there is a greater risk for myopathy and rhabdomyolysis such that the risks of treatment at this dose outweigh the benefits. This application is approvable for the proposed doses of 10 to 40 mg pending additional studies. These studies should include long-term safety exposure for the 20 and 40 mg dose and prospective evaluation of the potential for renal toxicity associated with rosuvastatin use. Specifically, the renal studies should address whether these findings progress to more severe renal deterioration, whether these findings are reversible, and what would be sensitive and specific monitoring tools for this toxicity should doses at 40 mg and below be approved.

Although the 10 mg dose and below appear safe, an adequate safety margin needs to be established with the 20 and 40 mg doses prior to their approval. Should the sponsor decide to pursue marketing of the — and 5.0 mg dosage strengths, sufficient chemistry and manufacturing data will be required in addition to the response to the other deficiencies in this approvable application.

PROPOSED INDICATIONS

The following indications are being sought with submission of the NDA:

1. as an adjunct to diet to reduce elevated total-C, LDL-C, apoB, nonHDL-C, — and TG levels and to increase HDL-C — in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Types IIa and IIb)
2. as an adjunct to diet for the treatment of patients with elevated serum TG levels (Fredrickson Type. — IV)
3. to reduce LDL-C, total-C, and apoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) if such treatments are unavailable

The definitions used by the sponsor for identification of specific dyslipidemic disorders are summarized in Table 1. The actual LDL-C inclusion criterion for the clinical development program, however, used a higher cut-off of 160 mg/dL.

Table 1. Classification of Dyslipidemia by Sponsor for Study Selection

Dyslipidemia	Lipid Criteria in mg/dL
Fredrickson Type IIa	LDL-C ≥ 130, TG < 200
Fredrickson Type IIb	LDL-C ≥ 130, TG ≥ 200
Fredrickson Type IV	LDL-C < 130, TG ≥ 200
Heterozygous FH	220 ≤ LDL-C < 500
Homozygous FH	LDL-C > 500

derived from sponsor's submission dated 6.26.01, item 3 Summary section 2.1 Categories of Dyslipidemia

CLINICAL STUDIES SUBMITTED

The clinical development program for rosuvastatin included 50 clinical trials designed to evaluate its clinical pharmacology, efficacy and safety at doses up to 80 mg administered once daily. The study population included healthy volunteers (Phase 1 studies), special populations (e.g., patients with renal and hepatic impairment), and patients with a broad range of dyslipidemia (Phase 2/3 trials). Only the Phase 2/3 studies reviewed by the medical and statistical reviewers will be addressed in this memo.

Rosuvastatin was studied in placebo-controlled studies, active-controlled studies against other marketed statins, and combination studies with niacin, fenofibrate, and cholestyramine. In total, there were 14 controlled, pivotal studies and one open-label extension trial submitted for the support of the proposed indications. The controlled studies are summarized below in Table 2:

Table 2. Summary of Controlled Clinical Trials for NDA 21-366

Trial No./Design	N	Rosu dose (mg/day)	Comparator (mg/day)	Primary endpoint % chg from baseline
Types IIa and IIb Dyslipidemia				
8 Rand, DB, PC, fixed-dose	142	1, 2.5, 5, 10, 20, 40	placebo atorvastatin 10, 80 OL	LDL-C at 6 wks
23 Rand, DB, PC, fixed-dose	64	40, 80	placebo	LDL-C at 6 wks
24 Rand, DB, PC, AC, fixed-dose	519	5, 10	placebo atorvastatin 10	LDL-C at 12 wks
25 Rand, DB, AC, force-titrated	383	5, 10, 20, 40, 80	atorvastatin 10, 40, 80	LDL-C at 24 wks
26 Rand, DB, AC, titrate to NCEP II	412	5, 10, 20, 40, 80	atorvastatin 10, 20, 40, 80	LDL-C at 12 wks
27 Rand, DB, AC, fixed-dose	502	5, 10	pravastatin 20 simvastatin 20	LDL-C at 12 wks
28 Rand, DB, AC, titrate to NCEP II	477	5, 10, 20, 40, 80	pravastatin 20, 40 simvastatin 20, 40, 80	LDL-C at 12 wks
33 Rand, DB, AC, fixed-dose	374	5, 10, 20, 40, 80	atorvastatin 10, 20, 40, 80	LDL-C at 6 wks
Types IIb and IV Dyslipidemia				
29 Rand, OL, force-titrated	270	10, 20, 40	niacin 0.5, 1.0, 1.5. 2.0 g combination with niacin	LDL-C at 24 wks
35 Rand, DB, PC, fixed-dose	156	5, 10, 20, 40, 80	placebo	TG at 6 wks
36 Rand, 6wk DB PC then 18wk OL, forced-titrate in Type II DM	216	5, 10 during DB phase 5, 10, 20, 40 during OL phase	placebo during DB phase fenofibrate 67 mg qd, bid, tid during OL phase *combination with* fenofibrate	TG at 24 wks
HeFH, HoFH, and Severe Hypercholesterolemia				

Trial No./Design	N	Rosu dose (mg/day)	Comparator (mg/day)	Primary endpoint % chg from baseline
30 Rand, DB, AC, force-titrated	623	20, 40, 80	atorvastatin 20, 40, 80	LDL-C at 18 wks
31 Rand, OL	153	40, 80	combination with cholestyramine	LDL-C at 6 wks
54 OL, force-titrated for 18 wks then Rand, cross-over, DB for 12 wk	44	20, 40, 80 during OL phase 80 mg during DB phase	atorvastatin 80	LDL-C at 18 wks

Many patients enrolled in the controlled trials were enrolled in Trial 34, an ongoing, open-label, extension study designed to assess the long-term safety of rosuvastatin treatment. This trial will be discussed in the Safety Results section of this memo.

EFFICACY RESULTS

The design, conduct, and results of the individual trials are discussed in detail in the two separate statistical reviews by Joy Mele, MS and Cynthia Liu, MA.

This memo will present the efficacy results from the placebo-controlled trials in an attempt to summarize the effects of rosuvastatin in Types IIa/IIb with respect to cholesterol-lowering (trials 8, 23, and 24) and in Types IIb/IV with respect to TG-lowering (trial 35).

The lipid-altering efficacy of rosuvastatin was also compared to 3 other marketed statins: atorvastatin; simvastatin; and pravastatin. The most comprehensive comparison was done between rosuvastatin and atorvastatin, the most efficacious LDL-lowering statin compared to other currently marketed statins on a mg per mg basis. Atorvastatin was the active comparator in 7 of the 14 controlled trials. Of these 7, only 3 trials will be summarized under this section (Trial 33, 25, and 30). Pravastatin and simvastatin were the active comparators in 2 trials. These trials were reviewed in detail by Joy Mele, MS and will not be discussed in this memo.

This section will also review the findings of rosuvastatin therapy on reaching NCEP goals in patients with Types IIa and IIb dyslipidemia (trials 26 and 28) and rosuvastatin therapy in homozygous FH (trial 54). Finally, the results of combination therapy with niacin (trial 29), fenofibrate (trial 36), and cholestyramine (trial 31) will be presented.

Treatment of Hypercholesterolemia (IIa/IIb)

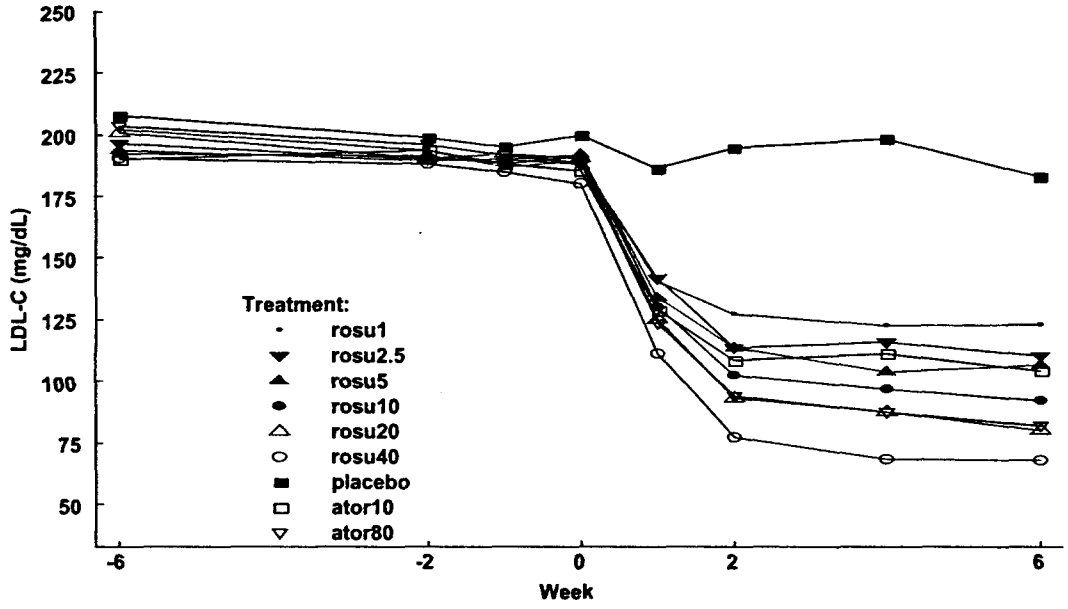
Treatment with rosuvastatin at doses of 1.0, 2.5, 5.0, 10, 20, 40, and 80 mg significantly reduced LDL-C, TC, and apo B from baseline relative to placebo. Average reductions in LDL-C ranged from –35% to –63% with reductions seen as early as 1 week after therapy and achieved by 2 weeks of therapy. These reductions were dose-dependent although titration from the 40 mg to 80 mg dose did not appear to confer any additional benefit to LDL-lowering. This conclusion is based on the results described below.

