In females, the frequencies of patients with ALT and /or AST ≥3xULN, and CPK≥3xULN, were none in the placebo group and 0.7%-1.3% in the ezetimibe 10 mg group, statin group, and ezetimibe 10 mg+statin group.

In males, the frequencies of patients with ALT and/or AST≥3xULN were none in the placebo group, 0.5%-0.9% in the ezetimibe 10 mg group and statin group, and 3.8% in the ezetimibe 10 mg+statin group These laboratory test results for liver function were similar to the AE results for the Liver And Biliary System, discussed above. In patients treated with ezetimibe+statin, the frequency of patients with ALT and/or AST ≥3xULN was higher in males compared to females.

In males, the frequencies of patients with CPK≥3xULN were 2.7% in the placebo group and 3.0-5.4% in the ezetimibe 10 mg, statin, and ezetimibe 10 mg+statin groups. In all treatment groups, the frequencies of patients with CPK≥3xULN were higher in males compared to females, and highest in Black males. In Black males with CPK ≥3xULN, the values were in the range of 3xULN to <5xULN for 7 patients, 5xULN to <10xULN for 3 patients, and >10xULN for 1 patient. These results appear to represent real differences between the sexes and racial groups.

7.1.2.1.2.2 Age

AEs of Any Intensity. The frequencies of patients with AEs of any intensity, by age, were as follows:

Age	Placebo	Ezetimibe 10 mg	Statin	Ezetimibe 10 mg+statin
<65 Years	120/183 (65.6%)	132/198 (66.7%)	451/676 (66.7%)	416/656 (63.4%)
≥65 Years	46/ 76 (60.5%)	45/ 64 (70.3%)	155/260 (59.6%)	177/269 (65.8%)
<75 Years	154/241 (63.9%)	164/248 (66.1%)	570/879 (64.8%)	547/859 (63.7%)
≥75 Years	12/ 18 (66.7%)	13/ 14 (92.9%)	36/ 57 (63.2%)	46/ 66 (69.7%)

In patients < 65 & <75 years of age, respectively, the frequencies of patients with AEs of any intensity were 1.1% & 2.2% higher in the ezetimibe 10 mg group compared to the placebo group, and 1.1% & 3.3% lower in the ezetimibe 10 mg+statin group compared to the statin group.

In patients ≥65 & ≥75 years of age, respectively, the frequencies of patients with AEs of any intensity were 9.8% & 26.2% higher in the ezetimibe 10 mg group compared to the placebo group, and 6.2% & 6.5% higher in the ezetimibe 10 mg+statin group compared to the statin group. The results for the ezetimibe 10 mg group compared to the placebo group are discussed in Section 7.1.2.1.1.2 above. Regarding the results for the ezetimibe 10 mg+statin group compared to the statin group the

frequencies of patients with myalgia, in patients ≥65 & ≥75 years of age, respectively, were 4.6% & 3.5% and in the statin group and 7.4% & 7.6% in the ezetimibe+statin group. These findings are difficult to interpret, because the frequencies of patients with CPK ≥3xULN were not increased in the ezetimibe 10 mg+statin group compared to the statin group (see below).

ALT, AST, And CPK. The frequencies of patients with postbaseline ALT and/or AST≥3xULN and CPK ≥3xULN, by age, as were follows:

Age	Placebo	Ezetimibe 10 mg	Statin	Ezetimibe 10 mg+statin
		ALT &/or AST>3xULN		
<65 Years	0/182	2/196 (1.0%)	6/670 (0.9%)	19/652 (2.9%)
≥65 Years	0/ 73	0/ 63	3/259 (1.2%)	0/265
<75 Years	0/237	2/246 (0.8%)	8/872 (0.9%)	19/852 (2.2%)
≥75 Years	0/ 18	0/13	1/ 57 (1.8%)	0/65
		CPK >3xULN		
<65 Years	3/182 (1.6%)	5/196 (2.6%)	21/670 (3.1%)	14/652 (2.1%)
≥65 Years	0/ 73	1/ 63 (1.6%)	4/259 (1.5%)	1/265 (0.4%)
<75 Years	3/237 (1.3%)	5/246 (2.0%)	24/872 (2.8%)	15/852 (1.8%)
≥75 Years	0/ 18	1/ 13 (7.7%)	1/ 57 (1.8%)	0/65

In patients <65 & <75 years of age, respectively, the frequencies of patients with ALT and/or AST ≥3xULN were none in the placebo group, 0.8%-1.0% in the ezetimibe 10 mg group and statin group, and 2.2%-2.9% in the ezetimibe 10 mg+statin group. In patients ≥65. & ≥75 years of age, respectively, the frequencies of patients with ALT and/or AST ≥3xULN were none in the placebo group or ezetimibe 10 mg group, 1.2%-1.8% in the statin group, and none in the ezetimibe 10 mg+statin group. Ezetimibe increased the frequency of patients with ALT and/or AST ≥3xULN, in patients <65 & <75 years of age, but not in older patients.

In patients <65 & <75 years of age, respectively, the frequencies of patients with CPK ≥3xULN were 1.3%-1.6% in the placebo group and 1.8%-3.1% in the ezetimibe 10 mg group, statin group, and ezetimibe 10 mg+statin group. In patients ≥65 & >75 years of age, respectively, the frequencies of patients with CPK ≥3xULN were none in the placebo group, 1.6%-7.7% (1 case) in the ezetimibe 10 mg group, 1.5%-1.8% in the statin group, and 0%-0.4% in the ezetimibe 10 mg+statin group. The frequency of patients with CPK≥3xULN was lower, and increased less in patients treated with ezetimibe, in patients ≥65 & ≥75 years of age compared to patients <65 & <75 years of age, respectively.

7.1.2.1.2.3 Race

AEs of Any Intensity. The frequencies of patients with AEs of any intensity, by race, were as follows:

Race	Placebo	Ezetimibe 10 mg	Statin	Ezetimibe 10 mg+statin
Caucasian	146/227 (64.3%)	160/235 (68.1%)	526/814 (64.6%)	532/813 (65.4%)
non-Cauc.	20/ 32 (62.5%)	17/ 27 (63.0%)	80/122 (65.6%)	61/112 (54.5%)

In Caucasian patients, the frequency of patients with AEs of any intensity was 3.8% higher in the ezetimibe 10 mg group compared to the placebo group and 0.9% higher in the ezetimibe 10 mg+statin group compared to the statin group. The higher frequency in the ezetimibe 10 mg group compared to the placebo group was not concentrated in individual AEs, and the frequencies of patients with AEs of any intensity in the statin and ezetimibe 10 mg+statin groups were similar by individual AE.

In non-Caucasian patients, the frequency of patients with AEs of any intensity was 0.5% higher in the ezetimibe 10 mg group compared to the placebo group, and the frequencies of patients with individual AEs were similar in the 2 treatment groups. The frequency of patients with AEs of any intensity was 11.1% lower in the ezetimibe 10 mg+statin group compared to the statin group, and this lower frequency was not concentrated in individual AEs. To the contrary, in the ezetimibe 10 mg+statin group compared to the placebo group, there were higher frequencies of patients with AEs in the Liver and Biliary System. In the ezetimibe 10 mg+statin group, these frequencies were 4.5% for GGT increased, 5.4% for SGOT (AST) increased, and 7.1% for SGPT (ALT) increased, whereas, in the statin group, these frequencies were 0.8% for GGT increased, 0.8% for SGOT (AST) increased, and 1.6% for SGPT (ALT) increased.

ALT, AST, And CPK. The frequencies of patients with postbaseline ALT and/or AST≥3xULN and CPK ≥3xULN, by race, as were follows:

Race	Placebo	Ezetimibe 10 mg	Statin	Ezetimibe 10 mg+statin
		ALT &/or AST>3xULN		
Caucasian	0/223	2/233 (0.9%)	6/808 (0.7%)	16/806 (2.0%)
non-Cauc.	0/ 32	0/ 26	3/121 (2.5%)	3/111 (2.7%)
		CPK >3xULN		
Caucasian	2/223 (0.9%)	4/233 (1.7%)	17/808 (2.1%)	10/806 (1.2%)
non-Cauc.	1/ 32 (3.1%)	2/ 26 (7.7%)	8/121 (6.6%)	5/111 (4.5%)
Black male	1/ 7 (14.3%)	2/ 4 (50.0%)	5/ 23 (21.7%)	3/ 16 (18.8%)
All other	0/ 25	0/ 22	3/ 98 (3.1%)	2/ 95 (2.1%)

In Caucasian and non-Caucasian patients, the frequencies of patients with ALT and/or AST ≥3xULN were none in the placebo group 0%-0.9% in

the ezetimibe 10 mg group, 0.7-2.5% in the statin group, and 2.0-2.7% in the ezetimibe 10 mg+statin group.

In Caucasian patients, the frequencies of patients with CPK ≥3xULN were 0.9% in the placebo group and -1.2%-2.1 % in the ezetimibe 10 mg group, statin group, and ezetimibe 10 mg+statin group. In non-Caucasian patients, these frequencies were 3.1% in the placebo group and 4.5%-7.7% in the ezetimibe 10 mg group, statin group, and ezetimibe 10 mg+statin group. The higher frequencies in non-Caucasian patients were largely due to higher frequencies in Black males (see Section 7.1.2.1.2.).

7.1.2.2 Homozygous Familial Hypercholesterolemia

In the RCT for Homozygous Familial Hypercholesterolemia, there were 17 patients in the statin 80 mg group and 33 patients in the ezetimibe 10 mg+statin 40/80 mg group. For these patients, AEs of any intensity and laboratory test results for postbaseline ALT, AST, and CPK were stratified by sex (female versus male), age (<18 versus ≥18 years of age), and race (Caucasian versus non-Caucasian). There were no obvious differences in the relationship between treatment group and the risk of AEs or ALT, AST, or CPK increases, between the sex, age, and racial groups.

7.2 Interactions Of Ezetimibe With Hepatic And Renal Dysfunction

In the Phase 2/3 RCTs, no safety results were reported as indicating an adverse interaction between ezetimibe and hepatic dysfunction, renal dysfunction, or other disorders.

The pharmacokinetics of ezetimibe were studied in Clinical Pharmacology studies of patients with hepatic dysfunction and renal dysfunction. The results are briefly summarized below. For more information, see Biopharmaceutics review.

7.2.1 Hepatic Dysfunction

In the first study, ezetimibe 10 mg in single doses was given to 8 patients with normal hepatic function and 12 patients with varying degrees of hepatic dysfunction. These patients were 18 males and 2 females, 39-64 years of age. There was a direct correlation between the extent of hepatic dysfunction and ezetimibe bioavailability. For example, the AUC for total ezetimibe was 916 ng hr/mL in normal patients, 1543 ng hr/mL in patients with mild hepatic dysfunction, 3001 ng hr/mL in patients with moderate hepatic dysfunction, and 3682 ng hr/mL in patients with severe

hepatic dysfunction. This result was considered unusual because ezetimibe is metabolized mainly by intestinal glucuronidation, and increases in drug bioavailability associated with hepatic dysfunction have generally been reported for drugs that are metabolized mainly by hepatic cytochrome P450 enzymes.

In the second study, ezetimibe 10 mg was given for 14 days was given to 11 patients with normal hepatic function and 11 patients with moderate hepatic dysfunction. These patients were 10 males and 12 females, 40-63 years of age. The results on Day 1 were similar to the results of the single-dose study, described above. Comparing Day 14 to Day 1, bioavailability increased in both the healthy patients and the patients with moderate hepatic dysfunction. For example, the area under the curve (AUC) for total ezetimibe increased from 529 ng hr/mL to 853 ng hr/mL in the healthy patients and from 2287 ng hr/mL to 3089 ng hr/mL in the patients with moderate hepatic dysfunction.

