled Analysis of C96-411/C96-345, C98-010 and C98-258						
	Ezetimibe Dose					
	– mg	– mg	– mg	10 mg	– mg	– mg
% with ≥15% ↓/total #	19/46	31/66	74/144	90/134	9/16	13/18
Percentage with ≥15% ↓	41%	47%	51%	67%	56%	72%

In these 3 studies, maximal or near-maximal effects on LDL-C lowering were observed at week 2 and continued for the study duration.

Phase II Studies: Secondary Efficacy Variables:

Mean Percent Changes From Baseline to Endpoint in Plasma Concentrations of Secondary Lipid Variables in the Placebo Group and the Range of these Mean Percent Changes Across All Ezetimibe Groups in a Given Study (C96-411/345, C98-010 and C98-258)						
	C96-411/C96-345		C98-010		C98-258	
	Placebo (n= 17)	Ez – mg (n= 107)	Placebo (n= 52)	Ez – 10 mg (n= 191)	Placebo (n= 36)	Ez – 10 mg (AM + PM) (n= 147)
Calc. LDL-C	+1.3%	-16.0 to -22.1[a]	+3.6	-9.3 to -18.9[a]	-3.7	-14.3 to -19.2[a]
TC	+0.9	-10.3 to -15.8[a]	+2.2	-6.8 to -12.6[a]	-3.6	-10.1 to -13.6[a]
TG	-6.4	-8.3 to +13.1[b]	-2.9	-3.8 to –10.4[c]	-5.9	-11.2 to -12.6[c]
HDL-C	+4.4	+1.8 to +4.6[c]	+2.2	+2.7 to +4.5[c]	-0.8	+2.4 to +6.4[d]
HDL_2-C	+0.4	-1.9 to +13.7[c]	+16.1	+10.4 to +16.9[c]	+10.3	+12.8 to +18.4[c]
HDL_3-C	+6.8	+2.7 to +8.8[c]	-0.1	-2.2 to +2.6[c]	-2.8	-3.4 to +4.8[b]
Apo A_1	-0.6	+0.9 to +9.6[b]	-2.9	-2.9 to +1.2[c]	-3.2	-1.2 to +3.6[b]
Apo B	+3.4	-7.9 to -13.5[a]	+2.4	-6.3 to -15.2[a]	-4.7	-12.0 to -15.7[a]
Lp(a)	+1.9	-8.9 to +7.3[c]	+9.1	-2.8 to +12.6[c]	+3.4	-4.5 to +13.9[c]
a= p< 0.01: each ezetimibe treatment group versus placebo; b= significant (i.e. p< 0.05) for one comparison only (TG: ezetimibe 10 mg vs. placebo: p= 0.03; Apo A_1: ezetimibe 10 mg vs. placebo: p< 0.01; HDL_3-C: ezetimibe 10 mg PM vs. placebo: p= 0.04; Apo A_1: ezetimibe 10 mg PM vs. placebo: p= 0.01) c= p> 0.05 (i.e. not significant) for each ezetimibe treatment group comparison to placebo; d= significant only for the following comparisons for HDL-C: ez – mg AM vs. placebo: p= 0.04; ezetimibe – mg PM vs. placebo: p= 0.01; ezetimibe 10 mg PM vs. placebo: p< 0.01						

Comments on the above table:
Ezetimibe significantly ($p< 0.01$) reduced LDL-C, total cholesterol and Apo B levels compared to placebo. Ezetimibe either did not significantly differ from placebo in its effect on the other lipid variables measured or there were no consistent differences between ezetimibe and placebo in the effects on other lipid variables.

See the Appendix for a tabulation of efficacy by ezetimibe dose by study for each of the 3 Phase II studies.

