

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 19-766/S040

STATISTICAL REVIEW(S)

**APPEARS THIS WAY  
ON ORIGINAL**

The following information is reproduced exactly as it  
appears in the Clinical and Statistical Documentation  
of the supplemental application.

**APPEARS THIS WAY  
ON ORIGINAL**

TABLE OF CONTENTS

	<u>PAGE</u>
List of Tables	2
1. Introduction	3
2. Effectiveness of Therapy According to the NCEP Guidelines	3
3. Conclusions	10

APPEARS THIS WAY  
ON ORIGINAL

LIST OF TABLES

		<u>PAGE</u>
Table 1	Percentage of U.S. Patients Older Than 20 Years of Age Achieving Treatment Target Levels With Simvastatin, by NCEP Risk Group and Dosage	4
Table 2	Percent of Patients From Two Phase III Studies With Specific Percent Reductions in LDL Cholesterol	6
Table 3	LDL Cholesterol Pretreatment Levels From Which a Reduction of >45% Would be Required to Achieve NCEP Treatment Target Levels	7

APPEARS THIS WAY  
ON ORIGINAL

## **1. Introduction**

It has long been known that high serum cholesterol is a major risk factor for coronary heart disease (CHD). The effectiveness of lipid-lowering therapy for reducing the risk of coronary events in patients with and without CHD is now firmly established, and the results of the Scandinavian Simvastatin Survival Study (4S) have shown unequivocally that simvastatin reduces total and coronary mortality and coronary morbidity [1], with very few adverse reactions [2]. Because of their excellent tolerability and powerful effect on low-density lipoprotein cholesterol (LDL-C), simvastatin and other inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase have made the treatment of hypercholesterolemia much easier. This class of drugs now accounts for the large majority of prescriptions written for lipid-lowering drugs in the United States and most other countries. Nevertheless, the adoption of treatment in clinical practice has fallen well short of the recommendations of national guidelines [3] and expert opinion [4], with many patients being either undertreated or not treated at all [5]. There are many reasons for this, including the need for higher doses of even a very effective HMG-CoA reductase inhibitor like simvastatin to bring many patients, especially those with CHD, to treatment target levels [6].

The current usual recommended starting dose for simvastatin is 20 mg/day given as a single dose in the evening. The purpose of this supplemental marketing application is to propose a revision to the DOSAGE AND ADMINISTRATION section of the product circular for simvastatin that would allow an alternative starting dose of 40 mg for patients who require large (>45%) reductions in LDL-C. Such patients usually have CHD or multiple risk factors coupled with relatively high LDL-C, and therefore, are at high risk of coronary events. Because 20 mg produces reductions of this magnitude in only a minority of patients, and because many physicians frequently do not titrate drugs past the recommended starting dose, providing this choice of starting doses should increase the numbers of patients reaching the National Cholesterol Education Program (NCEP) treatment target levels [3]. The benefit/risk relationship is favorable because the safety and tolerability of simvastatin 40 mg has been documented over the 14 years since it was first studied. Both in clinical studies and postmarketing experience.

## **2. Effectiveness of Therapy According to the NCEP Guidelines**

Guidelines for the use of lipid-lowering drugs vary by country and region; the U.S. NCEP Adult Treatment Guidelines [3] are a useful model because they are currently more explicit and quantitative than those guiding therapy in other parts of the world. The U.S. guidelines divide potential patients into 3 risk groups: those with known CHD, those without CHD but with two or more risk factors (the multiple risk factor [MRF] patients), and those without CHD and with less than two risk factors (<2 RF). The risk factors are age over 45 for men and 55 for women, diabetes mellitus, hypertension, cigarette smoking, family history of CHD, and a high-density lipoprotein cholesterol (HDL-C) concentration below 35 mg/dL. After dietary therapy and other nonpharmacological measures have been tried, the LDL-C levels above which drug therapy is recommended are 130, 160, and 190 mg/dL for CHD, MRF, and <2 RF patients, respectively. The

corresponding LDL-C treatment target levels are 100, 130, and 160 mg/dL, respectively. Table 1 shows the percentages of patients in each risk group who will reach these treatment target levels with simvastatin 10 to 80 mg. The values in the table were calculated from the National Health and Nutrition Examination Survey (NHANES) database [6]. Dietary therapy was assumed to produce a mean reduction in LDL-C of 5%, and simvastatin mean reductions of 28, 35, 41, and 47% with 10, 20, 40, and 80 mg, respectively, with a standard deviation of 12.5% [6].

