CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-766/S077

Trade Name: Zocor

Generic Name: simvastatin

Sponsor: Merck Sharp & Dohme Corp.

Approval Date: June 8, 2011

Purpose: Provides clinical trial data from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Trial showing an increased risk of myopathy, including rhabdomyolysis, in patients treated with 80 mg of simvastatin versus those treated with 20 mg.

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 19766/S-077 and S-082

SUPPLEMENT APPROVAL

Merck Sharp & Dohme Corp.
Attention: Carl Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Sparrow:

Please refer to your supplemental new drug applications dated June 12, 2009, received June 12, 2009 (S-077); and dated March 30, 2011, received March 30, 2011 (S-082), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ZOCOR (simvastatin) Tablets 10 mg, 20 mg, 40 mg, and 80 mg.

We acknowledge receipt of your amendments for S-077 dated December 9, 2009, and February 12, and October 8, 2010, and January 21, February 3, 18 and 25, March 29, April 4, May 6, 11, and June 3 (2), 2011. For supplement, S-082, we acknowledge receipt of your amendments dated April 22, May 11, 19, and June 3 (2), 2011.

We also refer to our letter dated February 28, 2011, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for ZOCOR (simvastatin). This information pertains to the risk of myopathy, including rhabdomyolysis, in patients treated with 80 mg of simvastatin based on new safety information about this risk identified since the product was approved. We also refer to our letter dated May 18, 2011 detailing the methodology and the need to submit prescription volume reports by 8 months, 14 months, 20 months, and 26 months from the date of approval of these supplements.

Supplemental new drug application, S-077, provides clinical trial data from the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Trial showing an increased risk of myopathy, including rhabdomyolysis, in patients treated with 80 mg of simvastatin versus those treated with 20 mg. Supplemental new drug application, S-082, provides for revisions to the **DOSAGE AND ADMINISTRATION**, **CONTRAINDICATIONS**, **WARNINGS AND PRECAUTIONS**, **ADVERSE REACTIONS**, **DRUG INTERACTIONS**, **USE IN SPECIFIC POPULATIONS**, and **CLINICAL PHARMACOLOGY** sections of the ZOCOR (simvastatin) package insert. The agreed upon changes to the labeling revisions required in our February 28, 2011 are attached in Appendix A (additions are noted by underline and deletions are noted by ~~strikethrough)~~.

Supplemental new drug application, S-082, was a response to our February 28, 2011 safety labeling change notification letter.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We request that the labeling approved with this letter be available on your website within 10 days of receipt of this letter.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Margaret Simoneau, M.S., RPh., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):
Appendix A: Agreed upon changes to labeling revisions
Content of Labeling

23 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC C COLMAN
06/08/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZOCOR safely and effectively. See full prescribing information for ZOCOR.

ZOCOR (simvastatin) Tablets

Initial U.S. Approval: 1991

---------- RECENT MAJOR CHANGES ----------

Dosage and Administration	
Recommended Dosing (2.1)	06/2011
Restricted Dosing for 80 mg (2.2)	06/2011
Coadministration with Other Drugs (2.3)	06/2011
Patients with Homozygous Familial Hypercholesterolemia (2.4)	06/2011
Chinese Patients Taking Lipid-Modifying Doses (≥1 g/day Niacin) of Niacin-Containing Products (2.7)	06/2011
Contraindications (4)	06/2011
Warnings and Precautions	
Myopathy/Rhabdomyolysis (5.1)	06/2011
Liver Dysfunction (5.2)	06/2011

---------- INDICATIONS AND USAGE ----------

ZOCOR® is an HMG-CoA reductase inhibitor (statin) indicated as an adjunctive therapy to diet to:

- Reduce the risk of total mortality by reducing CHD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events. (1.1)
- Reduce elevated total-C, LDL-C, Apo B, TG and increase HDL-C in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia. (1.2)
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and VLDL-C in patients with primary dysbeta-lipoproteinemia. (1.2)
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia. (1.2)
- Reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy. (1.2, 1.3)

Limitations of Use
ZOCOR has not been studied in Fredrickson Types I and V dyslipidemias. (1.4)

---------- DOSAGE AND ADMINISTRATION ----------

- Dose range is 5 to 40 mg/day. (2.1)
- Recommended usual starting dose is 10 or 20 mg once a day in the evening. (2.1)
- Recommended starting dose for patients at high risk of CHD is 40 mg/day. (2.1)
- Due to the increased risk of myopathy, including rhabdomyolysis, use of the 80-mg dose of ZOCOR should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity. (2.2)
- Patients who are currently tolerating the 80-mg dose of ZOCOR who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for the drug-drug interaction. (2.2)
- Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 80-mg dose of ZOCOR, patients unable to achieve their LDL-C goal utilizing the 40-mg dose of ZOCOR should not be titrated to the 80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering. (2.2)
- Adolescents (10-17 years of age) with HeFH: starting dose is 10 mg/day; maximum recommended dose is 40 mg/day. (2.5)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 5 mg; 10 mg; 20 mg; 40 mg; 80 mg (3)

---------- CONTRAINDICATIONS ----------

- Concomitant administration of strong CYP3A4 inhibitors. (4, 5.1)
- Concomitant administration of gemfibrozil, cyclosporine, or danazol. (4, 5.1)
- Hypersensitivity to any component of this medication. (4, 6.2)
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels. (4, 5.2)
- Women who are pregnant or may become pregnant. (4, 8.1)
- Nursing mothers. (4, 8.3)

---------- WARNINGS AND PRECAUTIONS ----------

- **Patients should be advised of the increased risk of myopathy including rhabdomyolysis with the 80-mg dose. (5.1)**
- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥65), female gender, uncontrolled hypothyroidism, and renal impairment. (4, 5.1, 8.5, 8.6)
- Patients should be advised to report promptly any symptoms of myopathy. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. See Drug Interaction table. (5.1)
- Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminase can occur. Monitor liver enzymes before and during treatment. (5.2)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥5.0%) are: upper respiratory infection, headache, abdominal pain, constipation, and nausea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis (2.3, 4, 5.1, 7.1, 7.2, 7.3, 12.3)

Interacting Agents	Prescribing Recommendations
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol	Contraindicated with simvastatin
Amiodarone, verapamil, diltiazem	Do not exceed 10 mg simvastatin daily
Amlodipine, ranolazine	Do not exceed 20 mg simvastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

- Coumarin anticoagulants: Concomitant use with ZOCOR prolongs INR. Achieve stable INR prior to starting ZOCOR. Monitor INR frequently until stable upon initiation or alteration of ZOCOR therapy. (7.6)

---------- USE IN SPECIFIC POPULATIONS ----------

- Severe renal impairment: patients should be started at 5 mg/day and be closely monitored. (2.6, 8.6)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2011

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with coronary heart disease (CHD) or at high risk of CHD, ZOCOR[1] can be started simultaneously with diet.

1.1 Reductions in Risk of CHD Mortality and Cardiovascular Events

In patients at high risk of coronary events because of existing coronary heart disease, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, ZOCOR is indicated to:

- Reduce the risk of total mortality by reducing CHD deaths.
- Reduce the risk of non-fatal myocardial infarction and stroke.
- Reduce the need for coronary and non-coronary revascularization procedures.

1.2 Hyperlipidemia

ZOCOR is indicated to:

- Reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia (Fredrickson type IIa, heterozygous familial and nonfamilial) or mixed dyslipidemia (Fredrickson type IIb).
- Reduce elevated TG in patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia).
- Reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia (Fredrickson type III hyperlipidemia).
- Reduce 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.

[1] Registered trademark of Merck Sharp & Dohme Corp., a subsidiary of **Merck & Co., Inc.**
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Reference ID: 2957153

1.3 Adolescent Patients with Heterozygous Familial Hypercholesterolemia (HeFH)

ZOCOR is indicated as an adjunct to diet to reduce total-C, LDL-C, and Apo B levels in adolescent boys and girls who are at least one year post-menarche, 10-17 years of age, with HeFH, if after an adequate trial of diet therapy the following findings are present:

1. LDL cholesterol remains ≥190 mg/dL; or
2. LDL cholesterol remains ≥160 mg/dL and

- There is a positive family history of premature cardiovascular disease (CVD) or
- Two or more other CVD risk factors are present in the adolescent patient.

The minimum goal of treatment in pediatric and adolescent patients is to achieve a mean LDL-C <130 mg/dL. The optimal age at which to initiate lipid-lowering therapy to decrease the risk of symptomatic adulthood CAD has not been determined.

1.4 Limitations of Use

ZOCOR has not been studied in conditions where the major abnormality is elevation of chylomicrons (i.e., hyperlipidemia Fredrickson types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

The usual dosage range is 5 to 40 mg/day. In patients with CHD or at high risk of CHD, ZOCOR can be started simultaneously with diet. The recommended usual starting dose is 10 or 20 mg once a day in the evening. For patients at high risk for a CHD event due to existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day. Lipid determinations should be performed after 4 weeks of therapy and periodically thereafter.

2.2 Restricted Dosing for 80 mg

Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80-mg dose of ZOCOR should be restricted to patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity *[see Warnings and Precautions (5.1)].*

Patients who are currently tolerating the 80-mg dose of ZOCOR who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for the drug-drug interaction.

Due to the increased risk of myopathy, including rhabdomyolysis, associated with the 80-mg dose of ZOCOR, patients unable to achieve their LDL-C goal utilizing the 40-mg dose of ZOCOR should not be titrated to the 80-mg dose, but should be placed on alternative LDL-C-lowering treatment(s) that provides greater LDL-C lowering.

2.3 Coadministration with Other Drugs

Patients taking Amiodarone, Verapamil, or Diltiazem

- The dose of ZOCOR should not exceed 10 mg/day *[see Warnings and Precautions (5.1), Drug Interactions (7.3), and Clinical Pharmacology (12.3)].*

Patients taking Amlodipine or Ranolazine

- The dose of ZOCOR should not exceed 20 mg/day *[see Warnings and Precautions (5.1), Drug Interactions (7.3), and Clinical Pharmacology (12.3)].*

2.4 Patients with Homozygous Familial Hypercholesterolemia

The recommended dosage is 40 mg/day in the evening *[see Dosage and Administration, Restricted Dosing for 80 mg (2.2)]*. ZOCOR should be used as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) in these patients or if such treatments are unavailable.

2.5 Adolescents (10-17 years of age) with Heterozygous Familial Hypercholesterolemia

The recommended usual starting dose is 10 mg once a day in the evening. The recommended dosing range is 10 to 40 mg/day; the maximum recommended dose is 40 mg/day. Doses should be

individualized according to the recommended goal of therapy [see NCEP Pediatric Panel Guidelines[2] and *Clinical Studies (14.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.6 Patients with Renal Impairment

Because ZOCOR does not undergo significant renal excretion, modification of dosage should not be necessary in patients with mild to moderate renal impairment. However, caution should be exercised when ZOCOR is administered to patients with severe renal impairment; such patients should be started at 5 mg/day and be closely monitored *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

2.7 Chinese Patients Taking Lipid-Modifying Doses (≥1 g/day Niacin) of Niacin-Containing Products

Because of an increased risk for myopathy in Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products, caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. The cause of the increased risk of myopathy is not known. It is also unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients. *[See Warnings and Precautions (5.1).]*

3 DOSAGE FORMS AND STRENGTHS

- Tablets ZOCOR 5 mg are buff, oval, film-coated tablets, coded MSD 726 on one side and ZOCOR 5 on the other.
- Tablets ZOCOR 10 mg are peach, oval, film-coated tablets, coded MSD 735 on one side and plain on the other.
- Tablets ZOCOR 20 mg are tan, oval, film-coated tablets, coded MSD 740 on one side and plain on the other.
- Tablets ZOCOR 40 mg are brick red, oval, film-coated tablets, coded MSD 749 on one side and plain on the other.
- Tablets ZOCOR 80 mg are brick red, capsule-shaped, film-coated tablets, coded 543 on one side and 80 on the other.

4 CONTRAINDICATIONS

ZOCOR is contraindicated in the following conditions:

- Concomitant administration of strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, HIV protease inhibitors, erythromycin, clarithromycin, telithromycin and nefazodone) *[see Warnings and Precautions (5.1)].*
- Concomitant administration of gemfibrozil, cyclosporine, or danazol *[see Warnings and Precautions (5.1)].*
- Hypersensitivity to any component of this medication *[see Adverse Reactions (6.2)]*.
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels *[see Warnings and Precautions (5.2)]*.
- Women who are pregnant or may become pregnant. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because HMG-CoA reductase inhibitors (statins) decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, ZOCOR may cause fetal harm when administered to a pregnant woman. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome

[2] National Cholesterol Education Program (NCEP): Highlights of the Report of the Expert Panel on Blood Cholesterol Levels in Children and Adolescents. *Pediatrics*. 89(3):495-501. 1992.

Reference ID: 2957153

of long-term therapy of primary hypercholesterolemia. There are no adequate and well-controlled studies of use with ZOCOR during pregnancy; however, in rare reports congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal reproduction studies, simvastatin revealed no evidence of teratogenicity. **ZOCOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, ZOCOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

- Nursing mothers. It is not known whether simvastatin is excreted into human milk; however, a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who require treatment with ZOCOR should not breastfeed their infants *[see Use in Specific Populations (8.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Myopathy/Rhabdomyolysis

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy is increased by high levels of statin activity in plasma. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment.

The risk of myopathy, including rhabdomyolysis, is dose related. In a clinical trial database in which 41,413 patients were treated with ZOCOR, 24,747 (approximately 60%) of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03% and 0.08% at 20 and 40 mg/day, respectively. The incidence of myopathy with 80 mg (0.61%) was disproportionately higher than that observed at the lower doses. In these trials, patients were carefully monitored and some interacting medicinal products were excluded.

In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with ZOCOR (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

The risk of myopathy, including rhabdomyolysis, is greater in patients on simvastatin 80 mg compared with other statin therapies with similar or greater LDL-C-lowering efficacy and compared with lower doses of simvastatin. Therefore, the 80-mg dose of ZOCOR should be used only in patients who have been taking simvastatin 80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity *[see Dosage and Administration, Restricted Dosing for 80 mg (2.2)]*. If, however, a patient who is currently tolerating the 80-mg dose of ZOCOR needs to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin, that patient should be switched to an alternative statin with less potential for the drug-drug interaction. Patients should be advised of the increased risk of myopathy, including rhabdomyolysis, and to report promptly any unexplained muscle pain, tenderness or weakness. If symptoms occur, treatment should be discontinued immediately. *[See Warnings and Precautions (5.2).]*

All patients starting therapy with simvastatin, or whose dose of simvastatin is being increased, should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. Simvastatin therapy should be discontinued immediately if myopathy is diagnosed or suspected. In most cases, muscle symptoms and CK increases resolved when treatment was promptly discontinued. Periodic CK determinations may

be considered in patients starting therapy with simvastatin or whose dose is being increased, but there is no assurance that such monitoring will prevent myopathy.

Many of the patients who have developed rhabdomyolysis on therapy with simvastatin have had complicated medical histories, including renal insufficiency usually as a consequence of long-standing diabetes mellitus. Such patients merit closer monitoring. Therapy with simvastatin should be temporarily stopped a few days prior to elective major surgery and when any major medical or surgical condition supervenes.

Drug Interactions

The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, and posaconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, the antidepressant nefazodone, or large quantities of grapefruit juice (>1 quart daily). Combination of these drugs with simvastatin is contraindicated. If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment. *[See Contraindications (4) and Drug Interactions (7.1).] In vitro* studies have demonstrated a potential for voriconazole to inhibit the metabolism of simvastatin. Adjustment of the simvastatin dose may be needed to reduce the risk of myopathy, including rhabdomyolysis, if voriconazole must be used concomitantly with simvastatin. *[See Drug Interactions (7.1).]*

The combined use of simvastatin with gemfibrozil, cyclosporine, or danazol is contraindicated *[see Contraindications (4) and Drug Interactions (7.1 and 7.2)].*

Caution should be used when prescribing other fibrates with simvastatin, as these agents can cause myopathy when given alone and the risk is increased when they are co-administered *[see Drug Interactions (7.2)]*.

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine *[see Drug Interactions (7.7)]*.

The benefits of the combined use of simvastatin with the following drugs should be carefully weighed against the potential risks of combinations: other lipid-lowering drugs (other fibrates or ≥1 g/day of niacin), amiodarone, verapamil, diltiazem, amlodipine, or ranolazine *[see Drug Interactions (7.3) and Table 3 in Clinical Pharmacology (12.3)]*.

Cases of myopathy, including rhabdomyolysis, have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In an ongoing, double-blind, randomized cardiovascular outcomes trial, an independent safety monitoring committee identified that the incidence of myopathy is higher in Chinese compared with non-Chinese patients taking simvastatin 40 mg coadministered with lipid-modifying doses of a niacin-containing product. Caution should be used when treating Chinese patients with simvastatin in doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. It is unknown if the risk for myopathy with coadministration of simvastatin with lipid-modifying doses of niacin-containing products observed in Chinese patients applies to other Asian patients *[see Drug Interactions (7.4)]*.

Prescribing recommendations for interacting agents are summarized in Table 1 *[see also Dosage and Administration (2.3), Drug Interactions (7), Clinical Pharmacology (12.3)]*.

TABLE 1
Drug Interactions Associated with Increased
Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone Gemfibrozil Cyclosporine Danazol	Contraindicated with simvastatin
Amiodarone Verapamil Diltiazem	Do not exceed 10 mg simvastatin daily
Amlodipine Ranolazine	Do not exceed 20 mg simvastatin daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

5.2 Liver Dysfunction

Persistent increases (to more than 3X the ULN) in serum transaminases have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity.

In the Scandinavian Simvastatin Survival Study (4S) *[see Clinical Studies (14.1)]*, the number of patients with more than one transaminase elevation to >3X ULN, over the course of the study, was not significantly different between the simvastatin and placebo groups (14 [0.7%] vs. 12 [0.6%]). Elevated transaminases resulted in the discontinuation of 8 patients from therapy in the simvastatin group (n=2,221) and 5 in the placebo group (n=2,223). Of the 1,986 simvastatin treated patients in 4S with normal liver function tests (LFTs) at baseline, 8 (0.4%) developed consecutive LFT elevations to >3X ULN and/or were discontinued due to transaminase elevations during the 5.4 years (median follow-up) of the study. Among these 8 patients, 5 initially developed these abnormalities within the first year. All of the patients in this study received a starting dose of 20 mg of simvastatin; 37% were titrated to 40 mg.

In 2 controlled clinical studies in 1,105 patients, the 12-month incidence of persistent hepatic transaminase elevation without regard to drug relationship was 0.9% and 2.1% at the 40- and 80-mg dose, respectively. No patients developed persistent liver function abnormalities following the initial 6 months of treatment at a given dose.

It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3X ULN or greater persist, withdrawal of therapy with ZOCOR is recommended. Note that ALT may emanate from muscle, therefore ALT rising with CK may indicate myopathy *[see Warnings and Precautions (5.1)].*

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver diseases or unexplained transaminase elevations are contraindications to the use of simvastatin.

As with other lipid-lowering agents, moderate (less than 3X ULN) elevations of serum transaminases have been reported following therapy with simvastatin. These changes appeared soon after initiation of therapy with simvastatin, were often transient, were not accompanied by any symptoms and did not require interruption of treatment.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

In the pre-marketing controlled clinical studies and their open extensions (2,423 patients with median duration of follow-up of approximately 18 months), 1.4% of patients were discontinued due to adverse reactions. The most common adverse reactions that led to treatment discontinuation were: gastrointestinal disorders (0.5%), myalgia (0.1%), and arthralgia (0.1%). The most commonly reported adverse reactions (incidence ≥5%) in simvastatin controlled clinical trials were: upper respiratory infections (9.0%), headache (7.4%), abdominal pain (7.3%), constipation (6.6%), and nausea (5.4%).

Scandinavian Simvastatin Survival Study

In 4S involving 4,444 (age range 35-71 years, 19% women, 100% Caucasians) treated with 20-40 mg/day of ZOCOR (n=2,221) or placebo (n=2,223) over a median of 5.4 years, adverse reactions reported in ≥2% of patients and at a rate greater than placebo are shown in Table 2.

TABLE 2
Adverse Reactions Reported Regardless of Causality by ≥2% of Patients Treated with ZOCOR and Greater than Placebo in 4S

	ZOCOR (N = 2,221) %	Placebo (N = 2,223) %
Body as a Whole		
Edema/swelling	2.7	2.3
Abdominal pain	5 9	5.8
Cardiovascular System Disorders		
Atrial fibrillation	5.7	5.1
Digestive System Disorders		
Constipation	2 2	1.6
Gastritis	4 9	3.9
Endocrine Disorders		
Diabetes mellitus	4 2	3.6
Musculoskeletal Disorders		
Myalgia	3.7	3.2
Nervous System/ Psychiatric Disorders		
Headache	2 5	2.1
Insomnia	4 0	3.8
Vertigo	4 5	4.2
Respiratory System Disorders		
Bronchitis	6.6	6.3
Sinusitis	2 3	1.8
Skin / Skin Appendage Disorders		
Eczema	4 5	3.0
Urogenital System Disorders		
Infection, urinary tract	3 2	3.1

Heart Protection Study

In the Heart Protection Study (HPS), involving 20,536 patients (age range 40-80 years, 25% women, 97% Caucasians, 3% other races) treated with ZOCOR 40 mg/day (n=10,269) or placebo (n=10,267) over a mean of 5 years, only serious adverse reactions and discontinuations due to any adverse reactions were recorded. Discontinuation rates due to adverse reactions were 4.8% in patients treated with ZOCOR compared with 5.1% in patients treated with placebo. The incidence of myopathy/rhabdomyolysis was <0.1% in patients treated with ZOCOR.

Other Clinical Studies

In a clinical trial in which 12,064 patients with a history of myocardial infarction were treated with ZOCOR (mean follow-up 6.7 years), the incidence of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase [CK] >10 times upper limit of normal [ULN]) in patients on 80 mg/day was approximately 0.9% compared with 0.02% for patients on 20 mg/day. The incidence of rhabdomyolysis (defined as myopathy with a CK >40 times ULN) in patients on 80 mg/day was approximately 0.4% compared with 0% for patients on 20 mg/day. The incidence of myopathy, including rhabdomyolysis, was highest during the first year and then notably decreased during the subsequent

years of treatment. In this trial, patients were carefully monitored and some interacting medicinal products were excluded.

Other adverse reactions reported in clinical trials were: diarrhea, rash, dyspepsia, flatulence, and asthenia.

Laboratory Tests

Marked persistent increases of hepatic transaminases have been noted *[see Warnings and Precautions (5.2)]*. Elevated alkaline phosphatase and γ-glutamyl transpeptidase have also been reported. About 5% of patients had elevations of CK levels of 3 or more times the normal value on one or more occasions. This was attributable to the noncardiac fraction of CK. *[See Warnings and Precautions (5.1).]*

Adolescent Patients (ages 10-17 years)

In a 48-week, controlled study in adolescent boys and girls who were at least 1 year post-menarche, 10-17 years of age (43.4% female, 97.7% Caucasians, 1.7% Hispanics, 0.6% Multiracial) with heterozygous familial hypercholesterolemia (n=175), treated with placebo or ZOCOR (10-40 mg daily), the most common adverse reactions observed in both groups were upper respiratory infection, headache, abdominal pain, and nausea *[see Use in Specific Populations (8.4) and Clinical Studies (14.2)]*.

6.2 Post-Marketing Experience

Because the below reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following additional adverse reactions have been identified during postapproval use of simvastatin: pruritus, alopecia, a variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails), dizziness, muscle cramps, myalgia, pancreatitis, memory impairment, paresthesia, peripheral neuropathy, vomiting, anemia, erectile dysfunction, interstitial lung disease, rhabdomyolysis, hepatitis/jaundice, hepatic failure, and depression.

An apparent hypersensitivity syndrome has been reported rarely which has included some of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, dermatomyositis, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inhibitors, cyclosporine, or danazol

Strong CYP3A4 inhibitors: Simvastatin, like several other inhibitors of HMG-CoA reductase, is a substrate of CYP3A4. Simvastatin is metabolized by CYP3A4 but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4.

Elevated plasma levels of HMG-CoA reductase inhibitory activity increases the risk of myopathy and rhabdomyolysis, particularly with higher doses of simvastatin. *[See Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).]* Concomitant use of drugs labeled as having a strong inhibitory effect on CYP3A4 is contraindicated *[see Contraindications (4)].* If treatment with itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin or telithromycin is unavoidable, therapy with simvastatin must be suspended during the course of treatment.

Although not studied clinically, voriconazole has been shown to inhibit lovastatin metabolism *in vitro* (human liver microsomes). Therefore, voriconazole is likely to increase the plasma concentration of simvastatin. It is recommended that dose adjustment of simvastatin be considered during concomitant use of voriconazole and simvastatin to reduce the risk of myopathy, including rhabdomyolysis. *[see Warnings and Precautions (5.1)]*

Cyclosporine or Danazol: The risk of myopathy, including rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol. Therefore, concomitant use of these drugs is contraindicated. *[see Contraindications (4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

7.2 Lipid-Lowering Drugs That Can Cause Myopathy When Given Alone

Gemfibrozil: Contraindicated with simvastatin *[see Contraindications (4) and Warnings and Precautions (5.1)].*

Other fibrates: Caution should be used when prescribing with simvastatin *[see Warnings and Precautions (5.1)].*

7.3 Amiodarone, Ranolazine, or Calcium Channel Blockers

The risk of myopathy, including rhabdomyolysis, is increased by concomitant administration of amiodarone, ranolazine, or calcium channel blockers such as verapamil, diltiazem, or amlodipine *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1), and Table 3 in Clinical Pharmacology (12.3)]*.

7.4 Niacin

Cases of myopathy/rhabdomyolysis have been observed with simvastatin coadministered with lipid-modifying doses (≥1 g/day niacin) of niacin-containing products. In particular, caution should be used when treating Chinese patients with simvastatin doses exceeding 20 mg/day coadministered with lipid-modifying doses of niacin-containing products. Because the risk for myopathy is dose-related, Chinese patients should not receive simvastatin 80 mg coadministered with lipid-modifying doses of niacin-containing products. *[See Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).]*

7.5 Digoxin

In one study, concomitant administration of digoxin with simvastatin resulted in a slight elevation in digoxin concentrations in plasma. Patients taking digoxin should be monitored appropriately when simvastatin is initiated *[see Clinical Pharmacology (12.3)]*.

7.6 Coumarin Anticoagulants

In two clinical studies, one in normal volunteers and the other in hypercholesterolemic patients, simvastatin 20-40 mg/day modestly potentiated the effect of coumarin anticoagulants: the prothrombin time, reported as International Normalized Ratio (INR), increased from a baseline of 1.7 to 1.8 and from 2.6 to 3.4 in the volunteer and patient studies, respectively. With other statins, clinically evident bleeding and/or increased prothrombin time has been reported in a few patients taking coumarin anticoagulants concomitantly. In such patients, prothrombin time should be determined before starting simvastatin and frequently enough during early therapy to ensure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of simvastatin is changed or discontinued, the same procedure should be repeated. Simvastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

7.7 Colchicine

Cases of myopathy, including rhabdomyolysis, have been reported with simvastatin coadministered with colchicine, and caution should be exercised when prescribing simvastatin with colchicine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X [See Contraindications (4).]

ZOCOR is contraindicated in women who are or may become pregnant. Lipid lowering drugs offer no benefit during pregnancy, because cholesterol and cholesterol derivatives are needed for normal fetal development. Atherosclerosis is a chronic process, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholesterolemia therapy. There are no adequate and well-controlled studies of use with ZOCOR during pregnancy; however, there are rare reports of congenital anomalies in infants exposed to statins *in utero*. Animal reproduction studies of simvastatin in rats and rabbits showed no evidence of teratogenicity. Serum cholesterol and triglycerides increase during normal pregnancy, and cholesterol or cholesterol derivatives are essential for fetal development. Because statins decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, ZOCOR may cause fetal harm when

administered to a pregnant woman. If ZOCOR is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

There are rare reports of congenital anomalies following intrauterine exposure to statins. In a review[3] of approximately 100 prospectively followed pregnancies in women exposed to simvastatin or another structurally related statin, the incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbirths did not exceed those expected in the general population. However, the study was only able to exclude a 3- to 4-fold increased risk of congenital anomalies over the background rate. In 89% of these cases, drug treatment was initiated prior to pregnancy and was discontinued during the first trimester when pregnancy was identified.

Simvastatin was not teratogenic in rats or rabbits at doses (25, 10 mg/kg/day, respectively) that resulted in 3 times the human exposure based on mg/m^2 surface area. However, in studies with another structurally-related statin, skeletal malformations were observed in rats and mice.

Women of childbearing potential, who require treatment with ZOCOR for a lipid disorder, should be advised to use effective contraception. For women trying to conceive, discontinuation of ZOCOR should be considered. If pregnancy occurs, ZOCOR should be immediately discontinued.

8.3 Nursing Mothers

It is not known whether simvastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women taking simvastatin should not nurse their infants. A decision should be made whether to discontinue nursing or discontinue drug, taking into account the importance of the drug to the mother *[see Contraindications (4)]*.

8.4 Pediatric Use

Safety and effectiveness of simvastatin in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial in adolescent boys and in girls who were at least 1 year post-menarche. Patients treated with simvastatin had an adverse reaction profile similar to that of patients treated with placebo. **Doses greater than 40 mg have not been studied in this population.** In this limited controlled study, there was no significant effect on growth or sexual maturation in the adolescent boys or girls, or on menstrual cycle length in girls. *[See Dosage and Administration (2.5), Adverse Reactions (6.1), Clinical Studies (14.2).]* Adolescent females should be counseled on appropriate contraceptive methods while on simvastatin therapy *[see Contraindications (4) and Use in Specific Populations (8.1)].* Simvastatin has not been studied in patients younger than 10 years of age, nor in pre-menarchal girls.

8.5 Geriatric Use

Of the 2,423 patients who received ZOCOR in Phase III clinical studies and the 10,269 patients in the Heart Protection Study who received ZOCOR, 363 (15%) and 5,366 (52%), respectively were ≥65 years old. In HPS, 615 (6%) were ≥75 years old. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Since advanced age (≥65 years) is a predisposing factor for myopathy, ZOCOR should be prescribed with caution in the elderly. *[See Clinical Pharmacology (12.3).]*

A pharmacokinetic study with simvastatin showed the mean plasma level of statin activity to be approximately 45% higher in elderly patients between 70-78 years of age compared with patients between 18-30 years of age. In 4S, 1,021 (23%) of 4,444 patients were 65 or older. Lipid-lowering efficacy was at least as great in elderly patients compared with younger patients, and ZOCOR significantly reduced total mortality and CHD mortality in elderly patients with a history of CHD. In HPS, 52% of patients were elderly (4,891 patients 65-69 years and 5,806 patients 70 years or older). The relative risk reductions of CHD death, non-fatal MI, coronary and non-coronary revascularization procedures, and stroke were similar in older and younger patients *[see Clinical Studies (14.1)]*. In HPS, among 32,145 patients entering the active run-in period, there were 2 cases of myopathy/rhabdomyolysis; these patients were aged 67 and 73. Of the 7 cases of

[3] Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy, *Reproductive Toxicology*, 10(6):439-446, 1996.

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myopathy/rhabdomyolysis among 10,269 patients allocated to simvastatin, 4 were aged 65 or more (at baseline), of whom one was over 75. There were no overall differences in safety between older and younger patients in either 4S or HPS.

Because advanced age (≥65 years) is a predisposing factor for myopathy, including rhabdomyolysis, ZOCOR should be prescribed with caution in the elderly. In a clinical trial of patients treated with simvastatin 80 mg/day, patients ≥65 years of age had an increased risk of myopathy, including rhabdomyolysis, compared to patients <65 years of age. *[See Warnings and Precautions (5.1) and Clinical Pharmacology (12.3).]*

8.6 Renal Impairment

Caution should be exercised when ZOCOR is administered to patients with severe renal impairment. *[See Dosage and Administration (2.6).]*

8.7 Hepatic Impairment

ZOCOR is contraindicated in patients with active liver disease which may include unexplained persistent elevations in hepatic transaminase levels *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

10 OVERDOSAGE

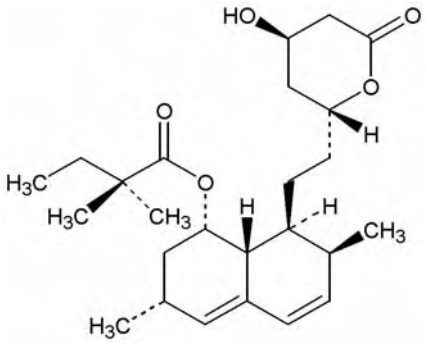
Significant lethality was observed in mice after a single oral dose of 9 g/m^2. No evidence of lethality was observed in rats or dogs treated with doses of 30 and 100 g/m^2, respectively. No specific diagnostic signs were observed in rodents. At these doses the only signs seen in dogs were emesis and mucoid stools.

A few cases of overdosage with ZOCOR have been reported; the maximum dose taken was 3.6 g. All patients recovered without sequelae. Supportive measures should be taken in the event of an overdose. The dialyzability of simvastatin and its metabolites in man is not known at present.

11 DESCRIPTION

ZOCOR (simvastatin) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate-limiting step in the biosynthesis of cholesterol.

Simvastatin is butanoic acid, 2,2-dimethyl-,1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α,3α,7β,8β(2*S**,4*S**),-8aβ]]. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Its structural formula is:



Simvastatin is a white to off-white, nonhygroscopic, crystalline powder that is practically insoluble in water, and freely soluble in chloroform, methanol and ethanol.

Tablets ZOCOR for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg or 80 mg of simvastatin and the following inactive ingredients: ascorbic acid, citric acid, hydroxypropyl cellulose,

hypromellose, iron oxides, lactose, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Butylated hydroxyanisole is added as a preservative.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Simvastatin is a prodrug and is hydrolyzed to its active β-hydroxyacid form, simvastatin acid, after administration. Simvastatin is a specific inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate limiting step in the biosynthetic pathway for cholesterol. In addition, simvastatin reduces VLDL and TG and increases HDL-C.

12.2 Pharmacodynamics

Epidemiological studies have demonstrated that elevated levels of total-C, LDL-C, as well as decreased levels of HDL-C are associated with the development of atherosclerosis and increased cardiovascular risk. Lowering LDL-C decreases this risk. However, the independent effect of raising HDL-C or lowering TG on the risk of coronary and cardiovascular morbidity and mortality has not been determined.

12.3 Pharmacokinetics

Simvastatin is a lactone that is readily hydrolyzed *in vivo* to the corresponding β-hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β-hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of simvastatin.

Following an oral dose of ^{14}C-labeled simvastatin in man, 13% of the dose was excreted in urine and 60% in feces. Plasma concentrations of total radioactivity (simvastatin plus ^{14}C-metabolites) peaked at 4 hours and declined rapidly to about 10% of peak by 12 hours postdose. Since simvastatin undergoes extensive first-pass extraction in the liver, the availability of the drug to the general circulation is low (<5%).

Both simvastatin and its β-hydroxyacid metabolite are highly bound (approximately 95%) to human plasma proteins. Rat studies indicate that when radiolabeled simvastatin was administered, simvastatin-derived radioactivity crossed the blood-brain barrier.

The major active metabolites of simvastatin present in human plasma are the β-hydroxyacid of simvastatin and its 6′-hydroxy, 6′-hydroxymethyl, and 6′-exomethylene derivatives. Peak plasma concentrations of both active and total inhibitors were attained within 1.3 to 2.4 hours postdose. While the recommended therapeutic dose range is 5 to 40 mg/day, there was no substantial deviation from linearity of AUC of inhibitors in the general circulation with an increase in dose to as high as 120 mg. Relative to the fasting state, the plasma profile of inhibitors was not affected when simvastatin was administered immediately before an American Heart Association recommended low-fat meal.

In a study including 16 elderly patients between 70 and 78 years of age who received ZOCOR 40 mg/day, the mean plasma level of HMG-CoA reductase inhibitory activity was increased approximately 45% compared with 18 patients between 18-30 years of age. Clinical study experience in the elderly (n=1522), suggests that there were no overall differences in safety between elderly and younger patients *[see Use in Specific Populations (8.5)]*.

Kinetic studies with another statin, having a similar principal route of elimination, have suggested that for a given dose level higher systemic exposure may be achieved in patients with severe renal insufficiency (as measured by creatinine clearance).

Although the mechanism is not fully understood, cyclosporine has been shown to increase the AUC of statins. The increase in AUC for simvastatin acid is presumably due, in part, to inhibition of CYP3A4.

The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Inhibitors of CYP3A4 can raise the plasma levels of HMG-CoA reductase inhibitory activity and increase the risk of myopathy *[see Warnings and Precautions (5.1) and Drug Interactions (7.1)]*.

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TABLE 3
Effect of Coadministered Drugs or Grapefruit Juice on Simvastatin Systemic Exposure

Coadministered Drug or Grapefruit Juice	Dosing of Coadministered Drug or Grapefruit Juice	Dosing of Simvastatin	Geometric Mean Ratio (Ratio* with / without coadministered drug) No Effect = 1.00		
				AUC	C_{max}
Contraindicated with simvastatin *[see Contraindications (4) and Warnings and Precautions (5.1)]*					
Telithromycin†	200 mg QD for 4 days	80 mg	simvastatin acid‡ simvastatin	12 8.9	15 5.3
Nelfinavir†	1250 mg BID for 14 days	20 mg QD for 28 days	simvastatin acid‡ simvastatin	 6	 6.2
Itraconazole†	200 mg QD for 4 days	80 mg	simvastatin acid‡ simvastatin		13.1 13.1
Posaconazole	100 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid simvastatin	7.3 10.3	9.2 9.4
	200 mg (oral suspension) QD for 13 days	40 mg	simvastatin acid simvastatin	8.5 10.6	9.5 11.4
Gemfibrozil	600 mg BID for 3 days	40 mg	simvastatin acid simvastatin	2.85 1.35	2.18 0.91
Avoid >1 quart of grapefruit juice with simvastatin *[see Warnings and Precautions (5.1)]*					
Grapefruit Juice§ (high dose)	200 mL of double-strength TID¶	60 mg single dose	simvastatin acid simvastatin	7 16	
Grapefruit Juice§ (low dose)	8 oz (about 237mL) of single-strength#	20 mg single dose	simvastatin acid simvastatin	1.3 1.9	
Avoid taking with >10 mg simvastatin, based on clinical and/or post-marketing experience *[see Warnings and Precautions (5.1)]*					
Verapamil SR	240 mg QD Days 1-7 then 240 mg BID on Days 8-10	80 mg on Day 10	simvastatin acid simvastatin	2.3 2.5	2.4 2.1
Diltiazem	120 mg BID for 10 days	80 mg on Day 10	simvastatin acid simvastatin	2.69 3.10	2.69 2.88
Diltiazem	120 mg BID for 14 days	20 mg on Day 14	simvastatin	4.6	3.6
Amiodarone	400 mg QD for 3 days	40 mg on Day 3	simvastatin acid simvastatin	1.75 1.76	1.72 1.79
Avoid taking with >20 mg simvastatin, based on clinical and/or post-marketing experience *[see Warnings and Precautions (5.1)]*					
Amlodipine	10 mg QD x 10 days	80 mg on Day 10	simvastatin acid simvastatin	1.58 1.77	1.56 1.47
Ranolazine SR	1000 mg BID for 7 days	80 mg on Day 1 and Day 6-9	simvastatin acid simvastatin	2.26 1.86	2.28 1.75
No dosing adjustments required for the following:					
Fenofibrate	160 mg QD X 14 days	80 mg QD on Days 8-14	simvastatin acid simvastatin	0.64 0.89	0.89 0.83
Niacin extended-release Þ	2 g single dose	20 mg single dose	simvastatin acid simvastatin	1.6 1.4	1.84 1.08
Propranolol	80 mg single dose	80 mg single dose	total inhibitor active inhibitor	0.79 0.79	↓ from 33.6 to 21.1 ng·eq/mL ↓ from 7.0 to 4.7 ng·eq/mL

* Results based on a chemical assay except results wi h propranolol as indicated.
† Results could be representative of the following CYP3A4 inhibitors: ketoconazole, erythromycin, clarithromycin, HIV protease inhibitors, and nefazodone.
‡ Simvastatin acid refers to the β-hydroxyacid of simvastatin.
§ The effect of amounts of grapefruit juice between hose used in these two studies on simvastatin pharmacokinetics has not been studied.
¶ Double-strength: one can of frozen concentrate diluted with one can of water. Grapefruit juice was administered TID for 2 days, and 200 mL together with single dose simvastatin and 30 and 90 minutes following single dose simvastatin on Day 3.
\# Single-strength: one can of frozen concentrate diluted with 3 cans of water. Grapefruit juice was administered with breakfast for 3 days, and simvastatin was administered in the evening on Day 3.
Þ Because Chinese patients have an increased risk for myopathy with simvastatin coadministered with lipid-modifying doses (≥ 1 gram/day niacin) of niacin-containing products, and the risk is dose-related, Chinese patients should not receive simvasta in 80 mg coadministered with lipid-modifying doses of niacin-containing products *[see Warnings and Precautions (5.1) and Drug Interactions (7.4)]*.

In a study of 12 healthy volunteers, simvastatin at the 80-mg dose had no effect on the metabolism of the probe cytochrome P450 isoform 3A4 (CYP3A4) substrates midazolam and erythromycin. This

indicates that simvastatin is not an inhibitor of CYP3A4, and, therefore, is not expected to affect the plasma levels of other drugs metabolized by CYP3A4.

Coadministration of simvastatin (40 mg QD for 10 days) resulted in an increase in the maximum mean levels of cardioactive digoxin (given as a single 0.4 mg dose on day 10) by approximately 0.3 ng/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 72-week carcinogenicity study, mice were administered daily doses of simvastatin of 25, 100, and 400 mg/kg body weight, which resulted in mean plasma drug levels approximately 1, 4, and 8 times higher than the mean human plasma drug level, respectively (as total inhibitory activity based on AUC) after an 80-mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males with a maximum incidence of 90% in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls. No evidence of a tumorigenic effect was observed at 25 mg/kg/day.

In a separate 92-week carcinogenicity study in mice at doses up to 25 mg/kg/day, no evidence of a tumorigenic effect was observed (mean plasma drug levels were 1 times higher than humans given 80 mg simvastatin as measured by AUC).

In a two-year study in rats at 25 mg/kg/day, there was a statistically significant increase in the incidence of thyroid follicular adenomas in female rats exposed to approximately 11 times higher levels of simvastatin than in humans given 80 mg simvastatin (as measured by AUC).

A second two-year rat carcinogenicity study with doses of 50 and 100 mg/kg/day produced hepatocellular adenomas and carcinomas (in female rats at both doses and in males at 100 mg/kg/day). Thyroid follicular cell adenomas were increased in males and females at both doses; thyroid follicular cell carcinomas were increased in females at 100 mg/kg/day. The increased incidence of thyroid neoplasms appears to be consistent with findings from other statins. These treatment levels represented plasma drug levels (AUC) of approximately 7 and 15 times (males) and 22 and 25 times (females) the mean human plasma drug exposure after an 80 milligram daily dose.

No evidence of mutagenicity was observed in a microbial mutagenicity (Ames) test with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

There was decreased fertility in male rats treated with simvastatin for 34 weeks at 25 mg/kg body weight (4 times the maximum human exposure level, based on AUC, in patients receiving 80 mg/day); however, this effect was not observed during a subsequent fertility study in which simvastatin was administered at this same dose level to male rats for 11 weeks (the entire cycle of spermatogenesis including epididymal maturation). No microscopic changes were observed in the testes of rats from either study. At 180 mg/kg/day, (which produces exposure levels 22 times higher than those in humans taking 80 mg/day based on surface area, mg/m^2), seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. In dogs, there was drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation at 10 mg/kg/day, (approximately 2 times the human exposure, based on AUC, at 80 mg/day). The clinical significance of these findings is unclear.

13.2 Animal Toxicology and/or Pharmacology

CNS Toxicity

Optic nerve degeneration was seen in clinically normal dogs treated with simvastatin for 14 weeks at 180 mg/kg/day, a dose that produced mean plasma drug levels about 12 times higher than the mean plasma drug level in humans taking 80 mg/day.

