

above prespecified limits that were set to identify patients with more clearly defined outlier values. Table 69 shows the mean and median values at baseline, and the mean and median changes from baseline, for the 4 treatment groups. These measurements of hematology 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.

4.1.2.2.3 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 ezetimibe 10 mg group compared to the placebo group, and in the ezetimibe 10 mg+statin group compared to the statin 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.

4.1.2.2.4 Fecal Occult Blood

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 5 (0.5%) patients in the ezetimibe 10 mg+statin group with positive postbaseline results for fecal occult blood.

4.1.2.3 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 these values for special attention.

4.1.2.3.1 Allergic Reaction/Rash Adverse Events (AEs)

Table 70 shows the Allergic Reaction/Rash AEs. There were 6 (2.3%) patients in the placebo group, 16 (6.1%) patients in the ezetimibe 10 mg group, 48 (5.1%) patients in the statin group, and 49 (5.3%) patients in the ezetimibe 10 mg +statin group with any Allergic Reaction/Rash AE. Within these totals, the higher frequency in the ezetimibe 10 mg group compared to the placebo group involved several AEs that could be related, although these AEs were not more frequent in the ezetimibe

10 mg group in the monotherapy pool analysis (see Section 4.1.1.3.1). The frequencies of patients with individual Allergic Reaction/ Rash AEs were similar in the statin group and the ezetimibe 10 mg+statin group.

4.1.2.3.2 Central and Peripheral Nervous System Adverse Events (AEs)

Table 71 shows the Central Nervous System/Peripheral Nervous System AEs. There were 12 (4.6%) patients in the placebo group, 10 (3.8%) patients in the ezetimibe 10 mg group, 51 (5.4%) patients in the statin group, and 34 (3.7%) patients in the ezetimibe 10 mg +statin group with any Central Nervous System/Peripheral Nervous System AE. Within these totals, the frequencies of patients with individual AEs were similar in the placebo group compared to the ezetimibe 10 mg group, and in the statin group compared to ezetimibe 10 mg+ statin group.

4.1.2.3.3 Psychiatric Adverse Events

Table 72 shows the Psychiatric AEs. There were 9 (3.5%) patients in the placebo group, 7 (2.7%) patients in the ezetimibe 10 mg group, 36 (3.8%) patients in the statin group, and 28 (3.0%) patients in the ezetimibe 10 mg+statin group with any Psychiatric AE. Within these totals, the frequencies of patients with individual AEs were similar in the placebo group compared to the ezetimibe 10 mg group, and in the statin group compared to the ezetimibe 10 mg+statin group.

4.1.2.3.4 Gastrointestinal System Adverse Events (AEs)

Table 73 shows the Gastrointestinal System AEs. There were 47 (18.1%) patients in the placebo group, 54 (20.6%) patients in the ezetimibe 10 mg group, 171 (18.3%) in the statin group, and 155 (16.8%) patients in the ezetimibe 10 mg+statin group with any Gastrointestinal System AE. Within these totals, the frequencies of patients with individual AEs were similar in the placebo group compared to the ezetimibe 10 mg group, and in the statin group compared to the ezetimibe 10 mg+statin group.

4.1.2.3.5 Gallbladder-related Adverse Events

Table 74 shows the Gallbladder-related AEs. There were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 2 (0.2%) in the statin group, and no patients in the ezetimibe 10 mg+statin group with any Gallbladder-related AE.

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

There were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 1 patient in the statin group, and no patients in the ezetimibe 10 mg+statin group with Hepatitis-related AEs.

Table 75 shows the Liver And Biliary System AEs. 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 any Liver And Biliary System AE. Within these totals, the frequencies of patients with individual AE, in the ezetimibe 10 mg group compared to the placebo group, were similar to those seen in the monotherapy pool analysis (see Section 4.1.1.3.6). In the ezetimibe 10 mg+statin group compared to the statin group, the largest increase was in the Hepatic Pool of AEs: hepatic enzymes increased, SGOT (AST) increased, and SGPT (ALT) increased. There were 16 (1.7%) patients in the statin group and 47 (5.1%) patients in the ezetimibe 10 mg+statin group with AEs in the Hepatic Pool. For SAEs in the Hepatic Pool, there were 1 (0.1%) patient in the statin group and 8 (0.9%) patients in the ezetimibe 10 mg+statin group, and for AEs that led to discontinuation from a study, there were 3 (0.3%) patients in the statin group and 10 (1.1%) patients in the ezetimibe 10 mg+ statin group.

Table 76 shows the frequencies of patients with of postbaseline values for ALT and AST that were $\geq 2xULN$. **ALT:** There were 6 (2.4) patients in the placebo group, 6 (2.3%) patients in the ezetimibe 10 mg group, 28 (3.1%) patients in the statin group, and 56 (6.1%) patients in the ezetimibe 10 mg+statin group with $ALT \geq 2xULN$. Within these totals, there were no patients in the placebo group , 2 (0.8%) patients in the ezetimibe 10 mg group, 8 (0.9%) patients in the statin group, and 18 (2.0%) patients in the ezetimibe 10 mg+statin group with $ALT \geq 3xULN$; there were no patients in the placebo group, 1 (0.4%) patient in the ezetimibe 10 mg group, no patients in the statin group, and 6 (0.7%) patients in the ezetimibe 10 mg+statin group with $ALT \geq 5xULN$; and there were no patients in any treatment group with $ALT \geq 10xULN$. With regard to persistent ALT elevations, there were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 4 (0.4%) patients in the statin group, and 12 (1.3%) patients in the ezetimibe 10 mg+statin group with consecutive ALT values $\geq 3xULN$. **AST:** There were 2 (0.8%) patients in the placebo group, 4 (1.5%) patients in the ezetimibe 10 mg group, 14 (1.5%) patients in the statin group, and 32 (3.5%) patients in the ezetimibe 10 mg+statin group with $AST \geq 2xULN$. Within these totals, there were no patients in the placebo group, 1 (0.4%) patient in the ezetimibe 10 mg group, 6 (0.6%) patients in the statin group, and 8 (2.0%) patients in the ezetimibe 10 mg+statin group

with AST $\geq 3xULN$; there were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 1 (0.1%) patient in the statin group, and 4 (0.4%) patients in the ezetimibe 10 mg +statin group with AST $\geq 5xULN$. There were no patients in any treatment group with AST $\geq 10xULN$. With regard to persistent AST elevations, 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 5 (0.5%) patients in the ezetimibe 10 mg+statin group with consecutive AST values $\geq 3xULN$.

Table 77 shows the frequencies of patients with postbaseline consecutive values for ALT and AST that were $\geq 3xULN$, by statin dose and type. For consecutive ALT and/or AST $\geq 3xULN$, there were: no patients in the placebo group or the ezetimibe 10 mg group; no patients in the statin 10 mg group, and 2 (0.7%) patients in the ezetimibe 10 mg +statin 10 mg group; 1 (0.4%) patient in the statin 20 mg group and 3 (1.2%) patients in the ezetimibe 10 mg+statin 20 mg group; 1 (0.4%) patient in the statin 40 mg group and 7 (2.6%) patients in the ezetimibe 10 mg+statin 40 mg group; 2 (1.6%) patients in the statin 80 mg group and 1 (0.8%) patient in the ezetimibe 10 mg+statin 80 mg group. The 4 statins (lovastatin, pravastatin, simvastatin, and atorvastatin) were studied in comparable numbers of patients across the statin dose interval of 10-40 mg. For consecutive ALT and/or AST $\geq 3xULN$ across this interval, there were no patients in the lovastatin group and 1 (0.5%) patient in the ezetimibe 10 mg+lovastatin group; 1 (0.5%) patient in the pravastatin group and 2 (1.0%) patients in the ezetimibe 10 mg+pravastatin group; 1 (0.5%) patient in the simvastatin group and 5 (2.4%) patients in the ezetimibe 10 mg+simvastatin group; no patients in the atorvastatin group and 4 (2.1%) patients in the ezetimibe 10 mg+atorvastatin group. Only simvastatin and atorvastatin were studied at the 80 mg. For consecutive ALT and/or AST at this dose, there were 1 (1.5%) patient in the simvastatin group and 1 (1.6%) patient in the ezetimibe 10 mg+simvastatin group; 1 (1.6%) patient in the atorvastatin group and no patients in the ezetimibe 10 mg+atorvastatin group.

There were no patients in the placebo group, 2 (0.8%) patients in the ezetimibe 10 mg group, 9 (1.0%) patients in the statin group, and 19 (2.1%) patients in the ezetimibe 10 mg+statin group with ALT and/or AST $\geq 3xULN$, of whom there were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 4 (0.4%) patients in the statin group, and 13 (1.4%) patients in the ezetimibe 10 mg+statin group with consecutive ALT and/or AST $\geq 3xULN$. No patient had ALT and/or AST $\geq 10xULN$ at any time.

Patient characteristics and histories were examined for the 17 patients with postbaseline consecutive ALT and/or AST $\geq 3xULN$. There were 4 (0.4%)

patients in the statin group and 13 (1.4%) patients in the ezetimibe 10 mg+ statin group. Of the 17 patients, 13 were Caucasian, 2 were Hispanic, and 2 were Black; 9 were male and 8 were female; the mean age was 65 years, and the age range was 32-65 years. The range of baseline ALT/AST values was 8-64 mU/mL; 8 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 $\geq 3xULN$ was 66-239 mU/mL. Study participation was discontinued for 8 patients. Of the 15 patients with follow-up, ALT/AST values declined to baseline in 9, declined to $<2xULN$ at last follow-up in 3, and remained over $\leq 2xULN$ in 3 patients. When all available ALT and AST values for the 17 patients were evaluated over time on study, there was no consistent difference in the time of ALT/AST elevations for the patients in the statin group and the ezetimibe 10 mg+ statin group.

Table 78 shows the changes from baseline in ALT. The grades or 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, ezetimibe 10 mg group, statin group, and ezetimibe 10 mg+statin group did not change ALT grade; (2) most increases that did occur during were of 1 grade; (3) the frequencies patients with increases of more than 1 grade were none in the placebo group, none in the ezetimibe 10-mg group, 12 (1.3%) in the statin group, and 17 (1.8%) in the ezetimibe 10 mg+statin group.

Table 79 shows the postbaseline values for GGT, alkaline phosphatase, and total bilirubin that were $\geq 2xULN$. There were 12 (4.7%) patients in the placebo group, 24 (9.3%) patients in the ezetimibe 10 mg group, 71 (7.6%) patients in the statin group, and 78 (8.5%) patients in the ezetimibe 10 mg+statin group with $GGT \geq 2xULN$, including 3 (1.2%) patients in the placebo group, 9 (3.5%) patients in the ezetimibe 10 mg group, 26 (2.8%) patients in the statin group, and 33 (3.6%) patients in the ezetimibe 10 mg+statin group with $GGT \geq 3xULN$. 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 3 (0.3%) patients in the ezetimibe 10 mg+statin group with alkaline phosphatase $\geq 2xULN$, including no 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 with alkaline phosphatase $\geq 3xULN$. 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 3 (0.3%) patients in the ezetimibe 10 mg+statin group with total bilirubin $\geq 2xULN$; none of these patients had values $\geq 3xULN$; in 2 of these patients, there was also an increase in liver enzymes.

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

Table 80 shows the increased CPK levels that were reported as AEs. There were 5 (1.9%) patients in the placebo group, 4 (1.5%) patients in the ezetimibe 10 mg group, 12 (1.3%) patients in the statin group, and 14 (1.5%) patients in the ezetimibe 10 mg+statin group with CPK AEs. Within these totals, there were 1 (0.4%) patient in the placebo group, no patients in the ezetimibe 10 mg group, no patients in the statin group, and 1 (0.1%) patient in the ezetimibe 10 mg+statin group with CPK AEs that were reported as SAEs, and there were 2 (0.8%) patients in the placebo group, no patients in the ezetimibe 10 mg group, 1 (0.1%) patient in the statin group, and 4 (0.4%) patients in the ezetimibe 10 mg+ statin group with CPK AEs that led to discontinuation from a study.

Table 81 shows the postbaseline values for CPK that were $\geq 3xULN$. There were 3 (1.2%) patients in the placebo group, 6 (2.4%) patients in the ezetimibe 10 mg group, 25 (2.6%) patients in the statin group, and 15 (1.6%) patients in the ezetimibe 10 mg+statin group with CPK $\geq 3xULN$. Within these totals, there were no patients in the placebo group, 3 (1.2%) patients in the ezetimibe 10 mg group, 10 (1.0%) patients in the statin group, and 5 (0.5%) patients in the ezetimibe 10 mg+statin group with CPK $\geq 5xULN$. There were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 4 (0.4%) patients in the statin group, and 1 (0.1%) patient in the ezetimibe 10 mg+statin group with CPK $\geq 10xULN$. The findings for ezetimibe 10 mg+statin were similar for the different statins (lovastatin, pravastatin, simvastatin, and atorvastatin).

Table 82 shows the postbaseline values for CPK that were 5 to $<10xULN$ and associated with muscle symptoms, or that were $\geq 10xULN$ regardless of muscle symptoms. There were no patients in the placebo group, 2 (0.8%) patients in the ezetimibe 10 mg group, no patients in the statin group, and 1 (0.1%) patient in the ezetimibe 10 mg+statin group with CPK 5 to $<10xULN$ who had associated muscle symptoms. There were no patients in the placebo group, no patients in the ezetimibe 10 mg group, 4 (0.4%) patients in the statin group, and 1 (0.1%) patient in the ezetimibe 10 mg+statin group with CPK $\geq 10xULN$; of these, there were 1 (0.1%) patient in the statin group and 1 (0.1%) patient in the ezetimibe 10 mg+statin group who had muscle symptoms.