Table 1

Percentage of U.S. Patients Older Than 20 Years of Age Achieving Treatment Target Levels With Simvastatin, by NCEP Risk Group and Dosage

Risk Group	Percent of U.S. Population	Threshold LDL-C (mg/dL) <sup>†</sup>	Percent of Risk Group With LDL-C Above Threshold	Percentage of Patients Achieving Treatment Target Level			
				Simvastatin Dosage			
				10 mg	20 mg	40 mg	80 mg
CHD	7	130	46	27	45	61	75
MRF	27	160	31	50	69	83	92
<2 RF	66	190	4	73	88	95	98

<sup>†</sup> Treatment target is 30 mg/dL below the threshold in each case. To convert to mmol/L, divide by 38.7.

[6]

The response to simvastatin is relatively consistent, with a standard deviation of approximately 12.5 percentage points in 4S around the mean reduction in LDL-C [7]. The standard deviation within the placebo group was virtually identical [7], indicating that much of this variability is attributable to day-to-day fluctuations in LDL-C within a given individual, rather than differences in drug responsiveness. The patients who cannot achieve treatment target levels thus tend to be those who have the highest concentrations of LDL-C at baseline and, for this reason, are at the highest risk of coronary events. Because the percentage reduction in LDL-C produced by simvastatin is essentially independent of baseline levels [8], it is relatively straightforward to estimate the probability that a given patient will be controlled at a particular dose. This raises the opportunity to improve therapy by tailoring the starting dose to the patient.

#### The Need for an Alternative 40-mg Starting Dose

In the United States, the current recommended usual starting dose for simvastatin is 20 mg [9]. Nearly all (88%) patients without multiple risk factors can reach treatment target levels with this dose. However, as shown in Table 1, titration to higher doses is required for 55 and 31% of CHD and MRF patients, respectively. These tend to be patients with high baseline concentrations of LDL-C. If therapy were started at 40 mg, only 39 and 17% of patients, respectively, would require titration. Titration of any

Simvastatin—40-mg Alternative Starting Dose  
Worldwide Clinical Summary

-5-

therapy adds complexity and cost; patients typically prefer not to have to return for repeat visits, and such visits tend to be discouraged under the managed care system that prevails in the United States today. Although titration of dosage is the ideal, the reality is that physicians frequently do not titrate drug dosage up from the recommended starting dose to achieve optimal therapeutic results. For example, in postmyocardial infarction patients,  $\beta$ -adrenergic blockers are usually not titrated up to the doses that have been proven to reduce mortality [10]. Similarly, several studies have shown that only a minority of hypercholesterolemic patients receiving lipid-lowering therapy achieve NCEP treatment target levels [5]. Marcelino, et al. [11] studied a population of 90 patients (73% with CHD) on HMG-CoA reductase inhibitor therapy at a university-affiliated Veterans Administration medical center. They found that despite the fact that only 30 of these patients attained their NCEP treatment target level, 53 patients were taking the starting dose, and only 9 had been titrated up to maximal dosage. Market research conducted by Merck Research Laboratories (MRL) has produced similar conclusions [12]. Therefore, a starting dose which provides the greatest likelihood of achieving the recommended treatment target level while maintaining the overall safety profile is recommended. Allowing an alternative recommended starting dose of 40 mg for patients who will require larger reductions in LDL-C to achieve their treatment target levels than can be expected with 20 mg, will facilitate more effective treatment.