7.2.2 Renal Dysfunction

Ezetimibe 10 mg in single doses was given to 9 healthy patients and 8 patients with severe chronic renal insufficiency. These patients were 14 males and 4 females, 31-68 years of age. AUC for total ezetimibe was 894 ng hr/mL in the healthy patients and 1317 ng hr/mL in the patients with severe chronic renal insufficiency, and the increase in AUC was associated with an increase in $T_{1/2}$. These results were considered as not being clinically significant.

7.3 Concomitant Medications

No adverse events or other safety findings in the Phase 2/3 RCTs were attributed to interaction between ezetimibe and other medication. However, these RCTs were not specifically designed to evaluate such interactions.

Pharmacokinetic and pharmacodynamic interactions between ezetimibe and other medications were evaluated in Clinical Pharmacology studies. The results are briefly summarized below. Terms such as "did not inhibit or induce," "did not alter," and "increased" or "decreased" are used to describe findings that appeared large enough to be clinically meaningful. For more information, see Biopharmaceutics review.

7.3.1 Effects Of Ezetimibe On Drug-metabolizing Enzymes

- Ezetimibe did not inhibit or induce Cytochrome P1A2, P2C8/9, P2D6, P3A4, or N-acetyltransferase enzymes, in an 8-day study of ezetimibe ~ mg, given to 12 males 22-43 years of age.

7.3.2 Effects Of Ezetimibe On Oral Contraceptives

- Ezetimibe did not alter the pharmacokinetics of ethinyl estradiol or norgestrel, in a 7-day study of ezetimibe 10 mg on days 8-14 of a 21 day oral contraceptive cycle, given to 18 females 25-35 years of age who were taking an oral contraceptive containing these steroids.

7.3.3 Effects Of Ezetimibe on warfarin, digoxin, and glipizide

- Ezetimibe did not alter the pharmacokinetics or pharmacodynamics (prothrombin time) of warfarin, in an 11-day study of ezetimibe 10 mg for 11 days and a single dose of warfarin 25 mg on day 7, given to 15 males 20-44 years of age.

- Ezetimibe did not alter the pharmacokinetics or pharmacodynamics (heart rate and PR, QT, and QTc Intervals) of digoxin, in a 10-day study of digoxin 0.5 mg on days 1 and 10, and ezetimibe 10 mg on days 3-10, given to 12 males 25-40 years of age.

- Ezetimibe did not alter the pharmacokinetics or pharmacodynamics (glucose-lowering) of glipizide, in a 9-day study of glipizide 10 mg on days 1 and 9, and ezetimibe 10 mg on days 2-9, given to 12 males 18-36 years of age.

7.3.4 Effects Of Cimetidine And Antacid On Ezetimibe

- Cimetidine increased the total ezetimibe C_{max} by 22%, with no increase in total ezetimibe AUC, in a 7-day study of ezetimibe 10 mg and ezetimibe 10 mg+cimetidine 800 mg (400 mg/ 12 hours), given to 6 males and 7 females 18-44 years of age.

- An antacid containing magnesium hydroxide (AlOH) 6 g/100 ml and aluminum hydroxide (MgOH) 9 g/100 ml decreased the total ezetimibe C_{max} by 30% with no decrease in total ezetimibe AUC, in a single-dose study of ezetimibe 10 mg and antacid 20 ml, given to 8 males and 4 females 19-31 years of age.

7.3.5 Effects Of Ezetimibe Coadministration With Cholestyramine And Cholestyramine+Simvastatin

- Cholestyramine decreased the total ezetimibe AUC by 55%, with no decrease in total ezetimibe C_{max}, and the addition of simvastatin did not further decrease total ezetimibe AUC, in a 14-day study of placebo, ezetimibe 10 mg, cholestyramine 8 grams(g) (4 g/12 hours), ezetimibe 10 mg+cholestyramine 8 grams (4 g/12 hours), and ezetimibe 10 mg+cholestyramine 8 grams (4 g/12 hours)+simvastatin 20 mg, given to 25 males and 13 females 19-48 years of age. The coadministration of cholestyramine and ezetimibe reduced LDL-C more than ezetimibe or placebo, and the addition of simvastatin further reduced LDL-C.

7.3.6 Effects Of Ezetimibe Coadministration With Gemfibrozil And Fenofibrate

- Gemfibrozil increased the total ezetimibe AUC by 68%, and increased total ezetimibe C_{max} by 80%, whereas ezetimibe did not alter the pharmacokinetics of gemfibrozil, in a 7-day study of ezetimibe 10 mg, gemfibrozil 1200 mg (600 mg/12 hours), and ezetimibe 10 mg+gemfibrozil 1200 mg (600 mg/12 hours), given to 12 males 25-45 years of age.

- Fenofibrate increased the total ezetimibe AUC by 36%, and increased total ezetimibe C_{max} by 63%, whereas ezetimibe did not alter the pharmacokinetics of fenofibrate, in a 14-day study of placebo, ezetimibe 10 mg, fenofibrate 200 mg, and ezetimibe 10 mg+fenofibrate 200 mg, given to 25 males and 8 females 25-53 years of age. The coadministration of fenofibrate and ezetimibe reduced LDL-C more than either drug alone.

7.3.7 Effects Of Ezetimibe Coadministration With Lovastatin, Pravastatin, Simvastatin, Atorvastatin, Cervistatin, and Fluvastatin

The coadministration of ezetimibe and lovastatin did not alter the pharmacokinetics of either drug, in a 7-day study of ezetimibe 10 mg, lovastatin 20 mg, and ezetimibe 10 mg+lovastatin 20 mg, given to 14 males and 5 females 18-41 years of age.

The coadministration of ezetimibe and lovastatin did not alter the pharmacokinetics of lovastatin, in a 14-day study of placebo, lovastatin 20 mg, ezetimibe -mg+lovastatin 20 mg, ezetimibe

10 mg+lovastatin 20 mg, ezetimibe ~ mg+lovastatin 20 mg, and ezetimibe 10 mg+lovastatin 40 mg, given to 48 males 24-50 years of age. The coadministration reduced LDL-C more than either drug alone.

The coadministration of ezetimibe and pravastatin did not alter the pharmacokinetics of either drug, in a 14-day study of placebo, ezetimibe 10 mg, pravastatin 20 mg, and ezetimibe 10 mg+pravastatin 20 mg, given to 30 males and 3 females 19-51 years of age.

The coadministration of ezetimibe and simvastatin did not alter the pharmacokinetics of simvastatin, in a 14-day study of placebo, simvastatin 10 mg, ezetimibe — mg+simvastatin 10 mg, ezetimibe _ mg+simvastatin 10 mg, and ezetimibe 10 mg+simvastatin 10 mg, given to 58 males 20-50 years of age. The coadministration reduced LDL-C in direct relation to the ezetimibe dose.

The coadministration of ezetimibe and simvastatin reduced LDL-C more that either drug alone, in a 14 day study of ezetimibe 10 mg, simvastatin 20 mg and ezetimibe 10 mg+simvastatin 20 mg. given to 24 males 22-49 years of age.

The coadministration of ezetimibe and atorvastatin did not alter the pharmacokinetics of either drug, in a 14-day study of placebo, ezetimibe 10 mg, atorvastatin 10 mg, and ezetimibe 10 mg+atorvastatin 10 mg, given to 28 males and 4 females 20-50 years of age. The coadministration reduced LDL-C more than either drug alone.

The coadministration of ezetimibe and cervistatin did not alter the pharmacokinetics of either drug, in a 14-day study of placebo, ezetimibe 10 mg, cerivastatin 0.3 mg, and ezetimibe 10 mg+cerivastatin 0.3 mg, given to 31 males and 1 female 22-51 years of age. The coadministration reduced LDL-C more than either drug alone.

The coadministration of ezetimibe and fluvastatin did not alter the pharmacokinetics of either drug, in a 14-day study of placebo, ezetimibe 10 mg, fluvastatin 20 mg, and ezetimibe 10 mg+fluvastatin 20 mg, given to 30 males and 2 females 22-50 years of age. The coadministration reduced LDL-C more than either drug alone.

8. CLINICAL INFORMATION FROM SOURCES OTHER THAN CLINICAL STUDIES

Ezetimibe has not been approved in any market. No clinical data are available except from clinical studies.

9. NON-CLINICAL INFORMATION

See chemistry, biopharmaceutics, and pharmacology reviews.

The main findings from animal toxicology studies that appear relevant to the clinical use of ezetimibe were in rats and dogs. In studies of ezetimibe monotherapy, there was heart and lymph node toxicity in both species, and kidney and bone marrow toxicity in rates, at ≥10x human exposure. In studies of ezetimibe coadministered with a statin, the main findings in rats were liver, skeletal muscle, and stomach toxicity; there was also spleen, heart, and prostate toxicity in individual studies. The main finding in dogs was liver toxicity; there was also testes, heart, and lung toxicity in individual studies. For methodologic reasons, a no-adverse-effect-level was difficult to establish in the coadministration studies. These animal toxicology findings were reviewed in the randomized clinical trial data.

10. PHARMACOLOGIC PROPERTIES OTHER THAN LIPID-LOWERING

No pharmacologic properties of ezetimibe have been reported other than lipid-lowering.

11. ABUSE AND OVERDOSE POTENTIAL

No withdrawal effects have been reported after stopping ezetimibe, and no overdose potential has been identified.

12. SAFETY UPDATES

12.1 4-Month Safety Update

The NDA was submitted on 27 December 2001, and the cutoff dates for inclusion of data were 31 July 2001 for completed studies, 15 July 2001 for ongoing studies with detailed analyses, and 15 August 2001 for ongoing studies with limited data. The 4-month Safety Update was submitted on 24 April 2002, and the cutoff date for inclusion of data was 30 November 2001.

12.1.1 Content

The 4-month Safety Update presented: (1) safety data from 2 14-week RCTs that were completed after the NDA cutoff date; (2) updated safety data from the ongoing UESs that are discussed in Section 5 above. In these UESs, the median Duration of Participation for all ezetimibe increased from 8.8 months in the NDA to 11.6 months in the 4-month

Safety update, and the median Duration of Participation for ezetimibe coadministered with a statin increased from increased from 5.6 in the NDA to 8.9 months in the Safety Update; (3) limited safety data from 8 other clinical studies that were ongoing as of the Safety Update cutoff date. Of these 8 other studies, 7 were discussed Under Ongoing Studies in Sections 4.5 and 5.3 above, and the remaining study was a UES for the Homozygous Sitosterolemia RCT.

12.1.2 The 14-week Randomized Clinical Trials (RCTs)

Enrollment and Randomization. The 2 14-week RCTs both enrolled patients with Primary Hypercholesterolemia who had known coronary heart disease or at least 2 cardiovascular risk factors, and patients with Heterozygous Familial Hypercholesterolemia.

During the run-in phase, patients were treated with open-label atorvastatin 10 mg (Study 1) or simvastatin 20 mg (Study 2), for at least 4 weeks. Patients who responded to the open-label statin with LDL-C <130 mg/dL were considered to be "filtered out." Patients with mean LDL-C ≥130 mg/dL and mean triglycerides ≤350 mg/dL during the run-in were continued on the open-label statin and randomized to: (1) add blinded statin to double the total dose (i.e., add blinded atorvastatin 10 mg or simvastatin 20 mg), or (2) add blinded ezetimibe 10 mg.