PHASE III STUDIES: EFFICACY ANALYSES- LIPID PARAMETERS
(Note: the following analyses for the lipid variables are presented for the ITT population only since the results for the Protocol-Evaluable Data Set were similar).
LDL-C:

MONOTHERAPY INDICATION:
Primary Efficacy Endpoint and Key Secondary Efficacy Endpoints:

Mean % Changes (SEM) From Baseline (mg/dl) to Endpoint (mg/dl) in Plasma Concentrations of the 1^0 and Key 2^0 Lipid/Apolipoprotein Variables in the Monotherapy Efficacy Pool (Combined Results From P00474 and P00475): Intent-to-Treat Data Set

Variables	Placebo[a,b] (n= 431)	Ez 10 mg[a,b] (n= 1,288)	Ez – Placebo (95% CI)	p-Value[c]
Direct LDL-C	0.3 (0.6)	-17.4 (0.3)	-17.7 (-19.0, -16.5)	≤0.01
Calc. LDL-C	0.9 (0.5)	-18.2 (0.3)	-19.1 (-20.3, -18.0)	≤0.01
TC	0.4 (0.4)	-12.7 (0.2)	-13.1 (-14.0, -12.2)	≤0.01
TG[d,e]	3.6 (1.4)	-4.2 (0.8)	-7.8 (-10.9, -4.7)	≤0.01
Apo B	-1.6 (0.5)	-15.7 (0.3)	-14.1 (-15.3, -12.9)	≤0.01
HDL-C[f]	-1.6 (0.5)	1.0 (0.3)	+2.6 (1.5, 3.7)	≤0.01

EZ= ezetimibe
a: values presented are least-squares (LS) means and standard errors of LS means (SEM)
b: not every subject had an end-of-treatment measurement for every variable; thus, "n" sizes varied from 430 to 431 for the placebo group and from 1,286 to 1,288 for the ezetimibe group
c: comparison between placebo and EZ 10 mg
d: median values for TG were 0.0 for placebo and –8.0 for EZ 10 mg ($p <0.01$)
e: TG, $p \leq 0.01$ for study P00475 (additional TG lowering of 11.4% compared to placebo) and for the combined analysis (see above); difference between ez and placebo not significant for P00474 (-4.1%, $p= 0.09$, see Appendix).
f: HDL-C, $p \leq 0.01$ for study P00475 and the combined analysis only (additional HDL-C increase of 2.9% and 2.6%, respectively, with ez compared to placebo). For study P00474, this difference was +2.3%, $p \leq 0.05$.

Time Course of Therapeutic Response:
As seen in the following figure, a significant reduction in calculated LDL-C in response to ezetimibe compared with placebo was observed as early as week 2, the first time point examined, and was maintained throughout the 12-week time course:

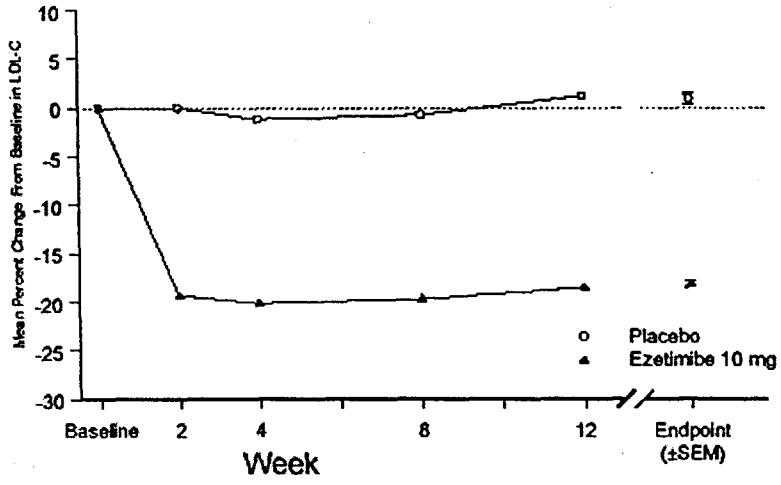

Figure 6 Mean percent change from baseline in plasma concentration of Calculated LDL-C over time and at endpoint for the two treatment groups: Phase III Ezetimibe Monotherapy (Intent-to-Treat Data Set) **(Appendix 12)**

This rapid onset was also seen for all the key secondary parameters analyzed: TC, TG, HDL-C and Apo B.