Reference ID: 2957153

A chemically similar drug in this class also produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean plasma drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose that resulted in a mean plasma drug level similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels were seen in dogs treated with simvastatin at a dose of 360 mg/kg/day, a dose that produced mean plasma drug levels that were about 14 times higher than the mean plasma drug levels in humans taking 80 mg/day. Similar CNS vascular lesions have been observed with several other drugs of this class.

There were cataracts in female rats after two years of treatment with 50 and 100 mg/kg/day (22 and 25 times the human AUC at 80 mg/day, respectively) and in dogs after three months at 90 mg/kg/day (19 times) and at two years at 50 mg/kg/day (5 times).

14 CLINICAL STUDIES

14.1 Clinical Studies in Adults

Reductions in Risk of CHD Mortality and Cardiovascular Events

In 4S, the effect of therapy with ZOCOR on total mortality was assessed in 4,444 patients with CHD and baseline total cholesterol 212-309 mg/dL (5.5-8.0 mmol/L). In this multicenter, randomized, double-blind, placebo-controlled study, patients were treated with standard care, including diet, and either ZOCOR 20-40 mg/day (n=2,221) or placebo (n=2,223) for a median duration of 5.4 years. Over the course of the study, treatment with ZOCOR led to mean reductions in total-C, LDL-C and TG of 25%, 35%, and 10%, respectively, and a mean increase in HDL-C of 8%. ZOCOR significantly reduced the risk of mortality by 30% (p=0.0003, 182 deaths in the ZOCOR group vs 256 deaths in the placebo group). The risk of CHD mortality was significantly reduced by 42% (p=0.00001, 111 vs 189 deaths). There was no statistically significant difference between groups in non-cardiovascular mortality. ZOCOR significantly decreased the risk of having major coronary events (CHD mortality plus hospital-verified and silent non-fatal myocardial infarction [MI]) by 34% (p<0.00001, 431 vs 622 patients with one or more events). The risk of having a hospital-verified non-fatal MI was reduced by 37%. ZOCOR significantly reduced the risk for undergoing myocardial revascularization procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 37% (p<0.00001, 252 vs 383 patients). ZOCOR significantly reduced the risk of fatal plus non-fatal cerebrovascular events (combined stroke and transient ischemic attacks) by 28% (p=0.033, 75 vs 102 patients). ZOCOR reduced the risk of major coronary events to a similar extent across the range of baseline total and LDL cholesterol levels. Because there were only 53 female deaths, the effect of ZOCOR on mortality in women could not be adequately assessed. However, ZOCOR significantly lessened the risk of having major coronary events by 34% (60 vs 91 women with one or more event). The randomization was stratified by angina alone (21% of each treatment group) or a previous MI. Because there were only 57 deaths among the patients with angina alone at baseline, the effect of ZOCOR on mortality in this subgroup could not be adequately assessed. However, trends in reduced coronary mortality, major coronary events and revascularization procedures were consistent between this group and the total study cohort. Additionally, ZOCOR resulted in similar decreases in relative risk for total mortality, CHD mortality, and major coronary events in elderly patients (≥65 years), compared with younger patients.

The Heart Protection Study (HPS) was a large, multi-center, placebo-controlled, double-blind study with a mean duration of 5 years conducted in 20,536 patients (10,269 on ZOCOR 40 mg and 10,267 on placebo). Patients were allocated to treatment using a covariate adaptive method[4] which took into account the distribution of 10 important baseline characteristics of patients already enrolled and

[4] D.R. Taves, Minimization: a new method of assigning patients to treatment and control groups. Clin. Pharmacol. Ther. 15 (1974), pp. 443-453

Reference ID: 2957153

minimized the imbalance of those characteristics across the groups. Patients had a mean age of 64 years (range 40-80 years), were 97% Caucasian and were at high risk of developing a major coronary event because of existing CHD (65%), diabetes (Type 2, 26%; Type 1, 3%), history of stroke or other cerebrovascular disease (16%), peripheral vessel disease (33%), or hypertension in males ≥65 years (6%). At baseline, 3,421 patients (17%) had LDL-C levels below 100 mg/dL, of whom 953 (5%) had LDL-C levels below 80 mg/dL; 7,068 patients (34%) had levels between 100 and 130 mg/dL; and 10,047 patients (49%) had levels greater than 130 mg/dL.

The HPS results showed that ZOCOR 40 mg/day significantly reduced: total and CHD mortality; non-fatal MI, stroke, and revascularization procedures (coronary and non-coronary) (see Table 4).

TABLE 4
Summary of Heart Protection Study Results

Endpoint	**ZOCOR** (N=10,269) n (%)†	**Placebo** (N=10,267) n (%)†	**Risk Reduction (%) (95% CI)**	**p-Value**
Primary				
Mortality	1,328 (12.9)	1,507 (14.7)	13 (6-19)	p=0.0003
CHD mortality	587 (5.7)	707 (6.9)	18 (8-26)	p=0.0005
Secondary				
Non-fatal MI	357 (3.5)	574 (5.6)	38 (30-46)	p<0.0001
Stroke	444 (4.3)	585 (5.7)	25 (15-34)	p<0.0001
Tertiary				
Coronary revasculariza ion	513 (5)	725 (7.1)	30 (22-38)	p<0.0001
Peripheral and other non-coronary revascularization	450 (4.4)	532 (5.2)	16 (5-26)	p=0.006

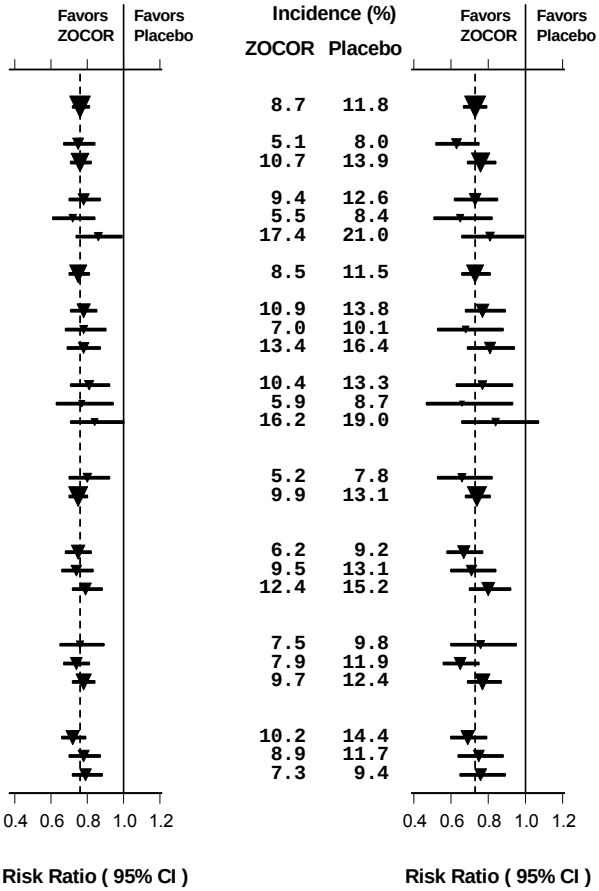
† n = number of patients with indicated event

Two composite endpoints were defined in order to have sufficient events to assess relative risk reductions across a range of baseline characteristics (see Figure 1). A composite of major coronary events (MCE) was comprised of CHD mortality and non-fatal MI (analyzed by time-to-first event; 898 patients treated with ZOCOR had events and 1,212 patients on placebo had events). A composite of major vascular events (MVE) was comprised of MCE, stroke and revascularization procedures including coronary, peripheral and other non-coronary procedures (analyzed by time-to-first event; 2,033 patients treated with ZOCOR had events and 2,585 patients on placebo had events). Significant relative risk reductions were observed for both composite endpoints (27% for MCE and 24% for MVE, p<0.0001). Treatment with ZOCOR produced significant relative risk reductions for all components of the composite endpoints. The risk reductions produced by ZOCOR in both MCE and MVE were evident and consistent regardless of cardiovascular disease related medical history at study entry (i.e., CHD alone; or peripheral vascular disease, cerebrovascular disease, diabetes or treated hypertension, with or without CHD), gender, age, creatinine levels up to the entry limit of 2.3 mg/dL, baseline levels of LDL-C, HDL-C, apolipoprotein B and A-1, baseline concomitant cardiovascular medications (i.e., aspirin, beta blockers, or calcium channel blockers), smoking status, alcohol intake, or obesity. Diabetics showed risk reductions for MCE and MVE due to ZOCOR treatment regardless of baseline HbA1c levels or obesity with the greatest effects seen for diabetics without CHD.

Reference ID: 2957153

Figure 1
The Effects of Treatment with ZOCOR on Major Vascular Events and Major Coronary Events in HPS

Baseline Characteristics	N	Major Vascular Events Incidence (%) ZOCOR	Major Vascular Events Incidence (%) Placebo	Major Coronary Events Incidence (%) ZOCOR	Major Coronary Events Incidence (%) Placebo
All patients	20,536	19.8	25.2	8.7	11.8
Without CHD	7,150	16.1	20.8	5.1	8.0
With CHD	13,386	21.8	27.5	10.7	13.9
Diabetes mellitus	5,963	20.2	25.1	9.4	12.6
Without CHD	3,982	13.8	18.6	5.5	8.4
With CHD	1,981	33.4	37.8	17.4	21.0
Without diabetes mellitus	14,573	19.6	25.2	8.5	11.5
Peripheral vascular disease	6,748	26.4	32.7	10.9	13.8
Without CHD	2,701	24.7	30.5	7.0	10.1
With CHD	4,047	27.6	34.3	13.4	16.4
Cerebrovascular disease	3,280	24.7	29.8	10.4	13.3
Without CHD	1,820	18.7	23.6	5.9	8.7
With CHD	1,460	32.4	37.4	16.2	19.0
Gender					
Female	5,082	14.4	17.7	5.2	7.8
Male	15,454	21.6	27.6	9.9	13.1
Age (years)					
≥ 40 to < 65	9,839	16.9	22.1	6.2	9.2
≥ 65 to < 70	4,891	20.9	27.2	9.5	13.1
≥ 70	5,806	23.6	28.7	12.4	15.2
LDL-cholesterol (mg/dL)					
< 100	3,421	16.4	21.0	7.5	9.8
≥ 100 to < 130	7,068	18.9	24.7	7.9	11.9
≥ 130	10,047	21.6	26.9	9.7	12.4
HDL-cholesterol (mg/dL)					
< 35	7,176	22.6	29.9	10.2	14.4
≥ 35 to < 43	5,666	20.0	25.1	8.9	11.7
≥ 43	7,694	17.0	20.9	7.3	9.4



N = number of patients in each subgroup. The inverted triangles are point estimates of the relative risk, with their 95% confidence intervals represented as a line. The area of a triangle is proportional to the number of patients with MVE or MCE in the subgroup relative to the number with MVE or MCE, respectively, in the entire study population. The ver ical solid line represents a relative risk of one. The vertical dashed line represents the point estimate of relative risk in the entire study population.

Angiographic Studies

In the Multicenter Anti-Atheroma Study, the effect of simvastatin on atherosclerosis was assessed by quantitative coronary angiography in hypercholesterolemic patients with CHD. In this randomized, double-blind, controlled study, patients were treated with simvastatin 20 mg/day or placebo. Angiograms were evaluated at baseline, two and four years. The co-primary study endpoints were mean change per-patient in minimum and mean lumen diameters, indicating focal and diffuse disease, respectively. ZOCOR significantly slowed the progression of lesions as measured in the Year 4 angiogram by both parameters, as well as by change in percent diameter stenosis. In addition, simvastatin significantly decreased the proportion of patients with new lesions and with new total occlusions.

Modifications of Lipid Profiles

Primary Hyperlipidemia (Fredrickson type lla and llb)

ZOCOR has been shown to be effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of hyperlipidemia and in mixed hyperlipidemia. Maximal to near maximal response is generally achieved within 4-6 weeks and maintained during chronic therapy. ZOCOR consistently and

significantly decreased total-C, LDL-C, total-C/HDL-C ratio, and LDL-C/HDL-C ratio; ZOCOR also decreased TG and increased HDL-C (see Table 5).

TABLE 5
Mean Response in Patients with Primary Hyperlipidemia and Combined (mixed) Hyperlipidemia
(Mean Percent Change from Baseline After 6 to 24 Weeks)

TREATMENT	N	TOTAL-C	LDL-C	HDL-C	TG[†]
Lower Dose Comparative Study [‡] (Mean % Change at Week 6)					
ZOCOR 5 mg q.p.m.	109	-19	-26	10	-12
ZOCOR 10 mg q.p.m.	110	-23	-30	12	-15
Scandinavian Simvastatin Survival Study [§] (Mean % Change at Week 6)					
Placebo	2223	-1	-1	0	-2
ZOCOR 20 mg q.p.m.	2221	-28	-38	8	-19
Upper Dose Comparative Study [‖] (Mean % Change Averaged at Weeks 18 and 24)					
ZOCOR 40 mg q.p.m.	433	-31	-41	9	-18
ZOCOR 80 mg q.p.m. [¶]	664	-36	-47	8	-24
Multi-Center Combined Hyperlipidemia Study [††] (Mean % Change at Week 6)					
Placebo	125	1	2	3	-4
ZOCOR 40 mg q.p.m.	123	-25	-29	13	-28
ZOCOR 80 mg q.p.m.	124	-31	-36	16	-33

[†] median percent change
[‡] mean baseline LDL-C 244 mg/dL and median baseline TG 168 mg/dL
[§] mean baseline LDL-C 188 mg/dL and median baseline TG 128 mg/dL
[‖] mean baseline LDL-C 226 mg/dL and median baseline TG 156 mg/dL
[¶] 21% and 36% median reduction in TG in patients with TG ≤200 mg/dL and TG >200 mg/dL, respectively. Patients with TG >350 mg/dL were excluded
[††] mean baseline LDL-C 156 mg/dL and median baseline TG 391 mg/dL.

Hypertriglyceridemia (Fredrickson type IV)

The results of a subgroup analysis in 74 patients with type IV hyperlipidemia from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 6.

TABLE 6
Six-week, Lipid-lowering Effects of Simvastatin in Type IV Hyperlipidemia
Median Percent Change (25th and 75th percentile) from Baseline[†]

TREATMENT	N	Total-C	LDL-C	HDL-C	TG	VLDL-C	Non-HDL-C
Placebo	74	+2 (-7, +7)	+1 (-8, +14)	+3 (-3, +10)	-9 (-25, +13)	-7 (-25, +11)	+1 (-9, +8)
ZOCOR 40 mg/day	74	-25 (-34, -19)	-28 (-40, -17)	+11 (+5, +23)	-29 (-43, -16)	-37 (-54, -23)	-32 (-42, -23)
ZOCOR 80 mg/day	74	-32 (-38, -24)	-37 (-46, -26)	+15 (+5, +23)	-34 (-45, -18)	-41 (-57, -28)	-38 (-49, -32)

[†] The median baseline values (mg/dL) for the patients in this study were: total-C = 254, LDL-C = 135, HDL-C = 36, TG = 404, VLDL-C = 83, and non-HDL-C = 215.

Reference ID: 2957153

Dysbetalipoproteinemia (Fredrickson type III)

The results of a subgroup analysis in 7 patients with type III hyperlipidemia (dysbetalipoproteinemia) (apo E2/2) (VLDL-C/TG>0.25) from a 130-patient, double-blind, placebo-controlled, 3-period crossover study are presented in Table 7.

TABLE 7
Six-week, Lipid-lowering Effects of Simvastatin in Type III Hyperlipidemia
Median Percent Change (min, max) from Baseline†

TREATMENT	N	Total-C	LDL-C + IDL	HDL-C	TG	VLDL-C + IDL	Non-HDL-C
Placebo	7	-8 (-24, +34)	-8 (-27, +23)	-2 (-21, +16)	+4 (-22, +90)	-4 (-28, +78)	-8 (-26, -39)
ZOCOR 40 mg/day	7	-50 (-66, -39)	-50 (-60, -31)	+7 (-8, +23)	-41 (-74, -16)	-58 (-90, -37)	-57 (-72, -44)
ZOCOR 80 mg/day	7	-52 (-55, -41)	-51 (-57, -28)	+7 (-5, +29)	-38 (-58, +2)	-60 (-72, -39)	-59 (-61, -46)

† The median baseline values (mg/dL) were: total-C = 324, LDL-C = 121, HDL-C = 31, TG = 411, VLDL-C = 170, and non-HDL-C = 291.

Homozygous Familial Hypercholesterolemia

In a controlled clinical study, 12 patients 15-39 years of age with homozygous familial hypercholesterolemia received simvastatin 40 mg/day in a single dose or in 3 divided doses, or 80 mg/day in 3 divided doses. In 11 patients with reductions in LDL-C, the mean LDL-C changes for the 40- and 80-mg doses were 14% (range 8% to 23%, median 12%) and 30% (range 14% to 46%, median 29%), respectively. One patient had an increase of 15% in LDL-C. Another patient with absent LDL-C receptor function had an LDL-C reduction of 41% with the 80-mg dose.

Endocrine Function

In clinical studies, simvastatin did not impair adrenal reserve or significantly reduce basal plasma cortisol concentration. Small reductions from baseline in basal plasma testosterone in men were observed in clinical studies with simvastatin, an effect also observed with other statins and the bile acid sequestrant cholestyramine. There was no effect on plasma gonadotropin levels. In a placebo-controlled, 12-week study there was no significant effect of simvastatin 80 mg on the plasma testosterone response to human chorionic gonadotropin. In another 24-week study, simvastatin 20-40 mg had no detectable effect on spermatogenesis. In 4S, in which 4,444 patients were randomized to simvastatin 20-40 mg/day or placebo for a median duration of 5.4 years, the incidence of male sexual adverse events in the two treatment groups was not significantly different. Because of these factors, the small changes in plasma testosterone are unlikely to be clinically significant. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown.

14.2 Clinical Studies in Adolescents

In a double-blind, placebo-controlled study, 175 patients (99 adolescent boys and 76 post-menarchal girls) 10-17 years of age (mean age 14.1 years) with heterozygous familial hypercholesterolemia (HeFH) were randomized to simvastatin (n=106) or placebo (n=67) for 24 weeks (base study). Inclusion in the study required a baseline LDL-C level between 160 and 400 mg/dL and at least one parent with an LDL-C level >189 mg/dL. The dosage of simvastatin (once daily in the evening) was 10 mg for the first 8 weeks, 20 mg for the second 8 weeks, and 40 mg thereafter. In a 24-week extension, 144 patients elected to continue therapy with simvastatin 40 mg or placebo.

ZOCOR significantly decreased plasma levels of total-C, LDL-C, and Apo B (see Table 8). Results from the extension at 48 weeks were comparable to those observed in the base study.

Reference ID: 2957153

TABLE 8
Lipid-Lowering Effects of Simvastatin in Adolescent Patients with Heterozygous Familial Hypercholesterolemia
(Mean Percent Change from Baseline)

Dosage	Duration	N		Total-C	LDL-C	HDL-C	TG†	Apo B
Placebo	24 Weeks	67	% Change from Baseline (95% CI)	1.6 (-2.2, 5.3)	1.1 (-3.4, 5 5)	3.6 (-0.7, 8.0)	-3.2 (-11 8, 5.4)	-0.5 (-4.7, 3.6)
			Mean baseline, mg/dL (SD)	278.6 (51.8)	211.9 (49.0)	46.9 (11.9)	90.0 (50.7)	186.3 (38.1)
ZOCOR	24 Weeks	106	% Change from Baseline (95% CI)	-26.5 (-29.6, -23.3)	-36.8 (-40.5, -33.0)	8.3 (4.6, 11.9)	-7.9 (-15 8, 0.0)	-32.4 (-35.9, -29.0)
			Mean baseline, mg/dL (SD)	270.2 (44.0)	203.8 (41.5)	47.7 (9.0)	78.3 (46.0)	179.9 (33.8)

† median percent change

After 24 weeks of treatment, the mean achieved LDL-C value was 124.9 mg/dL (range: 64.0-289.0 mg/dL) in the ZOCOR 40 mg group compared to 207.8 mg/dL (range: 128.0-334.0 mg/dL) in the placebo group.

The safety and efficacy of doses above 40 mg daily have not been studied in children with HeFH. The long-term efficacy of simvastatin therapy in childhood to reduce morbidity and mortality in adulthood has not been established.

16 HOW SUPPLIED/STORAGE AND HANDLING

No. 8360 — Tablets ZOCOR 5 mg are buff, oval, film-coated tablets, coded MSD 726 on one side and ZOCOR 5 on the other. They are supplied as follows:

NDC 0006-0726-31 unit of use bottles of 30
NDC 0006-0726-54 unit of use bottles of 90.

No. 8146 — Tablets ZOCOR 10 mg are peach, oval, film-coated tablets, coded MSD 735 on one side and plain on the other. They are supplied as follows:

NDC 0006-0735-31 unit of use bottles of 30
NDC 0006-0735-54 unit of use bottles of 90
NDC 0006-0735-82 bottles of 1000.

No. 8147 — Tablets ZOCOR 20 mg are tan, oval, film-coated tablets, coded MSD 740 on one side and plain on the other. They are supplied as follows:

NDC 0006-0740-31 unit of use bottles of 30
NDC 0006-0740-54 unit of use bottles of 90
NDC 0006-0740-82 bottles of 1000.

No. 8148 — Tablets ZOCOR 40 mg are brick red, oval, film-coated tablets, coded MSD 749 on one side and plain on the other. They are supplied as follows:

NDC 0006-0749-31 unit of use bottles of 30
NDC 0006-0749-54 unit of use bottles of 90
NDC 0006-0749-82 bottles of 1000.

No. 6577 — Tablets ZOCOR 80 mg are brick red, capsule-shaped, film-coated tablets, coded 543 on one side and 80 on the other. They are supplied as follows:

NDC 0006-0543-31 unit of use bottles of 30
NDC 0006-0543-54 unit of use bottles of 90
NDC 0006-0543-28 unit dose packages of 100
NDC 0006-0543-82 bottles of 1000.

Storage

Store between 5-30°C (41-86°F).

Storage of 1,000 count bottles

Dispense in a tightly-closed container.

17 PATIENT COUNSELING INFORMATION

Patients should be advised to adhere to their National Cholesterol Education Program (NCEP)-recommended diet, a regular exercise program, and periodic testing of a fasting lipid panel.

Patients should be advised about substances they should not take concomitantly with simvastatin *[see Contraindications (4) and Warnings and Precautions (5.1)]*. Patients should also be advised to inform other healthcare professionals prescribing a new medication or increasing the dose of an existing medication that they are taking ZOCOR.

17.1 Muscle Pain

All patients starting therapy with ZOCOR should be advised of the risk of myopathy, including rhabdomyolysis, and told to report promptly any unexplained muscle pain, tenderness or weakness. **Patients using the 80-mg dose should be informed that the risk of myopathy, including rhabdomyolysis, is increased with use of the 80-mg dose.** The risk of myopathy, including rhabdomyolysis, occurring with use of ZOCOR is increased when taking certain types of medication or consuming larger quantities of grapefruit juice. Patients should discuss all medication, both prescription and over the counter, with their healthcare professional.

17.2 Liver Enzymes

It is recommended that liver function tests be performed before the initiation of ZOCOR, and thereafter when clinically indicated.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of birth control to prevent pregnancy while using ZOCOR. Discuss future pregnancy plans with your patients, and discuss when to stop taking ZOCOR if they are trying to conceive. Patients should be advised that if they become pregnant they should stop taking ZOCOR and call their healthcare professional.

17.4 Breastfeeding

Women who are breastfeeding should not use ZOCOR. Patients who have a lipid disorder and are breastfeeding should be advised to discuss the options with their healthcare professional.

Manuf. for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

By:
MERCK SHARP & DOHME LTD.
Cramlington, Northumberland, UK NE23 3JU

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S077

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 27, 2011
From	Amy G. Egan, M.D., M.P.H.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	19-766 S-077
Applicant	Merck & Co, Inc.
Date of Submission	June 12, 2009
Proprietary Name / Established (USAN) names	ZOCOR (simvastatin)
Dosage forms / Strength	Tablet: 5 mg, 10 mg, 20, mg, 40 mg, and 80 mg
Recommended:	*Approval*

Reference ID: 2954462

1. Introduction

This memorandum summarizes the Agency's assessment of a labeling supplement submitted by the sponsor proposing new information concerning myopathy, based on the results of the clinical trial entitled Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

2. Background

Simvastatin, a member of the HMG-CoA reductase inhibitor (statin) class of medications, was approved in the U.S. in December 1991 in dosage strengths of 5, 10, 20, and 40 mg; the 80 mg dose was approved in July 1998. Simvastatin is indicated to:

- Reduce the risk of total mortality by reducing coronary heart disease (CHD) deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events.
- Reduce elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) in patients with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.
- Reduce elevated TG in patients with hypertriglyceridemia and reduce TG and very low-density lipoprotein cholesterol (VLDL-C) in patients with primary dysbetalipoproteinemia.
- Reduce total-C and LDL-C in adult patients with homozygous familial hypercholesterolemia.
- Reduce elevated total-C, LDL-C, and Apo B in boys and postmenarchal girls, 10 to 17 years of age with heterozygous familial hypercholesterolemia after failing an adequate trial of diet therapy.

Simvastatin, as with all statins, is associated with myopathy, ranging in severity from myalgia (unexplained muscle pain or weakness with or without an elevated serum creatine kinase [CK]) to rhabdomyolysis (unexplained muscle pain or weakness with a CK >40 times the upper limit of normal [ULN] generally with evidence of end-organ damage). The risk for myopathy is related to the plasma level of statin; as simvastatin is extensively metabolized by the CYP3A4 enzyme system, it is particularly prone to drug interactions which increase serum levels of simvastatin and thus increase the risk for developing myopathy.

In August 2001, a Citizen Petition was filed that requested that FDA take the following four actions on all marketed statins:

- Require a boxed warning of the risks of rhabdomyolysis
- Require labels to include an additional bolded warning of the risks of myopathy and measures doctors and patients can take to reduce these risks
- Require that an FDA-approved Medication Guide be distributed warning the public of the risk of muscle pain and weakness and rhabdomyolysis and measures to take should symptoms develop

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- Require sponsors to inform physicians about the risk of rhabdomyolysis through a "Dear Doctor" letter

A response to the Citizen Petition is still pending.

(b) (4)

[redacted]

3. CMC/Device

Not applicable, as no new CMC data were submitted for this supplement.

4. Nonclinical Pharmacology/Toxicology

Not applicable, as no new nonclinical data were submitted for this supplement.

5. Clinical Pharmacology/Biopharmaceutics

There was no clinical pharmacology review associated with this supplement. However, a review of an interaction between amiodarone and simvastatin was conducted under NDA 19-766/S-051, submitted May 15, 2001 and based on interim SEARCH data. As a result, changes to the simvastatin label adding precautionary language about the increased risk of myopathy in patients taking higher doses of simvastatin and amiodarone and limiting the dose of simvastatin to 20 mg in patients taking amiodarone were approved in May 2002. Please refer to reviews by Drs. Anne Pariser and Xiaoxiong Wei.

In addition, a Changes Being Effected supplemental new drug application (NDA 19-766/S-080) providing for a simvastatin dose cap of 40 mg was approved in April 2010, based on published medical literature and a preliminary review of postmarketing adverse events. Please refer to reviews by Drs. Amy Egan and Sang Chung.

6. Clinical Microbiology

Not applicable.

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7. Clinical/Statistical- Efficacy

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) was a 6.7-year, randomized, double-blind 2x2 factorial trial comparing the efficacy and safety of simvastatin 80 mg to simvastatin 20 mg with or without vitamin B12 and folate in survivors of myocardial infarction.

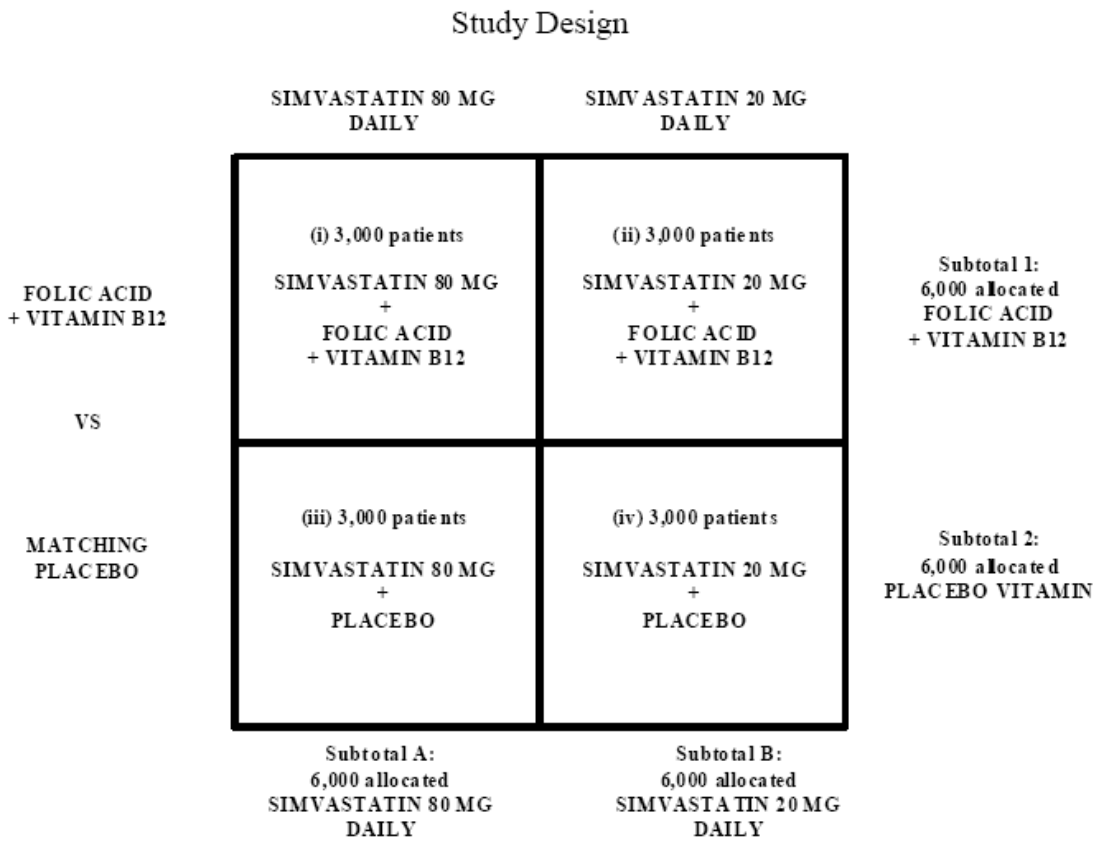

Figure 9-1 from sponsor's submission.

Inclusion criteria included men or women 18 to 80 years of age with a history of definite or probable diagnosis of myocardial infarction (>3 months before the study screening visit), clear indication for statin therapy, and a baseline total cholesterol ≥135 mg/dL in patients already on statin therapy, or ≥174 mg/dL in patients not already on statin therapy.

Exclusion criteria included the following screening lab values:

- ALT >1.5x ULN;
- ALT >1-1.5x ULN and AST or ALP >2x ULN;
- GGT, AST or ALP >4x ULN;
- Creatinine >2x ULN;
- CK >3x ULN; or

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- TC <135 mg/dL on a statin or <174 mg/dL if not on a statin

Patients taking fibrates, high-dose niacin (>1g per day), nefazodone, systemic azole antifungals, or the macrolide antibiotics clarithromycin or erythromycin were also excluded.

Pertinent discontinuation criteria during the trial included:

- *Elevation in CK according to the following algorithm: Elevation of CK>10x ULN with unexplained muscle symptoms (muscle pain or weakness) was to result in the study simvastatin treatment being stopped immediately and permanently, and an early recall visit arranged within about 1 week (with 3-weekly early recall visits, or referral to the patient's own doctor, until the CK level reverted to normal: i.e. ≤3x ULN). Any other CK elevation >5x ULN was to result in an early recall visit within about 1 week for a repeat sample, and if repeat CK remained >5xULN then study simvastatin treatment was to be stopped temporarily. CK was to be checked again in about 6 weeks and study simvastatin treatment stopped permanently if CK was still >3x ULN. If, on the other hand, CK was ≤3x ULN then the allocated study simvastatin treatment could be started again after review by one of the clinical coordinators, with a further 2 early recall visits at 4-weekly intervals. If CK did not remain ≤3x ULN, study simvastatin treatment was to be stopped permanently.*

The primary efficacy variables for the simvastatin dose allocation included major vascular events (MVE), defined as major coronary events (fatal CHD, non-fatal MI or coronary revascularization procedure [CABG or PTCA]), non-fatal or fatal stroke, or peripheral revascularization (peripheral artery angioplasty or arterial surgery, including amputations).

Secondary efficacy comparisons included:

- MVEs separately in the first year after randomization and in the later years of the scheduled treatment period;
- MVEs among patients subdivided into 3 similar-sized groups with respect to blood cholesterol levels at the end of the pre-randomization run-in period on simvastatin 20 mg daily;
- MVEs in the presence and in the absence of the allocated study folic acid + vitamin B_{12};
- Major coronary events (MCE); and
- Total strokes.

A total of 34,780 subjects were screened for participation in SEARCH. Of these, 19,190 subjects entered a 2-month run-in phase where they received simvastatin 20 mg plus vitamin therapy. Of those entering the run-in phase, 5,642 subjects dropped out before the randomization visit. The primary reason for dropping out was screening blood results, most notably cholesterol levels. Forty-five subjects (<1%) dropped out due to abnormal CK at screening; 102 subjects (1%) dropped out due to unexplained muscle pain, while another 376 subjects (2%) dropped out due to "unwell or possible side effects".

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An additional 1,484 subjects (11%) dropped out during the randomization appointment. Among those, 316 subjects (2%) dropped out due to new unexplained muscle pain. Approximately 12,000 subjects were ultimately randomized to simvastatin 20 mg (n=6033) or simvastatin 80 mg (n=6031). A total of 69% of randomized subjects completed the trial.

The two groups were well-matched for baseline demographic characteristics. Eighty-three percent of the patients in each treatment group were male and 50% were 65 years of age or older. All patients had a previous MI and about 42% had other cardiovascular disease as well. Approximately 10% of patients had diabetes mellitus. Ninety-eight percent of patients were White. Baseline lipid levels were similar between treatment groups.

Seventy-two percent of patients in each treatment group were using non-study statins at screening, the most common being simvastatin. Of note, ~27% of patients in each treatment group were receiving calcium channel blockers at randomization, and ~2.2% in each treatment group were receiving amiodarone.

Compliance between treatment groups was similar until ~36 months into the trial, when the compliance rate for simvastatin 20 mg declined more significantly. By 84 months, 77% of subjects in the simvastatin 80 mg treatment group versus 69% of subjects in the simvastatin 20 mg group were compliant with study medication (defined as >80% of study drug taken). In part, the decrease in compliance in the simvastatin 20 mg treatment group was offset by an increased use of non-study statin. At 36 months, 10% of simvastatin 80 mg subjects versus 14% of simvastatin 20 mg subjects were receiving non-study statin; by 84 months the percentages were 20% and 27%, respectively.

In the primary efficacy analysis, 24.5% of simvastatin 80 mg subjects vs. 25.7% of simvastatin 20 mg subjects had a major vascular event (p=0.10). The relative risk reduction was 6%.

	Simvastatin 80 mg N=6031		Simvastatin 20 mg N=6033			
	Number of events	Incidence (%)	Number of events	Incidence (%)	Risk Ratio (95% CI)	p-value
Major Vascular Events	1477	(24.5%)	1553	(25.7%)	0.94 (0.88, 1.01)	0.10

Table 11-1 from sponsor's submission.

There was no statistically significant difference between treatment groups in the incidence of MVEs during the first year of treatment versus during later years; or in the incidence of MVEs by tertile of baseline level of LDL-C; or in the incidence of MVEs in the presence or absence of folic acid + vitamin B_{12}; or in the incidence of MCE.

Consistency of treatment effect on the primary endpoint was observed in subgroups defined by age, gender, history of diabetes mellitus, and baseline lipid and apolipoprotein levels. There was apparent heterogeneity for diastolic and systolic BP levels, favoring the 80 mg group in subjects with diastolic BP of 75 mm Hg or greater, and with systolic BP of 125 mm Hg or greater, and the 20 mg group in subjects with lower values.

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According to protocol, "Lipids were measured in all participants at the screening visit, and both lipids and apolipoproteins at the randomization visit. After randomization, about 10% of all participants were selected each year for extensive analysis of non-fasting lipid and lipoprotein levels. Missing values were imputed based on randomization values. Samples were taken at any time of day, as opposed to restricting collection to the fasting."

Over the course of the trial the average LDL-C level was 84.0 ± 0.39 mg/dL in subjects allocated simvastatin 80 mg and 97.5 ± 0.39 mg/dL in subjects allocated simvastatin 20 mg. The absolute difference in LDL-C between the two groups declined during the trial; averaged over the entire study, the absolute difference in mean LDL-C was 13.5 ± 0.39 mg/dL.

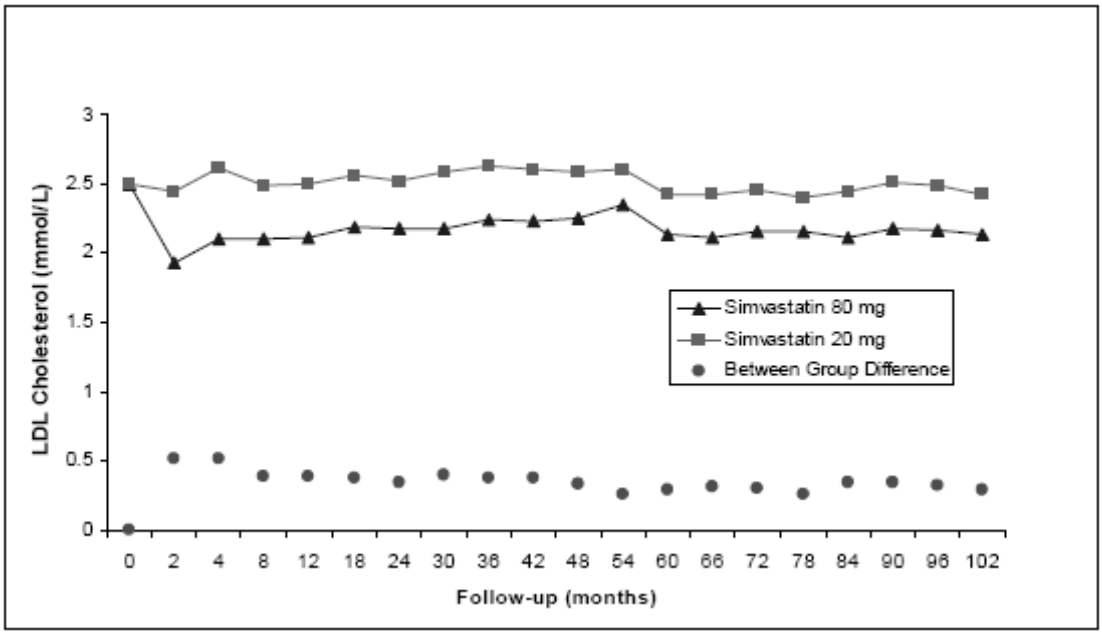

Figure 11-2 from sponsor's submission.

Mean TC at baseline was 163.7 ± 28.3 mg/dL and decreased to an average level of 148.2 ± 0.39 mg/dL in the simvastatin 80 mg group. In subjects allocated simvastatin 20 mg, average TC over the course of the study was similar to the baseline value of 163.7 mg/dL. On average the difference in TC between the simvastatin 80 mg and simvastatin 20 mg groups was 15.5 ± 0.39 mg/dL.

Mean HDL-C was 40.2 ± 13.9 mg/dL at baseline and remained stable over the course of the trial. The average HDL-C level over the study did not differ between the simvastatin 80 mg and 20 mg groups.

At baseline, mean TG levels were 168.1 ± 111.8 mg/dL in subjects who were subsequently randomized to simvastatin 80 mg and 170.7 ± 108.2 mg/dL in subjects who were randomized to simvastatin 20 mg. Over the course of the trial, TG levels declined to an average level of 149.6 ± 0.9 mg/dL in the simvastatin 80 mg group and to 162.8 ± 0.9 mg/dL) in the

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simvastatin 20 mg group. The average difference in triglycerides between the two groups was 13.2 ± 1.8 mg/dL).

In summary, there was a non-statistically significant 6% reduction in the relative risk of major vascular events in the simvastatin 80 mg group versus the simvastatin 20 mg group. Due in part to greater use of off-study LDL-C lowering medication in the simvastatin 20 mg group versus the 80 mg group, the difference in mean levels of LDL-C between the two treatment groups was 13 mg/dL instead of the expected difference of 20 mg/dL. The 6% relative risk reduction observed in the trial is consistent with the 13 mg/dL lower level of LDL-C in the 80 mg simvastatin group.

8. Safety

Person-years of follow-up were comparable between treatment groups, 40129.2 for the simvastatin 80 mg group and 40158.1 for the simvastatin 20 mg group.

There was no difference in CHD mortality (HR 1.02, CI: 0.89-1.13; p=0.78), vascular mortality (HR 0.99, CI: 0.88-1.11; p=0.89) or non-vascular mortality (HR 1.00, CI: 0.87-1.15; p=0.98) between treatment groups. All cause mortality was similarly balanced – HR 0.99 (0.91-1.09); p=0.90.

The number of cancer deaths in the simvastatin 80 mg and 20 mg groups was similar, as was the incidence of total cancer. However, the incidence of breast cancer was increased in the simvastatin 80 mg group relative to the 20 mg group. There were 35 (0.6%) cases of breast cancer in subjects allocated to simvastatin 80 mg and 18 cases (0.3%) in subjects allocated to simvastatin 20 mg. The hazard ratio was 1.90 (1.11-3.26) and the p-value was of nominal statistical significance, p=0.02.

> **Reviewer Comment:** A study published February 22, 2011 by Cancer Research, "Long-term Use of Cholesterol-Lowering Drugs and Cancer Incidence in a Large United States Cohort", noted that "long-term use of statins is unlikely to substantially increase or decrease overall cancer risk". Specifically, this study looked at the incidence of 10 common cancers among 133,255 participants in the Cancer Prevention Study-II (CPS-II) Nutrition Cohort. The incidence of breast cancer with current use of a statin for 5 years or more was 1.11 (0.98-1.25). Similarly, a study of long-term statin use and cancer using computerized pharmacy data from the Kaiser Permanente Medical Care Program in northern California did not find any associations between 5 years or more of statin use and incidence of any type of cancer in women.

Serious adverse events attributable to study treatment occurred in 56 (0.9%) subjects in the simvastatin 80 mg group and 7 (0.1%) subjects in the simvastatin 20 mg group. Of the 56 subjects with SAEs in the 80 mg treatment group, 52 experienced myopathy versus 2 of 7 in the 20 mg group. (b) (6) one of the two subjects with 'myopathy' in the 20 mg group was later diagnosed with polymyositis.) There were 2 SAEs of hepatitis in each treatment group.

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During the 6.7 years of the SEARCH trial, 27.4% of subjects in the simvastatin 80 mg group and 34.1% in the simvastatin 20 mg group stopped taking simvastatin study treatment. Of these subjects, 1.0% in the simvastatin 80 mg group versus 0.6% in the simvastatin 20 mg group discontinued due to muscle pain or weakness, while 1.7% versus 0.5% in the simvastatin 80 mg group and simvastatin 20 mg group, respectively, discontinued due to abnormal liver or muscle enzymes ("unknown which").

In the simvastatin 80-mg treatment arm, there were 52 cases (0.9%) of myopathy (defined as unexplained muscle weakness or pain with a serum creatine kinase (CK) >10 times upper limit of normal [ULN]) versus one case (0.02%) in the 20-mg treatment arm. Twenty-two subjects (0.4%) treated with simvastatin 80 mg developed rhabdomyolysis (defined as unexplained muscle pain or weakness with serum CK >40 times ULN) versus no subjects (0%) treated with simvastatin 20 mg. No deaths due to rhabdomyolysis were reported.