In Study 1, patients were randomized by a 1:1 ratio to a total atorvastatin dose of 20 mg or to ezetimibe 10 mg+atorvastatin 10 mg, and in Study 2, patients were randomized by a 1:2 ratio to a total simvastatin dose of 40 mg or to ezetimibe 10 mg+simvastatin 20 mg. Following randomization, there were 316 patients in the atorvastatin 20 mg group and 305 patients in the ezetimibe 10 mg+atorvastatin 10 mg group (Study 1); there were 34 patients in the simvastatin 20 mg group and 66 patients in the ezetimibe 10 mg+simvastatin 10 mg group (Study 2). Thus, there were 350 patients in the atorvastatin 20 mg or simvastatin 40 mg group and 371 patients in the ezetimibe 10 mg+atorvastatin 10 mg or simvastatin 20 mg group. This comprised the "Filter Coadministration Pool."

The term "statin" is used below to mean "atorvastatin 20 mg or simvastatin 40 mg" and "ezetimibe 10 mg+statin" is used to mean "ezetimibe 10 mg+atorvastatin 10 mg or simvastatin 20 mg."

Demographics And Other Baseline Characteristics. Of the 721 patients, 89.0% Caucasian and 53.0% male. The median age was 54 years and the range 18-82 years. The treatment groups were generally well-balanced for these and other baseline variables.

Patient Disposition. Of the 721 Patients, 656 (91.0%) completed treatment. Of the 65 (9.0%) discontinuations, 34 (4.7%) were for AEs, 15 (2.1%) were for noncompliance with protocol, 11 (1.5%) did not wish to continue, and 5 (0.7%) were lost to follow-up.

12.1.2.1 Adverse Events (AEs)

12.1.2.1.1 Overview

Table 101 presents an overview of the AEs. The main findings are shown below in Table 101A.

Table 101A: Filter Coadministration Pool AEs: Number (%) Of Patients

Adverse Event	Statin	Ezetimibe 10 mg+statin
Death	1 (0.3%)	0
Serious AE*	8 (2.3%)	16 (4.3%)
Discontinuation due to AE	15 (4.3%)	19 (5.1%)
AEs of Any Intensity	208 (59.4%)	238 (64.2%)
Any Severe or Life-Threatening AE	16 (4.6%)	28 (7.5%)

*See Section 1.5

12.1.2.1.2 Deaths And Other Serious Adverse Events (AEs)

12.1.2.1.2.1 Deaths

A 53 year old Caucasian male with a history of Heterozygous Familial Hypercholesterolemia, coronary artery bypass grafting, angina, stroke, and carotid bypass began atorvastatin 40 mg in November 2000 and died 99 days later due to myocardial infarction. No autopsy was performed. The investigator considered the event as unlikely to be related to treatment. There were no other deaths.

12.1.2.1.2.2 Serious Adverse Events (SAEs)

Table 102 shows the SAEs. SAEs were reported for 8 (2.3%) patients in the statin group and 16 (4.3%) patients in the ezetimibe 10 mg+statin group. The SAEs in the ezetimibe 10 mg+statin group included hepatitis, liver abcess, musculo-skeletal pain, myalgia, and others.

SAEs that were considered to be treatment-related were reported for 1 (0.3%) patient in the statin group and 2 (0.5%) patients in the ezetimibe 10 mg+statin group. The SAEs in the ezetimibe 10 mg+statin group that were considered to be treatment-related included hemolytic anemia and hepatitis for 1 patient and mylagia for 1 patient.

12.1.2.1.3 Discontinuations Due To Adverse Events (AEs)

AEs that led to discontinuation from a study were reported for 15 (4.3%) patients in the statin group and 19 (5.1%) patients in the ezetimibe 10 mg+statin group. The AEs in the ezetimibe 10 mg+statin group that led to discontinuation from a study included anemia, anemia hemolytic, hepatitis, liver abcess, musculo-skeletal pain, myalgia, myopathy, and others.
AEs that led to discontinuation from a study and were considered to be treatment-related were reported for 11 (3.1%) patients in the statin group and 14 (3.8) patients in the ezetimibe 10 mg+statin group. The AEs in the ezetimibe 10 mg+statin group that led to discontinuation from a study and were considered to be treatment-related included hemolytic anemia, hemoglobin decreased, hepatitis, musculoskeletal pain, myalgia, and others.

12.1.2.1.4 Treatment-Emergent Adverse Events (AEs) Of Any Intensity

AEs of any intensity were reported for 208 (59.4%) patients in the statin group and 238 (64.2%) patients in the ezetimibe 10 mg+statin group. The most frequent were: upper respiratory infection, myalgia, headache, abdominal pain, musculoskeletal pain, and nausea. These AEs could generally be expected in a middle-aged patient population. There were 22 (6.3%) patients in the statin group and 33 (9.9%) patients in the ezetimibe 10 mg+statin group with headache. For the other AEs of any intensity, the frequencies of patients with AEs of any intensity were similar or higher in the statin group and the ezetimibe 10 mg+statin group.

AEs of any intensity that were considered to be treatment related were reported for 80 (22.9%) patients in the statin group and 94 (25.3%) patients in the ezetimibe 10 mg+statin group. The frequencies of patients with AEs of any intensity that were considered to be treatment-related were similar in the statin group and the ezetimibe 10 mg+statin group.

AEs that were considered to be severe or life-threatening were reported for 16 (4.6%) patients in the statin group and 28 (7.5%) patients in the ezetimibe 10 mg+statin group. Table 103 shows the AEs that were considered to be severe or life threatening. The AEs in the ezetimibe

10 mg+statin group that were considered to be severe or life-threatening were diverse; of the 28 individual AEs, 23 were reported for 1 patient each, 4 were reported for 2 patients each, and 1 was reported for 4 patients.

12.1.2.2 Laboratory Tests

The results for blood chemistry, hematology, urinalysis, and fecal occult blood were similar to the results in the monotherapy pool (Section 4.1.1.2), the factorial coadministration pool (Section 4.1.2.2), and the add-on study (Section 4.1.3.2).

12.1.2.3 Clinical Adverse Events (AEs) And Laboratory Test Values Of Special Interest

The frequencies of patients with AEs in the statin group and the ezetimibe 10 mg+statin group were similar for Allergic Reaction/Rash AEs, Central and Peripheral Nervous System AEs, Psychiatric AEs, and Gastrointestinal AEs, and Gall-bladder-related AEs.

The frequencies of patients with Liver and Biliary System AEs, and elevated hepatic enzymes, in the statin group and the ezetimibe 10 mg+statin group, were similar to the results in the factorial coadministration pool (Section 4.1.2.3.6), and the add-on study (Section 4.1.3.3.1), with the exception of 2 patients: (1) 1 patient in the ezetimibe 10 mg+statin group was discontinued from the study after 42 days due to Coombs-positive hemolytic anemia and hepatitis. ALT, AST, alkaline phosphatase, and bilirubin were increased 1 day before discontinuation, and returned to baseline or near baseline 40 days later; (2) 1 patient in the ezetimibe 10 mg+statin group had a liver abcess; however, there was evidence of an amoebic liver abcess before the study began.

The frequencies of patients with elevated CPK activity and muscle-related AEs in the statin group and the ezetimibe 10 mg+statin group were similar to the results in the factorial coadministration pool (Section 4.1.2.3.7) and the add-on study (Section 4.1.3.3.2).

12.1.2.4 Vital Signs And Body Weight

The results for vital signs and body weight were similar to the results in the factorial coadministration pool (Section 4.1.2.4) and the add-on study (Section 4.1.3.4).

12.1.2.5 Electrocardiograms

In patients with normal baseline ECGs, the frequencies of patients with clinically significant postbaseline changes were 2 (1.1%) in the statin group and none in the ezetimibe 10 mg+statin group, and the frequencies of patients with changes that were not clinically significant were 26 (14.9%) in the statin group and 31 (18.2%) in the ezetimibe 10 mg+statin group. In patients with abnormal baseline ECGs, the frequencies of patients with clinically significant postbaseline changes were 4 (2.3%) in the statin group and 4 (2.0%) in the ezetimibe 10 mg+statin group, and the frequencies of patients with changes that were not clinically significant were 54 (30.9%) in the statin group and 83 (41.3%) in the ezetimibe 10 mg+statin group. An increase in ECG changes that were not clinically significant, in patients treated with ezetimibe 10 mg and statin compared to statin, was not seen in the factorial coadministration pool (Section 4.1.2.5).

12.1.2.6 Cardiopulmonary Examinations

Abnormal postbaseline cardiopulmonary examination results were reported for 22 (6.3%) patient in the statin group and 39 (10.5%) patients in the ezetimibe 10 mg+statin group. Most of this difference was in study 2, were abnormal results were reported for 3 (8.8%) patients in the simvastatin 40 mg group and 16 (24.4%) patients in the ezetimibe 10 mg+simvastatin 20 mg group. There was no qualitative difference between treatment groups in the nature of the abnormal findings, most of which were wheezing, other changes in breath sounds, and various heart sounds or murmurs. An increase in abnormal cardiopulmonary examination results, in patients treated with ezetimibe 10 mg and statin compared to statin, was not seen in the factorial coadministration pool (Section 4.1.2.6).

12.1.2.7 Effects of Sex, Age, and Race On Safety Results

There were only minor variations from the results in the factorial coadministration pool (see Section 7.1.2.1.2).

12.1.3 Ongoing UESs And Other Clinical Studies.

There were no new safety findings in the updated safety data from the ongoing UESs that are discussed in Section 5 above, or in the limited safety data from the 8 other clinical studies that were ongoing as of the Safety Update cutoff date.

12.1.4 Conclusion

The 4-month Safety Update identified no new or worsened adverse events or laboratory safety results that appear to have been related to treatment with ezetimibe.

12. 2 8-Month Safety Update

The 8-month Safety Update was submitted on 21 August 2002, and the cutoff date for inclusion of data was 15 March 2002.

12.2.1 Content

The 8-month Safety Update presented: (1) safety data from a 12-week factorial RCT of ezetimibe 10 mg and simvastatin (10, 20, 40, and 80 mg) that was completed after the 4-month Safety Update cutoff date; (2) safety data from the 6-week, open-label "reversibility phase" of the add-on study (see Section 4.1.3), which occurred after blinded study drug had been stopped; (3) updated safety data from the UESs that are discussed in Section 5 above. In these UESs, the median Duration of Participation for all ezetimibe increased from 11.6 months in the 4-month Safety Update to 18.5 months in the 8-month Safety Update, and the median Duration of Participation for ezetimibe coadministered with a statin increased from 8.9 months in the 4-month Safety Update to 11.6 months in the 8-month Safety Update; safety data from 3 small crossover Clinical Pharmacology studies; limited safety data from 8 other clinical studies that were ongoing as of the 8-month Safety Update cutoff date, and from 1 study that was terminated due to poor enrollment.

12.2.2 Conclusion

The 8-month Safety Update identified no new or worsened adverse events or laboratory safety results that appear to have been related to treatment with ezetimibe.

13. CONSULTS

A study to evaluate [redacted] was suggested in an informal discussion with Mark Avigan, M.D., Division of Gastrointestinal and Coagulation Drug Products. However, the NDA review raised no gastrointestinal safety issues, and evidence was presented that ezetimibe 10 mg does not inhibit the absorption of fat soluble vitamins. Therefore, a study [redacted]

[redacted] does not appear to be a safety issue. The potential value of study can be discussed as an addition to an ongoing or upcoming IND.

14. CONCLUSIONS

14.1 General

The NDA Integrated Summary of Safety, the individual study reports, and the reports on additional data requested during the review, were well-organized and clearly presented. The methods used to evaluate safety were generally appropriate and rigorous.