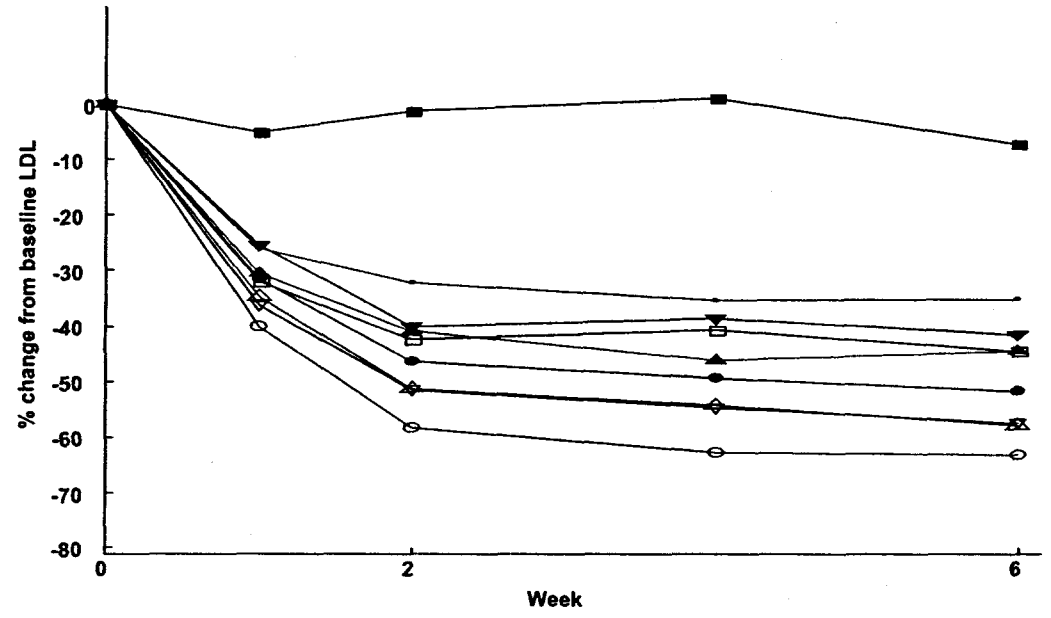
Trial 8

Trial 8 evaluated placebo versus rosuvastatin treatment in the dose range of 1.0 to 40 mg daily for 6 weeks after a 6-wk dietary run-in period. There were also open-label treatment arms with atorvastatin 10 and 80 mg for purposes of estimating treatment

effect and providing information for future comparative treatment studies. The results of trial 8 are summarized in the 2 graphs obtained from Joy Mele's review.

Figure 1. LDL-C (mg/dL) and mean % change from baseline across rosuvastatin dosage range 1.0-40 mg versus placebo in Trial 8 (*From Joy Mele, MS, FDA statistical review of NDA 21-366)*





Rosuvastatin treatment at daily doses of 1.0 to 40 mg resulted in average reductions in LDL-C of –35% to –63% from baseline that were statistically significant compared to placebo. Similarly, rosuvastatin treatment across all doses studied significantly reduced total-C and apoB levels after 6 weeks. The effect of rosuvastatin treatment on TG and HDL-C was highly variable and for the most part, not significantly different from placebo except for a marginally significant effect seen at the 5 and 10 mg dose for HDL-raising and 5 mg dose for TG-lowering.

Table 3. Mean changes from baseline in lipid parameters in Study 8 (*From Joy Mele, MS, FDA statistical review of NDA 21-366)*

	Placebo (n=13)	ROSU 1 (n=14)	ROSU 2.5 (n=15)	ROSU 5 (n=17)	ROSU 10 (n=17)	ROSU 20 (n=17)	ROSU 40 (n=18)
LDL Baseline % change	197 (14) -7% (7)	191 (18) -35% (9)	190 (15) -42% (9)	193 (16) -45% (7)	190 (16) -52% (9)	191 (22) -56% (13)	184 (19) -63% (9)
P-value vs. pla		<.001	<.001	<.001	<.001	<.001	<.001
TC Baseline % change	272 (12) -5% (6)	267 (21) -24% (7)	264 (24) -30% (8)	269 (20) -33% (6)	267 (16) -36% (7)	267 (21) -41% (10)	257 (27) -46% (8)
P-value vs. pla		<.001	<.001	<.001	<.001	<.001	<.001
HDL Baseline % change	49 (12) +3% (10)	55 (14) +8.5% (10)	48 (10) +8.8% (10)	52 (9) +13% (13)	50 (15) +14% (12)	50 (13) +7.5% (9)	52 (13) +9.4% (8)
P-value vs. pla		.4	.5	.04	.04	.4	.3
TG Baseline % change	130 (41) -3% (23)	116 (49) -16% (18)	132 (45) -14% (33)	123 (51) -35% (16)	135 (52) -12% (35)	134 (52) -27% (18)	107 (48) -25% (23)
P-value vs. pla		.2	.7	.001	.8	.07	.009
Apo-B Baseline % change	140 (16) -3% (10)	132 (14) -27% (11)	135 (12) -34%	139 (18) -38% (9)	143 (18) -42% (8)	136 (20) -46% (11)	130 (15) -55% (6)
P-value vs. pla		<.001	<.001	<.001	<.001	<.001	<.001

Trial 23

Trial 23 evaluated the effects of rosuvastatin 40 mg and 80 mg daily treatment versus placebo for 6 weeks following a 6-wk dietary run-in period. Both doses achieved statistically significant reductions in percent change in LDL-C from baseline compared to placebo. As expected, these results were accompanied by significant reductions in total-C and apoB levels at both doses. The effect of treatment on TG was marginally significant with both doses and only significant at the 80 mg dose for an effect on HDL-C. The inability to demonstrate a significant difference from placebo may also be a function of the small sample size per group.

Table 4. Mean % Changes from Baseline Lipid Parameters at Wk 6 in Trial 23

	Placebo N=17	Rosu 40 mg N=16	Rosu 80 mg N=31
Mean % Chg LDL	-0.8%	-61%	-63%
p-value vs pbo	NA	<0.001	<0.001
Mean % Chg TC	-0.2%	-44%	-45%
p-value vs pbo	NA	<0.001	<0.001
Mean % Chg ApoB	-1.8%	-52%	-54%
p-value vs pbo	NA	<0.001	<0.001
Mean % Chg HDL	+2.6%	+11%	+15%
p-value vs pbo	NA	0.10	0.04
Mean % Chg TG	-0.1%	-27%	-23%
p-value vs pbo	NA	0.05	0.06

From the figure below, comparison of the range of LDL-lowering in Trials 8 and 23 demonstrates a dose-related response with comparable results observed at the 40 mg dose in both trials. The figure on the right also illustrates the minimal additional benefit of titrating from 40 mg to 80 mg.