> **Reviewer Comment:** Reports on the SEARCH trial in the published literature cite different numbers for the incidence of rhabdomyolysis as the SEARCH investigators employed a more stringent definition, "CK >40x ULN plus evidence of renal damage". Based on that definition, the SEARCH investigators identified 7 patients with rhabdomyolysis, and imputed 4 additional patients as follows:
>
> *... there were 22 patients with CK>40xULN. In 7 of these 22 patients, serum creatinine was not available. Among the 13 patients with known serum creatinine, creatinine was increased in 5, and in 2 additional patients raised creatinine was inferred from very high CK levels (34,074 and 50,719 IU/L) together with the presence of dark urine believed to represent myoglobinuria, for a total of 7 of 15 patients. Thus where creatinine was known or inferred, it was raised in approximately half the cases. Therefore, in the remaining 7 patients where there was no information on creatinine, a raised level was imputed in about half, i.e. 4 patients. On this basis, the best estimate for the number of cases of rhabdomyolysis among patients taking simvastatin 80 mg, using the CTSU definition, is 11 (0.2%).*
>
> Due to the lack of uniform collection of renal status in patients with very high levels of CK in the SEARCH trial, and because "unexplained muscle pain or weakness with serum CK >40 times ULN" was the definition used by Merck in its 2005 report to the FDA on myopathy in SEARCH and other studies, this less stringent definition of rhabdomyolysis was used in FDA analyses.

Of the 52 cases of myopathy in the 80-mg treatment group, 13 (25%) occurred in subjects receiving concomitant treatment with diltiazem. Approximately half of the cases were detected in the first year of treatment, and approximately half of the cases were detected by routine monitoring of CK levels. Approximately 60% of the cases were associated with a genetic variant (the C variant in the SLCO1B1 gene) which affects the coding of an organic anion transporter polypeptide (OAT1B1) which is responsible for statin uptake into the liver. Older age and female sex both increased the risk of myopathy, 2.2-fold and 2.8-fold, respectively.

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Analyses conducted by the sponsor showed that the rates for myopathy and rhabdomyolysis with simvastatin 80 mg decreased from 5 per 1000 person-years and 2 per 1000 person-years, respectively, during the first 12 months of treatment to 1 per 1000 person-years and 0.4 per 1000 person-years, respectively, after the first 12 months of treatment. The rates observed in the subsequent years of the trial appear consistent with rates seen in clinical trials of other high dose statins.

No additional safety concerns arose as a result of the review of this trial.

9. Advisory Committee Meeting

This topic was not taken to an advisory committee. The SEARCH findings were discussed at a June 4, 2010 FDA Regulatory Briefing, a December 21, 2010 Safety First Steering Committee meeting, a February 3, 2011 Safety First Steering Committee meeting, and a March 17, 2011 Drug Safety Board meeting.

Dr. Woodcock's recommendation at both the Regulatory Briefing and the December SFSC meeting had been for market withdrawal of the 80 mg dose, given the availability of other safer, more potent statins. However, DMEP and ODE II did not agree with this recommendation, primarily because the risk seemed confined to the first year of use of simvastatin 80 mg, so the benefit in patients who had already been receiving this dose for 12 months or more outweighed the risk of myopathy, including rhabdomyolysis. DMEP and ODE II felt that if use of the simvastatin 80 mg dose could be restricted to those who had been taking it chronically (defined as 12 months or more), and if the package insert were updated to note the new contraindications and dose caps, that the risk of rhabdomyolysis could be successfully mitigated.

At the February 2011 SFSC meeting, DMEP presented additional background information and a proposed plan for a regulatory path forward for simvastatin 80 mg.

a. Drug utilization data conducted by OSE's Division of Epidemiology noted that in 2010, approximately 2.1 million individuals were being prescribed a simvastatin 80 mg-containing product. These individuals have already shown a tolerance to the muscle toxicity of simvastatin 80 mg.

b. The attributable risk for rhabdomyolosis is low; the attributable risk for myopathy is higher, but myopathy is not fatal. The occurrence of these adverse events is usually in the first year after initiating therapy with 80 mg simvastatin.

c. Hence, a reasonable risk management approach would be to allow continued marketing of the 80 mg dose, for the benefit of established users, and implement a program for eliminating new initiators, and ensuring that those receiving any dose of simvastatin do not receive concomitant medications that could increase plasma levels of simvastatin to levels that are inappropriate.

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To facilitate this plan, FDA would require safety labeling changes under FDAAA and, under its Safe Use initiative, would work with drug formularies, pharmacy benefit managers, and professional medical societies to increase awareness and implementation of the new safety labeling changes.

CDER would then monitor prescription use data to ensure that the safety labeling changes and the communication outreach were having their intended effects of limiting new initiators of high-dose simvastatin and guiding appropriate use of concomitant medications with simvastatin. If evidence indicated that these measures were not being effective, FDA would consider additional regulatory action, including withdrawal of high-dose simvastatin from the market.

The SFSC, including Dr. Woodcock, concurred with this proposed plan.

On March 17, 2011, the proposed Drug Safety Communication regarding the safety labeling changes and new contraindications and dose caps for simvastatin and simvastatin-containing products was discussed at the Drug Safety Board. Based on input from the board, the DSC was revised to note the other data streams (AERS data and other clinical trial data) that informed the regulatory decision, and to emphasize the drug-drug interaction portion of the DSC, in particular the new contraindications and new dose caps.

10. Pediatrics

This submission did not trigger PREA.

11. Other Relevant Regulatory Issues

None.

12. Labeling

Please see the safety labeling changes issued to the sponsor on February 28, 2011, and the final agreed upon labeling which will be appended to the supplement approval letter. The simvastatin approval letter also documents the differences between the labeling changes in the SLC notification letter and the final agreed upon labeling, a result of labeling negotiations with the sponsor.

13. Recommendations/Risk Benefit Assessment

Dr. Gortler did not make a regulatory recommendation in his review dated December 21, 2010.

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I recommend that based on the results of SEARCH, as well as other clinical trial data with high dose simvastatin, the 80 mg dose of simvastatin remain available to patients who have been taking this dose chronically, e.g., for 12 months or more, without signs or symptoms of significant muscle toxicity. For these individuals, I believe that the cardiovascular benefits of high-dose simvastatin outweigh the low absolute risk of rhabdomyolysis.

However, those patients who are currently tolerating the 80-mg dose of simvastatin who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for the drug-drug interaction. And, patients unable to achieve their LDL-C goal utilizing 40-mg simvastatin should be placed on appropriate LDL-C lowering therapy (e.g., a statin with greater potency and lower risk for drug interactions and lower risk for myopathy such as atorvastatin or rosuvastatin). For these patients the incremental increase in cardiovascular benefit may not be outweighed by the known increased risk of rhabdomyolysis noted in the first year of use.

In addition to labeling for restrictions in the use of simvastatin 80 mg, the label has also been updated with new contraindications and dose caps that have been modified based on a threshold for safe exposure consistent with exposure to simvastatin 40 mg. The safety findings from the SEARCH clinical trial have also been noted in the label.

The labels for Vytorin (ezetimibe/simvastatin) and Simcor (simvastatin/extended-release niacin) have been revised to be consistent with the simvastatin labeling changes.

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/s/

AMY G EGAN
06/01/2011

ERIC C COLMAN
06/01/2011
I agree with Dr. Egan's overall assessment and regulatory recommendations

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S077

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Prior Approval Supplement
Application Number(s)	NDA 19-766 E001
Priority or Standard	Standard (6-month)
Submit Date(s)	12 June 2009
Received Date(s)	12 June 2009
PDUFA Goal Date	12 December 2009
Division / Office	DMEP/ODE II
Review Name	David Gortler, PharmD, FCCP
Review Completion Date	December 12th 2009
Established Name	Zocor™
(Proposed) Trade Name	simvastatin
Therapeutic Class	3-hydroxy-3-methyl-glutaryl Co-enzyme A reductase inhibitors (“statins”)
Applicant	Merck
Formulation(s)	Oral tablet
Dosing Regimen	20 or 80mg orally each day, with and without folate plus vitamin B12.
Indication(s)	Hyperlipidemia; Reduction in risk of CHD mortality and cardiovascular events
Intended Population(s)	Adults

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List of Abbreviations and their Definitions

Abbreviation:	Definition:
4S	Scandinavian Simvastatin Survival Study
ACS	Acute Coronary Syndrome
ALT	Alanine Aminotransferas
ALP	Alkaline Phosphatase
Apo	Apolipoprotein
AST	Aspartate Aminotransferas
AUC	Area Under the Concentration-Time Curve
B_{12}	Vitamin B_{12}
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CCB	Calcium Channel Blocker
CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatine Kinase
CSR	Clinical Study Report
CTSU	Clinical Trial Service Unit
ECG	Electrocardiogram
GCP	Good Clinical Practice
GLP	Good Laboratory Pratice
GI	Gastrointestinal
GGT	Gamma-Glutamyltransferase
g	Gram
GTN	Glyceryl Trinitrate
HbA1c	Glycosylated Hemoglobin A1c
ICH	Conference on Harmonization
HDL-C	High-Density Lipoprotein Cholesterol
HMG CoA	Hydroxy-Methyl Coenzyme A
HRT	Hormone Replacement Therapy
HPS	Heart Protection Study
ICD-9	9th International Classification of Diseases
ICD-10	10th International Classification of Diseases
ICH	International Conference on Harmonization
IDEAL	Incremental Decrease in Endpoints Through Aggressive Lipid Lowering
ITT	Intention To Treat
LDL	Low-Density Lipoprotein Cholesterol
LREC	Local Research Ethics Committee
MCA	Medicines Control Agency
MCE	Major Coronary Events
Mg	Milligram
MI	Myocardial Infarction
MREC	Multicentre Research Ethics Committee
MSD	Merck Sharp & Dohme
MVE	Major Vascular Events
P-value	Probability Value
PE	Pulmonary embolism
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Treatment-Thrombolysis in Myocardial Infarction
PTCA	Percutanerous Transluminal Coronary Angioplasty
RR	Risk Ratio
SAE	Serious Adverse Experience
SD	Standard Deviation
SE	Standard Error

SEARCH	Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
SOP	Standard Operating Procedure
TG	Triglycerides
TIA	Transient Ischemic Attack
TNT	Treating to New Targets
TC	Total Cholesterol
UK	United Kingdom
ULN	Upper Limit of Normal
Var	Variance

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

A review of SEARCH's were formally presented at an FDA Regulatory Briefing. This presentation detailed the skeletal muscle safety and efficacy profile of simvastatin 80mg as well as the use pattern of simvastatin 80mg in the United States since becoming generic.

Following the Regulatory Briefing, further discussion took place with the sponsor and internally, including a Safety First Steering Committee (held on Tuesday, December 21, 2010). It was the final recommendation of members of the Immediate Office to withdraw simvastatin 80mg from the market.

1.2 Risk Benefit Assessment

- See Section 6.1.4 Analysis of Primary Endpoint
- See Section 6.1.5 Analysis of Secondary Endpoints

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

1.4 Recommendations for Postmarket Requirements and Commitments

See above

2 Introduction and Regulatory Background

2.1 Product Information

Simvastatin is an HMG-CoA reductase inhibitor or statin. It is approved as an adjunct to diet to reduce the risk of total mortality by reducing CAD deaths and reduce the risk of non-fatal myocardial infarction, stroke, and the need for revascularization procedures in patients at high risk of coronary events. Simvastatin is also indicated to reduce elevated total, LDL, Apo-B, TG, and

increase HDL in patients with primary hyperlipidemia (heterozygous familial and non-familial) and mixed dyslipidemia.

Safety concerns with simvastatin include skeletal muscle effects (ie, myopathy and rhabdomyolysis), persistent elevations in hepatic transaminase, and multiple drug interactions associated with an increased risk of myopathy/rhabdomyolysis, as well as postmarketing reports of an apparent hypersensitivity syndrome, memory impairment and peripheral neuropathy.

2.2 Currently Available Statins

The following statins are currently approved in the US: fluvastatin, lovastatin, pravastatin, simvastatin, atorvastatin, rosuvastatin, and pitavastatin.

2.3 Availability of Proposed Active Ingredient in the United States

Simvastatin was approved for use in the US on 23 December 1991 and is widely available as Zocor™ and as generic simvastatin. The 80mg dose strength was approved in the US on 10 July 1998 in Supplement 19766-028.

2.4 Important Safety Issues with Consideration to Related Drugs

See Section 7

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

7/98: NDA 19-766 S028: The 80mg dose strength was approved in the US on 10 July 1998 in Supplement 19766-028.

(b) (4)

3/05: Merck submission of 18 March 2005 (Supplement 069, which was a response to the September 29, 2004, AE action letter) concerning Zocor and the risk of myopathy. Merck included interim data on myopathy and rhabdomyolysis from SEARCH. Internal comments from

that review state that the risk of myopathy will need to be reevaluated after the SEARCH study is finalized to determine if the 80mg dose of simvastatin presents an unacceptable risk.

11/08: DMEP was informed on 6 Nov 08 that on Sunday 9 November 2008, Professor Jane Armitage and Professor Rory Collins of Oxford University will present data concerning simvastatin at the American Heart Association meeting in New Orleans. The presentation will summarize the results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), a clinical outcomes trial that included a comparison of simvastatin 80mg to simvastatin 20mg in myocardial infarction survivors. Merck expected that sometime in early 2009, Oxford University will publish a complete description of SEARCH. With the assistance of Oxford, Merck will generate a clinical study report which will be submitted to the agency.

01/09: On 22 Jan 09 DMEP had requested details on all the cases of myopathy and rhabdomyolysis that occurred during SEARCH. On 3 Feb 09 Merck responded to DMEP's questions concerning NDA 19-766 and myopathy in SEARCH. The draft Section 12.2.4 from the CSR for SEARCH that was being assembled by Merck and Oxford was submitted.

2.6 Other Relevant Background Information:

Publications based on this study:

- SEARCH Study Collaborative Group. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): Characteristics of a randomized trial among 12064 myocardial infarction survivors. Am Heart J 2007; 154: 815-823.
- SEARCH Study Collaborative Group. SLCO1B1 Variants and Statin-Induced Myopathy – A Genomewide Study. NEJM 2008; 359: 788-99.

SEARCH was conducted by the Clinical Trial Service Unit at Oxford University, and Oxford controls the primary data. This submission contains the Clinical Study report but does not include Case Report forms, SAS datasets, or any Case Report Tabulations.

3 Ethics and Good Clinical Practices:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human patients participating in biomedical research.

The application for SEARCH was submitted by the coordinating center (The Clinical Trial Service Unit at Oxford University) to the South Thames Multicentre Research Ethics Committee. The CTSU at Oxford University was responsible for the organization and conduct of the study, analysis of the data, and publication of the study results. In this capacity, CTSU was responsible for conducting the trial in compliance with applicable local (UK) regulations and ICH guidelines. The CTSU was responsible for obtaining MREC approval; for the training and

monitoring of all staff directly involved in the study; for the supply of packaged study drugs and other study materials; for the identification, with the assistance of the local medical collaborators and study clinic staff, of potentially eligible patients; for obtaining permission to invite suitable patients to each study clinic; for the initial invitation of patients to screening clinics and for allocation of subsequent clinic appointments; for central randomizations, unblinding when medically necessary, and reporting of any serious adverse events believed to be due to study treatment); and for the collection and analysis of data and blood samples. In addition, the CTSU was also responsible for obtaining information on possible endpoint events from the patient's GP and the UK Office of National Statistics which maintains a registry of death by cause as well as details of reported cancers. Financial support and drug supplies for the study were provided by Merck.

Eighty-eight (88) sites in the UK participated in this study. The primary investigators in each clinic obtained local ethics committee approval and appointed senior nurses to run the study clinics. No site audits were conducted specific to this protocol.

3.1 Financial Disclosures

Financial disclosures are not applicable to labeling supplements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

See Clinical Pharmacology section.

4.1 Clinical Pharmacology Review:

Not submitted

5 Sources of Clinical Data

This submission contains the results of one study, SEARCH, which was conducted by the Clinical Trial Service Unit at Oxford University. This study report will focus on the cholesterol lowering arm of SEARCH and not the homocysteine lowering with folic acid and vitamin B12 arm.

This submission contains the Clinical Study report but does not include Case Report forms, SAS datasets, or any Case Report Tabulations.

6 Study Design and Efficacy Analysis

Sponsor's Efficacy Summary

Simvastatin dose comparison:
Primary Comparison - MVE: MVEs were pre-defined as MCEs (fatal CHD, non-fatal MI or coronary revascularization procedure), non-fatal or fatal stroke, or peripheral revascularization (peripheral artery angioplasty, or arterial surgery including amputations).

The relative risk reduction in MVE in patients randomized to simvastatin 80mg compared with 20mg was 6%, although this was not statistically significant, (p=0.10).

Table 1: Risk reduction between simvastatin doses in SEARCH:

	Simvastatin 80mg N=6031		Simvastatin 20mg N=6033		Risk Ratio (95% CI)	p-value
	Number of events	Incidence (%)	Number of events	Incidence (%)		
Major Vascular Events	1477	(24.5%)	1553	(25.7%)	0.94 (0.88, 1.01)	0.10

Source: Sponsor's Table 11-1

Review comment: The risk absolute reduction between the 20 and 80mg simvastatin groups was 1.2% and the relative risk reduction was 6%. The p-value was 0.10 and therefore not statistically significant.

Many placebo-controlled clinical trials have shown that the benefit in risk reduction with statins related chiefly to the absolute reduction in LDL achieved. Using extrapolated data from a study from the LANCET[1] showed that a 13.5mg/dL change in LDL would be expected to convey a relative risk reduction of 8%.

To compare, TNT[2] examined 10 vs. 80mg of atorvastatin which showed a 2.2% absolute risk reduction and 22% relative risk reduction in major cardiovascular event (defined in TNT as coronary heart disease death, nonfatal myocardial infarction, resuscitated cardiac arrest, or stroke) between treatment groups. The risk reduction was statistically significant.

1 Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins *Lancet* 2005; 366: 1267–78
2 LaRosa JC, Grundy SM, Waters DD; Treating to New Targets (TNT) Investigators. Intensive lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005;352

Secondary Comparisons:

a) MVEs by year of follow-up:
There was no difference in the incidence of MVEs during the first year of follow-up. The relative risk reduction in MVE during two or more years of follow-up was 5%, although not statistically significant: RR 0.95; 95% CI (0.88, 1.03); p=0.23.

Review comment: The pre-randomization run-in period was 8-10 weeks long and dosed all patients with simvastatin 20mg.

Published data shows that vascular risk reduction with statin therapy takes 3-5 years, so a risk reduction during the first year would not be expected.

b) MVEs in subgroups of baseline LDL:
For subgroups of LDL <85 mg/dL, ≥85 to <104 mg/dL, and ≥104 mg/dL at baseline, which was the end of the pre-randomization run-in period on simvastatin 20mg daily, there was no evidence of heterogeneity of the effect on MVEs.

Review comment: There was no difference between the two different groups taking folate + B_{12} versus placebo. This report will focus on the safety and efficacy aspects of the 20 and 80mg dose comparisons of simvastatin.

d) MCEs and
e) Total strokes

The relative risk reduction for MCEs in patients randomized to simvastatin 80mg compared with 20mg was 4% and for fatal/nonfatal strokes 9%. These reductions in risk were not statistically significant. (see Table 2 below)

Table 2: MCE and total stroke difference between simvastatin doses

	Simvastatin 80 mg N=6031		Simvastatin 20 mg N=6033		Risk Ratio (95% CI)	p-value
	Number of events	Incidence (%)	Number of events	Incidence (%)		
Major Coronary Events	1189	(19.7%)	1225	(20.3%)	0.96 (0.89, 1.04)	0.37
Total Strokes	255	(4.2%)	279	(4.6%)	0.91 (0.77, 1.08)	0.30

Review comment: The risk reduction for MCEs and stroke between 20 and 80mg of simvastatin is lower than expected considering the tripling of a dose, and the difference was not statistically significant. Studies with newer statins examining the high/low doses have shown much larger differences between high and low doses.

Tertiary Comparisons:
Simvastatin 80mg compared with 20mg did not have an effect on total or vascular mortality, hemorrhagic or other strokes, or coronary revascularization procedures. In patients allocated simvastatin 80mg, the risk ratio for non-coronary revascularization was 0.77 (95% CI 0.62, 0.96; p=0.02).

Review comment: A difference might have been expected for vascular mortality, hemorrhagic or other strokes, or coronary revascularization procedures over the average 6.7-year duration of this trial.

Lipids:
The absolute difference between mean LDL levels in patients allocated to simvastatin 80mg and simvastatin 20mg over the course of the trial was 13.5 ± 0.39 mg/dL. There was a narrowing of the difference in LDL between the treatment groups during the course of the trial, probably due to the slow increase in LDL levels over time in patients taking 80mg of simvastatin. The reason for the increase in LDL over time with the use of simvastatin 80mg is not clear.

Review comment: Compliance was apparently not the reason for the increase in LDL in the 80mg group. The 84-month compliance for simvastatin 80mg was 77% and for 20mg it was 69%. LDL levels stayed very consistent in the 20mg group.

6.1 Indication

Merck does not seek an indication with this submission but seeks to add pertinent safety information to the Zocor label.

6.1.1 Methods

This was a multicenter, double-blind, active-treatment run-in, factorial-design study conducted in the UK only. Prior to randomization, potentially eligible patients entered a run-in period during which they received simvastatin 20mg daily and placebo-vitamin tablets for 8-10 weeks. Eligible patients who completed the run-in phase were then randomized in a 2x2 factorial blinded design between simvastatin higher-dose (80mg daily) versus standard-dose (20mg daily) and 2mg of folic acid + 1mg of vitamin B_{12} daily versus placebo. Follow-up visits after randomizations were scheduled at 2, 4, 8, and 12 months, and then every 6 months, for a mean follow-up period of 6.7 years.

Review comment: A total of 15,590 (45% of those screened) patients who entered the run-in did not enter randomization. The most common reason (23%) listed by the sponsor was "Serious concerns about the patient's willingness to comply with the study protocol." Additionally, of the 19,190 patients who entered the run-in, 7,123 (37%) dropped out. Of these 7,123 patients, 45 of these individuals dropped out because of elevated CK measurements, 105 dropped out due to elevated creatinine levels and 2,386 dropped out due to abnormal cholesterol laboratory values. Therefore, the 12,064 patients who ended up completing in this study would be considered to be an "enriched" population because of the various drop-outs during the run-in.

In 11% of patients screened, informed consent was not given. This is a fundamental violation of research protocol, but the sponsor did not provide an explanation for this. It is unclear if informed consent was obtained at a later time or not in these 11%.

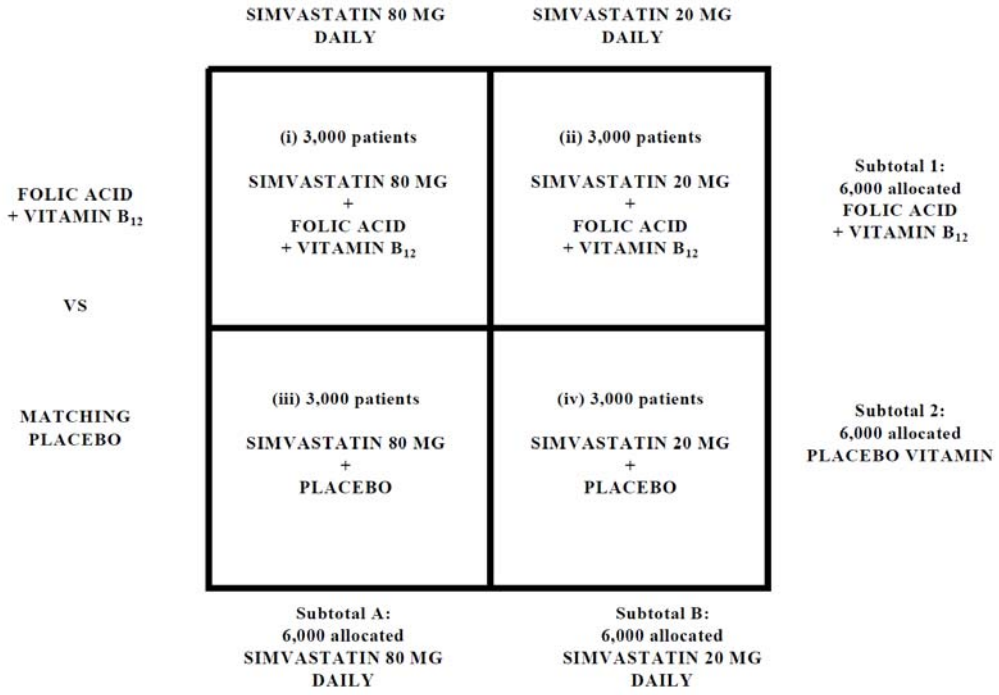
Lipid levels (TC, LDL, HDL, TG, apo-B, and apo- A1) were measured in non-fasting patients. To assess the overall effects of study treatment during follow-up on the detailed lipid profile and on homocysteine levels in the different treatment groups, the sponsor states that it was sufficient to assay levels in only 5-10% of the patients. Therefore, during the follow-up visits, lipids were assessed during a randomly selected period of a few weeks in each clinic each year. In addition, lipids and homocysteine were assessed in all participants during 2003 (during a nine month period beginning in mid February), and in all participants at the final visit between October 2007 and April 2008.

Review comment: Although more difficult in a trial of this size, measuring lipid levels in all patients in the fasting state would have provided more accurate cholesterol values. As an alternative to fasting measurements, direct cholesterol subfraction measurements could have also provided more accurate lipid readings. The sponsors' choice to measure detailed lipid profiles in only 5-10% of the population in this study is reasonable and has precedence in other large simple trials.

The simvastatin tablets (and folic acid 2mg and vitamin B_{12} 1mg tablets) were administered in the evening without regard to meals. The first dose of double-blind study drug was taken on 28-SEP-1998 and the last dose was taken on 21-MAY- 2008. The frozen file date was 27-JAN-2009.

The breakdown of doses are shown in the schematic which follows:

Figure 1: Study design schematic:



Study Objectives

Primary objectives
To assess, in high-risk patients, the effects on the incidence of total (i.e. fatal or not) MVE during the scheduled treatment period of the:

- Improved reduction in blood cholesterol produced by the higher simvastatin dose regimen; and
- Reduction in blood homocysteine produced by folic acid + vitamin B_{12}.

Secondary objective:
To assess the effects of the study treatments on total and fatal MVE in particular subgroups, and their effects on MCEs, strokes, major vascular procedures, total and cause specific mortality and on the incidence of cancer, and other conditions that require hospitalization.

Cholesterol reduction: Comparisons of Simvastatin 80mg versus 20mg daily:
For the cholesterol-lowering comparison with the different simvastatin doses, it was hypothesized that the more substantial cholesterol-lowering produced by simvastatin 80mg daily compared to simvastatin 20mg daily would reduce the incidence of non-fatal and fatal MVE without adversely affecting the incidence of other non-fatal or fatal serious adverse events (including: MCE, total stroke, arterial revascularization, total mortality, vascular mortality, CHD mortality) and that the same absolute reduction in cholesterol would be associated with similar proportional reductions in MVE risk throughout the blood cholesterol range studied.

Inclusion Criteria:
Men or women 18 to 80 years of age with a history of definite or "probable" diagnosis of myocardial infarction (MI) (>3 months before the study screening visit), clear indication for statin therapy while having no clear indication for routine folic acid, and a baseline total cholesterol ≥135 mg/dL in patients already on statin therapy, or ≥174 mg/dL in patients not already on statin therapy.

Review comment: the sponsor clarified that a "probable MI" meant that an MI was coded into the patient's study record based on the individual study physician's verbal history provided by the patients.

Exclusion Criteria:
Patients were excluded if they had the following laboratory values on their screening visit blood test:

- ALT >1.5xULN;
- ALT >1-1.5xULN and AST or ALP >2xULN;
- GGT, AST or ALP >4xULN;
- creatinine >2xULN; (v) CK >3xULN; or
- TC <3.5 mmol/L (<135mg/dL) on a statin or <4.5 mmol/L (<174mg/dL) if not on a statin.

Patients taking fibrates, high-dose niacin (>1 g per day), nefazodone, systemic azole antifungals, or the macrolide antibiotics clarithromycin or erythromycin were excluded as were patients with a clear contraindication to the study treatments (statins, folic acid or vitamin B12). Patients were also excluded if they had severe heart failure, or if they had a predominant medical problem (other than CHD) that might limit compliance with 5 years of study treatment. Pre-menopausal women not sterilized or not using a reliable method of contraception were also excluded from the study.

Method of Assigning Patient to Treatment Groups:
A computer generated randomization schedule was used for this study. Patients who did not have a MVE or other significant problem during the run-in period and were willing to take study medication for at least 5 years were randomized using a 24-hour computerized randomization service. A centralized randomization scheme was employed using a minimization algorithm to balance important patient characteristics (age, sex, previous medical history, BP, smoking, ethnic origin, prior statin use, and screening TC) ensuring even distribution among the different treatment groups.

6.1.2 Demographics

There were no clinically meaningful differences between treatment groups with regards to baseline characteristics. Eighty-three percent (83%) of the patients in each treatment group were male and 50% were 65 years of age or older. All patients had a previous MI, and about 42% had other cardiovascular disease as well. Approximately 10% of patients had diabetes mellitus.

Baseline lipids were measured when all participants had received simvastatin 20mg for 2 months, and mean LDL was 85 mg/dL in approximately 67%, and HDL-C was <35 mg/dL in approximately 37% of the patients in each treatment group.

Review comment: Baseline values are typically defined as values prior to study drug administration. In this study, the sponsor defined baseline as the lipid values following the run-in phase after patients have already received simvastatin 20mg for two months. LDL levels were not measured by the sponsor at the pre-run-in screening visit.

Baseline characteristics (following run-in) of randomized patients are provided in the table below for the simvastatin 80mg and simvastatin 20mg groups.

Table 3: Characteristics of Randomized Patients Following Run-in Period: (Number and Percentage or Mean ± SD)

	Simvastatin 80mg (N=6031)		Simvastatin 20mg (N=6033)	
Baseline characteristic	n	(%)	n	(%)
Prior disease				
MI alone	2955	(49%)	2890	(48%)
Other CHD (+ MI)	2484	(41%)	2557	(42%)
Cerebrovascular	417	(7%)	420	(7%)

	Simvastatin 80mg (N=6031)		Simvastatin 20mg (N=6033)	
Baseline characteristic	n	(%)	n	(%)
Peripheral vascular	138	(2%)	141	(2%)
Diabetes mellitus	633	(10%)	634	(11%)
Prior treated hypertension				
No	3495	(58%)	3495	(58%)
Yes	2536	(42%)	2538	(42%)
Gender				
Male	5005	(83%)	5007	(83%)
Female	1026	(17%)	1026	(17%)
Age at randomization (years)	64.2±8.9	---	64.2±8.9	---
<60	1880	(31%)	1885	(31%)
≥60<70	2414	(40%)	2414	(40%)
≥70	1737	(29%)	1734	(29%)
Diastolic BP (mmHg)	79±11	---	79±12	---
<75	2019	(33%)	2148	(36%)
≥75<85	2105	(35%)	1998	(33%)
≥85	1907	(32%)	1887	(31%)
Systolic BP (mmHg)	137±21	---	137±21	---
<125	1798	(30%)	1817	(30%)
≥125<145	2210	(37%)	2257	(37%)
≥145	2023	(34%)	1959	(32%)
Total cholesterol (mmol/L)	4.23±0.73	---	4.23±0.73	---
<4.0mmol/L (155mg/dL)	2460	(41%)	2397	(40%)
≥4.0<4.5 (≥155<174mg/dL)	1645	(27%)	1721	(29%)
≥4.5mmol (174mg/dL)	1926	(32%)	1915	(32%)
HDL cholesterol (mmol/L)	1.04±0.36	---	1.04±0.36	---
<0.9 (35mg/dL)	2238	(37%)	2320	(38%)
≥0.9<1.1	1516	(25%)	1446	(24%)
≥1.1 (43mg/dL)	2277	(38%)	2267	(38%)
LDL cholesterol (mmol/L)	2.50±0.61	---	2.50±0.61	---
<2.2 (85 mg/dL)	1975	(33%)	1958	(32%)
≥2.2<2.7	2015	(33%)	2012	(33%)
≥2.7 (105 mg/dL)	2041	(34%)	2063	(34%)
Apolipoprotein A1 (mg/dL)	135±22.3	---	135±22.3	---
<125	2078	(34%)	2102	(35%)
≥125<140	1742	(29%)	1709	(28%)
≥140	2211	(37%)	2222	(37%)
Apolipoprotein B (mg/dL)	89.8±16.7	---	90.0±16.8	---
<80	1765	(29%)	1736	(29%)
≥80<95	2184	(36%)	2202	(36%)
≥95	2082	(35%)	2095	(35%)
Triglycerides (mmol/L)	1.91±1.27	---	1.94±1.23	---
<1.3 (50 mg/dL)	2022	(34%)	1977	(33%)
≥1.3<2.0	1878	(31%)	1860	(31%)
≥2.0 (77 mg/dL)	2131	(35%)	2196	(36%)

Triglycerides (mmol/L)	1.91±1.27	---	1.94±1.23	---
<2.0 (177 mg/dL)	3900	(65%)	3837	(64%)
≥2.0<4.0	1831	(30%)	1851	(31%)
≥4.0 (355mg/dL)	300	(5%)	345	(6%)
Creatinine (µmol/L)	90±20	---	90±20	---
Normal	5747	(95%)	5721	(95%)
Elevated	284	(5%)	312	(5%)
Hemoglobin (g/dL)	14.3±1.2	---	14.3±1.2	---
<14	2175	(36%)	2198	(36%)
≥14<15	2053	(34%)	2104	(35%)
≥15	1803	(30%)	1731	(29%)
Platelets (1000/µL)	225±56	---	225±57	---
<200	1919	(32%)	1886	(31%)
≥200<240	2124	(35%)	2231	(37%)
≥240	1988	(33%)	1916	(32 %)
Mean cell volume (fL)	90.4±4.3	---	90.4±4.4	---
<89	1982	(33%)	2025	(34%)
≥89<92	1969	(33%)	1936	(32%)
≥92	2080	(34%)	2072	(34%)
Homocysteine (µmol/L)	13.4±4.5	---	13.5±5.1	---
<11	1727	(29%)	1744	(29%)
≥11<14	2283	(38%)	2287	(38%)
≥14	2021	(34%)	2002	(33%)
Folate (nmol/L)	16.8±10.2	---	16.9±10.7	---
<11	1935	(32%)	1980	(33%)
≥11<18	2131	(35%)	2070	(34%)
≥18	1965	(33%)	1983	(33%)
Vitamin B_{12} (pmol/L)	284.4±266.7	---	288.1±376.6	---
<220	1800	(30%)	1840	(30%)
≥220<300	2199	(36%)	2175	(36%)
≥300	2032	(34%)	2018	(33%)
Smoking				
Never regular	1373	(23%)	1370	(23%)
Ex-cigarette	3918	(65%)	3920	(65%)
Current	740	(12%)	743	(12%)
Alcohol (days/week)				
None	2324	(39%)	2312	(38%)
1-2	1377	(23%)	1445	(24%)
3-4	825	(14%)	814	(13%)
5-7	1505	(25%)	1462	(24%)
Alcohol (units/week)				
None	2321	(38%)	2310	(38%)
1-21	3015	(50%)	2989	(50%)
≥22	695	(12%)	734	(12%)
Body mass index (kg/m²)	28±4	---	28±4	---
Lean	1316	(22%)	1282	(21%)
Overweight	2814	(47%)	2904	(48%)

Obese	1901	(32%)	1847	(31%)
HbA_1c (%) in diabetics	7.41±1.6	---	7.42±1.6	---
<7.0	200	(3%)	203	(3%)
≥7.0	270	(4%)	261	(4%)
Ethnic origin				
White	5902	(98%)	5900	(98%)
Asian - Indian/Pakistani	76	(1%)	69	(1%)
Asian - Chinese	1	(0%)	1	(0%)
Black - African	0	(0%)	1	(0%)
Black - Caribbean	6	(0%)	14	(0%)
Black - other	4	(0%)	1	(0%)
Other	16	(0%)	16	(0%)
Estimated GFR (Cockcroft-Gault)(mL/min)	87±28	---	87±29	---
<60	958	(16%)	977	(16%)
≥60	5073	(84%)	5056	(84%)
Estimated GFR (MDRD) (mL/min)	79±18	---	79±19	---
<60	820	(14%)	866	(14%)
≥60	5211	(86%)	5167	(86%)
Conversion factor for mmol/L to mg/dL for cholesterol is 38.7 and 88.6 for triglycerides.				

Data Source: Sponsor Table 10-9

Approximately 72% of patients in each group were taking at least one lipid-lowering medication at the screening visit. The most common medication with prior use at screening was simvastatin.

Patients were instructed to stop taking non-study statin prior to beginning treatment with simvastatin 20mg during the run-in period. There were no clinically meaningful differences between treatment groups in the use of non-study treatments other than lipid lowering medications at baseline.

The use of non-study lipid lowering treatments at baseline are summarized in the following table.

Table 4: Use of Non-Study Lipid-Lowering Treatments at Baseline

	Simvastatin 80mg (N=6031)		Simvastatin 20mg (N=6033)	
	n	(%)	n	(%)
Non-study statins at Screening				
Atorvastatin	770	(12.8%)	793	(13.1%)
Cerivastatin	282	(4.7%)	287	(4.8%)
Fluvastatin	183	(3.0%)	164	(2.7%)
Pravastatin	475	(7.9%)	494	(8.2%)
Simvastatin	**2635**	**(43.7%)**	**2605**	**(43.2%)**
Lovastatin	0	(0.0%)	2	(0.0%)
Other lipid-lowering at Randomization				
Fibrates	0	(0.0%)	0	(0.0%)
Resins	2	(0.0%)	3	(0.0%)
Other	0	(0.0%)	0	(0.0%)
Any lipid-lowering	4345	(72.0%)	4347	(72.1%)

Source: Sponsor's Table 10-10

6.1.3 Patient Disposition

Patients were screened following which they entered a run-in phase for 8-10 weeks followed by a randomization to one of four different study groups for a period of 12 months. Following the 12-month randomization, patients were followed-up for an average of 6.7 years. The breakdown of the patient drop-outs for each stage of the study were as follows:

Drop outs during screening period:
A total of 34,780 patients were screened. Of these 15,590 (45% of those screened) did not enter the run-in phase of the study. In some cases, there were multiple reasons for not entering run-in. The most common reason was that there were serious concerns about the patient's willingness to comply with the study protocol (23%).

Table 5: Reasons that screened patients did not enter the run-in phase

Reason given (may give more than one)	n	(%)
Screened	34,780	(100%)
Denied having MI	453	(1%)
MI, angina admission, CABG or PTCA in last 3 months	684	(2%)
CABG or PTCA planned in next 3 months	264	(1%)
Severe heart failure	631	(2%)
Severely disabling stroke	74	(<1%)
Chronic liver disease	217	(1%)
Severe kidney disease	318	(1%)
Inflammatory muscle disease	182	(1%)
Childbearing potential	55	(<1%)
Other life-threatening non-vascular disease	1,153	(3%)
Serious concern about likely compliance or unwilling to comply	8,014	(23%)
Contraindicated drug	798	(2%)
Informed consent not given in otherwise eligible patient	3,789	(11%)
No reason given	76	(<1%)
Screened but did not enter run-in	15,590	(45%)
Entered run-in	19,190	(55%)

Source: Sponsor's Table 10-2

Drop outs during run-in period:
Of the total number of patients who were screened, entered run-in, and were randomized but who completed or were discontinued from simvastatin 80mg or simvastatin 20mg, are in shown in the following table:

Table 6: Disposition of Patients Entering Run-in.

	Simvastatin 80mg	Simvastatin 20mg	Total
Screened	---	---	34,780
Entered Run-In	---	---	19,190
Completed Run-In	---	---	13,548
Randomized	6,031	6,033	12,064
Completed Study Medication	4,377	3,973	8,350
Discontinued Study Medication†	1,654	2,060	3,714
Lost to Follow-up for Mortality	11	11	22
Lost to Follow-up for Morbidity	68	49	117
†Patients who discontinued study medication were still followed for outcomes.			

Source: Sponsor's Table 10-1.

Of the 19,190 patients who entered the run-in phase 12,064 were ultimately randomized: In the simvastatin 80mg 6,031 patients were randomized and in the simvastatin 20mg group and 6,033 patients were randomized.

There were 5,642 patients who entered run-in and then dropped out of the run-in phase before the randomization visit. The most common reason (in 2,811 patients) was "blood test results from the screening visit that did not meet the eligibility criteria for the study." In 2,386 patients (12%),

serum cholesterol was below the entry criteria cut-off. Liver function tests did not meet eligibility criteria in 343 patients (2%), elevated CK >3-fold ULN was present in 45 patients and elevated creatinine >2-fold ULN in 105 patients.

Table 7: Reasons for Dropping Out of Run-In Phase Before Randomization Appointment

Reason given (may give more than one)	n	(%)
Entered run-in	19,190	(100%)
Screening blood results	2,811	(15%)
Cholesterol	2,386	(12%)
Liver function	343	(2%)
ALT	253	(1%)
GGT	94	(<1%)
Other LFT	76	(<1%)
CK	45	(<1%)
Creatinine	105	(1%)
Vetoed	261	(1%)
GP	180	(1%)
Collaborator	86	(<1%)
Randomization appointment cancelled by patient	1,657	(9%)
Patient wishes	943	(5%)
Unexplained muscle pain	102	(1%)
Unwell or possible side effects	376	(2%)
MI or stroke during Run-in	24	(<1%)
CABG or PTCA planned in next 6 months	7	(<1%)
Medical advice	153	(1%)
Admitted with angina during Run-in	10	(<1%)
Cancer reported during Run-in	7	(<%)
Other SAE during Run-in	7	(<1%)
Missed randomization appointment, too late to rebook	6	(<1%)
On contraindicated drug	5	(<1%)
Not eligible	6	(<%)
In another trial	7	(<1%)
Other reasons	4	(<1%)
No reason given	968	(5%)
Dropped out of run-in before randomization appointment	5,642	(29%)
Completed run-in	13,548	(71%)

Source: Sponsor's Table 10-3

Review comment:
As shown in the preceding table, SEARCH's run-in period had a significant number of drop-outs. The 8-10 week run in period washed out ~7,000 patients (approx 37%) who had abnormal laboratory values or who were poor responders to simvastatin therapy. The ~12,000 patients who ended up completing in this study would therefore be considered an "enriched" population.

The number of adverse events which took place may have been larger had all 19,000+ patients been allowed to complete this study. Additionally, final efficacy findings were affected because patients not achieving their goal simvastatin 20mg were dropped during the run-in.

Drop outs during randomization period:

Table 8: Reasons for Dropping Out of Run-In Phase During Randomization Appointment

Reason given (may give more than one)	n	(%)
Completed run-in	13,548	(100%)
MI, hospitalization for angina, CABG or PTCA during Run-in	94	(1%)
New unexplained muscle pain	316	(2%)
Other SAE which renders patient ineligible	11	(0%)
Non-compliant with Run-in treatment	299	(2%)
Patient reluctant to continue	1,042	(8%)
Likely problems attending regular clinics	290	(2%)
CABG/PTCA planned in next 3 months	23	(<1%)
Other reasons for non compliance	167	(1%)
- Unwell/possible side effects	29	(<1%)
- Medical advice	17	(<1%)
- Awaiting surgery	5	(<1%)
- SAE during Run-in	3	(<1%)
- Cardiovascular symptoms	5	(<1%)
- Gastrointestinal symptoms	61	(<1%)
- Respiratory/ENT symptoms	2	(<1%)
- Urinary/gynecological symptoms	1	(<1%)
- Neuro/psychological symptoms	36	(<1%)
- Rash/skin symptoms	13	(<1%)
- Non-specific symptoms	16	(<1%)
- Other	5	(<1%)
Unknown reason	97	(1%)
Dropped out of run-in during randomization appointment	1,484	(11%)
Randomized	12,064	(89%)

Source: Sponsor's Table 10-4

Drop outs during follow-up period:
Reasons for stopping simvastatin 80mg or simvastatin 20mg before the end of the study are shown in following table.