14.2 Extent Of Safety Testing

The safety data from randomized, double-blind, placebo-controlled clinical trials (RCTs) provided sufficient information, on a sufficient number of patients, for detailed evaluation of the safety of ≤12 weeks of treatment with ezetimibe 10 mg (the only dose proposed for marketing). The RCTs investigated ezetimibe 10 mg as monotherapy for Primary Hypercholesterolemia, and as coadministered or added therapy, with a statin, for Primary Hypercholesterolemia, Homozygous Familial Hypercholesterolemia, and Homozygous Sitosterolemia. Most of the coadministered/added therapy was with lovastatin, pravastatin, simvastatin, or atorvastatin.

The safety data from uncontrolled extension studies provided sufficient information, on a sufficient number of patients, for general evaluation of longer treatment with ezetimibe 10 mg. For Primary Hypercholesterolemia, the median length of follow-up was 18.5 months for any treatment with ezetimibe 10 mg in patients from the 2 RCTs of ezetimibe monotherapy, and 11.6 months for treatment with ezetimibe 10 mg+statin in patients from the 2 RCTs of ezetimibe monotherapy and 3 of the 4 RCTs of ezetimibe coadministered with a statin. For patients with Homozygous Familial Hypercholesterolemia, the median length of follow-up was 6.1 months, for treatment with ezetimibe 10 mg+statin.

The above conclusions are in accordance with Division recommendations (see minutes of 25 April 2002 Pre-NDA meeting).

14.3 Adverse Events And Laboratory Results

14.3.1 Primary Hypercholesterolemia

14.3.1.1 Randomized Clinical Trials Of Ezetimibe Monotherapy

In pooled data from the randomized clinical trials of ezetimibe monotherapy, the placebo group, the ezetimibe 10 mg group, and the ezetimibe all doses group [redacted] mg) were similar in the overall frequencies of patients with postbaseline serious adverse events, discontinuations due to adverse events, adverse events of any intensity, and adverse events that were considered severe or life-threatening by the investigators.

14.3.1.1.1 Important Adverse Events And Laboratory Safety Results

The important postbaseline adverse events and laboratory safety results, that appear related to treatment with ezetimibe 10 mg, involved the liver and skeletal muscle.

Liver. There were 11 (1.4%) patients in the placebo group and 32 (1.9%) patients in the ezetimibe 10 mg group with Liver and Biliary System adverse events, including 7 (0.9%) patients in the placebo group and 26 (1.5%) patients in the ezetimibe 10 mg group with ≥1 adverse event in the Hepatic Pool of adverse events [hepatic enzymes increased, hepatic function abnormal, SGOT (AST) increased, and SGPT (ALT) increased].

With regard to laboratory results, there were 4 (0.5%) patients in the placebo group and 14 (0.8%) patients in the ezetimibe 10 mg group with ALT (SGPT) and/or AST (SGOT) ≥3xULN, of whom there were 3 (0.4%) patients in the placebo group and 9 (0.5%) patients in the ezetimibe 10 mg group with consecutive ALT and/or AST ≥3xULN. No patient had ALT and/or AST ≥10xULN. The findings for GGT, alkaline phosphate, and bilirubin were similar or less different between the 4 treatment groups.

Muscle. There were no reports of rhabdomyolysis. There were 12 (1.5%) patients 24 (1.4%) patients in the ezetimibe 10 mg group with elevated CPK as an adverse event.

With regard to laboratory results there were 11 (1.3%) patients in the placebo group and 42 (2.5%) patients in the ezetimibe 10 mg group with CPK ≥3xULN. There were no patients in the placebo group and 4 (0.2%) patients in the ezetimibe 10 mg group with CPK 5 to <10xULN and associated with muscle symptoms. There were 1 (0.1%) patient in the

placebo group and 4 (0.2%) patients in the ezetimibe 10 mg group with CPK ≥10xULN. The highest CPK value was 5540 mU/mL, in a 25 year old Caucasian male treated with ezetimibe 5 mg.

14.3.1.1.2 Other Adverse Events And Laboratory Safety Results

With regard to other postbaseline adverse events, that could possibly have been related to treatment with ezetimibe 10 mg, there were 7 (0.9%) patients in the placebo group and 39 (2.3%) patients in the ezetimibe 10 mg group with allergy or allergy aggravated; most of these events were considered seasonal or environmental, and rated mild or moderate in severity. There were 1 (0.1%) patient in the placebo group and 14 (0.9%) patients in the ezetimibe 10 mg group with gastroesophageal reflux or gastroesophageal reflux aggravated adverse events, most of these events were rated mild or moderate in severity.

With regard to other postbaseline laboratory safety results, that could possibly to have been related to treatment with ezetimibe 10 mg, there were 1 (0.1%) patient in the placebo group and 10 (0.6%) patients in the ezetimibe 10 mg group with ≥1 platelet count below $100x10^9$/L; all of these patients were asymptomatic, and in most a low platelet count was observed on only 1 occasion. There were 5 (0.6%) patients in the placebo group and 19 (1.1%) patients in the ezetimibe 10 mg group with ≥1 white blood cell count below $3.0x10^9$/L; all of these patients were asymptomatic and in most the difference between the lowest prerandomization count an the lowest postrandomization count was ≤$0.5x10^9$/L. There were no patients in the placebo group and 4 (0.3%) patients in the ezetimibe 10 mg group with prothrombin times >1.5xULN; the maximum prothrombin times were 17.3 seconds in the placebo group and 25.5 seconds in the ezetimibe 10 mg group.

Overall, the most frequent postbaseline adverse events were upper respiratory infection, headache, back pain, arthralgia, and musculoskeletal pain. The frequencies of patients with these events were similar in the placebo group and ezetimibe 10 mg group.

14.3.1.1.3 Effects Of Sex, Age, And Race On Adverse Events And Laboratory Safety Results

Treatment with ezetimibe 10 mg resulted in more frequent postbaseline CPK elevations in men compared to women, especially in Black males. The generally small numbers of patients in specific non-Caucasian racial/ethnic groups limited the potential for more detailed evaluation of racial/ethnic variation.

Sex. The frequencies of female patients with CPK ≥3xULN were none in the placebo group and 5 (0.6%) patients in the ezetimibe 10 mg group, whereas the frequencies of male patients with CPK ≥3xULN were 11 (3.0%) patients in the placebo group and 37 (4.6%) patients in the ezetimibe 10 mg group. In Black males, the frequencies of CPK ≥3xULN were 4 (21.1%) in the placebo group and 12 (26.7%) in the ezetimibe 10 mg group.

Race. The frequencies of Caucasian patients with CPK ≥3xULN were 7 (1.0%) patients in the placebo group and 26 (1.7%) patients in the ezetimibe 10 mg group, whereas the frequencies of non-Caucasian patients with CPK ≥3xULN were 4 (5.1%) patients in the placebo group and 16 (9.6%) patients in the ezetimibe 10 mg group. These differences were largely due to the higher frequencies of CPK ≥3xULN in Black males.

14.3.1.2 Uncontrolled Extension Study Of Patients From Randomized Clinical Trials Of Ezetimibe Monotherapy

The uncontrolled extension study of patients from the randomized clinical trials of ezetimibe monotherapy identified no new or worsened postbaseline adverse events or laboratory safety results that appear to have been related to treatment with ezetimibe.

14.3.1.3 Randomized Clinical Trials Of Ezetimibe Coadministered With A Statin

In pooled data from the randomized clinical trials of ezetimibe coadministered with a statin, the placebo group, ezetimibe 10 mg group, statin group, and ezetimibe 10 mg+statin group were similar in the overall frequencies of patients with postbaseline serious adverse events, discontinuations due to adverse events, adverse events of any intensity, and adverse events that were considered severe or life-threatening by the investigators.

14.3.1.3.1 Important Adverse Events And Laboratory Safety Results

The important postbaseline adverse events and laboratory safety results, that appear related to treatment with ezetimibe, involved the liver and skeletal muscle.

Liver. There were 4 (1.5%) patients in the placebo group, 5 (1.9%) patients in the ezetimibe 10 mg group, 23 (2.5%) patients in the statin group, and 53 (5.7%) patients in the ezetimibe 10 mg+statin group with Liver and Biliary System adverse events. Within these totals, the individual adverse event

frequencies in the ezetimibe 10 mg group compared to the placebo group were similar to those seen in the monotherapy pool analysis (see Section 14.3.1.1.1). In the ezetimibe 10 mg+statin group compared to the statin group, the largest increase was in the Hepatic Pool of adverse events [hepatic enzymes increased, SGOT (AST) increased, and SGPT (ALT) increased]. There were 16 (1.7%) patients in the statin group and 47 (5.1%) patients in the ezetimibe 10 mg+statin group with adverse events in the Hepatic Pool, including 1 (0.1%) patient in the statin group and 8 (0.9%) patients in the ezetimibe 10 mg+statin group with serious adverse events, and 3 (0.3%) patients in the statin group and 10 (1.1%) patients in the ezetimibe 10 mg+statin group with adverse events that led to discontinuation from a study.

With regard to laboratory results, there were no patients in the placebo group, 2 (0.8%) patients in the ezetimibe 10 mg group, 9 (1.0%) patients in the statin group, and 19 (2.1%) patients in the ezetimibe 10 mg+statin group with ALT (SGPT) and/or AST (SGOT) $\geq$3xULN, of whom there were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 4 (0.4%) patients in the statin group, and 13 (1.4%) patients in the ezetimibe 10 mg+statin group with consecutive ALT and/or AST $\geq$3xULN No patient had ALT and/or AST $\geq$10xULN. The findings for GGT, alkaline phosphate, and bilirubin were similar or less different between the placebo group and ezetimibe 10 mg group.

Muscle. There were no reports of rhabdomyolysis. There were 5 (1.9%) patients in the placebo group, 4 (1.5%) patients in the ezetimibe 10 mg group, 12 (1.3%) patients in the statin group, and 14 (1.5%) patients in the ezetimibe 10 mg+statin group with elevated CPK as an adverse event.

With regard to laboratory results, there were 3 (1.2%) patients in the placebo group, 6 (2.4%) patients in the ezetimibe 10 mg group, 25 (2.6%) patients in the statin group, and 15 (1.6%) patients in the ezetimibe 10 mg+statin group with CPK $\geq$3xULN. There were no patients in the placebo group, 2 (0.8%) patients in the ezetimibe 10 mg group, no patients in the statin group, and 1 (0.1%) patients in the ezetimibe 10 mg+statin group with CPK 5 to <10xULN who had associated muscle symptoms. There were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 4 (0.4%) in the statin group, and 1 (0.1%) patient in the ezetimibe 10 mg+statin group with CPK $\geq$10xULN. The highest CPK value was 6770 mU/mL, in a 39 year old Black woman treated with simvastatin 20 mg.

Note: The frequencies of CPK elevations were not higher in patients treated with ezetimibe 10 mg+statin group compared to the same type and dose of statin given alone.

14.3.1.3.2 Other Adverse Events And Laboratory Safety Results

With regard to other postbaseline adverse events or laboratory safety results, that could possibly have been related to treatment with ezetimibe, there were no particular results of concern

Overall, the most frequent postbaseline adverse events were upper respiratory infection, headache, myalgia, musculoskeletal pain, and nausea. The frequencies of patients with these events were similar in the placebo group, ezetimibe 10 mg group, statin group, and ezetimibe 10 mg+statin group.