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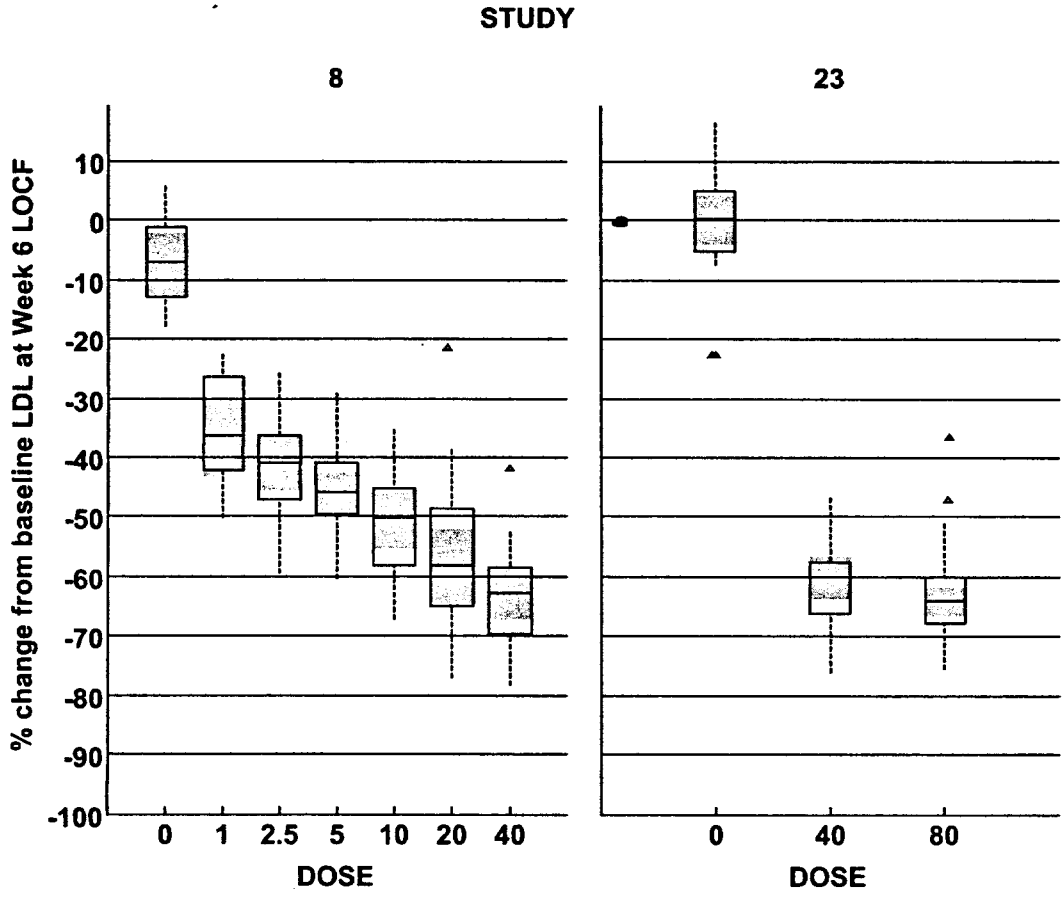
Figure 2. Range of Percent Change from Baseline Across the Rosuvastatin Dosage Range of 1.0 to 80 mg as Observed in Trial 8 and 23. (*From Joy Mele, MS, FDA statistical review of NDA 21-366*)

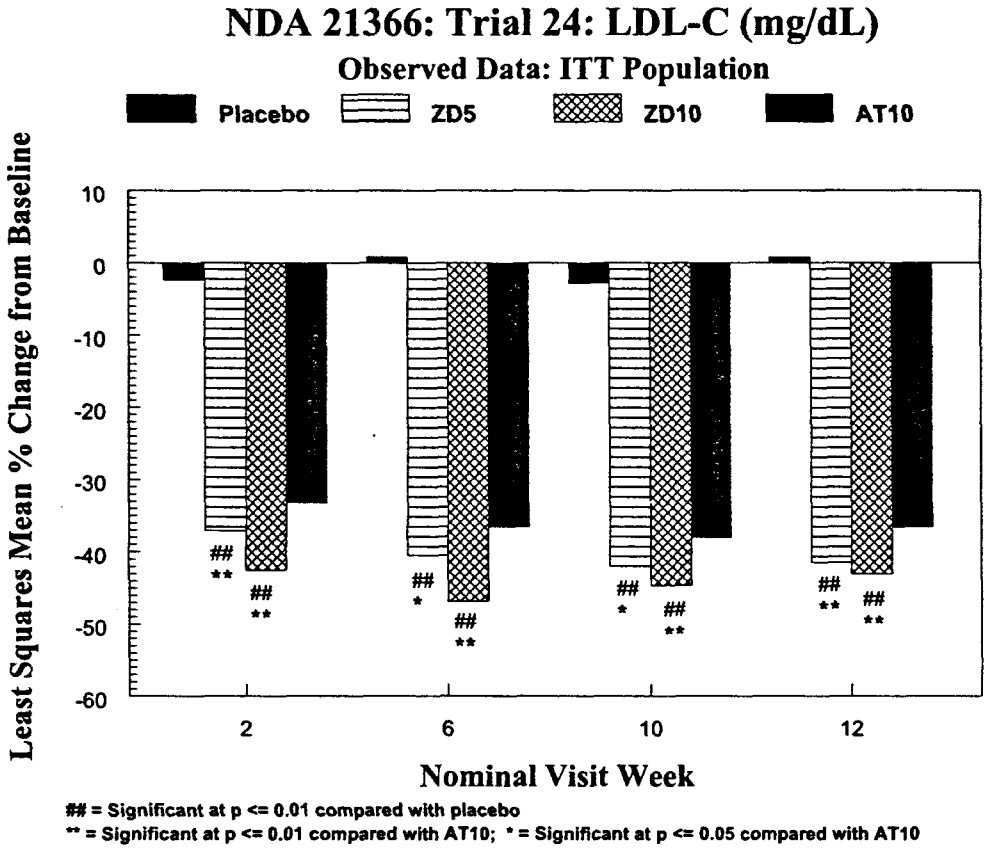


Trial 24

This was a 12-week trial comparing the effects of rosuvastatin 5 and 10 mg versus placebo and atorvastatin 10 mg daily. The double-blind treatment period was preceded by a 6-wk dietary run-in period. Treatment with rosuvastatin 5 or 10 mg daily resulted in statistically significant mean percent reductions in LDL-C from baseline relative to placebo. Significant changes in total-C, apoB, non-HDL-C, TG and HDL-C were also observed.

The following figure obtained from Cynthia Liu's statistical review shows significant reductions in LDL-C relative to baseline at endpoint and throughout all periods of efficacy assessment. At week 12, the rosuvastatin 5 and 10 mg groups had mean reductions in LDL-C of –40.4% and 42.9%, respectively, compared to the placebo group's +0.03%. In addition, both the 5 and 10 mg doses showed superior reductions in LDL-C compared to atorvastatin 10 mg. Comparative efficacy results will be discussed in a subsequent section of this review.

Figure 3. Mean %·Change in LDL-C Throughout Trial 24 (*From Cynthia Liu, MA FDA statistical review of NDA 21-366)*



Treatment of Hypertriglyceridemia (IIb/IV)

Three studies were conducted to evaluate the effect of rosuvastatin treatment on hypertriglyceridemia in the Type IIb/IV patient population. The TG inclusion criterion for these studies was 200 or 300 ≤ TG < 800 mg/dL. Trial 35 was the only randomized, placebo-controlled, fixed-dose study evaluating rosuvastatin across its entire dosage range. Trials 29 and 36 incorporated complex study designs involving force-titration, active-control, and combination therapy with either niacin extended-release or fenofibrate. These trials will be discussed in a separate section of the Efficacy Results section (see Effect of Rosuvastatin in Combination with Non-Statin Lipid-Altering Drugs).

Treatment with rosuvastatin across its dosage range of 5 to 80 mg significantly reduces TG levels in Type IIb/IV patients compared to placebo. This reduction occurs by Week 2 with a dose-response seen only at the 5 and 10 mg doses. Titrating beyond the 10 mg dose does not appear to provide any difference in TG-lowering as afforded by the 10 mg dose. Patients with HDL-C ≤ 39 have a greater TG-lowering response than those with HDL-C levels above 39 but this is likely a function of the former subgroup having higher baseline TG levels.

Trial 35

This trial was a double-blind, randomized trial comparing fixed-doses of rosuvastatin 5, 10, 20, 40, and 80 mg to placebo in patients with TGs between 300 and 800 mg/dL. After 6 weeks of dietary run-in, patients were randomized to 6 weeks of treatment.