Other Efficacy Endpoints:
In the combined analysis (P00474 and P00475), treatment with ezetimibe resulted in statistically significant ($p \leq 0.01$) mean changes from baseline in Lp(a) and the cholesterol ratios, direct LDL-C/HDL-C and TC/HDL-C relative to placebo. This change was not significant for either the HDL-C subfractions or for Apo A-1.

Summary of the Efficacy Results From the Combined Monotherapy Studies:
1,288 subjects with primary hypercholesterolemia were randomized to ezetimibe 10 mg/day for 12 weeks. Reductions in LDL-C, TC, TG and HDL-C by ezetimibe occurred as early as week 2. Treatment with ezetimibe resulted in statistically significant ($p \leq 0.01$) mean changes from baseline in calculated LDL-C of –19%, direct LDL-C of –18%, TC of –13%, TG of –8%, Apo B of –14% and HDL-C of +3%, relative to placebo.

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CO-ADMINISTRATION WITH STATINS INDICATION:
EZETIMIBE INITIATED CONCURRENTLY WITH A STATIN: FACTORIAL COADMINISTRATION STUDIES:

LDL-C: All Statins (Lovastatin, Simvastatin, Pravastatin and Atorvastatin): Assessment of the Effect of Ezetimibe on LDL-C Across Statins and Statin Doses:

Change in Plasma Concentration of Calculated LDL-C Between Baseline and Endpoint: Factorial Coadministration Studies: Pooled Across All Statins[a] (Intent-to-Treat Data Set)					
	Placebo	Ez 10 mg[b]	All Statin[c]	Ez+AllStatin[c]	[Pooled Ez + Statin] – [Pooled Statin] (95% CI)
Baseline calc. LDL-C (mg/dl)	179.3 (1.3) (n= 259)	179.6 (1.3) (n= 262)	179.5 (0.7) (n= 936)	178.5 (0.7) (n= 925)	-1.0 (-2.9, 0.9)
Week 2: mean % Δ from base (SEM)	-0.1 (0.6)	-19.5 (0.6)	-32.5 (0.4)	-48.9 (0.4)	-16.4 (-17.5, -15.3), p< 0.01
Week 8: mean % Δ from base (SEM)	-0.2 (0.7)	-20.6 (0.7)	-34.5 (0.5)	-49.2 (0.5)	-14.7 (-15.9, -13.4), p< 0.01
Endpoint: mean % Δ from base (SEM)	0.6 (0.8)	-19.3 (0.7)	-32.8 (0.5)	-46.6 (0.5)	-13.8 (-15.2, -12.4), p< 0.01

a= lovastatin, simvastatin, pravastatin and atorvastatin
b= means and standard errors are sample means and sample standard errors
c= means and standard errors are least-square means and standard errors based on the ANOVA model
All Statin= pool of all doses of statin; Ez + All Statin= pool of all doses of statin coadministered with Ez 10 mg

Comment on the above table:

The results of this analysis shows that the co-administration of ezetimibe with any of the four statins studied at any dose results in a mean percent decrease of –13.8% in calculated LDL-C concentrations at endpoint on top of what would be expected with statin alone. This effect is seen as early as week 2 (when first measured) and is maintained throughout the 12-week treatment period. (Note: the results obtained using direct LDL-C were similar demonstrating a mean percent decrease of –13.3%).

The above analysis was contingent on there being no statistically significant dose-by-treatment interaction for LDL-C with respect to coadministration of statin with ezetimibe. This was true in 3 of the 4 Factorial studies. In the simvastatin factorial, a significant treatment-by-dose interaction for the percent change from baseline in LDL-C was seen at endpoint across the simvastatin doses for the ITT analysis (p= 0.04 using direct LDL-C and p= 0.05 using calculated LDL-C). However, the sponsor determined that the best estimate of added ezetimibe effect was still the average effect across all doses of statin for the following reasons:

a. the protocol-evaluable analysis failed to show a significant interaction (p = 0.18);
b. there was no suggestion of a dose-by-treatment interaction at the 2, 4 or 8 week timepoints in this study;

c. the significant result was related to the change in LDL-C observed for the Ez + simvastatin 20 mg versus simvastatin 20 mg, which was not consistent with the overall average benefit of coadministration therapy over simvastatin monotherapy;
d. the differences between coadministration and simvastatin alone were not increasing/decreasing with dose.

