CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-445

MEDICAL REVIEW(S)

MEDICAL SAFETY REVIEW
Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 21-445
Application Type: New Drug Application (NDA)
Sponsor: Merck/Schering-Plough Pharmaceuticals
Proprietary Name: Zetia
USAN Name: Ezetimibe
Pharmaceutical Category: Lipid lowering agent
Route of Administration: Oral
Indications: Primary Hypercholesterolemia, Homozygous Familial Hypercholesterolemia, Homozygous Sitosterolemia
Dosage: 10 milligrams (mg) per day
Medical Safety Reviewer: Bruce V. Stadel, MD, MPH
Dates of Review: 7 January 2002 to 17 September 2002
Medical Efficacy Reviewer: Jean Temeck, MD
Pharmacology Reviewer: Indra Antonipillai, PhD
Statistics Reviewer: Japo Choudhury, PhD
Biopharmaceutics Reviewer: Wei Qiu, PhD
Chemistry Reviewer: Chen-Hua Niu, PhD

SUMMARY: Ezetimibe for cholesterol-lowering was studied in Primary Hypercholesterolemia, Homozygous Familial Hypercholesterolemia, and Homozygous Sitosterolemia. In 12 randomized, double-blind, clinical trials, 8-12 weeks long, 1443 patients received ezetimibe 10 mg/day as monotherapy and 2297 patients received ezetimibe 10 mg/day coadministered with a statin (mostly lovastatin, pravastatin, simvastatin, or atorvastatin). There were also uncontrolled extension studies, 6-18 months long. The studies were of good quality. The important safety results involved the liver and skeletal muscle. The main findings were elevations of ALT and/or AST (coadministration) and CPK (monotherapy and coadministration). In monotherapy studies of Primary Hypercholesterolemia, there were 4 (0.5%) patients in the placebo group and 14 (0.8%) in the ezetimibe 10 mg group with ALT &/or AST ≥3xULN, of whom 3 (0.4%) in the placebo group and 9 (0.5%) in the ezetimibe 10 mg had consecutive ALT &/or AST ≥3xULN. No patient had ALT &/or AST ≥10xULN. There were 11 (1.3%) patients in the placebo group and 42 (2.5%) in the ezetimibe 10 mg group with CPK ≥3xULN, of whom 1(0.1) in the placebo group and 4 (0.2%) in the ezetimibe 10 mg group had CPK ≥10xULN. CPK elevations were more frequent in males than females, and in Black males than other males. No patient had rhabdomyolysis. In coadministration studies of Primary Hypercholesterolemia, there were no patients in the placebo group, 2 (0.8%) in the ezetimibe 10 mg group, 9 (1.0%) in the statin group, and 19 (2.1%) in the ezetimibe 10 mg+statin group with ALT and/or AST ≥3xULN, of whom none in the placebo group, none in the ezetimibe 10 mg group, 4 (0.4%) in the statin group, and 13 (1.4%) in the ezetimibe 10 mg+statin group had consecutive ALT and/or AST ≥3xULN. No patient had ALT &/or AST ≥10xULN. There were 3 (1.2%) patients in the placebo group, 6 (2.4%) in the ezetimibe 10 mg group, 25 (2.6%) in the statin group, and 15 (1.6%) in the ezetimibe 10 mg+statin group with CPK ≥3xULN, of whom none in the placebo group, none in the ezetimibe 10 mg group, 4 (0.4%) in the statin group, and 1 (0.1%) in the ezetimibe 10 mg+statin group had CPK ≥10xULN. CPK elevations were not higher with ezetimibe 10 mg+statin compared to the same type and dose of statin alone. As with monotherapy, CPK elevations were more frequent in males than females, and in Black males than other males. No patient had rhabdomyolysis. The safety results were similar for Homozygous Familial Hypercholesterolemia and Homozygous Sitosterolemia.

OUTSTANDING ISSUES:

RECOMMENDED REGULATORY ACTION: N drive location:

New clinical studies _____ Clinical Hold _____ Study May Proceed
NDA, Efficacy/Label supplement: _____ Approvable _____ Not Approvable
__X__ Approve

SIGNATURES: Medical Safety Reviewer:_____ Date: _____

Medical Team Leader:
_____ Date: _____

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

1. INTRODUCTION

1.1 Background

Zetia® (ezetimibe) is a new molecular entity that has been developed for the treatment of Primary Hypercholesterolemia, Homozygous Familial Hypercholesterolemia, and Homozygous Sitosterolemia. Ezetimibe acts by reducing the intestinal absorption of cholesterol and related phytosterols, and does not appear to alter the absorption of other nutrients. The molecular mechanism of action is unknown. Ezetimibe is extensively glucuronidated in the intestinal wall, and appears within minutes in the portal plasma and bile. The parent drug and glucuronide undergo enterohepatic circulation. Elimination is mainly in the feces (~78%) and urine (~11%).

Ezetimibe is proposed for both monotherapy and coadministration with approved "statin" drugs, which reduce cholesterol synthesis in the liver by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A. The clinical studies of efficacy and safety therefore included studies of ezetimibe alone compared to placebo, and studies of ezetimibe coadministered with a statin compared to placebo coadministered with the same statin.

Due to the known adverse effects of statins on liver and muscle, a special effort was made, in the ezetimibe clinical studies, to identify all patients with persistent increases in alanine aminotransferase (ALT, formerly SGPT) or aspartate aminotransferase (AST, formerly SGOT), or other indications of liver injury, and patients with increases in creatine phosphokinase (CPK), with or without muscle pain or weakness. The data for ezetimibe coadministered with a statin, compared to placebo coadministered with the same statin, were evaluated at each statin dose, because the effects of statins on liver and muscle are known to be dose-related.

1.2 Proposed Indications And Dosing

Ezetimibe is proposed for 3 indications, at an oral dose of 10 mg:

- Primary Hypercholesterolemia (monotherapy or coadministered with a statin, as adjunctive to diet);
- Homozygous Familial Hypercholesterolemia (coadministered with a statin, as adjunctive to other lipid-lowering treatments such as apheresis, or as a substitute if other treatments are not available);
- Homozygous Sitosterolemia (as adjunctive to diet).

Note: In this review, "ezetimibe 10 mg" means "ezetimibe 10 mg/day." This convention is also used for other doses of ezetimibe and for the statins.

1.3 Clinical Studies And Numbers Of Patients

A total of 4584 patients were treated with ezetimibe in clinical studies for which full reports were presented in the NDA. This included 552 patients treated in 32 completed Clinical Pharmacology studies, 3350 patients treated in 12 completed Phase 2/3, randomized, double-blind, parallel-group clinical trials (RCTs), and 682 patients treated with ezetimibe for the first time in 4 uncontrolled, open-label extension studies (UESs). The 12 completed RCTs were all 8-12 weeks long, were begun in the interval April 1997 to May 2000, and had last patient visits on or before 31 July 2001. In addition, interim reports through 15 July 2001 were presented for 2038 patients who were in 6 of the 12 completed RCTs, and have since been treated with ezetimibe in 4 uncontrolled, open-label, extension studies (UESs) that began in the interval February to December 2000 and are still in progress.

Of the 4032 patients treated with ezetimibe in the 12 completed RCTs (n=3350) or UESs (n=682), 1735 received monotherapy only, including 1443 at 10 mg, and the other 2297 received 10 mg coadministered with a statin.

Tables 1 and 2 describe the 12 completed RCTs and 4 related UESs. For Primary Hypercholesterolemia, there were 3 Phase 2 RCTs, 7 Phase 3 RCTs, and 3 UESs. For Homozygous Familial Hypercholesterolemia, there were 1 Phase 3 RCT and 1 UES. For Homozygous Sitosterolemia, there was 1 Phase 3 RCT.

The NDA also presented limited safety data from other clinical studies. This included blinded data through 15 August 2001 on 4077 patients who signed informed consent to participate in 8 ongoing RCTs that were begun in the interval February 2000 to April 2001, and 136 patients in a related 1-year UES that was begun in October 2000. These RCTs are described in Table 3. The NDA also briefly discussed clinical studies done by the independent Japanese subsidiary of Schering-Plough.

Note: Of the 8 ongoing RCTs, 4 are long-term, and will provide controlled data on the effects of treatment with ezetimibe 10 mg for up to 1 year. These 4 RCTs are scheduled for last patients visits in June-November 2002, and for the completion of study reports in March-August 2003.

1.4 Safety Evaluation Data Sets

The main safety evaluations in the NDA were based on the 12 completed RCTs and 4 related UESs (Tables 1 and 2). RCT data and RCT+UES data were analyzed separately, and separate evaluations were done for the different treatment indications, because of differences in the patient populations and study designs. For Primary Hypercholesterolemia, separate evaluations were also done for ezetimibe monotherapy versus coadministration with a statin.

1.4.1 Primary Hypercholesterolemia

1.4.1.1 Randomized Clinical Trials (RCTs)

All of the 10 RCTs for Primary Hypercholesterolemia were 8-12 weeks long, and all randomized patients by equal allocation to the treatment groups in a particular study, except for 2 monotherapy RCTs that randomized by 3:1 allocation to ezetimibe and placebo.

Of the 10 RCTs, 9 had patient populations and study designs that were similar enough for pooling of the data. These 9 RCTs included: (1) 3 Phase 2 RCTs and 2 Phase 3 RCTs of ezetimibe monotherapy compared to placebo. The ezetimibe dose in these studies was primarily 10 mg; the range was —— mg; (2) 4 Phase 3 RCTs that were "factorial" in design, i.e., the patients were randomized, by equal allocation, to 1 of 2 daily doses of ezetimibe (0 mg [placebo] or 10 mg) and 1 of 4 or 5 daily doses of a statin (0 mg [placebo], 10 mg, 20 mg, 40 mg, or [in 2 studies] 80 mg). The statins were lovastatin, pravastatin, simvastatin, and atorvastatin.

In the 9 pooled RCTs, patients were eligible if they (1) had a clinical diagnosis of Primary Hypercholesterolemia, (2) were willing to maintain a National Cholestesterol Education Program (NCEP) Step 1 or stricter diet during the study, (3) were $\geq$18 years of age, (4) were males or females who were either postmenopausal or nonlactating, nonpregant, and using an effective method of birth control, (5) met run-in phase criteria for lipid levels, and (6) did not have any of the conditions listed as exclusion criteria. Patients recruited for the study were told to stop taking any current lipid-altering agent and, after a specified washout phase, selected plasma lipids and lipoproteins were measured several times during a 4-8 week single-blind placebo run-in phase. Patients were randomized if the average value of their calculated plasma low-density lipoprotein cholesterol (LDL-C) level (Friedewald equation) during the placebo run-in ranged from 130-160 mg/d/L to 220-250 mg/dL, depending on the study, and the average value of their triglyceride level

was ≤250-350 mg/dL, depending on the study. The exclusion criteria included secondary hypercholesterolemia, a requirement for concomitant therapy that could affect lipid/lipoprotein concentrations, a concomitant illness that made treatment with an investigational drug inadvisable or that might confound the results of the study, hypercholesterolemia severe enough that withholding approved treatment was inappropriate, hypersensitivity to the statin to be administered (for coadministration studies), and inability to participate optimally. Participating patients received randomized treatment assignment for 12 weeks in 8 RCTs and for 8 weeks in 1 RCT.

The 10th RCT differed from the preceding 9 in 2 important ways. First, patients were eligible only if they (1) had documented coronary heart disease (CHD) or diabetes mellitus, or in the absence of disease had documented cardiovascular disease (CVD) risk factors, (2) had been taking an approved dose of an approved statin for at least 6 weeks, and (3) had a LDL-C level that was equal to or higher than the NCEP Adult Treatment Panel goal for their clinical status. Second, eligible patients were randomized to receive placebo or ezetimibe 10 mg added to an established statin, for 8 weeks. Because of these differences, the data from this RCT were not pooled with data from the 9 other RCTs of Primary Hypercholesterolemia.

1.4.1.1.1 Randomized Clinical Trials (RCTs) Of Ezetimibe Monotherapy

The main safety evaluations of ezetimibe monotherapy were based on the 3 Phase 2 and 2 Phase 3 monotherapy RCTs, and those patients in the 4 factorial RCTs who received either placebo or ezetimibe monotherapy. These 9 RCTs provided data on 795 patients treated with placebo, 1691 patients treated with ezetimibe 10 mg, and 1983 patients treated with any dose of ezetimibe. This comprised the "monotherapy pool."

Table 4 shows the number of patients by study and treatment group. Table 5 shows that 2558 (92.1%) the 2778 patients randomized in these RCTs completed the studies, and that the patients in the different treatment groups had similar rates of discontinuation: 3.6-4.0% for adverse events (AEs), 0.6-0.9% for lost to follow-up, 2.4-3.0% for did not wish to continue, and 1.0% for other reasons.