Table 9: Reasons for Stopping Study Simvastatin Tablets Before Scheduled End

	Simvastatin 80mg (N=6031)		Simvastatin 20mg (N=6033)	
Reason(s) given	**n**	**(%)**	**n**	**(%)**
Patient wishes to stop	711	(11.8%)	792	(13.1%)
Unwilling to attend clinics	184	(3.1%)	225	(3.7%)
Contraindicated drug started	19	(0.3%)	20	(0.3%)
Abnormal liver or muscle enzymes (unknown which)	103	(1.7%)	30	(0.5%)
Abnormal LFTs	1	(0.0%)	0	(0.0%)
Muscle pain or weakness	63	(1.0%)	34	(0.6%)
Medical advice	654	(10.8%)	1,099	(18.2%)
Other symptoms	90	(1.5%)	100	(1.7%)
Other reasons	104	(1.7%)	95	(1.6%)
Any of the above	1,654	(27.4%)	2,060	(34.1%)

†This table includes patients who stopped study simvastatin tablets plus folic acid + B_{12} or placebo-folic acid + B_{12} tablets, as well as patients who stopped only study simvastatin tablets.

Source: Sponsor's Table 10-5.

During the 6.7 years of the study, 1,654 (27.4%) patients in the simvastatin 80mg group and 2,060 (34.1%) in the simvastatin 20mg group stopped taking simvastatin study treatment. This includes patients who stopped taking both simvastatin treatment and vitamin treatment, as well as patients who stopped taking study simvastatin treatment but continued study vitamin treatment.

Review comment:
It is not clear whether the reasons for stopping treatment in the table above are due to simvastatin or the folate or B12.

Patients Whose Treatment Was Prematurely Unblinded:
As shown in the table below, treatment was unblinded before study end in 72 patients allocated to simvastatin 80mg and nine patients allocated to simvastatin 20mg. The most common reason for unblinding were muscle -related issues, specifically myopathy.

Table 10: Patients Unblinded Before Scheduled End of Trial

	Simvastatin 80mg (N=6031)		Simvastatin 20mg (N=6033)	
Reason for unblinding	n	(%)	n	(%)
Need for open statin treatment	8	(0.1%)	1	(<0.1%)
Muscle related issues (myopathy/ rhabdomyolysis)	54	(0.9%)	2	(<0.1%)
Liver disease or elevated liver enzymes	2	(<0.1%)	1	(<0.1%)
Other biochemical abnormality	1	(<0.1%)	0	(0.0%)
Other	9	(0.1%)	5	(0.1%)
Total	74	(1.2%)	9	(0.1%)

Source: Sponsor's Table 10-8

Review comment:
Row 2 in the table above was originally labeled as "muscle related issues." In this review, the table was changed to specify the terms "myopathy" and "rhabdomyolysis." This review also updated the number of cases in the simvastatin 80mg group based on the more commonly accepted definition of rhabdomyolysis. There was a higher than expected incidence of myopathy/ rhabdomyolysis in SEARCH, and accordingly it will be one of the major focus points of this review.

It is unclear what "need for open statin treatment" means in the above table. The values shown above do not represent discontinuing a statin due to AEs or the need for better efficacy. (For these values, see 'nonstudy statin use,' Table 15, page 37)

6.1.4 Analysis of Primary Endpoint

The primary comparison for the simvastatin dose allocation was major vascular events (MVE), defined as major coronary events (MCE), non-fatal or fatal stroke, or peripheral revascularization (peripheral artery angioplasty or arterial surgery, including amputations), during the scheduled study treatment period. MCE was defined in this study as fatal CHD, non-fatal MI or coronary revascularization procedure (CABG or PCTA).

Review Comment:
This reviewer agrees with the MCE+stroke composite endpoint, however the addition of peripheral revascularization (amputation, carotid surgery, aortic aneurysm surgery, leg revascularization, and other revascularizations) may only represent a surrogate marker for atheroprogression, but they do not always represent a valid surrogate for CV mortality.

Pre-study-completion approximations on SEARCH:
In the initial protocol, the primary comparison was specified to be the incidence of MCEs during the scheduled treatment period. After randomization, study treatment was scheduled to continue for a minimum of 4 years median follow-up (i.e. at least 4 years after randomization of 6,000 patients) until at least 1,900 patients have had confirmed MCE defined as fatal CHD, non-fatal MI, or coronary revascularization procedure. It was estimated prior to the start of SEARCH that the annual rate of MCEs on simvastatin 20mg daily would be about 4% and the LDL difference between 80 and 20mg would be ~19.4 mg/dL. However, after a median of 3-4 years of follow-up, both the overall vascular event rate (annual MCE rate during the first 4 years of follow-up in both treatment groups of SEARCH combined was only about 2.7%) and the LDL difference (~13.5 mg/dL) were smaller than originally anticipated. Consequently based upon discussions at the March 2004 meeting of the Steering Committee, it was decided (blind to the interim results for clinical outcomes) to expand the primary outcome to MVE. In 2005 the Steering Committee agreed to continue the trial until a total of at least 2800 patients had confirmed MVEs.

Screening requirements for MI
The diagnosis of MI required:

1. The presence of two or more of the following:
   - Typical ischemic chest pain, pulmonary edema, syncope or shock;
   - Development of pathological Q-waves and/or appearance or disappearance of localized ST-elevation followed by T-wave inversion in two or more of 12 standard electrocardiograph leads; and
   - Increase in concentration of serum enzymes consistent with MI (e.g. troponins or CK >2xULN); or

Review comment:

In this study an MI required a diagnosis as per above. A "Probable MI" refers to the individual physician's diagnosis of MI in the medical history if the above criteria were not expressly articulated in the patient's chart.

2. Necropsy findings of MI of an age corresponding to time of onset of symptoms ("silent" MIs were not to be included). For any strokes reported, information was sought for review particularly of likely etiology (i.e. hemorrhagic or not) and severity.

Primary Endpoint:

Effect of Simvastatin 80mg and Simvastatin 20mg on Major Vascular Events (MVEs):
The MVE incidence comprised coronary and non-coronary vascular events. There were fewer MVEs over the entire study period in the simvastatin 80mg group compared to the simvastatin 20mg treated group.

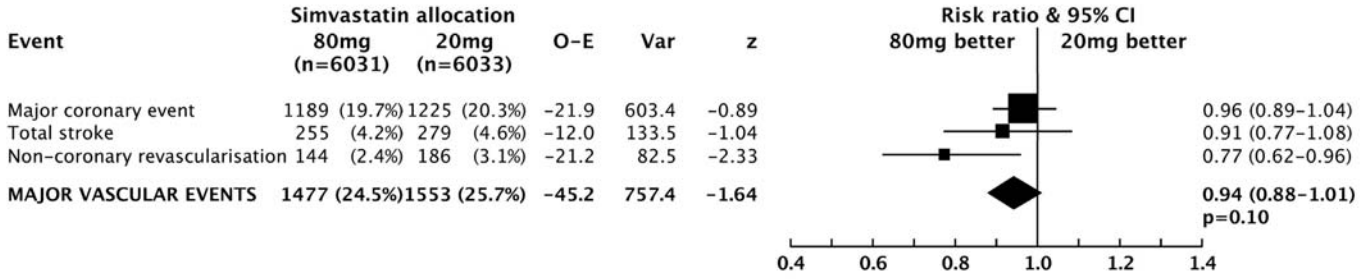
As shown in Table and Figure below, the relative risk reduction in MVEs was 6%, and not statistically significant (p=0.10). The absolute risk reduction between the 20 and 80mg groups was 1.2%.

Table 11: Effect of Simvastatin 80mg and Simvastatin 20mg on Major Vascular Events

	Simvastatin 80mg N=6031		Simvastatin 20mg N=6033		Risk Ratio (95% CI)	p-value
	Number of events	Incidence (%)	Number of events	Incidence (%)		
Major Vascular Events	1477	(24.5%)	1553	(25.7%)	0.94 (0.88, 1.01)	0.10

Source: Sponsor's Table 11-1

Figure 2: Primary Endpoint: Major Vascular Events (MVE)



Source: Sponsor's Figure 14-1

Review Comment:
The 6.7 year duration of this trial should have been adequate to show a decrease in MVE between the 20 and 80mg doses. Although there was a decrease in the incidence MVE with the 80mg dose when compared with the 20mg dose, the difference was less than what was expected, and there was an increased risk of skeletal muscle AEs associated with 80mg.

Prior to SEARCH, there was only one other study which compared a single statin at the high and low dose. The Treating to New Targets (TNT) trial was a parallel-group study that randomized 10,003 patients in who had stable CAD and an average baseline LDL cholesterol of 152mg/dL to either atorvastatin 10 or 80mg. During the run in period, atorvastatin 10mg was associated with an LDL reduction to 98mg/dL or 35%.

In TNT, atorvastatin 80mg/day was associated with a 48.3% reduction in LDL cholesterol to 77mg/dL and a 22% relative and 2.2% absolute risk reduction in CV events (defined as death from CHD, nonfatal, non-procedural-related myocardial infarction, fatal or non-fatal stroke) compared to 10mg/day of atorvastatin which reduced the mean LDL cholesterol to 101 mg/dL.

In contrast to TNT's results, the SEARCH study found that between 20 and 80mg of simvastatin the absolute difference in mean LDL was 13.5 ± 0.39 mg/dL (an approximate 13.9% difference).

Of note, TNT was not a perfect comparison to SEARCH, since SEARCH used low-dose simvastatin (20mg), but not the starting dose of simvastatin (10mg). (TNT's comparison was between the highest and lowest marketed dose of atorvastatin.) Event with this consideration, the relative CV event risk reduction seen in SEARCH (6%) is not comparable to that seen in TNT (22%).

6.1.5 Analysis of Secondary Endpoints

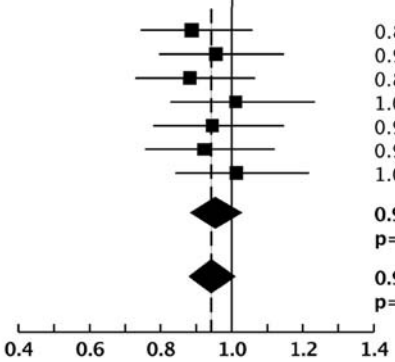
1. MVEs separately in the first year after randomization (when little difference is anticipated) and in the later years of the scheduled treatment period;

2. MVEs among patients subdivided into 3 similar-sized groups with respect to blood cholesterol levels at the end of the pre-randomization run-in period on simvastatin 20mg daily (with the hypothesis that the same absolute reduction in LDL will be associated with similar proportional reductions in vascular risk in each of these groups);
3. MVEs in the presence and in the absence of the allocated study folic acid + vitamin B12 (with the hypothesis that the effects will be similar);
4. MCEs; and
5. Total strokes.

MVEs separately in the first year after randomization:
The incidence of MVEs during the first year of treatment and during the later years of the treatment period (two or more years of treatment) was slightly lower in simvastatin 80mg treated patients compared to those treated with simvastatin 20mg but the risk ratio was not statistically significant.

Figure 3: Major Vascular Events by Year of Follow-Up

Year of follow-up	Simvastatin allocation 80mg		Simvastatin allocation 20mg		O-E	Var	z	Risk ratio & 95% CI (80mg better | 20mg better)
1	232/6031	(3.8%)	261/6033	(4.3%)	-14.8	123.2	-1.34	0.89 (0.74-1.06)
2	224/5782	(3.9%)	233/5752	(4.1%)	-5.3	114.2	-0.49	0.95 (0.79-1.15)
3	202/5519	(3.7%)	227/5474	(4.1%)	-13.5	107.2	-1.30	0.88 (0.73-1.07)
4	195/5257	(3.7%)	191/5201	(3.7%)	1.0	96.5	0.11	1.01 (0.83-1.23)
5	202/5012	(4.0%)	211/4955	(4.3%)	-5.8	103.2	-0.57	0.95 (0.78-1.15)
6	193/4741	(4.1%)	207/4687	(4.4%)	-8.2	100.0	-0.82	0.92 (0.76-1.12)
7+	229/4463	(5.1%)	223/4404	(5.1%)	1.4	113.0	0.13	1.01 (0.84-1.22)
2+	**1245/5782**	**(21.5%)**	**1292/5752**	**(22.5%)**	**-30.4**	**634.2**	**-1.21**	**0.95 (0.88-1.03) p=0.23**
ALL FOLLOW-UP	**1477/6031**	**(24.5%)**	**1553/6033**	**(25.7%)**	**-45.2**	**757.4**	**-1.64**	**0.94 (0.88-1.01) p=0.10**



Source: Sponsor's Figure 14-2

MVEs among patients by tertiles of baseline LDL:
The incidence of MVEs among patients subdivided by tertiles of baseline levels of LDL is summarized in the following table:

Table 12: Effect of Simvastatin 80mg and Simvastatin 20mg on Major Vascular Events by Baseline LDL Value

	Simvastatin 80mg		Simvastatin 20mg		
Baseline LDL (mg/dL)	Number of events	Incidence (%)	Number of events	Incidence (%)	Het χ^2
< 85	473/1975	(23.9%)	503/1958	(25.7%)	0.87 2 d.f.
≥ 85 to < 104	474/2015	(23.5%)	478/2012	(23.8%)	
≥ 104	530/2041	(26.0%)	572/2063	(27.7%)	

Source: Sponsor's Table 11-3

MVEs in the presence and in the absence of the allocated study folic acid + vitamin B12:
There was no significant heterogeneity in those who were receiving folate + B12 and those who were not. The incidence of MVEs in the presence or absence of folic acid + vitamin B12 is provided in following table:

Table 13: Effect of Simvastatin 80mg and Simvastatin 20mg on Major Vascular Events by Folate + B12 Allocation

	Simvastatin 80 mg		Simvastatin 20 mg		
Folate + B_{12} allocation	Number of events	Incidence (%)	Number of events	Incidence (%)	Het χ^2
Placebo	745/3015	(24.7%)	748/3016	(24.8%)	2.11 1 d.f.
Active	732/3016	(24.3%)	805/3017	(26.7%)	

Source: Sponsor's Table 11-4

Review Comment:
There does not appear to be any benefit to combining simvastatin with the combination of folate + B12 in this study. Accordingly, the differences between the groups taking folate+B12 and those not taking folate +B12 will not be discussed.

Major Coronary Events (MCEs):
MCE was pre-defined as a composite of fatal CHD, non-fatal MI, or coronary revascularization procedure (CABG or angioplasty). There was no statistically significant difference between the two groups.

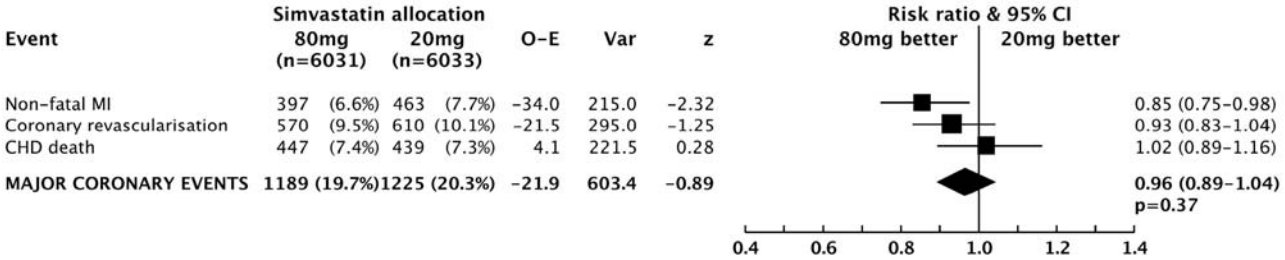
Table 14: Effect of Simvastatin 80mg and Simvastatin 20mg on Major Coronary Events

	Simvastatin 80 mg N=6031		Simvastatin 20 mg N=6033			
	Number of events	Incidence (%)	Number of events	Incidence (%)	Risk Ratio (95% CI)	p-value
Major Coronary Events	1189	(19.7%)	1225	(20.3%)	0.96 (0.89, 1.04)	0.37

Source: Sponsor's Table 11-5

The components of MCEs were evaluated separately are shown in the figure below.

Figure 4: Major Coronary Events (MCEs):



Source: Sponsor's Figure 14-4

The RR for nonfatal MI in patients allocated simvastatin 80mg versus simvastatin 20mg was 0.85 (95% CI 0.75-0.98). For CHD death, the RR was 1.02 (95% CI 0.89-1.16) and for coronary revascularization 0.93 (95% CI 0.83-1.04).

Total strokes:
There was no statistically significant difference between the two groups for the incidence of total strokes, as shown in the following table:

Table 15: Effect of Simvastatin 80mg and Simvastatin 20mg on Total Strokes

	Simvastatin 80 mg N=6031		Simvastatin 20 mg N=6033			
	Number of events	Incidence (%)	Number of events	Incidenc e (%)	Risk Ratio (95% CI)	p-value
Total Strokes	255	(4.2%)	279	(4.6%)	0.91 (0.77, 1.08)	0.30

Source: Sponsor's Table 11-6

6.1.6 Other Endpoints

1. Total mortality;
2. Cause-specific mortality (i.e. considering separately deaths from vascular causes, and non-vascular causes);
3. Vascular mortality excluding the first year after randomization (when little difference is anticipated);
4. Coronary revascularizations (i.e. CABG and/or PTCA) and non-coronary revascularizations (i.e., peripheral artery angioplasty, or arterial surgery including amputations);
5. Confirmed hemorrhagic and other strokes considered separately;
6. Pulmonary embolus;
7. Total and site-specific cancers;
8. Hospitalizations for various causes; and
9. Possible adverse effects of treatment, including, in particular, evidence of liver function abnormalities (defined as two or more consecutive elevations of ALT >4xULN) and evidence of muscle abnormalities (defined as any elevation of CK >10xULN).

6.1.7 Subpopulations

Consistency of treatment effect on the primary endpoint was evaluated by examining the 95% confidence intervals for the risk ratio within a variety of subgroups based upon baseline characteristics.

There is an apparent heterogeneity for diastolic and systolic BP levels, favoring the 80mg group in patients with diastolic BP of 75 mm Hg or greater, and with systolic BP of 125 mm Hg or greater, and the 20mg group in patients with lower values. The sponsor states that there is no biological rationale for this difference.

Review comment:
As shown in the figure which follows, the 20mg dose was favored by the tertile of patients that had the lowest blood pressure (diastolic <75mmHg and systolic <125mmHg)

Several studies have reported a slight beneficial reduction in blood pressure reduction associated with the administration of statins, [3,4,5] but none of them stratified the effect with regards to baseline blood pressures. In this review the blood pressure effect was more favorable in the 20mg group in those subjects with a low baseline BP. Therefore, the BP effect appears to be related to baseline characteristics and not simvastatin dose.

3 Do statins lower blood pressure? J Cardiovasc Pharmacol Ther. 2007 Jun;12(2):112-23

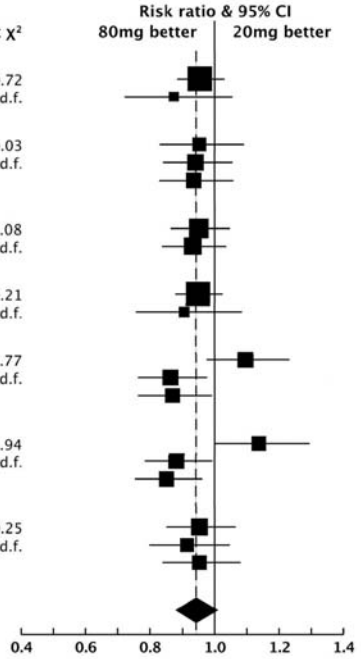
4 Statins and blood pressure: is there an effect or not? J Clin Hypertens (Greenwich). 2007 Jun;9(6):460-7

5 Beyond lipid lowering: the anti-hypertensive role of statins Cardiovasc Drugs Ther. 2007 Jun;21(3):161-9

Figure 5: Baseline Characteristics by Simvastatin Doses

The baseline data for age, gender, systolic and diastolic BP, history of diabetes mellitus, and baseline lipid and lipid levels are shown in the following figure:

Presentation feature	Simvastatin allocation 80mg	Simvastatin allocation 20mg	O−E	Var	z	Het χ^2
Gender						
Male	1277/5005 (25.5%)	1325/5007 (26.5%)	−30.8	650.4	−1.21	0.72
Female	200/1026 (19.5%)	228/1026 (22.2%)	−14.6	107.0	−1.41	1 d.f.
Age at randomisation (years)						
<60	406/1880 (21.6%)	424/1885 (22.5%)	−10.2	207.5	−0.71	0.03
≥60 <70	574/2414 (23.8%)	601/2414 (24.9%)	−17.9	293.7	−1.04	2 d.f.
≥70	497/1737 (28.6%)	528/1734 (30.4%)	−17.1	256.2	−1.07	
Treated hypertension						
No	811/3495 (23.2%)	847/3495 (24.2%)	−21.0	414.4	−1.03	0.08
Yes	666/2536 (26.3%)	706/2538 (27.8%)	−24.4	342.9	−1.32	1 d.f.
Diabetes mellitus						
No	1252/5398 (23.2%)	1308/5399 (24.2%)	−34.0	639.9	−1.35	0.21
Yes	225 /633 (35.5%)	245 /634 (38.6%)	−11.6	117.4	−1.07	1 d.f.
Diastolic blood pressure (mmHg)						
<75	567/2019 (28.1%)	556/2148 (25.9%)	25.6	280.3	1.53	9.77
≥75 <85	487/2105 (23.1%)	524/1998 (26.2%)	−37.2	252.4	−2.34	2 d.f.
≥85	423/1907 (22.2%)	473/1887 (25.1%)	−31.3	223.9	−2.09	
Systolic blood pressure (mmHg)						
<125	480/1798 (26.7%)	435/1817 (23.9%)	29.4	228.6	1.95	11.94
≥125 <145	512/2210 (23.2%)	579/2257 (25.7%)	−34.3	272.7	−2.07	2 d.f.
≥145	485/2023 (24.0%)	539/1959 (27.5%)	−41.2	255.8	−2.58	
Total cholesterol (mmol/L)						
<4.0	610/2460 (24.8%)	617/2397 (25.7%)	−15.0	306.6	−0.86	0.25
≥4.0 <4.5	392/1645 (23.8%)	442/1721 (25.7%)	−18.7	208.4	−1.29	2 d.f.
≥4.5	475/1926 (24.7%)	494/1915 (25.8%)	−11.8	242.2	−0.76	
ALL PATIENTS	**1477/6031 (24.5%)**	**1553/6033 (25.7%)**	**−45.2**	**757.4**	**−1.64**	



Source: Sponsor's Figure 14-3

6.1.8 Analysis of Clinical Information Relevant to Dose:

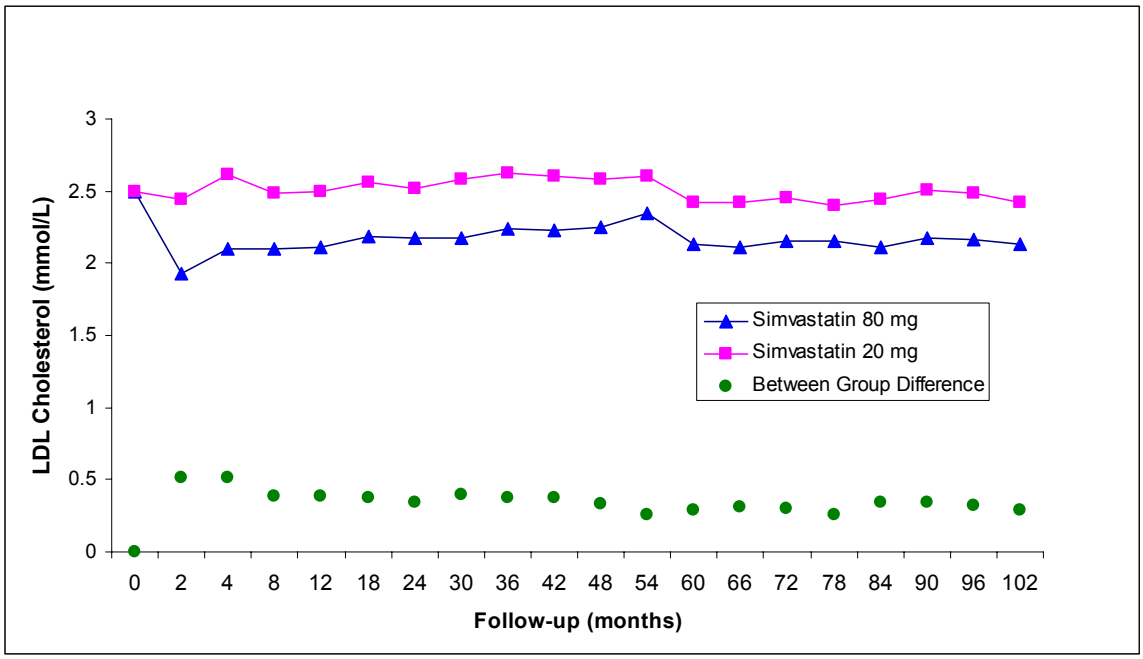
Lipids were measured in all participants at the screening visit, and both lipids and apolipoproteins at the randomization visit. After randomization, about 10% of all participants were selected each year for extensive analysis of non-fasting lipid and lipoprotein levels. Missing values were imputed based on randomization values. Samples were taken at any time of day, as opposed to restricting collection to the fasting state.

<u>LDL cholesterol:</u>
At baseline, after a two-month run-in period on simvastatin 20mg, mean LDL was 96.8 ± 24mg/dL in both study groups. In patients allocated simvastatin 80mg, mean LDL was reduced to 74.7 ± 1.5 mg/dL at 2 months of treatment, and subsequently rose slightly to mean levels ranging from 81.3 to 90.0 mg/dL (averaging 85.7mg/dL). In patients allocated simvastatin 20mg, mean LDL was 94.4 ± 1.5 mg/dL after 2 months of treatment, and subsequently ranged from 93.7 to 101.4 mg/dL (averaging 97.6mg/dL).

Over the course of the trial the average LDL level was 84.0 ± 0.39 mg/dL in patients allocated simvastatin 80mg and 97.5 ± 0.39 mg/dL in patients allocated simvastatin 20mg. There was some narrowing of difference in LDL over the course of the trial.

The mean LDL levels and the difference in mean LDL in addition to the percent change in LDL between the study groups at each study visit are shown in the following two figures.

Figure 6: Mean LDL and Between Group Differences in Mean LDL

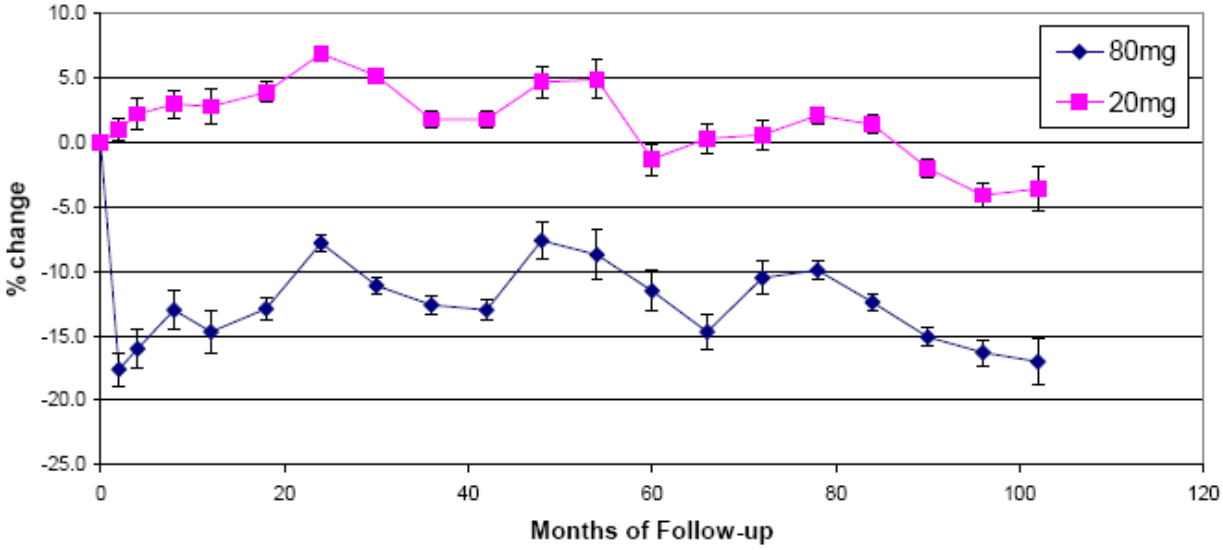


Source: Sponsor's Figure 11-2

Review Comment:
Following the run in period, (denoted by the 0 month time point in the figure above) LDL levels averaged 97mg/dL, staying just below the NCEP ATP III recommended LDL criteria of <100mg/dL. In the 20mg group, the average LDL level relatively constant over the 6.7 year trial period. In the 80mg group, the average LDL level was 85.7mg/dL over the 6.7 year trial period.

The absolute LDL difference between the 20 and 80mg statin groups at the 6.7 year trial endpoint was 13.5 mg/dL (97.6-84mg/dL) representing an approximate 13.9% difference between the 20 and 80mg groups.

Figure 7: Percentage change in LDL cholesterol



Source: 2/12/10 response to supplemental request from sponsor, Figure 1

Review Comment:
The average percentage change in LDL over time in Figure 7 above shows that LDL levels remained elevated above baseline levels in the simvastatin 20mg group during the majority of the SEARCH trial.

Total Cholesterol (TC):
Mean TC at baseline was 163.7 ± 28.3 mg/dL and decreased to an average level of 148.2 ± 0.39 mg/dL in the simvastatin 80mg group. In patients allocated simvastatin 20mg, average TC over the course of the study was similar to the baseline value 163.7 ± 28.3 mg/dL.

On average the difference in TC between the simvastatin 80mg and simvastatin 20mg groups was 15.5 ± 0.39 mg/dL.

Review Comment:
Simvastatin 80mg lowered TC levels by an additional 9.5%. TC levels in the simvastatin 20mg group remained similar to levels at baseline.

HDL cholesterol:
Mean HDL-C was 40.2 ± 13.9 mg/dL at baseline and remained stable over the course of the trial.

The average HDL-C level over the study did not differ between the simvastatin 80mg and 20mg groups.

Triglycerides:
At baseline, mean TG levels were 168.1 ± 111.8 mg/dL in patients who were subsequently randomized to simvastatin 80mg and 170.7 ± 108.2 mg/dL in patients who were then randomized to simvastatin 20mg.

Over the course of the trial, TG levels declined to an average level of 149.6 ± 0.9 mg/dL in the simvastatin 80mg group and to 162.8 ± 0.9 mg/dL in the simvastatin 20mg group.

The average difference in triglycerides between the two groups was 13.2 ± 1.8 mg/dL.

Review Comment:
Relative to baseline values, simvastatin 80mg lowered serum TG levels by 11% (149.6/168.1) compared to simvastatin 20mg group which lowered TG levels by 4.6% (162.8/170.7).

Apoprotein B:
At baseline apo B levels were 89.8 ± 16.7 mg/dL and 90.0 ± 16.8 mg/dL in patients subsequently allocated simvastatin 80mg and 20mg, respectively. During the course of the trial, average apo B levels were 81.5 ± 0.3 mg/dL in patients allocated simvastatin 80mg and 90.2 ± 0.3 mg/dL in those allocated to simvastatin 20mg.

The absolute difference in apo B levels between the two treatment groups declined over the course of the trial and on average was 8.7 ± 0.4 mg/dL.

Review Comment:
Simvastatin 80mg lowered apo B levels by 9.1% (81.5/89.8) relative to baseline, and apo B levels in the simvastatin 20mg group stayed approximately the same.

Apoprotein A1:
At baseline mean apo A1 was 135.2 ±22.3 mg/dL and 135.1 ± 22.3 mg/dL in patients allocated simvastatin 80mg and simvastatin 20mg, respectively.

The average level of apoA1 during follow-up was 141.9 ± 0.3 mg/dL in the simvastatin 80mg group, and 141.7 ± 0.3 in the simvastatin 20mg group.

Review Comment:
It would be expected that Apo A1 changes would more closely correlate to changes in HDL. Even though HDL levels remained relatively unchanged from baseline in both the 20 and 80mg dose groups, both doses of simvastatin equally increased Apo A1 by approximately 4.7% compared to baseline (135.2/141.9 and (135.1/141.7).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The absolute difference in LDL between the two groups declined during the trial. Averaged over the entire study, the absolute difference in mean LDL was 13.5 ± 0.39 mg/dL. Adherence to study medication declined in both treatment groups during follow-up, but in the simvastatin 20mg group this may have been offset by the use of non-study statins. Patients who began taking non-study statins were required to discontinue simvastatin study treatment.

Table 16: Use of Non-Study Statin at Each Scheduled Follow-Up Visit

Follow-up (months)	Simvastatin 80mg		Simvastatin 20mg	
	n/N	(%)	n/N	(%)
2	48/5887	(1%)	48/5889	(1%)
4	101/5895	(2%)	99/5932	(2%)
8	191/5838	(3%)	204/5865	(3%)
12	281/5832	(4%)	305/5815	(5%)
18	364/5723	(6%)	415/5720	(7%)
24	448/5642	(8%)	549/5634	(10%)
30	501/5533	(9%)	649/5556	(12%)
36	555/5455	(10%)	746/5440	(14%)
42	627/5379	(12%)	852/5393	(16%)
48	686/5321	(13%)	934/5305	(18%)
54	725/5219	(14%)	1012/5233	(19%)
60	760/5126	(15%)	1073/5143	(21%)
66	800/5028	(16%)	1115/5032	(22%)
72	805/4895	(16%)	1162/4901	(24%)
78	852/4738	(18%)	1218/4743	(26%)
84	655/3325	(20%)	891/3252	(27%)
90	386/1976	(20%)	561/1926	(29%)
96	182/851	(21%)	246/839	(29%)
102	28/143	(20%)	52/152	(34%)
108	2/4	(50%)	1/5	(20%)

Footnote: n represents the number of patients taking non-study statin medication, and N (the denominator) the number of patients who attended the follow-up visit.

Source: Sponsor's Table 11-9

More patients in the simvastatin 20mg group (n=1,400, 23.2%) compared to the simvastatin 80mg group (n=1,045, 17.3%) were taking non-study lipid lowering medications, most commonly simvastatin and atorvastatin. This also may help explain the narrowing difference in mean LDL levels throughout the trial since some of the non-study statins used likely provided greater reduction in LDL than simvastatin 20mg. Only a very small number of patients in the simvastatin 80mg and 20mg groups were taking non-statin lipid-lowering medications (fibrates, resins, niacin, and ezetimibe) either alone or in combination with a statin.

Review Comment:
A fair percentage of patients in both the simvastatin 20 and 80mg groups took nonstudy statins.

Although the sponsor doesn't specify the reasons why patients were put on nonstudy statins, it is plausible that more patients in the 20mg simvastatin group needed to be put on nonstudy statins due to poor efficacy (see *Percentage change in LDL cholesterol* in Figure 7). In the 80mg group, adverse events may have necessitated that patients be switched to a nonstudy statin.

The use of each particular non-study lipid lowering medication at the final follow-up visit is shown in following table:

Table 17: Use of Non-Study Lipid-Lowering Treatments at Final Follow-up

Treatment	Simvastatin 80mg (N=6031)		Simvastatin 20mg (N=6033)	
	n	(%)	n	(%)
Non-study statins				
Atorvastatin	300	(5.0%)	433	(7.2%)
Cerivastatin	0	(0.0%)	0	(0.0%)
Fluvastatin	6	(0.1%)	4	(0.1%)
Pravastatin	39	(0.6%)	40	(0.7%)
Rosuvastatin	43	(0.7%)	90	(1.5%)
Simvastatin	602	(10.0%)	768	(12.7%)
Any non-study statin	990	(16.4%)	1335	(22.1%)
Other lipid-lowering				
Fibrates	22	(0.4%)	21	(0.3%)
Resins	2	(0.0%)	2	(0.0%)
Other	92	(1.5%)	124	(2.1%)
Any lipid-lowering	1045	(17.3%)	1400	(23.2%)
Footnote: "Other" treatment includes niacin and ezetimibe.				

Source: Sponsor's Table 11-10

6.1.10 Simvastatin Compliance

Compliance declined over the course of the study. At the 12 month visit, more than 90% of patients in each of the simvastatin groups were taking at least 80% of the simvastatin tablets, while at the 78 month visit, 78% and 70% of patients allocated to simvastatin 80mg simvastatin 20mg, respectively, were taking at least 80% of the simvastatin tablets.

Table 18: Compliance with Study Simvastatin (>80% taken) at Each Scheduled Follow-up

	Simvastatin 80 mg		Simvastatin 20 mg	
Follow-up (months)	n/N	(%)	n/N	(%)
2	5701/5887	(97%)	5720/5889	(97%)
4	5585/5895	(95%)	5638/5932	(95%)
8	5378/5838	(92%)	5437/5865	(93%)
12	5275/5832	(90%)	5273/5815	(91%)
18	5086/5723	(89%)	5100/5720	(89%)
24	4939/5642	(88%)	4863/5634	(86%)
30	4785/5533	(86%)	4705/5556	(85%)
36	4666/5455	(86%)	4506/5440	(83%)
42	4534/5379	(84%)	4352/5393	(81%)
48	4425/5321	(83%)	4199/5305	(79%)
54	4297/5219	(82%)	4054/5233	(77%)
60	4160/5126	(81%)	3902/5143	(76%)
66	4038/5028	(80%)	3730/5032	(74%)
72	3909/4895	(80%)	3541/4901	(72%)
78	3716/4738	(78%)	3335/4743	(70%)
84	2555/3325	(77%)	2243/3252	(69%)
90	1512/1976	(77%)	1286/1926	(67%)
96	633/851	(74%)	562/839	(67%)
102	114/143	(80%)	95/152	(62%)
108	2/4	---	4/5	---

Footnote: n represents the number of patients taking > 80% study simvastatin, and N (the denominator) the number of patients who attended the follow-up visit (or had the interview conducted by telephone). Patients who had discontinued study simvastatin because of adverse effects or because their GP had started a non-study statin were considered to be non-compliant if during the period between study visits less than 80% of the allotted study simvastatin had been taken.

Source: Sponsor's Table 11-8

6.1.11 Additional Analyses:

none

7 Review of Safety

Serious Adverse Events:
Serious adverse events were attributed to study treatment in 57 (0.9%) patients allocated to simvastatin 80mg and in 7 (0.1%) patients allocated to simvastatin 20mg. There was a statistically significant increase in the RR for serious musculoskeletal adverse experiences in patients allocated to simvastatin 80mg versus 20mg: RR 1.11 (95% CI 1.02, 1.21); p=0.02. (all but two cases were myopathy/rhabdomyolysis). This difference was due to the increased incidence of myopathy in patients allocated to simvastatin 80mg.

Muscle-Related Adverse Events:
Myopathy, defined by the sponsor as unexplained muscle pain or weakness accompanied by an elevation of CK >10xULN, and attributable to study treatment, occurred in 53 patients (0.9% on an intention to treat basis) randomized to simvastatin 80mg and 1 patient (0.02%) randomized to simvastatin 20mg. Twenty-two patients with myopathy, all allocated to simvastatin 80mg, had CK elevations >40xULN (usually ≥10,000 IU/L).

Hepatic Adverse Events:
Hepatitis was reported in 8 patients, 3 allocated to simvastatin 80mg and 5 allocated to simvastatin 20mg. In 4 patients, (2 allocated to simvastatin 80mg and 2 allocated to simvastatin 20mg), serology for hepatitis was negative, and the patients' physicians attributed the hepatitis to treatment with simvastatin because another etiology could not be identified.

Two or more consecutive elevations in ALT >3xULN were observed in 27 patients (0.5%) allocated to simvastatin 80mg and 19 (0.3%) patients allocated to simvastatin 20mg. However, 7 of the 27 patients in the simvastatin 80mg group and 1 of the 19 patients in the simvastatin 20mg group had CK >10xULN at some point in the study, suggesting that the high levels of ALT originated from muscle in these individuals. Two or more consecutive elevations in ALT >4xULN were observed in 14 patients (0.2%) allocated to simvastatin 80mg and 10 patients (0.2%) allocated to simvastatin 20mg. Five of the 14 patients in the simvastatin 80mg group had CK levels >10x ULN at some time in the study, suggesting that the elevated ALT might have been of muscle origin. None of the 10 patients in the simvastatin 20mg group with ALT exceeding 4xULN ever had elevated CK >10xULN.

Review comment:
Hepatitis was assessed by individual study investigators using their own clinical definitions, therefore a universal definition of hepatitis was not provided by the sponsor in their study report.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This submission involved one study: Protocol 158 (ie, The SEARCH trial).

7.1.2 Categorization of Adverse Events

In SEARCH, only adverse events that were either serious, led to discontinuation of study treatment, or were believed with a reasonable probability to be due to study treatment, were recorded.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not analyzed in this submission.

7.2 Adequacy of Safety Assessments

CK Testing during SEARCH:
CK was measured at every study visit. The sponsor specified that "patients were queried about muscle symptoms, especially in the first year of the study." In the first year of the trial, study visits occurred more frequently (at 2, 4, 8, and 12 months) than in later years, when visits occurred every 6 months. The more frequent visits in the first year provided additional opportunity to evaluate CK levels and inquire about muscle symptoms.

Elevation in CK according to the following algorithm: Elevation of CK>10xULN with unexplained muscle symptoms (muscle pain or weakness) was to result in the study simvastatin treatment being stopped immediately and permanently, and an early recall visit arranged within about 1 week (with 3-weekly early recall visits, or referral to the patient's own doctor, until the CK level reverted to normal: i.e. ≤3xULN).

Review comment:

The limited assessments of CK required by the protocol was problematic and may have lead to an increased incidence of the progression of myopathy to rhabdomyolysis. Additionally, the follow-up intervals for patients who were found to have CK elevations >>10xULN should have been more stringent.

When CK elevations were found to be elevated, it would have been preferable to take daily serial CK measurements and carried forth sampling until levels returned to baseline. In this study the majority of follow-up was a single CK measurement taken after seven days or more, and not all

CK measurements had returned to baseline or within normal limits following the second measurement. An accurate downward CK trend can not be illustrated with two data points, especially two data points taken 7+ days apart.

Any other CK elevation >5xULN was to result in an early recall visit within about 1 week for a repeat sample, and if repeat CK remained >5xULN then study simvastatin treatment was to be stopped temporarily. CK was to be checked again in about 6 weeks and study simvastatin treatment stopped permanently if CK was still >3xULN. If, on the other hand, CK was ≤3xULN then the allocated study simvastatin treatment could be started again after review by one of the clinical coordinators, with a further two early recall visits at 4-weekly intervals. If CK did not remain ≤3xULN, study simvastatin treatment was to be stopped permanently.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

See Section 6.1.2 for demographic information.

There is adequate exposure at appropriate doses and duration to make a safety assessment of simvastatin. The numbers of surviving patients at each visit time point is shown in following table.

Table 19: Number of Surviving Patients at Each Scheduled Follow-Up Visit Time Point

Follow-up (Months)†	Simvastatin 80 mg (N=6031)	Simvastatin 20 mg (N=6033)
2	6023	6024
4	6016	6012
8	5991	5988
12	5971	5955
18	5917	5905
24	5864	5849
30	5794	5806
36	5725	5736
42	5656	5671
48	5602	5600
54	5534	5537
60	5445	5459
66	5355	5376
72	5267	5288
78	5168	5183
84	3607	3576
90	2174	2146
96	939	947
102	177	172
108	4	5

† The number of patients at each time point indicated represents the number of patients surviving up to that scheduled follow-up visit. It does not take clinic attendance or telephone follow-up into account. The numbers fall off sharply from 78 months onwards because the mean follow-up period in patients surviving to the end of the scheduled follow-up period was 6.7 years and, therefore, fewer follow-up visits were scheduled.

Source: Sponsor's Table 12-1.

7.2.4 Routine Clinical Testing and Laboratory Measurements

Laboratory safety and efficacy measurements were performed by the central laboratory in the Clinical Trial Service Unit. However, in cases of suspected myopathy, some measurements were also made by local laboratories. ALT and CK were measured in each patient at every visit. If ALT was >1.5xULN, GGT, AST, and ALP were measured. GGT and albumin were measured at the screening visit. Creatinine was measured at the screening visit in all patients and at any early recall visits after July 2002.