LDL-C: Direct and Caculated: Mean Baseline Values (mg/dl): Factorial Coadministration Studies:

	Placebo		Ezetimibe		Statin (all doses)		Ez + Statin (all doses)	
	Direct	Calc.	Direct	Calc.	Direct	Calc.	Direct	Calc.
Lovastatin	177.8	179.0	178.0	179.1	177.5	178.9	175.8	177.7
Simvastatin	177.4	179.1	181.3	183.4	178.6	180.2	176.3	177.6
Pravastatin	177.1	178.8	177.4	179.7	176.6	177.6	176.3	177.0
Atorvastatin	178.1	180.2	175.3	176.7	179.9	181.4	180.0	181.8

Comment on the above table:
Mean baseline direct and calculated LDL-C levels were similar across statins and between the placebo and ezetimibe groups for a given statin.

LDL-C: Mean % Change From Baseline to Endpoint For The Phase III Monotherapy Arms (Placebo and Ezetimibe Treatment Groups) of the Factorial Coadministration Studies: P00679 (Lovastatin), P00680 (Simvastatin), P00691 (Pravastatin) and P00692 (Atorvastatin):

Mean % Change in Plasma Concentration of LDL-C (Direct and Calculated) Between Baseline and Endpoint: Monotherapy Arm of Factorial Coadministration Studies (Intent-to-Treat)						
	Direct LDL-C			Calculated LDL-C		
	Placebo	Ez	Ez – Placebo (95% CI)[a]	Placebo	Ez	Ez – Placebo (95% CI)[a]
Lovastatin	-0.03 (n= 64)	-18.6 (n= 72)	-18.56 (-23.3, -13.9), $p \leq 0.01$	0.4 (n= 64)	-18.7 (n= 72)	-19.1 (-23.7, -14.5), $p \leq 0.01$
Simvastatin	-1.3 (n= 70)	-18.1 (n= 61)	-16.7 (-21.7, -11.7), $p \leq 0.01$	-1.5 (n= 70)	-19.1 (n= 61)	-17.6 (-22.7, -12.5), $p \leq 0.01$
Pravastatin	1.3 (n= 65)	-18.7 (n= 64)	-20.1 (-24.4, -15.7), $p \leq 0.01$	-0.6 (n= 65)	-19.6 (n= 64)	-19.1 (-23.3, -14.8), $p \leq 0.01$
Atorvastatin	5.9 (n= 60)	-18.4 (n= 65)	-24.3 (-29.6, -19.1), $p \leq 0.01$	4.3 (n= 60)	-20.0 (n= 65)	-24.3 (-29.6, -18.9), $p \leq 0.01$

a= difference between ezetimibe and placebo in mean percent change from baseline
Comments on the above table:
The mean % changes in LDL-C from baseline to endpoint for the placebo and ezetimibe alone treatment groups were similar for direct and calculated values. The mean % change from baseline to endpoint in LDL-C ranged from –1.5 to +5.9% for the placebo group and from –18% to –20% for the ezetimibe group. For each of the 4 factorial studies, the difference between ezetimibe and placebo was significant ($p \leq 0.01$) with reductions in LDL-C of –17 to –24%. These results are consistent with the findings of the Phase III Monotherapy Studies.

