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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-366

Medical Review(s)

CRESTOR (ZD4522, rosuvastatin calcium) TABLETS
NDA 21-366 N000 Resubmission Amendment

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1. EXECUTIVE SUMMARY

1.1 Recommendations on Approvability

It is recommended that the daily dose of 5 to 40mg of Rosuvastatin be approved for the treatment of patients with primary hypercholesterolemia and mixed dyslipidemia, as an adjunct to diet for the treatment of patients with elevated serum triglyceride levels (Fredrickson Type IV), and as an adjunct to apheresis and other lipid lowering treatments in patients with homozygous familial hypercholesterolemia.

The recommended starting dose should be 5 or 10mg in patients with primary hypercholesterolemia (LDL-C< 190mg/dL) and 20mg for patients with severe hypercholesterolemia (LDL-C> 190mg/dL).

The recommended start dose in patients of Asian ethnicity should be 5mg with a maximum of 20mg in most patients unless the benefits of lipid lowering outweigh the additional risk of higher doses in patients with severe hypercholesterolemia. This recommendation may be modified as additional information on the pharmacokinetics of this drug is obtained in Asian Americans.

The recommended start and maximal dose in patients receiving cyclosporin is 5mg.

The maximum recommended dose for patients with severe renal impairment (creatinine clearance < 30mL/,im/1.73m2) is 10mg once daily.

Then maximum recommended dose for combination with gemfibrozil is 10mg once daily.

The 40mg dose should be restricted to patients with severe hypercholesterolemia who have not responded adequately to all other available forms of therapy. Patients should be advised of the increased possibility of myopathy with higher doses of statins, and as recommended by the advisory committee, renal function monitoring should be initiated and continued while patients are maintained at this higher dose. If additional information should become available, that would alter the need for monitoring, this recommendation may be modified in the future.

1.2 Recommendations on Phase 4 Studies and Risk Management Steps

Additional pharmacokinetic studies should be performed including Asian Americans, Native Americans, and organ transplant recipients on chronic immunosuppresive therapy with drugs similar to cyclosporin, as recommended at the advisory committee meeting.

Ongoing clinical studies with patients receiving long term treatment with 40mg daily of Crestor (Study 0106-Polaris, Study 076-Asteroid and Study 0088-Meteor) should have regular renal monitoring with urinalysis and serum creatinine measurements in order to better describe the clinical course of the renal findings.

1.3 Summary

Rosuvastatin is the newest member of the statin class of lipid-lowering compounds, which inhibit HMG-CoA reductase and reduce cholesterol synthesis. The safety and effectiveness of rosuvastatin was reviewed under NDA 21-366 submitted to the Agency on June 26, 2001. In this original submission, rosuvastatin at daily doses of 1 to 80 mg effectively lowered total and LDL-C in patients with familial and nonfamilial hypercholesterolemia. The mean percent change from baseline in LDL-C ranged from –33% (1 mg) to –65% (80 mg) in this patient population. Rosuvastatin 80 mg provided an average 2 to 4% further reduction in LDL-C over the 40 mg dose; however, the range of efficacy overlapped markedly for these two doses. Rosuvastatin therapy significantly lowered TGs in patients with severe hypertriglyceridemia (200 or 300 mg/dL ≤ TG ≤ 800 mg/dL); however, a dose-relationship was not evident across the entire dosage range studied. Reductions in TGs were more pronounced in patients whose baseline TG levels exceeded 200 mg/dL. Although rosuvastatin therapy increased HDL-C from baseline at all doses studied, the results were highly variable. Increases in HDL-C were most notable in those patients with HDL-C < 34 mg/dL at entry.

The sponsor had originally proposed to market rosuvastatin at doses ranging from 10 to 80 mg. Review of the original application revealed safety concerns at the 80 mg dose that led to the conclusion that the risks of treatment at this dose outweighed the benefits associated with the modest incremental reduction in cholesterol. These safety concerns consisted of cases of myopathy and rhabdomyolysis observed at the 80 mg dose. In addition, proteinuria with and without hematuria and elevations in serum creatinine levels unrelated to myotoxicity were also documented at a greater frequency in the 80 mg dose group. An approvable action was taken on this application because the benefit-to-risk ratio at doses below 40 mg could not be assessed as a result of inadequate patient exposure. Clinical development of the 80 mg dose has since been discontinued and the sponsor has now resubmitted an application responding to the concerns raised by the Agency in its initial review of NDA 21-366. This resubmission includes an updated and expanded clinical development program with efficacy and safety data derived from approximately 12,500 patients to support the marketing of rosuvastatin 5 to 40 mg. More patients were studied at the 20 and 40 mg doses fulfilling the division's requirements, and patients previously treated with the 80 mg dose were back-titrated to 40 mg and analyzed separately.

Data presented by the sponsor showed that the development of severe myopathy or rhabdomyolysis requiring hospitalization for IV hydration occurred at an increased incidence only at the 80 mg dose. The incidences of CK elevations > 10xULN and myopathy in clinical trials of rosuvastatin 5 to 40 mg were between 0.2-0.4% and 0.1-0.2%, respectively, which are similar to rates seen with other currently approved statins. No cases of irreversible renal failure or death due to rhabdomyolysis were seen in these clinical trials.

While there have been rare case reports of proteinuria with other statins, this is not currently considered a class effect. Data from the clinical trials in this application show that patients receiving rosuvastatin had an increased rate of developing proteinuria with and without hematuria, and in a small percentage of these cases the findings were persistent and associated

with an increase in serum creatinine. Proteinuria was most pronounced at the 80 mg dose and the rate decreased in patients back-titrated from 80 to 40 mg suggesting reversibility. At the advisory committee meeting, the sponsor argued that isolated proteinuria is a class effect due to the inhibition of HMG-CoA reductase in proximal tubular cells as demonstrated in an Opossum kidney cell model, but they could not explain the hematuria or changes in serum creatinine seen primarily at the 80mg dose. There were two cases of renal failure and one case of renal insufficiency in patients receiving rosuvastatin 80 mg associated with proteinuria and hematuria. Renal biopsies in two of these cases suggested tubular inflammation and necrosis. The one case of renal insufficiency was diagnosed as chronic tubulointerstitial nephritis and had a positive rechallenge test to both rosuvastatin and atorvastatin suggesting that this may be due to a class effect.

At the 40mg dose the incidence of proteinuria ranged from 3.8 to 5% between the controlled trials and the open label extensions, while the incidence of combined proteinuria and hematuria was 1.3 to 1.5%, respectively. The incidence of combined proteinuria, hematuria and an increase in creatinine of > 30% from baseline was even lower at 0.2 to 0.3% at any visit (N=10). Only 3 out of these ten patients (0.1% of the total population exposed to the 40mg dose) continued to have elevations in serum creatinine of > 30% from baseline at the final visit. The sponsor interpreted the low incidence of serum creatinine elevations at the final visit as a suggestion that there was "no long-term detrimental effects on renal function" at doses of 40mg or lower.

A large percentage of the patients with abnormal renal findings were hypertensive and diabetic, so it is difficult to determine from these current studies if these findings are secondary to these comorbid conditions or due to rosuvastatin.

The risks of muscle and renal toxicity appear dose-related and are clearly evident at the 80 mg dose. Nine plasma concentrations of rosuvastatin were obtained from 6 patients receiving rosuvastatin 80 mg who developed muscle and/or renal toxicity. Rosuvastatin levels were > 50 ng/mL in all 9 samples. Drug levels corresponding to therapy with 20, 40, and 80 mg doses were obtained in a subset of asymptomatic patients enrolled in 5 different clinical studies. Drug levels across the 3 different doses in asymptomatic patients were compared to the drug levels in the patients experiencing muscle and/or renal toxicty. No patients treated with rosuvastatin 20 mg daily had drug levels in the range observed with clinical toxicity. Only a few patients treated with rosuvastatin 40 mg (2%) had drug levels within this range and a greater proportion of patients treated with 80 mg (33%) achieved drug levels > 50 ng/mL. This analysis suggests a potential threshold in the drug level at which risks of muscle and renal toxicity are increased. Treatment at the 20 mg and lower doses does not appear to raise drug levels into this 'range of concern'. However, clinical situations (e.g., drug-drug interactions, special populations), which may increase drug levels, require careful consideration as patients in these settings may be exposed to drug levels beyond what is typical for the 20 and 40 mg doses. The pharmacokinetic studies on patients in Japan and Singapore suggest that a subgroup of patients of Asian ethnicity will have a 2 fold increase in median exposure in response to rosuvastatin. Therefore, it is prudent to reserve the highest dose of rosuvastatin for only those patients not adequately treated with the lower doses where the benefits of therapy may still out weigh the potential risks. In patients of Asian ethnicity, treatment with rosuvastatin 40mg should include careful monitoring for symptoms of muscle toxicity and renal laboratory tests.

A final issue to be addressed in this review is the recommendation of a start dose of 10mg for most patients receiving rosuvastatin. While most patients could be adequately treated with a 5mg start dose, the sponsor argued that studies show that physicians do not adequately titrate patients on statins. Starting all patients at the 10mg dose is likely to result in more patients reaching goals in practice. However, since the issues surrounding the risks and benefits of a 10mg start dose are complex as I have described in my review, I think it is more reasonable to recommend a start dose of either 5 or 10mg and to let the physician decide which dose is best for each patient.

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2. EFFICACY REVIEW

2.1 Introduction-

Rosuvastatin is the newest member of the statin class of lipid-lowering compounds, which inhibit HMG-CoA reductase and reduce cholesterol synthesis. The clinical program was designed to show that rosuvastatin is effective at:

- lowering total and LDL-cholesterol in patients with familial and nonfamilial hypercholesterolemia (Fredrickson Type IIA and IIB)
- lowering total and LDL-cholesterol levels in patients with heterozygous familial hypercholesterolemia
- lowering total and LDL-cholesterol levels in patients with homozygous familial hypercholesterolemia as an adjunct to other treatment modalities (e.g., LDL-apheresis) or if such treatments were unavailable
- lowering triglycerides in patients with Fredrickson Type IIB and IV dyslipidemia as an adjunct to diet

2.2 Lowering LDL-Cholesterol In Patients with Familial and Nonfamilial Hypercholesterolemia (Fredrickson Type IIA And IIB)-

Therapy with rosuvastatin 1 to 40 mg daily results in significant mean % reductions from baseline in total cholesterol and LDL-cholesterol, in subjects with Fredrickson type IIA and IIB dyslipidemia relative to placebo (see Table 1). The mean % changes from baseline in LDL-cholesterol ranged from -33% (1 mg) to -62% (40 mg). Most patients reached NCEP target LDL-cholesterol on 5 or 10 mg of rosuvastatin (67 and 81%, respectively). Increasing the daily dose to 20 or 40 mg resulted in only an additional 6 and 2%, respectively, of patients reaching NCEP goals. While increases in HDL-cholesterol and decreases in triglycerides, from baseline, were seen for daily doses of 1 to 40 mg, there was no dose-response relationship and the mean % changes were not statistically significant at all doses. However, patients with low HDL-cholesterol at trial entry, <34 mg/dl, had greater increases in HDL-cholesterol on 5 to 10 mg of rosuvastatin than patients with HDL ≥ 35mg/dl (15.6% vs. 7.3%). Similarly, patients with Type IIB dyslipidemia (TG> 200mg/dl at baseline) had greater mean decreases from baseline in TG than patients with Type IIA (TG<200 mg/dl at baseline, -23.1% vs. -11.8%). An insufficient number of African Americans, Hispanics and Asians were included in these studies to independently confirm the effectiveness of rosuvastatin therapy in these subpopulations. The sponsor is currently studying these populations in ongoing trials.