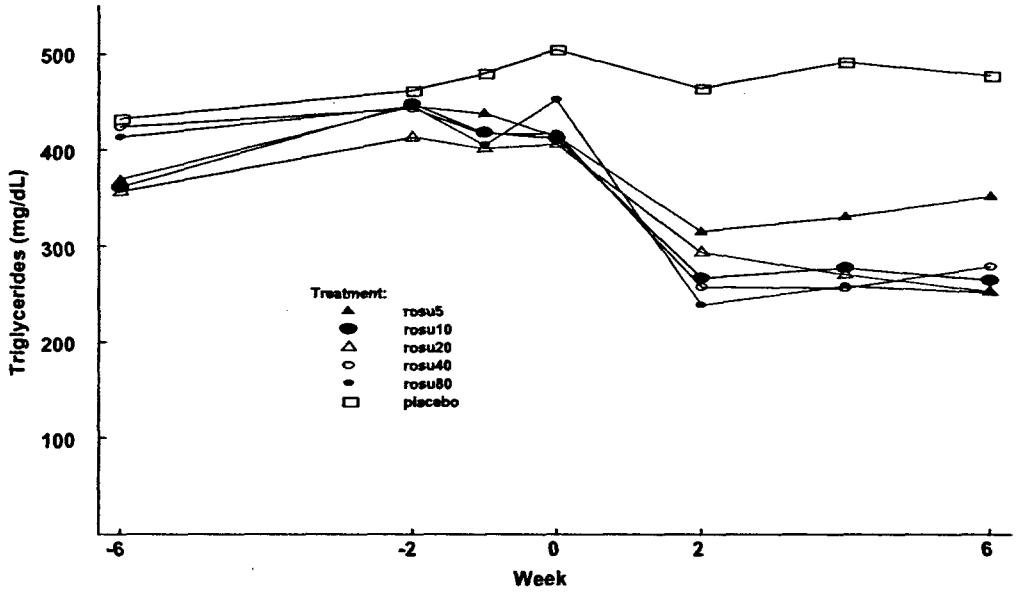
All doses of rosuvastatin achieved significant TG-lowering from baseline compared to placebo (Table 5).

Table 5. LS Mean (SE) % Chg in TG from Baseline at Week 6 in Trial 35 *(data obtained from Joy Mele, MS FDA statistical review of NDA 21-366)*

	Placebo N=26	Rosu 5mg N=25	Rosu 10mg N=23	Rosu 20mg N=27	Rosu 40mg N=25	Rosu 80mg N=27
Baseline TG	511 (138)	462 (104)	447 (96)	446 (119)	471 (142)	448 (138)
%Chg	+3% (4)	-21% (6)	-40% (6)	-40% (6)	-43% (6)	-40% (4)

However, the responses at the 10, 20, 40, and 80 mg were similar as illustrated in the figure below obtained from Joy Mele's review. This finding suggests that no additional benefit for TG-lowering is obtained with doses greater than 10 mg.

Figure 4. Study 35 Median TG (mg/dL) by week on study and treatment group (*From Joy Mele, MS FDA statistical review of NDA 21-366)*



Except for HDL-C, the effect of rosuvastatin treatment on secondary efficacy measures revealed similar responses to the primary measure of TG in that there were significant reductions from baseline relative to placebo but no notable differences among the 10, 20, 40, and 80 mg dose. For HDL-C, significant increases were only obtained with the 20 and 40 mg dose and there was clearly no dose response across the entire dosage range (Table 6).

Table 6. LS Mean (SE) % Chg in HDL from Baseline at Week 6 in Trial 35 *(data obtained from Joy Mele, MS FDA statistical review of NDA 21-366)*

	Placebo N=26	Rosu 5mg N=25	Rosu 10mg N=23	Rosu 20mg N=27	Rosu 40mg N=25	Rosu 80mg N=27
Baseline HDL	35 (7)	36 (9)	38 (6)	34 (7)	35 (7)	36 (9)
%Chg	-2% (2)	+4% (3)	+6% (3)	+18% (2)	+15% (2)	+10% (2)

Efficacy of Rosuvastatin Versus Other Marketed Statins

Rosuvastatin, at similar doses to atorvastatin, is more effective at lowering LDL-C, total-C, non-HDL-C, and apoB levels. The effect of rosuvastatin on LDL-C is as good as a doubling of the atorvastatin dose. Rosuvastatin 5 and 10 mg is also more effective at lowering these same lipid parameters than the 20 mg dose of either pravastatin or simvastatin.

Trial 33

This was a double-blind, randomized trial comparing multiple doses of rosuvastatin 5, 10, 20, 40, and 80 mg to atorvastatin 10, 20, 40, and 80 mg. This is the only study which compares the entire dosage range of both statins in a fixed-dose study design. Patients were treated for 6 weeks after a 6-week dietary run-in period.

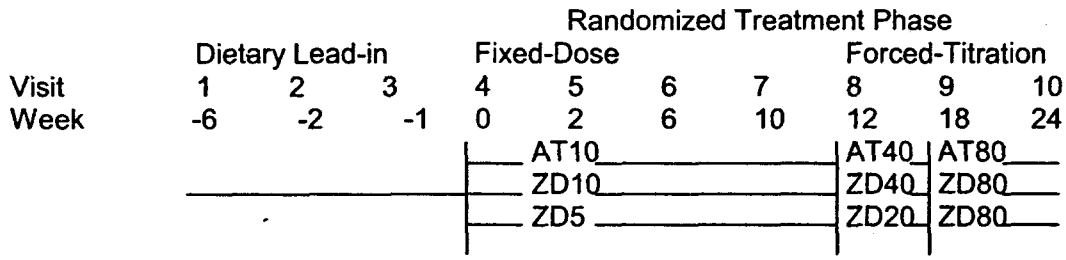
In both treatment groups, significant reductions in LDL-C were obtained after 1 week and achieved by 2 weeks. Rosuvastatin was statistically significantly better than atorvastatin at similar mg doses for LDL-lowering (Table 7).

Table 7. LDL results (mg/dL) at Week 6 in Study 33 *(from Joy Mele, MS FDA Statistical Review of NDA 21-366)*

	ROSU 5 (n=38)	**ROSU 10 (n=45)**	**ROSU 20 (n=38)**	**ROSU 40 (n=44)**	**ROSU 80 (n=42)**
Baseline mean (SD)	193 (22)	190 (18)	188 (24)	188 (20)	198 (22)
% change mean (SD)	**-42%** (10)	**-48%** (13)	**-50%** (19)	**-58%** (12)	**-61%** (14)
		ATOR 10 (n=43)	**ATOR 20 (n=39)**	**ATOR 40 (n=42)**	**ATOR 80 (n=41)**
Baseline mean (SD)		190 (24)	185 (19)	188 (22)	190 (18)
% change mean (SD)		-37% (13)	-46% (10)	-45.5% (14)	-55% (10)
p-value (Rosu vs. Ator)					
Sponsor's model		<.0001	<.0001	<.0001	<.0001
Alternative model		.0001	.13	<.0001	.03

Trial 25

This was a 24-wk trial preceded by a 6-wk dietary run-in period. Patients were randomized after the run-in period to either atorvastatin 10 mg, rosuvastatin 5 mg or rosuvastatin 10 mg as fixed-dosed treatments for 12 weeks. At the end of the 12 weeks patients entered a force-titration period with the atorvastatin patients titrated from 10 to 40 to 80 mg in 6 week intervals and the rosuvastatin 5 mg group titrated from 20 to 80 mg and the rosuvastatin 10 mg titrated from 40 to 80 mg also in 6 wk intervals. The following diagram, obtained from Cynthia Liu, MA's review, displays the study design.



The primary efficacy measure was obtained at Week 24 between the 80 mg doses of atorvastatin and rosuvastatin. Secondary efficacy measure for LDL-C was obtained at the 12 and 18 week timepoints of treatment.

At Wk 24, force titration to rosuvastatin 80 mg achieved mean LDL reductions from baseline of –58.4% in the 5/20/80 titrated group and –60.7% in the 10/40/80 titrated group. The atorvastatin 80 mg dose achieved a mean reduction of –52% in LDL-C from baseline after force titration (10/40/80). The treatment differences between both rosuvastatin groups and atorvastatin were statistically significant.

The figure below shows that rosuvastatin treatment at any timepoint in the study was significantly better than atorvastatin with respect to LDL-lowering. However, the increase from rosuvastatin 40 mg to 80 mg provided only an additional 3% reduction in LDL and titration of atorvastatin from 40 to 80 mg reduced LDL by an additional 5%.