Calculated LDL-C: Mean % Change From Baseline to Endpoint Pooled Across All Doses of a Given Statin: Factorial Coadministration Studies:

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

	Ez	Statin (all doses)	Ez +Statin (all doses)	[Ez + Statin] – [Ez][a] (95% CI)	[Ez + Statin] – [Statin][b] (95% CI)
Lovastatin	-18.7 (n= 72)	-25.4 (n= 220)	-40.4 (n= 192)	-21.7 (-25.4, -18.0), $p < 0.01$	-15.0 (-17.6, -12.3), $p \leq 0.01$
Simvastatin	-19.1 (n= 61)	-36.5 (n= 263)	-51.3 (n= 274)	-32.2 (-36.4, -28.1), $p < 0.01$	-14.8 (-17.3, -12.3), $p \leq 0.01$
Pravastatin	-19.6 (n= 64)	-25.2 (n= 205)	-38.6 (n= 204)	-19.0 (-22.4, -15.6), $p < 0.01$	-13.4 (-15.8, -11.1), $p \leq 0.01$
Atorvastatin	-20.0 (n= 65)	-44.2 (n= 248)	-56.3 (n= 255)	-36.4 (-40.5, -32.2), $p < 0.01$	-12.1 (-14.7, -9.4), $p \leq 0.01$

a= difference between pooled doses of a given statin coadministered with ezetimibe versus ezetimibe alone

b= difference between pooled doses of a given statin coadministered with ezetimibe versus pooled doses of a given statin alone

Comments on the above table:

The mean % change from baseline in calculated LDL-C ranged from –39 to –56% for the coadministration groups compared with –25 to –44% for the statin alone groups and to ~-19% for the ezetimibe alone groups. The difference between the coadministration groups and the statin alone group was significant ($p \leq 0.01$) and consistent, ~ -14% across the studies. The difference between the coadministration groups and the ezetimibe alone groups was also significant ($p < 0.01$) for all studies, ranging from 19 to 36%, being greatest in the simvastatin and atorvastatin studies. The results for direct LDL-C were very similar to those observed for calculated LDL-C (see Appendix).

Calculated LDL-C: Individual Treatment Groups: Mean % Δ Between Baseline & Endpoint

Mean Percent Change in Calculated LDL-C Between Baseline and Endpoint: Factorial Coadministration Studies: By Statin, By Dose (Intent-to-Treat Data Set)

	Plac	Ez	Statin 10 mg	Ez + Statin 10 mg	Statin 20 mg	Ez + Statin 20 mg	Statin 40 mg	Ez + Statin 40 mg	Statin 80 mg	Ez + Statin 80 mg
Lovastatin:	N= 64[a]	N= 72[a]	N= 73[a]	N= 65[a]	N= 74[a]	N= 62[a]	N= 73[a]	N= 65[a]	-	-
Mean % Δ	0.4	-18.7	-20.2	-34.2	-25.6	-40.8	-30.5	-46.1	-	-
Diff. in mean % Δ (95% CI)		-19.1 (-23.7, -14.5), p≤0.01[b]		-14.0 (-18.6, -9.5), p≤0.01[c]		-15.2 (-19.8, -10.6), p≤0.01[c]		-15.7 (-20.2, -11.1), p≤0.01[c]		
Lova label[d]			*-21*		*-27*		*-31*			
Simvastatin:	N= 70	N= 61	N= 70	N= 67	N= 61	N= 69	N= 65	N= 73	N= 67	N= 65
Mean % Δ	-1.5	-19.1	-27.2	-45.5	-36.5	-46.3	-37.5	-55.8	-44.7	-57.6
Diff. in mean % Δ (95% CI)		-17.6 (-22.7, -12.5), p≤0.01[b]		-18.3 (-23.2, -13.4), p≤0.01[c]		-9.8 (-14.9, -4.7), p≤0.01[c]		-18.2 (-23.2, -13.3), p≤0.01[c]		-13.0 (-18.1, -7.9), p≤0.01[c]
Simva label[d]			*-30*		*-38*		*-41*		*-47*	
Pravastatin:	N= 65	N= 64	N= 66	N= 71	N= 69	N= 66	N= 70	N= 67	-	-
Mean % Δ	-0.6	-19.6	-21.3	-33.8	-23.2	-39.7	-31.1	-42.4	-	-
Diff. in mean % Δ (95% CI)		-19.1 (-23.3, -14.8), p≤0.01[b]		-12.5 (-16.5, -8.4), p≤0.01[c]		-16.5 (-20.6, -12.4), p≤0.01[c]		-11.4 (-15.4, -7.3), p≤0.01[c]		
Prava label[d]			*-22*		*-32*		*-34*			
Atorvastatin:	N= 60	N= 65	N= 60	N= 65	N= 60	N= 62	N= 66	N= 65	N= 62	N= 63
Mean % Δ	4.3	-20.0	-36.5	-53.4	-41.8	-54.2	-44.8	-56.4	-53.8	-61.2
Diff. in mean % Δ (95% CI)		-24.3 (-29.6, -18.9), p≤0.01[b]		-16.9 (-22.2, -11.5), p≤0.01[c]		-12.4 (-17.8, -7.0), p≤0.01[c]		-11.7 (-16.9, -6.4), p≤0.01[c]		-7.3 (-12.7, -2.0), p≤0.01[c]
Atorva label[d]			*-39*		*-43*		*-50*		*-60*	