1.4.1.1.2 Randomized Clinical Trials (RCTs) Of Ezetimibe Coadministered With A Statin Or Added To An Established Statin

The main safety evaluations of ezetimibe coadministered with a statin or added to an established statin were based on the 4 factorial RCTs and the 1 RCT for patients with documented CHD, diabetes mellitus, or CVD risk factors.

The 4 factorial RCTs provided data on 259 patients treated with placebo, 262 patients treated with ezetimibe 10 mg, 936 patients treated with a statin (any dose), and 925 patients treated with ezetimibe 10 mg coadministered with a statin (any dose). This comprised the "factorial coadministration pool."

The RCT for patients with documented CHD, diabetes mellitus, or CVD risk factors provided data on 390 patients treated with placebo added to an established statin, and 379 patients treated with ezetimibe 10 mg added to an established statin. This comprised the "add-on RCT."

For the 4 factorial RCTs, Table 6 shows the number of patients by study and treatment group. Table 7 shows that 2157 (90.6%) of the 2382 patients randomized in these RCTs completed the studies, and that the patients in the different treatment groups had similar rates of discontinuation: 4.3-6.2 % for AEs, 0.3-1.0% for lost to follow-up, 1.2-3.5% for did not wish to continue, and 0.9-2.3% for noncompliance.

For the add-on RCT for patients with documented CHD, diabetes mellitus, or CVD risk factors, Table 8 shows that 729 (94.8%) of the 769 patients randomized completed the study, and that the patients in the 2 treatment groups had similar rates of discontinuation: 3.0-4.0% for AEs, 1.0% for lost to follow-up, 1.0% for did not wish to continue, and <1% for other reasons.

1.4.1.2 Uncontrolled Extension Studies (UESs)

All of the 3 UESs for Primary Hypercholesterolemia are still in progress and scheduled to be 1-2 years long. Data were analyzed for the RCT+UES data sets. Results presented in the NDA were through 15 July 2001.

Patients who completed any of 5 RCTs were eligible for longer treatment in 1 of these 3 UESs. The studies are described in Table 2. The numbers of patients, treatments, and scheduled durations are discussed below.

A total of 1313 patients who completed the 2 ezetimibe monotherapy RCTs entered a 2-year UES, in which all patients were to be treated with ezetimibe 10 mg. Initially, either lovastatin or simvastatin 10 mg could be added, after 1 month, if needed to achieve the patient's NCEP Adult Treatment Panel goal. This was later changed to the addition of simvastatin 10 mg if LDL-C was >130 mg/dL or 20 mg/day if LDL-C was >145 mg/dL.

A total of 321 patients who completed the ezetimibe/pravastatin factorial RCT entered a 1-year UES, in which all patients were to be treated with ezetimibe 10 mg and pravastatin 10 mg.

A total of 181 patients who completed the ezetimibe/lovastatin factorial RCT and 178 patients who completed the ezetimibe/simvastatin factorial RCT entered a 1-year UES, in which all patients were to be being treated with ezetimibe 10 mg and simvastatin 10 mg.

In all of the UESs, the dose of statin was to be increased as needed to achieve the target NCEP goal.

1.4.2 Homozygous Familial Hypercholesterolemia

1.4.2.1 Randomized Clinical Trial (RCT)

The main safety evaluation of ezetimibe for Homozygous Familial Hypercholesterolemia was based on the 1 RCT for this disorder, in which 50 patients receiving atorvastatin or simvastatin 40 mg were treated with additional atorvastatin or simvastatin 40 mg, ezetimibe 10 mg, or ezetimibe 10 mg+atorvastatin or simvastatin 40 mg.

Patients were eligible if they (1) had a clinical diagnosis of Homozygous Familial Hypercholesterolemia, (2) were willing to maintain a NCEP Step 1 or stricter diet during the study, (3) were ≥12 years old, (4) were males or females who were either postmenopausal or nonlactating, nonpregant, and using an effective method of birth control, (5) had an average LDL-C level of ≥100 mg/dL during at least 6 weeks of run-in treatment with open-label atorvastatin or simvastatin 40 mg, and (6) did not have any of the conditions listed as exclusion criteria. A total of 50 patients met all inclusion/exclusion criteria and were randomized to the double-blind addition of study drugs, while continuing the open-label statin. The patients taking open-label atorvastatin 40 mg were randomized to the addition of blinded atorvastatin 40 mg, ezetimibe 10 mg, or atorvastatin 40 mg and ezetimibe 10 mg. Likewise, the patients taking open-label simvastatin were randomized to the addition of blinded simvastatin

40 mg, ezetimibe 10 mg, or simvastatin 40 mg and ezetimibe 10 mg. Statins not specified in the protocol and fibric acid derivatives were not allowed during the study. However, other therapies were permitted, such as apheresis or bile acid sequestrants, provided the regimen remained stable and a schedule was followed regarding the timing of these therapies relative to treatment with study drug and measurement of lipid/lipoprotein concentrations. The exclusion criteria included a requirement for concomitant therapy that could affect lipid/lipoprotein concentrations (i.e., other than allowed lipid-lowering therapy), a concomitant illness that made treatment with an investigational drug inadvisable or that might confound that the results of the study, hypersensitivity to the statin to be administered, abnormal laboratory test values as specified in the protocol, and inability to participate optimally. Participating patients received randomized treatment assignment for 12 weeks.

Table 9 shows the number of patients by treatment group, and that only 2 patients discontinued.

1.4.2.2 Uncontrolled Extension Study (UES)

Patients who completed the RCT for Homozygous Familial Hypercholesterolemia were eligible for a 2-year UES. This study is described in Table 2 and is still in progress. Data were analyzed for the RCT+UES data set. Results presented in the NDA were through 15 July 2001.

A total of 41 patients entered, and were treated with ezetimibe 10 mg and either atorvastatin or simvastatin 40 mg, with possible up-titration of the statin dose based on the LDL-C level. Patients were treated with the same statin as in the RCT.

1.4.3 Homozygous Sitosterolemia Randomized Clinical Trial (RCT) Only

The main safety evaluation of ezetimibe for Homozygous Sitosterolemia was based on the 1 RCT for this disorder, in which 37 patients were treated with placebo or ezetimibe 10 mg in addition to previously established therapies such as apheresis or a bile acid sequestrant.

Patients were eligible if they (1) had a clinical diagnosis of Homozygous Sitosterolemia, (2) were willing to maintain a stable diet during the study, (3) were $\geq$10 years old, (4) were males or females who were either postmenopausal or nonlactating, nonpregant, and using an effective method of birth control, and (5) had a plasma sitosterol level of >5 mg/dL

at the end of a 1 week screening phase. A total of 37 patients met all inclusion/exclusion criteria and were randomized to the double-blind addition of placebo or ezetimibe 10 mg to their previously established therapy, such as apheresis or a bile acid sequestrant. The previously established therapies were to remain stable during the RCT, and a schedule was to be followed regarding the timing of these therapies relative to treatment with study drug and measurement of lipid/lipoprotein concentrations. Participating patients received randomized treatment assignment for 8 weeks.

Table 10 shows the number of patients by treatment group, and that no patients discontinued.

1.4.4 Other Clinical Studies

1.4.4.1 Clinical Pharmacology Studies

Data from the 32 Clinical Pharmacology studies were not pooled because these studies varied regarding the patient population (e.g., healthy people, patients with hypercholesterolemia, patients with chronic hepatic or renal dysfunction), study design (e.g., parallel-group versus crossover), and duration of treatment (single dose to 2 weeks). The safety findings are discussed in Section 4.4.

1.4.4.2 Ongoing Clinical Studies Without Full Reports

Full reports were not presented in the NDA for the 8 ongoing RCTs and 1 related UES, although a full report was presented for the completed, double-blind initial phase of 1 of the 8 ongoing RCTs, through 20 July 2001. For the studies without full reports, summaries and lists of blinded serious AEs were presented, through 15 August 2001.

1.4.4.3 Clinical Studies By The Japanese Subsidiary Of Schering-Plough

The NDA briefly discussed 5 completed clinical studies and 1 ongoing clinical study by the independent Japanese subsidiary of Schering-Plough. In these studies, a total of 99 patients were treated with ezetimibe [redacted] mg, as single doses or as daily doses for up to 4 weeks. Only limited information is available. The safety findings are discussed in Section 4.6.

1.5 Methods For Evaluating Safety

The methods for collecting and evaluating safety data in the clinical studies were standardized to the extent feasible. For study centers in North and South America, laboratory analyses were done by [redacted], and for study centers elsewhere, by [redacted] Consistent inclusion and exclusion safety criteria were used across studies and certain laboratory test results were defined as "serious AEs" to facilitate close evaluation and stop-treatment rules for certain types of adverse findings.

In all clinical studies, general health was evaluated before any treatment with study drugs by a medical history (including presence of CHD, family history of cardiac disease, and presence of cardiovascular risk factors according to the NCEP Adult Treatment Panel II guideline), physical examination, and screening laboratory tests. Thereafter, AEs were recorded at each study visit; blood pressure (BP), pulse, and body weight were measured at regular intervals; and samples for laboratory tests (including pregnancy tests for females) were collected at regular intervals. In most studies, a 12-lead electrocardiogram (ECG) was recorded before and after study drug treatment. In many studies, samples for fecal occult blood were collected before and after study drug treatment.

1.5.1 Adverse Events (AEs)

An AE was defined as any physical or clinical change or disease reported by a patient or observed by an investigator or staff member at any time during a study, regardless of potential relationship to study treatment. The definition of AEs included underlying disease, onset or discovery of new disorder, or exacerbation of pre-existing conditions.

At each study visit after initial enrollment, information about AEs was obtained by general questions (i.e., not focused on specific AEs). Results from physical examinations, laboratory tests, ECGs, could be reported as AEs if the investigator considered this warranted. Except for serious adverse events as defined below, there were no preset limits on the severity of events recorded as AEs.

For each AE identified, the following information was to be recorded in the patient's Case Report Form (CRF):

- Dates the AE began and ended, or a note that the AE was ongoing;
- Intensity according to investigator/staff opinion of impact on daily life:
  *Mild = easily tolerated;
  *Moderate = interfering with activity and may warrant intervention;
  *Severe = incapacitating and definitely warrants intervention;
  *Life-Threatening = immediate risk of death.
- Potential relationship to study drug according to investigator/staff:
  *Unlikely/unrelated = no temporal association, cause identified as something else, or drug cannot be implicated for another reason;
  *Possible = temporal association but other causes likely;
  *Probable = temporal association and other causes unlikely;
  *Related (Phase 2 only) = temporal or other association such as rechallenge, and no other cause reasonable.

Important AE terminology is discussed below.

Serious Adverse Events (SAEs). In accordance with FDA requirements, an AE was considered to be a Serious Adverse Event (SAE) if it was associated with any of the following:

- Death;
- Life-threatening;
- Significant or permanent disability;
- New or prolonged in-patient hospitalization;
- Congenital anomaly or birth defect;
- Any other medical event that was considered serious because of jeopardy to the patient and/or requirements for intervention.

Cancer and AEs associated with intentional or inadvertent overdose were not automatically defined as SAEs except in 2 RCTs, although these events could be reported as SAEs at the investigator's discretion.

In several studies, the first or both of the following events were defined as SAEs: (1) an increase in the activity of ALT or AST to $\geq$3 times the upper limit of normal (3xULN) on 2 consecutive occasions, and (2) an increase in the activity of CPK to $\geq$10xULN or $\geq$5xULN with symptoms of myopathy and in the absence of muscle trauma, on 2 consecutive occasions at least 48 hours apart.

"Treatment-emergent" Adverse Event. An AE was defined as "treatment-emergent" if the event was reported during treatment with study drug and was not present before randomization, or was not present with the same or greater intensity. In this review, the term "adverse event" or "AE" is used to mean "treatment-emergent" unless otherwise specified.

"Treatment-related" Adverse Event. An AE was defined as "treatment-related" "if the event was considered by the investigator(s) to be at least possibly related to treatment, or if the investigator did not describe the event in the CRF as unrelated to treatment.

AE Summaries. The overall AE summary tables show events that were "treatment-emergent" or "treatment-emergent and treatment-related." The summary tables for SAEs and AEs that led to discontinuation from a study show all such events and are not limited to events that were "treatment-emergent."

The nomenclature for AEs was standardized using a modification of the World Health Organization Adverse Reaction Terminology (WHO-ART), as maintained and updated by the Drug Safety Surveillance Department at Schering-Plough. Each literal term in a patient's CRF was linked to a preferred term that served to consolidate reports of a similar nature. Both the literal and preferred terms were stored. The preferred terms were used for consolidating data within a "Body System" or "Organ Class."