Table 1

Rosuvastatin Dose Response vs. Placebo
Mean % Change from Baseline to Week 6
Type IIA/IIB Dyslipidemia: Trials 8 and 23 Pooled[a]

Efficacy Endpoint	Placebo	Rosuvastatin Dose						
		1.0 mg	2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg
	(N=31)	(N=14)	(N=15)	(N=18)	(N=17)	(N=17)	(N=34)	(N=31)
LDL-C								
BL, mg/dL	194	191	190	191	190	191	185	188
Ls mean %	-3.8	-33.2***	-39.6***	-42.6***	-49.8***	-53.1***	-62.2***	-64.9***
change (SE)	(1.7)	(2.8)	(2.7)	(2.6)	(2.6)	(2.6)	(1.6)	(2.1)
TC								
BL, mg/dL	271	267	265	268	267	268	261	263
Ls mean %	-2.5	-22.5***	-28.1***	-31.1***	-34.4***	-38.4***	-45.1***	-46.8***
change (SE)	(1.4)	(2.3)	(2.2)	(2.1)	(2.1)	(2.1)	(1.4)	(1.7)
HDL-C								
BL, mg/dL	53	55	49	53	50	51	52	51
Ls mean %	3.2	9.4	8.8	13.7*	14.6*	8.2	10.1	14.1**
change (SE)	(2.1)	(3.5)	(3.3)	(3.2)	(3.2)	(3.2)	(2.0)	(2.6)
TG								
BL, mg/dL	122	116	133	121	135	134	117	119
Ls mean %	-1.9	-17.0	-11.6	-34.2**	-8.9	-21.9	-27.4**	-24.6**
change (SE)	(4.8)	(7.8)	(7.6)	(7.2)	(7.2)	(7.2)	(4.5)	(5.8)

Table 5 ISE Data derived from tables on pages A63, A66, A69, A72, A84, A87, A101, A597 to A604 in Appendix A.
[a] Main analysis of LOCF data from the ITT population. BL = baseline; N = All subjects in ITT population; SE = standard error.
* p<0.05 versus placebo; ** p<0.01 versus placebo; *** p<0.001 versus placebo.

2.3 Lowering LDL-Cholesterol Levels in Patients with Heterozygous Familial Hypercholesterolemia-

Rosuvastatin therapy at daily doses of 20 to 80 mg effectively reduced total cholesterol and LDL-cholesterol in subjects with severe hypercholesterolemia (LDL-cholesterol > 220mg/dL, see Table 2).

Table 2

Patients with Heterozygous Familial Hypercholesterolemia Treated with Rosuvastatin (ITT population)

0 mg (0wks)	20mg (6wks)		40mg (12wks)		80mg (18wks)	
Baseline LDL (mean)	% LDL	LDL (mean)	% LDL	LDL (mean)	% LDL	LDL (mean)
292	-47%	154	-54%	135	-58%	123

Data derived from sponsor's Table T10.1.1

The majority of the decrease in LDL-cholesterol was seen with 20 mg of rosuvastatin (wk 6). Titration from 20 mg to 40 mg provided an average 7% further reduction in LDL-cholesterol while titration from 40 mg to 80 mg produced an average 4% further reduction.

2.4 Lowering LDL-Cholesterol Levels in Patients with Homozygous Familial Hypercholesterolemia as an Adjunct to Other Treatment Modalities (e.g., LDL-Apheresis) or if Such Treatments Were Unavailable-

Therapy with rosuvastatin 20 mg significantly reduced total cholesterol and LDL-cholesterol in subjects with homozygous familial hypercholesterolemia (mean baseline LDL-cholesterol of 515 ± 115 mg/dl). There was little additional benefit for daily doses greater than 20 mg (see Table 3). The statistical review showed that approximately one-third of patients titrated to doses higher than 20 mg did achieve an additional 6% lowering in LDL-cholesterol, which corresponds to an additional decrease of about 30 mg/dl. It is unclear what clinical impact this small additional reduction will have in these patients whose mean LDL-cholesterol are still > 400 mg/dl. Changes in HDL-cholesterol and triglycerides were variable.

Table 3
All Patients with Homozygous Familial Hypercholesterolemia Treated with Rosuvastatin (ITT population)

0 mg (0wks)	20mg (6wks)		40mg (12wks)		80mg (18wks)	
Baseline LDL (mean)	**% LDL**	**LDL (mean)**	**% LDL**	**LDL (mean)**	**% LDL**	**LDL (mean)**
515	-19%	416	-22%	409	-22%	403

Data derived from sponsor's Table T10.2.1 to T10.1.1

2.5 Lowering Triglycerides in Patients with Fredrickson Type IIB And IV Dyslipidemia as an Adjunct to Diet-

Therapy at daily doses of 5 to 40 mg of rosuvastatin significantly reduced triglycerides in subjects with Fredrickson type IIB and IV dyslipidemia compared to placebo (see Table 4). The mean dose response curve was flat at doses above 10 mg.

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Table 4	Analysis of Mean % Change from Baseline to Week 6 LOCF in total TG levels in study 4522IL/0035 [a]					
	Placebo N=26	ZD4522 N=25	ZD4522 N=23	ZD4522 N=27	ZD4522 N=25	ZD4522 N=27
		5 mg	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Baseline(mean, SD): mg/dl	511 (138)	462 (104)	447 (96)	446 (119)	471 (142)	448 (138)
Final (mean, SD):mg/dl	521 (222)	376 (140)	271 (65)	278 (114)	270 (81)	267 (96)
Ls mean of % change (SE) median	2.9 (4.4) 0.8	-18.1 (4.5) -20.6	-37.0 (4.7) -36.5	-36.8 (4.3) -37.0	-40.0 (4.5) -43.1	-39.5 (4.3) -46.2
Difference (%) relative to placebo	NA	**-21.0 (6.3)**	**-39.9 (6.4)**	**-39.6 (6.2)**	**-42.9 (6.3)**	**-42.4 (6.1)**
95% CI of difference	NA	-33.4, -8.6	-52.5, -27.3	-51.8, -27.5	-55.3, -30.5	-54.5, -30.2
p-value of difference	NA	0.001	<0.001	<0.001	<0.001	<0.001

Table 16 study 4522IL/0035. Data derived from Tables T10.1.1, T10.1.2, T10.3.1, and H1.1.1.
[a] Main analysis of last observation carried forward from the intent-to-treat population.
CI = Confidence interval; LOCF = last observation carried forward; ls mean = Least squares mean; NA = Not Aplicable; SD = Standard deviation; SE = Standard error.

2. DOSING, REGIMEN AND ADMINISTRATION

Rosuvastatin was studied at daily oral doses of 1, 2.5, 5, 10, 20, 40 and 80 mg. The sponsor proposes a starting dose of 10 mg daily with a dose range of 10 mg to 40 mg once daily for patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIA and IIB). The 10mg start dose of rosuvastatin would result in a mean LDL-C lowering of 50% which would make it the highest approved start dose of all marketed statins. In one study of Fredrickson Type IIa and IIb patients the 5mg dose resulted in 67% of the cohort reaching ATP-III goals compared to 81% at the higher dose of 10mg, showing that most patients can be adequately treated with the lower dose. Although there are currently no clinical trial outcome data for rosuvastatin, it should be noted that the mean LDL-C lowering achieved with the 5 mg dose exceeds that observed with other statins studied in large prevention trials. It is reasonable to assume, that all else being equal, rosuvastatin 5mg would be clinically effective as well as effective in treatment to LDL-C goal. Furthermore, the 5mg dose may be more appropriate in patients with a predisposition to developing myopathy such as the elderly, hypothyroid and patients with renal insufficiency or in patients who need a lower level of LDL-lowering. However, the sponsor argued that studies show that physicians do not adequately titrate patients on statins, therefore starting all patients at the 10mg dose is likely to result in more patients reaching goals in practice. Since the current data show the two doses have similar safety profiles, the sponsor favors starting all patients, irrespective of their need for LDL-C lowering, at the higher starting dose. Since it is difficult to adequately weigh all the risks and benefits of a 10mg start dose, I think it is reasonable to recommend a start dose of either 5 or 10mg and to let the physician decide which dose is best for each patient, based on baseline CHD risks, LDL-C levels, and treatment goals.

The sponsor proposed the option of a daily start dose of 20 mg for patients with heterozygous or homozygous familial hypercholesterolemia, with severe

hypercholesterolemia (LDL-cholesterol >190mg/dl). Since there was an adequate number of patients started at the 20mg dose in these trials and these patients are likely to require titration to doses of 20mg and higher, it is reasonable to accept a 20mg start dose for this patient population.

3. DRUG-DRUG INTERACTIONS

3.1 Cyclosporine

Heart transplant patients treated with cyclosporine and receiving daily doses of 10 mg of rosuvastatin had a 10.6-fold increase in Cmax and a 6.8-fold increase in AUC (0-t) for rosuvastatin drug levels compared to values obtained in healthy subjects. The sponsor proposes limiting the dose of rosuvastatin to 5 mg in subjects receiving concomitant cyclosporine.

3.2 Gemfibrozil

Healthy subjects receiving 600 mg twice daily of gemfibrozil and a single dose of rosuvastatin 80 mg had a 2.2-fold increase in Cmax and a 1.9-fold increase in AUC (0-t) for rosuvastatin drug levels compared to placebo. The sponsor proposes limiting the daily dose of rosuvastatin to 10 mg in subjects receiving concomitant gemfibrozil.

3.3 Cytochrome-p450 inhibitors

In-vitro data suggest that rosuvastatin is not metabolized by CYP3A4 to a clinically significant extent. No clinically relevant changes in AUC (0-t) or Cmax for rosuvastatin were seen when it was administered with known CYP3A4 inhibitors such as itraconazole, ketoconazole and erythromycin.

No clinically relevant changes in AUC (0-t) or Cmax were seen for rosuvastatin when it was administered with the known CYP2C9 inhibitor fluconazole.

4. SPECIAL POPULATIONS

4.1 Renal Insufficiency

Subjects with severe renal impairment, (baseline CrCL < 30ml/min), had a 3.1-fold increase in Cmax and a 3.2 fold increase in AUC (0-24) for rosuvastatin compared to healthy subjects treated with 20 mg of rosuvastatin. The sponsor proposes limiting the daily dose of rosuvastatin to 10mg in subjects with severe renal impairment.

4.2 Liver Insufficiency

Two subjects with alcohol-induced cirrhosis of the liver described as severe by the Maddrey discriminant function (df≥54) had a 4 to 16-fold increase in Cmax and a 2 to 4-fold increase in AUC (0-24) for rosuvastatin compared to patients with normal hepatic function treated with 10 mg of rosuvastatin. The sponsor does not feel the need to cap the dose in patients with severe liver disease but instead proposes contraindicating the use of

rosuvastatin in patients with active liver disease or unexplained persistent elevations of serum transaminases.

