Endocrinologic and Metabolic Drugs Advisory Committee Meeting

November 2, 2011

New Drug Application 21-687/S-039: VYTORIN®
(ezetimibe/simvastatin)

New Drug Application 21-445/S-033: ZETIA® (ezetimibe)

Applicant: MSP (Merck/Schering-Plough) Singapore Company, LLC

Clinical Briefing Document

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Office of Drug Evaluation II, Office of New Drugs

Center for Drug Evaluation and Research

Food and Drug Administration

DISCLAIMER

This briefing document contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We are bringing a new proposed indication for VYTORIN and ZETIA, based on the results of the Study of Heart and Renal Protection, to the Advisory Committee in order to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation; instead, its intent is to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Introduction

Product Information

ZETIA (ezetimibe), a selective inhibitor of the absorption of intestinal cholesterol and related phytosterol, was initially approved in the United States on 25 October 2002. VYTORIN, which contains ezetimibe and the HMG-CoA reductase inhibitor simvastatin, was initially approved on 23 July 2004. Simvastatin has been available since 23 December 1991.

Currently, VYTORIN is indicated as an adjunct to diet for:

1. the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and non-high-density lipoprotein cholesterol (non-HDL-C), and to increase high-density-lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia; and
2. the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

The current VYTORIN label includes the limitation that "no incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established."

ZETIA is indicated as an adjunct to diet for the following:

1. primary hyperlipidemia
    a. administered alone, for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia;
    b. administered in combination with a statin, for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia;
    c. administered in combination with fenofibrate, for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in adult patients with mixed hyperlipidemia
2. homozygous familial hypercholesterolemia (HoFH)
    a. administered in combination with atorvastatin or simvastatin, for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable
3. homozygous sitosterolemia
    a. for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia

The current ZETIA label includes the limitation that "the effect of ZETIA on cardiovascular morbidity and mortality has not been determined."

Simvastatin is indicated for adults as an adjunct to diet for the following:

1. reduction in risk of coronary heart disease (CHD) mortality and cardiovascular events
    a. In patients at high risk of coronary events because of existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, simvastatin is indicated to reduce the risk of total mortality by reducing CHD deaths; reduce the risk of nonfatal myocardial infarction and stroke; and reduce the need for coronary and non-coronary revascularization procedures;
2. hyperlipidemia
    a. reduce elevated total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hyperlipidemia (Fredrickson type IIa, heterozygous familial and nonfamilial) or mixed dyslipidemia (Fredrickson type IIb);
    b. reduce elevated TG in patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia);
    c. reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia);
    d. reduce total-C and LDL-C in patients with HoFH as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;

The purpose of this meeting is to discuss NDA supplements that present data from one pivotal efficacy study: SHARP (Study for Heart and Renal Protection), a multicenter, randomized, double-blind, placebo-controlled trial that compared the effect of ezetimibe/simvastatin to placebo in the reduction of major vascular events among adult subjects (≥40 years old) with chronic kidney disease (serum creatinine ≥1.7 mg/dL for men and ≥1.5 mg/dL for women) who did not have a history of myocardial infarction or coronary revascularization. Based on the results of this study, MSP (Merck/Schering-Plough) Singapore Company, LLC proposes new indications for VYTORIN and ZETIA:

- *VYTORIN is indicated to reduce the risk of major cardiovascular events in patients with chronic kidney disease.*
- *The combination of ZETIA and simvastatin is indicated to reduce the risk of major cardiovascular events in patients with chronic kidney disease.*

The applicant proposes to add the following Limitations of Use:

- *VYTORIN has been shown to reduce major cardiovascular events in patients with chronic kidney disease; however, incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has not been definitively established.*
- *ZETIA combined with simvastatin has been shown to reduce major cardiovascular events in patients with chronic kidney disease; however, the effect of ZETIA alone on cardiovascular morbidity and mortality has not been definitively determined.*

Labeled Information Regarding Renal Impairment

The VYTORIN label states that no dosage adjustment is necessary in patients with mild or moderate renal impairment, but the drug should not be started in patients with severe renal insufficiency unless the patient has already tolerated treatment with simvastatin at a dose of 5 mg or higher. "Caution should be exercised when VYTORIN is administered to these patients, and they should be closely monitored." This recommendation derives from the simvastatin component, as pharmacokinetic studies with another statin, similar to simvastatin with regard to principal route of elimination, suggest that patients with severe renal impairment experience higher systemic exposures for a given dose level compared with other patients. The relatively low contribution of renal excretion (13% of a radiolabeled simvastatin dose) suggests that dosage modifications should not be necessary with lesser degrees of renal impairment.

Regarding ezetimibe, no dosage adjustment is necessary in patients with renal impairment. Ezetimibe is primarily metabolized in the small intestine and the liver via glucuronide conjugation with subsequent biliary and renal excretion. Following oral administration of radiolabeled ezetimibe to human subjects, ~78% and 11% was recovered in the feces and urine, respectively. The pharmacologically active ezetimibe-glucuronide metabolite was the major component in urine and accounted for 9% of the administered dose. After a single 10-mg dose of ezetimibe in patients with severe renal disease (n=8; mean CrCl ≤30 mL/min/1.73m2), the mean AUC values for total ezetimibe, ezetimibe-glucuronide, and ezetimibe were increased approximately 1.5-fold, compared to healthy subjects (n=9).

Both simvastatin and its β-hydroxyacid metabolite are ~95% bound to human plasma proteins; similarly, ezetimibe and ezetimibe-glucuronide are >90% bound. Because only unbound drug is free to cross the semipermeable membranes used for dialysis, dialysis should not contribute substantially to the total removal of ezetimibe or simvastatin under typical conditions.

Clinical Background

Cardiovascular Disease in Kidney Disease

Chronic kidney disease (CKD) is a public health problem worldwide. In the United States, an estimated 25 million adults, approximately 13% of the population, have CKD defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 or persistent albuminuria.[1, 2] In addition, approximately 570,000 individuals have end-stage renal disease (ESRD), with 370,000 receiving dialysis and 170,000 surviving as recipients of a kidney transplant.[3] Although patients with CKD and their physicians often worry about the progression to ESRD, many may lose sight of the fact that the risk of death from cardiovascular disease is greater than the risk of developing kidney failure.[4]

Traditional risk factors for cardiovascular disease, such as older age, hypertension, lower HDL-cholesterol (HDL-C) levels, and diabetes are highly prevalent in CKD.[4] Even after adjusting for multiple potential confounders, however, degree of renal impairment strongly associates with cardiovascular risk.[5, 6] This may, in part, reflect the relatively high prevalence of "nontraditional" risk factors in CKD, such as left ventricular hypertrophy, albuminuria, anemia,

deranged metabolism of calcium and phosphorus, volume overload, oxidative stress, inflammation, malnutrition, and altered endothelial function.[4] Among patients who survive to ESRD in the United States, approximately 20% have atherosclerotic heart disease, 32% have congestive heart failure, 14% have peripheral vascular disease, and 9% have a history of cerebrovascular disease at the time they start dialysis. The annual cardiovascular mortality among dialysis patients younger than 45 years is approximately 100-fold greater than individuals of similar age in the general population,[7] and 60% of incident ESRD patients will die within 5 years, nearly half from cardiovascular disease.[8] These dismal statistics highlight the need to modulate cardiovascular risk in the CKD population.

Several randomized controlled trials and subsequent meta-analyses have established that statins effectively reduce the risk of major cardiovascular events, but patients with kidney disease were largely excluded from these trials.[9] Despite this, nearly a decade ago, the Kidney Disease Outcomes Quality Initiative (K/DOQI) of the National Kidney Foundation suggested that all patients with CKD should be considered in the "highest risk" group for cardiovascular disease, thereby setting an LDL-C goal of <100 mg/dL for this population.[2, 10, 11] A scientific statement from the American Heart Association concurred.[4] At the same time, however, these groups encouraged the conduct of trials to test strategies to reduce cardiovascular risk in the CKD/ESRD population.

At the time these guidelines were put forward, there were reasons for uncertainty regarding the efficacy of statins to lower cardiovascular morbidity and mortality in patients with kidney disease. First, unlike other high-risk populations, a clear association between lower cholesterol levels and lower all-cause or cardiac mortality was not evident from observational studies, probably resulting from confounding and effect modification by inflammation and/or malnutrition.[12, 13] Second, the dyslipidemia that accompanies CKD generally manifests as low HDL-C levels and increased triglycerides.[14] LDL-C levels are typically low, although there may be a predominance of small, dense LDL particles.[15] Third, given the prevalence of structural heart disease, electrolyte imbalances, and volume overload among patients with ESRD, the proportion of cardiovascular events modifiable by statin therapy could be lower than the proportion in the general population. Among prevalent dialysis patients in 2005-2007, 26.3% of all deaths resulted from arrhythmia/cardiac arrest, 5.7% from acute myocardial infarction (MI), 5.3% from congestive heart failure, 4.0% from stroke, and 2.4% from other cardiac causes.[16]

On this background, the Clinical Trial Service Unit (CTSU) of Oxford University designed and initiated the Study of Heart and Renal Protection (SHARP), funded by an unrestricted grant from Merck Schering-Plough. The primary aim of SHARP was to assess the effects of lowering LDL-C on the time to a first "major vascular event" (defined as nonfatal myocardial infarction or cardiac death, nonfatal or fatal stroke, or revascularization) among patients with moderate to severe kidney disease (~6000 pre-dialysis and 3000 dialysis at baseline). Because patients with CKD typically do not have high LDL-C levels, the investigators anticipated that high-dose statin therapy would be necessary to achieve an average absolute LDL-C reduction of 1 mmol/L (~40 mg/dL). Because of a concern for muscle toxicity with a high-dose statin regimen, the investigators chose to use ezetimibe/simvastatin (10 mg/20 mg) as the lipid-lowering strategy in SHARP. Furthermore, this trial was designed to test the secondary hypothesis that reducing

lipid levels slows progression to ESRD.[17] SHARP was initiated in June 2003 and completed in August 2010.

While SHARP was ongoing, two randomized controlled trials of statin therapy for patients treated with hemodialysis were completed: 4D and AURORA.[18, 19] Table 1 summarizes these trials.

The Die Deutsche Diabetes Dialyse Studie (4D study) compared the effects of atorvastatin (20 mg once daily) with placebo on survival and cardiovascular events in patients with type 2 diabetes receiving maintenance hemodialysis. This multicenter, randomized, double-blind, placebo-controlled trial assigned 1255 patients with LDL 80-190 mg/dL to atorvastatin or placebo and followed them for a median 4.0 years. The primary endpoint was the time to death from cardiac causes, nonfatal MI, or stroke. Death from cardiac causes comprised fatal MI (including death within 28 days after an MI), sudden death, death resulting from congestive heart failure (CHF), death due to coronary heart disease (CHD) during or within 28 days after an intervention, and all other deaths attributed to CHD. At baseline, the mean age was 66 years, the mean time treated with dialysis was 8.3 months, mean LDL was 126 mg/dL, 19% were taking statins before entering the study, and 29% had a history of MI, revascularization, or coronary heart disease. The cumulative incidence of the primary composite endpoint was 37% in the atorvastatin group and 38% in the placebo group; time-to-event analysis demonstrated a non-significant relative risk reduction of 8% (HR 0.92; 95% CI 0.77-1.10; p=0.37). Examining the components of a non-significant composite endpoint should be considered exploratory and hypothesis-generating only, but the risk of fatal stroke was higher in the atorvastatin group (HR 2.03; 95% CI 1.05-3.93; p=0.04), the risk of nonfatal stroke was similar between groups (HR 1.04; 95% CI 0.64-1.69; p=0.89), and the risk of all cardiac events combined (death from cardiac cause, nonfatal MI, PTCA, CABG, other CHD interventions) was lower in the atorvastatin group (HR 0.82; 95% CI 0.68-0.99; p=0.03).[18]

AURORA ("**A** study to evaluate the **U**se of **R**osuvastatin in subjects **O**n **R**egular haemodialysis: an **A**ssessment of survival and cardiovascular events") compared the effects of rosuvastatin (10 mg once daily) with placebo on survival and cardiovascular events in patients receiving hemodialysis who had not taken statins in the preceding 6 months. This multicenter, randomized, double-blind, placebo-controlled trial assigned 2776 patients to rosuvastatin or placebo and followed them for a median 3.8 years. The primary endpoint was the time to nonfatal MI, nonfatal stroke, or death from cardiovascular causes. Death from cardiovascular causes comprised death resulting from definite or suspected CHD, sudden and unexpected death, fatal stroke, other cardiac deaths, and death resulting from other vascular causes. At baseline, the mean age was 64 years, the mean time receiving dialysis was 3.5 years, mean LDL was 100 mg/dL, 26% had diabetes, and clinical histories included cardiovascular disease (40%), myocardial infarction (10%), and coronary revascularization (6%). The cumulative incidence of the primary composite endpoint was 28.5% in the rosuvastatin group and 29.5% in the placebo group; time-to-event analysis demonstrated a non-significant relative risk reduction of 4% (HR 0.96; 95% CI 0.84-1.11; p=0.59). Exploratory analyses of endpoint components suggested no significant treatment effects on stroke (nonfatal or fatal), atherosclerotic cardiac events, or revascularization.[19]

Table 1. Summary of Randomized Controlled Trials of Statins in ESRD Prior to SHARP

Trial	ITT Population	Intervention	Median Duration	LDL Reduction	Primary Composite Endpoint	Primary Result
4D	N=1255 Type 2 DM, ESRD on HD < 2 yrs, LDL 80-190 mg/dL	atorvastatin 20 mg daily (reduce 50% if LDL < 50 mg/dL) vs. placebo (random dose reductions to maintain blind)	4.0 y	At 4wks: atorva: median -42% from baseline (median 121 to 72 mg/dL) placebo: median -1.3% from baseline (median 125 to 120 mg/dL)	Nonfatal MI (including silent) Stroke Death from cardiac cause (includes sudden death)	Atorva: 226 events (37%) Placebo: 243 events (38%) HR 0.92 (0.77-1.10); p=0.37
AURORA	N=2773 ESRD on HD, no statin x 6 mo	rosuvastatin 10 mg daily vs. placebo	3.8 y	At 3 mos: rosuva: mean -43% from baseline (mean 100 to 58 mg/dL) placebo: mean -1.9% from baseline (mean 99 to 97 mg/dL)	Nonfatal MI (including silent) Stroke Death from cardiovascular causes (includes sudden death)	Rosuva: 396 events (9.2 events/100 pt-yr) Placebo: 408 events (9.5 events/100 pt-yr) HR 0.96 (0.84-1.11); p=0.59

The failure of these trials to detect a cardiovascular benefit of statins underscored the possibility that results from trials in the general population may not be generalizable to patients with kidney disease, including those with the highest cardiovascular risk. Randomized, controlled trials investigating rosuvastatin in populations with CHF, another "end-stage" condition, also failed to demonstrate a significant treatment effect on their primary endpoints. The CORONA trial randomly assigned 5011 patients ≥60 years old with New York Heart Association (NYHA) class II-IV ischemic, systolic heart failure to daily rosuvastatin 10 mg or placebo. During a median follow-up of 2.75 years, there was a nonsignificant 8% reduction in the relative risk for the primary composite outcome of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (HR 0.92; 95% CI 0.83-1.02; P=0.12). A similar nonsignificant 8% reduction in the relative risk for any coronary event was observed (HR 0.92; 95% CI 0.82-1.04; P=0.18).[20] The Italian GISSI-HF trial randomly assigned 4574 adults with NYHA class II-IV heart failure, regardless of cause, to daily rosuvastatin 10 mg or placebo. During a median follow-up of 3.3 years, rosuvastatin did not demonstrate a reduction in the relative risk of the co-primary endpoints of all-cause death and all-cause death or admission for cardiovascular reasons. Furthermore, among the secondary outcomes, rosuvastatin did not demonstrate benefit with regard to MI (adjusted HR 0.89; 95% CI 0.63-1.27; P=0.52) or stroke (adjusted HR 1.23; 95% CI 0.89-1.70; P=0.21).

Ezetimibe (ZETIA) and Ezetimibe/Simvastatin (VYTORIN)

In the United States, ZETIA was initially approved in October 2002 and VYTORIN was initially approved in July 2004. Both agents were approved based on their ability to modulate various lipid parameters; neither has an indication to reduce cardiovascular morbidity or mortality.

Furthermore, the VYTORIN label specifically highlights the limitation that "no incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established."

The lack of clinical outcomes data for ZETIA and VYTORIN has been the focus of controversy, and the publication of the ENHANCE and SEAS trials in 2008 stimulated much debate. ENHANCE was a multicenter, double-blind, randomized, placebo-controlled trial in which 725 adults with heterozygous familial hypercholesterolemia were assigned to daily simvastatin (80 mg) in combination with either placebo or ezetimibe (10 mg). The primary outcome was the change in the mean carotid-artery intima-media thickness (CIMT) from baseline to 24 months. By 24 months, mean LDL had decreased from 318 mg/dL to 193 mg/dL (-39%) in the simvastatin-only group and from 319 mg/dL to 141 mg/dL (-56%) in the ezetimibe/simvastatin group. Despite the incremental LDL reduction with the addition of ezetimibe, this trial failed to detect a statistically significant difference in CIMT at 24 months (mean change from baseline: 0.0058±0.0037 mm vs. 0.0111±0.0038 mm for simvastatin monotherapy and ezetimibe/simvastatin, respectively; p=0.29). Despite several reasonable hypotheses to explain this result, the possibility remains that lowering LDL with ezetimibe/simvastatin yields outcomes distinct from lowering LDL with simvastatin alone. The ongoing IMPROVE-IT trial is examining whether treatment with VYTORIN reduces the risk for cardiovascular events compared with simvastatin alone in patients post acute coronary syndrome.[21] The estimated completion date of IMPROVE-IT is June 2013 (ClinicalTrials.gov NCT00202878).

SEAS was a multicenter, double-blind, randomized, placebo-controlled trial in which 1873 adults with mild-to-moderate, asymptomatic aortic stenosis were assigned to daily ezetimibe/simvastatin (10/40 mg) or placebo. Among the exclusion criteria were diabetes mellitus, current lipid-lowering therapy, and established coronary, cerebral, or peripheral vascular disease. The primary composite outcome of major cardiovascular events included death from cardiovascular causes, aortic-valve replacement, congestive heart failure resulting from progression of aortic-valve stenosis, nonfatal MI, hospitalization for unstable angina, CABG, PCI, or nonhemorrhagic stroke. By 8 weeks, mean LDL had decreased from 140 mg/dL to 53 mg/dL (-61%) in the ezetimibe/simvastatin group. During a median follow-up of 4.4 years, there was no evidence for a statistically significant difference between groups with regard to the primary outcome (HR 0.96; 95% CI 0.83-1.12; p=0.59). There was a suggestion, however, that ezetimibe/simvastatin may reduce the risk of ischemic events, a secondary composite outcome (HR 0.78; 95% CI 0.63-0.97; p=0.02).[22]

Not only did the SEAS trial strengthen the debate questioning the efficacy of ezetimibe to improve clinical outcomes, the trial also called its safety into question by generating the hypothesis that ezetimibe/simvastatin may increase the risk for cancer. Cancer was reported in 105 patients (11.1%) in the ezetimibe/simvastatin group and in 70 patients (7.5%) in the placebo group. In addition, 39 patients (4.1%) died from cancer in the ezetimibe/simvastatin group compared with 23 (2.5%) in the placebo group; this suggested a 67% increase in the relative risk of cancer-related death among those treated with ezetimibe/simvastatin (HR 1.67; 95% CI 1.00-2.79; p=0.05). There was a qualitatively similar imbalance in incident cancer diagnoses.[22] These data seem to conflict with the totality of evidence from randomized trials involving

statins.[9] To test the hypothesis that ezetimibe may increase the risk for cancer, Peto *et al.* analyzed unblinded interim data regarding cancer from 20,617 patients randomized in the ongoing SHARP and IMPROVE-IT[21] trials. During a combined 36,501 person-years, 313 cancers occurred among patients assigned to an ezetimibe-containing regimen and 326 cancers among patients not taking ezetimibe (p=0.61). There was neither a suggestion of site-specificity nor a trend in the relative risk for cancer death over time.[23] Based on a review of these studies, FDA issued a drug safety communication expressing the belief that it is unlikely that VYTORIN or ZETIA increase the risk of cancer or cancer-related death (22 December 2009). In addition to SHARP, the ongoing IMPROVE-IT trial will provide additional data to further assess cancer risk of ezetimibe.

Summary

At the time SHARP was designed, both observational data and the exclusion of patients with CKD/ESRD from previous statin trials supported an environment of clinical equipoise regarding the risk/benefit of lipid-lowering therapy in kidney disease. While SHARP was ongoing, the publication of 4D and AURORA – the only large randomized controlled trials of statins in hemodialysis patients – suggested that patients with ESRD may not experience similar benefit from statin therapy. It remained unknown, however, whether lipid-lowering therapy could improve clinical outcomes if initiated at earlier stages of CKD. SHARP was poised to answer this question, since the majority (2/3) of patients were recruited before they progressed to ESRD. The choice to compare ezetimibe/simvastatin with placebo does not shed light on the potential incremental benefit of adding ezetimibe to simvastatin. Nevertheless, SHARP provides the first randomized controlled evidence of cardiovascular benefit for ezetimibe-containing regimens.

Currently Available Treatments for Proposed Indications

No currently available treatments are specifically indicated to reduce cardiovascular events in patients with CKD. Six of the seven marketed statins have indications for primary and/or secondary prevention of cardiovascular events; only pitavastatin (approved 3 August 2009) does not.

SHARP: Study for Heart and Renal Protection

The remaining portion of this briefing document describes the design, conduct, and results from the SHARP trial. Table 2 presents a summary of the trial design for reference.

Table 2. Summary of SHARP Design and Objectives

Study & Location	Study Design Dose Duration	Population	Objectives
SHARP 380 sites in 18 countries	Double-blind, randomized*, placebo-controlled Year 1: placebo vs. ezetimibe/simvastatin 10/20 mg vs. simvastatin 20 mg QD (4:4:1) After Year 1: placebo vs. ezetimibe/simvastatin 10/20 mg QD; simvastatin-only group from 1st year re-randomized 1:1 Median 4.9 y follow-up * Minimization algorithm combined with a 10% random element	Age ≥40 y with advanced CKD (Men: Cr ≥150 μmol/L [≥1.7 mg/dL]; Women: Cr ≥130 μmol/L [≥1.5 mg/dL]) with no known history of MI or coronary revascularization. ~2/3 pre-dialysis, ~1/3 ESRD 11,792 screened 9,438 1st randomization 9,270 2nd randomization	Effect of ezetimibe/simvastatin vs. placebo on Primary (Arm 1 vs. Arm 2) • time to 1st "major vascular event" (nonfatal MI or cardiac death, nonfatal or fatal stroke, or any revascularization excluding dialysis access procedures. Secondary (Arms 1+3a vs. Arms 2+3b) • progression to ESRD • various causes of death • major cardiac events (nonfatal MI or cardiac death) • stroke (overall and subtypes) • hospitalization for angina • major vascular outcomes among subgroups Tertiary (Arms 1+3a vs. Arms 2+3b) • Hospital admission for heart failure • Site-specific cancers • Development of diabetes • Revision of dialysis access • Various other reasons for hospital admission

Trial Organization, Objectives, and Design

This section presents the objectives, study design, eligibility criteria, study conduct, and analytical plans for the SHARP trial as specified in the protocol and/or specific operating procedures submitted by the applicant, unless noted otherwise.

Trial Organization

SHARP was coordinated by the International Coordinating Center (ICC) based at the Clinical Trial Service Unit of Oxford University and six Regional Coordinating Centers (RCCs). Each RCC provided administrative support to Local Clinical Centers (LCCs) in their region. In countries without an RCC, a member of the SHARP Steering Committee served as a "National Coordinator" liaison with the relevant regulatory authority in the country. Each LCC identified a lead investigator (senior nephrologist or physician) and a research nurse (or medically qualified research fellow) to identify, recruit, and follow study participants.

SHARP was initiated and designed by the SHARP Steering Committee. A joint venture of Merck and Schering-Plough, which merged in November 2009 under the Merck name, provided an unrestricted grant to the University of Oxford to conduct the trial. The protocol states that the collection, analysis, and publication of data are independent of the source of funding. The SHARP Steering Committee included nephrologists, cardiologists, clinical trialists, and statisticians, with two non-voting observers from Merck.

Table 3 lists milestone dates of the SHARP trial.

Table 3. SHARP Milestones

Study initiation:	25 June 2003
First dose of double-blind study treatment:	20 August 2003
Last participant randomized (1st randomization):	31 August 2006
Steering Committee votes to change primary endpoint:	02 October 2009
Last dose of double-blind study treatment:	18 August 2010
Study completion:	19 August 2010
Statistical analysis plan finalized:	20 August 2010
Last data collection:	31 August 2010
Statistical analysis plan published:	21 September 2010
Unblinding:	07 October 2010
Final database lock:	05 January 2011

Trial Objectives

For each of the following objectives, the target population is patients with CKD, including both pre-dialysis and ESRD.

Primary Objective: To compare the effects of lowering LDL-C with combined simvastatin 20 mg daily and ezetimibe 10 mg daily ("ezetimibe/simvastatin") to placebo on the time to a first "major vascular event" (MVE), defined as nonfatal MI or cardiac death, any stroke, or revascularization (including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation, but excluding vascular access surgery for dialysis).

Secondary Objectives: To assess the effects of ezetimibe/simvastatin on

- progression to end-stage renal disease (ESRD) among pre-dialysis patients

- various causes of death
- major cardiac events (nonfatal MI or cardiac death)
- stroke
- hospitalization for angina
- major vascular events among subgroups of patients

Tertiary Objectives: To assess the effects of ezetimibe/simvastatin on

- hospitalization for heart failure
- site-specific cancers
- revision of vascular access for dialysis
- various other reasons for hospitalization

The SHARP investigators also aimed to obtain additional information regarding the safety of adding ezetimibe to simvastatin among patients with CKD by comparing ezetimibe/simvastatin with simvastatin monotherapy after one year of treatment.

Trial Design

SHARP was a multinational, double-blind, placebo-controlled, parallel-group trial that used a minimization algorithm to assign patients with 4:4:1 allocation to one of the following 3 arms for the first year: placebo (Arm 1), ezetimibe/simvastatin 10/20 mg (Arm 2), and simvastatin 20 mg (Arm 3) daily. After 1 year, those receiving simvastatin monotherapy were randomly assigned 1:1 to placebo (Arm 3a) or ezetimibe/simvastatin (Arm 3b) (Figure 1). The trial intended to enroll ~9000 patients with CKD, comprising ~6000 pre-dialysis patients and ~3000 dialysis patients at the time of the first treatment assignment. The trial was scheduled to continue until all patients had at least 4 years follow-up and at least 1100 major vascular events had occurred.

This study design provides very limited information regarding the safety and efficacy of ezetimibe as monotherapy or as add-on therapy to simvastatin. The investigators did not pre-specify any efficacy analyses at one year with the exception of biochemical (lipid) measures.

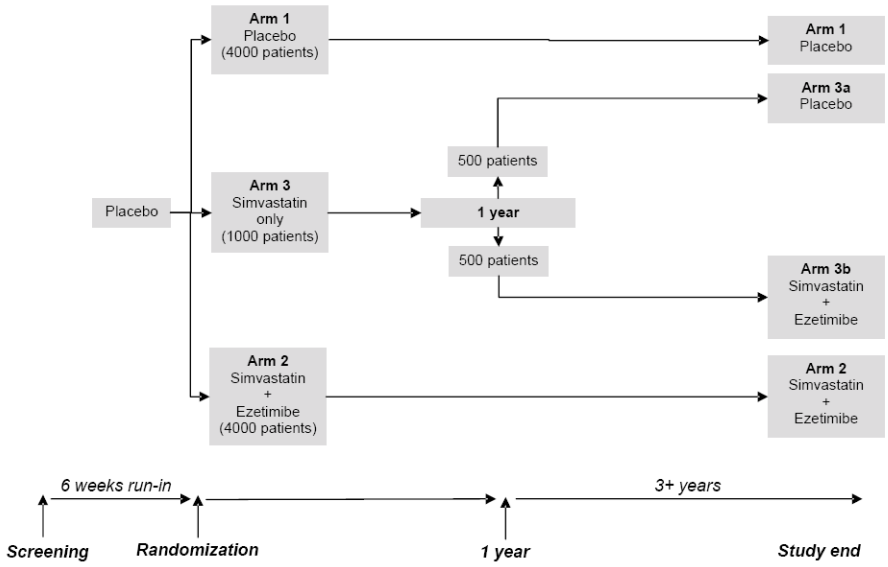


Figure 1. SHARP Study Design
Source: SHARP Protocol v4; 14 July 2003

Trial Population

Patients were eligible for randomization if (1) their nephrologist agreed with their participation after being made aware of the lipid profile results obtained during the screening period and (2) all inclusion/exclusion criteria were satisfied.

Inclusion Criteria

1. History of CKD
    a. Pre-dialysis (plasma or serum creatinine ≥150 μmol/L [≥1.7 mg/dL] in men or ≥130 μmol/L [≥1.5 mg/dL] in women, as measured at the most recent routine clinic visit and at the SHARP Screening Visit)
    b. Dialysis (hemodialysis or peritoneal dialysis)
2. Men or women aged ≥40 years

Exclusion Criteria

1. Definite history of myocardial infarction or coronary revascularization procedure
2. Functioning renal transplant, or living donor-related transplant planned [during the next year]
3. Less than 2 months since presentation as an acute uremic emergency (but may be entered later, if appropriate)
4. Definite history of chronic liver disease, or abnormal liver function (i.e. ALT > 1.5xULN or, if ALT not available at the LCC, AST >1.5xULN). (Note: Patients with a history of hepatitis are eligible provided these limits are not exceeded)
5. Evidence of active inflammatory muscle disease (e.g. dermatomyositis, polymyositis) or CK >3xULN
6. Definite previous adverse reaction to a statin or to ezetimibe

7. Concurrent treatment with a contraindicated drug (Note: Patients who are temporarily taking such drugs may be re-screened when they discontinue them, if appropriate.)
    a. HMG-CoA reductase inhibitor ("statin")
    b. fibric acid derivative ("fibrate")
    c. nicotinic acid
    d. macrolide antibiotic (erythromycin, clarithromycin)
    e. systemic use of imidazole or triazole antifungals (e.g., itraconazole, ketoconazole)
    f. protease inhibitors (e.g. antiretroviral drugs for HIV infection)
    g. nefazodone
    h. cyclosporine
    i. ezetimibe
8. Child-bearing potential (i.e. premenopausal woman who is not using a reliable method of contraception)
9. Known to be poorly compliant with clinic visits or prescribed medication
10. Medical history that might limit the individual's ability to take trial treatments for the duration of the study (e.g. severe respiratory disease, history of cancer other than non-melanoma skin cancer [unless completely free from cancer for at least 5 years], or recent history of alcohol or substance misuse).

Reviewer Comments

1. *Inclusion/exclusion did not depend on any lipid profile characteristics.*
2. *Pre-dialysis patients in this study could have had the following eGFRs (4-variable MDRD) given the sCr-based inclusion criterion:*

    Men: ≤45 mL/min/1.73m^2 (Non-black) Women: ≤33 mL/min/1.73m^2 (Non-black)
    ≤54 mL/min/1.73m^2 (Black) ≤40 mL/min/1.73m^2 (Black)

    Based on prevalence estimates from the National Health and Nutrition Examinations Survey (NHANES III 1999-2000, 2001-02, 2003-05, and 2005-06), approximately 14% of the U.S. population has chronic kidney disease. Patients with eGFR < 45 mL/min compose approximately 2% of the total U.S. population and 14% of the total U.S. CKD population (Table 4).

Table 4. Estimated Percentages of U.S. Population by eGFR and Albuminuria

eGFR	*Albuminuria (mg/g)*				
	<10	*10-29*	*30-299*	*>300*	*Total*
>105	23.6	5.7	1.9	0.1	31.4
90-104	20.0	4.7	1.7	0.3	26.7
75-89	17.3	4.1	1.6	0.2	23.0
60-74	8.2	2.7	1.3	0.1	12.2
45-59	2.5	1.1	0.8	0.2	4.7
30-44	0.6	0.4	0.4	0.2	1.5
15-29	0.1	0.1	0.1	0.1	0.4
<15	0.0	0.0	0.0	0.1	0.1
Total	72.2	18.8	7.8	1.3	100.0

Source: After Levey and Coresh (2011).[24]

The shaded portion (~86% of the US population) represents individuals that would not be classified as CKD according to the NKF or KDIGO definitions.

Study Visits

Identification, Invitation, Screening Visit (-6 weeks), and Placebo Run-in

Local coordinating center (LCC) research nurses identified possible participants from lists of renal consultants, outpatient clinics, hemodialysis units, peritoneal dialysis units, and biochemistry records. Potentially eligible participants were invited to a screening visit. Eligible patients who wished to participate provided written informed consent and initiated a 4- to 8-week placebo run-in period to identify participants who would be most likely to remain adherent with long-term study treatment and follow-up. During the run-in period, a patient's lipid profile was provided to their personal physician(s) so that they could assess the appropriateness of the patient's participation in the trial.

Randomization Visit (Month 0)

Compliant patients who did not experience a vascular event or other significant problems during run-in and were not on a contraindicated drug were asked if they were still willing to take study treatment for at least 4 years. If they were, non-fasting blood samples (and a urine sample for pre-dialysis patients) were collected for central laboratory analysis of lipid profile, creatinine, cystatin C, and urinary albumin:creatinine ratio.

A randomization program on the SHARP laptop assigned a patient to a treatment arm. The randomization procedure involved both a minimization algorithm and simple randomization. Participants had a 90% chance of having treatment assigned by the minimization algorithm and a 10% chance of having it assigned by simple randomization. At the first randomization visit, minimization was performed using both local and global elements. The minimization algorithm intended to produce treatment groups well balanced for the following characteristics:

- Age in 4 categories (40-49, 50-59, 60-69, ≥70 years)
- Sex
- Renal status at randomization visit (pre-dialysis, hemodialysis, peritoneal dialysis)
- Creatinine at screening visit (<200, 200-399, ≥400 μmol/l)
- Presence or absence of diabetes at screening visit (diabetes with vascular disease, diabetes with no vascular disease, no diabetes with vascular disease, no diabetes with no vascular disease)
- Systolic blood pressure at randomization (<140, 140-159 [or null], 160-179, ≥180 mmHg)
- Total cholesterol at screening visit (<3, 3-3.9, 4-4.9, ≥5 mmol/l)
- Ethnic origin at screening visit (White, Black, Asian, Other)

SHARP was double-blind and used a double-dummy technique. For the first year, patients were asked to take one tablet from each of two bottles in the evening (placebo-combination designates a placebo tablet resembling the ezetimibe/simvastatin tablet):

- Arm 1: Placebo (placebo-combination and placebo-simvastatin tablets);

- Arm 2: Ezetimibe/simvastatin 10/20 mg daily (ezetimibe/simvastatin and placebo-simvastatin tablets); or
- Arm 3: Simvastatin 20 mg daily (placebo-combination and simvastatin tablets).

At the first randomization, patients were allocated to Arms 1, 2, and 3 in a 4:4:1 ratio.

Reviewer Comments:

1. *The trial design did not allow for dose titration.*
2. *The Agency agreed that the design of Arm 3 was adequate to identify adverse effects attributable to simvastatin 20 mg or to ezetimibe in patients with CKD (14 November 2002 teleconference). During this meeting, Oxford stated that the simvastatin-only arm was extended only to one year because the number of patients in this arm was not powered for efficacy.*

Post-Randomization Follow-up (2 months, 6 months, and then 6-monthly)
At each follow-up appointment, study personnel collected details of all hospital admissions, other serious adverse events (SAEs), and unexplained muscle pain or weakness. A non-fasting blood sample was taken for measurement of CK, liver transaminase (ALT and/or AST), and creatinine by the local laboratory. Additional urine and non-fasting blood samples were collected from a 10% random sample at years 1 and 4, and from all patients at year 2.5, for central laboratory analysis, including a lipid profile.

All study patients were encouraged to continue attending follow-up visits, regardless of whether they continued study treatment. If a patient became unwilling or unable to attend, the LCC research nurse would telephone the patient at the time of each scheduled follow-up visit and complete the appropriate follow-up forms. If contacting the patient was not possible, the regional coordinating center (RCC) or LCC staff attempted to check a patient's progress by directly corresponding with one of the patient's physicians. Patients who stopped attending study visits were asked to discontinue study treatment because of the inability to monitor safety parameters.

1-year Follow-up Visit: At the 1-year follow-up visit, participants randomized to Arm 3 (simvastatin) were randomly re-allocated 1:1 either to Arm 3a (placebo-combination) or Arm 3b (ezetimibe/simvastatin). All patients discontinued simvastatin or placebo-simvastatin at this follow-up visit, thereby maintaining the blind. Minimization was performed using local elements only.

Reviewer Comment: Only using local-site elements in the minimization algorithm is reflected in the numerical imbalance of the reassignment of Arm 3: 429 patients were assigned to Arm 3a and 457 were assigned to Arm 3b. Also, since the algorithm did not incorporate characteristics of the global trial population when making this reassignment, baseline characteristics would not be as well balanced between Arms 3a and 3b. The study personnel at the local sites would have remained blind to the treatment assignment, however.

Protocol-Specified Study Endpoints & Assessments

This section describes the assessments of outcomes specified in both the SHARP protocol (v4; 14 July 2003) at the time of first randomization and in the statistical analysis plan (SAP), which was finalized 20 August 2010.

At one year, the primary comparison was ezetimibe/simvastatin (Arm 2) vs. simvastatin (Arm 3) with regard to safety outcomes (muscle-related, hepatic, or biliary events). With the exception of assessing changes in laboratory values at one year, efficacy analyses were not planned.

Primary Endpoint (End-of-Study)

The primary comparison pre-specified in the protocol involves a logrank-test-based intention-to-treat (ITT) analysis of *major vascular events (MVE)* during the scheduled treatment period of at least 4 years among ~4000 patients assigned to ezetimibe/simvastatin (Arm 2) vs. ~4000 patients assigned to placebo (Arm 1). This primary analysis does not include patients initially assigned to Arm 3. An MVE is the composite of:

- nonfatal MI or cardiac death (coronary or non-coronary death);
- nonfatal or fatal stroke; or
- revascularization, including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation (but excluding vascular access surgery for dialysis).

Reviewer Comment: Non-coronary death includes the event code "sudden cardiac death" but not "sudden death."

The "key outcome" specified in the SAP involves a logrank-test-based ITT analysis of *major atherosclerotic events (MAE)* during the scheduled treatment period of at least 4 years among ~4500 patients ever assigned to ezetimibe/simvastatin (Arms 2+3b) vs. ~4500 patients ever assigned to placebo (Arms 1+3a). An MAE is the composite of:

- coronary death or MI;
- ischemic stroke; or
- revascularization procedure (as above).

The rationale, timing, and consequences of the change in the primary comparison are discussed below (see "Statistical Analysis Plan").

Other End-of-Study Assessments

Both the protocol and the SAP planned to conduct all other analyses using the entire study population, i.e., ~4500 patients ever assigned to ezetimibe/simvastatin (Arms 2+3b) vs. ~4500 patients ever assigned to placebo (Arms 1+3a). The Appendix (p. 104) contains a comprehensive listing of the endpoints and subgroups identified in the protocol and/or SAP.

Reviewer Comment: In a 14 November 2002 teleconference between MSP, Oxford, and FDA, the Agency asked why secondary endpoints would be assessed in all 9000 patients instead of the 8000 patients used in the primary analysis. The sponsor stated that they would test for homogeneity between the 8000 and 1000 patient groups before combining the groups. The

intention of using the larger sample size was "to increase the power to compare the efficacy of the combination versus placebo."

Biochemical Efficacy
Biochemical efficacy was assessed in a 10% random sample of patients at 1 year and at 4 years, and in all patients at 2.5 years (the anticipated midpoint of the study). The planned analyses included the effects of ezetimibe/simvastatin vs. placebo on total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides, apolipoprotein B, apolipoprotein A_1, proteinuria (albumin:creatinine ratio), and creatinine.

SAP-specified Safety Outcomes
In addition to the efficacy and safety outcomes listed previously, the SAP specified safety assessments for muscle-related outcomes, liver-related outcomes, complications of gallstones, and pancreatitis. These are further described with the safety analyses in this document.

Trial Methods

Adjudication Procedures

Adjudication procedures are relevant to both safety and efficacy endpoints in the SHARP trial. According to the protocol, the LCC research nurse was to seek additional information from hospital records and other sources regarding SAEs reported as myocardial infarction, angina, heart failure, stroke, TIA, revascularization procedure (excluding dialysis access procedures), angiography, amputation, initiation of dialysis, kidney transplantation, cancer, rhabdomyolysis, hepatitis, or gallbladder disease. The LCC lead investigator was responsible for reviewing and confirming these events. A central Outcomes Adjudication Panel would then review, blind to treatment allocation, the following LCC-investigator-confirmed outcomes:

- specified causes of all deaths
- myocardial infarction
- angina
- stroke
- revascularization procedure (excluding dialysis access procedures)
- amputation
- initiation of dialysis
- kidney transplantation
- cancer
- rhabdomyolysis
- hepatitis
- gallbladder disease (i.e., cholecystectomy or complications of gallstones)

In addition, events with descriptions that may have corresponded to an outcome of interest were reviewed. For example, "chest pain/tightness" and "transient ischemic attack" would have been referred for adjudication to rule out myocardial infarction and stroke, respectively.

Event adjudication was carried out by medically qualified staff working under the direction of the Clinical Coordinator at CTSU. In addition to being blind to treatment allocation, references to lipid-lowering treatment or blood cholesterol were removed by LCC staff before sending documentation to the ICC. The ICC verified appropriate anonymization before scanning the records into the system used by clinical adjudicators.

The Appendix (p. 107) includes a summary of criteria for adjudicated events.

Protocol-specified Statistical Considerations

The initial power calculation for SHARP used the following assumptions:

- Expected mean rate of 3.7% per year for the primary outcome
  - Assumes 3% and 5% per year (based on observational data and "healthy volunteer" selection bias) for 6000 pre-dialysis and 3000 dialysis patients, respectively, and 2:1 enrollment of these populations
- Allocation to ezetimibe/simvastatin might be expected to produce a 20% reduction in major vascular events during the study
  - Assumed that ezetimibe/simvastatin would lower LDL-C, on average, 1 mmol/L compared to placebo (allows for some nonadherence to study treatment)
  - Assumed that 80% of non-CHD cardiac events would be modifiable by lowering cholesterol

To have 90% power to detect a 20% proportional reduction in major vascular events with a two-sided type I error rate < 1%, SHARP was scheduled to continue until all patients were followed for at least 4 years and ≥1100 major vascular events had occurred. The protocol allowed the Steering Committee to modify recruitment or the follow-up duration based on review of the blinded rate for major vascular events during follow-up and the unblinded differences in blood lipids observed between the treatment groups.

Regarding the secondary endpoint of progression to ESRD among patients with CKD, the cumulative incidence of ESRD in the placebo arm was expected to be ~20% by the end of the study based on the UK-HARP-I[25] pilot and the RENAAL[26] trial. SHARP, therefore, would have >95% power to detect a 20% proportional reduction in the risk of ESRD with a two-sided type I error rate < 1%.

Reviewer Comment: The rationale for the targeted 2:1 enrollment of pre-dialysis and dialysis patients was not stated.

Statistical Analysis Plan (SAP)

The SHARP SAP was finalized on 20 August 2010 and published 21 September 2010. The trial was unblinded on 07 October 2010, and the database was locked on 05 January 2011.

As previously mentioned, the protocol-specified primary composite endpoint was time to first major vascular event (MVE), comprising major cardiac events (nonfatal MI or cardiac death), any stroke, or revascularization (including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation, but excluding vascular access surgery for dialysis).

On 02 October 2009, the SHARP Steering Committee discussed emerging results from other trials (hemodialysis: 4D, AURORA; heart failure: CORONA, GISSI-HF) that suggested lipid-lowering therapy may not affect non-coronary cardiac deaths in all populations. Furthermore, the updated Cholesterol Treatment Trialists' meta-analysis suggested that LDL lowering does not reduce the risk of hemorrhagic stroke. These findings countered the original assumption that lipid-lowering therapy could modify 80% of non-coronary cardiac deaths.

There was widespread agreement that the inclusion of these presumably unmodifiable events would decrease the trial's power, but several members of the Committee expressed concern regarding the perception of a change in the primary endpoint. The committee ultimately voted to change the primary outcome from MVE to "major atherosclerotic events" (MAE), which excludes non-coronary cardiac death and hemorrhagic stroke from the original MVE endpoint.

Although Merck did not disagree with the scientific arguments for changing the primary endpoint, Merck declined Oxford's request given concerns regarding late-stage changes to the primary endpoint of an outcomes study. To reconcile these differences in opinion, the Oxford investigators wrote a SAP specifying that the chief emphasis of the analyses would be the "Key Outcome" of *MAE in all patients ever randomized to ezetimibe/simvastatin 10/20 mg versus all patients ever randomized to placebo* (Arms 2+3b vs. Arms 1+3a), with the primary endpoint as defined in the original protocol retained as one of the subsidiary analyses.

Table 5. Comparison of Main Outcomes

Main Outcome	Protocol Primary Comparison	SAP 'Key Outcome'
Composite Endpoint	Major vascular events (MVE)	Major atherosclerotic events (MAE)
Endpoint Components	Major *cardiac* events: MI, *cardiac* death	Major *coronary* events: MI, *coronary* death
	Any stroke	*Ischemic* stroke
	Any revascularization procedure	Any revascularization procedure
Population Analyzed	*Excludes* patients initially randomized to simvastatin. (Arm 2 versus Arm 1, total N=8,384)	*Includes* 886 initially randomized to simvastatin. (Arm 2+3b versus Arm 1+3a, total N=9,270)
MVE/MAE Differences	*Includes* non-coronary cardiac death and hemorrhagic stroke; *excludes* patients initially randomized to simvastatin	*Excludes* non-coronary cardiac death and hemorrhagic stroke; *includes* patients initially randomized to simvastatin

Source: Clinical Study Report (CSR) Table 7-2.

The decision to change the population analyzed (Protocol: Arm 2 vs. Arm 1; SAP: Arms 2+3b vs. Arms 1+3a) also resulted from mid-trial information: An unblinded review of the between-group LDL-C differences at 2.5 years revealed a mean LDL reduction of 33 mg/dL rather than the expected 39 mg/dL. Combined with the concern that LDL-lowering therapy may not influence ~30% of observed cardiac events, the investigators had concern for an unacceptable probability of type II error, which could be reduced by including the patients originally assigned to simvastatin monotherapy to increase the sample size.

Reviewer Comments:

1. *The protocol pre-specified, "Based on review of the blinded rate for major vascular events during follow-up, and the unblinded differences in blood lipids observed between the treatment groups, the Steering Committee may modify recruitment or the follow-up duration."*
2. *Combining Arms 3a and 3b with Arms 1 and 2 has the potential to reduce the relative treatment effect of ezetimibe/simvastatin compared with placebo (e.g., it should reduce the between-group difference in mean LDL-C for a period of time). The analyses involving the entire trial population adjust for this exposure to simvastatin (stratified log-rank analyses). If one considers the one-year adherence to simvastatin as a "baseline" characteristic, since time-at-risk for these patients starts at the time of re-assignment to ezetimibe/simvastatin or placebo, the effects of this initial assignment should be near-randomly distributed to Arms 1 and 2. Therefore, although this could conceivably affect the relative treatment effect between ezetimibe/simvastatin compared with placebo, it is unlikely to introduce differential bias.*

Table 6. Mid-Trial Power Calculations

Outcome	Anticipated Proportional Reduction*	n†	Expected No. of Events (Active Versus Placebo)‡	Power at α≤0.01 (2-Sided)
Major Vascular Events (MVE)	**13%**	**~8400**	**737 vs. 845**	**66%**
	13%	~9400	807 vs. 927	72%
Major Atherosclerotic Events (MAE)	18%	~8400	525 vs. 639	84%
	18%	**~9400**	**576 vs. 701**	**88%**

*Treatment effects estimated using data from the Cholesterol Treatment Trialists' Collaboration.
†Sample size is increased from ~8,400 to ~9,400 by the inclusion of patients randomized to simvastatin only for the first year and subsequently randomized to ezetimibe/simvastatin versus placebo. For these patients, events are only counted in the primary outcome if they occur after the second randomization.
‡Based on blinded outcome event rates in November 2009.
The protocol-specified primary endpoint and the SAP-specified 'key outcome' are shown in bold font.

Source: CSR Table 9-4.

The SAP was published on 21 September 2010 prior to unblinding individual patient-outcome data. Group-level unblinding had been performed by the study statistician for the purposes of

assessing between-group lipid differences and publishing one-year safety data, but outcome endpoints remained blinded.

Therefore, the protocol and SAP are discordant. Because Merck declined to agree with the modification of the primary endpoint, it considers itself bound to the protocol-specified endpoint of major vascular events for the purpose of seeking a new indication.

Reviewer Comments:

(b) (4)

Briefly, the SAP stated that analyses would be ITT comparisons (log-rank methods) of all patients ever assigned to ezetimibe/simvastatin vs. all patients ever assigned to placebo. All analyses would be stratified by whether patients were originally allocated to ezetimibe/simvastatin vs. placebo (Arm 2 vs. Arm 1) or were initially allocated simvastatin for 1 year (Arm 3b vs. Arm 3a). Tests for heterogeneity would be used to determine whether the treatment effects in various subgroups were different from the overall effect. Assessing for a linear trend in proportional effects would be performed if subgroups could be arranged in a meaningful order (e.g., stages of baseline renal function). The key outcome of MAE and the protocol-specified analysis of MVE would be assessed without adjustment for multiple comparisons. The subsidiary analyses of the separate components of MAEs would adjust for multiplicity using the Hochberg procedure.

Data and Safety Monitoring

The Data Monitoring Committee (DMC) was tasked with advising the Steering Committee if, in their view, "the randomized comparisons in SHARP have provided **both** (i) 'proof beyond reasonable doubt' that for all, or some specific types, of patient, prolonged use of ezetimibe/simvastatin is clearly indicated or clearly contraindicated in terms of a net difference in time to death; **and** (ii) evidence that might reasonably by expected to influence materially the patient management of many clinicians who are already aware of the main results of any other trials." In response, the Steering Committee could decide whether to modify the study or seek additional data.

The SHARP Clinical Study Report (CSR) states that there were no interim analyses conducted on the primary efficacy endpoint.

Reviewer Comments:

(b) (4)

[redacted]

Categorization of Adverse Events

In the SHARP trial, only serious adverse events (SAEs) were recorded. SAEs were defined as any adverse events that resulted in death, were life-threatening, required hospitalization or prolonged a hospitalization, resulted in persistent or significant disability or incapacity, resulted in congenital anomaly or birth defect, or were deemed important medical events. Important medical events included cancers, cholecystectomy or complications of gallstones, rhabdoymyolysis (CK >40xULN), myopathy (CK >10xULN and ≤40xULN associated with unexplained muscle pain or weakness), or hepatitis. In addition, at each study visit, participants were specifically asked whether they had experienced an episode of unexplained muscle pain or weakness since the last visit. Other non-serious AEs were not routinely captured.

CTSU has developed their own method of collection and categorization of adverse events. Verbatim terms for adverse events were not collected for the majority (~90%) of events; instead, study personnel selected an event description from a "pick tree" of approximately 800 event descriptions on the study laptop, grouped either by system or by cancer. For the remaining ~10%, study personnel wrote in an event description as free text. Coordinating clinicians reviewed these free text entries and assigned an appropriate event code. CTSU believes that the hierarchical menu of event codes allows the research nurse at the point-of-care to select the most detailed event code appropriate to describe a patient's adverse event.

Further descriptions of the definitions of safety events and their adjudication are presented in the Safety section of this document (p. 75).

Reviewer Comment: In this reviewer's opinion, whether computer-guided selection of adverse event codes leads to a more accurate description of adverse events, without introducing bias, than the recording of event descriptions (verbatim terms) with subsequent recoding is a hypothesis worth testing.

Demographics & Other Subject Characteristics

As discussed above, SHARP involved a second randomization for patients initially assigned to simvastatin (Arm 3). Table 7 presents baseline characteristics across treatment group for both initial randomization and final randomization, since each of these times can define the beginning of the follow-up period, depending on the analysis:

- For the primary efficacy analysis, which only includes Arms 1 and 2 (i.e., patients initially assigned to either placebo or ezetimibe/simvastatin, respectively, and kept on the same treatment for the duration of the trial), the "baseline" characteristics of the patients are best described by Arms 1 and 2 at "initial randomization." Note that for these patients, initial randomization is the same as their final randomization.

- For analyses involving "Year 1" comparisons (Arms 1, 2, and 3), the baseline characteristics of the patients are best described by the values at initial randomization.

- For analyses involving all patients *ever* randomized to ezetimibe/simvastatin or placebo (i.e., Arms 1+3a vs. 2+3b), the follow-up time begins at the time of randomization to ezetimibe/simvastatin or placebo for each patient. Thus, for ~90% of the patients (Arms 1 and 2), initial randomization is the same as their final randomization. For the ~10% of patients who were reassigned after approximately one year of simvastatin monotherapy, follow-up begins at their re-randomization ("final randomization"). Therefore, the baseline characteristics of this study population are best described by the values at final randomization.

Any available measurements or events that occurred between first and final randomization for Arm 3 subjects were used in the calculation of baseline characteristics in the "final randomization" columns (denoted with ‡) with the exception of lipid values. Because only 10% of the trial population had lipids measured at year 1, it was decided that the lipid values "at final randomization" should represent the untreated lipid characteristics for Arms 1+3b and 2+3a.

Reviewer Note to Aid Interpretation: From a practical standpoint, one will note few differences between characteristics at initial randomization and at final randomization. This is a consequence of the fact that these times are equivalent for 90% of trial participants. Although the phrase "at final randomization" is sometimes used within this document for brevity, it may be helpful to consider that this is synonymous with "at the time of randomization to ezetimibe/simvastatin or placebo."