In this review, individual AEs are lower case and Body System/Organ Class categories of AEs are capitalized.

1.5.2 Laboratory Tests

Samples for laboratory tests were collected before and at the end of treatment with study drug, and samples for many tests were collected at specified intervals during treatment, based on study schedules or as follow-up for abnormalities. In the 8-12 week RCTs, samples were collected every 2-4 weeks, and in the longer studies every 3 months.

Hematology and blood chemistry after an overnight fast were evaluated in all studies, and urinalysis was done in most studies. Other routine tests and certain special tests were also done. Standard method of data analysis were used The specific variables and methods of analysis are described below.

Hematology. Hemoglobin concentration , hematocrit , red blood cell count, platelet count, total and differential white blood cell count, prothrombin time, and partial thromboplastin time .Prothrombin time was usually measured only before and at the end of treatment, and partial thromboplastin time only before treatment.

Blood Chemistry. ALT (SGPT), AST (SGOT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase, total bilirubin, CPK, serum creatinine, blood urea nitrogen, albumin, total protein, calcium, inorganic phosphorous, glucose, uric acid, sodium potassium, chloride, and thyroid stimulating hormone. Tests for thyroxine and resin uptake of triiodothyronine could be performed in the thyroid stimulating hormone was abnormal).

Urinalysis. Specific gravity, pH, glucose, ketones, protein, red blood cells, and white blood cells.

Other Routine Laboratory Tests. Urine or serum samples were to be collected from female patients for pregnancy testing. Samples for fecal occult blood were to be collected before and at the end of treatment in the Phase 2 RCTs, the Phase 3 monotherapy RCTs, the Phase 3 RCT involving factorial coadministration of ezetimibe with lovastatin or simvastatin, and the 2-year UES for patients from 2 of the ezetimibe monotherapy RCTs.

Special Laboratory Tests. These were to be done before and at the end of treatment in 3 RCTs and 1 UES:

- In a monotherapy RCT: vitamins A and D (25-hydroxy vitamin D and 1,25-dihydroxy vitamin D), the 2 major components of vitamin E (alpha and gamma tocopherol), the alpha and beta carotenoids, prothrombin time (an indicator of vitamin K status), and the cortisol response to cosyntropin challenge.
- In the RCT involving factorial coadministration of ezetimibe and pravastatin: c-reactive protein, endothelin, fibrinogen, plasminogen activator inhibitor-1, tissue factor, and tissue factor pathway inhibitor;
- In the add-on RCT for patients with documented CHD, diabetes, or CVD risk factors: c-reactive protein, fibrinogen, follicle stimulating hormone, leutinizing hormone, and testosterone in male patients;
- In the 2-year UES of patients from 2 of the ezetimibe monotherapy RCTs: vitamins A, D (25-hydroxyvitamin D and 1,25-dihydroxy vitamin D), and carotenoids.

Analysis Of Laboratory Tests. Laboratory test results were evaluated for values during treatment with study drug (i.e., postbaseline values) that were below or above prespecified limits, regardless of change from baseline. The proportions of patients with values outside these prespecified limits at least once after baseline were summarized and compared between treatment groups when appropriate. For each laboratory variable, a patient was counted only once if multiple values were outside the prespecified limits, but a patient could be counted in both the "low" and "high" groups if values below and above the prespecified limits were observed after baseline. These "low" and "high" results are emphasized here, because they are sensitive for identifying potential safety issues.

In addition, summary statistics were calculated for each laboratory variable and compared between treatment groups when appropriate. The mean, standard deviation, and median were calculated for actual values, actual changes from baseline, percent changes from baseline, minimum postbaseline value, maximum postbaseline value, and endpoint value. Also, "shift tables" were constructed to show the proportions of patients in the different treatment groups that moved between categories of values, between baseline and endpoint, and between baseline and minimum or maximum value, depending on the variable.

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

Special attention was directed to evaluating certain clinical AEs and laboratory test values because ezetimibe is a new molecular entity or because of known actions of the drug, preclinical findings, issues raised by the FDA, or other considerations. These clinical AEs and laboratory test values included:

- Allergic Reaction/Rash AEs (ezetimibe is a new molecular entity of unknown allergenicity): allergic reaction, allergic reaction aggravated, allergy, allergy aggravated, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, dermatitis, dermatitis aggravated, eosinophilia, face edema, photosensitivity allergic reaction, photosensitivity reaction, photosensitivity toxic reaction, pruritis, pruritis aggravated, rash, rash aggravated, rash erythematous, rash follicular, rash maculopapular, rash maculopapular aggravated, rash psoriaform, rash pustular, rash vesicular, skin disorder, urticaria, urticaria aggravated, urticaria acute.

- Central Nervous System/Peripheral Nervous System and Psychiatric AEs (FDA request): all preferred terms in the Schering-Plough modification of the WHO-ART.
- Gastrointestinal System AEs (ezetimibe acts on intestinal epithelium): all preferred terms in the Schering-Plough modification of the WHO-ART.
- Gallbladder-related AEs (ezetimibe increases bile cholesterol concentration in dogs although there has been no increase in stone formation or biliary dysfunction): biliary pain, biliary sludge, bile duct obstruction, bile duct stricture, bile duct stone, cholecystectomy, cholangitis, cholelithiasis, cholecystitis, gallbladder disease, gallbladder disorder, gallbladder perforation.
- Hepatitis-related AEs (ezetimibe is proposed for coadministration with statins, which can increase ALT and AST, and in rare cases have reportedly caused clinical hepatitis): cholestasis, hepatitis, hepatitis aggravated, hepatitis cholestatic, hepatitis infectious, cytolytic hepatitis, hepatitis fulminant, hepatitis necrosis, hepatocellular damage, hepatic failure, hepatic failure aggravated, jaundice, jaundice cholestatic.
- Liver And Biliary System AEs (ezetimibe can increase ALT and AST): all preferred terms in the Schering-Plough modification of the WHO-ART.
- ALT or AST values $\geq$3xULN on at least 2 consecutive or presumed consecutive occasions (if records were incomplete) (ezetimibe sometimes increases ALT or AST),
- CPK values $\geq$10xULN or 5 to <10xULN and associated with muscle symptoms within 7 days of the CPK elevation (CPK elevations have predictive value for the risk of rhabdomyolysis associated with lipid-lowering drugs).

1.5.4 Vital Signs And Body Weight

At each study visit, BP and pulse were measured after the patient had been seated for at least 5 minutes, and body weight was measured without shoes or heavy clothing. In the 8-12 week RCTs, BP and pulse were usually recorded in the CRF only before and after study drug treatment, whereas body weight was usually recorded at each visit. In the longer studies, BP, pulse, and body weight were usually recorded at each visit. Changes in BP, pulse, or body weight could be reported as AEs, at the discretion of the investigator. In the analysis, treatment groups were compared for the frequency of patients with postbaseline values below or above the prespecified limits and for prespecified changes from baseline.

1.5.5 Electrocardiograms

In most studies, a standard 12-lead ECG was to be obtained before and after study drug treatment. Important features were recorded, including heart rate, the PR, QRS, and QT intervals, and the rhythm (normal sinus, sinus bradycardia, etc.) Overall findings were characterized as normal or abnormal, and if abnormal as clinically significant or not, with description of the abnormality. Results before and after study drug treatment were compared, and any changes from baseline were characterized as clinically significant or not. An ECG abnormality could be reported as an AE at the discretion of the investigator. In the analysis, treatment groups were compared for the frequency of patients with clinically significant changes from baseline, stratified on the presence or absence of baseline abnormalities, and the frequency of patients with prespecified changes from baseline in measured PR, QRS, and QT intervals, and derived QTc intervals using the corrections of both Bazett and Fridericia.

1.5.6 Cardiopulmonary Examination

Auscultation of the heart and lungs was scheduled at least once during drug treatment in the Phase 2/3 RCTs. The investigator was to note whether the result was normal or abnormal, and if abnormal to provide comment. Any abnormality could be reported as an AE at the discretion of the investigator.

1.5.7 General Data Conventions

In the 12 completed RCTs, time was measured in days. The day of randomization was "Study Day 1," and events or observations were reported by Study Day of occurrence, e.g. "Study Day 13." If an event or observation occurred after study drug was stopped, the Study Day was followed by the days since stopping in parenthesis, e.g., "Study Day 90 (6)" meant the 90th Study Day and 6th day since stopping study drug. In the 4 UESs, time was measured in "months" defined as having 30 days, e.g., <3 months = $\leq$89 days, 6 to <9 months = 180 to 269 days, etc.

In the RCTs, events or observations that occurred for up to 30 days after study discontinuation or completion were ascribed to a patient's randomly assigned treatment, which did not change during the study. However, in the UESs, treatments could change over time. Therefore, in reporting RCT+UES results, categories of events or observations were used such as: "All Reported After Assignment to Ezetimibe" (i.e., reported after assignment to ezetimibe, regardless of statin coadministration); "Reported During Ezetimibe Monotherapy" (i.e., reported after assignment to

ezetimibe and before any statin; pure monotherapy was a subset), and "Reported During Coadministration," (i.e., reported after a statin was first coadministered with ezetimibe).

Because the UESs were all ongoing at the time of the NDA submission, assumptions were made to deal with incomplete dosing records. If a patient was not known to have discontinued a UES, the patient was considered to have continued with the last treatment(s) recorded before 15 July 2001, which was the cutoff date for the NDA data. If a continuing patient had received both ezetimibe and a statin, the following assumptions were made on the basis of recorded dosing dates: If the last ezetimibe date was $\leq$7 days after the last statin date, the patient was considered to have been receiving coadministration through 15 July 2001. If the last ezetimibe date was >7 days after the last statin date, the patient was considered to have stopped the statin, and safety data were attributed to coadministration only through 30 days after the last statin date. If a patient had discontinued a study, and had received both ezetimibe and a statin, safety data were attributed to coadministration through 30 days after the last statin date.

Baseline. In the RCTs, AEs that occurred from the signing of informed consent up to Study Day 1 (day of randomization) comprised the "baseline" to which AEs that occurred after Study Day 1 were compared, to determine if the latter were "treatment emergent." For other events or observations, "baseline" was generally the last result obtained before randomization, or by Study Day 3 if no earlier result was available (patients without a result by Study Day 3 were considered to have no baseline value). In the UESs, "baseline" was considered to be the baseline of the RCT from which a patient came.

Treatment-Emergent AEs. In general, an AE was defined as "treatment emergent" if the AE was not present before Study Day 1 or not present at the same (or greater) intensity. However, in the UESs, an AE was defined as "treatment emergent" only if the start date was on or after the specific treatment (any ezetimibe, monotherapy, coadministration);an AE that was present when a specific treatment was started in a UES was not considered to be "treatment emergent" for that treatment.

Postbaseline Results. In general, postbaseline results were any results that occurred after baseline in a RCT or after the start of a specific treatment in a UES if the patient did not receive that specific treatment in the originating RCT.

Changes From Baseline. Change from baseline was calculated as the difference between postbaseline and baseline values. Patients without at least 1 baseline and postbaseline value for a variable were excluded from calculating change from baseline for that variable.

Multiple Laboratory Test Results. When multiple laboratory test results were obtained in a prespecified time interval, the maximum observed value was used to calculated summary statistics for the following variables:

- Hematology – counts of red cells, monocytes, basophils, eosinophils, and band-form neutrophils; prothrombin time and partial thromboplastin time;
- Blood Chemistry –ALT, AST, GGT, alkaline phosphatase, total bilirubin, CPK, BUN, creatinine, calcium, phosphorus sodium, potassium, chloride, glucose, and thyroid stimulating hormone;
- Urinalysis - All variables.

The minimum observed value was used for the remaining tests.

Summaries Of Postbaseline Laboratory Results. Maximum and minimum postbaseline values, for each patient and laboratory variable in a study, were displayed as a way of inspecting extreme values. When these displays refer to actual and percent changes from baseline, the terms "maximum" and "minimum" mean the postbaseline value itself, and not the magnitude of change from baseline.

ALT Or AST Values $\geq$3xULN in the UESs. In the UESs, a patient was considered to have consecutive values $\geq$3xULN for ALT or AST if the last recorded value while receiving a specific treatment (e.g., monotherapy) was $\geq$3xULN, even if the patient continued the study, received another treatment (e.g., coadministration), and the next recorded value was <3xULN. The accounting was therefore conservative of possibly meaningful ALT or AST elevations.

Endpoints. In general, endpoint for an event or observation was the last value during or shortly after treatment with study drug.

In the RCTs, endpoint was the last observation during or $\leq$ 3 days after study drug treatment.