14.3.1.3.3 Effects Of Sex, Age, And Race On Adverse Events And Laboratory Safety Results

Treatment with ezetimibe 10 mg, and statins, resulted in more frequent CPK elevations in men compared to women, especially in Black males. The generally small numbers of patients in specific non-Caucasian racial/ethnic groups limited the potential for more detailed evaluation of racial/ethnic variation.

Sex. The frequencies of female patients with CPK≥3xULN, were none in the placebo group, 2 (1.3%) patients in the ezetimibe 10 mg group, 4 (0.7%) patients in the statin group, and 3 (0.6%) patients in the ezetimibe 10 mg+statin group, whereas the frequencies of male patients with CPK≥3xULN were 3 (2.7%) patients in the placebo group, 4 (3.7%) patients in the ezetimibe 10 mg group, 21 (5.4%) patients in the statin group, and 12 (3.0%) patients in the ezetimibe 10 mg+statin group. In Black males, the frequencies of CPK ≥3xULN were 1 (14.3%) in the placebo group, 2 (50.0%) in the ezetimibe 10 mg group, 5 (21.7%) in the statin group, and 3 (18.8%) in the ezetimibe 10 mg+statin group.

Race. The frequencies of Caucasian patients with CPK ≥3xULN were 2 (0.9%) patients in the placebo group, 4 (1.7%) patients in the ezetimibe 10 mg group, 17 (2.1%) patients in the statin group, and 10 (1.2%) in the ezetimibe 10 mg+statin group, whereas the frequencies of non-Caucasian patients with CPK ≥3xULN were 1 (3.1%) in the placebo group, 2 (7.7%) in the ezetimibe 10 mg group, 8 (6.6%) in the statin group, and 5 (4.5%) in the ezetimibe 10 mg+statin group. These differences were largely due to

higher frequencies of CPK ≥3xULN in Black males compared to other non-Caucasian patients.

14.3.1.4 Uncontrolled Extension Study Of Patients From Randomized Clinical Trials Of Ezetimibe Coadministered With A Statin

The uncontrolled extension study of patients from the randomized clinical trials of ezetimibe monotherapy identified no new or worsened postbaseline adverse events or laboratory safety results that appear to have been related to treatment with ezetimibe.

14.3.1.5 Randomized Clinical Trial Of Ezetimibe Added to An Established Statin

The adverse events and laboratory safety results that appear to have been related to treatment with ezetimibe in the randomized clinical trial of ezetimibe added to an established statin were similar to the adverse events and laboratory safety results described above for ezetimibe coadministered with a statin.

14.3.2 Homozygous Familial Hypercholesterolemia And Homozygous Sitosterolemia.

The adverse events and laboratory safety results that appear to have been related to treatment with ezetimibe in the randomized clinical trials for Homozygous Familial Hypercholesterolemia and Homozygous Sitosterolemia, and in the uncontrolled extension study for Homozygous Sitosterolemia, were similar to the adverse events and safety results described above for ezetimibe coadministered with a statin.

14.4 Animal Toxicology In Relation To Clinical Safety Results

Safety issues raised by animal toxicology studies were evaluated in the data from randomized clinical trials and uncontrolled extension studies. There was agreement between the 2 sources of information in finding evidence of liver and muscle toxicity for ezetimibe.

14.5 Exposure in Clinical Studies Compared to Probable Marketplace Exposure

It is probable that large numbers of people will be treated with ezetimibe 10 mg for long periods of time. The number of patients treated with ezetimibe 10 mg in the clinical studies was sufficient for a thorough evaluation of safety. The duration of treatment in completed randomized

clinical trials was short in relation to probable marketplace durations of treatment, but was complemented by the uncontrolled extension studies, and randomized clinical trials with longer durations of treatment will soon be completed.

14.6 Composition Of Clinical Trial Populations Compared To Probable Marketplace Population

The randomized clinical trial populations appear to have been generally representative of the probable marketplace population, and the rates of discontinuation from the randomized clinical trials were low.

14.7 Relationship To Other Drugs For Hypercholesterolemia

It appears likely that ezetimibe will be used extensively in coadministration with a statin. It is possible that this could represent an improvement in the safety of the treatment of Hypercholesterolemia, since the frequencies of patients with CPK elevations in the clinical studies were not increased for ezetimibe 10 mg coadministered with a statin compared to the same statin type and dose given alone.(see efficacy review regarding greater effectiveness of ezetimibe 10 mg+statin compared to statin alone).

15. RECOMMENDATIONS

1. APPROVAL

2. Phase 4 Studies

A study should be requested to further evaluate racial/ethnic variation in responses to ezetimibe 10 mg, as monotherapy and in coadministration with a statin, with emphasis on the evaluation of adverse events involving skeletal muscle and the detection of CPK elevations.

3. Labeling

Labeling should address the important adverse events and laboratory safety issues (see Sections 14.3.1.1.1 and 14.3.1.3.), and will be negotiated with Merck/Schering-Plough.

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NDA 21-445
Zetia® (ezetimibe) for Hypercholesterolemia and Hypersitosterolemia
Integrated Review of Safety: Part II (Tables)
Bruce V. Stadel, MD, MPH

Table 1 The 12 Completed Randomized Clinical Trials

Protocol(s)	Study Title and Design	Treatment Duration	Number of Subjects Assigned Treatment With Ezetimibe[a] Total[b]	No Statin	With a Statin
	Primary Hypercholesterolemia				
C96-411 and C96-345[c]	Pilot Dose-Ranging Study of the Safety and Efficacy of SCH 58235 Compared to Placebo and Lovastatin in Patients With Primary Hypercholesterolemia R, DB, PC, PG - EZ ~ 10, ~ mg - QD before AM meal	8 weeks	89 (18 at 10 mg)	89 (18 at 10 mg)	0
C98-010	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 R, DB, PC, PG - EZ ~ 10 mg - QD before AM meal	12 weeks	191 (46 at 10 mg)	191 (46 at 10 mg)	0
C98-258	A Double-Blind Investigation of the Efficacy and Safety of Morning Versus Evening Dosing of Two Doses Of SCH 58235 Compared With Placebo in Subjects With Primary Hypercholesterolemia R, DB, PC, PG - EZ ~10 mg - QD before AM meal or at bedtime	12 weeks	153 (77 at 10 mg)	153 (77 at 10 mg)	0
P00474	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg Compared With Placebo in Subjects With Primary Hypercholesterolemia R, DB, PC, UPG - EZ 10 mg – QD before AM meal	12 weeks	622	622	0
P00475	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg Compared With Placebo in Subjects With Primary Hypercholesterolemia R, DB, PC, UPG - EZ 10 mg – QD before AM meal	12 weeks	666	666	0
P00679	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Lovastatin Compared With Placebo in Subjects With Primary Hypercholesterolemia R, DB, PC, PG - EZ 10 mg – lova 10, 20, 40 mg - EZ + lova 10, 20, 40 mg - QD with PM meal	12 weeks	264	72	192
P00680	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Simvastatin Compared With Placebo in Subjects With Primary Hypercholesterolemia R, DB, PC, PG - EZ 10 mg – simva 10, 20, 40, 80 mg - EZ + simva 10, 20, 40, 80 mg - QD in PM	12 weeks	335	61	274
P00691	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Pravastatin Compared With Placebo in Subjects With Primary Hypercholesterolemia R, DB, PC, PG - EZ 10 mg – prava 10, 20, 40 mg - EZ + prava 10, 20, 40 mg - QD at bedtime	12 weeks	268	64	204
P00692	A Phase III Double-Blind Efficacy and Safety Study of Ezetimibe (SCH 58235) 10 mg in Addition to Atorvastatin Compared With Placebo in Subjects With Primary Hypercholesterolemia R, DB, PC, PG - EZ 10 mg – atorva 10, 20, 40, 80 mg - EZ + atorva 10, 20, 40, 80 mg - QD in AM	12 weeks	320	65	255
P02173 and P02246[d]	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety, and Tolerability of SCH 58235 When Added to Ongoing Therapy With an HMG-CoA Reductase Inhibitor (Statin) in Patients With Primary Hypercholesterolemia, Known Coronary Heart Disease, or Multiple Cardiovascular Risk Factors R, DB, PC, PG - EZ 10 mg – subjects already taking any approved dose of any approved statin, then add placebo or EZ to present statin/dose - QD per statin label	8 weeks	379	0	379
	Subtotals for Primary Hypercholesterolemia		3287 (2995 at 10 mg)	1983 (1691 at 10 mg)	1304 (1304 at 10 mg)
	Homozygous Familial Hypercholesterolemia				
P01030	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 R, DB, PG - EZ 10 mg - lead in on atorva or simva 40 mg, then randomized assignment to add (1) additional atorva or simva 40 mg, or (2) EZ, or (3) EZ + additional atorva or simva 40 mg - QD with atorva in AM or with simva in PM	12 weeks	33	0	33

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Table 1 Completed.

Protocol(s)	Study Title and Design	Treatment Duration	Number of Subjects Assigned Treatment With Ezetimibe[a] Total[b]	No Statin	With a Statin
	Homozygous Sitosterolemia				
P02243 and P02257[e]	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 R, DB, PC, UPG - EZ 10 mg – subjects already receiving any standard of care, then add placebo or EZ - QD in AM, ≥2 h before or ≥4 h after bile acid binding resin	8 weeks	30	23	7
	Grand Totals for Controlled, Blinded Clinical Therapy Trials of 2 to 3 Months Treatment		3350 (3058 at 10 mg)	2006 (1714 at 10 mg)	1344 (1344 at 10 mg)

a: Randomized treatment assignment.

b: Regardless of any other concomitant therapy.

c: Protocol C96-411 was a no-treatment screening protocol; upon completing this protocol, subjects continued directly into Protocol C96-345 for placebo run-in and subsequent randomized treatment.

d: Protocol P02173 was for centers in the USA, and Protocol P02246 was for centers outside the USA — the study design and procedures were the same in both protocols. After the 8-week treatment phase, there was a 6-week recovery phase during which subjects continued to take their statin without ezetimibe. The protocols were amended to allow a 1-year blinded, long-term extension after the 6-week recovery phase. The report included in this submission includes results for the 8-week treatment phase only, as the remainder of the study was ongoing at the time of clinical cut-off.

e: Protocol P02243 was for centers in the USA, and Protocol P02257 was for centers outside the USA — the study design and procedures were the same in both protocols.

AM = morning; atorva = atorvastatin; DB = double blind; EZ = ezetimibe; lova = lovastatin; PC = placebo controlled; PG = parallel groups; PM = evening; prava = pravastatin; QD = once daily; R = randomized; simva = simvastatin; UPG = unbalanced parallel groups.