Table 7. Baseline Characteristics

	Initial Randomization			Final Randomization	
Characteristic	**Eze/Sim Arm 2 N=4193**	**Simva Alone Arm 3 N=1054**	**Placebo Arm 1 N=4191**	**Eze/Sim Arms 2+3b N=4650**	**Placebo Arms 1+3a N=4620**
Age (y)‡	61 (12)	61 (12)	61 (12)	61 (12)	62 (12)
40-49	865 (21%)	211 (20%)	848 (20%)	968 (21%)	908 (20%)
50-59	1037 (25%	266 (25%)	1039 (25%)	1161 (25%)	1149 (25%)
60-69	1123 (27%)	280 (27%)	1131 (27%)	1226 (26%)	1246 (27%)
≥70	1168 (28%)	297 (28%)	1173 (28%)	1295 (28%)	1317 (29%)
Male	2626 (63%)	656 (62%)	2618 (62%)	2915 (63%)	2885 (62%)
Race					
White	3006 (72%)	755 (72%)	3012 (72%)	3332 (72%)	3314 (72%)
Black	129 (3%)	27 (3%)	120 (3%)	137 (3%)	127 (3%)
Asian	932 (22%)	242 (23%)	936 (22%)	1043 (22%)	1043 (23%)
Other	116 (3%)	26 (2%)	109 (3%)	127 (3%)	120 (3%)
Diabetes‡	951 (23%)	240 (23%)	935 (22%)	1051 (23%)	1036 (22%)
Prior Vascular Disease‡					
Coronary disease	138 (3%)	39 (4%)	122 (3%)	169 (4%)	142 (3%)
Peripheral arterial disease	276 (7%)	62 (6%)	272 (6%)	304 (7%)	300 (6%)
Cerebrovascular disease	303 (7%)	77 (7%)	281 (7%)	337 (7%)	314 (7%)
≥1 of the above 3	633 (15%)	158 (15%)	608 (15%)	711 (15%)	682 (15%)
Renal Disease Etiology					
Diabetic nephropathy	625 (15%)	167 (16%)	602 (14%)	695 (15%)	668 (14%)
Glomerulonephritis	705 (17%)	178 (17%)	665 (16%)	790 (17%)	730 (16%)
Secondary GN / Vasculitis	112 (3%)	13 (1%)	100 (2%)	119 (3%)	103 (2%)
TIN/Pyelonephritis	395 (9%)	98 (9%)	406 (10%)	430 (9%)	454 (10%)
HTN/Lg Vessel Disease	786 (19%)	221 (21%)	809 (19%)	882 (19%)	902 (20%)
Cystic, Hereditary, or Congenital	526 (13%)	136 (13%)	569 (14%)	590 (13%)	621 (13%)
Neoplasms/Tumors	52 (1%)	10 (1%)	42 (1%)	57 (1%)	44 (1%)
Miscellaneous	312 (7%)	78 (7%)	316 (8%)	344 (7%)	350 (8%)
Unknown/Missing	680 (16%)	153 (15%)	682 (16%)	743 (16%)	748 (16%)
Smoking Status					
Current	556 (13%)	151 (14%)	550 (13%)	626 (13%)	608 (13%)
Former	1479 (35%)	368 (35%)	1488 (36%)	1639 (35%)	1633 (35%)
Systolic BP (mmHg) ‡	139 (22)	139 (22)	139 (22)	139 (22)	139 (22)
Diastolic BP (mmHg)‡	79 (13)	79 (12)	79 (13)	79 (13)	79 (13)
BMI (kg/m^2) ‡	27.1 (5.7)	27.1 (5.4)	27.1 (5.6)	27.1 (5.7)	27.1 (5.6)
≤25	1637 (39%)	378 (36%)	1597 (38%)	1795 (39%)	1755 (38%)
>25 and ≤30	1497 (36%)	397 (38%)	1520 (36%)	1674 (36%)	1667 (36%)
>30	973 (23%)	255 (24%)	984 (23%)	1085 (23%)	1101 (24%)
Waist circ (cm) ‡	97 (15)	97 (15)	97 (15)	97 (15)	97 (15)
Renal Status‡					
CKD	2831 (68%)	714 (68%)	2837 (68%)	3112 (67%)	3125 (68%)
Functioning transplant	0	0	1	5 (0.1%)	5 (0.1%)
Hemodialysis	1138 (27%)	283 (27%)	1135 (27%)	1275 (27%)	1252 (27%)
Peritoneal dialysis	224 (5%)	57 (5%)	219 (5%)	258 (6%)	238 (5%)
On dialysis (subtotal)	1362 (32%)	340 (32%)	1354 (32%)	1533 (33%)	1490 (32%)

(Continued on next page)

Characteristic	Initial Randomization			Final Randomization	
	Eze/Sim Arm 2 N=4193	Simva Alone Arm 3 N=1054	Placebo Arm 1 N=4191	Eze/Sim Arms 2+3b N=4650	Placebo Arms 1+3a N=4620
Co-Medication‡					
Antiplatelet	940 (22%)	228 (22%)	932 (22%)	1056 (23%)	1049 (23%)
Oral anticoagulant	137 (3%)	29 (3%)	153 (4%)	156 (3%)	165 (4%)
ACE/ARB	2275 (54%)	585 (56%)	2255 (54%)	2531 (54%)	2499 (54%)
Beta blocker	1533 (37%)	389 (37%)	1620 (39%)	1716 (37%)	1798 (39%)
CCB	1760 (42%)	439 (42%)	1682 (40%)	1968 (42%)	1873 (41%)
Diuretic	1768 (42%)	396 (38%)	1724 (41%)	1942 (42%)	1890 (41%)
ESA	1125 (27%)	301 (29%)	1087 (26%)	1293 (28%)	1218 (26%)
Sevelamer	349 (8%)	76 (7%)	329 (8%)	385 (8%)	358 (8%)
Labs					
Serum Cr (mg/dL)*‡	2.5 [1.9-3.6]	2.4 [1.9-3.6]	2.5 [1.9-3.5]	2.5 [1.9-3.6]	2.5 [1.9-3.5]
Cystatin C (g/L)*‡	2.4 [1.8-3.2]	2.3 [1.8-3.1]	2.4 [1.8-3.1]	2.3 [1.8-3.1]	2.3 [1.8-3.1]
eGFR (MDRD)*§‡	25.5 [16.9-34.7]	25.8 [16.4-34.6]	25.7 [16.9-34.5]	25.5 [16.8-34.7]	25.6 [16.9-34.7]
≥60	40 (1%)†	15 (2%)†	35 (1%)†	44 (1%)†	46 (1%)†
≥45 and <60	134 (5%)	24 (3%)	143 (5%)	147 (5%)	161 (5%)
≥30 and <45	908 (32%)	227 (32%)	849 (30%)	998 (32%)	932 (30%)
≥15 and <30	1177 (42%)	303 (42%)	1244 (44%)	1292 (41%)	1364 (44%)
<15	570 (20%)	145 (20%)	563 (20%)	634 (20%)	624 (20%)
Urine alb/Cr (mg/g)*‡	225 [44-811]	200 [39-746]	201 [45-756]	217 [44-788]	196 [43-748]
<30	492 (17%)†	136 (19%)†	497 (18%)†	545 (17%)†	562 (18%)†
30-300	923 (33%)	228 (32%)	977 (34%)	1032 (33%)	1076 (34%)
>300	1112 (39%)	264 (37%)	1053 (37%)	1203 (39%)	1156 (37%)
Missing	304 (11%)	86 (12%)	310 (11%)	337 (11%)	336 (11%)
Total chol. (mg/dL)	189 (47)	188 (44)	190 (45)	189 (46)	190 (45)
≥200	1512 (36%)	370 (35%)	1535 (37%)	1668 (36%)	1696 (37%)
LDL-C (mg/dL)	108 (34)	107 (33)	108 (33)	107 (34)	108 (33)
<70	507 (12%)	123 (12%)	463 (11%)	556 (12%)	506 (11%)
≥70 and <100	1257 (30%)	326 (31%)	1249 (30%)	1402 (30%)	1384 (30%)
≥100 and <130	1320 (32%)	348 (33%)	1349 (32%)	1479 (32%)	1492 (32%)
≥130	934 (22%)	216 (20%)	953 (23%)	1023 (22%)	1048 (23%)
HDL-C (mg/dL)	43 (13)	42 (13)	43 (13)	43 (13)	43 (13)
<40	1858 (44%)	503 (48%)	1879 (45%)	2056 (44%)	2095 (45%)
≥40 and <60	1721 (41%)	414 (39%)	1736 (41%)	1926 (41%)	1896 (41%)
≥60	436 (10%)	96 (9%)	399 (10%)	475 (10%)	439 (10%)
TG (mg/dL)	168 [118-244]	175 [119-250]	169 [119-251]	169 [118-244]	170 [119-252]
<150	1691 (40%)	394 (37%)	1646 (39%)	1871 (40%)	1799 (39%)
≥150 and < 200	811 (19%)	234 (22%)	805 (19%)	915 (20%)	897 (19%)
≥200	1516 (36%)	385 (37%)	1562 (37%)	1674 (36%)	1733 (38%)
Apo B (mg/dL)	96 (26)	96 (25)	97 (25)	96 (26)	97 (25)
Apo A1 (mg/dL)	134 (29)	132 (28)	133 (29)	134 (29)	133 (28)
Hgb (g/dL)	12.3 (1.7)	12.3 (1.7)	12.3 (1.7)	12.3 (1.7)	12.3 (1.7)
Albumin (g/dL)	4.0 (0.5)	4.0 (0.5)	4.0 (0.5)	4.0 (0.5)	4.0 (0.5)
Phosphate (mg/dL)	4.4 (1.5)	4.4 (1.4)	4.4 (1.5)	4.4 (1.5)	4.4 (1.5)

Source: FDA reviewer analysis from submitted raw data.
Values are frequency (%); mean (SD); or median [IQR]. Missingness ≤ 5% and equally distributed across groups.
* Non-dialysis patients only.

† Percentages for eGFR and albuminuria categories indicate proportions of the non-dialysis population.
‡ Updated to reflect any measurements and events prior to second randomization for Arm 3 patients.
§ Some values may differ from applicant's analysis based on the substitution of local laboratory results in the FDA analysis when central laboratory results were missing (supported by a strong correlation between local and central values for the 6112 (96%) pre-dialysis subjects for whom both values were measured at randomization; Pearson's r=0.96, P<0.0001).

At the time of initial randomization, the mean age was 61 years (range, 39 to 94 years) and 63% of participants were men. The study population consisted of 72% whites, 22% Asians, and 3% blacks. Consistent with the trial's enrollment plan, 68% were not on dialysis and 32% were treated with either hemodialysis (27%) or peritoneal dialysis (5%). Approximately 23% of participants had a history of diabetes mellitus and 85% were free from any history of coronary artery disease, peripheral arterial disease, or cerebrovascular disease. The mean BMI was 27 kg/m^2 and 24% had a BMI > 30 kg/m^2.

Categorizing the reported causes of CKD based on the groupings listed on the Centers for Medicare/Medicaid Services 2728 form used in the United States, the three most common categories of CKD etiology in the SHARP trial were hypertension/large-vessel disease (19%), glomerulonephritis (16%), and diabetes (15%).

Of the 6382 participants not on dialysis, most had moderate to severe kidney disease, with 94% having an estimated GFR < 45 $mL/min/1.73m^2$. Furthermore, among the 5682 CKD patients with an available urinary albumin:creatinine ratio (UACR), 80% had micro- or macroalbuminuria. The cross-tabulation of eGFR and albuminuria category at the time of first randomization is shown in Table 8.

Table 8. Cross-tabulation of eGFR and Albuminuria Categories

eGFR*	Albuminuria at 1st Randomization (mg/g)				TOTAL
	<30	30-300	>300	Missing	
≥60	35 (0.6%)	25 (0.4%)	14 (0.2%)	16 (0.3%)	90 (1.4%)
≥45 and <60	100 (1.6%)	102 (1.6%)	69 (1.1%)	30 (0.5%)	301 (4.7%)
≥30 and <45	514 (8.1%)	651 (10.2%)	565 (8.9%)	254 (4.0%)	1984 (31.1%)
≥15 and <30	425 (6.7%)	970 (15.2%)	1049 (16.4%)	280 (4.4%)	2724 (42.7%)
<15	51 (0.8%)	380 (6.0%)	732 (11.5%)	115 (1.8%)	1278 (20.0%)
Missing	0	0	0	5 (0.1%)	5 (0.1%)
TOTAL	1125 (17.6%)	2128 (33.3%)	2429 (38.1%)	700 (11.0%)	6382 (100%)

Source: FDA reviewer's analysis of submitted raw data.
Percentages represent proportions of the overall pre-dialysis population (n=6382) at first randomization.
* Local laboratory creatinine values used to calculate eGFR when central laboratory values were missing.

The mean LDL at randomization was 108 mg/dL; 43% of participants had an LDL < 100 mg/dL and approximately 12% had an LDL < 70 mg/dL. Because SHARP excluded patients taking concomitant statins, fibrates, or nicotinic acid, these values should represent untreated LDL levels.

Reviewer Comment: Although the use of statins, fibrates, or nicotinic acid was an exclusion criterion, the proportion of patients who had used these agents within the previous 6 or 12 months, for example, was not reported.

The SHARP trial was multinational; more than 95% of participants resided outside of the United States (Table 9).

Table 9. Number Ever Randomized in Each Country

Country	# Patients Randomized (%)
United Kingdom	1987 (21%)
Germany	1678 (18%)
Australia	1043 (11%)
China	994 (11%)
Malaysia	701 (7%)
Canada	505 (5%)
United States	**394 (4%)**
New Zealand	285 (3%)
France	264 (3%)
Denmark	258 (3%)
Thailand	253 (3%)
Sweden	219 (2%)
Norway	194 (2%)
Czech Republic	191 (2%)
Poland	160 (2%)
Austria	111 (1%)
Netherlands	108 (1%)
Finland	93 (1%)
TOTAL	**9438 (100%)**

Source: CSR Table 10-1.

Compared with all participants outside of the United States, the 394 participants from the U.S. were more likely to be non-white, diabetic, and obese. In the U.S., 38% of participants had a BMI > 30 kg/m^2 compared to 23% of non-U.S. participants. The U.S. study population had a greater proportion of dialysis patients, and the eGFR among U.S. pre-dialysis patients was higher than non-U.S. pre-dialysis patients. Furthermore, the distribution of CKD etiologies was different between U.S. and non-U.S. participants. Last, U.S. participants had lower levels of total cholesterol, LDL-C, triglycerides, and apo B levels at the time of randomization. In the U.S., 28% and 66% of participants had LDL-C levels less than 70 and 100 mg/dL, respectively, compared with 12% and 43% of non-U.S. participants; given that SHARP excluded patients treated with lipid-lowering therapy, these proportions presumably do not reflect regional differences in prescribing lipid-lowering therapy. There did not appear to be substantial differences between U.S. and non-U.S. participants with regard to age, sex, or history of prior vascular disease (Table 10).

Table 10. Characteristics at Initial Randomization by U.S./non-U.S. status

Characteristic	U.S. (N=394)	Non-U.S. (N=9044)
Age	61 (12)	61 (12)
Male	264 (67%)	5636 (62%)
Race		
White	170 (43%)	6603 (73%)
Black	178 (45%)	98 (1%)
Asian	3 (1%)	2107 (23%)
Other	42 (11%)	209 (2%)
Diabetes	133 (34%)	1993 (22%)
Renal Disease Etiology		
Diabetic nephropathy	69 (18%)	1325 (15%)
Glomerulonephritis	16 (4%)	1532 (17%)
Secondary GN / Vasculitis	4 (1%)	221 (2%)
TIN/Pyelonephritis	17 (4%)	882 (10%)
HTN/Lg Vessel Disease	151 (38%)	1665 (18%)
Cystic, Hereditary, or Congenital	24 (6%)	1207 (13%)
Neoplasms/Tumors	4 (1%)	100 (1%)
Miscellaneous	58 (15%)	1143 (13%)
Unknown/Missing	76 (19%)	1439 (16%)
Systolic BP	137 (22%)	139 (22)
Diastolic BP	77 (13)	79 (13)
BMI	29.3 (7.0)	27.0 (5.5)
Waist circumference	101.7 (16.5)	96.7 (14.9)
On Dialysis	155 (39%)	2901 (32%)
eGFR (MDRD)*	30.6 [20.9-40.1]	25.5 [16.8-34.3]
Total Cholesterol	163 (38)	190 (45)
LDL-C	89 (29)	108 (34)
HDL-C	42 (14)	43 (13)
TG	146 [99-212]	170 [119-250]
Apo B	82 (22)	97 (26)
Apo A1	135 (30)	134 (29)

Source: FDA reviewer analysis from submitted raw data.
Values are frequency (%), mean (SD), or median [IQR].
* Non-dialysis patients only.

Subject Disposition

Figure 2 summarizes the disposition of subjects from initial screening through complete follow-up.

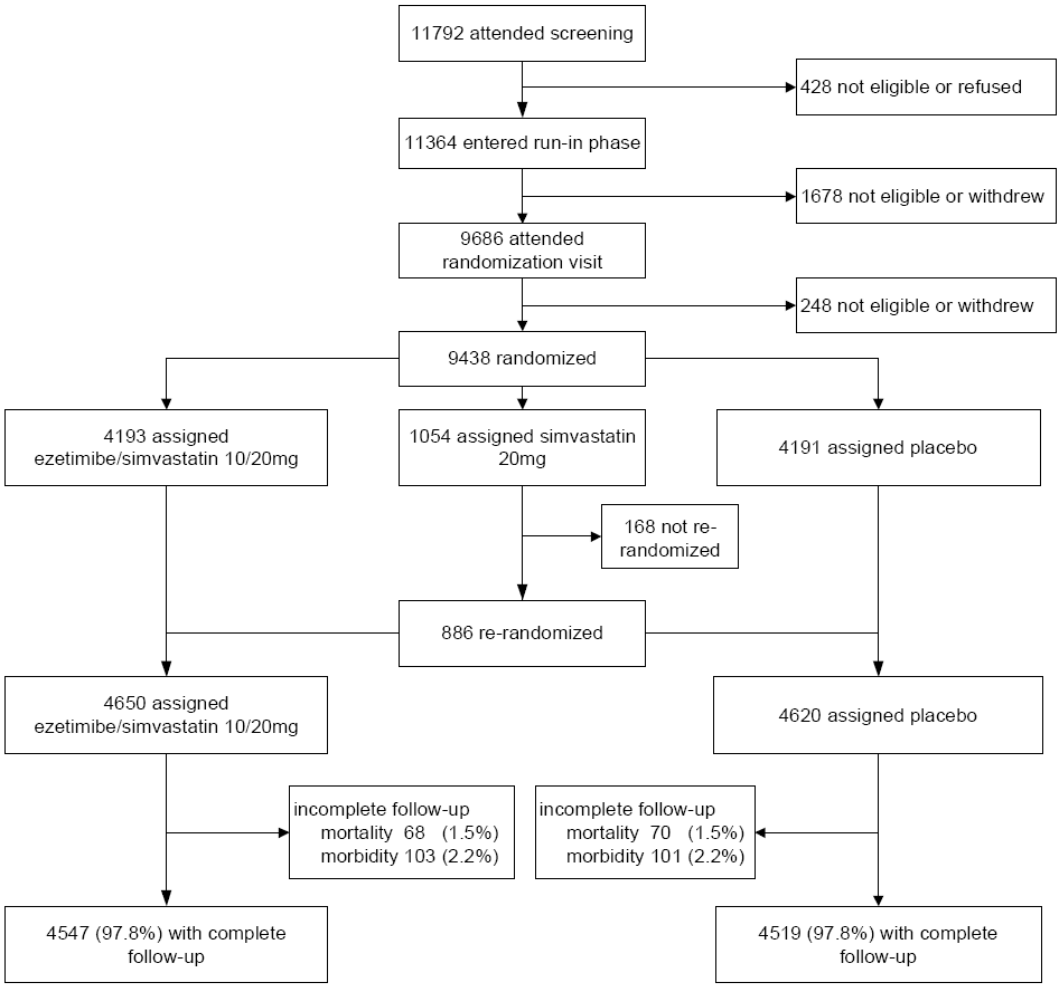


Figure 2. Summary of Subject Disposition
Source: CSR Figure 10-1.
Incomplete follow-up includes those without direct contact (in person or by telephone) at the scheduled final visit and with ≤ 4 years of follow-up.

Of the 11792 subjects screened, 11364 (96%) entered the placebo run-in period. The most common reasons for screened patients not entering the run-in phase were identification of previous MI, CABG, or PTCA (n=128); concomitant use of a contraindicated drug (n=65); and/or failure to complete the screening visit (n=63) (Table 11).

Table 11. Reasons Screened Patients Did not Enter Placebo Run-in

Reason for not entering placebo run-in	n (%)
SCREENED	**11,792 (100%)**
On contraindicated drug	65 (0.6%)
Did not complete screening visit	63 (0.5%)
Concern about long-term compliance	32 (0.3%)
Informed consent not given	22 (0.2%)
Previous adverse reaction to statin	16 (0.1%)

Reason for not entering placebo run-in	n (%)
Screening blood sample not obtained	2 (0.02%)
Previous adverse reaction to ezetimibe	1 (0.01%)
Did not Meet Inclusion Criteria	
• Did not meet CKD definition	35 (0.3%)
• Functioning transplant	1 (0.01%)
Fulfilled Exclusion Criteria	
• Previous MI, CABG, PCI	128 (1.1%)
• Chronic liver disease	39 (0.3%)
• Other life-threatening disease	30 (0.3%)
• Living-donor transplant anticipated within 1 yr	11 (0.1%)
• Acute uremic emergency in past 2 mo	9 (0.1%)
• Inflammatory muscle disease	8 (0.1%)
• Child-bearing potential	4 (0.03%)
• Believed ineligible at screening	3 (0.03%)
SCREENED, DID NOT ENTER RUN-IN	**428 (3.6%)**

Source: CSR Table 10-2.
Each subject could contribute more than one reason.

Of the 11364 subjects who entered the placebo run-in phase, 1678 (15%) dropped out before the randomization appointment with the most common cause being the request of the subject's personal physician (n=743). For 149 (1.3%) subjects, their physician wanted to start lipid-lowering therapy (Table 12). An additional 248 subjects dropped out of the study during the randomization visit, largely as a result of non-compliance with run-in treatment (n=153), serious concerns about long-term compliance/attendance (n=94), and/or at the patient's request (n=129) (Table 13). As a result, the first randomization assigned 9438 subjects to once-daily doses of either ezetimibe/simvastatin 10/20 mg (n=4193), simvastatin 20 mg (n=1054), or placebo (n=4191).

Table 12. Reasons for Drop-out During Placebo Run-in

Reason for drop-out during placebo run-in	n (%)
ENTERED PLACEBO RUN-IN	**11,364 (100%)**
Doctor's request	743 (6.5%)
• Approval for randomization not granted	561 (4.9%)
• Wishes to start lipid-lowering treatment	149 (1.3%)
• Other reason	85 (0.7%)
Patient's request	385 (3.4%)
• Intolerant of study treatment	111 (1.0%)
• Difficult to attend study visits	58 (0.5%)
• Other reason	216 (1.9%)
Did not meet CKD definition	376 (3.3%)
Elevated ALT, AST, or CK	175 (1.5%)
Died during run-in	31 (0.3%)
Required blood test missing	12 (0.1%)
SAE during run-in	8 (0.1%)

Reason for drop-out during placebo run-in	n (%)
Unspecified reason	139 (1.2%)
None of the above	3 (0.03%)
DROPPED OUT BEFORE RANDOMIZATION APPT	**1,678 (14.8%)**

Source: CSR Table 10-3.
Each subject could contribute more than one reason.

Table 13. Reasons for Drop-out at Initial Randomization Visit

Reason for drop-out at initial randomization visit	n (%)
COMPLETED RUN-IN	**9,686 (100%)**
Non-compliant with run-in treatment	153 (1.6%)
Patient's request	129 (1.3%)
Serious concern about long-term compliance	94 (1.0%)
SAE during run-in	16 (0.2%)
On contraindicated drug	14 (0.1%)
Functioning transplant	6 (0.1%)
Living-donor transplant anticipated within 1 yr	4 (0.04%)
Acute uremic emergency in past 2 mo	4 (0.04%)
Unknown reason	2 (0.02%)
DROPPED OUT AT RANDOMIZATION APPT	**248 (2.6%)**

Source: CSR Table 10-4.
Each subject could contribute more than one reason.

Of the 1054 subjects initially assigned to simvastatin, 168 (16%) were not re-randomized after year 1: 103 (10%) had stopped treatment, 46 (4%) died during the first year, and 19 (2%) did not attend the second randomization visit. The remaining 886 subjects initially assigned to simvastatin were re-assigned to ezetimibe/simvastatin (n=457) or placebo (n=429).

Study Treatment Discontinuation

During the first year of the study, 659 (15.7%) patients in the ezetimibe/simvastatin group, 161 (15.3%) in the simvastatin group, and 668 (15.9%) in the placebo group discontinued study treatment. Reasons for discontinuation of study treatment during year 1 were similar across Arms 1, 2, and 3 (Table 14).

Discontinuation of study treatment was more common among patients ever randomized to placebo compared with those ever randomized to ezetimibe/simvastatin (35.9% vs. 32.7%). This net imbalance primarily resulted from more frequent discontinuation because of contraindicated medication in the placebo group (9.7% vs. 5.3%). More ezetimibe/simvastatin-treated patients than placebo-treated patients stopped study treatment because of non-serious AEs and abnormal safety blood results (Table 14).

Renal transplant was the most frequent SAE that led to study treatment discontinuation in all groups (overall, accounting for 99 [44%] of the 225 "other SAE" events during year 1 and for 300 [49%] of the 613 "other SAE" events from the time of final randomization). See page 86 for further discussion of SAEs and AEs that led to discontinuation.

Table 14. Reasons for Stopping Study Treatment

Reason for Stopping*	During Year 1 Only			From Final Randomization	
	Eze/Sim Arm 2 N=4193	Simva Alone Arm 3 N=1054	Placebo Arm 1 N=4191	Eze/Sim Arms 2+3b N=4650	Placebo Arms 1+3a N=4620
SSAR	1 (<0.05%)†	0 †	4 (0.1%)†	17 (0.4%)‡	12 (0.3%)‡
Other SAE (not SSAR or primary endpoint)	102 (2.4%)	31 (2.9%)	92 (2.2%)	303 (6.5%)	310 (6.7%)
AE (non-serious)	81 (1.5%)	14 (0.9%)	79 (1.6%)	165 (3.5%)	131 (2.8%)
Abnormal safety blood result (non-serious)	17 (0.4%)	4 (0.4%)	13 (0.3%)	43 (0.9%)	28 (0.6%)
Other Reason					
Patient wishes	165 (3.9%)	32 (3.0%)	159 (3.8%)	417 (9.0%)	409 (8.9%)
Contraindicated medication	60 (1.4%)	19 (1.8%)	85 (2.0%)	248 (5.3%)	449 (9.7%)
Difficulty/concern taking tablets	40 (1.0%)	4 (0.4%)	28 (0.7%)	95 (2.0%)	81 (1.8%)
Difficulty attending clinic	19 (0.5%)	7 (0.7%)	31 (0.7%)	82 (1.8%)	90 (1.9%)
Awaiting bloods	5 (0.1%)	3 (0.3%)	1 (0%)	5 (0.1%)	1 (<0.05%)
Other reasons	3 (0.1%)	1 (0.1%)	3 (0.1%)	16 (0.3%)	10 (0.2%)
Reason not specified	25 (0.6%)	5 (0.5%)	26 (0.6%)	83 (1.8%)	86 (1.9%)
Subtotal: Other Reason	**317 (7.6%)**	**71 (6.7%)**	**333 (7.9%)**	**946 (20.3%)**	**1126 (24.4%)**
None of the Above					
No follow-up form but known to be alive	156 (3.7%)	44 (4.2%)	156 (3.7%)	86 (1.8%)	70 (1.5%)
No reason recorded	2 (<0.05%)	1 (0.1%)	4 (0.1%)	5 (0.1%)	9 (0.2%)
Subtotal: None of the Above	**158 (3.8%)**	**45 (4.3%)**	**160 (3.8%)**	**91 (2.0%)**	**79 (1.7%)**
Any Reason	**659 (15.7%)**	**161 (15.3%)**	**668 (15.9%)**	**1522 (32.7%)**	**1658 (35.9%)**

Source: Derived from *revised* CSR Tables 10-5, 10-6, 14-30, 14-31.
SSAR = Suspected serious adverse reaction; i.e., SAE thought to be related to study drug by blinded study investigator in consultation with ICC.
* One patient may contribute more than one reason.
† During year 1, six additional patients had SSARs but did not stop: four in Arm 2 and one in each of Arms 3 and 1.
‡ Four additional patients had SSARs but did not stop: three in Arms 2+3b and one in Arms 1+3a.

Follow-up

Study personnel encouraged all patients to attend follow-up visits, even after discontinuation of study treatment. If patients did not attend visits in person, the study nurse would attempt to contact the patient or a relative/caregiver by telephone. If still unsuccessful, study personnel would review notes from medical records and/or contact the patient's primary care physician or nephrologist. Last, national registries could be used for follow-up information in the UK, United States, and some states in Germany. As shown in Figure 2, incomplete follow-up was equal in each group: 1.5% with respect to mortality and 2.2% with respect to morbidity when all of these sources were used.

Median follow-up from final randomization was 4.9 years for both treatment arms. Table 15 provides the person-years of follow-up by year among these patients.

Table 15. Person-years of Follow-up by Year

Years since Final Randomization*	Eze/Sim Arms 2+3b N=4650	Placebo Arms 1+3a N=4620
<1	4545.6	4510.1
≥1 and <2	4321.3	4279.4
≥2 and <3	4032.3	4000.1
≥3 and <4	3602.4	3605.7
≥4 and <5	2219.0	2232.8
≥5 and <6	942.3	954.7
≥6 and <7	119.5	131.8
Total	**19782.5**	**19714.6**
Median follow-up (survivors)	**4.9**	**4.9**

Source: Table 10-9 (Revised in 02 Aug 2011 response to FDA information request.)
* Recall that final randomization is the only randomization for Arms 1 and 2 (n=8384) but is the time of re-assignment to ezetimibe/simvastatin or placebo for Arms 3a/3b (n=886).

SHARP: Efficacy Results

Primary Efficacy Endpoint: Major Vascular Events

The protocol-specified primary endpoint is the first occurrence of major vascular event (MVE) among patients initially randomized to ezetimibe/simvastatin or placebo (i.e., Arm 2 vs. Arm 1). An MVE is defined as cardiac death, MI, any stroke, or any revascularization procedure (excluding dialysis access-related procedures). Assessments of endpoint components are presented as secondary/exploratory analyses later in this document.

The primary efficacy analysis demonstrates that assignment to ezetimibe/simvastatin reduced the risk of an MVE. Overall, 639 (15.2%) of 4193 ezetimibe/simvastatin-treated patients and 749 (17.9%) of 4191 placebo-treated patients experienced an MVE. Survival analysis shows that assignment to ezetimibe/simvastatin reduced the relative risk of an MVE by 16% (95% CI, 7% to 25%; log-rank p=0.001) compared with placebo (Figure 3).

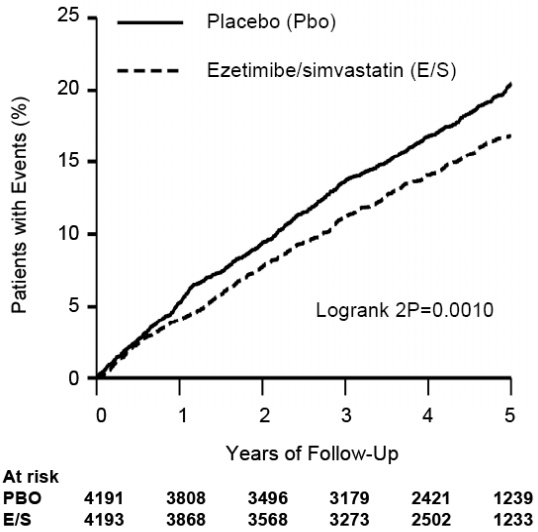


Figure 3. Kaplan-Meier of Protocol-specified Primary Endpoint
Source: CSR Figure 11-2.

A Kaplan-Meier analysis yields the following cumulative probabilities of an MVE, absolute risk reduction (ARR) associated with treatment, and the corresponding number needed to treat (NNT) to prevent one MVE:

Table 16. Cumulative Incidence and NNT for Primary Endpoint (MVE)

Year	Placebo	Eze/Sim	ARR (95% CI)	NNT (95% CI)
1	5.3%	4.1%	1.2% (0.3% - 2.1%)	83 (47-336)
2	9.4%	7.8%	1.6% (0.4% - 2.8%)	60 (35-250)
3	13.7%	11.1%	2.5% (1.1% - 4.0%)	39 (25-92)
4	16.8%	14.1%	2.7% (1.1% - 4.3%)	37 (23-92)
5	20.4%	16.9%	3.6% (1.7% - 5.4%)	28 (18-59)

Source: FDA reviewer analysis using submitted analysis dataset.

SAP-specified "Key Outcome": Major Atherosclerotic Events

As discussed previously, the SHARP Steering Committee voted to change the primary endpoint from MVE to MAE in October 2009. Furthermore, the SAP specifies that the population for the primary analysis would include patients originally assigned to simvastatin, in contrast to the protocol-specified plan and previous discussions with the Agency prior to study initiation (14 November 2002). For these reasons, Merck declined to accept the change to the primary endpoint.

For completeness, the results of this "key outcome" are presented below. Note that for the subset of patients initially randomized to simvastatin (Arms 3a and 3b), time-at-risk began at the time of second randomization, i.e., approximately one year after their initial assignment to simvastatin monotherapy. Any events that occurred while taking simvastatin monotherapy *were excluded*

from the primary endpoint; instead, these events were used to "update" the baseline characteristics for these patients (e.g., a patient in Arm 3 who had an MI while receiving simvastatin monotherapy would be noted as having a "history of MI" in the baseline characteristics of patients ever randomized to ezetimibe/simvastatin or placebo).

Table 17 describes the event codes, assigned after adjudication, that distinguish coronary and non-coronary causes of death in SHARP.

Table 17. Possible Adverse Events Comprising Coronary vs. Non-coronary Deaths

CORONARY DEATHS ***(Included in both MAE and MVE)***	**NON-CORONARY DEATHS** ***(Included in MVE but not MAE)***
Myocardial infarction/heart attack	Cardiac arrest
Myocardial infarction – definite	Sudden cardiac death
Myocardial infarction – probable	Cardiac death
Myocardial infarction – possible	Other cardiac death (not CHD)
Acute coronary syndrome/hospitalization with angina	Coronary angiogram/cardiac catheterization
Heart failure – ischemic	Arrhythmia
Coronary artery bypass graft (CABG)	Atrial fibrillation/flutter
Coronary angioplasty (PTCA) ± stent	Conduction disorder/heart block
Laser transmyocardial revascularization	Tachycardia
CHD death (not MI)	Supraventricular tachycardia (SVT)
	Ventricular tachycardia (VT)
	Bradycardia
	Palpitations/fluttering of heart
	Pacemaker insertion/change/battery change
	Cardioversion
	Electrophysiological studies (EPS)
	Internal cardiac defibrillator insertion/problem/battery change or check
	Conduction system ablation
	Cardiomyopathy
	Hypertrophic obstructive cardiomyopathy
	Heart failure/pulmonary edema/congestive cardiac failure
	Heart failure – not ischemic
	Cor pulmonale or right heart failure
	Cardiac congestion of liver
	Heart surgery
	Heart valve surgery
	Aortic valve repair/replacement
	Mitral valve repair/replacement
	Heart valve problem
	Heart transplant
	Pericardial surgery/pericardial drainage
	Pericarditis including Dressler's
	Pericardial effusion
	Infective endocarditis/subacute bacterial endocarditis

Source: *aecats.xpt*

Assignment to ezetimibe/simvastatin reduced the risk of an MAE. Overall, 526 (11.3%) of 4650 ezetimibe/simvastatin-treated patients and 619 (13.4%) of 4620 placebo-treated patients experienced an MAE. Survival analysis shows that assignment to ezetimibe/simvastatin reduced the relative risk of an MAE by 17% (95% CI, 6% to 26%; log-rank p=0.002) compared with placebo (Figure 4).

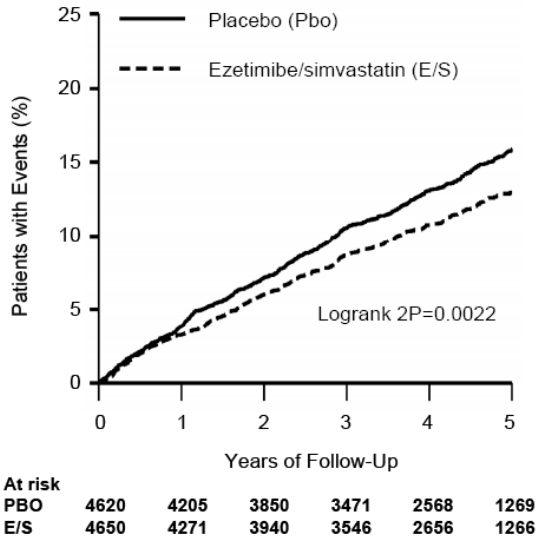


Figure 4. Kaplan-Meier of SAP-specified "Key Outcome"
Source: CSR Figure 11-4.

A Kaplan-Meier analysis yields the following cumulative probabilities of an MAE, ARR associated with treatment, and the corresponding NNT to prevent one MAE:

Table 18. Cumulative Incidence and NNT for "Key Outcome" (MAE)

Year	Placebo	Eze/Sim	ARR (95% CI)	NNT (95% CI)
1	3.8%	3.3%	0.6% (-0.2% - 1.3%)	175 (-∞ to -522 and 75 to ∞)
2	7.1%	6.0%	1.1% (0.1% - 2.2%)	88 (46-1051)
3	10.6%	8.6%	2.0% (0.7% - 3.2%)	51 (31-139)
4	13.1%	10.8%	2.3% (0.9% - 3.2%)	43 (27-109)
5	15.8%	12.9%	2.9% (1.3% - 4.5%)	34 (22-80)

Source: FDA reviewer analysis using submitted analysis dataset.

Recall that removing hemorrhagic strokes and non-coronary deaths ("other cardiac deaths") from the MVE composite resulted in the MAE composite. Sudden cardiac death, cardiac arrest, and deaths resulting from congestive heart failure accounted for 70% and 66% of non-coronary deaths in the ezetimibe/simvastatin and placebo groups, respectively. The frequencies of

individual event codes that composed the non-coronary deaths in SHARP are presented in Table 64 (Appendix, p. 114).

Reviewer Comment: Misclassification of non-coronary vs. coronary deaths is expected. Blinded adjudication should reduce the potential for the introduction of differential misclassification bias.

Analysis of Secondary Endpoints

Reviewer Comment to Aid Interpretation: All analyses except for the primary efficacy comparison were pre-specified in the protocol to include all patients ever randomized to ezetimibe/simvastatin or placebo (Arms 2+3b vs. Arms 1+3a). Recall that follow-up for these analyses begins at the time of assignment to either ezetimibe/simvastatin or placebo, i.e., the initial randomization for the 8384 patients in Arms 1 and 2 and the second randomization for the 886 patients in Arms 3a and 3b. Therefore, the time of "randomization" in subsequent sections refers to this time of assignment to ezetimibe/simvastatin or placebo, unless otherwise specified.

Cardiovascular Endpoints

Each component of the primary composite endpoint was a composite endpoint itself: for example, "major cardiac event" comprises cardiac deaths and nonfatal MI; "any stroke" comprises fatal and nonfatal hemorrhagic or ischemic/other stroke; and "any revascularization procedure" comprises coronary or non-coronary revascularization and non-traumatic amputation. The applicant typically designated these subcomponents as secondary or tertiary endpoints (see Table 56 in Appendix).

Table 19 summarizes analyses of MVE components, derived from the applicant's presentation of these results. These analyses describe the time to first event after assignment to ezetimibe/simvastatin or placebo for each component endpoint; therefore, the total number of first component events exceeds the total number of first MVE. For patients initially randomized to simvastatin, only events following the second randomization are included.

Table 19. Number of First Events for MVE Components – Arms 2+3b vs. 1+3a

Endpoint	Eze/Sim (N=4650)	Placebo (N=4620)	Risk Ratio (95% CI)	P
MVE	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.0012
Major cardiac event	367 (7.9%)	403 (8.7%)	0.90 (0.78-1.04)	0.16
Major coronary event	213 (4.6%)	230 (5.0%)	0.92 (0.76-1.11)	0.37
Coronary (CHD) death	91 (2.0%)	90 (1.9%)	1.01 (0.75-1.35)	0.95
Nonfatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Coronary (CHD) death	91 (2.0%)	90 (1.9%)	1.01 (0.75-1.35)	0.95
Other cardiac (non-CHD) death	162 (3.5%)	182 (3.9%)	0.89 (0.72-1.09)	0.26
Any stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038

Endpoint	Eze/Sim (N=4650)	Placebo (N=4620)	Risk Ratio (95% CI)	P
Non-hemorrhagic stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011*
Ischemic stroke	114 (2.5%)	157 (3.4%)	0.72 (0.57-0.92)	0.0073
Unknown stroke	18 (0.4%)	19 (0.4%)	0.94 (0.49-1.79)	0.85
Hemorrhagic stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any revascularization procedure	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.0036*
Coronary revascularization	149 (3.2%)	203 (4.4%)	0.73 (0.59-0.90)	0.0027
CABG	50 (1.1%)	66 (1.4%)	0.75 (0.52-1.09)	0.13
PCI	106 (2.3%)	148 (3.2%)	0.71 (0.56-0.91)	0.0063
Non-coronary revascularization	154 (3.3%)	169 (3.7%)	0.90 (0.73-1.12)	0.36
Vascular surgery / intervention	109 (2.3%)	130 (2.8%)	0.83 (0.65-1.07)	0.15
Non-traumatic amputation	75 (1.6%)	76 (1.6%)	0.98 (0.71-1.35)	0.9

Source: CSR Figures 11-3, 11-5, 11-6, 11-7, 11-8, 11-9, and 12-1.
The two-sided P value derives from the log-rank O-E statistic. P values are not adjusted for multiple comparisons.
* The SAP specified that components of the MAE endpoint (major coronary event, non-hemorrhagic stroke, and revascularization) would be assessed using the Hochberg procedure to adjust for multiplicity. The adjusted P values for non-hemorrhagic stroke and revascularization are 0.022 and 0.011, respectively.

Reviewer Comment: The proposed change in the primary endpoint hypothesized that lipid-lowering would not favorably affect hemorrhagic strokes or non-coronary deaths. In SHARP, the number of coronary (CHD) deaths were similar between the ezetimibe/simvastatin and placebo groups (91 vs. 90, respectively), whereas there were fewer non-coronary deaths among the ezetimibe/simvastatin group (162 vs. 182), although this difference was not statistically significant.

As an exploratory analysis, Table 20 summarizes analyses of MVE components using the same population as the primary efficacy analysis (Arms 1 and 2), i.e., excluding patients initially assigned to simvastatin.

Table 20. Number of First Events for MVE Components – Arm 2 vs. Arm 1

Endpoint	Eze/Sim (N=4193)	Placebo (N=4191)	HR (95% CI)	P
MVE	**639 (15.2%)**	**749 (17.9%)**	**0.84 (0.76-0.93)**	**0.001**
Major cardiac event	344 (8.2%)	369 (8.8%)	0.93 (0.80-1.07)	0.30
Major coronary event	205 (4.9%)	215 (5.1%)	0.95 (0.78-1.15)	0.57
Coronary (CHD) death	88 (2.1%)	86 (2.1%)	1.02 (0.76-1.37)	0.89
Nonfatal MI	128 (3.1%)	147 (3.5%)	0.86 (0.68-1.10)	0.22
Cardiac death	235 (5.6%)	249 (5.9%)	0.94 (0.79-1.13)	0.51
Coronary (CHD) death	88 (2.1%)	86 (2.1%)	1.02 (0.76-1.37)	0.89
Other cardiac (non-CHD) death	147 (3.5%)	163 (3.9%)	0.90 (0.72-1.12)	0.35
Any stroke	148 (3.5%)	192 (4.6%)	0.77 (0.62-0.95)	0.02
Non-hemorrhagic stroke	116 (2.8%)	158 (3.8%)	0.73 (0.57-0.93)	0.01
Ischemic stroke	102 (2.4%)	142 (3.4%)	0.71 (0.55-0.92)	0.01
Unknown stroke	14 (0.3%)	17 (0.4%)	0.82 (0.40-1.66)	0.58

Endpoint	Eze/Sim (N=4193)	Placebo (N=4191)	HR (95% CI)	P
Hemorrhagic stroke	36 (0.9%)	35 (0.8%)	1.02 (0.64-1.63)	0.92
Any revascularization procedure	261 (6.2%)	327 (7.8%)	0.79 (0.67-0.92)	0.004
Coronary revascularization	142 (3.4%)	190 (4.5%)	0.74 (0.59-0.92)	0.006
CABG	47 (1.1%)	62 (1.5%)	0.75 (0.52-1.10)	0.14
PCI	102 (2.4%)	139 (3.3%)	0.73 (0.56-0.94)	0.01
Non-coronary revascularization	136 (3.2%)	157 (3.8%)	0.86 (0.68-1.08)	0.19
Vascular surgery / intervention	95 (2.3%)	121 (2.9%)	0.78 (0.60-1.02)	0.07
Non-traumatic amputation	68 (1.6%)	72 (1.7%)	0.94 (0.67-1.31)	0.71

Source: FDA reviewer's analysis of submitted raw data (*sradata.xpt*).

These analyses suggest that the effects of ezetimibe/simvastatin on time to first nonfatal MI, ischemic stroke, and coronary revascularization contribute substantially to the overall effect on MVE (and MAE) outcomes. Figure 5, Figure 6, and Figure 7 are the Kaplan-Meier curves for these component events.

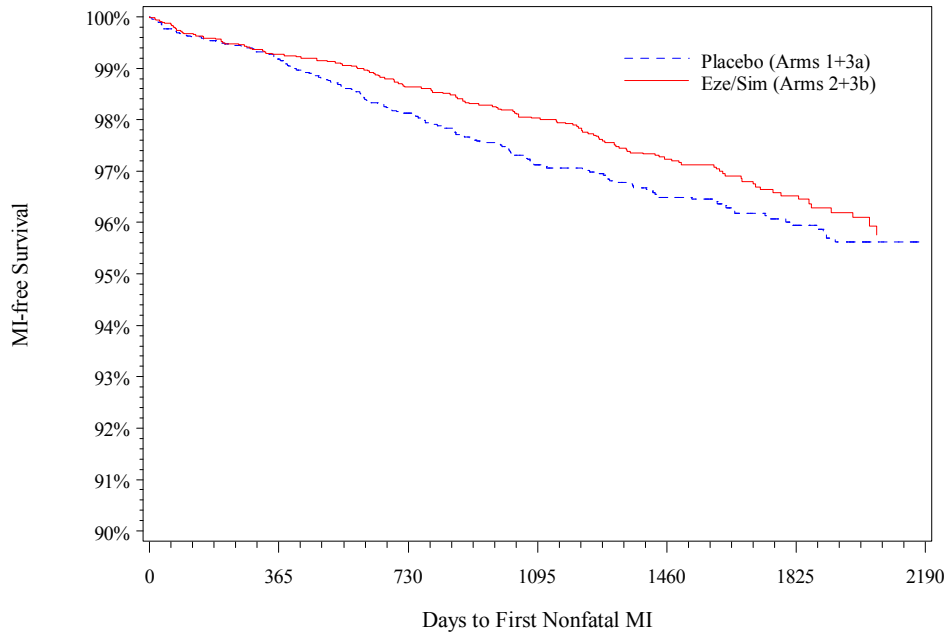


Figure 5. Kaplan-Meier of First Nonfatal MI
Source: FDA reviewer's analysis from submitted analysis dataset (*sradata.xpt*).

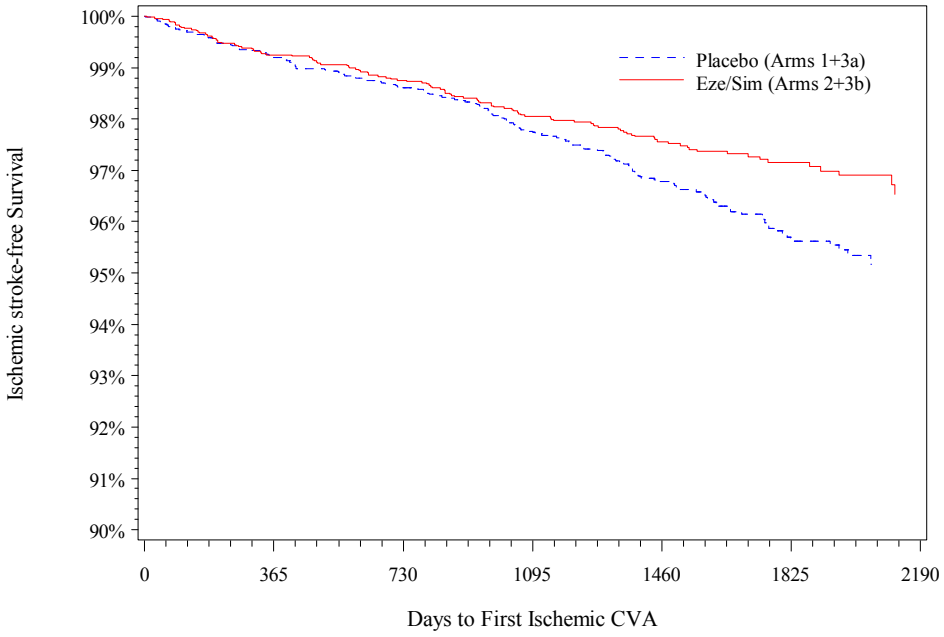


Figure 6. Kaplan-Meier of First Ischemic Stroke
Source: FDA reviewer's analysis from submitted analysis dataset (*sradata.xpt*).

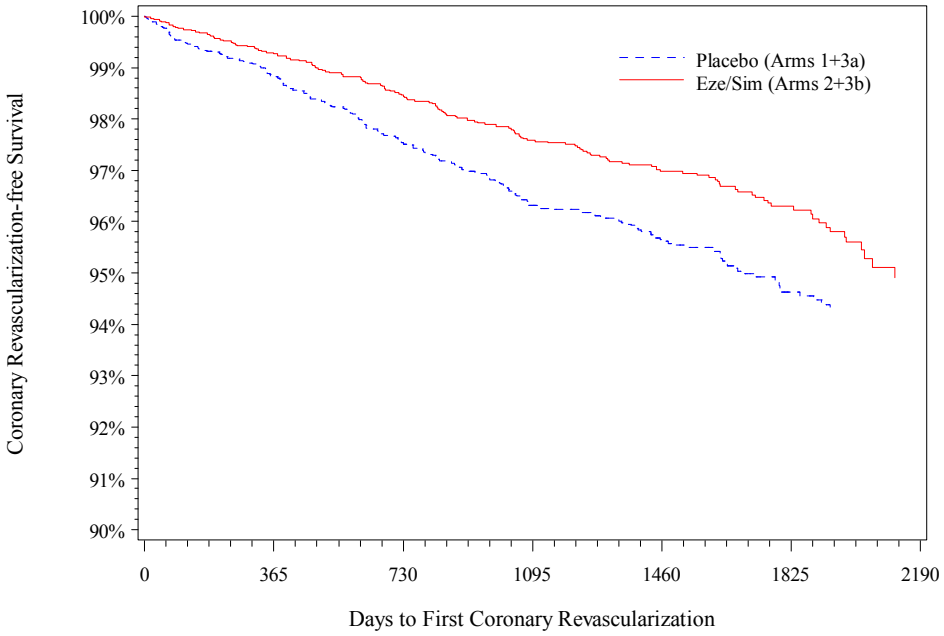


Figure 7. Kaplan-Meier of First Coronary Revascularization
Source: FDA reviewer's analysis from submitted analysis dataset (*sradata.xpt*).

The point estimates for all endpoints except for hemorrhagic stroke favored ezetimibe/simvastatin or were extremely close to 1. There were 45 (1.0%) subjects who had at least one hemorrhagic stroke in the ezetimibe/simvastatin group compared with 37 (0.8%) subjects in the placebo group (Risk Ratio 1.21 [95% CI 0.78-1.86; p=0.4]). Although the number of hemorrhagic strokes is low, it is interesting to note that hemorrhagic stroke was also

the only outcome with a point estimate >1 (favoring less statin) in the Cholesterol Treatment Trialists' (CTT) Collaboration's 2010 meta-analysis of data from 170,000 participants in 26 randomized trials.[9] Combining 5 trials of more vs. less statin, more statin conferred a non-significant 1.21-fold higher risk of hemorrhagic stroke (95% CI 0.76-1.91). Combining 21 trials of statin vs. control, statin conferred a non-significant 1.15-fold higher risk of hemorrhagic stroke (95% CI 0.87-1.51).

Ischemic strokes were classified as definite or presumed (see Table 60 and Table 61). Briefly, an ischemic stroke was "presumed" if (1) imaging was performed and was either normal or equivocal, (2) duration of symptoms was >24 hrs or was not specified but the original SAE form recorded a stroke, and (3) if fatal, no infarct was observed on post-mortem (if performed). A "definite" ischemic stroke required observing an infarct on imaging and/or post-mortem examination. Table 21 summarizes the event codes recorded for the 271 first ischemic stroke events. Among all patients ever randomized to placebo, 104/157 (66%) of ischemic strokes were adjudicated as "definite" compared with 66/114 (58%) among all patients ever randomized to ezetimibe/simvastatin.

Table 21. Ischemic/non-hemorrhagic Stroke Event Codes

Ischemic/non-hemorrhagic Stroke Classification		Arm 1	Arm 3a	Arms 1+3a	Arm 2	Arm 3b	Arms 2+3b
Definite	Nonfatal	66	6	72	39	4	43
	Fatal	26	6	32	19	4	23
	Subtotal	92	12	104	58	8	66
Presumed	Nonfatal	43	1	44	36	4	40
	Fatal	7	2	9	7	0	7
	Subtotal	50	3	53	43	4	47
Not specified	Nonfatal	0	0	0	1	0	1
	TOTAL	142	15	157	102	12	114

Source: FDA reviewer's analysis of submitted raw data.

The frequencies of events that compose other endpoints (e.g., first occurrence of other cardiac death, vascular surgery/intervention, etc.) are summarized in the Appendix (p. 113).

Subgroup analyses of the MVE and MAE outcomes are presented later in this document (p. 56).

Renal Endpoints

The SAP designated ESRD (need for long-term dialysis or transplantation) as a subsidiary outcome (and the "main renal outcome") among the patients who were not on dialysis at the time of assignment to ezetimibe/simvastatin or placebo. The SHARP trial does not provide evidence that ezetimibe/simvastatin reduces the risk of ESRD among patients with CKD (Risk Ratio 0.97; 95% CI, 0.89-1.05; p=0.41). Among the 3130 non-dialysis patients assigned to placebo, 1083 (34.6%) developed ESRD; among the 3117 non-dialysis patients assigned to

ezetimibe/simvastatin, 1057 (33.9%) developed ESRD. Furthermore, the applicant's analysis suggests that the treatment effect on progression to ESRD does not vary by baseline CKD stage (eGFR >60, 30-60, 15-30, or <15 mL/min/1.73m^2) or baseline level of albuminuria. Tertiary renal outcomes included composite endpoints: (1) ESRD or death and (2) ESRD or doubling of serum creatinine; the SHARP trial does not support significant effects of ezetimibe/simvastatin on either of these renal composite endpoints.

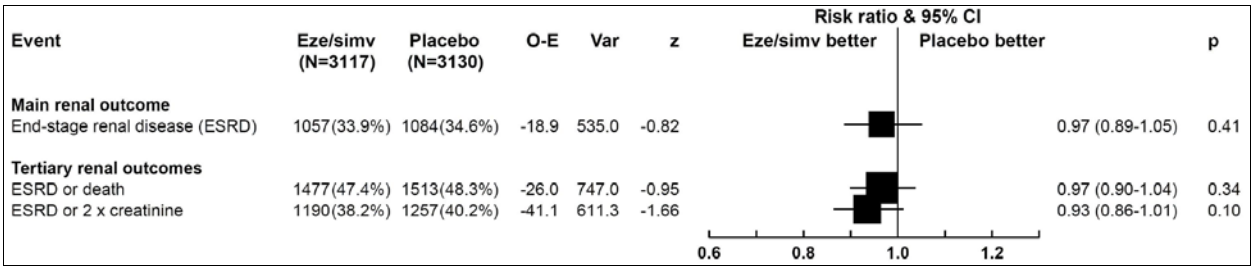


Figure 8. Renal Endpoints
Source: CSR Fig. 11-21.

Among patients who were not on dialysis at the time of randomization but progressed to ESRD during the trial, the median (IQR) time to progression was 2.0 [0.8, 3.2] years in the ezetimibe/simvastatin group and 1.8 [0.9, 3.1] years in the placebo group (Figure 9).

