AstraZeneca

CRESTOR® tablets

(rosuvastatin calcium)

NDA 21-366

FDA Advisory Committee Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee
09 July 2003

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EXECUTIVE SUMMARY

NDA 21-366 submitted by AstraZeneca Pharmaceuticals LP provides for the use of CRESTOR® (rosuvastatin calcium) 10 to 40 mg as an adjunct to diet to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), ApoB/ApoA-I, and triglyceride (TG) levels and to increase HDL-C and ApoA-I in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb); as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IIb and IV); and to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable. The Division of Metabolic and Endocrine Drug Products has requested that AstraZeneca participate in an Advisory Committee review of this application and this briefing document has been prepared to support that review.

The NDA for CRESTOR currently includes data for over 12,500 patients treated with rosuvastatin in Phase II/III clinical trials. This makes the clinical data package to be reviewed by the Advisory Committee the largest of any new statin development program to date.

In this briefing document, AstraZeneca will provide the information necessary to make an overall assessment of the benefit-risk profile for rosuvastatin and will highlight how rosuvastatin compares with currently marketed statins and how these all are distinct from cerivastatin which was withdrawn from the market shortly after the CRESTOR NDA was filed. To facilitate this evaluation, this document and the presentation to the committee will briefly address the following key areas:

Development objectives

The development program for rosuvastatin was designed to evaluate additional benefit to patients in all key lipid parameters beyond that achieved with existing statins. The failure of the current treatment options to adequately control dyslipidemia is reflected by the fact that the majority of patients do not meet even the older ATP II goals, much less the new, more aggressive goals in ATP III. This partially reflects a reluctance on the part of physicians to titrate patients to higher doses of the existing statins. One consequence of this has been the recent trend to higher starting doses with the existing statins and the approval of add-on treatment for dyslipidemia. A new statin which brings more patients to their lipid goals at the start dose and across the dose range without compromising safety would be a valuable addition to the treatment options available to patients.

Efficacy of rosuvastatin

In discussions with the Division of Metabolic and Endocrine Drug Products, it is clear that the extensive clinical trial program conducted with rosuvastatin has demonstrated its efficacy in relation to each of the key lipid parameters. As the program is very large, it is only possible to

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briefly describe key aspects of the program in this document and the presentation to the committee, but it is important to highlight these to have a clear basis for consideration of the benefit side of the benefit-risk profile. The data presentations in this document are representative of and consistent with the efficacy data from the entire clinical development program. The data show that rosuvastatin (at a dose range of 10 mg to 40 mg) was more efficacious than atorvastatin (10 mg to 80 mg), simvastatin (10 mg to 80 mg), and pravastatin (10 mg to 40 mg) in reducing LDL-C, non-HDL-C, and important lipid ratios such as ApoB/ApoA-1. In addition, treatment with rosuvastatin raised HDL-C levels more than treatment with atorvastatin. The effects seen on lipid levels following rosuvastatin treatment translated into a greater percentage of patients achieving NCEP ATP II and III goals with rosuvastatin treatment compared to treatment with other statins.

Safety of rosuvastatin

This document will present the overall safety results based on studies in more than 12,500 patients in Phase II/III trials. It will be demonstrated that across the dose range studied (up to and including 80-mg), the overall safety profile is similar to currently marketed statins. One safety consideration for all statins is liver safety; the data show that rosuvastatin compares favorably with approved statins in terms of liver safety. Another safety variable for statins is muscle effects, particularly following the cerivastatin withdrawal; the data show that rosuvastatin is similar to currently marketed statins in terms of muscle safety. One explanation for this is provided in the preclinical data which demonstrate the selectivity of rosuvastatin (and other statins) for liver tissue compared to muscle tissue, particularly when compared to similar data for cerivastatin. Finally, this document will discuss the renal effects of rosuvastatin. During the rosuvastatin clinical trial program an increased frequency of proteinuria was observed early in the course of treatment with the 80-mg dose. More extensive evaluation of this finding has demonstrated that this phenomenon is seen predominantly at doses above the 10 to 40-mg dose range currently being requested and is believed to be an effect of HMG-CoA reductase inhibition in renal tubules. Preclinical data are presented supporting this mechanism both for rosuvastatin as well as for the currently approved statins. Proteinuria, when observed at doses up to and including 40 mg, was usually transient and not associated with worsening renal function or clinically significant increases in serum creatinine.

The data support that, over the requested dose range (10 mg to 40 mg), rosuvastatin does not present any additional safety concerns beyond those already present with the currently approved statins.

In addition to considering potential adverse safety signals from the clinical trial program for rosuvastatin, it is also important to consider potentially beneficial aspects of rosuvastatin in terms of safety in the broad patient population. In this respect, the absence of significant metabolism and drug-drug interactions will be highlighted.

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Benefit-risk profile of rosuvastatin

Based on the data showing the beneficial effect of rosuvastatin on all key lipid parameters compared with currently marketed statins, as well as a safety profile that is similar AstraZeneca believes that the overall benefit-risk profile of rosuvastatin supports the availability of the 10-mg to 40-mg doses of CRESTOR.

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ABBREVIATIONS

Abbreviation	Term
4S	Scandinavian Simvastatin Survival Study Group
ACCESS	Atorvastatin Comparative Cholesterol Efficacy and Safety Study
AFCAPS/TexCAPs	Air Force/Texas Coronary Prevention Study
ALT	Alanine aminotransferase
ApoA-I	Apolipoprotein A-I
ApoB	Apolipoprotein B
ASCOT	Anglo-Scandinavian Cardiac Outcomes Trial
AST	Aspartate aminotransferase
ATP	Adult treatment panel
AU-INR	Area under the INR time curve
AUC	Area under the plasma concentration-time curve
$AUC_{(0\text{-}24)}$	area under the plasma concentration-time curve from time zero to 24 hours
CABG	Coronary artery bypass grafting
CARE	Cholesterol and Recurrent Events
CHD	Coronary heart disease
CK	Creatine kinase
Cmax	Maximum concentration
CrCl	Creatinine clearance
CYP450	Cytochrome P450
FH	Familial hypercholesterolemia
FITC-BSA	Fluorescein-5-isothiocyanate isomer I-bovine serum albumin
FPP	Farnesyl pyrophosphate
GGPP	Geranylgeranylpyrophospate
gmean	Geometric mean
HDL-C	High density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HPS	Heart Protection Study
IC_{50}	Concentration giving 50% of the drug-induced inhibitory effect
IgG	Immunoglobulin G

Abbreviation	Term
IgM	Immunoglobulin M
INR	International normalized ratio
ITT	Intention-to-treat
L	Liter
LIPID	The Long-term Intervention with Pravastatin in Ischaemic Disease
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
lsmean	Least squares mean
LTE	Long-term extension
NAG	N-acetyl-beta-D-glucosaminidase
NCEP	National Cholesterol Education Program
NDA	New drug application
Non-HDL-C	Non-high density lipoprotein cholesterol
OATP-C	Organic anion transporter
PgP	P-glycoprotein
PTCA	Percutaneous transluminal coronary angioplasty
RR	Relative risk
RTLD	Real-time laboratory data
SBA	Summary basis of approval
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
$t_{1/2}$	Half-life
t_{max}	Time to reach peak or maximum concentration or maximum response following drug administration
TC	Total cholesterol
TG	Triglyceride
ULN	Upper limit of normal
VLDL	Very-low-density lipoprotein
WOSCOPS	West of Scotland Coronary Prevention Study

1. INTRODUCTION

AstraZeneca Pharmaceuticals LP submitted an original New Drug Application (NDA) for rosuvastatin calcium (CRESTOR® Tablets, ZD4522) to the FDA-CDER Division of Metabolic and Endocrine Drug Products in June 2001 (NDA 21-366). The initial NDA submission proposed a dose range of 10 mg to 80 mg qd rosuvastatin (see Section 1.1). The development program was designed to evaluate the safety of this proposed dose range by "force-titrating" patients in clinical trials from the 10-mg to the 80-mg dose. This approach produced an NDA patient safety exposure database where a majority of the patient exposures were acquired at the 10-mg and 80-mg doses, thereby "bracketing" the proposed dose range. The NDA was amended with updated patient exposure and safety information in October 2001 and February 2002 bringing the NDA safety database at that time to 4549 patients treated with rosuvastatin.

In March 2002, AstraZeneca and the Division NDA Team agreed to discontinue further development of the 80-mg dose of rosuvastatin in the general dyslipidemic population in response to an evaluation of the benefit-risk of this dose. While the clinical data demonstrated potential benefits of this dose in patients with dyslipidemias that were difficult to control, the clinical data did not support a superior benefit-risk profile for the 80-mg dose in the general dyslipidemic population. Patients in ongoing trials who were receiving the 80-mg dose of rosuvastatin at that time were down titrated to the 40-mg dose of rosuvastatin.

The NDA Action Letter was issued in May 2002, noting that the proposed 10-mg, 20-mg and 40-mg doses of rosuvastatin were approvable. The NDA Action Letter centered on the request for additional safety exposure information for patients receiving rosuvastatin 20 mg and 40 mg to fully assess the therapeutic profile of rosuvastatin at these doses. In addition, further data to clarify the nature, magnitude, and frequency of renal effects observed in patients treated with rosuvastatin was requested.

AstraZeneca and Division representatives met in July 2002 to outline the data package needs for continued NDA review of rosuvastatin. At the meeting it was agreed that 600 patients treated with 20-mg and 40-mg doses of rosuvastatin for 6 months were necessary. The conclusions from this meeting culminated in a NDA amendment submitted on 12 February 2003, which supported the proposed 10-mg to 40-mg dose range for the general dyslipidemic population. With this amendment, the NDA safety database increased to over 11,000 patients treated with rosuvastatin and provided the requested additional patient data for the 20-mg and 40-mg doses. An interim safety update was submitted in June 2003 to complete the NDA review database. The current rosuvastatin NDA safety database contains over 12,500 patients treated with rosuvastatin.

1.1 Indication and proposed dosing

Rosuvastatin is intended for:

1. use as an adjunct to diet to reduce elevated total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (ApoB), non-high density lipoprotein cholesterol (non-HDL-C), ApoB/ApoA-I, and triglyceride (TG) levels and to increase HDL-C and apolipoprotein A-I (ApoA-I) in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb)

2. use as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IIb and IV)

3. reduction of LDL-C, TC, and ApoB in patients with homozygous familial hypercholesterolemia (FH) as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable

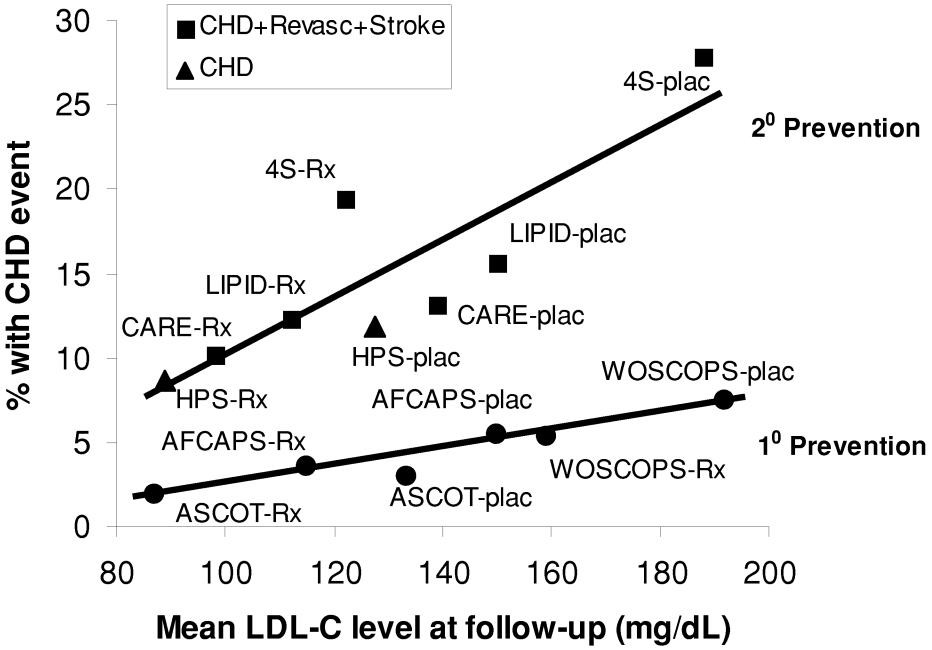
The recommended starting dose of CRESTOR is 10 mg once daily. For patients with severe hypercholesterolemia (LDL-C >190 mg/dL) and aggressive lipid targets, a 20-mg start dose is optional. The maximum recommended dose is 40 mg. The recommended starting dose is 20 mg once daily in patients with homozygous familial hypercholesterolemia. In patients taking cyclosporine, therapy should be limited to 5 mg once daily.

CRESTOR is currently approved for marketing at a dose range of 10 to 40 mg in 17 markets in North America, Europe, and Asia.

1.2 Rationale and objectives for the CRESTOR clinical development program

The benefits of statin therapy are well documented. Long-term event trials (ie, events measured for approximately 5 years) with statins show that improving lipid profiles, in particular lowering LDL-C levels, is strongly related to improving cardiovascular survival, reducing a range of vascular event rates, and extending life in patients with and without established cardiovascular disease (LaRosa 1999; 4S [Scandinavian Simvastatin Survival Study Group 1994]; WOSCOPS [West of Scotland Coronary Prevention Study; Shepherd et al 1995]; CARE [Cholesterol and Recurrent Events; Sacks et al 1996]; LIPID [The long-term Intervention with Pravastatin in Ischaemic Disease; The Lipid Study Group 1998]; AFCAPS/TexCAPS [Air Force/Texas Coronary Prevention Study; Downs et al 1998]; and ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial; Sever et al 2003]). Furthermore, analysis of clinical trial data (Figure 1) suggests that treating patients more aggressively in order to obtain lower LDL-C target goals provides added benefit by reducing cardiovascular event rates and disease progression (Ballantyne 1998).

Figure 1 Primary and secondary prevention trials with statins



Adapted from Ballantyne 1998, Heart Protection Study Collaborative Group 2002, and Sever 2203.
Plac placebo; Rx treatment; CHD Coronary heart disease; CHD+Revasc+Stroke CHD including with revascularization and stroke

The benefits of more aggressive lipid therapy were shown in a follow-up evaluation of patients from the Post-CABG (coronary artery bypass grafting) Trial where, after 7.5 years of follow-up, patients treated to more aggressive LDL-C goals (mean LDL-C at 1 year: 93 mg/dL) had a 30% reduction in the incidence of percutaneous transluminal coronary angioplasty (PTCA) or CABG (P=0.0006), a 24% reduction in the composite clinical endpoint (P=0.001; the composite clinical outcome included death from cardiovascular or unknown causes, nonfatal myocardial infarction, stroke, bypass surgery, or angioplasty;), and a trend toward reduced overall mortality compared to those treated less aggressively (mean LDL-C at 1 year: 134 mg/dL; Knatterud 2000). The relative risk and p-value for the trend in reduced overall mortality was RR=0.8, p=0.16

Recognizing the importance of lowering lipids in patients, especially those with or at high risk of cardiovascular events, the National Cholesterol Education Program (NCEP) guidelines were recently revised (Table 1).

Table 1 **NCEP Adult Treatment Panel III (ATP III): LDL-C and non-HDL-C goals**

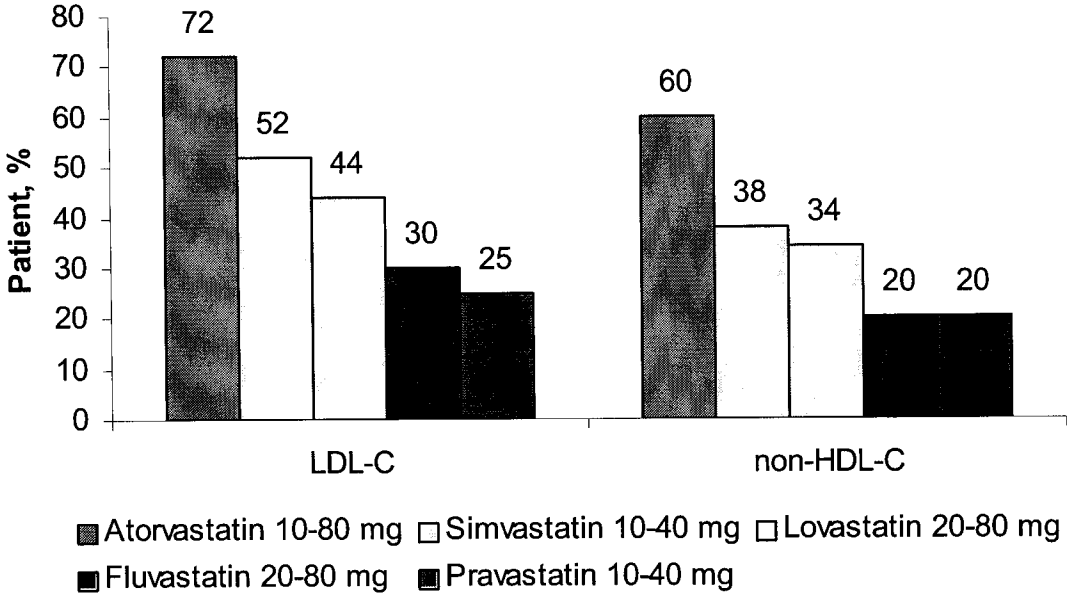
Risk category	LDL-C (mg/dL)	Non-HDL-C (mg/dL)
CHD and CHD risk equivalent (10 year risk >20%)	<100	<130
Multiple (2+) risk factors (10-year risk ≤20%)	<130	<160
Zero to one risk factor	<160	<190

The new guidelines lower the LDL-C for therapy initiation in high-risk patients, and they dramatically increase the number of patients in the high-risk group by including patients with a ≥20% risk of coronary heart disease over 10 years. In addition to the continued emphasis on LDL-C, the guidelines also include non-HDL-C as a secondary target in patients with elevated TG and placed an increased focus on HDL-C. The latter changes were made to emphasize the fact that other lipids in addition to LDL-C contribute to overall cardiovascular risk. As a result of these changes, the number of patients who would require the most aggressive lipid lowering therapy has increased from about 5 million to over 20 million (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults 2001).

Despite the availability of several, marketed HMG-CoA reductase inhibitors and the documented evidence for benefit from treatment with these agents, three points are clear. First, a large number of patients who should be treated with statins are not treated. Second, where therapy is initiated, physicians often don't titrate. And finally, despite titration, many patients who are treated are not achieving recommended treatment targets (Simpson 2001; Ballantyne 2001). Part of the reason for the latter finding is that primary care physicians who regularly treat patients with dyslipidemia tend to avoid the use of combinations of lipid-regulating drugs.

Simpson et al examined a cohort of 2,989 patients at high risk for a cardiovascular event. They found that 53% were not at goal at the start dose of therapy, and over half of these patients (53%) were not titrated to higher doses of medication. In those subjects that were titrated, 31% still did not reach goal following titration (Simpson 2001). In ACCESS (Atorvastatin Comparative Cholesterol Efficacy and Safety Study), which evaluated currently used statin therapies, many patients with coronary heart disease (CHD) failed to reach LDL-C and non-HDL-C targets even with dose titration (Figure 2).

Figure 2 **Percent of patients with CHD who achieve LDL-C and non-HDL-C target goals at week 54 (maximum titration)**



Adapted from Ballantyne 2001.

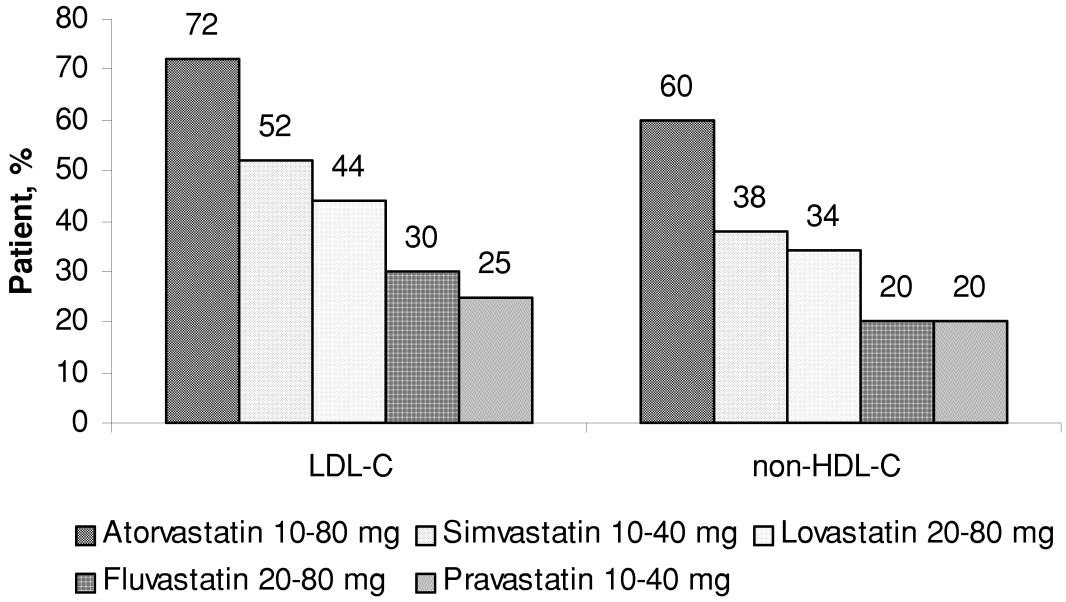
These data clearly indicate that a new statin capable of additional lipid effects (enhanced LDL-C and non-HDL-C reductions, as well as better HDL-C raising), which allows a higher percentage of patients to achieve goal at both the starting dose and following dose titration, should be beneficial to patients. The preclinical and early clinical data from Shionogi Pharmaceutical Company suggested that rosuvastatin could safely satisfy this objective.

For rosuvastatin to have clinical utility, the development program for rosuvastatin needed to meet three major objectives with regard to the proposed dose range:

- Additional lipid-modifying benefits at both the start dose and across the dose range compared to currently marketed statins.
- A low potential for drug-drug interactions.
- A safety profile similar to currently marketed statins.

The efficacy and safety data along with supporting preclinical and clinical pharmacology findings presented in this briefing document show that rosuvastatin within the proposed dose range for the desired indications meets these objectives and has an overall favorable benefit-risk profile.

Figure 2 **Percent of patients with CHD who achieve LDL-C and non-HDL-C target goals at week 54 (maximum titration)**



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2. OVERVIEW OF PRECLINICAL PHARMACOLOGY

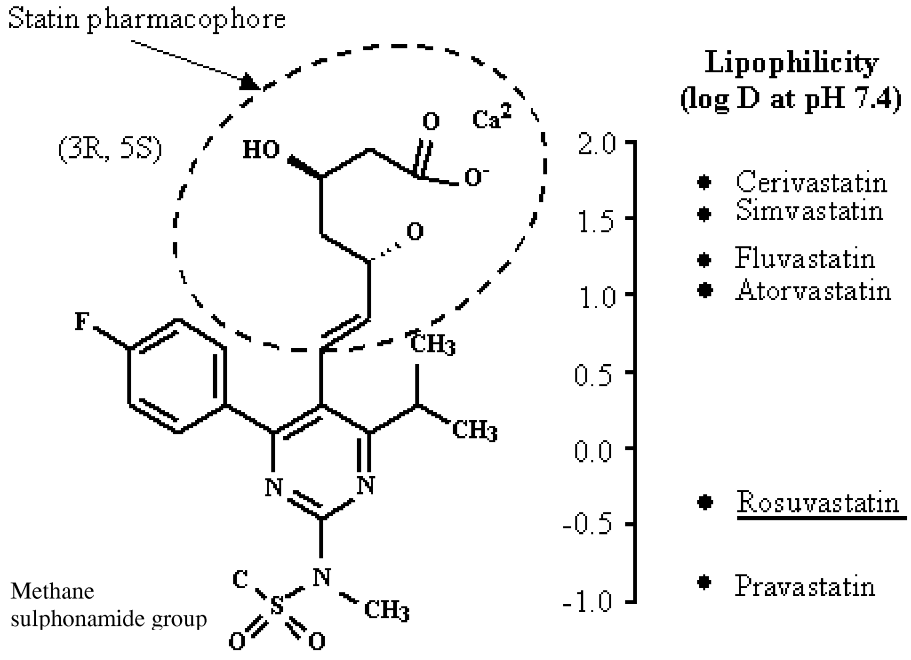
2.1 Introduction

The major pharmacodynamic effect of inhibition of cellular 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase by statins (HMG-CoA reductase inhibitors) is a reduction in cholesterol synthesis and a reduction in other products of the mevalonate pathway. The consequent homeostatic response of cells to inhibition of HMG-CoA reductase includes up-regulation of this enzyme, up-regulation of other enzymes of the sterol pathway, and enhanced expression of cell surface LDL receptors. The induction of LDL receptor expression, particularly in the liver, increases the rate of uptake of atherogenic apolipoprotein B and E-containing lipoproteins (eg, LDL and VLDL) from the circulation. Thus, the major therapeutic action of statins is a reduction in levels of circulating atherogenic lipoproteins as a result of inhibition of HMG–CoA reductase in the liver.

2.1.1 Structure and physiochemical properties

Rosuvastatin is a novel HMG-CoA reductase inhibitor. It has an HMG-like side chain (statin pharmacophore), typical of the statin class (Figure 3), which binds to the active site of HMG-CoA reductase. Rosuvastatin is a synthetic, single enantiomer (3R, 5S) formulated and administered as the calcium salt of the active hydroxy acid. The relatively hydrophilic nature of rosuvastatin is largely a result of the polar methane sulphonamide substituent on the pyrimidine ring.

Figure 3 Chemical structure and lipophilicity of rosuvastatin

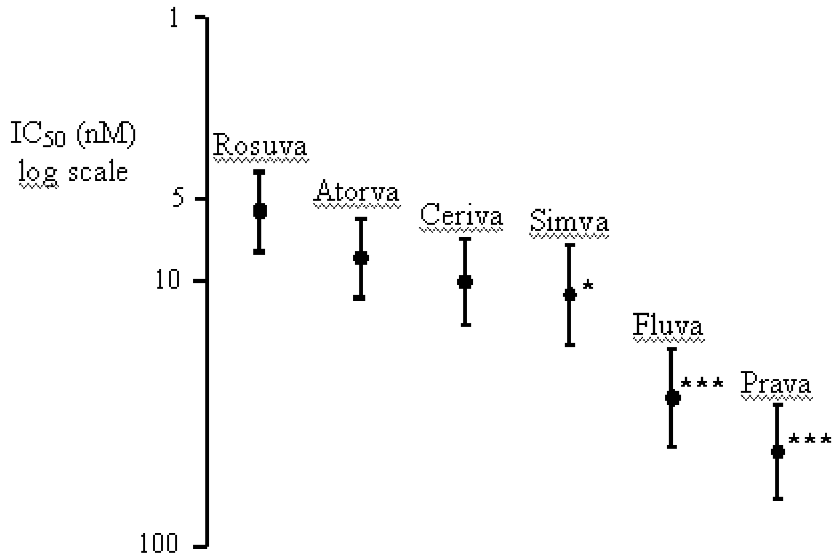


The rate of diffusion of hydrophilic compounds into cells is expected to be low and this suggests that rosuvastatin, like pravastatin, could have the potential for selective uptake into liver cells with low rate of passive uptake into non-hepatic cells, such as skeletal muscle cells. Moreover, hydrophilic molecules in general show a lower propensity for metabolism by CYP450 enzymes compared to more lipophilic molecules.

2.1.2 Inhibition of HMG-CoA reductase

Rosuvastatin is a relatively potent, reversible inhibitor of human HMG-CoA reductase compared to other statins. The data shown in Figure 4 was obtained from steady state observations of reductase inhibition in a soluble preparation of the catalytic domain of the human enzyme. The data demonstrate that rosuvastatin is numerically more potent than statins such as atorvastatin, simvastatin and cerivastatin but is about 8-fold more potent than the hydrophilic comparator, pravastatin. Like other statins, the inhibition by rosuvastatin is competitive with substrate HMG-CoA and non-competitive with co-substrate NADPH. Similar results have been obtained using the whole enzyme in human and rat hepatic microsomes.

Figure 4 Relative potencies of rosuvastatin and other statins for inhibition of human HMG-CoA reductase



The measurements are of steady state inhibition using a soluble preparation of the catalytic domain of human HMG-CoA reductase. The data are expressed as means and 95% confidence limits. Significance of differences from rosuvastatin, *p < 0.05, *** p < 0.001, (From Holdgate 2001).