4.3 Japanese

After single or seven-day repeat oral dosing with 20 mg of rosuvastatin, Cmax was 1.9 to 2.3-fold higher and AUC (0-24) was 2.0 to 2.5-fold higher for rosuvastatin in healthy Japanese male volunteers compared to Caucasians. The sponsor has not proposed limiting the daily dose of rosuvastatin in patients of Asian ethnicity in the US. They currently have an application in Japan with a dose range of 10 to 20 mg with 5mg recommended for special treatment circumstances. The sponsor admits that at this time they do not know if the increased exposure in Japanese patients is related to genetic or environmental factors and whether these findings apply to other Asian populations or to patients with mixed genetic profiles.

4.4 Special Populations Patient Exposure

No specific safety concerns were identified in these special population trials with respect to rosuvastatin. However, since the number of subjects enrolled in these trials was low (Renal-impaired study N=26, Hepatically impaired study N=18, Japanese study N=18), and these PK studies lasted at most 2 weeks, the safety profile of rosuvastatin in these special populations can not be adequately assessed based on the results of these trials alone.

5. SAFETY REVIEW

5.1 Description of Patient Exposure

The original application, including the Pre-Approval Safety Update submitted by the sponsor, included data from 3,900 patients exposed to daily doses of 5 to 80 mg of rosuvastatin. However, because of the force-titration design of many of the trials, exposures were greatest at 5, 10 and 80 mg with fewer than 200 patients exposed to 20 or 40 mg of rosuvastatin for greater than 24 weeks and fewer than 100 patients exposed to these doses for greater than 48 weeks. Because of muscle and renal safety issues associated with exposure to the 80 mg dose in these trials, (to be discussed in more detail later in this review) the 80 mg dose was not approved and the sponsor was asked to submit additional safety data on the 20 and 40 mg doses. Table 5 shows the cumulative exposure to all doses in the current clinical trial program, which now includes data on over 11,000 patients. Note that once the agency was aware of the potential toxicity of the 80 mg dose the sponsor was asked to withdraw all patients from the 80 mg dose and to follow them at lower doses as appropriate. Most of these patients were down-titrated to 40 mg and are included as a separate column in this table.

Table 5
Maximum continuous duration of treatment for each dose of rosuvastatin in the All Controlled / Uncontrolled and RTLD Pool

	Rosuvastatin dose [a,b]						
Cumulative duration of treatment [c]	5 mg N=1,324	10 mg N=7,246	20 mg N=3,391	40 mg N=3,021	Originally on 80 mg then down titrated to 40 mg N=826	80 mg N=1,580	Total rosuvastatin [d,e] N=11,210
≥6 weeks	1235	6919	3032	2554	785	1419	10,658
≥24 weeks	647	4,787	940	657	209	977	7,695
≥48 weeks	341	2,631	285	195	1	398	4,786
≥60 weeks	349	1,466	189	164	0	868	3,238
≥96 weeks	274	831	89	73	0	639	2,260
Mean weeks of treatment	49	45	20	17	18	65	55
Subject years	1,248	6,199	1,296	959	282	1,952	11,725

RTLD= Real Time Lab Data

Data derived from ISSU Table S2.8.3 and S2.8.4. from Table 24 Integrated Summary of Safety Update Jan. 31, 2003

[a] Subjects are counted in each dose group to which they are exposed; therefore, subjects may be counted in more than 1 treatment group. For subjects with more than 1 exposure to a given rosuvastatin dose, only the longest duration of exposure to that dose is counted. [b] Subjects were down titrated from rosuvastatin 80 mg as a result of a protocol amendment for Studies 34, 65, and 81. Not all subjects given rosuvastatin 40 mg were down-titrated from 80 mg; these subjects were either up-titrated to 40 mg from a lower start dose or were directly randomized to 40 mg. c If a subject received 40 mg prior to the protocol amendments for Studies 34, 65, and 81 and then were down-titrated from 80 mg to 40 mg after the protocol amendments were put into effect, the subject is counted in both the "not down-titrated to 40 mg" and "down-titrated to 40 mg" columns. [d] Maximum continuous exposure in the Total rosuvastatin column includes all rosuvastatin continuous exposure, regardless of titration of dose. For

this reason, counts of subjects in the individual duration categories cannot be added across doses to obtain the count in the Total rosuvastatin column. [c] The reason for the missing counts is that there were no return dates to calculate the treatment durations. In most of these cases, the subjects 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 subject. Note: Participation in Phase II/III controlled and uncontrolled clinical studies includes participation in any controlled clinical study and/or participation in an extension study. Subjects received rosuvastatin either alone or with another lipid-lowering agent at any point during a feeder study and/or an extension study. ND not determined

ICH guidelines recommend that the total number of patients exposed to an investigational drug for long-term treatment of non-life-threatening conditions should be at least 1500, with 300 to 600 exposed at 6 months and at least 100 patients exposed at one year. The Division of Metabolic and Endocrine Drug Products has routinely required a minimum of 200 patients exposed for at least one year for the approval of medications intended for chronic use. While the sponsor has now roughly achieved these guidelines even at the highest to be marketed dose of 40 mg, the total patient-years of exposure at 40 mg is still about half (i.e. 959 pt-years) of what was seen with the 80 mg dose (i.e. 1,952 pt-years) where the main safety concerns were identified. The total patient exposure in clinical trials submitted for initial approval for rosuvastatin (N=11,210) is considerably greater than the 2,000-3,000 patients submitted for most of the currently approved statins (See Table 10).

The rest of this briefing packet will focus on three areas of potential concern, which were identified during the pre-approval safety review:

- Liver-related adverse events
- Musculoskeletal-related adverse events
- Renal-related adverse events

5.2 Liver-Related Adverse Events

SUMMARY-As a group, statins have been associated with liver transaminase elevations and rarely hepatitis and liver failure. The data presented by the sponsor show a frequency of transaminase elevations similar to that seen in currently approved statins. No cases of irreversible liver disease or liver failure were seen in these clinical trials.

LIVER TRANSAMINASE ELEVATIONS -

Liver transaminase elevations have been widely used to screen statins for potential hepatotoxicity. Since patients can have random isolated elevations which turn out to be nonspecific and unrelated to the study drug, sponsors typically present data for persistent elevations to try to identify patients who are more likely to have clinically significant elevations.

Total single elevations are also useful for analysis and comparison between control groups as long as it is taken into account that they may over represent the incidence of significant disease. Data for single elevations are typically obtained at scheduled study visits or if clinically warranted. Pre-specified criteria for consecutive elevations in liver transaminases often include a time restriction between measurements (e.g., measurements must be made 4 to 10 days apart). Consequently, the incidence of LFT abnormalities reported as consecutive transaminase elevations may miss clinically relevant cases if repeat tests occur beyond the arbitrary time frame defined by the protocol. When analyzing single elevations it is useful to compare the drug to active controls or placebo and by degree of enzyme elevation, such as >6xULN or >9xULN. Higher single elevations are more likely to represent relevant toxicity.

An analysis of single, and multiple ALT elevations was performed. Multiple elevations do not depend on the time of the measurement and therefore do not necessarily represent consecutive elevations as reported by the sponsor.

Table 6
ALT Elevations in the Rosuvastatin All Controlled/Uncontrolled and RTLD Pool

	5mg		10mg		20mg		40mg		80mg	
Single elevations	N (1317)	%	N (7726)	%	N (3882)	%	N (3957)	%	N (1574)	%
>3xULN	14[a]	1.1	61[a]	0.8	26	0.7	44[a]	1.1	62[a]	3.9
>6xULN	0	0	9	0.1	2	0.05	4	0.1	15[b]	1.0
>9xULN	0	0	3	0.04	1	0.03	1	0.03	8[b]	0.5
Multiple elevations										
>3xULN	5	0.4	9	0.1	4	0.1	15	0.4	22	1.4
>6xULN	0	0	3	0.04	0	0	1	0.03	6	0.4
>9xULN	0	0	0	0	0	0	1	0.03	4	0.3

[a]While rhabdomyolysis can also be associated with elevations in transaminases most of the mild elevations in Alt > 3xULN reported here were not associated with CK elevations > 10xULN. Only 19/207 pts with Alt > 3xULN also had CK elevations >10xULN. One on 5 mg, two on 10 mg, four on 40 mg and 12 on 80mg.

[b]At the higher transaminase elevations 6/30 patients with ALT>6xULN and 2/13 with ALT >9xULN also had CK > 10xULN but all were at the 80 mg dose of rosuvastatin

Data were derived from AV_LUBR.xpt data file submitted 5/20/03, Where the lab ULN was not known from data in the Lab.xpt dataset submitted 6/26/01, it was assumed that 3xULN=75 which was true for most values in the dataset.

There is a clear increase in the incidence of single and multiple transaminase elevations >3xULN, > 6xULN and >9xULN only at the 80 mg dose of rosuvastatin. The frequency of elevations >3xULN at doses of 5 to 40 mg was in the range of 0.7 to 1.1% which is less than the frequency of transaminase elevations >3xULN reported in healthy patients in Phase 1 trials receiving placebo i.e. < 2% (Rosenzweig et al. 1999). Even though direct comparisons of data from independent trials are difficult because of different patient populations, study eligibility criteria and different lengths of drug exposure, these data suggest that the occurrence of transaminase elevations at the lower doses in these clinical trials may not be due to the study drug.

The frequency of single elevations >3xULN at 80 mg is increased (3.9%) in comparison to rates observed at the 40 mg and lower doses (0.7 to 1.1%). This might suggest the potential for a clinically significant signal. In comparison to other currently approved statins however, similar elevations in transaminases have also been seen at the highest approved doses and careful monitoring has shown statins to be relatively safe and rarely associated with cases of liver failure. The incidence of persistent elevations in transaminases, as it is currently reported in the labels of these drugs, is shown in the Table 7 below. These data are in the same range as the frequency of multiple elevations >3xULN reported above for 80 mg of rosuvastatin (1.4%).

Table 7
Dose Related Incidence of Persistent Transaminase Elevations in Statins in Clinical Trials

Statin	Placebo	10 mg	20 mg	40 mg	80 mg
Pravachol	0.3%			0.3%	
Mevacor	0.1%		0.1%	0.9%	1.5%
Lipitor		0.2%	0.2%	0.6%	2.3%
Zocor				0.9%	2.1%
Lescol			0.2%	1.5%	2.7%

Data taken from currently approved labels or NDA19898/Se8-042.

Liver function monitoring appears to identify a small group of subjects with evidence of liver injury for which the study drug should be discontinued. Out of 45 different subjects with 2 or more consecutive elevations identified by the sponsor in the All Controlled/Uncontrolled and RTDL Pools (data obtained from Tables 37 and 38 in sponsor's ISS dated 1/31/03), at least 21 had the drug withdrawn, two had the dose lowered and four had the drug withheld temporarily. Hence about half of these patients were able to continue on treatment despite consecutive ALT elevations. For all subjects, for whom follow up data were available, transaminase levels improved. A small number of subjects (n=5) continued to have mild low grade elevations <3xULN when continued on the study drug.