Patient characteristics and histories were examined for the 8 patients with postbaseline CPK 5 to $<10xULN$ and associated muscle symptoms, or CPK $\geq 10xULN$, regardless of muscle symptoms. The specific treatments and numbers of patients were: ezetimibe 10 mg (n=2); pravastatin 10 mg (n=1);

pravastatin 40 mg (n=1); simvastatin 20 mg (n=1); simvastatin 40 mg (n=1) ezetimibe 10 mg+atorvastatin 40 mg (n=1); ezetimibe 10 mg+ simvastatin 80 mg (n=1). Of the 8 patients, 3 were Caucasian, 4 were Black, and 1 was Hispanic; 4 were male and 4 were female; the mean age was 48 years, and the age range was 37-62 years. The range of baseline CPK values was 36-302 mU/mL; 2 patients had baseline values >1xULN (ULN = 120 mU/mL) The range of peak postbaseline CPK values was 659-6770 mU/mL. The highest postbaseline value was 6770 mU/mL, in a 39 year old Black woman treated with simvastatin 20 mg. The time from baseline to peak CPK ranged from 11-85 days. Study participation was discontinued for 3 patients. For 5 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 5 patients and after treatment stopped in 3 patients.

4.1.2.4 Vital Signs And Body Weight

Table 83 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 ezetimibe 10 mg group compared to the placebo group, and the ezetimibe 10 mg+statin group compared to the statin 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 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.

4.1.2.5 Electrocardiograms

Table 84 shows changes from baseline in ECGs. The frequencies of patients in the ezetimibe 10 mg group compared to the placebo group, and the ezetimibe 10 mg+statin group compared to the statin 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 15/246 (6.1%) patients in the placebo group, 16/277 (5.9%) patients in the ezetimibe 10 mg group, 68/902 (7.5%) patients in the statin group, and 48/890 (5.4%) patients in the ezetimibe 10 mg+statin group with increases of $\geq 10\%$ from baseline to endpoint by the method of Bazette, and there were 11/246

(4.5%) patients in the placebo group, 15/255 (5.9%) patients in the ezetimibe 10 mg group, 47/902 (5.2%) patients in the statin group, and 41/890 (4.6%) patients in the ezetimibe 10 mg+statin group with increases of $\geq 10\%$ from baseline to endpoint by the method of Fridericia. There were 9/247 (3.6%) patients in the placebo group, 7/257 (2.7%) patients in the ezetimibe 10 mg group, 34/902 (3.8%) patients in the statin group, and 44/890 (4.9%) patients in the ezetimibe 10 mg+statin group with postbaseline QTc intervals above the upper limit of normal (450 milliseconds for men or 470 milliseconds for women), by either method.

4.1.2.6 Cardiopulmonary Examinations

Abnormal postbaseline cardiopulmonary examination results were reported for 21 (8.1%) patients in the placebo group, 16 (6.1%) patients in the ezetimibe 10 mg group, 55 (5.9%) patients in the statin group, and 52 (5.6%) patients in the ezetimibe 10 mg+statin group.

4.1.3 Ezetimibe Added To An Established Statin

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 statin.

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

4.1.3.1 Adverse Events (AEs)

4.1.3.1.1 Deaths And Other Serious Adverse Events (SAEs)

There were no deaths.

Table 85 shows the SAEs. SAEs were reported for 9 (2.3%) patients in the statin group and 19 (5.0%) patients in the statin+ezetimibe 10 mg group. There were 1 (0.3%) patient in the statin group and 6 (1.6%) patients in the statin+ezetimibe 10 mg group with Cardiovascular SAEs; the SAEs in the statin+ezetimibe 10 mg group included angina pectoris, angina pectoris aggravated, and coronary artery disorder. There were no patients in the statin group and 6 (1.6%) patients in the statin+ezetimibe 10 mg group with Gastrointestinal System AEs; the SAEs in the ezetimibe 10 mg group included abdominal pain, appendicitis perforated, gastritis,

gastroenteritis, and others. For other SAEs, the frequencies of patients in the statin group and statin+ezetimibe 10 mg group were similar.

4.1.3.1.2 Discontinuation Due To Adverse Events (AEs)

Table 86 shows the AEs that led to discontinuation from the study. AEs that led to discontinuation from the study were reported for 13 (3.3%) patients in the statin group and 12 (3.2%) patients in the statin+ezetimibe 10 mg group. There were no patients in the statin group and 3 (0.8%) patients in the statin+ezetimibe 10 mg group with discontinuations due to Cardiovascular AEs; the AEs in the statin+ezetimibe 10 mg group included angina pectoris, angina pectoris aggravated, and coronary artery disorder. For other AEs that led to discontinuation from the study, the frequencies of patients in the statin group and statin+ezetimibe 10 mg group were similar.

4.1.3.1.3 Adverse Events (AEs) Of Any Intensity

AEs of any intensity were reported for 198 (50.8%) patients in the statin group and 226 (59.6%) patients in the statin+ezetimibe 10 mg group. The higher frequency in the statin+ezetimibe 10 mg group was related to higher frequencies of patients with Gastrointestinal System or Musculoskeletal System AEs of any intensity. There were 58 (14.9%) patients in the statin group and 75 (19.8%) in the statin+ezetimibe 10 mg group with Gastrointestinal System AEs; the AEs in the statin+ezetimibe 10 mg group included constipation, diarrhea, flatulence, and others. There were 40 (10.3%) patients in the statin group and 62 (16.4%) patients in the ezetimibe 10 mg group and with Musculoskeletal System AEs; the AEs in the ezetimibe 10 mg group included arthralgia, musculoskeletal pain, myalgia, and others.

Table 87 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, abdominal pain, headache, fatigue, and myalgia. Of the AEs in Table 87, 2 were reported more frequently for patients in the statin group than in the ezetimibe 10 mg group, 9 were reported more frequently for patients in the statin+ezetimibe 10 mg group than in the statin group, and 5 were reported at the same frequency in the 2 groups. These AEs could generally be expected in a middle-aged population, although the higher frequencies of patients with Gastrointestinal System and Musculoskeletal System AEs in the statin+ezetimibe 10 mg group would not be generally expected.

For the 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 statin group compared to the ezetimibe 10 mg+statin group.

AEs of any intensity that were considered to be treatment-related were reported for 66 (16.9%) patients in the statin group and 81 (21.4%) patients in the statin+ezetimibe 10 mg group. The higher frequency in the statin+ezetimibe 10 mg group was not concentrated in any Body System/Organ Class or individual AE.

AEs that were considered to be severe or life-threatening were reported for 12 (3.1%) patients in the statin group and 20 (5.3%) patients in the statin+ezetimibe 10 mg group. Table 88 shows the AEs that were considered to be severe or life-threatening. There were 1 (0.3%) patient in the statin group and 7 (1.8%) patients in the statin+ezetimibe 10 mg group with Gastrointestinal System AEs; the AEs in the ezetimibe 10 mg group included abdominal distension, appendicitis perforated, diverticulitis, 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 statin group compared to the statin+ezetimibe 10 mg group.

4.1.3.2 Laboratory Tests

4.1.3.2.1 Blood Chemistry

The results of laboratory tests for hepatobiliary function (ALT, AST, GGT alkaline phosphatase, and total bilirubin) are discussed in Section 4.1.3.3.2, and the results of laboratory tests for muscle breakdown (CPK) are discussed in Section 4.1.3.3.2. The results of other blood chemistry tests are discussed below.

Renal Function. The renal function variables were BUN and serum creatinine. Table 89 shows the frequencies of patients in the statin group and the statin+ezetimibe 10 mg group with postbaseline values below or above the prespecified limits. Table 90 shows the mean values at baseline, and the mean changes from baseline, for the statin group and the statin+ezetimibe 10 mg group. The statin group and the statin+ezetimibe 10 mg group were similar in these measurements of renal function.

Uric Acid, Chloride, Sodium, Potassium, Glucose, Hemoglobin A_{1c}. The frequencies of patients in the statin group and the statin+ezetimibe

10 mg group with postbaseline values below or above the prespecified limits were similar for these variables. The prespecified limits, in US units, were: uric acid: female ≤ 10 mg/dL, male ≤ 12 mg/dL; chloride = 95-110 meq/L; sodium = 133-145 meq/L; potassium = 3.5-5.5 meq/L; glucose = 60-180 mg/dL; Hemoglobin A_{1c} $\leq 9\%$.

4.1.3.2.2 Hematology

The hematology variables were platelet count, white blood cell count, hematocrit, prothrombin time, and fibrinogen. Table 91 shows the frequencies of patients in the statin group and statin+ezetimibe 10 mg group with postbaseline values below or above the prespecified limits. The 2 treatment groups were similar in these measurements of hematology, and were also similar in the mean values at baseline and mean changes from baseline (data not shown).

4.1.3.2.3 Urinalysis

The urinalysis variables included protein, red blood cells, white blood cells, and glucose. The frequencies of patients in the statin group and statin+ezetimibe 10 mg group with postbaseline values below or above the prespecified limits were similar for these variables. The prespecified limits, were: protein = ≤ 30 dipstick units; red blood cells ≤ 5 per high power field; white blood cells ≤ 5 per high power field; glucose = ≤ 100 dipstick units.

4.1.3.2.4 Hormones

Follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone were measured in men at baseline and endpoint. The frequencies of patients in the statin group and statin+ezetimibe 10 mg group with postbaseline values below or above the prespecified limits were similar for these variables.

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

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

There were no patients in the statin group or the statin+ezetimibe 10 mg group with hepatitis, cholecystitis, or cholecystectomy AEs.

There were no patients in the statin group and 3 (0.8%) patients in the statin+ezetimibe 10 mg group with consecutive ALT ≥ 3 xULN, and there

were 1 (0.3%) patient in the statin group and 2 (0.5%) patients in the statin+ezetimibe 10 mg group with consecutive AST ≥ 3 xULN. Of the 3 patients in the statin+ezetimibe 10 mg group with consecutive ALT ≥ 3 xULN, 2 also had consecutive AST ≥ 3 xULN. There was 1 additional patient in the statin+ezetimibe 10 mg group with ALT/AST elevations that began 54 days after completion of study treatment. Details are as follows: Statin+ezetimibe 10 mg group:

- A 51 year old male taking simvastatin 40 mg was randomized to the addition of ezetimibe 10 mg. On Study Day 30, laboratory tests were normal. On Study Day 42 the patient developed abdominal pain, syncope, and diarrhea while vacationing in Egypt, and stopped taking study drug. Tests 2 days later showed ALT/AST = 208/241 mU/mL, respectively (local reference range for ALT/AST = <41/<38 mU/mL). Tests done 4 days after stopping study drug showed ALT/AST = 806/457 mU/mL, respectively (local reference range for ALT/AST = 21-72/16-48 mU/mL). Tests 25 days after stopping study drug showed normal ALT/AST. Tests were negative for viral or parasitic infection, or autoimmune disease.
- A 59 year old male taking simvastatin 80 mg was randomized to the addition of ezetimibe 10 mg. At baseline, tests showed ALT = 33 mU/mL; AST not stated. On Study Day 28, tests showed ALT/AST = 72/45 mU/mL. On Study Day 56, the last day of treatment, tests showed ALT/AST = 77/42 mU/mL. On Study Day 70, 14 days after treatment was completed, tests showed ALT/AST = 64/37 mU/mL. (reference range for ALT/AST = 5-25/8-22 mU/mL). This patient was presumed to have consecutive ALT elevations because the last result on study drug was elevated.
- A 57 year old female taking simvastatin 40 mg was randomized to the addition of ezetimibe 10 mg. At baseline, ALT/AST = 33/29 mU/mL. On Study Day 55, the last day of treatment, tests showed ALT/AST = 107/96 mU/mL. On study day 61, 6 days after treatment was completed, tests showed ALT/AST = 87/80 mU/mL. On Study Day 69, 14 days after treatment was completed, ALT/AST were both <2xULN. (reference range for ALT/AST = 5-25/8-22 mU/mL).
- A 67 year-old female taking cervistatin 0.8 mg was randomized to the addition of ezetimibe 10 mg. ALT/AST/CPK values were normal during the study. On Study Day 19, the patient developed angina, was hospitalized, and subsequently discontinued from the study. Tests 54 days after discontinuation showed ALT/AST/CPK = 122/108/2202 mU/mL, and these values were confirmed. Tests 24 days later showed

ALT/AST/CPK = 17/23/63. (reference range for ALT/AST/CPK = 0-48/ 0-55/0-190 mU/mL).

Statin group:

- A 72 year old female taking cervistatin 0.8 mg was randomized to the addition of placebo. On Study day 17, tests showed AST/CPK = 61/1313 mU/mL; ALT not stated. On Study Day 19, tests showed AST/CPK = 94/2232 mU/mL; ALT not stated. The patient stopped study drug (both statin and placebo), due to the CPK elevation and associated muscle pain. After 5 days, tests showed ALT/AST/CPK = 84/84/1166 mU/mL. After 10 days, tests showed AST/CPK within normal limits, and after another week, tests showed ALT within normal limits.

Table 92 shows the frequencies of patients with any postbaseline (consecutive or non-consecutive) values for ALT, AST, GGT, alkaline phosphatase, and total bilirubin that were $\geq 2xULN$. There were 6 (1.6%) patients in the statin group and 15 (4.0%) patients in the statin+ezetimibe 10 mg group with ALT $\geq 2xULN$. Within these totals, there were no patients in the statin group and 5 (1.3%) patients in the statin+ezetimibe 10 mg group with ALT $\geq 3xULN$. The highest ALT was 375 mU/mL, in a patient in the statin+ezetimibe 10 mg group. There were 3 (0.8%) patients in the statin group and 7 (1.8%) patients in the statin+ezetimibe 10 mg group with AST $\geq 2xULN$. Within these totals, there were 1 (0.3%) patient in the statin group and 2 (0.5%) patients in the statin+ezetimibe 10 mg group with AST $\geq 3xULN$. The highest AST was 489 mU/mL, in a patient in the statin+ezetimibe 10 mg group. There were 26 (6.7%) patients in the statin group and 18 (4.7%) patients in the statin+ezetimibe group with GGT $\geq 2xULN$. Within these totals, there were 8 (2.1%) patients in the statin group and 11 (2.9%) patients in the statin+ezetimibe 10 mg group with GGT $\geq 3xULN$. There was 1 (0.3%) patient in the statin group with alkaline phosphatase $2xULN$ to $<3xULN$, and 1 (0.3%) patient in the statin+ezetimibe 10 mg group with alkaline phosphatase $\geq 3xULN$. There were 2 (0.5%) patients in the statin group with bilirubin $2xULN$ to $<3xULN$ and no other patients with bilirubin elevations.