Rosuva rosuvastatin; Atorva atorvastatin; Ceriva cerivastatin; Simva simvastatin; Fluva fluvastatin; Prava pravastatin

Studies of the interaction of rosuvastatin and other statins with the catalytic portion of HMG-CoA reductase have shown that in addition to the contacts with the active site, which

are common to all statins, rosuvastatin forms an additional interaction between its polar methane sulfonamide group and an arginine residue of the reductase enzyme. Overall, compared to other statins, rosuvastatin has the greatest number of binding interactions with HMG–CoA reductase. The methane sulphonamide group provides both additional binding to the enzyme and higher polarity to the molecule, explaining the unique combination of high inhibitory potency and relatively hydrophilic properties observed with rosuvastatin (Istvan and Deisenhofer 2001).

2.1.3 Inhibition of hepatic cholesterol synthesis in the liver

Rosuvastatin has also been shown to be an effective inhibitor of human HMG-CoA reductase in intact hepatocytes. Studies in freshly prepared rat hepatocytes showed that rosuvastatin inhibits cholesterol synthesis in liver cells with an IC_{50} of 0.2 nM, significantly more potent than atorvastatin, simvastatin acid, cerivastatin, fluvastatin, and pravastatin (IC_{50} values 1.2, 2.7, 3.5, 3.8, and 6.9 nM, respectively) in the range, 1.2 to 6.9 nM; Buckett 2000). Rosuvastatin did not inhibit the conversion of mevalonate to cholesterol, indicating selectivity for inhibition of HMG-CoA reductase. Additional experiments have shown that rosuvastatin has a similar high degree of inhibition of HMG-CoA reductase in primary human hepatocytes (TNO Study report).

Following intravenous administration to rats, rosuvastatin was taken up into the liver at a considerably greater rate than other organs with uptake clearance rates of 0.9, 0.2, and <0.02 mL/min/g for liver, kidney, and other tissues, respectively (Nezasa 2001).

Repeated oral administration of rosuvastatin reduced serum cholesterol levels in the dog and total and LDL-C in Cynomolgus monkeys. Moreover, rosuvastatin reduced VLDL and LDL levels and VLDL production rates in a transgenic mouse model. Finally, rosuvastatin reduced total and LDL-C in a genetically hyperlipidemic rabbit resulting in a reduction in the extent and degree of aortic atherosclerotic lesions.

2.1.4 Cell selectivity of rosuvastatin

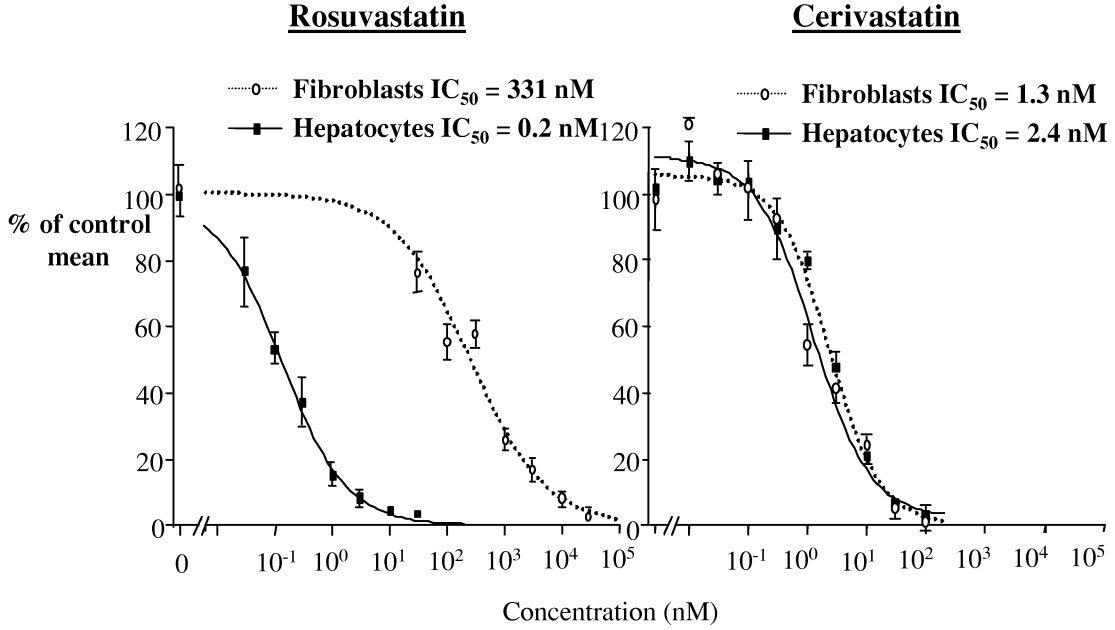
Ideally, a statin should be highly selective for inhibition in liver compared to non-liver cells, such as skeletal muscle cells. This is important given the need to minimize the potential for adverse effects in muscle. Since rosuvastatin is a relatively hydrophilic molecule, the rate of entry by diffusion into non-liver cells is expected to be low. This expectation was tested first using a rat fibroblast cell line (a non-hepatic cell line) (Figure 5).

Rosuvastatin is taken up into hepatocytes by a high affinity active transport process (Nezasa 2000a). Rosuvastatin is a substrate for the liver-specific human Organic Anion Transporter-C protein (OATP-C) with relatively high affinity (Km = 8.5 ± 1.12 μM, mean ± SEM). Cis inhibition studies with [^{3}H]-rosuvastatin showed that other statins also had affinity for OATP-C with either similar (atorvastatin) or lower affinity (simvastatin, pravastatin) than rosuvastatin, (Brown 2001).

The results (Figure 5) show that, in contrast to the high potency of effect of rosuvastatin on cholesterol synthesis in liver cells, rosuvastatin was found considerably less potent when

tested in the same manner in a rat fibroblast cell line, with a 1000-fold difference in the IC_{50} values (0.2 versus 331 nM for liver cells and fibroblasts respectively). In contrast, cerivastatin, which is a relatively lipophilic compound, was non-selective between the two cell types, (2.4 versus 1.3 nM).

Figure 5 **Effects of rosuvastatin and cerivastatin on cholesterol synthesis in rat hepatocytes and rat fibroblasts**



Monolayers of hepatocytes in serum-free medium were pre-incubated with statins for 30 min before addition of [2-14C] acetate for 3 h and assay of cholesterol synthesis. The data are shown as means with 95% confidence limits. Significance of differences from rosuvastatin, *** $p < 0.001$. (From Buckett 2000). The data presented are from representative experiments.

A range of statins was examined in the same way. Both of the relatively hydrophilic compounds, pravastatin and rosuvastatin were highly selective for their effects in liver cells compared to fibroblasts although rosuvastatin is more potent than pravastatin. Atorvastatin was intermediate and the more lipophilic compounds such as simvastatin and cerivastatin were non-selective. A number of human cell lines (fibroblasts, umbilical vein endothelial cells, smooth muscle cells and myoblasts) have also been examined and the results show similar degrees of selectivity to those determined above. In the non-hepatic cells, the rank order of potency follows the rank order of lipophilicity of the statins shown in Figure 3.

Results of studies of rosuvastatin uptake into tissues in vivo are consistent with the cell culture studies. As mentioned above, the uptake clearance rate of rosuvastatin from the circulation into the liver was considerably greater than other organs. In addition, whole body autoradiography and studies of the tissue distribution of radioactivity after oral administration of single or multiple doses of labeled rosuvastatin showed the distribution of radioactive rosuvastatin to be highly selective for liver.

2.1.5 Metabolism of rosuvastatin

No metabolism of rosuvastatin was demonstrated in a preparation of human liver microsomes or in the presence of microsomes from cells transfected with individual human P450 isoenzymes. These results suggest that rosuvastatin is a poor substrate for P450 mediated metabolism in man.

In human hepatocytes, [^{14}C]-rosuvastatin was metabolized slowly over a 48-hour period, the principal metabolite formed was N-desmethyl rosuvastatin. CYP2C9 was found to be the principal isozyme responsible for the formation of N-desmethyl rosuvastatin with some additional minor contribution by CYP2C19, CYP3A4 and CYP2D6. Incubation of rosuvastatin with probe substrates for CYP isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 in human microsomes revealed no enzyme inhibition, suggesting that it is unlikely to be an inhibitor of drugs metabolized by these enzymatic pathways.

Rosuvastatin appears to undergo relatively little metabolism by CYP P450 enzymes in vivo. Principal metabolites in all species other than Cynomolgus monkey and man appear to be derived from metabolism of the pharmacophore side chain. Such metabolites have little or no pharmacological activity. In Cynomolgus monkey rosuvastatin was the major drug-related component in the feces. Also identified in urine and/or feces was rosuvastatin triol, N-desmethyl rosuvastatin, rosuvastatin lactone and N-desmethyl rosuvastatin lactone.

2.2 Summary of rosuvastatin preclinical pharmacology

In summary, all of the effects of rosuvastatin observed in in vitro and in vivo investigations have been found to be typical of the statin class and result from the sole mechanism of inhibition of HMG-CoA reductase. The pharmacological and toxicological properties of rosuvastatin are consistent with those of other statins.

The distinctive feature of rosuvastatin compared to other statins is the relatively high potency for inhibition of HMG-CoA reductase, combined with a marked selectivity for action in liver compared to non-liver cells.

The cell selectivity observed with rosuvastatin is related to the relatively hydrophilic nature of the compound. Consistent with its relatively hydrophilic character, in vitro and in vivo studies have demonstrated that rosuvastatin undergoes minimal metabolism by the cytochrome P450 (CYP) system and, in particular, little or no metabolism by CYP 3A4, the isoenzyme implicated in a variety of drug–drug interactions.

3. OVERVIEW OF THE ROSUVASTATIN CLINICAL PROGRAM

The clinical development program for rosuvastatin was comprised of 33 Phase I trials and 27 Phase II/III trials conducted worldwide. The clinical pharmacology program (Phase I) was designed to evaluate the profile of rosuvastatin in healthy volunteers and special populations. In addition, the program would meet the important objective of evaluating whether there was a low potential for drug-drug interactions. Over 690 subjects participated in these trials.

The Phase II/III clinical program was designed to evaluate the efficacy and safety of rosuvastatin at doses up to 80 mg in a patient population representative of those requiring lipid-lowering therapy in the general population. The Phase II/III clinical program consisted of controlled trials typically ranging from 6 to 52 weeks in duration. However, in order to collect additional long-term safety data, patients were permitted to enter into long-term follow-up protocols (Trials 34, 91, 65 LTE (long term extension), and 81 LTE). Trials were designed to obtain detailed comparative efficacy and safety versus other lipid lowering agents (ie, atorvastatin, simvastatin, pravastatin, fenofibrate, and niacin) and to establish utility in the following indications:

- As an adjunct to diet to reduce elevated LDL-C, TC, ApoB, non-HDL-C, ApoB/ApoA-I, and TG levels and to increase HDL-C and ApoA-I in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb)

- As an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type IIb and IV)

- To reduce LDL-C, TC, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (eg, LDL apheresis) or if such treatments are unavailable

Overall, approximately 12,500 patients are part of the efficacy and safety database for rosuvastatin. The majority of patients recruited into the clinical trial program had Fredrickson Type IIa, IIb, or IV dyslipidemia, which are the most commonly encountered types of dyslipidemia in clinical practice. Specific trials were also performed in patients with heterozygous (Trial 30) and homozygous (Trial 54) familial hypercholesterolemia and patients with hypertriglyceridemia (Trials 29, 35, 36). In addition, several trials were designed to evaluate rosuvastatin in key patient groups such as high-risk patients (Trials 25 and 81), post-menopausal women (Trial 32) and patients with diabetes (Trial 36). There are no completed trials studying the effects of rosuvastatin on clinical outcomes.

The entry criteria for clinical trials were designed to be inclusive. For example:

- No upper age limit was defined for Phase III trials.

- The upper limit of creatinine for entry into a trial was generally 2.5 mg/dL. (The only exceptions were Trials 29, 36, and 65. The entry criterion was lowered to 1.8 mg/dL for Trials 29 and 36 due to use of combination therapy with niacin [Trial 29] and fenofibrate [Trial 36]. The entry criterion was lowered to 2.0 mg/dL because of incorporation of cerivastatin into the initial trial design [Trial 65]).

- Women of childbearing potential were permitted to enter provided they were not pregnant and used appropriate contraception.

- Patients with co-morbidities such as hypertension, cardiovascular disease, and diabetes mellitus were permitted to enter provided their conditions were stable.

The result of these design considerations was a comprehensive clinical trial database, which permitted a thorough assessment of rosuvastatin at doses up to and including 80 mg. In the following sections the clinical pharmacology, efficacy, and safety of rosuvastatin are reviewed.

4. CLINICAL PHARMACOLOGY

4.1 Overview

A total of 33 Phase I studies were conducted to define the clinical pharmacology profile of rosuvastatin. The following types of studies were conducted:

- Studies to determine the pharmacokinetic profile of rosuvastatin in healthy volunteers and special populations

- Drug interaction studies with inhibitors of CYP450 enzymes and multidrug resistance protein P-glycoprotein (PgP) transport protein (ketoconazole, erythromycin, itraconazole, fluconazole and cyclosporin). Additionally, drug interaction studies with gemfibrozil and fenofibrate, digoxin, warfarin, oral contraceptive, and antacid.

Data from the Phase I clinical pharmacology studies provided important information regarding the overall potential for drug-drug interactions with rosuvastatin.

4.2 Human pharmacokinetics

The pharmacokinetics of rosuvastatin was determined following both oral and intravenous administration. Plasma clearance of rosuvastatin was 48.9 L/h after single intravenous administration of 8 mg rosuvastatin. Renal clearance accounts for approximately 28% (13.6 L/h) of total clearance. Since the observed renal clearance exceeds the maximum value possible by glomerular filtration alone it is assumed that active tubular secretion plays an important role in rosuvastatin elimination. Elimination via the liver is likely responsible for 72% of rosuvastatin clearance. The mean volume of distribution at steady-state was estimated as 134 L.

Rosuvastatin is administered orally in the active form; peak plasma concentrations are achieved 3 to 5 hours following administration. Both peak concentration (Cmax) and area under the plasma concentration-time curve (AUC) increased in approximate proportion to rosuvastatin dose. Post-peak plasma concentrations decline bi-exponentially with mean terminal half-lives ranging from 16 to 20 hours. The absolute bioavailability of rosuvastatin is 20.1%. Steady-state rosuvastatin plasma concentrations are predictable from single-dose data; accumulation in plasma after multiple daily dosing is minimal.

In man, in-vitro protein binding of rosuvastatin was 88% and was independent of plasma concentration over the range of 10 to 150 ng/mL. The major binding protein was albumin and the binding was reversible. Blood cell binding was 35% across the concentration range of 10 to 150 ng/mL.

One hundred percent of a 20-mg oral dose of [^{14}C]-rosuvastatin was recovered in excreta: 90% in feces and 10% in urine. Rosuvastatin was the principle drug-derived component in both urine and feces. In plasma, rosuvastatin was the principal circulating drug-related species and was responsible for all circulating active HMG-CoA reductase inhibitor activity, and over 90% of circulating total HMG-CoA reductase inhibitor activity.

Rosuvastatin is not extensively metabolized; approximately 10% of a radiolabeled dose is recovered as metabolites. The major metabolite N-desmethyl rosuvastatin is formed principally by cytochrome P450 2C9. In vitro studies have demonstrated N-desmethyl rosuvastatin to have approximately one-sixth to one-half the HMG-CoA reductase inhibitory activity of rosuvastatin. Rosuvastatin lactone, an inactive metabolite, was also present in plasma and excreta.

Table 2 summarizes the single-dose pharmacokinetics of rosuvastatin at doses of 5 to 80 mg.

Table 2 Pharmacokinetic parameters of rosuvastatin following single oral dose administration of rosuvastatin 5, 10, 20, 40 and 80 mg to healthy volunteers

Dose (mg)	N	C_{max} (ng/mL) gmean (CV%)	t_{max} (h) Median (range)	AUC (ng.h/ml) gmean (CV%)	$t_{1/2}$ (h) Mean (SD)
5	4	3.12 (42.2)	5.0 (5.0 – 6.0)	25.0 (25.5)	NC
10	34	4.79 (56.7)	5.0 (1.0 – 6.0)	38.7 (60.7)	NC
20	121	11.0 (71.8)	4.5 (0.5 – 6.0)	99.4 (62.9)	16.4 (4.15)
40	75	17.5 (69.2)	4.5 (1.0 – 6.0)	167 (56.6)	20.3 (8.16)
80	176	51.5 (66.2)	3.5 (0.5 – 6.0	399 (53.6)	17.4 (5.02)

NC not calculable; CV coefficient of variation; SD standard deviation; h hour; N number of subjects; gmean geometric mean.

4.3 Special populations

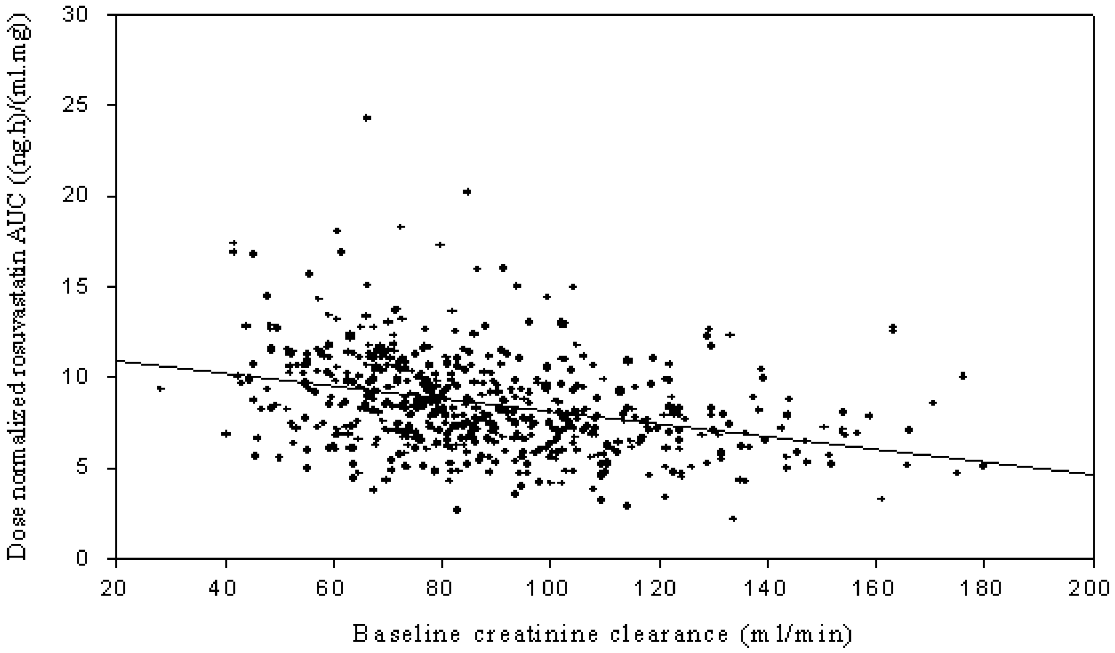
4.3.1 Subjects with renal impairment

A Phase I study in 22 subjects with varying degrees of renal impairment indicated a 3-fold increase in Cmax and AUC in subjects with severe renal impairment (creatinine clearance [CrCl]<30 mL/min) compared with subjects with normal renal function (CrCl ≥80 mL/min). Post-hoc Bayesian estimates of steady-state rosuvastatin AUC in 386 subjects with dyslipidemia were derived from a population pharmacokinetic analysis incorporating data from 5 trials. Predicted exposure was plotted as a function of estimated creatinine clearance

(Figure 6) and indicates that mild to moderate renal impairment is not an important determinant of rosuvastatin exposure in subjects with dyslipidemia.

Because of the 3-fold increase in exposure in patients with severe renal impairment, the dose of rosuvastatin should be limited to 10 mg in this population.

Figure 6 **Predicted dose-normalized AUC at steady state versus estimated creatinine clearance for subjects with dyslipidemia receiving from 1- to 80-mg doses of rosuvastatin (Studies 8, 23, 33, 34 substudy, and 35)**



Doses included are rosuvastatin 1 mg to 80 mg. Baseline creatinine clearance was calculated using the Cockroft-Gault formula.

Dose-normalized AUC = -0.03517*baseline creatinine clearance (mL/min) + 11.63395. (p,0.0001, adjusted R2=12%)

4.3.2 Subjects with hepatic impairment

Results from a Phase I study demonstrated no statistically significant differences in rosuvastatin Cmax and AUC in subjects with mild (Childs-Pugh A classification) or moderate (Childs-Pugh B classification) hepatic impairment compared to subjects with normal hepatic function. However, two subjects with the highest score in the Childs- Pugh B group had the highest values for Cmax and $AUC_{(0-24)}$. These observations suggest that subjects with mild liver impairment will have a similar pharmacokinetic profile compared to normal subjects but subjects with more severe hepatic impairment may have significant increases in rosuvastatin plasma concentrations.

4.3.3 Effects of age and gender

Results from Phase I studies and a population pharmacokinetic analysis demonstrate a lack of a significant effect of age or gender on rosuvastatin pharmacokinetics

4.3.4 Ethnicity

No differences in rosuvastatin pharmacokinetics were observed among Caucasian, black, or Hispanic subjects in the population pharmacokinetic analysis. Phase I studies conducted in healthy Japanese volunteers living in Japan indicated an approximate 2-fold increase in rosuvastatin Cmax and $AUC_{(0-24)}$ compared to similar studies conducted in Caucasian volunteers in Europe and that the absolute bioavailability in Japanese subjects from Japan was 29% compared to 20% in Caucasians. A population pharmacokinetic analysis that incorporated race as a categorical variable also demonstrated an approximate 2-fold increase in plasma concentrations in Asian subjects, most of whom were Japanese subjects residing in Japan.

4.3.5 Pediatric studies

A Phase I study conducted in subjects 10 to 17 years of age with heterozygous familial hypercholesterolemia demonstrated that the pharmacokinetic profile of rosuvastatin in this population was similar to that in adult volunteers.

4.4 Rosuvastatin drug-drug interactions

In vitro studies strongly indicated that rosuvastatin was unlikely to interact significantly with CYP P450 enzymes. These in vitro studies were substantiated by drug interaction studies with CYP3A4 inhibitors and an inhibitor of CYP2C9. Because interactions at transport proteins are also possible, the effects of inhibitors of the PgP transporter were examined. Drug interaction studies were also conducted with cyclosporin and gemfibrozil as previous published studies had documented a pharmacokinetic interaction between these drugs and other statins. Other drug interaction studies included fenofibrate, digoxin, warfarin, an oral contraceptive, and an antacid.

4.4.1 Cytochrome P450 and PgP inhibitors

These studies were powered to determine if the 90% CI for the ratio of rosuvastatin AUC during inhibitor treatment as compared to placebo treatment fell within the margins of 0.7 to 1.43. These margins were considered to be the relevant margins for assessing the clinical significance of any drug interaction observed.

Table 3 summarizes the results of rosuvastatin drug interaction studies performed using cytochrome P450 and PgP inhibitors.

Table 3 **Summary of results of rosuvastatin drug interaction studies performed with CYP P450 and PgP inhibitors**

Interacting drug	Characteristics	Rosuvastatin AUC ratio[a]	90% CI
Ketoconazole	3A4 and PgP inhibitor	1.02	0.84 to 1.23
Erythromycin	3A4 and PgP inhibitor	0.80	0.68 to 0.94
Itraconazole	3A4 and PgP inhibitor	1.28	1.15 to 1.43
Fluconazole	2C9 and 2C19 inhibitor	1.14	0.97 to 1.34

[a] Ratio of AUC with interacting drug to AUC with placebo.
CI confidence interval; PgP P-glycoprotein

The lack of an increase in rosuvastatin AUC in the presence of ketoconazole and erythromycin indicates that CYP3A4 and PgP do not contribute to the disposition of rosuvastatin. The reduction of rosuvastatin AUC with erythromycin may reflect an increase in gut motility produced by erythromycin. The modest increase in rosuvastatin AUC produced by itraconazole is unlikely to be due to inhibition of CYP3A4 or PgP since ketoconazole and erythromycin do not increase rosuvastatin AUC. The mechanism for this interaction may be due to an interaction of itraconazole with an unknown transporter contributing to rosuvastatin disposition. The lack of interaction with fluconazole indicated that CYP2C9 does not contribute significantly to rosuvastatin clearance.

A Phase I study in healthy volunteers demonstrated that rosuvastatin had no significant effect on digoxin pharmacokinetics. This result provides further evidence for a lack of interaction of rosuvastatin with the transport protein, PgP.

4.4.2 Cyclosporin

Drug interaction studies with other statins in transplant patients on stable cyclosporin dosing regimens have demonstrated significant increases in statin plasma concentrations (Figure 7).

Figure 7 **AUC ratio of cyclosporin treated patients versus values reported in historical volunteer controls**

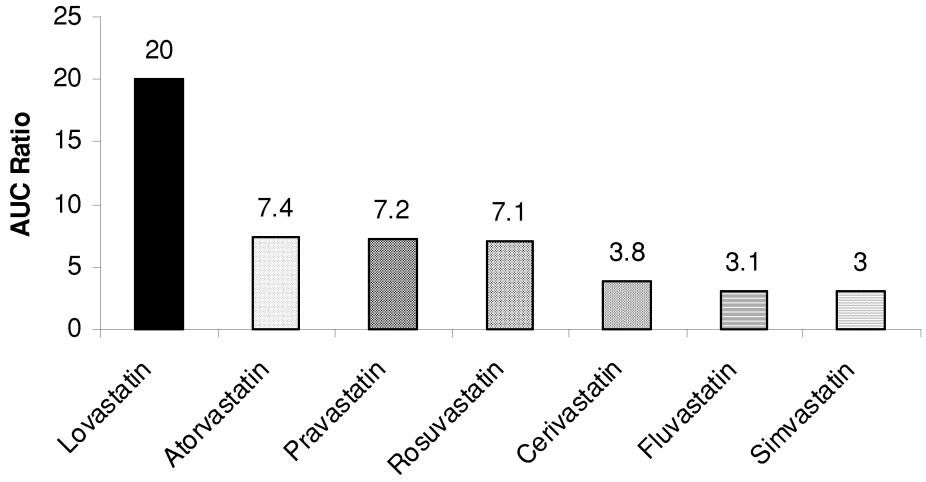


Figure derived from Arnadottir 1993; Asberg 2001; Muck 1999, Olbrict 1997, and Park 2001.

The effect of cyclosporin on rosuvastatin pharmacokinetics was investigated in stable cardiac transplant patients. Compared to historical volunteer controls cyclosporin treatment increased rosuvastatin AUC by 7.1-fold.

The mechanism of the cyclosporin-rosuvastatin interaction is not known, but is unlikely to involve CYP3A4 or PgP since ketoconazole and erythromycin do not increase rosuvastatin plasma concentrations. In vitro studies with cells transfected with the hepatic influx organic anion transporter (OATP-C) have demonstrated that cyclosporin competitively inhibits rosuvastatin uptake by these cells. All statins are ligands for this transporter. Inhibition of this transporter by cyclosporin may make an important contribution to the cyclosporin-statin interaction. As a result of the interaction with cyclosporine, a 5-mg dose of rosuvastatin will be made available. The dose of rosuvastatin in patients receiving cyclosporine should be limited to 5 mg.

4.4.3 Gemfibrozil and fenofibrates

Previous drug interaction studies between gemfibrozil and cerivastatin, simvastatin, and lovastatin demonstrated significant increases in statin plasma concentrations particularly with cerivastatin (Figure 8).

Figure 8 Effect of gemfibrozil on statin plasma concentrations

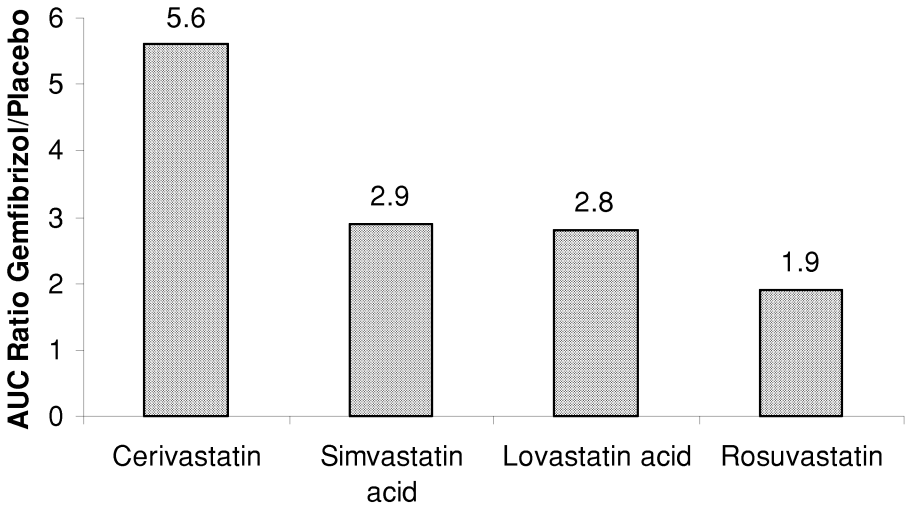


Figure derived from Backman 2000, Backman 2002, Kryklund 2001.