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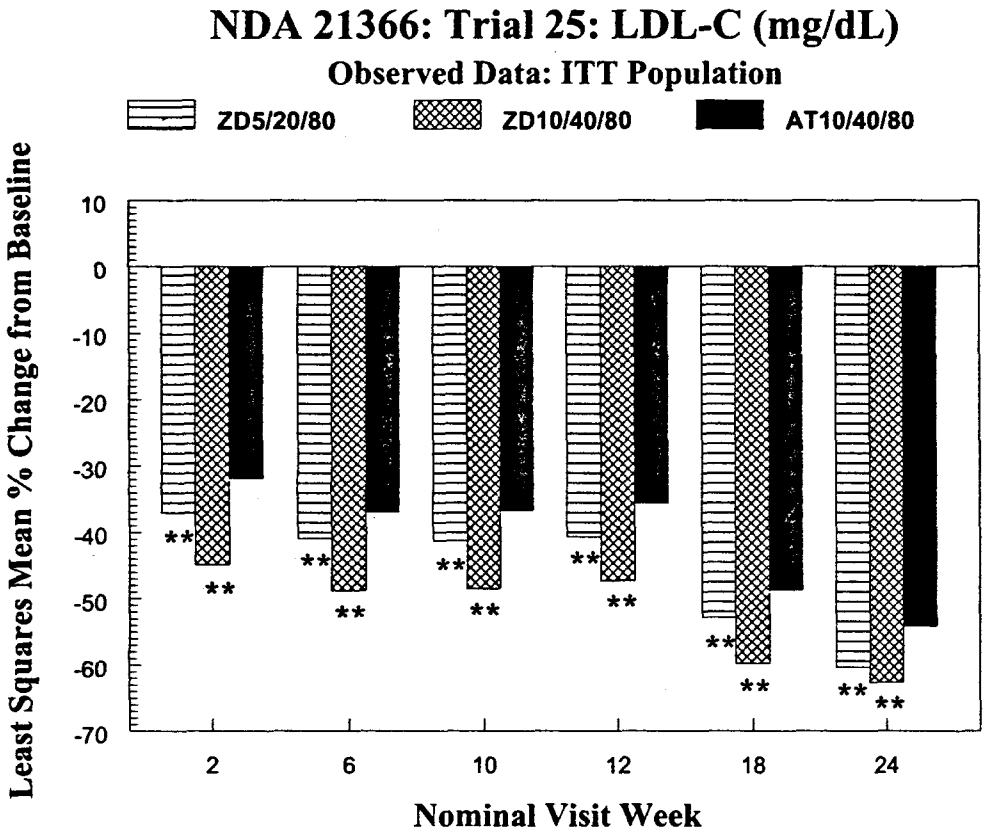
Figure 5. LDL-lowering response by treatment group and study visit in Study 25 (*from Cynthia Liu, MA FDA Statistical Review of NDA 21-366*).



Dosing by Week

Treatment Group	Wk 2	Wk 6	Wk 10	Wk 12	Wk 18	Wk 24
Rosu 5/20/80	5 mg	5 mg	5 mg	5 mg	20mg	80 mg
Rosu 10/40/80	10 mg	10 mg	10 mg	10 mg	40 mg	80 mg
Atorva 10/40/80	10 mg	10 mg	10 mg	10 mg	40 mg	80 mg

Trial 30

This trial evaluated the 20, 40, and 80 mg dose of rosuvastatin to atorvastatin in a force-titrated study design in patients with heterozygous FH. Treatment duration was 18 weeks preceded by a 6-wk dietary run-in period. Upward titration took place at 6 wk intervals.

Similar to results from Trial 33 and 25, this study reveals statistically significant LDL-lowering of rosuvastatin over atorvastatin (Table 8).

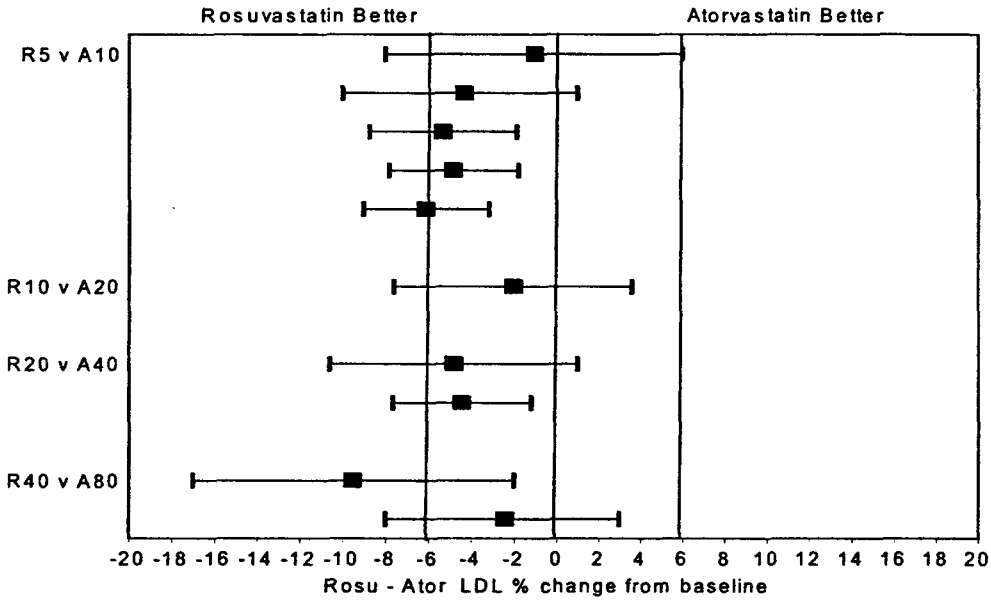
Table 8. LDL% Chg from Baseline by Week and Dose in Trial 30 (*from Joy Mele, MS FDA Statistical Review of 21-366*)

	ROSU (n=435)	ATOR (n=187)	Difference (CI)	p-value
Baseline	293 (51)	288 (49)		
Week 6 20 mg	-47.1%	-37.9%	-9% (-11%, -7%)	.0001
Week 12 40 mg	-55.4%	-47.3%	-8% (-10%, -6%)	.0001
Week 18 80 mg	-59.9%	-51.8%	-8% (-10%, -6%)	.0001
Week 18 LOCF	-57.9%	-50.4%	-7% (-10%, -5%)	.0001

Rosuvastatin vs. Atorvastatin

Joy Mele compared the LDL-lowering efficacy of rosuvastatin versus atorvastatin by computing the 95% confidence intervals for the treatment difference of rosuvastatin minus atorvastatin (negative values favor rosuvastatin) from 5 trials (8, 33,24, 25, 26). Her results reveal that rosuvastatin's LDL-lowering efficacy is comparable or better to that of twice the dose of atorvastatin.

Figure 6. Rosuvastatin LS mean minus atorvastatin LS mean and 95% CI by comparison and study where atorvastatin was 2x the dose of rosuvastatin (*from Joy Mele, MS FDA statistical review of NDA 21-366).*



Effect of Rosuvastatin on Treatment to NCEP LDL-C Goals

The description of statin efficacy by proportion of patients achieving NCEP LDL-C goals was first introduced in the atorvastatin label in December 1996. Since then it has been acknowledged that the presentation of proportion of individuals reaching treatment goals as a summary of efficacy and, in most cases, comparative efficacy with other statins, is

not appropriate for drug labeling as the proportion reaching goal is dependent on baseline LDL-C values and CHD risk categories.[1]

Although the reasons for selecting one statin over another would include efficacy at achieving a recommended LDL level to lower the risk of heart disease, other factors including safety and potential for drug interactions need to be considered as well. The presentation of LDL-lowering efficacy by mean percent reduction from baseline is adequate for prescribers to determine which statin and what dose would be appropriate given the patient's medical history.

It is self-evident that in any given population with similar baseline cholesterol levels, CHD risks, and treatment goals, a very potent statin will be more effective at getting the majority of patients to that treatment goal at lower doses than a less potent statin. To this end, the sponsor has conducted 2 studies - the results of which prove this point.

In Trial 26, patients with Types IIa/IIb dyslipidemia were randomized to atorvastatin 10 mg, rosuvastatin 5 mg, or rosuvastatin 10 mg for 12 weeks. At the end of this period, patients entered a dose-titration phase of 40 weeks duration in order to achieve NCEP II goals.[2] At the end of the study (Wk 52), 76% and 82.2% of the patients in the rosuvastatin group achieved their NCEP II goal on the dose their randomized starting dose (5 and 10 mg, respectively) in contrast to 62.9% of the patients in the atorvastatin group who achieved NCEP goals at the 10 mg start dose. In other words, more patients in the rosuvastatin group achieved treatment goals at their start dose of 5 or 10 mg then patients initiated on treatment with atorvastatin 10 mg.