There were two cases of jaundice for which relationship to rosuvastatin therapy could not be excluded. Both cases occurred on the 10 mg dose of rosuvastatin and resolved after the discontinuation of therapy (see appendix for MedWatch forms D3560L0001/0310/01237 and D3560L0001/2265/09060). No cases of liver failure or irreversible liver disease were observed in these trials. In these clinical trials liver function tests appear to adequately monitor for hepatotoxicity in patients on rosuvastatin.

In conclusion, statins have been associated with liver transaminases elevations but rarely hepatitis and liver failure. Rosuvastatin, like other statins, shows a dose-related increase in liver transaminases. The incidence of multiple transaminase elevations is similar at 80 mg of rosuvastatin to that seen at the highest approved doses of other statins. Liver function monitoring, as currently recommended for all members of the statin drug class, is also recommended for patients receiving treatment with rosuvastatin.

5.3 Musculoskeletal-Related Adverse Events

SUMMARY- Myopathy and rare cases of rhabdomyolysis, which can lead to acute renal failure and death, have been reported post-marketing for all currently approved statins. The data presented here show, for the first time, the development of severe myopathy and rhabdomyolysis in clinical trials submitted for the original approval of a new statin. This risk is clearly increased at the highest dose studied (80 mg), which has subsequently been discontinued from development. While the risks of myopathy at lower doses appear comparable to other marketed statins, these risks may increase in special populations in which patients are exposed to higher levels of drug (drug-drug interactions, renal impairment, Japanese descent).

CK ELEVATIONS IN PATIENTS TAKING ROSUVASTATIN

Skeletal muscle damage results in the release of intracellular proteins into the bloodstream. One of these proteins, myoglobin, is normally filtered out of the body by the kidneys. Under conditions in which there is a large degree of skeletal muscle damage, excessive amounts of myoglobin can be released, overwhelming the kidney's filtering capacity, occluding it and leading to renal failure and possibly death. Adequate IV hydration during this time can maintain renal output and prevent the progression to renal failure.

Other intracellular muscle proteins have been commonly used as markers to estimate the extent of muscle damage. The best example of this is creatine phosphokinase (CK) which has isoenzymes also present in heart muscle and brain. Mild elevations of CK are common after vigorous exertion but typically do not lead to myopathy (CK>10xULN and muscle symptoms) or the more severe condition of rhabdomyolysis. Rhabdomyolysis is a clinical diagnosis, which unlike myopathy has been poorly defined. For example, in this current database there was one patient on 80 mg of rosuvastatin with muscle weakness, myalgia, back pain, CK=34,548 (288xULN), and a plasma myoglobin of 13,810ng/ml who developed acute renal failure and was diagnosed with "myoglobin associated renal failure due to toxicity of myoglobin on the renal tubules" but not "rhabdomyolysis". Clearly this case was misclassified. While most reviewers would include CK elevations > 10,000 IU/L with muscle symptoms, there are reports of rhabdomyolysis with CK <10xULN (Omar et al. Annals of Pharm Sept. 2001) and not all patients have myalgia. Some patients can have nonspecific symptoms such as loss of appetite, fatigue, weakness, malaise, nausea, vomiting and abdominal distention. For the purpose of this review I will refer to cases of rhabdomyolysis (i.e. severe myopathy) as those patients with myopathy (CK>10xULN and muscle symptoms) who required hospitalization for IV hydration, with the reasoning that in such cases the level of muscle toxicity is so severe that it would likely have lead to renal failure if left untreated.

CK elevations have been commonly used to screen for potentially myotoxic drugs even though there is no clear indication that patients who develop transient unexplained CK elevations are more likely to progress to myopathy or rhabdomyolysis in the future. Therefore, while monitoring CK levels may not predict who is at risk of developing rhabdomyolysis, it is a useful marker to compare potentially myotoxic drugs. For example, the frequency of CK elevations for cerivastatin, which was eventually removed

from the market because it was associated with a higher unexceptable risk of rhabdomyolysis, was higher in clinical trials than had been seen for other marketed statins (see Table 10).

In addition to CK, transaminases (AST > ALT) are also released from necrotic muscle cells and can be used to identify more severe cases of myopathy. Also, an increase in creatinine as a result of decreasing renal function associated with myopathy is likely to signal more severe muscle damage. While serum and urine myoglobin tests would be useful to diagnose rhabdomyolysis they are rarely done and can not be relied upon to make the diagnosis.

The clinical manifestations of myotoxicity are observed over a continuum. Most patients with normal baseline renal function and who are otherwise healthy can handle certain levels of myoglobinuria. These patients may experience only CK elevations without symptoms or myopathy without renal function deterioration. Co-morbid medical conditions, dehydration, age, mental status, certain concomitant medications or genetic factors may play a role in making some patients more susceptible at certain times to potentially myotoxic drugs. Increased serum levels of myotoxic drugs have clearly been associated with an increased risk for developing rhabdomyolysis. In addition, conditions which result in increased levels of these drugs, such as drug-drug interactions or renal dysfunction, may also increase the risk of developing rhabdomyolysis.

The data presented in Table 8 compare CK elevations seen in patients with rosuvastatin to placebo and other statins in the All Controlled Data Pool. There is clearly an increase in the frequency of CK elevations for all statins compared to placebo. The increase is greatest in patients taking the rosuvastatin 80 mg dose (CK>10xULN=0.9%). The frequency observed at 40 mg of rosuvastatin is similar to what was seen for 80 mg of simvastatin (CK>10xULN=0.4%). It is likely that the high frequency of 1.2% for 10 mg of simvastatin is an over estimation because of the small number of patients in this subgroup (N=163) especially since there is no clear dose response (0.1 and 0% for 20 and 40 mg simvastatin doses, respectively). It is also likely that no CK elevations >10xULN were seen for cerivastatin in these trials because of the low number of patients in these groups (N=45 to 64).

Table 8

CK ELEVATIONS IN THE ALL CONTROLLED POOL[a]

	5mg		10mg		20mg		40mg		80mg	
Rosuvastatin	N=833	%	N=3193	%	N=2113	%	N=2804	%	N=988	%
CK >5xULN	7	0.8	8	0.3	7	0.3	28	1.0	11	1.1
CK>10xULN	3	0.4	4	0.1	3	0.1	11	0.4	9	0.9
	Placebo		10mg		20mg		40mg		80mg	
Atorvastatin	N=381	%	N=1573	%	N=1772	%	N=522	%	N=555	%
CK >5xULN	0	0	8	0.5	7	0.4	3	0.6	2	0.4
CK>10xULN	0	0	1	0.1	2	0.1	0	0	0	0
			10mg		20mg		40mg		80mg	
Simvastatin			N=163	%	N=1272	%	N=532	%	N=501	%
CK >5xULN			2	1.2	2	0.2	0	0	3	0.6
CK>10xULN			2	1.2	1	0.1	0	0	2	0.4
			10mg		20mg		40mg			
Pravastatin			N=161	%	N=416	%	N=751	%		
CK >5xULN			2	1.2	2	0.5	0	0		
CK>10xULN			0	0	0	0	0	0		
					0.3mg		0.4mg		0.8mg	
Cerivastatin					N=64	%	N=54	%	N=45	%
CK >5xULN					0	0	0	0	1	2.2
CK>10xULN					0	0	0	0	0	0

[a]Data were derived from AV_LBUR.xpt submitted 5/20/03 to the EDR. Data includes only patients on monotherapy lipid lowering drugs and excludes patients in OLE (open label extension), i.e. ISS-ALL CONTROLLED STUDIES= Yes.

In the All Controlled/Uncontrolled and RTLD Patient Pools, which contain many more patients exposed to rosuvastatin for longer periods of time, it is possible to get a better estimate of the true frequency of dose-related CK elevations (see Table 9). These data show that 80 mg of rosuvastatin has a high frequency of elevations (CK>10xULN=1.9%), between what was seen in clinical trials for cerivastatin doses of 0.4 mg (1.55%) and 0.8 mg (2.1%) and higher than seen for all other currently approved statins (see Table 10). This increased frequency at 80 mg is true even when you look at more severe cases of myopathy with multiple CK elevations, or CK elevations associated with transaminase elevations or myalgias (see Table 9). There is also a slight increase in CK elevations for 40 mg of rosuvastatin but it is not clear if this represents a clear signal of a substantial risk of myotoxicity. The frequency at 40 mg (CK>10xULN=0.4%) is not higher than seen in clinical trials submitted for initial approval of other currently approved statins (Table 10) or in published clinical trials (Table 11).

Table 9

CK ELEVATIONS IN PATIENTS TAKING ROSUVASTATIN IN THE ALL CONTROLLED/UNCONTROLLED and RTLD POOLS [a]

	5mg		10mg [b]		20mg		40mg		80mg	
	N (1317)	%	N (7727)	%	N (3883)	%	N (3700)	%	N (1574)	%
Single CK elevations										
CK >5xULN	14	1.1	69	0.9	19	0.5	39	1.1	55	3.5
CK>10xULN	5	0.4	17	0.2	7	0.2	15	0.4	30	1.9
Multiple CK elevations										
CK >5xULN	3	0.2	11	0.1	3	0.08	7	0.2	21	1.3
CK>10xULN	3	0.2	1	0.01	1	0.03	5	0.1	12	0.8
Single CK elevations associated with Alt >3xULN [c]										
CK >5xULN	1	0.08	2	0.03	0	0	4	0.1	16	1.0
CK>10xULN	1	0.08	2	0.03	0	0	4	0.1	12	0.8
Single CK Elevations associated with clinical symptoms										
Myopathy (All)	3	0.2	9	0.1	4	0.1	6	0.2	16	1.0
Myopathy (Not related to exercise or injury)	0	0	1	0.01	1	0.03	1	0.03	11	0.7
Rhabdo or IV hydration [d]	0	0	1	0.01	0	0	0	0	7	0.4

[a] Data were derived from AV_LBUR.xpt submitted 5/20/2003 to the EDR. Data includes only patients on monotherapy with rosuvastatin and includes patients in double-blind controlled and open-label extension phases. Data includes RTLD pool and data from local labs. Data on 40mg patients does not included patients down titrated from 80mg. Patients with CK elevations in both controlled pool and open label extension were counted only once.

[b] Includes data from a initial Med Watch report on a 75 y/o female in the GISSI-HF study diagnosed with rhabdomyolysis on 4/20/03 see appendix for full case report

[c] ALT≥ 75U/L, [d] All patients diagnosed with rhabdomyolysis received IV hydration, two other patients who had peak CK's of 34,548 and 16,280 U/L with increased plasma myoglobulin were also hospitalized for IV hydration but did not get a formal diagnosis of rhabdomyolysis.