The effect of gemfibrozil on the pharmacokinetics of rosuvastatin was assessed in healthy volunteers. Rosuvastatin AUC was 1.9-fold higher in the presence of gemfibrozil as compared to placebo. The AUC increase was similar for simvastatin acid (2.9-fold) and lovastatin acid (2.8-fold), but less than that for cerivastatin (5.6-fold). The mechanism of the pharmacokinetic interaction between gemfibrozil and statins has not been well defined in humans. Based on the pharmacokinetic interaction with gemfibrozil and the well-known risks of myopathy when gemfibrozil is used in combination with statins, the dose of rosuvastatin should be limited to 10 mg in patients receiving gemfibrozil.

Fenofibrate had no effect on rosuvastatin pharmacokinetics in healthy volunteers.

4.4.4 Warfarin

A Phase I pharmacokinetic and pharmacodynamic study was conducted in healthy volunteers. Compared to placebo, rosuvastatin increased maximal international normalized ratio (INR) by 19% and area under the INR (AU-INR) curve by 10%. The pharmacokinetic profile for the S and R enantiomers of warfarin was unchanged.

The effect of rosuvastatin on the INR of patients on stable warfarin anticoagulation was also studied. Rosuvastatin was administered to patients on stable warfarin dosing regimens (INR 2 to 3 range). Several patients had INR values exceed 4 following treatment with rosuvastatin. The mechanism of this interaction is unknown. Such increases are known to occur with other statins (Lin 1999).

In patients taking coumarin anti-coagulants, the INR should be determined before and following initiation of rosuvastatin therapy or dose titration and frequently enough during early therapy to ensure no significant alteration of INR occurs. Once a stable INR has been documented, it can be monitored at intervals usually recommend for patients on coumarin anti-coagulants. In the clinical development program, 206 patients received concomitant rosuvastatin and oral anticoagulant therapy. A review of the data shows that the two drugs can be safely co-prescribed provided that INR is monitored as described.

4.4.5 Oral contraceptive steroids

A Phase I drug interaction study was conducted in healthy female volunteers taking a commonly prescribed oral contraceptive (triorthcyclen containing ethinyl estradiol and the progestin norgestimate) to assess the effect of rosuvastatin on the plasma concentrations of the steroids. Rosuvastatin increased the plasma concentration of ethinyl estradiol and norgestrel (the active metabolite of norgestimate) 25 to 35 % respectively. The mechanism for the increase in these plasma concentrations is unknown, but is unlikely to involve CYP3A4 since rosuvastatin is not an inhibitor of this enzyme and this enzyme is responsible for the metabolism of the contraceptive steroids.

4.4.6 Antacid

Co-administration of rosuvastatin (40mg) with Co-magaldrox (20 ml, a magnesium hydroxide and aluminum hydroxide combination) reduced rosuvastatin Cmax and AUC by 50%.

4.5 Summary of rosuvastatin clinical pharmacology

Rosuvastatin demonstrates linear kinetics over the dose range 5 to 80 mg. The terminal $t_{1/2}$ is approximately 20 hours.

Subjects with severe renal impairment have a 3-fold increase in Cmax and AUC compared to normal subjects whereas subjects with mild and moderate renal impairment have Cmax and AUC values similar to normal subjects. Subjects with mild hepatic impairment have Cmax and AUC values similar to normal subjects; subjects with more severe liver impairment may have higher systemic exposure to rosuvastatin.

Japanese subjects living in Japan have an approximate 2 fold increase in Cmax and AUC compared to Caucasian subjects.

Rosuvastatin does not interact to a clinically significant extent with CYP3A4, 2C9, 2C19, and the PgP transporter. Additionally, rosuvastatin did not affect the disposition of digoxin. The lack of interaction with digoxin demonstrates a lack of interaction with the PgP transporter. Fenofibrate had no effect on rosuvastatin plasma concentrations. Clinically significant interactions occurred with cyclosporin and gemfibrozil. The mechanism for these interactions is unknown but may involve transporter proteins other than PgP. Rosuvastatin enhanced the anticoagulant effect of warfarin by an unknown pharmacodynamic mechanism. Rosuvastatin produced modest increases in the plasma concentrations of ethinyl estradiol and norgestrel.

5. EFFICACY OF ROSUVASTATIN IN THE TREATMENT OF DYSPLIPIDEMIAS

5.1 Introduction

As discussed in Section 1.2, the NCEP ATP III guidelines identified the need for more aggressive lipid target goals for patients, particularly for those with or at high risk of cardiovascular events. The preclinical and clinical pharmacology profile, along with initial dose-ranging data from a Phase II study, suggested that rosuvastatin could safely deliver greater efficacy with regard to lowering LDL-C and non-HDL-C, as well as raising HDL-C, compared to other marketed statins without additional safety risks. Thus, a key objective of the rosuvastatin development program was to determine whether rosuvastatin provided additional lipid-modifying benefits at both the start dose and across the dose range compared to currently marketed statins.

5.2 Overview of efficacy program

Of the 27 Phase II/III trials in the rosuvastatin clinical program presented in this briefing document, 24 trials were performed to evaluate the efficacy of rosuvastatin. Key patient populations in which efficacy was evaluated included patients with heterozygous familial and nonfamilial hypercholesterolemia and mixed dyslipidemia, patients with hypertriglyceridemia, and patients with homozygous familial hypercholesterolemia. Comparative trials of rosuvastatin with other statins focused primarily on patients with Type IIa and IIb dyslipidemia. All comparative trials were randomized.

Following an extensive development program, the efficacy data from controlled clinical trials showed that rosuvastatin at a dose range of 10 mg to 40 mg was more efficacious than atorvastatin (10 mg to 80 mg), simvastatin (10 mg to 80 mg), and pravastatin (10 mg to 40 mg) in reducing LDL-C, non-HDL-C, and important lipid ratios such as ApoB/ApoA-1. In addition, treatment with rosuvastatin raised HDL-C levels more than treatment with atorvastatin. The effects seen on lipid levels following rosuvastatin treatment translated into a high percentage of patients achieving NCEP ATP II and III goals.

In this section, the efficacy data supporting a 10-mg to 40-mg dose range for rosuvastatin in the general population of patients with dyslipidemias are presented. Supporting data includes clinical trials designed to evaluate comparative efficacy at the 10-mg start dose with commonly prescribed starting doses of other statins, as well as comparative efficacy to other statins across dose ranges. This section concludes with a brief overview of the efficacy of rosuvastatin in patients with familial forms of hypercholesterolemia and in patients with hypertriglyceridemia.

All efficacy analyses were based on Intention-to Treat (ITT) populations, which included all subjects in clinical trials who had a baseline and at least one post-baseline lipid measurement. For analysis of lipids, the last observed values were carried forward (LOCF) for subjects who withdrew early. Least square means are presented.

- Percent change from baseline LDL-C was analyzed using Analysis of Variance for trial 8/23, adjusting for baseline LDL-C and dose.

- The primary analysis of Trial 33 was a comparison of the dose-response curves using Analysis of Covariance, adjusting for baseline LDL-C, center, treatment, and log dose.

- In the pooled data (Trials 24 to 26; Trials 27 to 28) the comparisons of percent change LDL-C used Analysis of Variance, adjusting for trial and treatment.

- Comparisons of dose-response in Trial 65 were done using Analysis of Covariance, adjusting for baseline LDL-C, treatment, log dose, and center. Separate comparisons were done for each of the comparator statins. There were also pair-wise comparisons done between dose groups in trial 65. These were done using Analysis of Variance, adjusting for treatment dose and center. The alpha level used to determine statistical significance was 0.002, representing a Bonferroni adjustment for the pre-specified comparisons.

LOCF imputation was used in the primary ITT analyses because it was commonly used in previous trials of currently marketed statins. Adapting trial designs and statistical methods from published trials allows context for interpretation of results from new trials. The potential for LOCF to introduce bias into analyses is small, because statins' effect on LDL-C is seen in 2 to 4 weeks; and the treatment effect is maintained. Further, the frequency of missing data at the primary endpoints of trials typically was low, and it was balanced between treatment groups.

When regression analyses across the dose range were performed, all doses in the trial were included in the analysis, in order to increase the precision of the estimate of the dose-response curve.

Percentages of patients reaching NCEP goal were analyzed in the pooled trials using logistic regression, adjusting for trial, treatment group, baseline LDL-C, and risk category. Results are shown using ATP III guidelines. In trials that were conducted before NCEP ATP III guidelines were available, results from only the fixed dose periods were reanalyzed using ATP III guidelines.

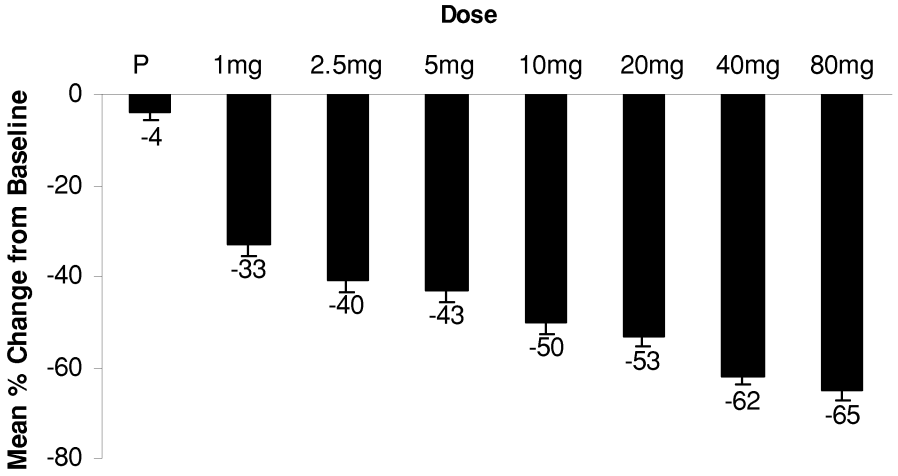
Although the data for all trials are not presented within this briefing document, the results of the trials described are representative of the overall results observed with rosuvastatin in the development program. The information presented supports a rosuvastatin start dose of 10 mg for patients with Fredrickson Types IIa, IIb, and IV dyslipidemia, and a dose range up to 40 mg. In patients with severe hypercholesterolemia (LDL-C >190 mg/dL) and aggressive LDL-C targets a 20-mg start dose is optional. In patients with homozygous familial hypercholesterolemia, the recommended start dose is 20 mg.

5.3 Selection of the rosuvastatin dose range for the general population of patients with Type IIa and IIb dyslipidemia

The initial dose ranging efficacy data was derived from a pool of two Phase II trials (Trials 8 and 23). Both trials were multicenter, double-blind, placebo-controlled, parallel group designs that included a 6-week dietary lead-in period and a 6-week treatment period. Trial 8 randomized patients to rosuvastatin (1, 2.5, 5, 10, 20 or 40 mg), placebo, or atorvastatin (10 or 80 mg [open-label]); trial 23 randomized patients to rosuvastatin (40 or 80 mg) or placebo. These studies were conducted at the same centers and used the same investigators; however, patients from Trial 8 were not permitted in Trial 23. The primary endpoint for both trials was the change from baseline to week 6 in LDL-C.

At baseline, the groups were well matched. The mean age was 56 years (range 24 to 70) and 62% of patients were male. The mean baseline LDL-C levels ranged from 185 mg/dL to 194 mg/dL, and the mean baseline HDL-C levels from 49 mg/dL to 55 mg/dL. The results of the pooled efficacy analysis are shown in Figure 9.

Figure 9 **Comparison of doses of rosuvastatin in % change from baseline in LDL-C at Week 6 in patients with Type IIa/IIb dyslipidemia: Trials 8 and 23 pooled**



p <0.001 for all doses compared to placebo; P placebo; N = All patients in ITT population, as follows: placebo, N = 31, rosuvastatin doses: 1.0 mg, N = 14; 2.5 mg, N = 15; 5 mg, N = 18; 10 mg, N = 17; 20 mg, N = 17; 40 mg, N = 34; and 80 mg, N = 31.

The data shows that rosuvastatin was highly efficacious with mean LDL-C reductions up to 65%. Similar to the effects on LDL-C, rosuvastatin was highly effective in modifying other lipid parameters. Compared to placebo, statistically significant dose-dependent reductions in TC, ApoB, non-HDL-C and the ratios LDL-C/HDL-C, TC/HDL-C, non-HDL-C/HDL-C, and ApoB/ApoA-I were also observed. Increases in HDL-C at all doses were seen. As with other statins, no dose-dependent relationship was identified. For benchmarking purposes two open-

label atorvastatin doses were included in Trial 8, which produced LDL-C reductions of 43% and 54% at the 10 mg and 80 mg doses, respectively. Based on the results of this study, two potential start doses were selected for study in Phase III, 5 mg and 10 mg. The maximum rosuvastatin dose studied in Phase III was 80 mg.

Following completion of the Phase III program, a benefit-risk assessment of the various doses of rosuvastatin indicated that a 10-mg to 40-mg dose range was appropriate for the general population of patients with dyslipidemias. Based on pooled data from 5 randomized clinical trials in patients with Type IIa and IIb hypercholesterolemia (Trials 24 to 28), the 10-mg dose provided additional lipid benefits over the 5-mg dose (Table 4), and brought a higher percentage of patients to NCEP ATP III targets (79.8% versus 68.3% respectively).

Table 4 Comparison of rosuvastatin 5 and 10 mg in % change from baseline to Week 12 in lipids in Type IIa/IIb patients: Trials 24 to 28 pooled

Efficacy endpoint	Rosuvastatin 5 mg (N=630)			Rosuvastatin 10 mg (N=615)		
	Baseline (mg/dL)	Final (mg/dL)	% change from baseline (SE)[a]	Baseline (mg/dL)	Final (mg/dL)	% change from baseline (SE)[a]
LDL-C	188	110	-41.4 (0.5)	186	98	-47.2 (0.6)
TC	275	194	-29.4 (0.4)	272	181	-33.4 (0.4)
HDL-C	51	55	7.7 (0.5)	51	55	9.0 (0.5)
TG	179	146	-15.8 (1.1)	174	137	-19.6 (1.0)
Non-HDL-C	224	140	-37.8 (0.5)	221	125	-43.1 (0.5)

[a] Main analysis of LOCF data from the ITT population.
Note: No statistical analysis was performed.
N All patients in the ITT population; SE standard error

Importantly, no differences in safety were observed between the 5 mg and 10 mg doses (See Section 6), and the safety profile of the 10 mg dose was similar to the safety profile of starting doses of other statins evaluated in the program. The 40 mg maximum dose was chosen because the 10 mg to 40 mg dose range for rosuvastatin was superior to atorvastatin (10 mg to 80 mg), simvastatin (10 mg to 80 mg) and pravastatin (10 to 40 mg) in modifying key lipids and bringing patients to NCEP lipid targets. The 80-mg dose was not selected as the maximum dose in response to an evaluation of the benefit-risk of this dose which would limit its use in the general dyslipidemic population.

The information that follows demonstrates the benefits of the rosuvastatin 10-mg to 40-mg dose range relative to the dose ranges of other statins.

5.4 Comparison of the rosuvastatin 10 mg start dose to starting doses of atorvastatin, simvastatin, and pravastatin

5.4.1 Comparisons to atorvastatin

A key attribute of the starting dose of a new HMG-CoA reductase inhibitor is that it provides additional lipid modifying benefits, which allow more patients to achieve lipid guidelines compared to start dose(s) of other statins. With this in mind, the efficacy of rosuvastatin 10 mg was compared to atorvastatin 10 mg, simvastatin 20 mg, and pravastatin 20 mg in several trials.

Table 5 shows the pooled lipid results from three trials (Trials 24 to 26) which evaluated the efficacy of rosuvastatin 10 mg compared to atorvastatin 10 mg in patients with Type IIa and IIb hypercholesterolemia. All studies were multicenter, double-blind, randomized and included a 6-week dietary lead-in period followed by at least 12 weeks of active treatment at the start dose. The baseline demographics for the two treatment groups were similar. The mean age was 59 years (range 23 to 88), 55% percent of patients were male, and over 90% of patients in each group were Caucasian.

Table 5 **Rosuvastatin versus atorvastatin in % change from baseline to Week 12 in lipids in patients with Type IIa/IIb dyslipidemia: Trials 24 to 26 pooled**

Efficacy endpoint[a]	Rosuvastatin 10 mg (N=389)			Atorvastatin 10 mg (N=393)		
	Baseline	Final	Lsmean % change (SE)	Baseline	Final	Lsmean % change (SE)
LDL-C	185	99	-46.7 (0.7)[b]	187	119	-36.4 (0.7)
TC	271	182	-33.0 (0.5)[b]	274	200	-26.7 (0.5)
HDL-C	50.8	55.2	8.9 (0.6)[b]	50.4	53	5.5 (0.6)
TG	176	139	-19.2 (1.3)	181	145	-17.6 (1.3)
Non-HDL-C	221	127	-42.6 (0.6)[b]	223	147	-33.9 (0.6)

[a] Main analysis of LOCF data from the ITT population

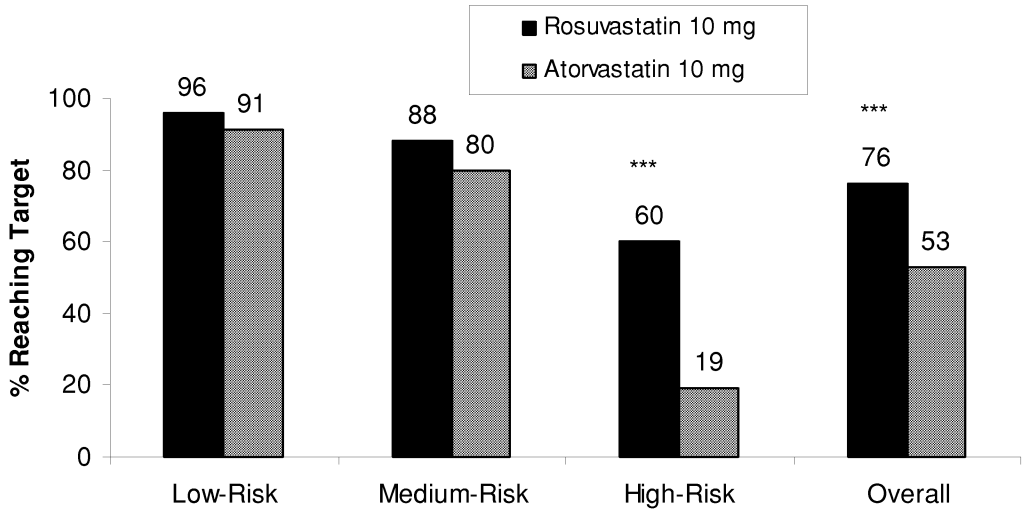
[b] $p<0.001$ versus atorvastatin.

N All patients in ITT population in the pool; For Trials 24, 25, 26 N=128, 127, 135 (rosuvastatin 5 mg), N=129, 128, 132 (rosuvastatin 10 mg), N=127, 127, 139 (atorvastatin 10 mg); SE standard error.

The data show that rosuvastatin provided significantly greater reductions in LDL-C and non-HDL-C and greater increases in HDL-C compared to atorvastatin. These parameters are critical parameters identified in the current NCEP ATP III guidelines for directing patient management. In addition to these findings rosuvastatin-treated patients demonstrated significant improvements in all lipid ratios compared to atorvastatin, including ApoB/ApoA-1.

As shown in Figure 10, the benefits on LDL-C translated into significantly more patients achieving NCEP ATP III goals at the 10-mg dose compared to atorvastatin 10 mg.

Figure 10 **Rosuvastatin 10 mg versus atorvastatin 10 mg in reaching NCEP ATP III LDL-C targets at Week 12 in patients with Type IIa/IIb dyslipidemia: Trials 24 to 26 pooled**

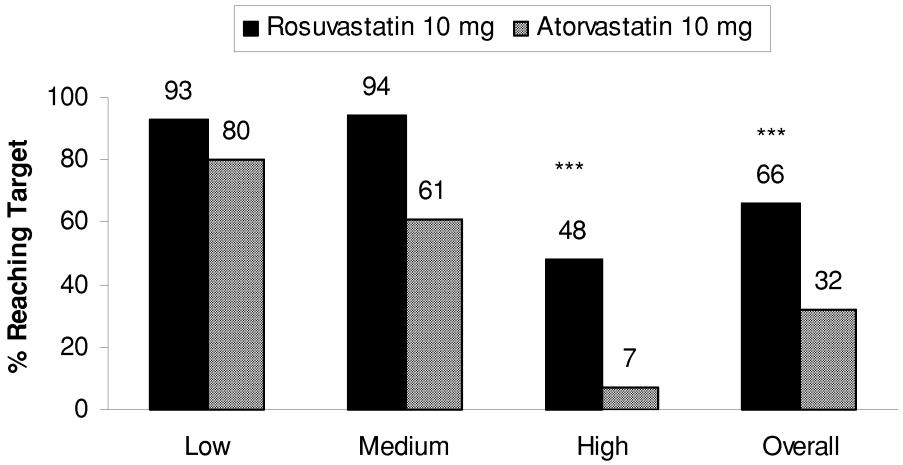


NCEP ATP III LDL-C treatment goals of risk categories: Low <160 mg/dL; Medium <130 mg/dL; High <100 mg/dL.
Main analysis of last observation carried forward (LOCF) data from the intent-to-treat (ITT) population.
***p<0.001 versus atorvastatin.
N = patients: rosuvastatin 10 mg: 121, 69, 199, and 389 patients (low, medium high, and overall, respectively); atorvastatin 10 mg: 116, 88, 189, and 393 patients (low, medium, high, and overall, respectively)

Overall, 76% of patients receiving rosuvastatin 10 mg achieved NCEP ATP III LDL-C target levels, compared to 53% on atorvastatin 10 mg. In the high-risk category patients with the most aggressive LDL-C target (LDL-C goal <100 mg/dL) the difference in the percentage of patients achieving their goal was more pronounced for subjects receiving rosuvastatin 10 mg than atorvastatin 10 mg.

The percentage of patients with baseline values of TG ≥200 mg/dL who achieved NCEP ATP III LDL-C and non-HDL-C target goals is shown in Figure 11.

Figure 11 **Rosuvastatin 10 mg versus atorvastatin 10 mg in reaching NCEP ATP III non-HDL-C target goals at Week 12 in patients with Type IIa/IIb dyslipidemia: Trials 24 to 26 pooled**



NCEP ATP III LDL-C treatment goals of risk categories: Low <160 mg/dL; Medium <130 mg/dL; High <100 mg/dL. Patients had baseline TG ≥200 mg/dL and reached LDL-C goal.
***p<0.001 versus atorvastatin.
N= patients: rosuvastatin 10 mg: 20, 18, 73, 121 patients (low, medium high, and all, respectively) and atorvastatin 10 mg: 20, 33, 76, and 129 patients (low, medium, high, and all, respectively)

Overall, 66% of patients receiving rosuvastatin 10 mg achieved NCEP ATP III non-HDL-C target levels, compared to 32% on atorvastatin 10 mg. In the high-risk category patients with the most aggressive LDL-C target (LDL-C goal <100 mg/dL and non-HDL-C goal <130 mg/dL) the difference in the percentage of patients achieving their goal was more pronounced for subjects receiving rosuvastatin 10 mg than atorvastatin 10 mg.

Another important piece of evidence regarding the importance of having patients achieve NCEP ATP III targets at the start dose is the fact that higher starting doses of other HMG-CoA reductase inhibitors were approved over the past couple years. Although early studies comparing rosuvastatin with atorvastatin did not evaluate the relative benefits of rosuvastatin 10 mg compared to atorvastatin 20 mg, a later trial (Trial 65) did permit a comparison. Trial 65 enrolled a patient population similar to those in Trials 24 to 26. The results of Trial 65 are as follows:

- Rosuvastatin 10 mg lowered LDL-C by 46%, non-HDL-C by 42%, and ApoB/ApoA-1 by 41% compared with the effects of atorvastatin 20 mg on these same parameters (43%, 40%, and 38%, respectively)

- Rosuvastatin 10 mg raised HDL-C by 7.6% compared with 4.8% for atorvastatin 20 mg

The results were not statistically different. With regard to achievement of NCEP ATP III LDL-C goals, overall 82% of patients achieved target with rosuvastatin 10 mg compared to 75% with atorvastatin 20 mg.

5.4.2 Comparisons to simvastatin and pravastatin

Two randomized trials (Trials 27 and 28) were designed in a manner similar to Trials 24 to 26 to allow for pooled comparisons between rosuvastatin 10 mg and simvastatin 20 mg and pravastatin 20 mg. The results of 12 weeks of double-blind treatment are shown in Table 6. At baseline the treatment groups were similar with regard to age (mean age 59, range 19 to 86), gender (57% female), and race (92% Caucasian).

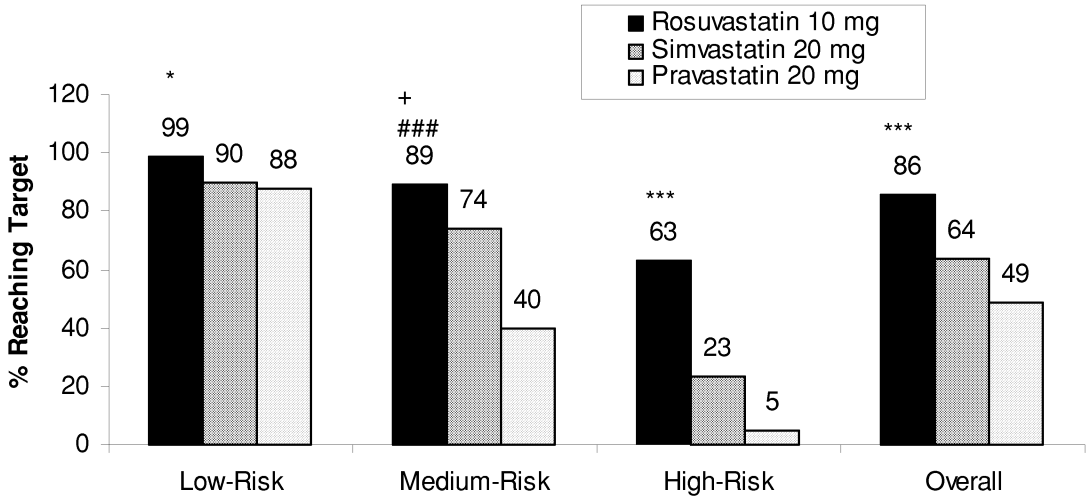
Table 6 **Rosuvastatin versus pravastatin or simvastatin in % change from baseline to Week 12 in lipids in patients with Type IIa/IIb dyslipidemia: Trials 27 to 28 pooled**

Efficacy endpoint[a]	Rosuvastatin 10 mg (N=226)			Pravastatin 20 mg (N=252)			Simvastatin 20 mg (N=249)		
	Baseline	Final	Lsmean % change (SE)	Baseline	Final	Lsmean % change (SE)	Baseline	Final	Lsmean % change (SE)
LDL-C	187	97	-48.1 (0.9)[b]	189	138	-27.1 (0.9)	188	121	-35.7 (0.9)
TC	272	179	-34.0 (0.7)[b]	275	221	-19.2 (0.6)	274	205	-25.1 (0.6)
HDL-C	51	56	9.1 (0.8)[d]	52	55	6.2 (0.8)	53	56	6.2 (0.8)
TG	170	134	-20.2 (1.9)[c]	169	145	-12.4 (1.8)	166	143	-12.2 (1.8)
Non-HDL-C	221	123	-44.0 (0.8)[b]	222	167	-25.0 (0.8)	221	149	-32.5 (0.8)

[a] Main analysis of LOCF data from the ITT population.
[b] $p<0.001$ versus pravastatin and simvastatin
[c] $p<0.01$ versus pravastatin and $p<0.01$ versus simvastatin
[d] $p<0.05$ versus pravastatin and $p<0.05$ versus simvastatin
LDL-C low-density lipoprotein; TC total cholesterol; HDL-C high-density lipoprotein cholesterol; TG triglycerides; lsmean least square mean; SE standard error

As shown, rosuvastatin 10 mg produced statistically significantly greater reductions in LDL-C than pravastatin 20 mg and simvastatin 20 mg. Additionally, rosuvastatin 10 mg produced statistically significantly greater reductions in all major lipid parameters and ratios. Figure 12 shows the impact of the LDL-C reductions observed in these trials on the percentage of patients achieving NCEP ATP III LDL-C target goals.