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

Myalgia was reported as an AE for 10 (2.6%) patients in the statin group and 17 (4.5%) patients in the statin+ezetimibe 10 mg group, including 2 (0.5%) patients in the statin group and 1 (0.3%) patient in the statin+ezetimibe 10 mg group who were discontinued from the study due to myalgia. There was also 1 patient in the statin group who discontinued due to elevated CPK.

Table 93 shows the postbaseline values for CPK that were ≥ 3 xULN. There were 4 (1.0%) patients in the statin group and 6 (1.6%) patients in the statin+ezetimibe 10 mg group with CPK ≥ 3 xULN. Within these totals, there were 1 (0.3%) patient in the statin group and 2 (0.5%) patients in the statin+ezetimibe 10 mg group with CPK 5 to <10 xULN, and there was 1 (0.3%) patient in the statin group and no patients in the statin+ezetimibe 10 mg group with CPK ≥ 10 xULN.

4.1.3.4 Vital Signs And Body Weight

Table 94 shows last observation values and decreases or increases from baseline in pulse rate, systolic BP, diastolic BP, and body weight. The frequencies of patients in the statin group and the statin+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 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 ≥ 2 kg; a decrease or increase in waist circumference of ≥ 7 centimeters

4.1.3.5 Electrocardiograms

Table 95 shows numbers of patients according to changes from baseline in ECGs. The frequencies of patients in the statin group and the statin+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 19/368 (5.2%) patients in the statin group and 15/354 (4.2%) patients in the statin+ezetimibe 10 mg group with increases of $\geq 10\%$ from baseline to endpoint by the method of Bazette, and there were 15/368 (4.1%) patients in the statin group and 12/354 (3.4%) patients in the statin+ezetimibe 10 mg+statin group with increases of $\geq 10\%$ from baseline to endpoint by the method of Fridericia. There were 45/376 (12.0%) patients in the statin group and 37/366 (10.1%) patients in the statin+ezetimibe 10 mg group with postbaseline QTc intervals above the upper limit of normal (450 milliseconds for men or 470 milliseconds for women), by either method.

4.1.4 Statistical Screening Of Adverse Events (AEs) And Laboratory Safety Results For Ezetimibe Monotherapy, Ezetimibe Coadministered With A Statin, And Ezetimibe Added To An Established Statin

A statistical screening test was applied to differences between treatment groups in the frequencies of patients with AEs or values for laboratory safety results that were below or above the prespecified limits. The screening was done for AEs and laboratory safety results with ≥ 4 patients in at least 1 of the 2 treatment groups being compared. "Statistically significant" was defined as a difference in frequency between the 2 treatment groups which had a 95% confidence interval that did not include zero. The screening was applied in analyses of the monotherapy pool, factorial coadministration pool, and add-on RCT. In the monotherapy pool, the placebo group and ezetimibe 10 mg group were compared; in the factorial coadministration pool, the statin group and ezetimibe 10 mg+statin group were compared; and in the add-on RCT, the statin group and statin+ezetimibe 10 mg group were compared. (The placebo group and ezetimibe 10 mg group in the factorial coadministration pool were not compared because these groups were subsets of the corresponding groups in the monotherapy pool).

4.1.4.1 Adverse Events

There were 30 individual AEs and 6 Body System/Organ Class AE categories with ≥ 4 patients in at least 1 of the 2 treatment groups that were compared in the 3 analyses (i.e., monotherapy pool, factorial coadministration pool, and add-on RCT), and showed statistically significant differences in frequency between treatment groups. Of these 36 AEs/AE categories, 10 were more frequent in the control (placebo or statin) groups and 26 were more frequent in the ezetimibe 10 mg or ezetimibe 10 mg/statin groups, as shown below:

Number Of AEs/AE Categories With >4 Patients In At Least 1 Treatment Group And Statistically Significant Differences Between Treatment Groups:

	Control*	Ezetimibe 10 mg**
Monotherapy pool	2	17
Factorial coadministration pool	8	6
Add-on RCT	0	3

*Placebo in the monotherapy pool, statin in the factorial coadministration pool, and statin in the add-on RCT (see Section 1.4.1).

**Ezetimibe 10 mg in the monotherapy pool, ezetimibe 10 mg coadministered with a statin in the factorial coadministration pool, and ezetimibe 10 mg added to an established statin in the add-on RCT.

Monotherapy Pool. In the monotherapy pool, patients were treated with placebo or ezetimibe 10 mg. There were 19 AEs/AE categories with ≥ 4 patients in at least 1 of the 2 treatment groups that showed statistically significant differences in frequency between treatment groups. Of these 19 AEs/AE categories, 2 were more frequent in the placebo group compared to the ezetimibe 10 mg group, and 17 were more frequent in the ezetimibe 10 mg group compared to the placebo group. The 2 AEs/AE categories that were more frequent in the placebo group compared to the ezetimibe 10 mg group were AEs of TSH increased and mouth ulceration. The increases in the frequency of these AEs, in the placebo group compared to the ezetimibe 10 mg group, were 0.7% for increased TSH and 0.5% for mouth ulceration. The 17 AEs/AE categories that were more frequent in the ezetimibe 10 mg group compared to the placebo group were syncope, hypertonia, neuralgia, Disorders Of The Immune System, allergy, allergy aggravated, gastroesophageal reflux aggravated, infection fungal, skin infection fungal, contusion, hepatic function abnormal, arthralgia aggravated, joint stiffness, dysuria, epistaxis, wheezing, and erythema. The increases in the frequency of these AEs/AE categories, in the ezetimibe 10 mg group compared to the placebo group, ranged from 0.2% to 1.2%. The monotherapy pool data have already been reviewed regarding the frequency of several of these AEs/AE categories, including allergy and allergy aggravated (see Section 4.1.1.3.1), gastroesophageal reflux aggravated, (see Section 4.1.1.3.4) and hepatic function abnormal (see Section 4.1.1.3.6). Regarding the other AEs, the statistical screening test appears to have been biased, in the monotherapy pool analyses, toward finding statistically significant increases in the frequency of AEs in the ezetimibe 10 mg group compared to the placebo group, because the screening was done for AEs and laboratory safety results with ≥ 4 patients in at least 1 of the 2 treatment groups, and there were 1691 patients in the ezetimibe 10 mg group compared to only 795 patients in the placebo group. The statistical screening test was not biased in the analyses of the factorial coadministration pool and add-on RCT, because the numbers of patients were similar in the treatment groups compared: In the factorial coadministration study, there 936 patients in the statin group and 925 patients in the ezetimibe 10 mg+statin group, and in the add-on RCT, there were 390 patients in the statin group and 379 patients in the statin+ezetimibe 10 mg group.

Factorial Coadministration Pool and Add-on RCT. In the factorial coadministration pool and the add-on RCT, patients were treated with statin or statin and ezetimibe 10 mg. In these RCTs, there were 17 AEs/AE categories with ≥ 4 patients in at least 1 of the 2 treatment groups that

showed statistically significant differences in frequency between treatment groups. Of these 17 AEs/AE categories, 8 were more frequent in the statin group compared to the ezetimibe 10 mg+statin group in the factorial coadministration pool, 6 were more frequent in the ezetimibe 10 mg+statin group compared to the statin group in the factorial coadministration pool, and 3 were more frequent in the statin+ezetimibe 10 mg group compared to the statin group in the add-on RCT.

The 8 AEs/AE categories that were more frequent in the statin group compared to the ezetimibe 10 mg+statin group in the factorial coadministration pool were asthenia, edema, Cardiovascular Disorders/General, hypertension aggravated, gastroenteritis, palpitation, bruise, and Renal/Urinary System Disorders. The increases in the frequency of these AEs/AE categories, in the statin group compared to the ezetimibe 10 mg+statin groups, ranged from 0.6% to 1.5%. The 6 AEs/AE categories that were more frequent in the ezetimibe 10 mg+statin group compared to the statin group in the factorial coadministration pool were fatigue, tinnitus, gingivitis, Liver/Biliary System Disorders, SGOT (AST) increased, and SGPT (ALT) increased. The increases in the frequency of these AEs/AE categories, in the ezetimibe 10 mg/statin group compared to the statin group, ranged from 0.4% to 1.4% except for the Liver And Biliary System Disorders, where the range was 2.5% to 3.3%. The 3 AEs/AE categories that were more frequent in the statin+ezetimibe 10 mg group compared to the statin group in the add-on RCT were hot flushes, Central/Peripheral Nervous System Disorders, and Musculoskeletal System Disorders. The increases in frequency of these AEs/AE categories, in the statin+ezetimibe 10 mg group compared to the statin group, were 1.1% for hot flushes, 2.4% for central/peripheral nervous system disorders, and 6.1% for musculoskeletal system disorders.

The factorial coadministration pool and add-on RCT data have already been reviewed regarding the frequency of patients with AEs in the liver and biliary system and the musculoskeletal system (see Sections 4.1.2.3.6, 4.1.2.3.7, 4.1.3.3.1, and 4.1.3.3.2). In the add-on RCT, the Central/Peripheral Nervous system individual AEs in the statin+ezetimibe 10 mg group were diverse, including restless leg syndrome, dysphagia, hypoesthesia, and others.

4.1.4.2 Laboratory Safety Results

There were 22 postbaseline laboratory safety results with ≥ 4 patients in at least 1 of the 2 treatment groups that were compared in the 3 analyses (i.e., monotherapy pool, factorial coadministration pool, and add-on RCT), and showed statistically significant differences in frequency

between treatment groups. Of these 22 laboratory safety results, 12 involved increases in ALT, AST, bilirubin, or CPK; these data have already been reviewed (see Sections 4.1.1.3.6, 4.1.1.3.7, 4.1.2.3.6, 4.1.2.3.7, 4.1.3.3.1, and 4.1.3.3.2).

Of the 10 other laboratory safety results, 8 were in the monotherapy pool and 2 were in the factorial coadministration pool.

Monotherapy Pool. In the ezetimibe 10 mg group compared to the placebo group, the frequencies of patients with platelet count $<100 \times 10^9$ and prothrombin time $>1.5 \times \text{ULN}$ were increased by 0.5% and 0.3% respectively. The result for platelet count has already been reviewed (see Section 4.1.1.2.2). The result for prothrombin time was based on no patients in the placebo group and 4 patients in the ezetimibe 10 mg group, of whom 3 were on long-term treatment with warfarin and had elevated prothrombin times before randomization. In the placebo group compared to the ezetimibe 10 mg group, the frequency of patients with total protein $>8 \text{ g/dL}$ was decreased by 1.8%, and the frequencies of patients with segmented neutrophils $>8 \times 10^9/\text{L}$, lymphocytes $>4 \times 10^9/\text{L}$, monocytes $>0.8 \times 10^9/\text{L}$, eosinophils $>0.45 \times 10^9/\text{L}$, and basophils $>0.2 \times 10^9/\text{L}$ were decreased by 3.2-5.0%. These findings in the placebo group compared to the ezetimibe 10 mg group have no apparent importance.

Factorial Coadministration Pool. In the ezetimibe 10 mg+statin group compared to the statin group, the frequency of patients with phosphorus $>4.5 \text{ mg/dL}$ was increased by 2.7%, and the frequency of patients with potassium $>5.5 \text{ mEq/dL}$ was increased by 1.7%. Regarding the result for phosphorus, there were no associated changes in calcium, albumin, alkaline phosphatase, TSH, or electrolytes. The highest phosphorus values were 5.5 mg/dL in the ezetimibe 10 mg+statin group and 5.7 mg/dL in the statin group, and the largest increases in phosphorus from baseline to endpoint were 1.7 mg/dL in the ezetimibe 10 mg+statin group and 1.4 mg/dL in the statin group. Regarding the result for potassium, there were no associated changes in BUN, creatinine, other electrolytes, or CP. The highest potassium values were 6.7 mEq/L in the ezetimibe 10 mg+statin group and 6.2 mEq/L in the statin group, and the largest increases in potassium from baseline to endpoint were 2.4 mEq/L in the ezetimibe 10 mg+statin group and 1.7 mg in the statin group. The 2.4 mEq/L increase from baseline was in the patient who also had the highest value (6.7 mEq/L), and 8 days after the highest value was obtained, the patient had a value of 5.1 mEq/L.

4.2 Homozygous Familial Hypercholesterolemia

The RCT for patients with Homozygous Familial Hypercholesterolemia provided data on 50 patients who were treated with open-label simvastatin or atorvastatin 40 mg for ≥ 6 weeks and then randomized to treatment for 12 weeks with the same open-label statin and the addition of study drug. The 16 patients treated with open-label simvastatin 40 mg were randomized to the addition of blinded simvastatin 40 mg (n=5), ezetimibe 10 mg (n=4), or ezetimibe 10 mg+simvastatin 40 mg (n=5). The 36 patients treated with open-label atorvastatin 40 mg were randomized to the addition of blinded atorvastatin 40 mg (n=12), ezetimibe 10 mg (n=12), or ezetimibe 10 mg+atorvastatin 40 mg (n=12). Because the numbers of patients in the individual treatment groups were small, the groups were pooled for some analyses to form a "statin 80 mg group," consisting of patients treated with open-label simvastatin or atorvastatin 40 mg plus blinded simvastatin or atorvastatin 40 mg, and an "ezetimibe+statin 40/80 group," consisting of patients treated with open-label simvastatin or atorvastatin 40 mg plus blinded ezetimibe 10 mg, ezetimibe 10 mg+simvastatin 40 mg, or ezetimibe 10 mg+atorvastatin 40 mg.

4.2.1 Adverse Events

4.2.1.1 Deaths And Other Serious Adverse Events (SAEs)

There were no deaths.