Table 10
CK Elevations, Myopathy and Rhabdomyolysis in Pre-Approval Clinical Trials

Statin	Approval	NDA Dose	Pts N	CK>10xULN % (N)	Myopathy % (N)	Drug Stopped % (N)	Hospitalized IV Hydration % (N)
Pravastatin 19-898	Oct. 1991	5-40	1,925	0.1% (2)	0.1% (2) (1 clofibrate)	0.2% (3)	0
S-046 Se-000 4F	Dec. 2001 (Phase IV)	80	581	0.9% (5)	0.4% (2)	0.3% (2)	0
Unapproved	(Phase IV)	160	604	0.3% (2)	0	0.2% (1)	0
Simvastatin 19-766	Dec. 1991	5-40	2,423	0.6% (13)	0.04% (1)	0.1% (2)	0
S-026	July 1998 IIb, III	80	669	0.7% (5)	0.5% (5) (1 nefazodone + clarithromycin, 1 verapamil)	0.7% (5)	0
Merck press release 5/19/97	GEM extended release form	160	~400	~0.8% (3)	~0.8% (3)		~0.8% (3)
Fluvastatin 20-261	Dec. 93	20-40	2,342	0.1% (3)		0.1% (2)	0
21-192	Nov. 1999	40	543	0.4% (2)			0
21-192	Nov. 1999	80 XL	912	0%			0
Atorvastatin 20-702	Dec. 1996	10-40	1,965	0.4% (8)			0
	April 2000	80	346	0.9% (3)			0
Protocol A2581042	Phase IV	10-40	688	0.3% (2)	0%	0.1% (1) (20mg)	0
	"	80	231	0%			0
Lovastatin 19-643	Aug. 1997	5-80	873	N/A	N/A	0	0
Cerivastatin	June 1997	0.05-0.3	2,815	0%			0
S-002	May 1999	0.4	448	0.2% (1)		0.7% (3)	0
S-008	July 2000	0.4	193	1.55% (3)	1.55% (3) (1 gemfibrozil)		0*
S-008	July 2000	0.8	770	2.1% (16)	1.0% (8)		0*
Rosuvastatin		5	1,317	0.4% (5)	0.2% (3)	0.2% (2)	0
		10	7,728	0.2% (17)	0.1% (9)	0.04% (3)	0.01% (1)
		20	3,883	0.2% (7)	0.1% (4)	0.08% (3)	0
		40	3,700	0.4% (15)	0.2% (6)	0.1% (4)	0
		80	1,574	1.9% (30)	1.0% (16)	0.8% (13)	0.4% (7)

*Possible cases of rhabdomyolysis may have been labeled as myopathy only.

Table 11

CK Elevations, Myopathy and Rhabdomyolysis in Published Clinical Trials or Approved Label

Statin	Data Source	NDA Dose	Pts N	CK >10xULN		All Myopathy		Rhabdomyolysis	
				%	N	%	N	%	N
Pravastatin	Approved Label	5-80		-	-	<0.1	-		
		40	115	0	0	0	0		
		80	464	0.9	4	0	0		
	WOSCOPS *NEJM* 333, Nov.1995	Placebo	3293	0.03	1	0	0		
		40	3302	0.09	3	0	0		
Simvastatin	Approved Label	20		-	-	0.02			
		40		-	-	0.07			
		80		-	-	0.3			
	4S- Lancet 344, Nov. 1994	Placebo	2,223	0.04	1	0	0		
		10-40	2,221	0.3	6	0	0	0.05	1 (20mg)
	J-LIT Japanese Pts *Circ J* 67, April 2003	5-10	51,321	0.01	6	0.01	4 (1 hosp)	0	0
	HPS (*Lancet* 360, July 2002)	Placebo	10,267	0.06	6	0.04	4	0.03	3
		40	10,269	0.11	11	0.1	10	0.05	5
Fluvastatin	Approved Label	20-40		-	-	-	-		
		80XL		-	-	-	-		
	American Journal of Cardiology 89, Jan 2002	Placebo	2,323	0.2	5	-	-		
		20	2,590	0.2	4	-	-		
		40	4,369	0.3	13	-	-		
		80 XL	1,724	0	0	-	-		
Atorvastatin	Approved Label	10-40		-	-	-	-		
		80		-	-	-	-		
Lovastatin	Approved Label	10		-	-	-	-		
		20-40	4,933	-	-	0.02	1		
		80	1,649	-	-	0.2	4		
	EXCEL study *Arch Int Med* 151, Jan. 1991	placebo	1,663	0.4	7	0	0		
		20	1,642	0.2	3	0	0		
		40	3,291	0.2	6	0.03	1		
		80	1,649	0.5	8	0.2	4		
	AFCAPS/TexCAPS JAMA 279, May 1998	Placebo	3,248	0.6	21	0	0	0.06	2
		20	1,586	0.7	11	0	0	0.03	1(s/p cancer surgery)
		40	1,657	0.6	10	0	0		
Cerivastatin	Last Approved Label	0.2-0.8		-	-	0.4	-		
	J Int Med Res 28, Mar 2000	placebo	198	0	0	0	0	0	0
		0.4mg	194	1.0	2	1.0	2 (1 gem-fibrozil)	0	0
		0.8mg	774	1.3	10	0.9	7	0	0

FREQUENCY of CK ELEVATIONS and MYOPATHY DOES NOT CORRELATE with CHANGE in LDL

It has been reported in the literature that there is no clear association between final LDL level or percent decrease in LDL and the risk of myopathy or rhabdomyolysis (Berg et al. 1996). Similarly, data from trials with atorvastatin (Bakker-Akema et al. 2000) showed that lowering LDL-cholesterol to < 50 mg/dl did not alter the safety profile of that statin. One possible explanation for these observations is that changes in LDL reflect drug activity at the level of the liver in contrast to myopathy and rhabdomyolysis which may be more likely to reflect serum drug levels and drug penetration into muscle.

Data from the clinical studies with rosuvastatin all show that there is no correlation between the baseline LDL, the % decrease in LDL, or final LDL value, and the development of myopathy at any of the doses of rosuvastatin. Patients with LDL values above 100mg/dL, who had not yet met NCEP goals, developed myopathy and rhabdomyolysis (see Table 12).

Yet out of 149 subjects identified in the rosuvastatin All Controlled Pool who achieved LDL-cholesterol < 50mg/dl, only one (0.7%) had increased CK (>1xULN) and two (1.3%) had myalgia. The frequency of these events was less than observed in the total rosuvastatin group. In addition nine patients in this All Controlled Pool achieved LDL-cholesterol below 30 mg/dl and only two adverse events, both unlikely to be related to the study drug i.e. pharyngitis and lacrimation disorder, were observed.

Table 12
Change In LDL-Cholesterol associated with CK >10xULN and Myopathy in Patients on Rosuvastatin in the All Controlled/Uncontrolled Pool

Dose (mg)	Max CK (U/L)	LDL (mg/dL) Baseline	LDL (mg/dL) Treated[a]	% decrease in LDL	(*) Rhabdo/ IV hydration (#) unknown etiology (e) Exercise or injury related
5	3,954	165	114	-31	e
	3,492	204	139	-32	e
	2,496	183	106	-42	e
10	21,632	N/A	N/A	N/A	*
	5,810	165	112	-32	e
	2,730	171	69	-60	e
	1,888	117	66	-44	e
	1,626	195	119	-39	e
	1,490	167	71	-57	e
	1,490	187	118	-37	e
	1,421	159	82	-48	e
	1,312	135	91	-33	e
20	7,580	185	101	-45	#
	4,550	202	94	-53	e
	1,266	174	77	-56	e
	1,211	177	92	-48	e
40	15,858	178	63	-65	#
	8,470	251	148	-41	e
	3,636	194	80	-59	e
	2,577	179	66	-63	e
	1,836	179	83	-54	e
	1,518	200	88	-56	e
80	34,548	221	75	-66	*
	>20,000	272	74	-73	*
	16,280	237	59	-75	*
	11,132	58	38	-34	*
	7,484	217	126	-42	*
	3,486	385	163	-58	*
	2,509	211	80	-62	*
	5,480	167	48	-71	#
	5,380	287	N/A	N/A	#
	2,154	105	N/A	N/A	#
	1,780	226	96	-58	#
	3,610	244	122	-50	e
	2,570	334	131	-61	e
	2,294	232	113	-51	e
	2,184	211	66	-69	e
	1,393	288	122	-58	e

[a] Data taken from AV_LUBR 5/16/03 submission. When no LDL value available at the time of CK elevation the nearest available value was taken. LDL> 100mg/dL is highlighted

MYOPATHY IN CLINICAL TRIALS with ROSUVASTATIN

The frequency of myopathy (CK>10xULN and muscle symptoms) associated with the use of 80 mg rosuvastatin (i.e. 1.0%) was higher than had been seen in the pre-approval clinical trials (Table 10) or in current labels or published clinical trials for all marketed statins (Table 11) except for 0.4 to 0.8 mg doses of cerivastatin. While most of the

rosuvastatin cases at 80 mg and all but one of the cases at doses of 5 to 40 mg were associated with muscle injury or excessive exercise, this does not necessarily mean that these episodes were not drug-related. By comparison there were no cases of exercise-induced myopathy in any of the other statins in the All Controlled Pool. Similarly, exercise is rarely a contributing factor in the few cases of statin related myopathy reported in the literature.

RHABDOMYOLYSIS in CLINICAL TRIALS with ROSUVASTATIN

All 7 cases of rhabdomyolysis at the 80 mg dose occurred during the open-label extension trials. The average length of time on the current drug dose prior to the development of rhabdomyolysis was 282 days (9.4 months) with a standard deviation of 212 days (7 months). The median was 246 days (8.2 months) with a range of 29 to 698 days. Most patients were titrated up to the 80 mg dose so the total time on rosuvastatin at any dose was even greater at 386 days (12.9 months). Clearly these patients were able to tolerate the medication for a long time prior to the adverse event. Most hospitalizations were preceded by a 3 to 28 day prodrome suggesting a viral illness with subsequent dehydration as a possible precipitating event. Typical symptoms included loss in appetite, fatigue, malaise, muscle soreness, muscle weakness, nausea, vomiting, diarrhea and abdominal distension. This is in contrast to rhabdomyolysis produced by other clearly myotoxic drugs reviewed by this division that primarily produced muscle symptoms in healthy individuals within two to four weeks after starting therapy. These medications still show individual variability so that not all patients exposed develop myopathy by 4 weeks, but as the dose is increased and the length of exposure is increased a higher percentage of patients developed rhabdomyolysis.

None of the patients who developed rhabdomyolysis on rosuvastatin had CK elevations noted prior to the actual episode so periodic CK monitoring is unlikely to be of benefit in identifying the patients at risk for rhabdomyolysis.

The one case of rhabdomyolysis on the 10 mg dose occurred in the double blind study GISSI-HF. This patient had been randomized on Nov 26, 2002 and developed rhabdomyolyis on April 20, 2003 (after 145 days). This occurred about one week after a 3-day hospitalization for worsening CHF (see appendix for full case report). While the occurrence of rhabdomyolysis at the 10 mg dose may be a worrisome sign, it must be taken into account that there were 7,728 patients exposed at that dose in these clinical trials. Therefore, the incidence of rhabdomyolysis at the 10 mg dose is only 0.01% which is lower than was seen for the 40 mg dose of simvastatin in the recent HPS trial (0.05%) (see Table 11).

DEMOGRAPHIC ANALYIS OF PATIENTS WITH CK ELEVATIONS

Available patient characteristics were screened to see if any were associated with a higher risk of developing CK elevations since such patient populations might require different safety labeling. Data were analyzed to see if there was an association with CK elevations and the patient's age, sex, baseline (creatinine, CK, or LDL-C) levels or past medical history of cardiovascular heart disease, diabetes, or hypertension (see Table 13).