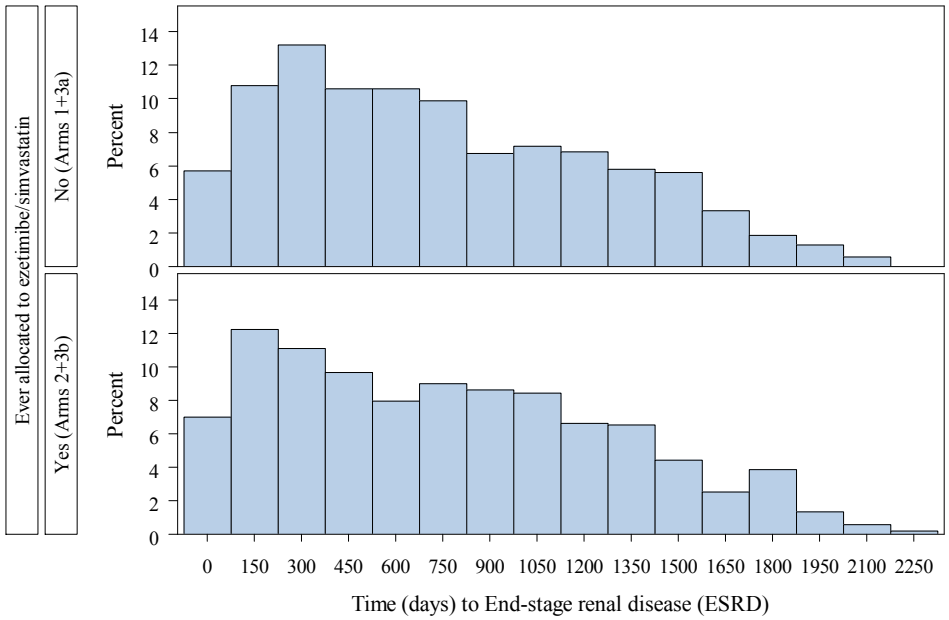


Figure 9. Time to ESRD Among Non-Dialysis Patients who Progressed
Source: FDA reviewer's analysis of submitted analysis dataset (*sradata.xpt*).

Other Clinical Endpoints

Analyses of all-cause mortality, cause-specific mortality, incident cancer, and incident diabetes are discussed in the Safety section (p. 75).

Additional endpoints specified in the protocol and/or SAP included hospitalization for angina, hospitalization for heart failure, revision of vascular access, and transient ischemic attack. Although the point estimates for the treatment effect of ezetimibe/simvastatin on TIA, hospitalization for heart failure, and access revision favor ezetimibe/simvastatin, these effects did not achieve nominal statistical significance.

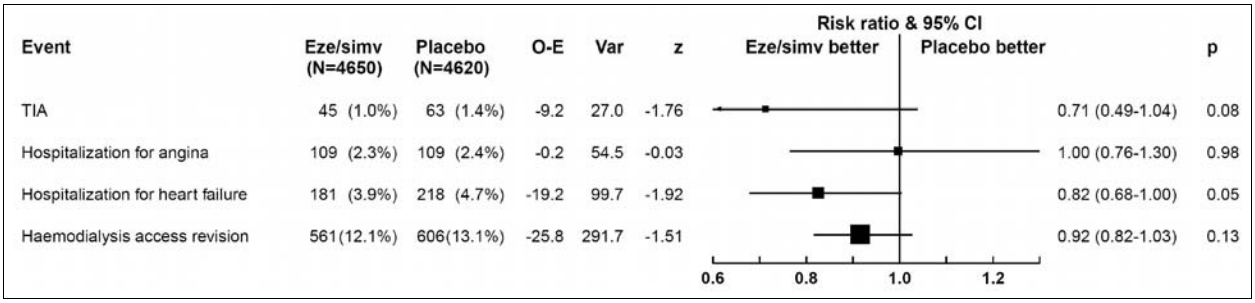


Figure 10. TIA, Hospitalizations for Angina or Heart Failure, Access Revision
Source: CSR Fig. 11-10.

Reviewer Comment: Transient ischemic attacks were not adjudicated except to exclude the possibility of stroke. Hospitalizations for angina and hospitalization for heart failure were adjudicated primarily to exclude myocardial infarction. The adjudication criteria for heart failure included guidance regarding the incorporation of evidence for inadequate ultrafiltration of dialysis patients.

Biochemical Efficacy

The central laboratory measured lipid profiles from non-fasting samples at the initial randomization visit and ~2.5 years later from all patients and at years 1 and 4 from a 10% random sample. LDL-C was measured directly. Treatment decisions (e.g., dose adjustments) were not made based on these data.

Table 22 summarizes the lipid and apolipoprotein values one year after initial randomization in the 10% random sample. At the time these levels were drawn, the applicant reports that 75%, 74%, and 76% of patients in the ezetimibe/simvastatin, simvastatin, and placebo groups, respectively, demonstrated ≥80% adherence to therapy.

Table 22. Mean Lipid and Apolipoprotein Levels at End of Year 1

	Placebo (N=365*)	Simvastatin (N=108)	Eze/Sim (N=391)
Total chol. (mg/dL)	189 ± 2	151 ± 4	135 ± 2
LDL-C (mg/dL)	108 ± 2	79 ± 3	66 ± 2
HDL-C (mg/dL)	43 ± 1	45 ± 1	44 ± 1
Non-HDL-C (mg/dL)	146 ± 2	106 ± 4	91 ± 2
Triglycerides (mg/dL)	209 ± 12	152 ± 10	159 ± 5
Apolipoprotein B (mg/dL)	94 ± 1	73 ± 2	66 ± 1
Apolipoprotein A1 (mg/dL)	136 ± 2	140 ± 3	139 ± 2

Source: CSR Table 11-4. Values are mean ± SE.
* n=364 for Apo B.

Table 23 summarizes the absolute and relative differences between mean values in the ezetimibe/simvastatin group compared with either placebo or simvastatin. The mean LDL-C level among patients in the ezetimibe/simvastatin arm was 42 mg/dL (39%) lower than the mean LDL-C level among patients in the placebo arm at the end of the first year. Compared to placebo, ezetimibe/simvastatin also significantly lowered total cholesterol, non-HDL-C, triglycerides, and apolipoprotein B, but did not appear to have an appreciable effect on HDL-C or apolipoprotein A1.

The mean LDL-C among patients in the ezetimibe/simvastatin arm was 13 mg/dL (17%) lower than the mean LDL-C among patients in the simvastatin arm at the end of the first year. Compared to simvastatin alone, ezetimibe/simvastatin also significantly lowered non-HDL-C and apolipoprotein B but did not further reduce triglycerides.

Table 23. Mean Between-group Differences in Lipids at End of Year 1

	Eze/Sim Relative to Placebo			Eze/Sim Relative to Simvastatin		
	Absolute Difference (95% CI)	Percentage Difference	P*	Absolute Difference (95% CI)	Percentage Difference	P*
Tot. chol.	-54 (-60 to -48)	-29%	<0.0001	-16 (-25 to -7)	-11%	0.0002
LDL-C	-42 (-47 to -38)	-39%	<0.0001	-13 (-20 to -6)	-17%	0.0001
HDL-C	+1 (-2 to +3)	+1%	0.54	-1 (-4 to +2)	-3%	0.47
Non-HDL-C	-55 (-61 to -49)	-37%	<0.0001	-15 (-25 to -6)	-15%	0.0004
Triglycerides	-51 (-75 to -26)	-24%	<0.0001	+6 (-16 to +28)	+4%	0.58
Apo B	-28 (-31 to -25)	-30%	<0.0001	-7 (-13 to +2)	-10%	0.003
Apo A1	+3 (-1 to +7)	+2%	0.13	-1 (-7 to +5)	-1%	0.75

Source: Derived from CSR Table 11-4. All units are mg/dL.

* P value reflects comparison of mean values between ezetimibe/simvastatin and either placebo or simvastatin at the end of the first year.

Figure 11 depicts mean LDL-C over time in the SHARP trial. Because the timing of lipid measurements was determined from initial randomization, only patients initially assigned to simvastatin compose the 18-month time point in this figure (i.e., 30 months after their initial assignment to simvastatin). In contrast, the 12-, 30-, and 48-month time points only reflect values from Arms 1 and 2.

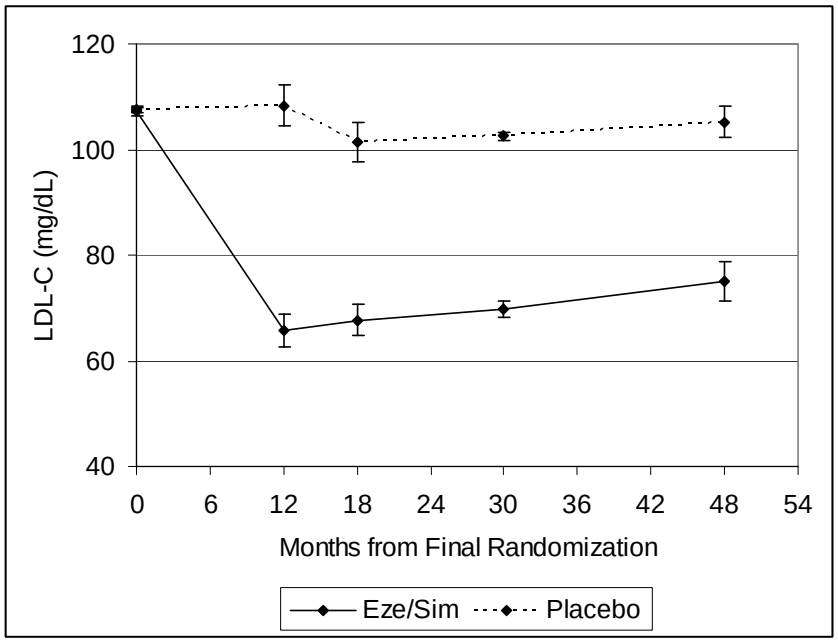


Figure 11. Mean LDL-C Over Time
Source: Derived from CSR Table 11-5. Error bars represent 95% CI.

The difference in mean LDL-C between the ezetimibe/simvastatin and placebo groups narrowed over time. At one year after randomization, the mean LDL-C in the ezetimibe/simvastatin group was 42 mg/dL (39%) lower than in the placebo group. At 2.5 years and 4 years, mean LDL-C was 33mg/dL (32%) and 30 mg/dL (29%) lower than the placebo group, respectively. The applicant suggests that this attenuation is a result of (1) increased non-compliance to study treatment over time and (2) a differential increase in the use of non-study statins in the placebo group (see below).

Reviewer Comment: Increased use of non-study statins in the placebo group would lead to a reduction in mean LDL-C levels over time in the placebo group. This does not appear to be the primary contributor to the narrowing in between-group differences in mean LDL-C over time in SHARP. The use of non-study statins is discussed on p. 55.

Table 24 summarizes the absolute and relative mean differences between additional lipid and apolipoprotein levels at 2.5 years after initial randomization in the ezetimibe/simvastatin group compared to placebo.

Table 24. Mean Between-group Differences in Lipids at Year 2.5

	Eze/Sim (Mean ± SE)	Placebo (Mean ± SE)	Eze/Sim Relative to Placebo		
			Absolute Difference (95% CI)	Percentage Difference	P
Tot. chol.	142 ± 1 (n=3474)	183 ± 1 (n=3452)	-41 (-44 to -39)	-23%	<0.0001
LDL-C	70 ± 1 (n=3473)	103 ± 0.4 (n=3452)	-33 (-34 to -31)	-32%	<0.0001
HDL-C	44 ± 0.4 (n=3470)	44 ± 0.4 (n=3452)	+1 (0 to +2)	+2%	0.029
Non-HDL-C	98 ± 1 (n=3470)	139 ± 1 (n=3452)	-42 (-44 to -40)	-30%	<0.0001
Triglycerides	223 ± 2 (n=3473)	188 ± 3 (n=3450)	-25 (-32 to -18)	-13%	<0.0001
Apo B	70 ± 0.4 (n=3466)	93 ± 0.4 (n=3451)	-23 (-24 to -22)	-24%	<0.0001
Apo A1	145 ± 0.5 (n=3480)	143 ± 0.5 (n=3455)	+2 (+1 to +4)	+1%	0.003

Source: Derived from CSR Table 11-6.
Lipids measured 2.5 years after randomization in Arms 1 (placebo) and 2 (ezetimibe/simvastatin) only. Missing values were replaced with the corresponding value at randomization, thereby assuming a return to baseline as a result of non-compliance with therapy.

Patients with more advanced CKD and patients on dialysis exhibited a smaller difference in LDL-C reduction between ezetimibe/simvastatin and placebo at 2.5 years after initial randomization (Table 25). The mean difference in LDL-C between ezetimibe/simvastatin and placebo was 37 mg/dL among patients who were not on dialysis and 23 mg/dL among patients who were on dialysis at randomization (P<0.0001). The applicant suggests that this difference reflects the lower compliance with therapy among patients on dialysis.

Table 25. Mean Between-group Differences in LDL-C at Year 2.5 by Renal Function

		LDL-C in Eze/Sim Relative to Placebo	
	N_1 / N_2 (Eze/Sim / Placebo)	Absolute Difference (95% CI)	Percentage Difference
eGFR (mL/min/1.73m^2)			
≥60	39 / 40	-38 (-54 to -22)	-30%
≥30 and <60	1006 / 966	-38 (-41 to -35)	-34%
≥15 and <30	1121 / 1161	-41 (-43 to -38)	-35%
<15	490 / 494	-28 (-32 to -23)	-26%

		LDL-C in Eze/Sim Relative to Placebo	
	N_1 / N_2 (Eze/Sim / Placebo)	**Absolute Difference (95% CI)**	**Percentage Difference**
Subtotal: Pre-dialysis	2656 / 2661	-37 (-39 to -36)	-34%
Hemodialysis	1005 / 978	-24 (-27 to -21)	-26%
Peritoneal dialysis	211 / 197	-19 (-26 to -12)	-20%
Subtotal: Dialysis	1216 / 1175	-23 (-26 to -20)	-23%

Source: Derived from CSR Table 11-8.
Missing values were replaced with the corresponding value at randomization, thereby assuming a return to baseline as a result of non-compliance with therapy.

Compliance with Therapy

At each follow-up visit, the LCC nurse was instructed to "estimate the percentage of tablets taken" since study treatment was last issued by examining the pill bottles and calculating the number of weeks since last issue. Greater than 80% was considered "good compliance;" less than this prompted a discussion of ways to improve adherence to therapy. Patients were also considered non-compliant if they did not attend a study visit or had stopped study treatment for any reason, including adverse events or initiation of a non-study statin.

A slightly larger proportion of patients in the ezetimibe/simvastatin group remained compliant with study therapy over time than the placebo group. At the time when all patients were scheduled to have lipids measured (2.5 years after initial randomization), 66% patients in the ezetimibe/simvastatin group and 64% in the placebo group reported ≥80% compliance. Table 26 presents reported compliance data from a few representative time points during the trial.

Table 26. Reported Compliance Over Time

Months Since Randomization	Placebo (Arms 1+3a)	Eze/Sim (Arms 2+3b)
8 – 13 (~ 1 yr)	3344/4396 (76%)	3334/4435 (75%)
26 – 31 (~2.5 yr)	2570/4014 (64%)	2659/4058 (66%)
44 – 49 (~4 yr)	1982/3525 (56%)	2096/3512 (60%)

Source: CSR Table 10-16.

Dialysis patients were reportedly less compliant than non-dialysis patients at both year 1 and year 2.5 (Table 27) after initial randomization.

Table 27. Reported Compliance by Renal Function

	Reported Compliance ≥80% at End of Year 1			Reported Compliance ≥80% at Year 2.5	
Subgroup	**Placebo**	**Simvastatin**	**Eze/Sim**	**Placebo**	**Eze/Sim**
Non-dialysis	2113/2715 (78%)	530/683 (78%)	2116/2722 (78%)	1884/2780 (68%)	1934/2781 (70%)
Dialysis	902/1263 (71%)	212/321 (66%)	904/1284 (70%)	686/1234 (56%)	725/1277 (57%)
All Patients	3015/3978 (76%)	742/1004 (74%)	3020/4006 (75%)	2570/4014 (64%)	2659/4058 (66%)

Source: CSR Tables 10-17 and 14-11.

Use of Non-study Lipid-Lowering Therapy

As noted above, the use of non-study statins increased over the duration of the study (Figure 12). By the end of the first year, 2-3% of patients in each of the three arms were using a non-study statin. By 2.5 years after initial randomization, 10% of patients in the placebo group were using non-study lipid-lowering medications compared to 6% of patients in the ezetimibe/simvastatin group. By the time of each patient's final follow-up visit, 15% of those in the placebo group had started a non-study lipid-lowering medication compared to 10% of those in the ezetimibe/simvastatin group (Table 28).

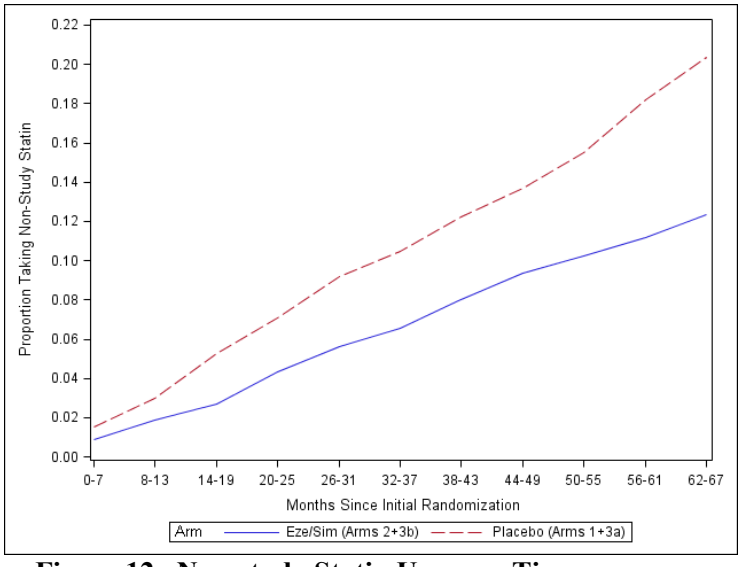


Figure 12. Non-study Statin Use over Time
Source: Derived from CSR Table 10-18. Truncated at 62-67 months.

Table 28. Non-study Lipid-Lowering Therapy Use by Arm

	2.5 Years from Initial Randomization		Final Study Visit	
	Eze/Sim (N=3760)	Placebo (N=3735)	Eze/Sim (N=3512)	Placebo (N=3506)
Non-study statin				
Simvastatin	91 (2%)	156 (4%)	148 (4%)	269 (8%)
Atorvastatin	82 (2%)	127 (3%)	98 (3%)	143 (4%)
Fluvastatin	20 (1%)	24 (1%)	45 (1%)	42 (1%)
Rosuvastatin	4 (0%)	15 (0%)	20 (1%)	33 (1%)
Pravastatin	14 (0%)	16 (0%)	26 (1%)	22 (1%)
Lovastatin	1 (0%)	3 (0%)	1 (0%)	5 (0%)
Subtotal: Any Statin	**212 (6%)**	**341 (9%)**	**337 (10%)**	**513 (15%)**
Other LDL-lowering				
Ezetimibe	12 (0%)	28 (1%)	28 (1%)	36 (1%)
Cholestyramine	3 (0%)	3 (0%)	3 (0%)	6 (0%)
Subtotal: Any LDL-lowering	**217 (6%)**	**351 (9%)**	**350 (10%)**	**529 (15%)**
Fibrate	5 (0%)	7 (0%)	7 (0%)	10 (0%)
Nicotinic acid	5 (0%)	3 (0%)	5 (0%)	6 (0%)
TOTAL Lipid-lowering	**225 (6%)**	**358 (10%)**	**359 (10%)**	**541 (15%)**

Source: CSR Tables 10-19, 10-20.
Includes all patients ever randomized to ezetimibe/simvastatin or placebo (Arms 2+3b vs. 1+3a).
Some patients were taking more than one non-study lipid-lowering therapy.

Subpopulations

The protocol and SAP specified subgroup analyses for the MVE and MAE outcomes, respectively, based on baseline renal and cardiovascular disease, demographics, and baseline lipid profiles. Subgroup analyses were pre-specified to be performed using data from all patients ever randomized to ezetimibe/simvastatin (Arms 2+3b) or placebo (Arms 1+3a).

Reviewer Comments to Aid Interpretation:

1. Many of the applicant-generated figures presented within this document include a column of numbers titled "Het or trend χ^2_1." Note that these values are *not* P values. Instead, these are the χ^2 values for the statistical test performed to assess for differences in treatment effect across categories within a given subgroup. P values that correspond to these test statistics are *not* presented. For your reference, $\chi^2_{(1)} > 2.70$ corresponds to $p < 0.10$; $\chi^2_{(1)} > 3.84$ corresponds to $p < 0.05$; $\chi^2_{(1)} > 6.64$ corresponds to $P < 0.01$; and $\chi^2_{(1)} > 10.83$ corresponds to $P<0.001$. The applicant applied a test for trend when there was a biologically plausible ordering of subgroup categories (e.g., eGFR categories) and a test for heterogeneity in other cases (e.g., race). Therefore, a significant test for trend does *not* indicate that at least one of the categories within the subgroup shows a treatment effect significantly different from the rest; instead, it indicates that there exists a trend in the magnitude of treatment

effect with increasing level (usually tertile) of the value defining the subgroup (e.g., baseline LDL-C).

2. Similar to the secondary efficacy analyses, follow-up for nearly all subgroup analyses begins at the time of assignment to either ezetimibe/simvastatin or placebo, i.e., the initial randomization for the 8384 patients in Arms 1 and 2 and the second randomization for the 886 patients in Arms 3a and 3b. Therefore, the time of "randomization" in subsequent sections refers to this time of assignment to ezetimibe/simvastatin or placebo, unless otherwise specified.

Renal Function

Among the 6,247 patients who were not on dialysis at randomization, ezetimibe/simvastatin reduced the relative risk of MVE by 22% (95% CI, 11% to 31%) and MAE by 22% (95% CI, 9% to 33%) compared to placebo. Among the 3,023 patients who were on dialysis at randomization, ezetimibe/simvastatin reduced the relative risk of MVE by 6% (95% CI, -9% to 20%) and MAE by 10% (95% CI, -8% to 25%) compared to placebo. The tests for heterogeneity of treatment effect across dialysis status at randomization yield P values of 0.08 and 0.25 for MVE and MAE, respectively (Table 29).

Table 29. Treatment Effects on MVE/MAE by Renal Status

	Risk Ratio (95% CI)		P (heterogeneity)
Outcome	**Non-dialysis**	**Dialysis**	
MVE	0.78 (0.69-0.89)	0.94 (0.80-1.09)	0.08
MAE	0.78 (0.67-0.91)	0.90 (0.75-1.08)	0.25

Source: Derived from CSR Fig. 11-11 and 11-12.
Population: all patients ever randomized to ezetimibe/simvastatin or placebo

Among those patients who were not on dialysis at the time of randomization, the treatment effect of ezetimibe/simvastatin on MVE and MAE was compared in subgroups defined by eGFR, tertiles of cystatin C, and levels of proteinuria. The applicant's analysis suggests no statistically significant trend across categories within each subgroup for either MVE or MAE (Figure 13 and Figure 14). Among those who were on dialysis at the time of randomization, there was no evidence for heterogeneity of treatment effect across dialysis modality (hemodialysis vs. peritoneal dialysis) for either MVE or MAE ($\chi^2_{(1)}$=0.38, p=0.54 and $\chi^2_{(1)}$=1.54, p=0.23, respectively), although the peritoneal dialysis subgroup composed only 16% of dialysis patients (Figure 13 and Figure 14).

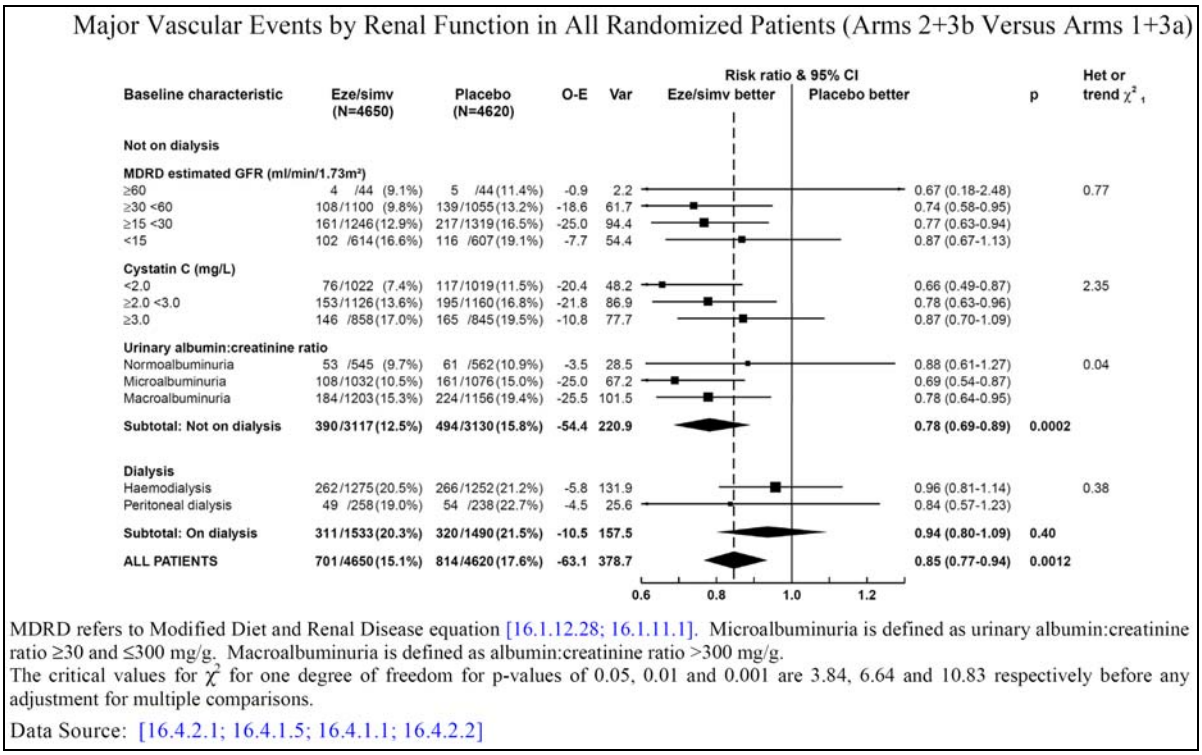


Figure 13. Subgroup Analyses - MVE by Renal Function
Source: CSR Fig. 11-11.

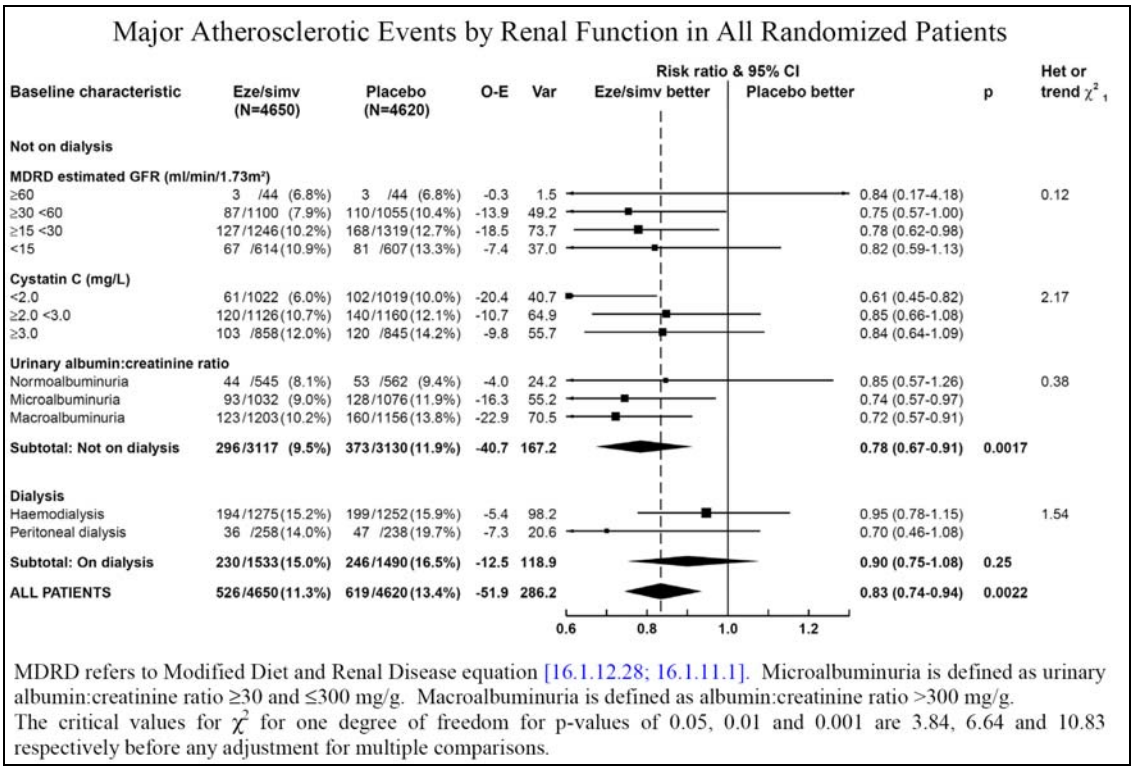


Figure 14. Subgroup Analyses - MAE by Renal Function
Source: CSR Fig. 11-12

The applicant hypothesized that differences in the magnitude of LDL-C reduction within various subgroups could confound the relationship between the defining characteristic of the subgroup (e.g., dialysis status) and treatment effect. In an attempt to address this, the subgroup analyses listed above were repeated after weighting the risk reduction by the magnitude of LDL-C reduction, defined by the absolute difference in mean LDL-C at 2.5 years between the ezetimibe/simvastatin and placebo arms in a particular subgroup. This weighting narrowed, but did not eliminate, the difference in treatment effects between subgroups (e.g., non-dialysis vs. dialysis) (Appendix, Figure 31 and Figure 32).

Reviewer Comment: These weighted analyses use mid-trial observations of population averages at a single point in time to "adjust" the time-to-event analysis of the entire trial. This reviewer considers these analyses exploratory and hypothesis-generating.

Demographics

The effect of ezetimibe/simvastatin on MVE and MAE appears consistent across age categories and race. The applicant excluded patients initially randomized to simvastatin alone in these analyses of MVE to maintain consistency with the protocol-specified primary endpoint (Figure 15). The MAE analysis includes all patients ever randomized to ezetimibe/simvastatin or placebo as specified in the SAP (Figure 16).

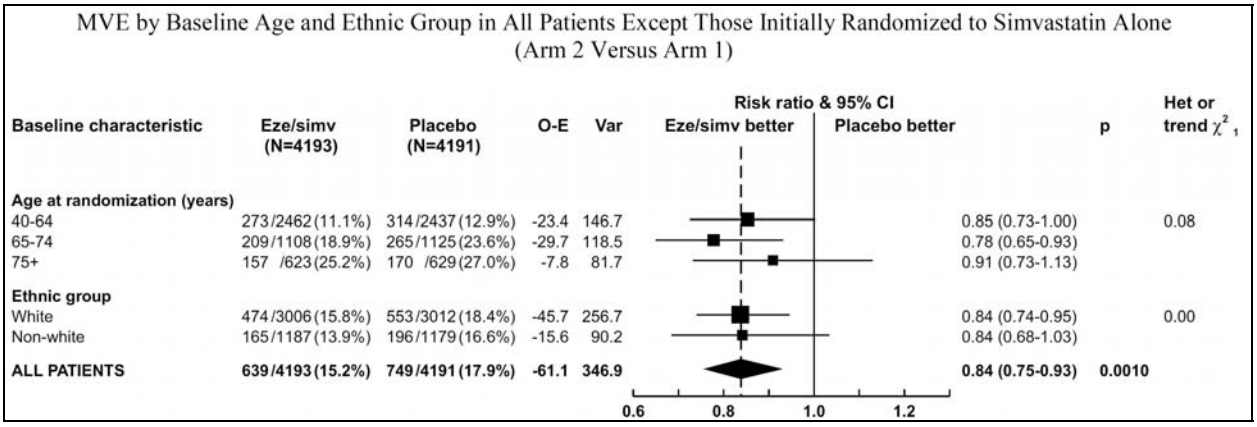


Figure 15. Subgroup Analyses - MVE by Demographic Characteristics
Source: CSR Fig. 11-19

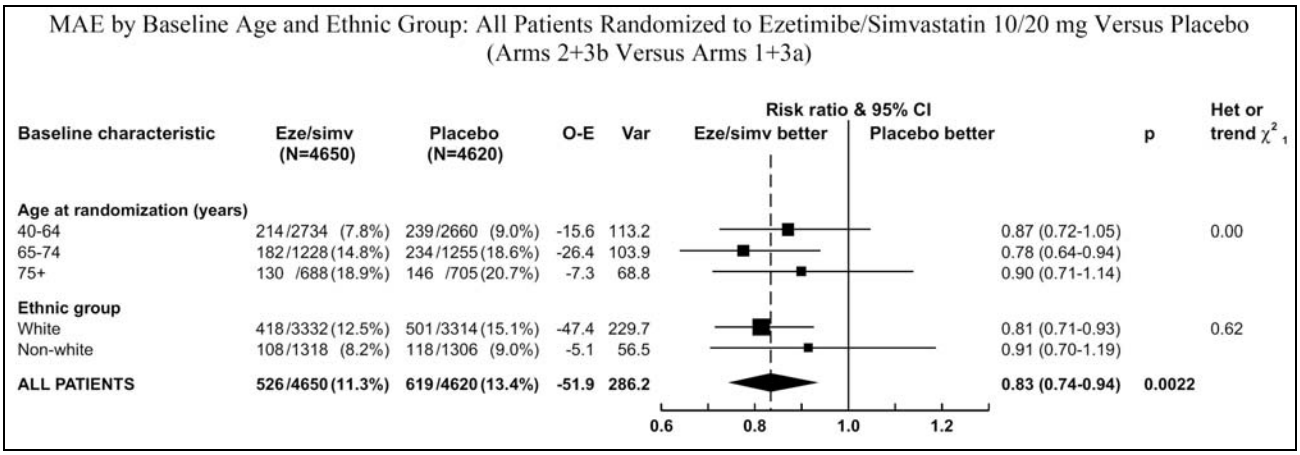


Figure 16. Subgroup Analyses - MAE by Demographic Characteristics
Source: CSR Fig. 11-20

Reviewer Comment: Given the relatively small number of non-white patients in this trial, the applicant chose not to subdivide this group further in subgroup analyses. The FDA statistical reviewer (Dr. Dongmei Liu) reports a treatment effect of 0.84 (0.74-0.95) in whites, 1.08 (0.61-1.92) in blacks, and 0.80 (0.63-1.01) in Asians.

Other Baseline Clinical Characteristics

The applicant compared the treatment effect of ezetimibe/simvastatin on MVE and MAE within several subgroups defined by clinical characteristics at the time of randomization. For most continuous variables, potential differences in treatment effect were assessed across tertiles. Without adjusting for multiple comparisons, there was evidence for a statistically significant trend in treatment effect for both MVE and MAE in groups defined by total cholesterol, non-HDL-C, and apolipoprotein B, with greater treatment effects observed in patients with higher baseline values. Additionally, patients with higher baseline levels of LDL-C experienced a statistically significantly greater treatment effect on MVE but the evidence for a trend in treatment effect was not as strong for MAE (test for trend p=0.01 and p=0.06 for MVE and MAE, respectively).

Patients with BMI in higher tertiles demonstrated a greater treatment effect on both MVE and MAE, although the evidence was slightly less strong for MVE (test for trend p=0.06 and p=0.04 for MVE and MAE, respectively). Patients with larger waist circumference demonstrated a greater treatment effect on MAE but not MVE (test for trend p=0.14 and p=0.04 for MVE and MAE, respectively).

Among the 15% of trial participants with a history of either coronary disease, peripheral arterial disease, or cerebrovascular disease, ezetimibe/simvastatin reduced the risk of MVE by 10% (Rate ratio 0.90; 95% CI 0.75-1.09) and MAE by 9% (RR 0.91; 95% CI 0.74-1.13) compared with placebo. Among the 85% of trial participants with a history of none of these vascular

conditions, ezetimibe/simvastatin reduced the risk of MVE by 18% (RR 0.82; 95% CI 0.72-0.92) and MAE by 21% (RR 0.79; 95% CI 0.69-0.91).

Figure 17 and Figure 18 summarize the analyses of treatment effect on MVE within subgroups defined by baseline clinical characteristics; Figure 19 and Figure 20 present the analogous analyses of treatment effect on MAE. Note that in these figures, the test for heterogeneity or trend within each subgroup is presented as the $\chi^2_{(1)}$ statistic. For reference, $\chi^2_{(1)} > 2.70$ corresponds to $p < 0.10$; $\chi^2_{(1)} > 3.84$ corresponds to $P < 0.05$; $\chi^2_{(1)} > 6.64$ corresponds to $P < 0.01$; and $\chi^2_{(1)} > 10.83$ corresponds to $P<0.001$.

As explained previously, the applicant hypothesized that differences in the magnitude of LDL-C reduction within various subgroups could confound the relationship between the defining characteristic of the subgroup (e.g., BMI) and treatment effect. Weighting the risk reduction by the absolute difference in mean achieved LDL-C at 2.5 years did not substantially change the results except for the attenuation, but not elimination, of the differences in treatment effect observed across levels of baseline lipid characteristics (total cholesterol, LDL-C, non-HDL-C, and apolipoprotein B). These data are presented in the Appendix (p. 116).

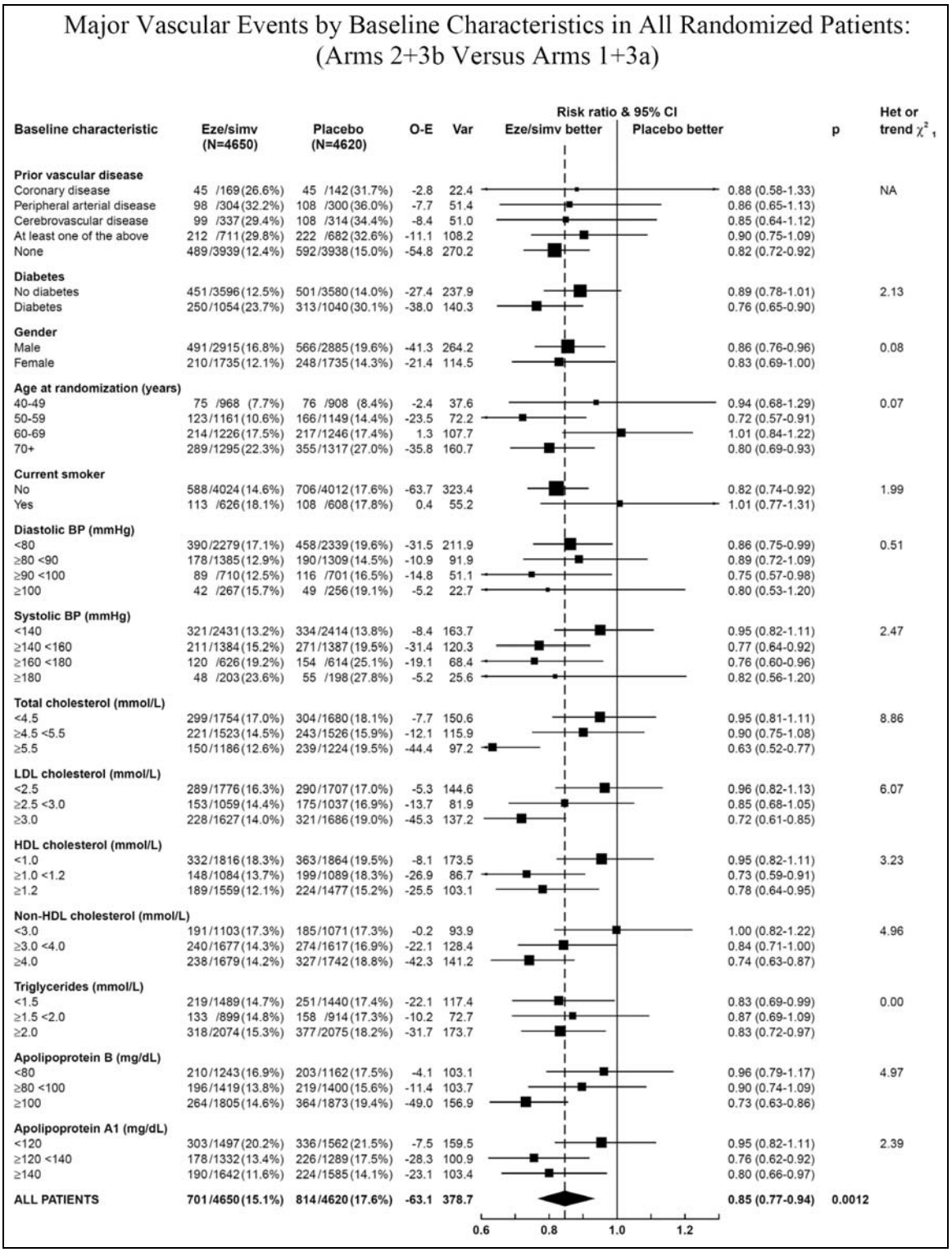


Figure 17. Subgroup Analyses - MVE by Baseline Clinical Characteristics I
Source: CSR Fig 11-13
Categories in conventional units: total cholesterol <174, 174-212, ≥212 mg/dL; LDL <97, 97-116, ≥116 mg/dL; HDL <39, 39-46, ≥46 mg/dL; TG <133, 133-177, ≥177 mg/dL.

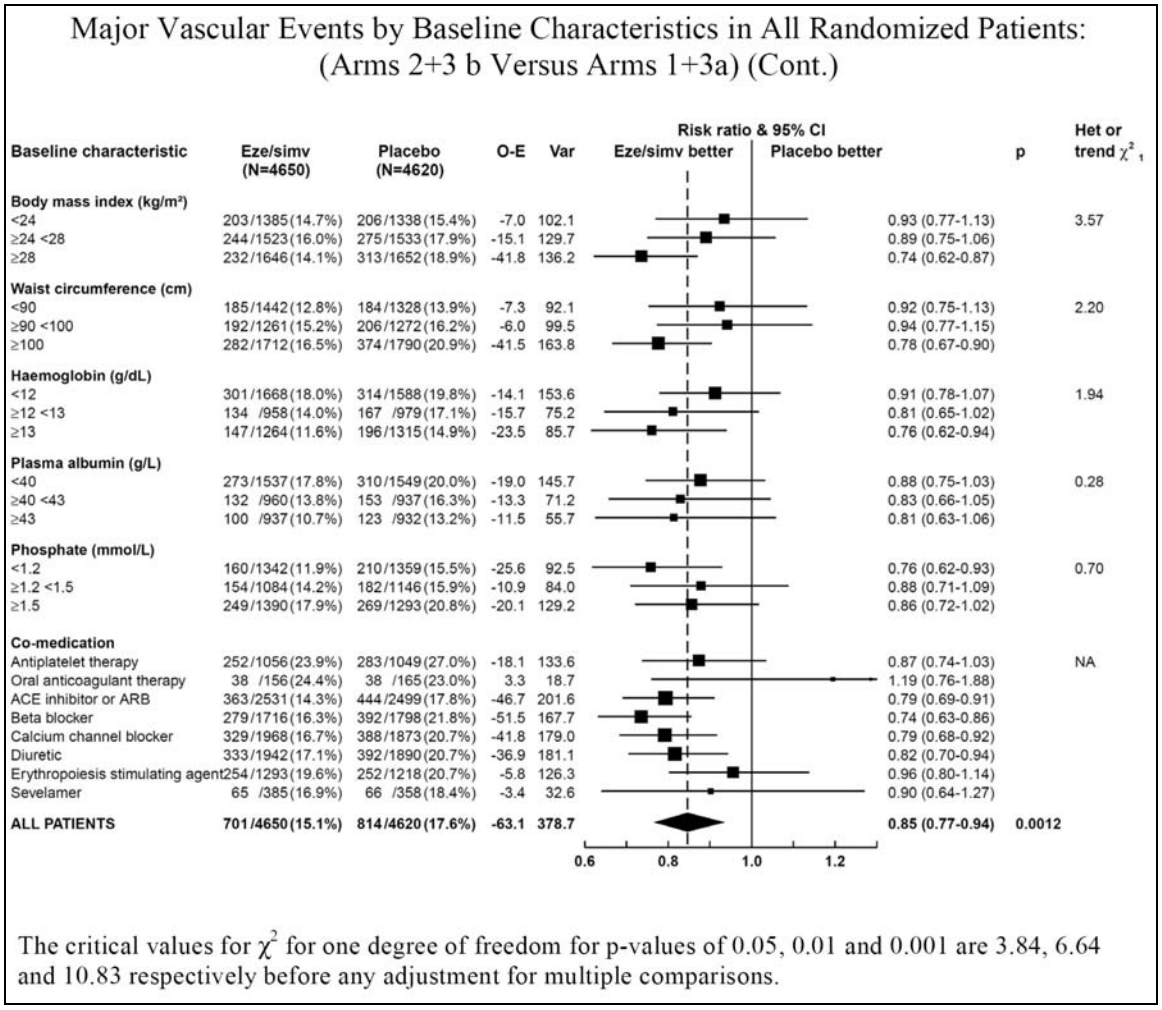


Figure 18. Subgroup Analyses - MVE by Baseline Clinical Characteristics II
Source: CSR Fig. 11-13

The test for heterogeneity or trend within each subgroup is presented as the $\chi^2_{(1)}$ statistic. For reference, $\chi^2_{(1)} > 2.70$ corresponds to $p < 0.10$; $\chi^2_{(1)} > 3.84$ corresponds to $P < 0.05$; $\chi^2_{(1)} > 6.64$ corresponds to $P < 0.01$; and $\chi^2_{(1)} > 10.83$ corresponds to $P<0.001$.

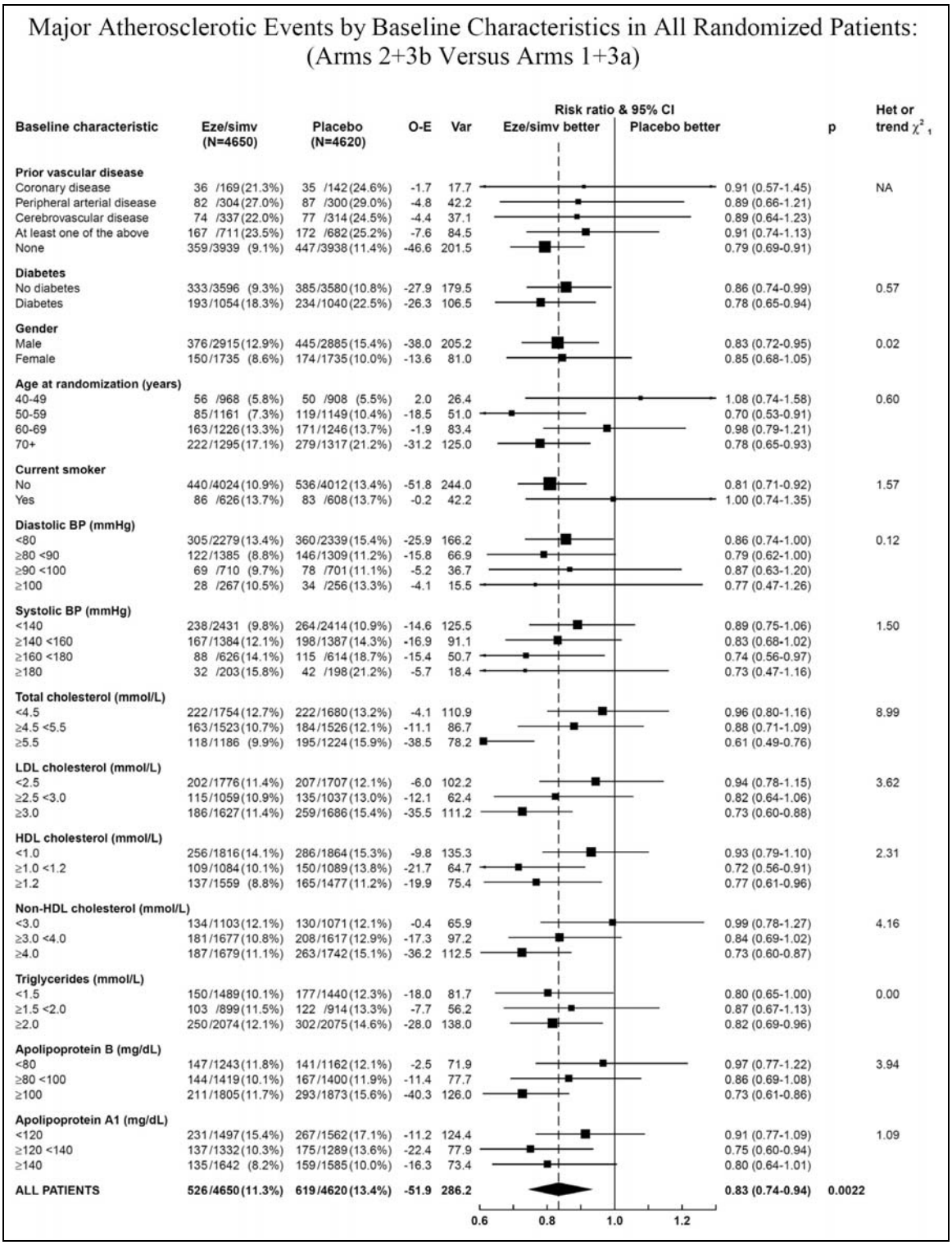


Figure 19. Subgroup Analyses - MAE by Baseline Clinical Characteristics I
Source: CSR Fig. 11-14
Categories in conventional units: total cholesterol <174, 174-212, ≥212 mg/dL; LDL <97, 97-116, ≥116 mg/dL; HDL <39, 39-46, ≥46 mg/dL; TG <133, 133-177, ≥177 mg/dL.

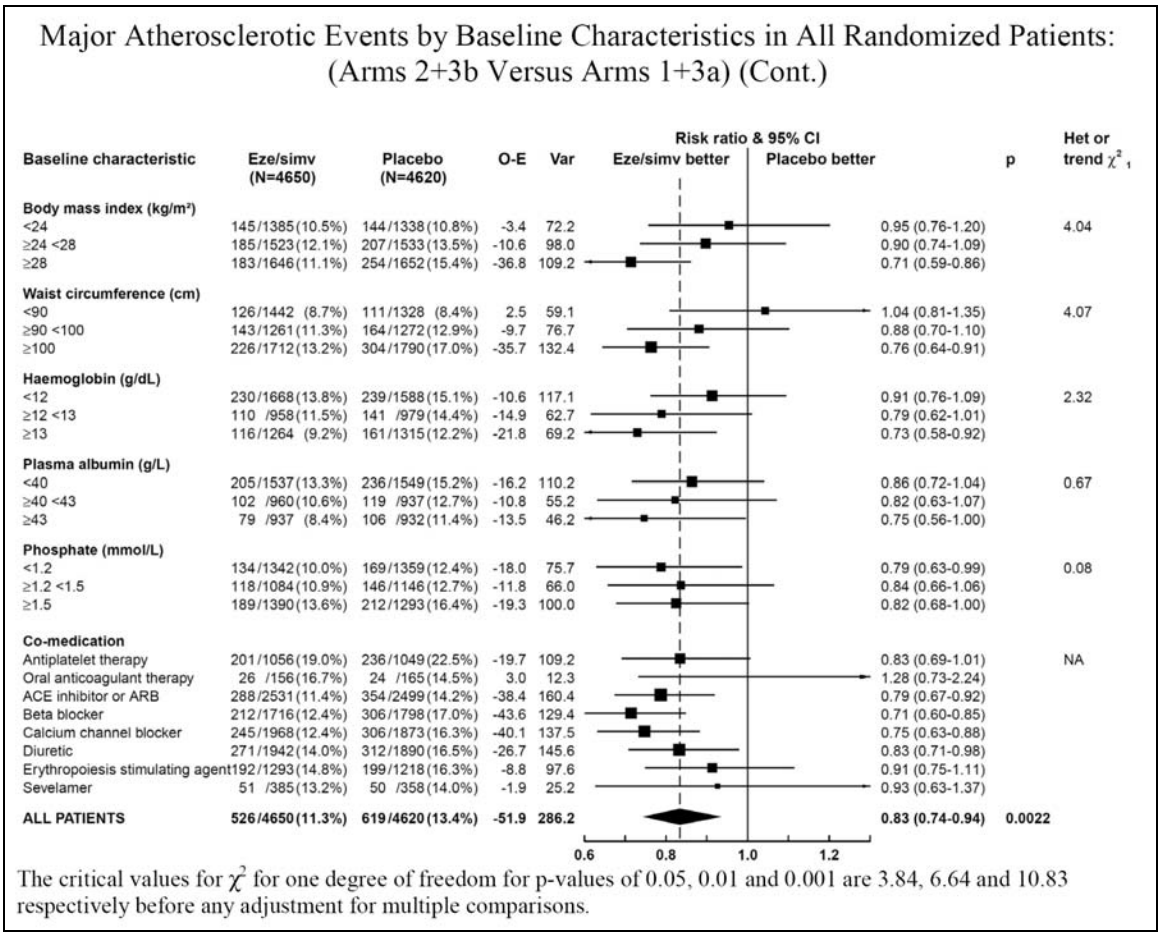


Figure 20. Subgroup Analyses - MAE by Baseline Clinical Characteristics II
Source: CSR Fig. 11-14

The test for heterogeneity or trend within each subgroup is presented as the $\chi^2_{(1)}$ statistic. For reference, $\chi^2_{(1)} > 2.70$ corresponds to $p < 0.10$; $\chi^2_{(1)} > 3.84$ corresponds to $P < 0.05$; $\chi^2_{(1)} > 6.64$ corresponds to $P < 0.01$; and $\chi^2_{(1)} > 10.83$ corresponds to $P<0.001$.

Exploratory FDA Analyses

MVE Excluding Revascularization

The primary composite endpoints for AURORA and 4D did not include revascularization events. In an exploratory analysis, revascularization events were removed from the primary composite endpoint (MVE) for SHARP. Similar to other exploratory analyses, patients initially assigned to simvastatin were included. There were 527 (11.3%) first non-revascularization MVEs among those ever assigned to ezetimibe/simvastatin and 593 (12.8%) among those ever assigned to placebo; in a Cox model that included adjustment for previous simvastatin exposure, assignment to ezetimibe/simvastatin conferred a 12% risk reduction (HR 0.88; 95% CI, 0.78-0.99; p=0.03) (Figure 21). Exclusion of those initially assigned to simvastatin produced nearly identical results.

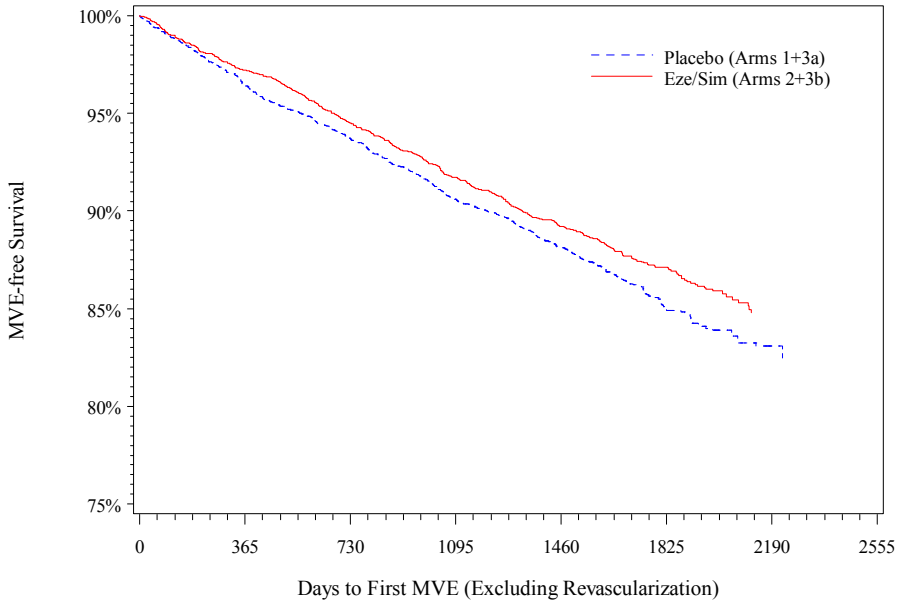


Figure 21. Kaplan-Meier of MVE (Excluding Revascularization)
Source: FDA reviewer's analysis of submitted dataset (*sradata.xpt*).
Similar to other exploratory analyses, all patients ever randomized to ezetimibe/simvastatin or placebo are included (i.e., Arms 2+3b vs. Arms 1+3a).