In the UESs, endpoint was based upon recorded dates of study drug use through 15 July 2001, and defined as follows:

- Endpoint for "All Reported After Assignment to Ezetimibe " depended on whether the patient was known to have discontinued the study. For patients who had not discontinued, endpoint was the last reported value, and for patients who had discontinued, endpoint was the last reported value during or ≤3 days after ezetimibe treatment (regardless of statin coadministration).
- Endpoint for "Reported During Monotherapy" was the last reported value during ezetimibe treatment, before any statin treatment was begun, or ≤3 days after the last monotherapy dose for patients who discontinued during monotherapy.
- Endpoint for "Reported During Coadministration" depended on whether the patient was known to have discontinued the study. For patients who had not discontinued, endpoint was defined as follows.
- For a patient whose last ezetimibe date was ≤7 days after the last statin date, endpoint was the last reported value during coadministration or through 15 July 2001; and, for a patient whose last ezetimibe date was >7 days after the last statin date, endpoint was the last reported value during coadministration or up to 30 days after the last recorded statin date. For patients who had discontinued, endpoint was defined as the last reported value during coadministration or whichever of the following resulted in the least number of study days: the greater of the last ezetimibe date plus 3 days or the last statin date plus 3 days, or the last statin date plus 30 days.

For patients who discontinued or completed a study, safety data collected for 30 days thereafter were generally associated with the treatment received at the time of discontinuation or completion. Analyses of these data were included in overall summaries for that treatment, even if the data did not met the predefined "endpoint" for the study.

Denominators. The denominators for time intervals in the RCT+UES data were derived as follows. If a patient had an observation or measurement in an interval (e.g., vital signs recorded or sample taken for laboratory test), the patient contributed to the denominator for that interval; and, if a patient had an AE, the patient contributed to the denominator for all intervals up to the interval containing the last study visit recorded before the AE. However, because the UESs are ongoing and data collection is not complete, some AEs were recorded in intervals beyond those of the preceding study visits. Because of this, the number of patients with an AE recorded in an interval was sometimes greater than the number of patients documented as contributing to the denominator for that interval. When this occurred, the percentage of patients with an AE could exceed 100% and not be meaningful.

Data recorded on the CRF were used to estimate the length of time that a patient was treated with study drug, and the investigators recorded changes in treatment (addition of statin, up-titration, etc.) However, patients were often unable to specify exact dates of missed doses during the intervals between study visits, and investigators sometimes did not completed the dates when a treatment started or stopped. Therefore, the length of time a patient was treated was defined in 2 ways: First, "Duration of Participation" was defined as the total interval between the first and last recorded dates of dosing with a treatment, ignoring missed doses and gaps in the record; second, "Extent of Exposure" was defined as the number of days a treatment was actually taken, as estimated by subtracting missed doses and gaps in the record from the duration of participation, whenever the record was complete enough to identify the intervals of missed doses and gaps.

Finally, part of the UES safety evaluation included the display of data by time of occurrence. Time was stratified by intervals of 3 to 6 months and, in each interval, only patients who were receiving a treatment at the beginning of the interval contributed data.

2. LENGTH OF STUDY DRUG TREATMENT

As discussed above, length of treatment was defined in 2 ways: "Duration of Participation" was the interval between the first and last recorded dates of dosing with a treatment (ignoring missed doses and gaps in the record), and "Extent of Exposure" was the number of days a treatment was actually taken (estimated by subtracting missed doses and gaps in the record from the Duration of Participation).

2.1 Randomized Clinical Trials (RCTs)

2.1.1 Primary Hypercholesterolemia

2.1.1.1 Randomized Clinical Trials (RCTs) Of Ezetimibe Monotherapy

The main safety evaluations of ezetimibe monotherapy were based on the monotherapy pool, consisting of the 3 Phase 2 and 2 Phase 3 monotherapy RCTs, and those patients in the 4 factorial RCTs who received either placebo or ezetimibe monotherapy. These 9 RCTs provided data on 795 patients treated with placebo, 1691 patients treated with ezetimibe 10 mg, and 1983 patients treated with any dose of ezetimibe. About 90% of patients randomized to placebo or ezetimibe

10 mg had Durations of Participation of at least 10 weeks, and the median was about 12.0 weeks. Table 11 shows more information about Duration of Participation for the monotherapy pool.

2.1.1.2 Randomized Clinical Trials (RCTs) Of Ezetimibe Coadministered With A Statin Or Added To An Established Statin

The main safety evaluations of ezetimibe coadministered with a statin or added to an established statin were based on the factorial coadministration pool and the add-on RCT for patients with documented CHD, diabetes mellitus, or CVD risk factors.

The 4 factorial RCTs provided data on 259 patients treated with placebo, 262 patients treated with ezetimibe 10 mg, 936 patients treated with a statin (any dose), and 925 patients treated with ezetimibe 10 mg and a coadministered statin (any dose). About 89% of patients randomized had Durations of Participation of at least 10 weeks, and the median was about 12 weeks. Table 12 shows more information about Duration of Participation for the factorial coadministration pool.

The add-on RCT for patients with documented CHD, diabetes mellitus, or CVD risk factors provided data on 390 patients treated with placebo added to an established statin, and 379 patients treated with ezetimibe 10 mg added to an established a statin. About 95% of patients randomized had Durations of Participation of at least 6 weeks, and the median was about 8 weeks. Table 13 shows more information about Duration of Participation for this study.

2.1.2 Homozygous Familial Hypercholesterolemia

The main safety evaluations of ezetimibe for Homozygous Familial Hypercholesterolemia were based on the 1 RCT for this disorder, in which 17 patients were treated with 80 mg of a statin and 33 patients were treated with ezetimibe 10 mg and 40 mg or 80 mg or a statin. About 92% of patients randomized had Durations of Participation of at least 10 weeks, and the median was about 12 weeks. Table 14 shows more information about Duration of Participation for this study.

2.1.3 Homozygous Sitosterolemia

The main safety evaluations of ezetimibe for Homozygous Sitosterolemia were based on the 1 RCT for this disorder, in which 7 patients were treated with placebo and 30 patients were treated with ezetimibe 10 mg, in addition to previously established therapies such as apheresis or a bile

acid sequestrant. About 84% of patients randomized had Durations of Participation of at least 7 weeks; the median was about 8 weeks. Table 15 shows more information about Duration of Participation for this study.

2.2 Uncontrolled, Extension Studies (UESs); RCT+UES Analyses

In all UESs, all patients received ezetimibe 10 mg, as monotherapy or in coadministration with a statin. Analyses were generally done using RCT+UES data sets.

2.2.1 Primary Hypercholesterolemia

In the RCT+UES data sets for Primary Hypercholesterolemia, the Duration of Participation for all ezetimibe treatment was at least 6 months for 1341 patients and at least 12 months for 1018 patients; the median was 8.8 months. Tables 16-18 show more information about Duration of Participation and Extent of Exposure for all ezetimibe, ezetimibe monotherapy, and ezetimibe coadministered with a statin.

2.2.2 Homozygous Familial Hypercholesterolemia

In the RCT+UES data sets for Homozygous Familial Hypercholesterolemia, the Duration of Participation for ezetimibe coadministered with a statin was at least 6 months for 25 patients; the median was 6.1 months. Tables 19-20 show more information about Duration of Participation and Extent of Exposure.

3. ENROLLMENT IN THE RANDOMIZED CLINICAL TRIALS (RCTs); DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Information about RCT enrollment was summarized for Primary Hypercholesterolemia (monotherapy pool, factorial coadministration pool, add-on RCT), the Homozygous Familial Hypercholesterolemia RCT, and the Homozygous Sitosterolemia RCT. These summaries included the total number of study centers and the number of centers in the United States; the total number of patients randomized and the number randomized in the United States; the total number of patients enrolled in the studies, and the numbers discontinued before randomization according to general reasons for discontinuation. (The case report forms did not record exact reasons for discontinuation before randomization.)

Demographic and other baseline characteristics were summarized for patients in the completed RCTs and related UESs for which full reports were included in the NDA, by indication for treatment and monotherapy

versus coadministration. Baseline characteristics were not summarized for patients in the Clinical Pharmacology studies or the ongoing RCTs.

3.1 Primary Hypercholesterolemia

3.1.1 Randomized Clinical Trials (RCTs)

3.1.1.1 Randomized Clinical Trials (RCTs) Of Ezetimibe Monotherapy

The monotherapy pool consisted of the 3 Phase 2 and 2 Phase 3 monotherapy RCTs and those patients in the 4 factorial RCTs who received either placebo or ezetimibe monotherapy.

The total number of study centers was 366, of which 337 (92.1%) were in the United States. The total number of patients randomized was 2778, of whom 2724 (98.1%) were in the United States.

Data on the numbers of patients enrolled but discontinued before randomization were pooled for 4 of the Phase 2/3 monotherapy RCTs. (For methodological reasons, 1 Phase 2 RCT was analyzed separately). In the 4 pooled RCTs, a total of 5536 patients were enrolled, of whom 3385 (61.1%) were discontinued before randomization. Of the 3385 discontinued patients, the reasons were: adverse event, n=60 (1.8%); lost to follow-up, n=98, (2.9%); patient declined to continue, n=487 (14.4%), non-compliance with protocol, n=75 (2.2%), did not meet protocol eligibility, n=2613 (77.2%), and administrative, n=52 (1.5%). Of the 2613 patients discontinued because of not meeting protocol eligibility, screening/placebo lead-in data were available for 2196 (84.0%). From these data, it appears that >50% of discontinuations before randomization that were due to not meeting protocol eligibility were a result of calculated LDL-C <130 mg/dL, variability between qualifying values of calculated LDL-C>14 %, and/ or triglycerides >350 mg/dL. In the 1 separately analyzed Phase 2 RCT, the reasons for discontinuation before randomization were similar to the reasons discussed above.

Tables 21-24 show demographic and other baseline characteristics for the monotherapy pool. Of the 2778 patients, 795 were treated with placebo, 1983 were treated with ezetimibe (any dose), and 1691 were treated with ezetimibe 10 mg.

Of the 2778 patients, about 90.2% were Caucasian, 5.2% were Black, 3.0% were Hispanic, and the remainder were other ethnicities. About 51.8% were female and 48.2% were male. The median age was about 59 years and the range was 18-86 years. The treatment groups were generally

well-balanced for sex, age, race, body weight, body mass index, smoking status, "washout" treatments (treatments used prior to study), cardiovascular risk factors, cardiovascular history and physical findings,, and general medical history and physical findings.

3.1.1.2 Randomized Clinical Trials (RCTs) Of Ezetimibe Coadministered With A Statin

The factorial coadministration pool consisted of the 4 factorial RCTs.

The total number of study centers with randomized patients was 225, of which 191 (84.9%) were in the United States. The total number of patients randomized was 2382, of whom 2106 (88.4%) were in the United States.

A total of 8405 patients were enrolled, of whom 6023 (71.1%) were discontinued before randomization. Of the 6023 discontinued patients, the reasons were: adverse event, n=131 (2.2%); lost to follow-up, n=136 (2.3%); patient declined to continue, n=665 (11.0%); non-compliance with protocol, n=127 (2.1%); did not meet protocol eligibility, n=4917 (81.6%), and administrative, n=47 (0.8%). Of the 4917 patients discontinued because of not meeting protocol eligibility, screening/placebo lead-in data were available for 4556 (92.7%). From these data, it appears that >70% of discontinuations before randomization that were due to not meeting protocol eligibility were a result of calculated LDL-C <160 mg/dL, variability between qualifying values of calculated LDL-C>14%, and/ or triglycerides >350 mg/dL.

Tables 25-28 show demographic and other baseline characteristics for patients in the factorial coadministration pool. Of the 2382 patients, 259 were treated with placebo, 262 were treated with ezetimibe 10 mg, 936 were treated with a statin (any dose), and 925 patients treated ezetimibe 10 mg and coadministered statin (any dose).

Of the 2382 patients, about 87.7% were Caucasian, 5.3% were Black, 4.8% were Hispanic, and the remainder were other ethnicities. About 57.3% were female and 42.7% were male. The median age was about 57 years and the range was 18-87 years. The treatment groups were generally well-balanced for sex, age, race, body weight, body mass index, smoking status, "washout" treatments (treatments used prior to study), cardiovascular risk factors, cardiovascular history and physical findings, and general medical history and physical findings.

3.1.1.3 Randomized Clinical Trial (RCT) Of Ezetimibe Added To An Established Statin

Ezetimibe added to an established statin was studied in the RCT for patients with documented CHD, diabetes mellitus, or CVD risk factors.

The total number of study centers with randomized patients was 77, of which 48 (62.3%) were in the United States. The total number of patients randomized was 769, of whom 473 (61.5%) were in the United States.