Figure 12 **Rosuvastatin 10 mg versus pravastatin 20 mg and simvastatin 20 mg in reaching NCEP ATP III LDL-C target goals**



NCEP ATP III LDL-C treatment goals of risk categories: Low <160 mg/dL; Medium <130 mg/dL; High <100 mg/dL
Main analysis of last observation carried forward (LOCF) data from the intent-to-treat (ITT) population.
*p<0.05 versus pravastatin; **p<0.01 versus pravastatin; ***p<0.001 versus pravastatin
#p<0.05 versus simvastatin; ##p<0.01 versus simvastatin; ###p<0.001 versus simvastatin
N= patients: rosuvastatin 10 mg: 96, 65, 65, and 226 patients (low, medium, high, and overall, respectively); simvastatin 20 mg: 102, 75, 75, and 252 patients (low, medium, high, and overall, respectively); pravastatin 20 mg: 100, 69, 80, and 249 patients (low, medium, high, and overall, respectively)

A statistically significantly higher proportion of patients achieved NCEP ATP III LDL-C target goals for LDL-C with rosuvastatin 10 mg (86%) than with simvastatin 20 mg (64%) and pravastatin 20 mg (49%). Although more patients achieved goal with rosuvastatin in all risk categories, the differences were greatest in the high-risk group. Similar to the findings observed versus atorvastatin 10 mg, more patients achieved the NCEP ATP III non-HDL-C goal with rosuvastatin 10 mg than with simvastatin 20 mg or pravastatin 20 mg.

The results of studies evaluating the efficacy of the rosuvastatin 10-mg start dose demonstrate that this dose will provide potential benefits versus commonly prescribed start doses of other statins. This benefit should translate to a high percentage of patients achieving lipid targets at the start dose and decrease the need for additional patient visits for dose titration.

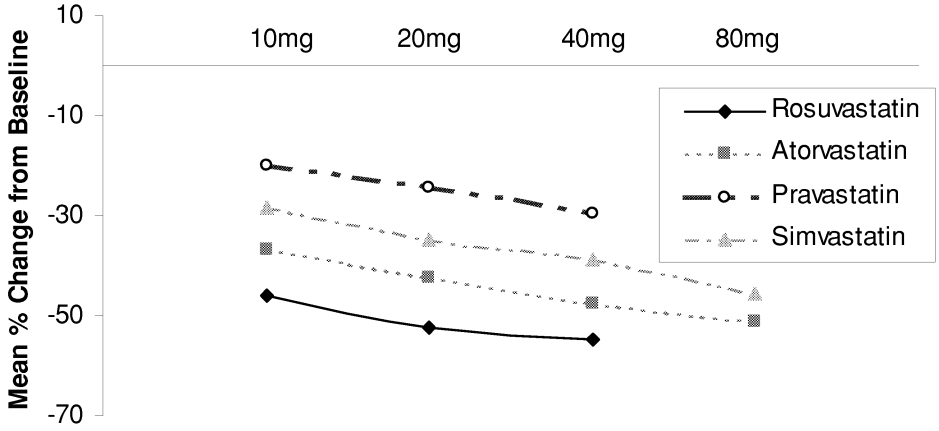
5.5 Assessments of the utility of a rosuvastatin 10 mg to 40 mg dose range

5.5.1 Comparative effects on lipid parameters

Four clinical trials permit an assessment of the overall utility of a rosuvastatin 10 mg to 40 mg dose range versus dose ranges of other marketed statins. Two of these trials (Trials 33 and 65) were 6-week, fixed dose, parallel group trials designed to compare treatment effects on lipid parameters across the dose range. The two other trials (Trials 26 and 28) were one-year trials which assessed the percentage of patients achieving guidelines when titrated based on need in order to achieve NCEP LDL-C goals.

Trial 65 was a multicenter, randomized, open-label, fixed dose, parallel group trial, which randomized 2401 patients with Type IIa and IIb hypercholesterolemia to treatment with rosuvastatin (10, 20, 40, or 80 mg), atorvastatin (10, 20, 40, or 80 mg), simvastatin (10, 20, 40, or 80 mg), and pravastatin (10, 20, or 40 mg) for 6 weeks (Entry LDL-C ≥160 mg/dL and <250 mg/dL). At baseline, the treatment groups were similar with regard to their demographic characteristics and baseline lipids. The results of this trial are shown in Figure 13.

Figure 13 **Linear regression and mean percent reduction in LDL-C values at Week 6 (LOCF): Trial 65**



Main analysis (log dose scale) on LOCF data from ITT population. Linear regression lines are shown for rosuvastatin (solid line) and atorvastatin (dashed line).

The results of Trial 65 demonstrated that rosuvastatin provided an 8.8% additional LDL-C reduction compared to atorvastatin. Doubling the dose of rosuvastatin and atorvastatin provided an additional 4.3% LDL-C reduction. The LDL-C lowering observed with rosuvastatin 40 mg could not be achieved by simply doubling the dose of atorvastatin to 80 mg. Similar to the results observed with atorvastatin, the across the dose range

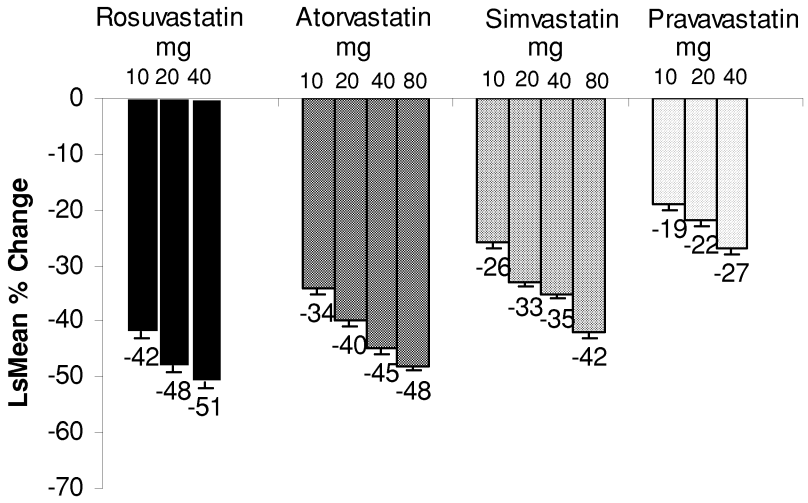
comparisons of rosuvastatin to simvastatin and pravastatin on LDL-C also showed that rosuvastatin would provide better LDL-C reductions. On a mg per mg basis, rosuvastatin provided an additional 16.7% LDL-C reduction compared to simvastatin and an additional 26.3% reduction compared to pravastatin. Doubling the doses of simvastatin and pravastatin gave approximately an additional 5% LDL-C reduction for each.

Trial 33, a multicenter, randomized, double-blind, fixed-dose, parallel group trial comparing rosuvastatin and atorvastatin had results similar to those observed in Trial 65. This trial was conducted in patients with Type IIa and IIb hypercholesterolemia (Entry LDL-C ≥160 mg/dL and < 250 mg/dL). Following a 6-week dietary lead-in period, patients were randomized to treatment with rosuvastatin (5, 10, 20, 40, or 80 mg) or atorvastatin (10, 20, 40, or 80 mg) for 6 weeks. The demographic characteristics and baseline lipids were similar for the patients randomized to atorvastatin or rosuvastatin and similar among treatment dose arms. The mean age of the population was 57 years. In this trial the proportion of men and women and the ethnic distribution was similar to that observed in Trials 24 to 28.

On a mg-per-mg basis, rosuvastatin therapy provided an additional 8.4% LDL-C reduction compared with atorvastatin therapy. Also, doubling the dose of both rosuvastatin and atorvastatin resulted in an additional LDL-C reduction of approximately 5%. The results of this double-blind trial are similar to the results of the larger, open-label Trial 65. Across the dose range of 10 to 40 mg, rosuvastatin provides greater efficacy than atorvastatin 10 to 80 mg.

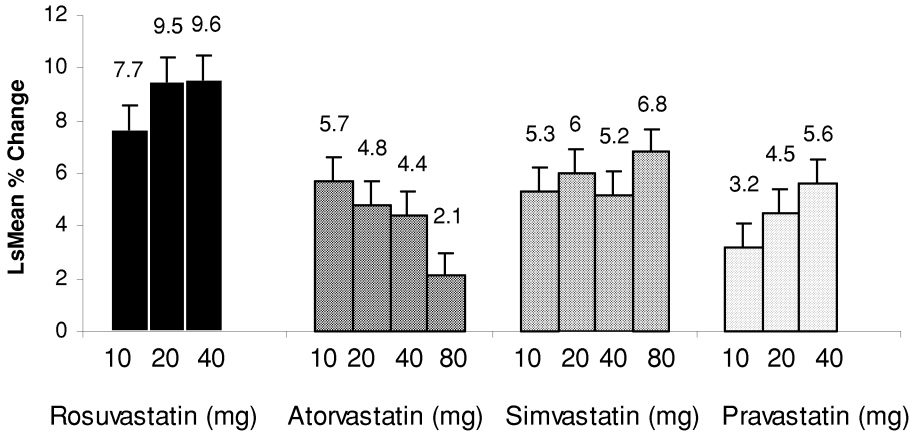
The data from Trials 33 and 65 comparing LDL-C efficacy across the dose range demonstrate that rosuvastatin provides effective LDL-C lowering. However, Trial 65 was also designed to allow for pairwise dose-dose comparisons on other lipid parameters. To account for the multiple pair-wise comparisons performed, the statistical inference for each comparison was determined to be at the $p<0.002$ level (the Bonferroni correction). Figure 14 and Figure 15 show the results of the various statin treatments on non-HDL-C and HDL-C, respectively.

Figure 14 Non-HDL-C reductions at Week 6 for rosuvastatin and comparators



p<0.002 rosuvastatin 10 mg versus atorvastatin 10 mg, pravastatin 10 to 40 mg, simvastatin 10 to 40 mg
p<0.002 rosuvastatin 20 mg versus atorvastatin 20 mg, pravastatin 20 to 40 mg, simvastatin 20 to 80 mg
p<0.002 rosuvastatin 40 mg versus atorvastatin 40 mg, pravastatin 40 mg, simvastatin 40 to 80 mg

Figure 15 HDL-C increases at Week 6 for rosuvastatin and comparators



p<0.001 rosuvastatin 10 mg versus pravastatin 10mg
p<0.001 rosuvastatin 20 mg versus atorvastatin 20 mg, 40mg, 80mg; pravastatin 20mg, 40mg; simvastatin 40mg
p<0.001 rosuvastatin 40 mg versus atorvastatin 40mg, 80mg; pravastatin 40mg; simvastatin 40mg

The data from Trials 33 and 65 demonstrate the benefits of a rosuvastatin 10 mg to 40 mg dose range compared to atorvastatin, simvastatin, and pravastatin on the modification of various lipid parameters and several lipid ratios, including ApoB/ApoA-1.

5.5.2 Comparative effects on achieving NCEP LDL-C goals

Trials 26 and 28 demonstrated the utility of a rosuvastatin 10 mg to 40 mg dose range in bringing patients to NCEP ATP II LDL-C goals. These trials were 52-week, multicenter, randomized, double-blind, titration-to-goal trials in patients with Type IIa and IIb hypercholesterolemia (Entry LDL-C ≥160 mg/dL and < 250 mg/dL). Trial 26 compared rosuvastatin to atorvastatin while Trial 28 compared rosuvastatin to simvastatin and pravastatin. After a 12-week treatment period, patients were randomized to start doses. Following a 12-week treatment period at this start dose, patients were titrated to their NCEP ATP II goals at 12-week intervals. Both trials used rosuvastatin at doses up to 80 mg. For the purposes of assessing the utility of the 10-mg to 40-mg dose range of rosuvastatin, the analysis was modified so that all patients receiving rosuvastatin 80 mg were considered to have not reached their goal in this presentation of results. This modification affected the rosuvastatin treatment arms only.

Table 7 presents results of the analysis of the percentage of patients reaching NCEP ATP II targets for LDL-C at Week 52 for the proposed dose range of rosuvastatin (10, 20, and 40 mg) compared to atorvastatin (10, 20, 40, and 80 mg). The baseline demography and lipids were similar for all treatments groups.

Table 7 Number (%) of patients reaching NCEP ATP II targets for LDL-C levels at Week 52

NCEP ATP II risk category[a]	Rosuvastatin 10-mg to 40-mg group			Atorvastatin 10-mg to 80-mg group		
	N	Baseline LDL-C (mg/dL)	At goal, n (%)	N	Baseline LDL-C (mg/dL)	At goal, n (%)
Low	40	186	40 (100.0)	43	188	43 (100.0)
Medium	35	187	33 (94.3)	45	188	41 (91.1)
High	31	184	29 (93.5)	28	189	17 (60.7)
All categories	106	186	102 (96.2)[b]	116	188	101 (87.1)

[a] The NCEP ATP II risk categories are as follows:
Low risk: No CHD/PVD and ≤1 risk factor; Target LDL-C <160 mg/dL
Medium risk: No CHD/PVD and ≥2 risk factors; Target LDL-C <130 mg/dL
High risk: Clinically evident CHD/PVD or diabetes; Target LDL-C ≤100 mg/dL

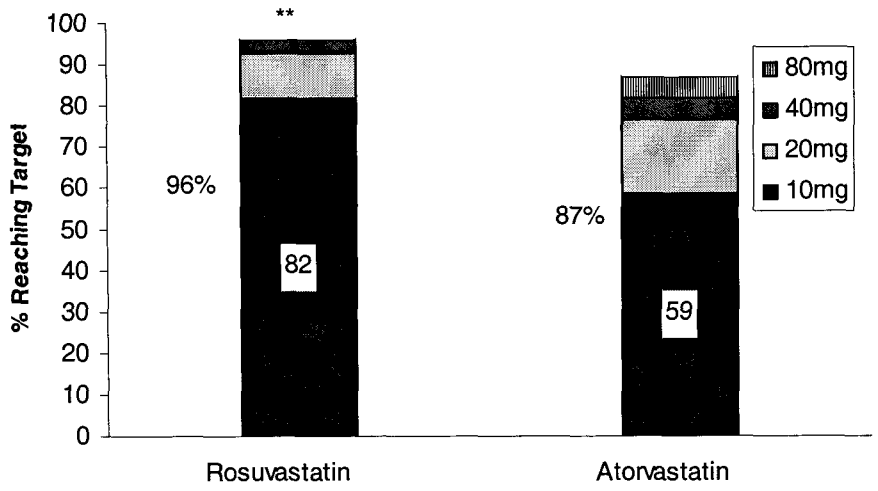
[b] p=0.006 versus atorvastatin 10-mg to 80-mg group.

ATP Adult Treatment Panel; CHD coronary heart disease; LDL-C low-density lipoprotein cholesterol; N Number of patients in the category; n Number of patients in that group who reached the NCEP ATP target; NCEP National Cholesterol Education Program; ATP adult treatment panel; LDL-C low-density lipoprotein C; ns not statistically significant (versus atorvastatin 10 mg); PVD peripheral vascular disease.

The percentage of patients achieving NCEP ATP II targets was higher in the rosuvastatin 10-mg to 40-mg group (96%) compared with the atorvastatin 10-mg to 80-mg group (87%). The difference between the rosuvastatin 10-mg to 40-mg group and the atorvastatin 10-mg to 80-mg group was statistically significant (p=0.006).

Figure 16 shows the dose at which patients achieved their LDL-C targets. Of note, 82% of patients achieved their NCEP target with rosuvastatin 10 mg compared to 59% with atorvastatin 10 mg. The data clearly show that fewer patients required titration to higher doses with rosuvastatin compared to atorvastatin.

Figure 16 **Percentage of patientts achieving NCEP ATP II target goals for LDL-C levels at rosuvastatin and atorvastatin by dose**



**p <0.01 versus atorvastatin

Table 8 presents the results for Trial 28 comparing the percentage of patients achieving goal with rosuvastatin (10, 20, and 40 mg), simvastatin (20, 40, and 80 mg), and pravastatin (20 and 40 mg).

Table 8 **Number (%) of patients reaching NCEP ATP II targets for LDL-C levels**

NCEP ATP II risk category[a]	Rosuvastatin 10-mg to 40-mg group			Pravastatin 20-mg to 40-mg group			Simvastatin 20-mg to 80-mg group		
	N	Baseline LDL-C (mg/dL)	At goal, n (%)	N	Baseline LDL-C (mg/dL)	At goal, n (%)	N	Baseline LDL-C (mg/dL)	At goal, n (%)
Low	47	188	44 (93.6)	44	189	35 (79.5)	42	192	41 (97.6)
Medium	35	188	30 (85.7)	34	188	21 (61.8)	33	185	25 (75.8)
High	14	183	10 (71.4)	17	188	1 (5.9)	27	27	8 (29.6)
All categories	96	187	84 (87.5)[b,c]	95	188	57 (60.0)	102	102	74 (72.5)

[a] The NCEP ATP II risk categories are as follows:
Low risk:No CHD/PVD and ≤1 risk factor; Target LDL-C <160 mg/dL
Medium risk: No CHD/PVD and ≥2 risk factors; Target LDL-C <130 mg/dL
High risk: Clinically evident CHD/PVD or diabetes; Target LDL-C ≤100 mg/dL

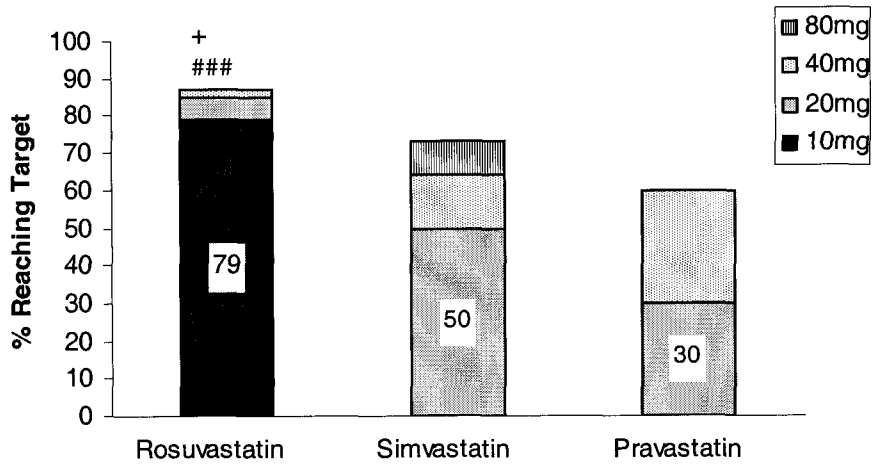
[b] $p<0.001$ versus pravastatin 20-mg to 40-mg group.

[c] $p<0.05$ versus simvastatin 20-mg to 80-mg group.

N Number of patients in the category; n Number of patients in that group who reached the NCEP target; NCEP National Cholesterol Education Program

The percentage of all patients achieving NCEP ATP II targets was statistically significantly higher in the rosuvastatin group compared with both the pravastatin and simvastatin groups (all $p<0.05$). Figure 17 shows the distribution by dose for patients achieving their NCEP LDL-C targets. Of note, 79% of patients achieved their LDL-C goal at 52 weeks with rosuvastatin 10 mg compared to 31% of patients receiving pravastatin 20 mg and 50% of patients receiving simvastatin 20 mg.

Figure 17 **Percentage of patientts achieving NCEP ATP II targets for LDL-C levels for rosuvastatin versus simvastatin or pravastatin**



+ $p<0.05$ versus simvastatin; ### $p<0.001$ versus pravastatin

The results from Trials 26 and 28 demonstrate that the 10-mg to 40-mg dose range for rosuvastatin brings a high percentage of patients within NCEP ATP II LDL-C targets at the 10-mg start dose, thus reducing the need for dose titration.

5.6 Efficacy of rosuvastatin in patients with severe forms of hypercholesterolemia

5.6.1 Heterozygous familial hypercholesterolemia

A new statin which lowers LDL-C more than currently marketed medications would be a significant benefit to patients with more severe forms of hypercholesterolemia. Heterozygous familial hypercholesterolemia (FH) occurs with a frequency of approximately 1 in 500 in the general population. Patients with this disorder represent a difficult to treat patient group who are at high risk for coronary heart disease (CHD) at a young age. Trial 30 was conducted specifically in patients with documented heterozygous familial hypercholesterolemia. Following a 6-week dietary lead-in period, patients were randomized to treatment with rosuvastatin 20 mg or atorvastatin 20 mg for 6 weeks. At week 6 and week 12, patients were force-titrated to 40 mg and 80 mg of their respective treatments. The primary endpoint was the change from baseline in LDL-C at week 18.

The treatment groups were similar at baseline. On average, patients enrolled in this study were younger than those enrolled in previously discussed studies. The mean age for patients randomized to rosuvastatin was 48 years (range 19 to 79 years) and was 47 years (range 20 to 78 years) for those randomized to atorvastatin. Approximately 55% of patients were male and most were Caucasian.

Table 9 summarizes the results of this study comparing lipid results at weeks 6, 12, and 18. Because of potential influences of dose and time on overall lipid response, statistical comparisons between the rosuvastatin 12-week data and the atorvastatin 18-week data were not performed. Although AstraZeneca is not seeking approval of the 80-mg dose of rosuvastatin, the data is shown for this trial since it allows for a complete picture of the results of this study in this particularly difficult to treat population.

Table 9 Summary of changes of efficacy parameters at Weeks 6, 12, and 18 (ITT population)

Efficacy endpoint	Week 6 (20 mg)		Week 12 (20/40 mg)		Week 18 (20/40/80 mg)	
	Rosuvastatin (N=435)	Atorvastatin (N=187)	Rosuvastatin (N=435)	Atorvastatin (N=187)	Rosuvastatin (N=435)	Atorvastatin (N=187)
lsmean of percentage change from baseline (LOCF) in lipids and lipid ratios						
LDL-C						
Baseline	292.5	287.6	292.5	287.6	292.5	287.6
Final	154.4	178.1	136.3	156.9	125.0	144.9
lsmean	–47.07[a]	–37.98	–53.89[a]	–46.02	-57.88[a]	-50.41
TC						
Baseline	372.0	367.0	372.0	367.0	372.0	367.0
Final	231.4	252.2	212.1	229.2	200.1	214.3
lsmean	–37.42[a]	–31.17	–43.13[a]	–38.01	-46.35[a]	-42.13
HDL-C						
Baseline	47.9	47.4	47.9	47.4	47.9	47.4
Final	53.5	50.3	53.0	49.3	53.3	48.4
lsmean	11.74[a]	5.29	10.39[a]	2.74	12.36[a]	2.91
TG						
Baseline	159.5	158.7	159.5	158.7	159.5	158.7
Final	117.8	119.1	113.9	116.2	110.3	105.3
lsmean	–22.93[ns]	–22.07	–25.23[ns]	–24.75	-27.82[ns]	-31.60
Non-HDL-C						
Baseline	324.1	319.6	324.1	319.6	324.1	319.6
Final	177.9	201.9	159.0	179.9	146.8	165.9

Table 9 Summary of changes of efficacy parameters at Weeks 6, 12, and 18 (ITT population)

Efficacy endpoint	Week 6 (20 mg)		Week 12 (20/40 mg)		Week 18 (20/40/80 mg)	
	Rosuvastatin (N=435)	Atorvastatin (N=187)	Rosuvastatin (N=435)	Atorvastatin (N=187)	Rosuvastatin (N=435)	Atorvastatin (N=187)
lsmean	–44.98[a]	–36.85	–51.37[a]	–44.37	-55.3[a]	-49.1
Percentage of patients reaching NCEP ATP III targets for LDL-C levels						
NCEP, all patients	36.6[a]	24.6	49.2[a]	32.6	60.5	46.0
NCEP, patients in high-risk category	6.5	1.5	16.8[b]	3.0	23.9	3.2

[a] $p<0.001$ in favor of rosuvastatin (ANOVA for lipids and lipid ratios, logistic regression for percentage of patients reaching NCEP ATP III targets for LDL-C).

[b] $p<0.05$ in favor of rosuvastatin (logistic regression).

Note: Statistical analyses not performed for rosuvastatin 40 mg versus atorvastatin 80 mg because the treatment groups were at different timepoints.

LDL-C low-density lipoprotein; TC total cholesterol; HDL-C high-density lipoprotein cholesterol; TG triglycerides; NCEP National Cholesterol Education Program; ATP Adult treatment panel; ANOVA analysis of variance; lsmean least square mean

The results were consistent with previous results comparing rosuvastatin to atorvastatin. At week 12, when almost all patient in both groups were receiving the 40 mg dose, rosuvastatin treatment produced significantly greater LDL-C reductions than atorvastatin 40 mg. Despite titration of atorvastatin to 80 mg, the LDL-C reductions were still less than those observed with rosuvastatin 40 mg. Once again, the additional LDL-C lowering translated into more patients achieving NCEP ATP III LDL-C goals with rosuvastatin 40 mg than with atorvastatin 40 mg or 80 mg.

In this trial, a 20-mg start dose of rosuvastatin was selected since these patients are difficult to treat and typically require high doses of statin therapy. Over 400 patients initiated therapy with 20 mg. The mean LDL-C reduction was 47% and overall, approximately 37% of patients achieved their LDL-C target compared to 25% achieving target with atorvastatin 20 mg. In this program, approximately 750 patients initiated therapy with rosuvastatin 20 mg and the safety profile was similar to rosuvastatin 5 and 10 mg. Based on this data and the need for added efficacy in this population, an optional 20 mg start dose is recommended.

5.6.2 Homozygous familial hypercholesterolemia

Homozygous familial hypercholesterolemia is the most severe form of hypercholesterolemia. Patients with this disorder have various degrees of LDL-C receptor dysfunction and are usually refractory to all current therapies. More intensive measures such as plasma apheresis and hepato-portal shunting are often required to lower their LDL-C levels.

The initial period of Trial 54 was an open-label, uncontrolled, force-titration study in patients with documented homozygous familial hypercholesterolemia. Patients were evaluated for their response to rosuvastatin 20 mg, 40 mg, and 80 mg, with the results of 20 mg and 40 mg discussed below. The mean baseline age of this population was 28 years (range 8 to 63 years) and the mean baseline LDL-C was 515 mg/dL.

After 6-weeks of treatment with rosuvastatin 20 mg, the mean LDL-C reduction was 19%. After 6 additional weeks of treatment at 40 mg, the mean LDL-C reduction was 22%. In the 27 patients with at least a 15% reduction in LDL-C by week 12 (ie, considered to be the responder population), the mean LDL-C reduction was 26% at the 20 mg dose, and 30% at the 40 mg dose. Of the 13 patients with an LDL-C reduction of <15%, only 3 had no change or an increase in LDL-C. In this study, LDL-C reductions were observed in patients with defective receptors, in patients with unknown receptor status, and in 3 of 5 patients with known receptor negative status.

Trial 54 demonstrates the efficacy of rosuvastatin in patients with homozygous familial hypercholesterolemia. Because of the severe nature of this disorder, a 20 mg start dose is recommended in this population.

5.7 Efficacy of rosuvastatin in patients with hypertriglyceridemia

Clinical trials with both atorvastatin and simvastatin have demonstrated that HMG-CoA reductase inhibitors are efficacious in reducing triglyceride (TG) levels in patients with Types IIb and IV dyslipidemias. The efficacy of rosuvastatin in this patient population was

evaluated in a multicenter, randomized, double-blind, placebo-controlled, parallel group trial. Patients with elevated baseline triglycerides (entry levels between 300 and 800 mg/dL) entered a six week dietary lead-in period; after which, they were randomized to rosuvastatin (5, 10, 20, 40, and 80 mg) or placebo for 6 weeks. The primary endpoint for the study was the percentage change from baseline in TG levels.

Compared to placebo, rosuvastatin treatment resulted in statistically significant reductions in LDL-C, TC, VLDL-C, VLDL-TG, non-HDL-C, and ApoB; statistically significant increases in HDL-C; and numerically greater increases in ApoA-I. Table 10 summarizes the efficacy results (median % change) for rosuvastatin at doses from 10 mg to 40 mg.

Table 10 Rosuvastatin dose response versus placebo: median % change from baseline to Week 6 in lipids in Type IIb or IV dyslipidemia

Efficacy endpoint[a]		Rosuvastatin dose		
	Placebo (N=26)	10 mg (N=23)	20 mg (N=27)	40 mg (N=25)
TG	0.8	-36.5	-37.0	-43.1
LDL-C	4.5	-45.2	-31.5	-42.5
TC	1.2	-40.5	-33.7	-40.4
HDL-C	-2.9	7.9	21.6	17.0
Non-HDL-C	1.7	-48.5	-42.8	-50.9

[a] Main analyses of LOCF from ITT population
N all patients in ITT population
LDL-C low-density lipoprotein; TC total cholesterol; HDL-C high-density lipoprotein cholesterol; TG triglycerides

Two other studies, Trials 29 and 36 also enrolled patients with Types IIb and IV dyslipidemia and demonstrated the efficacy of rosuvastatin. In clinical trials enrolling both Type IIb and IV patients (Studies 29, 35, and 36), the effects of rosuvastatin on LDL-C, TG, and HDL-C were similar in these two Fredrickson categories. The efficacy results from trials in patients with hypertriglyceridemia support a 10 mg to 40 mg dose range in patients with Type IIb and IV dyslipidemia.