Similarly, there were 336 (7.2%) first non-revascularization MAEs (i.e., major coronary event or non-hemorrhagic stroke) in the ezetimibe/simvastatin group and 390 (8.4%) in the placebo group; in a Cox model that included adjustment for previous simvastatin exposure, assignment to ezetimibe/simvastatin conferred a 15% risk reduction (HR 0.85; 95% CI, 0.74-0.99; p=0.03).

Treatment Effect on MVE Components by Renal Status at Randomization

Figure 22 depicts the point estimates of the treatment effects for components of the primary composite outcome stratified by dialysis status at randomization. This analysis includes all patients ever randomized to ezetimibe/simvastatin (Arms 2+3b) or placebo (Arms 1+3a). No hypothesis testing was performed for this exploratory analysis given the caution that must be exercised when attempting to interpret treatment effects on components of a composite endpoint in a subgroup. This reviewer regards these data as hypothesis-generating.

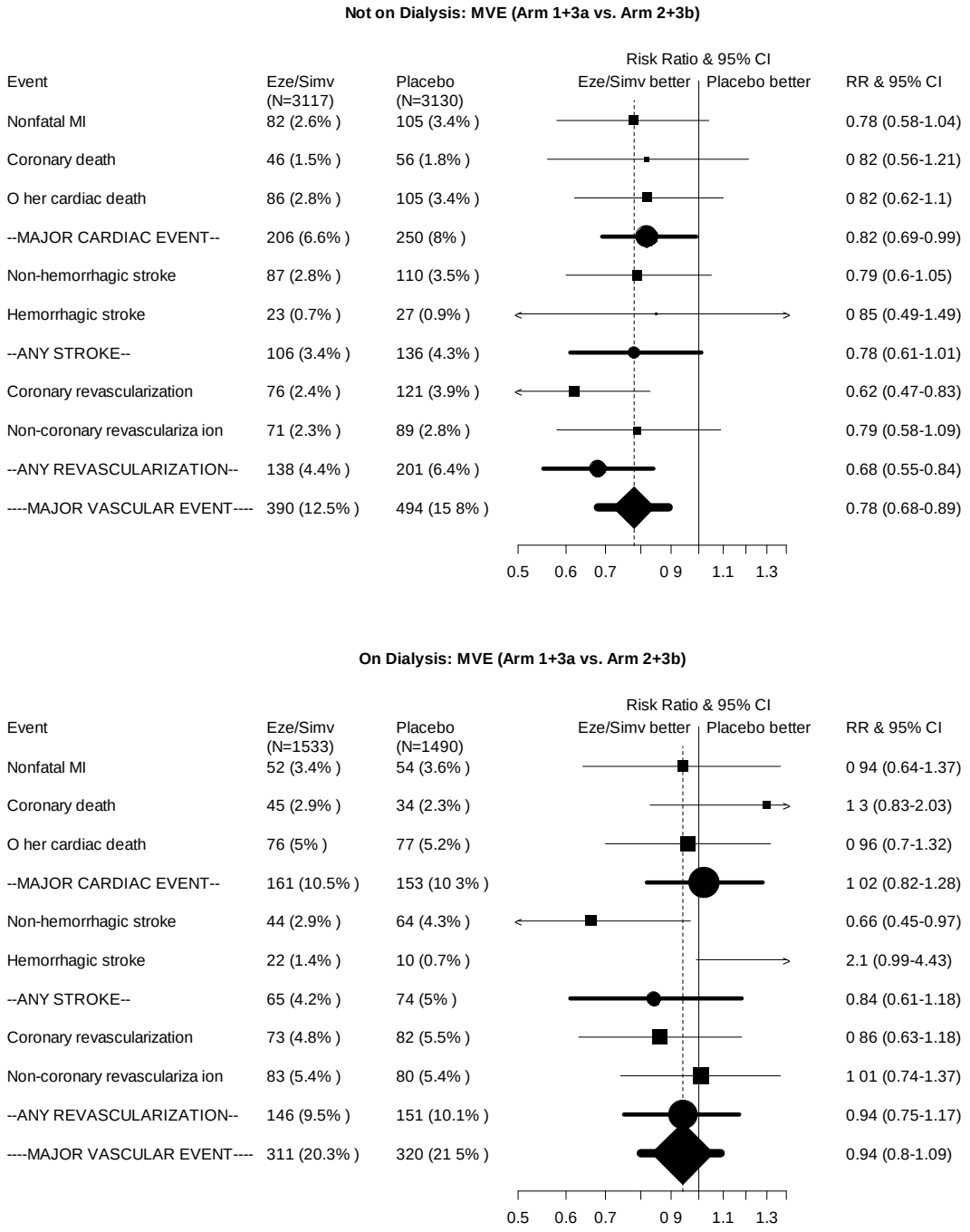


Figure 22. Treatment Effect on MVE Components by Renal Status (Exploratory)
Source: FDA statistical reviewer's analysis using submitted analysis dataset (*sradata.xpt*).

Efficacy by Country

Figure 23 depicts the average treatment effect and 95% CI for the primary protocol-specified endpoint (MVE), including patients initially assigned to simvastatin. Despite several differences between the U.S. and non-U.S. populations (Table 10), the point estimate in the relatively small U.S. study population was qualitatively similar to the overall result.

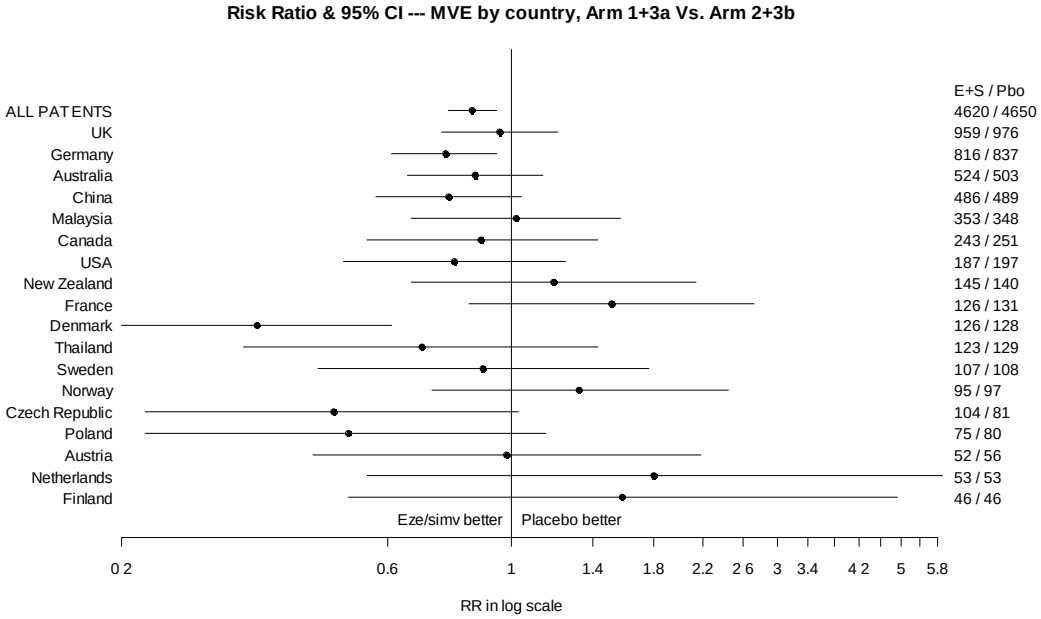


Figure 23. Treatment Effect on MVE by Country
Source: FDA statistical reviewer's analysis.

To describe geographical variation in the incidence of endpoints, Table 30 shows the cumulative incidence of various endpoints that compose the primary composite MVE in the placebo group.

Table 30. Frequency of 1st Events by Region (Placebo Only)

Outcome	North America (N=430)	Europe (N=2559)	Australia/NZ (N=669)	Asia (N=962)
Nonfatal MI	17 (4%)	94 (4%)	32 (5%)	16 (2%)
Coronary (CHD) death	3 (1%)	51 (2%)	15 (2%)	21 (2%)
Other cardiac (non-CHD) death	25 (6%)	77 (3%)	25 (4%)	55 (6%)
Major cardiac event	42 (10%)	211 (8%)	62 (9%)	88 (9%)
Non-hemorrhagic stroke	13 (3%)	86 (3%)	34 (5%)	41 (4%)
Hemorrhagic stroke	2 (0.5%)	10 (0.4%)	1 (0.2%)	24 (2.5%)
Any stroke	15 (3%)	96 (4%)	35 (5%)	64 (7%)
Coronary revascularization	16 (4%)	146 (6%)	28 (4%)	13 (1%)
Non-coronary revascularization	14 (3%)	127 (5%)	25 (4%)	3 (0.3%)

Any revascularization	27 (6%)	257 (10%)	52 (8%)	16 (2%)
MAJOR VASCULAR EVENT	73 (17%)	462 (18%)	125 (18.7%)	154 (16.0%)

Source: FDA reviewer's analysis of submitted raw data (*sradata.xpt*).
Population: Arms 1+3a only.

Reviewer Comment: Although no hypothesis testing was performed on these data given their descriptive nature, it appears that hemorrhagic strokes were most commonly reported from Asia. In addition, revascularization procedures were less commonly performed in Asia.

SHARP, 4D, and AURORA

Neither of the previous trials of statins in hemodialysis populations, 4D and AURORA, demonstrated a statistically significant benefit of statin therapy on their primary composite endpoints (nonfatal MI, stroke, cardiovascular death). Similarly, as described above, SHARP did not demonstrate a statistically significant treatment effect in the pre-specified dialysis subgroup (Rate Ratio 0.94; 95% CI 0.80-1.09 for MVE and RR 0.90; 95% CI 0.75-1.08 for MAE).

In SHARP, the difference in the observed point estimates of the treatment effect across dialysis status could reflect differences in patient characteristics, adherence to therapy, or response to therapy. Here, comparative data within the SHARP trial (non-dialysis vs. dialysis patient characteristics) and across trials are summarized.

Table 31 describes patient characteristics at randomization by renal status. On average, dialysis patients were younger, had lower BMI, and had lower total cholesterol and LDL-C before receiving study treatment. Before receiving any study treatment, approximately 37% of non-dialysis patients had LDL-C levels < 100 mg/dL compared with 51% of dialysis patients.

Table 31. Patient Characteristics by Renal Status

Characteristic	**Renal Status at Randomization to Eze/Sim or Placebo**	
	Non-dialysis (N=6247)	**Dialysis (N=3023)**
Age (y)	62 (12)	59 (12)
40-49	1070 (17%)	806 (27%)
50-59	1490 (24%)	820 (27%)
60-69	1744 (28%)	728 (24%)
≥70	1943 (31%)	669 (22%)
Male	3884 (62%)	1916 (63%)
Race		
White	4483 (72%)	2163 (72%)
Black	120 (2%)	144 (5%)
Asian	1523 (24%)	563 (19%)
Other	106 (2%)	141 (5%)

Characteristic	Renal Status at Randomization to Eze/Sim or Placebo	
	Non-dialysis (N=6247)	Dialysis (N=3023)
Diabetes	1423 (23%)	664 (22%)
Prior Vascular Disease		
Coronary disease	217 (3%)	94 (3%)
Peripheral arterial disease	367 (6%)	237 (8%)
Cerebrovascular disease	461 (7%)	190 (6%)
≥1 of the above 3	932 (15%)	461 (15%)
Renal Disease Etiology		
Diabetic nephropathy	887 (14%)	476 (16%)
Glomerulonephritis	908 (15%)	612 (20%)
Secondary GN / Vasculitis	152 (2%)	70 (2%)
TIN/Pyelonephritis	623 (10%)	261 (9%)
HTN/Lg Vessel Disease	1303 (21%)	481 (16%)
Cystic, Hereditary, or Congenital	775 (12%)	436 (14%)
Neoplasms/Tumors	58 (1%)	43 (1%)
Miscellaneous	499 (8%)	195 (6%)
Unknown/Missing	1042 (17%)	449 (15%)
Smoking Status		
Current	763 (12%)	471 (16%)
Former	2240 (36%)	1032 (34%)
Systolic BP (mmHg)	139 (21)	138 (24)
Diastolic BP (mmHg)	80 (12)	78 (13)
BMI (kg/m^2)	27.4 (5.5)	26.5 (5.9)
≤25	2212 (35%)	1338 (44%)
>25 and ≤30	2359 (38%)	982 (32%)
>30	1560 (25%)	626 (21%)
Waist circ (cm)	97 (15)	97 (16)
Renal Status		
CKD	6237 (99.8%)	NA
Functioning transplant	10 (0.2%)	NA
Hemodialysis	NA	2527 (84%)
Peritoneal dialysis	NA	496 (16%)
Labs*		
Total chol. (mg/dL)	194 (45)	180 (45)
≥200	2516 (40%)	848 (28%)
LDL-C (mg/dL)	111 (33)	100 (33)
<70	555 (9%)	507 (17%)
≥70 and <100	1767 (28%)	1019 (34%)
≥100 and <130	2141 (34%)	830 (27%)
≥130	1563 (25%)	508 (17%)
HDL-C (mg/dL)	44 (13)	42 (13)
TG (mg/dL)	169 [120, 250]	170 [115, 246]
Apo B (mg/dL)	99 (25)	92 (26)
Apo A1 (mg/dL)	136 (29)	129 (27)

Characteristic	Renal Status at Randomization to Eze/Sim or Placebo	
	Non-dialysis (N=6247)	Dialysis (N=3023)
Co-Medication†	**N=6382**	**N=3056**
Antiplatelet	1207 (19%)	871 (29%)
Oral anticoagulant	211 (3%)	167 (5%)
ACE	2537 (40%)	813 (27%)
ARB	1657 (26%)	488 (16%)
Beta blocker	2349 (37%)	1181 (39%)
CCB	2819 (44%)	1087 (36%)
Diuretic	2869 (45%)	1062 (35%)
ESA	779 (12%)	1724 (56%)
Phosphate binder	1021 (16%)	2479 (81%)

Source: FDA reviewer's analysis of submitted raw data and SHARP baseline paper.[27]
* For patients in Arms 3a and 3b, lipid levels at initial randomization were used.
† Co-medications as presented in the SHARP baseline paper,[27] which includes Arm 3 patients at *initial* randomization (N=6382 non-dialysis and 3056 dialysis).

Table 32 compares the study populations and designs of the 4D, AURORA, and SHARP trials.

Table 32. Study Designs of 4D, AURORA, SHARP

	4D	AURORA	SHARP
Population	Type 2 DM ESRD on HD ≤ 2y LDL 80-190 mg/dL Age 18-80 (20% taking statins)	ESRD on HD ≥3mo No statin x 6 mo	2/3 non-dialysis (men Cr ≥1.7 mg/dL; women Cr ≥1.5 mg/dL); 1/3 ESRD No h/o MI or coronary revasc Age ≥40 Not on statin
N	1255	2773	9270
Location	178 centers in Germany	~300 centers, multinational, no US sites	308 centers in 18 countries (4% subjects in US)
Years of trial	1998-2004	2003-2008	2003-2010
Sponsor	Pfizer	AstraZeneca	Merck/Oxford
Intervention	atorva 20 mg daily (reduce 50% if LDL < 50 mg/dL) vs. placebo	rosuvastatin 10 mg daily vs. placebo	eze/sim (10/20 mg) daily vs. placebo
Primary Endpoint	Nonfatal MI (including silent), stroke, cardiovascular death	Nonfatal MI (including silent), stroke, cardiovascular death	Nonfatal MI (not silent), stroke, cardiac death, any revascularization
Median duration	4.0 y	3.8 y	4.9 y

Baseline characteristics of the trial participants are summarized in Table 33.

Table 33. Patient Characteristics in 4D, AURORA, SHARP

	4D	AURORA	SHARP (All)	SHARP (Dialysis subgroup)
Age (mean)	66	64	61	59
Male	54%	62%	63%	63%
Race	NR	85% white 4% black 5% Asian 4% Hispanic	72% white 3% black 23% Asian 3% Other	72% white 5% black 19% Asian 5% Other
Years on RRT (mean)	0.7	3.7 on HD	-	3.7 (median 2.2)
Cause of renal disease	NR			
HTN		20%	19%	16%
DM		19%	15%	16%
GN/vasculitis		19%	19%	22%
Reflux/pyelo/IN		14%	10%	9%
Genetic		13%	13%	14%
Other		15%	8%	8%
Unknown			16%	15%
Diabetes	100%	26%	23%	22%
PVD	45%	15%	7%	8%
Coronary disease	29%	10% h/o MI (40% with "Cardiovascular disease")	3%	3%
Cerebrovascular disease	18%	NR	7%	6%
Tot. chol (mean)	219	174	189	180
LDL-C (mean)	126	100	108	100
HDL-C (mean)	36	45	43	42
hsCRP (mg/L; median)	NR	5.0 [2.1, 14.0]	NR	NR
Antiplatelet drugs	52%	42%	23%	29%
Beta-blockers	38%	37%	38%	39%
Diuretics	NR	31%	42%	35%
ACE	48%	-	-	27%
ARB	12%	-	-	16%
ACE/ARB	(See above)	37%	54%	-

Overall, all-cause mortality was higher in 4D and AURORA than SHARP. Approximately 49% of participants died in 4D, 47% in AURORA, and 24% in SHARP (33% of those on dialysis at final randomization).

The proportions of deaths attributable to either MI or other CHD-related causes were 11% in 4D, 32% in AURORA, and 8% in SHARP.

Similar to the observation that dialysis patients were reportedly less adherent to study therapy in SHARP, adherence was challenging in 4D and AURORA as well. In 4D, 72% of subjects completed the course of study treatment per protocol; at 2 years, among those surviving without having had an event, 51% and 48% continued receiving study treatment in the atorvastatin and placebo arms, respectively. In AURORA, approximately 50% in each group remained on study therapy until the end of study or death.

Because of differences in when LDL-C levels were measured in each study, it is difficult to compare the relationships between compliance, LDL-C reduction, and treatment effects. The median placebo-subtracted LDL reduction in 4D was 41% at 4 weeks (72 vs. 120 mg/dL in atorvastatin and placebo arms, respectively). The mean placebo-subtracted LDL reduction in AURORA was 42% at 3 months (58 vs. 99 mg/dL in rosuvastatin and placebo arms, respectively). The mean placebo-subtracted LDL reduction in SHARP was 39% at 1 year and 32% at 2.5 years (70 vs. 103 mg/dL in ezetimibe/simvastatin and placebo, respectively).

In the overall SHARP population, the treatment effects on nonfatal MI, ischemic stroke, and coronary revascularization appear to contribute substantially to the overall effect on major vascular events. In 4D, 70 (11%) patients in the atorvastatin group and 79 (12%) in the placebo group experienced at least one nonfatal MI (RR 0.88; 95% CI 0.64-1.21; p=0.42). This trial included both silent and symptomatic nonfatal MI, and silent MI were more common. There were 41 and 50 patients in the atorvastatin and placebo groups, respectively, who experienced at least one silent MI compared with 33 and 35 patients who experienced at least one symptomatic MI. In AURORA, 91 (7%) patients in the rosuvastatin group and 107 (8%) in the placebo group experienced at least one nonfatal MI (HR 0.84; 95% CI 0.64-1.11; p=0.23).

In 4D, there was a 2-fold *increased* risk of fatal stroke among those receiving atorvastatin (RR 2.03; 95% CI 1.05-3.93; p=0.04), which seemed to reflect an imbalance in the numbers of fatal ischemic strokes (18 vs. 7 in the atorvastatin and placebo groups, respectively). There was not, however, a suggestion of an increase in the risk of nonfatal strokes with atorvastatin (RR 1.04; 95% CI 0.64-1.69; p=0.89). This observation with respect to fatal strokes could be the result of chance given the number of individual component endpoints examined in secondary/exploratory analyses. Revascularization was included as part of the secondary "All cardiac events combined" secondary endpoint in 4D, along with death from cardiac causes and nonfatal MI. Atorvastatin reduced the relative risk of this secondary composite endpoint by 18% (RR 0.82; 95% CI 0.68-0.99; p=0.03). There were 45 (7%) PTCA events in the placebo group and 34 (5%) in the atorvastatin group; similarly, there were fewer CABG events in the atorvastatin group (30 [5%] vs. 24 [4%]).

In AURORA, there was no statistically significant effect of rosuvastatin on nonfatal stroke (HR 1.17; 95% CI 0.79-1.75), death from ischemic stroke (0.4 vs. 0.3 events per 100 patient-years in

the rosuvastatin and placebo groups, respectively), death from hemorrhagic stroke (0.3 vs. 0.4 events per 100 patient-years), or revascularization (HR 0.98; 95% CI 0.78-1.23; p=0.88).

SHARP: Efficacy Summary

- In patients with moderate-to-severe chronic kidney disease (men with Cr ≥1.7 mg/dL, women with Cr ≥1.5 mg/dL) and no history of myocardial infarction or coronary revascularization, treatment with ezetimibe/simvastatin reduced the relative risk of major vascular events (cardiac death, nonfatal MI, stroke, or any revascularization) by 16% (95% CI, 7% to 25%; p=0.001) compared with placebo.
- The results are similar whether one includes or excludes the ~10% of patients initially assigned to simvastatin and whether one limits the composite endpoint to major atherosclerotic events (coronary death, nonfatal MI, non-hemorrhagic stroke, or any revascularization).
- In secondary and exploratory analyses, nonfatal MI, ischemic stroke, and coronary revascularization seem to contribute substantially to the composite endpoint.
- Among patients assigned to ezetimibe/simvastatin, 45 (1.0%) had at least one hemorrhagic stroke compared with 37 (0.8%) among those assigned to placebo (RR 1.21; 95% CI 0.78-1.86).
- In a pre-specified subgroup analysis:
    - Among the 6,247 patients who were not on dialysis at randomization, ezetimibe/simvastatin reduced the relative risk of MVE by 22% (95% CI, 11% to 31%) compared with placebo.
    - Among the 3,023 patients who were on dialysis at randomization, ezetimibe/simvastatin reduced the relative risk of MVE by 6% (95% CI, -9% to 20%) compared with placebo.
    - A test for heterogeneity of treatment effect on MVE across dialysis status yields P=0.08.
- In a pre-specified subgroup analysis involving pre-dialysis patients, there was no statistically significant trend of treatment effect on MVE across stages of chronic kidney disease (eGFR ≥60, 30-60, 15-30, <15 mL/min/1.73m^2) (p=0.38).
- This trial does not provide evidence for an effect of ezetimibe/simvastatin on slowing the progression of chronic kidney disease.
- At 2.5 years after initial randomization, the mean LDL-C level in the ezetimibe/simvastatin group was 32% lower than the placebo group (70 mg/dL vs, 103 mg/dL). The relative reduction in LDL-C was greater among non-dialysis patients than dialysis patients (-34% vs. -23%); it is possible that this reflects the reported difference in compliance with study medication between non-dialysis and dialysis patients.

SHARP: Safety Results

Exposure to Study Treatment

SHARP used only one dose of ezetimibe/simvastatin (10/20 mg) and simvastatin (20 mg). Mean duration of exposure to study drug during the "year 1" analyses was 321 days. In all three treatment groups of year 1, 89% of patients took study drug for ≥6 months and 33% for 12-13 months (Table 34).

Table 34. Exposure for Specified Durations During Year 1

Months of Exposure	Eze/Sim Arm 2 (N=4193)	Simvastatin Arm 3 (N=1054)	Placebo Arm 1 (N=4191)
12 – 13	1372 (33%)	343 (33%)	1351 (32%)
6 – 11	2330 (56%)	586 (56%)	2365 (56%)
0 – 5	491 (12%)	125 (12%)	475 (11%)

Source: 02 August 2011 response to FDA information request.
A report of compliance <10% was analyzed as if the subject was not taking study drug.

Among patients ever randomized to ezetimibe/simvastatin or placebo, the mean exposure durations to study drug were 1187 and 1160 days, respectively. Approximately 60% of those ever randomized to ezetimibe/simvastatin or placebo were exposed to study treatment for more than 3 years and 17% were exposed for less than one year. Table 35 describes the cumulative distribution function of drug exposure by treatment arm by 6-month intervals.

Table 35. Exposure for Specified Durations From Final Randomization

Months of Exposure	Eze/Sim Arms 2+3b (N=4650)		Placebo Arms 1+3a (N=4620)	
	n (%)	Cumulative % Exposed ≥ Specified Duration	n (%)	Cumulative % Exposed ≥ Specified Duration
78 – 83	6 (0.1%)	0.1%	4 (0.1%)	0.1%
72 – 77	104 (2%)	2%	86 (2%)	2%
66 – 71	282 (6%)	8%	254 (5%)	7%
60 – 65	409 (9%)	17%	380 (8%)	16%
54 – 59	444 (10%)	27%	445 (10%)	25%
48 – 53	586 (13%)	39%	549 (12%)	37%
42 – 47	645 (14%)	53%	629 (14%)	51%
36 – 41	296 (6%)	60%	312 (7%)	58%
30 – 35	300 (6%)	66%	286 (6%)	64%
24 – 29	239 (5%)	71%	264 (6%)	70%
18 – 23	252 (5%)	77%	287 (6%)	76%
12 – 17	285 (6%)	83%	288 (6%)	82%
6 – 11	325 (7%)	90%	381 (8%)	90%
0 – 5	477 (10%)	100%	455 (10%)	100%

Source: Derived from 02 August 2011 response to FDA information request.
A report of compliance <10% was analyzed as if the subject was not taking study drug.

Safety Results

The applicant conducted two evaluations of SHARP safety data (Figure 24):

1. The Year 1 safety evaluation comprised the 9,438 patients assigned to Arm 1 (placebo), Arm 2 (ezetimibe/simvastatin), or Arm 3 (simvastatin). All SAEs that occurred during the first year after initial randomization compose the safety database for this time period.
2. The safety evaluation involving all patients ever randomized to placebo or ezetimibe/simvastatin comprised the 8,384 patients assigned to Arm 1 (placebo), Arm 2 (ezetimibe/simvastatin), and the subset of 886 Arm 3 patients who underwent reassignment to placebo or ezetimibe/simvastatin. These analyses excluded events that occurred during the first year in Arm 3 (see open markers in Figure 24). Events occurring during the first year in Arms 1 and 2 were included.

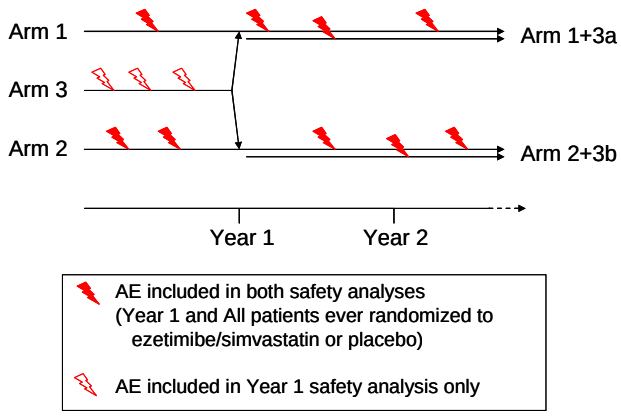


Figure 24. Schematic of Safety Analyses
Source: FDA.

Unless otherwise indicated, all analyses adhere to the ITT principle; i.e., adverse events are included whether or not the patient was taking study drug at the time of the event.

Deaths

The criteria for adjudicating deaths are listed in the Appendix (p. 107). In the United States, some German states, and the United Kingdom, study staff could seek confirmation and dates of death from civil registries. The United Kingdom registry provided a cause of death.

First Year
During the first year, 184/4193 (4.4%) patients died in the ezetimibe/simvastatin group, 51/1054 (4.8%) died in the simvastatin group, and 209/4191 (5.0%) died in the placebo group. Table 36 summarizes cause-specific mortality for these patients.

Table 36. Cause-specific Mortality for Year 1

Cause of Death	Eze/Sim Arm 2 (N=4193)	Simvastatin Arm 3 (N=1054)	Placebo Arm 1 (N=4191)
CHD death	11 (0.3%)	5 (0.5%)	21 (0.5%)
Other cardiac death	31 (0.7%)	5 (0.5%)	47 (1.1%)
Cardiac death	**42 (1.0%)**	**10 (0.9%)**	**68 (1.6%)**
Ischemic stroke	8 (0.2%)	2 (0.2%)	5 (0.1%)
Hemorrhagic stroke	3 (0.1%)	2 (0.2%)	10 (0.2%)
Unspecified stroke	2 (0.05%)	0	2 (<0.05%)
Stroke (any type)	**13 (0.3%)**	**4 (0.4%)**	**17 (0.4%)**
Any other vascular death	9 (0.2%)	1 (0.1%)	4 (0.1%)
Subtotal: Vascular death	**64 (1.5%)**	**15 (1.4%)**	**89 (2.1%)**
Any cancer (including complications)	21 (0.5%)	5 (0.5%)	16 (0.4%)
Renal death	30 (0.7%)	10 (0.9%)	34 (0.8%)
Any respiratory death	11 (0.3%)	5 (0.5%)	19 (0.5%)
Gastrointestinal	14 (0.3%)	4 (0.4%)	10 (0.2%)
Other medical causes	20 (0.5%)	4 (0.4%)	24 (0.6%)
Trauma/fracture	5 (0.1%)	1 (0.1%)	2 (<0.05%)
Subtotal: Non-vascular death	**101 (2.4%)**	**29 (2.8%)**	**105 (2.5%)**
Sudden death	10 (0.2%)	5 (0.5%)	9 (0.2%)
Death (reason unclear)	9 (0.2%)	2 (0.2%)	6 (0.1%)
Subtotal: Unknown causes	**19 (0.5%)**	**7 (0.7%)**	**15 (0.4%)**
TOTAL: All-cause	**184 (4.4%)**	**51 (4.8%)**	**209 (5.0%)**

Source: 02 August 2011 response to FDA information request.
For this analysis, the applicant defined the cut-off date for year 1 by first determining the "year 1" follow-up date (for Arm 3, the visit corresponding to 2nd randomization; otherwise, the first follow-up visit >333 days after initial randomization and after the last date of dispensing study medication). If this follow-up date was <396 days after initial randomization, this date marks the end of year 1; otherwise, year 1 ends 395 days after initial randomization.

Reviewer Comment: Efficacy analyses after year 1 were neither pre-specified nor performed. This table shows that fatal cardiac events or fatal strokes occurred in 1.3%, 1.3%, and 2.0% of the ezetimibe/simvastatin, simvastatin, and placebo groups, respectively.

All Patients Ever Randomized to Ezetimibe/simvastatin or Placebo

During follow-up, 1142/4650 (24.6%) patients ever randomized to ezetimibe/simvastatin died compared to 1115/4620 (24.1%) patients ever randomized to placebo; survival analysis yielded a risk ratio of 1.02 (95% CI 0.94-1.11) for all-cause mortality. Figure 25 summarizes cause-specific mortality for these patients.

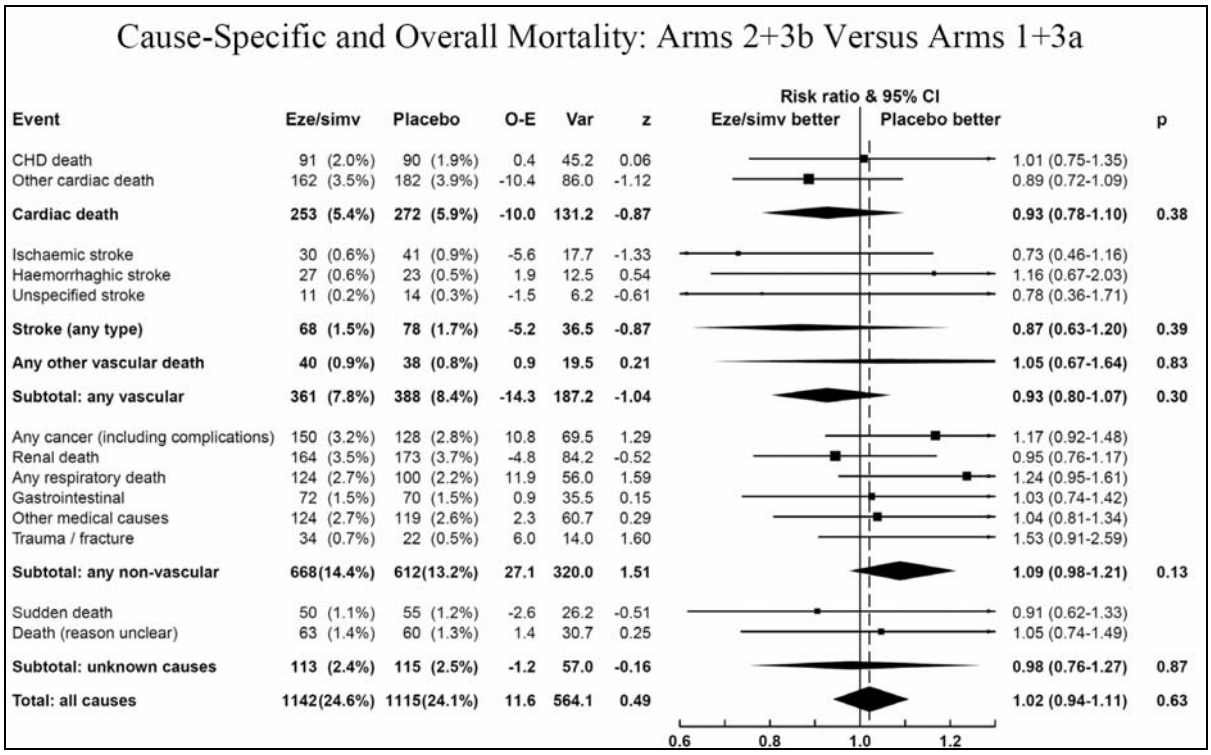


Figure 25. Cause-specific and Overall Mortality From Final Randomization
Source: CSR Fig. 12-1.

Overall, 1272 (20%) of the 6247 patients who were not on dialysis at randomization died during the trial compared with 985 (33%) of the 3023 dialysis patients. Causes of death and their individual contributions to all-cause death (i.e., column percentages) are described in Table 37, stratified by treatment group and renal status at the time of assignment to ezetimibe/simvastatin or placebo. These data are intended to be descriptive only; therefore, no hypothesis testing was performed. Coronary deaths, as defined by the SHARP investigators, and ischemic strokes composed 8.0% and 3.1% of all-cause deaths, respectively. Cardiac *or* sudden deaths accounted for 630/2257 (28%) of all-cause deaths with 181/630 (29%) of these attributed to coronary disease. These percentages were similar regardless of dialysis status at randomization.

Cancer deaths are described in greater detail on page 100.

The three most common causes of renal-related death were withdrawal of dialysis, uremia, and conservative care for ESRD. These causes contributed 81 deaths (47% of renal deaths) to the placebo group and 87 deaths (53% of renal deaths) to the ezetimibe/simvastatin group.

Table 37. Causes of Death by Renal Status and Treatment

Cause of Death	Non-dialysis			Dialysis			
	Eze/Sim	Placebo	Total	Eze/Sim	Placebo	Total	TOTAL
CHD death	46 (7.2%)	56 (8.8%)	102 (8.0%)	45 (8.9%)	34 (7.1%)	79 (8.0%)	181 (8.0%)
Other cardiac death	86 (13.5%)	105 (16.5%)	191 (15.0%)	76 (15.0%)	77 (16.1%)	153 (15.5%)	344 (15.2%)
Cardiac death	**132 (20.8%)**	**161 (25.3%)**	**293 (23.0%)**	**121 (23.9%)**	**111 (23.2%)**	**232 (23.6%)**	**525 (23.3%)**
Ischemic stroke	17 (2.7%)	22 (3.5%)	39 (3.1%)	13 (2.6%)	19 (4.0%)	32 (3.2%)	71 (3.1%)
Hemorrhagic stroke	15 (2.4%)	16 (2.5%)	31 (2.4%)	12 (2.4%)	7 (1.5%)	19 (1.9%)	50 (2.2%)
Unspecified stroke	7 (1.1%)	11 (1.7%)	18 (1.4%)	4 (0.8%)	3 (0.6%)	7 (0.7%)	25 (1.1%)
Stroke (any type)	**39 (6.1%)**	**49 (7.7%)**	**88 (6.9%)**	**29 (5.7%)**	**29 (6.1%)**	**58 (5.9%)**	**146 (6.5%)**
Any other vascular death	18 (2.8%)	17 (2.7%)	35 (2.8%)	22 (4.3%)	21 (4.4%)	43 (4.4%)	78 (3.5%)
Subtotal: Vascular death	**189 (29.7%)**	**227 (35.7%)**	**416 (32.7%)**	**172 (34.0%)**	**161 (33.6%)**	**333 (33.8%)**	**749 (33.2%)**
Any cancer (including complications)	99 (15.6%)	76 (11.9%)	175 (13.8%)	51 (10.1%)	52 (10.9%)	103 (10.5%)	278 (12.3%)
Renal death	107 (16.8%)	101 (15.9%)	208 (16.4%)	57 (11.3%)	72 (15.0%)	129 (13.1%)	337 (14.9%)
Any respiratory death	67 (10.5%)	58 (9.1%)	125 (9.8%)	57 (11.3%)	42 (8.8%)	99 (10.1%)	224 (9.9%)
Gastrointestinal	35 (5.5%)	36 (5.7%)	71 (5.6%)	37 (7.3%)	34 (7.1%)	71 (7.2%)	142 (6.3%)
Other medical causes	62 (9.7%)	53 (8.3%)	118 (9.3%)	62 (12.3%)	63 (13.2%)	125 (12.7%)	243 (10.8%)
Trauma/fracture	16 (2.5%)	11 (1.7%)	27 (2.1%)	18 (3.6%)	11 (2.3%)	29 (2.9%)	56 (2.5%)
Subtotal: Non-vascular death	**386 (60.7%)**	**338 (53.1%)**	**724 (56.9%)**	**282 (55.7%)**	**274 (57.2%)**	**556 (56.4%)**	**1280 (56.7%)**
Sudden death	29 (4.6%)	37 (5.8%)	66 (5.2%)	21 (4.2%)	18 (3.8%)	39 (4.0%)	105 (4.7%)
Death (reason unclear)	32 (5.0%)	34 (5.3%)	66 (5.2%)	31 (6.1%)	26 (5.4%)	57 (5.8%)	123 (5.4%)
Subtotal: Unknown causes	**61 (9.6%)**	**71 (11.2%)**	**132 (10.4%)**	**52 (10.3%)**	**44 (9.2%)**	**96 (9.7%)**	**228 (10.1%)**
TOTAL: All-cause	**636 (100%)**	**636 (100%)**	**1272 (100%)**	**506 (100%)**	**479 (100%)**	**985 (100%)**	**2257 (100%)**

Source: FDA reviewer's analysis of submitted analysis dataset (*sradata.xpt*).
Percentages are column %, reflecting the relative contribution of each cause to all-cause death for each group.

Patients assigned to ezetimibe/simvastatin had a non-significant 24% increased risk for respiratory death, on average, compared with those assigned to placebo (95% CI, -5% to 61%), although the absolute risk increase was modest at 0.5%. The majority of these deaths were the result of pneumonia or other infectious respiratory complications. Table 38 summarizes the event codes that contributed at least 4 respiratory deaths in the total study population.

Table 38. Causes of Respiratory Death

Cause of Respiratory Death	Eze/Sim (N=124)	Placebo (N=100)
Pneumonia	88 (71%)	64 (64%)
COPD Exacerbation	16 (13%)	10 (10%)
Aspiration pneumonia/pneumonitis	5 (4%)	11 (11%)
Cough with fever / chest congestion / bronchitis	6 (5%)	3 (3%)
Empyema	4 (3%)	1 (1%)
Other	5 (4%)	11 (11%)

Source: FDA reviewer's analysis of submitted data.
Only individual events that contributed ≥4 respiratory deaths are listed; the remaining events are combined in the "Other" category.

The category Trauma/Fracture had the largest point estimate for an increased risk of death associated with ezetimibe/simvastatin, although the numbers were few as reflected in the wide confidence interval (HR 1.53, 95% CI 0.91-2.59); the absolute risk increase was 0.2%. Table 39 summarizes the event codes that contributed to these trauma/fracture-related deaths.

Table 39. Causes of Trauma/Fracture Death

Cause of Trauma/Fracture Death	Eze/Sim (N=34)	Placebo (N=22)
Traumatic intracranial hemorrhage	10	5
Fracture*	10	9
Traffic accident	7	3
Accident (not further specified)	3	1
Hypoxic brain damage	1	2
Chest injury	1	1
Assault	1	0
Post-traumatic wound infection	1	0
Head injury	0	1

Source: FDA analysis of submitted raw data.
* Femoral neck/hip fracture accounted for 8 (eze/sim) and 5 (placebo) deaths.

By the judgment of the applicant and investigators, only one death in SHARP was reported to be possibly related to study medication:

- **Subject 172-0130 (Arm 2: Eze/Sim).** 66-y/o Southeast Asian female (Malaysia) with diabetic nephropathy who was randomized to ezetimibe/simvastatin on 12 October 2004 and initiated hemodialysis on 11 November 2006. She appeared well at dialysis on March 4 and March 7 but developed acute epigastric pain on 08 March 2007. She was found to have hyperamylasemia; within hours, she became hypotensive (BP 64/36, HR 56) with acidemia (pH 7.23) and severe

metabolic acidosis (HCO_3 4 mEq/L). The next morning, ultrasound revealed a swollen pancreas suggestive of acute pancreatitis, supporting her biochemical abnormalities. The patient became asystolic after insertion of a central venous line intended for the initiation of continuous renal replacement therapy; the family declined further active resuscitation. Post-mortem was not performed. Time from onset of symptoms to death was approximately 32 hours. According to the family, the patient had no history of alcohol consumption, steroid use, gallstones/biliary disease, autoimmune disease, abdominal trauma, or taking supplements/traditional medicine. Concomitant medications at the time of the event were amlodipine besylate, atenolol, telmisartan, furosemide, insulin, epoetin, alfacacidol, and iron dextran infusions.

Nonfatal Serious Adverse Events

First Year

LCC study personnel, in consultation with the ICC, determined whether each SAE was likely related to study treatment (suspected serious adverse reactions [SSARs]). The applicant reported 5 SSARs (0.12%) among the 4193 patients assigned to ezetimibe/simvastatin, 1 SSAR (0.09%) among the 1054 assigned to simvastatin, and 5 SSARs (0.12%) among the 4191 assigned to placebo during the first year of treatment (Table 40).

Table 40. Suspected Serious Adverse Reactions - Year 1

Suspected Serious Adverse Reaction	Ezetimibe/ simvastatin 10/20 mg (N=4193) n	Simvastatin 20 mg (N=1054) n	Placebo (N=4191) n
CK>10 ≤40xULN, muscle symptoms[†]	1	0	1
CK>40xULN, no muscle symptoms	0	0	1
Cholelithiasis	1	0	0
Acute pancreatitis-drug induced	1	0	0
Gastritis	0	0	1
Difficulty controlling INR	1	0	0
Eczema/dermatitis	1	0	0
Psoriasis	0	0	1
Allergic or anaphylactic reaction	0	1	1
Total	**5 (0.12%)**	**1 (0.09%)**	**5 (0.12%)**

[†] These patients meet the criteria for myopathy, as traditionally defined and used by Merck.
Note: Suspected serious adverse reaction refers to an unwanted or harmful reaction that is considered by the reporting investigator to be both serious and thought likely to be directly related to the study treatment based upon information from the patient and/or the patient's physician.

Source: CSR Table 12-1.

Table 67 in the Appendix (p. 122) summarizes the nonfatal SAEs that occurred during the first year of follow-up, excluding events presented elsewhere in this document (e.g., endpoint events, pre-specified safety events such as myopathy/rhabdomyolysis, etc.).

All Patients Ever Randomized to Ezetimibe/simvastatin or Placebo

Nonfatal SAEs occurred in 70% of patients ever randomized to ezetimibe/simvastatin and 71% of patients ever randomized to placebo, excluding major vascular events, cancer, TIA, hospitalization for angina or heart failure, dialysis access revision, diabetes and hypoglycemia, initiation of dialysis, renal transplantation, pancreatitis, hepatitis, myopathy, and rhabdomyolysis (all of which are reported separately).

Renal SAEs affected 42% of patients, with the majority being events related to hemodialysis vascular access excluding revision (23% vs. 25% in ezetimibe/simvastatin and placebo groups, respectively). The second most common organ system contributing to SAEs was gastrointestinal (excluding hepatobiliary/pancreas-related events), which led to nonfatal SAEs in ~21% of each treatment group.

Table 41 summarizes the counts of all nonfatal SAEs that are not reported elsewhere in this review.

Table 41. Nonfatal SAEs From Final Randomization

Event	Eze/Sim Arms 2+3b (N=4650)	Placebo Arms 1+3a (N=4620)
Cardiac (excluding endpoints reported elsewhere)	**527 (11.3%)**	**557 (12.1%)**
Angina (not hospitalized)	3 (0.1%)	0 (0.0%)
Heart failure (not hospitalized)	9 (0.2%)	5 (0.1%)
Arrhythmia	277 (6.0%)	291 (6.3%)
Valvular and pericardial disease	103 (2.2%)	131 (2.8%)
Other heart disease	203 (4.4%)	212 (4.6%)
Vascular (excluding cardiac)	**324 (7.0%)**	**367 (7.9%)**
Cerebrovascular (excluding stroke)	12 (0.3%)	16 (0.3%)
Other artery disease	106 (2.3%)	106 (2.3%)
Hypertension	73 (1.6%)	96 (2.1%)
Venous disease (including pulmonary embolus)	87 (1.9%)	96 (2.1%)
Other and unspecified circulatory disorders *	70 (1.5%)	83 (1.8%)
Cancer (not incident)	**73 (1.6%)**	**63 (1.4%)**
Pre-randomization cancer	26 (0.6%)	20 (0.4%)
Cancer treatment or complication	51 (1.1%)	47 (1.0%)
Renal	**1958 (42.1%)**	**1966 (42.6%)**
Acute-on-chronic renal failure	207 (4.5%)	226 (4.9%)
Uremia / withdrawal of dialysis	47 (1.0%)	41 (0.9%)
Hemodialysis access (excluding revision)	1074 (23.1%)	1159 (25.1%)
Peritoneal dialysis access problem / procedure	415 (8.9%)	421 (9.1%)
Fluid/metabolic complication	368 (7.9%)	358 (7.7%)
Transplant rejection / complication	130 (2.8%)	114 (2.5%)
Other investigation / surgery	204 (4.4%)	189 (4.1%)
Renal / ureteric obstruction / intervention	147 (3.2%)	148 (3.2%)
Bladder/lower urinary tract disorder	97 (2.1%)	95 (2.1%)
Urinary Tract Infection	239 (5.1%)	227 (4.9%)

Event	Eze/Sim Arms 2+3b (N=4650)	Placebo Arms 1+3a (N=4620)
Miscellaneous renal	245 (5.3%)	220 (4.8%)
Respiratory	**654 (14.1%)**	**666 (14.4%)**
Pneumonia / bronchitis	424 (9.1%)	397 (8.6%)
Other chest infection	90 (1.9%)	77 (1.7%)
COPD / asthma	60 (1.3%)	59 (1.3%)
Other respiratory disease	103 (2.2%)	115 (2.5%)
Respiratory symptoms/investigations/surgery	132 (2.8%)	144 (3.1%)
Liver/pancreas/biliary	**82 (1.8%)**	**76 (1.6%)**
Gallstones (excluding complications)	22 (0.5%)	14 (0.3%)
Liver (excluding hepatitis)	31 (0.7%)	26 (0.6%)
Miscellaneous liver/pancreas/biliary	36 (0.8%)	43 (0.9%)
Gastrointestinal	**957 (20.6%)**	**988 (21.4%)**
Esophageal disorder / investigation	53 (1.1%)	63 (1.4%)
Gastroduodenal disorders	126 (2.7%)	127 (2.7%)
Upper GI investigation/procedure	133 (2.9%)	146 (3.2%)
Large bowel disease	154 (3.3%)	151 (3.3%)
Large bowel investigation/procedure	235 (5.1%)	243 (5.3%)
GI hemorrhage	85 (1.8%)	83 (1.8%)
Infective gastroenteritis/colitis	96 (2.1%)	115 (2.5%)
Other GI symptoms	210 (4.5%)	225 (4.9%)
Other GI disorder/intervention	149 (3.2%)	153 (3.3%)
Hernia / repair	137 (2.9%)	137 (3.0%)
Skin	**238 (5.1%)**	**240 (5.2%)**
Skin infection	93 (2.0%)	86 (1.9%)
Skin biopsy / surgery	55 (1.2%)	52 (1.1%)
Dermatitis and eczema/ rash	32 (0.7%)	29 (0.6%)
Miscellaneous skin	89 (1.9%)	95 (2.1%)
Genital disorders & Breast	**176 (3.8%)**	**185 (4.0%)**
Gynecological disorder	64 (1.4%)	72 (1.6%)
Breast disorder / intervention	15 (0.3%)	16 (0.3%)
Prostate disorder / intervention	72 (1.5%)	72 (1.6%)
Penis/testis	26 (0.6%)	29 (0.6%)
Psychiatric	**68 (1.5%)**	**62 (1.3%)**
Neurological	**220 (4.7%)**	**222 (4.8%)**
Musculoskeletal	**483 (10.4%)**	**471 (10.2%)**
Muscle (excluding myopathy)	11 (0.2%)	4 (0.1%)
Vasculitis and related disorders	23 (0.5%)	20 (0.4%)
Orthopedic	269 (5.8%)	288 (6.2%)
Rheumatological	229 (4.9%)	205 (4.4%)
Hematological	**224 (4.8%)**	**200 (4.3%)**
Anemia (including transfusion)	181 (3.9%)	151 (3.3%)
Platelet and clotting disorder	34 (0.7%)	39 (0.8%)
Other hematological disorder	18 (0.4%)	20 (0.4%)
Eye	**184 (4.0%)**	**179 (3.9%)**

Event	Eze/Sim Arms 2+3b (N=4650)	Placebo Arms 1+3a (N=4620)
Cataract / cataract surgery	96 (2.1%)	108 (2.3%)
Other eye disorder/intervention	105 (2.3%)	82 (1.8%)
Ear/nose/throat/mouth	**72 (1.5%)**	**82 (1.8%)**
Endocrine	**58 (1.2%)**	**39 (0.8%)**
Hyperthyroid	8 (0.2%)	9 (0.2%)
Hypothyroid	9 (0.2%)	6 (0.1%)
Unknown thyroid disorder	27 (0.6%)	15 (0.3%)
Other endocrine	15 (0.3%)	11 (0.2%)
Other SAE	**891 (19.2%)**	**896 (19.4%)**
Allergy / hypersensitivity	29 (0.6%)	30 (0.6%)
Septicemia	110 (2.4%)	115 (2.5%)
Other infection	200 (4.3%)	216 (4.7%)
Metabolic	78 (1.7%)	70 (1.5%)
Surgical	118 (2.5%)	139 (3.0%)
Symptoms of cardiovascular compromise *	195 (4.2%)	167 (3.6%)
Adjustment of treatment	106 (2.3%)	109 (2.4%)
Rehabilitation / impaired mobility	118 (2.5%)	91 (2.0%)
Miscellaneous episode	173 (3.7%)	177 (3.8%)
Fracture	265 (5.7%)	246 (5.3%)
Other trauma	107 (2.3%)	103 (2.2%)
Non-medical SAE	**340 (7.3%)**	**333 (7.2%)**
Any SAE (except those reported elsewhere)	**3258 (70.1%)**	**3270 (70.8%)**

Source: CSR Table 12-7.
Recall that final randomization is the only randomization for Arms 1 and 2 (n=8384) but is the time of re-assignment to ezetimibe/simvastatin or placebo for Arms 3a/3b (n=886).
* *Other and unspecified circulatory disorders*, listed as a Vascular (non-cardiac) SAE, comprises "other cardiovascular procedures," "cardiovascular investigations," "hypotension," and "postural hypotension." *Symptoms of cardiovascular compromise*, listed as an Other SAE, comprises "chest pain/tightness," "peripheral edema," "collapse/vasovagal syncope," "faintness/lightheadedness/presyncope," "multi-organ failure," and "fall/collapse."

The applicant reported 20 SSARs (0.43%) among the 4650 patients ever assigned to ezetimibe/simvastatin and 13 SSARs (0.28%) among the 4620 patients ever assigned to placebo (Table 42). CK elevations (page 87) were the most common SSARs.

Narratives for these 32 patients (33 SSARs) were provided by the applicant. Study medication was discontinued as a result of a SSAR in 17 (0.4%) patients ever randomized to ezetimibe/simvastatin group and 12 (0.3%) ever randomized to placebo; the remaining patients continued study medication despite the SSAR.

Table 42. Suspected Serious Adverse Reactions - from Final Randomization

Suspected Serious Adverse Reaction	Ezetimibe/ simvastatin 10/20 mg (N=4650) n	Placebo (N=4620) n
CK>10 ≤40xULN, muscle symptoms†	4	3
CK>40xULN, muscle symptoms‡	3	0
CK>40xULN, no muscle symptoms	0	1
Non-infective hepatitis	1	0
Hepatitis, unknown etiology	0	1
Complications of gallstones	1	0
Acute pancreatitis (without gallstones)	3	1#
Chronic pancreatitis	0	2
Gastritis	0	1
GI hemorrhage	1	0
Diarrhea	1	0
Difficulty controlling INR	1	0
Peripheral neuropathy	0	1
Acute interstitial nephritis	1	0
Eczema/dermatitis	2	0
Psoriasis	0	1
Allergic or anaphylactic reaction	2	3
Total	**20 (0.43%)**	**13 (0.28%)**

† These patients meet the criteria for myopathy, as defined by Merck.
‡ These patients meet the criteria for rhabdomyolysis, as defined by Merck.
# This patient had both acute and chronic pancreatitis and therefore also appears in the row below.
Note: Suspected serious adverse reaction refers to an unwanted or harmful reaction that is considered by the reporting investigator to be both serious and likely to be directly related to the study treatment based upon information from the patient and/or the patient's physician.

Source: CSR Table 12-8.

Reviewer Comment: Narratives for all SSARs were reviewed and were consistent with the diagnoses listed in Table 42. Additionally,

- *GI hemorrhage (subject 289-0117) occurred in the setting of concomitant warfarin and an elevated INR (5.9). The patient had not had an INR checked during the 2 months prior to this event; the preceding INR had been 3. The reporting investigator felt that supratherapeutic anticoagulation was possibly related to study therapy; study drug was discontinued permanently 28 May 2006. Despite this, he had 4 subsequent hospitalizations between (b) (6) and (b) (6) for GI hemorrhages, suggesting that study therapy was likely not responsible for this event;*
- *the case of acute pancreatitis listed here (subject 172-0130) is the only death in SHARP thought related to study drug by the applicant/investigators (see p. 80).*

Dropouts and/or Discontinuations

A summary of the reasons for drop-out or discontinuation of study drug was presented in Table 14 (p. 39). Here, Table 43 provides a further breakdown of the serious and non-serious AEs that led to permanent discontinuation. Recall that non-serious AEs were not captured in SHARP unless the event was the reason for discontinuing study drug.