Review comment:
There were long periods of time following the first year of randomization during which laboratory measurements were not taken. Interim laboratory measurements from non-study related physician visits is were not reported in SEARCH. It appears that bilirubin was only measured in some patients who presented with abnormal laboratory values.

Table 20: Schedule of Clinical Observations and Laboratory Measurements

Visit:	Screening (Baseline)	Randomization (Baseline for lipids)	Follow-Up Visits	Final Visit
	-2 Months	0 Months	Months 2, 4, 8, and 12, Then Every 6 Months	
Single-blind run-in period	X			
Double-blind treatment period		- - - - - - - - - - - X - - - - - - - - - - - -		
Informed consent[†]	X			
Medical history	X			
Prior/concomitant medications review	X	X	X	X
Review inclusion/exclusion eligibility factors	X			
Verify eligibility		X		
Assess compliance		X	X	X
Lipid profile[§]	X	X	X[‖]	X
ALT[¶]	X	X*	X*	X
Gamma-glutamyltransferase (GGT)[#]	X			
CK	X	X	X	X
Albumin	X			
AST	X			
Alkaline phosphatase	X			
Creatinine	X			
HbA1c		X[§§]		
Full blood count		X	X[‡‡]	
Discuss diet and risk factor modification	X			
Archive samples[##]		X	X[‖]	
Treatment dispensed	X[‡]	X	X	
Record major clinical event, vascular events, serious adverse events		X	X	X
Record non-serious adverse experiences attributed to study treatment			X	X
Hearing function assessment				X
Memory and mental function assessment				X
Vital signs[††]	X			X

[†] Consent had to be signed before performing screening tests.
[‡] Run-in treatment consisted of 10 week supply of simvastatin 20 mg and placebo vitamin tablets.
[§] Included TC, TG, HDL-C, LDL-C, Apolipoprotein (Apo) A-I, Apo B except at screening when TC, HDL-C and TG only were measured.
[‖] Follow-up lipid profile done during selected period of a few weeks each year in each clinic for patients scheduled for follow-up, on about 1000 patient samples total from each year. Only these patient samples were archived during follow-up. Also was done in all patients scheduled for follow-up (intention to treat) for a 9 month period in 2003, beginning in about mid February, and at the final visit between October 2007 and April 2008.
[¶] At the screening visit, if ALT >45 IU/L, then aspartate aminotransaminase (AST) and alkaline phosphatase (ALP) also measured. At randomization visit, if ALT >67 IU/L, then GGT, AST, and ALP also measured. At follow-up visits, if ALT >67 IU/L, then GGT, AST, ALP, and albumin were measured.
[#] If GGT >2 x ULN, then AST and ALP measured; GGT also measured.
[††] Screening visit included height, weight, and blood pressure measurements. Final visit included blood pressure only. Blood pressure measured after the patient had been seated for at least 5 minutes and the 2nd of 2 measurements was recorded.
[‡‡] Full blood count was assessed at the 1-year and 4-year follow-up visits.
[§§] Measured in participants reporting diabetes.
[##] Samples (as well as buffy coats containing DNA and collected at the randomization visit) stored in liquid nitrogen for subsequent analyses.
For schedule of folate, vitamin B_{12} and homocysteine measurements, see Table 9-3.

Screening Visit: ALT† (if ALT >1 x ≤1.5 x ULN (ULN=45 IU/L), then also AST and alkaline phosphatase (ALP) GGT (if GGT >2 x ULN, then also AST and ALP) Albumin Creatinine CK (ULN = 250 IU/L) Lipid Profile: (TC, TG, HDL-C,) Patients started in Run-in were to have study treatment stopped by the coordinating center and not be randomized if (i) ALT >1.5 x ULN; (ii) ALT >1 x ≤1.5 x ULN and GGT, AST, or ALP >2 x ULN; (iii) creatinine >2 x ULN; (iv) CK >3 x ULN; or (v) GGT, AST, or ALP >4 x ULN.
Randomization Visit: ALT† (if >1.5 x ULN, then also GGT, AST, and ALP) CK Lipid Profile: (TC, TG, LDL-C, HDL-C, Apo A-I, Apo B) Folate Vitamin B12 Homocysteine Full blood count Hemoglobin A1C in patients with diabetes Samples Stored including Buffy Coats If ALT >2 x ULN, then the patient came in for an early recall visit (see below for details). Any GGT, AST or ALP >4 x ULN was reviewed by the clinical coordinators.
Follow-Up Visit and Early Recall Visit: ALT† (if >1.5 x ULN, then also GGT, AST, ALP, and albumin) CK Full blood count (1-year and 4-year visits only) If ALT >2 x ULN or CK >5 x ULN, then the patient came in for an Early recall. Any GGT, AST, or ALP >4 x ULN was reviewed by the clinic coordinators.
Follow-Up Visit During a Randomly Selected Period of a Few Weeks Each Year (About 1000 Patient Samples Total During Each Year): Lipid Profile: (TC, TG, LDL-C, HDL-C, Apo A-I, Apo B) Folate Vitamin B12 Homocysteine Samples Stored
Follow-Up Visits for a 9 Month Period in 2003 in all patients: Lipid profile (TC, TG, LDL-C, HDL-C) Homocysteine
Final Visit in all patients: Lipid profile (TC, TG, LDL-C, HDL-C) Homocysteine
†Additional liver function tests GGT, AST, and ALP (and albumin at follow-up visits) triggered by ALT >1.0 x ULN until 23/11/00 and by ALT >1.5 x ULN thereafter. AST = Aspartate aminotransferase; ALT = Alanine aminotransferase; Apo = Apolipoprotein; HbA1c = Hemoglobin A1c; GGT = Gamma-glutamyltransferase; TC = Total cholesterol; TG = Triglycerides; LDL-C = Low-density lipoprotein cholesterol; HDL-C = High-density lipoprotein cholesterol; ULN = Upper limit of normal.

Source: Sponsor's Table 9-2.

7.3 Major Safety Results (Myopathy and Rhabdomyolysis)

Myopathy:
Although there is no consistent definition of myopathy in the literature, statin-induced myopathy has traditionally been defined as unexplained muscle pain or weakness accompanied by an elevation of CK 10xULN, or 2,500 IU/L. In the CTSU laboratory, ULN for CK was 250 IU/L. However, in some cases (noted in the narrative summaries Table 21), CK was measured in local laboratories that may have had different normal ranges.

Myopathy with or without rhabdomyolysis is the only SAE clearly attributable to simvastatin with a greater incidence with simvastatin 80mg. One patient who was allocated to simvastatin 20mg was later discovered to have polymyositis rather than myopathy, which was not attributed to study treatment:

Myopathy and Rhabdomyolysis:
The number of patients who developed myopathy in SEARCH, or those who had myopathy with rhabdomyolysis, is represented by patients with CK elevations greater than 10,000 IU/L, are briefly listed in the following table.

Review Comment:

The table below reflects the more widely accepted definition of rhabdomyolysis in the medical literature and not the sponsor's definition.

Table 21: Number of Patients with Myopathy (see Review comment immediately following):

Event	Simvastatin 80mg N=6031	Simvastatin 20mg N=6033
Myopathy (CK > 2,500, <10,000 IU/L)	54 (0.9%)	2[†] (0.03%)
Rhabdomyolysis (CK >10,000 IU/L)	22 (0.4%)	0 (0%)
Attributed to study treatment	53 (0.9%)	1 (0.02%)

Notes:
This table includes one patient with CK of 2155 measured 2 days after stopping simvastatin treatment due to muscle symptoms, 1 patient with CK of 2040 with characteristic clinical presentation, 1 patient in whom CK was not measured but who had symptoms of myopathy, markedly elevated ALT (947 IU/L), normal bilirubin, normal serum creatinine, and dark urine and 1 patient (allocated to simvastatin 20mg) who was admitted to the hospital with chest pain, CK 1013, troponin negative, and was discharged with a diagnosis of myositis. The latter event was classified as myopathy "not attributed to simvastatin treatment."

[†]Of 2 patients allocated to simvastatin 20mg with myopathy attributed to study treatment, 1 patient was later found to have polymyositis rather than myopathy.

Source: Sponsor's table 12-6 (edited)

Review comment:
Rhabdomyolysis was originally defined in the Sponsor's protocol with the more widely accepted definition of myopathy with a CK>40xULN with or without renal changes.

Following the study completion, a high number of patients met this criteria and the sponsor revised its definition of rhabdomyolysis as: myopathy with CK >40xULN plus evidence of renal damage (including brown urine, creatinine elevation or an increase in urinary myoglobin).

Based on the new definition, the sponsor revised the number of rhabdomyolysis cases, now stating that only 7 patients (1 female, 6 males) in the simvastatin 80mg group and none in the simvastatin 20mg group had rhabdomyolysis. Creatinine measurements were not available in an additional 7 patients with myopathy with CK >40xULN. In addition to these 7 patients the sponsor believed that a raised creatinine was "inferred" in four additional patients without creatinine measurements who reported muscle pain, for a total of 11 patients.

The sponsors' definition is further problematic due to the fact that few creatinine measurements (or any other measurements of renal function) were made during this large-simple trial. Accordingly, the 7 to 11 patients determined by the sponsor to have had rhabdomyolysis is an underestimation. Upon discussion with The Division, it was decided that the review should revert to the definition originally specified in the protocol.

The number of patients with rhabdomyolysis vs. myopathy in the tables/text in this review were updated based on the more widely accepted definition of rhabdomyolysis/ myopathy reported in the medical literature (CK >40 xULN or 10,000 IU/L) independent of changes in renal function, or muscle symptoms. Based on this more widely accepted definition, 22 or 0.4% or patients in this study met the criteria for rhabdomyolysis, and one additional patient may have also had rhabdomyolysis, but insufficient laboratory data was provided by the sponsor to definitively make this decision.

Almost all of the cases of myopathy/rhabdomyolysis occurred in with the 80mg dose group. Simvastatin 80mg had a 0.4% incidence of rhabdomyolysis and a 0.9% incidence of myopathy with or without rhabdomyolysis on an intention to treat basis. In comparison, there was only one patient (0.02%) allocated to simvastatin 20mg with myopathy which was attributable to study drug. Relatively, there was an approximate 20-fold increase in the incidence of myopathy in the simvastatin 80mg group versus the simvastatin 20mg group in this study.

No patients developed myopathy during the active run-in period. Myopathy occurred in a total of 54 patients (0.9%) randomized to simvastatin 80mg and 2 patients (0.03%) randomized to simvastatin 20mg. In 2 of these 54 patients (1 patient allocated to simvastatin 80mg and 1 patient allocated to simvastatin 20mg), the myopathy was not attributed to simvastatin. The case narratives are as follows:

Case Narratives:

A 73 year old white female (study ref 112 (b) (6) 1L) was admitted to the hospital because of chest pain and elevated CK of 1013 IU/L (with ULN of local laboratory not known) approximately 4 years following randomization to simvastatin 20mg. Troponin was negative. The diagnosis on the hospital discharge summary was "elevated CK, myositis." Due to the rise in CK, the local managing doctor discontinued study statin use but did not report the case to CTSU. When the hospital discharge summary came to the attention of CTSU at the end of the study, The CTSU, still blinded to the treatment allocation of the patient, coded the adverse event as myopathy, not attributed to study treatment, because in the SEARCH database the term "myositis" codes to "myopathy". However, the sponsor believes that this case does not meet the traditional criteria for myopathy because the CK elevation was well below 10xULN.

Review comment:
This was a small, clinically unimportant increase in CK. The elevation in CK is not high enough to be considered myopathy and the lack of change in renal function also points towards this case not being myopathy.

A patient allocated to simvastatin 80mg who developed myopathy that was not attributed to study treatment was a 54 year old male (study ref 144 H396) who was found to have elevated CK of 8223 IU/L with raised ALT of 83 IU/L in July 2001, approximately 7 to 8 months after randomization to simvastatin 80mg. He was asymptomatic at that time. Study simvastatin was stopped. The patient's general practitioner was unblinded to the patient's treatment allocation, and advised to treat the patient cautiously. The patient was prescribed non-study statin treatment, beginning in 2002 with simvastatin 20mg. The dose of simvastatin was increased to 40 mg in 2003 and to 80mg in 2004. At a routine follow-up visit on 20-May-2004, 42 months after randomization, the patient complained of aching thighs, and was diagnosed with myopathy. CK was 6784 IU/L. Serum creatinine was normal. Medications included simvastatin 80mg (non-study medication), captopril, atenolol, aspirin and GTN (glycerol trinitrate spray). The event was coded as myopathy not attributed to study treatment because the patient had discontinued simvastatin study treatment in 2001. However, from a clinical perspective, the myopathy was related to the use of simvastatin 80mg.

Review comment:
Although the sponsor is proposing not attributing the above case to simvastatin, it seems that this would be considered related to study medication and it was included with the other myopathy cases.

One additional patient allocated to simvastatin 20mg was originally diagnosed with myopathy, but was later found to have polymyositis. This patient was a 77 year old white male who was found to have an elevated CK (3058 IU/L) on a routine visit, on 08 July 2002, one year after randomization to simvastatin 20mg. Concomitant medications were "coodamol" (a codeine/APAP combination), furosemide, aspirin, enalapril, and prednisolone. He complained of leg and shoulder pain, and was diagnosed with myopathy. Subsequent investigations by local physicians showed that he had polymyositis, rather than statin-related myopathy. This patient

with polymyositis is therefore not included in the 55 cases of myopathy, as noted in the table above.

Review comment:

It is unclear if this patient had a history of polymyositis prior to study enrollment. Therefore, it is unknown whether or not this elevation in CK is due to a new diagnosis of polymyositis or if the administration of simvastatin acutely exacerbated an underlying polymyositis which lead to the myopathy.

Had there been a prior history of polymyositis, this patient should have been excluded at screening. Due to the lack of collection of appropriate laboratory information, this patient should be excluded from the analysis.

Further details on patients with myopathy or rhabdomyolysis:
Of the 54 patients in the simvastatin 80mg group who were diagnosed with myopathy after randomization, 2 patients (study ref 276 JK41 and 130 JKRM) had CK elevations of 2,155 IU/L and 2,040 IU/L, which were slightly less than 10xULN. In the former patient (study ref 276 JK41), CK was measured 2 days after stopping study simvastatin treatment for suspected myopathy.

Review comment:

Although these two patients did not strictly meet the definition of myopathy based upon the degree of CK elevation, it would have been reasonable to include them in the group with myopathy based on the timing of the CK elevation relative to drug discontinuation. The inclusion of these two patients does not dramatically change the myopathy and rhabdomyolysis findings in this study.

A third patient allocated to simvastatin 80mg (study id 163 F86J) did not have a CK measured at the time of the onset of myopathy, but was diagnosed with myopathy based on symptoms of muscle pain, weakness, and markedly elevated ALT (947 IU/L) that was greater than 20xULN, with normal bilirubin. This patient did not have symptoms of hepatitis and the elevated ALT is presumed to be of muscle origin. Although he reported dark urine, he had a normal serum creatinine and therefore is not classified with having rhabdomyolysis (see below for discussion of rhabdomyolysis).

Review comment:
Patients 276 JK41 and 130 JKRM were myopathy cases.

163 F86J may have been a rhabdomyolysis case but a lack of laboratory information prevents making a definitive conclusion. The normal bilirubin prevents making a definitive rhabdomyolysis diagnosis. It is not known why patient 163 F86J did not have a CK measured when it was found that the ALT was more than 20x ULN. This patient also reported passing dark urine, which is suggestive of a diagnosis of rhabdomyolysis.

No additional information was available on this patient.

Table 22: Patients with Myopathy but not Rhabdomyolysis

Drugs known to interact with simvastatin have been underlined in the concomitant medications column.
Drugs representing potential new drug-drug interaction elucidated in SEARCH (specifically, amlodipine and diltiazem) are boxed in the concomitant medications column.

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 20mg											
224 K22R	15Mar2002	1 year	(b) (6)	White/M/ 65	Leg and shoulder pain	Amlodipine, Aspirin, Atenolol, Nicorandil	3,214	Unknown	No	No	None
112 HY1L	02Feb2005	50 months		White/F/ 72	Chest pain thought to be gastric in origin	Aspirin, atenolol, rabeprazole, fosamax	1,013 (local lab ULN not known)	No	Yes	No	Consulted GP with chest pain thought to be gastric in origin. Troponin negative. Discharge diagnosis myositis. Local team stopped statin treatment but did not report case to CTSU. Although not a clear case of myopathy, the event was coded at end of trial as myopathy (not attributed to study treatment) due to the hospital discharge diagnosis of myositis.
Patients Randomized to Simvastatin 80											
203 F1LF	Oct2000	6 weeks		White/F/ 58	Generalized muscle pain	Atenolol, Aspirin, Frusemide, Diltiazem, Isosorbide mononitrate Nicorandil, GTN	2,944	Unknown	No	No	None
170 A9YP	Dec2000	1 year		White/F/ 69	Moderate muscle pain	Atenolol, Bendrofluazide, Thyroxine, Diltiazem	3,701	Unknown	No	Yes	None

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
110 A39B	Dec2000	13 months	(b) (6)	White/F/ 69	Leg weakness	Bendrofluazide, Enalapril, Aspirin Glibenclamide, **Amiodarone**	6,723	Unknown	No	Yes	Saw other physicians, recovered while on study treatment.

Table 22 (Cont'd): Patients with Myopathy but not Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont.)											
296 FB4X	12Feb2001	4 months	(b) (6)	White/M/ 72	Muscle pain and stiffness	Aspirin, Allopurinol	>1,600 (ULN = 205)	Unknown	No	No	CK measured in local laboratory – no further dilution done.
136 J08A	12Feb2001	4 weeks		White/F/ 63	Leg pain and weakness	Atenolol, Lisinopril, Metformin, Aspirin, Glibenclamide, Lercanidipine	3,112 (ULN = 180)	Unknown	No	Yes	CK measured in local laboratory. In central lab CK was 2509 on the following day.
276 JK41	05Apr2001	3 weeks		White/M/ 71	Leg, back and shoulder pain	Losartan, Isosorbide mononitrate, Aspirin, Temazepam, Atenolol	2,155	Unknown	No	Yes	CK measured 2 days after stopping study medication. Therefore counted as a myopathy even though peak CK<10xULN.
270 BJL7	30Apr2001	10 months		White/M/ 59	Leg and arm pain and weakness	Aspirin, Atenolol, Enalapril	2,601	Unknown	No	No	None
248 HL7F	24May2001	4 months		White/M/ 60	Leg and shoulder pain	Warfarin, Elantan, Frusemide, Coproxamol, Lactulose, GTN	5,314	Unknown	No	Yes	None
171 K8YL	19Jun2001	2 months		White/F/ 79	Leg stiffness	Aspirin, Enalapril, Bendrofluazide	3,355	Unknown	No	Yes	None
168 J832	25Jun2001	5 months		White/M/ 79	Leg and arm weakness	Frusemide, Warfarin, Lisinopril, **Amiodarone**	9,020 (ULN = 195 IU/L)	Unknown	No	Yes	None

Table 22 (Cont'd): Patients with Myopathy but not Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont.)											
130 JKRM	29Jun2001	15 weeks	(b) (6)	White/M/ 80	Leg and back pain	Ramipril, Amlodipine Omeprazole, Persantin, Cod liver oil	2,040	Unknown	No	No	CK not quite 10xULN, but the diagnosis of myopathy was made because of the patient's history.
130 FYJ1	01Aug2001	8 months		White/M/ 70	Leg pain and weakness	Diltiazem, Insulin, Aspirin, Metformin	3,806	Unknown	No	No	None
110 LRFJ	22Aug2001	2 months		White/M/ 80	Leg pain and weakness	Amlodipine, Atenolol, Isosorbide mononitrate, Aspirin, Ciprofloxacin	4,417	Unknown	No	No	None
137 HYFR	02Oct2001	8 months		White/M/ 74	Mild leg ache	Insulin, Becotide, Ventolin, Lisinopril, Aspirin, Danazol, Isosorbide mononitrate, Domperidone, Bumetanide	4,619	Unknown	No	No	None
228 JB66	04Dec2001	10 months		White/F/ 78	Leg pain and weakness	Aspirin, **Amiodarone**, Loratidine	6,650 (ULN = 220)	Unknown	No	No	None
150 FM05	29Aug2002	2 year		White/M/ 60	Aching in legs	Metoprolol, **Amiodarone**, Losartan, Frusemide, Aspirin, Gabapentin	2,680	No (128)	No	Yes	Symptoms longstanding – not clearly worse in lead up to diagnosis of myopathy.
284 H0AA	05Nov2002	18 months		White/M/ 58	Leg aches	Nicorandil, Bisoprolol, Aspirin, Diltiazem and Ramipril	7,815	No (89)	No	Yes	None

Table 22 (Cont'd): Patients with Myopathy but not Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont.)											
231 MP99	07Oct2002	1 year	(b) (6)	White/M/ 73	Leg pain	Diltiazem, Isosorbide mononitrate, Nicorandil, Lisinopril, Budesonide, Terbutaline, Esomeprazole, Aspirin, Cocodamol, GTN spray	3,371	No (140; 145 at screening)	No	Yes	Symptoms initially reported as longstanding, but resolved after stopping study simvastatin.
267 H921	29May2003	30 months		White/F/ 74	Aching legs Nausea and vomiting	Isosorbide mononitrate, lisinopril, atenolol, aspirin, glyceryl trintrate	4,408	No (65)	No	Yes	Routine CK 4408 with history of muscle pain in legs for months
141 B11L	14Jul2003	39 months		White/M/ 68	1 month generalized aches and lethargy	Aspirin, warfarin, lisinopril, bisoprolol, GTN, lactulose, gaviscon	3,785 (ULN 195)	Unknown	Yes	No	None
242 B4B3	24Nov2003	42 months		White/M/ 67	Generalized stiffness	Aspirin, frusemide, carvedilol, ramipril, zoladex, casodex, amoxycillin	2,350	No (72)	No	No	Had a course of erythromycin from 7Nov2003 to 19Nov2003. Study treatment taken concurrently.
233 M711	06Apr2004	31 months		White/M/ 61	Aching thighs	Aspirin, atenolol, GTN	4,430	No (82)	No	Yes	None
225 ML8M	19Aug2004	36 months		White/F/ 66	Shoulder, leg and back pain. Generalized stiffness	Cocodamol, Metformin, Nicorandil, Elantan, Human insulin, Calcium and vitamin D, Aspirin, Candesartan, Bisoprolol, Furosemide	3,041	No (61)	No	Not on SC form but NB drugs	None

Table 22 (Cont'd): Patients with Myopathy but not Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont.)											
161 HYU4	08Jan2005	47 months	(b) (6)	White/F/ 76	Proximal muscle weakness (legs)	Aspirin, propranolol, furosemide, diltiazem human insulin, ISMN, ramipril, omega-3, glucosamine, tumeric caps	6,514	No	Yes	Yes	Patient had type 2 DM. Treated with steroids for polymyalgia rheumatica (no CK done) in Dec 2004 with complete resolution. Symptoms recurred on cessation of steroids.
214 JUKA	24Mar2005	47 months		White/F/ 84	Leg weakness	Diltiazem, irbesartan, rutoside, bendrofluazide, aspirin, spironolactone, lansoprazole	2,742	No (111)	No	Yes	CK found to be high at routine check-up. Retrospectively she reported a 2 month history of marked bilateral leg weakness and moderate pain
228 H083	05May2005	51 months		White/F/ 80	Bilateral leg weakness	Amlodipine, perindopril, atenolol, furosemide, clopidogrel, lansoprazole	3,329	No (126)	No	Yes	CK high at routine follow-up. Did not report muscle symptoms in clinic but on direct questioning by CTSU clinician described a 2 month history of bilateral leg weakness. Coincident gastrointestinal symptoms (dyspepsia, flatulence) which resolved along with muscle symptoms
247 FFUR	24Aug2006	73 months		White/M/ 76	Leg pain and weakness	Carvedilol, ramipril, furosemide, spironolactone (started after symptoms reported), omeprazole, allopurinol, warfarin, GTN, diclofenac	3,927	No (136; No change from early 2005)	No	Not known	A 2 week history of bilateral thigh and knee pains. Also increased fatigue and vague back and shoulder aches. Asymptomatic rise in CK and ALT in 2005.

Table 22 (Cont'd): Patients with Myopathy but not Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont.)											
214 LKK8	22Jan2007	66 months	(b) (6)	White/M/ 72	Moderate muscle pain in his legs	tamsulosin, dutasteride, aspirin, atenolol, ramipril, (amoxicillin)	5,803	Unknown	No	Yes	Recent history of a chest infection for which he had been prescribed amoxicillin.
129 HRFX	26Jul2007	74 months		White/F/ 67	Moderate pain and weakness in arms and legs	Ramipril, isosorbide mononitrate, aspirin, temazepam, amlodipine propranolol	7,503	No	No	Yes	None
144 H396	20May2004	42 months		White/M/ 57	Aching thighs	Simvastatin 80mg, captopril, atenolol, aspirin, GTN	6,784	No	No	Yes	In July 2001 pt was asymptomatic with CK 8223, ALT 83). Study statin stopped, GP unblinded and advised to treat cautiously. Started 20mg simvastatin in 2002, increased to 40mg in 2003 and to 80mg in 2004.

Data Source: Sponsor's table 12-7

Temporal Relationship of Myopathy to Study Treatment, as Defined by The Sponsor:
Myopathy or rhabdomyolysis occurred within 12 months of randomization in 27 patients (51%) allocated to simvastatin 80mg. In 11 patients (21%) allocated to simvastatin 80mg, myopathy or rhabdomyolysis developed very early, within 2 months after starting study simvastatin.

The time of onset of myopathy in patients allocated to simvastatin 80mg and 20mg is shown in the following table:

Table 23: Temporal Relationship of Myopathy/Rhabdomyolysis, as Defined by The Sponsor:

	Simvastatin 80 mg	Simvastatin 20 mg
Follow-up (Months)	n	n
0-2	11	0
3-4	4	0
5-6	1	0
7-8	6	0
9-12	5	1
13-18	3	0
19-24	2	0
25-30	1	0
31-36	4	0
37-42	4	0
43-48	3	0
49-54	2	0
55-60	1	0
61-66	1	0
67-72	1	0
73-78	3	0
TOTAL	52	1

Review comment:
This table provided by the sponsor does not differentiate between myopathy and rhabdomyolysis.

SEARCH Annual Rate of Myopathy in Patients Taking Study Simvastatin 80mg:
The rate of myopathy is highest (0.5%) during the first year of the study, and in subsequent years decreases to approximately 0.1% per year, or about 1 per 1000 patient-years. The overall rate of myopathy in patients taking at least 80% of the allocated simvastatin 80mg (averaged over the course of the study) is 1.2% (52/4427, per below), compared to 0.9% as calculated on an intention-to-treat basis.

Review comment:
For the purpose of this review, myopathy/rhabdomyolysis cases were calculated on an intent-to-treat basis. The sponsor only included patients who were ≥80% medication compliant.

The annual rate of myopathy in patients taking simvastatin 80mg in the first year of the study and in subsequent years is shown in the following table:

Table 24 Annual Rate of Myopathy in Patients Taking Study Simvastatin 80mg

Follow-up (Years)	No. Patients with Myopathy	No. Patients with >80% Compliance	Annual Rate of Myopathy %
1	27	5432	0.50
2 and 3	10	4869	0.10
4 and 5	10	4354	0.11
6 and 7	5	3555	0.07
TOTAL	52†	4427††	---

† This table does not include the patient (study ref 144 H396) who stopped study simvastatin but developed myopathy 42 months after randomization while taking non study simvastatin 80 mg.
†† Weighted average over all follow-up visits.

Source: Sponsor table 12-10

Review comment:
The total number of myopathy and rhabdomyolysis cases attributed to study simvastatin 20 and 80mg was 54 using the more widely published definition of rhabdomyolysis and myopathy. (Two additional cases were added following a review of the case reports.) The above table shows that the highest incidence of myopathy occurred during the first year of therapy at a rate of 0.5% but this rate was 0.11% to 0.07% in subsequent years, as calculated using the sponsor's definition.

Study Monitoring and the Detection of Myopathy:
Of the sponsor's assessment of myopathy attributable to simvastatin 80mg, 19 were diagnosed independently of the study follow-up system by the patients' own physicians after they complained of muscle symptoms. Of the 33 cases of myopathy diagnosed at the study visits, 12 did not volunteer muscle complaints, but admitted to such symptoms in response to further inquiry by the study nurse when CK was found to exceed 10xULN.

Older age and female sex both increased the risk of myopathy, and these differences were statistically highly significant. For age, the increase in risk was approximately two-fold. Compared to men, the observed risk in women was 2.8 times greater for myopathy alone.

According to the sponsor, the risk of myopathy in women was about twice that in men, and similarly about twice in patients ≥65 than in patients <65.

Review comment:
The underlined above was taken verbatim and appears to be an error in the sponsor's report. The sponsor contradicts itself in the study report once saying that "Compared to men, the observed risk in women was 2.8 times greater for myopathy alone" but later states "The risk of myopathy in women was about twice that in men."

Although the sponsor reports that a higher number of female patients reported myopathy, Tables 22 and 25 shows that only 40% of females (13/32) had myopathy and 27% (6/22) of female patients had rhabdomyolysis.

The literature does report that female gender is a traditional risk factor associated with statin-induced myopathy[6], but this is not the case in SEARCH where more male patients were diagnosed with myopathy/rhabdomyolysis.

The sponsor's table and analysis of the rhabdomyolysis cases in the table and narrative above differs from that of this Review.

The average age of the 32 patients experiencing myopathy was determined to be 70 years old, with the range being 57 to 84 years.

Rhabdomyolysis:

Rhabdomyolysis is a more severe form of myopathy that leads to the accumulation of toxic products in the blood and urine. Using the sponsor's proposed definition or rhabdomyolysis, only seven patients (1 female, 6 males) in the simvastatin 80mg group and none in the simvastatin 20mg group had rhabdomyolysis.

Review comment:
There is no perfect consensus on the definition of rhabdomyolysis, but a CK>40xULN (ULN is typically 200-250 IU/L) or 10,000 IU/L is a conservative definition which is commonly used in the medical literature, and has precedence in other FDA medical officer reviews. The original SEARCH 2005 protocol proposed this definition as well. Publications have shown that a CK elevation of 40xULN represents a sufficient degree of muscle cell injury, independent of whether or not any change in renal function has occurred.

Following the study results, the sponsor revised its original rhabdomyolysis definition to be a CK >40xULN, but additionally included the text: "plus evidence of renal damage." This definition is problematic, firstly because it is not a widely accepted definition, and secondly because not all patients with significant CK elevations in this study had creatinine measurements in order to assess renal damage.

As shown in the Table 25 below, 22 patients were determined to have rhabdomyolysis based on this Review's more widely accepted definition of rhabdomyolysis, based wholly on a CK

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>40xULN. This Review's definition did consider definitive renal damage as assessed by creatinine levels since creatinine levels were not reliably measured by the sponsor.

One additional patient listed at the bottom of Table 25 (163 F86J) had limited laboratory data, however this participant was highly suspect of rhabdomyolysis based on an raised ALT (947 IU/L) and dark urine which is suggestive of myoglobinuria, but with normal bilirubin and without a CK measurement. However, since there was no measurement of CK and creatinine, there is inadequate data to definitively diagnose rhabdomyolysis.

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Table 25: Patients with Rhabdomyolysis

Drugs known to interact with simvastatin have been underlined in the concomitant medications column.
Drugs representing potential new drug-drug interaction elucidated in SEARCH (specifically, amlodipine and diltiazem) are boxed in the concomitant medications column.

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (creatinine µmol/L)	Hospitalized for Myopathy	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg											
292 B1A4	20Jul2000	3 weeks	(b) (6)	White/M/ 68	Muscle pain and stiffness	**Amiodarone**, Aspirin, Cod liver oil, Diazepam, Furosemide, Garlic extract, Isosorbide mononitrate, Lactulose, Trandolapril	50,719	Unknown	No	Yes	Reported passing very dark urine. Serum creatinine not measured at onset of myopathy, but 2 weeks later, after symptoms had improved, creatinine was normal (72 µmol/L)
276 FJUX	15Mar2001	7 months		White/M/ 76	Back pain	Diltiazem, Aspirin, Isosorbide Mononitrate, Frusemide, Lansoprazole, Chlorpheniramine, Human Insulin, Quinine Sulphate, Beclomethasone, Fentanyl patch, Senna, Lactulose, Temazepam	43,870 (ULN = 200 IU/L)	Yes (205; 117 at Screening)	Yes	No	Admitted following a fall. Rhabdomyolysis attributed to the fall since the admitting team was unaware of simvastatin use. Back pain attributed to bony metastases from prostate cancer.
270 JBRX	18Jun2001	2 weeks		White/F/ 76	Leg and arm pain and weakness	Diltiazem, **Amiodarone**, Aspirin, Omeprazole, Atenolol, Thyroxine, Isosorbide mononitrate, Co-amilofruse, GTN, Garlic tablets	34,074	Unknown	No	Yes	Reported dark urine, but serum creatinine was not available.
125 M33F	14Nov2001	4 months		White/M/ 78	Generalized muscle pain and weakness	Clopidogrel, Metoprolol, Amlodipine, Isosorbide Mononitrate, Nicorandil, Lisinopril, Frusemide, GTN, Garlic tablets, Fish oil	161,000 (ULN = 200 IU/L)	Yes (344; 186 at Screening, 119 Aug 2003)	Yes	No	CK rose to 1569 (one week after the first follow up visit), but fell while still on treatment. Patient had no symptoms with initial CK elevation.

Table 25 (Cont'd): Patients with Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (creatinine µmol/L)	Hospitalized for Myopathy	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont)											
287 H195	24Oct2002	22 months	(b) (6)	White/M/ 74	Leg pain	Perindopril, Aspirin, Isosorbide Mononitrate, Frusemide, Diclofenac, Unspecified vitamins, GTN, Allopurinol, Thyroxine	19,145	Yes (302; 165 at screening)	No	No	Amiodarone stopped 2 weeks previously by GP. Creatinine 169 May 2003
143 AY8P	16Mar2006	70 months		White/M/ 72	Leg weakness	warfarin, GTN spray, candesartan, bisoprolol, ISMN, fluticasone inhaler, goserelin	15,200	Yes (300 on16-Mar-2006)	Yes	Not on SC form but NB drugs	Diagnosed with prostate cancer Feb 2006 and started goserelin. Hospitalized (b) (6) with leg weakness, worsening renal function, and CK 15,200. Discharged on high dose steroids with evidence of resolving myopathy (CK 670 IU/L). Readmitted late (b) (6) with GI bleed due to hemorrhagic gastritis. Developed disseminated intravascular coagulopathy (DIC), neutropenia, sepsis, and renal failure. Died (b) (6) Certified cause of death: septicemia
267 KR51	15Sep2007	76 months		Other/M/ 58	Generalized muscle aches	Diltiazem, metformin, aspirin	57,000	Yes, (300 and Ur 23)	Yes	Yes	Transferred to ITU and died (b) (6) Death certificate listed cause of death as congestive heart failure with ischemic heart disease.

Table 25 (Cont'd): Patients with Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont.)											
170 AK5B	27Sep2000	8 months	(b) (6)	White/M/ 55	Muscle pain and stiffness	Axid, Flomax, Gaviscon, Tylex Aspirin, Atenolol, Bendroflumethiazide, Lactulose	28,300	Unknown	No	No	Hospitalized for planned prostatectomy which was cancelled because of myopathy.
176 F9X8	Oct2000	3 weeks		White/F/ 75	Generalized muscle pain	Insulin, Nicorandil, GTN, Aspirin, Amlodipine, Cod liver oil, Omeprazole, Lisinopril, Frumil, Vitamin E, Isosorbide mononitrate	16,163	Unknown	No	No	None
270 BFJJ	29Mar2001	10 months		White/M/ 50	Back and shoulder pain	Lisinopril, Diltiazem Atenolol, Paroxetine, Aspirin	18,604 (ULN = 190)	No (84)	Yes	No	CK measured in local laboratory.
262 AYRP	28Jun2001	14 months		White/M/ 58	Generalized muscle pain and stiffness	Warfarin, Perindopril, **Amiodarone**, Cod liver oil, **Erythromycin**	11,462	Unknown	No	No	Took erythromycin 1g bd from 22Jun01 to 28Jun01. Continued study treatment throughout.
147 J80M	16Oct2001	8 months		White/F/ 78	Generalized muscle pain	Imdur, Gaviscon, Amlodipine, Bisoprolol, Aspirin, Codyramol, Lansoprazole, Frusemide	22,206	Unknown	No	Yes	CK rose to 2063 at the first follow-up visit but fell while still on treatment. Patient described "arthritic" symptoms at the time which did not resolve when study simvastatin was stopped.

Table 25 (Cont'd): Patients with Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont)											
231 LJ37	11Feb2002	8 months	(b) (6)	White/M/ 75	Leg weakness	Sotalol, Bumetanide, Losartan, Aspirin, **Clarithromycin**	27,530	Yes (176; 135 at screening; 170 Feb2003)	Yes	Yes	Clarithromycin taken from 30Jan2002 to 04Feb2002.
277 A5FF	27Jan2003	3 years		White/M/ 59	Leg pain	Atenolol, Aspirin, Ranitidine, Isosorbide mononitrate, Co-amilofruse, GTN	15,229	No (91)	No	No	CK rose to 860 a month before onset of myopathy and decreased while continuing treatment. No associated symptoms at the time.
224 FF44	08Apr2003	31 months		White/F/ 75	Generalized muscle pain and weakness	Propranolol, ramipril, oxazepam, flunisolide, aspirin, brewers yeast, cod liver oil, insulin, meloxicam, frusemide, isosorbide mononitrate	11,156	No (88)	No	Yes	CK rose to 1048 1 month before but then decreased to 448 while continuing study treatment
155 ALY3	03Aug2003	41 months		White/M/ 73	Generalized muscle pain and weakness	frusemide, lisinopril, aspirin, ranitidine, paracetamol	11,900 (local ULN 210 IU/l)	Unknown	Yes	No	CK increased from 70 at randomization to 593 at first follow-up visit. Also had early recall for CK 2278 in March 2001 but CK decreased while remaining on treatment.
214 AR6F	22Sep2003	42 Months		White/M/ 70	3 months generalized muscle pain and weakness	prednisolone 10mg, losartan, Co-tenidone, aspirin, ranitidine, goserelin injections	17,876	No (97)	No	No	Metastatic prostate cancer May 2003. Started on Bicalutamide June 2003. Pain started a few weeks later. Stopped bicalutamide Aug 2003 but pain continued.

Table 25 (Cont'd): Patients with Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont.)											
130 K3F3	28Jan2005	46 months	(b) (6)	White/M/ 79	Leg weakness and pain	Mesalazine, budesonide inhaler and telmisartan	52,409	No (104)	Yes	Not clear	1 week history of muscle weakness and pain. Recent history of melanoma with regional spread (axilla) treated surgically. Staging investigations not available
139 FX52	19Jan2006	59 months		White/F/ 79	Very mild general aches (possibly worse in right arm)	Furosemide, lisinopril, ISMN, aspirin, Adcal, GTN spray, **clarithromycin**	15,958 on 21Jan06	No (84 on (22Jan06)	Yes	Yes	Course of claithromycin 12Jan2006 to 19Jan2006. Admitted to hospital (b) (6) with dizziness. Neurologically intact. Raised CK on admission. Retrospectively, 1 week after admission the patient described profound weakness in both legs (without pain) the morning of admission. A different history was provided by the admitting team when the SAE was reported.
150 JF86	02Jul2005	53 month		White/M/ 81	Bilateral proximal leg muscle weakness	Diltiazem, candesartan, metoprolol, isosorbide mononitrate, aspirin, nicorandil, GTN spray, glargine insulin	11,847	No (132)	Yes	Yes	Admitted on (b) (6) with a 7 day history of proximal leg muscle weakness. Symptoms and CK resolved on stopping study statin therapy (the former within 4 days).

Table 25 (Cont'd): Patients with Rhabdomyolysis

Study Ref	Onset Date	Time From Randomization	Date of Birth	Ethnicity/ Gender/ age at diagnosis	Muscle Symptoms	Concomitant Medications	Peak CK (ULN 250 IU/L)	Renal damage (serum creatinine µmol/L)	Hospitalized	Treated HTN	Other AEs/ Comments
Patients Randomized to Simvastatin 80mg (Cont.)											
246 B565	04Jul2000	8 weeks	(b) (6)	White/M/ 65	Muscle pain and difficulty bending	Alfuzosin HCl, Aspirin, Atenolol, Furosemide	17,510	Unknown	No	No	None
181 F36B	Jul2000	3 weeks		White/F/ 65	Muscle pain and stiffness	Frumil, GTN, Aspirin, Atenolol, Diltiazem Herbal remedies	20,686	Unknown	No	Yes	None

Patient with Suspected Rhabdomyolysis

The following patient was suspected to have had rhabdomyolysis but a limited amount of laboratory information prevented making a conclusive decision.

163 F86J	01Sep2000	4 weeks	(b) (6)	White/M/ 60	Muscle pain and weakness	Coodamol, Aspirin, Atenolol, Isosorbide mononitrate, Lisinopril Nicardipine	N/A (*see comments*)	No (91)	No	No	CK not measured on 01Sep2000, but assumed to be high because of raised ALT (947 IU/L) with normal bilirubin. The patient reported passing dark urine.

Data Source: Sponsor's table 12-8

Review comment:
Rhabdomyolysis was diagnosed in 22 (0.4%) patients based on CK levels >40xULN (CK >10,000 IU/L). CK levels ranged form 11,142 to 161,000 IU/L. There was one additional suspected case of rhabdomyolysis based on an AST >20x ULN, however a definitive diagnosis could not be made based on the lack of CK data provided by the sponsor. All rhabdomyolysis cases occurred in patients taking the 80mg dose of simvastatin.

Use of Concomitant Medications in Patients with Myopathy:
Medications known to increase the risk of myopathy in patients taking simvastatin include potent CYP3A4 inhibitors (itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone), verapamil, gemfibrozil, cyclosporine, danazol, and amiodarone. At the time that SEARCH was initiated, the interaction of simvastatin with some of these medications, such as amiodarone and danazol (see below) had not yet been identified. In SEARCH, 4 patients allocated to simvastatin 80mg had taken macrolide antibiotics for short periods of time (ranging from about 6 days to 12 days) prior to developing myopathy. Details about these patients' concomitant medications can be found in the "Concomitant Medications" column in Tables 22 and 25.

Review comment:
Despite the fact that no dosage adjustment is stated to be needed in the package insert, concomitant therapy with diltiazem (n=13) or amlodipine (n=8) appeared to increase the risk of myopathy/rhabdomyolysis about three-fold and two-fold, respectively, in patients taking simvastatin 80mg. (See: '*clinical pharmacology*')

On 16-MAR-2010, during the SEARCH review process, The Agency sent a supplement request letter (19766, S-80) to Merck Inc. requesting the establishment of a simvastatin dose cap of 40mg for patients taking diltiazem or amlodipine. This labeling action was completed on 08-APR-2010.

The Sponsor's Report did not provide the start date of concomitant medications relative to the onset of rhabdomyolysis.

The average age of the 31 patients experiencing rhabdomyolysis was calculated and found to be 66 years old, with the range being 55 to 81 years.

Two patients (study ref 242 B4B3, 262 AYRP) had taken erythromycin and the latter patient was also taking amiodarone. Two patients (study ref 231 LJ37 and 139 FX52) had taken clarithromycin. One patient (study ref 137 HYFR) was taking danazol concomitantly with simvastatin 80mg prior to the onset of myopathy on 02-Oct-2001.

In SEARCH, increased risk of myopathy in patients taking amiodarone and simvastatin 80mg concomitantly was identified in 2002 when it was found that as of 04-Dec-2001, with a median duration of follow-up of 9 months, 7 patients (study refs 292 B1A4, 270 JBRX, 181 F36B, 262 AYRP, 168 J832, 110 A39B, 228 JB66) allocated to simvastatin 80mg, who were also taking

Amiodarone, developed myopathy. There were no cases of myopathy in patients taking amiodarone who were allocated to simvastatin 20mg. According to the preliminary data available at the time, 259 patients were taking amiodarone at randomization and it was assumed that about half were allocated to simvastatin 80mg, thus giving a rate of myopathy of approximately 5.4% in these patients. This information was summarized in a report dated 05-Sept-2002. The final data indicate that at randomization, 268 patients were taking amiodarone, of whom 138 were allocated to simvastatin 80mg. It should be noted that the report dated 05-Sept-2002 incorrectly identifies patient 181 F36B as taking amiodarone. This does not change the conclusions of this review.