A total of 1197 patients were enrolled, of 428 (35.8%) were discontinued before randomization. Of the 428 discontinued patients, the reasons were: adverse event, n=2 (0.5%); lost to follow-up, n=3 (0.7%); patient declined to continue, n=35 (8.2%); non-compliance with protocol, n=3 (0.7%); did not meet protocol eligibility, n=374 (87.4%), administrative, n=6 (1.4%), and missing reason, n=4 (0.9%). Of the 374 patients discontinued because of not meeting protocol eligibility, screening/placebo lead-in data were available for 338 (90.4%). From these data, it appears that >35% of discontinuations before randomization that were due to not meeting protocol eligibility were a result of calculated LDL-C <100 mg/dL in patients with documented CHD or diabetes mellitus, glucose ≥140 mg/dL, calculated LDL-C<130 mg in patients with ≥2 CHD risk factors and without documented CHD, and /or calculated LDL-C <160 mg/dL in patients with <2 CHD risk factors and without documented CHD.

Table 29 shows demographic and other baseline characteristics for the RCT for patients with documented CHD, diabetes mellitus, or CVD risk factors. Of the 769 patients, 390 were treated with placebo and a statin (any dose) and 379 were treated with ezetimibe 10 mg and a statin (any dose).

Of the 769 patients, about 90.1% were Caucasian, 6.0% were Black, 2.0% were Hispanic, and the remainder were other ethnicities. About 42.4% were female and 57.6% were male. The median age was about 61 years and the range was 22-85 years. The treatment groups were generally well-balanced for these and other baseline variables.

3.1.2 Uncontrolled Extension Studies (UESs); RCT+UES Data

The demographic and other baseline characteristics of patients in the RCT+UES data sets for were generally similar to those of patients in the contributing RCTs.

3.2 Homozygous Familial Hypercholesterolemia

3.2.1 Randomized Clinical Trial (RCT)

There was 1 RCT for Homozygous Familial Hypercholesterolemia.

The total number of study centers with randomized patients was 17, of which 4 (23.5%) were in the United States. The total number of patients randomized was 50, of whom 5 (10.0%) were in the United States.

A total of 55 patients were enrolled, of whom 5 (9.1%) were discontinued before randomization. Of the 5 discontinued patients, the reasons were: adverse event, n=1; lost to follow-up, none; patient declined to continue, n=3; non-compliance with protocol, none; did not meet protocol eligibility, n=1; administrative, none.

Table 30 shows demographic and other baseline characteristics for patients in the RCT for Homozygous Familial Hypercholesterolemia. Of the 50 patients, 17 were treated with 80 mg of a statin and 33 were treated with ezetimibe 10 mg and 40 mg or 80 mg of a statin. Of the 50 patients, about 90.0% were Caucasian, 2.0% were Black, and 8.0% were Hispanic. About 58.0% were female and 42.0% were male. The median age was about 30 years and the range was 11-74 years. The treatment groups were generally well-balanced for these and other baseline variables.

3.2.2 Uncontrolled Extension Study; RCT+UES Data

The demographic and other baseline characteristics of patients in the RCT+UES data set were generally similar to those of patients in the contributing RCT.

3.3 Homozygous Sitosterolemia

There was 1 RCT for Homozygous Sitosterolemia.

The total number of study centers with randomized patients was 23, or which 12 (52.2%) were in the United States. The total number of patients randomized was 37, of whom 23 (62.2%) were in the United States.
A total of 39 patients were enrolled, of whom 2 (5.1%) were discontinued before randomization. Of the 2 discontinued patients, neither met protocol eligibility. In 1 case, baseline ALT and AST were above 5xULN, and in the other case baseline HbA1c was >10%.

Table 31 shows demographic and other baseline characteristics for patients in the RCT for Homozygous Sitosterolemia. This RCT provides data on 7 patients treated with placebo and 30 patients treated with ezetimibe 10 mg, in addition to previously established therapies such as apheresis or a bile acid sequestrant.

Of the 37 patients, about 89.2% were Caucasian, 8.1% were Hispanic, and the remainder were other ethnicities. About 64.9% were female and 35.1% were male. The median age was about 39 years and the range was 13-72 years. The treatment groups were generally well-balanced for these and other baseline variables.

4. SAFETY RESULTS IN CLINICAL STUDIES ≤14 WEEKS LONG

The results shown below are for the safety evaluation data sets as a whole. Possible interactions between ezetimibe and baseline demographic characteristics (sex, age, race), concomitant illnesses, or concomitant therapy are discussed in Section 7.

4.1 Primary Hypercholesterolemia

Results are shown for (1) ezetimibe monotherapy, from the 3 Phase 2 and 6 Phase 3 RCTs in the monotherapy pool, (2) ezetimibe coadministered with a statin, from the 4 RCTs in the factorial coadministration pool, and (3) ezetimibe added to an established statin, from the RCT for patients with documented CHD, diabetes mellitus, or CVD risk factors.

4.1.1 Ezetimibe Monotherapy

The monotherapy pool consisted of 795 patients treated with placebo, 1691 patients treated with ezetimibe 10 mg, and 1983 patients treated with any dose of ezetimibe, from — mg (see Section 1.4.1.1.1). In this review the results for placebo and ezetimibe 10 mg are emphasized in the text, since the number of patients receiving other ezetimibe doses was small, and the results for patients receiving all doses were similar to those for patients receiving 10 mg. The results for all 3 treatment groups are shown in the tables.

4.1.1.1 Adverse Events (AEs)

4.1.1.1.1 Overview

Table 32 presents an overview of the AEs. The main findings are shown below in Table 32A (Table 32 abbreviated).

Table 32A: Monotherapy Pool AEs: Number (%) of Patients

Adverse Event	Placebo	Ezetimibe 10 mg
Death	0	1 (0.1%)
Serious AE*	19 (2.4%)	35 (2.1%)
Discontinuation due to AE	30 (3.8%)	68 (4.0%)
AEs of Any Intensity	511 (64.3%)	1061 (62.7%)
Any Severe or Life-Threatening AE	32 (4.0%)	79 (4.7%)

*See Section 1.5

4.1.1.1.2 Deaths And Other Serious Adverse Events (AEs)

4.1.1.1.2.1 Deaths

A 68 year old Caucasian male began ezetimibe 10 mg in April 2000 and in June 2000 was reported missing. In September 2000, his body was found in his car submerged in a lake. An autopsy was performed; the results were not released. Review of the patient's records revealed nothing to suggest an adverse effect of ezetimibe. There were no other deaths.

4.1.1.1.2.2 Serious Adverse Events (SAEs)

Table 33 shows the SAEs. SAEs were reported for 19 (2.4%) patients in the placebo group and 35 (2.1%) patients in the ezetimibe 10 mg group. The frequencies of patients with individual SAEs were similar in the placebo group and the ezetimibe 10 mg group.

Table 34 shows the SAEs that were considered to be treatment-related. SAEs that were considered to be treatment-related were reported for no patients in the placebo group and 6 (0.4%) of patients in the ezetimibe 10 mg group.

The main reason for the difference in results between Tables 33 and 34 was that 4 of the 5 patients in the ezetimibe 10 mg group who had SAEs of the Liver And Biliary System were considered to have treatment-related SAEs, whereas neither of the 2 patients in the placebo group who had Liver And Biliary System SAEs considered to have treatment-related SAEs. The individual SAEs involved were GGT increased, hepatic function abnormal, SGOT (AST) increased, and SGPT (ALT) increased. The difference suggests that the investigators may have called these SAEs

treatment-related more frequently for patients in the ezetimibe 10 mg group than patients in the placebo group. (see Section 4.1.1.3.6). Non-fatal, life-threatening SAEs were reported for 2 (0.3%) patients in the placebo group and 3 (0.2%) patients in the ezetimibe 10 mg group. All of these SAEs led to discontinuation from the study, although all were considered unrelated or unlikely to be related to treatment. Of the 2 patients in the placebo group: 1 had a history of CVD, was treated with placebo for 2 months, and was then discontinued and hospitalized for a coronary bypass; the other had a history of muscle aches, had elevations of ALT, AST, and CPK on the day of randomization, and was discontinued without receiving study drug. Of the 3 patients in the ezetimibe 10 mg group: 1 had prostate cancer diagnosed from a biopsy performed during the placebo run-in, was treated with ezetimibe 10 mg for 2 weeks, and was then discontinued because of the cancer; 1 had a history of CVD and ECG abnormalities, was treated with ezetimibe 10 mg for 6 days, then developed chest pain and was discontinued, after which further work-up led to a coronary bypass; 1 was treated with ezetimibe 10 mg for 4 weeks, was hit by a motor vehicle and sustained fractures of the right leg and pelvis, was discontinued , and was hospitalized for reparative surgery.

4.1.1.1.3 Discontinuation Due To Adverse Events (AEs)

Table 35 shows the AEs that led to discontinuation from a study. AEs that led to discontinuation from a study were reported for 30 (3.8%) patients in the placebo group and 68 (4.0%) patients in the ezetimibe 10 mg group. Within these totals, there were 1 (0.1%) patient in the placebo group and 7 (0.4%) patients in the ezetimibe 10 mg group with discontinuations due to Benign And Malignant Neoplasms, but the AEs in the ezetimibe 10 mg group were diverse, including breast neoplasm, meningioma, prostate cancer, and others. There were 2 (0.3%) patients in the placebo group and 10 (0.6%) in the ezetimibe 10 mg group with discontinuations due to Liver And Biliary System AEs; the AEs in the ezetimibe 10 mg group included GGT increased, hepatic function abnormal, SGOT (AST) increased, and others (see Section 4.1.1.3.6). For the other AEs that led to discontinuation, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group.

Table 36 shows the AEs that led to discontinuation from a study and were considered to be treatment-related. AEs that led to discontinuation from a study and were considered to be treatment-related were reported for 17 (2.1%) patients in the placebo group and 39 (2.3%) patients in the ezetimibe 10 mg group. Within these totals, there were 1 (0.1%) patient in the placebo group and 9 (0.5%) patients in the ezetimibe 10 mg group with discontinuations due to Liver And Biliary System AEs that were

considered to be treatment-related; the AEs in the ezetimibe 10 mg group included GGT increased, hepatic function abnormal, SGOT (AST) increased, and others. There were 1 patient (0.1%) in the placebo group and 5 patients (0.3%) in the ezetimibe 10 mg group with discontinuations due to elevations in CPK that were considered to be treatment related (see Section 4.1.1.3.6). For the other AEs that led to discontinuation and were considered to be treatment-related, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group.

4.1.1.1.4 Adverse Events (AEs) Of Any Intensity

AEs of any intensity were reported for 511 (64.3%) patients in the placebo group and 1061 (62.7%) patients in the ezetimibe 10 mg group. Table 37 shows the AEs or any intensity that were reported for ≥2% of patients in at least 1 treatment group. The most frequent were upper respiratory infection, headache, back pain, arthralgia, and musculoskeletal pain. Of the AEs in Table 37, 8 were more frequent in the placebo group than in the ezetimibe 10 mg group, 9 were more frequent in the ezetimibe 10 mg group than in the placebo group, and 1 was at the same frequency in the 2 groups. These AEs could generally be expected in a middle-aged population, and did not show meaningful associations with treatment group.

Of the AEs of any intensity that were reported for <2% of patients in all treatment groups, there were 6 (0.8%) patients in the placebo group and 22 (1.3%) patients in the ezetimibe 10 mg group with Benign And Malignant Neoplasms, but the AEs in the ezetimibe 10 mg group were diverse, including benign neoplasm, meningioma, prostate cancer and others. There were no patients in the placebo group and 8 (0.5%) patients in the ezetimibe 10 mg group with hypertonia (see Section 4.1.1 3.2). There were 10 (1.3%) patients in the placebo group and 41 (2.4%) patients in the ezetimibe 10 mg group with Immune System AEs; the AEs in the ezetimibe 10 mg group included allergy, allergy aggravated, and others (see Section 4.1.1.3.1). 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 AEs; the AEs in the ezetimibe 10 mg group included hepatic function abnormal and SGOT (AST) increased (see Section 4.1.1.3.6). There were 12 (1.5%) patients in the placebo group and 24 (1.4%) patients in the ezetimibe 10 mg group with CPK elevated (see Section 4.1.1.3.7). For the other AEs of any intensity that were reported for <2% of patients in all treatment groups, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group.

AEs of any intensity that were considered to be treatment-related were reported for 123 (15.5%) patients in the placebo group and 235 (13.9%) patients in the ezetimibe 10 mg group. Table 38 shows the 2 AEs of any intensity that were considered to be treatment-related and were reported for ≥2% of patients in at least 1 treatment group. These 2 AEs, headache and constipation, were both reported more often in the placebo group than in the ezetimibe 10 mg group.