Meta-analyses of lipid-lowering intervention studies strongly suggest that in both primary and secondary prevention studies, reduction in coronary mortality and morbidity is proportional to the degree of cholesterol-lowering achieved, at least up to the 25% reduction in total cholesterol (equivalent to 35% reduction in LDL-C) observed thus far in clinical studies with coronary endpoints [13; 14; 15]. Improved survival has been unequivocally demonstrated in hypercholesterolemic CHD patients receiving simvastatin 20 to 40 mg daily for more than 5 years [1], 256 patients (11.5%) in the placebo group died compared with 182 (8.2%) in the simvastatin group. This represents a 30% reduction in the risk of death in the simvastatin group ( $p=0.0003$ ), resulting from a 42% reduction in coronary deaths. Moreover, the risk of major coronary events (myocardial infarction plus CHD death) was reduced by 34% ( $p<0.00001$ ). Other benefits of treatment included a 37% reduction ( $p<0.00001$ ) in the risk of undergoing a myocardial revascularization procedure. In 4S, there was a continuous relationship between the risk of a major CHD event and reduction in LDL-C, with no evidence for a threshold below which further lipid lowering is futile [16]. Therefore, it is likely that an even better outcome could have been achieved if all patients had received 40 mg, instead of only the 37% [1] who were titrated up from 20 mg. These results support the NCEP guidelines and suggest that more lives could be saved if physicians more frequently achieved treatment target levels by using the appropriate dosage. Providing an alternative starting dose of 40 mg for patients unlikely to reach the target level on 20 mg would certainly make this easier.

**APPEARS THIS WAY  
ON ORIGINAL**

**Magnitude of LDL-C Reduction Required in Relation to Starting Dose**

In order to provide physicians with a practical choice of starting doses, it is necessary to supply guidance on when to start with 40 mg as opposed to 20 mg. While there are various ways in which this could be done, the simplest solution is to base the choice of starting dose on the goal, expressed as the percentage reduction in LDL-C that the prescriber is hoping to achieve. This will apply across the range of pretreatment LDL-C values, as the percentage reduction in LDL-C produced by simvastatin is essentially independent of baseline levels [8]. In order to minimize the number of patients started on 40 mg who do not need it, the goal needs to be set at a point that can be reached in only a minority of patients taking 20 mg. Two Phase III studies [17; 18] in the original 1987 marketing application for simvastatin have been examined to determine the appropriate goal. Both studies, one using cholestyramine as a control agent [17] and the other, probucol [18], were conducted in the United States and randomized patients to 20 or 40 mg. (There are several studies in which patients were titrated from 20 to 40 mg, but these do not permit an unbiased comparison of the efficacy of 20 and 40 mg.)

Table 2 shows the results from these studies, expressed as the percentage of patients achieving different LDL-C reductions (in 5% increments). The intention-to-treat approach was used, with the percentage reductions based on the last available value.

Table 2

Percent of Patients From 2 Phase III Studies With Specific Percent Reductions in LDL Cholesterol

Study: Daily Dose:	Simvastatin Versus Cholestyramine		Simvastatin Versus Probucol	
	20 mg	40 mg	20 mg	40 mg
(Number of Patients)	(86)	(82)	(83)	(81)
Mean Baseline LDL-C (mg/dL)	251	246	258	240
LDL-C Reduction $\geq$ %	Percent of Patients	Percent of Patients	Percent of Patients	Percent of Patients
25%	80	88	77	91
30%	70	85	65	82
35%	61	77	49	69
40%	34	65	41	59
45%	14	40	25	37
50%	4	23	10	26
55%	1	9	1	11

[17; 18; 19]

In the cholestyramine study, the percentages of patients achieving a 40% reduction were 34 and 65% on 20 and 40 mg, respectively; in the probucol study, the corresponding

percentages were 41 and 59%. However, with more than one-third of the patients in both studies reaching a 40% reduction with simvastatin 20 mg, that cutpoint is probably too low. The percentages of patients achieving a 45% reduction in LDL-C on 20 and 40 mg were 14 and 40%, respectively, in the cholestyramine study, and 25 and 37% in the probucol study. Pooling the 2 studies, these percentages were 19.5 and 38.7%. Thus, if the treatment goal is a 45% reduction in LDL-C, 20 mg is an inadequate dose because it achieves the goal in less than 20% of patients; a prescriber with a patient who requires a treatment effect of this magnitude might well consider beginning treatment at 40 mg to avoid the probable need for titration to 40 mg. Table 3 shows the LDL-C pretreatment levels from which a reduction >45% would be required to achieve NCEP treatment target levels.