Similarly, in Trial 28, patients with Types IIa/IIb dyslipidemia were randomized to rosuvastatin 5 and 10 mg or 20 mg of pravastatin or simvastatin for 12 weeks. After this period the dose could be titrated to achieved NCEP II treatment goals. The total duration of treatment was 52 weeks. At the end of the study, 74% and 85% of the rosuvastatin-treated groups achieved goal with the 5 or 10 mg dose, respectively, while 41% of the pravastatin group achieved goal at a start dose of 20 mg and 60% of the simvastatin group achieved goal at a start dose of 20 mg.

Again, the results of these 2 studies are not unexpected given the LDL-lowering efficacy of rosuvastatin compared to these individual statins.

Treatment of Homozygous Familial Hypercholesterolemia

Only one study was conducted in this patient population (Trial 54). This study included an 18-week, open-label forced-titration period where patients received rosuvastatin 20, 40, then 80 mg on 6 week intervals. Primary efficacy measure was performed at Week 18. After this time point patients entered a double-blind, cross-over period of 12 weeks' duration. In this period patients were treated with either atorvastatin 80 mg or rosuvastatin 80 mg for 6 weeks then crossed-over to the other treatment for 6 weeks.

At Wk 18, treatment with rosuvastatin 20, 40, and 80 mg daily resulted in mean reductions from baseline in LDL-C of –20%, -24%, and –22%, respectively, suggesting

[1] the label for atorvastatin has been modified with the approval of NDA 20-702/S029
[2] NCEP II goals were used as efficacy endpoints in these trials because the NCEP III treatment guidelines had not been finalized and published during the rosuvastatin clinical development program.

little additional benefit with upward titration from 20 mg in this patient population. However, from the FDA statistical review approximately 1/3 of patients achieve additional LDL-lowering of > 6% with titration from 20 to 40 mg. Only about 1/5 of the patients titrated from 40 to 80 mg achieved additional LDL-lowering of the same magnitude.

During the double-blind, cross-over treatment period the mean change from baseline in LDL-C was –25% for the rosuvastatin 80 mg group and –22% for the atorvastatin 80 mg group. The difference in treatment was not statistically significant.

Efficacy of Rosuvastatin in Combination with Non-Statin Lipid Altering Drugs
There were 2 studies conducted with treatment arms combining rosuvastatin with either niacin extended-release (Trial 29) or fenofibrate (Trial 36). Despite the study designs containing combination treatment arms, the sponsor's proposed label describes under the CLINICAL PHARMACOLOGY; Clinical Studies subsection the montherapy results of rosuvastatin and the comparator only. Such an analysis would be an unbalanced comparison of the drugs since rosuvastatin is a potent LDL-lowering drug whereas the benefits of the comparators used are primarily HDL-raising, TG-lowering, or both but not LDL-lowering.

In these trials a more appropriate comparison would be whether the combined use of rosuvastatin plus niacin or fenofibrate provides additional benefit over the individual components. An example in which such combination therapies would be clinically useful would be in patients whose lipid abnormalities include elevated LDL-C and TGs and low HDL-C levels. The LDL-lowering effectiveness of rosuvastatin, even at its lowest dose, could be complimented with the HDL-raising and TG-lowering effects of niacin or fenofibrate. This may be particularly useful as the effects of rosuvastatin on HDL and TGs are highly variable with little additional benefit beyond the 10 mg dose.

A third study included the combination of chlolestyramine with rosuvastatin (trial 31). This trial will not be reviewed in this memo; however, it should be noted that the addition of cholestyramine to rosuvastatin did not improve lipids significantly.

Trial 29
In this 24-week, open-label study patients were randomized to 4 different treatment groups: rosuvastatin monotherapy; niacin monotherapy; rosuvasatin 40 mg plus niacin 1.0 g; and rosuvastatin 10 mg plus niacin 2.0 g. All treatment groups required force-titration as illustrated in the following figure:

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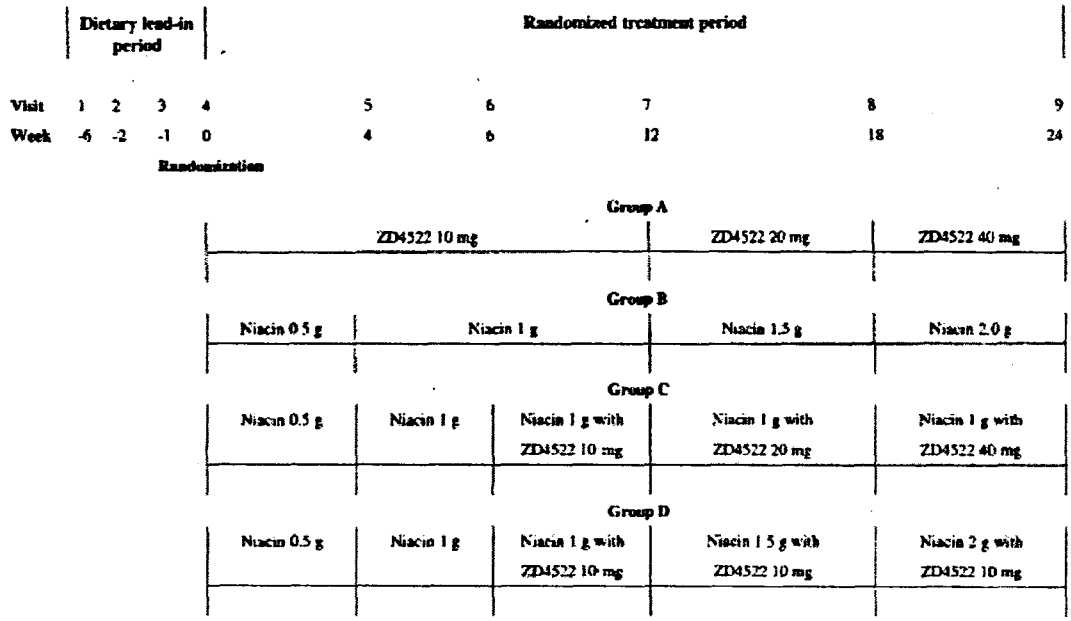
Figure 7. Study Design as Diagrammed by Sponsor

Figure 1 Trial design



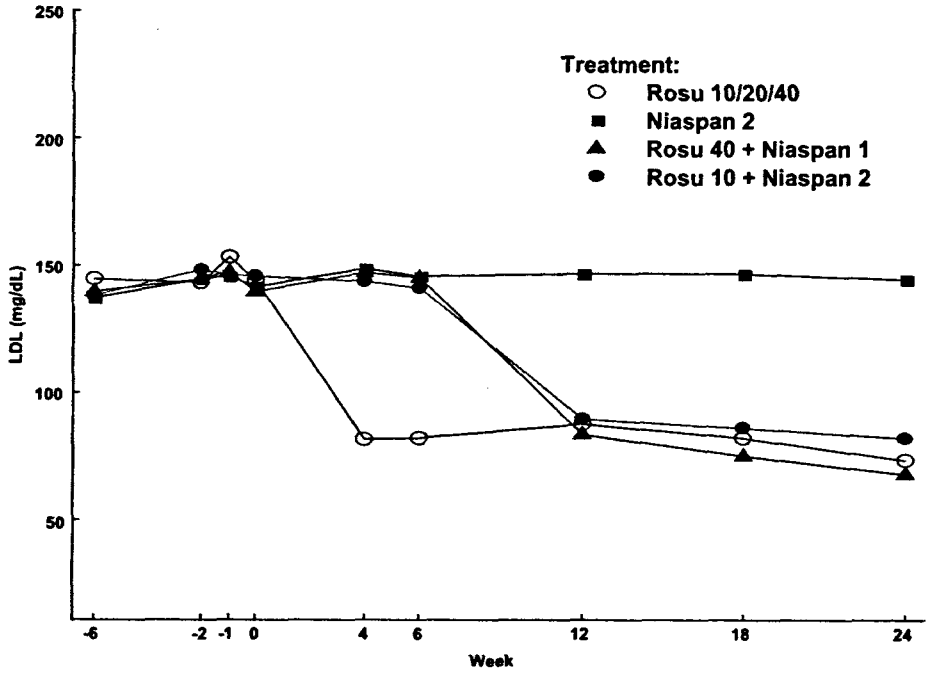


Figure 8. LDL-response over time by treatment group in Study 37 (*from Joy Mele, MS FDA Statistical Reviewer of NDA 21-366*)

From the figure above, it is clear that the effect of rosuvastatin on LDL-lowering is evident in all treatment arms and one can reasonably conclude that the addition of rosuvastatin will always provide superior LDL-lowering over niaspan alone. The benefits of niaspan to rosuvastatin will therefore be evaluated with respect to TG-lowering and HDL-raising.