Table 13-
Demographic Information on Patients with CK Elevations >10xULN [a]

Dose	Age (yrs, Mean±SD)	Sex (male)	Baseline (Mean ± SD)			>30% inc in Cr	CHD	Htn	DM
			LDL-C (mg/dL)	CK (U/L)	Cr (Umol/L)				
Control (all randomized subjects) N=12,371	58 ± 12	53%	190 ± 47	70 ± 71	97 ± 17	3.5%	36%	52%	17%
Control[b] (trials with rhabdo patients i.e. 25, 30, 31 and 35) N=1,315	54 ± 14	57%	237 ± 76	64 ± 46	99 ± 17	7%	49%	37%	6%
CK>10xULN (N=73)	52 ± 15	77%	206 ± 51	92 ± 57	107 ± 19	20.5%	42%	45%	11%
Rhabdomyolysis (N=7)	67 ± 7	29%	229 ± 97	66 ± 53	103 ± 15	86%	86%	71%	14%

[a] Data were taken from the latest submission LV_LUBR submitted to the EDR on 5/20/03 and submission DDEMOG1-3[b] submitted 2/12/03

Patients, who developed rhabdomyolysis, were more likely to be older women with cardiovascular heart disease and hypertension. It is possible that these co-morbid conditions may impact on their baseline renal function or alternatively this may reflect a potential interaction with cardiac or antihypertensive medications and rosuvastatin.

Concomitant medications for the seven patients with rhabdomyolysis at 80mg (COMMED.xpt files from the 2/12/03 submission) and from the single patient with rhabdomyolysis at 10mg (MedWatch report) were reviewed. No clear association between the development of rhabdomyolysis and the use of the listed concomitant medications was established. Five out of the eight patients had been on aspirin, and a diuretic (hydorchlorothiazide or furosemide), and an ACE inhibitor (lisinopril, ramipril or benazeprilat). Four out of eight had been on a quinilone (ciprofloxacin, ofloxacin or levofloxacin). None of these drugs had previously been reported as a potentially interacting drug in statin-associated rhabdomyolysis (Omar and Wilson, 2002). However, a recent review (Jan 2002) of rhabdomyolysis associated with Baycol performed by the FDA's Office of Drug Safety did find spontaneous reports of drug interactions with norfloxacin, trovafloxacin and levofloxacin.

In conclusion, there is a higher incidence of myopathy (1.0%) and rhabdomyolysis (0.4%) observed in the clinical trials with 80 mg of rosuvastatin than reported in the original NDA or current labels for any of the currently approved statins. Most cases of myopathy not associated with exercise or physical injury, including seven out of the eight cases of rhabdomyolysis, occurred at the 80 mg dose. The risk for 5 to 40 mg doses appears to be comparable to rates observed in clinical trials for other approved statins. However, drug interactions (e.g., cyclosporine or gemfibrozil) and special populations (co-morbid medical conditions, renal impairment) pose a special challenge to the safe use of this product in the general population and will clearly need to be addressed in product labeling.

APPEARS THIS WAY
ON ORIGINAL

5.4 Renal-Related Adverse Events

SUMMARY- In contrast to currently approved statins, rosuvastatin was also associated with renal findings not previously reported with other statins. A small percentage of patients exposed primarily to the 80 mg dose of rosuvastatin had an increased frequency of persistent proteinuria and hematuria, which in some patients was also associated with an increase in serum creatinine. The sponsor argues that these findings are likely to be a previously unobserved class effect due to inhibition of HMG-CoA reductase in proximal tubular cells as demonstrated in Opossum kidney cells and are reversible following down titration to lower doses. However, the animal model would not account for the hematuria, and creatinine increase from baseline which was also seen in the clinical studies. Finally there were two cases of renal failure and one case of renal insufficiency on rosuvastatin 80 mg associated with hematuria and proteinuria and not associated with rhabdomyolysis. Renal biopsies in two of these cases suggested tubular inflammation or necrosis. The one case of renal insufficiency was diagnosed as chronic tubulointerstitial nephritis and had a positive rechallenge test to both rosuvastatin and atorvastatin, suggesting that this may be due to a class effect.

PROTEINURIA IS SEEN in PATIENTS TAKING 40 and 80 mg DAILY DOSES of ROSUVASTATIN

In the All Controlled Pool it was observed that there was an increase from baseline in the frequency of proteinuria in the rosuvastatin group. The number of patients with all grades of proteinuria, from trace to ++++, went from 20.5% at baseline to 29.5% at the end of the controlled phase of the trials on rosuvastatin. This is in contrast to a decrease from 21.0% to 17.3% for patients on total other statins and a decrease of 27.6% to 23.3% for patients on placebo (see Table 56 ISS).

In response to these unexpected findings in the All Controlled Pool, the sponsor amended the protocols in the open label extension to add urinalysis testing and serum creatinine measurements for all subjects at follow-up visits. Data in Table 14 was separated by drug dose at the onset of proteinuria. These data show an increase of proteinuria at rosuvastatin 40 and 80 mg for patients with 1, 2 or 3 grade increases in proteinuria and an increase of 4 grades in proteinuria in patients on 80 mg of rosuvastatin as well.

Table 14
Proteinuria from Open Label Extension Trials Submitted in PreApproval SUR

Increase from baseline	Rosuvastatin Dose									
	5 mg		10 mg		20 mg		40 mg		80 mg	
	N=270	%	N=577	%	N=123	%	N=155	%	N=631	%
≥1 grade	34	12.6	56	9.7	17	13.8	39	25.2	201	31.9
≥2 grades	12	4.4	12	2.1	7	5.7	17	11.0	106	16.8
≥3 grades	0	0	2	0.3	1	0.8	3	1.9	34	5.4
≥4 grades	0	0	1	0.2	0	0	0	0	5	0.8

Data from Table 14 PreApproval SUR 1/30/02

The sponsor did not perform 24 hour urine collections to quantify urine protein in these patients. Instead the sponsor used (total urine protein-to-urine creatinine) ratios from spot collections to estimate total urinary protein. 28.8% of the subjects who had at least a two

category shift in urine protein dipstick measurements had a (total urine protein-to-creatinine) ratio of >0.5 representing a urine protein excretion > 3XULN according to the sponsor.

In an attempt to focus on patients likely to have more significant levels of proteinuria, the most current urinalysis data (i.e. AV_LBUR.xpt) were analyzed to look for patients who had at least a (++) grade of proteinuria and an increase of at least one grade above their baseline value. In addition, these data were screened to identify patients with urine dipstick positive hematuria of ≥ (+) grade that had an increase of at least one grade above their baseline value. In the few patients with no baseline urinalysis data, it was assumed that they had no baseline hematuria or proteinuria. Data from patients using other statins or from all patients in the dietary-run in period were used as controls. The duration of treatment, number of patients and number of samples per patient in the rosuvastatin Uncontrolled and Real Time Data Pool far exceeded that of the other statins in the Controlled Pool.

These data showed an increase in dipstick-positive proteinuria (12-17%), hematuria (12-22%) and proteinuria associated with hematuria (6-11%), at the rosuvastatin 80 mg dose (see Table 15). There is a trend suggesting an intermediate effect at 40 mg whereas the 20 mg and lower doses have rates that are similar to the background seen with other statins.

Table 15
PROTEINURIA AND HEMATURIA in the ALL Controlled and Uncontrolled and RTLD Pools[a]

Treatment (mg)	Total patients	Urine Dipstick Proteinuria ≥ ++	Urine Dipstick Hematuria ≥ +	Proteinuria ≥ ++ & Hematuria ≥ +
	N	%	%	%
Dietary Run-In	5,811	1	3	0.1
Placebo	372	3	5	0
Pravastatin				
20	191	1	7	0.5
40	67	0	4	0
Atorvastatin				
10	710	2	4	0.6
20	667	2	3	0.3
40	245	0.4	2	0.4
80	377	0.5	2	0
Simvastatin				
20	517	4	5	0.6
40	356	2	5	0.8
80	337	0.6	8	0.3
Rosuvastatin				
5	653	1	6	0
5 OLE[b]	438	4	14	1.6
10	1,202	2	7	0.3
10 OLE[b]	5,011	3	10	0.8
20	1,460	2	4	0.3
20 OLE[b]	1,894	4	8	0.7
40[c]	2,384	4	10	1.3
40 OLE[b]	1,684	5	10	1.5
80	804	12	12	6.1
80 OLE[b]	959	17	22	10.5

[a] This data includes only patients with an increase of at least one protein category above baseline. In the few cases where no baseline values were present it was assumed the baseline value was no protein and no blood.
Data taken from AV_LBUR.xpt data file 5/20/03
[b] OLE-Refers to samples from the Open Label Extension [c] There was one less patient with hematuria results i.e. N=2,383

CHANGES IN SERUM CREATININE IN PATIENTS TAKING ROSUVASTATIN

The sponsor's analysis of serum creatinine levels in the All Controlled and RTLD Pools (see Table 27 Sponsor's briefing packet) showed a slight decrease from baseline in mean creatinine levels of 1 to 4% for all statins including rosuvastatin doses up to 40 mg. At the rosuvastatin 80 mg dose there was a slight increase of 2.2% in the mean serum creatinine. The significance of such a finding is hard to interpret since the standard deviation about the mean of the baseline creatinine values range from 15 to 18%. Substantial changes in a small subgroup of patients could be easily missed by such an analysis.

Table 16 shows the percentage of patients with proteinuria (≥ ++) subgrouped by increase in serum creatinine. Table 17 shows similar data for patients with combined proteinuria (≥ ++) and hematuria (≥ +). These tables show there is a clear increase in serum creatinine in patients on 80mg. About 3- 4% of the patients treated with 80mg had proteinuria associated with a >30% increase in creatinine and about 2-3% of the patients treated with 80mg had combined proteinuria, hematuria and an increase in creatinine of >30% from baseline, in at least one visit. At doses below 80mg the incidence is much lower with only 0.4% of patients treated with 40mg having proteinuria and an increase of >30% in creatinine and only 0.2 to 0.3% of patients treated with 40mg having combined proteinuria, hematuria and an increase in creatinine of >30% from baseline, in at least one visit.