Table 3

LDL Cholesterol Pretreatment Levels From Which a Reduction  
of >45% Would be Required to Achieve  
NCEP Treatment Target Levels

Risk Group	Pretreatment Level (mg/dL)	Treatment Target Level (mg/dL)
CHD	182	100
MRF	237	130
<2 RF	291	160

The proposed change to the DOSAGE AND ADMINISTRATION section of the product circular for simvastatin is to insert the sentence in italics:

*Doses should be individualized according to baseline LDL-C levels, the recommended goal of therapy (see NCEP Treatment Guidelines), and the patient's response. The recommended usual starting dose is 20 mg once a day in the evening. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg/day in the evening.*

Other proposed changes to this section are indicated in the annotated label. These are intended to improve conciseness and clarity and to remove outdated information.

There is an established precedent for setting the starting dose at a level that achieves a large reduction in LDL-C. Simvastatin 40 mg produces a mean reduction in LDL-C of 41% [9]. This is only slightly more than the 10-mg starting dose approved for the recently introduced HMG-CoA reductase inhibitor atorvastatin, which, according to the product circular [20], produces a mean reduction in LDL-C of 39%. In contrast to simvastatin 40 mg, there is no alternative lower starting dose, and long-term safety and tolerability data on atorvastatin are not available at any dose.

### Safety of Simvastatin 40 mg

The safety and tolerability of simvastatin 40 mg has been documented. The only important adverse reactions of HMG-CoA reductase inhibitors including simvastatin are myopathy and marked but asymptomatic increases in hepatic transaminases. Both are uncommon and rapidly reversible when treatment is stopped. In addition to 11 years of worldwide postmarketing surveillance, detailed safety data are available from 4S [2]. This study randomized patients up to age 70, who were 75 by the end of the study, for a median follow-up period of 5.4 years, thus documenting safety and efficacy in both elderly and younger patients [21]. Patients were randomly allocated to simvastatin 20 mg or placebo. Thirty seven percent of patients were titrated to 40 mg during the first 6 months of the study [1], so that the mean dose of simvastatin was 27 mg. This produced a long-term 35% mean reduction in LDL cholesterol, accompanied by an 8% increase in HDL cholesterol. After 1 year, 72 % of the simvastatin treated patients had achieved the goal defined by the study protocol (total cholesterol < 5.2 mmol/L). More recently, data have been published from the Heart Protection Study (HPS), in which more than 20,000 patients at high risk of CHD up to 80 years of age were randomized to simvastatin 40 mg or placebo. Lipid changes and safety data after approximately 2 years of treatment have been published [22]. In 1998, the dosage range of simvastatin was extended to 80 mg/day. The incidence of myopathy and marked increases in hepatic transaminases is somewhat higher at this dose than at 40 mg (see below) but still low (0.7 and 2.1% in the 2 Phase III studies with 80 mg) [9].

Simvastatin 10-mg tablets will continue to be available and can be used for patients who need only a moderate reduction in LDL-C. In addition, 5 mg will remain an appropriate starting dose for patients with severe renal insufficiency and patients undergoing cyclosporine immunosuppression. Patients receiving concomitant therapy with a fibrate or niacin should generally not take more than 10 mg of simvastatin, so that the starting dose for these patients should be 5 to 10 mg [9].

### Safety of Simvastatin 40 mg in Megatrials

#### Scandinavian Simvastatin Survival Study

In 4S, 4444 patients with angina pectoris or previous MI and serum total-C of 213 to 310 mg/dL (5.5 to 8.0 mmol/L) on a lipid-lowering diet were initially randomized to double-blind treatment with simvastatin 20 mg or placebo and were followed for a median period of 5.4 years [1]. The protocol specified that patients with serum total cholesterol above 5.2 mmol/L during the first 6 months after randomization were to be titrated to 40 mg [1]; 822 (37%) of the 2221 patients taking simvastatin were titrated to 40 mg during the first 6 months after randomization. Because patients were not randomized to 40 mg, statistical comparisons of patients taking 20 and 40 mg are of questionable value.

#### Myopathy

A single case of myopathy was reported, after 4 years of therapy in a woman taking simvastatin 20 mg [2].