a= sample size at baseline

b= pairwise comparison of ezetimibe versus placebo

c= pairwise comparison of ez + statin to the same dose of statin

d= approved labeling for the given statin

Comments on the above table:

Ezetimibe alone resulted in a significant ($p \leq 0.01$) difference in LDL-C lowering compared to placebo in each of the factorial studies. Coadministration resulted in a significant ($p \leq 0.01$) difference in LDL-C lowering compared to the same dose of statin alone in each of the factorial studies (lovastatin: additional 14 to 16% LDL-C lowering with coadministration compared to same dose of statin alone; simvastatin: additional 10 to 18% LDL-C ↓; pravastatin: additional 11 to 17% ↓ and atorvastatin, additional 7 to 17% decrease in LDL-C). This incremental or additive effect of ezetimibe appears to be independent of the statin dose. (Note: the results for direct LDL-C were very similar to those observed for calculated LDL-C, see Appendix).

Comparison of the mean percent changes in calculated LDL-C from baseline to endpoint reported for a given dose of statin monotherapy reported in the ezetimibe factorial studies to that

reported in the approved labeling for the corresponding dose of that statin were within 3% of expected with the following 3 exceptions: prava 20 mg, 9% less in the factorial study; atorva 40 mg and atorva 80 mg, 5% and 6% less in the factorial study.

Pairwise Comparisons in Mean % Change from Baseline to Endpoint in Calculated LDL-C[a] (ITT):

Lovastatin:

	[Ezetimibe] – [Placebo]	[Ezetimibe] – [Lova 10 mg]
Diff. in mean % Δ from baseline to endpoint for calc. LDL-C (95% CI) (p value)	-19.1 (-23.7, -14.5), p < 0.01	1.5 (-3.0, 5.9), not significant: p=0.51

	Ez+ Lova 10mg	Ez+ Lova 20mg	Ez+ Lova 40mg
Diff. from same dose of lova alone in mean % Δ from base (95% CI) (p value)	-14.0 (-18.6, -9.5) p < 0.01	-15.2 (-19.8, -10.6) p < 0.01	-15.7 (-20.2, -11.1) p < 0.01
Diff, from next higher dose of lova alone in mean % Δ from base (95% CI)(p value	-8.6 (-13.2, -4.0) p < 0.01	-10.3 (-14.9, -5.7) p < 0.01	Not applicable
Diff. from second higher dose of lova alone in mean % Δ from base(95%CI)(p)	-3.8 (-8.3, +0.8) not significant: p= 0.11	Not applicable	Not applicable

a= the corresponding results obtained with direct LDL-C were very similar (see Appendix).