As a result of this information, the simvastatin label was changed to add a precaution about the increased risk of myopathy in patients taking higher doses of simvastatin and amiodarone and to limit the dose of simvastatin to 20mg in patients taking amiodarone. At the final visit, 110 patients (2.3%) originally allocated to simvastatin 80mg, were taking amiodarone, but had been re-assigned to simvastatin 20mg. This may have contributed to the narrowing LDL difference between the simvastatin 80mg and 20mg groups over the course of the trial.

Deaths in Association with Rhabdomyolysis:

No patients died directly due to rhabdomyolysis, although in one patient rhabdomyolysis was listed as a secondary diagnosis on the death certificate. This patient (study ref 267 KR51), a 58 year old man with diabetes and hypertension, was admitted to the hospital on (b) (6) months after randomization to simvastatin 80mg) with a few days history of generalized aches and malaise. Concomitant medications included diltiazem, metformin, and aspirin. He had moderately impaired renal function and a provisional diagnosis of pyelonephritis was made. On (b) (6), the patient's CK was found to be elevated at 40,000 IU/L. Simvastatin study treatment was discontinued. On (b) (6), CK was 57,000 IU/L, ALT 849 IU/L, serum creatinine 300µmol/L and BUN 23mmol/L. A probable diagnosis of simvastatin-induced myopathy was made. The patient's renal function deteriorated and he became anuric. On (b) (6) he was transferred to an intensive care unit and provided ventilation, hemofiltration, and inotropic support. He was also treated for suspected sepsis. On (b) (6), the patient died. The death certificate listed congestive heart failure with ischemic heart disease as the primary cause of death. Secondary diagnoses included renal failure secondary to statin-induced rhabdomyolysis and pneumonia.

The reporting investigator considered the simvastatin induced myopathy and renal failure due to rhabdomyolysis to be related to therapy with simvastatin. The investigator felt that the death, sepsis, cardiac failure and ischemic heart disease were not related to simvastatin therapy.

Another patient who was recovering from rhabdomyolysis, died about 3 weeks later. This patient (study ref 143 AY8P) was a 72 year old man recently diagnosed with prostate cancer who developed leg weakness and worsening renal function. He was admitted to the hospital (b) (6), (b) (6) months after randomization to simvastatin 80mg. CK was 15,200 IU/L and serum creatinine 300 µmol/L on (b) (6). Concomitant medications were warfarin, NTG spray, candesartan, bisoprolol, isosorbide mononitrate, fluticasone inhaler, and goserelin (a lutenizing hormone for the prostate cancer). Study simvastatin was discontinued. He was discharged from the hospital on high dose steroids with evidence of resolution of myopathy. (CK had decreased

to 670 IU/L.). He was re-admitted to the hospital at the end of (b) (6) with a gastrointestinal bleed due to hemorrhagic gastritis. He developed disseminated intravascular coagulopathy (DIC), neutropenia, sepsis, and renal failure.

The patient died on (b) (6). The certified cause of death was septicemia. Rhabdomyolysis was not mentioned on the death certificate.

7.2.6 Evaluation of rhabdomyolysis/myopathy for selected statins in clinical trials:

Rhabdomyolysis rates with selected statins:

Review comment:

In order to compare the occurrence of myopathy/rhabdomyolysis in SEARCH to those found in other studies, a literature review was conducted and those results are summarized below**.**

Cumulative FDA database reports of Rhabdomyolysis:
Historically, rhabdomyolysis was most commonly produced by crushing injuries of the muscle and extreme exertion. Medications were a rare and unusual cause of rhabdomyolysis prior to the advent of statin drugs.

The FDA Adverse Event Reporting System database contains 601 cases of statin- associated rhabdomyolysis from November 1997 through March 2000.[7]

All records that appeared in the AERS database between November 1997 and March 2000 (a total of 29 months) were included in the analysis. A series of queries were conducted to extract the records from the Drug File that contained the brand or generic names for each of the six listed statins, and then these were further limited to matching records that had the term "rhabdomyolysis" in the Reaction File. There were a total of 38 deaths (representing 6.3% of the unique cases) due to statin-associated rhabdomyolysis.

The percentage of total reported cases associated with each drug were as follows:

- simvastatin, 36%;
- cerivastatin, 32%; (voluntarily withdrawn on Aug 8th 2001)
- atorvastatin, 12%;
- pravastatin, 12%;
- lovastatin, 7%;
- fluvastatin, 2%,

7 FDA adverse event reports on satin-associated rhabdomyolysis. Ann Pharmacother. 2002 Feb;36(2):288-95.

Review comment:
The above data are from AERS which is a voluntary reporting system. It is therefore not necessarily reflective of the actual occurrence of rhabdomyolysis. Using this reporting system, simvastatin shows a relatively higher reporting rate. Doses were not specified.

Reports of Rhabdomyolysis in Clinical Trials:
Clinical trial results support a low incidence of severe muscle problems with statin therapy.[8] A compilation of all randomized controlled statin trials identified by one search revealed that among 83,858 patients randomly assigned to receive either statin treatment or placebo, there were only 49 cases of myositis and 7 cases of rhabdomyolysis in the statin treatment groups vs. 44 cases of myositis and 5 cases of rhabdomyolysis among placebo controls.

In this review, 5 of the 7 reported cases of rhabdomyolysis occurred during the heart Protection Study where patients took 40mg of simvastatin, or placebo. (see publication table which follows).

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8 Thompson, PD et al Statin-Associated Myopathy *JAMA*, 2003;289:1681-1690

Table 26: Myopathy rates in randomized controlled trials with statin therapy

Table 3. Myopathy in Randomized Controlled Trials of Statin Therapy

Studies*	Type of Patients†	Duration, y	Statin Dosage, mg/d	No. of Patients		No. With Rhabdomyolysis		No. With Myositis‡		% With CK Elevation		% With Myalgia	
				Statin	Control	Statin	Control	Statin	Control	Statin	Control	Statin	Control
Lovastatin													
AFCAPS/ TexCAPS[4]	No CAD	5.2 (Mean)	20-40	3304	3301	1	2	21	21	NR		NR	
FATS[30]	CAD (men)	2.5	20 (×2)§	38	46	NR		NR		NR		NR	
CCAIT[31]	CAD	2	40-80	165	166	NR		NR		NR		NR	
Post-CABG[32]	CAD	4.3 (Mean)	76 (Mean)§	628	628	0	0	NR		0.64	0.15	NR	
Pravastatin													
CARE[7,37]	CAD	5 (Median)	40	2078	2081	0	0	0	4	0.57	0.33	NR	
WOSCOPS[3]	No CAD (men)	4.9 (Mean)	40	3302	3293	0	0	NR		0.09	0.03	3.5	3.7
PLAC-I[33]	CAD	3	40	206	202	0	0	0	0	NR		NR	
PLAC-II[34]	CAD	3	10-40	75	76	NR		NR		NR		NR	
REGRESS[35,36]	CAD	2	40	323	330	0	0	0	0	NR		0.3	0
PREDICT[38]	CAD	0.5	40	347	348	NR		NR		NR		NR	
LIPID[39]	CAD	6.1 (Median)	40	4512	4502	0	0	8	10			NR	
L-CAD[40]	CAD	2	NR§	70	56	NR		NR		NR		NR	
GISSI-P[41]	CAD	0.4 (Median)	20-40	2138	2133	0	0	NR		NR		NR	
PRINCE[42]	No CAD	0.5	40	666	673	NR		NR		NR		NR	
ALLHAT-LLT[43]	Both	4.8 (Median)	40	5170	5185	NR		NR		NR		NR	
PROSPER[44]	Both, aged 70-82 y	3.2 (Mean)	40	2891	2913	0	0	0	0	NR		1.2	1
FAST[45]	No CAD	2	10	83	81	NR		NR		NR		NR	
Simvastatin													
4S[1]	CAD	5.4 (Median)	10-40	2221	2223	1	0	6	1	NR		NR	
CIS[46]	CAD	2.3 (Mean)	40	129	125	NR		NR		NR		NR	
Wenke et al[47]	Heart transplantation	4	10 (Mean)	35	37	0	0	0	0	0	0	NR	
Heart Protection Study[25]	Both	5 (Median)	40	10 269	10 267	5	3	11	6	0.19	0.13	32.9	33.2
Fluvastatin													
LCAS[48]	CAD	2.5	20 (×2)§	214	215	0	0	1	2	NR		NR	
LISA[49]	CAD	1	40-80	187	178	0	0	0	0	0	0.56	NR	
FLARE[50]	CAD	0.8	40	409	427	0	0	0	0	NR		NR	
Holdaas et al[51]	Renal transplantation	0.2	40	182	182	0	0	0	0	4.9	3.8	NR	
Atorvastatin													
AVERT[52,53]	CAD	1.5	80	164	177	0	0	0	0	0	0	1.2	1.2
MIRACL[54]	CAD	0.3	80	1538	1548	0	0	0	0	NR		NR	
GAIN[55]	CAD	1	33 (Mean)	65	66	0	0	0	0	NR		NR	
GREACE[56]	CAD	3 (Median)	10-80	800	800	0	0	0	0	NR		NR	
Cerivastatin													
ENCORE[57]	CAD	0.5	0.4	114	119	NR		2	0	0.61	0.58	NR	
Total				**42 323**	**41 535**	**7**	**5**	**49**	**44**				

Abbreviations: CAD, coronary artery disease; CK, creatine kinase; NR, not reported.
*See references for explanations of study abbreviations.
†"Both" indicates both patients with and without CAD.
‡Myositis was defined by study investigators or as a CK elevation of greater than 10 times the upper limit of normal.
§Plus another medication.

Individual statin trials which assessed rhabdomyolysis:

ASCOT-LLA:
The Anglo-Scandinavian Cardiovascular Outcomes Trial Lipid Lowering Arm (ASCOT-LLA) was a lipid-lowering sub-trial of a still-ongoing parent hypertension treatment trial (ASCOT). ASCOT-LLA was intended to be the first large-scale long-term study to evaluate the benefits of cholesterol lowering with atorvastatin 10mg in the primary prevention of coronary heart disease in a total of 19,342 hypertensive adult male and female hypertensive patients with normal to mildly elevated lipid levels and a number of additional cardiovascular risk factors.

In this study, rhabdomyolysis was defined as muscle symptoms with CK >10xULN, plus elevated serum creatinine. The definition further added that "brown urine and urinary myoglobin usually occur." Two rhabdomyolysis cases in over 10,000 patients occurred in this study, both in the atorvastatin group. The sponsor reported that both patients recovered "after a few days" of hydration and both patients had contributing factors (excess ethanol intake and concomitant simvastatin therapy).

Summary narratives of these two rhabdomyolysis cases are as follows:

Case 2002062397 involved a 67 year old woman who developed symptoms of gastroenteritis on day 1,152 of study medication. This patient was simultaneously receiving simvastatin, prescribed by her primary care physician. The simvastatin had been stared about one year prior to the event, and about two years after she entered the study and was randomized to atorvastatin. She was admitted to the hospital and developed "symptoms of rhabdomyolysis," renal failure and myoglobinemia. Atorvastatin was stopped and her study antihypertensive therapy was temporarily stopped. Simvastatin was also stopped. With intravenous hydration, she recovered in four to five days.

Case 2003005632 involved a 56 year old man who was admitted to the hospital with weakness and fainting on Day 1,155 of study medication. He was a heavy drinker of ethanol. He was found to have elevated myoglobin and liver function tests, a CPK of 1,765 U/L, and acute renal failure. He was discharged after four days.

Both these cases have additional predisposing factors for rhabdomyolysis. The incidence of rhabdomyolysis did not exceed that seen with statin therapy in general.

Other muscle-related SAEs occurred in four atorvastatin-treated and 11 placebo patients. Pfizer reports that contributing etiologies included angina, embolism, pneumonia, "disc disease," and anemia. In the medical officer's review of these additional "muscle-related" adverse event cases, none appear attributable to atorvastatin.

There were no cases of increased CPK reported as SAEs in either the placebo or atorvastatin group.

Heart Protection Study (HPS):
The HPS randomized 20,536 patients (10,269 on active 10,267 on placebo) to 40mg simvastatin per day, and/or antioxidant vitamins (vitamin E 600 mg, vitamin C 250 mg, and beta carotene 20mg) in a 2 x 2 factorial study design. Over the mean 5 year duration of this trial, rhabdomyolysis defined as CK > 40 times the ULN, occurred in 5 statin and 3 placebo participants, but one of the placebo patients was taking a nonstudy statin. (the names of the nonstudy statins were not specified).

Review comment:
The HPS study documented a low, but comparatively higher incidence of rhabdomyolysis associated with simvastatin therapy compared to other available statins. It should be noted that such results, when elucidated in a controlled trial, monitored by lipid researchers, may be under-estimating the incidence in the general population when statins users are likely be followed with less precise care, and where myopathy could more easily progress to rhabdomyolysis or fatal rhabdomyolysis.

In this trial serious cases of rhabdomyolysis or severe myopathy were defined using the following criterion:

- CK>10,000 and/or
- hospitalization for myopathy (i.e. CK >10xULN and unexplained muscle symptoms).

Using these definitions, there were 8 cases of rhabdomyolysis or myopathy on simvastatin (0.08%) compared to two cases on placebo. However, one of these placebo patients was on cerivastatin, so in actuality there was only one placebo patient with rhabdomyolysis or myopathy not associated with statin use in this trial (0.01%). Even though the incidence is relatively small, there is a higher risk of rhabdomyolysis or myopathy on simvastatin compared to placebo.

Review Comment:
Cases of rhabdomyolysis and myopathy were grouped together in the Summary Analysis section. Specific details of the individual cases were not provided.

Four out of the 8 cases of rhabdomyolysis or myopathy observed in this study occurred in patients taking other drugs know to interact with simvastatin. Two patients were on erythromycin (2/12=17%), a potent inhibitor of cytochrome P-450 (CYP3A4), and two were on verapamil (2/202=1.0%), a CYP3A4 substrate. In contrast, no patients in the placebo group receiving concomitant erythromycin (n=16) or verapamil (n=169) experienced rhabdomyolysis/myopathy. The current approved labeling for simvastatin warns about the increased risk of myopathy with concomitant administration of erythromycin or verapamil.

One of the cases of rhabdo/myopathy occurred in a patient who was started on 20mg simvastatin in addition to the 40mg study simvastatin. This combined dose of 60mg is within the currently approved maximal daily dose of simvastatin (80mg). However, it is known that the incidence of myopathy/rhabdomyolysis is dose related with statins. The current label for Zocor estimates the incidence from clinical trials as 0.07% at 40mg and 0.3% at 80mg.

One case of rhabdo/myopathy occurred in a 66y/o male with chronic renal failure. Patients with severe renal disease or creatinine > 2.3mg/dL (>2xULN) were excluded from the study. This patient had a creatinine measurement of 1.9mg/dL noted at screening. Higher systemic exposure has been reported in patients with severe renal insufficiency and the current label recommends starting patients with severe renal insufficiency on a daily dose of 5mg of simvastatin.

The A to Z Trial:
In this trial, patients with ACS receiving simvastatin 40mg for 1 month followed by 80mg/d thereafter (n=2265) compared with ACS patients receiving placebo for 4 months followed by 20mg/d of simvastatin (n=2232), who were enrolled in phase Z of the A to Z trial between December 29, 1999, and January 6, 2003.

Discontinuation of the study drug due to a muscle-related adverse event occurred in 1.5% (34/2230) of patients in the placebo plus simvastatin group and 1.8% (41/2263) in the simvastatin only group (P=0.49). A total of 10 patients developed myopathy (creatine kinase level >10 times the ULN with associated muscle symptoms); 1 patient was in the 20mg simvastatin group and 9 patients were in the 80mg simvastatin only group (P=0.02).

Three of the 9 patients with myopathy had creatine kinase levels higher than 10,000 units/L therefore meeting the definition for rhabdomyolysis. Of these 3 patients, 1 patient had contrast-induced renal failure and 1 patient was receiving concomitant verapamil, which is a known inhibitor of CYP3A4. In addition, 1 patient receiving 80mg of simvastatin had a creatine kinase level higher than 10x ULN without muscle symptoms, which was associated with alcohol abuse. There were no cases of myopathy when patients were taking 20mg of simvastatin or 40 mg of simvastatin.

CARDS (Collaborative AtoRvastatin Diabetes Study)
A total of 2838 patients aged 40-75 years with type 2 DM were randomized to placebo (n=1410) or atorvastatin 10 mg daily (n=1428). There were two reports of myopathy and no reports of rhabdomyolysis.

Review Comment:
Atorvastatin's major trials including AVERT, MIRACL, GAIN and GREACE had zero reported cases of rhabdomyolysis or myopathy.

The CARDS atorvastatin study had two cases of myopathy and zero cases of rhabdomyolysis. In CARDS, rhabdomyolysis was defined as: "muscle symptoms with marked CPK elevation (>10xULN) and with creatinine elevation."

In addition, over two dozen other clinical trials examining lovastatin, pravastatin, fluvastatin and atorvastatin had zero reported cases of rhabdomyolysis, however the numbers of patients examined in those studies were all smaller in size and involved the administration of lower statin doses.

Treating to New Targets (TNT):
The closest comparable study to SEARCH was The Treating to New Targets (TNT). This trial randomized 10,003 patients to either atorvastatin 10 or 80mg.

Review comment:
TNT had a total of five cases of rhabdomyolysis: two in the 80mg atorvastatin group and three in the 10mg atorvastatin group. Unlike SEARCH, the incidence of rhabdomyolysis occurred less often in TNT and did not appear to be dose-related. The incidence of rhabdomyolysis in TNT was 0.05% compared to 0.4% in SEARCH. The number of myopathy cases in TNT was not reported.

Rhabdomyolysis in TNT was defined by the same criteria as the American College of Cardiology, American Heart Association, and National Heart, Lung, and Blood Institute which is muscle symptoms plus a CK >10xULN plus an elevation in creatinine or urinary abnormalities (e.g., myoglobinuria).

Cerivastatin 0.8mg NDA review:
This was a 52-week study examining 1,170 patients taking 0.8 mg of cerivastatin daily.

The percentage of patients with any treatment-emergent elevations of CK through week 52 (Week 8 shown in parentheses) regardless of baseline status is shown in the following table:

Table 27: Comparison of cerivastatin 0.4 and 0.8mg to placebo/pravastatin

	CER 0.4 mg (n=193)	CER 0.8mg (n=770)	PLA/PRAVA 40mg (n=198)
Any elevation*	38% (28%)	49% (35%)	35% (22%)
>ULN to ≤3xULN	30% (22.7%)	40% (29.7%)	30.3% (20.2%)
>3xLN to ≤5xULN	3.6% (2.1%)	4.3% (2.8%)	2.0% (1.0%)
>5xULN to<10xULN	2.6% (2.1%)	2.5% (1.3%)	2% (1.0%)
>10xULN	1.5% (1.0%)	2.1% (1.3%)	0.5% (0.0%)
>10xULN with symptoms	1.5% (1.0%)	1.0% (0.9%)	0.0% (0.0%)
Sustained High+	18% (11%)	27% (17%)	16% (7%)

* Normal Range: 0 to 120 U/L
\+ >ULN at 2 consecutive visits or patient's last visit.

The development of CK elevation >l0xULN at Week 8 and Week 52-week time-points (week 8 shown in parentheses) were higher in cerivastatin 0.8mg patients compared to cerivastatin 0.4mg

and placebo/pravastatin 40mg-treated patients. There were 20 patients (one in the placebo/pravastatin group, three in the cerivastatin 0.4mg group, and 16 in the cerivastatin 0.8 mg group) with CK elevation >10XULN post-randomization.

Although there were no reported deaths in this study due to rhabdomyolysis, cerivastatin was eventually withdrawn when Bayer received post-marketing surveillance reports of 52 US deaths due to severe rhabdomyolysis associated with use of cerivastatin. In addition, there were 385 nonfatal cases reported among the estimated 700,000 users in the United States, giving it an approximate rhabdomyolysis incidence of 0.06% at any dose.[9] In many of the fatal cases, patients had received the full dose of cerivastatin (0.8 mg/day) or were using gemfibrozil concomitantly. This drug-drug interaction was implicated in 12 of the 31 fatalities in the United States.

Clinical Trial Myopathy Data:
To provide a point of reference for the simvastatin data from SEARCH, The Division obtained myopathy data from long-term, controlled trials of high doses of statins other than simvastatin.

As shown in the data in Table which follows, the incidence of myopathy is higher with the 80mg dose of simvastatin compared with doses of rosuvastatin and atorvastatin.

9 Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. Curr Control Trials Cardiovasc Med 2001;2:205-207.

Table 28: Incidence of Myopathy in High-Dose Statin Trials:

Trial	Treatment	Sample Size	CK >10xULN-40xULN	CK > 40xULN	"Rhabdo-myolysis"†
JUPITER	20mg rosuvastatin	8900	1 (0.01%)	1	1
	placebo	8900	1 (0.01%)	0	0
HPS	40mg simvastatin	10000	7 (0.07%)	7	4
	placebo	10000	4 (0.04%)	4	1
A-Z	**40/80 mg simvastatin**	**2200**	**22 (1.0%)**	**4**	**3**
	placebo/20mg simvastatin	2200	5 (0.23%)	1	0
SEARCH	**80mg simvastatin**	**6000**	**47 (0.80%)**	**23**	**11**
	20mg simvastatin	6000	12 (0.20%)	0	0
TNT	80mg atorvastatin	5000	9 (0.18%)	4	2
	10mg atorvastatin	5000	5 (0.10%)	1	3
IDEAL	80mg atorvastatin	4400	9 (0.20%)	1	2
	20/40mg simvastatin	4400	6 (0.10%)	0	3
SPARCL	80mg atorvastatin	2300	6 (0.30%)	0	2
	placebo	2300	3 (0.13%)	1	3
PROVE-IT	80mg atorvastatin	2000	3 (0.15%)	0	1
	40mg pravastatin	2000	3 (0.15%)	0	0
LIPS	80mg fluvastatin	840	0	0	0
	placebo	840	3 (0.40%)	0	0

†Rhabdomyolysis was defined by individual investigators without regard to uniform criteria

It should be noted that for the trials listed there was no correction for time on drug. In most trials, individuals with CK > 3xULN at screening were not allowed to continue to participate in the trial, and participants were permanently discontinued if they developed unexplained muscle pain or weakness with CK >10xULN. Unfortunately, a uniform definition of rhabdomyolysis was not used across these trials, limiting the usefulness of the reports of "rhabdomyolysis".

Observational Myopathy Data:
As a post-marketing requirement following the recent approval of Trilipix (fenofibric acid) for the treatment of dyslipidemia, The Division obtained observational data on the risk for hospitalized rhabdomyolysis in subjects exposed to statin monotherapy, fenofibrate

monotherapy, gemfibrozil monotherapy, statin-fibrate combination therapy, and statin-gemfibrozil combination therapy.

Using the Normative Health Informatics database, 1,116,805 patients were identified based on the following eligibility criteria: age greater than 17 years, commercial insurance coverage, complete medical and pharmacy benefits, at least 183 days of continuous enrollment in the health plan, and at least one dispensing of any statin (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin) or of any fibrate (fenofibrate, gemfibrozil). Outpatient pharmacy records were used to identify all dispensing of statins and fibrates during the study period. Patients who had never received cerivastatin or clofibrate were excluded. An inception cohort was constructed by identifying new initiators of statins or fibrates. Cohort entry (index date) was the date of the first dispensing of a statin or of a fibrate after being continuously enrolled for at least a 183-day period prior to the index date and fulfilling all eligibility criteria. Follow-up continued through the earliest of the date of health plan disenrollment, the date of confirmed rhabdomyolysis diagnosis, or December 31, 2008 (the end of the study). Each follow-up day was classified according to current exposure status to statins and fibrates.

The following diagnostic codes were used to identify potential cases of hospitalized rhabdomyolysis: rhabdomyolysis, myoglobinuria, polymyositis, myositis, muscle weakness, myopathy, musculoskeletal symptoms of the limb, other disorder of muscle, ligament, or fascia, and adverse effect of antihyperlipidemic agent.

The largest incidence rate was observed with simvastatin, followed by lovastatin and pravastatin. The 95% confidence interval for the incidence rate for simvastatin excluded unity.

The incidence rate for hospitalized rhabdomyolysis for individual statins is provided in table which follows:

Table 29: Incidence Rates for Hospitalized Rhabdomyolysis:

Statin	# Cases	Person-Years	Incidence Rate	95% CI
Simvastatin	**11**	**329,639**	**3.34**	**1.67, 5.97**
Lovastatin	2	62,556	3.20	0.39, 11.55
Pravastatin	3	95,874	3.13	0.65, 9.14
Atorvastatin	11	557,173	1.97	0.99, 3.53
Rosuvastatin	1	78,228	1.28	0.03, 7.12
Fluvastatin	0	14,444	0	0.00, 20.7

*One case occurred with 40 mg lovastatin and one case with lovastatin/niacin

Of the 11 cases of hospitalized rhabdomyolysis identified in users of simvastatin monotherapy, 4 cases occurred with the 20 mg dose, 3 with the 40 mg dose, and 4 with the 80 mg dose. Of the 11 cases identified in users of atorvastatin, 4 cases occurred with the 10 mg dose, 5 with the 20 mg dose, 1 with the 40 mg dose, and 1 with the 80 mg dose.

Nonetheless, currently available data on patient exposure to individual statin doses at the time of entry into the study suggest that the risk for hospitalized rhabdomyolysis is considerably higher with 80 mg simvastatin compared to doses of other statins that provide equal or superior lowering of LDL.

Primo Study:
In a naturalistic study of nearly 8000 statins users in France, investigators reported that 18.2% of patients treated with 40 mg or 80 mg of simvastatin reported muscle pain compared with 14.9%, 10.9%, and 5.1% of patients treated with 40 mg or 80 mg atorvastatin, 40 mg pravastatin, and 80 mg fluvastatin, respectively.[10]

In contrast to the above, in a prospective, open-cohort assessment of 2 million patients followed by general practitioners in England and Wales, the risks for moderate-to-severe myopathy were similar in users of low versus moderate and high doses of simvastatin.[11] Moreover, the risk estimate for myopathy with moderate and high doses of simvastatin was intermediate to the risk estimate calculated with a range of doses of other statins. The authors do not provide the definitions used to define moderate-to-severe myopathy.

Pooled Statin Efficacy Data:

Lancet Meta-analysis:
In 2005, The LANCET did a meta-analysis pooling data from 90K patients from 14 statin trials over a 20 year interval in effort to quantify the combined benefit.[12]

The LANCET data were composed of older studies including: 4S and WOSCOPS, CARE, AFCAPS and so on and almost all studies used low-to-moderate doses of lovastatin, pravastatin fluvastatin, simvastatin, or atorvastatin. Additionally, these trials combined *both primary and secondary prevention*. Only LIPS used the maximum marketed dose, fluvastatin. None of the trials examined rosuvastatin.

10 Bruckert E, et al. Mild to moderate muscular symptoms with high-dose statin therapy in hyperlipidemic patients – The Primo Study. Cardiovascular Drugs and Therapy 19; 403-414: 2005.
11 Hippisley-Cox J, et al. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ 340; 2197:2010.
12 Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins ***Lancet* 2005; 366: 1267–78**

Table 30: Pooled data from the Lancet Meta- Analysis.

Trial	year	treatment*	n
4S	1994	S20-40vs pbo	4,444
WOSCOPS	1995	P40 vs pbo	6,595
CARE	1996	P40 vs pbo	4,159
Post CABG	1997	L20-40 vs pbo	1,351
AFCAPS	1998	L20-40 vs pbo	6,605
LIPID	1998	P40 vs pbo	9,014
GISSI	2000	P20 vs pbo	4,271
LIPS	2002	F80 vs pbo	1,677
HPS	2002	S40 vs pbo	20,536
PROSPER	2002	P40 vs pbo	5,804
ALLHAT-LLT	2002	P40 vs pbo	10,355
ASCOT-LLA	2003	A10 vs pbo	10,305
ALERT	2003	F40 vs pbo	2,102
CARDS	2004	A10 vs pbo	2,838
TOTAL			**90,056**

*Treatment: S=simvastatin P=pravastatin L=lovastatin, F=fluvastatin, A=atorvastatin, pbo=placebo

The Lancet study concluded that the absolute benefit relates chiefly to the absolute reduction in LDL cholesterol achieved. Specifically, the study concluded: "statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about 20% per ~39mg/dL reduction in LDL, irrespective of the initial LDL or other presenting characteristics."

Extrapolating findings from The Lancet, the 13.5mg/dL decrease in LDL found in SEARCH should have achieved an 8% decrease in MVEs ($p<0.0001$). The actual difference in LDL due to the 13.5mg/dL decrease in LDL was 6% and was not statistically significant.

Statin Utilization Data: Year 2007 through September 30th 2009:

The Office of Surveillance and Epidemiology used outpatient drug utilization databases to assess statin utilization because sales data for the 12-month period ending in August 2009. These data indicated that around 66% of statin single-ingredient tablets or capsules and 62% statin combination product tablet or capsule sales were distributed to outpatient retail pharmacies; 25% and 32% were to mail order pharmacies, respectively; and 10% and 7% to non-retail settings, respectively.[13] Neither mail order nor non-retail settings were included in this analysis.

From January 2007 to September 2009, simvastatin-containing products were most commonly dispensed as the generic simvastatin product ([redacted] (b) (4) prescriptions; [redacted] (b) (4) %).

The decrease in the use of atorvastatin was associated with an increase in the use of simvastatin, as show in the in figure below.

Figure 8: Projected Number of Dispensed Outpatient Retail Prescriptions (in thousands)

[redacted] (b) (4)

As shown in the figure above, there was an increase in the total number of prescriptions written between 2007 and 2008, and during this period, a majority of patients on a statin took simvastatin or atorvastatin. There was also a corresponding increase in simvastatin use and a corresponding decrease in the use of atorvastatin associated with the timing of simvastatin losing patent protection. This trend would be expected to continue through 2009.

13 IMS Health, IMS National Sales Perspectives™, MAT September 2009, Extracted 11-9-09. File: 0911stat.dvr

From January 2007 to September 2009:

- Of the (b) (4) simvastatin single-ingredient products dispensed, the (b) (4) mg strength ((b) (4) prescriptions; (b) (4)%) was followed closely by the (b) (4) strength ((b) (4) prescriptions; (b) (4)%) as the most commonly dispensed. The (b) (4) strength accounted for around (b) (4)% of the simvastatin single-ingredient dispensed prescription market.
- Of the (b) (4) Vytorin dispensed prescriptions, the product containing the (b) (4) strength of simvastatin was most commonly dispensed ((b) (4) prescriptions, (b) (4)%) followed closely by the product containing the (b) (4) strength of simvastatin ((b) (4) prescriptions; (b) (4)%). The product containing the (b) (4) strength of simvastatin accounted for around (b) (4)% or (b) (4) prescriptions of the Vytorin dispensed prescription market.

Figure 9: Total number of dispensed <u>retail prescriptions</u> for simvastatin and combination simvastatin products:

Total Number of Dispensed Retail Prescriptions for Statins and Combination Statin Products by Strength

(b) (4)

<u>Data for the use of Simvastatin 80mg as a single and combined product:</u>
The patent for simvastatin expired on June 23 2006. From year 2007 to year 2008, dispensed prescriptions for simvastatin-containing products (i.e. generic products) increased by (b) (4)%. This was heavily weighted by the new availability of generic simvastatin products. During this same period, brand-name Vytorin decreased by (b) (4)% and brand-name Zocor decreased by (b) (4)%.

Review comment:
The use of simvastatin 80mg was projected for 2009 based on data available though September 30th 2009 (ie 273 days worth of data). As shown, there was a (b) (4)% increase in the use of simvastatin 80 between January 2007 and September of 2009.

Of important note: drug use data is highly estimated data based on a very small sample of mail order and retail data. Of the approximately 60,000 retail pharmacies in the United States, data is obtained from about 20,000 pharmacies and extrapolated. The mail order extrapolation details are not clear, but they are also highly estimated from a small sample. Additional extrapolations are made to include mail order houses, non-retail settings, hospitals, LTC facilities, hospital pharmacies, on line pharmacies, and other non-retail settings.

Rhabdomyolysis summary:
The relative rates of myopathy/ rhabdomyolysis relative to their achieved LDL are shown in the figure and table which follow:

Figure 10: Relative myopathy and rhabdomyolysis rates in long-term trials

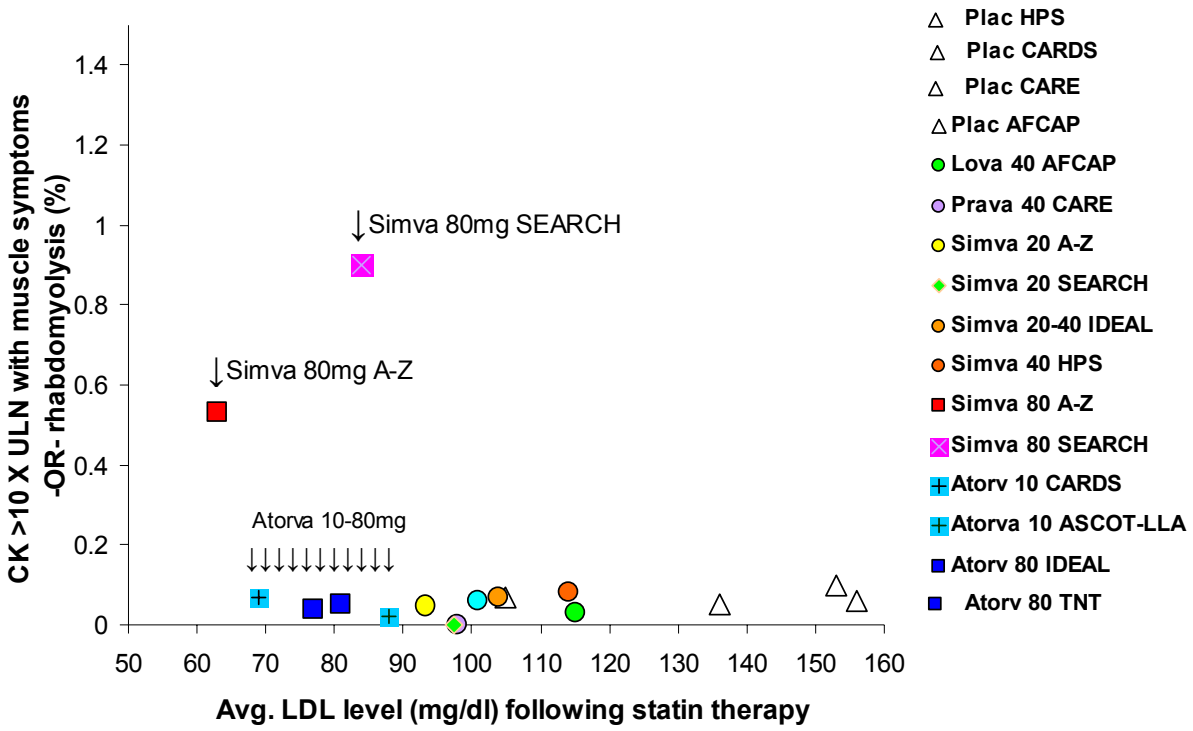


Table 31: Relative myopathy and rhabdomyolysis rates in long-term trials

Study:	Treatment:	Avg. LDL level (mg/dl) following statin therapy	CK >10 X ULN w/ muscle sx -OR- rhabdomyolysis (%)
AFCAP	plac	156	0.061
CARDS	plac	105	0.07
CARE	plac	136	0.05
HPS	plac	153	0.1
AFCAP	lova 40	115	0.03
CARE	prava 40	98	0
AtoZ	simva 20	77	0.04
IDEAL	simva 20-40	104	0.07
HPS	simva 40	114	0.08
CARDS	atorva 10	69	0.07
TNT	atorva 10	101	0.06
AtoZ	simva 80	63	0.53
TNT	atorva 80	77	0.04
IDEAL	atorva 80	81	0.05
SEARCH	simva 80	84	0.9
SEARCH	simva 20	97.5	0
ASCOT-LLA	atorva 10	88	0.02

As shown in the figure above, in comparative long-term event trials, the rate of myopathy and rhabdomyolysis were rather low and comparable for all statin groups except simvastatin 80mg the A to Z and SEARCH trials.

Review Comment:
In relative terms, it appears that simvastatin at its maximum dose of 80mg is less safe in terms of myopathy/rhabdomyolysis than simvastatin 20mg as well as comparative statins at their range of doses.

In absolute terms, it is likely that the clinical benefit of simvastatin 80mg would hypothetically outweigh the risk of myopathy/ rhabdomyolysis if no safer statin alternatives existed.

The finding of an increased incidence of rhabdomyolysis in SEARCH is in agreement with The A to Z trial which also showed in increased incidence in rhabdomyolysis specifically with the 80mg dose of simvastatin.

In SEARCH, using an on-treatment basis, the incidence of myopathy in patients taking simvastatin 80mg over the course of the study was 1.2%, with an incidence of 0.5% in the first year of the study and about 0.1% in each subsequent year, (based on the sponsor's definition of

rhabdomyolysis.) The majority (0.9%) of these myopathy cases were simvastatin 80mg associated myopathy with CK elevations.

During SEARCH and A to Z the use concomitant interacting medications such as amiodarone, diltiazem, erythromycin and amlodipine appeared to increase the risk of myopathy when given with simvastatin 80mg.

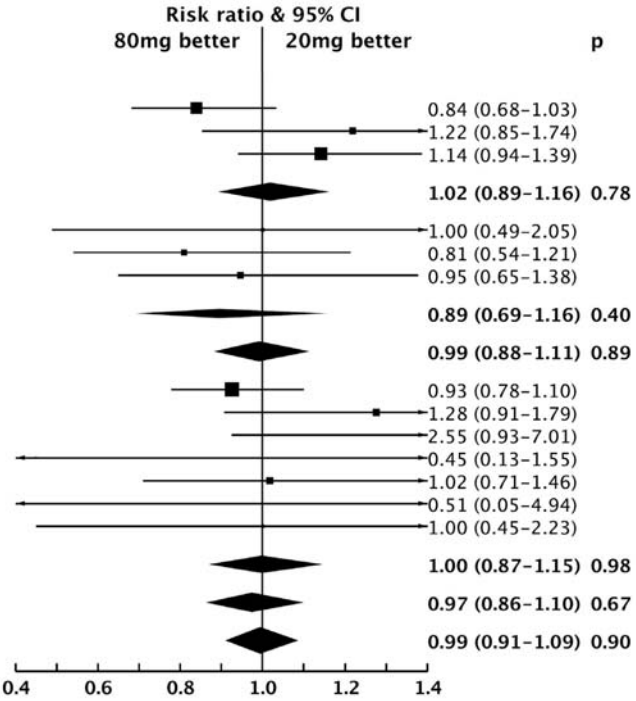
7.3.1 Deaths

There was no difference between the simvastatin 80mg and 20mg groups in total mortality, mortality due to CHD, mortality due to vascular causes, or mortality from non-CHD or non-vascular causes, including cancer.

The total and cause-specific mortality, including CHD mortality, vascular mortality and non-vascular mortality are show in the following figure.

Figure 11: Total and Cause-Specific Mortality

Cause of death	Simvastatin allocation 80mg (n=6031)	Simvastatin allocation 20mg (n=6033)	O-E	Var	z	Risk ratio & 95% CI (80mg better / 20mg better)	p
Acute MI	162 (2.7%)	193 (3.2%)	-15.5	88.7	-1.65	0.84 (0.68-1.03)	
Heart failure	67 (1.1%)	55 (0.9%)	6.0	30.5	1.09	1.22 (0.85-1.74)	
Other CHD	218 (3.6%)	191 (3.2%)	13.6	102.2	1.34	1.14 (0.94-1.39)	
ALL CHD	**447 (7.4%)**	**439 (7.3%)**	**4.1**	**221.5**	**0.28**	**1.02 (0.89-1.16)**	**0.78**
Haemorrhagic stroke	15 (0.2%)	15 (0.2%)	0.0	7.5	0.00	1.00 (0.49-2.05)	
Other stroke (isch & unknown)	42 (0.7%)	52 (0.9%)	-5.0	23.5	-1.03	0.81 (0.54-1.21)	
Other vascular	53 (0.9%)	56 (0.9%)	-1.5	27.2	-0.29	0.95 (0.65-1.38)	
OTHER VASCULAR	**110 (1.8%)**	**123 (2.0%)**	**-6.5**	**58.2**	**-0.85**	**0.89 (0.69-1.16)**	**0.40**
ALL VASCULAR	**557 (9.2%)**	**562 (9.3%)**	**-2.4**	**279.7**	**-0.14**	**0.99 (0.88-1.11)**	**0.89**
Neoplastic	246 (4.1%)	266 (4.4%)	-9.9	128.0	-0.87	0.93 (0.78-1.10)	
Respiratory	74 (1.2%)	58 (1.0%)	8.0	33.0	1.40	1.28 (0.91-1.79)	
Hepatic	11 (0.2%)	4 (0.1%)	3.5	3.7	1.81	2.55 (0.93-7.01)	
Renal	3 (0.0%)	7 (0.1%)	-2.0	2.5	-1.26	0.45 (0.13-1.55)	
Other medical	60 (1.0%)	59 (1.0%)	0.5	29.7	0.10	1.02 (0.71-1.46)	
Suicide	1 (0.0%)	2 (0.0%)	-0.5	0.8	-0.58	0.51 (0.05-4.94)	
Other non-medical	12 (0.2%)	12 (0.2%)	0.0	6.0	0.00	1.00 (0.45-2.23)	
ALL NON-VASCULAR	**407 (6.7%)**	**408 (6.8%)**	**-0.3**	**203.7**	**-0.02**	**1.00 (0.87-1.15)**	**0.98**
ALL NON-CHD	**517 (8.6%)**	**531 (8.8%)**	**-6.8**	**262.0**	**-0.42**	**0.97 (0.86-1.10)**	**0.67**
ALL CAUSES	**964(16.0%)**	**970(16.1%)**	**-2.7**	**483.5**	**-0.12**	**0.99 (0.91-1.09)**	**0.90**



Source: Sponsor's Figure 12-1.

The above figure shows total mortality by baseline characteristics, vascular death by year of follow-up, vascular death by baseline characteristics, CHD death by year of follow-up, CHD death by baseline characteristics, and non-vascular death by baseline characteristics. There was no difference between the various subgroups in the simvastatin 80mg and 20mg groups in regard to total mortality, vascular mortality, CHD mortality, or non-vascular mortality.

Cancer Deaths
There was no meaningful difference in the rate of cancer deaths in patients allocated to simvastatin 80mg or simvastatin 20mg. Two hundred forty-six (4.1%) patients allocated to simvastatin 80mg had neoplasm as the cause of death compared to 266 (4.4%) patients allocated to simvastatin 20mg (RR 0.93; 95% CI 0.78, 1.10).

7.3.2 Nonfatal Serious Adverse Events

The table below summarizes SAEs in all patients randomized to simvastatin 80mg versus simvastatin 20mg.