Table 43. Adverse Events Leading to Discontinuing Study Treatment

Event	During Year 1 Only			From Randomization to Eze/Sim or Placebo	
	Eze/Sim Arm 2 N=4193	Simva Alone Arm 3 N=1054	Placebo Arm 1 N=4191	Eze/Sim Arms 2+3b N=4650	Placebo Arms 1+3a N=4620
SSAR	**1 (0.0%)**	**0**	**4 (0.1%)**	**17 (0.4%)**	**12 (0.3%)**
SAE (not SSAR)	**102 (2.4%)**	**31 (2.9%)**	**92 (2.2%)**	**303 (6.5%)**	**310 (6.7%)**
Cardiac disorder	13 (0.3%)	8 (0.8%)	13 (0.3%)	37 (0.8%)	53 (1.1%)
Stroke	1 (0.02%)	1 (0.1%)	7 (0.2%)	9 (0.2%)	15 (0.3%)
Other vascular disorder	1 (0.02%)	1 (0.1%)	4 (0.1%)	7 (0.2%)	10 (0.2%)
Cancer	9 (0.2%)	1 (0.1%)	9 (0.2%)	30 (0.6%)	20 (0.4%)
Renal transplant	50 (1.2%)	14 (1.3%)	35 (0.8%)	152 (3.3%)	148 (3.2%)
Other renal	1 (0.02%)	1 (0.1%)	5 (0.1%)	8 (0.2%)	12 (0.3%)
Respiratory	2 (0.04%)	0	1 (0.02%)	2 (0.04%)	5 (0.1%)
Gastrointestinal	4 (0.1%)	1 (0.1%)	9 (0.2%)	13 (0.3%)	21 (0.5%)
Other medical	19 (0.5%)	4 (0.4%)	8 (0.2%)	37 (0.8%)	22 (0.5%)
Non-medical	0	0	0	2 (0.04%)	1 (0.02%)
Death*	1 (0.02%)	0	1 (0.02%)	2 (0.04%)	1 (0.02%)
Unspecified SAE	1 (0.02%)	0	0	4 (0.1%)	2 (0.04%)
Non-serious AE	**81 (1.9%)**	**14 (1.3%)**	**79 (1.9%)**	**165 (3.5%)**	**131 (2.8%)**
General / miscellaneous	6 (0.1%)	0	8 (0.2%)	10 (0.2%)	15 (0.3%)
Chest pain / palpitations	0	0	1 (0.02%)	2 (0.04%)	5 (0.1%)
Dizziness / blackouts	1 (0.02%)	0	0	1 (0.02%)	0
Respiratory symptoms	0	0	0	1 (0.02%)	2 (0.04%)
Upper GI symptoms	5 (0.1%)	3 (0.3%)	10 (0.2%)	10 (0.2%)	9 (0.2%)
Lower GI symptoms	10 (0.2%)	1 (0.1%)	11 (0.3%)	10 (0.2%)	13 (0.3%)
Abdominal pain/distention	2 (0.04%)	0	3 (0.1%)	4 (0.1%)	4 (0.1%)
Genitourinary symptoms	0	0	1 (0.02%)	0	1 (0.02%)
Skin symptoms	11 (0.3%)	1 (0.1%)	3 (0.1%)	19 (0.4%)	8 (0.2%)
Bleeding symptoms	0	0	1 (0.02%)	0	1 (0.0%)
Headache	0	1 (0.02%)	0	0	0
Other neuro symptoms	3 (0.1%)	0	4 (0.1%)	3 (0.1%)	7 (0.2%)
Psych / mood disorders	0	0	2 (0.04%)	3 (0.1%)	2 (0.0%)
Joint symptoms	4 (0.1%)	0	3 (0.1%)	10 (0.2%)	8 (0.2%)
Muscle pain	22 (0.5%)	4 (0.4%)	19 (0.5%)	49 (1.1%)	28 (0.6%)
Abnormal safety bloods	17 (0.4%)	4 (0.4%)	13 (0.3%)	43 (0.9%)	28 (0.6%)

Source: *Revised* CSR Tables 14-30 and 14-31 (12 September 2011 response to FDA information request).
Year 1 events are listed for subjects who were not taking study treatment *at the end of the year 1 period*; some of these subjects may have restarted at a later date. The events listed from final randomization

are those that led to discontinuation in subjects *who never restarted study treatment*. Therefore, events that led to study drug interruption during year 1 may not be represented in the tally of events "from final randomization" if study treatment was resumed later during the trial.

* For a few cases, a fatal SAE was recorded as the reason for discontinuing treatment. Because it was unclear whether study medication was discontinued because of the SAE that resulted in death or whether study medication was continued until the time of death, these events are recorded in this table as "death."

The most common SAE leading to the discontinuation of study treatment in patients ever randomized to ezetimibe/simvastatin or placebo was renal transplantation (152 [3.3%] vs. 148 [3.2%]), often because of starting cyclosporine. Muscle pain, abnormal safety bloods (CK, transaminases), and cancer-related events are explored below.

Muscle-related AEs

At each visit, patients were specifically asked if they had developed muscle pain or weakness. CK was measured in the local laboratory at each study visit and whenever a patient complained of unexplained muscle pain. Safety thresholds for CK values were determined based on multiples of the local laboratory's ULN. Sex- and race-specific normal ranges of CK were *not* used.

The applicant defined the following terms related to muscle-related events:

- *Myopathy*: CK >10xULN with unexplained muscle pain or weakness
- *Rhabdomyolysis*: myopathy with CK >40xULN (i.e., CK >40xULN with unexplained muscle pain or weakness)

Oxford adjudicated SAEs coded as rhabdomyolysis or myositis/myopathy. During adjudication, myopathy was defined as CK >10x and ≤40xULN with unexplained muscle pain or weakness, and rhabdomyolysis was defined as CK >40xULN *regardless of symptoms*. Adjudicators were instructed to use the peak recorded CK and to record evidence of end-organ damage, defined as an otherwise unexplained 20% increase in serum creatinine compared with previous values or the need for dialysis. End-organ damage was not ascertained for patients already on maintenance dialysis at the time of the event. Cases that were "believed to be fully explained by recent strenuous exercise do not fulfill the criteria for Serious Adverse Event and [were to] be marked as invalid."

Table 44 summarizes the muscle-related events defined by CK elevations.

Table 44. CK-related Events– Most Severe Event/Patient

Event	First Year			From Randomization to Eze/Sim or Placebo	
	Eze/Sim Arm 2 (N=4193)	Simvastatin Arm 3 (N=1054)	Placebo Arm 1 (N=4191)	Eze/Sim Arms 2+3b (N=4650)	Placebo Arms 1+3a (N=4620)
CK >5x but ≤10xULN	**18 (0.43%)**	**6 (0.57%)**	**14 (0.33%)**	**50 (1.1%)**	**47 (1.0%)**
Without symptoms	17	5	11	43	40
With symptoms	1	1	3	7	7
CK >10x but ≤ 40xULN	**4 (0.10%)**	**1 (0.09%)**	**6 (0.14%)**	**17 (0.37%)**	**16 (0.35%)**
No symptoms / no renal damage	0	1	0	3	3
With symptoms / no renal damage	0	0	0	3	1†
No symptoms / with renal damage	1	0	3	3§	4
With symptoms / with renal damage	0	0	1	0	3
Without symptoms / on dialysis	2	0	2	6	5
With symptoms / on dialysis	1	0	0	2*	0
Symptomatic Subtotal	**1**	**0**	**1**	**5***	**4†**
CK >40xULN	**0**	**0**	**1 (0.02%)**	**4 (0.09%)**	**5 (0.11%)**
No symptoms / no renal damage	0	0	0	0	1
With symptoms / no renal damage	0	0	0	1	0
No symptoms / with renal damage	0	0	1	0	1
With symptoms / with renal damage	0	0	0	1	1‡
Without symptoms / on dialysis	0	0	0	0	2
With symptoms / on dialysis	0	0	0	2	0
Symptomatic Subtotal	**0**	**0**	**0**	**4**	**1‡**
Myopathy (CK >10xULN with symptoms)	**1 (0.02%)**	**0**	**1 (0.02%)**	**9* (0.19%)**	**5†‡ (0.11%)**
Rhabdomyolysis (CK >40xULN with symptoms)	**0**	**0**	**0**	**4 (0.09%)**	**1‡ (0.02%)**

Source: Derived from CSR Tables 12-2, 12-11, 12-12, 12-16. NR = Not reported.
Each patient contributes a maximum of *one event* to this table based on peak CK.
CK values were available for 4615 and 4587 patients in the eze/sim and placebo groups, respectively.
Renal damage was defined as >20% increase in serum creatinine or the initiation of dialysis.
***** Includes patient 430-0121, who was not taking study medication when CK rose to >10xULN.
† Patient 121-0164 was taking a non-study statin when CK rose to >10xULN.
‡ Patient 517-0105 was taking a non-study statin when CK rose to >40xULN.
§ Includes patient 138-0159, who was not taking study medication when CK rose to >10xULN.

Table 45 stratifies these events by renal status (dialysis vs. non-dialysis) at time of randomization to ezetimibe/simvastatin or placebo.

Table 45. CK-related Events by Renal Status at Randomization

Event	Non-dialysis		Dialysis	
	Eze/Sim (N=3117)	**Placebo (N=3130)**	**Eze/Sim (N=1533)**	**Placebo (N=1490)**
CK >10x but ≤40xULN	9 (0.29%)	11 (0.35%) (inc. 1 on NSS)	8 (0.52%) (inc. 1 off drug)	5 (0.34%)
CK >40xULN	2 (0.06%)	3 (0.10%) (inc. 1 on NSS)	2 (0.13%)	2 (0.13%)
Myopathy (CK >10xULN with symptoms)	5 (0.16%)	5 (0.16%) (inc. 2 on NSS)	4 (0.26%) (inc. 1 off drug)	0
Rhabdomyolysis (CK >40xULN with symptoms)	2 (0.06%)	1 (0.03%) (on NSS)	2 (0.13%)	0

Source: Derived from CSR Tables 12-2, 12-11, 12-12, 12-16.
NSS = non-study statin

Using the definitions listed above, two patients developed myopathy and no patients developed rhabdomyolysis during the first year:

1. **Subject 220-0105 (Arm 2: Eze/Sim).** 53-y/o Hispanic male (USA) who commenced hemodialysis 6 months before randomization to ezetimibe/simvastatin on 23 Aug 2005. Approximately one week before his first follow-up visit, he stopped study medication because of abdominal discomfort, nausea, "bone ache," headaches, generalized weakness, and muscle pain. At his first visit (25 Oct 2005), CK was 3028 IU/L (15xULN), up from his previously normal CK 131 IU/L. All symptoms resolved after stopping study treatment (permanently). There was no other explanation for the high CK. Troponin-I was 0.066 ng/mL (ULN 0.08 ng/mL). Concomitant medications were Fe-cap folic capsules, ascorbic acid, metoprolol, insulatard, sevelamer, and amlodipine.
   Reviewer Comment: Amlodipine can increase simvastatin systemic exposure.

2. **Subject 492-0113 (Arm 1: Placebo).** 73-y/o Chinese male (China), who was randomized to placebo on 20 Feb 2006, was found to have an asymptomatic CK elevation at his first follow-up visit (19 Apr 2006) to 1078 IU/L (5.5xULN), up from 352 (2.2xULN) and 458 (2.3xULN) at screening and randomization, respectively. He reported muscle symptoms at an early recall visit 5 days later, but also reported recent moderate-intensity exercise. CK peaked at 2285 (11.7xULN) on April 29. Renal function remained stable with serum creatinine ~7.4 mg/dL. He was diagnosed with hypothyroidism (TSH >100 U/mL, FT_4 4.38 pmol/L [ref 9.45-22.5]). Euthyrox was initiated, study treatment was held, and his CK fell to 398 (2xULN) by May 17. Dialysis was initiated in June 2006, leading to the applicant's attribution of renal damage to this event.
   Reviewer Comment: Creatinine seems to have been relatively stable around the time of peak CK. Multiple concomitant medications were added around the time of hospitalization, including valsartan and furosemide, in this patient with severe CKD at baseline. Evidence that the renal damage is attributable to the CK abnormality is weak.

Table 46 presents a brief summary of the myopathy and rhabdomyolysis cases observed in SHARP.

Table 46. Summary of Myopathy and Rhabdomyolysis Cases

ID	Rx	Demog.	Date of Rand.	Date of Onset	Renal Status	Hosp?	Related to Rx? *	Peak CK (xULN)
MYOPATHY								
151-0163	Eze/Sim	59 F White (Australia)	11Mar04	28Sep06	CKD (Cr 2.4) no damage	No	Yes	2984 (17x)
220-0105	Eze/Sim	53 M Hispanic (USA)	23Aug05	25Oct05	HD	No	Yes	3028 (15x)
430-0121	Eze/Sim ***(Not taking Rx)***	47 M Chinese (Canada)	30Mar06	09Apr09	PD	Yes (bleeding)	No	6887 (35x)
436-0126	Eze/Sim	46 M White (Germany)	17Aug05	17Aug07	CKD (Cr 3.3) no damage	No	Yes†	1841† (11x)
112-0102	Eze/Sim	70 F White (UK)	13Jan04	09Aug06	CKD (Cr 2.5) no damage	No	Yes	2575 (13x)
121-0164	Placebo ***(Taking non-study simva)***	45 M White (UK)	07Mar05	07May09	CKD (Cr 1.7) no damage	No	No	1755 (13x)
464-0102	Placebo	65 F White (Germany)	23Jan06	21Nov07	CKD (Cr NR) + damage	Yes (Complete heart block)	Yes	2563 (18x)
492-0113	Placebo	73 M Chinese (China)	20Feb06	29Apr06	CKD (Cr 7.6) + damage‡	Yes (Myopathy, TSH > 100)	Yes	2285 (12x)
527-0112	Placebo	73 F White (Czech)	15Jun06	08Jun10	CKD (Cr 3.4 to 4.8) + damage; few days NSAIDs	No	Yes	1556 (13x)
RHABDOMYOLYSIS								
135-0119	Eze/Sim	42 M White (UK)	15Sep04	13Mar06	CKD (Cr 2.7) no damage	No	Yes	9530 (50x)
273-0125	Eze/Sim	61 F White (Germany)	18Jan06	29Jul09	HD	Yes (volume depletion, rhabdo)	No	7020 (41x)

ID	Rx	Demog.	Date of Rand.	Date of Onset	Renal Status	Hosp?	Related to Rx? *	Peak CK (xULN)
491-0150	Eze/Sim	76 M Chinese (China)	09May06	16Nov09	HD	Yes (rhabdo)	Yes	30906 (183x)
113-0123	Eze/Sim	47 M Black (UK)	08Nov04	24Jun09	CKD (Cr 2.9 to 3.6) + damage	No	Yes	7241 (42x)
517-0105	Placebo (***Taking non-study lovastatin)***	56 M Black (USA)	16Jun06	16Jan10	CKD (Cr 4.2 to HD) + damage	Yes (weakness; inpatient x months)	No	8414 (45x)

Source: CSR Table 12-15 and submitted laboratory & AE data. NR=not reported.
* Relation to study treatment as recorded by local investigator (blind to treatment).
† Patient 436-0126 had a CK 2.4xULN at screening and 4.1xULN at randomization.
‡ In this reviewer's opinion, the evidence for renal damage as a result of the CK abnormality is weak based on the data provided for this case (see preceding narrative).

The time to onset of myopathy among the 4 patients compliant with ezetimibe/simvastatin ranged from 2 months to ~2.5 years after randomization. None of these patients were hospitalized and none experienced significant deterioration in renal function. Myopathy resolved in all of these patients, defined by CK falling to <3xULN.

The time of onset of rhabdomyolysis among the 4 patients taking ezetimibe/simvastatin ranged from 1.5 to 4.6 years after randomization. Study medication was discontinued and CK fell to <3xULN in all patients. One pre-dialysis patient experienced acute kidney injury. Two patients, both of whom were on hemodialysis at the time of onset, were hospitalized:

1. **Subject 491-0150.** 76-y/o Chinese male who was randomized to ezetimibe/simvastatin on 09 May 2006. At a routine SHARP clinic visit on 17 Oct 2009, he was asymptomatic with a CK 183 IU/L. He reported ≥80% compliance with study treatment at the time. He developed muscle symptoms approximately 4 weeks later on November 13, but did not immediately alert study staff. On (b) (6) study medication was stopped and he was admitted to the hospital; the first available CK during the admission was 26,416 IU/L (ULN 169) with AST 688 (ULN 40) on (b) (6) CK peaked at 30,906 on November 21 and fell to 2501 by (b) (6) and to 274 by (b) (6) the day before discharge. Thyroid function tests were normal. No alternative cause for the elevated CK was found.
2. **Subject 273-0125.** 61-y/o white female (Germany) who was randomized to ezetimibe/simvastatin on 18 Jan 2006. At a routine SHARP clinic visit on 23 Jul 2009, CK was 7020 (41xULN). She was told to stop medication, and she was hospitalized on (b) (6), primarily for "dehydration." She reported falling several times in the preceding few weeks, but it was unknown whether she spent a prolonged period lying on the floor. Bruising was evident. The local investigator reported a history of bulimia and chronic complaints of generalized body aches at most dialysis sessions, not necessarily related to these events. By August 15, the CK had fallen to 47 IU/L.

Asymptomatic CK Elevations >10xULN

Although asymptomatic CK elevations >10xULN do not meet the definitions of myopathy or rhabdomyolysis, CK elevations associated with a decline in renal function could be clinically significant in a population with moderate-to-severe kidney disease at baseline. Of the 25 CK >10xULN events in *pre-dialysis* patients described in Table 44, 8 events were asymptomatic but associated with renal damage: 3 in the ezetimibe/simvastatin group and 5 in the placebo group. Narratives for the ezetimibe/simvastatin patients follow:

1. **Subject 207-0120 (Arm 2: Eze/Sim).** 76-y/o white female (New Zealand), who was randomized 30 Jun 2005 to ezetimibe/simvastatin, was hospitalized on (b) (6) with an inferior STEMI and cardiac failure, treated with streptokinase. Troponin-T rose to 13.6 µg/L (ULN <0.03). She stopped SHARP study medication and initiated open-label simvastatin. On 03 Feb 2009, CK was 2050 IU/L with no CK-MB recorded, and creatinine was 2.3 mg/dL (207 µmol/L). CK fell to 349 IU/L on 05 Feb 2009, and creatinine rose to 4.6 mg/dL (408 µmol/L) by 12 Feb 2009. Plans were made for dialysis and she started PD within 2 months of this hospitalization.
   Reviewer Comment: CK elevation associated with MI. Renal damage likely multifactorial; probability of drug-induced CK elevation contributing is very low.

2. **Subject 172-0127 (Arm 2: Eze/Sim)**. 51-y/o Malaysian female, who was randomized 24 Aug 2004 to ezetimibe/simvastatin, was noted to have an asymptomatic elevation in CK to 2733 (16xULN) at a routine SHARP clinic visit on 04 Sep 2007. The patient strongly believed that her elevated CK was related to eating "duku/dokong" (Lansium domesticum), a local fruit that the local community believes causes muscle aches in adults. The patient remained on study drug and one week later her CK had fallen to 461 IU/L. The patient's creatinine was 1.9 mg/dL (170 µmol/L) at her SHARP visit in Aug 2007, 2.4 mg/dL (210 µmol/L) at the time of peak CK, and 2.4 mg/dL (210 µmol/L) in Apr 2008. This change led the applicant to adjudicate this CK event as having caused renal damage.
   Reviewer Comment: Prior to the Aug 2007 creatinine value of 1.9 mg/dL (170 µmol/L), her creatinine had fluctuated between 2.1 and 2.5 mg/dL (190 and 220 µmol/L) since randomization. The evidence that this CK event was associated with renal damage is weak.

3. **Subject 491-0198 (Arm 2: Eze/Sim)**. 45-y/o Chinese male (China) with diabetic nephropathy, who was randomized 10 Jul 2006 to ezetimibe/simvastatin, was noted to have an asymptomatic elevation in CK to 4342 IU/L (39xULN) at a routine SHARP clinic visit on 21 Jul 2007. At this visit, his creatinine had risen to 3.2 mg/dL (280 µmol/L) from 2.5 mg/dL (220 µmol/L) in Jan 2007. No cause for the CK elevation was identified; thyroid function was normal. Study treatment was stopped 22 Jul 2007; repeat CK on 27 Jul 2007 was 234 IU/L with creatinine 2.8 mg/dL (250 µmol/L). He restarted study treatment on 06 Aug 2007 and continued until study end on 11 Jun 2010 without further CK elevation. Creatinine fluctuated between 2.5 and 3.2 mg/dL (220 and 280 µmol/L) during the remainder of follow-up.
   Reviewer Comment: Rechallenged with study treatment for nearly 2 additional years without a recurrence in CK elevation. Creatinine was 3.4 mg/dL (300 µmol/L) at screening and ranged 2.3 to 2.8 mg/dL (200 to 250 µmol/L) between randomization and the event. Nevertheless, a drug-related elevation in CK with associated renal damage remains plausible.

These narratives suggest that there may have been only one case of an asymptomatic drug-related CK elevation >10xULN contributing to renal decline among pre-dialysis patients taking ezetimibe/simvastatin.

Less Severe CK Elevations

The routine measurement of CK in SHARP provides information regarding CK elevations of smaller magnitude. As shown in Table 44, 50 (1.1%) subjects ever randomized to ezetimibe/simvastatin experienced their greatest CK elevation in the >5x to ≤10xULN range compared with 47 (1.0%) subjects ever randomized to placebo. Among these patients, 7 in each group complained of concomitant muscle symptoms.

Muscle Symptoms

It is well recognized that muscle symptoms can occur in the absence of CK elevations, and these symptoms can lead to nonadherence to therapy. Consistent with this, as noted previously, more patients in the ezetimibe/simvastatin group (49; 1.1%) than the placebo group (29; 0.6%) discontinued treatment because of muscle pain (Table 43).

During the first year, there was a modestly higher incidence of muscle symptoms in the ezetimibe/simvastatin group (11.2%) compared with both simvastatin and placebo (10.6% in each). From the time of randomization to ezetimibe/simvastatin or placebo until study end, 21.5% of patients in the ezetimibe/simvastatin group ever complained of muscle symptoms compared with 20.9% of patients in the placebo group.

Hepatobiliary/Pancreas-related AEs

ALT and/or AST was measured at the LCC at each study visit. Patients with ALT or AST elevations >3xULN were asked to have a repeat measurement at an early recall visit in approximately 2 weeks. Study treatment was stopped temporarily but restarted, at the discretion of the LCC investigator, if liver transaminases were subsequently stable <3xULN.

Adjudication assigned an event code to the etiology of liver disease associated with liver-related SAE. These codes were grouped into the following categories: viral causes, alcoholic liver disease, toxic (drug-induced) liver disease, liver failure not elsewhere classified (required encephalopathy thought secondary to liver disease), chronic hepatitis not elsewhere classified, fibrosis/cirrhosis (excluding cases thought related to alcohol, drugs, or viral causes), other inflammatory liver diseases, other diseases of liver, or other causes of liver disease (hemochromatosis, Wilson's).

The event codes "ALT >2 ≤3xULN" or "ALT >3xULN" were used for single elevated ALT or AST readings, which would not meet the SHARP criteria for acute hepatitis.

Table 47. Liver-related Events

Event	First Year			From Randomization to Eze/Sim or Placebo	
	Eze/Sim Arm 2 (N=4193)	Simvastatin Arm 3 (N=1054)	Placebo Arm 1 (N=4191)	Eze/Sim Arms 2+3b (N=4650)	Placebo Arms 1+3a (N=4620)
Persistently elevated transaminases	**13 (0.31%)**	**1 (0.09%)**	**6 (0.14%)**	**30 (0.65%)**	**26 (0.56%)**
With hepatitis	6	1	4	14	10
With any other SAE	0	0	1	5	5
Without alternative explanation	7	0	1	11	11
Hepatitis	**10† (0.24%)**	**1 (0.09%)**	**7 (0.17%)**	**21*† (0.45%)**	**18‡ (0.39%)**
Infective	6	1	6	12	12‡
Non-infective	2	0	1	6*	4
No cause identified	2†	0	1	3†	2§

Source: CSR Tables 12-3, 12-20

* Includes subject 265-0130, who d/c'd study treatment 1.5 years before the event.

† Includes subject 274-0123, who had elevated transaminases at randomization.

‡ Includes subject 176-0102, who was initially classified non-infective hepatitis based on negative screening results for viral hepatitis but repeat testing and confirmatory results diagnosed hepatitis C.

§ Includes subject 225-0143, who was found to have ALT 371 (7xULN) at the 2nd randomization visit (switch to placebo after 1-yr simvastatin).

Local investigators reported two cases of hepatitis suspected to be the result of study treatment:

1. **Subject 346-0109 (Arm 2: Eze/Sim).** 70-y/o white male (Germany),who was randomized to ezetimibe/simvastatin on 12 January 2005, was found to have increased AST and ALT (145 and 355 IU/L, respectively) at a SHARP clinic visit on 05 May 2009. Study treatment was stopped along with azathioprine, cotrimoxazole, benalapril, and benzbromaron. AST and ALT increased into the 200s and 500s, respectively; abdominal ultrasound revealed diffuse parenchymal disease without masses. Other than immunity to Hep A (IgG pos), all other hepatitis serologies were negative (HBsAg, HBsAb, HBcAb, HCV, CMV IgG and IgM, ANA, anti-histone, anti-mitochondrial, anti-LKM-1, anti-SLA/LP Abs, EBV). A liver biopsy on 28 July 2009 demonstrated metabolic-toxic liver damage with focal fatty degeneration, no hemochromatosis, and a high rate of hepatocyte apoptosis. The peak AST and ALT in the submitted dataset are 876 and 1074, respectively, on 06 November 2009. A repeat liver biopsy that month showed "medical toxic liver damage and fibrosis / incomplete cirrhosis." LFTs subsequently trended down; ALT was 116 IU/L at the final study visit on 16 June 2010.
2. **Subject 225-0143 (Arm 3a: Simvastatin → Placebo).** 78-y/o SE Asian male (Canada) who was initially randomized to simvastatin (Arm 3) on 30 June 2005. At his routine SHARP clinic visit on 07 December 2005, his ALT was 17 IU/L (ULN=55 IU/L). At his SHARP clinic visit six months later (30 June 2006), ALT was 371 IU/L; at this visit, he was re-randomized to placebo (Arm 3a). Study treatment was discontinued. He was admitted to the hospital (b) (6) with RUQ tenderness, ALT 663 (12xULN) and AST 584 (13xULN). Transaminases peaked the next day at ALT 710 and AST 605. Abdominal ultrasound was unrevealing. Treating physician thought abnormalities were like a result of SHARP study treatment. Concomitant medications were Tylenol arthritis, Tylenol with codeine, nifedipine, allopurinol, colchicine, salbutamol, fluticasone, Pepto-bismol suspension. Hepatitis serologies were consistent with previous

Hepatitis B exposure (HBsAg neg, HBsAb pos, HBeAb pos). ALT fell to 215 IU/L by July 13 and to 23 IU/L by a routine SHARP visit on 19 December 2007.
Reviewer Comment: Although the applicant includes this case among those assigned to placebo, the liver abnormality was present on the day that the patient finished 1-yr of simvastatin as part of Arm 3.

Table 48. Summary of Hepatitis Cases

ID	Demog.	Date of Rand.	Date of Onset	Adjudicated Outcome	Hosp?	D/C & Rechallenge?	Notes
EZETIMIBE/SIMVASTATIN							
150-0145	63 M White (UK)	20Apr05	24Mar06	Toxic w/ acute hepatitis	No	Temp D/C 24Mar06; restarted Apr09 without recurrence	ALT/AST abnormality the day following addition of clarithromycin; study drug stopped w/ rapid return to baseline
196-0102	57 F White (Australia)	20Jan04	04Jul05	EtOH hepatitis	Yes	D/C 07Jul05	Biopsy consistent w/ NASH or EtOH hepatitis
265-0130	48 M White (Germany)	04Nov04	02Nov06	Toxic w/ hepatitis	Yes	D/C Jan 05 (>1.5 y before event)	***Not taking Rx at time of event.*** On fluvastatin.
346-0109	70 M White (Germany)	12Jan05	15May09	Toxic w/ hepatitis	Yes (biopsy)	D/C 15May09	See narrative above.
346-0115	71 F White (Germany)	18Mar05	27Aug09	Toxic w/ hepatitis	Yes	D/C 28Aug09	
418-0127	51 F White (Germany)	20Jul06	02Apr07	Toxic w/ acute hepatitis	Yes	Temp D/C peri-op; restarted Aug07 without recurrence	
263-0120	89 M Asian (Thailand)	31May05	27Nov06	Non-infective hepatitis	No	Temp D/C 27 Nov06; restarted Dec06 without recurrence	ALT 63 on 27Dec06 (restart); ALT 137 on 24Jan07 → drug d/c'd again → ALT 55 on 08Feb07 → Restart 21Feb07 → ALT 29 on 07Jun07 (death, "spinal cord disorder")
274-0123	70 F White (Germany)	02Nov05	01Nov05	Non-infective hepatitis	Yes	Temp D/C Nov05; restarted May06 without recurrence	Increased transaminases at randomization (ALT 147 [4xULN]), which rose to peak ALT 530 on 14Nov05]
408-0104	64 M White (Sweden)	15Dec05	30Jan06	Non-infective hepatitis	Yes	Temp D/C Feb06; restarted Spring '06 without recurrence	Concurrent idiopathic pancreatitis
PLACEBO							
120-0118	58 M White (UK)	21Apr04	09Sep09	Other specified inflammatory liver disease	Yes	D/C at final visit Apr10	Biliary obstruction/ascending cholangitis on background of primary sclerosing cholangitis
163-0103	49 F Chinese (Malaysia)	11Dec03	12Nov07	Toxic liver disease	No	Temp D/C 29Nov07; restart 03Dec07 until	History of taking traditional Chinese herbs

ID	Demog.	Date of Rand.	Date of Onset	Adjudicated Outcome	Hosp?	D/C & Rechallenge?	Notes
						Aug08 (start of non-study statin)	
164-0142	62 M Chinese (Malaysia)	22Dec04	22Feb05 and Mar07	Toxic liver disease	No	No	'05: *Klebsiella* peritonitis; '07: chronic hep B / cirrhosis
197-0109	61 M Oceanian (Australia)	13May05	07Oct08	Toxic liver disease w/ cholelithiasis	Yes	D/C'd May08 before event	? Augmentin. Off-treatment simvastatin in 2009-2010 without transaminase abnormalities
176-0102	54 M Asian (Malaysia)	07Jan04	28Jun04	Chronic HCV (see notes)	Yes	D/C'd Jun04; restart Oct04 x 1 mo, then on/off until Jul06 (death from Hep C)	Initially non-infective hepatitis; later adjudicated to have acute, then chronic, Hep C
225-0143	58 M Asian (Canada)	30Jun05	30Jun06	Non-infective hepatitis	Yes	D/C 29Jun06	***Increased transaminases noted on day of randomization to placebo (from simva)***
269-0107	73 M Black (Canada)	19Dec05	04Jul07	Non-infective hepatitis	Yes	Temp D/C Jul07 (ran out of Rx), otherwise on Rx throughout	? sepsis-related

Source: CSR Tables 14-24 and 14-25.

All Transaminase Elevations >2xULN

During the first year, 43 (1.0%) patients in the ezetimibe/simvastatin group, 6 (0.6%) in the simvastatin group, and 22 (0.5%) in the placebo group experienced at least one event of transaminases >3xULN. Lesser degrees of elevation occurred more commonly in the ezetimibe/simvastatin and simvastatin groups than placebo: the number of patients in each group who experienced a year-one peak ALT and/or AST elevation >2x but ≤3xULN was 76 (1.8%), 16 (1.5%), and 34 (0.8%) for the ezetimibe/simvastatin, simvastatin, and placebo groups, respectively. From the time of randomization to ezetimibe/simvastatin or placebo until last follow-up, 105 (2.3%) patients in the ezetimibe/simvastatin group and 76 (1.7%) in the placebo group experienced at least one event of transaminases >3xULN. Lesser degrees of elevation also occurred more commonly in the ezetimibe group than placebo (162 [3.5%] vs. 112 [2.4%], respectively). Table 49 summarizes these data.

Table 49. Incidence of Increased Transaminases

	First Year			From Randomization to Eze/Sim or Placebo	
Peak ALT and/or AST	**Eze/Sim (N=4170)***	**Simva (N=1051)***	**Placebo (N=4166)***	**Eze/Sim (N=4615)***	**Placebo (N=4587)***
>2x but ≤3xULN	**76 (1.8%)**	**16 (1.5%)**	**34 (0.8%)**	**162 (3.5%)**	**112 (2.4%)**
>3xULN	**43 (1.0%)**	**6 (0.6%)**	**22 (0.5%)**	**105 (2.3%)**	**76 (1.7%)**
>3x but ≤5xULN	26 (0.6%)	2 (0.2%)	13 (0.3%)	66 (1.4%)	49 (1.1%)
>5x but ≤10xULN	14 (0.3%)	3 (0.3%)	5 (0.1%)	29 (0.6%)	15 (0.3%)
>10xULN	3 (0.07%)	1 (0.1%)	4 (0.1%)	10 (0.2%)	12 (0.3%)

Source: Tables 12-4, 12-19.
* N reflects number of subjects with post-baseline AST or ALT data. Percentages do not change if N is changed to reflect the total ITT population.

Gallbladder- and Pancreas-related AEs

Biliary/gallstone-related events were adjudicated using clinical judgment. Events were classified as complications of gallstones, hospitalization with gallstones (and no reported complications), and pancreatitis without gallstones. Complications of gallstones included acute pancreatitis and "other" (cholecystectomy, gallstones with cholecystitis, bile duct stones with or without cholecystitis, and bile duct stones with cholangitis). A patient who had acute gallstone pancreatitis followed by cholecystectomy would appear in both subcategories of "Complications of gallstones," but a patient who had acute cholecystitis followed by cholecystectomy would appear once in "Other complications."

Pancreatitis was *not* a pre-specified event for adjudication in the protocol, except for pancreatitis that occurred secondary to gallstones. For events assigned to adjudication, cases of pancreatitis must have met pre-specified criteria that appear reasonable to this reviewer.

Table 50. Gallstone- and Pancreas-related Events

	First Year			From Randomization to Eze/Sim or Placebo	
Event	**Eze/Sim Arm 2 (N=4193)**	**Simvastatin Arm 3 (N=1054)**	**Placebo Arm 1 (N=4191)**	**Eze/Sim Arms 2+3b (N=4650)**	**Placebo Arms 1+3a (N=4620)**
Complications of gallstones	**19 (0.45%)**	**3 (0.28%)**	**23 (0.55%)**	**85 (1.83%)**	**76 (1.65%)**
Acute pancreatitis	3	0	5	11	12
Other complications	17	3	20	78	71
Hospitalization with gallstones but no reported complications	**2 (0.05%)**	**4 (0.38%)**	**4 (0.10%)**	**21 (0.45%)**	**30 (0.65%)**
Pancreatitis (without gallstones)	**2 (0.05%)**	**1 (0.09%)**	**6 (0.14%)**	**12 (0.26%)**	**27 (0.58%)**
Acute pancreatitis	2	1	5	11	22
Chronic pancreatitis	0	0	1	2	6

Source: CSR Tables 12-3 and 12-21.

Patients with other types of nonfatal biliary disease are reported in Table 41 in the "Miscellaneous liver/pancreas/biliary" category: 36 events in the ezetimibe/simvastatin group and 43 events in the placebo group. Patients with gallstones not associated with complications, hospitalization, or death (e.g., incidental gallstones on ultrasound) are reported in Table 41 in the "Gallstones (excluding complications)" category: 22 events in the ezetimibe/simvastatin group and 14 events in the placebo group.

Incident Diabetes / Complications of Diabetes

Incident diabetes mellitus, a tertiary endpoint in SHARP, was defined by reports of diabetes as an SAE and by the initiation of medications to treat diabetes among patients not known to have diabetes mellitus at randomization. Hemoglobin A1c was not measured. Complications of diabetes were defined by the following SAEs: pancreas transplant, diabetic eye disease, laser treatment for diabetic eye disease, diabetes (newly diagnosed), unstable diabetes/hyperglycemia, diabetic coma, diabetic ketoacidosis, diabetic non-ketotic hyperosmolar state, and diabetic ulcer (foot, toe, or leg).

The group of patients ever randomized to ezetimibe/simvastatin had numerically more cases of incident diabetes and diabetic complications, but the differences were rather small. Hypoglycemic episodes were also reported more often among those treated with ezetimibe/simvastatin (Table 51).

Table 51. Incident Diabetes and Diabetic Complications

Endpoint	Eze/Sim (N=4650)	Placebo (N=4620)	HR (95% CI)	P
Incident Diabetes	172 (4.8%)	162 (4.5%)	1.06 (0.85-1.32)	0.59
Diabetic Complication				
Among those *with* DM at randomization	83 (7.9%)	67 (6.4%)	1.22 (0.89-1.68)	
Among those *without* DM at randomization	53 (1.5%)	59 (1.6%)	0.90 (0.62-1.30)	
All patients	**136 (2.9%)**	**126 (2.7%)**	**1.07 (0.84-1.37)**	**0.56**
Hypoglycemia				
Among those *with* DM at randomization	51 (4.8%)	32 (3.1%)	1.58 (1.03-2.43)	0.06
Among those *without* DM at randomization	2 (0.1%)	3 (0.1%)	0.67 (0.12-3.88)	
All patients	**53 (1.1%)**	**35 (0.8%)**	**1.50 (0.99-2.28)**	**0.06**

Source: CSR Figures 12-2 and 12-3.

Reviewer Comment: SHARP neither pre-specified the collection of diabetes-related AEs nor required adjudication of these events.

Cancer-related Events

Cancer-related events were pre-specified for adjudication:

- The first post-randomization occurrence of each cancer type was recorded;
- Subsequent events relating to the same cancer were coded according to the procedure (e.g. chemotherapy, resection) or as "recurrent cancer;"
- If the same type of cancer clearly led to 2 separate cancer events at different sites of the body, the first occurrence of each was coded;
- Cancer was coded as the cause of death if death resulted directly from the cancer, from a complication of the cancer (e.g. infection, surgery, chemotherapy, etc.), or from withdrawal of other therapies (e.g., dialysis) because of poor prognosis associated with

the cancer. Deaths resulting from cancers present before randomization had "pre-randomization cancer" recorded as cause of death.

Table 52 summarizes cancer incidence by site in all patients ever randomized to ezetimibe/simvastatin or placebo. Any incident cancer occurred in 438 (9.4%) patients in the ezetimibe/simvastatin group and 439 (9.5%) patients in the placebo group (Rate Ratio 0.99; 95% CI 0.87-1.13). Excluding non-melanoma skin cancers, any incident cancer occurred in 322 (6.9%) patients in the ezetimibe/simvastatin group and 307 (6.6%) in the placebo group (RR 1.04; 95% CI 0.89-1.22).

Forty-two patients (20 ezetimibe/simvastatin and 22 placebo) had an incident cancer in more than one body site; skin cancer accounted for 22 of these cases.

Table 52. Cancer Incidence by Body Site

Cancer Site	Eze/Sim (N=4650)	Placebo (N=4620)	Rate Ratio (95% CI)
Lip/mouth/pharynx/esophagus	14	16	0.87 (0.43-1.78)
Stomach	11	14	0.78 (0.36-1.72)
Large bowel or intestine	53	35	1.50 (0.99-2.28)
Pancreas	9	10	0.90 (0.36-2.20)
Liver/gallbladder/bile ducts	8	4	1.94 (0.63-6.02)
Lung	42	35	1.19 (0.76-1.87)
Other respiratory	3	4	0.75 (0.17-3.29)
Skin	136	153	0.88 (0.70-1.11)
Breast	29	21	1.37 (0.79-2.39)
Prostate	39	52	0.75 (0.49-1.12)
Kidney	31	23	1.34 (0.79-2.28)
Bladder and urinary tract (excluding kidney)	26	32	0.81 (0.48-1.35)
Genital	12	14	0.85 (0.40-1.84)
Hematological	26	27	0.96 (0.56-1.65)
Other known site	9	12	0.75 (0.32-1.76)
Unspecified cancer	13	7	1.81 (0.75-4.35)
Any incident cancer	**438 (9.4%)**	**439 (9.5%)**	**0.99 (0.87-1.13)**
All except non-melanoma skin cancer	**322 (6.9%)**	**307 (6.6%)**	**1.04 (0.89-1.22)**

Source: CSR Table 12-5.
In addition, there were 3 cancers in a transplanted kidney (2 eze/sim, 1 placebo).

For reference, Table 53 summarizes numbers of subjects with incident cancer (fatal or nonfatal) in the SEAS trial as reported in the analysis by Peto *et al.*[23]

Table 53. Incident Cancer in SEAS Trial

Cancer Site	Eze/Sim (N=944)	Placebo (N=929)
Lip/mouth/pharynx/esophagus	1	1
Stomach	5	1
Large bowel or intestine	9	8

Cancer Site	Eze/Sim (N=944)	Placebo (N=929)
Pancreas	3	1
Liver/gallbladder/bile ducts	2	3
Lung	7	10
Other respiratory	1	0
Skin	18	8
Breast	8	5
Prostate	21	13
Kidney	2	2
Bladder	7	7
Genital	4	4
Hematological	7	5
Other known site	3	1
Unspecified cancer	9	6
Any incident cancer	**101**	**65**

Source: Derived from Table 1 of Peto *et al. NEJM* 359:1357-1366*;* 2008.

Similar to SEAS, the difference in risk for incident cancer between ezetimibe/simvastatin and placebo did not appear to increase with duration of follow-up in SHARP (Figure 26).

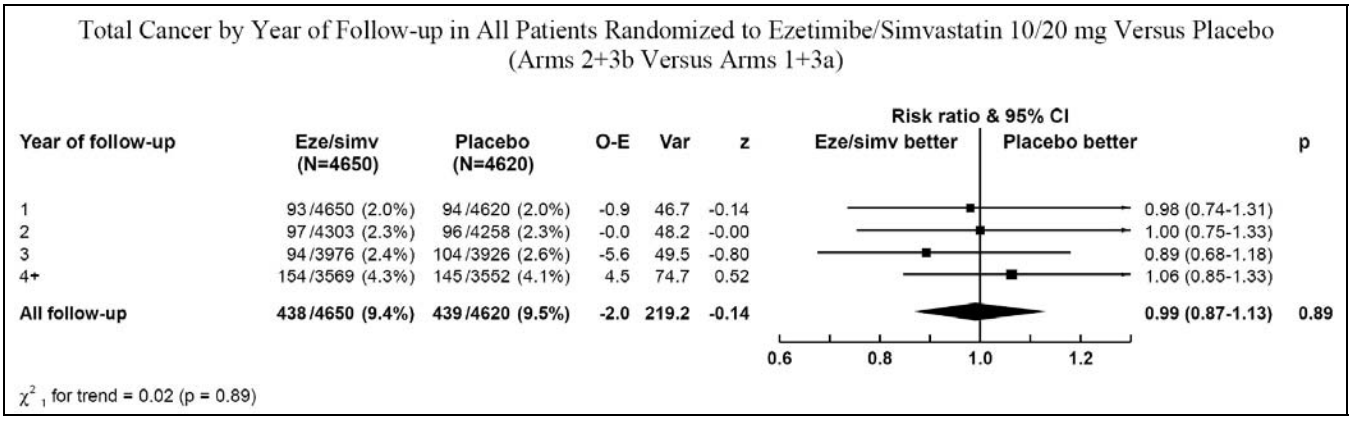


Figure 26. Incident Cancer by Year of Follow-up
Source: CSR Figure 14-1.

There were 18 more deaths resulting from incident cancer in those ever randomized to ezetimibe/simvastatin compared with placebo (132 [2.8%] vs. 114 [2.5%]). There were 22 more deaths resulting from any cancer (i.e., including cancers diagnosed before randomization) in those ever randomized to ezetimibe/simvastatin compared with placebo (150 [3.2%] vs. 128 [2.8%]). Table 54 summarizes cancer deaths by body site.

Table 54. Cancer Deaths by Body Site

Cancer Site	Eze/Sim (N=4650)	Placebo (N=4620)	Rate Ratio (95% CI)
Lip/mouth/pharynx/esophagus	9	8	1.12 (0.43-2.89)
Stomach	10	11	0.91 (0.39-2.14)
Large bowel or intestine	20	15	1.33 (0.68-2.57)
Pancreas	7	10	0.70 (0.27-1.81)
Liver/gallbladder/bile ducts	4	4	1.00 (0.25-3.99)
Lung	32	22	1.44 (0.84-2.45)
Other respiratory	2	3	0.67 (0.12-3.85)
Skin	4	4	1.00 (0.25-4.00)
Breast	1	1	0.99 (0.06-15.87)
Prostate	6	2	2.79 (0.70-11.17)
Kidney	5	1	3.77 (0.76-18.69)
Bladder and urinary tract (excluding kidney)	8	7	1.14 (0.41-3.14)
Genital	4	2	1.94 (0.39-9.62)
Hematological	6	14	0.45 (0.19-1.08)
Other known site	3	5	0.60 (0.15-2.41)
Unspecified cancer	11	5	2.11 (0.79-5.61)
Any incident cancer	**132 (2.8%)**	**114 (2.5%)**	**1.15 (0.90-1.48)**
Pre-randomization cancer	18	14	1.27 (0.64-2.55)
Any cancer (including pre-randomization)	**150 (3.2%)**	**128 (2.8%)**	**1.17 (0.92-1.48)**

Source: CSR Table 12-6.
In addition, there were 2 deaths from cancer in a transplanted kidney (1 eze/sim, 1 placebo).
Review of the raw data verified that each cancer death was recorded only one time in this table, even if the patient had incident cancer in more than 1 site.

For reference, Table 55 summarizes numbers of subjects who died from cancer in the SEAS trial as reported in the analysis by Peto *et al.*[23]

Table 55. Cancer Deaths in SEAS Trial

Cancer Site	Eze/Sim (N=944)	Placebo (N=929)
Lip/mouth/pharynx/esophagus	1	0
Stomach	4	1
Large bowel or intestine	3	1
Pancreas	2	0
Liver/gallbladder/bile ducts	2	3
Lung	6	8
Other respiratory	1	0
Skin	0	0
Breast	1	0
Prostate	2	0
Kidney	1	0
Bladder	4	1
Genital	3	2
Hematological	3	2

Cancer Site	Eze/Sim (N=944)	Placebo (N=929)
Other known site	1	0
Unspecified cancer	3	2
Any incident cancer	**37**	**20**

Source: Derived from Table 2 of Peto *et al. NEJM* 359:1357-1366*;* 2008.

Reviewer Comments:

1. *In SHARP, there were numerically more incident cancers of the "large bowel or intestine" in the ezetimibe/simvastatin group with a 95% CI lower bound of 0.99. This imbalance was not observed in SEAS. Furthermore, the sites with the greatest imbalances in SEAS (e.g., prostate, skin) do not appear to be sites of concern in SHARP.*
2. *Similar to SEAS, risk of cancer did not increase consistently over time with longer use of ezetimibe/simvastatin, as would be expected if a drug caused cancer or promoted the growth of pre-existing cancers.*

SHARP: Safety Summary

- All-cause mortality was similar between patients ever randomized to ezetimibe/simvastatin or placebo (24.6% vs. 24.1%, respectively)
- Nonfatal serious adverse events (SAEs) occurred in 70% of patients ever randomized to ezetimibe/simvastatin and 71% ever randomized to placebo.
- The proportion of patients discontinuing study treatment as a result of an SAE was similar between those ever randomized to ezetimibe/simvastatin and placebo (6.5% vs. 6.7%, respectively). The most common SAE that led to premature discontinuation of study treatment was renal transplantation, accounting for ~50% of all SAE-related discontinuations in each group.
- The proportion of patients discontinuing study treatment as a result of a non-serious AE was higher among those randomized to ezetimibe/simvastatin (3.5% vs. 2.8%). Non-serious AEs that led to premature discontinuation and that occurred more frequently among those assigned to ezetimibe/simvastatin included skin symptoms (0.4% vs. 0.2%), muscle pain (1.1% vs. 0.6%), and abnormal safety bloodwork (0.9% vs. 0.6%).
- Myopathy (symptomatic CK >10xULN) occurred in 9 patients assigned to ezetimibe/simvastatin and 5 patients assigned to placebo. An "on-treatment" comparison reduces these counts to 8 vs. 3. Rhabdomyolysis (symptomatic CK >40xULN) occurred in 4 patients assigned to ezetimibe/simvastatin and 1 patient assigned to placebo (who was taking a non-study statin at the time of the event).
- Persistently elevated transaminases (>3xULN for two consecutive measurements) occurred in 30 (0.7%) patients assigned to ezetimibe/simvastatin and 26 (0.6%) patients assigned to placebo.
- Any incident cancer occurred in 438 (9.4%) patients assigned to ezetimibe/simvastatin and 439 (9.5%) patients assigned to placebo. There was no statistically significant trend

detected between duration of follow-up and risk difference of incident cancer between patients assigned to ezetimibe/simvastatin and placebo.

- There were 18 more deaths resulting from incident cancer among those ever randomized to ezetimibe/simvastatin compared with placebo (132 [2.8%] vs. 114 [2.5%]).

Appendix

Pre-specified Endpoints & Subgroups

Table 56. SHARP Pre-specified Endpoints

Endpoint	Protocol Designation	SAP Designation
MVE (Arm 1 vs. Arm 2) *	Primary	Subsidiary
MAE	-	"Key"
Major cardiac events (nonfatal MI or cardiac death)	Secondary	-
Major coronary events (nonfatal MI or coronary death)	-	Subsidiary
All stroke (fatal or nonfatal)	Secondary	Tertiary
Ischemic stroke (fatal or nonfatal)	-	Subsidiary
Coronary or non-coronary revascularization	Secondary	Subsidiary
All-cause mortality	Secondary	Tertiary
Death from coronary heart disease (CHD)	Secondary	Tertiary
Death from other cardiac cause	Secondary	Tertiary
Death from stroke (including subtypes in SAP)	Secondary	Tertiary
Death from other vascular cause	Secondary	Tertiary
Death from neoplasm	Secondary	Tertiary
Death from renal cause	Secondary	Tertiary
Death from other cause	Secondary	Tertiary
Hospitalization for angina (symptoms suggestive of cardiac chest pain and no other cause identified)	Secondary	Tertiary
ESRD (need for long-term dialysis or transplantation) among pre-dialysis patients at the time of randomization†	Secondary*	Subsidiary ("Main renal outcome")
ESRD or death from any cause among pre-dialysis patients at the time of randomization†	Secondary*	Tertiary
Doubling of plasma creatinine or ESRD among pre-dialysis patients at the time of randomization†	-	Tertiary
Hospitalization for heart failure	Tertiary	Tertiary
Site-specific cancers‡ (SAP: subdivided by site with appropriate statistical adjustment for multiplicity, and excluding any recurrences of cancers known to be present prior to randomization†)	Tertiary	Tertiary
Incident diabetes from the time of randomization†	Tertiary	Tertiary
Revision of vascular access for dialysis	Tertiary	Tertiary
Coronary revascularization	Tertiary	-
Non-coronary revascularization procedures (excluding vascular access revisions)	Tertiary	-
Hemorrhagic stroke	Tertiary	Tertiary
Unknown type of stroke	-	Tertiary
Transient ischemic attack	-	Tertiary
Possible adverse effects of combination treatment during the entire scheduled treatment period	Tertiary	-

* Arm 1 vs. 2; all other endpoints compare Arms 1+3a vs. 2+3b.

† Randomization to ezetimibe/simvastatin (i.e., second randomization for Arm 3).
‡ SAP specifies that site-specific cancers will be subdivided by site, in categories previously defined in a published interim analysis of SHARP cancers (Peto R, et al. 2008)[23] with appropriate statistical adjustment for multiplicity, and excluding any recurrences of cancers known to be present prior to randomization to ezetimibe/simvastatin.

Table 57. SHARP Pre-specified Subgroups

Subgroup	Specified in Protocol	Specified in SAP
Patients with or without evidence of a disease that is associated with an increased risk of coronary heart disease, including:		
• peripheral arterial disease,	X	X
• cerebrovascular disease,	X	X
• diabetes mellitus	X	X
• coronary disease (i.e., angina)		X
• at least one of peripheral arterial disease, cerebrovascular disease, or diabetes mellitus (vs. none)	X	-
• at least one of peripheral arterial disease, cerebrovascular disease, or coronary disease (vs. none)	-	X
Various other categories of patient determined at randomization:		
• men and women	X	X
• age 40-49; 50-59; 60-69; ≥70	X	X
• pre-dialysis and dialysis	X	X
• smokers and non-smokers	X	X
• blood creatinine ≤200; 201-400; >400 μmol/L [pre-dialysis patients only]	X	-
• tertiles of blood cystatin C [pre-dialysis patients only]	X	X
• tertiles of Cockcroft-Gault-estimated creatinine clearance [pre-dialysis patients only]	X	-
• tertiles of MDRD eGFR [pre-dialysis patients only]	X	-
• MDRD eGFR ≥60, 30-59, 15-29, <15 mL/min/1.73m^2	-	X
• hemodialysis and peritoneal dialysis [dialysis patients only]	X	X
• diastolic blood pressure <80; 80-89; 90-99; ≥100 mmHg	X	X
• systolic blood pressure <140; 141-159; 160-179; ≥180 mmHg	X	X
• tertiles of total cholesterol	X	X
• tertiles of LDL-C	X	X
• tertiles of HDL-C	X	X
• tertiles of non-HDL-C	X	X
• tertiles of triglycerides	X	X
• tertiles of apolipoprotein B	X	X
• tertiles of apolipoprotein A	X	X
• tertiles of body mass index	X	X
• tertiles of waist circumference	X	X
• tertiles of hemoglobin	X	X
• tertiles of blood creatinine (surrogate for nutritional status) [among dialysis patients only]	X	-

Subgroup	Specified in Protocol	Specified in SAP
• tertiles of plasma albumin	X	X
• tertiles of calcium-phosphate product	X	-
• tertiles of plasma phosphate	-	X
• tertiles of proteinuria (as measured by albumin:creatinine ratio)	X	-
• normoalbuminuria, microalbuminuria, macroalbuminuria (based on albumin:creatinine ratio)	-	X
The presence or absence of particular non-study treatments at randomization:		
• aspirin	X	-
• anti-platelet therapy	-	X
• ACE inhibitors	X	-
• ARBs	X	-
• ACE or ARB	-	X
• diuretic	X	X
• calcium-channel blockers	X	X
• beta-blockers	X	X
• erythropoietin	X	X
• sevelamer	X	X
• oral anticoagulants	-	X

The outcome of interest for each subgroup analysis is MVE (protocol) or MAE (SAP).
Randomization refers to the time of allocation to ezetimibe/simvastatin or placebo (i.e., second randomization for Arm 3).

Selected Endpoint Definitions & Adjudication Criteria

Death

- The fact and the date of death must be adjudicated from hospital records, pathology results, imaging or treatment records, death certificates, routine data sources, or, in rare circumstances, relevant information from relatives, caregivers, or local physicians.
- "The disease or injury which initiated the chain of morbid events leading directly to death" should be coded as the cause of death.