### Hepatic Effects

The study protocol called for discontinuation of patients with increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) above 4 times the upper limit of normal (ULN) confirmed by a repeat measurement [2]. Only 8 patients (0.36%) in the simvastatin group, versus 5 (0.23%) in the placebo group, were discontinued because of elevated liver transaminases. Six of the 8 simvastatin patients were taking 40 mg. There was 1 case of nonviral hepatitis in the simvastatin group (in a patient taking 20 mg) and 2 in the placebo group [2].

### Heart Protection Study

In HPS, 20,536 patients with or at high risk of CHD due to diabetes mellitus or non-coronary vascular disease have been randomized [22]. HPS is an ongoing study in the United Kingdom in which the interventions are simvastatin 40 mg versus placebo, and an antioxidant vitamin mixture (C, E, and  $\beta$ -carotene) versus placebo, in a 2 x 2 factorial design. There was a 10-week run-in period prior to randomization, which consisted of 4 weeks on placebo followed by 6 weeks on simvastatin 40 mg and the vitamin mixture. As of Aug-1998, the mean duration of treatment was more than 2 years, and virtually all patients had received at least 1 year of treatment.

### Myopathy

Two of 32,145 patients entering the run-in period developed myopathy [23]. As of Aug-1998, 2 of the 10,269 patients randomized to simvastatin 40 mg and 2 of the 10,267 patients randomized to placebo developed myopathy. One of the 2 placebo patients developed frank rhabdomyolysis following coronary revascularization, apparently precipitated by thrombolytic therapy with streptokinase; rhabdomyolysis is a recognized but rare complication of such treatment [23]. The other placebo patient was hypothyroid, a condition known to cause muscle weakness.

Following the preparation of the paper by the Oxford investigators, as of March 1999, MRL has received 3 additional reports of myopathy in patients randomized to simvastatin [23], bringing the total in the simvastatin group to 5. Thus, after a median duration of therapy of approximately 3 years, the incidence of myopathy in the simvastatin group is 0.05%.

### Hepatic Effects

Thirty-nine patients randomized to simvastatin and 32 to placebo developed an asymptomatic elevation in ALT to  $>3 \times$  ULN [22]. In 1 of the patients in the simvastatin group, ALT values remained abnormal after stopping simvastatin, and approximately 1 year later the patient developed clinical hepatitis. Viral serology was negative. The patient recovered although ALT values remained abnormal. While simvastatin is a possible cause, drug-induced hepatotoxicity with symptomatic disease appearing 1 year after cessation of treatment is most unusual.

### Drug Interactions

Several drug interactions have been identified with simvastatin and other inhibitors of HMG-CoA reductase. The risk of myopathy is increased by concomitant administration of fibrates and niacin [9], and by potent inhibitors of the cytochrome P-450 isoform 3A4 that metabolizes simvastatin [24], such as cyclosporine, the antifungal azoles itraconazole and ketoconazole, the macrolide antibiotics erythromycin and clarithromycin, human immunodeficiency virus (HIV) protease inhibitors, and the antidepressant nefazodone. In addition, like many drugs, simvastatin slightly augments the effect of coumarin anticoagulants [9; 25], but this has never been a significant clinical problem. All of these interactions are described in detail in the product circular for simvastatin [9], along with the appropriate course of action to avoid or control them. While these interactions may be slightly more likely to occur at 40 than at 20 mg, they are very uncommon at both doses: as noted above, the incidence of myopathy in both 4S and HPS was very low, despite the fact that of the interacting drugs, only fibrates, niacin, and cyclosporine were excluded. (The product circular for simvastatin recommends a maximal dose of 10 mg in patients taking these drugs.) These data show that the risk of drug interactions is too low to materially affect the choice of 40 versus 20 mg.

### 3. Conclusions

The use of lipid-lowering therapy in clinical practice has fallen well short of the recommendations of national guidelines and expert opinion, with many patients inadequately treated. As a result, many preventable fatal and nonfatal coronary events are not being prevented. Because of the excellent safety and tolerability profile of simvastatin 40 mg and the fact that many physicians do not titrate the starting dosage to achieve treatment target levels, providing prescribers with the option of starting simvastatin at 40 mg in appropriate patients will improve the effectiveness of treatment.