Table 32: Serious Adverse Events Summary

	Simvastatin 80 mg (N=6031)		Simvastatin 20 mg (N=6033)	
Adverse Experience	n	(%)	n	(%)
Any reported SAE	5024	(83.3%)	5037	(83.5%)
SAE attributed to study treatment	56	(0.9%)	7	(0.1%)
Stopped study treatment	1591	(26.4%)	2039	(33.8%)
Adverse experience	287	(4.8%)	229	(3.8%)
Other reasons	1304	(21.6%)	1810	(30.0%)

Source: Sponsor's Table 12-2

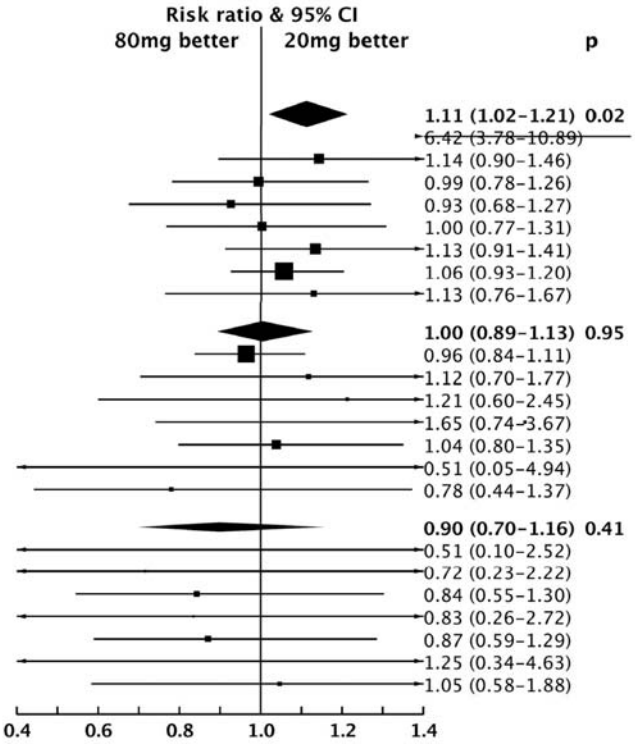
There was a statistically significant increase in the RR for serious musculoskeletal adverse reactions in patients allocated to simvastatin 80mg vs 20mg: RR 1.11 (95% CI 1.02,1.21); p = 0.02. This difference is due to the increased incidence of myopathy in patients allocated to simvastatin 80mg. The sponsor notes that throughout the table, risk ratios are estimated by the approximation exp ((O-E)/V), which is satisfactory up to ratios of about 1.5, but becomes increasingly inaccurate as risk ratios increase further. For this reason, the risk ratio of 6.42 given in the table for myopathy or rhabdomyolysis is not appropriate. For this extreme difference (52 vs. 2 cases) the risk ratio was subsequently calculated by Cox regression, yielding 26.6 (95% CI 6.7-109.3).

There was no difference between the simvastatin 80mg group and the 20mg group for serious adverse events in the neurological and psychological areas which includes memory loss, dementia, and confusion. Given the large number of comparisons, there were occasional instances where the 95% confidence interval did not overlap unity. The lower risk of DVT, ventricular arrhythmia, esophageal disease/surgery, other gastrointestinal (GI) disease, including colitis, and of kidney/renal tract surgery in patients allocated simvastatin 80mg is likely due to chance, and is not statistically significant when account is taken of the multiple comparisons. In the 20mg group, there was a lower risk for breast disease/surgery (80mg: 29/0.5% vs 20mg: 16/0.3%) and 'other endocrine problem' (80mg: 29/0.5% vs 20mg: 16/0.3%).

The figure which follows shows part of the sponsor's table of all patients with serious adverse events that were not adjudicated endpoints of the trial.

Figure 12: Serious Adverse Events Other Than Adjudicated Endpoints

Event	Simvastatin allocation 80mg (n=6031)	Simvastatin allocation 20mg (n=6033)	O-E	Var	z	Risk ratio & 95% CI (80mg better / 20mg better)	p
Musculoskeletal	**1035(17.2%)**	**941(15.6%)**	**52.2**	**493.9**	**2.35**	**1.11 (1.02-1.21)**	**0.02**
Myopathy or rhabdomyolysis	53 (0.9%)	2 (0.0%)	25.6	13.7	6.89	6.42 (3.78-10.89)	
Other muscle problem	139 (2.3%)	122 (2.0%)	8.6	65.2	1.07	1.14 (0.90-1.46)	
Arthritis	132 (2.2%)	133 (2.2%)	-0.4	66.2	-0.05	0.99 (0.78-1.26)	
Other bone/joint disease	74 (1.2%)	80 (1.3%)	-3.0	38.5	-0.48	0.93 (0.68-1.27)	
Back/spinal problem	108 (1.8%)	108 (1.8%)	0.1	54.0	0.01	1.00 (0.77-1.31)	
Hip surgery	173 (2.9%)	153 (2.5%)	10.2	81.5	1.13	1.13 (0.91-1.41)	
Other bone/joint surgery	459 (7.6%)	436 (7.2%)	12.1	223.7	0.81	1.06 (0.93-1.20)	
Soft tissue surgery/disease	53 (0.9%)	47 (0.8%)	3.0	25.0	0.61	1.13 (0.76-1.67)	
Neurological	**566 (9.4%)**	**563 (9.3%)**	**1.1**	**282.2**	**0.06**	**1.00 (0.89-1.13)**	**0.95**
Neuro symptom/investigation	386 (6.4%)	400 (6.6%)	-7.2	196.5	-0.52	0.96 (0.84-1.11)	
Chronic neurological disease	38 (0.6%)	34 (0.6%)	2.0	18.0	0.47	1.12 (0.70-1.77)	
Sleep problem	17 (0.3%)	14 (0.2%)	1.5	7.7	0.54	1.21 (0.60-2.45)	
Peripheral neuropathy	15 (0.2%)	9 (0.1%)	3.0	6.0	1.23	1.65 (0.74-3.67)	
Peripheral nerve surgery	113 (1.9%)	109 (1.8%)	2.1	55.5	0.28	1.04 (0.80-1.35)	
Benign brain tumour	1 (0.0%)	2 (0.0%)	-0.5	0.8	-0.58	0.51 (0.05-4.94)	
Other neuro problem/surgery	21 (0.3%)	27 (0.4%)	-3.0	12.0	-0.86	0.78 (0.44-1.37)	
Psychological	**115 (1.9%)**	**128 (2.1%)**	**-6.5**	**60.7**	**-0.83**	**0.90 (0.70-1.16)**	**0.41**
Accidental overdose/poisoning	2 (0.0%)	4 (0.1%)	-1.0	1.5	-0.83	0.51 (0.10-2.52)	
Deliberate self harm/overdose	5 (0.1%)	7 (0.1%)	-1.0	3.0	-0.58	0.72 (0.23-2.22)	
Dementia	37 (0.6%)	44 (0.7%)	-3.5	20.2	-0.77	0.84 (0.55-1.30)	
Confusion/psychosis	5 (0.1%)	6 (0.1%)	-0.5	2.8	-0.30	0.83 (0.26-2.72)	
Depression or bipolar disease	47 (0.8%)	54 (0.9%)	-3.5	25.2	-0.70	0.87 (0.59-1.29)	
Memory loss	5 (0.1%)	4 (0.1%)	0.5	2.2	0.34	1.25 (0.34-4.63)	
Other psych problem/symptom	23 (0.4%)	22 (0.4%)	0.5	11.2	0.15	1.05 (0.58-1.88)	



Source: Sponsor's Figure 12-5

Musculoskeletal and hepatic adverse events are discussed in Section 7.3.5: Submission Specific Primary Safety Concerns.

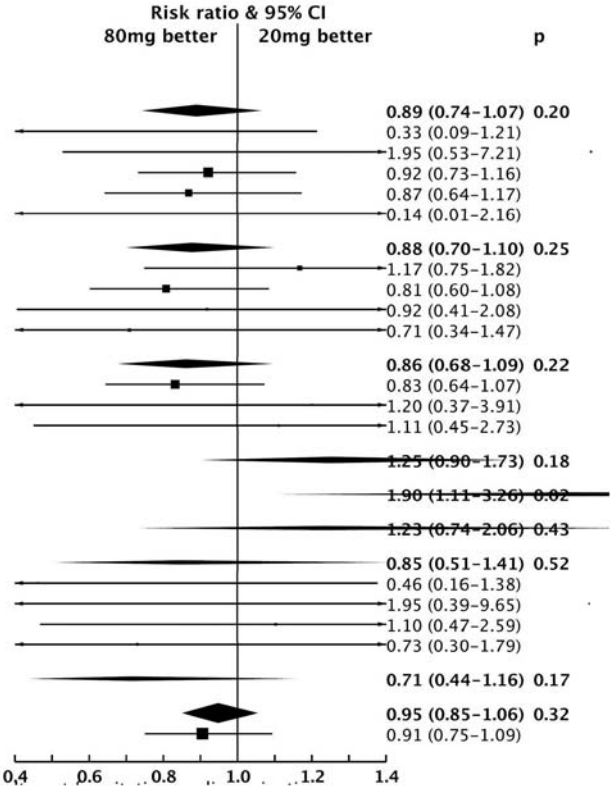
Cancer:
Cancer was a pre-defined safety outcome of the trial, and the incidence of new cancers and deaths from cancer were recorded. In addition, cancer events were checked with the UK National Registry, and follow-up for cancer at the end of the trial was complete with the exception of 22 (0.2%) patients who had immigrated out of the country.

The incidence of cancer by site in the two simvastatin treatment groups was very similar, with the exception of breast cancer. There were 35 (0.6%) cases of breast cancer in patients allocated to simvastatin 80mg and 18 cases (0.3%) in patients allocated to simvastatin 20mg. The nominal p-value is 0.02 (not adjusted for multiple comparisons).

The incidence of cancer is shown in the figure which follows:

Figure 13: Simvastatin Comparison: Cancer Incidence by Site

Cancer site	Simvastatin allocation 80mg (n=6031)	Simvastatin allocation 20mg (n=6033)	O-E	Var	z	Risk ratio & 95% CI (80mg better / 20mg better)	p
Genitourinary	**220 (3.6%)**	**247 (4.1%)**	**-13.8**	**116.7**	**-1.27**	**0.89 (0.74-1.07)**	**0.20**
Uterus, cervix	2 (0.0%)	7 (0.1%)	-2.5	2.2	-1.67	0.33 (0.09-1.21)	
Ovary	6 (0.1%)	3 (0.0%)	1.5	2.2	1.00	1.95 (0.53-7.21)	
Prostate	141 (2.3%)	153 (2.5%)	-6.1	73.5	-0.71	0.92 (0.73-1.16)	
Kidney, bladder, urinary	79 (1.3%)	91 (1.5%)	-6.0	42.5	-0.92	0.87 (0.64-1.17)	
Other GU	0 (0.0%)	2 (0.0%)	-1.0	0.5	-1.42	0.14 (0.01-2.16)	
Gastrointestinal	**141 (2.3%)**	**161 (2.7%)**	**-9.9**	**75.5**	**-1.14**	**0.88 (0.70-1.10)**	**0.25**
Oesophagus, stomach	42 (0.7%)	36 (0.6%)	3.0	19.5	0.68	1.17 (0.75-1.82)	
Colorectal	79 (1.3%)	98 (1.6%)	-9.5	44.2	-1.42	0.81 (0.60-1.08)	
Pancreas	11 (0.2%)	12 (0.2%)	-0.5	5.7	-0.21	0.92 (0.41-2.08)	
Other gastrointestinal	12 (0.2%)	17 (0.3%)	-2.5	7.2	-0.93	0.71 (0.34-1.47)	
Respiratory & intrathoracic	**123 (2.0%)**	**143 (2.4%)**	**-10.0**	**66.5**	**-1.23**	**0.86 (0.68-1.09)**	**0.22**
Lung	108 (1.8%)	130 (2.2%)	-11.0	59.5	-1.42	0.83 (0.64-1.07)	
Larynx	6 (0.1%)	5 (0.1%)	0.5	2.8	0.30	1.20 (0.37-3.91)	
Other respiratory	10 (0.2%)	9 (0.1%)	0.5	4.8	0.23	1.11 (0.45-2.73)	
Haematological	**80 (1.3%)**	**64 (1.1%)**	**8.1**	**36.0**	**1.35**	**1.25 (0.90-1.73)**	**0.18**
Breast	**35 (0.6%)**	**18 (0.3%)**	**8.5**	**13.2**	**2.34**	**1.90 (1.11-3.26)**	**0.02**
Melanoma	**32 (0.5%)**	**26 (0.4%)**	**3.0**	**14.5**	**0.79**	**1.23 (0.74-2.06)**	**0.43**
Other	**27 (0.4%)**	**32 (0.5%)**	**-2.5**	**14.7**	**-0.65**	**0.85 (0.51-1.41)**	**0.52**
Musculoskeletal/connective tissue	4 (0.1%)	9 (0.1%)	-2.5	3.2	-1.38	0.46 (0.16-1.38)	
Endocrine	4 (0.1%)	2 (0.0%)	1.0	1.5	0.82	1.95 (0.39-9.65)	
Head and neck	11 (0.2%)	10 (0.2%)	0.5	5.2	0.22	1.10 (0.47-2.59)	
Central nervous system	8 (0.1%)	11 (0.2%)	-1.5	4.8	-0.69	0.73 (0.30-1.79)	
Unspecified	**27 (0.4%)**	**38 (0.6%)**	**-5.5**	**16.2**	**-1.36**	**0.71 (0.44-1.16)**	**0.17**
ANY CANCER	**640(10.6%)**	**677(11.2%)**	**-17.9**	**329.2**	**-0.99**	**0.95 (0.85-1.06)**	**0.32**
except non-melanoma skin	207 (3.4%)	228 (3.8%)	-10.8	108.7	-1.03	0.91 (0.75-1.09)	

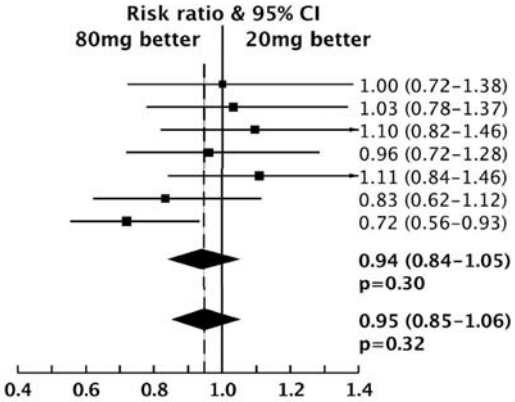


Source: Sponsor's Figure 12-2

The incidence of total cancer by year of follow-up is shown in the figure which follows:

Figure 14: Total Cancer by Year of Follow-up

Year of follow-up	Simvastatin allocation 80mg	Simvastatin allocation 20mg	O-E	Var	z	Risk ratio & 95% CI (80mg better / 20mg better)
1	73/6031 (1.2%)	73/6033 (1.2%)	0.0	36.5	0.00	1.00 (0.72-1.38)
2	98/5907 (1.7%)	95/5896 (1.6%)	1.5	48.2	0.22	1.03 (0.78-1.37)
3	96/5734 (1.7%)	88/5733 (1.5%)	4.2	46.0	0.62	1.10 (0.82-1.46)
4	89/5538 (1.6%)	93/5569 (1.7%)	-1.8	45.5	-0.27	0.96 (0.72-1.28)
5	106/5373 (2.0%)	96/5379 (1.8%)	5.2	50.5	0.74	1.11 (0.84-1.46)
6	82/5160 (1.6%)	99/5190 (1.9%)	-8.2	45.2	-1.22	0.83 (0.62-1.12)
7+	96/4954 (1.9%)	133/4970 (2.7%)	-18.8	57.2	-2.48	0.72 (0.56-0.93)
2+	**567/5907 (9.6%)**	**604/5896 (10.2%)**	**-17.9**	**292.7**	**-1.04**	**0.94 (0.84-1.05) p=0.30**
ALL FOLLOW-UP	**640/6031 (10.6%)**	**677/6033 (11.2%)**	**-17.9**	**329.2**	**-0.99**	**0.95 (0.85-1.06) p=0.32**



Source: Sponsor's Figure 12-3

Review comment:
Despite some experimental observations suggesting that statins have antitumor activity,[14] clinical studies have reached mixed conclusions about the relationship between statin use and breast cancer risk.[15, 16]

SEARCH showed a low, but two-fold higher incidence in the occurrence of breast cancer between the two different doses of simvastatin. The statin class has been extensively studied in the past in large clinical trials, and some of these trials have shown a low overall, but relatively increased incidence of breast cancer in patients treated with certain statins.[17, 18]

Other serious adverse events:

Hemorrhagic Stroke:
There was no difference in the rate of hemorrhagic stroke in patients allocated to simvastatin 80mg or simvastatin 20mg. In the simvastatin 80mg group, 24 (0.4%) patients had a hemorrhagic stroke compared to 25 (0.4%) patients in the simvastatin 20mg group (RR 0.96; 95% CI 0.55, 1.68).

Pulmonary Embolism:
There was no meaningful difference in the rate of pulmonary embolism in patients allocated to simvastatin 80mg or simvastatin 20mg. Fifty-nine (1.0%) patients allocated to simvastatin 80mg had a pulmonary embolus compared to 53 (0.9%) patients allocated to simvastatin 20mg (RR 1.11; 95% CI 0.77, 1.61; p=0.57). Thirteen (0.2%) patients allocated to simvastatin 80mg had a fatal pulmonary embolus compared to 11 (0.2%) patients allocated to simvastatin 20mg. Forty-seven (0.8%) patients allocated to simvastatin 80mg had a non-fatal pulmonary embolus compared to 43 (0.7%) patients allocated to simvastatin 20mg.

Simvastatin 80mg did not have a statistically significant or clinically meaningful effect on the tertiary efficacy endpoints of total or vascular mortality, hemorrhagic or other strokes, pulmonary embolus, coronary revascularization procedures, or cancer.

Total Mortality:
In patients allocated to simvastatin 80mg versus 20mg, there was no evidence of increased total mortality (RR 0.99; 95% CI 0.91, 1.09; p=0.90), mortality due to CHD (RR 1.02; 95% CI 0.89, 1.16; p=0.78), mortality due to vascular causes (RR 0.99; 95% CI 0.88, 1.11; p=0.89) or non-vascular causes (RR 1.0; 95% CI 0.87, 1.15; p=0.98).

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14 Potential antitumor effects of statins. International journal of oncology 2003, vol. 23, n°4, pp. 1055-1069

15 Statins and cancer prevention. *Nat. Rev. Cancer* (2005) 5(12):930-942

16 Statin Use and Breast Cancer: Prospective Results From the Women's Health Initiative JNCI Journal of the National Cancer Institute 2006 98(10):700-707

17 Carcinogenicity of lipid-lowering drugs. *JAMA* (1996) 275(1):55-60

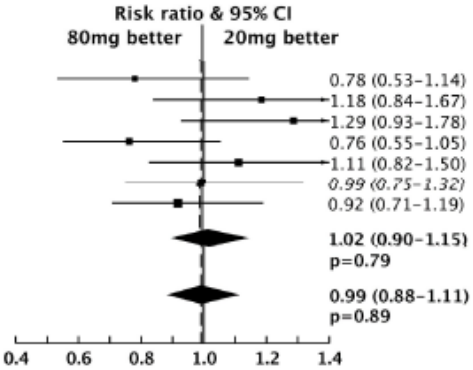
18 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and the risk of cancer. *Arch. Intern. Med.* (2000) 160:2363-2368

Vascular and non-vascular mortality

Lipid reduction with simvastatin 80mg did not increase all-cause mortality or deaths due to any particular cause. There was no difference between the treatment groups in vascular or non-vascular mortality. Subgroup analyses of mortality, vascular mortality, CHD mortality, and non-vascular mortality by baseline characteristics found no evidence for an imbalance based upon demographic characteristics, baseline lipids, or concomitant medical therapies. This lack of effect is consistent with earlier placebo-controlled trials with simvastatin and other statins.

Figure 15: Vascular Mortality by Year of Follow-Up (simvastatin comparison)

Year of follow-up	Simvastatin allocation 80mg		Simvastatin allocation 20mg		O-E	Var	z	Risk ratio & 95% CI (80mg better / 20mg better)
1	46/6031	(0.8%)	59/6033	(1.0%)	-6.5	26.2	-1.27	0.78 (0.53-1.14)
2	70/5970	(1.2%)	59/5955	(1.0%)	5.4	32.2	0.96	1.18 (0.84-1.67)
3	81/5863	(1.4%)	63/5848	(1.1%)	9.1	36.0	1.51	1.29 (0.93-1.78)
4	63/5720	(1.1%)	83/5735	(1.4%)	-9.9	36.5	-1.64	0.76 (0.55-1.05)
5	91/5600	(1.6%)	82/5596	(1.5%)	4.5	43.2	0.69	1.11 (0.82-1.50)
6	96/5438	(1.8%)	97/5454	(1.8%)	-0.3	48.2	-0.04	0.99 (0.75-1.32)
7+	110/5252	(2.1%)	119/5268	(2.3%)	-4.7	57.2	-0.62	0.92 (0.71-1.19)
2+	**511/5970**	**(8.6%)**	**503/5955**	**(8.4%)**	**4.1**	**253.5**	**0.26**	**1.02 (0.90-1.15) p=0.79**
ALL FOLLOW-UP	**557/6031**	**(9.2%)**	**562/6033**	**(9.3%)**	**-2.4**	**279.7**	**-0.14**	**0.99 (0.88-1.11) p=0.89**



Stroke:

In patients allocated simvastatin 80mg, the risk ratio for non-coronary revascularization was 0.77 (95% CI 0.62-0.96; p=0.02). Fifty-nine (1.0%) patients allocated to simvastatin 80mg had a pulmonary embolus compared to 53 (0.9%) patients allocated to simvastatin 20mg (RR 1.11; 95% CI 0.77, 1.61; p=0.57).

Review comment:
In agreement with SEARCH, another large trial (n=20,536) comparing simvastatin 40mg to placebo has shown only a very modest reduction in all cause and vascular mortality, major coronary events, stroke, and revascularization over a 5-year follow-up period. [19]

Figure 16: Simvastatin versus placebo in high risk patients at mean 5 year follow up:

Outcomes	Simvastatin	Placebo	RRR (95% CI	NNT (CI)
All cause mortality	13%	15%	13% (6 to 19)	58 (37 to 128)
Vascular mortality	7.6%	9.1%	17% (9 to 25)	66 (44 to 134)
Nonvascular mortality	5.3%	5.6%	5% (–7 to 15)	Not significant
Major coronary event‡	8.7%	12%	27% (21 to 33)	33 (26 to 46)
Stroke	4.3%	5.7%	25% (15 to 34)	73 (51 to 131)
Revascularisation	9.1%	12%	24% (17 to 30)	39 (29 to 58)

†Abbreviations defined in glossary; RRR, NNT, and CI calculated from data in article.
‡Nonfatal myocardial infarction or death from coronary disease.

One would expect a dose response relationship between the 20 and 80mg groups would have a more meaningful effect on LDL, stroke and vascular outcomes over a 6.7 year period.

In contrast to SEARCH, newer statins have shown a dose-response relationship between stroke risk, alongside LDL lowering. In addition to the myopathy/rhabdomyolysis cases the lack of this hard CV benefit raises issue with the 80mg simvastatin dose.

In contrast to SEARCH, in TNT, atorvastatin 80mg/day of was associated with a 48.3% reduction in LDL cholesterol to 77mg/dL and a 22% relative risk reduction in CV events (defined as death from CHD, nonfatal, non-procedural-related myocardial infarction, fatal or non-fatal stroke) when compared to 10mg/day of atorvastatin which reduced the mean LDL cholesterol to 101 mg/dL.

There was a lower incidence of pulmonary embolism in patients taking 20 vs 80mg of simvastatin.

19 MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7–22.

7.3.3 Dropouts and/or Discontinuations

During the 6.7 years of the study, 1,654 (27.4%) patients in the simvastatin 80mg group and 2,060 (34.1%) in the simvastatin 20mg group stopped taking simvastatin study treatment.

Of these, 626 (10.4%) patients in the simvastatin 80mg group and 911 (15.1%) patients in the simvastatin 20mg group stopped taking simvastatin tablets, but continued treatment with folic acid + B_{12} or folic acid + B_{12}-placebo tablets. The reasons for discontinuation of simvastatin treatment in this subgroup of patients therefore relate only to simvastatin.

The most common reason for stopping study simvastatin treatment was "medical advice," and more patients in the simvastatin 20mg group (n=707 (11.7%)) compared to the simvastatin 80mg group (n=374 (6.2%)) stopped simvastatin study treatment because of medical advice.

Reasons for stopping simvastatin 80mg or simvastatin 20mg before the end of the study are in the following table.

	Simvastatin 80 mg (N=6031)		Simvastatin 20 mg (N=6033)	
Reason(s) given	n	(%)	n	(%)
Patient wishes to stop	711	(11.8%)	792	(13.1%)
Unwilling to attend clinics	184	(3.1%)	225	(3.7%)
Contraindicated drug started	19	(0.3%)	20	(0.3%)
Abnormal liver or muscle enzymes (unknown which)	103	(1.7%)	30	(0.5%)
Abnormal LFTs	1	(0.0%)	0	(0.0%)
Muscle pain or weakness	63	(1.0%)	34	(0.6%)
Medical advice	654	(10.8%)	1,099	(18.2%)
Other symptoms	90	(1.5%)	100	(1.7%)
Other reasons	104	(1.7%)	95	(1.6%)
Any of the above	1,654	(27.4%)	2,060	(34.1%)

†This table includes patients who stopped study simvastatin tablets plus folic acid + B_{12} or placebo-folic acid + B_{12} tablets, as well as patients who stopped only study simvastatin tablets.

Data Source: Sponsor's Table 10-5

7.3.5 Submission Specific Primary Safety Concerns

Hepatic Safety

Hepatitis, as diagnosed separately by each study physician, was reported in 8 patients, 3 allocated to simvastatin 80mg and 5 allocated to simvastatin 20mg. All patients recovered from hepatitis. In 4 patients, 2 allocated to simvastatin 80mg and 2 allocated to simvastatin 20mg, serology for hepatitis was negative, and the patients' physicians attributed the hepatitis to treatment with simvastatin because another etiology could not be identified. Simvastatin treatment was unblinded in these 4 patients, and study simvastatin permanently discontinued. One of these patients (study ref 110 AOJU), a 69 year old white female allocated to simvastatin 80mg, developed elevated AST, GGT and ALP without jaundice 4 days after being randomized to simvastatin 80mg and about 2.5 weeks after starting azathioprine. It is therefore unclear if the increase in liver function tests may have been due, at least in part, to azathioprine. Both

simvastatin and azathioprine were discontinued, and about 9 days later, AST had decreased to near normal, although GGT and ALP remained elevated.

In the other 4 patients with hepatitis, the event was not attributed to simvastatin treatment. Serology was positive for hepatitis A in 1 patient, and for hepatitis C in another. After recovery from hepatitis, these two patients continued on simvastatin study treatment. In patient 141 AK85, a 65 year old white male, allocated to simvastatin 20mg, hepatitis was diagnosed 5 days after a CABG procedure. The patient had been taking amiodarone for a few days with study simvastatin. Study simvastatin was permanently discontinued and the patient fully recovered from the hepatitis. In the remaining patient (study ref 113B5AF) with hepatitis not attributed to study treatment, a 59 year old white male, allocated to simvastatin 20mg, and treated concomitantly with aspirin lisinopril and atenolol, hepatitis serology was negative. The hepatitis occurred at the same time as a serious adverse event of colitis. It is not known whether simvastatin study treatment was interrupted. The patient continued taking simvastatin treatment after the event.

Details are provided for the clinically relevant patients in following table:

Table 33: Patients with Hepatitis Possibly Related to Simvastatin

Study Ref	Date of randomization	Date of Birth	Ehnic Origin/ Gender	Attributed to Simvastatin	Event Description / Date	Hepatitis Serology	Peak ALT IU/L	Concomitant Medications	Alcohol Use	Comments
Patients Randomized to Simvastatin 80 mg										
110 AOJU	22Jun1999	(b) (6)	White/F	Yes	Hepatitis unspecified 28Jun1999	Hepatitis A,B, C negative	AST 231	azathioprine (started 11Jun1999), prednisolone, co-amilozide, verapamil, aspirin, diclofenac, salbutamol	No	Had polymyalgia rheumatica since Jan- 1998 which had been controlled on steroids. On 11Jun1999, while in the Run-in phase, she was started on azathioprine so that steroids could be tapered. She remained well until 26Jun1999, 4 days after randomization. Liver function tests on 28Jun1999 showed hepatitis without jaundice with AST 231 IU/l, ALP 988 IU/l, GGT 521.Azathioprine and simvastatin were stopped on 29Jun1999 and by 5Jul1999 liver function tests were improved with ALP 564 IU/l, AST 47 IU/l and GGT 377 IU/l. ALT 15 IU/L on 17Aug1999. The GP felt that the hepatitis may have been due to the combination of azathioprine and high dose simvastatin. The patient fully recovered. Simvastatin therapy was not re-started. The patient died on (b) (6) The cause of death was stroke.

Study Ref	Date of randomization	Date of Birth	Ehnic Origin/ Gender	Attributed to Simvastatin	Event Description / Date	Hepatitis Serology	Peak ALT IU/L	Concomitant Medications	Alcohol Use	Comments
Patients Randomized to Simvastatin 80 mg (Cont.)										
277 M743	20Aug2001	(b) (6)	White/F	Yes	Hepatitis unspecified 22Oct2001	Hepatitis B and C negative	624	metformin, aspirin, bendroflumethiazide, atenolol	No	At first follow-up visit on 15Oct2001 she had raised ALT at 128 IU/l with a normal CK. She felt well. She was recalled for an extra visit and on 22Oct2001. ALT was 624 IU/l. Apart from epigastric pain she felt well. Admitted to hospital on (b) (6) at her GPs request. The admitting doctor requested unblinding of her study simvastatin allocation as he felt that the hepatitis might be related to high dose simvastatin. Simvastatin was permanently discontinued on (b) (6) Abdominal ultrasound showed that the liver had a somewhat coarse parenchyma echo-texture, without focal abnormalities, raising the possibility of parenchymal disease. The gall bladder, biliary tree, kidneys, spleen and aorta appeared normal. The pancreas showed generalized increased echogenicity in keeping with diffused fatty infiltration. The patient recovered from hepatitis. Repeat ALT 87 IU/L on 21Nov2001 and 20 on 15Apr2003. Reported to have pancreatitis 18Mar2005 and cholecystectomy 13Feb2006.

Study Ref	Date of randomization	Date of Birth	Ehnic Origin/ Gender	Attributed to Simvastatin	Event Description/ Date	Hepatitis Serology	Peak ALT IU/L	Concomitant Medications	Alcohol Use	Comments
Patients Randomized to Simvastatin 20 mg										
141 AH09	12Jan2000	(b) (6)	White/F	Yes	Hepatitis unspecified 24Jun2000	Hepatitis A,B,C negative	1500	captopril, paracetamol, insulin, bumetanide, gtn, aspirin, digoxin, slow K, ferrous sulphate	No	Admitted to hospital (b) (6) with a 2 week history of feeling unwell with left sided abdominal pain, vomiting, and fever. Lab tests showed ALT about 1500 IU/l, creatinine 165 µmol/l and a normal CK. Hepatitis serology was normal and liver and renal ultrasound did not show anything abnormal. All medication including study drug was stopped in hospital. The patient was managed on a dextrose and insulin infusion for a few days and made a slow recovery. ALT was 71 IU/L on discharge from the hospital. The managing doctors felt she may have had drug induced hepatitis. Simvastatin study treatment was not re-started.
217 LP13	03Jul2001		White/ M	Yes	Hepatitis unspecified 20Feb2006	"Full screen negative"	228	aspirin, lisinopril, atenolol	4 glasses wine per week	Admitted to hospital (b) (6) having been generally unwell for over 1 week. (He had recently returned from a holiday in Malta). On admission the patient was noted to be jaundiced with abnormal liver function tests; Bilirubin 48 µmol/L, ALT 228 IU/L, AST 134 IU/L, ALP 422 IU/L, GGT 759 IU/L. At the previous study clinic appointment on 4Jan2006, ALT had been 15 IU/L. A full hepatitis screen and liver ultrasound scan were negative. Study medications were stopped and the liver function tests improved. The patient made a full recovery with ALT 34 IU/L on 1Mar2006 and 23 IU/L on 6Jul2006. As no other cause for the abnormalities had been found a diagnosis of statin-related hepatitis was made by the patient's managing consultant. Study simvastatin was not re-started.

Source: Sponsor's Table 12-6

Review comment:
The incidence of hepatitis was low and simvastatin was not clearly implicated as a cause of hepatitis in any of the cases.

ALT/AST/GGT elevations are discussed below in Section 7.4.2: Laboratory Findings.

7.4 Supportive Safety Results

The incidence of non-serious adverse reactions that patients attributed to study treatment was similar in patients allocated to simvastatin 80mg and simvastatin 20mg, with the following exceptions: Impotence attributed to study treatment was reported in 25 (0.4%) patients allocated to simvastatin 80mg and 13 patients (0.2%) allocated to simvastatin 20mg. Memory loss was attributed to study treatment in 17 (0.3%) patients allocated to simvastatin 80mg, and 8 (0.1%) patients allocated to simvastatin 20mg. The identical imbalance, but in the opposite direction, was observed in the folate + vitamin B_{12} comparison, with fewer patients in the folate + vitamin B_{12} group, compared to the placebo-vitamin group, reporting memory loss. These data are inconclusive given the small numbers of adverse events and the multiple comparisons.

Assessment of cognitive function (a tertiary endpoint for the folate arm of the trial) at the final visit showed no difference in the TICS-m score in patients allocated to simvastatin 80mg and simvastatin 20mg. (The TICS-m score reflects memorizing ability)

7.4.1 Common Adverse Events

With the exception of myopathy/rhabdomyolysis, simvastatin 80mg did not appear to increase the occurrence of other serious adverse events. The apparent lower risk of ventricular arrhythmia, esophageal disease/surgery, other GI disease including colitis, and of kidney/renal

tract surgery in patients allocated to simvastatin 80mg appeared to be due to chance and was not statistically significant.

7.4.2 Laboratory Findings

Non-serious laboratory adverse experiences were not captured as this trial was designed as a large simple study.

ALT Abnormalities
ALT and GGT were measured by the central laboratory in blood collected at the screening visit. Samples from participants with ALT >1.5xULN or GGT above 2xULN at the screening visit were also assayed for AST and ALT. Patients entering the run-in period had study treatment stopped and were not randomized if they met one of the following criteria.

- ALT>1.5xULN;
- ALT>1≤1.5xULN and GGT, AST, or ALP >2xULN; or
- GGT, AST, or ALP>4xULN.

Of 19,190 patients entering the run-in period, 343 (2%) were not randomized because liver function tests at the screening visit met the above criteria. Patients were considered ineligible for randomization because of ALT levels (n=253), GGT levels (n=94), and/or other liver function test abnormalities (n=76).

As shown in the table below, following the randomization visit, 100 patients (1.7%) allocated to simvastatin 80mg and 65 (1.1%) to simvastatin 20mg had one or more elevation of ALT >3xULN. Elevated ALT >3xULN on 2 consecutive visits was observed in 27 (0.5%) patients allocated to simvastatin 80mg and in 19 (0.3%) patients allocated to simvastatin 20mg. However, 7 of the 27 patients in the simvastatin 80mg group and 1 of the 19 patients in the simvastatin 20mg group had elevated CK >10xULN at some time in the study.

Fifty-one patients (0.9%) allocated to simvastatin 80mg and 40 patients (0.7%) allocated to simvastatin 20mg had one or more elevations in ALT greater than 4xULN. Fourteen patients (0.2%) allocated to simvastatin 80mg and 10 patients (0.2%) allocated to simvastatin 20mg had >4xULN elevations in ALT on two consecutive visits. In the simvastatin 80mg group, five of these 14 patients also had maximum CK >10xULN at some point in the study. None of the patients in the simvastatin 20mg group, ever had elevated CK >10xULN.

Table 34: Elevated ALT at Any Follow-up Visit

	Simvastatin 80mg		Simvastatin 20mg	
	n	(%)	n	(%)
ALT				
≥3xULN one or more times	100	(1.7)	65	(1.1)
>3xULN on 2 consecutive visits	27	(0.5)	19	(0.3)
> 4xULN one or more times	51	(0.9)	40	(0.7)
>4xULN on 2 consecutive visits	14	(0.2)	10	(0.2)

Discontinuation was recorded by the clinic nurses as due to liver or muscle enzyme abnormalities in 71 (1.2%) patients in the simvastatin 80mg group and 15 (0.2%) patients in the simvastatin 20mg group.

7.4.3 Hematological effects

At 1 year and 4 years of follow-up, there was no clinically meaningful change in hemoglobin, mean cell volume, packed cell volume and white cell count in patients allocated to simvastatin 80mg and simvastatin 20mg, and the mean change from baseline did not differ between the groups.

However, at 1 year of follow-up, platelet counts increased by 3,800/µL from a baseline of 250,000/µL in patients allocated to simvastatin 80mg and by 9,100/µL from a baseline of 250,000/µL in patients allocated to simvastatin 20mg. At 4 years of follow-up, platelet counts had decreased by a mean of 6,300/µL in the simvastatin 80mg group and by 1,900/µL in the simvastatin 20mg group, in comparison to baseline. Thus, at both 1 and 4 years of follow-up, platelet counts were slightly lower in patients allocated to simvastatin 80mg. This is unlikely to be of clinical significance.

Review comment:
Variable outcomes on the effect of statins on platelets have been shown in the literature. Publications have shown that platelets can be less reactive with statin use, [20] [21] platelets can be more reactive with statin use,[22] or have no effect with statin use. [23] The change in platelet counts in SEARCH does not appear to be clinically meaningful.

7.4.4 Electrocardiograms (ECGs)

Analysis of the effect of simvastatin on specific intervals of the ECG was not conducted in SEARCH. Myocardial infarction was a primary efficacy endpoint.

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20 Simvastatin reduces activation of normal platelets by LDL isolated from patients with familial hypercholesterolaemia and familial defective apolipoprotein B Eur J Clin Pharmacol (1997) 53: 277±279

21 HMG-CoA reductase inhibitor attenuates platelet adhesion in intestinal venules of hypercholesterolemic mice. *Am J Physiol Heart Circ Physiol* 286: H1402-H1407, 2004

22 The effect of high dose simvastatin on, platelet size in patients with type 2 diabetes mellitus Platelets, August 2006; 17(5): 292–295 "drug treatment caused the platelets to be more responsive to the ex vivo stimuli applied"

23 No Influence of Simvastatin Treatment on Platelet Function In Vivo in Patients With Hypercholesterolemia Arteriosclerosis, Thrombosis, and Vascular Biology. 1997;17:273-278.

7.4.5 Special Safety Studies

Cognitive Function

Assessment of cognitive function (i.e. <22 for TICS-m score), which was a tertiary endpoint for the folate arm of the trial, at the final visit showed no difference in the TICS-m score in patients allocated to simvastatin 80mg and simvastatin 20mg. The TICS-m score reflects memorizing ability in large part. Verbal fluency scores also did not differ among patients allocated to simvastatin 80mg and simvastatin 20mg. Hearing thresholds were assessed at final follow-up and did not differ between the simvastatin groups.

Table 35: Cognitive Function by TICS-m at Final Follow-Up

	Simvastatin 80 mg (n=4473)		Simvastatin 20 mg (n=4418)	
	n	%	n	%
TICS-m score	24.3 ± 4.1		24.3 ± 4.2	
<20	517	(12%)	523	(12%)
≥20<22	465	(10%)	441	(10%)
≥22<25	1175	(26%)	1140	(26%)
≥25<30	1949	(44%)	1958	(44%)
≥30	367	(8%)	356	(8%)

Source: Sponsor Table 12-5

7.4.6 Blood pressure effects

At the final follow-up there was a 3 to 4 mm decrease in systolic and diastolic blood pressure in both simvastatin groups, although the mean change from baseline in blood pressure did not differ between the groups.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See Section 7.3: Major Safety Results

7.5.2 Time Dependency for Adverse Events

- See Table 23: Temporal Relationship of Myopathy/Rhabdomyolysis, as Defined by The Sponsor
- See Table 24: Annual Rate of Myopathy in Patients Taking Simvastatin 80mg, as Defined by The Sponsor

7.5.3 Drug-Demographic Interactions

Compared to men, the observed risk in women was 2.8 times greater for myopathy (as defined by the sponsor). Additionally, the risk of myopathy (as defined by the sponsor) was about twice that in patients ≥65 than in patients <65.

See "Study Monitoring and the Detection of Myopathy"

7.5.4 Drug-Disease Interactions

Not applicable

7.5.5 Drug-Drug Interactions

During SEARCH and A to Z the use concomitant interacting medications such as amiodarone, diltiazem, erythromycin and amlodipine appeared to increase the risk of myopathy when given with simvastatin 80mg.

- See Table 22: Patients with Myopathy but not Rhabdomyolysis
- See Table 25: Patients with Rhabdomyolysis (and the Review Comments which follow)

7.6 Additional Safety Evaluations

Not applicable

7.6.1 Human Carcinogenicity

There was no meaningful difference in the rate of cancer deaths in patients allocated to simvastatin 80mg or simvastatin 20mg.

See Section 7.3.1

7.6.2 Human Reproduction and Pregnancy Data

Not applicable; Women of childbearing potential were excluded from the SEARCH trial.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable; Children were excluded from the SEARCH trial.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

7.7 Additional Submissions / Safety Issues

Not applicable

8 Postmarket Experience

9 Appendices

9.1 Literature Review/References

See footnotes in report body.

9.2 Labeling Recommendations

Pending

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/s/

DAVID S GORTLER
12/21/2010

ERIC C COLMAN
12/22/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S077

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

RISK MANAGEMENT OPTIONS REVIEW

Date:	May 24, 2011
To:	Mary Parks, MD, Director Division of Metabolism and Endocrinology Products (DMEP)
Through:	Claudia Karwoski, PharmD, Director Division of Risk Management (DRISK)
From:	Suzanne Robottom, PharmD Team Leader, DRISK
Subject:	Risk Management Options
Drug Name (Established Name) and Application Type/Number	Zocor (simvastatin) 80 mg; NDA 19-766 Vytorin (ezetimibe/simvastatin)10/80; NDA 21-687
Applicant:	Merck and MSP Singapore
OSE RCM #:	2011-163
TSI #	746

Reference ID: 2951567

EXECUTIVE SUMMARY

The purpose of this review is to provide an analysis of the risk managment options to address the increased risk of rhabdomyolysis associated with simvastatin 80mg during the first year of treatment, state the Safety First Steering Committe (SFSC) guidance, and provide recommendations with how to proceed based on SFSC guidance.

(b) (4) . The option of voluntary outreach measures proposed by Merck and amplified by FDA outreach would be faster to implement but the impact on utilization is unknown.

On February 3, 2011, the SFSC agreed with the proposal to allow simvastatin 80 mg to remain on the market, revise the labeling to recommend against new initiators, allow Merck to proceed with the voluntary measures proposed, pursue outreach efforts through FDA initiatives (stakeholder call, Medscape interview) and to follow drug utilization data to determine if these efforts substantially reduced new initiators.

OND and OSE will monitor drug use data through reports submitted by Merck every 6 months after the safety labeling changes are approved. We expect the following reductions (as proposed by Merck) to be met.

Predicted % reduction vs. current prescribing		
+6 months from label change	*+1 year from label change*	*+2 years from label change*
(b) (4)		

This path forward, in particular, FDA outreach and monitoring drug use to assess the overall impact of the collaboration has not been tested post-FDAAA. If these measures do not prove to limit distribution, further regulatory action (withdrawal) must be re-considered.

1. INTRODUCTION

The purpose of this review is to document DRISK's analysis of the risk managment options to address the increased risk of rhabdomyolysis associated with simvastatin 80mg during the first year of treatment.

Simvastatin was first approved in 1991. The 80mg strength was approved several years later (1998) due to concerns regarding heaptic and muscle toxicities. At present, simvastatin does not have a formal risk evaluation and mitigation strategy (REMS). There is an approved patient package insert.

2. MATERIALS REVIEWED

The following materials were reviewed

- Merck's May 6, 2011 submission "Response to Agency for PAS-077"

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- Merck's October 8, 2010 submission "Response to Agency for PAS-077"

3. RISK BENEFIT CHARACTERIZATION

3.1. Severity of the Risk

Cases of simvastatin-induced rhabdomyolysis have resulted in hospitalization and death. The incidence of rhabdomyolysis (unexplained muscle weakness or pain with a CK>40xULN) in SEARCH[1] was 0.2% (n=11) for patients treated with simvastatin 80 mg versus no patients in the 20 mg arm. No deaths occurred. However, these patients were closely monitored and drug was discontinued with CK values > 10xULN.