AEs that were considered to be severe or life-threatening were reported for 32 (4.0%) patients in the placebo group and 79 (4.7%) patients in the ezetimibe 10 mg group. Table 39 shows the AEs that were considered to be severe or life-threatening. There were 1 (0.1%) patient in the placebo group and 8 (0.5%) patients in the ezetimibe 10 mg group with Benign Or Malignant Neoplasms, but the AEs in the ezetimibe 10 mg group were diverse, including breast neoplasm, meningioma, prostate cancer, and others. There were 5 (0.6%) patients in the placebo group and 19 (1.1%) patients in the ezetimibe 10 mg group with Musculoskeletal System AEs, but the AEs in the ezetimibe 10 mg group were diverse, including arthralgia, back pain, musculoskeletal pain, and others. For the other AEs that were considered to be severe or life-threatening, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group.

4.1.1.2 Laboratory Tests

4.1.1.2.1 Blood Chemistry

The results of laboratory tests for hepatobiliary function (ALT, AST, GGT alkaline phosphatase, and total bilirubin) are discussed in Section 4.1.1.3.6, and the results of laboratory tests for muscle breakdown (CPK) are discussed in Section 4.1.1.3.7. The results of other blood chemistry tests are discussed below.

LDL-C. In an additional analysis not prespecified in the protocol, low LDL-C was defined as a calculated value of <70 mg/dL. The frequencies patients with low postbaseline LDL-C were 1 (0.1%) in the placebo group and 1 (0.1%) in the ezetimibe 10 mg group. The lowest postbaseline LDL-C values reported were 62 mg/dL in the placebo group and 68 mg/dL in the 10 mg group. Study drug was not changed in response to low cholesterol and there is no evidence that any patient was discontinued from the study due to low cholesterol.

Renal Function. The renal function variables were BUN and serum creatinine. Tables 40 shows the frequencies of patients in the placebo group and the ezetimibe 10 mg group with postbaseline values below or above prespecified limits corresponding to the laboratory reference ranges, and Table 40 A shows the frequencies of patients in the placebo group and the ezetimibe 10 mg group with postbaseline values below or above prespecified limits that were set to identify patients with more clearly defined outlier values. Table 41 shows the mean and median values at baseline, and the mean and median changes from baseline, for the placebo group and the ezetimibe 10 mg group. The placebo group and the ezetimibe 10 mg group were similar in these measurements of renal function.

Total Protein, Albumin, Calcium, Phosphorus, Uric Acid, Chloride, Sodium, Potassium, Glucose, TSH. The frequencies of patients in the placebo group and the ezetimibe 10 mg group with postbaseline values below or above the prespecified limits were similar for these variables. The prespecified limits, in United States (US) units, were: total protein = 6-8 g/dL; albumin = 3.5-5.5 g/dL; calcium = 8.5-10.5 mg/dL; phosphorus = 2.5-4.5 mg/dL; uric acid: female $\leq$10 mg/dL, male $\leq$12 mg/dL; chloride = 95-110 meq/L; sodium = 135-145 meq/L; potassium = 3.5-5.5 meq/L; glucose = 60-180 mg/dL; TSH = 0.3-10 mcU/mL.

4.1.1.2.2 Hematology

The hematology variables were platelet count, white blood cell count, hemoglobin concentration, hematocrit, and prothrombin time. Table 42 shows the frequencies of patients in the placebo group and the ezetimibe 10 mg group with postbaseline values below or above prespecified limits corresponding to the laboratory reference ranges, and Table 42 A shows the frequencies of patients in the placebo group and the ezetimibe 10 mg group with postbaseline values below or above prespecified limits that were set to identify patients with more clearly defined outlier values. Table 43 shows the mean and median values at baseline, and the mean and median changes from baseline, for the placebo group and the ezetimibe 10 mg group. Other than as noted below, the placebo group and the ezetimibe 10 mg group were similar in these measurements of hematology.

Platelet count. There were 1 (0.1%) patient in the placebo group and 13 (0.7%) patients treated with ezetimibe, including 10 (0.6%) patients in the ezetimibe 10 mg group, with postbaseline platelet counts below $100x10^9$/L. These patients were all asymptomatic. In 9 of the 13 patients treated with ezetimibe, there was a single postbaseline count of $32\text{-}61x10^9$

obtained during treatment (n=3), on the first day after treatment was stopped (n=5), or later (n=1); the count returned to normal on the next measurement in 8 patients and was not measured again in 1 patient. There was 1 patient with a prior history of thrombocytopenia who had a count of $65x10^9$ during treatment and was discontinued from the study; the count 22 days after stopping ezetimibe was $54x10^9$ and the count 57 days after stopping was $92x10^9$. There were 3 patients who each had 2 counts of $81\text{-}94x10^9$ during or $\leq$8 days after stopping ezetimibe; 1 had a subsequent count of $103x10^9$ of the first day after treatment was stopped, and the other 2 did not have follow-up counts.

White Blood Cell Count. There were 5 (0.6%) patients in the placebo group and 21 (1.1%) patients treated with ezetimibe, including 19 (1.1%) patients in the ezetimibe 10 mg group, with postbaseline white blood cell counts below $3.0x10^9$/L. These patients were all asymptomatic. In 18 of the 21 patients treated with ezetimibe, the difference between the lowest pre-randomization count and lowest post-randomization value was $\leq 0.5x10^9$/L. Of the remaining 3 patients, the count returned to normal during ezetimibe treatment in 1 patient, concomitant treatment with allopurinol may have been contributory in 1 patient, and in 1 patient treatment with ezetimibe 10 mg was discontinued after about 2 months due to the leukopenia. This patient began screening with a count of $4.8x10^9$/L, which increased to $7.0x10^9$/L at randomization, decreased to $3.50x10^9$/L after about 1 month of treatment with ezetimibe 10 mg, increased again to $5.0x10^9$/L, and finally decreased to $3.2x10^9$/L, at which time treatment was stopped. Neutrophil counts were also below the lower limit of the reference range during this time. The count 10 days after treatment was stopped was $4.3x10^9$/L. The event was considered to be probably treatment-related.

Prothrombin Time. There were no patients in the placebo group and 4 (0.3%) patients in the ezetimibe 10 mg group with postbaseline 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.

4.1.1.2.3 Urinalysis

The urinalysis variables included specific gravity, pH, glucose, ketones, protein, red blood cells, and white blood cells. The frequencies of patients with postbaseline values below or above the prespecified limits were similar in the placebo group and the ezetimibe 10 mg group. The prespecified limits were: specific gravity = 1.002-1.035; pH = 5-8 pH units;

glucose ≤100 dipstick units; ketones ≤5 dipstick units; protein =≤30 dipstick units; red blood cells ≤5 per high power field; white blood cells ≤5 per high power field.

4.1.1.2.4 Fecal Occult Blood

There were 7 (0.9%) patients in the placebo group and 8 (0.5%) patients in the ezetimibe 10 mg group with positive postbaseline results for fecal occult blood.

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

Section 1.5.3 describes the Clinical Adverse Events And Laboratory Test Values Of Special Interest and the reasons for selecting these events and test values for special attention.

4.1.1.3.1 Allergic Reaction/Rash Adverse Events (AEs)

Table 44 shows the Allergic Reaction/Rash AEs. There were 28 (3.5%) patients in the placebo group and 79 (4.7%) patients in the ezetimibe 10 mg group with any Allergic Reaction/Rash AE. Within these totals, there were 7 patients (0.9%) in the placebo group and 39 patients (2.3%) in the ezetimibe 10 mg group with allergy or allergy aggravated. Most of these events were seasonal or environmental allergies, and were rated as mild or moderate in severity. For the other Allergic Reaction/Rash AEs, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group.

4.1.1.3.2 Central and Peripheral Nervous System Adverse Events (AEs)

Table 45 shows the Central Nervous System/Peripheral Nervous System AEs. There were 26 (3.3%) patients in the placebo group and 58 (3.4%) patients in the ezetimibe 10 mg group with any Central Nervous System/Peripheral Nervous System AE. Within these totals, there were no patients in the placebo group and 8 (0.5%) patients in the ezetimibe 10 mg group with hypertonia, and there were no patients in the placebo group and 5 (0.3%) patients in the ezetimibe 10 mg group with neuralgia. Most of these AEs were rated as mild or moderate in severity. For the other Central Nervous System/ Peripheral Nervous System AEs, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group.

4.1.1.3.3 Psychiatric Adverse Events (AEs)

Table 46 shows the Psychiatric AEs. There were 25 (3.1%) patients in the placebo group and 59 (3.5%) patients in the ezetimibe 10 mg with any Psychiatric AE. Within these totals, there were 3 (0.4%) patients in the placebo group and 13 (0.8%) patients in the ezetimibe 10 mg group with anxiety, and there were 1 (0.3%) patients in the placebo group and 5 (0.6%) patients in the ezetimibe 10 mg group with impotence. Most of these AEs were rated mild or moderate in severity. For the other Psychiatric AEs, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group.

4.1.1.3.4 Gastrointestinal System Adverse Events (AEs)

Table 47 shows the Gastrointestinal System AEs. There were 155 (19.5%) patients in the placebo group and 303 (17.9%) patients in the ezetimibe 10 mg group with any Gastrointestinal System AE. Within these totals, 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; most of these AEs were rated as mild or moderate in severity. For the other Gastrointestinal System AEs, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group.

4.1.1.3.5 Gallbladder-related Adverse Events (AEs)

Table 48 shows the Gallbladder-related AEs. There were 2 (0.3%) patients in the placebo group and 1 (0.1%) patient in the ezetimibe 10 mg group with any Gallbladder-related AEs.

4.1.1.3.6 Liver And Biliary System Adverse Events (AEs) And Laboratory Test Values

There were no patients in the placebo group and no patients in the ezetimibe 10 mg group with Hepatitis-related AEs.

Table 49 shows the Liver And Biliary System AEs. There were 11 (1.4%) patients in the placebo group and 32 (1.9%) patients in the ezetimibe 10 mg group with any Liver and Biliary System AE. Within these totals, there were 7 (0.9%) patients in the placebo group and 26 (1.5%) patients in the ezetimibe 10 mg group with $\geq$1 AE in the Hepatic Pool, which consisted of hepatic enzymes increased, hepatic function abnormal, SGOT (AST) increased, and SGPT (ALT) increased. For SAEs in the Hepatic Pool, there were 2 (0.3%) patients in the placebo group and 4 (0.2%) patients in the

ezetimibe 10 mg group, and for AEs in the Hepatic Pool that led to discontinuation from a study, there were 2 (0.3%) patients in the placebo group and 9 (0.5%) in the ezetimibe 10 mg group. For the other Liver And Biliary System AEs, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group.
Table 50 shows the postbaseline values for ALT and AST that were ≥2xULN. **ALT:** There were 14 (1.8%) patients in the placebo group and 41 (2.5%) patients in the ezetimibe 10 mg group with ALT ≥2xULN. Within these totals, there were 3 (0.4%) patients in the placebo group and 10 (0.6%) patients in the ezetimibe 10 mg group with ALT ≥3xULN, there were no patients in the placebo group and 2 (0.1%) patients in the ezetimibe 10 mg group with ALT ≥ 5xULN; and there were no patients in either treatment group with ALT ≥10xULN. With regard to persistent ALT elevations, there were 2 (0.3%) patients in the placebo group and 5 (0.3%) patients in the ezetimibe 10 mg group with consecutive ALT ≥3xULN. **AST:** There were 9 (1.2%) patients in the placebo group and 21 (1.3%) patients in the ezetimibe 10 mg group with AST ≥2xULN. Within these totals, there were 3 (0.4%) patients in the placebo group and 8 (0.5%) patients in the ezetimibe 10 mg group with AST ≥3xULN, and there no patients in the either treatment group with AST ≥ 5xULN. With regard to persistent AST elevations, there were 2 (0.3%) patients in the placebo group and 5 (0.3%) patients in the ezetimibe 10 mg group with consecutive AST values ≥3xULN.

There were 4 (0.5%) patients in the placebo group and 14 (0.8%) patients in the ezetimibe 10 mg group with ALT and/or AST ≥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 at any time.