Table 2 The 4 Ongoing Uncontrolled Extension Studies Related To The 12 Completed Randomized Clinical Trials

Protocol(s)	Study Title and Design	Treatment Duration[b]	Number of Subjects Treated: All (New Since Base Study)[a] Total EZ	EZ / No Statin[c]	EZ With a Statin
	Primary Hypercholesterolemia				
P00476	Long-Term, Open-Label, Safety and Tolerability Study of Ezetimibe (SCH 58235) in Subjects with Primary Hypercholesterolemia OL - EZ 10 mg - subjects to continue directly into P00476 from base protocols P00474 or P00475 - all subjects to receive EZ monotherapy at start, then could have lova or simva 10 mg added, and subsequently up-titrated, based on LDL-C response - monotherapy QD in AM; coadministration QD per statin label	2 years	1313 (336)	783 (+208[d]; -402[e] monoRx in base, but coad in P00476; Table 13)	530 (530)
P01416	Long-Term, Open-Label, Safety and Tolerability Study of Ezetimibe (SCH 58235) in Addition to Pravastatin in Patients With Primary Hypercholesterolemia OL - EZ 10 mg - subjects to continue directly into P01416 from base study P00691 - all subjects to receive EZ plus prava 10 mg at start, with possible up-titration of prava based on LDL-C response - QD in PM	1 year	321 (153)	0 (-35[e] monoRx in base, but coad in P01416; Table 14)	321 (188)
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) OL - EZ 10 mg - subjects who completed P00679 or P00680 and left these studies were later offered the opportunity to return and participate in P02134; long-term experience begins with treatment in P02134 - all subject to receive EZ plus simva 10 mg at start, with possible up-titration of simva based on LDL-C response - QD in PM	1 year	359 (181)	0 (-42[e] monoRx in base, but coad in P02134; Table 15)	359 (223)
	Subtotals for Primary Hypercholesterolemia		1993 (670)	783 (+208[d]; -479[e] monoRx in base, but coad in extension)	1210 (941)
	Homozygous Familial Hypercholesterolemia				
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 OL - EZ 10 mg - subjects to continue directly into P01417 from base study P01030 - all subjects to receive EZ plus atorva or simva (per assignment in P01030) 40 mg at start, with possible up-titration of atorva or simva based on LDL-C response - QD with atorva in AM or with simva in PM	2 years	45 (12)	0	45 (12)
	Grand Totals for Ongoing Uncontrolled, Open-Label, Long-Term Extension Trials		2038 (682)	783 (+208[d]; -479[e] monoRx in base, but coad in extension)	1255 (953)

a: "New since base study" indicates subjects who were not assigned to receive ezetimibe or ezetimibe/statin coadministration during the controlled, blinded base study in which subjects initially participated, but received ezetimibe or ezetimibe/statin coadministration in the extension, and "(All)" indicates all subjects in the extension data base regardless of whether they previously received ezetimibe or ezetimibe/statin coadministration in the previous base study. Note that for P00476, P01416, and P01417, these numbers reflect ONLY the extension data base, and not the entire data base for reporting long-term experience from P00474/P00475/P00476, P00691/P01416, and P01030/P01417, respectively (see the explanation prior to Table 1).

b: Protocol-specified duration of this protocol; the study is ongoing.

c: Subject was receiving ezetimibe monotherapy as of July 15, 2001 (subject had received no statin during the base study or the extension).

d: Subjects received placebo in P00474 or P00475 and ezetimibe 10 mg without coadministered statin in P00476.

e: Subjects counted as EZ monotherapy in base protocol, but received coadministration in extension protocol; negative number is for overall accounting.

AM = morning; atorva = atorvastatin; base = base protocol(s); EZ = ezetimibe; LDL-C = low-density-lipoprotein cholesterol; lova = lovastatin; monoRx = monotherapy; PM = evening; prava = pravastatin; OL = open label; QD = once daily; simva = simvastatin.

Table 3 The 8 Ongoing Randomized Clinical Trials And The 1 Related Uncontrolled Extension Study

Protocol(s)[a]	Study Title and Design
P00693	A Phase III Double-Blind Efficacy and Safety Study of SCH 58235 (10 mg) 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 R, DB, AC, PG; atorva 10-mg lead-in, then randomized assignment of EZ 10 mg plus additional atorva 10 mg versus additional atorva 10 mg alone; LDL-C-response-based up-titration of atorva dose at 4- to 5-wk intervals to maximum of 80 mg - QD in AM for 14 weeks
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 of Simvastatin (20 mg) R, DB, AC, PG; simva 20-mg lead-in, then randomized assignment of EZ 10 mg plus additional simva 20 mg versus additional simva 20 mg alone; LDL-C-response-based up-titration of simva dose at 4- to 5-wk intervals to maximum of 80 mg - QD in AM for 14 weeks
005 (Base Phase) (Extension Phase)	Base: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, "Factorial" Design, 12-Week Study to Evaluate the Efficacy of SCH 58235 10 mg/day Coadministered With Multiple Doses of Simvastatin in Patients With Primary Hypercholesterolemia Extension: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, "Factorial" Design, 48-Week Extension Study to Evaluate the Safety of SCH 58235 10 mg/day Coadministered With Multiple Doses of Simvastatin in Patients With Primary Hypercholesterolemia R, DB, PC, PG; base phase -- effect of EZ 10 mg coadministered with simva 10, 20, 40, and 80 mg daily - QD in PM for 12 weeks; extension phase -- long term safety/tolerability/efficacy of EZ 10 mg coadministered with simva 10, 20, 40, and 80 mg in subjects who completed treatment in the base phase - QD in PM for 48 weeks
P01418	Long-Term, Open-Label, Safety and Tolerability Study of SCH 58235 in Addition to Atorvastatin in Subjects With Coronary Heart Disease or Multiple Risk Factors and with Primary Hypercholesterolemia Not Controlled by a Starting Dose (10 mg) of Atorvastatin OL; long term safety/tolerability of EZ 10 mg coadministered with atorva 10 mg in subjects who completed treatment under Protocol P00693; LDL-C-response-based up-titration of atorva dose to maximum of 80 mg - QD in AM for 12 months
P02154	Long-Term Safety and Tolerability Study of Ezetimibe (SCH 58235) or Placebo in Addition to Atorvastatin in Subjects with Primary Hypercholesterolemia R, DB, PC, PG; long term safety/tolerability of EZ 10 mg coadministered with atorva vs atorva alone in subjects who completed treatment under Protocol P00692; LDL-C-response-based up-titration of atorva dose from 10 mg to maximum of 80 mg - QD in AM for 12 months
P02156	Long-Term, Safety and Tolerability Study of SCH 58235 or Placebo in Addition to Simvastatin in Subjects With Primary Hypercholesterolemia R, DB, PC, PG; assess long term safety/tolerability of EZ coadministered with simva vs simva alone in subjects who completed treatment under Protocol P00680; LDL-C-response-based up-titration of simva dose from 10 mg to maximum of 80 mg - QD in PM for 12 months
P02173 and P02246 (Extension Phase)	A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Lipid-Altering Efficacy, Safety, and Tolerability of SCH 58235 When Added to Ongoing Therapy With an HMG-CoA Reductase Inhibitor (Statin) in Patients With Primary Hypercholesterolemia, Known Coronary Heart Disease, or Multiple Cardiovascular Risk Factors R, DB, PC, PG; extension to base treatment phase wherein subjects run in on any approved dose of any approved statin, then add placebo or EZ 10 mg - switch subjects to equipotent dose of simva, then add placebo or EZ 10 mg; LDL-C-response-based up-titration of simva dose - QD in PM for 48 weeks
[redacted]	A Pilot Study to Examine the Efficacy and Safety of Ezetimibe [redacted]
[redacted]	A Pilot Study to Examine the Effects of Ezetimibe [redacted]

a: A list of the reported serious adverse events is included.

AC = active controlled; AM = morning; atorva = atorvastatin; DB = double blind; EZ = ezetimibe; OL = open label; PC = placebo controlled; PG = parallel groups; PM = evening; QD = once daily; R = randomized; simva = simvastatin; XO = crossover

Table 4 Primary Hypercholesterolemia
Ezetimibe Monotherapy
Completed Randomized Clinical Trials
Number Of Patients By Study

Number of Patients

		Ezetimibe Monotherapy[a]	
Study[c]	Placebo[a]	10 mg	All Doses[b]
C96-411/345	17	18	89
C98-010	52	46	191
C98-258	36	77	153
P00474	205	622	622
P00475	226	666	666
P00679	64	72	72
P00680	70	61	61
P00591	65	64	64
P00592	60	65	65
POOL	795	1691	1993

a: Randomized treatment assignment.

b: Ezetimibe [redacted] 10, [redacted] mg were studied during Phase II.

c: See Table 1 for study designs

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Table 5 Primary Hypercholesterolemia
Ezetimibe Monotherapy
Completed Randomized Clinical Trials
Number Of Patients, Rates Of Completion, And Reasons For Discontinuation

Number And (Percent) Of Patients

Disposition of Subjects	Placebo	Ezetimibe 10 mg	Ezetimibe All Doses
Received Randomized Treatment Assignment	795	1691	1983
Completed Treatment	728 (91.6)	1549 (91.6)	1830 (92.3)
Discontinued Treatment	67 (8.4)	142 (8.4)	153 (7.7)
adverse event	30 (3.8)	68 (4.0)	71 (3.6)
lost to follow-up	5 (0.6)	15 (0.9)	15 (0.8)
did not wish to continue	24 (3.0)	43 (2.5)	48 (2.4)
noncompliance with protocol	8 (1.0)	13 (0.8)	14 (0.7)
did not meet protocol eligibility	0	0	1 (0.1)
administrative	0	3 (0.2)	4 (0.2)

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Table 6 Primary Hypercholesterolemia
Ezetimibe Coadministered With A Statin
Completed Factorial Randomized Clinical Trials
Number Of Patients By Study

	Number Of Patients			
Study[a] - Statin	Placebo	EZ	All Statins	EZ + All Statins
P00692 - atorvastatin	60	65	248	255
P00680 - simvastatin	70	61	263	274
P00691 - pravastatin	65	64	205	204
P00679 - lovastatin	64	72	220	192
POOL	259	262	936	925

a: See Table 1 for design details

EZ = ezetimibe 10 mg; All Statins = pool of all doses of statin; EZ + All Statins = pool of all doses of statin coadministered with ezetimibe 10 mg

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Table 7 Primary Hypercholesterolemia Ezetimibe Coadministered With A Statin Completed Factorial Randomized Clinical Trials Number Of Patients, Rates Of Completion, And Reasons For Discontinuation

	Number And (Percent) Of Patients			
Disposition of Subjects	Placebo	Ezetimibe 10 mg	All Statins	EZ + All Statins
Received Randomized Treatment Assignment	259	262	936	925
Completed Treatment	227 (87.6)	239 (91.2)	859 (91.8)	832 (90.0)
Discontinued Treatment	32 (12.4)	23 (8.8)	77 (8.2)	93 (10.1)
adverse event	16 (6.2)	13 (5.0)	40 (4.3)	53 (5.7)
Lost to follow-up	2 (0.8)	1 (0.4)	9 (1.0)	3 (0.3)
did not wish to continue	9 (3.5)	3 (1.2)	20 (2.1)	25 (2.7)
noncompliance with protocol	5 (1.9)	6 (2.3)	8 (0.9)	12 (1.3)

EZ = ezetimibe 10 mg; All Statins = all doses of all statins;.