Table 16
Change in Serum Creatinine in Patients with Urine Proteinuria (Dipstick ≥++) at any visit

Treatment Period	All Patients [a] (N)	All Cr values		Between 20 -30% in Cr		Inc > 30% Inc in Cr	
		N	100 x %	N	100 x %	N	100 x %
Dietary Run-in	5811	59	1.0	1	0.02	1	0.02
Rosuvastatin (mg)							
5	653	7	1.1	0	0	0	0
5 OLE	438	18	4.1	0	0	2	0.5
10	1202	26	2.2	0	0	0	0
10 OLE	5011	135	2.7	7	0.1	6	0.1
20	1460	30	2.1	1	0.1	0	0
20 OLE	1894	79	4.2	5	0.3	6	0.3
40	2384	90	3.8	6	0.3	9	0.4
40 OLE	1684	84	5.0	6	0.4	6	0.4
80	804	95	11.8	17	2.1	21	2.6
80OLE	959	165	17.2	25	2.6	36	3.8

[a] Includes all data from final combined dataset AV_LBUR submitted to EDR 5/20/03 for patients with at least one urinalysis data point. OLE-open label extension

Table 17
Change in Serum Creatinine in Patients with Urine Proteinuria (Dipstick ≥++) with Urine Bld (Dipstick ≥+) at any visit

Treatment Period	All Patients[a] (N)	All Cr values		Between 20 -30% Inc in Cr		Inc > 30% Inc in Cr	
		N	100 x %	N	100 x %	N	100 x %
Dietary Run-in	5811	8	0.1	0	0	0	0
Rosuvastatin (mg)							
5	653	0	0	0	0	0	0
5 OLE	438	7	1.6	0	0	0	0
10	1202	4	0.3	0	0	0	0
10 OLE	5011	39	0.8	1	0.02	4	0.1
20	1460	5	0.3	1	0.1	0	0
20 OLE	1894	13	0.7	0	0	3	0.2
40	2384	30	1.3	3	0.1	6	0.3
40 OLE	1684	25	1.5	2	0.1	4	0.2
80	804	49	6.1	9	1.1	20	2.5
80OLE	959	101	10.5	17	1.8	26	2.7

[a] Includes all data from final combined dataset AV_LBUR submitted to EDR 5/20/03 for patients with at least one urinalysis data point. OLE-open label extension

A similar earlier analysis by the sponsor also showed an increase in serum creatinine in patients with combined hematuria and proteinuria (see appendix 9.2). These data suggest that some patients with greater levels of proteinuria and hematuria may have progressive renal disease.

PERSISTENCE OF PROTEINURIA FROM THE CONTROLLED TRIALS DURING THE OPEN LABEL EXTENSION

To get an estimate for the persistence of the proteinuria identified during the controlled feeder trials, the sponsor originally looked at a subgroup of 297 patients who demonstrated an increase in urine protein in their last feeder trial visit. These patients were screened to see how many had no change or a further increase in their level of proteinuria at the last recorded visit of the open label extension. Out of these patients 71.4% improved, 20.9% showed no change, and 7.7% showed worsening of proteinuria on therapy with rosuvastatin. While the data for no change are mixed across all doses, it is clear that patients on 80 mg are more likely to have progressive proteinuria.

Table 18-

Urine Protein Change in Patients with an Increase in Urine Protein Noted During the Feeder Trial

	5 mg N=18		10 mg N=60		20 mg N=21		40 mg N=37		80 mg N=161		All doses N=297	
	N	%	N	%	N	%	N	%	N	%	N	%
No change in proteinuria	5	28	12	20	1	5	3	8	41	25	62	20.9
Increase in proteinuria	0	0	1	2	1	5	2	5	19	12	23	7.7

Data taken from Table 15 PreApproval SUR 1/30/02

The sponsor emphasized that most patients (71.4%) with proteinuria improve on continued therapy (including data from all doses). While the number of patients who progress on therapy may be small, this may still be clinically significant if it can be associated with increases in creatinine and renal insufficiency.

In an analysis of the 55 patients with (≥++) proteinuria and (≥+) hematuria, while on the 40mg dose, taken from the final All controlled/Uncontrolled and Real Time Data Pool (i.e. AV_LBUR), 47 had a baseline urine value and 8 did not. Out of those with baseline urine values, 27/47=57% had protein and 22/47=47% had blood above their baseline value on their final visit. Of the 8 patients with no baseline value 4/8=50% had abnormal protein and 4/8=50% had abnormal blood measurements on their last visit. So the proteinuria and hematuria continue even though some of these patients (9/55=16%) were down titrated from 40mg to lower doses. But the degree of proteinuria and hematuria is less, only 14/55=25% had proteinuria of grade ++ or greater and 20/55=36% had blood of + or greater at the final visit.

Individual patient profiles were generated by Ana Szarfman for these patients with combined proteinuria and hematuria on rosuvastatin 40mg. These profiles show that most patients had multiple elevations over the course of the open label extension, and there were at least 17 patients with proteinuria or hematuria above baseline levels after 1000 days of treatment with rosuvastatin.

Following down titration of the patients on rosuvastatin 80 mg to 40 mg the sponsor reports that the frequency of patients with proteinuria ≥++ fell from 7.5% to 1.9% on the first follow–up visit suggesting that proteinuria at 80 mg is reversible.

A prospective analysis of the incidence of proteinuria would be more informative than the down-titration of patients from rosuvastatin 80 to 40 mg. The sponsor attempted such an analysis in Trial 99, which has yet to be completed. This was a 6-week, open-label, randomized trial comparing rosuvastatin 40 mg to simvastatin 80 mg in patients with type IIa and IIb hypercholesterolemia. Frequent monitoring of proteinuria, hematuria, creatinine, and urinary protein excretion pattern was incorporated into the trial. Preliminary results from the trial suggest, as might have been predicted, that it will be more difficult to clarify the frequency and duration of the proteinuria associated with

rosuvastatin 40 mg since it is much less frequent than seen with 80 mg. The frequency of proteinuria (≥ ++) in this 6-week trial was much lower than was seen in the larger ALL Controlled/Uncontrolled and RTLD Pools (Table 15), which included data from the long-term extension trials. Consequently, data for the occurrence of a lower degree of proteinuria (≥ +) were also included for comparison. Clearly six weeks may be insufficient time to detect enough cases of proteinuria, yet there is a suggestion that rosuvastatin 40 mg is still more likely to cause proteinuria than simvastatin 80 mg. It is not clear why there is such a high frequency of dipstick positive (≥ +) hematuria in both the simvastatin and rosuvastatin groups in this trial.

Table 19

Frequency of Proteinuria in Trial 99[a]

	Patient (N)	**≥ + proteinuria**		**≥ ++ proteinuria**		**≥ + hematuria**	
		N	%	N	%	N	%
Dietary Lead-In	620	21	3.4	4	0.6	49	7.9
Simvastatin 80 mg	315	6	1.9	2	0.6	27	8.6
Rosuvastatin 40 mg	316	25	7.9	5	1.6	27	8.6

[a]Data derived from AV_LUBR.xpt dat file 5/20/03
Because of the low frequency of (++) proteinuria seen at 6 weeks in this trial the frequency of (+) proteinuria was also calculated.

COMORBID CONDITIONS IN PATIENTS WITH ABNORMAL URINALYSES ON THE 40MG DOSE

Most patients with abnormal renal findings on rosuvastatin 40mg had atherosclerotic disease, hypertension and/or diabetes. For the 55 patients with (≥ ++) proteinuria, and (≥ +) hematuria the ratios were 64%, 47%, and 18% respectively. For the 15 patients with (≥ ++) proteinuria and an increase in creatinine of >30% from baseline the ratios were 60%, 87% and 53%, respectively. And for the 10 patients with (≥ ++) proteinuria, (≥ +) hematuria and an increase in creatinine of >30% from baseline the ratios were 60%, 80% and 50%, respectively, showing that creatinine increases were more common in patients with hypertension and diabetes. It is not known, however, what degree of these abnormal renal findings is directly due to rosuvastatin and independent of these comorbid conditions.

POSSIBLE RENAL TUBULAR DAMAGE ASSOCIATED WITH ROSUVASTATIN

Analysis of the urine protein in patients taking rosuvastatin revealed elevated levels of beta-2-microglobulin and N-acetyl-beta-D-glucosaminidase suggesting a renal tubular etiology according to the sponsor. Drug insolubility or crystallization in the renal tubules would be an alternative hypothesis of a potential mechanism for renal tubular damage.

KIDNEY FAILURE/ INSUFFICIENCY in PATIENTS on 80 MG of ROSUVASTATIN
Two cases of renal failure and one case of renal insufficiency, all with unknown etiology were seen in the open label extensions and ongoing trials in patients receiving 80 mg of rosuvastatin. Narratives for these three patients will be presented below but additional information from the latest MedWatch forms can be found in the appendix.

A 46 year old female **(0065/0044/0014)** with normal baseline lab values presented with nausea, anorexia, and fatigue and an abnormal urinalysis [proteinuria (30mg/dL), hematuria (small), 15-20 RBC/hpf, 10-15 WBC/hpf, coarse granular and hyaline casts in the urine sediment] after 31 days on rosuvastatin. The urine culture grew mixed organisms. Her creatinine went from 1.1 to 13.7 mg/dL. CPK was normal at 41 U/L. A renal scan showed multiple cystic masses in both kidneys. The drug was stopped. She responded to IV hydration and was discharged from the hospital with a serum creatinine of 3.8 mg/dl. Azithromycin and candesartan were possible contributing medications.

A 70 y/o female **(0065/0026/0049)** taking rosuvastatin 80 mg developed acute tubular necrosis on Day 15 of ongoing Trial 65. She was also taking rofecoxib, valsartan and amlodipine at the time of the adverse event. She presented with generalized body aches, right-sided abdominal pain radiating to the right flank, nausea and vomiting. A CT urogram showed no evidence of hydronephrosis or urinary calculi. At least 3 gallstones were seen in the gallbladder but the f/u HIDA scan was negative. Her serum creatinine was 3.4mg/dl and her urinalysis showed protein, moderate occult blood, 0-1 granular casts and 1+ calcium oxalate crystals. She was treated with hydration and the study drug was discontinued. Her serum creatinine continued to rise to 9 mg/dL and she needed to be dialyzed. CPK went from 69 to 137 U/L (10-130 U/L) and myoglobin was 195 ηg/dl (19-51 ηg/dl), both only mildly elevated (not c/w rhabdomyolysis). Renal biopsy showed tubular degenerative changes with prominent vacuolization consistent with of acute tubular necrosis. Dialysis was stopped after about 2 months, and her last reported serum creatinine was 1.8 mg/dl.

A 69-y/o male **(0034/0316/0025)** developed chronic tubulo-interstitial nephritis with proteinuria, active urine sediment and a rise in serum creatinine after he had been on 80 mg of rosuvastatin for 1 year and 6 months. He had a h/o hospitalization at 8 years of age for inflammation of the kidneys, which resolved without known sequelae. (Probably, "minimal change disease" and unrelated to the present episode). During the 6-week dietary lead-in he had one urine sample with no protein but active sediment? (Not described), and one urine sample with 1+ protein and some bacteria but no active sediment. He also had a normal baseline serum creatinine 1.1 mg/dl. At the one-year visit his creatinine was up to 1.6 mg/dl but a urinalysis was not done. His urinalysis at the time of the renal biopsy was 1+ protein, 3+ blood and numerous granular casts with moderate numbers of renal tubular cells. Daily protein excretion was 1.6 g/day, serum creatinine was still 1.6 mg/dL. The biopsy showed moderate increase in fibrous tissue and occasional inflammatory cells in the interstitium, suggestive of a chronic process present for many months and resulting in gradual collagen deposition within the interstitium rather than an acute process. Rosuvastatin was officially stopped at 2 years (Dec. 14, 2001) to see if renal function improved. It was restarted Dec. 24, 2001 and a follow up urine sample from Jan. 16th was cloudy with innumerable casts of all varieties, 1+

protein, 2+ blood, 24 hour urine protein was 600mg, serum creatinine was 1.3 mg/dL. A nephrology consult initially attributed this, after a positive paracetamol challenge test, to three tablets of paracetamol taken 4-10 days prior to the visit and the patient was continued on the study drug. On a follow up visit on April 10, a repeat 24 hour urine protein had 1300 mg of protein and the serum creatinine was 1.4mg/dL. Rosuvastatin was finally stopped on April 15, 2002. Follow up laboratory tests in May 2002 were 24 hour urine protein of 110 to 159mg, serum creatinine of 1.2 mg/dL, corrected serum creatinine clearance of 57 ml/min.