5.8 Summary of rosuvastatin efficacy

A key objective of the rosuvastatin development program was to determine whether rosuvastatin provided additional lipid-modifying benefits at both the start dose and across the dose range compared to currently marketed statins. The data presented in this section shows that a rosuvastatin 10 mg to 40 mg dose range is appropriate for the general population of patients with dyslipidemias. This dose range will provide additional lipid modifying benefits and bring more patients to currently established lipid guidelines than the dose ranges of currently marketed statin therapies. For those patients with more severe levels of hypercholesterolemia (LDL-C >190 mg/dL) and aggressive lipid targets an optional 20-mg

start dose is proposed. For patients with homozygous familial hypercholesterolemia, a 20-mg start dose is considered appropriate. Adjustments to the recommended dose range are suggested based on safety considerations.

6. SAFETY

6.1 Introduction

The third major objective of the clinical program was to show that the proposed dose range provides additional benefits without added safety risks. The data presented in this section will show that the 10-mg to 40-mg dose range for rosuvastatin has a safety profile similar to other marketed statins.

6.1.1 Studies used to assess safety

The safety summary for this briefing document presents data from 27 Phase II/III clinical trials. Trials 8, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 40, 54, 55, 65, and 81 are completed trials. Interim data from 8 ongoing trials (Trials 34, 65 LTE, 68, 81 LTE, 91, 99, US02, and US06) are integrated into the clinical safety database.

For the purposes of reviewing safety data in the NDA, trials were pooled according to their design characteristics. The data pools were chosen to provide a thorough review of safety across all studies by obtaining the largest yet most appropriate set of data upon which to base the summary tables and reviews. Several of these safety data pools are presented in this review and are listed in Table 11.

In creating an updated safety database for the rosuvastatin clinical trial program, AstraZeneca and the FDA agreed that safety information from an overall integrated clinical safety database could be updated with "real-time laboratory data" (RTLD). RTLD were obtained from the central laboratory for Trials 34, 65, 68, 81, 91, 99, US02, and US06. Briefly, data for specific laboratory parameters (creatine kinase [CK], alanine aminotransferase [ALT], aspartate aminotransferase [AST], urinalysis, and serum creatinine) from the central laboratory were linked with subjects' exposure and demography information. The RTLD is important because it provides additional data for key safety parameters (ie, liver, muscle, and renal) critical to the overall evaluation of the safety of rosuvastatin.

The safety database for rosuvastatin is comprised of information on over 12,500 patients from Phase II/III clinical trials. Safety information in this section is presented in the following order:

- Description of the data pools used in this section
- Patient demographics
- Patient exposure to doses of rosuvastatin

- Summary of adverse event data
- Evaluation of liver, muscle, and renal effects of rosuvastatin

6.1.2 Data pooling

Table 11 shows the data pooling method for the clinical studies used to evaluate safety in the rosuvastatin clinical program. The RTLD was used to supplement information presented in two pools in this document, the **All Controlled Pool** and the **All Controlled/Uncontrolled Pool.**

Table 11 Safety population data pools and study groupings

Data pool	Trials included in data pool or group	Number of patients given rosuvastatin
All Controlled	**08, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 35, 36,40, 54, 55, 65** (first 6 weeks only), **81** (first 16 weeks only), **91** (start of study until interim database lock)	5721
Combined All Controlled and RTLD	**US02** (first 6 weeks only), **US06** (first 6 weeks only), **08, 23, 24,25,26, 27, 28, 29, 30, 31, 32, 33, 35, 36, 40, 54, 55, 65** (first 6 weeks only), **68, 81** (first 16 weeks only), **91** (start of study until interim database lock), **99** (first 6 weeks only)	8135
Fixed-dose Controlled	**08, 23, 24, 25** (first 12 weeks only), **26** (first 12 weeks only), **27, 28** (first 12 weeks), **29** (first 12 weeks only for rosuvastatin patients, first 4 weeks only for niacin subjects), **30** (first 6 weeks only), **31** (first 6 weeks only), **32, 33, 35, 36** (first 6 weeks only), **40** (first 8 weeks only) **54** (first 6 weeks only), 55, 65 (first 6 weeks only), **81** (first 8 weeks for patients who switched treatment at Week 8, first 16 weeks for patients who did not switch at Week 8), **91** (first 12 weeks)	4239
Combined All Controlled/ Uncontrolled and RTLD	**08, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34[a], 35, 36, 40, 54, 55, 65, 65 LTE, 68, 81, 81 LTE, 91**	12569

[a] Study 34 is an ongoing, uncontrolled study that is an extension of most of the controlled studies listed.
NA Not available; LTE long-term extension; RTLD real time laboratory data.

The **All Controlled Pool** consists of all the completed Phase II/III controlled studies and an interim database lock of Study 91. This pool is helpful for making comparisons of the adverse event profile of rosuvastatin with the profiles of other statins. Placebo event rates are included in these in-text tables for benchmarking purposes. Note, however, the number of exposures and the duration of exposure are greater for rosuvastatin than for placebo in this pool. When supplemented with RTLD, the new pool is referred to as the **Combined All Controlled and**

RTLD Pool and is used to compare rosuvastatin with other statins on laboratory parameters of interest (CK, ALT, AST, urinalysis, and serum creatinine).

The **Fixed-dose Controlled Pool** consists of fixed-dose studies and initial fixed-dose portions of all the Phase II/III controlled studies in which titration subsequently took place. This pool provides one method for assessing the dose relationship of various adverse events. Since all comparisons with placebo occurred during fixed-dose studies or during the fixed-dose portion of a study, placebo data is also presented in these tables.

The **All Controlled/Uncontrolled Pool** consists of all completed Phase II/III controlled studies; Study 34, an ongoing, uncontrolled study that is an extension of most of the studies comprising the **All Controlled Pool**; the LTEs for Studies 65 and 81; and an interim database lock of Study 91. This pool is the largest patient pool that provides adverse event data and the opportunity to examine longer-term exposure to rosuvastatin. When supplemented with RTLD, the new pool is referred to as the **Combined All Controlled/Uncontrolled and RTLD Pool.** This is the largest pool and provides the most comprehensive description of exposure to rosuvastatin in the clinical trial program. It is used to evaluate long-term liver, muscle, and renal effects of treatment with rosuvastatin and to assess the dose relationship of laboratory abnormalities of interest.

6.2 Patients included in the analyses of safety and patient exposure

6.2.1 Demography and baseline medical conditions

The demographic characteristics of patients exposed to rosuvastatin in the largest pool of clinical safety data are presented in Table 12.

Table 12 **Demographic characteristics of patients: Combined All Controlled/Uncontrolled and RTLD Pool**

Demographic characteristic	Rosuvastatin (N=12569)[a]
Age, yr	
Mean (SD)	58.1 (11.8)
Range	8 to 92
Age distribution (n, %)	
<18 years	8 (0.1)
18 to 64 years	8624 (68.6)
≥65 years	3936 (31.3)
≥75 years	915 (7.3)
Ethnic origin (n, %)	
Caucasian	11081 (88.2)
Hispanic[b]	297 (2.4)
Black[c]	820 (6.5)
Asian[d]	234 (1.9)
Other[e]	137 (1.1)
Sex (n, %)	
Men	6626 (52.7)
Women	5943 (47.3)
Postmenopausal[f]	4019 (67.6)

[a] Includes patients receiving rosuvastatin either alone or with another lipid-lowering agent at any point during a feeder trial or an extension trial.
[b] Hispanic of Latino origin.
[c] Includes African, African-American, African-Caribbean, and other.
[d] Includes Japanese, Chinese/East Asian, South Asian, Oriental, and other.
[e] Includes American Indian/Alaska Native, American Indian/Pacific Islander, mixed, and other.
[f] Includes all female patients in Trials 08, 23, and 40, all patients in Trial 32, and women aged 50 years or more in all other trials.
SD Standard deviation.

The demographic characteristics of patients in the safety population shows that the population studied covered a broad age range (8 to 92 years old) with 31% of the patients ≥65 years of age. Men and women were approximately equally represented, and the majority of women were postmenopausal.

A substantial number of patients treated with rosuvastatin had medical conditions prior to entry into the rosuvastatin clinical trial program as shown in Table 13.

Table 13 Number (%) of patients who had baseline medical conditions of interest: All Controlled/Uncontrolled and RTLD Pool

Medical condition	Rosuvastatin dose (n, [%])[a] (N=12,569)
Diabetes	2080 (16.5)
Hypertension	6529 (51.9)
Cardiovascular disease	4530 (36.0)
Hepatic function	
ALT and AST ≤1 x ULN	11202 (89.1)
ALT and/or AST >1 to 3 x ULN	1349 (10.7)
ALT and/or AST >3 x ULN	13 (0.1)
Unknown	5 (0.0)
Renal function at baseline[b]	
Normal	5909 (47.0)
Mild impairment	5579 (44.4)
Moderate impairment	983 (7.8)
Severe impairment	41 (0.3)
Unknown	57 (0.5)

[a] Patients may have more than 1 disease or abnormality at entry. Patients who had altered hepatic or renal function at baseline were included in the category of their highest value.

[b] Renal function at baseline was calculated retrospectively and is based on calculated creatinine clearance (Cockcroft and Gault 1976): normal renal function = calculated CrCl >80 mL/min; mild renal impairment = calculated CrCl 50 to ≤80 mL/min; moderate renal impairment = calculated CrCl 30 to <50 mL/min; severe impairment = calculated CrCl <30 mL/min.

ALT Alanine aminotransferase; AST Aspartate aminotransferase; ULN Upper limit of normal; CrCl Creatinine clearance

Over half of the patients enrolled in the rosuvastatin clinical trial program had hypertension and over half had some level of renal impairment. A large percentage of patients also had diabetes mellitus and/or cardiovascular disease (atherosclerotic disease) at baseline.

A comparison of the demographic and baseline medical conditions for patients included in the **All Controlled Pool** and **Fixed-dose Controlled Pool** revealed that baseline characteristics were similar between patients treated with rosuvastatin and comparator statins and were also similar between the various rosuvastatin dose groups.

6.2.2 Exposure

The maximum continuous duration of treatment for each dose of rosuvastatin in the rosuvastatin Phase II/III clinical trial program is presented in Table 14.

Over 7800 patients were treated with the 10 mg proposed starting dose for the general dyslipidemia population; 1700 of these patients initiated rosuvastatin therapy at this dose at the beginning of a controlled trial. Over 3900 patients were treated with the 20 mg proposed starting dose for patients with severe hypercholesterolemia and aggressive LDL-C targets (1184 patients started at this dose in a controlled trial) and over 4000 patients were treated with the 40 mg proposed top dose of rosuvastatin of which 2126 patients initiated rosuvastatin therapy at this dose. In total, the current database represents 14,231 patient-years of continuous exposure to rosuvastatin. With regard to long-term exposure data, 4055, 545, and 276 patients were treated with rosuvastatin for ≥48 weeks at doses of 10 mg, 20 mg, and 40 mg, respectively. Patients with ≥48 weeks of rosuvastatin therapy were those not down-titrated from 80 mg. The exposures accumulated during the rosuvastatin clinical trial program are appropriate for assessing the safety profile of rosuvastatin at doses up to and including 80 mg.

Table 14 **Maximum continuous duration of treatment for each dose of rosuvastatin in the Combined All Controlled/Uncontrolled and RTLD Pool**

	Rosuvastatin daily dose[a]							
Duration of treatment	**5 mg**	**10 mg**	**20 mg**	**Not down-titrated to 40 mg[b]**	**Down-titrated to 40 mg[b]**	**Total at 40 mg[c]**	**80 mg**	**Total[d] rosuvastatin**
	(N=1325)	**(N=7819)**	**(N=3939)**	**(N=3742)**	**(N=825)**	**(N=4007)**	**(N=1583)**	**(N=12569)**
≥6 weeks	1234 (93.1)	7467 (95.5)	3582 (90.9)	3381 (90.4)	820 (99.4)	3705 (92.5)	1417 (89.5)	12049 (95.9)
≥12 weeks	995 (75.1)	6219 (79.5)	2143 (54.4)	2001 (53.5)	803 (97.3)	2758 (68.8)	1055 (66.6)	10603 (84.4)
≥24 weeks	647 (48.8)	5041 (64.5)	1353 (34.3)	1227 (32.8)	686 (83.2)	1893 (47.2)	971 (61.3)	8860 (70.5)
≥48 weeks	542 (40.9)	4055 (51.9)	545 (13.8)	276 (7.4)	0	276 (6.9)	891 (56.3)	6646 (52.9)
≥72 weeks	324 (24.5)	1546 (19.8)	235 (6.0)	159 (4.2)	0	159 (4.0)	783 (49.5)	3423 (27.2)
≥96 weeks	283 (21.4)	903 (11.5)	120 (3.0)	110 (2.9)	0	110 (2.7)	642 (40.6)	2356 (18.7)
Not calculated[e]	1 (0.1)	4 (0.1)	20 (0.5)	7 (0.2)	2 (0.2)	6 (0.1)	7 (0.4)	1 (<0.1)
Mean (SD) duration of treatment (days)	362.8 (394.3)	348.6 (289.0)	167.8 (179.8)	142.9 (164.2)	211.8 (53.1)	169.5 (157.2)	450.5 (352.8)	413.6 (349.7)
Patient-years of treatment	1315	7458	1800	1461	477	1857	1944	14,231

[a] Patients were counted in each dose group to which they are exposed; therefore, patients may be counted in more than 1 treatment group. For patients with more than 1 exposure to a given rosuvastatin dose, only the longest duration of exposure to that dose is counted.

[b] Patients were back-titrated from rosuvastatin 80 mg as a result of a protocol amendment. Not all patients given rosuvastatin 40 mg were down-titrated from rosuvastatin 80 mg; these patients were either up-titrated to 40 mg from a lower start dose or were directly randomized to 40 mg.

[c] If a patient received 40 mg prior and then was back-titrated from 80 mg to 40 mg, the patient is counted in both the "not down-titrated to 40 mg" and "down-titrated to 40 mg" columns. Thus, the total 40 mg column does not equal the sum of the 2 individual 40 mg columns.

[d] Maximum continuous exposure in the Total rosuvastatin column included all rosuvastatin continuous exposure, regardless of titration of dose. For this reason, counts of patients in the individual duration categories cannot be added across doses to obtain the count in the Total rosuvastatin column. Also includes 63 patients exposed to 1 mg or 2.5 mg rosuvastatin.

[e] The reason for the missing counts is that there were no return dates to calculate the treatment durations. In most of these cases, the patients were not only dispensed these doses for the first time, but also these doses were the last dispensed dose before the database lock for the patient.

SD standard deviation

6.3 Evaluation of adverse events

6.3.1 Adverse events

The frequencies of overall adverse events and individual adverse events for rosuvastatin, comparator statins, and placebo in controlled clinical trials are presented in Table 15.

Table 15 Percent of patients with an adverse event: All Controlled Pool

COSTART preferred term	Treatment				
	Rosuva[a]	Atorva	Simva	Prava	Placebo
	(N=5721)	(N=2940)	(N=1457)	(N=1278)	(N=382)
% of patients with any adverse event	**50.5**	**46.0**	**44.3**	**43.3**	**56.8**
Pharyngitis	7.5	6.5	6.0	6.1	7.6
Pain	4.6	4.0	4.5	4.0	6.5
Headache	4.2	3.6	2.9	3.1	5.0
Myalgia	3.5	3.4	3.4	2.3	1.3
Asthenia	2.8	2.4	1.6	2.3	2.6
Back pain	2.8	2.4	2.3	1.8	2.4
Abdominal pain	2.7	2.4	2.0	2.3	4.7
Diarrhea	2.7	2.6	1.8	2.1	2.9
Flu syndrome	2.7	2.4	2.3	1.9	1.8
Nausea	2.6	1.9	2.4	2.4	3.1

[a] Includes doses up to 80 mg.

Note: Laboratory abnormalities were not required to be reported as adverse events; reporting of these abnormalities as adverse events was left to investigator discretion.

During the controlled trials, the mean duration of exposure to rosuvastatin was greater than for the comparator groups. The mean duration of treatment with rosuvastatin was 98 days compared to 86, 85, 91, and 62 days for the atorvastatin, simvastatin, pravastatin, and placebo groups, respectively. Taking into account the fact that the mean duration of exposure was greater in the rosuvastatin group than for the comparator groups and that the highest frequency of any adverse event was observed in the placebo group (56.8%), the overall adverse event frequency for rosuvastatin was similar to that observed with the other statins studied in the program.

When evaluating the specific types of adverse events observed following treatment with rosuvastatin in comparison with other statins and placebo, the adverse event profile for rosuvastatin was similar to that of the comparator statins. The adverse event profile for patients on statin therapy also compared favorably with that for placebo. The one exception

was the frequency of myalgia, which tended to be higher for patients receiving statin therapy and similar across the statin groups. The most frequent drug-related adverse events observed with rosuvastatin were myalgia, asthenia, nausea, and abdominal pain. Most adverse events observed with rosuvastatin were mild in intensity.

The adverse event profile for rosuvastatin was evaluated based on age, gender, ethnic origin, and menopausal status, as well as the presence of comorbid conditions such as diabetes, hypertension, cardiovascular disease, and altered hepatic function. The overall frequency of adverse events in patients <65 years old was 68.8% compared to 65.9% in patients ≥65 years old. Using age <75 years old or ≥75 years old, the overall frequency of adverse events was 68.3% and 62.8%, respectively. The incidence of myalgia was similar in young and older patients regardless of the age cut-off. No major differences in the adverse event profiles were observed based on gender, race, menopausal status, ethnic origin, or the presence of baseline co-morbidities.

Rosuvastatin was safely administered along with a variety of other medications used to treat either comorbid medical conditions or underlying lipid profile abnormalities. In particular, no significant changes in the overall adverse event frequency or the adverse event profile were observed when rosuvastatin was given with antidiabetic agents, antihypertensive agents, drugs known to effect the cytochrome P450 enzyme system, hormone replacement therapy, oral contraceptives, digitalis glycosides, or drugs known to prolong the QTc interval. The data also show that rosuvastatin can be safely administered in combination with the lipid-lowering agent cholestyramine to patients with dyslipidemia; however, a higher incidence of gastrointestinal side effects were observed with the combination compared to rosuvastatin monotherapy.

The frequency of adverse events at different doses of rosuvastatin was evaluated using the **Fixed-dose Controlled Pool** (Table 16). Patients presented in this pool initiated rosuvastatin therapy at the doses listed in the table.

Table 16 **Percent of patients with an adverse event: Fixed-dose Controlled Pool**

COSTART preferred term	5 mg (N=838)	10 mg (N=1573)	20 mg (N=749)	40 mg (N=752)	80 mg (N=264)	Placebo (N=365)
% of patients with any adverse event	**59.3**	**50.8**	**42.7**	**49.5**	**59.1**	**56.2**
Pharyngitis	10.9	6.0	6.1	3.6	9.5	7.4
Headache	4.5	4.1	3.5	3.6	5.7	4.9
Pain	4.9	3.6	4.4	2.3	8.0	6.6
Myalgia	3.9	3.3	3.3	1.6	7.2	1.4
Diarrhea	3.6	3.2	1.5	2.3	3.0	3.0
Abdominal pain	3.1	3.1	2.7	1.7	3.4	4.9
Nausea	3.0	2.6	2.9	1.6	6.1	3.3
Asthenia	2.4	2.5	2.7	1.7	5.7	2.7
Constipation	2.3	2.4	1.2	3.1	4.2	2.5
Back pain	2.7	2.8	1.6	1.2	1.9	2.2

Note: Laboratory abnormalities were not required to be reported as adverse events; reporting of these abnormalities as adverse events was left to investigator discretion.

The overall adverse event frequency was similar at rosuvastatin doses from 5 to 80 mg. The adverse event profile was similar at doses up to and including 40 mg. At 80 mg, an increase in some adverse events (pain, myalgia, nausea, asthenia, and constipation) was observed. Importantly, no significant differences in safety were observed between the 5-mg and 10-mg doses, thus making the 10-mg dose an appropriate start doses from the standpoint of adverse event frequency. Also, the 40-mg dose was well tolerated with an adverse event profile similar to lower doses of rosuvastatin.

The most frequent adverse events thought to be related to rosuvastatin were myalgia, asthenia, abdominal pain, and nausea.

6.3.2 Nonfatal serious adverse events and adverse events leading to withdrawal

As shown in Table 17, the frequencies of nonfatal serious adverse events and adverse events leading to withdrawal were low and similar to other statin in the controlled trials. Table 18 shows that the frequencies of these events were similar at rosuvastatin doses from 5 to 40 mg but were increased slightly at the 80-mg dose.

Table 17 **Percent of patients in various categories of adverse events during the treatment phase: All Controlled Pool**

	Treatment[a]				
	Rosuva[b] (N=5721)	Atorva (N=2940)	Simva (N=1457)	Prava (N=1278)	Placebo (N=382)
Nonfatal serious adverse events	2.6	2.1	2.3	1.7	1.3
Adverse events leading to withdrawal	3.4	3.6	3.0	3.1	4.7

[a] Patients are counted according to each treatment received, therefore patients may be counted in more than 1 treatment group.

[b] Includes doses up to 80 mg.

Rosuva rosuvastatin; Atorva atorvastatin; Simva simvastatin; Prava pravastatin; SD standard deviation

Table 18 **Percent of patients in various categories of adverse events during the treatment phase: Fixed-dose Controlled Pool**

	Rosuvastatin dose					
	5 mg (N=838)	10 mg (N=1573)	20 mg (N=749)	40 mg (N=752)	80 mg (N=264)	Placebo (N=365)
Nonfatal serious adverse events	2.1	1.8	1.2	2.3	2.7	1.4
Adverse events leading to withdrawal	3.4	3.6	3.0	3.1	6.1	4.9

[a] Patients are counted according to each treatment received, therefore patients may be counted in more than 1 treatment group.

Note: Numbers of patients with adverse events based on actual treatment received at onset, death or withdrawal. Patients may be included in more than one category.

The **All Controlled/Uncontrolled Pool** is the largest patient pool with the longest duration of exposure to rosuvastatin with adverse event data. In this pool, the most frequent serious adverse events observed in the program were angina pectoris (0.8%), chest pain (0.8%), and pathological fracture (0.6%); these types of serious adverse events would be expected in the patient population in this clinical development program. As a serious adverse event, myalgia occurred with a frequency of 0.1%. The frequency of adverse events and drug-related adverse events leading to withdrawal was low, 7.1% and 4.4%, respectively. The most common adverse event leading to withdrawal was myalgia (1.1%).

6.3.3 Deaths

Among the 12,569 patients treated with rosuvastatin (with 14,231 patient-years of treatment) in the **Combined All Controlled/Uncontrolled and RTLD Pool**, there were 68 deaths, giving a rate of deaths of 68/14,231 (0.5%). Similarly, calculated rates for deaths in patients

treated with atorvastatin, simvastatin, and pravastatin in the **Combined All Controlled and RTLD Pool** were 5/864 (0.6%), 4/524 (0.8%), and 1/318 (0.3%), respectively.

The number of deaths in all treatment groups was low and paralleled the number of treatment years for each group. There were no deaths attributed to rosuvastatin by an investigator; there was no evidence of a relationship between dose or duration of dose and deaths in patients given rosuvastatin.

Deaths were mostly attributed to cardiovascular events or other illnesses, which would be expected in this study population. There is no evidence that rosuvastatin increases cardiovascular or noncardiovascular deaths.

6.3.4 Summary of adverse event data

A review of adverse events from the rosuvastatin clinical trial program reveals that the overall frequency of any adverse event, as well as the adverse event profile for patients receiving rosuvastatin (5 mg to 80 mg) was similar to atorvastatin (10 mg to 80 mg), simvastatin (10 mg to 80 mg), and pravastatin (20 mg to 40 mg). The overall frequency of nonfatal serious adverse events and adverse events leading to withdrawal or to death was also similar between the statin groups. With regard to the individual doses of rosuvastatin, the overall frequency of adverse events and the adverse event profiles were very similar for rosuvastatin doses up to and including 40 mg. An increase in some adverse events was observed following treatment with the 80-mg dose.

6.4 Liver, skeletal muscle, and renal effects of rosuvastatin

Evaluations were performed in patients to assess the effects of rosuvastatin treatment on several organs including the liver, skeletal muscle, kidney, eye, and heart as well as on adrenal function. Rosuvastatin treatment did not result in cataract formation, electrophysiologic changes, or impairment in adrenal function. This section will focus on the findings pertaining to treatment-related effects on the liver, skeletal muscle, and kidney.

6.4.1 Liver effects

6.4.1.1 Background

The primary site of action for HMG-CoA reductase inhibitors is the liver. The degree to which different statins are taken up by the liver varies (Blumenthal 2000). Following initiation of therapy with other statins, transaminase elevations may occur. Transaminase elevations tend to occur early and usually reverse with continued therapy (Tolman 2000). Statins cause elevated transaminase levels in approximately 1 to 3% cases and for some statins, clinical study evidence has demonstrated that the elevations appear to be dose-related (Farmer 2000; Physician's Desk Reference, 2001 [atorvastatin]). There is some evidence for severe or persistent hepatic toxicity caused by statins in humans, but the frequency appears to be very low (Tolman 2000).

Because rosuvastatin is a member of the statin class of drugs, clinical biochemistry assessments of liver function were carefully followed in the rosuvastatin clinical development

program in order to investigate the hepatotoxic potential of rosuvastatin. For presentation purposes in this section, the major focus is on presentation of ALT data and, where appropriate, bilirubin data are discussed. Elevations in AST are not presented since changes in this laboratory parameter paralleled the ALT changes but were generally smaller in magnitude. In this section, "clinically significant ALT changes" are defined as changes >3 x ULN on 2 consecutive occasions. This definition is consistent with the description of "persistent ALT elevations" which appears in US labeling for other statins.

6.4.1.2 Clinical laboratory ALT data

A review of ALT data for patientss given rosuvastatin or a comparator in the **Combined All Controlled and RTLD Pool** shows that the frequency of ALT values >3 x ULN on at least 1 occasion, as well as the frequency of clinically significant ALT rises (>3 x ULN on 2 consecutive occasions), were similar for the rosuvastatin and the other statin treatment groups (Table 19).

Table 19 ALT elevations in patients in the Combined All Controlled and RTLD Pool

	Treatment				
	Rosuva[a] (N=8190)	**Atorva (N=3749)**	**Simva (N=2398)**	**Prava (N=1260)**	**Placebo (N=380)**
% >3 x ULN	0.9	0.7	0.5	0.4	0.3
% >3 x ULN on 2 consecutive occasions	0.2	0.2	0.2	0.2	0

[a] Includes data for patients who received rosuvastatin 80 mg.

Note: The numbers of patients in each treatment group in laboratory data tables may differ from those seen in other tables in this document since not all patients had baseline and at least 1 postbaseline laboratory evaluation for a particular laboratory parameter.

ULN Upper limit of normal; ALT alanine aminotransferase

In this pool, the mean duration of treatment to rosuvastatin was greater than for the comparator groups (104 days, 83 days, 79 days, 91 days for rosuvastatin, atorvastatin, simvastatin, and pravastatin, respectively). The rosuvastatin group also reflects data for doses up to and including 80 mg. Removing the 80 mg data, so that the table only reflects doses up to 40 mg, the frequency of ALT elevations >3x ULN is 0.7% while the frequency of ALT elevations >3 x ULN on 2 occasions is 0.2%.

The frequencies of ALT elevations in the **Combined All Controlled/Uncontrolled and RTLD Pool** for doses of rosuvastatin from 5 to 80 mg are shown in Table 20. Of the 12,458 patients who had a baseline and at least 1 postbaseline laboratory evaluation, 0.7% of patients had ALT elevations >3 x ULN on a single occasion and 0.4% of patients had ALT elevations >3 x ULN on a least 2 occasions.