SAEs were reported for 4 patients. A 35 year old Caucasian female treated with simvastatin 80 mg developed asthenia, cardiomegaly, chest pain, and other AEs, on Study Days 62-78, and was hospitalized, with an interruption of study drug. A 24 year old Caucasian male treated with ezetimibe 10 mg+simvastatin 80 mg developed consecutive ALT levels ≥ 3 xULN on Study Days 1-8, and was discontinued from the study; this patient had ALT ≥ 3 xULN prior to randomization, and should have been excluded from randomization according to the protocol. A 42 year old Caucasian male treated with ezetimibe 10 mg+ atorvastatin 40 mg developed hemiparesis on study day 50 and was hospitalized, but continued study drug. A 27 year old male treated with ezetimibe 10 mg+atorvastatin 40 mg developed abdominal pain, angina pectoris, abnormal hepatic function, and other AEs on Study Days 74-83 and was hospitalized and discontinued; the patient was later found to have an intrahepatic echinococcal cyst. All of the SAEs were considered unlikely to be treatment-related.

4.2.1.2 Discontinuation Due To Adverse Events (AEs)

There were 2 patients with SAEs that led to discontinuation from the study, as described in Section 4.2.1.1 above. There were no other patients with AEs that led to discontinuation.

4.2.1.3 Adverse Events (AEs) Of Any Intensity

AEs of any intensity were reported for 11 (64.7%) of patients in the statin 80 mg group and 24 (72.7%) patients in the ezetimibe 10 mg+statin 40/80 mg group. The higher frequency in the ezetimibe 10 mg+statin 40/80 mg group was related to higher frequencies of patients with Central and Peripheral Nervous System or Musculoskeletal System AEs. There were no patients in the statin 80 mg group and 5 (15.2%) patients in the ezetimibe 10 mg+statin 40/80 mg group with Central and Peripheral Nervous System AEs; the AEs in the ezetimibe 10 mg+statin 40/80 mg included hemiparesis, hypertonia (n=2), migraine, and neuralgia. However, the patient with hemiparesis had cervical arthrosis and the patient with neuralgia had a history of sciatica. There were 1 (5.9%) patients in the statin 80 mg group and 7 (21.2%) patients in the ezetimibe 10 mg+statin 40/80 mg group with Musculoskeletal System AEs; the AEs in the ezetimibe 10 mg+statin 40/80 mg group included arthralgia, arthrosis, back pain, and others. There were 1 (5.9%) patients in the statin 80 mg group and 3 (9.0%) patients in the ezetimibe 10 mg+statin 40/80 mg group with Liver And Biliary System AEs; the AEs in the ezetimibe 10 mg+statin 40/80 mg group included hepatic function abnormal, ALT increased and AST increased.

4.2.2 Laboratory Tests

4.2.2.1 Blood Chemistry

The results of laboratory tests for hepatobiliary function (ALT, AST, GGT, alkaline phosphatase, and total bilirubin) are discussed in Section 4.2.2.1.1, and the results of laboratory tests for muscle breakdown (CPK) are discussed in Section 4.2.2.1.2. The results of other blood chemistry tests are discussed below.

BUN, Creatinine, Total Protein, Albumin, Calcium, Phosphorus, Uric Acid, Chloride, Sodium, Potassium, Glucose, TSH. The frequencies of patients in the statin 80 mg group and the ezetimibe 10 mg+statin 40/80 mg group with postbaseline values below or above the prespecified limits were similar for these variables. The prespecified limits were, in US units, were: BUN 5-30 mg/dL; creatinine ≤ 2 mg/dL; 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 <10 mg/dL, male <12 mg/dL; chloride 95-110 meq/L; sodium 133-145 meq/L; potassium 3.5-5.5 meq/L; glucose 60-180 mg/dL; TSH 0.3-10 mU/mL.

4.2.2.1.1 Liver and Biliary System

There were no patients in the statin 80 mg group and 2 (6.0%) patients in the ezetimibe 10 mg+statin 40/80 mg group with consecutive ALT ≥ 3 xULN and 1 of the 2 patients in the ezetimibe 10 mg+statin 40/80 mg group also had consecutive AST ≥ 3 xULN. However, 1 of these 2 patients was found to have an intrahepatic echinococcal cyst and 1 was found to have had ALT and AST elevations at baseline which persisted but did not increase on treatment with ezetimibe 10 mg+simvastatin 80 mg. This patient was discontinued after 8 days.

The frequencies of patients with any (consecutive or non-consecutive) postbaseline value ≥ 2 xULN for ALT, AST, GGT, alkaline phosphatase, and total bilirubin were as follows. There were 2 (11.8%) patients in the statin 80 mg group and 6 (18.2%) patients in the ezetimibe 10 mg+statin 40/80 mg group with ALT ≥ 2 xULN. Within these totals, there were 1 (5.9%) patient in the statin 80 mg group and 2 (6.1%) patients in the ezetimibe 10 mg+statin 40/80 mg group with ALT ≥ 3 xULN. There were 1 (5.9%) patient in the statin 80 mg group and 3 (9.1%) patients in the ezetimibe 10 mg+statin 40/80 mg group with AST ≥ 2 xULN. Within these totals, there were no patients in the statin 80 mg group and 2 (6.1%) patients in the ezetimibe 10 mg+statin 40/80 mg group with ALT ≥ 3 xULN. There were no patients in the statin 80 mg group and 2 (6.1%) patients in the ezetimibe 10 mg+statin 40/80 mg group with GGT ≥ 2 xULN, including no patients in the statin 80 mg group and 1 (3.0%) patient in the ezetimibe 10 mg+statin 40/80 mg group with GGT ≥ 3 xULN. There were no patients in the statin 80 mg group and 2 (6.0%) patients in the ezetimibe 10 mg+statin 40/80 mg group with alkaline phosphatase ≥ 2 xULN, including no patients in the statin 80 mg group and 1 (3.0%) patient in the ezetimibe 10 mg+statin 40/80 mg group with alkaline phosphatase ≥ 3 xULN. There were 1 (5.9%) patient in the statin 80 mg group and no patients in the ezetimibe 10 mg+statin 40/80 mg group with total bilirubin ≥ 2 xULN. The ULN were ALT = 25 mU/mL, AST = 22 mU/mL, GGT = 29 mU/mL, alkaline phosphatase = 72 mU/mL, and total bilirubin = 1.1 mg/dL.

4.2.2.1.2 Creatine Phosphokinase

There were 2 (11.8%) patients in the statin 80 mg group and 3 (9.1%) patients in the ezetimibe 10 mg+statin 40/80 mg group with postbaseline

CPK ≥ 3 x ULN. Within these totals, there were no patients in the statin 80 mg group and no patients in the ezetimibe 10 mg+statin 40/80 mg group with CPK ≥ 5 xULN. The ULN for CPK was 120 mU/mL.

4.2.2.2 Hematology

The hematology variables were platelet count, white blood cell count, hemoglobin, and hematocrit. The frequencies of patients in the statin 80 mg group and the ezetimibe 10 mg+statin 40/80 mg group were similar for postbaseline platelet counts below or above the prespecified limits of 100-450 $\times 10^9$ /L. There were 1 (5.9%) patient in the statin 80 mg group and 4 (12.5%) patients in the ezetimibe 10 mg group with white blood cell counts $< 3.0 \times 10^9$ /L, and there were no patients in the statin 80 mg group or the ezetimibe 10 mg+statin 40/80 mg group with white blood cell counts $> 10.8 \times 10^9$ /L. There were 3 (17.6%) patients in the statin 80 mg group and 9 (28.1%) patients in the ezetimibe 10 mg+statin 40/80 mg group with hemoglobin < 11 g/dL female or < 13 g/dL male, and there were 1 (5.9%) patients in the statin 80 mg group and no patients in the ezetimibe 10 mg group+statin 40/80 mg group with hemoglobin > 16 g/dL female or > 18 g/dL male. There were 4 (23.5%) patients in the statin 80 mg group and 13 (40.6%) patients in the ezetimibe 10 mg+statin 40/80 mg group with hematocrit $< 33\%$ female or $< 39\%$ male, and there were 2 (11.8%) patients in the statin 80 mg group and no patients in the ezetimibe 10 mg+statin 40/80 mg group with hematocrit $> 46\%$ female or $> 54\%$ male. Most of the patients with hematology values outside the prespecified limits were found to have values only slightly outside the limits. At endpoint, the lowest hemoglobin level was 8.7 g/dL in the statin 80 mg group and 9.0 g/dL in the ezetimibe 10 mg+ statin 40/80 mg group, the lowest hematocrit was 25.0% in the statin 80 mg group and 27.8% in the ezetimibe 10 mg+statin 40/80 mg group, and the lowest leukocyte count was 2.9×10^9 /L in the statin 80 mg group and 2.1×10^9 /L in the ezetimibe 10 mg+statin 40/80 mg group.

4.2.2.3 Urinalysis

The urinalysis variables included pH, protein, blood, specific gravity, red blood cells, white blood cells, glucose, and ketones. The frequencies of patients in the statin 80 mg group and ezetimibe 10 mg+statin 40/80 mg group with postbaseline values below or above the prespecified limits were similar for these variables. The prespecified limits were: pH 5-8 units; protein = ≤ 30 dipstick units; specific gravity 1.002-1.035; red blood cells ≤ 5 per high power field; white blood cells ≤ 5 per high power field; glucose = ≤ 100 dipstick units; ketones ≤ 5 dipstick units.

4.2.3 Vital Signs and Body Weight

The frequencies of patients in the statin 80 mg group and the ezetimibe 10 mg+statin 40/80 mg group were similar for: last observation pulse rate <60 or >100 bpm, or a decrease or increase in pulse rate from baseline of >20 bpm; postbaseline systolic BP >150 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.

4.2.4 Electrocardiograms

The frequencies of patients in the statin 80 mg group and the ezetimibe 10 mg+statin 40/80 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. The patient with an echinococcal cyst (See Section 4.2.2.1), who was treated with ezetimibe 10 mg+atorvastatin 40 mg, also had inverted T waves in L3 AVF during the study, and was hospitalized for unstable angina, with ST depression in 2 leads. Coronary catheterization showed 4-vessel coronary stenosis.

With regard to changes in QTc intervals, there were 0/17 patients in the statin 80 mg group and 3/30 (10%) patients in the ezetimibe 10 mg+statin 40/80 mg group with increases of $\geq 10\%$ from baseline to endpoint by the method of Bazette and by the method of Fridericia. There were 0/17 patients in the statin 80 mg group and 2/30 (6.7%) patients in the ezetimibe 10 mg +statin 40/80 mg group with postbaseline QTc intervals above the upper limit of normal (450 milliseconds for men or 470 millisecond for women), by either method.

4.2.2.5 Cardiopulmonary Examinations

The frequencies of patients with abnormal postbaseline cardiopulmonary examinations were similar in the statin 80 mg group and the ezetimibe 10 mg+statin 40/80 mg group.

4.3 Homozygous Sitosterolemia

The RCT for patients with Homozygous Sitosterolemia provided data on 37 patients who were being treated with established therapies such as apheresis or a bile acid sequestrant, and were randomized to additional treatment, for 8 weeks, with placebo (n=7) or ezetimibe 10 mg (n=30).

The randomization was stratified by whether the established therapies included a bile acid sequestrant.

4.3.1. Adverse Events

4.3.1.1 Deaths And Other Serious Adverse Events (SAEs)

There were no deaths.

SAEs were reported for 2 patients. A 50 year Caucasian old female treated with placebo had increased blood pressure, and a 48 year old Hispanic male treated with ezetimibe 10 mg was hospitalized for stent placement for iliofemoral arteriosclerosis. Both of these SAEs were considered not to be treatment-related.

4.3.1.2 Discontinuation Due To Adverse Events (AEs)

There were no discontinuations due to AEs.

4.3.1.3 Adverse Events (AEs) Of Any Intensity

AEs of any intensity were reported for 2 (28.6%) patients in the placebo group and 21 (70.0%) patients in the ezetimibe 10 mg group. The higher frequency in the ezetimibe 10 mg group was related to a higher frequency of patients with Gastrointestinal System AEs. There were no patients in the placebo group and 12 (40.0%) in the ezetimibe 10 mg group with Gastrointestinal System AEs; the AEs in the ezetimibe 10 mg group included abdominal pain, diarrhea, nausea, and others. There were 1 (14.3%) patient in the placebo group and no patients in the ezetimibe 10 mg group with Liver and Biliary System AEs. There were 1 (14.3%) patient in the placebo group and 5 (16.7%) patients in the ezetimibe 10 mg group with Musculoskeletal System AEs; the AEs in the ezetimibe 10 mg group included arthralgia and musculoskeletal pain.

4.3.2 Laboratory Tests

4.3.2.1 Blood Chemistry

The results of laboratory tests for hepatobiliary function (ALT, AST, GGT, alkaline phosphatase, and total bilirubin) are discussed in Section 4.3.2.1.1, and the results of laboratory tests for muscle breakdown (CPK) are discussed in Section 4.2.3.1.2. The results of other blood chemistry tests are discussed below.

BUN, Creatinine, Uric Acid, Chloride, Sodium, Potassium, Bicarbonate, Glucose. 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 US units, were: BUN 5-20 mg/dL; creatinine 0.7-1.4 mg-dL; uric acid: female 2-6 mg/dL, male 4-8 mg/dL; chloride 95-110 meq/L; sodium 133-145 meq/L; potassium 3.5-5 meq/L; bicarbonate 21-33 meq/L; glucose 60-115 mg/dL. In addition, hemoglobin A_{1c} was used in screening diabetic patients and Qualitative Human Chorionic Gonadotropin was used for pregnancy screening.

4.3.2.1.1 Liver and Biliary System

There were 1 (14.3%) patient in the placebo group and no patients in the ezetimibe 10 mg group with consecutive ALT ≥ 3 xULN; the patient in the placebo group also had consecutive AST ≥ 3 xULN.

The frequencies of patients with any (consecutive or non-consecutive) postbaseline value ≥ 2 xULN for ALT, AST, GGT, alkaline phosphatase, and total bilirubin were as follows. There were 2 (28.6%) patients in the placebo group and no patients in the ezetimibe 10 mg group with ALT ≥ 2 xULN, including 2 patients in the placebo group with ALT ≥ 3 xULN. There was 1 (14.3%) patient in the placebo group and no patients in the ezetimibe 10 mg group with AST ≥ 2 xULN, including 1 patient in the placebo group with AST ≥ 3 xULN. There were 1 (14.3%) patient in the placebo group and 2 (6.7%) patients in the ezetimibe 10 mg group with GGT ≥ 2 xULN including 1 patient in the placebo group with GGT ≥ 3 xULN. There were 1 (14.3%) patient in the placebo group and 4 (13.3%) patients in the ezetimibe 10 mg group with alkaline phosphatase ≥ 2 xULN, including 1 (3.3%) patient in the ezetimibe 10 mg group with alkaline phosphatase ≥ 3 xULN. There were no patients in the placebo group and 1 (3.3%) patient in the ezetimibe 10 mg group with total bilirubin between 2xULN and <3xULN. In all patients in the ezetimibe 10 mg group with ALT, AST, GGT, alkaline phosphatase, or total bilirubin elevations during treatment, the abnormalities were present at baseline and generally stable during treatment.