These three cases of renal insufficiency of unknown etiology are of concern because they present with a clinical pattern, which is similar to the renal disease seen with rosuvastatin in these clinical trials. There is mild proteinuria associated with hematuria and the suggestion of tubular inflammation or necrosis. All cases occurred at the 80 mg dose which was also associated with the greatest number of patients with abnormal renal findings in these clinical trials. Proteinuria and hematuria could be potentially managed with regular urinalysis screening. However, if they are the signals for the potential progression to renal failure in a small number of patients, this may represent an unacceptable risk since currently approved statins do not have similar renal effects.

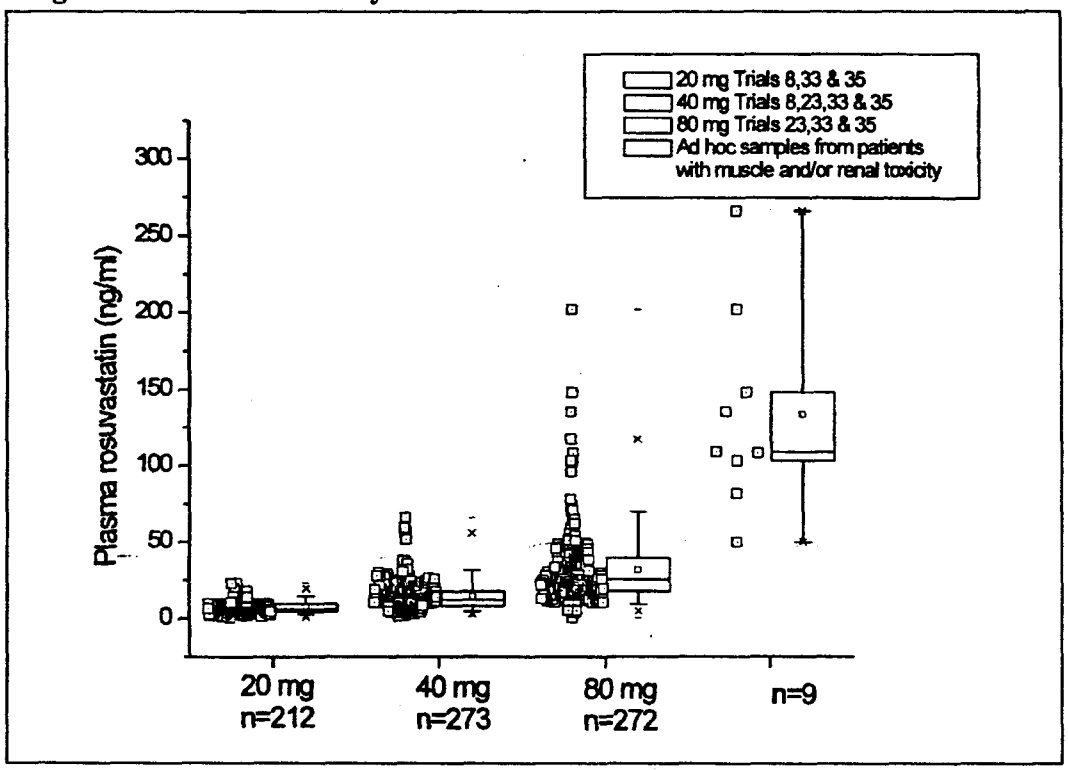
In conclusion, in addition to the known association of statins with rhabdomyolysis and elevation in liver transaminases, rosuvastatin appears to be associated with the development of proteinuria with and without hematuria at higher doses.

The mechanism for proteinuria is unknown although the sponsor postulates that protein uptake by renal tubular cells is inhibited by the statin effect on HMG-CoA reductase activity in renal proximal tubule cells. The finding of increased beta-2-microglobulin and N-acetyl-beta-D-glucosaminidase may also suggest renal tubular damage.
The incidence of proteinuria is clearly higher in patients treated with rosuvastatin 80 mg. The frequency of proteinuria with and without hematuria is lower in the 40 mg dose group but remains slightly higher than the lower dose groups. It is not clear from the current trials if the proteinuria is transient, waxes and wanes or is likely to progress to renal failure in a small number of patients. Such concerns may potentially be addressed in phase IV trials.

5.5 Correlation with Serious Adverse Events and Serum Rosuvastatin Levels

At the request of the agency, the sponsor submitted the limited data they had for rosuvastatin serum levels in patients with serious adverse events. Plasma concentrations for asymptomatic patients receiving 20, 40 or 80 mg of rosuvastatin in clinical trials 8, 23, 33, and 35 are shown in Figure 1 below. These values are compared to nine plasma samples obtained from six patients with serious adverse events involving muscle and or renal toxicity. These data correspond to Figure 22 in the sponsor's submission.

Figure 1 **Steady State Plasma Rosuvastatin Levels**



Two of these patients had myopathy with peak CK values of 5,380 and 2,154, two patients had rhabdomyolysis with peak CK values of 16,280 and >20,000 and two patients had renal failure of unknown etiology with normal CK values.

There is no overlap in exposure among patients receiving 20 mg and those showing evidence of toxicity. 5/273 patients (<2%) at 40 mg and 33/272 (33%) at 80 mg had steady-state plasma concentrations above 50ng/ml, the lowest observed plasma concentration associated with toxicity in these six patients. These data are derived from only a subset of patients studied in the entire clinical development program. Furthermore, one cannot definitively conclude from this analysis that a cut-off in drug level has been identified which will divide patients into an "at-risk" and "no-risk" category as other predisposing factors aside from drug levels may contribute to clinical toxicity. These data, however, support the recommendation for dose limitation in special populations wherein drug exposure would be increased secondary to drug-drug

interactions, diminished metabolism, or compromised clearance. While appropriate labeling restricting drug doses in certain situations can attempt to address potential safety concerns, labeling changes alone have not proven to be effective in changing prescriber behavior.

7. FINANCIAL DISCLOSURE

There was only one new trial, 0065, requiring financial disclosure information in the resubmission. Two investigators at two different sites in this trial reported [redacted]. They were Dr. [redacted] at site [redacted] and Dr. [redacted] at site [redacted]. These sites enrolled only 34/2579=1%, and 33/2579=1% respectively, of the total number of patients in this trial (data taken from AV_LUBR.xpt). Since these investigators enrolled only a small fraction of the patients in this double blind controlled trial it is unlikely that they could have biased the trials results. All other investigators in this trial provided information of " No Financial Arrangements" to the sponsor. There were no "No Response to Date" reports from this trial.

8. OVERVIEW OF METHODS USED TO EVALUATE DATA QUALITY AND INTEGRITY

DSI audited three domestic sites during the original NDA submission and found them to adhere to pertinent federal regulations and/or good clinical investigational practices governing conduct of clinical investigations and protections of human subjects. There were no new sites audited from the trials submitted in the resubmission.

9. APPENDIX

9.1 MedWatch Forms for Cases of Special Interest:

1. MedWatch Report of a case of 68 year old patient with Jaundice and Transaminase elevation on 10mg of Rosuvastatin D3560L0001/0310/01237
2. MedWatch Report of a case of 73 year old patient with Jaundice and Transaminase elevation on 10mg of Rosuvastatin D3560L0001/2265/09060
3. MedWatch Report of a case of Rhabdomyolysis on 10mg of Rosuvastatin 2003SE02255
4. MedWatch Report of a case of 46 year old patient with Renal Failure on 80mg of Rosuvastatin 0065/0044/0014
5. MedWatch Report of a case of 70 year old patient with Renal Failure on 80mg of Rosuvastatin 0065/0026/0049
6. MedWatch Report of a case of 69 year old patient with Interstitial Nephritis on 80mg of Rosuvastatin 0034/0316/0025

1. MedWatch Report of a case of 68 year old patient with Jaundice and Transaminase elevation on 10mg of Rosuvastatin D3560L0001/0310/01237

AstraZeneca Pharmaceuticals

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 4

Mfr report # 2002PK01036

FDA Use Only

A. Patient information

1. Patient identifier: [redacted] in confidence
2. Age at time of event: 68 yrs or Date of birth: [redacted]
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or 91 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   ☐ death ____ (mm/dd/yy)
   ☐ life-threatening
   ☒ hospitalization - initial or prolonged
   ☐ disability
   ☐ congenital anomaly
   ☐ required intervention to prevent permanent impairment/damage
   ☐ other: ____
3. Date of event (mm/dd/yy): 10/08/2002
4. Date of this report (mm/dd/yy): 10/28/2002
5. Describe event or problem:

15-DAY IND ALERT

CORRECTED REPORT: THE CLOCK START DATE G-4 HAS BEEN CHANGED TO 11-OCT-2002

Clinical Event(s):
1 HEPATOPATHY
2 ICTERUS

A report has been received from an investigator concerning a 68-year-old male patient who was enrolled in the ORBITAL study D3560L00001, an open, randomised parallel group study evaluating the effects of six months rosuvastatin treatment plus additional compliance initiatives compared to rosuvastatin alone on long-term *

6. Relevant tests/laboratory data, including dates:

*

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concomitant Disease(s): DIABETES MELLITUS, DIABETES MELLITUS TYPE II, FATTY LIVER, HEART DISEASE, HYPERTENSION, PERIPHERAL OCCLUSIVE ARTERY DISEASE

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 ROSUVASTATIN
   #2
2. Dose, frequency & route used
   #1 10 mg daily PO
   #2
3. Therapy dates (if unknown, give duration)
   #1 06/07/2002 to 10/09/2002
   #2
4. Diagnosis for use (indication)
   #1 HYPERCHOLESTEROLEMIA
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1 NI
   #2
7. Exp. date (if known)
   #1 NI
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # - for product problems only (if known)
   #1 NI
   #2
10. Concomitant medical products and therapy dates (exclude treatment of event)

Name: GLUCOPHAGE 850 Dates: NI to NI
Name: CAPTOBETA Dates: NI to NI
Name: ESCOR Dates: NI to NI *

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
   AstraZeneca Pharmaceuticals
   A Business Unit of AstraZeneca LP,
   1800 Concord Pike, P.O. Box 15437,
   Wilmington, DE 19850-5437
2. Phone number: 302 886 2127
3. Report source (check all that apply)
   ☒ foreign
   ☒ study
   ☐ literature
   ☐ consumer
   ☒ health professional
   ☐ user facility
   ☐ company representative
   ☐ distributor
   ☐ other: *
   DE
4. Date received by manufacturer (mm/dd/yy): 11-OCT-2002
5. (A)NDA # IND # [redacted] PLA # ____ pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #: D3560L00001
7. Type of report (check all that apply)
   ☐ 5-day ☒ 15-day
   ☐ 10-day ☐ periodic
   ☒ initial ☐ follow-up #____
8. Adverse event term(s)
   Hepatocellular damage, Jaundice NOS
9. Mfr. report number: 2002PK01036

E. Initial reporter

1. Name, address & phone # [redacted]
2. Health professional? ☒ yes ☐ no
3. Occupation: MEDICAL DOCTOR
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☒ unk

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.