Table 8 Primary Hypercholesterolemia/Patients With Documented CHD Or Diabetes Mellitus, Or Cardiovascular Risk Factors Ezetimibe Coadministered With A Statin Completed Randomized Clinical Trial Number Of Patients, Rates Of Completion, And Reasons For Discontinuation

	Number And (Percent) Of Patients	
Disposition of Subjects	Statin + *Placebo*	Statin + *Ezetimibe 10 mg*
Received Randomized Treatment Assignment	390 (100)	379 (100)
Completed Treatment	369 (95)	360 (95)
Discontinued Treatment	21 (5)	19 (5)
adverse event	14 (4)	13 (3)
treatment failure	0	0
lost to follow-up	2 (1)	2 (1)
subject did not wish to continue	4 (1)	3 (1)
noncompliance with protocol	1 (<1)	0
administrative	0	1 (<1)

Table 9 Homozygous Familial Hypercholesterolemia Ezetimibe Coadministered With A Statin Completed Randomized Clinical Trial Number Of Patients, Rates Of Completion, And Reasons For Discontinuation

Number Of Patients

	Atorvastatin			Simvastatin		
Disposition of Subjects	Statin 80 mg	EZ + Statin 40 mg	EZ + Statin 80 mg	Statin 80 mg	EZ + Statin 40 mg	EZ + Statin 80 mg
Received Randomized Treatment Assignment	12	12	12	5	4	5
Completed Treatment	12	11	12	5	4	4
Discontinued Treatment: Adverse Event	0	1	0	0	0	1

Table 10 Homozygous Sitosterolemia
Ezetimibe Coadministered With Established Therapy
Completed Randomized Clinical Trial
Number Of Patients, Rates Of Completion,
And Reasons For Discontinuation

	Number And (Percent) Of Patients	
Disposition of Subjects	Placebo	Ezetimibe 10 mg
Received Randomized Treatment Assignment	7 (100)	30 (100)
Completed Treatment	7 (100)	30 (100)
Discontinued Treatment	0	0

Table 11 Primary Hypercholesterolemia Monotherapy Pool Completed Randomized Clinical Trials Number Of Patients By Duration Of Participation

	Placebo (n=795)[a]	Ezetimibe 10 mg (n=1691)[a]	Ezetimibe All Doses (n=1983)[a]
Days in Randomized Treatment Phase			
n	780	1675	1967
Median	84	84	84
Mean	81.2	81.4	80.6
SD	15.2	15.9	16
Minimum	—	—	—
Maximum	—	—	—
Frequency by Interval: Number (%) of Subjects with the Indicated Number of Days Participation in the Randomized Treatment Phase			
0 day	1 (0.1)	3 (0.2)	3 (0.2)
1-7 days	6 (0.8)	15 (0.9)	15 (0.8)
8-21 days	14 (1.8)	32 (1.9)	37 (1.9)
22-42 days	13 (1.6)	33 (2.0)	37 (1.9)
43-70 days	38 (4.8)	50 (3.0)	120 (6.1)
71-98 days	707 (88.9)	1521 (90.0)	1732 (87.3)
>98 days	11 (1.4)	21 (1.2)	23 (1.2)
Missing	5 (0.6)	16 (1.0)	16 (0.8)

a: Number includes all subjects who received randomized treatment assignment, regardless of actual subsequent treatment.

Table 12 Primary Hypercholesterolemia
Factorial Coadministration Pool
Completed Randomized Clinical Trials
Number Of Patients By Duration Of Participation

	Placebo (n=259)[a]	EZ (n=262)[a]	All Statins (n=936)[a]	EZ + All Statins (n=925)[a]
Days in Randomized Treatment Phase				
n	256	261	928	922
Median	84	84	84	84
Mean	80.4	80.8	81.5	80.5
SD	17.1	17.5	15.9	17.1
Minimum	[illegible]	[illegible]	[illegible]	[illegible]
Maximum	[illegible]	[illegible]	[illegible]	[illegible]
Frequency by Interval: Number (%) of Subjects with the Indicated Number of Days Participation in the Randomized Treatment Phase				
0 day	1 (0.4)	1 (0.4)	2 (0.2)	3 (0.3)
1-7 days	1 (0.4)	4 (1.5)	7 (0.8)	5 (0.5)
8-21 days	7 (2.7)	6 (2.3)	18 (1.9)	21 (2.3)
22-42 days	7 (2.7)	4 (1.5)	23 (2.5)	31 (3.4)
43-70 days	9 (3.5)	5 (1.9)	17 (1.8)	27 (2.9)
71-98 days	227 (87.6)	236 (90.1)	843 (90.1)	821 (88.8)
>98 days	4 (1.5)	5 (1.9)	18 (1.9)	14 (1.5)
Missing	3 (1.2)	1 (0.4)	8 (0.9)	3 (0.3)

a: Number includes all subjects who received randomized *treatment assignment, regardless of actual subsequent* treatment.

Treatments: EZ = ezetimibe 10 mg; All Statins = all doses of all statins.

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Table 13 Primary Hypercholesterolemia/Patients With Documented CHD, Diabetes Mellitus, CVD Risk Factors *Ezetimibe Added To An Established Statin* Completed Randomized Clinical Trial Number Of Patients By Duration Of Participation

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

a: Number includes all subjects who received randomized treatment assignment, regardless of actual subsequent treatment.

SD = standard deviation.

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Table 14 Homozygous Familial Hypercholesterolemia
Ezetimibe Coadministered With A Statin
Completed Randomized Clinical Trial
Number Of Patients By Duration Of Participation

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	Statin 80 mg (n=17)	EZ + Statin 40/80 mg (n=33)	Ator 80 mg (n=12)	EZ + Ator 40 mg (n=12)	EZ + Ator 80 mg (n=12)	Sim 80 mg (n=5)	EZ + Sim 40 mg (n=4)	EZ + Sim 80 mg (n=5)
Days in Randomized Treatment Phase								
Median	84	84	84	86	85	85	81	84
Mean	84	83.1	82.1	86.7	87.5	88.6	77	69
SD	9.3	15.5	9.7	6.3	6.2	6.8	9.9	34.1
Minimum	[							]
Maximum								
Frequency by Interval: Number (%) of Subjects with the Indicated Number of Days Participation in the Randomized Treatment Phase								
8–21 Days	0	1 (3)	0	0	0	0	0	1 (20)
22–42 Days	0	0	0	0	0	0	0	0
43–70 Days	1 (6)	2 (6)	1 (8)	1 (8)	0	0	1 (25)	0
71–101 Days	16 (94)	30 (91)	11 (92)	11 (92)	12 (100)	5 (100)	3 (75)	4 (80)

Ator = atorvastatin; EZ = ezetimibe 10 mg; SD = standard deviation; Sim = simvastatin

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Table 15 Homozygous Sitosterolemia
Ezetimibe Coadministered With Established Therapy
Completed Randomized Clinical Trial
Number Of Patients By Duration Of Participation

	Placebo (n=7)	Ezetimibe 10 mg (n=30)
Days in Randomized Treatment Phase		
Median	53	56
Mean (SD)	53.3 (6.7)	55.9 (4.3)
Min-Max	—	—
Frequency by Interval: Number (%) of Subjects with the Indicated Number of Days Participation in the Randomized Treatment Phase		
36 - 49 days	2 (28.6)	4 (13.3)
50 - 62 days	5 (71.4)	23 (76.7)
>62 days	0	3 (10.0)

Min-Max = minimum to maximum values; SD=standard deviation.

Table 17 Primary Hypercholesterolemia
Ezetimibe Coadministered With A Statin
Randomized Clinical Trial + Uncontrolled Extension Study Data
Number Of Patients By Duration Of Participation

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Primary Hypercholesterolemia

Treatment	Number (%) of Subjects Participating for Indicated Total Duration							Summary of Duration in Months[a]	
	Months[a]								
	Missing	<3	3 to <6	6 to <9	9 to <12	12 to <18	≥18	Mean	Median
All Long-Term Coadministration Experience (n=1281)[b]	3 (<1)	418 (33)	411 (32)	212 (17)	137 (11)	100 (8)	0	5.5	5.6
Ezetimibe and Simvastatin (n=697)	2 (<1)	254 (36)	235 (34)	99 (14)	54 (8)	53 (8)	0	5.2	5.5
Ezetimibe and Pravastatin (n=392)	1 (<1)	147 (38)	150 (38)	75 (19)	19 (5)	0	0	4.2	3.2
Ezetimibe and Lovastatin (n=192)	0	17 (9)	26 (14)	38 (20)	64 (33)	47 (25)	0	8.9	9.6

a: 1 month = 30 days.

b: Total duration of participation in coadministration treatment, beginning with randomized assignment of treatment with ezetimibe 10 mg and pravastatin in P00691, or beginning of treatment with ezetimibe 10 mg and a statin in any of long-term protocols P00476 (lovastatin or simvastatin), P01416 (pravastatin), or P02134 (simvastatin), to the end of the available coadministration treatment record (eg, last recorded dose, discontinuation, cut-off date for data collection).

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Table 18 Primary Hypercholesterolemia
Ezetimibe Coadministered With A Statin
Randomized Clinical Trial + Uncontrolled Extension Study Data
Number Of Patients By Extent Of Exposure

Treatment[b]	Number (%) of Subjects Exposed for Indicated Duration							Summary of Duration in Months[a]	
		Months[a]							
	Missing	<3	3 to <6	6 to <9	9 to <12	12 to <18	≥18	Mean	Median
All Long-Term Coadministration Experience (n=1281)[c]	3 (<1)	465 (36)	432 (34)	186 (15)	143 (11)	52 (4)	0	5.24	5.17
Ezetimibe and Simvastatin (n=697)	2 (<1)	279 (40)	249 (36)	79 (11)	56 (8)	32 (5)	0	5.03	5.03
EZ and Simvastatin 10 mg (n=656)	1 (<1)	288 (44)	219 (33)	66 (10)	55 (8)	27 (4)	0	4.85	4.23
EZ and Simvastatin 20 mg (n=95)	0	54 (57)	29 (31)	9 (9)	3 (3)	0	0	3.27	2.80
EZ and Simvastatin 40 mg (n=5)	0	4 (80)	1 (20)	0	0	0	0	1.47	1.20
EZ and Simvastatin 80 mg (n=1)	0	1 (100)	0	0	0	0	0	1.43	1.43
Ezetimibe and Pravastatin (n=392)	1 (<1)	168 (43)	148 (38)	64 (16)	11 (3)	0	0	4.07	3.13
EZ and Pravastatin 10 mg (n=338)	0	174 (51)	126 (37)	36 (11)	2 (1)	0	0	3.41	2.97
EZ and Pravastatin 20 mg (n=98)	1 (1)	82 (84)	15 (15)	0	0	0	0	2.45	2.80
EZ and Pravastatin 40 mg (n=74)	0	50 (68)	24 (32)	0	0	0	0	2.74	2.80
Ezetimibe and Lovastatin (n=192)	0	18 (9)	35 (18)	43 (22)	76 (40)	20 (10)	0	8.40	9.00
EZ and Lovastatin 10 mg (n=192)	0	40 (21)	44 (23)	38 (20)	57 (30)	13 (7)	0	7.00	7.02
EZ and Lovastatin 20 mg (n=46)	0	17 (37)	16 (35)	5 (11)	7 (15)	1 (2)	0	4.73	3.37
EZ and Lovastatin 40 mg (n=11)	0	5 (45)	1 (9)	5 (45)	0	0	0	4.72	4.90
EZ and Lovastatin 80 mg (n=1)	0	1 (100)	0	0	0	0	0	0.03	0.03

a: 1 month = 30 days.

b: Note that treatments by dose are not mutually exclusive; a subject appears in as many treatments as actually received and for the duration that that treatment was received. Therefore, overall extent of exposure for the statin as a whole cannot be the sum of the individual doses.

c: Extent of exposure to coadministration treatment, beginning with randomized assignment of treatment with ezetimibe 10 mg and pravastatin in P00691, or beginning of treatment with ezetimibe 10 mg and a statin in any of long-term protocols P00476 (lovastatin or simvastatin), P01416 (pravastatin), or P02134 (simvastatin), to the end of the available coadministration treatment record (eg, last recorded dose, discontinuation, cut-off date for data collection).

EZ = ezetimibe 10 mg.