4.3.2.1.2 Creatine Phosphokinase

All postbaseline values for CPK were <3xULN, in the placebo group and the ezetimibe 10 mg group.

4.3.2.2 Hematology

The hematology variables included platelet count, white blood cell count, hemoglobin, and hematocrit. The frequencies of patients with below or above the prespecified limits were similar in the placebo group and the ezetimibe 10 mg group for these variables. The prespecified limits were: platelet count 125-375 x 10⁹/L; white blood cell count 3.7-11 x 10⁹/L; hemoglobin: female 11-15.5 g/dL, male 12.5-17 g/dL; hematocrit: female 33-47%, male 37-51%.

4.3.2.3 Urinalysis

The urinalysis variables included protein, red blood cells, white blood cells, and glucose. The frequencies of patients with postbaseline values above the prespecified limits/number of patients with postbaseline tests were: protein 0/3 for placebo versus 1/13 for ezetimibe 10 mg; red blood cells 0/1 for placebo versus 2/3 for ezetimibe 10 mg; white blood cells: 0/3 for placebo versus 3/6 for ezetimibe 10 mg; glucose 0/3 for placebo versus 0/13 for ezetimibe 10 mg. The prespecified limits were: protein >30 dipstick units; red blood cells >5/high power field; white blood cells >5/high power field; glucose >100 dipstick units.

4.3.3 Vital Signs and Body Weight

There were no patients in the placebo group and 3 (10.0%) patients in the ezetimibe 10 mg group with last observation systolic BP >150 mm Hg and with systolic BP change from baseline >20 mm Hg. The frequencies of patients in the placebo group and ezetimibe 10 mg group were similar for: last observation pulse rate <60 or >100 bpm, or a decrease or increase in pulse rate from baseline of >20 bpm; 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 \geq 3 kg.

4.3.4 Electrocardiograms

There were no patients in the placebo group or ezetimibe 10 mg group with ECG changes from baseline that were considered to be clinically significant. There were 0/7 patients in the placebo group and 8/30 (26.7%) patients in the ezetimibe 10 mg group with ECG changes that were not considered clinically significant.

With regard to changes in QTc intervals, there were 2/7 (28.6%) patients in the statin group and 1/28 (3.6%) patients in the statin+ezetimibe 10 mg group with increases of \geq 10% from baseline to endpoint by the method of

Bazette and the method of Fridericia. There were no patients in the statin group and no patients in the statin+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.

4.3.5 Cardiopulmonary Examinations

Cardiopulmonary examinations were not specified in the protocol of the RCT for patients with Homozygous Sitosterolemia.

4.4 Clinical Pharmacology

There were 756 patient enrollments in the 32 completed Phase 1 Clinical Pharmacology studies. Ezetimibe 10 mg was given in 587 of these enrollments, to a total of 552 patients (patients could enroll more than once). In 9 studies, 154 patients were given single doses of ezetimibe on 1 or more occasions. In the other 23 studies, 433 patients were given ezetimibe once daily for 7-14 consecutive days. Of the 552 patients treated with ezetimibe, 407 received ezetimibe alone, and 145 received ezetimibe with another lipid-lowering drug. The numbers of patients receiving the other lipid-lowering drugs were: 109 patients -a marketed statin (lovastatin, pravastatin, simvastatin atorvastatin, fluvastatin, or cervistatin); 20 patients - gemfibrozil or fenofibrate; 8 patients - cholestyramine; 8 patients - simvastatin and cholestyramine.

There were 13 multiple-dose, parallel-group Clinical Pharmacology studies. The data from these studies about AEs of any intensity were analyzed for patients treated with ezetimibe 10 mg, ezetimibe 10 mg, placebo, statin, and ezetimibe+statin (In the ezetimibe+statin group, the ezetimibe dose range was mg, but most patients received 10 mg.). The duration of treatment was 14 days in 10 studies, 10 days in 2 studies, and 7 days in 1 study, which could imbalance the comparisons slightly, since not all studies used the same doses of ezetimibe and the other study drugs. However, the comparisons are is satisfactory as an overview.

In the 13 studies referred to above, there were 56 (37.3%) patients in the ezetimibe 10 mg group, 34 (31.5%) patients in the ezetimibe 10 mg group, 29 (37.7%) patients in the placebo group, 23 (38.3%) patients in the statin group, and 42 (39.3%) patients in the ezetimibe+statin group with AEs of any intensity. The lower rate in the ezetimibe 10 mg group compared to the other treatment groups was not due to any Body System/Organ Class or individual AE. There were 25 (16.7%) patients in the ezetimibe 10 mg group, 20 (18.5%) patients in the ezetimibe 10 mg

group, 11 (14.3%) patients in the placebo group, 8 (13.3%) patients in the statin group, and 14 (13.1%) patients in the ezetimibe +statin group with Gastrointestinal System AEs; the AEs in the ezetimibe groups included abdominal distension, constipation, nausea, and others. The frequencies of patients with the other AEs of any intensity were similar in the 5 treatment groups. These findings are consistent with the results of the Phase 2/3 RCTs.

The results of laboratory tests for liver and muscle enzymes in the 13 multiple-dose, parallel-group Clinical Pharmacology studies were as follows. **ALT:** There were 7 (5.3%) patients in the ezetimibe 10 — mg group, 4 (4.4%) patients in the ezetimibe 10 mg group, 3 (3.9%) patients in the placebo group, 2 (3.3%) patients in the statin group, and 3 (2.8%) patients in the ezetimibe+statin group ALT $\geq 2xULN$. Within these totals, there were 4 (3.0%) patients in the ezetimibe 10 —mg group, 1 (1.1%) patient in the ezetimibe 10 mg group, 1 (1.3%) patient in the placebo group, no patients in the statin group, and no patients in the ezetimibe+statin group with ALT $\geq 3xULN$. **AST:** There were 1 (0.7%) patient in the ezetimibe 10 —mg group, 1 ((0.9%) patient in the ezetimibe 10 mg group, no patients in the placebo group, 1 (1.7%) patient in the statin group, and no patients in the ezetimibe+statin group. with AST $\geq 2xULN$. Within these totals, there were no patients in any treatment group with AST $\geq 3xULN$. **OTHER:** There were no patients in any treatment group with GGT $\geq 2xULN$ or alkaline phosphatase $\geq 2xULN$. There were 3 (2.0%) patients in the ezetimibe 10 — mg group, 3 (3.3%) patients in the ezetimibe 10 mg group, 1 (1.3%) patient in the placebo group, 1 (1.6%) patient in the statin group, and 2 ((1.9%) patients in the ezetimibe+statin group with CPK $\geq 2xULN$. Within these totals, there were no patients in the ezetimibe 10 — mg group, the ezetimibe 10 mg group, or the placebo group with CPK $\geq 3xULN$; there were 1 ((1.7%) patient in the statin group and 1 ((0.9%) patient in the ezetimibe+statin group with CPK $\geq 3xULN$. These findings are consistent with the results of the Phase 2/3 RCTs.

4.5 Ongoing 12-14 Week Randomized Clinical Trials (RCTs)

The NDA provided limited safety data for 5 ongoing 12-14 week RCTs, through 15 August 2001. No new safety issues were raised by these data. The RCTs included: (1) 2 14-week, controlled dose-titration RCTs of ezetimibe coadministered with atorvastatin (RCT #1) or simvastatin (RCT #2) in patients who failed to achieve LDL-C ≤ 100 mg/dL with atorvastatin 10 mg or simvastatin 20 mg, and who have coronary heart disease or multiple cardiovascular risk factors and hypercholesterolemia;

(2) [

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_____, (3) 1 12-week, placebo-controlled RCT of ezetimibe coadministered with simvastatin doses of 10, 20, 40, and 80 mg/day in patients with primary Hypercholesterolemia (RCT #5).

A total of 3261 patients have been enrolled in these 5 RCTs: 1832 in RCT #1, 756 in RCT #2, 4 in RCT #3, 7 in RCT #4, and 652 in RCT #5. There have been 4 deaths, in RCT #1. SAEs have been reported for 59 patients: 42 in RCT #1, 10 in RCT #2, and 7 in RCT #5. The reported causes of deaths and SAEs have been characteristic of the treatment populations. There have been 2 patients with SAEs in the Liver and Biliary System: 1 patient had cholelithiasis, urinary tract infection, increased CPK, and other AEs, and 1 patient had a liver abscess and protozoa infection. There have been no SAEs of myopathy or increased CPK.

4.6 Studies In Japan

The NDA briefly described 6 RCTs sponsored by the independent subsidiary of Schering-Plough in Japan. Schering-Plough was not the sponsor and does not have access to case report forms, a data base, or formal study summaries. These RCTs were: 3 Phase 1, placebo-controlled RCTs to evaluate the safety, tolerability, and pharmacokinetic profile of single and multiple oral dose of ezetimibe in healthy males or hyperlipidemic patients with no other significant disease; 1 Phase 1 crossover RCT to evaluate the effect of food ingestion on the bioavailability of ezetimibe in healthy males; 2 placebo-controlled, dose-ranging RCTs to evaluate the safety and efficacy of ezetimibe given once daily for 4 weeks and once daily for 12 weeks in males with Primary Hypercholesterolemia. Of the 6 RCTs, 5 have been completed and 1 is ongoing, with no available results. In the 5 completed studies, a total of 79 patients received at least 1 dose of ezetimibe. There were no deaths, no SAEs, and no discontinuations due to AEs. All reported AEs were mild to moderate in intensity. Laboratory abnormalities included elevations of ALT and AST. The findings were consistent with the findings in the Phase 2/3 RCTs discussed in Section 4 above.

5. SAFETY RESULTS IN CLINICAL STUDIES \geq 14 WEEKS LONG

Interim results were presented from the 4 UESs, which are all ongoing (see Sections 1.4.1.2 and 4.2.2). The data from these studies were combined to provide results for Primary Hypercholesterolemia on

long-term experience with (1) all ezetimibe treatment (i.e., with or without coadministered statin), (2) ezetimibe monotherapy, and (3) ezetimibe coadministered with a statin), and to provide data for Homozygous Familial Hypercholesterolemia on long-term experience with ezetimibe coadministered with a statin.

Because the UESs have no control groups, the discussion below is focused on AEs and laboratory tests of the liver (ALT, AST) and muscle (CPK). The intent of this focus is to screen for any clusters of unusual clinical events, and to evaluate the long-term frequency of the known effects of ezetimibe and statins on liver and muscle. The Phase 2/3 RCTs discussed in Section 4 above provide more reliable data about possible effects of ezetimibe and statins on the frequency of clinical events that are usual in the patient populations studied, and the frequency of changes in routine laboratory tests such of hematology, blood chemistry, and renal function.

In the discussion below, "ezetimibe" means ezetimibe 10 mg, "monotherapy" means "ezetimibe monotherapy," and "coadministration" means ezetimibe 10 mg coadministered with any dose of any statin used in the UESs.

5.1 Primary Hypercholesterolemia

5.1.1 Long-term Ezetimibe Experience

This was an analysis of RCT+UES data for patients who completed the 2 monotherapy RCTs and enrolled in the UES. Data were to be obtained at baseline in the RCT and at 1, 3, 6, 9, 12, 18, and 24 months. Results were presented in 3 categories: (1) "all reported after assignment of ezetimibe," i.e., during monotherapy in the RCTs, or during either monotherapy or coadministration in the UES. There were 1624 patients with data in this category, of whom 995 (61.1%) participated in the study for 12-18 months; the median duration was 12.8 months; (2) "reported during ezetimibe monotherapy," i.e., during monotherapy in the RCTs or UES, regardless of whether there was prior or later coadministration. There were 1624 patients with data in this category, and the median duration of participation was 9.0 months; (3) "reported during 'pure' ezetimibe monotherapy," i.e., during monotherapy in the RCTs or UES, without coadministration at any time. There were 1094 patients with data in this category, and the median duration of study participation was 12.1 months.

The discussion below focuses on category of results called "all reported after assignment to ezetimibe" because the results were similar in this category and the 2 monotherapy categories.

5.1.1.1 Adverse Events (AEs)

Table 96 presents an overview of the AEs.

In the category of results called "all reported after assignment of ezetimibe," the frequencies of patients with AEs were: 4 (0.2%) patients died, 136 (8.4%) patients had SAEs, 172 (10.6%) patients had AEs that led to discontinuation from a study, 1353 (83.3%) patients had AEs of any intensity, 187 (11.5%) patients had AEs that were considered to be severe, and 20 (1.2%) of patients had AEs that were considered to be life-threatening.

5.1.1.1.1 Deaths And Other Serious Adverse Events (SAEs)

5.1.1.1.1.1 Deaths

There were 4 deaths, all of which were considered unlikely to be treatment-related. A 68 year old Caucasian male died after 75 days of monotherapy; the probable cause was accidental drowning (see Section 4.1.1.1.2.1). A 73 year old Caucasian male died 7 days after 127 days of monotherapy followed by 155 days of coadministration; the cause was unclear. A 66 year old Caucasian male died 15 days after 488 days of monotherapy; the cause was myocardial infarction. A 70 year old Caucasian male died 151 days after completing 409 days of monotherapy; the cause was chronic obstructive pulmonary disease.

5.1.1.1.1.2 Serious Adverse Events (SAEs)

Table 97 Shows the SAEs. SAEs were reported for 136 (8.4%) patients. Within this total, there were 30 (1.8%) patients who had Surgical And Medical Procedures, including 20 patients who had elective procedures such as cardiac catheterization or colonoscopy. The frequencies of patients with SAEs were <1.5% for all other Body System/Organ Class groups, and <1% for all individual SAEs.