Simvastatin: Pairwise Comparisons in Mean % Change from Baseline to Endpoint in Calculated LDL-C[a] (ITT):

	[Ezetimibe] – [Placebo]	[Ezetimibe] – [Simva 10 mg]
Diff. in mean % Δ from baseline to endpoint for calc. LDL-C (95% CI) (p value)	-17.6 (-22.7, -12.5), p < 0.01	Not performed

	Ez +Simva10mg	Ez +Simva20mg	Ez +Simva40mg	Ez +Simva80mg
Diff. from same dose of simva alone in mean % Δ from base (95% CI) (p value)	-18.3 (-23.2, -13.4), p < 0.01	-9.8 (-14.9, -4.7), p < 0.01	-18.2 (-23.2, -13.3), p < 0.01	-13.0 (-18.1, -7.9), p < 0.01
Diff, from next higher dose of simva alone in mean % Δ from base (95% CI) (p value)	-9.0 (-14.1, -3.9), p < 0.01	-8.7 (-13.7, -3.7), p < 0.01	-11.1 (-16.0, -6.2), p < 0.01	Not applicable
Diff. from second higher dose of simva alone in mean % Δ from base(95%CI) (p value)	-8.0 (-13.0, -2.9), p < 0.01	-1.6 (-6.6, 3.4) not significant: p = 0.53	Not applicable	Not applicable
Diff. from highest dose of simva alone in mean % Δ from base(95%CI) (p value)	-0.8, p= 0.74	Not applicable	Not applicable	Not applicable

a= the corresponding results obtained with direct LDL-C were very similar (see Appendix).

Pravastatin: Pairwise Comparisons in Mean % Change from Baseline to Endpoint in Calculated LDL-C[a] (ITT):

	[Ezetimibe] – [Placebo]	[Ezetimibe] – [Prava 10 mg]
Diff. in mean % Δ from baseline to endpoint for calc. LDL-C (95% CI) (p value)	-19.1 (-23.3, -14.8), p < 0.01	1.7 (-2.5, +5.9), not significant: p=0.44

	Ez+ Prava 10mg	Ez+ Prava 20mg	Ez+ Prava 40mg
Diff. from same dose of prava alone in mean % Δ from base (95% CI) (p value)	-12.5 (-16.5, -8.4) p < 0.01	-16.5 (-20.6, -12.4) p < 0.01	-11.4 (-15.4, -7.3) p < 0.01
Diff, from next higher dose of prava alone in mean % Δ from base (95% CI)(p	-10.5 (-14.5, -6.5) p < 0.01	-8.6 (-12.7, -4.5) p < 0.01	Not applicable
Diff. from second higher dose of prava alone in mean % Δ from base(95%CI)(p)	-2.7 (-6.7, +1.3) not significant: p = 0.19	Not applicable	Not applicable

a= the corresponding results obtained with direct LDL-C were very similar (see Appendix) with the exception of the comparison of ez + prava 10 mg vs. prava 40 mg. This difference was significant for direct LDL-C but not for calculated LDL-C.

Atorvastatin: Pairwise Comparisons in Mean % Change from Baseline to Endpoint in Calculated LDL-C[a] (ITT):

	[Ezetimibe] – [Placebo]	[Ezetimibe] – [Atorva 10 mg]
Diff. in mean % Δ from baseline to endpoint for calc. LDL-C (95% CI) (p value)	-24.3 (-29.6, -18.9), p < 0.01	Not performed

	Ez +Atorv10mg	Ez +Atorv20mg	Ez +Atorv40mg	Ez +Atorv80mg
Diff. from same dose of atorva alone in mean % Δ from base (95% CI) (p value)	-16.9 (-22.2, -11.5), p < 0.01	-12.4 (-17.8, -7.0), p < 0.01	-11.7 (-16.9, -6.4), p < 0.01	-7.3 (-12.7, -2.0), p < 0.01
Diff, from next higher dose of atorva alone in mean % Δ from base (95% CI) (p value)	-11.6 (-16.9, -6.3), p < 0.01	-9.4 (-14.7, -4.1), p < 0.01	-2.6 (-7.9, 2.7), not significant: p = 0.34	Not applicable
Diff. from second higher dose of atorva alone in mean % Δ from base(95%CI) (p value)	-8.6 (-13.9, -3.4), p < 0.01	-0.4 (-5.7, 5.0) not significant: p = 0.90	Not applicable	Not applicable
Diff. from highest dose of atorva alone in mean % Δ from base(95%CI) (p value)	+0.4, p= 0.87	Not applicable	Not applicable	Not applicable

a= the corresponding results obtained with direct LDL-C were very similar (see Appendix).