Across all statins, 148 cases of fatal rhabdomyolysis have been reported in AERS. Of those, 50% of the cases involved simvastatin. This disparity cannot be explained due to proportional drug utilization. Simvastatin accounts for roughly 30% of all statin prescriptions. Cases and exposures were proportional for all other statins with the exception of lovastatin (17% of cases versus 11% of exposure).

Concomitant use with CYP3A4 inhibitors, older age, female sex increase the risk of myopathy based on SEARCH data.

3.1.1. *Risk in context of drugs in class, among other drugs used to treat diseease prescribers familiary with risk, monitoring and management*

Myopathy and rhabdomyolysis, including fatal cases, are associated with all statins. Very broadly speaking the risk increases as the dose and plasma level of the statin increases. Available data suggest the risk of rhabdomyolysis is not uniform across the statins (stronger signal with simvastatin, lovastatin). Although serious cases are rare, rhabdomyolysis is a well-known risk. Prescribers should be familiar with appropriate monitoring. However, serious cases resulting in hospitalization and death continue to occur.

3.1.2. *How the risk is managed across other products and/or diseases*

Many drug products are associated with rhabdomyolysis. At present, this risk is addressed through labeling and no drugs have a REMS (beyond a Medication Guide) to address this risk.

Of note, cerivastatin was removed from the market in 2001 due to an unacceptably high risk for fatal rhabdomyolysis compared to other statins.

3.2. Size of Population

Merck estimates that (b) (4) people are treated currently (2009 data) with statins in the US. Of those, (b) (4)% (~ (b) (4) million) are treated with simvastatin. Of those (b) (4) million, approximately (b) (4)% ((b) (4) million) are treated with the simvastatin 80 mg dose. Simvastatin statin market penetration ((b) (4)%) that Merck estimates is higher than the drug utilization analysis by FDA ((b) (4)).

3.3. Seriousness of Disease[2]

[1] SEARCH: Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
[2] www.cdc.gov accessed November 29, 2010.

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High cholesterol is one of the major controllable risk factors for coronary heart disease, heart attack and stroke. Of the risk factors, about 15% of adults in the US have high cholesterol (2005-2006 data).

- In 2006, heart disease caused 26% of death, more than 1 in every 4, in the US States. Stroke accounted for 1 in every 17 deaths.
- Heart disease is the leading cause of death for both men and women. Stroke is the third leading cause of death.
- Coronary heart disease is the most common type of heart disease. In 2005, 445,687 people died from coronary heart disease.
- In 2010, heart disease will cost the US $316.4 billion. This total includes the cost of health care services, medications, and lost productivity.
- In 2009, stroke will cost the US $68.9 billion. This total includes the cost of health care services, medications, and missed days of work.
- Stroke is a leading cause of serious long-term disability.

3.4. Expected Benefit

As stated above, coronary heart disease is a major public health concern. Statin-related reductions in LDL-c decrease the risk for major adverse cardiac events (MACE). For every 39 mg/dl statin-related lowering of LDL-c, the risk for MACE is reduced by approximately 25%. Simvastatin 40 and 80 mg provides a 41 and 47% reduction in LDL-c, respectively.

There are five other statins currently available. Two (atorvastatin, rosuvastatin) can provide even greater reductions in LDL-c.

3.5. Expected Duration of Treatment

Hyperlipidemia, cardio- and cerebro-vascular disease are chronic conditions. Patients may be treated indefinitely (years/decades) with simvastatin.

3.6. Products Affected

Simvastatin is available as a generic. In addition to the innovator, there are 13 different approved generic manufacturers. Merck states that generic simvastatin accounts for (b) (4)% of *all* 80 mg prescribing. Merck also states that five generic manufacturers account for (b) (4)% of *all generic* prescriptions dispensed in 2009.

Further, Vytorin (ezetimibe/simvastatin; MSP Distribution Services which may be owned by Merck) includes a 10/80 dose. Simcor (niacin/simvastatin; Abbott) does not include an 80 mg strength tablet but is available as a 500/40 mg tablet. The labeling states that "the recommended maintenance dose for SIMCOR is 1000/20 mg to 2000/40 mg (two 1000/20 mg tablets) once daily…. The efficacy and safety of doses of Simcor greater than 2000/40 mg daily have not been studied and are therefore not recommended."

Finally, given that there is a possibly comparable signal with lovastatin, the path forward for simvastatin 80 mg take into account how to incorporate lovastatin.

4. RISK MANAGEMENT OPTIONS

4.1. Applicant's Proposed Strategy

Merck proposes the following measures:

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- labeling changes (which would include revisions to the existing PPIs)
- a "communication package" to prescribers to include a Dear HCP letter, revised highlighted PI, and revised PPI
- non-specific pharmacy directed communication
- possible payer/system interventions that could be adopted
    - Prior Authorization
    - Step Therapy

  Merck states that (b)(4)% of all prescriptions for simvastatin are processed by (b)(4) payers. These payers include the Department of Defense and Veteran's Administration among others.

Targeting payer/system interventions is an interesting idea and one that has not been utilized thus far under REMS. These systems are well-established point of leverage between the patient and a drug product. Because simvastatin is the "highest potency" statin available as a generic currently, it is most likely a statin of choice on most insurance formularies. The upward sales trend in drug use data supports this assertion. Prior authorizations and step therapy are often more cost-driven than safety driven. It is not clear how likely payers are to adopt these interventions, if requested. We do believe the sponsors would be able to assess which payers have adopted interventions and what the interventions are.

Three important points are not clear from the Merck's proposal: 1) to what extent substantive labeling changes alone would result trigger these changes; 2) to what extent payers have independently decided to implement these measures already; and 3) if and how the generic manufacturers and combination product manufacturers would be involved. In addition, it is not clear how likely these interventions would drive patients to pay "out of pocket" or cash.[3] Moreover, beyond passive prescriber education, Merck's approach does not provide additional intervention for uninsured patients (who account for an estimated (b)(4)% of patients). Although we would assume that insurance interventions would drive changes in prescriber behavior across all patients.

Merck projects their proposal will reduce new prescriptions for simvastatin 80 mg by (b) (4)% over 2 years. DMEP has stated that they are uncomfortable with *any* new initiators but acknowledge that any of the options discussed below would not eliminate new initiators.

4.2. Analysist of Options

The goal is to prevent new patients from starting simvastatin 80 mg.

In conjunction with safety labeling changes, the following options have been considered:

(b) (4)

[3] 30 day supply of simvastatin 80 mg costs $35.99; 90 day costs $95.97. Among the top 4 chain drug stores (CVS, Walgreens, Walmart, Rite Aid), only the Rite Aid prescription savings plan includes simvastatin ($9 for 30 days; $16 for 90 days).

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5. DISCUSSION

(b) (4)

The option of agreeing with the voluntary outreach measures proposed by Merck and amplifying them with FDA outreach would be faster to implement but the impact on utilization is unknown. Merck estimates (b) (4) decline over 2 years. In addition, atorvastatin may be available as a generic within 2011which should reduce simvastatin sales.

The issue of how to address this increased risk with simvastatin 80 mg was discussed at two Safety First Steering Committee (SFSC) meetings. On December 21, 2010, Dr. Woodcock advised withdrawing the 80 mg strength from the market. Upon further consideration, this issue was re-addressed at the February 3, 2011 SFSC meeting. The committee agreed with the proposal to allow simvastatin 80 mg to remain on the market, revise the labeling to recommend against new initiators, allow Merck to proceed with the voluntary measures proposed, pursue outreach efforts through FDA initiatives (stakeholder call, Medscape interview) and to follow drug utilization data to determine if these efforts substantially reduced new initiators. This path forward, in particular FDA outreach to pharmacy benefit managers, has not been tested.

DMEP and DRISK met to discuss the outreach effort and to define a benchmark for program success. DRISK believes it is appropriate to accept Merck's predicted estimates.

6. RECOMMENDATIONS

Given, the SFSC decision, DRISK recommends the following FDA initiatives to amplify the safety labeling changes.

Outreach:

- Stakeholder call to include pharmacy benefit managers, prescriber organizations, pharmacist organizations, and federal partners (DOD, VA, and other members of the Drug Safety Oversight Board) . The call will be audiotaped for podcast and transcribed for posting on fda.gov.
- Medscape interview posted on Medscape's FDA webpage. For viewing this interview, prescribers may be able to receive continuing education credit

Benchmark:

DRISK recommends accepting Merck's estimates because we are accepting their voluntary proposal. The Division of Epidemiology was consulted to provide expertise on the methodology to further clarify our expectations. DMEP recommended communicating these expectations in a General Advice Letter to Merck. The following was included:

> *Employing the methods below, you will need to submit 6 months of baseline data encompassing the time period December 1, 2010 through May 31, 2011. This should be submitted within 30 days of the approval date of sNDA 19-766/S-077 and S-082 and sNDA 21-687/S-033 and S-040.*
>
> ***Methodology:***
>
> - *Estimate the number of outpatient retail prescriptions, dispensed by product and by strength, for simvastatin (brand and generic) and VYTORIN*

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(simvastatin/ezetimibe), excluding mail order pharmacies, by month and cumulative for a 6-month time period.

- *Analyze dispensed retail outpatient prescriptions by prescription type to evaluate which are being dispensed to new patients, continuing patients, or switch/add-on patients, by month and cumulative for a 6-month time period.*
- *Prescriptions should be classified as new patient prescriptions if no prescriptions were dispensed for a product within the cholesterol market to a patient within the previous 12 months.*
- *Prescriptions should be classified as continuing if prescriptions were dispensed for current therapy to a patient in the previous 12 months.*
- *Prescriptions should be classified as switch/add-on patient prescriptions if a different prescription for a statin and/or simvastatin 80 mg was dispensed to a patient in the previous 12 months (these prescriptions are either added onto current therapy or switched from one therapy to another, e.g., going from simvastatin 40 mg to simvastatin 80 mg or Lipitor 40 mg to simvastatin 80 mg) .*

Employing this methodology, please provide the following benchmarks for follow-up.

1. *Keep the "new" transactions separate from the "add/switch" transactions as we would like to see proportions that were changed from strength to strength.*

2. *For monthly counts, additionally provide total prescription volume (cumulative) for new, continuing, and add/switch patient transactions for the time period analyzed.*

3. *Do not increase prescription volume based on mail order sales estimates.*

4. *In addition to providing monthly and total prescription volumes for new, continuing, add/switch, please provide percent reduction of 80 mg products by reporting period.*

On October 8, 2010, you provided an estimate of the predicted impact on new patient transactions that would be achieved in the first two years from label change. These are summarized in the table below.

Predicted % reduction vs. current		
+6 months from label change	*+1 year from label change*	*+2 years from label change*
(b) (4)		

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We accept these benchmarks for the purpose of monitoring the effect of the labeling changes in reducing the number of new users of simvastatin 80 mg-containing products to guide further regulatory action.

In addition to drug use monitoring data in each report, provide a summary of the outreach efforts undertaken during the reporting period to include but not limited to the following information:

- *A timeline of when the communication occurred and what the communication was*
- *Number of healthcare providers who received each communication*
- *Identify the PBMs targeted and the resulting formulary decision(s) for each PBM*

7. CONCLUSION

(b) (4)

. The decision to accept Merck's proposal and amplify the message with additional FDA outreach is faster to implement. This path forward, in particular, FDA outreach and monitoring drug use to assess the overall impact of a voluntary and collaborative effort has not been tested post-FDAAA. If these measures do not prove to limit distribution, further regulatory action (withdrawal) must be re-considered.

Reference ID: 2951567

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/s/

SUZANNE C BERKMAN ROBOTTOM
05/25/2011

CLAUDIA B KARWOSKI
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concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-766/S077

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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03 June 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR® (simvastatin)

Response to FDA Request for Information

Reference is made to the New Drug Application #19766 cited above for ZOCOR®, and to the June 12, 2009 supplement (S-077) based on the results of the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial. Reference is also made to the April 22, 2011 supplement (S-082).

This submission is in response to the letter from Dr. Colman to Dr. Sparrow, dated May 18, 2011, which outlined the methods, benchmarks, and timelines for assessing the future use of simvastatin 80 mg and Vytorin 10/80 mg. To ensure that there is agreement on the nature of future Merck submissions of these data, this submission contains further details of our proposed methods (Module 1.11), as well as an example Microsoft Excel file that will be populated with new data for future submissions.

Reference is also made to the e-mail sent on May 30, 2011 from Dr. Egan to Dr. Tucker, which stated in part:

> *In your October 8, 2010, you indicated that you would have "community pharmacist communications" and "payer communications". You further indicated that you would "propose the implementation of a series of payer and pharmacy system interventions that would be consistent with the revised labeling"; however, in your response below, you do not address these additional communications or interventions. Please provide more detailed information on your proposals. It is unlikely you will be able to achieve the reduction in new initiators that has been agreed to with the interventions you have proposed to date.*

More detailed information on our proposals is included in Module 1.11 of this submission.

With respect to whether reduction in new initiators can be achieved, Merck acknowledges the importance of this goal. The sponsor will use the approved materials, including the Dear HCP letter, the patient resource, and the updated labels, to engage directly with payers and pharmacists on the label updates, including discussions of the Merck-proposed system interventions, to limit the number of new patients receiving simvastatin 80mg or VYTORIN 10/80mg.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

We consider the information included in this submission to be a confidential matter and request that the Food and Drug Administration not make its content, or any future communications in regard to it, public without first obtaining the written permission of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

If you have any questions, please contact Carl P. Sparrow, Ph.D. (732-594-7570) on this matter, or in my absence, Scott Korn, M.D. (267-305-6769).

Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

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APPEARS THIS WAY ON ORIGINAL

Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

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03 June 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR® (simvastatin)

Amendment to Pending Application

Reference is made to the New Drug Application cited above for ZOCOR® and to the above NDA, 19-766. Reference is made to the June 12, 2009 supplement (S-077) based on the results of the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial. Reference is also made to the February 28, 2011 safety labeling notification from the FDA and subsequent related communications between Merck and FDA, including reference made to the April 22, 2011 supplement (S-082) and May 19, 2011 response. This submission contains revised labeling as requested by the agency.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

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Carl P. Sparrow, Ph.D.
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19 May 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR® (simvastatin)

Amendment to Pending Application

Reference is made to the New Drug Application cited above for ZOCOR® and to the above NDA, 19-766. Reference is made to the June 12, 2009 supplement (S-077) based on the results of the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial. Reference is also made to the February 28, 2011 safety labeling notification from the FDA and subsequent related communications between Merck and FDA, including reference made to the April 22, 2011 supplement (S-082).

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 019766/S-077

GENERAL ADVICE

Merck Sharp & Dohme Corp.
Attention: Carl Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs
P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Sparrow:

Please refer to your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ZOCOR (simvastatin) Tablets 10 mg, 20 mg, 40 mg, and 80 mg.

We acknowledge receipt of your October 8, 2010 submission, which provided a proposal to address concerns regarding the safety of the 80 mg dose of ZOCOR (simvastatin) that were raised at our September 23, 2010 Type C Meeting. We also refer to your May 6, 2011 submission, which contained your response to our April 26, 2011 email requesting further clarification of the methodology you employed to generate the 2010 monthly patient volume for simvastatin 80 mg and VYTORIN (simvastatin/ezetimibe) 10/80 mg and your definition of patient volume, as reported in your February 25, 2011 submission.

We have reviewed your responses and recommend that you follow the FDA methods, as well as the expected benchmarks for follow-up, that we have outlined below. Additionally, employing the methods below, you will need to submit 6 months of baseline data encompassing the time period December 1, 2010 through May 31, 2011. This should be submitted within 30 days of the approval date of sNDA 19-766/S-077 and S-082.

Methodology:

- Estimate the number of outpatient retail prescriptions, dispensed by product and by strength, for simvastatin (brand and generic) and VYTORIN (simvastatin/ezetimibe), excluding mail order prescriptions, by month and cumulative for a 6-month time period.
- Analyze dispensed retail outpatient prescriptions by prescription type to evaluate which are being dispensed to new patients, continuing patients, or switch/add-on patients, by month and cumulative for a 6-month time period.
    - Prescriptions should be classified as new patient prescriptions if no prescriptions were dispensed for a product within the cholesterol market to a patient within the previous 12 months.

- Prescriptions should be classified as continuing if prescriptions were dispensed for current therapy (by product and strength) to a patient in the previous 12 months.
- Prescriptions should be classified as switch/add-on patient prescriptions if a prescription in the cholesterol market (by product and strength), other than simvastatin 80 mg, was dispensed to a patient in the previous 12 months (these prescriptions are either added onto current therapy or switched from one therapy to another, e.g., going from simvastatin 40 mg to simvastatin 80 mg or Lipitor 40 mg to simvastatin 80 mg).

Employing this methodology, please provide the following benchmarks for follow-up.

1. Keep the "new" transactions separate from the "add/switch" transactions as we would like to see proportions that were changed from strength to strength.

2. For monthly counts, additionally provide total prescription volume (cumulative) for new, continuing, and add/switch patient transactions for the time period analyzed.

3. Do not increase prescription volume based on mail order sales estimates.

4. In addition to providing monthly and total prescription volumes for new, continuing, add/switch, please provide percent reduction of 80 mg products by reporting period.

In addition to the drug use monitoring data in each report, please provide a summary of the outreach efforts undertaken during the reporting period, including but not limited to the following:

1. The types of communications sent, the dates they were sent, and the target audience.

2. The number of targeted healthcare providers who received each communication.

3. The names of all Pharmacy Benefit Managers (PBMs) that were targeted and a summary of each PBMs resultant formulary recommendations/modifications.

On October 8, 2010, you provided an estimate of the predicted impact on new patient numbers that would be achieved in the first two years from label change. These are summarized in the table below.

	Predicted % reduction vs. current		
	+6 months from label change	+1 year from label change	+2 years from label change
New patient transactions	(b) (4)		

We accept these benchmarks for the purpose of monitoring the effect of the labeling changes in reducing the number of new users of simvastatin 80 mg-containing products to guide further regulatory action.

Please submit your prescription volume reports to this NDA, with a cross reference to NDA 21687 for VYTORIN (simvastatin/ezetimibe), by 8 months, by 14 months, by 20 months, and by 26 months from the date of approval of sNDA 19-766/S-077 and S-082. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each report should conclude no earlier than 60 days before the submission date for that report. Please submit each report so that it will be received by the FDA on or before the dates listed above.

If you have any questions, please call Margaret Simoneau, M.S., R.Ph., Regulatory Project Manager, at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Eric Colman, M.D.
Deputy Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC C COLMAN
05/18/2011

Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

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13 May 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR® (simvastatin)

Response to FDA Request for Information

Reference is made to the New Drug Application cited above for ZOCOR® and to the above NDA, 19-766. Reference is made to the June 12, 2009 supplement (S-077) based on the results of the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial. Reference is also made to the Prior Approval Supplement (S-082) submitted on March 30, 2011. Final reference is made to labeling discussions held via teleconference on April 13, 2011 between the Agency and Merck.

As previously discussed with the FDA, clear and coordinated communications of the label updates will be in the best interest of patient care and will be necessary to help minimize potential confusion among patients and physicians. Merck remains committed to working with the agency in this regard. To that end, Merck includes for the agency's review the following updated communications materials:

- Dear Health Care Professional Letter: This is an updated version of the draft letter that Merck submitted to the agency on March 30, 2011. Per the agency's request, we have revised this letter consistent with the current draft labeling. Following receipt of FDA's approval of the draft labels, and following issuance of its drug safety communication, Merck plans to broadly distribute this letter to U.S. health care providers and managed care organizations via field representatives, direct mail and/or email. The letter would be accompanied by the updated Prescribing Information for ZOCOR, the updated Prescribing Information and Patient Product Information for VYTORIN, and the Patient Resource described below.

- Patient Resource: This is an updated version of the draft patient resource that Merck submitted to the agency on March 30, 2011. Per the agency's request, we have

revised this resource consistent with the current draft labeling. The purpose of this resource is to provide information for patients potentially affected by the label updates to help them to learn about the label changes and have informed discussions with their health care providers. The patient communication would accompany the Dear Health Care Professional letter for distribution to health care providers and managed care organizations. In addition, the information in this Patient Resource would serve as content for an informational web site (www.simvastatininfocenter.com) that Merck is creating and would reference in other public communications. The questions and answers in the Patient Resource would be posted on the web site in their entirety, and visitors to the site would be able to download and/or print a pdf of the Patient Resource as well as view, download and/or print updated Prescribing Information for ZOCOR and updated Prescribing Information and Patient Product Information for VYTORIN.

- News Release: Merck plans to issue this news release in the United States following receipt of FDA's approval of the draft labels and roughly contemporaneously with FDA's issuance of its drug safety communication. In general, the content of the release derives from the updated labels, the Dear Health Care Professional letter, the Patient Resource, and the FDA's March 19, 2010 drug safety communication about its ongoing review of the risk of muscle injury with high dose simvastatin. The release describes the anticipated label updates, describes Merck's intent to communicate them, advises patients who think they might be affected by these updates to talk to their doctors, provides additional background on simvastatin, myopathy/rhabdomyolysis and the relevant populations, and presents updated selected risk and dosing information for simvastatin and VYTORIN.

Based on prior discussions, we understand that the Division will be the point of contact for agency review of these materials and will coordinate further review within the FDA as appropriate. Merck appreciates the Division's role in this regard, as we believe this approach is well-suited to coordinated communications about the label changes and can facilitate timely and consistent FDA feedback to Merck. In light of FDA's goal to finalize the labels during or near the week of May 23, we respectfully request any feedback on these communications materials by Friday, May 20 to enable us to finalize and ready them for prompt dissemination as described above.

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If you have any questions, please contact Carl P. Sparrow, Ph.D. (732-594-7570) on this matter, or in my absence, Scott Korn, M.D. (267-305-6769).

Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

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Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

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06 May 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Prior Approval S-077
Agency Request for Information

Reference is made to the above NDA, 19-766, related to Prior Approval: S-077 (SEARCH). This submission is in response to an e-mail received from Ms. Margaret Simoneau on 26 April 2011 asking to provide the following clarifications concerning our submission of 25 February 2011:

- The methodology used to generate the 2010 monthly patient volume.
- A definition for the term "Patient Volume"
- Indicate whether the numbers submitted include mail order data

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Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

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Carl P. Sparrow, Ph.D.
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04 April 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Prior Approval S-077 (SEARCH)
Agency Request for Information

Reference is made to the above NDA, 19-766, related to Prior Approval: S-077 (SEARCH).

Merck submitted additional requested analyses from SEARCH by e-mail on 25 March 2011, followed by a formal electronic submission on March 29. After reviewing that submission, the FDA sent an e-mail on 29 March 2011, asking:

> *Please confirm that no cases of myopathy or rhabdomyolysis were excluded from these analyses based on limiting the at-risk population (the denominator) to patients with >80% compliance with study drug.*

In response to this question, Merck confirms that no cases of study-drug-related myopathy were excluded from these analyses based on the use of the "at-risk population" consisting of patients with >80% compliance with study drug for purposes of estimating myopathy rate as events per 1000 years of follow-up. The intention behind the use of that denominator was to be conservative in the rate estimation, avoiding a lower estimate that would result from inclusion of patients who had discontinued study drug or otherwise were not compliant with study drug. Myopathy events in patients still taking study drug that may have occurred despite less than 80% compliance were not excluded.

As fully described in the SEARCH CSR section 12.2.4.1, there was one patient among the intention-to-treat population allocated to 80 mg who had myopathy long after permanent discontinuation of study drug due to elevation of CK to 8223 IU/L in 2001, which occurred 7 to 8 months following randomization. He was asymptomatic, and hence did not meet criteria for myopathy. The patient's general practitioner was

unblinded to the patient's treatment allocation, and advised to treat the patient cautiously. In 2004 he was titrated to 80 mg simvastatin by his primary physician, independent of the study, and then presented with CK 6784 IU/L, thigh pain and normal creatinine. This case was classified as myopathy not attributable to study drug, and was not included in the total of 52 study-drug-related myopathy cases. No other cases of myopathy in patients who had discontinued study drug were reported.

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Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

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Carl P. Sparrow, Ph.D.
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30 March 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Safety Labeling Changes under 505(o)(4) – Prior Approval Supplement

Pursuant to Section 505(o)(4)(B) of the Food, Drug and Cosmetic Act, we submit for the agency's review and approval a supplement to NDA 19-766.

Reference is made to the 12 June 2009 supplement (S-077) based on the results of the Study of Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial. Reference is also made to the responses by Merck to Agency questions concerning SEARCH, submitted on 9 December 2009, 12 February 2010, 5 March 2010, 15 March 2010, 14 May 2010, 21 January 2011, and February 3, 18 and 25 in 2011. Reference is also made to the CBE submission concerning diltiazem on 30 March 2010. Reference is also made to the 11 August 2010 teleconference between the FDA and Merck, and the subsequent submission on 19 August 2010 addressing issues from that teleconference. Reference is also made to the 23 September 2010 Type C meeting between the FDA and Merck, and the subsequent 8 October 2010 submission of Merck proposals for labeling and communication. Reference is also made to the 9 February 2011 teleconference between the FDA and Merck. Final reference is made to the 28 February 2011 safety labeling notification from the FDA.

As indicated on the attached Form FDA 356h, this supplemental application provides for changes in the Labeling Section, of the approved New Drug Application for Zocor®. Additional details to support Merck's proposed labeling text are located in Module 1.11.3.

In response to the agency's communication of 28 February, Merck includes with this submission proposed changes to the approved labeling for Zocor to reflect information from the SEARCH trial showing an increased risk of myopathy, including

rhabdomyolysis, in patients treated with 80 mg of simvastatin versus those treated with 20 mg. Merck's proposed labeling incorporates much of the language included in the FDA's communication of 28 February. Our proposed approach, however, differs from that of the FDA's 28 February communication in certain important respects:

- **Continued use of the 80 mg dose by patients currently tolerating that dose:** Most significantly, Merck proposes that the risk-benefit profile of the 80 mg dose favors allowing its continued use in patients at high cardiovascular risk who are currently tolerating that dose and are not taking potentially interacting drugs that may increase the risk of myopathy/rhabdomyolysis. We are extremely concerned about language contained in the 28 February communication to restrict continued use of the 80 mg dose of simvastatin only to patients currently tolerating that dose "who cannot be switched to an alternative statin with similar or greater LDL-C lowering efficacy." We respectfully submit that a requirement that physicians actively attempt to switch the approximately (b) (4) patients who are currently tolerating high dose simvastatin (overwhelmingly in generic form) to other statin options is likely to have significant unintended, adverse consequences for patient care, and is neither in the interest of public health nor justified by available data. In particular, Merck believes that a requirement for active switching will affect not just those who take high dose simvastatin, but also potentially millions more who take lower doses of simvastatin or other lipid lower therapies and may have the counterproductive effect of causing patients to stop their therapy altogether. This, in turn, predictably may cause more people to experience cardiovascular morbidity and mortality in the form of additional deaths and serious cardiovascular events than are likely to be spared from fatal rhabdomyolysis.

  It is Merck's perspective that the unintended safety consequences of an active switching requirement are not justified by any safety advantage of such a requirement, considering the significantly reduced incidence of myopathy and rhabdomyolysis with the 80 mg dose following the first several months to 1 year of use, the clinical nature of myopathy, proposed labeling to further limit potential drug interactions, currently available data on myopathy and rhabdomyolysis (including fatal rhabdomyolysis) with other statins, and other associated risks of statin therapy. Understanding the agency's desire to further limit the use of simvastatin 80 mg, Merck instead proposes language that would enable only those patients (b) (4) currently tolerating 80 mg" to continue on that dose. Merck submits that this proposal is more appropriately tailored to permit continued use of the 80 mg dose by those patients who require its proven efficacy and who are unlikely to be at significantly increased risk of myopathy/rhabdomyolysis compared with other statin options.

- **Starting dose for patients at high risk of a CHD event:** It is Merck's perspective that principles of evidence-based medicine dictate retaining a 40 mg starting dose for patients, such as those studied in the Heart Protection Study (HPS), at high risk for a CHD event due to existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease. Labeling

language contained in the agency's 28 February communication would reduce the starting dose for this population to 20 mg. We believe that this reduction in the starting dose would be inconsistent with evidence-based practice because HPS demonstrated a clear morbidity and mortality benefit for such patients with use of the 40 mg dose.

- **Use of add-on lipid lowering therapy for patients on simvastatin 40 mg unable to achieve LDL-C goal:** To avoid any potential for misinterpretation, Merck believes that labeling direction for patients on simvastatin 40 mg (b) (4) [redacted]. Language included in the FDA's 28 February 2011 communication directing that these patients [redacted] (b) (4) " (b) (4) [redacted].

These issues, as well as others that Merck has identified in its review of the communication received from the FDA on 28 February, are discussed in greater detail in the accompanying justification document and proposed labeling.

Those documents reflect our commitment to address use of the 80 mg dose by new initiators as well as to support appropriate prescribing direction regarding potential drug interactions. In addition to labeling, we believe that clear and coordinated communications to healthcare providers and patients about the proposed label updates will be in the best interest of patient care and will be necessary to minimize potential confusion among physicians and patients. Merck therefore is including in Module 1.11.3 of this submission, for the agency's review, two communication documents that are aligned to Merck's labeling proposal. The first is a proposed letter to health care professionals, which is formatted in consideration of the FDA's November 10, 2010 draft guidance document entitled *Dear Health Care Provider Letters: Improving Communication of Important Safety Information*. The second document is a patient communication that would accompany the proposed letter to health care professionals and also would serve as content for an informational patient website. We recognize that any final communications will require alignment to the final, approved labels. However, in the interest of transparency and message consistency, we are providing these drafts now to foster efforts toward mutual coordination.

We remain committed to working with FDA to expeditiously address the issues discussed in the agency's communication of 28 February 2011. After the Agency has reviewed Merck's proposed labeling text, we would appreciate the opportunity to discuss the labeling and to coordinate related communications with the agency.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance

Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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If you have any questions, please contact Carl P. Sparrow, Ph.D. (732-594-7570) on this matter, or in my absence, Scott Korn, M.D. (267-305-6769).

Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

Merck Sharp & Dohme Corp.,
P.O. Box 2000, RY 33-208
Rahway NJ 07065-0900
Tel: +1-732 594 7570
Fax: +1-732 594 4980
carl_sparrow@merck.com

29 March 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Prior Approval S-077 (SEARCH)
Agency Request for Information

Reference is made to the above NDA, 19-766, related to Prior Approval: S-077 (SEARCH). This submission is in response to an e-mail received from Margaret Simoneau on 18 March 2011.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

Q:\Benebe\ZOCOR – MK-0733\US\US (NDA 19-766)\ Agency Response_S077_AbsoluteRisk_Mar11_

Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

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25 February 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Prior Approval S-077 (SEARCH)
Agency Request for Information

Reference is made to the above NDA, 19-766, related to Prior Approval: S-077 (SEARCH). This submission is in response to questions posed during a teleconference on 9 February 2011.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

Q:\Benebe\ZOCOR – MK-0733\US\US (NDA 19-766)\ Agency Response_S077_InfoRequest_25Feb11

Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

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18 February 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Prior Approval S-077 (SEARCH)
Agency Request for Information

Reference is made to the above NDA, 19-766, related to Prior Approval: S-077 (SEARCH). This submission is in response to an e-mail received from Margaret Simoneau on 1 February 2011.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

Q:\Benebe\ZOCOR – MK-0733\US\US (NDA 19-766)\ Agency Response-S077_InfoRequest2_Feb11

Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

Merck Sharp & Dohme Corp.,
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03 February 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Prior Approval S-077 (SEARCH)
Agency Request for Information

Reference is made to the above NDA, 19-766, related to Prior Approval: S-077 (SEARCH). This submission is in response to an e-mail received from Margaret Simoneau on 31 January 2011.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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If you have any questions, please contact Carl P. Sparrow, Ph.D. (732-594-7570) on this matter, or in my absence, Scott Korn, M.D. (267-305-6769).

Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

Q:\Benebe\ZOCOR – MK-0733\US\US (NDA 19-766)\ Agency Response-S077_InfoRequest_Feb11

Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

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21 January 2011

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Prior Approval S-077 (SEARCH)
Response to Agency

Reference is made to the above NDA, 19-766, related to Prior Approval: S-077 (SEARCH). This submission is in response to an e-mail received from Margaret Simoneau on 10 January 2011.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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If you have any questions, please contact Carl P. Sparrow, Ph.D. (732-594-7570) on this matter, or in my absence, Scott Korn, M.D. (267-305-6769).

Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

Q:\Benebe\ZOCOR – MK-0733\US\US (NDA 19-766)\ Agency Response-S077_Data_Jan11

MEMORANDUM OF INTERNAL MEETING MINUTES

MEETING DATE: August 11, 2010
TIME: 10 to 10:30 AM
LOCATION: 3376 WO Bldg. 22
APPLICATION: NDA 19766
DRUG NAME: Zocor (simvastatin) 80 mg
TYPE OF MEETING: Teleconference

ATTENDEES (FDA):

Mary Parks, M.D.
Eric Colman, M.D.
Amy Egan, M.D., M.P.H.
David Joy, J.D. (Reg counsel)
David Gortler, PharmD
John Bishai, Ph.D.
Margaret Simoneau, R.Ph.

ATTENDEES (Merck):

Scott Korn, M.D.
Mike Stepanavage, M.D.
Sandra Mackenzie
Sharon Olmstead
Yale Mitchel, M.D.
Jeff Tucker, M.D.
Larry Reich, J.D. (counsel)

BACKGROUND:

On June 12, 2009, Merck submitted a prior approval labeling supplement (NDA 19766/S-077) to provide new safety information concerning myopathy, based on the results of the clinical trial entitled Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). This trial was a seven-year, randomized, double-blind trial comparing the efficacy and safety of simvastatin 80 mg to simvastatin 20 mg with or without vitamin B12 and folate in survivors of myocardial infarction.

A Regulatory Briefing Meeting (June 4, 2010) discussed the clinical trial/observational/AERS data related to the risk for myopathy with 80 mg simvastatin relative to other statins. OSE presented a review from the AERS database of the Analysis of Rhabdomyolysis and Deaths Associated with Statins. At the Regulatory Briefing Meeting, Dr. Woodcock and the panel recommended withdrawal from the market of the 80 mg dose of simvastatin based on the benefit/risk assessment and the availability of other newer/more potent statins on the market. The meeting minutes (with slides) are archived in DARRTS under the NDA, supplement and TSI numbers for additional information.

An internal meeting took place on August 9, 2010, to discuss the panel recommendations from the Regulatory Briefing held on June 4, 2010, to withdraw from the market the 80 mg dose of simvastatin due to safety concerns (myopathy and rhabdomyolysis). Attendees were:

Mary Parks, Eric Colman, Amy Egan, David Gortler, John Bishai, Mitchell Weitzman, Nancy Hayes and David Joy. Discussion involved the possibility of withdrawal of the supplement for the 80 mg dose (S-028, approved on July 10, 1998). It was decided that the division would conduct a teleconference with the sponsor on August 11, 2010 to discuss the Agency's position regarding the 80 mg dose of simvastatin.

MEETING OBJECTIVES:

- Discuss the Agency review of SEARCH
- Discuss the Regulatory Briefing Recommendations

DISCUSSION POINTS:

Agency:
The risk is increased with the highest simvastatin dose (80 mg) when compared to other drugs that are therapeutically equivalent. The 80 mg simvastatin dose should not be marketed. Decision was derived from the SEARCH trial, other high dose statin clinical trials, observational myopathy data, drug utilization data, and AERS data.

Sponsor:
Merck was concerned with the ramifications of withdrawal of simvastatin 80 mg on Vytorin, an approved fixed-dose combination of simvastatin and ezetimibe (a cholesterol absorption inhibitor) indicated to lower LDL-C. Regulatory action taken on 80 mg simvastatin monotherapy could affect high-dose Vytorin (ezetimibe 10 mg/simvastatin 80 mg) and the development of any fixed-dose combination that contains 80 mg of simvastatin. Merck's additional concern included the impact the withdrawal would have on their ongoing cardiovascular outcome trial: IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT). This trial is a study of ezetimibe/simvastatin 10/40 mg vs. simvastatin 40 mg alone; however, patients who do not achieve LDL-C goal during the course of the trial can be uptitrated to ezetimibe/simvastatin 10/80 mg or simvastatin 80 mg alone.

Agency:
(b) (4)

Merck was asked if there were any patients who would benefit from the 80 mg dose and were unable to tolerate any other statin. The sponsor was not able to respond to this question.

A boxed warning and labeling were discussed but no agreements were made.

AGREEMENTS REACHED:

1. Agency will provide Merck the AERS analysis report.
2. Merck will discuss with their management and respond to the division by August 20, 2010.

Minutes concurrence: A. Egan 8.18.10

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-19766	SUPPL-77	MERCK RESEARCH LABORATORIES DIV MERCK CO INC	ZOCOR (SIMVASTATIN)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARGARET A SIMONEAU
08/18/2010

Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

Merck & Co., Inc.
P.O. Box 2000, RY 33-208
Rahway NJ 07065-0900
Tel: +1-732 594 7570
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carl_sparrow@merck.com

12 February 2010

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Request for Information

With reference to the above NDA, 19-766, the e-mail request for information, received from Ms. Margaret Simoneau on 22 December 2009, this submission is a duplicate of an e-mail sent on 05 February 2010, in response to Ms Simoneau's 22 December 2010 e-mail with the following requests:

1. **Question 1: Indicate where in the report you provide the average <u>pre-screening</u> lipid parameters for the 20 and 80mg groups. We would like these values as well as a calculation of percent change in LDL in the simvastatin 20 and 80mg groups from beginning to end.**

2. **Question 2: Provide the age at the time of the diagnosis of myopathy or rhabdomyolysis. The tables in your study report only provides date of birth. Indicate if there was any relation of myopathy or rhabdomyolysis to age or gender.**

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communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions, please contact Carl P. Sparrow, Ph.D. (732-594-7570) on this matter, or in my absence, Joseph P. Arena, Ph.D. (267-305-6772).

Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

Q:\Benebe\ZOCOR – MK-0733\US\US (NDA 19-766)\Agency Request Feb10

Sandra Mackenzie, B.Sc
Director
Worldwide Regulatory Affairs

Merck Sharpe & Dohme Corp.,
P.O. Box 2000, RY 33-208
Rahway NJ 07065-0900
Tel: +1-732 594 7729
Fax: +1-732 594 5235
sandra_mackenzie@merck.com

08 October 2010

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)
Prior Approval S-077 (SEARCH)
Response to Agency

Reference is made to the Prior Approval Supplement (S-077) dated 12 June, 2009 and the FDA meeting of the 11 August, 2010 related to the SEARCH study. Reference is also made to the FDA request to consider withdrawal of the simvastatin 80mg dose and the Company response submitted August 19, 2010. Further reference is made to the request of 23 August, 2010 for a Type C Meeting by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., (Merck) and to the subsequent Type C meeting of September 23, 2010 and Company minutes submitted October 5, 2010.

With this submission, Merck is now providing a full response to address the FDA concerns raised at the Type C meeting. The company proposes a number of changes to the Product Circular (PC) for Zocor to limit the use of simvastatin 80mg to patients currently tolerating 80mg or who have failed to tolerate other statin-based therapies with similar LDL-C lowering where the benefit outweighs the risk. The company has addressed the FDA concerns related to drug-drug interactions by contraindicating the potent CYP 3A4 inhibitors, cyclosporine, danazol and gemfibrozil, lowering the dose cap to simvastatin (b) (4) . In addition, a Patient Package Insert (PPI) and a Dear Healthcare Professional Letter are proposed to communicate the changes to the appropriate audiences.

The sponsor will support the proposed labeling changes, which would be applicable to all of the sponsor's simvastatin containing products, through a variety of measures designed to facilitate adoption by health care providers and patients. Further details are provided in the enclosed response document. The sponsor believes that the proposed label changes

along with the multichannel communication plan and the system interventions will help ensure appropriate use of simvastatin by those patients in whom the benefit outweighs the risk.

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Questions concerning this submission should be directed to Sandra Mackenzie, B.Sc. (732-594-7729), or in my absence to Jeff Tucker M.D. (267-305-6715).

Sincerely,
Sandra Mackenzie, B.Sc.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

Q:\Benebe\ZOCOR – MK-0733\US\US (NDA 19-766)\ Response_to_Agency_Oct10

Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

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P.O. Box 2000, RY 33-208
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carl_sparrow@merck.com

09 December 2009

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Request for Information

With reference to the above NDA, 19-766, this submission is a duplicate of an e-mail sent on 30 November 2009, in response to Ms Simoneau's e-mails of 17 November 2009 and 23 November 2009. Both those e-mails contained questions concerning the SEARCH study which was submitted as part of Supplement 77. The questions asked are reproduced in the attached response documents.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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If you have any questions, please contact Carl P. Sparrow, Ph.D. (732-594-7570) on this matter, or in my absence, Joseph P. Arena, Ph.D. (267-305-6772).

Sincerely,
Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products

Q:\Benebe\ZOCOR - MK-0733\US\US (NDA 19-766)\Agency Request_Dec09

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-766/S-077 **PRIOR APPROVAL SUPPLEMENT**

Merck & Co., Inc.
Attention: Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs
126 E. Lincoln Avenue, P.O. Box 2000, RY33-208
Rahway, NJ 07065-0900

Dear Dr. Sparrow:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Zocor (simvastatin) Tablets

NDA Number: 19-766

Supplement number: S-077

Date of supplement: June 12, 2009

Date of receipt: June 12, 2009

This supplemental application proposes new information concerning myopathy, based on the results of the clinical trial entitled Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 11, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 12, 2009.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, please call me at (301) 796-1295.

Sincerely,

{See appended electronic signature page}

Margaret Simoneau, M.S., R.Ph.
Regulatory Project Manager
Division of Metabolism and Endocrine Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

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 /s/
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Margaret Simoneau
6/18/2009 03:36:59 PM
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Carl P. Sparrow, Ph.D.
Director
Worldwide Regulatory Affairs

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12 June 2009

Mary H. Parks, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Dear Dr. Parks:

NDA 19-766: ZOCOR (simvastatin)

Prior Approval Supplement

Pursuant to Section 505(b) of the Food, Drug and Cosmetic Act, we submit, for the Agency's review and approval, a supplement to NDA 19-766. The purpose of this supplement is to provide new information concerning myopathy, based partly on the results of the clinical trial entitled Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). Reference is made to previous correspondence concerning SEARCH, Zocor and diltiazem between Michael Elia at Merck and David Orloff at the FDA in March of 2003. Reference is also made to previous correspondence concerning Zocor and the risk of myopathy, submitted to David Orloff (FDA) by Vijay Tammara (Merck) on May 18, 2005. Reference is also made to the February 2009 submission of preliminary myopathy data from SEARCH.

The Clinical Study Report for SEARCH is provided as part of this submission. As outlined through a telephone conversation, and e-mail, between Carl Sparrow (Merck) and Margaret Simoneau (FDA) on March 13, 2009, SEARCH was conducted by the Clinical Trial Service Unit at Oxford University, and Oxford controls the primary data. This submission, therefore, does not include the original Case Report Forms or any Case Report Tabulations.

As per FDA Guidance to Industry: Providing Regulatory Submissions in Electronic Format – Content of Labeling, the proposed labeling is provided in SPL format. Content of labeling [(201.100(d)(3)] has been included in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil.spl.html.

The Microsoft WORD version of the proposed labeling text is also supplied as PROPOSED.DOC within Section 1.14.1.3 Draft labeling text.

This submission is formatted as required in Title 21 paragraph 314.50 of the Code of Federal Regulations and is being submitted in accordance with the current FDA Guidance Documents for the electronic common technical document including, but not limited to the following: *Comprehensive Table of Contents Heading and Hierarchy, Study Tagging Files Specification, Organization of The Common Technical Document – Annex – Granularity Document, and the International Conference on Harmonization, ICH M2 EWG, Electronic Common Technical Document Specification.* This submission is being transmitted through the FDA's electronic submission gateway.

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If you have any questions, please contact Carl P. Sparrow, Ph.D. (732-594-7570) on this matter, or in my absence, Joseph P. Arena, Ph.D. (267-305-6772).

Sincerely,

Carl P. Sparrow, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Margaret Simoneau, Regulatory Project Manager (cover letter)
Division of Metabolism and Endocrinology Products