There were 18 (1.1%) patients with nonfatal SAEs that were considered to be life-threatening. In 2 patients, these SAEs began during a RCT, and were considered unlikely to be related to treatment (see Section 4.1.1.1.2.2). In the other 16 patients, these SAEs began during the UES; in

1 patient, the SAE was considered to be possibly related to treatment, and in the other 15 patients, the SAEs were considered unlikely to be related to treatment. Of the 18 patients, all were Caucasian, 11 were male and 7 were female; the mean age was 63 years, and the age range was 48-79 years. The first-listed AE terms for these 18 patients were: angina pectoris (aggravated), aortic aneurysm (abdominal), acute myocardial infarction, breast cancer, cellulitis (cat bite), cerebral infarction (brain stem), chest pain, cholelithiasis, colonic polyps, concussion, esophageal carcinoma, fracture, hemorrhage (spleen), meningitis (bacterial), myocardial infarction, pericarditis, positive cardiac catheterization, and procedures (pacemaker insertion and valve replacement).

5.1.1.1.2 Discontinuation Due To Adverse Events (AEs)

There were 172 (10.6%) patients with AEs that led to discontinuation from a study. In the Gastrointestinal System, there were 47 (2.9%) patients with AEs that led to discontinuation; the most frequent were abdominal pain, diarrhea, and flatulence. In the Musculoskeletal System, there 35 (2.2%) patients were AEs that led to discontinuation; the most frequent were myalgia, arthralgia, and back pain. In the Body As A Whole, there were 32 (2.0%) patients with AEs that led to discontinuation; the most frequent were fatigue, dizziness, and headache. The frequencies of patients with AEs that led to discontinuation were <1.0% in all other Body System/Organ Class groups, and for all individual AEs.

5.1.1.1.3 Adverse Events (AEs) Of Any Intensity

There were 1353 (83.3%) patients with AEs of any intensity. The most frequent were upper respiratory tract infection (20.1%), musculoskeletal pain (11.7%), headache (11.5%), arthralgia (10.0%), and back pain (9.7%).

AEs that were considered to be severe or life-threatening were reported for 187 (11.5%) patients. In the Musculoskeletal System, there were 45 (2.8%) patients with these AEs, and the most frequent AEs were back pain, musculoskeletal pain, and arthralgia. In the Gastrointestinal System, there were 38 (2.3%) patients with these AEs, and the most frequent AEs were abdominal pain, diarrhea, and flatulence. In the Body As A Whole, there were 29 (1.8%) patients with these AEs, and the most frequent AEs were chest pain, headache, leg edema, and fatigue. In Infections And Infestations, there were 29 (1.8%) patients with these AEs, and the most frequent AEs were upper respiratory tract infection, sinusitis, and pharyngitis. The frequencies of patients with AEs that were considered to be severe or life-threatening were <1.0% for all other Body System/Organ Class groups, and for all individual AEs.

AEs of any intensity that were reported for $\geq 2\%$ of patients were reviewed for frequency and intensity by time intervals since the assignment of ezetimibe. The frequency of patients with these AEs increased from 61.6% at <3 months to 69.7% at 12 to <18 months. This appeared to represent a gradual accumulation of ongoing AEs. There was no evidence of unexpected, late-emerging AEs, or of a trend toward worsening of AEs over time.

5.1.1.1.4 Clinical Events And Laboratory Test Values Of Special Interest

5.1.1.1.4.1 Allergic Reaction/Rash Adverse Events (AEs)

There were 168 (10.3%) patients with any Allergic Reaction/Rash AEs; the most frequent AEs were allergy (4.0%), rash (2.7%), allergy aggravated (1.3%), and pruritis (1.0%).

The frequency of patients with any Allergic Reaction/Rash AE increased from 4.5% at <3 months after first assignment to ezetimibe to 7.0% at 12 to <18 months. This was related to increases in the frequency of patients with allergy and rash AEs.

5.1.1.1.4.2 Central And Peripheral Nervous System Adverse Events (AEs)

There were 135 (8.3%) patients with any Central Nervous System/Peripheral Nervous System AE; the most frequent AEs were hypoesthesia (2.2%), paresthesia (1.4%), and migraine (1.0%).

The frequency of patients with any Central Nervous System/Peripheral Nervous System AE increased from 3.4% at <3 months after first assignment to ezetimibe to 5.3% at 12 to <18 months. This was related to increases in the frequency of patients with hypoesthesia AEs and paresthesia AEs.

5.1.1.1.4.3 Psychiatric Adverse Events (AEs)

There were 149 (9.2%) patients with any psychiatric AE; the most frequent AEs were insomnia (4.2%), anxiety (1.8%), and depression (1.6%).

The frequency of patients with any psychiatric AE increased from 3.8% at <3 months after assignment of ezetimibe to 6.9% at 12 to <18 months. This was related to increases in the frequency of patients with insomnia and depression AEs.

5.1.1.1.4.4 Gastrointestinal System Adverse Events (AEs)

There were 559 (34.4%) patients with any Gastrointestinal System AE; the most frequent AEs were abdominal pain (6.8%), diarrhea (6.7%), and nausea (5.8%).

The frequency of patients with any Gastrointestinal System AE decreased from 18.4% at <3 months after assignment to ezetimibe to 15.9% at 12 to <18 months. This was related to decreases in the frequency of patients with abdominal pain, diarrhea, and nausea AEs.

5.1.1.1.4.5 Gallbladder-related Adverse Events (AEs)

There were 13 (0.8%) patients with any Gallbladder-related AE; the AEs were cholecystectomy, cholecystitis, cholelithiasis, and gallbladder disease.

The frequency of patients with any Gallbladder-related AE was in the range of 0.1%-0.3% across time intervals from <3 months to 12 to <18 months after assignment to ezetimibe; there was no pattern of increasing or decreasing frequency over time.

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

Adverse Events. There were 69 (4.2%) patients with any Liver And Biliary System AE; the AEs were alpha-fetoprotein increased (0.1%), bilirubinemia ((0.1%), cholecystitis (0.6%), cholelithiasis (0.4%), gallbladder cholesterolosis (0.1%), gallbladder disease (0.1%), GGT increased (0.9%), liver fatty (0.1%), hepatic enzymes increased (1.0%), hepatic function abnormal (0.4%), SGOT (AST) increased (1.0%), and SGPT (ALT) increased (1.3%).

There were 48 (3.0%) patients with ≥ 1 AE in the Hepatic Pool (hepatic enzymes increased, hepatic function abnormal, SGOT (AST) increased, and SGPT (ALT) increased). There were 6 (0.4%) patients with SAEs in the Hepatic Pool and 16 (1.0%) patients with AEs in the Hepatic Pool that led to discontinuation from a study.

Laboratory Test Values. The denominator was 1603 for postbaseline ALT (ULN = 25 mU/mL) and AST (ULN = 22 mU/mL). **ALT:** There were 71 (4.4%) patients with ALT ≥ 2 xULN. Within this total, there were 24 (1.5%) patients with ALT ≥ 3 xULN, 3 (0.2%) patients with ALT ≥ 5 xULN, and no patients with ALT ≥ 10 xULN. With regard to persistent ALT elevations, there were 11 (0.7%) patients with consecutive ALT ≥ 3 xULN. **AST:** There were 40 (2.5%) patients

with AST ≥ 2 xULN. Within this total, there were 12 (0.7%) patients with AST ≥ 3 xULN, 2 (0.1%) patients with ALT ≥ 5 xULN, and no patients with AST ≥ 10 xULN. With regard to persistent AST elevations, there were 4 (0.2%) patients with consecutive AST ≥ 3 xULN.

Patient characteristics and histories were examined for the 13 (0.8%) patients with postbaseline consecutive ALT and/or AST ≥ 3 xULN. Of the 13 patients, 8 were identified during the RCTs (see Section 4.1.1.3.6) and 5 were identified during the UES. Of the 13 patients, 11 were Caucasian and 2 were Hispanic; 10 were male and 3 were female; the mean age was 54 years and the age range was 28-78 years. The range of baseline ALT/AST values was 14-56 mU/mL; 8 patients had baseline values > 1 xULN. The range of the consecutive postbaseline ALT/AST values ≥ 3 xULN was 66-138 mU/mL. The time from assignment of ezetimibe to the first consecutive ALT or AST ≥ 3 xULN ranged from 15-418 days. Study participation was discontinued for 4 patients during the RCTs and 2 patients during the UES. Of the 12 patients with follow-up, ALT/AST values returned to baseline or near baseline in 11 and remained elevated in 1 patient.

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

Adverse Events. There were 42 (2.6%) patients with increased CPK levels reported as AEs, including 1 ($< 0.1\%$) patient with a SAE and 7 (0.4%) patients with AEs that led to discontinued from a study.

Laboratory Test Values. The denominator was 1603 for postbaseline CPK (ULN = 120 mU/mL): There were 59 (3.7%) patients with CPK ≥ 3 xULN. Within this total, there were 22 (1.4%) patients with CPK ≥ 5 xULN, and 6 (0.4%) patients with CPK ≥ 10 xULN.

There were 13 (0.8%) patients with postbaseline values for CPK that were 5 to < 10 xULN and associated with muscle symptoms, or that were ≥ 10 xULN, regardless of muscle symptoms. There were 7 (0.4%) patients with CPK 5 to < 10 xULN who had associated muscle symptoms. There were 6 (0.4%) patients with CPK ≥ 10 xULN, of whom 1 had muscle symptoms.

Patient characteristics and histories were examined for the 13 patients with postbaseline CPK 5 to < 10 xULN and associated muscle symptoms or postbaseline CPK ≥ 10 xULN regardless of muscle symptoms. Of the 13 patients, 5 were identified during the RCTs (see Section 4.1.1.3.7) and 8 were identified during the UES. Of the 13 patients, 12 were Caucasian and 1 was Black; all 13 were male; the mean age was 49 years, and the

age range was 33-72 years. The range of baseline CPK values was 51-681 mU/mL; 7 patients had baseline values >1xULN. The range of peak postbaseline CPK values was 614-5452 mU/mL. The time from first assignment to ezetimibe to peak CPK ranged from 14 to 380 days. Study participation was discontinued for 3 patients during the RCTs and 2 patients during the UES. For 6 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 6 patients and after study discontinuation or cessation in 2 patients; the values remained elevated in 5 patients.

5.1.2 Long-term Experience With Ezetimibe Coadministered With A Statin

This was an analysis of RCT+UES data for patients who completed the 2 ezetimibe monotherapy RCTs and 3 of 4 the factorial coadministration RCTs, and enrolled in a UES. Data were to be obtained at baseline and at 1, 3, 6, 9, 12, 18, and 24 months.

All results were presented as "reported during coadministration," i.e., during coadministration of ezetimibe with a statin during a RCT or UES, regardless of whether there were intervals of other treatment. There were 1281 patients with data in this results category, and the median duration of participation was 5.6 months. (There is some overlap between these patients and the patients discussed in Section 5.1.1 above).

5.1.2.1 Adverse Events (AEs)

Table 98 presents an overview of the AEs. The frequencies of patients with AEs were: 2 (0.2%) patients died, 75 (5.9%) patients had SAEs, 64 (5.0%) patients had AEs that led to discontinuation from a study, 885 (69.1%) patients had AEs of any intensity, and 19 (1.5%) patients had AEs that were considered to be severe or life-threatening.

5.1.2.1.1 Deaths And Other Serious Adverse Events (SAEs)

5.1.2.1.1.1 Deaths

There were 2 deaths. Both of these AEs were considered unlikely to be treatment-related. A 73 year old Caucasian male died 7 days after completing 127 days of ezetimibe monotherapy followed by 155 days of coadministration; the cause was uncertain. A 56 year old Caucasian male died after completing 136 days of coadministration; the cause was cardiopulmonary arrest.

5.1.2.1.1.2 Serious Adverse Events (SAEs)

Table 99 Shows the SAEs. SAEs were reported for 75 (5.9%) patients. Within this total, there were 21 (1.6%) patients with disorders of the Cardiovascular System, including angina pectoris, coronary artery disorder, and myocardial infarction. The frequencies of patients with SAEs were <1.5% for all other Body System/Organ Class groups, and <1% for all individual SAEs.

There were 12 (0.9%) patients with nonfatal SAEs that were considered to be life-threatening. (For 7 patients, these SAEs were also discussed in the review of Long Term Ezetimibe Experience: see Section 5.1.1). In 2 of the 12 patients, these SAEs began during a RCT, and were considered unlikely to be related to treatment. In the other 10 patients, these SAEs began during a UES; in 1 patient, the SAE was considered to be possibly related to treatment, and in 9 as unlikely to be related to treatment. Of the 12 patients, all were Caucasian, 6 were male and 6 were female; the mean age was 65 years, and the age range was 41-78 years. The first-listed AE terms for these 12 patients were: angina pectoris (aggravated), aortic aneurysm (abdominal), acute myocardial infarction, breast cancer, breast cancer (ductal carcinoma), cardiac failure (aggravated), cerebral infarction, cholelithiasis, coronary artery disease, myocardial infarction, and peritonitis.

5.1.2.1.2 Discontinuation Due To Adverse Events (AEs)

AEs that led to discontinuation from a study were reported for 64 (5.0%) patients. There were 15 (1.2%) patients with musculoskeletal disorders that led to discontinuation, including 8 (0.6%) patients with myalgia. The frequencies of patients with AEs that led to discontinuation were <1.0% in all other Body System/Organ Class groups, and for all individual AEs.

5.1.2.1.3 Adverse Events (AEs) Of Any Intensity

AEs of any intensity were reported for 885 (69.1%) patients. The most frequent were upper respiratory tract infection (13.0%), headache (7.1%), arthralgia (6.2%), sinusitis (5.4%), and musculoskeletal pain (5.4%).

AEs were considered to be severe or life-threatening were reported for 105 (8.2%) patients. In the Body As A Whole, there were 18 (1.4%) patients with this type of AE, and the most frequent AEs were chest pain and headache. In the Gastrointestinal System, there were 17 (1.3%) patients with this type of AE, and the most frequent AEs were abdominal pain, diarrhea, nausea, and toothache. In the Musculoskeletal System, there

were 17 (1.3%) patients with this type of AE, and the most frequent AEs were musculoskeletal pain and myalgia. In the Cardiovascular System, there were 16 (1.2%) patients with this type of AE, and the most frequent were myocardial infarction, angina pectoris, and coronary artery disorder.