Nonfatal Myocardial Infarction

- Presentation must include typical ischemic chest pain, pulmonary edema, syncope, or shock without other likely diagnosis to explain the presentation.
- Assignment of qualifier (definite, probable, possible) depended on the results of cardiac biomarkers, ECG findings, post-mortem findings, and whether the patient was dependent on dialysis or a functioning renal transplant at the time of presentation (see Table 58).
- Patients treated with thrombolysis or primary PCI *for acute MI* were to be coded as Definite MI unless there was strong evidence to the contrary.
- *Cardiac Biomarkers*
    - Diagnostic: Either a gross elevation of a single result (troponin I >2.5x lower limit of detection [LLD] or troponin T >25xLLD) *or* a change of ≥20% on sequential troponin measurements (with peak troponin I ≥1.1xLLD or peak troponin T ≥10xLLD) made within the presenting episode.
    - Equivocal: Not "Diagnostic" and at least one of the following occurs: (1) Moderate elevation of a single result (troponin I >1x and ≤2.5xLLD *or* troponin T >10x and ≤25xLLD) and a change of ≥20% compared with usual troponin measurement taken outside of the context of acute ischemia (e.g., at routine dialysis session) *OR* (2) CK-MB results or serial CK results consistent with a diagnosis of MI (e.g., serial rise and fall of CK >2xULN).
    - Missing: No results available ≤10 days after date of presentation
    - Normal: Results available ≤10 days after date of presentation but do not fulfill "Diagnostic" or "Equivocal" criteria.
- *ECG Findings*
    - New ST elevation in ≥2 contiguous leads
    - New horizontal or downsloping ST depression in ≥2 contiguous leads *or* new T-wave inversion with prominent R wave or R/S ratio >1 in ≥2 contiguous leads
    - New-onset LBBB
    - Other changes not known to be chronic
    - Missing: no ECGs available from time of event
    - No new abnormality: Normal ECG *or* old changes only

Table 58. Diagnosis of Nonfatal MI

Biomarker ► ECG ▼	Diagnostic	Equivocal		Missing		Normal	
		No RRT	RRT	No RRT	RRT	No RRT	RRT
ST elevation	Definite	Definite	Definite	Definite	Definite	Definite	Definite
ST depression or T wave inversion	Definite	Probable	Possible	Possible	Possible	Not MI	Not MI
New LBBB	Definite	Probable	Possible	Possible	Possible	Not MI	Not MI
Other changes (not known to be old)	Definite	Possible	Possible	Not MI	Not MI	Not MI	Not MI
Missing	Definite	Possible	Not MI	Not MI	Not MI	Not MI	Not MI
No new abnormality	Definite	Possible	Not MI	Not MI	Not MI	Not MI	Not MI

[RRT = Renal Replacement Therapy (participant dependent on dialysis or a functioning renal transplant at time of presentation with the SAE)].

Reviewer Comment: (1) The troponin cut-off values reflect the fact that stable, asymptomatic patients with kidney disease, especially those on dialysis, frequently have values that could be diagnostic of myocardial infarction in the general population. The applicant cites Apple et al. Circulation 2002; 106:2941-5 for troponin cut-offs and Wu et al. Clin Chem 2007; 53:2086-96 for changes in repeated measures of troponin. (2) ECG criteria are not specified in detail (e.g., mV elevation to define ST elevation). (3) The development of pathological Q waves is not specifically included in the adjudication criteria for MI except for falling into the "other changes (not known to be old)" category. (4) Silent MIs are excluded per protocol. (5) No distinction is made between types of MI (e.g., spontaneous MI, peri-PCI MI, or peri-CABG MI; STEMI or NSTEMI; or other classification systems).

Fatal Myocardial Infarction

- Death that occurred as a result of an MI within the preceding 30 days
- In addition, results from post-mortem examination should be taken into account (see Table 59).
- *Post-mortem examination*
  - Diagnostic: Findings of MI of an age corresponding to clinical history *and* no other cause of death identified
  - Equivocal: Findings of ischemic heart disease (e.g., coronary artery atheroma) or old MI *and* no findings of acute MI of an age corresponding to clinical history *and* no other cause of death identified
  - Missing: Post-mortem done but no results available

- Not MI: Other cause of death identified

Table 59. Diagnosis of Fatal MI

Standard criteria ► Post mortem ▼	Definite	Probable	Possible	Not MI
Diagnostic	Definite	Definite	Definite	Definite
Equivocal	Definite	Probable	Possible	Not MI
Missing	Definite	Probable	Possible	Not MI
Notdone	Definite	Probable	Possible	Not MI
Not MI	Not MI	Not MI	Not MI	Not MI

Source: Event Adjudication SOP.

Reviewer Comment: Statistical analysis plan indicates that the dichotomous MI outcome comprises definite, probable, and possible MI.

Hospitalization for Angina (not in primary composite)

- Evidence for typical ischemic chest pain *and* hospitalization
- Criteria for MI must not be met

Hospitalization for Heart Failure (not in primary composite)

- Primary objective of reviewing reports of heart failure is to ensure that there is no evidence of heart failure.

Reviewer Comment: The SOP appropriately recognizes the complexity of adjudicating this type of event, especially in the ESRD population where fluid overload can occur for a multitude of reasons.

Cardiac Death

- Cardiac mortality comprises MI death (see above), CHD death (not MI), and Other cardiac death (not CHD).
- Sudden cardiac death is not specified as a separate outcome but rather defined as any death that is considered to be "cardiac in origin and which occurs suddenly and unexpectedly."
- *CHD Death (not MI)*
  - Criteria for MI not met *and* cause of cardiac death believed to be coronary atherosclerosis, including:
    - Death following admission with acute coronary syndrome/angina

        - Death from ischemic cardiomyopathy
        - Death from ischemic heart disease that does not meet the definition for acute MI (e.g., necropsy findings of coronary artery disease but without a lesion of an age corresponding to time of symptom onset) and is believed to be due to coronary atherosclerosis
- *Other Cardiac Death*
    - Criteria for MI not met *and* cause of cardiac death not believed to be atherosclerotic ischemic heart disease, including:
        - Death from non-ischemic cardiomyopathy or heart failure (unspecified)
        - Death from heart disease without evidence of underlying coronary atherosclerosis (e.g., sudden cardiac death)
        - Death from cardiac arrest, ventricular tachycardia, or other arrhythmia with *no* evidence of underlying coronary atherosclerosis
        - Death from other cardiac diseases (e.g., valvular heart disease)

Reviewer Comment: Accurate subclassification of cardiac death is prone to misclassification. For example, with regard to "Other cardiac death," the absence of evidence for underlying coronary atherosclerosis does not equate to evidence for absence of underlying coronary atherosclerosis. Successful blinding of the adjudicator should reduce the introduction of bias, however.

Nonfatal Stroke

- Rapid (or uncertain) onset of focal or global neurological deficit lasting >24 hours or leading to death
- *Excludes* primary subarachnoid hemorrhage, subdural or extradural hemorrhage/hematoma, primary or secondary tumor, venous sinus thrombosis, trauma, neurological deficit due to metabolic or hemodynamic disturbance, transient ischemic attack (resolution within 24 hours), or amaurosis fugax.
- If recovery time is unknown and neuro-imaging is either equivocal, normal, missing, or was not done, then the event should be coded per the original report if additional information cannot be obtained.
- *Brain imaging*
    - Infarct: Cerebral/cerebellar infarct seen of concomitant age and site to clinical presentation
    - Hemorrhage: Intra-cerebral/cerebellar hemorrhage seen of concomitant age and site to clinical presentation
    - Equivocal: Relevant abnormality detected but not of concomitant age to clinical presentation (e.g., old infarct), and no alternative diagnosis
    - Normal: No relevant abnormality detected and no alternative diagnosis
    - Missing: No result available
    - Other diagnosis: Definite changes compatible with alternative diagnosis (e.g. trauma, tumor, subdural hematoma)

Table 60. Diagnosis of Nonfatal Stroke

Resolution ► Imaging ▼	Death	>24 hours	<24 hours	Not known
Infarct	Ischaemic stroke – definite	Ischaemic stroke – definite	TIA	Ischaemic stroke – definite
Haemorrhage	Haemorrhagic stroke	Haemorrhagic stroke	TIA	Haemorrhagic stroke
Equivocal	Ischaemic stroke – presumed	Ischaemic stroke – presumed	TIA	Ischaemic stroke – presumed or TIA, according to original SAE report
Normal	Ischaemic stroke – presumed	Ischaemic stroke – presumed	TIA	Ischaemic stroke – presumed or TIA, according to original SAE report
Missing	Stroke – unknown type	Stroke – unknown type	TIA	Stroke – unknown type or TIA, according to original SAE report
Not done	Stroke – unknown type	Stroke – unknown type	TIA	Stroke – unknown type or TIA, according to original SAE report
Other diagnosis	Other diagnosis	Other diagnosis	Other diagnosis	Other diagnosis

Source: Event Adjudication SOP.

Fatal Stroke

- If stroke results in an inexorable decline in the condition of the participant and ultimately results in death, then stroke should be recorded as the underlying cause of death.
- Results from post-mortem examination should also be considered (see Table 61).
- *Post-mortem examination*
  - Infarct: Cerebral/cerebellar infarct seen of concomitant age and site to clinical presentation *and* no other cause of death identified
  - Hemorrhage: Intra-cerebral/cerebellar hemorrhage seen of concomitant age and site to clinical presentation *and* no other cause of death identified
  - Equivocal: Abnormality detected but not of concomitant age to clinical presentation *and* no findings of infarct or hemorrhage of concomitant age to clinical presentation *and* no other cause of death identified
  - Other diagnosis: Definite changes compatible with alternative diagnosis

Table 61. Diagnosis of Fatal Stroke

Standard criteria ► Post mortem ▼	Ischaemic stroke – definite	Ischaemic stroke – presumed	Haemorrhagic stroke	Stroke – unknown type	Other diagnosis
Infarct	Ischaemic stroke – definite	Ischaemic stroke – definite	Ischaemic stroke – definite	Ischaemic stroke – definite	Clinical judgement
Haemorrhage	Ischaemic stroke – definite	Ischaemic stroke – presumed	Haemorrhagic stroke	Haemorrhagic stroke	Clinical judgement
Equivocal	Ischaemic stroke – definite	Ischaemic stroke – presumed	Haemorrhagic stroke	Stroke – unknown type	Clinical judgement
Normal	Ischaemic stroke – definite	Ischaemic stroke – presumed	Haemorrhagic stroke	Stroke – unknown type	Clinical judgement
Missing	Ischaemic stroke – definite	Ischaemic stroke – presumed	Haemorrhagic stroke	Stroke – unknown type	Other diagnosis
Not done	Ischaemic stroke – definite	Ischaemic stroke – presumed	Haemorrhagic stroke	Stroke – unknown type	Other diagnosis
Other diagnosis	Clinical judgement	Clinical judgement	Clinical judgement	Clinical judgement	Other diagnosis

Source: Event Adjudication SOP.

Revascularization Events & Amputation

- Includes coronary or non-coronary artery grafting or angioplasty (with or without endovascular stenting) or amputation for arterial disease.
- *Excludes* vascular access surgery for dialysis.
- Must include evidence for either a percutaneous revascularization procedure, a surgical bypass or revascularization procedure (e.g., embolectomy, arterectomy), or amputation.
- For amputation due to trauma or other non-vascular causes (e.g., primary infection), the underlying diagnosis should be coded and the term "amputation" should not be used.
- For peri-procedural death, the revascularization procedure should be recorded as a nonfatal event and the underlying disease leading to the revascularization should be recorded as the cause of death.

End-stage Renal Disease Events

- *Initiation of Maintenance Dialysis*: Among patients not on dialysis at the screening visit, there must be evidence of initiation of maintenance dialysis. If there is evidence that dialysis is temporary and followed by no need for maintenance dialysis or for transplantation, the event should not be coded as initiation of dialysis. Evidence consists

of either (1) a record that dialysis has been initiated, (2) supporting documentation that indicates that dialysis is planned for the near future, accompanied by a subsequent SHARP follow-up visit form that records the change in renal status, or (3) two SHARP follow-up forms >3 months apart with status = dialysis on both.

- *Renal Transplantation*
- *Death from Renal Failure*
    - Among patients not on dialysis, there must be evidence that renal failure (either acute or chronic) was the cause of death.
    - Among patients on dialysis, there must be evidence that the death was due to either withdrawal of dialysis or failure of dialysis (either due to compliance or technical issues).
    - Among patients who have been transplanted, there must be evidence that death was due to transplant failure and either subsequent conservative renal care or withdrawal/failure of dialysis.
    - There must be no evidence that any other major pathology was the cause of death or withdrawal of dialysis.

Cancer Events

- The first post-randomization occurrence of each cancer type.
- The date and type of cancer must be confirmed from hospital records, pathology results (histology, cytology, post-mortem findings), imaging, or treatment records as well as from routine data sources.
- In the case of 2 separate cancers of the same type but at different sites, then the first occurrence of each cancer should be coded.
- *Death from Cancer*: Death results directly from the cancer, from a complication of the cancer, or from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer.

Frequency of Events Composing Primary Endpoint Components

Table 62. Frequency of Events Composing First Nonfatal MI

Event Code	Eze/Sim		Placebo	
	Arm 2	Arm 3b	Arm 1	Arm 3a
MI – Definite	116	5	135	10
MI – Probable	1	0	1	1
MI – Possible	10	1	11	1
MI/heart attack	1	0	0	0
TOTAL	**128**	**6**	**147**	**12**

Source: FDA reviewer's analysis from submitted raw data.

Table 63. Frequency of Events Composing Cardiac Death

Event Code	Eze/Sim		Placebo	
	Arm 2	Arm 3b	Arm 1	Arm 3a
MI – Definite	37	1	36	1
MI – Probable	2	0	0	0
MI – Possible	1	0	1	0
CHD death (not MI)	30	1	32	2
Heart failure – ischemic	11	0	12	1
Acute coronary syndrome / hosp with angina	7	1	5	0
TOTAL	**88**	**3**	**86**	**4**

Source: FDA reviewer's analysis from submitted raw data.

Table 64. Frequency of Events Composing Other Cardiac (non-CHD) Death

Event Code	Eze/Sim		Placebo	
	Arm 2	Arm 3b	Arm 1	Arm 3a
Sudden cardiac death	48	9	58	5
Heart failure/pulmonary edema/congestive cardiac failure	36	4	39	2
Cardiac arrest	15	1	10	5
Other cardiac death (not CHD)	7	0	14	0
Infective endocarditis/subacute bacterial endocarditis	8	0	7	4
Heart failure – not ischemic	7	0	10	2
Heart valve problem	8	1	9	0
Cardiac death	8	0	5	1
Arrhythmia	3	0	2	0
Cardiomyopathy	1	0	4	0
Ventricular tachycardia	1	0	1	0
Bradycardia	1	0	1	0
Aortic valve repair/replacement	0	0	2	0
Pericardial effusion	2	0	0	0
Conduction disorder/heart block	0	0	1	0
Mitral valve repair/replacement	1	0	0	0
Heart transplant	1	0	0	0
TOTAL	**147**	**15**	**163**	**19**

Source: FDA reviewer's analysis from submitted raw data.

Table 65. Frequency of Events Composing First Non-coronary Revascularization

Event Code	Eze/Sim		Placebo	
	Arm 2	Arm 3b	Arm 1	Arm 3a
Leg artery angioplasty ± stent	38	6	58	5
Fem-pop bypass/leg artery bypass	18	4	19	1
Aortic aneurysm repair or stent	18	2	11	1
Carotid surgery	8	0	9	1
Renal artery angioplasty ± stent	4	0	10	1
Popliteal, femoral, or iliac aneurysm repair	3	0	4	0
Arterial graft reconstruction/excision (not dialysis access)	2	1	1	0
Arterial surgery (not dialysis access)	1	0	2	0
Non-coronary angioplasty ± stent	1	0	2	0
Carotid angioplasty ± stent	1	0	2	0
Embolectomy	0	1	2	0
Non-coronary arterial surgery/intervention (not dialysis access)	1	0	0	0
Cerebral artery aneurysm surgery or clipping	0	0	1	0
TOTAL	**95**	**14**	**121**	**9**

Source: FDA reviewer's analysis from submitted raw data.

Table 66. Frequency of Events Composing First Amputation

Event Code	Eze/Sim		Placebo	
	Arm 2	Arm 3b	Arm 1	Arm 3a
Amputation of toe	34	3	34	0
Below-knee amputation	21	2	19	2
Above-knee amputation	7	0	12	1
Amputation of foot	6	1	6	1
Amputation of finger/thumb	0	1	1	0
TOTAL	**68**	**7**	**72**	**4**

Source: FDA reviewer's analysis from submitted raw data.

Subgroup Analyses Weighted for LDL Reduction

Major Vascular Events by Baseline Characteristics (Per mmol/L Reduction in LDL-C):
All Patients Randomized to Ezetimibe/Simvastatin Versus Placebo
(Arms 2+3b Versus Arms 1+3a)

Baseline characteristic	Eze/simv (N=4650)	Placebo (N=4620)	O-E	Var	Risk ratio & 95% CI	p	Het or trend χ^2_1
					Eze/simv better / Placebo better		
Prior vascular disease							
Coronary disease	45 /169 (26.6%)	45 /142 (31.7%)	-2.4	16.2	0.86 (0.53-1.40)		NA
Peripheral arterial disease	98 /304 (32.2%)	108 /300 (36.0%)	-6.8	39.8	0.84 (0.62-1.15)		
Cerebrovascular disease	99 /337 (29.4%)	108 /314 (34.4%)	-6.3	28.7	0.80 (0.56-1.16)		
At least 1 of above 3 conditions	212 /711 (29.8%)	222 /682 (32.6%)	-9.4	78.2	0.89 (0.71-1.11)		
None	489/3939 (12.4%)	592/3938 (15.0%)	-46.6	195.2	0.79 (0.68-0.91)		
Diabetes							
No diabetes	451/3596 (12.5%)	501/3580 (14.0%)	-23.0	167.9	0.87 (0.75-1.01)		1.87
Diabetes	250/1054 (23.7%)	313/1040 (30.1%)	-33.8	111.2	0.74 (0.61-0.89)		
Gender							
Male	491/2915 (16.8%)	566/2885 (19.6%)	-34.3	182.0	0.83 (0.72-0.96)		0.03
Female	210/1735 (12.1%)	248/1735 (14.3%)	-19.1	90.7	0.81 (0.66-1.00)		
Age at randomization (years)							
40-49	75 /968 (7.7%)	76 /908 (8.4%)	-1.8	20.0	0.92 (0.59-1.42)		0.01
50-59	123/1161 (10.6%)	166/1149 (14.4%)	-20.2	53.4	0.68 (0.52-0.90)		
60-69	214/1226 (17.5%)	217/1246 (17.4%)	1.2	87.2	1.01 (0.82-1.25)		
70+	289/1295 (22.3%)	355/1317 (27.0%)	-31.8	127.3	0.78 (0.65-0.93)		
Current smoker							
No	588/4024 (14.6%)	706/4012 (17.6%)	-55.5	244.8	0.80 (0.70-0.90)		1.38
Yes	113 /626 (18.1%)	108 /608 (17.8%)	0.3	27.0	1.01 (0.69-1.47)		
Diastolic BP (mmHg)							
<80	390/2279 (17.1%)	458/2339 (19.6%)	-27.1	156.7	0.84 (0.72-0.98)		0.61
≥80 <90	178/1385 (12.9%)	190/1309 (14.5%)	-9.2	64.8	0.87 (0.68-1.11)		
≥90 <100	89 /710 (12.5%)	116 /701 (16.5%)	-12.6	36.9	0.71 (0.52-0.98)		
≥100	42 /267 (15.7%)	49 /256 (19.1%)	-4.0	13.8	0.75 (0.44-1.26)		
Systolic BP (mmHg)							
<140	321/2431 (13.2%)	334/2414 (13.8%)	-7.2	121.1	0.94 (0.79-1.13)		2.67
≥140 <160	211/1384 (15.2%)	271/1387 (19.5%)	-27.0	89.0	0.74 (0.60-0.91)		
≥160 <180	120 /626 (19.2%)	154 /614 (25.1%)	-15.1	42.7	0.70 (0.52-0.95)		
≥180	48 /203 (23.6%)	55 /198 (27.8%)	-4.4	18.5	0.79 (0.50-1.24)		
Total cholesterol (mmol/L)							
<4.5	299/1754 (17.0%)	304/1680 (18.1%)	-4.8	57.9	0.92 (0.71-1.19)		5.51
≥4.5 <5.5	221/1523 (14.5%)	243/1526 (15.9%)	-11.2	98.1	0.89 (0.73-1.09)		
≥5.5	150/1186 (12.6%)	239/1224 (19.5%)	-48.9	117.6	0.66 (0.55-0.79)		
LDL cholesterol (mmol/L)							
<2.5	289/1776 (16.3%)	290/1707 (17.0%)	-3.3	57.4	0.94 (0.73-1.22)		2.74
≥2.5 <3.0	153/1059 (14.4%)	175/1037 (16.9%)	-11.8	60.6	0.82 (0.64-1.06)		
≥3.0	228/1627 (14.0%)	321/1686 (19.0%)	-48.5	157.1	0.73 (0.63-0.86)		
HDL cholesterol (mmol/L)							
<1.0	332/1816 (18.3%)	363/1864 (19.5%)	-6.2	100.2	0.94 (0.77-1.14)		2.21
≥1.0 <1.2	148/1084 (13.7%)	199/1089 (18.3%)	-23.9	68.7	0.71 (0.56-0.89)		
≥1.2	189/1559 (12.1%)	224/1477 (15.2%)	-23.2	85.4	0.76 (0.62-0.94)		
Non-HDL cholesterol (mmol/L)							
<3.0	191/1103 (17.3%)	185/1071 (17.3%)	-0.1	30.5	1.00 (0.70-1.42)		1.97
≥3.0 <4.0	240/1677 (14.3%)	274/1617 (16.9%)	-18.5	90.6	0.82 (0.66-1.00)		
≥4.0	238/1679 (14.2%)	327/1742 (18.8%)	-44.0	152.7	0.75 (0.64-0.88)		
Triglycerides (mmol/L)							
<1.5	219/1489 (14.7%)	251/1440 (17.4%)	-17.4	73.3	0.79 (0.63-0.99)		0.01
≥1.5 <2.0	133 /899 (14.8%)	158 /914 (17.3%)	-9.2	60.2	0.86 (0.67-1.10)		
≥2.0	318/2074 (15.3%)	377/2075 (18.2%)	-27.3	128.5	0.81 (0.68-0.96)		
Apolipoprotein B (mg/dL)							
<80	210/1243 (16.9%)	203/1162 (17.5%)	-2.4	35.9	0.94 (0.67-1.30)		2.54
≥80 <100	196/1419 (13.8%)	219/1400 (15.6%)	-9.8	76.7	0.88 (0.70-1.10)		
≥100	264/1805 (14.6%)	364/1873 (19.4%)	-50.0	163.3	0.74 (0.63-0.86)		
Apolipoprotein A1 (mg/dL)							
<120	303/1497 (20.2%)	336/1562 (21.5%)	-5.7	92.2	0.94 (0.77-1.15)		1.47
≥120 <140	178/1332 (13.4%)	226/1289 (17.5%)	-23.5	69.5	0.71 (0.56-0.90)		
≥140	190/1642 (11.6%)	224/1585 (14.1%)	-21.4	89.4	0.79 (0.64-0.97)		
ALL PATIENTS	**701/4650 (15.1%)**	**814/4620 (17.6%)**	**-53.7**	**273.6**	**0.82 (0.73-0.93)**	**0.0012**	

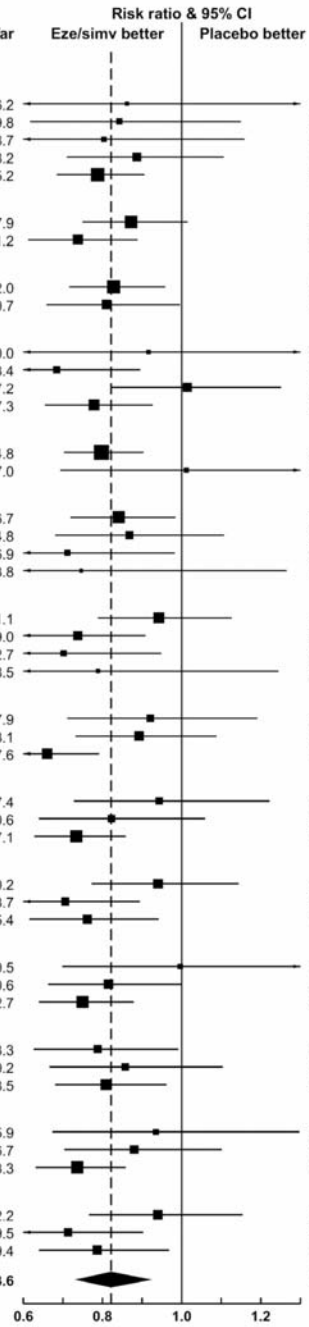
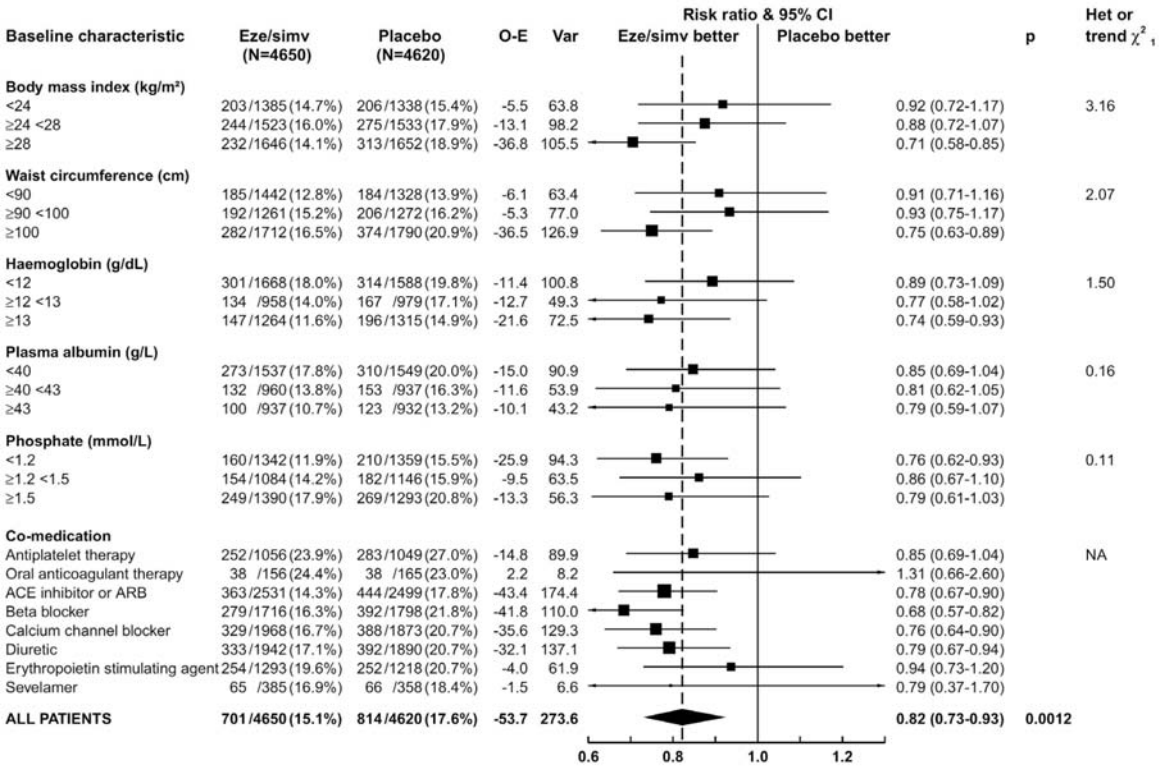


Figure 27. MVE by Baseline Clinical Characteristics per mmol/L LDL Reduction – I
Source: CSR Fig. 11-17

Major Vascular Events by Baseline Characteristics (Per mmol/L Reduction in LDL-C):
All Patients Randomized to Ezetimibe/Simvastatin Versus Placebo
(Arms 2+3b Versus Arms 1+3a) (Cont.)



The mean absolute difference in LDL-C (mmol/L) after 2.5 years between those allocated active treatment and those allocated control in a particular subgroup is designated w. The logrank (O-E) for that subgroup is multiplied by the weight w, and its variance by w^2, and a risk ratio (RR) per 1.0 mmol/L reduction in LDL-C is calculated using the weighted parameters.

Figure 28. MVE by Baseline Clinical Characteristics per mmol/L LDL Reduction – II
Source: CSR Fig. 11-17

The test for heterogeneity or trend within each subgroup is presented as the $\chi^2_{(1)}$ statistic. For reference, $\chi^2_{(1)} > 2.70$ corresponds to $p < 0.10$; $\chi^2_{(1)} > 3.84$ corresponds to $P < 0.05$; $\chi^2_{(1)} > 6.64$ corresponds to $P < 0.01$; and $\chi^2_{(1)} > 10.83$ corresponds to $P<0.001$.

Major Atherosclerotic Events by Baseline Characteristics (Per mmol/L Reduction in LDL-C): All Patients Randomized to Ezetimibe/Simvastatin Versus Placebo (Arms 2+3b Versus Arms 1+3a)

Baseline characteristic	Eze/simv (N=4650)	Placebo (N=4620)	O-E	Var	Risk ratio & 95% CI	p	Het or trend χ^2_1
					Eze/simv better / Placebo better		
Prior vascular disease							
Coronary disease	36 /169 (21.3%)	35 /142 (24.6%)	-1.4	12.8	0.89 (0.52-1.55)		NA
Peripheral arterial disease	82 /304 (27.0%)	87 /300 (29.0%)	-4.2	32.6	0.88 (0.62-1.24)		
Cerebrovascular disease	74 /337 (22.0%)	77 /314 (24.5%)	-3.3	20.8	0.85 (0.56-1.31)		
At least 1 of above 3 conditions	167 /711 (23.5%)	172 /682 (25.2%)	-6.4	61.1	0.90 (0.70-1.16)		
None	359/3939 (9.1%)	447/3938 (11.4%)	-39.6	145.6	0.76 (0.65-0.90)		
Diabetes							
No diabetes	333/3596 (9.3%)	385/3580 (10.8%)	-23.4	126.6	0.83 (0.70-0.99)		0.44
Diabetes	193/1054 (18.3%)	234/1040 (22.5%)	-23.4	84.3	0.76 (0.61-0.94)		
Gender							
Male	376/2915 (12.9%)	445/2885 (15.4%)	-31.5	141.4	0.80 (0.68-0.94)		0.05
Female	150/1735 (8.6%)	174/1735 (10.0%)	-12.1	64.1	0.83 (0.65-1.06)		
Age at randomization (years)							
40-49	56 /968 (5.8%)	50 /908 (5.5%)	1.4	14.1	1.11 (0.66-1.87)		0.34
50-59	85/1161 (7.3%)	119/1149 (10.4%)	-15.9	37.7	0.66 (0.48-0.90)		
60-69	163/1226 (13.3%)	171/1246 (13.7%)	-1.7	67.6	0.97 (0.77-1.24)		
70+	222/1295 (17.1%)	279/1317 (21.2%)	-27.8	99.0	0.76 (0.62-0.92)		
Current smoker							
No	440/4024 (10.9%)	536/4012 (13.4%)	-45.1	184.6	0.78 (0.68-0.90)		1.06
Yes	86 /626 (13.7%)	83 /608 (13.7%)	-0.1	20.7	0.99 (0.65-1.53)		
Diastolic BP (mmHg)							
<80	305/2279 (13.4%)	360/2339 (15.4%)	-22.3	122.9	0.83 (0.70-1.00)		0.15
≥80 <90	122/1385 (8.8%)	146/1309 (11.2%)	-13.2	47.2	0.76 (0.57-1.00)		
≥90 <100	69 /710 (9.7%)	78 /701 (11.1%)	-4.4	26.5	0.85 (0.58-1.24)		
≥100	28 /267 (10.5%)	34 /256 (13.3%)	-3.2	9.4	0.71 (0.37-1.35)		
Systolic BP (mmHg)							
<140	238/2431 (9.8%)	264/2414 (10.9%)	-12.5	92.8	0.87 (0.71-1.07)		1.63
≥140 <160	167/1384 (12.1%)	198/1387 (14.3%)	-14.5	67.4	0.81 (0.64-1.02)		
≥160 <180	88 /626 (14.1%)	115 /614 (18.7%)	-12.2	31.6	0.68 (0.48-0.96)		
≥180	32 /203 (15.8%)	42 /198 (21.2%)	-4.8	13.3	0.70 (0.41-1.19)		
Total cholesterol (mmol/L)							
<4.5	222/1754 (12.7%)	222/1680 (13.2%)	-2.5	42.6	0.94 (0.70-1.27)		5.53
≥4.5 <5.5	163/1523 (10.7%)	184/1526 (12.1%)	-10.2	73.4	0.87 (0.69-1.09)		
≥5.5	118/1186 (9.9%)	195/1224 (15.9%)	-42.4	94.7	0.64 (0.52-0.78)		
LDL cholesterol (mmol/L)							
<2.5	202/1776 (11.4%)	207/1707 (12.1%)	-3.7	40.5	0.91 (0.67-1.24)		1.29
≥2.5 <3.0	115/1059 (10.9%)	135/1037 (13.0%)	-10.4	46.2	0.80 (0.60-1.06)		
≥3.0	186/1627 (11.4%)	259/1686 (15.4%)	-38.0	127.3	0.74 (0.62-0.88)		
HDL cholesterol (mmol/L)							
<1.0	256/1816 (14.1%)	286/1864 (15.3%)	-7.4	78.2	0.91 (0.73-1.14)		1.49
≥1.0 <1.2	109/1084 (10.1%)	150/1089 (13.8%)	-19.3	51.2	0.69 (0.52-0.90)		
≥1.2	137/1559 (8.8%)	165/1477 (11.2%)	-18.1	62.4	0.75 (0.58-0.96)		
Non-HDL cholesterol (mmol/L)							
<3.0	134/1103 (12.1%)	130/1071 (12.1%)	-0.2	21.4	0.99 (0.65-1.51)		1.65
≥3.0 <4.0	181/1677 (10.8%)	208/1617 (12.9%)	-14.6	68.6	0.81 (0.64-1.02)		
≥4.0	187/1679 (11.1%)	263/1742 (15.1%)	-37.6	121.6	0.73 (0.61-0.88)		
Triglycerides (mmol/L)							
<1.5	150/1489 (10.1%)	177/1440 (12.3%)	-14.2	51.0	0.76 (0.58-1.00)		0.02
≥1.5 <2.0	103 /899 (11.5%)	122 /914 (13.3%)	-7.0	46.6	0.86 (0.65-1.15)		
≥2.0	250/2074 (12.1%)	302/2075 (14.6%)	-24.1	102.0	0.79 (0.65-0.96)		
Apolipoprotein B (mg/dL)							
<80	147/1243 (11.8%)	141/1162 (12.1%)	-1.5	25.0	0.94 (0.64-1.39)		1.79
≥80 <100	144/1419 (10.1%)	167/1400 (11.9%)	-9.8	57.5	0.84 (0.65-1.09)		
≥100	211/1805 (11.7%)	293/1873 (15.6%)	-41.1	131.0	0.73 (0.62-0.87)		
Apolipoprotein A1 (mg/dL)							
<120	231/1497 (15.4%)	267/1562 (17.1%)	-8.5	71.8	0.89 (0.70-1.12)		0.53
≥120 <140	137/1332 (10.3%)	175/1289 (13.6%)	-18.6	53.7	0.71 (0.54-0.92)		
≥140	135/1642 (8.2%)	159/1585 (10.0%)	-15.2	63.5	0.79 (0.62-1.01)		
ALL PATIENTS	**526/4650 (11.3%)**	**619/4620 (13.4%)**	**-44.1**	**206.8**	**0.81 (0.70-0.93)**	**0.0022**	

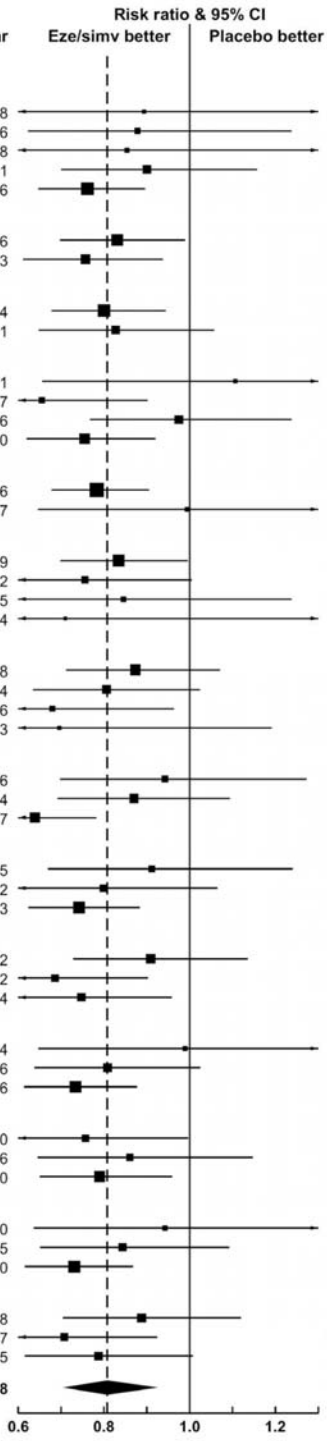
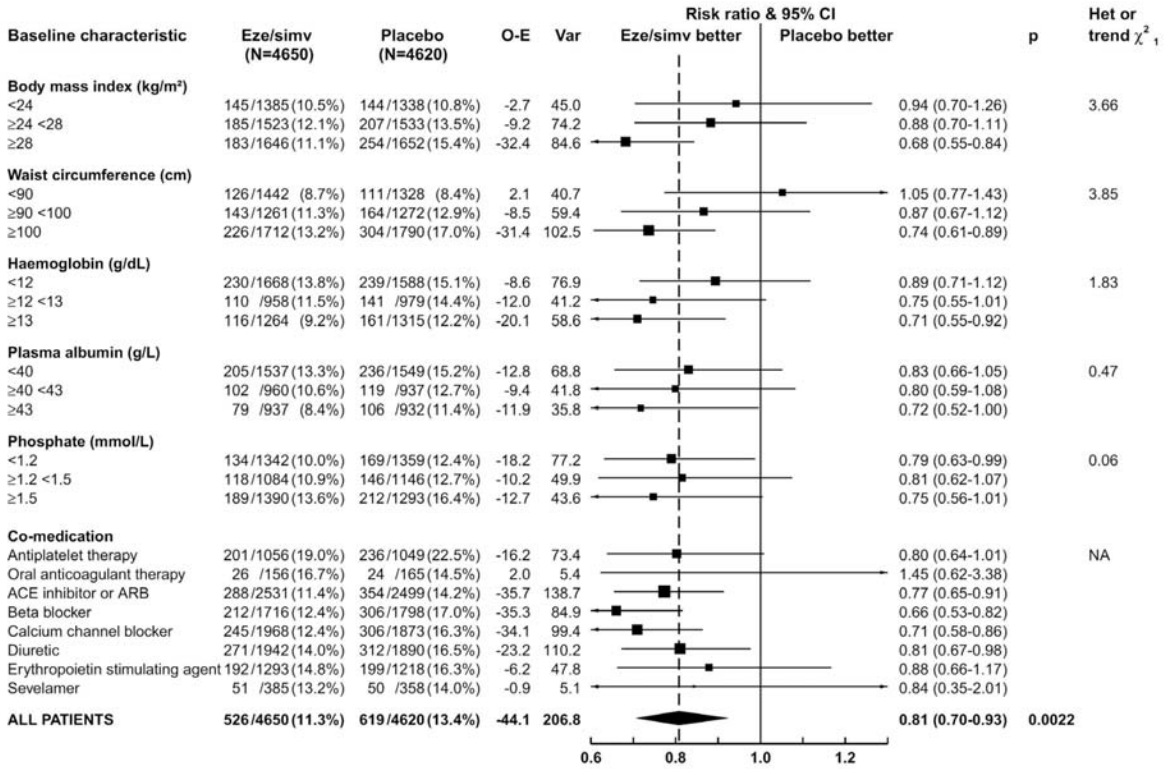


Figure 29. MAE by Baseline Characteristics per mmol/L LDL Reduction - I
Source: CSR Fig. 11-18

Major Atherosclerotic Events by Baseline Characteristics (Per mmol/L Reduction in LDL-C): All Patients Randomized to Ezetimibe/Simvastatin Versus Placebo (Arms 2+3b Versus Arms 1+3a) (Cont.)



Baseline characteristic	Eze/simv (N=4650)	Placebo (N=4620)	O-E	Var	Risk ratio & 95% CI	p	Het or trend χ^2_1
Body mass index (kg/m²)							
<24	145/1385 (10.5%)	144/1338 (10.8%)	-2.7	45.0	0.94 (0.70-1.26)		3.66
≥24 <28	185/1523 (12.1%)	207/1533 (13.5%)	-9.2	74.2	0.88 (0.70-1.11)		
≥28	183/1646 (11.1%)	254/1652 (15.4%)	-32.4	84.6	0.68 (0.55-0.84)		
Waist circumference (cm)							
<90	126/1442 (8.7%)	111/1328 (8.4%)	2.1	40.7	1.05 (0.77-1.43)		3.85
≥90 <100	143/1261 (11.3%)	164/1272 (12.9%)	-8.5	59.4	0.87 (0.67-1.12)		
≥100	226/1712 (13.2%)	304/1790 (17.0%)	-31.4	102.5	0.74 (0.61-0.89)		
Haemoglobin (g/dL)							
<12	230/1668 (13.8%)	239/1588 (15.1%)	-8.6	76.9	0.89 (0.71-1.12)		1.83
≥12 <13	110 /958 (11.5%)	141 /979 (14.4%)	-12.0	41.2	0.75 (0.55-1.01)		
≥13	116/1264 (9.2%)	161/1315 (12.2%)	-20.1	58.6	0.71 (0.55-0.92)		
Plasma albumin (g/L)							
<40	205/1537 (13.3%)	236/1549 (15.2%)	-12.8	68.8	0.83 (0.66-1.05)		0.47
≥40 <43	102 /960 (10.6%)	119 /937 (12.7%)	-9.4	41.8	0.80 (0.59-1.08)		
≥43	79 /937 (8.4%)	106 /932 (11.4%)	-11.9	35.8	0.72 (0.52-1.00)		
Phosphate (mmol/L)							
<1.2	134/1342 (10.0%)	169/1359 (12.4%)	-18.2	77.2	0.79 (0.63-0.99)		0.06
≥1.2 <1.5	118/1084 (10.9%)	146/1146 (12.7%)	-10.2	49.9	0.81 (0.62-1.07)		
≥1.5	189/1390 (13.6%)	212/1293 (16.4%)	-12.7	43.6	0.75 (0.56-1.01)		
Co-medication							
Antiplatelet therapy	201/1056 (19.0%)	236/1049 (22.5%)	-16.2	73.4	0.80 (0.64-1.01)		NA
Oral anticoagulant therapy	26 /156 (16.7%)	24 /165 (14.5%)	2.0	5.4	1.45 (0.62-3.38)		
ACE inhibitor or ARB	288/2531 (11.4%)	354/2499 (14.2%)	-35.7	138.7	0.77 (0.65-0.91)		
Beta blocker	212/1716 (12.4%)	306/1798 (17.0%)	-35.3	84.9	0.66 (0.53-0.82)		
Calcium channel blocker	245/1968 (12.4%)	306/1873 (16.3%)	-34.1	99.4	0.71 (0.58-0.86)		
Diuretic	271/1942 (14.0%)	312/1890 (16.5%)	-23.2	110.2	0.81 (0.67-0.98)		
Erythropoietin stimulating agent	192/1293 (14.8%)	199/1218 (16.3%)	-6.2	47.8	0.88 (0.66-1.17)		
Sevelamer	51 /385 (13.2%)	50 /358 (14.0%)	-0.9	5.1	0.84 (0.35-2.01)		
ALL PATIENTS	**526/4650 (11.3%)**	**619/4620 (13.4%)**	**-44.1**	**206.8**	**0.81 (0.70-0.93)**	**0.0022**	

The mean absolute difference in LDL-C (mmol/L) after 2.5 years between those allocated active treatment and those allocated control in a particular subgroup is designated w. The logrank (O-E) for that subgroup is multiplied by the weight w, and its variance by w^2, and a risk ratio (RR) per 1.0 mmol/L reduction in LDL-C is calculated using the weighted parameters.

Figure 30. MAE by Baseline Characteristics per mmol/L LDL Reduction – II
Source: CSR Fig. 11-18

The test for heterogeneity or trend within each subgroup is presented as the $\chi^2_{(1)}$ statistic. For reference, $\chi^2_{(1)} > 2.70$ corresponds to $p < 0.10$; $\chi^2_{(1)} > 3.84$ corresponds to $P < 0.05$; $\chi^2_{(1)} > 6.64$ corresponds to $P < 0.01$; and $\chi^2_{(1)} > 10.83$ corresponds to $P<0.001$.

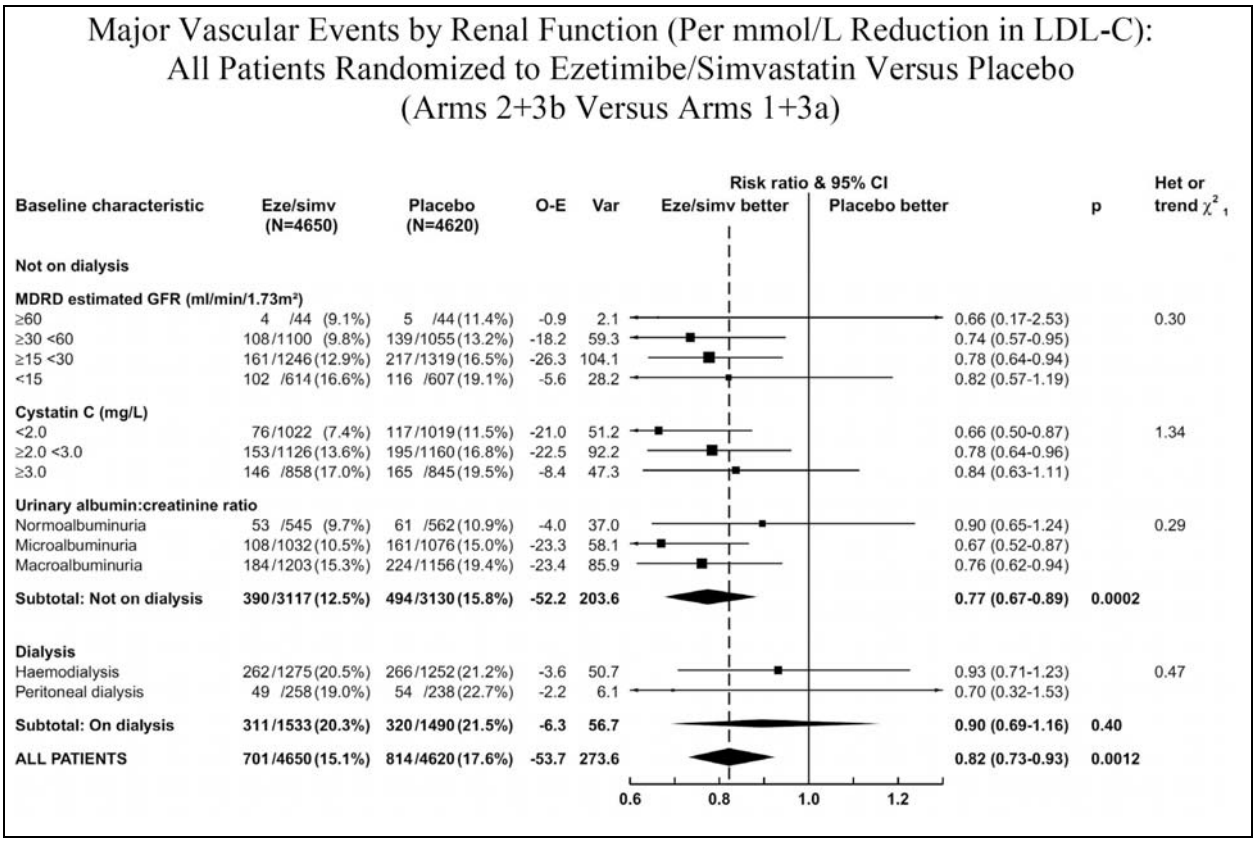


Figure 31. MVE by Renal Function per mmol/L LDL Reduction

Source: CSR Fig. 11-5. Methods are similar to the preceding figures.

The test for heterogeneity or trend within each subgroup is presented as the $\chi^2_{(1)}$ statistic. For reference, $\chi^2_{(1)} > 2.70$ corresponds to $p < 0.10$; $\chi^2_{(1)} > 3.84$ corresponds to $P < 0.05$; $\chi^2_{(1)} > 6.64$ corresponds to $P < 0.01$; and $\chi^2_{(1)} > 10.83$ corresponds to $P<0.001$.

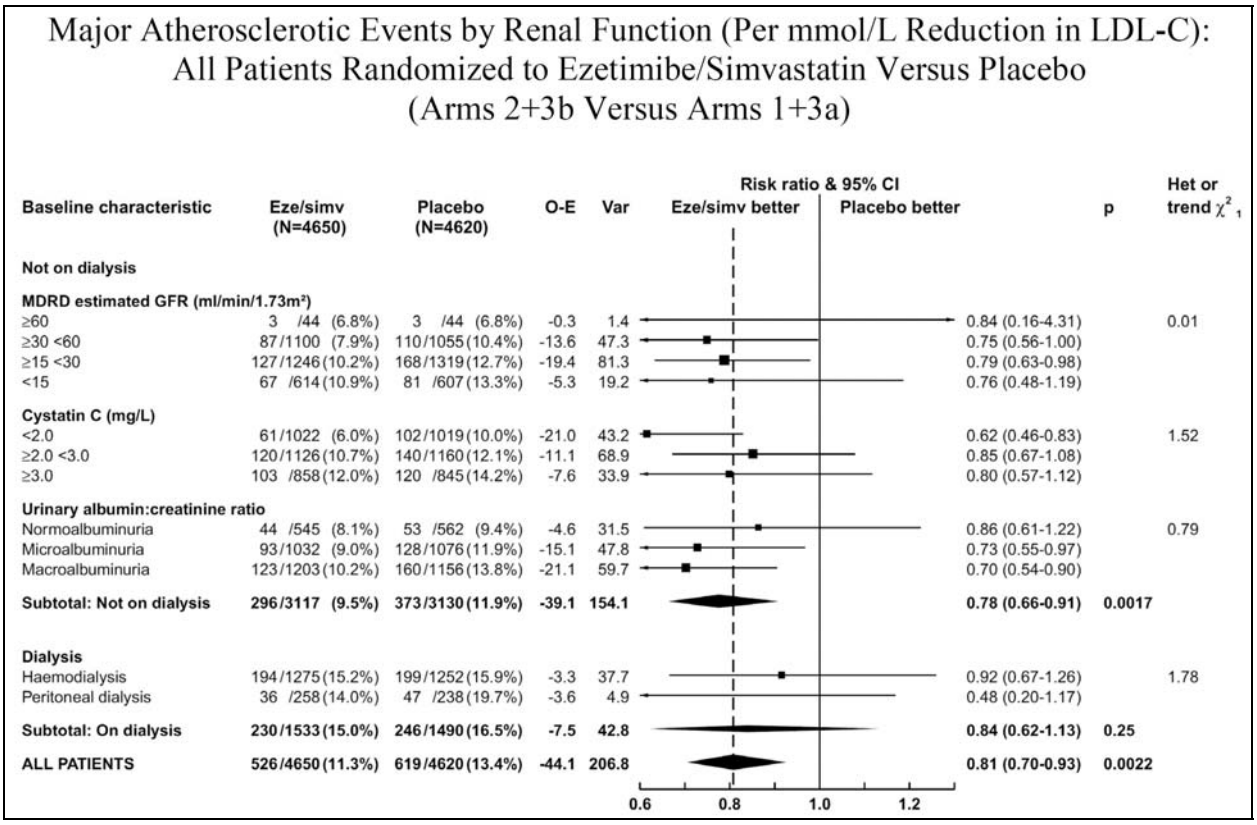


Figure 32. MAE by Renal Function per mmol/L LDL Reduction

Source: CSR Fig. 11-6. Methods are similar to the preceding figures.

The test for heterogeneity or trend within each subgroup is presented as the $\chi^2_{(1)}$ statistic. For reference, $\chi^2_{(1)} > 2.70$ corresponds to $p < 0.10$; $\chi^2_{(1)} > 3.84$ corresponds to $P < 0.05$; $\chi^2_{(1)} > 6.64$ corresponds to $P < 0.01$; and $\chi^2_{(1)} > 10.83$ corresponds to $P<0.001$.