Summary Statement for the 4 Pairwise Comparison Tables:

For a given dose of statin, the incremental mean % change in calculated LDL-C afforded by the addition of ezetimibe ranged from -14 to -16% for lovastatin, -10 to -18% for simvastatin, -11 to -17% for pravastatin and -7 to -17% for atorvastatin. Therefore, across all 4 statins, the incremental mean percent change in LDL-C gained by the coadministration of ezetimibe and each dose of statin ranged from –7 to –18%. With the exception of ez + atorva 40 mg vs. atorva

80 mg, coadministration resulted in a significant ($p \leq 0.01$) difference in LDL-c lowering compared to the same or next higher dose of statin alone. In addition, coadministration of ezetimibe with the lowest dose of statin, 10 mg, resulted in LDL-C concentrations similar to that seen with the highest dose tested of statin alone. Comparison of LDL-C lowering with coadministration to that reported for these doses of statin alone in the approved labeling for these products, corroborated this finding of comparable efficacy for lova, simva and prava. However, using the efficacy data reported in the label for atorvastatin, the 80 mg dose resulted in an additional 7% lowering in LDL-C compared to the LDL-C reduction reported for ezetimibe + atorva 10 mg in study P00692.

The incremental reduction in LDL-C at different statin doses produced by coadministration with ezetimibe is shown graphically in the following figure:

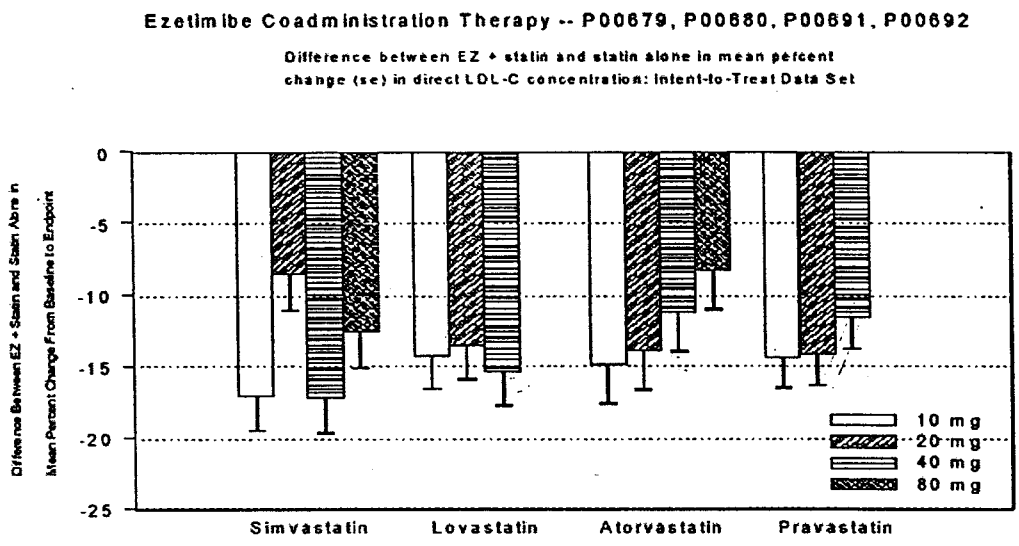

Figure 1 Incremental Mean Percent Change (SE) in Direct LDL-C when Ezetimibe is Co-Administered with Statin Treatment: Factorial Coadministration Studies (Intent-to-Treat Data Set)

The incremental mean percent change gained by the coadministration of ezetimibe and each dose of statin ranged from –8.3 to –17.2% for direct LDL-C and –7.3 to –18.3% for calculated LDL-C.