From figure 7 (sponsor trial design schematic), it is evident that assessments of niacin contribution to rosuvastatin therapy can only be conducted at Week 12 for niacin 1g plus rosuvastatin 10 mg vs. rosuvastatin 10 mg monotherapy, Week 18 for niacin 1g plus rosuvastatin 20 mg vs. rosuvastatiaan 20 mg monotherapy, and at Week 24 for niacin 1g plus rosuvastatin 40 mg vs. rosuvastatin 40 mg monotherapy. These efficacy assessments are summarized in the following table:

Table 9. Study 29 LS Means for LDL, TG and HDL % Chg from Baseline (*from Joy Mele, MS FDA Statistical Review of NDA 21-366*)

	Combination Rosu+Niacin	Rosuvastatin	p-value	95% CI
Week 12	10 mg + 1 g (n=140)	10 mg (n=40)		
LDL	-32%	-38%	.10	-1%, +14%
TG	-32%	-31.5%	.91	-11%, +10%
HDL	+17%	+10%	.005	+2%, +12%
Week 18	20 mg + 1 g (n=70)	20 mg (n=44)		
LDL	-37%	-43%	.24	-4%, +14%
TG	-36%	-36%	.94	-12%, +11%
HDL	+16%	+12%	.19	-2, +10%
Week 24	40 mg + 1 g (n=70)	40 mg (n=44)		
LDL	-42%	-48%	.21	-3%, +14%
TG	-39%	-37%	.73	-14%, +10%
HDL	+17%	+11%	.08	-1%, +13%

Addition of niacin 1.0 g to rosuvastatin 10 mg provides significantly greater HDL-raising than rosuvastatin 10 mg alone. This dose of niacin combined with rosuvastatin 20 and 40 mg did not show a significant difference to rosuvastatin monotherapy at the respective doses. It is conceivable that the addition of higher doses of niacin (maximum dose 2.0 g) to rosuvastatin could further enhance HDL-raising but this study design did not allow for appropriate comparisons of the 1.5 and 2.0 g dose of niaspan plus rosuvastatin to a rosuvastatin monotherapy group. Such a study may be clinically relevant as rosuvastatin does not appear to have a dose-related effect on HDL with little additional benefit at higher doses.

Trial 36

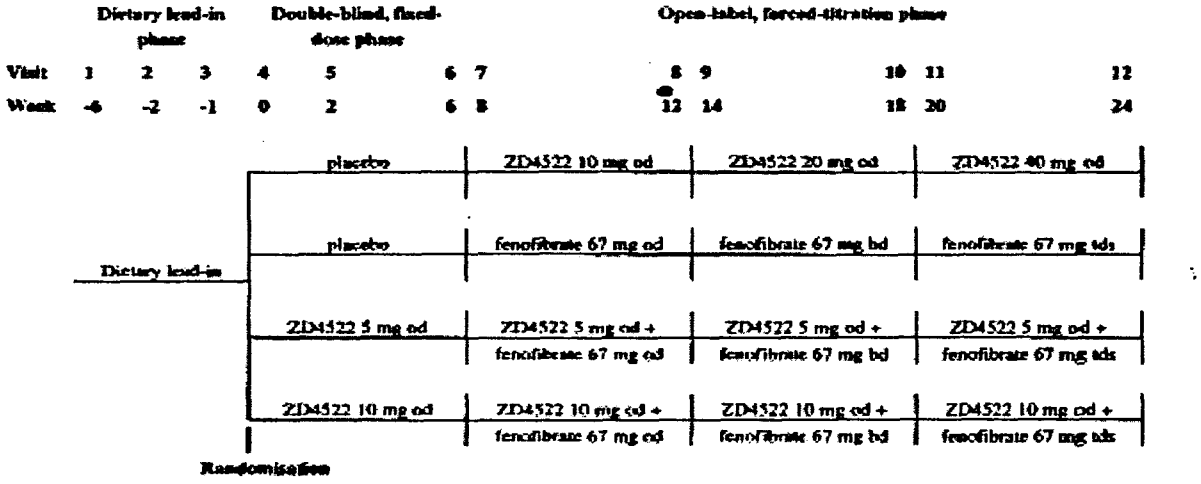
This study evaluated rosuvastatin monotherapy, fenofibrate monotherapy, and two different combinations of rosuvastatin and fenofibrate (R5mg + Feno 67 mg qd and R 10 mg + Feno 67 mg tid). This study was conducted in Type IIb/IV Type 2 diabetics; however, there is no reason to expect a difference in lipid-altering for Type IIb/IV dyslipidemics diabetics vs. non-diabetics. The presence of diabetes in these individuals will more likely increase the risk of cardiovascular clinical events but as this trial is only a

lipid-altering trial this reviewer places little emphasis on the recruitment of only diabetics for purposes of labeling.

Similar to Trial 29, this study employed a forced-titration dosing regimen although it is unclear why the sponsor chose such a design since neither rosuvastatin nor fenofibrate requires dose-titration for tolerability and could have therefore been studied as a fixed-dose regimen. The study design is illustrated below as presented by the sponsor.

Figure 9.

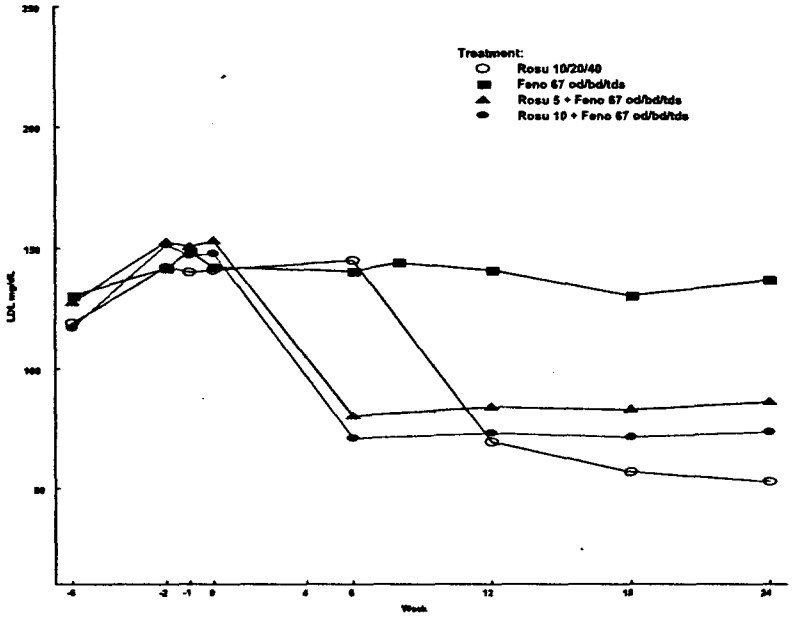
Figure 1 Trial design



od = once daily; bd = twice daily; tds = three-times daily.

Similar to combination rosuvastatin/niacin treatment, the addition of rosuvastatin 5 and 10 mg to fenofibrate results in significantly greater LDL-reduction than fenofibrate alone at any dose.