Other Nonfatal SAEs During Year 1

Table 67. Other Nonfatal SAEs During Year 1

Event	Eze/Sim Arm 2 (N=4193)	Simva Arm 3 (N=1054)	Placebo Arm 1 (N=4191)	P (2 vs. 1)	P (2 vs. 3)
Cardiac (excluding events reported elsewhere)	**105 (2.5%)**	**35 (3.3%)**	**125 (3.0%)**	**0.19**	**0.15**
Angina (not hospitalized)	0	0	0		
Heart failure (not hospitalized)	3 (0.1%)	0	0		
Arrhythmia	56 (1.3%)	9 (0.9%)	62 (1.5%)		
Valvular and pericardial disease	18 (0.4%)	5 (0.5%)	25 (0.6%)		
Other heart disease	38 (0.9%)	22 (2.1%)	48 (1.1%)		
Vascular (excluding cardiac)	**88 (2.1%)**	**23 (2.2%)**	**77 (1.8%)**	**0.39**	**0.87**
Cerebrovascular (excluding stroke)	4 (0.1%)	1 (0.1%)	4 (0.1%)		
Other artery disease	31 (0.7%)	6 (0.6%)	22 (0.5%)		
Hypertension	19 (0.5%)	8 (0.8%)	19 (0.5%)		
Venous disease (including pulmonary embolus)	21 (0.5%)	5 (0.5%)	20 (0.5%)		
Other and unspecified circulatory disorders	15 (0.4%)	4 (0.4%)	12 (0.3%)		
Cancer (not incident)	**17 (0.4%)**	**7 (0.7%)**	**6 (0.1%)**	**0.02**	**0.26**
Pre-randomization cancer	13 (0.3%)	4 (0.4%)	3 (0.1%)		
Cancer treatment or complication	4 (0.1%)	3 (0.3%)	4 (0.1%)		
Renal	**645 (15.4%)**	**180 (17.1%)**	**674 (16.1%)**	**0.41**	**0.19**
Acute-on-chronic renal failure	54 (1.3%)	16 (1.5%)	62 (1.5%)		
Uremia / withdrawal of dialysis	14 (0.3%)	0	12 (0.3%)		
Hemodialysis access (excluding revision)	330 (7.9%)	77 (7.3%)	384 (9.2%)		
Peritoneal dialysis access problem / procedure	123 (2.9%)	36 (3.4%)	137 (3.3%)		
Fluid/metabolic complication	77 (1.8%)	24 (2.3%)	75 (1.8%)		
Transplant rejection / complication	17 (0.4%)	9 (0.9%)	16 (0.4%)		
Other investigation / surgery	38 (0.9%)	14 (1.3%)	36 (0.9%)		
Renal / ureteric obstruction / intervention	43 (1.0%)	10 (0.9%)	39 (0.9%)		
Bladder/lower urinary tract disorder	17 (0.4%)	6 (0.6%)	23 (0.5%)		
Urinary Tract Infection	51 (1.2%)	14 (1.3%)	48 (1.1%)		
Miscellaneous renal	41 (1.0%)	19 (1.8%)	45 (1.1%)		
Respiratory	**174 (4.1%)**	**40 (3.8%)**	**158 (3.8%)**	**0.36**	**0.59**
Pneumonia / bronchitis	116 (2.8%)	23 (2.2%)	90 (2.1%)		
Other chest infection	22 (0.5%)	3 (0.3%)	13 (0.3%)		
COPD / asthma	12 (0.3%)	6 (0.6%)	20 (0.5%)		
Other respiratory disease	22 (0.5%)	5 (0.5%)	20 (0.5%)		
Respiratory symptoms/investigations/surgery	28 (0.7%)	7 (0.7%)	27 (0.6%)		
Liver/pancreas/biliary	**20 (0.5%)**	**3 (0.3%)**	**19 (0.5%)**	**0.87**	**0.40**
Gallstones (excluding complications)	6 (0.1%)	1 (0.1%)	6 (0.1%)		
Liver (excluding hepatitis)	7 (0.2%)	2 (0.2%)	6 (0.1%)		
Miscellaneous liver/pancreas/biliary	9 (0.2%)	0	8 (0.2%)		
Gastrointestinal	**242 (5.8%)**	**66 (6.3%)**	**259 (6.2%)**	**0.43**	**0.56**
Esophageal disorder / investigation	10 (0.2%)	2 (0.2%)	11 (0.3%)		
Gastroduodenal disorders	30 (0.7%)	5 (0.5%)	34 (0.8%)		

Event	Eze/Sim Arm 2 (N=4193)	Simva Arm 3 (N=1054)	Placebo Arm 1 (N=4191)	P (2 vs. 1)	P (2 vs. 3)
Upper GI investigation/procedure	29 (0.7%)	6 (0.6%)	28 (0.7%)		
Large bowel disease	44 (1.0%)	10 (0.9%)	38 (0.9%)		
Large bowel investigation/procedure	50 (1.2%)	15 (1.4%)	48 (1.1%)		
GI hemorrhage	16 (0.4%)	4 (0.4%)	20 (0.5%)		
Infective gastroenteritis/colitis	17 (0.4%)	2 (0.2%)	20 (0.5%)		
Other GI symptoms	44 (1.0%)	15 (1.4%)	54 (1.3%)		
Other GI disorder/intervention	36 (0.9%)	8 (0.8%)	43 (1.0%)		
Hernia / repair	29 (0.7%)	9 (0.9%)	33 (0.8%)		
Skin	**54 (1.3%)**	**8 (0.8%)**	**54 (1.3%)**	**0.99**	**0.16**
Skin infection	21 (0.5%)	1 (0.1%)	23 (0.5%)		
Skin biopsy / surgery	11 (0.3%)	2 (0.2%)	12 (0.3%)		
Dermatitis and eczema/ rash	10 (0.2%)	2 (0.2%)	11 (0.3%)		
Miscellaneous skin	13 (0.3%)	3 (0.3%)	11 (0.3%)		
Genital disorders & Breast	**39 (0.9%)**	**13 (1.2%)**	**50 (1.2%)**	**0.24**	**0.38**
Gynecological disorder	10 (0.2%)	5 (0.5%)	19 (0.5%)		
Breast disorder / intervention	6 (0.1%)	1 (0.1%)	6 (0.1%)		
Prostate disorder / intervention	20 (0.5%)	5 (0.5%)	20 (0.5%)		
Penis/testis	3 (0.1%)	2 (0.2%)	5 (0.1%)		
Psychiatric	**9 (0.2%)**	**2 (0.2%)**	**14 (0.3%)**	**0.30**	**0.87**
Neurological	**59 (1.4%)**	**9 (0.9%)**	**54 (1.3%)**	**0.63**	**0.16**
Musculoskeletal	**129 (3.1%)**	**31 (2.9%)**	**116 (2.8%)**	**0.40**	**0.83**
Muscle (excluding myopathy)	7 (0.2%)	1 (0.1%)	0		
Vasculitis and related disorders	11 (0.3%)	4 (0.4%)	9 (0.2%)		
Orthopedic	58 (1.4%)	18 (1.7%)	63 (1.5%)		
Rheumatological	58 (1.4%)	9 (0.9%)	51 (1.2%)		
Hematological	**61 (1.5%)**	**12 (1.1%)**	**41 (1.0%)**	**0.05**	**0.43**
Anemia (including transfusion)	44 (1.0%)	7 (0.7%)	29 (0.7%)		
Platelet and clotting disorder	12 (0.3%)	4 (0.4%)	9 (0.2%)		
Other hematological disorder	5 (0.1%)	3 (0.3%)	4 (0.1%)		
Eye	**48 (1.1%)**	**7 (0.7%)**	**44 (1.0%)**	**0.67**	**0.17**
Cataract / cataract surgery	25 (0.6%)	7 (0.7%)	27 (0.6%)		
Other eye disorder/intervention	27 (0.6%)	0	19 (0.5%)		
Ear/nose/throat/mouth	**17 (0.4%)**	**3 (0.3%)**	**17 (0.4%)**	**0.50**	**0.57**
Endocrine	**10 (0.2%)**	**5 (0.5%)**	**10 (0.2%)**	**0.99**	**0.20**
Hyperthyroid	2 (0.0%)	0	3 (0.1%)		
Hypothyroid	2 (0.0%)	2 (0.2%)	1 (0.0%)		
Unknown thyroid disorder	6 (0.1%)	1 (0.1%)	5 (0.1%)		
Other endocrine	0	2 (0.2%)	1 (0.0%)		
Other SAE	**223 (5.3%)**	**56 (5.3%)**	**200 (4.8%)**	**0.24**	**0.98**
Allergy / hypersensitivity	8 (0.2%)	2 (0.2%)	9 (0.2%)		
Septicemia	21 (0.5%)	10 (0.9%)	20 (0.5%)		
Other infection	40 (1.0%)	7 (0.7%)	36 (0.9%)		
Metabolic	14 (0.3%)	1 (0.1%)	15 (0.4%)		
Surgical	28 (0.7%)	9 (0.9%)	28 (0.7%)		

Event	Eze/Sim Arm 2 (N=4193)	Simva Arm 3 (N=1054)	Placebo Arm 1 (N=4191)	P (2 vs. 1)	P (2 vs. 3)
Symptoms of cardiovascular compromise	55 (1.3%)	7 (0.7%)	33 (0.8%)		
Adjustment of treatment	23 (0.5%)	5 (0.5%)	26 (0.6%)		
Rehabilitation / impaired mobility	20 (0.5%)	5 (0.5%)	15 (0.4%)		
Miscellaneous episode	37 (0.9%)	12 (1.1%)	35 (0.8%)		
Non-medical SAE	**77 (1.8%)**	**24 (2.3%)**	**53 (1.3%)**	**0.03**	**0.35**
Fracture	57 (1.4%)	15 (1.4%)	33 (0.8%)		
Other trauma	24 (0.6%)	9 (0.9%)	21 (0.5%)		
Any SAE (except those reported elsewhere)	**1375 (32.8%)**	**374 (35.5%)**	**1382 (33.0%)**	**0.98**	**0.13**

Source: Table 12-7a, 12 September 2012 response to FDA information request.

This table excludes major vascular events, cancer, TIA, hospitalization for angina or heart failure, dialysis access revision, diabetes and hypoglycemia, initiation of dialysis, renal transplantation, pancreatitis, hepatitis, myopathy, and rhabdomyolysis.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

DRAFT STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA/Serial Number:	NDA 21687 / 0039
Drug Name:	Vytorin (Ezetimibe/Simvastatin 10mg/20mg combination tablet)
Indication(s):	As an adjunct to diet to reduce risk of major cardiovascular events in patients with chronic kidney disease
Applicant:	Merck
Date(s):	Receipt date: (b) (4) PDUFA date: (b) (4)
Review Priority:	Standard (Efficacy Supplement)
Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Dongmei Liu, Ph.D.
Concurring Reviewers:	Jon Todd Sahlroot, Ph.D., Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	James Smith, M.D., Medical Officer Eric Colman, M.D., Medical Team Leader
Project Manager:	Margaret Simoneau

Keywords: NDA review, clinical studies, outcome study

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Vytorin, a fixed dose combination of ezetimibe and simvastatin, was originally approved in July 2004 for treatment of primary hypercholesterolemia, mixed hyperlipidemia or homozygous familial hypercholesterolemia as adjunctive therapy to diet. In this efficacy supplement, Merck proposes a new indication for Vytorin, reducing the risk of major cardiovascular events in patients with chronic kidney disease (CKD). Based on evaluation of risk reduction in MVE, a composite endpoint for major vascular events, after 4 years of treatment, the applicant claims by lowering low density lipoprotein-cholesterol (LDL-C) level, Vytorin is effective in reducing cardiovascular risk in CKD patients. My review of the statistical evidence suggests support for the claim. However, the treatment effect appears to be heterogeneous among patients with different renal function status. It appears the treatment effect of ezetimibe/simvastatin 10/20 mg on MVE was largely driven by the effect in pre-dialysis patients. Whether it could be claimed that Vytorin is effective in reducing cardiovascular risk in all patients with CKD is a question up for discussion at the advisory committee meeting scheduled for November 2, 2011.

1.2 Brief Overview of Clinical Studies

Only one study SHARP (Study of Heart and Renal Protection) was submitted in this efficacy supplement. It was a double-blinded, placebo-controlled, parallel-arm, multicenter study, conducted from June 2003 to August 2010 at 380 centers in 18 countries. The study enrolled 9438 patients who were above 40 years of age, with advanced CKD including about 1/3 who were on maintenance dialysis at baseline, and with no known history of MI or coronary revascularization procedure.

After the run-in period, patients were randomized in a ratio of 4:4:1 to placebo (arm 1) vs. ezetimibe/simvastatin 10/20 mg (Arm 2) vs. simvastatin 20 mg (Arm 3). After one-year, patients initially randomized to simvastatin 20 mg daily were re-randomized to ezetimibe/simvastatin 10/20 mg (Arm 3b) vs. placebo (Arm 3a) for the remainder of the trial. The double blinded treatment period was at least 4 years for each patient, with median duration of 4.9 years in survivors. During the scheduled treatment period, follow-up visits after randomization were scheduled at 2 and 6 months, and then every 6 months. The study was scheduled to continue until all patients have been followed for at least 4 years and at least 1100 major vascular event had occurred.

1.3 Statistical Issues and Findings

The primary efficacy endpoint specified in the protocol was major vascular event (MVE). MVE is a composite endpoint comprising non-fatal MI or cardiac death, non-fatal or fatal stroke; or revascularization procedures including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation (but excluding vascular access surgery for dialysis) during the scheduled treatment period. The primary comparison specified in the protocol was the effects on

the first MVE during the scheduled treatment period in patients originally randomized to ezetimibe/simvastatin (Arm 2) vs. patients originally randomized to placebo (Arm 1).

Based on blinded review on MVE and unblinded review on LDL-C level during the trial, the independent steering committee decided for the statistical analysis plan (SAP) that the key outcome to be major atherosclerotic event (MAE), which is a composite endpoint comprising major coronary events (i.e., coronary death or non-fatal MI), ischemic stroke, or any revascularization procedure. This endpoint corresponds to MVE minus non-coronary cardiac deaths and hemorrhagic stroke. The main comparison also changed to the effect on the first MAE in all randomized patients of ezetimibe/simvastatin (Arm 2 + Arm 3b) vs. all randomized patients of placebo (Arm 1 + Arm 3a).

It turned out the difference between protocol-defined main outcome and the key outcome in SAP was very small. Ezetimibe/simvastatin 10/20mg produced a 16% risk reduction (risk ratio=0.84) of MVE in Arm 2 vs. Arm 1, with a 95% confidence interval (CI) of (0.75, 0.93) for risk ratio and a p value of 0.001. The risk reduction on MAE in Arm 2+3b vs. Arm 1+3a was 0.83 in risk ratio with a 95% CI of (0.74, 0.93) and a p value of 0.002.

Among patients who were pre-dialysis at randomization, the effect of ezetimibe/simvastatin 10/20 mg on MVE in Arm 2 vs. Arm 1 showed a risk ratio of 0.77, with a 95% CI of (0.67, 0.88) and a p value less than 0.001. Among patients who were on dialysis at randomization, the effect of ezetimibe/simvastatin 10/20 mg on MVE in Arm 2 vs. Arm 1 showed a risk ratio of 0.94, with a 95% CI of (0.8, 1.11) and a p value of 0.5. Test of heterogeneity among pre-dialysis and dialysis subgroups gave p=0.07 for MVE.

In SHARP, patients were allocated to treatments based on a minimized randomization method. This method was applied to ensure that treatment groups were balanced with respect to prognostically important variables. Since minimization may produce predictable allocation sequences and the probability of error in significance testing may be high, re-randomization tests should be used when evaluating the endpoints or the analysis should be done with adjustment on variables used in the minimization. Re-randomization test shows that p values from re-randomization tests were similar to the applicant's reported p values.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Vytorin is a fixed-dose combination of Ezetimibe and Simvastatin, which are lipid altering drugs that have additive effects to lower low density lipoprotein-cholesterol (LDL-C). Ezetimibe inhibits the intestinal absorption of cholesterol and was approved in 2002 for the treatment of primary hypercholesterolemia, both as monotherapy and in combination with statins. Simvastatin is an HMG-CoA reductase inhibitor which blocks the rate-limiting enzyme in cholesterol synthesis and has been marketed in US since 1991. Clinical studies with simvastatin have demonstrated risk reductions for several cardiovascular clinical events, including CV mortality.

Vytorin was originally approved in July 2004 for treatment of primary hypercholesterolemia, mixed hyperlipidemia or homozygous familial hypercholesterolemia as adjunctive therapy to diet. In this efficacy supplement, Merck proposes a new indication for Vytorin, reducing the risk of major cardiovascular events in patients with chronic kidney disease (CKD).

The proposed dose range is ezetimibe/simvastatin 10/10 mg/day through 10/80 mg/day. The recommended usual starting dose is 10/20 mg/day, a single daily dose in the evening, with or without food.

2.1.2 History of drug development

Patients with CKD are at a greatly increased risk of cardiovascular morbidity and mortality, yet have been largely excluded from cardiovascular outcome trials with statins. The rationale for this exclusion includes concerns about reduced elimination of statins and consequently more risk of adverse effects in patients with severely impaired renal function, and doubts about the ability of lipid-lowering treatments to affect major components of the cardiovascular disease of CKD patients, especially deaths due to arrhythmias or heart failure that may have non-atherosclerotic causes. SHARP was designed to address the question: can a substantial reduction of LDL-C reduce cardiovascular risk in CKD patients?

The applicant stated before SHARP was conducted, an initial 1-year placebo-controlled pilot study showed that simvastatin 20 mg alone could be used safely and effectively in patients with CKD. However, the reduction of LDL-C level by simvastatin 20 mg alone was not enough to provide a test of hypothesis that cardiovascular risk in CKD patients could be reduced by lipid-lowering treatments. Another study SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine) showed that risk of myopathy was much higher with increased dose of simvastatin. Thus to achieve further reduction of LDL-C level by increasing simvastatin dose was not considered. Ezetimibe was known to be well tolerated with very few adverse effects and no known serious safety issues, and to provide an additional reduction in LDL-C when added to therapy with a statin. Using it in a combination product with simvastatin was thus thought to be an appropriate route to obtaining greater LDL-C reduction

than that obtainable with simvastatin alone at any dose, with a high likelihood of excellent tolerability and a good safety profile during long-term use. SHARP was designed to test if Vytorin, the combination of ezetimibe 10 mg and simvastatin 20mg, would reduce the risk of cardiovascular risk in CKD patients by a substantial reduction of LDL-C level.

SHARP was conducted and sponsored by the Clinical Trial Service Unit (CTSU) at the University of Oxford with financial support from Merck. The data of this study are proprietary to CTSU. The CTSU at Oxford is responsible for the data and the conduct of all analyses submitted in the clinical study report (CSR).

2.1.3 Specific studies reviewed

Only one study SHARP (Study of Heart and Renal Protection) was submitted in this efficacy supplement. Detailed description of this study is given in Section 3.

2.2 Data Sources

All data was supplied by the applicant to the CDER electronic data room in SAS transport format. The data and final study report for the electronic submission were archived under the network path location < \\CDSESUB1\EVSPROD\NDA021687\021687.enx>. The information needed for this review was contained in modules 1, 2.5, 2.7, and 5.3.5. This review focuses on documents submitted to serial number 0039, 0040, 0045 and 0065.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

3.1.1 Information Missing from Clinical Study Report

In SHARP, patients were allocated to treatments based on a minimized randomization method. This method was applied to ensure that treatment groups were balanced with respect to prognostically important variables. However, no detail about the minimized randomization was given in the clinical study report (CSR) in the original submission. In addition, since minimization may produce predictable allocation sequences and the probability of error in significance testing may be high, re-randomization tests should be used when evaluating the endpoints or the analysis should be done with adjustment on variables used in the minimization. However, neither was done by the applicant in this case. Without re-randomization test or analysis with adjustment on variables use in the minimization, there is possibility that the positive result in this study is false. We sent out an information request on details of minimized randomization method used for SHARP on August 12, 2011 and got a response on September 14, 2011. Based on the information we got, I did re-randomization test for this review.

3.1.2 Information Missing from Submitted Data

Neither the raw data nor the analysis data submitted in this application contains all necessary information to validate results in Tables 11-4 to 11-9 in the CSR. Those tables summarize the information on lipid differences between treatment arms at different time points. We sent out an information request on July 26, 2011 to ask for the dataset and SAS code used to generate those tables. The applicant responded on August 5, 2011 that some additional data would be needed to generate those tables and it requires time to prepare for it. We had not received yet the additional data when this review was written.

In the original submission, the algorithms to calculate derived variables, e.g. the primary efficacy endpoint ─ time to the first MVE, censoring date for fatal or non-fatal events, were not available. They were submitted on May 13, 2010 to FDA in a response to an information request for those algorithms.

3.1.3 Problems and Errors in Submitted Data

The raw data were submitted in CDISC-like standard and are in SDTM format. However, the analysis data were not submitted in ADaM format. Instead, the applicant submitted a dataset ready for analysis, which was SAS transport files generated by SAS CPORT procedure, different from the FDA Study Data Specification Guidance recommended SAS transport file created by XPORT engine. In addition, a standardized classification system for adverse events (e.g., MedDRA) was not used for this submission. Instead, the applicant used a self-created classification system for this study. This brought difficulties and problems to the safety review on this application.

There are some obvious errors in the raw data. For example, in DS.xpt (the dataset with patients disposition information), patient with USUBJID 4700106 had a record of death on February 15, 2010. Two days later on February 17, 2010, there was another record for this patient with entry "LAST KNOW TO BE ALIVE". One and a half months later, on March 29, 2010, this patient appeared to successfully complete the study. Problems like this cause errors in the derived variables. Censoring dates for fatal and nonfatal events were derived based on information from raw data including adverse events, subject visits, disposition, etc. In the originally submitted analysis dataset, censoring date for fatal event for this patient was 2010-03-29. It was corrected to 2010-02-15 later in a response to our information request for algorithms to calculate censoring time variable.

In addition, there were some inconsistencies in how derived variables were calculated. For example, when there was a record of death for a patient, in some cases censoring date for nonfatal events was considered to be one day before the death (e.g. for patient 1050132). The information on nonfatal events was considered complete all the way up until patient died. While in other cases (e.g. patient 3970108), the censoring date for nonfatal event was considered to be the last date with subject visit information. The information for nonfatal events between the last visit and the death was considered not available. The complete information of these two patients is available in appendix. The algorithms for calculation of censoring dates are also included in appendix for reference.

By systematic validation, I found 63 cases with problems in censoring dates. However, the problems in the censoring dates do not appear to substantially affect analysis result. It turned out analyses with different censoring dates have approximately the same result.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Design of the study SHARP is given in Figure 1. It was a double-blinded, placebo-controlled, parallel-arm, multicenter study, conducted from June 2003 to August 2010 at 380 centers in 18 countries. The study planned to enroll 9000 patients who were above 40 years of age, with advanced CKD including about 1/3 who were on maintenance dialysis at baseline, and with no known history of MI or coronary revascularization procedure.

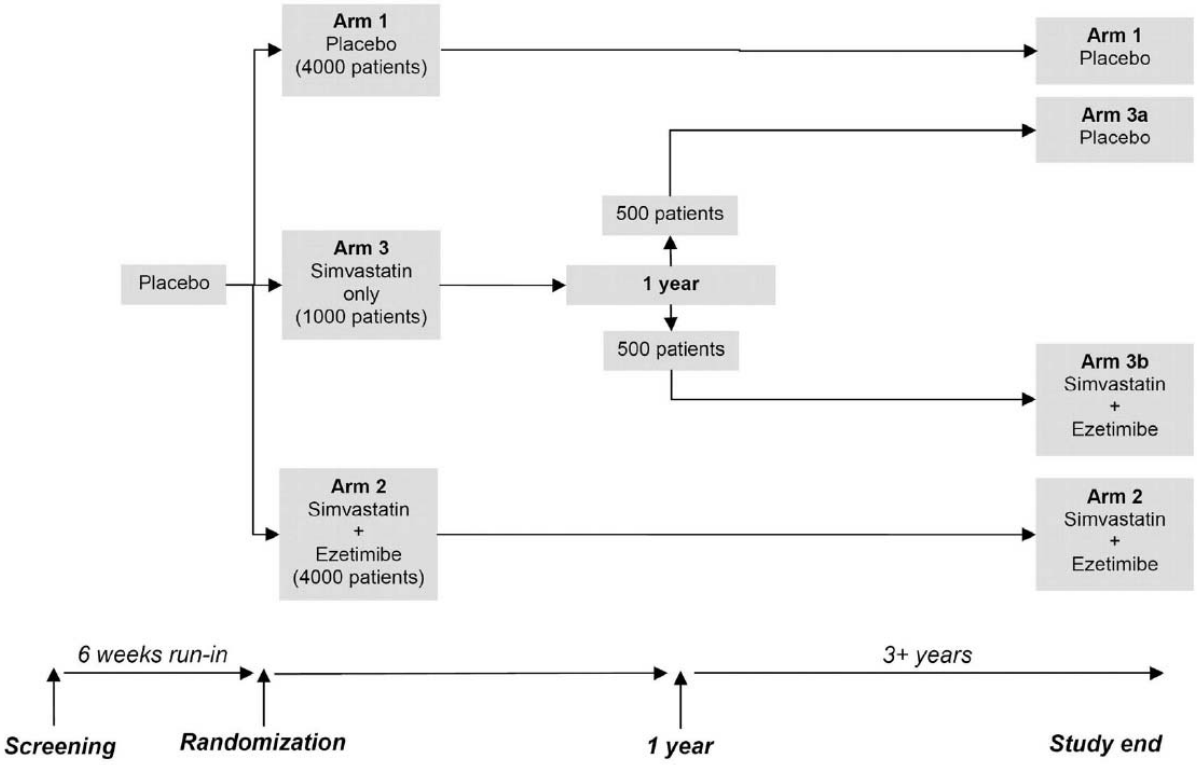


Figure 1 Design of the study SHARP (quoted from CSR).

Prior to randomization, potentially eligible patients entered a run-in period during which they received one placebo-combination tablet and one placebo-simvastatin tablet daily for about 6 weeks. The run-in period was to help ensure that only those likely to continue taking study treatment for an extended period were randomized. During run-in, details of each patient's lipid profile were provided to their own doctors, so that they were able to decide whether it was appropriate for their patient to be randomized.

After the run-in period, patients were randomized in a ratio of 4:4:1 to placebo (arm 1) vs. ezetimibe/simvastatin 10/20 mg (Arm 2) vs. simvastatin 20 mg (Arm 3). After one-year, patients initially randomized to simvastatin 20 mg daily were re-randomized to ezetimibe/simvastatin 10/20 mg (Arm 3b) vs. placebo (Arm 3a) for the remainder of the trial. The double blinded treatment period was at least 4 years for each patient, with median duration of 4.9 years in survivors. Follow-up visits after randomization were scheduled at 2 and 6 months, and then every 6 months, during the scheduled treatment period. The study was scheduled to continue until all patients have been followed for at least 4 years and at least 1100 major vascular event had occurred.

The reasons to include arm 3 in the design were 1) to provide a safety control for ezetimibe+simvastatin. If unexpected adverse effect of simvastatin emerges, the comparison of arm 2 and arm 3 would provide a randomized comparison of ezetimibe vs. placebo on a background of simvastatin. This would enable discrimination between a new adverse effect of simvastatin specific to CKD patients and an adverse effect specific to ezetimibe; and 2) to allow

assessment of the proportion of LDL-C reduction attributable to addition of ezetimibe to simvastatin in the study population.

The primary efficacy endpoint specified in the protocol was major vascular event (MVE). MVE is a composite endpoint comprising non-fatal MI or cardiac death, non-fatal or fatal stroke; or revascularization procedures including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation (but excluding vascular access surgery for dialysis) during the scheduled treatment period. The primary comparison specified in the protocol was the effects on the first MVE during the scheduled treatment period in patients originally randomized to ezetimibe/simvastatin (Arm 2) vs. patients originally randomized to placebo (Arm 1).

In the clinical study report, the applicant claimed that

> *During the study, blinded adjudication for MVE showed that about one third of these events were non-coronary cardiac deaths or hemorrhagic strokes. Knowledge gained following the start of SHARP and from other studies indicated that non-coronary cardiac deaths or haemorrhagic strokes were unlikely to be prevented by LDL-C lowering therapy. In addition, the mean LDL-C reduction at 2.5 years (the midpoint of the trial) was lower than the anticipated difference, thus a smaller risk reduction in MVE was anticipated, which, if true, would apply that there were not enough power to detect a difference in a test with pre-specified significant level of P<0.01 (2-sided). In order to potentially increase statistical power, in October 2009 the steering committee decided to change the primary outcome to MAE. The new proposed primary outcome excluded non-coronary cardiac death and hemorrhagic stroke to avoid, as far as possible, dilution of a potential benefit on atherosclerotic outcomes by a lack of benefit on non-atherosclerotic components. In addition, because slightly better power could be achieved by including those patients who were originally allocated to simvastatin for one year, the steering committee decided that the main comparisons should include them.*

There was no interim analysis on the primary efficacy endpoint planned for the study. However, LDL-C level was unblinded at the midpoint of the trial. The steering committee's knowledge on achieved LDL-C reduction was cited as one of the reasons for the committee to make the decision to change the primary treatment comparison. Based on blinded review on MVE and unblinded review on LDL-C level during the trial, the independent steering committee decided for the statistical analysis plan (SAP) that the key outcome to be major atherosclerotic event (MAE), which is a composite endpoint comprising major coronary events (i.e., coronary death or non-fatal MI), ischemic stroke, or any revascularization procedure. This endpoint corresponds to MVE minus non-coronary cardiac deaths and hemorrhagic stroke. The main comparison also changed to the effect on the first MAE in all randomized patients of ezetimibe/simvastatin (Arm 2 + Arm 3b) vs. all randomized patients of placebo (Arm 1 + Arm 3a). The comparison between the two main outcomes is given in Table 1.

Merck did not disagree with the scientific arguments for changing the primary endpoint. However, Merck declined the Oxford request to modify the primary endpoint, given general concerns around late-stage changes to outcome study primary endpoints and the belief that the relevant findings of SHARP could be scientifically communicated without such a change. While

still blinded, Oxford investigators wrote a statistical analysis plan (SAP) specifying the changes. The end result is that the protocol and SAP are not completely concordant. In the submitted CSR, analyses based on both protocol and SAP were reported. It is discussed in detail in Section 3.2.4.

Table 1 Comparison of the definition of two main outcomes MVE and MAE (quoted from CSR).

Main outcome	Protocol Primary Comparison	SAP Key Outcome
Composite endpoint	Major vascular events (MVE)	Major atherosclerotic events (MAE)
Endpoint components	Major cardiac events: MI, cardiac death	Major coronary events: MI, coronary death
	Any stroke	Ischemic stroke
	Any revascularization procedure†	Any revascularization procedure†
Population analyzed	All patients randomized to ezetimibe/simvastatin or placebo, excluding patients initially randomized to simvastatin.	All patients randomized to ezetimibe/simvastatin or placebo, including patients initially randomized to simvastatin.
	Arm 2 vs. Arm 1	Arm 2 + 3b vs. Arm 1 + 3a
	Total N=8384	Total N=9270
MVE/MAE difference	Includes non-coronary cardiac death and hemorrhagic stroke, excluding patients initially randomized to simvastatin.	Excludes non-coronary cardiac death and hemorrhagic stroke, including patients initially randomized to simvastatin.
†Coronary or non-coronary angioplasty or grafting, and non-traumatic amputation (but excluding vascular access surgery for dialysis).		

The specified causes of all deaths and any serious adverse events reported by the local centers were reviewed by a central outcomes adjudication panel blind to treatment allocation.

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

Figure 2 provides a summary of the disposition of patients from initial screening through complete follow-up. Incomplete follow-up includes those without direct contact (in person or telephone) at the scheduled final visit and with less than 4 years of follow-up.

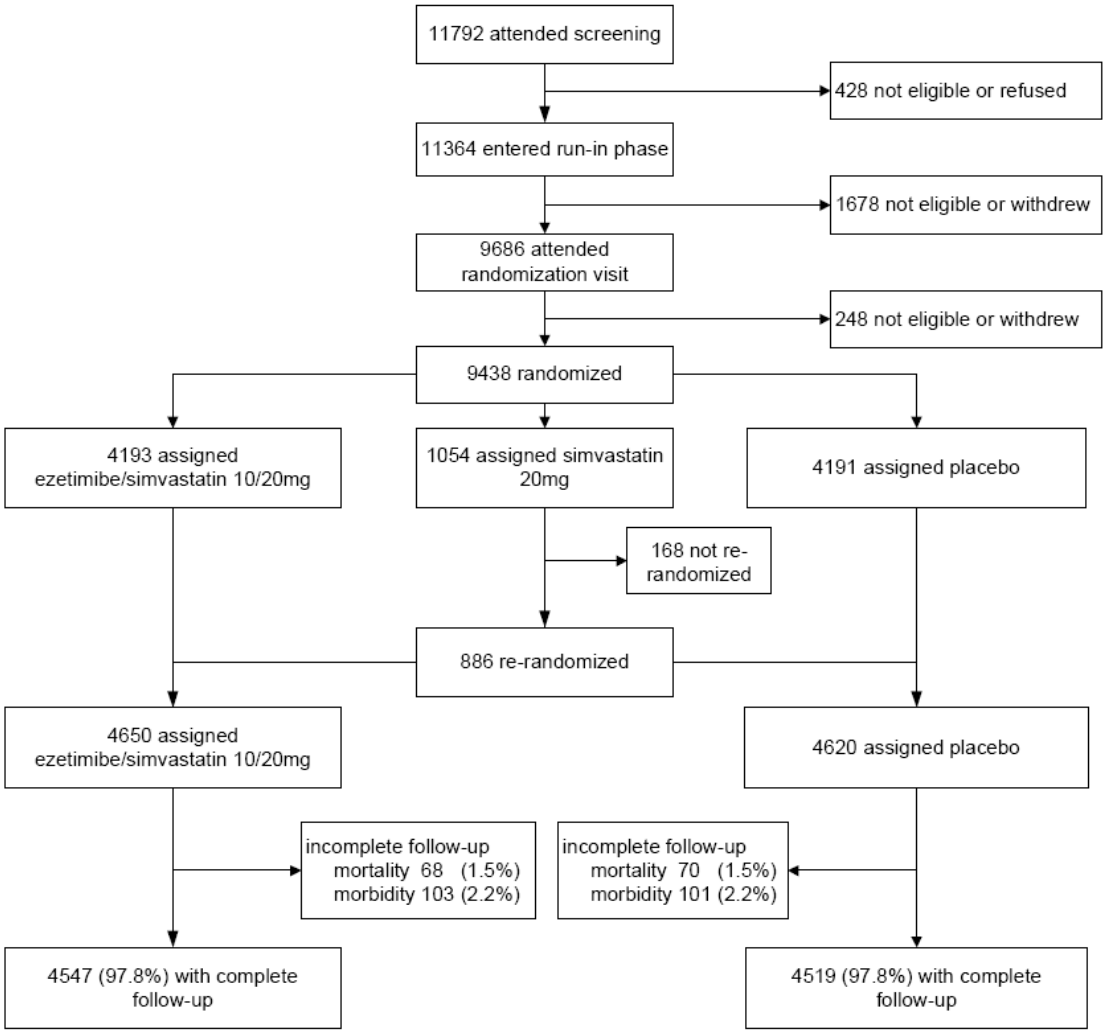


Figure 2 Summary of patients disposition (quoted from CSR).

Number of patients randomized in each country is summarized in Table 2. More than half of the patients were recruited from four countries: UK, Germany, Australia and China. US patients only counted for about 4% of the total study population.

Table 2 Number of patients randomized in each country: First Randomization.

Country	Ezetimibe / Simvastatin 10/20mg (N=4193)	Simvastatin 20mg (N=1054)	Placebo (N=4191)	Total (N=9438)	Percentage (%)
UK	888	229	870	1987	21
Germany	768	164	746	1678	18
Australia	450	120	473	1043	11
China	438	120	436	994	11
Malaysia	308	77	316	701	7
Canada	222	70	213	505	5

USA	176	46	172	394	4
New Zealand	125	31	129	285	3
France	119	28	117	264	3
Denmark	118	25	115	258	3
Thailand	116	28	109	253	3
Sweden	100	20	99	219	2
Norway	88	17	89	194	2
Czech Republic	69	26	96	191	2
Poland	71	20	69	160	2
Austria	50	13	48	111	1
Netherlands	46	12	50	108	1
Finland	41	8	44	93	1

Table 3 summarizes the reasons for stopping study treatment before scheduled end. During the first year of the study, about 15%~16% patients stopped taking study treatment. During the whole scheduled treatment period, about 33%~36% percent patients stopped taking study treatment. Patient wishes and adverse events were the two most common reasons for stopping study treatment. The next most common reason for discontinuing study treatment was the use of contraindicated medication, which was more frequent in patients allocated to placebo. Other than that, the percentage of patients stopped taking study medication was balanced across treatment arms.

Table 3 Reason for stopping study treatment before scheduled end (quoted from CSR).

	During Year one			From Final Randomization	
Reasons for stopping	Ezetimibe / Simvastatin 10/20mg (N=4193)	Simvastatin 20mg (N=1054)	Placebo (N=4191)	Ezetimibe / Simvastatin 10/20mg (N=4650)	Placebo (N=4620)
SSAR[†]	1	0	4	17	12
Other serious adverse event	102	31	92	303	310
Non-serious adverse event	81	14	79	165	131
Other reason	317	71	333	946	1126
Difficulty attending clinic	*19*	*7*	*31*	*82*	*90*
Awaiting bloods	*5*	*3*	*1*	*5*	*1*
Difficulty taking tablets	*40*	*4*	*28*	*95*	*81*
Contraindicated medication	*60*	*19*	*85*	*248*	*449*
Patient wishes	*165*	*32*	*159*	*417*	*409*
Other reasons	*3*	*1*	*3*	*16*	*10*
Reason not specified	*25*	*5*	*26*	*83*	*86*
None of the above	158	45	160	91	79
Any reason	659 (16%)	161 (15%)	668 (16%)	1522 (33%)	1658 (36%)
Had SSAR but did not stop	4	1	1	3	1

More than one reason may apply to a patient. ([†]SSAR=suspected serious adverse reaction)

The total person-years of follow-up was 19783.2 person-years in ezetimibe/simvastatin 10/20 mg (Arm 2+3b) vs. 19714.9 person-years in placebo (Arm 1+3a). After the second randomization, those patients who were randomized to Arm 3a and Arm 3b were considered as starting the study at time 0, i.e. their time under risk started from the second randomization. The median follow-up among survivors was 4.9 years in both Arm 1+3a and Arm 2+3b.

Compliance with study medication is summarized in Table 8 in appendix. The overall compliance to treatment declined steadily over the course of the study in both treatment arms. In the later stage of the study, the percentage of patients compliant with more than 80% of study medication was greater in ezetimibe/simvastatin 10/20mg arm than in placebo arm. This difference was partly the result of the greater use of non-study statins in the placebo group (as shown by contraindicated medication in Table 3). Patients who began taking non-study statins were required to discontinue study treatment. Compliance in the two arms at 2.5 years by renal status is summarized in Table 9 in appendix. Compliance was lower in patients on dialysis compared to patients not on dialysis.

The main baseline characteristics and demographics of randomized patients are summarized in Table 4. Complete baseline characteristics of randomized patients are available in appendix.

Table 4 Summary of main baseline characteristics and demographics of patients randomized to Arm 2+3b vs. Arm 1+3a.

Baseline characteristics	Ezetimibe/Simvastatin 10/20mg (N=4650)	Placebo (N=4620)
Age at randomization (years)		
40-49	968 (21%)	908 (20%)
50-59	1161 (25%)	1149 (25%)
60-69	1226 (26%)	1246 (27%)
70+	1295 (28%)	1317 (29%)
Mean ± SD	62 ± 12	62 ± 12
Gender		
Male	2915 (63%)	2885 (62%)
Female	1735 (37%)	1735 (38%)
Race		
White	3332 (72%)	3314 (72%)
Black	137 (3%)	127 (3%)
Asian	1043 (22%)	1043 (23%)
Other	138 (3%)	136 (3%)
Renal status		
Not on dialysis	3117 (67%)	3130 (68%)
On dialysis	1533 (33%)	1490 (32%)

Among 9270 patients who were randomized to ezetimibe/simvastatin 10/20 mg vs. placebo, there were no clinically meaningful differences between the groups in the baseline characteristics.

3.2.3 Statistical Methodologies

In SHARP, patients were allocated to treatments based on a minimized randomization method, which CTSU at Oxford University has previously used in another study (HPS, Heart Protection Study). This minimized randomization method was applied to ensure that treatment groups are balanced with respect to prognostically important variables, including age, gender, renal status, creatinine, history of vascular disease or diabetes, systolic blood pressure, total cholesterol, and ethnic origin. About 10% patients were allocated to treatment arms stochastically that used simple randomization method, the rest of the patients entered the study with treatment allocated by minimization method deterministically. Since minimization may produce predictable allocation sequences and the probability of error in significance testing may be high, re-randomization tests should be used when evaluating the endpoints or the analysis should be done with adjustment on variables used in the minimization. However, neither was done by the applicant in this case. We sent out an information request on details of minimized randomization method used for SHARP on August 12, 2011 and got a response on September 14, 2011. Based on the information we got, I did re-randomization test for this review.

The primary comparison was on time to the first MVE in Arm 2 vs. Arm 1 as specified in the original protocol. In SAP, the primary comparison was on time to the first MAE in Arm 2+3b vs. Arm 1+3a. Both were done by a log-rank test to calculate average event rate ratios, with stratification on whether patients were originally randomized to ezetimibe/simvastatin vs. placebo or were re-randomized after about one year on allocated simvastatin to ezetimibe/simvastatin vs. placebo.

For multiplicity, the Hochberg procedure was employed for the evaluation of the separate components of the MAE.

The primary analysis was performed in the ITT population, which was defined as all randomized patients. Randomized patients were followed for outcome information until the scheduled final follow-up visit regardless of whether or not they continued on study therapy. Patients who were lost to follow-up were included in outcome analyses by censoring their observation period after lost to follow up.

3.2.4 Results and Conclusions

The protocol-defined primary endpoint is the first occurrence of MVE in Arm 2 vs. Arm 1. It only includes patients randomized to ezetimibe/simvastatin 10/20 mg vs. placebo at the first randomization, excluded those originally allocated to simvastatin alone.

In the SAP, the endpoint of chief emphasis, also referred to as the "key outcome", is the first occurrence of MAE, defined as major coronary events (coronary death or non-fatal MI), ischemic stroke, or any revascularization procedure, in all patients randomized to ezetimibe/simvastatin 10/20 mg (Arm 2+3b) vs. placebo (Arm 1+3a). It Included those originally allocated to simvastatin alone on the beginning of the study and were re-randomized to ezetimibe/simvastatin 10/20 mg or placebo at the end of year one.

The reason for the change of main comparison from MVE in Arm 2 vs. Arm 1 to MAE in Arm 2+3b vs. Arm 1+3a is given in section 3.2.1. The effects of treatment with ezetimibe/simvastatin 10/20 mg vs. placebo are shown in Figure 3 in form of Kaplan-Meier plot. It summarizes all the possible comparisons with different combination of endpoints and comparison arms. The results are very similar numerically regardless of whether the emphasis is on the MVE or MAE, Arm 2 vs. Arm 1 or Arm 2+3b vs. Arm 1+3a, and are highly significant in all cases. Table 5 gives the corresponding numeric results. Ezetimibe/simvastatin 10/20mg produced a 15% to 17% reduction in the risk of suffering a major vascular or atherosclerotic event, with a 95% confidence interval (CI) around 7% to 26% reduction.

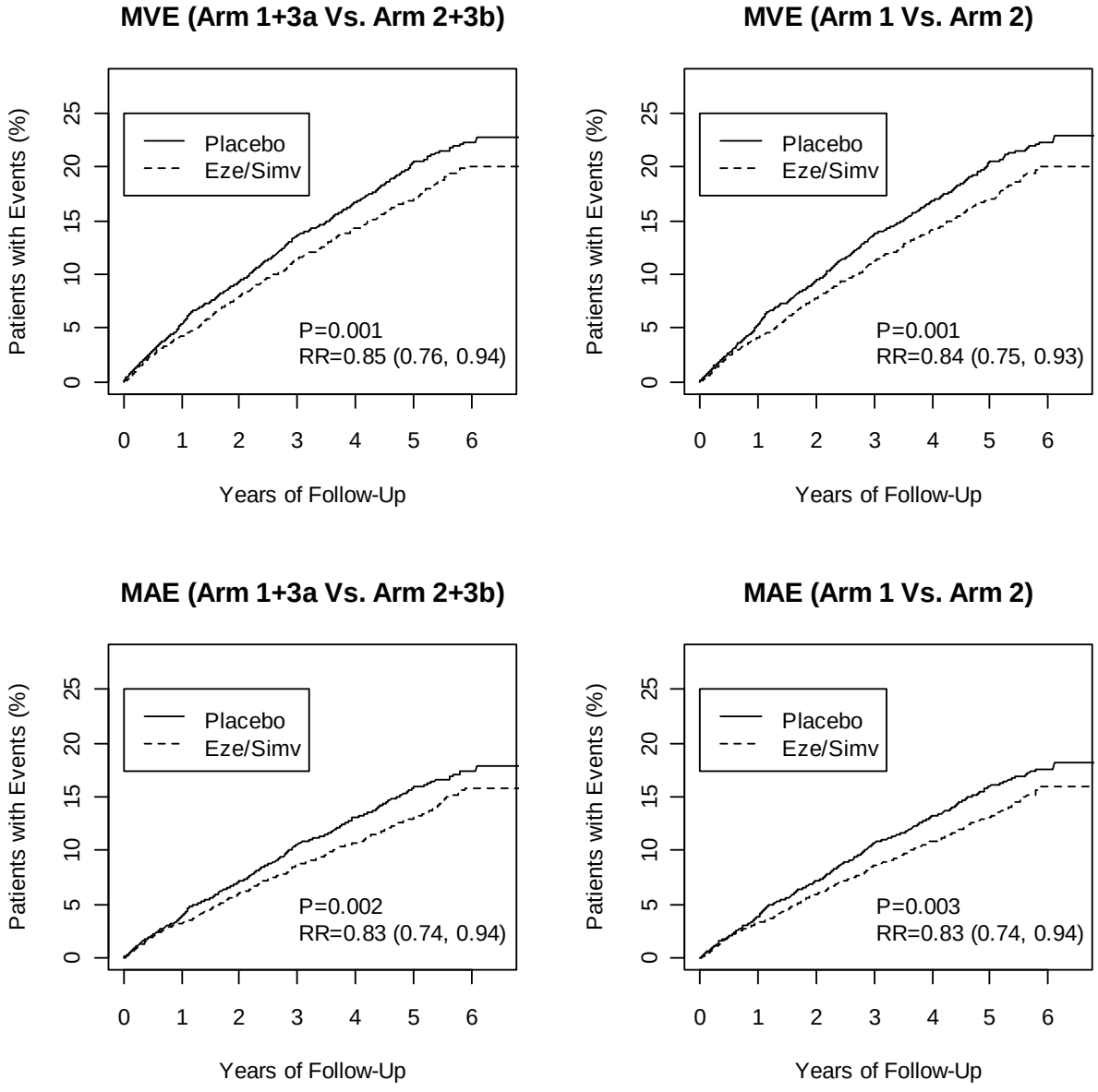


Figure 3 Effects of Ezetimibe/Simvastatin on MVE or MAE in randomized patients.

Table 5 Effects of Ezetimibe/Simvastatin on MVE or MAE in randomized patients.

EP	Arms compared	Ezetimibe/Simvastatin n/N (rate)	Placebo n/N (rate)	RR	95% CI	P
MVE	1+3a vs. 2+3b	701 / 4650 (15.1%)	814 / 4620 (17.6%)	0.85	(0.76, 0.94)	0.001
	1 vs. 2	639 / 4193 (15.2%)	749 / 4191 (17.9%)	0.84	(0.75, 0.93)	0.001
MAE	1+3a vs. 2+3b	526 / 4650 (11.3%)	619 / 4620 (13.4%)	0.83	(0.74, 0.94)	0.002
	1 vs. 2	486 / 4193 (11.6%)	574 / 4191 (13.7%)	0.83	(0.74, 0.94)	0.003

The results of re-randomization test on the two main comparisons, MVE in Arm 1 vs. Arm 2 and MAE in Arm 1+3a vs. Arm 2+3b, are given in Figure 4. It shows the distribution of risk ratios from 1000 permutations of treatment allocation by the same minimized randomization procedure used for the trial with the observed MVE/MAE result. It confirms that p values from the re-randomization test remain highly significant and are very close to the observed p values by log-rank test.

In Figure 5, breaking down MVE by components shows that except haemorrhagic stroke, all other components had a positive treatment effect, although not all of them were statistically significant. Overall, there was little apparent effect on those "other major vascular events", which were included in MVE but not included in MAE.

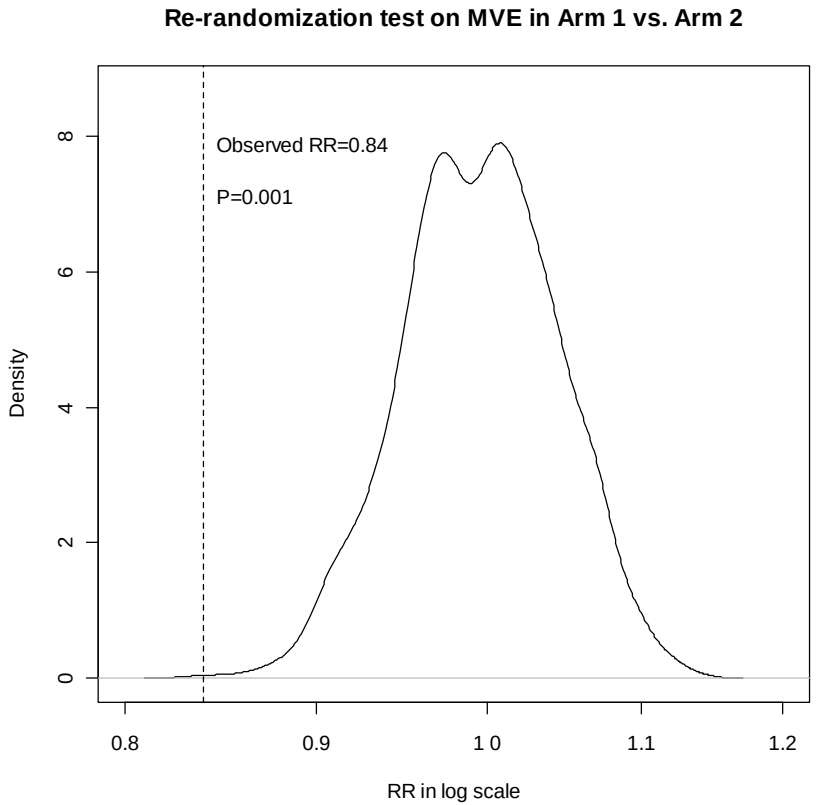
Figure 6 shows the effects of ezetimibe/simvastatin 10/20mg on MAE in Arm 1+3a vs. Arm 2+3b by components. After adjusting multiplicity by Hochberg procedure, the risk reductions in non-hemorrhagic stroke and any revascularization procedure remain statistically significant, with adjusted p-values of 0.022 and 0.011 respectively.

Since the difference between protocol-defined main outcome and the key outcome in SAP is very small, only comparisons of MVE in Arm 2 vs. Arm 1 are reported in the following sections.

Reduction of LDL-C level at different time points during the scheduled treatment period are given in Table 10 in appendix. This result is not validated by us yet, since we are still waiting for the applicant to submit the complete data. The absolute reduction of LDL-C by ezetimibe/simvastatin 10/20 mg at one year was about 1.1 mmol/L (42 mg/dL) and declined through the trial to 0.78 mmol/L (30 mg/dL) at 4 years. This decline was likely due to the difference in compliance of study treatment between the placebo arm and the ezetimibe/simvastatin 10/20mg arm.

As mentioned in section 3.2.1, one of the reasons for the change of primary efficacy endpoint in this study was due to the mean LDL-C reduction at 2.5 years (the midpoint of the trial) was 33 mg/dL, rather than the expected 39 mg/dL, thus a lower risk reduction in MVE was anticipated. If this turned out to be true, then the study was expected to only have 66% power at p=0.01 (2-sided) to detect a difference in MVE. Based on this interim analysis on reduction of LDL-C level and other findings, the steering committee decided to change the primary efficacy endpoint of this study and change the main comparison from Arm 1 vs. Arm 2 to Arm 1+3a vs. Arm 2+3b to increase the sample size.

There was no interim analysis on MVE planned or conducted for SHARP. However, since the study was designed based on the assumption that there is a correlation between reduction of LDL-C level and reduction in risk of MVE (or MAE), the applicant intended the interim evaluation of LDL-C level to serve as an indicator for the potential need to change sample size. Because there was little difference between the two sets of results, overall study conclusions and interpretations are the same. Otherwise if the comparison of MVE in Arm 1 vs. Arm 2 and the comparison of MAE in Arm 1+3a vs. Arm 2+3b had very different results, it would be problematic to make conclusions with the discordance.



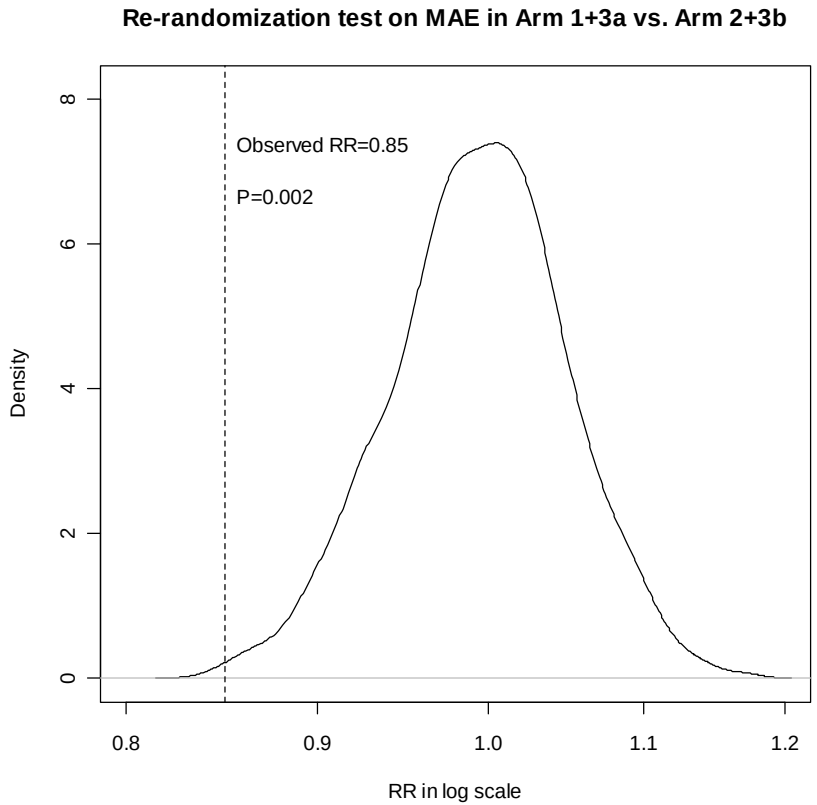


Figure 4 Re-randomization test on the primary comparisons.

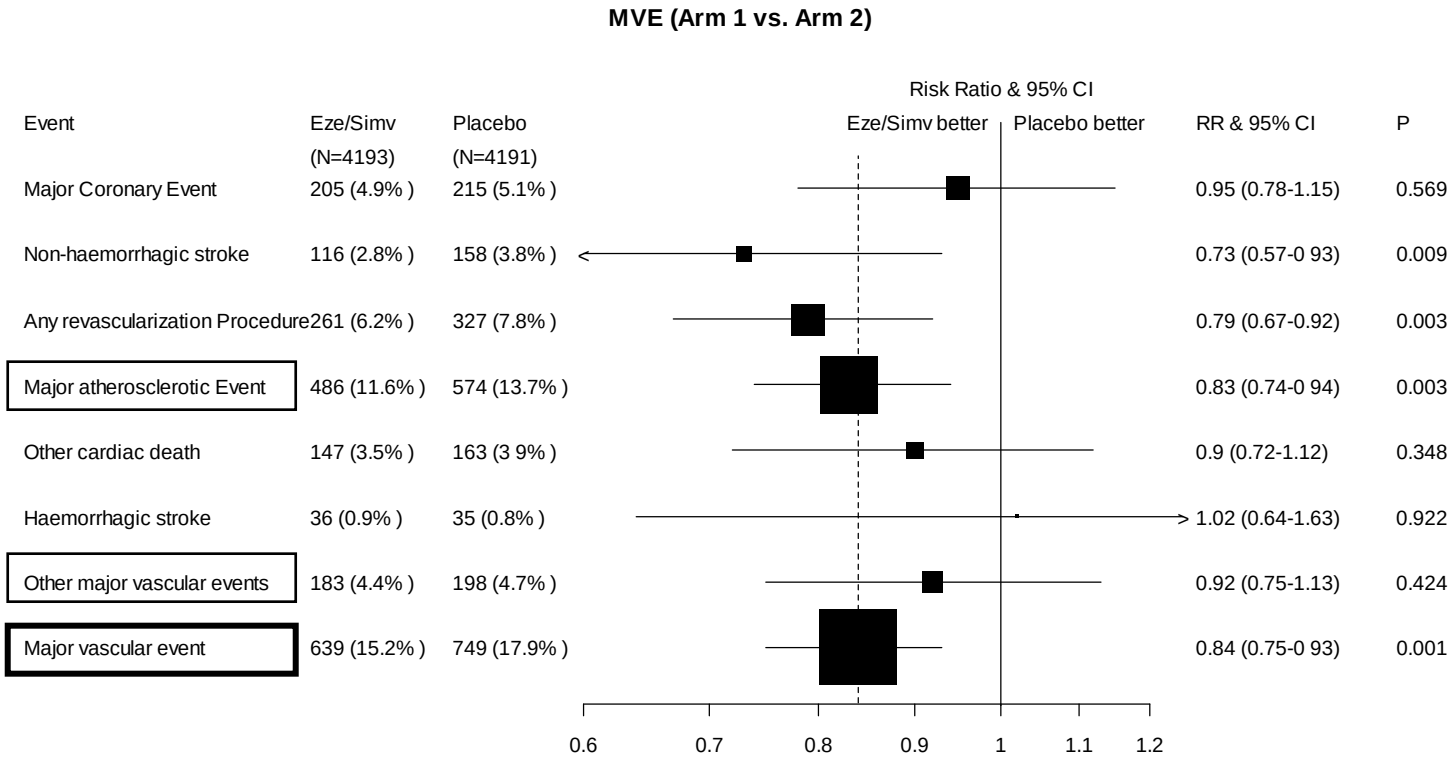


Figure 5 Effects of Ezetimibe/Simvastatin on components of MVE (Arm 1 vs. Arm 2).