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Table 19 Homozygous Familial Hypercholesterolemia
Ezetimibe Coadministered With A Statin
Randomized Clinical Trial + Uncontrolled Extension Study Data
Number Of Patients By Duration Of Participation

Treatment	Number (%) of Subjects Participating for Indicated Total Duration							Summary of Duration in Months[a]	
		Months[a]							
	Missing	<3	3 to <6	6 to <9	9 to <12	12 to <18	≥18	Mean	Median
All Long-Term Coadministration Experience (n=45)[b]	0	11 (24)	9 (20)	22 (49)	3 (7)	0	0	5.6	6.1
Ezetimibe and Atorvastatin (n=33)	0	7 (21)	4 (12)	19 (58)	3 (9)	0	0	6.1	6.8
Ezetimibe and Simvastatin (n=12)	0	4 (33)	5 (42)	3 (25)	0	0	0	4.1	4.0

a: 1 month = 30 days.

b: Total duration of participation in coadministration treatment, beginning with randomized assignment of treatment with ezetimibe 10 mg and atorvastatin or simvastatin in P01030, or beginning of treatment with ezetimibe 10 mg and atorvastatin or simvastatin in protocol P01417, to the end of the available coadministration treatment record (eg, last recorded dose, discontinuation, cut-off date for data collection).

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Table 20 Homozygous Familial Hypercholesterolemia
Ezetimibe Coadministered With A Statin
Randomized Clinical Trial + Uncontrolled Extension Study Data
Number Of Patients By Extent Of Exposure

Treatment[b]	Number (%) of Subjects Exposed for Indicated Duration							Summary of Exposure in Months[a]	
	Months[a]								
	Missing	<3	3 to <6	6 to <9	9 to <12	12 to <18	≥18	Mean	Median
All Long-Term Coadministration Experience (n=45)[c]	0	12 (27)	21 (47)	10 (22)	2 (4)	0	0	5.0	5.6
Ezetimibe and Atorvastatin (n=33)[c]	0	8 (24)	13 (39)	10 (30)	2 (6)	0	0	5.5	5.7
EZ and Atorvastatin 40 mg (n=33)	0	21 (64)	10 (30)	1 (3)	1 (3)	0	0	2.6	2.2
EZ and Atorvastatin 60 mg (n=2)	0	2 (100)	0	0	0	0	0	1.4	1.4
EZ and Atorvastatin 80 mg (n=29)	0	18 (62)	8 (28)	3 (10)	0	0	0	3.2	2.8
Ezetimibe and Simvastatin (n=12)[c]	0	4 (33)	8 (67)	0	0	0		3.7	3.9
EZ and Simvastatin 40 mg (n=11)	0	9 (82)	2 (18)	0	0	0		2.3	2.1
EZ and Simvastatin 80 mg (n=8)	0	6 (75)	2 (25)	0	0	0		2.4	2.4

a: 1 month = 30 days.

b: Note that treatments by dose are not mutually exclusive; a subject appears in as many treatments as actually received and for the duration that that treatment was received. Therefore, overall extent of exposure for the statin as a whole cannot be the sum of the individual doses.

c: Extent of exposure to coadministration treatment, beginning with randomized assignment of treatment with ezetimibe 10 mg and atorvastatin or simvastatin in P01030, or beginning of treatment with ezetimibe 10 mg and atorvastatin or simvastatin in protocol P01417, to the end of the available coadministration treatment record (eg, last recorded dose, discontinuation, cut-off date for data collection), subtracting out identifiable treatment gaps and missed doses.

EZ = ezetimibe 10 mg.

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Table 21 Primary Hypercholesterolemia
Randomized Controlled Trials
Monotherapy Pool
Baseline Demographic Characteristics

Characteristics	Placebo (n=795)	Ezetimibe 10 mg (n=1691)	Ezetimibe All Doses (n=1983)
Age (y)			
Mean	57.4	57.8	57.8
SD	11.7	11.6	11.3
Median	58	59	59
Min	18	18	18
Max	85	86	86
Age (no. subjects, %)			
<65 y	548 (68.9)	1158 (68.5)	1372 (69.2)
≥65 y	247 (31.1)	533 (31.5)	611 (30.8)
Age (no. subjects, %)			
<75 y	751 (94.5)	1593 (94.2)	1881 (94.9)
≥75 y	44 (5.5)	98 (5.8)	102 (5.1)
Sex (no. subjects, %)			
Female	425 (53.5)	880 (52.0)	1014 (51.1)
Male	370 (46.5)	811 (48.0)	969 (48.9)
Race (no. subjects, %)			
Caucasian	715 (89.9)	1523 (90.1)	1790 (90.3)
Black	41 (5.2)	89 (5.3)	104 (5.2)
American Indian	2 (0.3)	3 (0.2)	4 (0.2)
Asian	15 (1.9)	20 (1.2)	21 (1.1)
Hispanic	22 (2.8)	53 (3.1)	61 (3.1)
Pacific Islander	0	2 (0.1)	2 (0.1)
Body Weight (kg)	(n=795)	(n=1690)	(n=1982)
Mean	82	82.2	81.9
SD	16.7	16.8	16.5
Median	80	80.9	80.9
Min	43.2	44.5	36.8
Max	146.3	174.3	174.3
Body Mass Index (kg/m^2)	(n=774)	(n=1667)	(n=1885)
Mean	28.7	28.7	28.7
SD	4.8	5.1	5
Median	27.9	27.9	28
Min	19	17	17
Max	49.5	75.4	75.4
Smoker (no. subjects, %)			
No	703 (88.4)	1459 (86.3)	1708 (86.1)
Yes	92 (11.6)	232 (13.7)	275 (13.9)
Washout Info[a] (no. subjects, %)			
No	567 (71.3)	1181 (69.8)	1406 (70.9)
Yes	228 (28.7)	510 (30.2)	577 (29.1)
Statins	183 (23.0)	384 (22.7)	434 (21.9)
Fibric Acid Derivative	6 (0.8)	4 (0.2)	4 (0.2)
Bile Acid Sequestrant	4 (0.5)	6 (0.4)	6 (0.3)
Nicotinic Acid	11 (1.4)	29 (1.7)	35 (1.8)
Other	36 (4.5)	126 (7.5)	139 (7.0)

a: Prior therapy discontinued before investigational treatment.
SD = standard deviation.

Table 22 Primary Hypercholesterolemia
Randomized Controlled Trials
Monotherapy Pool
Baseline Cardiovascular Risk Factors/Family History/Known CHD Or Cardiovascular Medical History/Physical Findings

Number And (Percent) Of Patients

Risk Factors/History/Finding	Placebo (n=795)	Ezetimibe 10 mg (n=1691)	Ezetimibe All Doses (n=1983)
CV Risk Factor/History or CV Medical History/Physical Findings	456 (57.4%)	953 (56.4%)	1062 (53.6%)
CV Risk Factor/History[a]	421 (53.0%)	871 (51.5%)	967 (48.8%)
CV Medical History/Physical Finding	164 (20.6%)	350 (20.7%)	391 (19.7%)

a: Any subject with "Yes" for any of the following: hypertension, diabetes mellitus, stroke, transient ischemia attack, peripheral vascular disease, myocardial infarction, congestive heart failure, angina, coronary angioplasty, history of arrhythmias, CABG, family history of CAD if premature, other significant CV History, known CHD. Does not include postmenopausal condition for women.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHD = coronary heart disease; CV = cardiovascular.

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Table 23 Primary Hypercholesterolemia
Randomized Controlled Trials
Monotherapy Pool
Baseline Cardiovascular Risk Factors/Family History/Known CHD

Number And (Percent) Of Patients

Risk Factors/History/Known CHD	Placebo (n=795)	Ezetimibe 10 mg (n=1691)	Ezetimibe All Doses (n=1983)
Hypertension			
Yes	242 (30.4)	527 (31.2)	584 (30.0)
No	553 (69.6)	1164 (68.8)	1389 (70.0)
Diabetes Mellitus			
Yes	29 (3.6)	83 (4.9)	85 (4.3)
No	766 (96.4)	1608 (95.1)	1898 (95.7)
Stroke			
Yes	10 (1.3)	21 (1.2)	22 (1.1)
No	785 (98.7)	1670 (98.8)	1961 (98.9)
Transient Ischemic Attack			
Yes	13 (1.6)	15 (0.9)	17 (0.9)
No	782 (98.4)	1675 (99.1)	1965 (99.1)
Missing	0	1 (0.1)	1 (0.1)
Peripheral Vascular Disease			
Yes	11 (1.4)	34 (2.0)	37 (1.9)
No	784 (98.6)	1657 (98.0)	1946 (98.1)
Myocardial Infarction			
Yes	21 (2.6)	55 (3.3)	64 (3.2)
No	774 (97.4)	1634 (96.6)	1917 (96.7)
Unknown	0	1 (0.1)	1 (0.1)
Missing	0	1 (0.1)	1 (0.1)
Congestive Heart Failure			
Yes	2 (0.3)	15 (0.9)	15 (0.8)
No	793 (99.7)	1676 (99.1)	1968 (99.2)
Angina			
Yes	37 (4.7)	80 (4.7)	85 (4.3)
No	757 (95.2)	1611 (95.3)	1898 (95.7)
Unknown	1 (0.1)	0	0
Coronary Angioplasty			
Yes	11 (1.4)	36 (2.1)	39 (2.0)
No	784 (98.6)	1655 (97.9)	1943 (98.0)
Unknown	0	0	1 (0.1)
History of Arrhythmias			
Yes	49 (6.2)	86 (5.1)	88 (4.4)
No	729 (91.7)	1584 (93.7)	1803 (90.9)
Unknown	0	3 (0.2)	3 (0.2)
Missing	17 (2.1)	18 (1.1)	89 (4.5)
Coronary Artery Bypass Graft (CABG)			
Yes	11 (1.4)	41 (2.4)	44 (2.2)
No	784 (98.6)	1649 (97.5)	1938 (97.7)
Unknown	0	1 (0.1)	1 (0.1)
Other Significant Cardiovascular History			
Yes	130 (16.4)	225 (13.3)	249 (12.6)
No	664 (83.5)	1463 (86.5)	1730 (87.2)
Unknown	1 (0.1)	3 (0.2)	4 (0.2)
Post Menopausal[a]			
Yes	314 (73.9)	631 (71.7)	631 (62.2)
No	64 (15.1)	178 (20.2)	178 (17.6)
Missing	47 (11.1)	71 (8.1)	205 (20.2)
Family History of Coronary Artery Disease			
Yes	275 (34.6)	561 (33.2)	625 (31.5)
No	508 (63.9)	1115 (65.9)	1339 (67.5)
Unknown	12 (1.5)	15 (0.9)	19 (1.0)

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Table 23 Completed.

	Number And (Percent) Of Patients		
(Other) Known (Indicator of) Coronary Heart Disease[b]			
Yes	15 (1.9)	48 (2.8)	48 (2.4)
No	675 (84.9)	1498 (88.6)	1498 (75.5)
Unknown	0	4 (0.2)	4 (0.2)
Missing	105 (13.2)	141 (8.3)	433 (21.8)
Known Coronary Heart Disease[c]			
Known CHD	36 (4.5)	106 (6.3)	116 (5.8)
No CHD			
NCEP ATP II Risk Factor:			
<1	17 (2.1)	44 (2.6)	44 (2.2)
0	168 (21.1)	358 (21.2)	400 (20.2)
1	346 (43.5)	669 (39.6)	841 (42.4)
2	180 (22.6)	402 (23.8)	467 (23.6)
>2	48 (6.0)	112 (6.6)	115 (5.8)

a: Female subjects only.

b: Represents data captured in a check box in the case report form to identify indicators of coronary heart disease other than those already specified.

c: Derived variable: comprises any one or combination of myocardial infarction, coronary angioplasty, CABG, and "known coronary heart disease" from the Cardiovascular Risk Factors/History module of the case report form.

NCEP ATP II = National Cholesterol Education Program Adult Treatment Panel II.

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