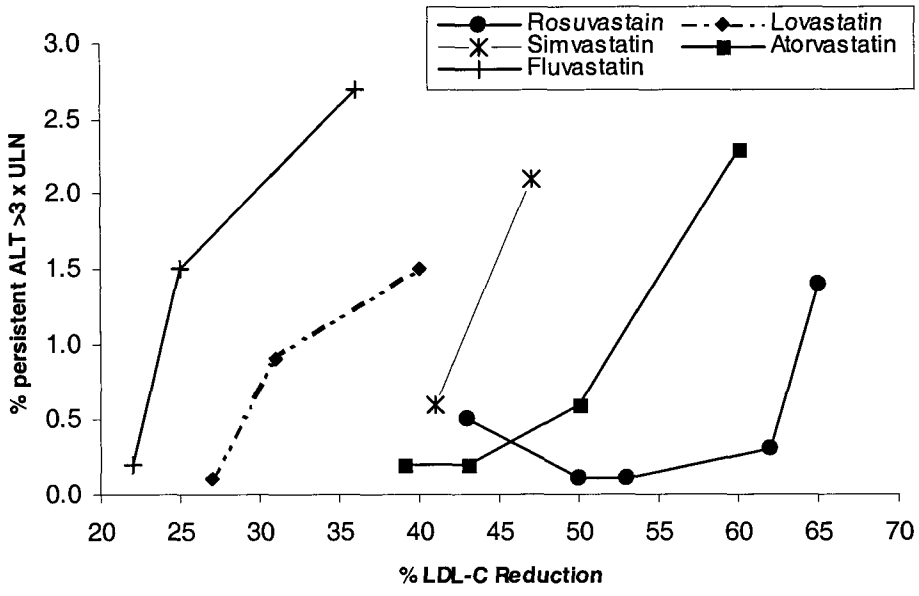
Table 20 **ALT elevations by dose in patients in the Combined All Controlled/Uncontrolled and RTLD Pool**

Dose of rosuvastatin	Number of patients (N)	>3 x ULN, n(%)	>3 x ULN on 2 occasions, n(%)
All doses	12,458	181 (1.5)	50 (0.4)
5 mg	1317	15 (1.1)	6 (0.5)
10 mg	7726	60 (0.8)	9 (0.1)
20 mg	3882	20 (0.5)	3 (0.1)
40 mg	3957	30 (0.8)	10 (0.3)
80 mg	1574	56 (3.6)	22 (1.4)

At doses from 5 to 40 mg, the frequencies of ALT elevations were low and similar. An increase in the frequency of ALT elevations was observed at the 80-mg dose. In the 50 patients receiving rosuvastatin who experienced clinically significant ALT elevations, the onset of the elevations ranged between Day 1 and Day 785 of initiation or dose titration of rosuvastatin therapy. Twenty-eight of these clinically significant elevations occurred within the first 12 weeks of initiation or dose titration. Of patients receiving rosuvastatin below the 80-mg dose, 16/28 patients had clinically significant ALT elevations occurring within the first 12 weeks of initiation or dose titration.

The frequency of persistent ALT elevations from the **Combined All Controlled/Uncontrolled and RTLD Pool** is similar to data contained within the prescribing information for other marketed statins and the Heart Protection Study (Figure 18).

Figure 18 **Percent of persistent ALT elevations (ALT >3 x ULN on 2 occasions) normalized for the percent reduction of LDL-C**



As shown, an increased frequency of persistent ALT elevations with increasing dose is observed for all statins. At doses of rosuvastatin from 5 mg to 40 mg, the frequency of persistent ALT elevations is low and similar to low doses of comparator statins. Importantly, the increase in frequency with rosuvastatin is observed at the 80 mg dose where a 65% LDL-C reduction occurs. In contrast, the increased frequency of persistent ALT elevations with comparator statins occurs at doses, which obtain lower levels of LDL-C reduction.

In accordance with the CDER-PhRMA-AASLD Conference 2000 Clinical White Paper (November 2000), cases of elevated ALT and/or AST with concurrent bilirubin elevation to 1.5 x ULN or greater were examined. A total of 9 patients met this criterion. Investigators attributed 5 of the 9 cases to other etiologies (ie, 1 case of bile duct malignancy, 1 case of pancreatic carcinoma, 1 case of hepatitis B, and 2 cases of hepatitis A). A sixth case appears secondary to hepatitis B (patient with elevated IgM HB core antibody, negative HBsAg). The remaining 3 cases were considered by investigators to be related to study treatment. In 2 of the cases, the bilirubin values were >ULN at baseline, and the values returned to baseline on continued therapy. In the third case, the ALT and bilirubin levels were just above the threshold (ALT >3.4 x ULN, bilirubin >2.1 x ULN) and normalized following withdrawal of treatment.

6.4.1.3 Conclusions of liver effects

A careful evaluation of the liver findings observed during the rosuvastatin clinical development program revealed a low incidence of ALT elevations that was similar at doses from 5 to 40 mg, but increased at the 80-mg dose. The elevations observed with rosuvastatin compared favorable to data observed for atorvastatin, simvastatin, and pravastatin within the rosuvastatin development program and with the prescribing information for atorvastatin.

Overall, the data obtained from this large trial program indicates that rosuvastatin has a low potential for causing significant adverse liver effects. Based on the timing of onset of clinically significant ALT elevations (>3 x ULN on 2 consecutive occasions), liver function tests should be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended.

6.4.2 Skeletal muscle effects

6.4.2.1 Background

Two serious complications of statin therapy are myopathy and rhabdomyolysis. Myopathy, defined as muscle pain or weakness associated with creatine kinase levels >10 x ULN, occurs in about 1 in 1000 patients treated with marketed statins and is dose-related. Symptoms may include fever and malaise, and cases have been associated with elevated serum statin drug levels (Maron 2000). Rhabdomyolysis is a more severe form of myopathy characterized by severe destruction of skeletal muscle associated with myoglobinuria and the potential for renal

failure. Clinically, rhabdomyolysis has been rare (<0.1%) in patients in large-scale studies with statins (Farmer 2000).

The recent worldwide withdrawal of cerivastatin has raised concerns about the myotoxic potential of statins and placed increased scrutiny on new agents being developed for the treatment of lipid disorders. In order to understand the potential effects of rosuvastatin on skeletal muscle, a large number of patients were exposed to doses up to and including 80 mg. Patients were carefully monitored in the clinical trial program for the effects of therapy on laboratory CK values and for possible muscle side effects. In addition to the clinical evaluations, preclinical evaluations were also performed to assess the potential for rosuvastatin to effect muscle cells relative to other HMG-CoA reductase inhibitors, including cerivastatin.

6.4.2.2 Pre-clinical evaluation of statin effects on skeletal muscle

As noted above, adverse effects on skeletal muscle have been found with all statins. However, the recent worldwide withdrawal of cerivastatin from the market has raised questions about the use of high doses of any statin where myopathy may be an issue. This section presents preclinical data which clearly differentiate rosuvastatin from cerivastatin with regard to potency for effect on HMG-CoA reductase in human skeletal muscle cells.

(a) Pre-clinical toxicology

In toxicology studies, damage to skeletal muscle have been found to occur with all statins administered at high doses to animals including rat (Reijneveld 1996, atorvastatin, cerivastatin, fluvastatin, simvastatin and pravastatin SBAs), mouse (atorvastatin SBA), hamster (atorvastatin SBA), rabbit (Fukami 1993, Fukushige and Tani 1998, Nakahara 1998, AZ Report No. S-4522 B-52-N, cerivastatin and pravastatin SBAs) and dog (Reijneveld 1996, Walsh 1996, atorvastatin and cerivastatin SBAs). The doses needed to elicit muscle damage are often those that approach the maximum tolerated doses. Characteristically, the histopathology findings are of necrosis of the myofibrils, interstitial edema and inflammatory cell infiltration. These are similar to the characteristics that have been identified in patients with statin-induced myopathy (Giordanon 1997). Rosuvastatin produced the same muscle changes in the rat and rabbit at doses approaching the maximum tolerated doses.

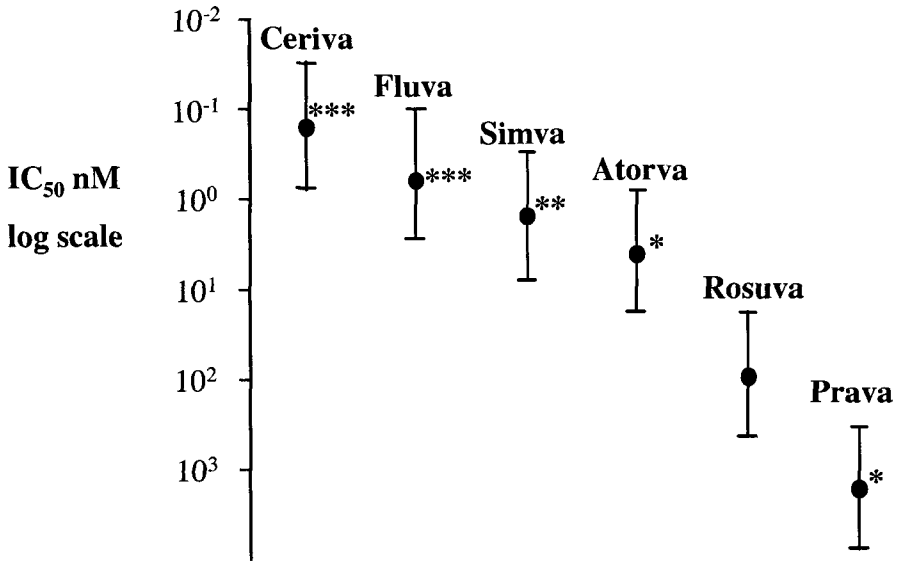
Studies have shown that muscle toxicity can be prevented or ameliorated by co-administration of mevalonate (von Keutz and Schluter 1998 and Hrab 1994). Similarly, in rabbit experiments with rosuvastatin, muscle changes could be prevented by mevalonate. Thus, there is strong evidence that the effects of statins on muscle cells are driven by a high degree of inhibition of HMG-CoA reductase in muscle cells. However, the downstream effects of HMG-CoA reductase inhibition that result in muscle damage are not known.

(b) Human skeletal muscle cells

In order to evaluate the relative effects of statins on skeletal muscle, cell studies in fibroblasts and other cell types were repeated in human skeletal muscle. As shown in Figure 19, cerivastatin was the most potent inhibitor, about 500-fold more potent than rosuvastatin. The

rank order of potency was similar to the rank order of lipophilicity shown previously in Figure 3.

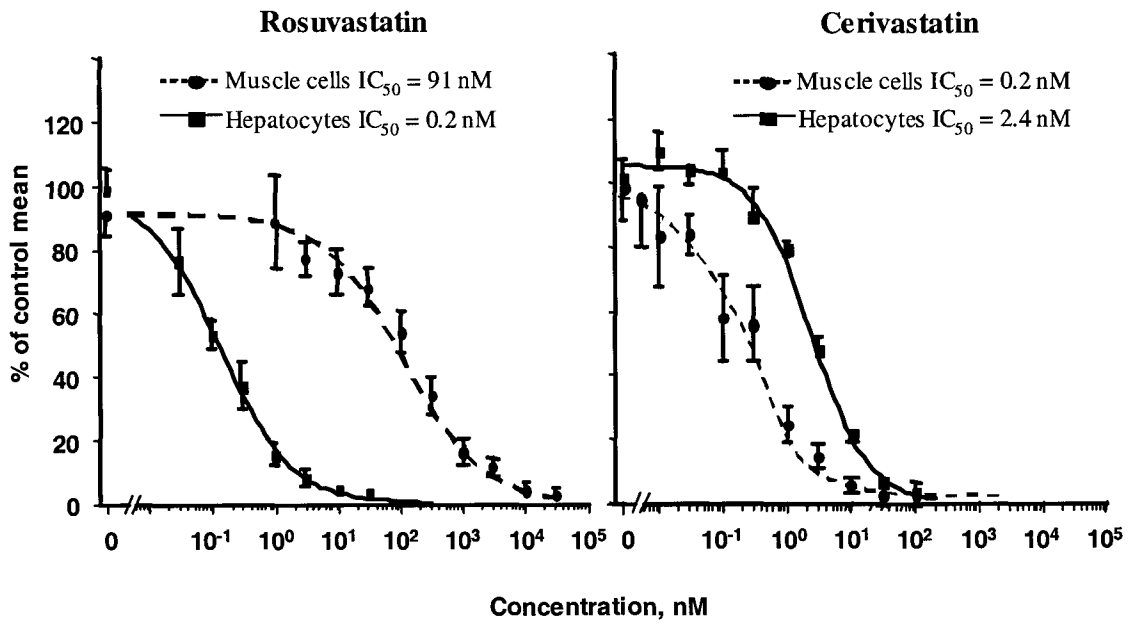
Figure 19 **Relative potencies of rosuvastatin and other statins for inhibition of cholesterol synthesis in human skeletal muscle cells**



Monolayers of human skeletal muscle cells in serum-free medium were pre-incubated with statins for 30 min before addition of [2-^{14}C] acetate for 3 h and assay of cholesterol synthesis. Data are shown as means and 95% confidence limits. Significance of differences from rosuvastatin, *p<0.05, **p<0.01, *** p<0.001.
Ceriva cerivastatin; Fluva fluvastatin; Simva simvastatin; Atorva atorvastatin; Rosuva rosuvastatin; Prava pravastatin

The cell selectivity studies that had been performed for fibroblasts and other cell types were repeated for human skeletal muscle cells and the results are shown in Figure 20.

Figure 20 **Hepatoselectivity of rosuvastatin compared to cerivastatin in human skeletal muscle cells**



These data illustrate the high selectivity of rosuvastatin as between hepatocytes (rat) and human skeletal muscle cells (IC_{50} values of 0.2 versus. 91 nM in liver and muscle cells respectively). In contrast, cerivastatin is a potent inhibitor in the muscle cells and is non-selective.

In summary, data from preclinical studies show that similar to other statins, rosuvastatin does have effects on skeletal muscle in animal models at very high doses approaching the maximum tolerated doses. Studies in cells show that cerivastatin appears to be different from other statins because of its high degree of potency in skeletal muscle cells compared to other HMG-CoA reductase inhibitors.

6.4.2.3 Clinical evaluation of skeletal muscle effects

The data presented in this section will focus on CK elevations and cases of myopathy. Brief narratives are presented for those myopathy cases that required hospitalization. In some cases, the investigator classified the myopathy as rhabdomyolysis or possible rhabdomyolysis; this is noted in the narrative. The adverse event "myalgia" was discussed in Section 6.3.1.

(a) Clinical laboratory CK data

Table 21 presents the frequencies of CK elevations of >5 x ULN, >10 x ULN, and >10,000 U/L observed in the **Combined All Controlled and RTLD Pool**. Note that for entry into the rosuvastatin clinical trial program, patients were required to have a CK value of <3 x ULN.

Table 21 **CK elevations in patients in the Combined All Controlled and Controlled RTLD Pool**

	Treatment				
	Rosuva[a] (N=8192)	**Atorva (N=3749)**	**Simva (N=2398)**	**Prava (N=1260)**	**Placebo (N=380)**
>5 x ULN, %	0.7	0.5	0.3	0.3	0
>10 x ULN, %	0.3	0.1	0.2	0	0
>10,000 U/L, %	0.04	0	0.08	0	0

[a] Includes data for patients who received rosuvastatin 80 mg.

Ceriva cerivastatin; Fluva fluvastatin; Simva simvastatin; Atorva atorvastatin; Rosuva rosuvastatin; Prava pravastatin.

As discussed in Section 6.4.1.2, the duration of therapy with rosuvastatin in this pool was longer than that for the comparator statins. In general, the frequencies of CK elevations for the various statin therapies in this pool were low. The slightly higher frequency of elevations in the rosuvastatin group was due to the contribution of elevations at the 80-mg dose. Table 22 shows the total number of patients with CK elevations > 10 x ULN in the **Combined All Controlled/Uncontrolled and RTLD Pool**. In this pool, some patients were exposed to more than one dose of rosuvastatin. The CK elevation was counted against the dose at which it occurred.

Table 22 **CK elevations >10 x ULN by dose in patients in the Combined All Controlled/Uncontrolled and RTLD Pool, including cases recorded at a local laboratory**

Rosuvastatin dose[a]	**Number of patients**	**N (%) >10 x ULN**
Total rosuvastatin	12,457[b,c]	73 (0.6)
5 mg	1317	5 (0.4)
10 mg	7727	16 (0.2)
20 mg	3883	8 (0.2)
40 mg	3957	14 (0.4)
Not down-titrated from 80 mg	3700	12 (0.3)
Down-titrated from 80 mg	825	2 (0.2)
80 mg	1574	30 (1.9)[b]

[a] Rosuvastatin dose at onset and number of patients with follow-up laboratory assessments at that dose (patients are counted in each dose group to which they were exposed; therefore, patients may be counted in more than 1 dose group).

[b] Total number of patients who received rosuvastatin and who had at least one postbaseline value.

[c] Number of patients includes 8 patients with CK elevations > 10 x ULN recorded at a local laboratory.

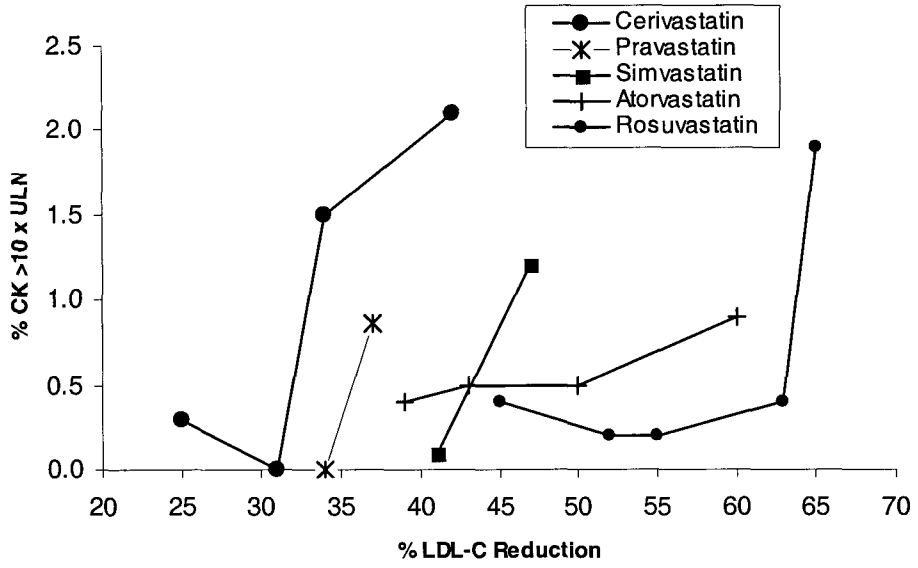
ULN upper limit of normal

At rosuvastatin doses from 5 mg to 40 mg, the frequencies of CK elevations >10 x ULN were low and similar in magnitude. Following a decision by AstraZeneca to suspend development of the 80-mg dose of rosuvastatin, additional clinical development for the 40-mg dose was initiated. Because of the possibility that the patients down-titrated from 80 mg may be a select population with demonstrated tolerability to high dose statin therapy, an analysis was performed on patients back-titrated from 80 mg versus those who were never exposed to the 80-mg dose. Of the 3957 patients at the 40-mg dose within this pool, 3700 were never exposed to 80 mg. The frequency of CK elevations >10 x ULN in this group was 0.3%, similar to that observed with lower doses of rosuvastatin.

Approximately half of the occurrences of CK elevations >10 x ULN (36 of 73) observed in the rosuvastatin clinical development program were not associated with any muscle symptoms and many were transient and resolved on continued rosuvastatin therapy. Since CK elevations are common in patients who exercise or experience muscle trauma (common occurrences in patients who will be prescribed rosuvastatin) and are an uncommon complication of statin therapy, routine monitoring for asymptomatic CK elevations is not warranted.

In order to provide context for the frequency data observed in the **Combined All Controlled/Uncontrolled and RTLD Pool** relative to other statin therapies, the data for rosuvastatin was compared with data for other statins obtained from either Summary Basis of Approval documents or prescribing information.

Figure 21 CK values >10 x ULN normalized for the percent reduction of LDL-C



Derived from Summary Basis of Approval documents, prescribing information, and Heart Protection Study Collaborative Group 2002 for comparators.

The data show that for rosuvastatin doses up to and including 40 mg, which can give LDL-C reductions greater than observed for other statins, the frequency of CK elevations >10 x ULN

was low and similar to other marketed statins. The frequency of CK elevations begins to increase only at the 80-mg dose where a 65% reduction in LDL-C is observed. Contrast this to cerivastatin where the frequency of CK elevations began to increase at LDL-C reductions of only 35% to 42%. Thus, when treating patients with cerivastatin, more patients would need to be exposed to potentially myotoxic doses in order to achieve only modest reductions in LDL-C.

(b) Cases of myopathy

For the purposes of this program, myopathy was defined as CK elevations >10 x ULN with associated muscle symptoms. All cases of myopathy were carefully reviewed to assess possible relationship to therapy. Table 23 summarizes the total number of symptomatic cases of CK elevations >10 x ULN and those considered possibly related to treatment, by dose. No cases of myopathy nor significant CK elevations were observed in studies where rosuvastatin was administered concomitantly with fenofibrate (n=103) niacin (n=128), gemfibrozil (n=20), or cyclosporine (n=10).

Table 23 CK elevations >10 x ULN plus associated muscle symptoms by dose: Combined All Controlled/Uncontrolled and RTLD Pool

Rosuvastatin dose[a]	Number of patients (N)	All cases CK >10 x ULN plus symptoms (%)	Possibly treatment-related cases (%)[b]
Total	12,457[c,d]	37 (0.3)	13 (0.1)
5 mg	1317	3 (0.2)	0
10 mg	7727	8 (0.1)	0
20 mg	3883	5 (0.1)	1 (0.03)
40 mg	3957	5 (0.1)	1 (0.03)
Not down-titrated from 80 mg	3700	5 (0.1)	1 (0.03)
Down-titrated from 80 mg	825	0	0
80 mg	1565	16 (1.0)	11 (0.7)

[a] Rosuvastatin dose at onset and number of patients with follow-up laboratory assessments at that dose (patients are counted in each dose group to which they were exposed; therefore, patients may be counted in more than 1 dose group).
[b] Per preliminary FDA assessment as of 06 June 2003.
[c] Total number of patients who received rosuvastatin and who had at least one postbaseline value.
[d] Includes 6 patients identified by CK values from a local laboratory.
ULN upper limit of normal.

An evaluation of all CK elevations >10 x ULN with symptoms regardless of causality reveals a pattern similar to that observed with CK elevation alone. The frequency of symptomatic elevations was similar for rosuvastatin doses up to and including 40 mg. An increase in frequency was observed at the 80-mg dose.

A careful evaluation of these symptomatic CK elevations revealed that a significant number (n=24) were related to other causes. Twenty-three cases were related to heavy exercise or physical activity; 19 of these cases resolved on continued therapy or following a brief interruption in therapy. Four of the 23 patients discontinued therapy, 2 patients were receiving rosuvastatin 5 mg and had CK elevations secondary to weightlifting; 1 patient was receiving rosuvastatin 10 mg and had shoulder soreness and leg cramps after house painting; and 1 patient receiving rosuvastatin 20 mg had leg cramps and pain following exercise. One patient had a symptomatic CK elevation after a fall with significant bruising just prior to her final study visit.

Of the 13 remaining cases of symptomatic CK elevations (shown in Table 23 as possibly treatment-related), 11 cases were in patients receiving 80 mg. In the two remaining lower dose cases, the relationship to therapy remains questionable. One patient was a 57-year old Caucasian male receiving rosuvastatin 20 mg for 337 days who had CK elevations (peak CK of 7,580 U/L) associated with cold sweats, muscle pains, and a markedly swollen, discolored tongue with canker sores. Rosuvastatin was discontinued at the time of the peak CK observation. Because of the prominent oral findings, Coxsackie B titres were drawn which revealed a recent type 4 infection (Coxsackie B type 4 has been associated with myopathy). The second patient was a 51-year old Caucasian male receiving rosuvastatin 40 mg for 104 days with a history of CK elevations as high as 10,000 U/L related to exercise (without statin therapy) who had CK elevations (peak CK – 15,828 U/L) along with atypical chest pain and arm pain three days after resuming a weightlifting program. The patient was admitted to the hospital because of the chest and arm pain; the patient was hydrated and a myocardial infarction was ruled out. The patient was discharged two days later and resumed treatment with rosuvastatin 40 mg. The patient has now been on treatment with rosuvastatin 40 mg for over 100 additional days without adverse effects.

An evaluation of the 11 cases of myopathy at the 80 mg dose with a possible relationship to rosuvastatin therapy revealed that 6 occurred in women and 8 occurred in patients ≥65 years of age. Nine of the 11 cases occurred in patients with baseline renal impairment (ie, creatinine clearance [CrCl] <80 mL/min [Cockcroft and Gault 1976]), and another in a patient with a baseline CrCl of 81 mL/min. Two of the cases had associated hypothyroidism prior to the event. None of the cases had a fulminant onset and resolution of the myopathy occurred soon after discontinuation of rosuvastatin therapy. None of the patients died and none needed dialysis. Seven patients receiving the 80 mg dose were hospitalized in order to administer intravenous fluids. A brief description of each of the hospitalized cases follows:

- Subject 0034/0037/0006 was a 67-year-old Caucasian male with a history of hypercholesterolemia, prostatic hypertrophy, glaucoma, cataracts, and cervical radiculopathy treated with aspirin, timolol, and tamsulosin. While receiving rosuvastatin therapy, the subject underwent an EMG for eyelid weakness. Two days later, he developed flu-like symptoms with myalgias for which he took ibuprofen. Several days later he was admitted to the hospital with rhabdomyolysis (peak CK > 20,000 U/L; peak creatinine approximately 13 mg/dL). Rosuvastatin

was discontinued at this time. He was treated with intravenous fluids and recovered.

- Subject 0034/0224/0003 was a 55-year-old Caucasian male with a history of hypercholesterolemia and hypertension treated with lisinopril/hydrochlorothiazide. After returning from a trip to Japan, he experienced generalized muscle pains along with nausea and watery diarrhea, which he attributed to food poisoning. He stopped rosuvastatin therapy and was subsequently hospitalized for evaluation of his symptoms. He was found to have a peak CK of 2509 U/L (urine myoglobin negative) and peak serum creatinine of 5.7 mg/dL. The investigator considered this patient to have rhabdomyolysis. He was treated with intravenous fluids and recovered.

- Subject 0034/0393/0012 was a 73-year-old Caucasian female with a history of hypercholesterolemia, hypertension, coronary artery disease, hypothyroidism, asthma, bronchitis, and cataracts treated with aspirin, potassium supplements, furosemide, amlodipine, and hormone replacement therapy. After approximately 10 months of therapy, she reported ongoing muscle aches. One week following an exacerbation of her bronchitis for which she received treatment, she noticed bilateral lower extremity weakness and was admitted to the hospital with a diagnosis of rhabdomyolysis. In the hospital, she had a peak CK of 11,123 U/L and her creatinine was 2.3 mg/dL (baseline serum creatinine 1.2 mg/dL). Rosuvastatin was discontinued, and she was treated with intravenous fluids and recovered.

- Subject 0034/0437/0012 was a 67-year-old Caucasian female with a history of hypercholesterolemia, coronary heart disease (EF 35%), pulmonary edema, peripheral vascular disease, diabetes, acute renal failure, and elevated CK levels treated with aspirin, glimepiride, hydrochlorothiazide, amlodipine/benazepril, pioglitazone, oxycodone, acetaminophen, nitrates, clopidogrel, and carvedilol. The subject was admitted to the hospital with lethargy and weakness, and diagnosed with rhabdomyolysis. Rosuvastatin was discontinued. Her peak CK during the hospitalization was 7484 U/L and her peak serum creatinine was 10.7 mg/dL. She was treated with intravenous fluids and recovered.

- Subject 0025/0264/0017 was a 75-year-old Caucasian female with a history of hypercholesterolemia, hypertension, glaucoma, peripheral edema, insomnia, and peripheral vascular disease treated with aspirin, hydrochlorothiazide, cortisone, Valium, and ofloxacin. She was admitted to the hospital with acute renal failure and myopathy. Her peak CK was 34, 548 U/L (plasma myoglobin was 13,810 ng/ml) and her peak serum creatinine was 1.9 mg/dL (baseline serum creatinine was 1.2 mg/dL). She was treated with intravenous fluids and recovered.

- Subject 0034/0229/0004 was a 72-year-old Caucasian female with a history of hypercholesterolemia who experienced muscle pains and weakness. She subsequently experienced weakness in her legs and fell and was hospitalized. Her

peak CK was 16,280 U/L (serum myoglobin 12,373 ng/ml) and her serum creatinine was 0.9 mg/dL. She was treated with intravenous fluids and recovered.

- Subject 0034/0317/0003 was a 63-year-old Caucasian female with a history of hypercholesterolemia and treated hypertension hospitalized with severe gastroenteritis and dehydration. During the hospitalization a consultant made a notation regarding "possible rhabdomyolysis" (peak CK 3486). The investigator stated that the evidence was insufficient to make this diagnosis; however, the case is included here for completeness. The patient recovered following treatment with intravenous fluids.

The estimated frequency of treatment-related myopathy with the 80-mg dose of rosuvastatin is 0.7% (11/1574). Of these 11 cases, 5 occurred within 6 months of initiating treatment with rosuvastatin 80 mg; 9 occurred within one year of initiating treatment with rosuvastatin 80 mg. No evidence for a sex-based predisposition is evident from these cases; however, most cases of myopathy observed with the 80-mg dose were in elderly patients.