The frequencies of patients with AEs that were considered to be severe or life-threatening were <1.0% in all other Body System/Organ Class groups, and for all individual AEs.

AEs of any intensity that were reported for $\geq 2\%$ of patients were reviewed for frequency and intensity by time intervals since the assignment of ezetimibe. The frequency of patients with these AEs increased from 58.9% at <3 months to 65.9% at 9 to <12 months. This appeared to represent a gradual accumulation of ongoing AEs. There was no clear evidence of unexpected, late-emerging AEs, or of a trend toward worsening of AEs over time.

5.1.2.1.4 Clinical Events And Laboratory Test Values Of Special Interest

5.1.2.1.4.1 Allergic Reaction/Rash Adverse Events (AEs)

There were 102 (8.0%) patients with any Allergic Reaction/Rash AE; the most frequent AEs were allergy (2.4%), rash (2.3%), and allergy aggravated (1.2%).

The frequency of patients with any Allergic Reaction/Rash AE increased from 5.0% at <3 months from first coadministration to 10.8% at 9 to <12 months. This was related to increases in the frequency of patients with allergy and rash AEs.

5.1.2.1.4.2 Central And Peripheral Nervous System Adverse Events (AEs)

There were 65 (5.1%) patients with any Central Nervous System/Peripheral Nervous System AE. The most frequent AEs were hypertonia (0.9%), hyporeflexia (0.9%), and migraine (0.8%).

The frequency of patients with any Central Nervous System/Peripheral Nervous System AE increased from 3.7% at < 3 months after first coadministration to 5.2 % at 9 to <12 months. This increase was not concentrated in individual AEs.

5.1.2.1.4.3 Psychiatric Adverse Events (AEs)

There were 80 (6.2%) patients with any psychiatric AE. The most frequent AEs were insomnia (2.9%), anxiety (1.1%), and depression (0.9%). The frequency of patients with any psychiatric AE increased from 4.2% at <3 months after first coadministration to 7.3% at 9 to <12 months. This was related to increases in the frequency of patients with insomnia and depression AEs.

5.1.2.1.4.4 Gastrointestinal System Adverse Events (AEs)

There were 277 (21.6%) patients with any Gastrointestinal System AE; the most frequent AEs were abdominal pain (4.1%), nausea (4.1%), dyspepsia (3.2%), constipation (2.6%), and diarrhea (2.5%).

The frequency of patients with any Gastrointestinal System AE decreased from 17.5% at <3 months after first coadministration to 11.2% at 9 to <12 months. This was related to decreases in the frequency of patients with abdominal pain, nausea, constipation, and diarrhea AEs.

5.1.2.1.4.5 Gallbladder-related Adverse Events (AEs)

There were 4 (0.3%) patients with any Gallbladder-related AE; the AEs were cholecystectomy (0.2%), cholecystitis (0.2%), cholelithiasis (0.2%), and gallbladder disease (0.1%).

All of the Gallbladder-related AEs occurred at <3 months after first coadministration.

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

Adverse Events. There were 38 (3.0%) patients with any Liver And Biliary System AE; the AEs included alpha-fetoprotein increased (0.1%), bilirubinemia (0.1%), cholecystitis (0.2%), cholelithiasis (0.2%), gallbladder disease (0.1%), GGT increased (1.1%), liver fatty (0.2%), hepatic enzymes increased (0.7%), hepatic function abnormal (none) SGOT (AST) increased (0.8%), and SGPT (ALT) increased (1.1%).

There were 24 (1.9%) patients with ≥ 1 AE in the Hepatic Pool (hepatic enzymes increased, hepatic function abnormal, SGOT (AST) increased, and SGPT (ALT) increased). There were 4 (0.3%) patients with SAEs in the Hepatic Pool and 7 (0.5%) patients with AEs in the Hepatic Pool that led to discontinuation from a study.

Laboratory Test Values. Postbaseline ALT (ULN = 25 mU/mL) and AST (ULN for AST = 22 mU/L). **ALT:** There were 39 (3.0%) patients with ALT $\geq 2x$ ULN. Within this total, there were 13 (1.0%) patients with ALT $\geq 3x$ ULN, 1 (0.1%) patient with ALT $\geq 5x$ ULN, and no patients with ALT $\geq 10x$ ULN. With regard to persistent ALT elevations, there were 6 (0.5%) patients with consecutive ALT $\geq 3x$ ULN. **AST (ULN = 22 mU/mL):** There were 23 (1.8%) patients with AST $\geq 2x$ ULN. Within this total, there were 9 (0.7%) patients with AST $\geq 3x$ ULN, 2 (0.2%) patients with AST $\geq 5x$ ULN, and no patients with AST $\geq 10x$ ULN. With regard to persistent AST elevations, there were 4 (0.3%) patients with consecutive AST $\geq 3x$ ULN.

Patient characteristics and histories were examined for the 7 (0.6%) patients with postbaseline consecutive ALT and/or AST $\geq 3x$ ULN. Of the 7 patients, 2 were identified during the RCTs (see Section 4.1.2.3.6) and 5 were identified during a UES. Of the 7 patients, 6 were Caucasian and 1 was Hispanic; 4 were male and 3 were female; the mean age was 59 years and the age range was 45-78 years. The range of baseline ALT/AST values was 10-36 mU/mL; 4 patients had baseline values $> 1x$ ULN (ULN = 25 mU/mL). The range of consecutive postbaseline ALT/AST values $\geq 3x$ ULN was 77-237 mU/mL. Study participation was discontinued for 1 patient during the RCTs and 2 patients during a UES. In follow-up, ALT/AST values returned to baseline or near baseline in 6 patients and remained elevated in 1 patient.

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

Adverse Events. There were 17 (1.3%) patients with increased CPK levels reported as AEs, including no patient with a SAE and 1 (0.1%) patient with an AE that led to discontinued from a study.

Laboratory Test Values. Postbaseline CPK (ULN =120 mU/mL): There were 26 (2.0%) patients with CPK $\geq 3x$ ULN. Within this total, there were 12 (0.9%) patients with CPK $\geq 5x$ ULN, and 2 (0.2%) patients with CPK $\geq 10x$ ULN.

There were 5 (0.4%) patients with postbaseline values for CPK that were 5 to $< 10x$ ULN and associated with muscle symptoms, or that were $\geq 10x$ ULN, regardless of muscle symptoms. Of these, there were 3 (0.2%) patients with CPK 5 to $< 10x$ ULN who had associated muscle symptoms, and 2 (0.2%) patients with CPK $\geq 10x$ ULN, of whom neither had muscle symptoms.

Patient characteristics and histories were examined for the 5 patients with postbaseline CPK ≥ 5 to $< 10x$ ULN and associated muscle symptoms or

postbaseline CPK $\geq 10 \times \text{ULN}$ regardless of muscle symptoms. All were identified during a UES. All 5 patients were Caucasian and all were male; the mean age was 49 years, and the age range was 37-60 years. The range of baseline CPK values was 51-681 mU/mL; 3 patients had baseline values $> 1 \times \text{ULN}$ ($\text{ULN} = 120 \text{ mU/mL}$). The range of peak postbaseline CPK values was 834-5452 mU/mL. The time from first coadministration to peak CPK ranged from 30-246 days. Study participation was discontinued for no patients during the RCTs and 1 patient during a UES; 2 patients discontinued statin treatment. For 3 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 1 patient and remained elevated in 4 patients.

5.2 Long-term Experience In Homozygous Familial Hypercholesterolemia

This was an analysis of RCT+UES data for patients who completed the Homozygous Familial Hypercholesterolemia RCT and enrolled in the UES. Data were to be obtained at baseline in the RCT and at 1,3,6,9,12,18, and 24 months. Results were presented for all patients assigned to ezetimibe+statin 40/80 mg ($n=45$), and for the subsets assigned to ezetimibe+atorvastatin 40/80 mg ($n=33$) and ezetimibe+simvastatin

40/80 mg ($n=12$). The median duration of study participation was 6.1 months. This discussion will focus on the results for all patients assigned to ezetimibe+statin 40/80 mg.

5.2.1 Adverse Events

5.2.1.1 Deaths And Other Serious Adverse Events (SAEs)

There were no deaths.

SAEs were reported for 8 (17.8%) patients. In 2 patients, these SAEs began during the RCT, and were considered unlikely to be related to treatment (See Section 4.2.1.1). In the other 6 patients, the SAEs began during the UES; in 1 patient, the SAE was considered to be possibly related to treatment, and in the other 5 patients, the SAEs were considered as unlikely to be related to treatment. Of the 8 patients, all were Caucasian; 5 were male and 3 were female; the mean age was 31 years, and the age range was 15-45 years. The first-listed AE terms for these 8 patients were: coronary artery disease, elevated CPK ($> 10 \times \text{ULN}$), elevated SGPT (AST) ($> 3 \times \text{ULN}$), epigastric pain, heavy headache, hepatic steatosis, seizures, and unstable angina.

5.2.1.2 Discontinuation Due To Adverse Events

There were 2 (4.4%) patients with AEs that led to discontinuation from the RCT (see Section 4.2.1.2). There were no patients with AEs that led to discontinuation from the UES.

5.2.1.3 Adverse Events (AEs) Of Any Intensity

There were 32 (71.1%) patients with AEs of any intensity. The most frequent were upper respiratory tract infection (20.0%), headache (15.6%), and pharyngitis (15.6%).

No life-threatening AEs were reported. AEs that were considered to be severe were reported for 11 (24.4%) patients. In the Body As A Whole, there were 5 (11.1%) patients with this type of AE, and the AEs were chest pain, headache, edema legs, and headache aggravated. In the Gastrointestinal System, there were 3 (6.7%) patients with this type of AE, and the AEs were abdominal pain and diarrhea. In the Central/Peripheral Nervous System, there were 2 (4.4%) patients with this type of AE, and the AEs were convulsions and hemiparesis. In the Cardiovascular System, there were 2 (4.4%) patients with this type of AE, both of whom had angina pectoris. In the Liver And Biliary System, there was 1 (2.2%) patient with this type of AE, and the AE was SGOT (AST) increased. In Metabolic And Nutritional Disorders, there were 2 (4.4%) patients with this type of AE, and the AEs were creatine phosphokinase increased and hypoalbuminemia. The frequencies of patients with severe AEs were ≤ 1 (2.2%) patient in all other Body System/Organ Class groups.

5.2.2 Laboratory Tests

5.2.2.1 Blood Chemistry

5.2.2.1.1 Liver And Biliary System

There were 44 (97.8%) patients with postbaseline test results for ALT (ULN = 25 mU/mL), AST (ULN = 22 mU/mL), and CPK (ULN = 12 mU/mL).

There were 6 (13.6%) patients with ALT ≥ 3 xULN, including 3 (6.8%) patients with ALT ≥ 3 xULN, of whom 2 (4.5%) patients had consecutive ALT ≥ 3 xULN. There were also 6 (13.6%) patients with AST ≥ 2 xULN, including 3 (6.8%) patients with AST ≥ 3 xULN, of whom 2 (4.5%) had consecutive AST ≥ 3 xULN.

Patient characteristics and histories were examined for the 3 patients with postbaseline consecutive ALT and/or AST ≥ 3 xULN. Of the 3 patients 2 were

identified during the RCT (see Section 4.2.2.1.1) and 1 was identified during the UES. Of the 3 patients, all were Caucasian; 2 were male and 1 was female; the mean age was 32 years and the age range was 24-44 years. The range of baseline ALT/AST values was 13-102 mU/L; 1 patient had elevated baseline ALT/AST values of 102/77 mU/L. The range of consecutive postbaseline AST/AST values $\geq 3 \times \text{ULN}$ was 76-121 mU/mL. Study participation was discontinued for 2 patients during the RCT. In follow-up, ALT/AST values returned to baseline or near baseline in 2 patients and remained elevated in 1 patient.

5.2.2.1.2 Creatine Phosphokinase (CPK) Activity

There were 4 (9.0%) patients with CPK $\geq 3 \times \text{ULN}$, including no patients with CPK 5 to $< 10 \times \text{ULN}$ and 1 patient with CPK $\geq 10 \times \text{ULN}$. The 1 patient with CPK $\geq 10 \times \text{ULN}$ was identified during the UES, and was a Caucasian female 44 years of age. Her baseline CPK was 75 mU/mL. The peak postbaseline CPK was 1772 mU/mL, and the time first ezetimibe+statin to peak CPK was 148 days. There was associated calf pain. The statin was discontinued, and 1 week later the symptoms had improved and the CPK was normal. The patient continued the study.

5.3 Ongoing Studies

The NDA provided limited safety data for 4 ongoing long-term studies. No new safety issues were raised by these data. The studies included 2 RCTs of ezetimibe coadministered with simvastatin or atorvastatin for up to 12 months in patients with Primary Hypercholesterolemia; 1 RCT of ezetimibe coadministered with atorvastatin for up to 54 weeks in patients with coronary heart disease or multiple risk factors and Primary Hypercholesterolemia, and 1 open-label study of ezetimibe coadministered with atorvastatin in patients with coronary heart disease or multiple risk factors and Primary Hypercholesterolemia not controlled by atorvastatin 10 mg.

6. EFFECTS OF DOSE ON SAFETY RESULTS IN CLINICAL STUDIES

Controlled, dose-response safety data for ezetimibe were available only from the Clinical Pharmacology studies and the 3 Phase 2 dose-ranging RCTs performed early in the development of ezetimibe.

In the Phase 1 Clinical Pharmacology studies, generally healthy people were given ezetimibe 10 mg, as a single dose or in daily doses for up to 2 weeks (see Section 4.4). Systemic exposure increased with dose, but was less than dose-proportional. There were no clearly dose-related safety findings.