**APPEARS THIS WAY  
ON ORIGINAL**

## REFERENCES

1. Scandinavian Simvastatin Survival Study group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-89.
2. Pedersen TR, Berg K, Cook TJ, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study. *Arch Intern Med* 1996;156:2085-92.
3. Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel II). *JAMA* 1993;269(23):3015-23.
4. Smith SC, Blair SN, Criqui MH, et al. AHA consensus panel statement: preventing heart attack and death in patients with coronary disease. *Circulation* 1995; 92(1):2-4.
5. Hoerger TJ, Bala MV, Bray JW, Wilcosky TC, LaRosa J. Treatment patterns and distribution of low-density lipoprotein cholesterol levels in treatment-eligible United States adults. *Am J Cardiol* 1998;82:61-5.
6. Memo to J. Tobert/D. Shapiro from Linda Nelsen: Analysis of NHANES III data: percentage of patients reaching NCEP=ATP II goal for LDL-C, 05JUN1997.
7. Memo to Dr. J. Tobert from Mr. T. Cook. 4S - Similarity of variability in LDL cholesterol in the treatment groups, 07MAY99.
8. Memo to Dr. J. Tobert from Mr. T. Cook. Use of percent change in assessing lipid response, 27APR99.
9. U.S. Package Circular: ZOCOR (simvastatin) Tablets. Merck & Co., Inc., December 1998.
10. Viskin S, Kitzis I, Lev E, et al. Treatment with beta-adrenergic blocking agents after myocardial infarction: from randomized trials to clinical practice. *J Am Coll Cardiol* 1995;25(6):1327-32.
11. Marcelino JJ, Feingold KR. Inadequate treatment with HMG-CoA reductase inhibitors by health care providers. *Am J Med* 1996;100:605-10.
12. Memo to J. Tobert from K. Smith. Patients achieving goal, 04APR99.
13. Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: Impact of statin trials. *Circulation* 1998;97:946-52.

REFERENCES (continued)

14. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308:367-72.
15. Gordon DJ. Cholesterol lowering and total mortality. In: Rifkind BM, ed. Lowering cholesterol in high-risk individuals and populations. New York: Marcel Dekker. 1995:33-47.
16. Pedersen TR, Olsson AG, Faergeman O, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998;97:1453-60.
17. MRL Clinical Study Report (Synopsis), Multicenter Study: A Multicenter Study to Compare the Safety, Tolerability, and Efficacy of Simvastatin and Cholestyramine in the Treatment of Hypercholesterolemia and to Study the Concomitant Use of the Two Drugs (Protocol 004).
18. MRL Clinical Study Report (Synopsis), Multicenter Study: A Multicenter Study to Compare the Safety, Tolerability, and Efficacy of Simvastatin and Probucol in the Treatment of Hypercholesterolemia (Protocol 005).
19. Memo to Dr. Y. Mitchel from Dr. D. Shapiro. Effect of simvastatin 20 vs 40 mg qpm - Protocols 004 and 005, 12APR99.
20. U.S. Package Circular: Lipitor (atorvastatin calcium) Tablets: 1999.
21. Miettinen TA, Pyorala K, Olsson AG, et al. Cholesterol-lowering therapy in women and elderly patients with myocardial infarction or angina pectoris: findings from the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1997;96(12):4211-8.
22. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol-lowering drug therapy and of antioxidant vitamin supplementation in patients at increased risk of coronary heart disease: design, study population and early experience. *Eur Heart J* 1999;20:725-41.
23. Memo to J. Tobert from A. Tate. Heart Protection Study - CK elevations and myopathies, 06MAY99.
24. MRL Preclinical Report: *In Vitro* Metabolism of Simvastatin Using Human Liver Microsomal Preparations: Identification of Responsible Enzymes. November 26, 1996.
25. Keech A, Collins R, MacMahon S, et al. Three-year follow-up of the Oxford Cholesterol Study: assessment of the efficacy and safety of simvastatin in preparation for a large mortality study. *Eur Heart J* 1994;15:255-69.