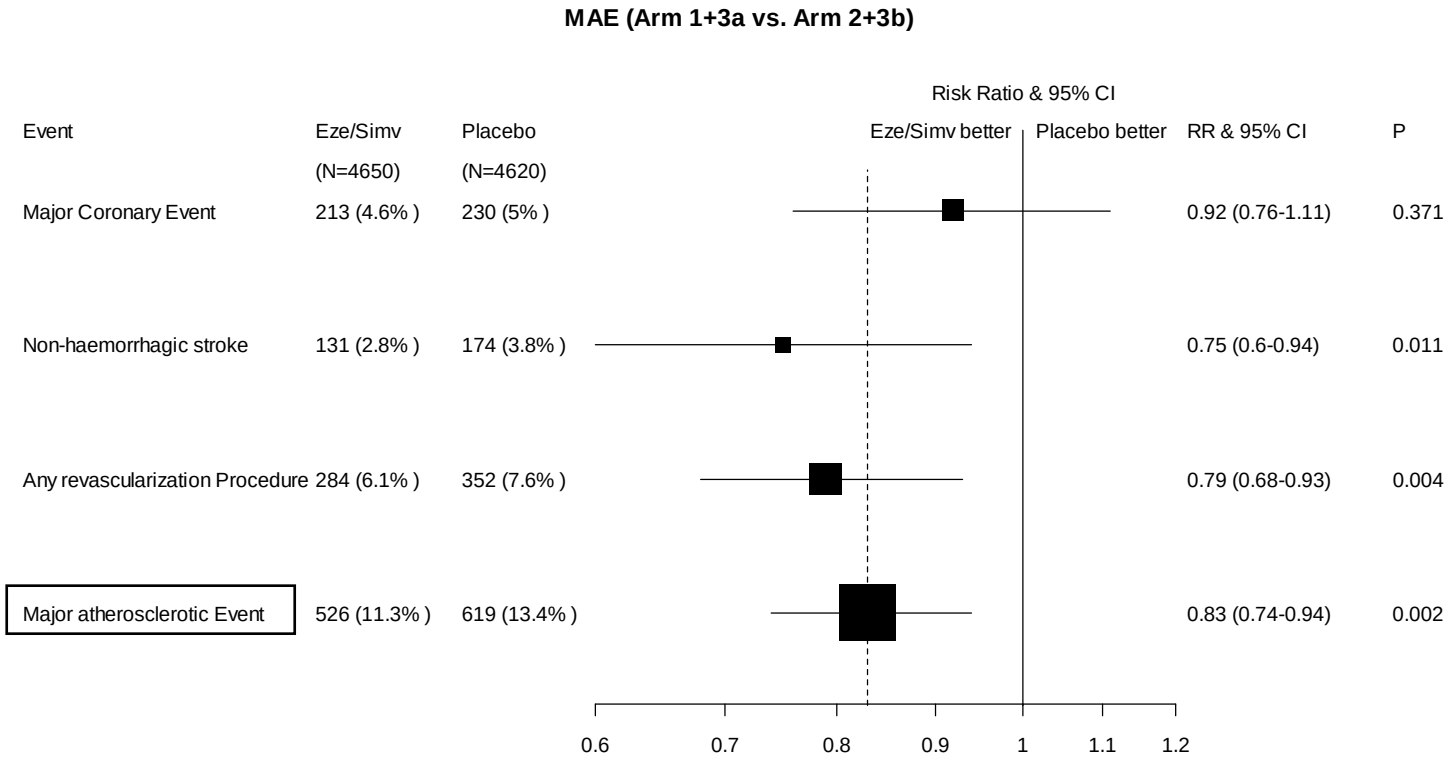


Figure 6 Effects of Ezetimibe/Simvastatin on components of MAE (Arm 1+3a vs. Arm 2+3b).

3.3 Evaluation of Safety

The evaluation of safety was conducted by Dr. James Smith. Reader is referred to Dr. James Smith's review for this section.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

The summary of subgroup analysis on the primary efficacy endpoint is given in Figure 7. The subgroups are categorized by gender, age group and race, based on the categories summarized in Table 4. In general, the subgroup analysis results are consistent with the results of overall population. In the subgroup analysis on race, ezetimibe/simvastatin showed a non-significant negative treatment effect on black patients. However, due to the small sample size of this subgroup, the estimation of the treatment effect for this subgroup had a wide 95% CI (0.61, 1.92). So the negative treatment effect of ezetimibe/simvastatin 10/20mg in black patients was not a reliable estimate.

4.2 Other Special/Subgroup Populations

There were two other studies, 4D[1] and AURORA[2], conducted before SHARP with the similar hypothesis test, namely whether lowering LDL-C would reduce cardiovascular risk in patients on hemodialysis.

4D compared atorvastatin 20 mg vs. placebo in 1255 patients with diabetes undergoing hemodialysis over a follow up period of 4 years. The primary endpoint was a composite of non-fatal MI, stoke and cardiac death, 469 patients had primary events. The relative risk of the primary endpoint was 0.92 with a 95% CI of (0.77, 1.10) and a p value of 0.37. The result is shown in Figure 8.

AURORA compared rosuvastatin 10 mg against placebo in 2776 patients undergoing dialysis. The primary endpoint was a composite of non-fatal MI, non-fatal stroke and cardiovascular death, 804 patients had primary events. The risk ratio was 0.96 with a 95% CI of (0.84, 1.11) and a p value of 0.59. The result is shown in Figure 9.

SHARP is different from 4D and AURORA in both the patient population and primary efficacy endpoint. Both 4D and AURORA included only patients on dialysis at randomization, the primary efficacy endpoint in the two studies excluded revascularization procedures, and the adjudication methods may have differed from those used in SHARP as well. In this review, we compared SHARP result to the other two studies by excluding revascularization procedure from MVE and only including patients on dialysis at randomization. The result is shown in Figure 10. There is no significant positive treatment effect of ezetimibe/simvastatin on MVE without revascularization procedure in the patients who were on dialysis at randomization. The risk ratio is 1.01 with a 95% CI of (0.83, 1.23) and a p value of 0.95. The result of SHARP with modified MVE in this subset of patients is similar to the result of 4D and AURORA.

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[1] Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. New England Journal of Medicine 2005; 353:238-48

[2] Fellström B, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. New England Journal of Medicine 2009; 360:1395-407.

It then becomes important to check if the treatment effect of ezetimibe/simvastatin 10/20 mg was different in patients on dialysis at randomization from that in patients who were pre-dialysis at randomization. The comparison of the primary efficacy endpoints in these subgroups is shown in Figure 11. The treatment effect of ezetimibe/simvastatin 10/20mg on MVE was significant only in patients not on dialysis at randomization (p=0.001), but was not significant in patients on dialysis at randomization (p=0.947).

The test of heterogeneity among pre-dialysis and dialysis subgroups gave p=0.07 for MVE and p=0.25 for MAE. The applicant claimed that, because neither was significant (i.e. p>0.05), there was no evidence of heterogeneity of risk reduction in either MVE or MAE. I think this is debatable. The reasons are listed below.

The test of heterogeneity among pre-dialysis and dialysis subgroups gave P=0.07 for MVE, which was significant at the 10% significance level. For subgroup analyses, due to reduced power, test of heterogeneity (or treatment interaction by subgroups) is often conducted at the 10% level instead of the usual 5% level for main effects.

The applicant conducted an analysis by weighting the risk reduction in each subgroup by the degree of LDL-C reduction. Specifically the weight for a particular subgroup was defined as the difference in mean LDL-C at 2.5 years between ezetimibe/simvastatin 10/20 mg and placebo groups in that subgroup. The purpose of the analysis was to adjust for the heterogeneity associated with differences in the magnitude of the reduction in LDL-C in different subgroups from that associated with intrinsic differences between subgroups. The applicant's weighted analysis narrowed the difference in risk reduction between pre-dialysis and dialysis patients.

The applicant's analysis has several shortcomings. First, although this method has been used in previous publications, it was not specified in the statistical analysis plan and therefore was post-hoc.

The second issue arises from the well known potential hazards that arise when a statistical analysis is adjusted on the basis of post-randomization outcomes. Adjusting for variables measured after randomization can confuse the notions of cause and effect. It is possible that the differential reduction in LDL-C level, rather than acting as an independent predictor of relative risks in the two subgroups, was in fact the result of intrinsic differences between the subgroups themselves. The adjustment is difficult to interpret due to the multiple possible causal pathways. Therefore, I think the unadjusted (for LDL-C) risk ratios represent the best estimates of risk in the two subgroups.

I have already shown above that by removing revascularization procedure from MVE and only including patients on dialysis at randomization, result of SHARP is very similar to the other two studies in dialysis patients, which did not show significant risk reduction on cardiovascular events in CKD patients by reducing LDL-C level. Subgroup analysis shows only patients who were pre-dialysis at randomization showed a significant different treatment result on MVE as originally defined. It appears the treatment effect of ezetimibe/simvastatin 10/20 mg on MVE was largely driven by the effect in pre-dialysis patients.

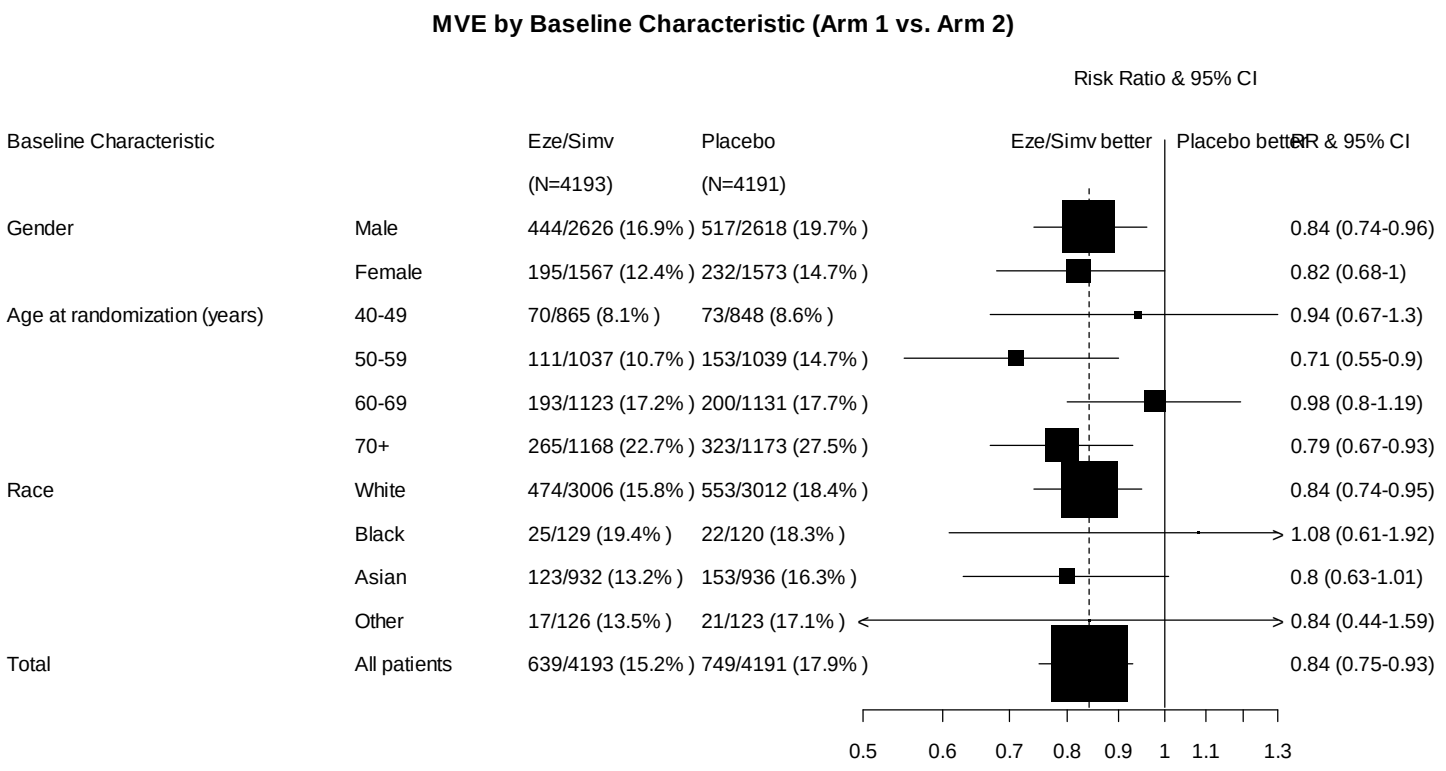

Figure 7 Effects of ezetimibe/simvastatin on MVE by baseline characteristics (Arm 1 vs. Arm 2).

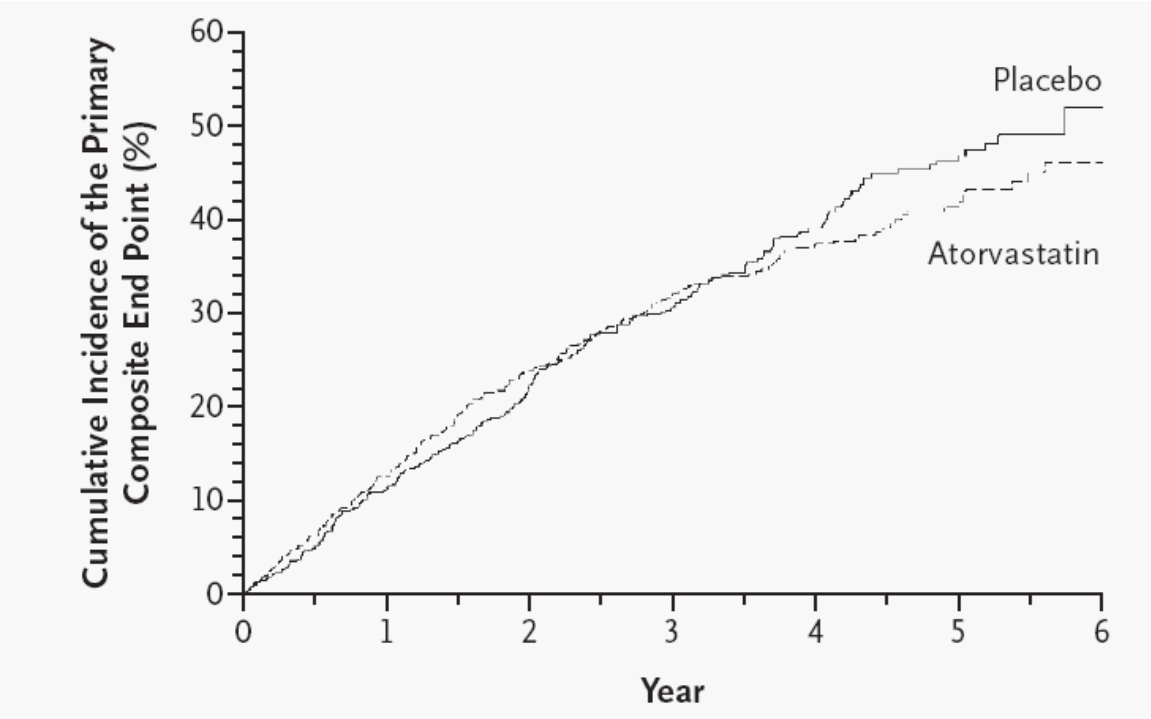

Figure 8 Main result of 4D study (quoted from Warner et al., 2005).

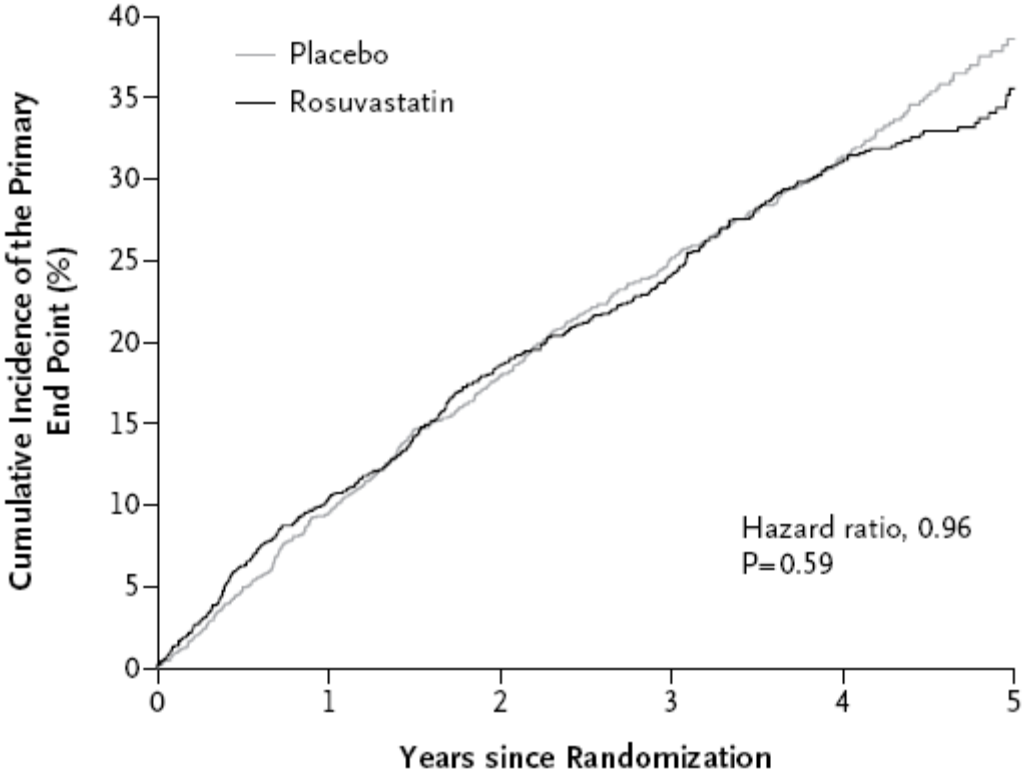

Figure 9 Main result of AURORA study (quoted from Fellström et al., 2009).

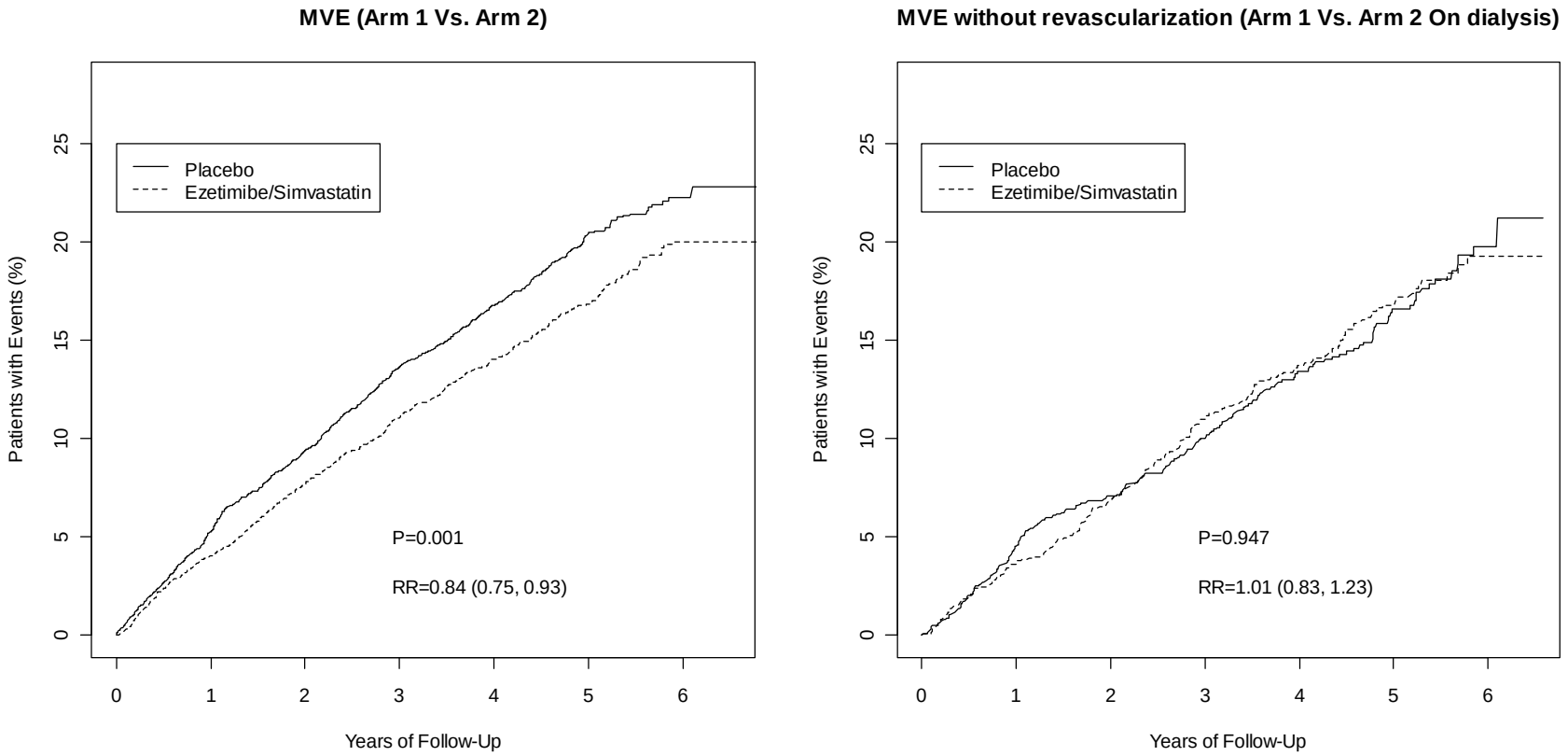

Figure 10 Effects of ezetimibe/simvastatin on MVE excluding revascularization procedure in Arm 1 vs. Arm 2, only including patients on dialysis at randomization.

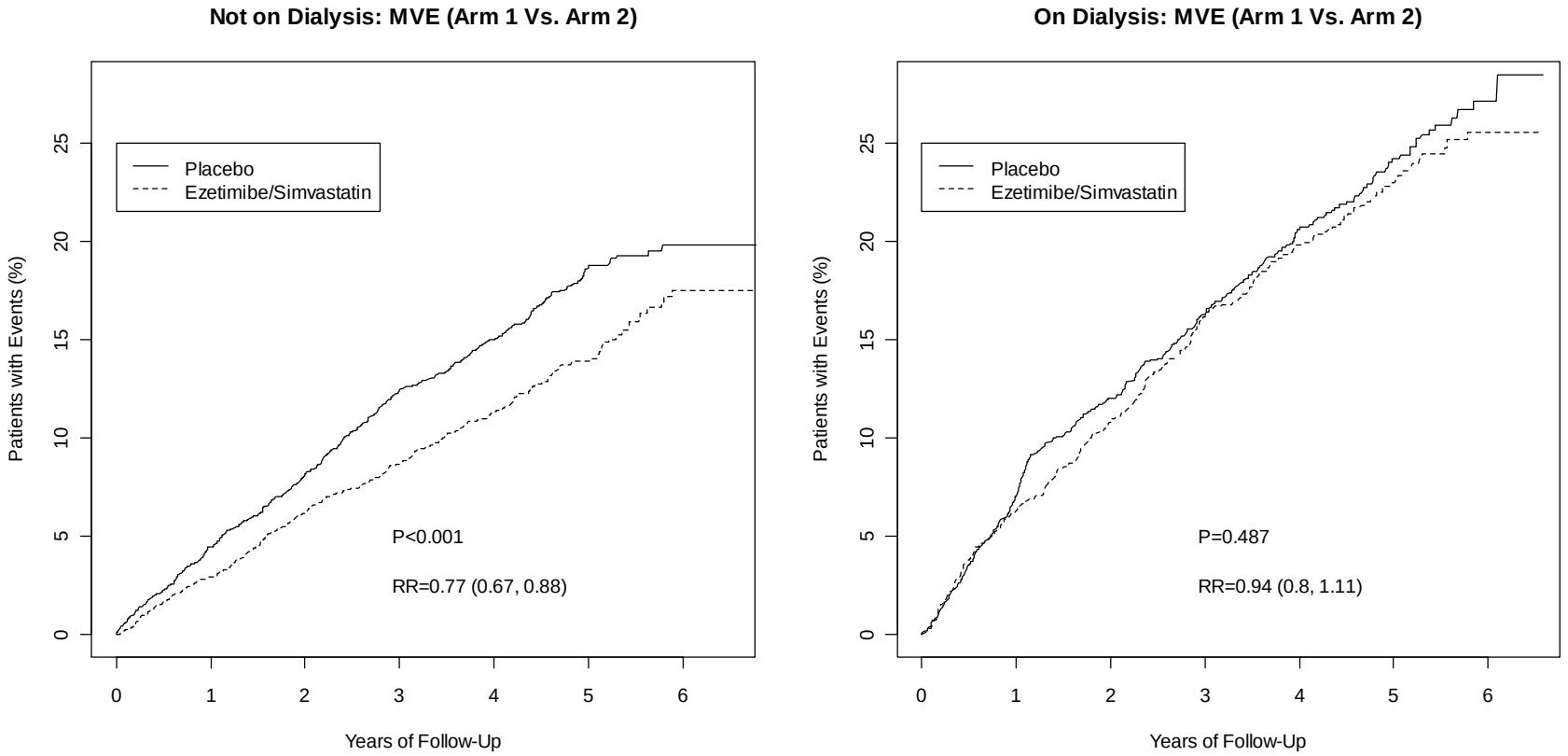

Figure 11 Effects of ezetimibe/simvastatin on MVE in Arm 1 vs. Arm 2 by dialysis status at randomization.

APPENDICES

Table 6 Examples of raw data error (quoted from submitted DS.xpt).

USUBJID	DSSEQ	DSTERM	EPOCH	DSDTC	DSSTDTC	DSSTDY
4700106	1	COMPLETED	SCRN	2/6/2006	2/6/2006	-45
4700106	2	INFORMED CONSENT OBTAINED		2/6/2006	2/6/2006	-45
4700106	3	COMPLETED	RUNIN	3/24/2006	3/24/2006	1
4700106	4	RANDOMIZED		3/24/2006	3/24/2006	1
4700106	5	SUPPLEMENTARY CONSENT (BLOOD) OBTAINED		3/24/2006	3/24/2006	1
4700106	6	SUPPLEMENTARY CONSENT (GENETIC) OBTAINED		3/24/2006	3/24/2006	1
4700106	7	SUPPLEMENTARY CONSENT (URINE) OBTAINED		3/24/2006	3/24/2006	1
4700106	8	COMPLETED	YEAR1	3/14/2007	3/14/2007	356
4700106	9	DEATH	RAND	3/29/2010	2/15/2010	1425
4700106	10	LAST EVENT INFORMATION		3/29/2010	2/17/2010	1427
4700106	11	LAST KNOWN TO BE ALIVE		3/29/2010	2/17/2010	1427
4700106	12	COMPLETED	RAND	3/29/2010	3/29/2010	1467

Record in sradata.xpt (analysis dataset)

patient_id	rand_arm	censor_nonfatal_days	censor_fatal_days	Randomization_date	censor_nonfatal_date	censor_fatal_date
1050132	1	1535	1535	10/8/2004	12/21/2008	12/21/2008

Record in DS.xpt (raw data for information on patient disposition)

DOMAIN	USUBJID	DSSEQ	DSDECOD	EPOCH	DSDTC	DSSTDTC	DSSTDY
DS	1050132	1	COMPLETED	SCRN	8/12/2004	8/12/2004	-56
DS	1050132	2	INFORMED CONSENT OBTAINED		8/12/2004	8/12/2004	-56
DS	1050132	3	COMPLETED	RUNIN	10/8/2004	10/8/2004	1
DS	1050132	4	RANDOMIZED		10/8/2004	10/8/2004	1
DS	1050132	5	SUPPLEMENTARY CONSENT (BLOOD) OBTAINED		10/8/2004	10/8/2004	1
DS	1050132	6	SUPPLEMENTARY CONSENT (GENETIC) OBTAINED		10/8/2004	10/8/2004	1
DS	1050132	7	SUPPLEMENTARY CONSENT (URINE) OBTAINED		10/8/2004	10/8/2004	1
DS	1050132	8	COMPLETED	YEAR1	12/20/2005	12/20/2005	439
DS	1050132	9	DEATH	RAND	5/15/2009	12/21/2008	1536

Record in SV.xpt (raw data for information subject visit)

DOMAIN	USUBJID	VISITNUM	VISIT	SVSTDTC	SVENDTC	SVSTDY	SVENDY
SV	1050132	1	Screening	2004-08-12T15:39:51	2004-08-12T16:17:49	-56	-56
SV	1050132	2	Randomization	2004-10-08T13:52:21	2004-10-08T13:54:43	1	1
SV	1050132	3.01	Early Recall 3.01	2005-01-25T11:40:51	2005-01-25T11:50:31	110	110
SV	1050132	4.01	Early Recall 4.01	2005-06-29T14:52:17	2005-06-29T15:21:04	265	265
SV	1050132	4.02	Early Recall 4.02	2005-09-05T14:29:02	2005-09-05T14:32:43	333	333
SV	1050132	5.01	Early Recall 5.01	2005-12-20T14:42:41	2005-12-20T14:49:28	439	439
SV	1050132	6	18 month follow-up	2006-05-02T14:49:20	2006-05-02T14:57:34	572	572

Record in SUPPSV.xpt (raw data for supplementary information on subject visit)

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
SV	1050132	VISITNUM	3.01	FINAL	Was this intended to be the final visit?	N
SV	1050132	VISITNUM	3.01	WITHYOU	Whether patient was physically present	Y
SV	1050132	VISITNUM	4.01	FINAL	Was this intended to be the final visit?	N
SV	1050132	VISITNUM	4.01	WITHYOU	Whether patient was physically present	Y
SV	1050132	VISITNUM	4.02	FINAL	Was this intended to be the final visit?	N
SV	1050132	VISITNUM	4.02	WITHYOU	Whether patient was physically present	Y
SV	1050132	VISITNUM	5.01	FINAL	Was this intended to be the final visit?	N
SV	1050132	VISITNUM	5.01	WITHYOU	Whether patient was physically present	Y
SV	1050132	VISITNUM	6	FINAL	Was this intended to be the final visit?	N
SV	1050132	VISITNUM	6	WITHYOU	Whether patient was physically present	Y

Record in AE.xpt (raw data for information on adverse event)

DOMAIN	USUBJID	AESEQ	AEDECOD	AECAT	AESDTH	AESTDTC	AEENDTC	AESTDY	AEENDY	AEDUR
AE	1050132	1	1021: breast cancer	SAE	N	12/7/2004		61	NA	
AE	1050132	2	1275: rectal or colon polypectomy	SAE	N	6/17/2005		253	NA	
AE	1050132	3	1292: colonoscopy	SAE	N	6/17/2005		253	NA	
AE	1050132	5	1073: bradycardia	SAE	N	9/5/2005		333	NA	
AE	1050132	6	1610: soft tissue injury to leg or foot	SAE	N	2005-10		359	NA	
AE	1050132	7	1601: manipulation of joint	SAE	N	2/20/2006		501	NA	P49D
AE	1050132	8	1307: acute on chronic renal failure requiring dialysis	SAE	N	12/21/2008		1536	NA	
AE	1050132	9	1787: CHD death (not MI)	SAE	Y	12/21/2008	12/21/2008	1536	1536	

Record in SUPPAE.xpt (raw data for supplementary information on adverse event)

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
AE	1050132	AESEQ	4	MPEX3D	Patient exercise in previous 3 days	NO EXERCISE
AE	1050132	AESEQ	9	DTHCAUSE	Whether event was primary cause of death	Y

Record in sradata.xpt (analysis dataset)

patient_id	rand_arm	censor_nonfatal_days	censor_fatal_days	Randomization_date	censor_nonfatal_date	censor_fatal_date
3970108	2	1267	1369	10/31/2005	4/20/2009	7/31/2009

Record in DS.xpt (raw data for information on patient disposition)

DOMAIN	USUBJID	DSSEQ	DSDECOD	EPOCH	DSDTC	DSSTDTC	DSSTDY
DS	3970108	1	COMPLETED	SCRN	9/20/2005	9/20/2005	-40
DS	3970108	2	INFORMED CONSENT OBTAINED		9/20/2005	9/20/2005	-40
DS	3970108	3	COMPLETED	RUNIN	10/31/2005	10/31/2005	1
DS	3970108	4	RANDOMIZED		10/31/2005	10/31/2005	1
DS	3970108	5	SUPPLEMENTARY CONSENT (BLOOD) OBTAINED		10/31/2005	10/31/2005	1
DS	3970108	6	SUPPLEMENTARY CONSENT (GENETIC) OBTAINED		10/31/2005	10/31/2005	1
DS	3970108	7	SUPPLEMENTARY CONSENT (URINE) OBTAINED		10/31/2005	10/31/2005	1
DS	3970108	8	COMPLETED	YEAR1	11/14/2006	11/14/2006	380
DS	3970108	9	DEATH	RAND	12/17/2009	7/31/2009	1370

Record in SV.xpt (raw data for information on subject visit)

DOMAIN	USUBJID	VISITNUM	VISIT	VISITDY	SVSTDTC	SVENDTC	SVSTDY	SVENDY
SV	3970108	1	Screening	-42	2005-09-20T15:37:49	2005-09-20T15:49:37	-40	-40
SV	3970108	2	Randomization	1	2005-10-31T15:40:34	2005-10-31T15:54:38	1	1
SV	3970108	3	2 month follow-up	60	2006-01-18T15:21:39	2006-01-18T15:34:52	80	80
SV	3970108	4	6 month follow-up	182	2006-05-03T14:21:07	2006-05-03T14:39:18	185	185
SV	3970108	5	12 month follow-up	365	2006-11-14T16:19:36	2006-11-14T17:09:05	380	380
SV	3970108	7	24 month follow-up	730	2007-10-12T08:36:55	2007-10-12T09:08:42	712	712
SV	3970108	8	30 month follow-up	912	2008-04-17T16:35:25	2008-04-17T16:52:34	900	900
SV	3970108	9	36 month follow-up	1095	2008-11-11T14:15:42	2008-11-11T14:41:15	1108	1108
SV	3970108	10	42 month follow-up	1277	2009-04-20T14:41:00	2009-04-20T14:44:35	1268	1268
SV	3970108	11	48 month follow-up	1460	2009-11-20T15:44:57	2009-11-20T15:48:02	1482	1482

Record in SUPPSV.xpt (raw data for supplementary information on subject visit)

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
SV	3970108	VISITNUM	10	FINAL	Was this intended to be the final visit?	N
SV	3970108	VISITNUM	10	HOWCOND	How interview was conducted	Telephone to patient
SV	3970108	VISITNUM	10	WITHYOU	Whether patient was physically present	N
SV	3970108	VISITNUM	11	FINAL	Was this intended to be the final visit?	N
SV	3970108	VISITNUM	11	HOWCOND	How interview was conducted	Telephone to relative/carer
SV	3970108	VISITNUM	11	WITHYOU	Whether patient was physically present	N
SV	3970108	VISITNUM	3	FINAL	Was this intended to be the final visit?	N
SV	3970108	VISITNUM	3	WITHYOU	Whether patient was physically present	Y
SV	3970108	VISITNUM	4	FINAL	Was this intended to be the final visit?	N
SV	3970108	VISITNUM	4	WITHYOU	Whether patient was physically present	Y
SV	3970108	VISITNUM	5	FINAL	Was this intended to be the final visit?	N
SV	3970108	VISITNUM	5	WITHYOU	Whether patient was physically present	Y
SV	3970108	VISITNUM	7	FINAL	Was this intended to be the final visit?	N
SV	3970108	VISITNUM	7	HOWCOND	How interview was conducted	Telephone to patient
SV	3970108	VISITNUM	7	WITHYOU	Whether patient was physically present	N
SV	3970108	VISITNUM	8	FINAL	Was this intended to be the final visit?	N
SV	3970108	VISITNUM	8	HOWCOND	How interview was conducted	Telephone to patient
SV	3970108	VISITNUM	8	WITHYOU	Whether patient was physically present	N
SV	3970108	VISITNUM	9	FINAL	Was this intended to be the final visit?	N
SV	3970108	VISITNUM	9	WITHYOU	Whether patient was physically present	Y

Record in AE.xpt. (raw data for information on adverse event)

DOMAIN	USUBJID	AESEQ	AEDECOD	AECAT	AESDTH	AESTDTC	AEENDTC	AESTDY	AEENDY
AE	3970108	1	1341: creation of permanent arteriovenous fistula	SAE	N	3/2/2006		123	NA
AE	3970108	2	1339: insertion of tunnelled venous line	SAE	N	5/15/2006		196	NA
AE	3970108	3	1315: initiation of peritoneal dialysis	SAE	N	6/19/2006		231	NA
AE	3970108	4	1301: abdominal pain	SAE	N	9/2/2006		306	NA
AE	3970108	5	1319: cadaveric renal transplantion	SAE	N	5/2/2007		548	NA
AE	3970108	6	1068: atrial fibrillation/flutter	SAE	N	6/4/2007		581	NA
AE	3970108	7	1499: psychological/psychiatric problem	SAE	N	2007-07		608	NA
AE	3970108	8	1067: arrhythmia	SAE	N	2007-10		700	NA
AE	3970108	9	1504: deliberate self harm	SAE	Y	7/31/2009	7/31/2009	1369	1370
AE	3970108	10	1505: attempted suicide	SAE	N	2009-08		1370	NA

Record in SUPPAE.xpt (raw data for supplementary information on adverse event)

RDOMAIN	USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL
AE	3970108	AESEQ	9	DTHCAUSE	Whether event was primary cause of death	Y

SHARP study

Algorithms for calculation of censoring dates

1. OVERVIEW

Two censoring dates for events are used in the SHARP analysis, one for fatal and one for non-fatal events. The intention is to capture the latest in-trial date at which we have definite information on the absence or occurrence of events. The use of two dates reflects the fact that in some cases we have definite information on vital status at a given date, but no definite information on non-fatal events.

The general approach is to determine the latest contact date for each subject at which relevant event information was collected.

2. ALGORITHMS

2.1 Basic algorithm

The same basic algorithm is used to derive the fatal and non fatal censoring dates, and consists of:

1. Determine the dates of all contact events for a subject at which relevant event data was obtained. If a date was only partial (i.e. only a month and year without a day), the date used was the first of the recorded month.
2. If the subject was recorded as withdrawing consent, disregard any date after the withdrawal of consent.
3. If the subject had a confirmed death, disregard any date after the date of death (interpreted as a data error).
4. Disregard any date after 31 August 2010. This was the last date of study data collection therefore any event with a later date is interpreted as an error.
5. The censoring date is the latest remaining date for the subject

2.2 Non-fatal censoring date

Contact events for non-fatal censoring date were:

	Event	***Derivation***
2.2.1	Randomization date	DSSTDTC where DSDECOD='RANDOMIZED'
2.2.2	Valid, non-fatal serious adverse event prior to final follow up visit	AESTDTC where (AECAT='SAE' *OR* 'BLOODS') *AND*: • AESTDTC <= final follow up SVSTDTC, defined as SV record with SUPPSV.QNAM='FINAL' *AND* SUPPSV.QVAL='Y' (if one exists) *AND* ◦ SUPPAE.QVAL='N' for corresponding supplemental qualifier with SUPPAE.QNAM='DTHCAUSE' (if one exists) *OR* ◦ Any corresponding record exists in SUPPAE with QNAM='SUBCODE'[1]
2.2.3	Clinic visit by subject in person or by telephone to subject at or prior to final follow up visit	SVENDTC where: • (SUPPSV.QVAL='Y' for supplemental qualifier with SUPPAE.QNAM='WITHYOU') *OR* (SUPPSV.QVAL='Telephone to patient' for supplemental qualifier with

1 The reason for this condition is that subsidiary codes are treated as independent events in the analysis and are always non-fatal. There is one case where the subsidiary code matches the primary code, this is an error and this subsidiary code is not taken into account in the calculation of the non-fatal censoring date

		SUPPAE.QNAM='HOWCOND') *AND* • SVSTDTC <= final follow up SVSTDTC, defined as SV record with supplemental qualifier SUPPSV.QNAM='FINAL' AND SUPPSV.QVAL='Y' (if one exists)
2.2.4	Withdrawal of consent	DSSTDTC when DSTERM='WITHDREW CONSENT'
2.2.5	Last event information date from final follow up visit	DSSTDTC when DSDECOD='LAST EVENT INFORMATION'

2.3 Fatal censoring date

Contact events for fatal censoring date were:

	Event	***Derivation***
2.3.1	Any contact event for non-fatal censoring	See above
2.3.2	Valid, non-fatal serious adverse event after final follow up visit[2]	AESTDTC where (AECAT='SAE' *OR* 'BLOODS') *AND*: • SUPPAE.QVAL='N' for corresponding supplemental qualifier with SUPPAE.QNAM='DTHCAUSE' (if one exists) *AND* • AESTDTC > final follow up SVSTDTC defined as SV record with SUPPSV.QNAM='FINAL' and SUPPSV.QVAL='Y'
2.3.3	Valid, fatal serious adverse event	AEENDTC where (AECAT='SAE' *OR* 'BLOODS') *AND*: • SUPPAE.QVAL='Y' for corresponding supplemental qualifier with SUPPAE.QNAM='DTHCAUSE'
2.3.4	Clinic visit by subject in person or by telephone to subject after final follow up visit[2]	SVENDTC where: • (SUPPSV.QVAL='Y' for supplemental qualifier with SUPPSV.QNAM='WITHYOU') *OR* (SUPPSV.QVAL='Telephone to patient' for supplemental qualifier with SUPPSV.QNAM='HOWCOND') *AND* • SVSTDTC > final follow up SVSTDTC for SV record with supplemental qualifier SUPPSV.QNAM='FINAL' AND SUPPSV.QVAL='Y' (if one exists)
2.3.5	Date last known to be alive from final follow up visit	DSSTDTC when DSDECOD='LAST KNOWN TO BE ALIVE'
2.3.6	For living UK subjects only, date of last death record update from central registry.[3]	31/08/10 when DM.COUNTRY='GBR'

2 Not relevant to non-fatal censoring because clinic visits and AE recording after final follow up only occurred in a small number of cases generally in response to a specific adverse reaction or abnormal laboratory results, therefore any event information obtained was not necessarily complete.

3 This data covered vital status for all UK patients

Table 7 Baseline characteristics of randomized patients (Arm 2+3b vs. Arm 1+3a) (Quoted from CSR).

Baseline Characteristic	Ezetimibe/simvastatin 10/20 mg (N=4650) n (%)	Placebo (N=4620) n (%)
Prior vascular disease*		
Coronary disease	169 (4%)	142 (3%)
Peripheral arterial disease	304 (7%)	300 (6%)
Cerebrovascular disease	337 (7%)	314 (7%)
At least one of the above 3 conditions	711 (15%)	682 (15%)
None	3939 (85%)	3938 (85%)
Diabetes*		
No	3596 (77%)	3580 (77%)
Yes	1054 (23%)	1040 (23%)
Gender		
Male	2915 (63%)	2885 (62%)
Female	1735 (37%)	1735 (38%)
Age at randomization (years)*	62 ± 12	62 ± 12
40-49	968 (21%)	908 (20%)
50-59	1161 (25%)	1149 (25%)
60-69	1226 (26%)	1246 (27%)
70+	1295 (28%)	1317 (29%)
Current smoker		
No	4024 (87%)	4012 (87%)
Yes	626 (13%)	608 (13%)
Diastolic BP (mmHg)*	79 ± 13	79 ± 13
<80	2279 (49%)	2339 (51%)
≥80 <90	1385 (30%)	1309 (28%)
≥90 <100	710 (15%)	701 (15%)
≥100	267 (6%)	256 (6%)
Systolic BP (mmHg)*	139 ± 22	139 ± 22
<140	2431 (52%)	2414 (52%)
≥140 <160	1384 (30%)	1387 (30%)
≥160 <180	626 (13%)	614 (13%)
≥180	203 (4%)	198 (4%)

Baseline Characteristic	Ezetimibe/simvastatin 10/20 mg (N=4650)	Placebo (N=4620)
	n (%)	n (%)
Total cholesterol (mmol/L)	4.88 ± 1.20	4.90 ± 1.17
<4.5	1754 (38%)	1680 (36%)
≥4.5 <5.5	1523 (33%)	1526 (33%)
≥5.5	1186 (26%)	1224 (26%)
Not available	187 (4%)	190 (4%)
LDL cholesterol (mmol/L)	2.77 ± 0.88	2.78 ± 0.87
<2.5	1776 (38%)	1707 (37%)
≥2.5 <3.0	1059 (23%)	1037 (22%)
≥3.0	1627 (35%)	1686 (36%)
Not available	188 (4%)	190 (4%)
HDL cholesterol (mmol/L)	1.12 ± 0.35	1.11 ± 0.34
<1.0	1816 (39%)	1864 (40%)
≥1.0 <1.2	1084 (23%)	1089 (24%)
≥1.2	1559 (34%)	1477 (32%)
Not available	191 (4%)	190 (4%)
Non-HDL cholesterol (mmol/L)	3.75 ± 1.12	3.79 ± 1.11
<3.0	1103 (24%)	1071 (23%)
≥3.0 <4.0	1677 (36%)	1617 (35%)
≥4.0	1679 (36%)	1742 (38%)
Not available	191 (4%)	190 (4%)
Triglycerides (mmol/L)	2.31 ± 1.76	2.34 ± 1.68
<1.5	1489 (32%)	1440 (31%)
≥1.5 <2.0	899 (19%)	914 (20%)
≥2.0	2074 (45%)	2075 (45%)
Not available	188 (4%)	191 (4%)
Apolipoprotein B (mg/dL)	95.91 ± 25.98	96.67 ± 25.53
<80	1243 (27%)	1162 (25%)
≥80 <100	1419 (31%)	1400 (30%)
≥100	1805 (39%)	1873 (41%)
Not available	183 (4%)	185 (4%)
Apolipoprotein A1 (mg/dL)	134.51 ± 29.02	133.38 ± 28.46
<120	1497 (32%)	1562 (34%)
≥120 <140	1332 (29%)	1289 (28%)
≥140	1642 (35%)	1585 (34%)
Not available	179 (4%)	184 (4%)

Baseline Characteristic	Ezetimibe/simvastatin 10/20 mg (N=4650)	Placebo (N=4620)
	n (%)	n (%)
Body mass index (kg/m²)*	27.1 ± 5.7	27.1 ± 5.6
<24	1385 (30%)	1338 (29%)
≥24 <28	1523 (33%)	1533 (33%)
≥28	1646 (35%)	1652 (36%)
Not available	96 (2%)	97 (2%)
Waist circumference (cm)*	97 ± 15	97 ± 15
<90	1442 (31%)	1328 (29%)
≥90 <100	1261 (27%)	1272 (28%)
≥100	1712 (37%)	1790 (39%)
Not available	235 (5%)	230 (5%)
Hemoglobin (g/dL)	12.3 ± 1.7	12.3 ± 1.7
<12	1668 (36%)	1588 (34%)
≥12 <13	958 (21%)	979 (21%)
≥13	1264 (27%)	1315 (28%)
Not available	760 (16%)	738 (16%)
Plasma albumin (g/L)	39.9 ± 4.6	39.8 ± 4.7
<40	1537 (33%)	1549 (34%)
≥40 <43	960 (21%)	937 (20%)
≥43	937 (20%)	932 (20%)
Not available	1216 (26%)	1202 (26%)
Phosphate (mmol/L)	1.43 ± 0.47	1.42 ± 0.48
<1.2	1342 (29%)	1359 (29%)
≥1.2 <1.5	1084 (23%)	1146 (25%)
≥1.5	1390 (30%)	1293 (28%)
Not available	834 (18%)	822 (18%)
Co-medication*		
Antiplatelet therapy	1056 (23%)	1049 (23%)
Oral anticoagulant therapy	156 (3%)	165 (4%)
ACE inhibitor or ARB	2531 (54%)	2499 (54%)
Beta blocker	1716 (37%)	1798 (39%)
Calcium channel blocker	1968 (42%)	1873 (41%)
Diuretic	1942 (42%)	1890 (41%)
Erythropoiesis stimulating agent	1293 (28%)	1218 (26%)
Sevelamer	385 (8%)	358 (8%)

* Variables updated at 1 year for patients originally allocated simvastatin only who were re-randomized to ezetimibe/simvastatin or placebo.
Conversion factors for mmol/L to mg/dL are 38.7 for cholesterol and 88.6 for triglycerides

Table 8 Compliance with ezetimibe/simvastatin or placebo by visit (Arm 2+3b vs. Arm 1+3a) (quoted from CSR).

Months Since Randomization	Ezetimibe/simvastatin 10/20 mg		Placebo	
	n/N	(%)	n/N	(%)
0 - 7	3737 /4614	(81%)	3770 /4583	(82%)
8 - 13	3334 /4435	(75%)	3344 /4396	(76%)
14 - 19	3063 /4322	(71%)	3079 /4284	(72%)
20 - 25	2859 /4188	(68%)	2785 /4153	(67%)
26 - 31	2659 /4058	(66%)	2570 /4014	(64%)
32 - 37	2484 /3903	(64%)	2391 /3893	(61%)
38 - 43	2283 /3701	(62%)	2180 /3698	(59%)
44 - 49	2096 /3512	(60%)	1982 /3525	(56%)
50 - 55	1486 /2597	(57%)	1419 /2629	(54%)
56 - 61	1052 /1911	(55%)	951 /1925	(49%)
62 - 67	676 /1236	(55%)	601 /1264	(48%)
68 - 73	334 /602	(55%)	273 /595	(46%)
74 - 85	81 /154	(53%)	66 /154	(43%)

Table 9 Compliance with ezetimibe/simvastatin or placebo at 2.5 years by renal function (Arm 2+3b vs. Arm 1+3a) (quoted from CSR).

Baseline Characteristic	Ezetimibe/simvastatin 10/20 mg		Placebo	
	n/N	(%)	n/N	(%)
Not on dialysis				
MDRD estimated GFR (ml/min/1.73m²)				
≥60	29 /38	(76%)	27 /39	(69%)
≥30 <60	724 /1011	(72%)	671 /977	(69%)
≥15 <30	825 /1133	(73%)	822 /1173	(70%)
<15	304 /498	(61%)	319 /503	(63%)
Not available	52 /101	(51%)	45 /88	(51%)
Cystatin C (mg/L)				
<2.0	692 /955	(72%)	685 /970	(71%)
≥2.0 <3.0	738 /1021	(72%)	700 /1032	(68%)
≥3.0	454 /706	(64%)	453 /689	(66%)
Not available	50 /99	(51%)	46 /89	(52%)
Urinary albumin:creatinine ratio				
Normoalbuminuria	385 /502	(77%)	373 /531	(70%)
Microalbuminuria	643 /943	(68%)	674 /971	(69%)
Macroalbuminuria	726 /1037	(70%)	666 /987	(67%)
Not available	180 /299	(60%)	171 /291	(59%)
Subtotal: Not on dialysis	1934 /2781	(70%)	1884 /2780	(68%)
On dialysis				
Dialysis				
Hemodialysis	621 /1056	(59%)	590 /1028	(57%)
Peritoneal dialysis	104 /221	(47%)	96 /206	(47%)
Subtotal: On dialysis	725 /1277	(57%)	686 /1234	(56%)
All patients	2659 /4058	(66%)	2570 /4014	(64%)

Table 10 LDL-C level (mean ± SD) at follow-up visit in all randomized patients (Arm 2+3b vs. Arm 1+3a) (quoted from CSR).

Time From Final Randomization (Months)	Ezetimibe/ simvastatin 10/20 mg	Placebo	Absolute Difference	Percentage Difference	p-Value
0	n=4462 2.77 ± 0.01	n=4430 2.78 ± 0.01	-0.01 ± 0.02	0%	0.49
12	n=391 1.70 ± 0.04	n=365 2.80 ± 0.05	-1.09 ± 0.06	-39%	<0.0001
18	n=399 1.75 ± 0.04	n=384 2.62 ± 0.05	-0.87 ± 0.06	-33%	<0.0001
30	n=3473 1.80 ± 0.02	n=3452 2.65 ± 0.01	-0.85 ± 0.02	-32%	<0.0001
48	n=385 1.94 ± 0.05	n=407 2.72 ± 0.04	-0.78 ± 0.06	-29%	<0.0001

Timings relate to final randomization to ezetimibe/simvastatin or placebo. Patients with missing values at randomization were not included in this analysis. Patients with missing values at the follow-up visit were assigned their value at randomization. Conversion factor for mmol/L to mg/dL for cholesterol is 38.7.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Dongmei Liu, Ph.D.
Date: Sep. 28, 2011

Statistical Team Leader: Jon Todd Sahlroot, Ph.D.

Draft Discussion Points and Voting Question

In the SHARP trial, after a median follow-up of 4.9 years, 639 (15.2%) of 4193 Vytorin (10 mg ezetimibe/20 mg simvastatin)-treated patients and 749 (17.9%) of 4191 placebo-treated patients had a major vascular event, defined as cardiac death, myocardial infarction, any stroke, or revascularization (excluding dialysis access-related procedures); RR 0.84, 95% confidence interval (0.75, 0.93), log-rank p=0.001.

The risk ratios for the individual components of the primary composite endpoint are shown in the following table.

	Vytorin 10/20 N=4193	Placebo N=4191	Risk Ratio (95% CI)	p-value
MVE	639 (15.2%)	749 (17.9%)	0.84 (0.75, 0.93)	0.001
Cardiac death	235 (5.6%)	249 (5.9%)	0.94 (0.79, 1.13)	0.51
Non-fatal MI	128 (3.1%)	147 (3.5%)	0.86 (0.68, 1.10)	0.22
Any Stroke	148 (3.5%)	192 (4.6%)	0.77 (0.62, 0.95)	0.02
Revascularization	261 (6.2%)	327 (7.8%)	0.79 (0.67, 0.92)	0.004

In a subgroup analysis by baseline dialysis status, the risk ratio for MVE in the Vytorin 10/20 group versus the placebo group was 0.77 (0.67, 0.88) in pre-dialysis patients, and the risk ratio in the Vytorin 10/20 group versus the placebo group was 0.94 (0.80, 1.11) in dialysis patients. The interaction p-value was 0.07.

1. Provide your interpretation of:

   a. the primary efficacy result for MVE
   b. the treatment effects for the individual components of the MVE endpoint
   c. the pre-dialysis versus dialysis subgroup result for MVE

2. Discuss whether you believe that the lack of lipid inclusion criteria in SHARP (e.g., LDL-C) was appropriate.

The standard accepted definition of chronic kidney disease, according to National Kidney Foundation guidelines, is evidence of kidney damage (including proteinuria) or GFR <60 mL/min/1.73m^2 for >= 3 months. The inclusion criteria for SHARP were age > 40 years and a) pre-dialysis: plasma or serum creatinine $\geq$ 150 umol/L ($\geq$ 1.7 mg/dL in men or $\geq$ 130 umol/L ($\geq$ 1.5 mg/dl in women, as measured at the most recent routine clinic visit AND at the SHARP screening visit or b) on dialysis (hemo or peritoneal).

3. Discuss whether you believe that the criteria used for enrollment of pre-dialysis patients provided an appropriate study population to generalize the results from SHARP to the real-world population of all patients with pre-dialysis chronic kidney disease.

4. Provide your interpretation of the safety data from the SHARP trial, in particular, the findings related to muscle, liver, and cancer.

5. Do the available efficacy and safety data provide substantial evidence to support approval of Vytorin 10/20 mg for the prevention of major vascular events in patients with:

a. pre-dialysis chronic kidney disease?
b. end-stage renal disease receiving dialysis?

Vote (yes/no) and provide your rationale