Myopathy was also observed with comparator statins during the program. Two cases were observed with simvastatin at the 80-mg dose, giving a frequency of 0.4% (2/501) at this dose. These cases are described below:

- Subject 0099/4004/0322 was a 77-year-old Caucasian female with a history of hypertension being treated with candesartan, hydrochlorothiazide, and bisoprolol. She was hospitalized on day 28 of simvastatin therapy with myalgias and a diagnosis of rhabdomyolysis (peak CK value of 26,400 U/L, plasma myoglobin of 14,517μg/L). She was treated with intravenous fluids and recovered.

- Subject 0099/8007/0443 was a 79-year-old African American female with a history of Alzheimer's Disease being treated with hormone replacement therapy and aspirin. She was found to have a peak CK value of 13, 420 U/L and urine myoglobin of 95,000 μg/L after 4 weeks of treatment with simvastatin. The CK elevations resolved after discontinuation of therapy.

The frequency of myopathy observed for rosuvastatin at doses up to and including 40 mg was lower than that observed for simvastatin 80 mg, as seen within this clinical development program and as reported in the simvastatin prescribing information (0.3% for 80 mg; PDR 2001 [simvastatin]). In addition, the frequency of hospitalizations for myopathy was similar.

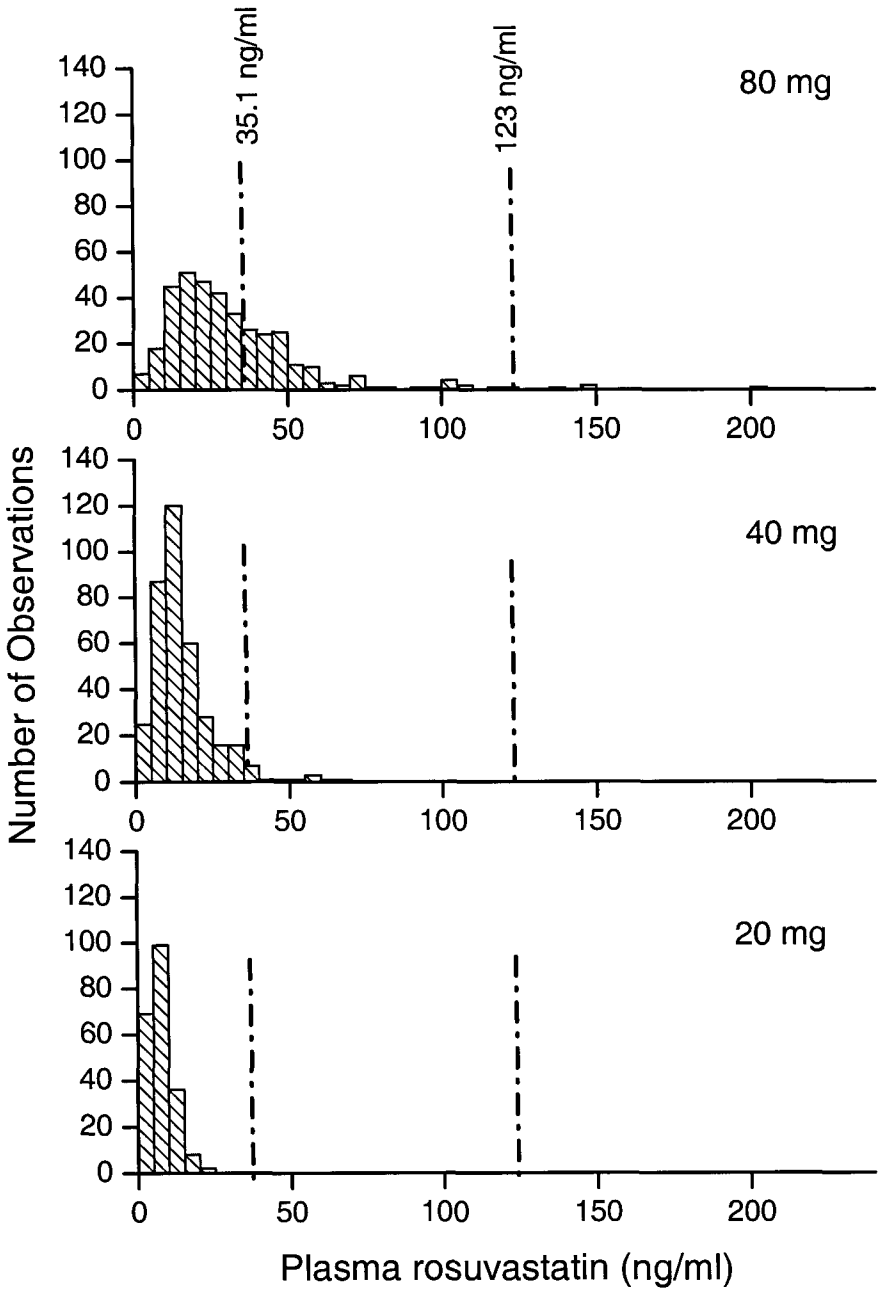
(c) Rosuvastatin exposure in patients with myopathy

The systemic exposure of 9 patients with myopathy was compared to the exposure in 387 patients from a pool of Phase II/III trials (Trials 8, 23, 33, 35, and 34 substudy) who did not experience myopathy. In Trials 8, 23, 33, and 35, rosuvastatin plasma concentrations were measured following 2, 4, and 6 weeks of exposure. In the Trial 34 substudy, patients had rosuvastatin plasma concentrations determined while receiving rosuvastatin 80 mg and

following down titration to 40 mg. In the Phase II/III studies blood samples were obtained 8 to 16 hours after the previous days dose. Serum rosuvastatin concentrations in patients with myopathy were determined from samples obtained for safety assessments and collected approximately 10 hours post the previous days dose.

In Figure 22 rosuvastatin serum concentrations in patients with myopathy are compared to the plasma concentrations in asymptomatic patients receiving rosuvastatin 20, 40, and 80 mg. For the 20-mg dose, 84 patients contributed 214 measurements; at the 40 mg dose 203 patients contributed 367 measurements; and at the 80-mg dose, 198 patients contributed 366 measurements. Based on these values the percent of patients at each dose above the threshold value for myopathy is 0 (20 mg), 3% (40 mg), and 17% (80 mg). All these measurements were plotted in the figure as a frequency distribution relative to the plasma concentration values. The lowest value observed for a patient with myopathy and the median value for the nine patients are shown as dotted lines.

Figure 22 **Rosuvastatin steady-state plasma exposure in patients (Trials 8, 23, 33, 34 substudy, and 35) compared to minimum and median exposure among 9 patients with myopathy**



The serum concentrations of rosuvastatin in patients with myopathy are substantially higher than those of asymptomatic patients dosed at the 20- and 40-mg doses. No overlap of values was observed at the 20-mg dose and approximately 6% of values at the 40 mg dose had overlap with the patients with myopathy. At the 80-mg dose approximately 30% of values

had overlap with the patients with myopathy. The incidence of myopathy at the 80-mg dose for possibly treatment-related cases is 0.7%. Higher plasma exposure contributes to risk for myopathy. However, other factors must also contribute since plasma exposure alone does not account for myopathy risk.

6.4.2.4 Conclusions of skeletal muscle effects

Myalgia, creatine kinase elevations, myopathy, and rhabdomyolysis are well-recognized complications of statin therapy. The frequency of these complications in patients given rosuvastatin is consistent with the data reported for other statins (Maron 2000, PDR 2001 [simvastatin]). This finding would be expected based on the preclinical pharmacology data presented in Section 6.4.2.2 of this document, which showed that, like pravastatin and in striking contrast to cerivastatin, rosuvastatin is a relatively low potency inhibitor in human skeletal muscle cells. This is in accord with the relative hydrophilicity of rosuvastatin which results in a low rate of passive diffusion across cell membranes.

Data presented in Section 6.3.1 from the **All Controlled Pool** showed that myalgia was reported as an adverse event for rosuvastatin with an overall frequency of 3.5% which was similar to that reported for atorvastatin (3.4%) and simvastatin (3.4%). In the **Fixed-dose Controlled Pool**, the frequency of myalgia at rosuvastatin doses of 5 mg to 40 mg was low and similar in magnitude across the dose range (3.9% at 5 mg, 3.3% at 10 and 20 mg, 1.6% at 40 mg); however, an increased frequency was observed at 80 mg (7.2%).

An evaluation of CK elevations >10 x ULN from the **All Controlled Pool** showed that the overall frequency was low and similar to that for comparator statins in the program. As shown in the **Combined All Controlled/Uncontrolled and RTLD Pool**, the frequency of CK elevations >10 x ULN was low and similar at rosuvastatin doses of 5 to 40 mg, but increased at the 80-mg dose. The frequency of CK elevations at doses from 5 to 40 mg compared favorably to similar data reported for other marketed statins.

The incidence of myopathy at rosuvastatin doses up to and including 40 mg irrespective of causality was ≤0.2% at each dose. This value compares favorably to the incidence of myopathy observed for simvastatin 80 mg in this program (0.4%) and reported in the simvastatin prescribing information (0.3% for 80 mg; PDR 2001 [simvastatin]). The overall incidence of myopathy did increase at the 80 mg dose (1.0%) of rosuvastatin. However, careful evaluation of the cases of myopathy at all doses of rosuvastatin that were observed in the rosuvastatin clinical development program revealed that rosuvastatin was not the most likely causative factor in many instances. In the majority of cases, exercise or muscle trauma, not drug-induced myopathy, was the most likely explanation, and many cases resolved with continued rosuvastatin therapy or after a transient interruption in therapy. An evaluation of these cases of myopathy at the 80-mg dose gives some clues to potential risk factors that may predispose patients treated with rosuvastatin to myopathy. The factors identified were known risk factors for other statins; they are advanced age, hypothyroidism, and renal insufficiency (Maron 2000). The importance of age as a risk factor for myopathy at the 80-mg dose is demonstrated by the fact the incidence of myopathy was 0.2% (2/1200) in patients <65 years of age compared to 2.3% (9/383) in patients ≥65 years of age.

In summary, the current data supports the safety of rosuvastatin at doses up to 40 mg with regard to skeletal muscle effects.

6.4.3 Renal effects

6.4.3.1 Background

Early data from controlled clinical trials from the rosuvastatin development program suggested that proteinuria could be an effect of high dose statin therapy. Because of this early finding, the nature, frequency, and magnitude of the renal effects of rosuvastatin were extensively evaluated in both clinical and preclinical studies. The data showed that proteinuria, primarily tubular in nature, was observed in patients predominantly at the 80-mg dose of rosuvastatin. Preclinical data suggested that these findings were an effect of HMG-CoA reductase inhibition in renal tubular cells. Potentially adverse effects of statin therapy on the kidney are not well documented except in the context of renal failure associated with rhabdomyolysis. In this instance, the renal effects are due to the toxic effects of myoglobin. The development of proteinuria in patients following therapy with simvastatin 40 mg has been reported (Deslypere 1990); however, this finding was refuted in a subsequent report (La Belle and Mantel 1991).

In this section, the clinical and preclinical data are presented. Data from the **Combined All Controlled and RTLD Pool** are used to compare the dose-related frequency of proteinuria and serum creatinine changes observed with rosuvastatin and the comparator statins included in the program. Data from the **Combined All Controlled/Uncontrolled and RTLD Pool** are used to assess the long-term effects (≥48 and ≥96 weeks) of rosuvastatin on renal function. In addition to evaluation of these pools to assess effects on laboratory parameters, clinical adverse events relevant to the renal findings are reviewed.

In the evaluation of renal laboratory parameters, the following conventions are used. The development of dipstick positive proteinuria is evaluated based on changes from none or trace at baseline. Serum creatinine changes are expressed as mean percentage changes from baseline and elevations > 30% from baseline (Ruilope 2001). In the pools presented in this section, the number of patients with serum creatinine measurements is greater than the number of patients with urine protein measurements because serum creatinine measurements were performed more frequently than urinalysis measurements in the clinical trial program.

6.4.3.2 Evaluation of urinalysis data

The finding of proteinuria on urine dipstick testing led to additional studies to determine the most appropriate method for evaluating urine dipstick results. Normal individuals excrete <150 mg of protein per day (or <0.15 mg protein/mg creatinine; Wingo 2000, Schwab 1987, Rodby 1995). An evaluation of the amount of urine protein excreted in patients with "none or trace" urine dipstick protein levels at baseline who developed "+" proteinuria (n=502) or "++ or greater" (n=278) revealed that only 35% of patients in the former category had elevated urinary protein levels compared to over 90% in the later category (based on the finding of a urine protein-to-creatinine ratio >0.15 mg protein/mg creatinine). In those patients who developed 2+ or greater proteinuria, mean (SD) and median total protein excretion were

estimated to be 800 (550) mg per day and 600 mg per day, respectively. Based on these findings, proteinuria analyses presented in this section focus on patients who develop "++ or greater" proteinuria since this identifies with a high degree of certainty, patients whose urinary protein excretion increased from a normal to an elevated level.

Table 24 shows the proportion of patients with urine dipstick protein levels that were "none or trace" at baseline who, following treatment with either rosuvastatin or comparator statins, developed an increase in dipstick protein level to "++ or greater" at any follow-up visit. The data presented is derived from the **Combined All Controlled and RTLD Pool**. Trials in this pool ranged from 6 to 52 weeks in duration.

Table 24 Proportion of patients who developed dipstick-positive proteinuria at any time: Combined All Controlled and RTLD Pool

		% (95% CI) with urine dipstick protein shifts
Treatment	**N[a]**	**"none or trace" to "++ or greater"**
Placebo	330	0.6 (0.07 to 2.2)
Rosuvastatin		
5 mg	602	0.5 (0.1 to 1.4)
10 mg	1080	0.8 (0.4 to 1.6)
20 mg	1319	0.5 (0.2 to 1.1)
40 mg	2375	2.8 (2.2 to 3.5)
80 mg	747	11 (8.8 to 13.4)
Pravastatin		
20 mg	174	1.1 (0.1 to 4.1)
40 mg	64	0 (0 to 5.6)
Atorvastatin		
10 mg	638	0.6 (0.2 to 1.6)
20 mg	609	0.8 (0.3 to 1.9)
40 mg	225	0.4 (0.01 to 2.5)
80 mg	342	0.3 (0.01 to 1.6)
Simvastatin		
20 mg	458	1.1 (0.4 to 2.5)
40 mg	323	0.6 (0.08 to 2.2)
80 mg	325	0.3 (0.01 to 1.7)

[a] Number of patients with available urinalysis results.
N Number of patients; CI confidence interval

As shown, the overall frequency of proteinuria at doses from 5 mg to 20 mg of rosuvastatin was similar to that observed with marketed dose ranges of other statins. The frequency of proteinuria was increased at the 80-mg dose. Although an increase in proteinuria was observed at the 40-mg dose, the frequency was more like that observed at lower doses of rosuvastatin than that observed at the 80-mg dose. In a prospective comparison of urine dipstick protein shifts in patient receiving rosuvastatin 40 mg (n=410) versus simvastatin 80 mg (n=304) shifts to ++ or greater were observed in 1% versus 0.3% of the study participants, respectively.

An evaluation of hematuria from this same pool of patients showed that there was no dose-related increase in frequency of isolated hematuria in patients receiving doses up to and including 80 mg of rosuvastatin. Hematuria (++ or greater) was observed in 3.8% of patients who developed proteinuria while receiving the 80-mg dose of rosuvastatin, ≤0.3% of patients receiving lower doses of rosuvastatin or a comparator statin had combined proteinuria/hematuria.

Many patients who entered a controlled clinical trial subsequently went on to receive rosuvastatin in a long-term extension trial. Table 25 shows data from the **Combined All Controlled/Uncontrolled and RTLD Pool** from patients who developed "++ or greater" proteinuria from baseline at any time.

Table 25 Percentage of patients with proteinuria following treatment with rosuvastatin: Combined All Controlled/Uncontrolled and RTLD Pool

Dose of rosuvastatin	N	% (95% CI) with proteinuria at any time
5 mg	906	1.0 (0.5 to 1.9)
10 mg	2279	1.4 (0.9 to 1.9)
20 mg	1992	1.6 (1.1 to 2.2)
40 mg	3172	3.5 (2.9 to 4.2)
Not down-titrated from 80 mg	2860	3.1 (2.5 to 3.8)
Down-titrated from 80 mg	724	3.2 (2.0 to 4.7)
80 mg	1157	16.2 (14.2 to 18.5)

N Number of patients; CI confidence interval

The results of the proteinuria analysis observed in this pool were similar to the results seen in the **Combined All Controlled and RTLD Pool** (Table 24).

Note that in the 724 patients who were down-titrated from the 80-mg dose, the frequency of proteinuria was similar to that observed in patients receiving the 40-mg dose who never received therapy with 80 mg, suggesting that proteinuria was reversible. This was confirmed in an analysis of urine protein data during therapy with both the 80-mg and 40-mg dose in

over 700 patients. The percentage of patients with shifts from "none or trace" to "++ or greater" fell from 7.4% to 1.9% on the first follow-up visit following down-titration.

Many patients who entered a controlled clinical trial subsequently went on to receive rosuvastatin in a long-term extension trial. Data from patients in the **Combined All Controlled/Uncontrolled and RTLD Pool** showed that the frequency of proteinuria at the last visit in patients who continued therapy with rosuvastatin was 0.3. 0.5, 0.7, 1.2 and 10.1% for the 5-, 10-, 20-, 40-, and 80-mg doses of rosuvastatin, respectively.

Since the duration of exposure to rosuvastatin for some of the patients included in Table 25 was shorter term, an evaluation of the effects of ≥96 weeks of treatment was performed. In this analysis, the 40-mg dose group included patients who completed therapy at 80 mg as well as patients receiving 40 mg who were down-titrated or not down-titrated from rosuvastatin 80 mg (Table 26).

Table 26 Percentage of patients with proteinuria after ≥96 weeks of rosuvastatin treatment: Combined All Controlled/Uncontrolled and RTLD Pool

Dose of rosuvastatin	N	% (95% CI) with proteinuria at any time	% (95% CI) with proteinuria at last visit
5 mg	261	1.1 (0.2 to 3.3)	0 (0 to 1.4)
10 mg	838	2.0 (1.2 to 3.2)	0.5 (0.1 to 1.2)
20 mg	112	4.5 (1.5 to 10.1)	0.9 (0 to 4.9)
40 mg	100	4.0 (1.1 to 9.9)	2.0 (0.2 to 7.0)
≥40 mg[a]	807	16.9 (14.3 to 19.6)	1.2 (0.6 to 2.3)
80 mg	590	16.8 (13.9 to 20.0)	6.1 (4.3 to 8.3)

[a] Includes patients who back-titrated from the 80-mg dose.

The data show that the frequency of development of "++ or greater" proteinuria remained low at doses up to and including 40 mg after therapy for over 96 weeks. Importantly, the frequency of proteinuria observed at the last visit was less than that observed at any time indicating that the proteinuria was transient in many cases. Finally, the fact that the frequency of proteinuria was low in the ≥40-mg dose group provides evidence that irreversible renal parenchymal injury did not occur following treatment with the 80-mg dose of rosuvastatin.

6.4.3.3 Nature of proteinuria

(a) Preclinical toxicology

In a number of experimental animals including rat (Pisipirigos 1999, fluvastatin and cerivastatin SBAs), mouse (simvastatin SBA), hamster (fluvastatin SBA), rabbit (Kornbrust 1988, Gerson 1989, Fukushige 1998, pravastatin SBA) and mini-pig (von Keutz 1998), degenerative changes in the proximal tubules of the kidney have been observed following administration of statins, albeit at doses sufficiently high to cause morbidity in the animals.

Similarly, high doses of rosuvastatin that cause morbidity in rat and rabbit have also been found to result in the same changes to the renal tubules. In the Cynomolgus monkey, with rosuvastatin, minimal or mild proximal tubular epithelial cell necrosis and regeneration was found following 6 months treatment at the high dose (30 mg/kg/day) in animals that showed few other treatment-related changes. At the no-effect level for this change in the Cynomolgus monkey, the mean AUC exposure was 4 times greater than in humans at the 40-mg dose of rosuvastatin. It is of note that pravastatin has also been reported to induce renal tubular degenerative changes in the Cynomolgus monkey, at non-morbid doses (Manabe S 1989).

(b) Clinical findings

Measurements of urinary proteins used as markers for renal handling of proteins at the glomerular (IgG and transferrin) and tubular (alpha-1 microglobulin, beta-2 microglobulin, retinol binding protein, N-acetyl-beta-D-glucosaminidase [NAG]) level were assessed in order to evaluate the origin of the proteinuria. Nearly all of this data was obtained from patients who received the 80-mg dose of rosuvastatin in an open-label extension trial and who were subsequently down-titrated to the 40 mg dose. In addition to these measurements, qualitative assessments of the pattern of proteinuria were performed using gel electrophoresis (SDS-PAGE).

The results showed that the proteins excreted in patients who developed dipstick positive proteinuria reflected a tubular, rather than glomerular, alteration of protein handling. The data supporting this conclusion are as follows. First, estimated total urine protein excretion was less than 1.5 mg protein/mg creatinine in approximately 90% of patients, which is similar to levels reported for patients with tubular proteinuria (Wingo 2000). Second, quantitative measurements of the proteins excreted revealed elevated levels of beta-2-microglobulin, NAG, and albumin, consistent with a tubular etiology. And third, the pattern of proteins observed on gel electrophoresis was primarily tubular.

No other evidence of altered renal proximal tubular function (eg, glucose, phosphate, calcium, or potassium handling) was apparent in patients receiving any of the doses of rosuvastatin.

The fact that urinary myoglobin concentrations were within the normal range in over 90% of the patients who had a urine dipstick protein shift from "none or trace" to "++ or greater" suggested that subclinical myopathy was not indicated in the etiology of the proteinuria. Similarly, there was no association between on-treatment LDL-C levels and the frequency of increased urine dipstick protein levels indicating the proteinuria did not result from low levels of LDL-C. The proteinuria data for patients receiving the 80-mg dose suggested that older individuals, particularly older women, were at increased risk for development of proteinuria.

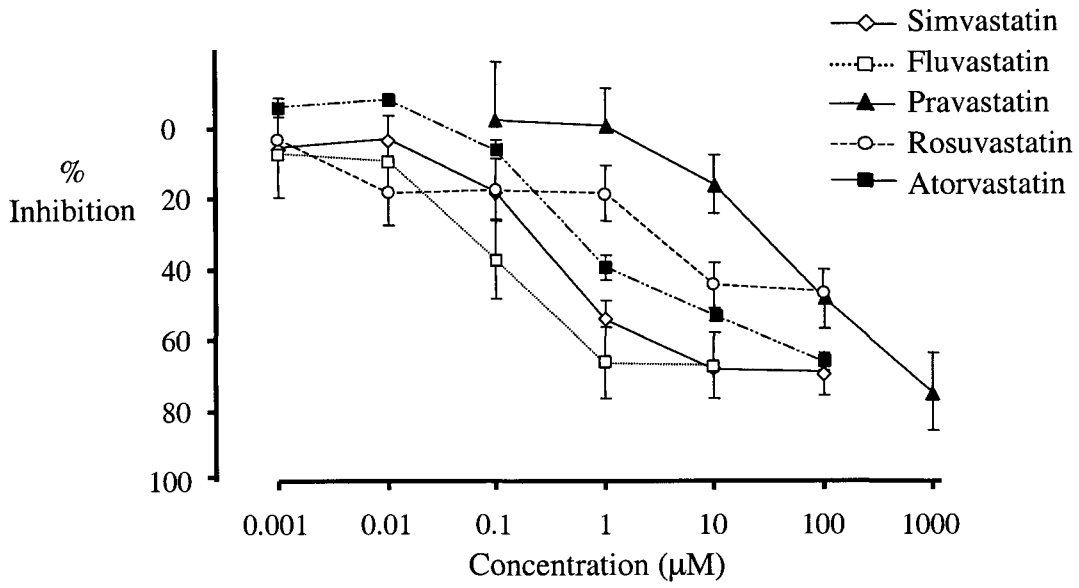
(c) Pre-clinical investigation of the effects of statins in proximal renal tubular cells

Based on the similar pattern of effect of statins on renal tubular histopathology from pre-clinical toxicology and the dose-related, tubular pattern of proteinuria observed clinically for rosuvastatin, a hypothesis was proposed. Inhibition of HMG-CoA reductase in renal proximal tubule cells leads to reduced efficiency of protein re-absorption from the lumen of proximal tubule cells.

It is well documented in the statin literature that a wide range of cell functions can be altered or abrogated as a result of reduced levels of mevalonate and particularly mevalonate metabolites such as the isoprenoid pyrophosphates, including farnesyl (FPP) and geranylgeranyl pyrophosphates (GGPP). These metabolites are required for the secondary modification and normal function of many cell proteins, in particular, the GTPases (G proteins) that are responsible for a wide variety of regulatory functions within cells.

The effects of statins on tubular protein re-absorption were studied using a line of cells derived from Opossum kidney (OK cells) since these cells have been used extensively to study the mechanisms and regulation of protein re-absorption (Malstron 1987). Figure 23 shows that five statins inhibited the uptake of fluorescently labeled albumin (FITC-BSA) by OK cells in a concentration-dependent manner.

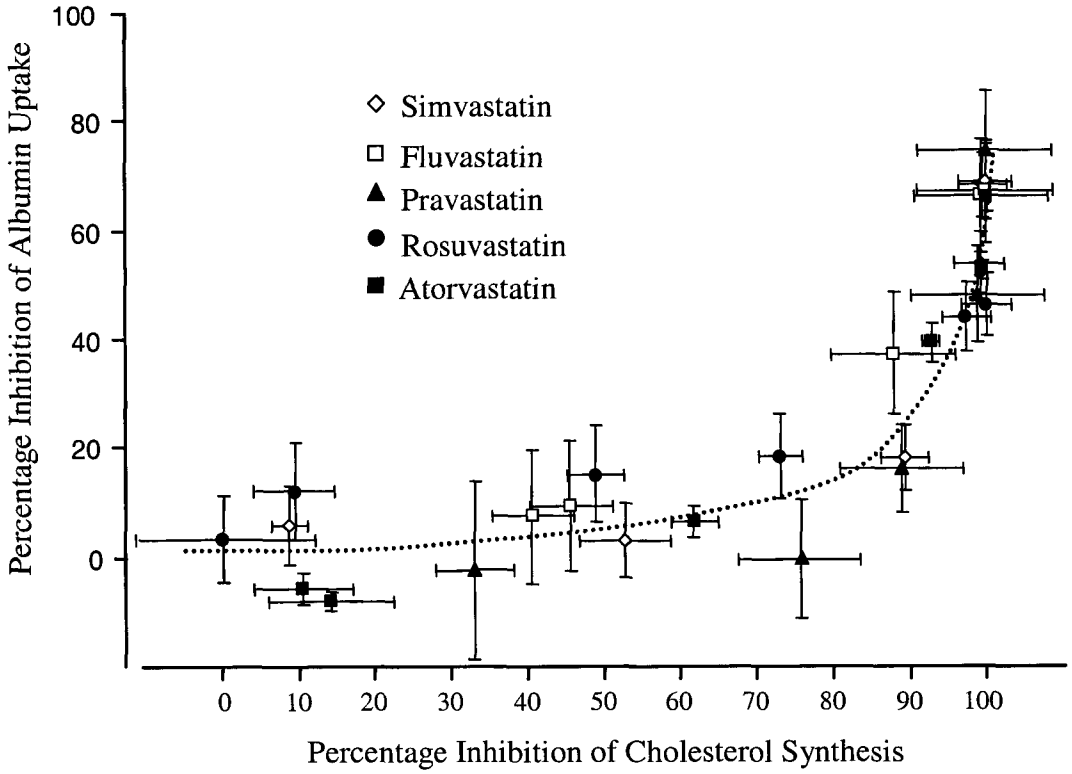
Figure 23 Effects of statins on albumin uptake by opossum kidney cells



Results are expressed as percentage inhibition of FITC-albumin uptake in the statin-treated cells compared to cells treated with vehicle medium. The data are the combined results of 2-4 independent experiments with 24-hour exposure to statins and are expressed as mean and standard errors.