Patient characteristics and histories were examined for the 13 patients with postbaseline consecutive ALT and/or AST ≥3xULN. There were 3 (0.4%) patients in the placebo group, 9 (0.5%) patients in the ezetimibe 10 mg group, and 1 patient treated with ezetimibe —— Of the 13 patients, 12 were Caucasian and 1 was Hispanic; 8 were male and 5 were female; the mean age was 52 years, and the age range was 25-76 years. The range of baseline ALT/AST values was 12-56 mU/mL; 6 patients had baseline values >1xULN (ULN = 25 mU/mL for ALT and 22 mU/mL for AST). The range of the consecutive postbaseline ALT/AST values ≥3xULN was 66-129 mU/mL. Study participation was discontinued for 5 patients. Of the 12 patients with follow-up, ALT/AST values returned to baseline in 11 and to <2xULN at the last visit in 1 patient. When all available ALT and AST values for the 13 patients were evaluated over time on study, there was no

consistent difference in the time of ALT/AST elevations for the patients in the placebo group and the patients treated with ezetimibe.

Table 51 shows the changes from baseline in ALT and AST. The grades of change correspond to multiples of the normal range, i.e., grade 0 means <1xULN, grade 1 means 1 to <2xULN, etc. The main findings are: (1) most patients in the placebo group and the ezetimibe 10 mg group did not change ALT or AST grade; (2) a greater proportion of patients in the ezetimibe 10 mg group compared to the placebo group had an increase of at least 1 grade in ALT or AST; (3) most of these changes in the ezetimibe 10 mg group were from within normal to <2xULN.

Table 52 shows the postbaseline values for GGT, alkaline phosphatase, and total bilirubin that were ≥2xULN. There were 38 (4.9%) patients in the placebo group and 96 (5.7%) patients in the ezetimibe 10 mg group with GGT≥2xULN, including 13 (1.7%) patients in the placebo group and 40 (2.4%) patients in the ezetimibe 10 mg group with GGT ≥3xULN. There were 2 (0.3%) patients in the placebo group and 1 (0.1%) patients in the ezetimibe 10 mg group with alkaline phosphatase ≥2xULN; none these patients had values ≥3xULN. There were no patients in the placebo group and 4 (0.2%) patients in the ezetimibe 10 mg group with total bilirubin ≥2xULN; none of these patients had values ≥3xULN, and there was no concomitant increase in the liver enzymes.

4.1.1.3.7 Creatine Phosphokinase (CPK) Activity And Muscle-related Adverse Events (AEs)

Table 53 shows the increased CPK levels that were reported as AEs. There were 12 (1.5%) patients in the placebo group and 24 (1.4%) patients in the ezetimibe 10 mg group with CPK AEs. Within these totals, there were 1 (0.1%) patient in the placebo group and 1 (0.1%) patient in the ezetimibe 10 mg with CPK AEs that were reported as SAEs, and there were 2 (0.3%) patients in the placebo group and 5 (0.3%) patients in the ezetimibe 10 mg group with CPK AEs that led to discontinuation from a study.

Table 54 shows the postbaseline values for CPK that were ≥3xULN. There were 11 (1.3%) patients in the placebo group and 42 (2.5%) patients in the ezetimibe 10 mg group with CPK ≥3xULN. Within these totals, there were 2 (0.2%) patients in the placebo group and 16 (0.9%) patients in the ezetimibe 10 mg group with CPK ≥5xULN, and there were 1 (0.1%) patient in the placebo group and 4 (0.2%) patients in the ezetimibe 10 mg group with CPK ≥10xULN.

Table 55 shows the postbaseline values for CPK that were 5 to <10xULN and associated with muscle symptoms, or that were ≥10xULN regardless of muscle symptoms. There were no patients in the placebo group and 4 (0.2%) patients in the ezetimibe 10 mg group with CPK 5 to <10xULN who had associated 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, of whom none had muscle symptoms.

Patient characteristics and histories were examined for the 12 patients with postbaseline CPK 5 to 10xULN and associated muscle symptoms or postbaseline CPK ≥ 10xULN regardless of muscle symptoms. There were 1 (0.1%) patient in the placebo group, 8 (0.5%) patients in the ezetimibe 10 mg group, 3 patients treated with ezetimibe 5 mg, plus 1 patient treated in the ezetimibe 10 mg group whose muscle symptoms were not discovered until after the patient had entered a UES (this patient is not shown in Table 55.) Of the 12 patients, 10 were Caucasian and 2 were Black; 11 were male and 1 was female; the mean age was 48 years, and the age range was 25-72 years. The range of baseline CPK values was 47-391 mU/mL; 5 patients had baseline values >1xULN (ULN = 120 mU/mL). The range of peak postbaseline CPK values was 715-5540 mU/mL. The highest postbaseline value was 5540 mU/mL, in a 25 year old Caucasian male treated with ezetimibe 5 mg. The time from baseline to peak CPK ranged from 11 to 85 days. Study participation was discontinued for 3 patients. For 7 patients, the investigators noted physical exercise or muscle trauma associated with the increased CPK values. The high postbaseline values declined to baseline or near baseline with continued treatment in 8 patients and after study discontinuation or cessation in 4 patients.

4.1.1.4 Vital Signs And Body Weight

Table 56 shows postbaseline values and decreases or increases from baseline in pulse rate, systolic BP, diastolic BP, and body weight. The frequencies of patients in the placebo group and the ezetimibe 10 mg group were similar for: postbaseline pulse rate <60 or >100 bpm, or a decrease or increase in pulse rate from baseline of >20 bpm; postbaseline systolic BP >150 millimeters of mercury (mm Hg), or a decrease or increase in systolic BP from baseline of >20 mm Hg; postbaseline diastolic BP >100 mm Hg, or a decrease or increase in diastolic BP from baseline of >20 mm Hg; a decrease or increase in body weight of ≥3 kg.

4.1.1.5 Electrocardiograms

Table 57 shows changes from baseline in ECGs. The frequencies of patients in the placebo group and the ezetimibe 10 mg group were similar for ECG changes from baseline that were considered to be clinically significant and for ECG changes from baseline that were not considered to be clinically significant, in both patients with normal ECGs at baseline and patients with abnormal ECGs at baseline.
With regard to changes in QTc intervals, there were 37/768 (4.8%) patients in the placebo group and 76/1614 (4.7%) patients in the ezetimibe 10 mg group with increases of ≥10% from baseline to endpoint by the method of Bazette, and there were 29/768 (3.8%) patients in the placebo group and 60/1614 (3.7%) patients in the ezetimibe 10 mg group with increases of ≥10% from baseline to endpoint by the method of Fridericia. There were 30/771 (3.9%) patients in the placebo group and 82/1622 (5.1%) patients in the ezetimibe 10 mg group with postbaseline QTc intervals above the upper limit of normal (450 milliseconds for men or 470 millisecond for women), by either method.

4.1.1.6 Cardiopulmonary Examinations

Abnormal postbaseline cardiopulmonary examination results were reported for 45 (5.7%) patients in the placebo group, 96 (5.7%) patients in the ezetimibe 10 mg group, and 112 (5.6%) patients treated with any dose of ezetimibe.

4.1.1.7 Vitamins And Cosyntropin Challenge

In 1 of the 2 monotherapy RCTs, measurements were obtained from 28 patients in the placebo group and 85 patients in the ezetimibe 10 mg group for vitamins A and D (including both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D), vitamin E (alpha and gamma tocopherol), the alpha and beta carotenoids, and prothrombin time (an indicator of vitamin K status); also, measurements were obtained from 28 patients in the placebo group and 90 patients in the ezetimibe 10 mg group for the cortisol response to cosyntropin challenge. The results were similar in the placebo group and ezetimibe 10 mg group.

4.1.2 Ezetimibe Coadministered With A Statin

The factorial coadministration pool consisted of 259 patients treated with placebo, 262 patients treated with ezetimibe 10 mg, 936 patients treated with a statin, and 925 patients treated with ezetimibe 10 mg

coadministered with a statin (see Section 1.4.1.1.2). The statins were lovastatin, pravastatin, simvastatin, and atorvastatin. The statin doses were 10 mg, 20 mg , 40 mg (for all statins), and 80 mg (simvastatin and atorvastatin only). The comparisons of the statin group and the ezetimibe 10 mg+statin group were controlled for statin dose and type because randomization in each of the pooled studies was by equal allocation to each statin group and ezetimibe 10 mg+statin group in the study.
In the factorial coadministration pool, the results for the statin group and ezetimibe 10 mg+statin group are the most important, since the results for the placebo group and ezetimibe 10 mg group are based on a subset of the patients in the monotherapy pool (see Section 4.1.1).

The term "statin" is used below to mean "statin (all doses and types)," and "ezetimibe 10 mg+statin" is used to mean "ezetimibe 10 mg+statin (all doses and types)."

4.1.2.1 Adverse Events

4.1.2.1.1 Overview

Table 58 presents an overview of the AEs. The main findings are shown below in Table 58A.

Table 58A: Factorial Coadministration Pool AEs: Number (%) Of Patients

Adverse Event	Placebo	Ezetimibe 10 mg	Statin	Ezetimibe 10 mg +Statin
Death	0	0	0	1 (0.1%)
Serious AE*	11 (4.2%)	7 (2.7%)	20 (2.1%)	22 (2.4%)
Discontinuation Due to AE	16 (6.2%)	13 (5.0%)	40 (4.3%)	53 (5.7%)
AEs of Any Intensity	166 (64.1%)	177 (67.6%)	606 (64.7%)	593 (64.1%)
Any Severe or Life-Threatening AE	13 (5.0%)	14 (5.3%)	52 (5.6%)	56 (6.1%)

*See Section 1.5

4.1.2.1.2 Deaths And Other Serious Adverse Events

4.1.2.1.2.1 Deaths

A 67 year old Hispanic female with a history of hypertension, heart murmur, irregular heart rate, cardiomegaly, and other disorders began taking ezetimibe 10 mg and simvastatin 20 mg in December 2000. In January 2001, she was found unresponsive in her home, and was admitted to an emergency room, where computer-assisted tomography

showed a left middle cerebral artery infarction. She was admitted to the hospital, where magnetic resonance imaging showed occlusion of the left internal carotid artery. She went into atrial fibrillation 2 days later, with a rapid ventricular response, and died due to hypotension and respiratory failure.

4.1.2.1.2.2 Serious Adverse Events (SAEs)

Table 59 shows the SAEs. SAEs were reported for 11 (4.2%) patients in the placebo group, 7 (2.7%) patients in the ezetimibe 10 mg group, 20 (2.1%) patients in the statin group, and 22 (2.4%) patients in the ezetimibe 10 mg+statin group. The frequencies of patients with individual SAEs were similar in the ezetimibe 10 mg group compared to the placebo group, and in the ezetimibe 10 mg+statin group compared to the statin group.

Table 60 shows the SAEs that were considered to be treatment-related. SAEs that were considered to be treatment-related were reported for no patients in the placebo group, 1 (0.4%) patient in the ezetimibe 10 mg group, 1 (0.1%) patient in the statin group, and 10 (1.1%) patients in the ezetimibe 10 mg+statin group.

The main reason for the difference in results between Tables 59 and 60 was that all of the 8 patients in the ezetimibe 10 mg+statin group who had Liver And Biliary System SAEs were considered to have treatment- related SAEs, whereas only 2 of the other 6 patients with Liver And Biliary System SAEs were considered to have treatment-related SAEs. The Liver and Biliary System AEs that were considered to be treatment-related were hepatic enzymes increased, ALT increased, and AST increased. These findings suggest that Liver and Biliary System SAEs were called treatment-related more frequently for patients in the ezetimibe 10 mg+statin group compared to the statin group (see Section 4.1.2.3.6).

Non-fatal, life-threatening SAEs were reported for 1 (0.4%) patients in the placebo group, no patients in the ezetimibe 10 mg group, 2 (0.2%) patients in the statin group, and 1 (0.1%) patient in the ezetimibe 10 mg+statin group. Of these SAEs, the 1 in the ezetimibe 10 mg+statin group was considered to be possibly treatment-related and the other 3 were considered unlikely to be related to treatment. The 1 patient in the placebo group had a history of muscle aches, had elevations of ALT, AST, and CPK on the day of randomization, and was discontinued without receiving study drug. Of the 2 patients in the statin group, 1 had a history of transient ischemic attack and gastroesophageal reflux disease, underwent endoscopy and gastric biopsy the day after starting treatment with atorvastatin 40 mg, developed chest pain the following night,

received a diagnosis of myocardial infarction, and underwent coronary angioplasty the next day; this patient discontinued the study after taking only 1 dose of atorvastatin 40 mg. The other patient in the statin group was treated with simvastatin 20 mg for about 6 weeks, developed abdominal pain, underwent laparascopic cholecystectomy, developed postoperative bronchospasm and acute respiratory failure, was intubated, and recovered; this patient completed the study. The 1 patient in the ezetimibe 10 mg+statin group was treated with ezetimibe 10 mg+atorvastatin 80 mg for about 2 months, developed chest pain, received a diagnosis of myocardial infarction, was hospitalized and discharged 10 days later; this patient completed the study.