In the 3 Phase 2 dose-ranging RCTs, the ezetimibe dose range was — mg. All 3 RCTs were placebo-controlled and double-blind, 1 was 8 weeks long and the other 2 were 12 weeks long. The patients were otherwise healthy adults with Primary Hypercholesterolemia. There were no clearly dose-related safety findings. In pooled data from the 3 RCTs, there were 538 patients (286 males and 252 females), 22-75 years of age. There were 105 patients in the placebo group and 433 patients in the ezetimibe groups: — mg (n=47); —mg (n=66); — mg (n=145); 10 mg (n=141); — mg (n=16); — mg (n=18). The safety results were as follows:

- the frequencies of patients with any SAE were 1 (1.0%) in the placebo group and 4 (0.9%) in the ezetimibe groups, including none at — mg, 1 (1.5%) at —mg, 1 (0.7%) at —mg, 2 (1.4%) at 10 mg, and none at —mg or — mg.
- the frequencies of patients with AEs leading to discontinuation from a study were 3 (2.9%) in the placebo group and 7 (1.6%) in the ezetimibe groups, including 1 (2.1%) at — mg, 2 (3.0%) at —mg, none at — mg, 4 (2.8%) at 10 mg, and none at —mg or — mg.
- the frequencies of patients with any AE were 61 (58.1%) in the placebo group and 268 (61.9%) in the ezetimibe groups, including 27 (57.4%) at — mg, 41 (62.1%) at —mg, 89 (61.4%) at —mg, 88 (62.4%) at 10 mg, 11 (68.8%) at — mg, and 12 (66.7%) at — mg.
- the frequencies of patients with ALT and/or AST $\geq 3 \times \text{ULN}$ were 1 (1.0%) in the placebo group and 4 (0.9%) in the ezetimibe groups, including none at — mg, none at —mg, 2 (1.4%) at — mg, 2 (1.4%) at 10 mg, and none at —mg or — mg.
- the frequencies of patients with CPK $\geq 3 \times \text{ULN}$ were 1 (1.0%) in the placebo group and 8 (1.8%) in the ezetimibe groups, including none at — mg, 1 (1.5%) at —mg, 4 (2.8%) at —mg, 3 (2.1%) at 10 mg, and none at —mg or —mg.

7. EFFECTS OF INTERACTIONS BETWEEN EZETIMIBE AND OTHER FACTORS ON SAFETY RESULTS IN CLINICAL STUDIES

7.1 Interactions Of Ezetimibe With Demographic Characteristics

7.1.1 Effects of Sex And Age On Pharmacokinetics

The effects of sex and age on the pharmacokinetics of ezetimibe were investigated in 3 Clinical Pharmacology studies. The participants were generally healthy people. Systemic exposure was about 20% higher in females compared to males, in an open-label, parallel-group, study of ezetimibe — mg given for 10 days to 12 males and 12 females 21-44 years

of age. Also, systemic exposure was about 2 times higher in males ≥ 65 years of age compared to males 18-45 years of age, in an open-label, parallel group study of ezetimibe 10 mg given for 10 days to 12 males 18-45 years of age and 12 men ≥ 65 years of age. The pharmacokinetics of ezetimibe in adolescents were similar to those in adults, except that unconjugated ezetimibe concentrations were about 1.3-2.7 higher in adolescents, in an open-label, parallel group study of ezetimibe 10 mg given for 7 days to 9 males and 9 females 10-18 years of age.

7.1.2 Effects of Sex, Age, and Race On Safety Results In Randomized Clinical Trials (RCTs) 8-12 Weeks Long

Possible effects of sex, age, and race on safety results in the 8-12 week RCTs were evaluated by stratifying on sex (female versus male), age (<65 versus ≥ 65 and <75 versus ≥ 75), and race (Caucasian versus non-Caucasian), in analyses of AEs of any intensity that were reported for $\geq 2\%$ of patients in any treatment group, and analyses of laboratory test results for postbaseline ALT, AST, and CPK. The laboratory results for the frequency of patients with postbaseline ALT and/or AST $\geq 3 \times \text{ULN}$ and CPK $\geq 3 \times \text{ULN}$ were generally representative of the more detailed results, and are emphasized below.

7.1.2.1 Primary Hypercholesterolemia

7.1.2.1.1 Ezetimibe Monotherapy

The monotherapy results were derived from the monotherapy pool of RCT data (see Section 1.4.1.1.1).

7.1.2.1.1.1 Sex

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

<u>Sex</u>	<u>Placebo</u>	<u>Ezetimibe 10 mg</u>
Female	305/425 (71.8%)	599/880 (68.1%)
Male	206/370 (55.7%)	462/811 (57.0%)

Within each sex, the frequencies of patients with AEs of any intensity were similar in the placebo group and ezetimibe 10 mg group. In both treatment groups, the frequency of patients with AEs of any intensity was higher in females compared to males.

Within each sex, the frequencies of patients with AEs of any intensity in the placebo group and ezetimibe 10 mg group were similar by individual AE.

ALT, AST And CPK. The frequencies of patients with postbaseline ALT and/or AST $\geq 3xULN$ and CPK $\geq 3xULN$, by sex, were as follows:

<u>Sex</u>	<u>Placebo</u>	<u>Ezetimibe 10 mg</u>
----- <u>ALT&/orAST>3xULN</u> -----		
Female	4/420 (1.0%)	4/867 (0.5%)
Male	0/366	10/807 (1.2%)
----- <u>CPK>3xULN</u> -----		
Female	0/420	5/867 (0.6%)
Male	11/366 (3.0%)	37/807 (4.6%)
Caucasian	7/ 329 (2.1%)	23/722 (3.2%)
Black	4/ 19 (21.1%)	12/ 45 (26.7%)
Other	0/ 18	2/ 40 (5.0%)

In females, the frequency of patients with ALT and/or AST $\geq 3xULN$ was 0.5% lower, and the frequency of patients with CPK $\geq 3xULN$ was 0.6% higher, in the ezetimibe group compared to the placebo group. In males, the frequency of patients with ALT and/or AST $\geq 3xULN$ was 1.2% higher, and the frequency of patients with CPK $\geq 3xULN$ was 1.6% higher, in the ezetimibe 10 mg group compared to the placebo group. In both treatment groups, the frequencies of patients with CPK $\geq 3xULN$ were higher in males compared to females, and highest in Black males. In Black males with CPK $\geq 3xULN$, the values were in the range of 3xULN to <5xULN for 10 patients, 5xULN to <10xULN for 5 patients, and >10xULN for 1 patient. These results appear to represent real differences between the sexes and racial groups.

7.1.2.1.1.2 Age

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

<u>Age</u>	<u>Placebo</u>	<u>Ezetimibe 10 mg</u>
<65 Years	356/548 (65.0%)	706/1158 (61.0%)
≥ 65 Years	155/247 (62.8%)	355/ 533 (66.6%)
<75 Years	486/751 (64.7%)	993/1593 (62.3%)
≥ 75 Years	25/ 44 (56.8%)	68/ 98 (69.4%)

In patients <65 & <75 years of age, the frequencies of patients with AEs of any intensity were lower in the ezetimibe 10 mg group compared to the placebo group.

In patients ≥ 65 & ≥ 75 years of age, respectively, the frequencies of patients with AEs of any intensity were 3.8% & 12.6% higher in the ezetimibe 10 mg group compared to the placebo group. These results were related to higher frequencies of patients with Musculoskeletal System AEs, including arthralgia, back pain, musculoskeletal pain, and others. These AEs are difficult to interpret because the frequencies of patients with CPK ≥ 3 xULN were lower in patients ≥ 65 & ≥ 75 years of age compared to patients < 65 & < 75 years of age, respectively, and the differences between treatment groups in the frequency of patients with CPK ≥ 3 xULN were not increased in patients ≥ 65 & ≥ 75 years of age compared to the patients < 65 & < 75 years of age (see below).

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

<u>Age (Years)</u>	<u>Placebo</u>	<u>Ezetimibe 10 mg</u>
	<u>ALT&/orAST>3XULN</u>	
<65 Years	4/544 (0.7%)	12/1145 (1.0%)
≥ 65 Years	0/242	2/ 529 (0.4%)
<75 Years	4/743 (0.5%)	13/1577 (0.8%)
≥ 75 Years	0/ 43	1/ 97 (1.0%)
	<u>CPK>3xULN</u>	
<65 Years	9/544 (1.7%)	36/1145 (3.1%)
≥ 65 Years	2/242 (0.8%)	6/ 529 (1.1%)
<75 Years	11/743 (1.5%)	41/1577 (2.6%)
≥ 75 Years	0/ 43	1/ 97 (1.0%)

In all age groups, the frequencies of patients with ALT and/or AST ≥ 3 xULN, and with CPK ≥ 3 xULN, were 0.3%-1.4% higher in the ezetimibe 10 mg group compared to the placebo group. In both treatment groups, these frequencies were similar or lower in patients ≥ 65 & ≥ 75 years of age compared to patients < 65 & < 75 years of age, respectively.

7.1.2.1.1.3 Race

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

<u>Race</u>	<u>Placebo</u>	<u>Ezetimibe 10 mg</u>
Caucasian	463/715 (64.8%)	961/1523 (63.1%)
non-Caucasian	48/ 80 (60.0%)	100/ 168 (59.5%)

In both racial groups, the frequencies of patients with AEs of any intensity were similar in the placebo group and the ezetimibe 10 mg group. In both

treatment groups, the frequencies were higher in Caucasian patients compared to non-Caucasian patients. The reason for this was not clear.

Within each racial group, the frequencies of patients with AEs of any intensity in the placebo group and ezetimibe 10 mg group were similar by individual AE, with the exception that ,for dyspepsia, the frequencies in Caucasian patients were 3.5% in the placebo group and 2.3% patients in the ezetimibe 10 mg group, whereas the frequencies in non-Caucasian patients were none in the placebo group and 3.0% patients in the ezetimibe 10 mg group.

ALT, AST, And CPK. The frequencies of patients with postbaseline CPK \geq 3XULN, by race, were as follows:

Race	Placebo	Ezetimibe 10 mg
	<u>ALT&/orAST>3xULN</u>	
Caucasian	3/707 (0.4%)	14/1508 (0.9%)
non-Caucasian	1/ 79 (1.3%)	0/ 166
	<u>CPK>3xULN</u>	
Caucasian	7/707 (1.0%)	26/1508 (1.7%)
non-Caucasian	4/ 79 (5.1%)	16/ 166 (9.6%)
Black male	4/ 19 (21.1%)	12/ 45 (26.7%)
All other	0/ 60	4/ 121 (3.3%)

In Caucasian patients, the frequency of patients with ALT &/or AST \geq 3xULN was 0.5% higher in the ezetimibe 10 mg group compared to the placebo group, and in non-Caucasian patients, this frequency was lower in the ezetimibe 10 mg group compared to the placebo group.

In Caucasian patients, the frequencies of patients with CPK \geq 3xULN were 1.0% in the placebo group and 1.7% in the ezetimibe 10 mg group, whereas in non-Caucasian patients, these frequencies were 5.1% in the placebo group and 9.6% in the ezetimibe 10 mg group. The higher frequencies in non-Caucasian patients were largely due to higher frequencies in Black males (see Section 7.1.2.1.1.1).

7.1.2.1.2 Ezetimibe Coadministered With A Statin

The results for ezetimibe coadministered with a statin were derived from the factorial coadministration pool of RCT data (see Section 1.4.1.1.2).

7.1.2.1.2.1 Sex

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

<u>Sex</u>	<u>Placebo</u>	<u>Ezetimibe 10 mg</u>	<u>Statin</u>	<u>Ezetimibe 10 mg+statin</u>
Female	103/144 (71.5%)	107/155 (69.0%)	370/542 (68.3%)	340/523(65.0%)
Male	63/115 (54.8%)	70/107 (65.4%)	236/394 (59.9%)	253/402 (62.9%)

In females, the frequency of patients with AEs of any intensity was 2.5% higher in the placebo group compared to the ezetimibe 10 mg group, and 3.3% higher in the statin group compared to the ezetimibe 10 mg+statin group. These higher frequencies were not concentrated in individual AEs.

In males, the frequency of patients with AEs of any intensity was 10.6% higher in the ezetimibe 10 mg group compared to the placebo group. This higher frequency is difficult to interpret, because it was not concentrated in individual AEs, and because the placebo group and ezetimibe 10 mg group in the factorial coadministration pool were subsets of the corresponding groups in the monotherapy pool, where the frequency in males of patients with AEs of any intensity was only 1.3% higher in the ezetimibe 10 mg group compared to the placebo group.

In males, the frequency of patients with AEs of any intensity was 3.0% higher in the ezetimibe 10 mg+statin group compared to the statin group. This was related to AEs in the Liver And Biliary System. In the statin group, there were 3 (0.8%) patients with hepatic enzymes increased, no patients with SGOT (AST) increased, and 3 (0.8%) patients with SGPT (ALT) increased; in the ezetimibe 10 mg+statin group, there were 8 (2.0%) patients with hepatic enzymes increased, 18 (4.5%) patients with SGOT (AST) increased, and 23 (5.7%) patients with SGPT (ALT) increased.

ALT, AST And CPK. The frequencies of patients with postbaseline ALT and/or AST $\geq 3 \times \text{ULN}$ and CPK $\geq 3 \times \text{ULN}$, by sex, as were follows:

<u>Sex</u>	<u>Placebo</u>	<u>Ezetimibe 10 mg</u>	<u>Statin</u>	<u>Ezetimibe 10 mg+statin</u>
----- <u>ALT &/or AST > 3xULN</u> -----				
Female	0/142	1/152 (0.7%)	7/539 (1.3%)	4/521 (0.8%)
Male	0/113	1/107 (0.9%)	2/390 (0.5%)	15/396 (3.8%)
----- <u>CPK > 3xULN</u> -----				
Female	0/142	2/152 (1.3%)	4/539 (0.7%)	3/521 (0.6%)
Male	3/113 (2.7%)	4/107 (3.7%)	21/390 (5.4%)	12/396 (3.0%)
Caucasian	2/ 98 (2.0%)	2/ 93 (2.2%)	15/343 (4.4%)	7/347 (2.0%)
Black	1/ 7 (14.3%)	2/ 4 (50.0%)	5/ 23 (21.7%)	3/ 16 (18.8%)
Other	0/ 8	0/ 10	1/ 24 (4.2%)	2/ 33 (6.1%)