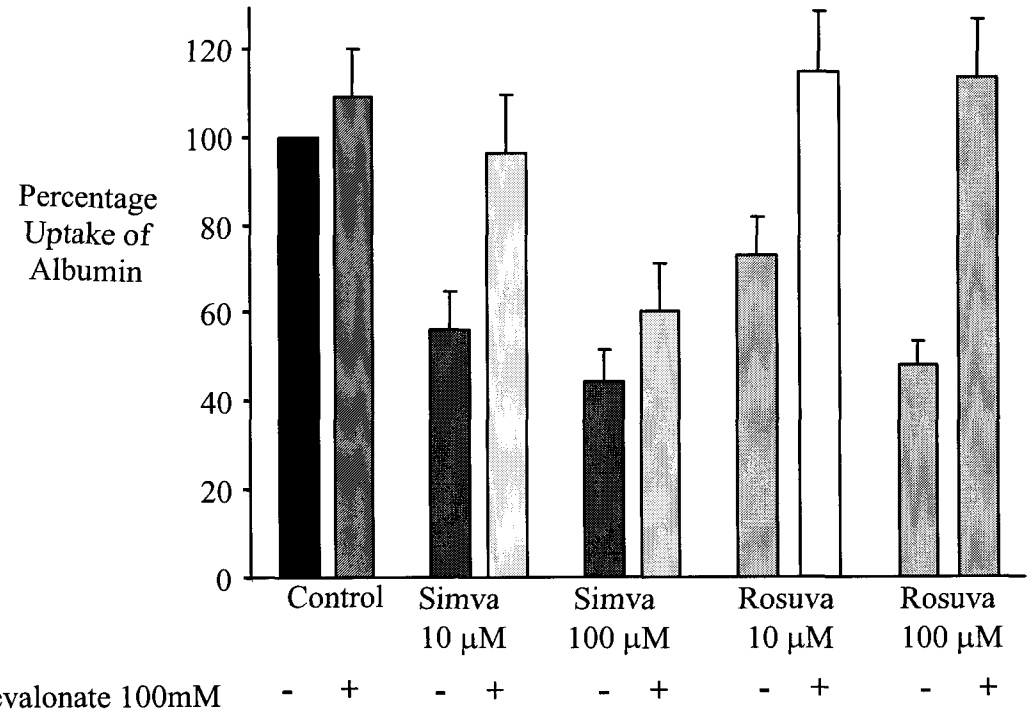
As expected, cholesterol synthesis was inhibited by all the statins in OK cells. As shown in Figure 24, the degree of inhibition of protein uptake (measured after 24-hour exposure to statins) was found to be proportional to the inhibition of sterol synthesis in the cells (measured 3.5 hours after addition of statin). The relationship was independent of the particular statin (Figure 24). The N-desmethyl metabolite of rosuvastatin was also tested and found to be less potent than rosuvastatin and to conform to the same relationship. In general, the effect of statins on protein uptake was apparent at statin concentrations that resulted in relatively high degree (>80%) inhibition of cholesterol synthesis. Importantly, measurements of cell protein and cell ATP levels showed that the effect of statins on albumin uptake was not related to cell toxicity.

Figure 24 **Relationship of inhibition of albumin uptake to degree of inhibition of cholesterol synthesis in OK cells**



The statin-induced inhibition of tubular protein uptake was reversed by the co-incubation of OK cells with mevalonate, the immediate product of HMG-CoA reductase (Figure 25). This is strong evidence that the effect on protein uptake is linked to inhibition of HMG-CoA reductase in the cells. Further experiments demonstrated the inhibition of albumin uptake by statins could be completely prevented also by the addition of the intracellular metabolite of mevalonate, GGPP. This was in accord with the hypothesis that the statin effect on protein uptake could be due to reduced isoprenylation of regulatory GTPases which are known to be involved in the process of receptor-mediated endocytosis. Similar statin-induced inhibition of tubular protein uptake was observed in a human kidney cell line. Co-administration with mevalonate also reversed the inhibition of protein uptake in these cells.

Figure 25 **Amelioration of statin inhibition of albumin uptake by mevalonate**



OK cells were incubated with simvastatin or rosuvastatin (10 and 100 μM), or vehicle control medium for 24 h with (light bars) and without (dark bars) the co-addition of 100 μM mevalonate. The results are expressed as percentage of the control. The data are the combined results of two independent experiments and are expressed as mean and standard errors.

In summary, the results described in this section show that statins inhibit the process of protein uptake in proximal tubular cells and that his effect is linked to inhibition of HMG-CoA reductase and to reduced availability of mevalonate and its metabolites.

6.4.3.4 Evaluation of serum creatinine data

The principal concern with the observation of proteinuria is that it may predate development of an impairment of renal excretory function (clinically recognized by an increase in serum creatinine level). Table 27 shows the effects of statin treatment on serum creatinine from patients in the **Combined All Controlled and RTLD Pool** based on creatinine measurements from the central laboratory. The data presented show the percent change in serum creatinine from baseline to the last visit in a controlled trial.

Table 27 Serum creatinine levels: Combined All Controlled and RTLD Pool

Dose	N	Serum creatinine (μmol/L)	
		Mean baseline[a] (SD)	% change (SD)
Placebo	313	94.7 (18.2)	0.3 (8.7)
Rosuvastatin			
5 mg	635	96.6 (15.8)	-1.6 (7.8)
10 mg	2871	97.7 (16.8)	-1.4 (10.3)
20 mg	1413	96.1 (17.9)	-1.6 (10.6)
40 mg	2090	93.7 (16.5)	-1.3 (9.8)
80 mg	964	97.2 (16.4)	2.2 (49.2)
Atorvastatin			
10 mg	973	98.2 (18.4)	-1.7 (8.9)
20 mg	822	97.4 (17.8)	-2.3 (8.9)
40 mg	220	97.4 (17.0)	-2.2 (8.1)
80 mg	533	97.4 (17.3)	-3.9 (8.2)
Simvastatin			
10 mg	161	93.2 (15.6)	-0.4 (8.5)
20 mg	789	97.7 (16.5)	-1.7 (8.6)
40 mg	362	95.5 (16.6)	-2.1 (9.1)
80 mg	495	92.2 (15.9)	-1.3 (9.9)
Pravastatin			
10 mg	158	96.0 (18.0)	-1.8 (8.4)
20 mg	342	97.3 (15.2)	-2.1 (7.8)
40 mg	489	97.8 (16.8)	-1.3 (8.5)

[a] Baseline is defined as the baseline from the controlled study.
N number of patients; SD standard deviation

Mean serum creatinine levels decreased following treatment with rosuvastatin at doses up to and including 40 mg. This finding was similar to that observed with other statins. At the 80-mg dose, the mean serum creatinine increased; however, a single patient with acute renal failure influenced this value. Excluding this patient, the mean % change in serum creatinine (SD) in the 80-mg dose group was 0.6 (13.7). Table 28 shows the percentage of patients from

the **Combined All Controlled and RTLD Pool** who had a >30% increase in serum creatinine at any time during a controlled trial.

Table 28 Percentage of patients with a >30% increase in serum creatinine at any time: Combined All Controlled and RTLD Pool

Dose	N	% (95% CI) with a >30% increase in serum creatinine
Placebo	371	0.3 (0.01 to 1.5)
Rosuvastatin		
5 mg	658	0.5 (0.09 to 1.3)
10 mg	2976	1.0 (0.7 to 1.4)
20 mg	1492	1.2 (0.7 to 1.9)
40 mg	2261	1.4 (1.0 to 2.0)
80 mg	983	4.1 (2.9 to 5.5)
Atorvastatin		
10 mg	1410	0.6 (0.2 to 1.1)
20 mg	1579	0.8 (0.4 to 1.4)
40 mg	232	0 (0 to 1.6)
80 mg	535	0 (0 to 0.7)
Simvastatin		
10 mg	161	0 (0 to 2.3)
20 mg	1225	0.5 (0.2 to 1.1)
40 mg	515	0.4 (0.05 to 1.4)
80 mg	500	0.8 (0.2 to 2.0)
Pravastatin		
10 mg	159	0 (0 to 2.3)
20 mg	358	0.3 (0.01 to 1.5)
40 mg	745	0.4 (0.08 to 1.2)

N number of patients; CI confidence intervals

The data show that the frequency of serum creatinine increases >30% for rosuvastatin at doses from 5 to 40 mg and the comparator statins was low and comparable. An increased frequency was observed at the 80-mg dose of rosuvastatin.

The rate of serum creatinine elevations >30% per 1000 patient-years exposure was 10, 38, 51, 42, and 331 at the 5-, 10-, 20-, 40-, and 80-mg doses of rosuvastatin, respectively. The rate of serum creatinine elevations for comparator statins ranged as high as 38 for atorvastatin (20 mg), 60 for simvastatin (80 mg), and 16 for pravastatin (40 mg).

Serum creatinine data from patients in the **Combined All Controlled/Uncontrolled and RTLD Pool** can be used to evaluate the effects of long-term rosuvastatin treatment on serum creatinine levels (Table 29) since many patients who entered a controlled clinical trial subsequently went on to receive rosuvastatin in a long-term extension trial.

Table 29 Serum creatinine changes following long-term treatment with rosuvastatin: Combined All Controlled/Uncontrolled and RTLD Pool

Dose at last scheduled visit	Serum creatinine (µmol/L) at last scheduled visit		Serum creatinine increase >30% at any time	
	N[a]	% (SD) change	N[b]	% (95% CI)
5 mg	348	-3.7 (10.8)	990	2.6 (1.7 to 3.8)
10 mg	5138	-1.1 (10.7)	6851	2.3 (1.9 to 2.6)
20 mg	1698	0.3 (11.3)	2860	2.4 (1.9 to 3.0)
40 mg	1650	-2.7 (12.0)	3726	1.8 (1.4 to 2.3)
Not down-titrated from 80 mg	840	-0.6 (11.3)	3056	1.8 (1.4 to 2.3)
Down-titrated from 80 mg	810	-4.8 (12.4)	824	1.8 (1.0 to 3.0)
80 mg	104	1.6 (14.0)	1449	6.9 (5.7 to 8.3)

[a] Patients were counted only at the last visit.

[b] Patients were assessed for maximum increases in serum creatinine at each dose to which they were exposed, thus patients could be included at more than one dose group.

N *number of patients*; SD *standard deviation*

The data revealed similar effects on mean serum creatinine levels at rosuvastatin doses from 5 mg to 40 mg. Note that in a large population of patients down-titrated from the 80-mg dose to the 40-mg dose, the mean serum creatinine level decreased 4.8 µmol/L.

The frequency of serum creatinine increases >30% at any time was similar at rosuvastatin doses of 5 to 40 mg and was at higher the 80-mg dose of rosuvastatin. Note that the frequency at the 40-mg dose was 1.8%, both in patients who were down-titrated, as well as those not down-titrated to 40 mg from 80 mg.

The rate of serum creatinine elevations >30% per 1000 patient-years exposure was 19, 20, 36, 34, and 50 at the 5-, 10-, 20-, 40-, and 80-mg doses of rosuvastatin, respectively. These rates were comparable to those seen in controlled clinical trials with rosuvastatin 5 to 40 mg and the comparator statins as described above.

The effects of rosuvastatin treatment on serum creatinine changes in patients who had ≥48 weeks and ≥96 weeks of treatment (a subset of patients from the pool presented in Table 29) are summarized in Table 30.

Table 30 Serum creatinine changes following long-term (≥48 or ≥96 weeks) treatment with rosuvastatin: Combined All Controlled/Uncontrolled and RTLD Pool

Dose at last scheduled visit	≥48 weeks exposure		≥96 weeks exposure	
	N	Mean (SD) creatinine	N	Mean (SD) creatinine
5 mg	468	-3.6	262	-4.7
10 mg	3132	-1.5	887	-5.0
20 mg	465	-1.2	118	-4.3
40 mg	266	-2.2	105	-6.2
≥40 mg	1010	-4.8	872	-5.6
80 mg	857	-1.9	630	-2.9

N number of patients; SD standard deviation

At ≥48 and ≥96 weeks of treatment with rosuvastatin, mean serum creatinine levels decreased at all doses up to and including 80 mg.

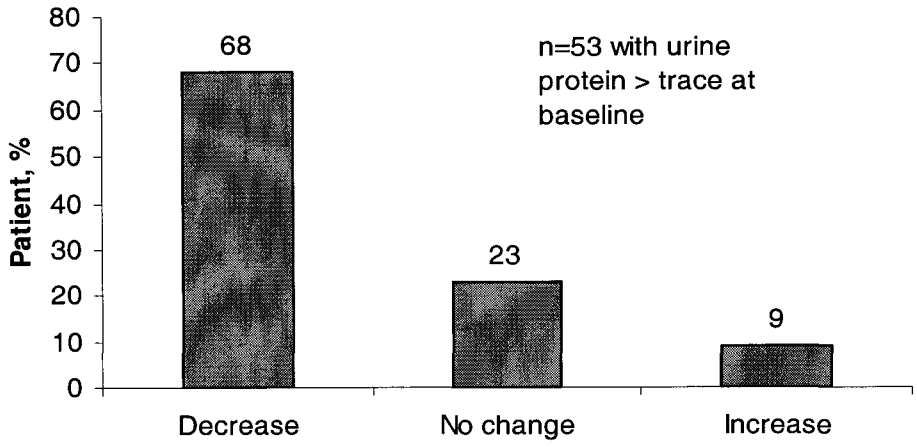
The Hypertension Optimal Treatment (HOT) study provides an historical context for the serum creatinine data in the rosuvastatin clinical development program. The HOT study was a blood pressure treatment study in 18,000 hypertensive patients who were treated to various predefined blood pressure goals for a mean duration of 3.8 years (Ruilope 2001). Demographic features of the HOT study population were similar to the population of patients receiving rosuvastatin in terms of age, gender, diabetic and cardiovascular status at entry. All of the patients in the HOT study were hypertensive (compared to 52% in the rosuvastatin development program) while all of the rosuvastatin treated patients were hypercholesterolemic. At the last follow-up visit in the HOT study, 7.8% of patients had a serum creatinine elevation >30%. At ≥96 weeks of exposure to rosuvastatin, the frequency of >30% creatinine elevations at the last visit was 1.1, 0.6, 0.8, 0.3, and 2.7 for the 5-, 10-, 20-, 40-, and 80-mg doses of rosuvastatin, respectively. The data suggests that the elevations observed with long-term rosuvastatin treatment at all doses are not unexpected for a population of dyslipidemic patients where over 50% were hypertensive and over half had some degree of renal impairment at baseline.

6.4.3.5 Effect of high dose rosuvastatin therapy in patients with baseline laboratory abnormalities

In order to assess the long-term renal safety of the 40-mg dose, an analysis was performed to assess the effect of treatment among patients with baseline renal laboratory abnormalities (ie, proteinuria and renal impairment.).

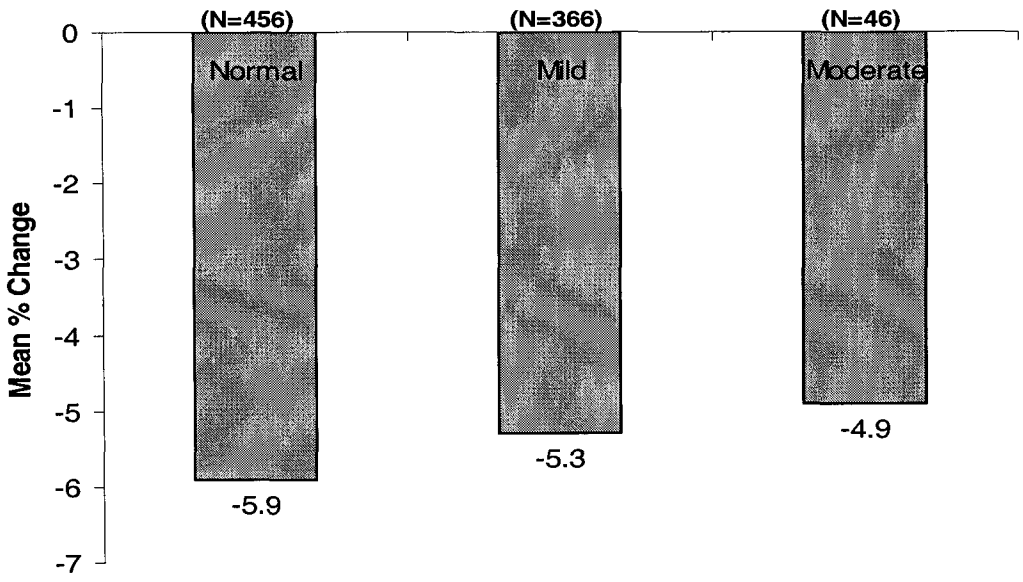
Of the 860 patients who received at least 40 mg of rosuvastatin for ≥96 weeks, 6.2% of these patients had urine dipstick protein levels that were ≥+ at baseline (Figure 26). Of these patients, 68% decreased on continued therapy.

Figure 26 Effect of rosuvastatin treatment in patients with baseline proteinuria ≥40 mg for ≥96 weeks



As seen in Figure 27, patients with normal or impaired renal function (creatinine clearance <80 mL/min) who received at least 40 mg of rosuvastatin per day for ≥48 weeks (N=1010) had a decrease in mean serum creatinine levels.

Figure 27 Mean % change in serum creatinine normal versus impaired renal function at baseline ≥40 mg for ≥96 weeks



These data indicate that higher dose rosuvastatin was well tolerated from the renal standpoint even among patients with baseline renal abnormalities.

6.4.3.6 Renal cases of interest

An additional parameter used when evaluating the potential effects of a drug on kidney function are cases of renal failure. Five patients had renal failure reported as an adverse event at doses up to 40 mg (2 at 10 mg; 1 at 20 mg; 2 at 40 mg). None of these cases were attributed to study medication.

Six cases of acute renal failure were reported in patients receiving the 80-mg dose of rosuvastatin. Four cases were in myopathy patients. In the two remaining patients (46-year-old Hispanic female and 69-year-old Caucasian female), acute renal failure occurred within 4 weeks of initiation of therapy. Both patients had gastrointestinal symptoms suggesting a volume-depleted state prior to the onset on renal failure. These cases are summarized below.

- A 70-year-old woman with a history of hypercholesterolemia, hypertension, and osteoporosis who was receiving multiple medications including rofecoxib, valsartan, and amlodipine reported generalized aches, right sided abdominal pain, nausea and vomiting and was noted to have an increase in serum creatinine level

from a baseline of 1.0 mg/dL to 2.3 mg/dL approximately 2 weeks after institution or rosuvastatin 80 mg treatment. Rosuvastatin was discontinued on Day 16 but the subject's symptoms persisted and serum creatinine increased to 8.0 mg/dL by Day 20. Hemodialysis treatment was initiated the following day. Renal biopsy indicated a diagnosis of acute tubular necrosis; no glomerular lesion was identified. The patient's renal function recovered after approximately 2 months.

- A 46-year-old woman with a history of hypercholesterolemia, fibrous arterial disease (renal and extra-renal) and hypertension treated with candesartan and aspirin reported fatigue, weakness, anorexia, and increased thirst while receiving the 80-mg dose of rosuvastatin. Serum creatinine around this time increased from 0.7 mg/dL at baseline to 1.1 mg/dL. Azithromycin was initiated for her symptoms. Rosuvastatin was discontinued. Serum creatinine increased to a maximum level of 13.6 mg/dL. Patient was hospitalized and treated with intravenous fluids. Her renal function recovered.

In addition to the cases described above, two additional patients receiving the 80-mg dose of rosuvastatin had renal biopsies because of an abnormal urinalysis and creatinine increase.

- A 69-year-old male with a history of heterozygous FH, stasis leg ulcers treated intermittently with penicillin and flamazine, and an unspecified renal disease in childhood was found to have proteinuria/hematuria with a creatinine increase from 1.1 mg/dL at baseline to 1.6 mg/dL after 18 months of treatment with rosuvastatin 80 mg. The subject, who was also treated with analgesics, had a renal biopsy, which showed histologic evidence of interstitial inflammation but normal glomeruli. The renal abnormalities resolved on discontinuation of rosuvastatin, but proteinuria recurred during treatment with atorvastatin 40 mg.

- A 65-year-old female with a history of heterozygous FH was found to have proteinuria/hematuria and an increase in serum creatinine from 1.1 mg/dL at baseline to 1.8 mg/dL after approximately 2 years of treatment with rosuvastatin 80 mg. The patient had a tubular pattern of proteinuria based on gel electrophoresis and a normal renal biopsy. The renal laboratory abnormalities normalized within 4 weeks of down-titration from the 80-mg to the 40-mg dose.

Overall more than 12,500 patients were treated with rosuvastatin in clinical trials. The data presented in this section show that at doses up to and including 40 mg rosuvastatin was well tolerated from the renal perspective.

6.4.3.7 Conclusions of renal effects

The nature, frequency, and magnitude of renal effects of rosuvastatin have been thoroughly reviewed. The preclinical and clinical data indicate that proteinuria is likely a class effect related to HMG-CoA reductase inhibition in the renal tubules.

Based on the findings from this development program, routine monitoring of renal function during therapy with rosuvastatin at doses from 10 mg to 40 mg is not recommended. The reasons for this are as follows: First, routine creatinine monitoring would not be appropriate since at doses up to and including 40 mg, rosuvastatin therapy did not cause an acute or chronic deterioration in renal function. Even at the 80-mg dose, the vast majority of patients tolerated the dose without an adverse effect on renal function. Second, although a small increase in the frequency of proteinuria may have occurred at the 40-mg dose, the fact that proteinuria can be caused by numerous more common factors such as exercise, infection, postural changes, and dehydration would make routine urinalysis impractical especially since the 40-mg dose did not have long-term deleterious effects on renal function.

The recommended labeling for rosuvastatin should reflect the fact that dipstick positive proteinuria, primarily tubular in nature, was observed with rosuvastatin subjects predominantly dosed above 40 mg per day. Although a small frequency of proteinuria was observed with subjects taking rosuvastatin 40 mg was usually transient and not associated with worsening renal function or clinically significant increases in serum creatinine. Moreover, patients with evidence of renal disease at entry (either dipstick positive proteinuria or a reduced calculated creatinine clearance) tended to have improvement, rather than deterioration of their renal laboratory parameters even with 40 mg or greater doses of rosuvastatin.

6.5 Summary of rosuvastatin safety

Over 12,500 patients were treated with rosuvastatin in Phase II/III clinical studies, providing substantial data for the evaluation of safety at all doses of rosuvastatin. The population evaluated in the development program was diverse and included a large percentage of patients with associated co-morbidities including hypertension, diabetes, and cardiovascular disease, as well as some degree of renal impairment. The population also had a large percentage of elderly patients. Overall, rosuvastatin was well tolerated with a small percent of patients who withdrew from clinical studies due to treatment-related adverse events. Rosuvastatin was well tolerated in a wide range of patients independent of gender, age, race or the presence of concomitant diseases such as hypertension, diabetes, renal or hepatic impairment, or cardiovascular disease. The overall adverse event profile of rosuvastatin was similar to that of other statins evaluated in this program.

With regard to the effect of rosuvastatin on liver function, the overall frequency of ALT elevations was low and similar to other statins. Muscle-related findings (ie, creatine kinase increases, myalgia, and myopathy) were observed with a low frequency in the 5- to 40-mg dose groups and an increased frequency at the 80-mg dose. The frequency of these adverse experiences at doses up to and including 40 mg for rosuvastatin was similar to that reported for other currently available statins (based on data from this program and the prescribing information of statins). Additionally, based on the careful evaluation of urinalysis, serum creatinine, and adverse event data, rosuvastatin at doses up to 40 mg should be well tolerated from a renal perspective.

7. BENEFIT-RISK EVALUATION

The major objectives of the clinical development program for rosuvastatin were:

- To demonstrate that rosuvastatin provided additional lipid-modifying benefits at both the start dose and across the dose range compared to currently marketed statins, thus allowing a greater percentage of patients to achieve national and international lipid goals at both the start dose and across the dose range.

- To demonstrate that rosuvastatin had a low potential for drug-drug interactions with commonly co-prescribed medications.

- To demonstrate a safety profile similar to other marketed statins.

The proposed rosuvastatin 10-mg to 40-mg dose range accomplishes these goals and has a favorable benefit-risk profile.

The rosuvastatin 10-mg to 40-mg dose range allows better lipid-modification at the starting dose compared to commonly prescribed starting doses of other statins, and it provides greater lipid-modification across the dose range when compared to other marketed statins. This is achieved with a similar safety profile. In addition, rosuvastatin has a low potential for drug-drug interactions. Rosuvastatin is not significantly metabolized by cytochrome P450 3A4; it undergoes very limited metabolism by cytochrome P450 2C9; and it does not interact with drugs handled by the p-glycoprotein transporter. Pharmacokinetic interactions with gemfibrozil and cyclosporin are similar to other marketed statins, and no pharmacokinetic interaction is observed with fenofibrate.

The rosuvastatin clinical development program is the largest program ever submitted to evaluate the safety and efficacy of a new statin. Over 12,500 patients are included in the safety database with 3939 patients treated with the 20 mg dose and 4007 patients treated with the 40-mg dose. Of these, 545 and 276 patients were treated with these doses for over 48 weeks. Rosuvastatin was studied in a broad range of patients in the Phase II/III program, including a high percentage of elderly patients (≥65 years; 31%), and patients with renal impairment (creatinine clearance <80 mL/min; 52%), hypertension (52%), cardiovascular disease (36%), and diabetes (17%). In addition, a large number of non-Caucasian patients were enrolled in trials.

The benefits of rosuvastatin were demonstrated in multiple clinical trials. The data showed that a rosuvastatin 10 mg to 40 mg dose range provided greater efficacy than other statin dose ranges while the safety profile is similar. As presented in Section 5.5.1, this dose range provided on average an additional 3.5% to 4.0% LDL-C reduction compared to atorvastatin (10 mg to 80 mg). The differences between rosuvastatin and the simvastatin (10 mg to 80 mg) and pravastatin (10 mg to 40 mg) dose ranges were even larger. The LDL-C benefits translated to a greater percentage of patients achieving NCEP ATP III goals at the rosuvastatin 10-mg start dose compared to commonly prescribed start doses of other statins, as well as to

more patients achieving goal with a rosuvastatin 10 mg to 40 mg dose range compared to other statin dose ranges when titrating based on lipid response. Rosuvastatin also allowed many patients with combined dyslipidemias to reach their secondary target of non-HDL-C.

A 10-mg start dose is readily supported by the efficacy and safety data from the rosuvastatin clinical development program. The 10-mg dose provided better lipid modification (decreases in LDL-C, non-HDL-C, and TG, as well as increases in HDL-C) compared to the 5-mg dose and brought a greater of patients to their NCEP ATP III targets. Importantly, the 10-mg dose had a safety profile that was indistinguishable from that of the 5-mg dose.

At doses up to and including 40 mg, rosuvastatin was well tolerated. The adverse events reported occurred at a frequency similar to comparator statins used in the program, and for most adverse events the frequency was similar to placebo. The most commonly reported treatment-related adverse events were myalgia, abdominal pain, nausea, and asthenia. Liver and skeletal muscle side effects are recognized complications of statin therapy. The frequency of persistent ALT elevations, CK elevations >10 x ULN, and cases of myopathy were low within the proposed rosuvastatin dose range and comparable to data with other statins, reported either within the program or in Summary Basis of Approval Documents or prescribing information. Although the finding of proteinuria was not previously reported as a known statin effect, the information presented in this document showed that the frequency of proteinuria at doses up to and including 40 mg was low and proteinuria could be observed with other statins. Importantly, no adverse effects on renal function were observed within the proposed dose range. In fact, on average, serum creatinine levels decreased following long-term treatment with rosuvastatin.

The efficacy and safety data from the clinical development program support a rosuvastatin dose range of 10 mg to 40 mg for the treatment of the general population of patients with hypercholesterolemia (heterozygous familial and nonfamilial), hypertriglyceridemia, and mixed dyslipidemia. This dose range is appropriate regardless of age, gender, and presence of CHD risk factors, or mild to moderate renal impairment. The exceptions to the 10-mg start dose are in patients with severe hypercholesterolemia (LDL-C >190 mg/dL) and aggressive LDL-C targets for whom a 20-mg start dose is optional, patients with homozygous familial hypercholesterolemia for whom a 20-mg start dose is recommended, and in patients receiving concomitant cyclosporine in whom the dose is restricted to 5 mg. The exception to the upper dose range is for patients with severe renal impairment and patients on gemfibrozil. For both of these patient groups, the maximum recommended dose of rosuvastatin is 10 mg.

For those patients who do not achieve the desired lipid-regulating effect at the 10-mg or 20-mg start dose, the dose of rosuvastatin can be doubled at 2- to 4-week intervals to achieve lipid targets. The maximum dose of rosuvastatin is 40 mg. The dose-response curve for rosuvastatin generated from Study 8 shows that for each doubling of dose, one can expect an additional 5% LDL-C reduction.

In summary, rosuvastatin is a new agent for the management of dyslipidemias. In a worldwide clinical trial program, rosuvastatin demonstrated superior efficacy to currently marketed statins. Within the proposed dose range, the safety profile was comparable to other

statins. When used according to the dosing instructions, rosuvastatin has a favorable benefit-risk profile.

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