4.1.2.1.3 Discontinuation Due To Adverse Events (AEs)

Table 61 shows the AEs that led to discontinuation from a study. AEs that led to discontinuation from a study were reported for 16 (6.2%) patients in the placebo group, 13 (5.0%) patients in the ezetimibe 10 mg group, 40 (4.3%) patients in the statin group, and 53 (5.7%) patients in the ezetimibe 10 mg+statin group. Within these totals, there were no patients in the placebo group, 3 (1.1%) patients in the ezetimibe 10 mg group, 1 (0.1%) patient in the statin group, and 1 (0.1%) patient in the ezetimibe 10 mg+statin group with discontinuations due to Benign And Malignant Neoplasms, but the AEs in the ezetimibe 10 mg group were diverse (see Section 4.1.1.1.3). There were 1 (0.4%) patient in the placebo group, 2 (0.8%) patients in the ezetimibe 10 mg group, 3 (0.3%) patients in the statin group, and 10 (1.1%) patients in the ezetimibe 10 mg+statin group with discontinuations due to Liver And Biliary System AEs; the AEs in the ezetimibe 10 mg+statin group included GGT increased, hepatic enzymes increased, SGOT (AST) increased, and SGPT (ALT) increased (see Section 4.1.2.3.6). There were 1 (0.4%) patient in the placebo group, no patients in the ezetimibe 10 mg group, 5 (0.5%) patients in the statin group, and 9 (1.0%) patients in the ezetimibe 10 mg+statin group with discontinuations due to myalgia or myalgia aggravated (see Section 4.1.2.3.7) For the other AEs that led to discontinuation, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group, and in the statin group compared to the ezetimibe 10 mg+statin group.

Table 62 shows the AEs that led to discontinuation from a study and were considered to be treatment-related. AEs that led to discontinuation from a study and were considered to be treatment-related were reported for 10 (3.9%) patients in the placebo group, 7 (2.7%) patients in the ezetimibe 10 mg group, 23 (2.5%) patients in the statin group, and 34 (3.7%) patients in the ezetimibe 10 mg+statin group. Within these totals, there were no

patients in the placebo group, 1 (0.4%) patient in the ezetimibe 10 mg group, 3 (0.3%) patients in the statin group, and 10 (1.1%) patients in the ezetimibe 10 mg+statin group with discontinuations due to Liver And Biliary System AEs that were considered to be treatment-related (see Section 4.1.2.3.6). There were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 3 (0.3%) patients in the statin group, and 7 (0.8%) patients in the ezetimibe 10 mg+statin group with discontinuations due to myalgia that was considered to be treatment related (see Section 4.1.1.3.7). For the other AEs that led to discontinuation and were considered to be treatment-related, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group, and in the statin group compared to the ezetimibe 10 mg+statin group.

4.1.2.1.4 Adverse Events (AEs) Of Any Intensity

AEs of any intensity were reported for 166 (64.1%) patients in the placebo group, 177 (67.6%) of patients in the ezetimibe 10 mg group, 606 (64.7%) patients in the statin group, and 593 (64.1%) patients in the ezetimibe 10 mg+statin group. Table 63 shows the AEs of any intensity that were reported for $\geq$2% of patients in at least 1 treatment group. The most frequent were upper respiratory infection, headache, myalgia, musculo-skeletal pain, and nausea. These AEs could generally be expected in a middle-aged patient population.

There were 2 (0.8%) patients in the placebo group, 3 (1.1%) patients in the ezetimibe 10 mg group, 7 (0.7%) patients in the statin group, and 30 (3.2%) patients in the ezetimibe 10 mg+statin group with increased SGPT (ALT); and there were 1 (0.4%) patient in the placebo group, 1 (0.4%) patient in the ezetimibe 10 mg group, 3 (0.3%) patients in the statin group, and 26 (2.8%) patients in the ezetimibe 10 mg+statin group with increased SGOT (AST) (see Section 4.1.2.3.6). For the other AEs of any intensity in Table 63, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group, and in the statin group compared to the ezetimibe 10 mg+statin group.

Of the AEs of any intensity that were reported for <2% of patients in all treatment groups, there were 1 (0.4%) patients in the placebo group, 4 (1.5%) patients in the ezetimibe 10 mg group, 6 (0.6%) patients in the statin group, and 10 (1.1%) patients in the ezetimibe 10 mg+statin group with Autonomic System Disorders, including flushing and hot flushes. There were 3 (1.2%) patients in the placebo group, 8 (3.1%) patients in the ezetimibe 10 mg group, 6 (0.5%) patients in the statin group, and 9 (1.0%)

patients in the ezetimibe 10 mg+statin group with Benign or Malignant Neoplasms, but the AEs in the ezetimibe 10 mg group and ezetimibe 10 mg+statin group were diverse, including breast neoplasm, meningioma, prostate cancer, and others. 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 Disorders; the AEs in the ezetimibe 10 mg and ezetimibe 10 mg+statin group included GGT increased and hepatic enzymes increased. There were 1 (0.4%) patient in the placebo group, 2 (0.8%) patients in the ezetimibe 10 mg group, 3 (0.3%) patients in the statin group, and 7 (0.8%) patients in the ezetimibe 10 mg+statin group with hyperglycemia. There were no patients in the placebo group, 1 (0.4%) patient in the ezetimibe 10 mg group, 4 (0.4%) patients in the statin group, and 8 (0.9%) patients in the ezetimibe 10 mg+statin group with Vascular (Extracardiac) Disorders; the AEs in the ezetimibe 10 mg and ezetimibe 10 mg+statin group included artery occlusion, carotid artery stenosis, vascular disorder, and vein pain. For the other AEs of any intensity that were reported for <2% of patients in all treatment groups, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group, and in the statin group compared to the ezetimibe 10 mg+statin group.

AEs of any intensity that were considered to be treatment-related were reported for 47 (18.1%) patients in the placebo group, 41 (15.6%) patients in the ezetimibe 10 mg group, 158 (16.9%) patients in the statin group, and 180 (19.5%) patients in the ezetimibe 10 mg+statin group. Table 64 shows the AEs of any intensity that were considered to be treatment related and were reported for ≥2% of patients in at least 1 treatment group. There were 1 (0.4%) patient in the placebo group, 2 (0.8%) patients in the ezetimibe 10 mg group, 7 (0.7%) patients in the statin group, and 25 (2.7%) patients in the ezetimibe 10 mg+statin group with increased ALT (SGOT); and there were no patients in the placebo group, 1 (0.4%) patient in the ezetimibe 10 mg group, 3 (0.3%) patients in the statin group, and 21 (2.3%) patients in the ezetimibe 10 mg+statin group with SGPT (ALT) (see Section 4.1.2.3.6). There were 4 (1.5%) patients in the placebo group, 3 (1.1%) patients in the ezetimibe 10 mg group, 20 (2.1%) patients in the statin group, and 23 (2.5%) patients in the ezetimibe 10 mg+statin group with myalgia (see Section 4.1.1.3.7). There were no other AEs of any intensity that were considered to be treatment-related and were reported for ≥2% of patients in at least 1 treatment group.

AEs that were considered to be severe or life-threatening were reported for 13 (5.0%) patients in the placebo group, 14 (5.3%) patients in the ezetimibe 10 mg group, 52 (5.6%) patients in the statin group, and

56 (6.1%) patients in the ezetimibe 10 mg+statin group. Table 65 shows the AEs that were considered to be severe or life-threatening. There were no patients in the placebo group, 4 (1.5%) patients in the ezetimibe 10 mg group, 1 (0.1%) patient in the statin group, and 2 (0.2%) patients in the ezetimibe 10 mg+statin group with Benign And Malignant Neoplasms, but the AEs in the ezetimibe 10 mg group were diverse, including breast neoplasm, gastric carcinoma, meningioma, and brain neoplasm. There were 2 (0.8%) patients in the placebo group, 6 (2.3%) patients in the ezetimibe 10 mg group, 10 (1.1%) patients in the statin group, and 13 (1.4%) patients in the ezetimibe 10 mg+statin group with Gastrointestinal System AEs; the AEs in the ezetimibe 10 mg group or ezetimibe 10 mg+statin group included abdominal pain, gastritis, nausea, and others. There were 1 (0.4%) patient in the placebo group, no patients in the ezetimibe 10 mg group, 2 (0.2%) patients in the statin group, and 5 (0.5%) patients in the ezetimibe 10 mg+statin group with Liver and Biliary System Disorders (see Section 4.1.2.3.6). For the other AEs that were considered to be severe or life-threatening, the frequencies of patients were similar or higher in the placebo group compared to the ezetimibe 10 mg group, and in the statin group compared to the ezetimibe 10 mg+statin group.

4.1.2.2. Laboratory Tests

4.1.2.2.1 Blood Chemistry

The results of laboratory tests for hepatobiliary function (ALT, AST, GGT alkaline phosphatase, and total bilirubin) are shown in Section 4.1.2.3.6, and the results of laboratory tests for muscle breakdown (CPK) are shown in Section 4.1.2.3.7. The results of other blood chemistry tests are summarized below.

LDL-C. In an additional analysis not prespecified in the protocol, low LDL-C was defined as a calculated value of <70 mg/dL. The frequencies of patients with postbaseline low LDL-C were none in the placebo group, 1 (0.1%) in the ezetimibe 10 mg group, 64 (6.8%) in the statin group, and 343 (37.1%) in the ezetimibe 10 mg+statin group. The lowest postbaseline LDL-C values reported were 36 mg/dL in the statin group and 32 mg/dL in the ezetimibe 10 mg+statin group. (see Section 4.1.1.2.1 for lowest values in the placebo group and ezetimibe 10 mg group). Study drug was not changed in response to low cholesterol and there is no evidence that any patient was discontinued from the study due to low cholesterol.

Renal Function. The renal function variables were BUN and serum creatinine. Table 66 shows the frequencies of patients in the 4 treatment

groups with postbaseline values below or above prespecified limits corresponding to the laboratory reference ranges, and Table 66 A shows the frequencies of patients in the 4 treatment groups with postbaseline values below or above prespecified limits that were set to identify patients with more clearly defined outlier values. In Table 66, the frequencies of patients with postbaseline BUN >20 mg/dL were 47 (18.5%) patients in the placebo group and 58 (22.4%) patients in the ezetimibe 10 mg group, and 153 (16.6%) patients in the statin group and 176 (19.3%) patients in the ezetimibe 10 mg+statin group. However, in Table 66 A, the frequencies of patients with BUN>30 mg/dL were 4 (1.6%) patients in the placebo group and 1 (0.4%) patients in the ezetimibe 10 mg group, and 7 (0.8%) patients in the statin group and 10 (1.1%) in the ezetimibe 10 mg+statin group. In Table 66, the frequencies of patients with postbaseline creatinine >1.4 mg/dL were 5 (2.0%) in the placebo group and 11 (4.2%) in the ezetimibe 10 mg group, and 30 (3.2%) in the statin group and 25 (2.7%) in the ezetimibe 10 mg+statin group. However, in Table 66 A, the frequencies of patients with postbaseline creatinine >2.0 mg/dL were none in the placebo group, none in the ezetimibe 10 mg group, none in the statin group, and 1 (0.1%) in the ezetimibe 10 mg+statin group. Table 67 shows the mean and median values at baseline, and the mean and median changes from baseline, for the 4 treatment groups. These measurements of renal function were similar for the ezetimibe 10 mg group compared to the placebo group, and for the ezetimibe 10 mg+statin group compared to the statin group.

Total Protein, Albumin, Calcium, Phosphorus, Uric Acid, Chloride, Sodium, Potassium, Glucose, TSH The frequencies of patients with postbaseline values below or above the prespecified limits for these variables were similar, in the ezetimibe 10 mg group compared to the placebo group, and for the ezetimibe 10 mg+statin group compared to the statin group. The prespecified limits, in US units, were: total protein = 6-8 g/dL; albumin = 3.5-5.5 g/dL; calcium = 8.5-10.5 mg/dL; phosphorus = 2.5-4.5 mg/dL; uric acid: female $\leq$10 mg/dL, male $\leq$12 mg/dL; chloride = 95-110 meq/L; sodium = 135-145 meq/L; potassium = 3.5-5.5 meq/L; glucose = 60-180 mg/dL; TSH = 0.3-10 mcU/mL.

4.1.2.2.2 Hematology

The hematology variables were platelet count, white blood cell count, hemoglobin concentration, hematocrit, and prothrombin time. Table 68 shows the frequencies of patients in the 4 treatment groups with postbaseline values below or above prespecified limits corresponding to the laboratory reference ranges, and Table 68 A shows the frequencies of patients in the 4 treatment groups with postbaseline values below or