Figure 10. LDL-lowering response by treatment group and week (*from Joy Mele, MS FDA Statistical Review of NDA21-366*)



To address whether the combined use of rosuvastatin and fenofibrate provides any additional lipid-altering benefit over the individual components with respect to TG-lowering and HDL-raising the following timepoints were assessed:

Week 12: R10 mg + Feno 67 mg qd versus R10 mg
R10 mg + Feno 67 mg qd versus Feno 67 mg qd

Week 18: R10 mg + Feno 67 mg bid versus R 20 mg
R10 mg + Feno 67 mg bid versus Feno 67 mg bid

Week 24: R10 mg + Feno 67 mg tid versus R 40 mg
R10 mg + Feno 67 mg tid versus Feno 67 mg tid

(*Note: a more appropriate comparison at Wks 18 and 24 would be of the combination product to the individual components at identical doses. This study design does not allow for comparison of rosuvastatin 10 mg + fenofibrate to rosuvastatin 10 mg alone. However, since there is no evidence of a dose-response for HDL and TG with rosuvastatin therapy, the above comparisons will be imputed as being similar to a comparison with rosuvastatin 10 mg.)*

The following table from Joy Mele's review summarizes these results:

Table 10. Results of Analyses of TG and HDL by Week (*from Joy Mele, MS FDA Statistical Review of NDA 21-366*)

	Rosu + Feno	Feno	Rosu	Combo vs. Rosu	Combo vs. Feno
Week 12	R10 + F67qd	67 qd	10mg	10 mg + 67 od vs. 10 mg	10 mg + 67 od vs. 67 od
TG	-42%	-20%	-33%	.05*	<.001*
HDL	+13%	+6%	+10%	.17	.008*
Week 18	R10 + F67bid	67bid	20mg	10 mg + 67 bd vs. 20 mg	10 mg + 67 bd vs. 67 bd
TG	-46%	-32%	-35%	.06*	.006*
HDL	+15%	+8%	+11%	.10	.005*
Week 24[3]	R10 + F67tid	67tid	40mg	10 mg + 67 tds vs. 40 mg	10 mg + 67 tds vs. 67 tds
TG	-47%	-34%	-30%	.002*	.002*
HDL	+12%	+9%	+6%	.06*	.28

Addition of rosuvastatin to any dose of fenofibrate provides greater TG-lowering than fenofibrate alone. Similarly, the addition of fenofibrate to rosuvastatin also provides greater TG-lowering than rosuvastatin alone; however, the contribution of rosuvastatin to TG-lowering in the combination therapy is greater than from that of fenofibrate. It appears that the TG-lowering effect at the lowest dose of rosuvastatin studied (10 mg) can be complemented with addition of fenofibrate in lieu of upward titration of rosuvastatin. With the exception for fenofibrate 67 mg tid, addition of rosuvastatin provides greater HDL-raising than fenofibrate alone.

Conclusions on Efficacy Results

Rosuvastatin across the entire dosage range studied (1.0 mg to 80 mg) is an effective LDL-lowering agent with average reductions from baseline in the range of -35% to 63%. This agent is more potent than any currently marketed statin on a mg per mg basis with its LDL-lowering effect as good as twice the dose of atorvastatin. This efficacy appears to plateau at the 40 mg dose with little additional benefit when titrated to 80 mg. Across several studies this increase in dose (40 to 80 mg) confers an additional 2 to 4% LDL-lowering with similar distribution of responses. This minimal increase in benefit is offset by the safety concerns associated with the 80 mg dose discussed in the Safety Results section.

The effect of rosuvastatin on TG and HDL are not dose-related. In Types IIb/IV studies there was no difference in TG-lowering for doses above 10 mg and in Types IIa/IIb studies the responses were not different from placebo in most doses.

Rosuvastatin 20 to 80 mg was effective in lowering LDL-C in homozygous FH patients with an average reduction of -20% from baseline. The responses were quite similar in all 3 doses with only about 1/3 of the patients titrated from 20 to 40 mg achieving a further lowering > 6%. The lack of a dose-effect in this patient population, particularly at the 80 mg dose, does not support the approval of this dose in view of its toxicities.

Although the design of the combination studies with niacin extended-release and fenofibrate did not allow for appropriate comparisons of the combined therapies with many doses of the individual constituents, it does appear that niacin and fenofibrate may provide additional HDL-raising (niacin) and TG-lowering (fenofibrate) to rosuvastatin. This may be of clinical relevance as there is no dose response for these lipid parameters with rosuvastatin treatment beyond 10 mg.

[3] At Week 24, both LOCF and observed cases analyses yielded essentially the same analyses.

SAFETY RESULTS

A total of 4497 subjects were exposed to rosuvastatin in this clinical development with 3,903 individuals receiving treatment for 6 weeks or more (data from 1/30/02 safety update). Long-term safety exposure data came primarily from the extension study to the controlled (feeder) trials. The goal of this trial (Trial 34) was to assess the long-term safety of rosuvastatin treatment while targeting or maintaining LDL-C or LDL-C/TG goals. Patients entering Trial 34 were divided into 3 groups as follows:

- Group 1: Trials 23-28, 30, and 33 (treatment of hypercholesterolemia) → LDL-C target
- Group 2: Trials 29, 35, and 36 (treatment of hypertriglyceridemia) → LDL-C and TG target
- Group 3: Trial 54 (HoFH) → LDL-C target

From Dr. Lubas's review of the most recent safety exposure database, the majority of patients exposed to rosuvastatin beyond 1 year was at the 80 mg and 10 mg doses. There were fewer than 100 patients exposed at the intermediate doses of 20 and 40 mg beyond one year (Table 11).

(From William Lubas, MD, PhD Medical Review of NDA 21-366)

Table 11 Maximum continuous duration of treatment for each dose of rosuvastatin in the All Controlled / Uncontrolled Pool from Pre-Approval Safety Update 1/30/02

	Rosuvastatin dose [a,b]					
Cumulative duration of treatment [c]	5 mg N=1293	10 mg N=2174	20 mg N=1220	40 mg N=1249	80 mg N=1365	Total rosuvastatin [d,e] N=3903
≥6 weeks	1200	2009	1033	1084	1247	3722
≥12 weeks	974	1642	308	302	1003	3416
≥24 weeks	621	1122	183	184	927	2988
≥48 weeks	445	730	67	82	810	2471
≥72 weeks	145	311	11	8	446	1449
≥96 weeks	85	59	0	0	0	396
Mean days of treatment	240	251	92	93	338	394
Subject years ISS	673	930	197	179	645	2595
Subject years 4MSU	735	1112	220	212	792	3073
Subject years PASU	846	1482	303	317	1260	4209

Table 3 PreApproval SUR.
Data derived from PASU Tables S2.4.3 and 2.4.4, 4MSU Tables S2.4.3 and S2.4.4, and ISS Tables S2.4.3 and S2.4.4.
[a] Subjects are counted in each dose group to which they were exposed; therefore, subjects may be counted in more than 1 dose group.
[b] Subjects received rosuvastatin either alone or with another non-statin lipid regulating agent as combination treatment at any point during a feeder trial and/or Trial 34.
[c] For subjects with more than 1 exposure to a given rosuvastatin dose, only the longest duration of exposure to that dose is counted.
[d] Each subject is counted only once in the Total rosuvastatin column.
[e] 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.
SD = Standard deviation.

The deficient number of patients studied long-term at the 20 and 40 mg dose is problematic as the 80 mg dose is associated with myopathy and 6 cases of rhabdomyolysis reported during the open-label extension study. Such a finding is absent in the NDAs of all previously approved statin. Although no cases of rhabdomyolysis were observed at the lower doses, the inadequate number of patients studied beyond 1 year for the 20 and 40 mg doses does not allow for a conclusion that muscle toxicity is not associated with these intermediate doses.

Another unique but more unexpected safety concern raised in the review of this NDA is proteinuria and proteinuria/hematuria at the 40 and 80 mg doses.

This memo will summarize only the muscle and kidney-related safety findings. Liver enzyme elevation, a finding observed in all statins, is discussed in detail in Dr. Lubas's review. Although there are dose-related increases in the incidence of ALT elevations, these rates appear similar to other statins and there were no cases of liver failure or unexplained hepatitis observed.

Myopathy

Incidence of Myopathy

The incidence of CK elevations > 5x and > 10x ULN was higher at the 80 mg dose versus any of the lower doses. In addition, about one-third to half of these CK elevations had accompanying ALT elevations > 3x ULN. The incidence of myopathy (CK elevations > 10x ULN with muscle symptoms) was higher at the 80 mg dose (1.1%) than any of the lower doses (0 to 0.2%). Compared to historical data from some of the other statin safety databases, this rate also appears higher than the currently marketed statins. The following table from Dr. Lubas's review summarizes the incidence of CK elevations with and without associated clinical signs and symptoms. Across the spectrum of terminologies used to describe muscle toxicity, the incidence of event is always highest at the 80 mg dose.

(From William Lubas, MD, PhD Medical Review of NDA 21-366)

Table 12
CK ELEVATIONS IN PATIENTS TAKING ROSUVASTATIN IN THE ALL CONTROLLED/UNCONTROLLED POOL

	5mg		10mg		20mg		40mg		80mg	
	N (1221)	%	N (1967)	%	N (1125)	%	N (1123)	%	N (1314)	%
Single CKelevations[a]										
CK >5xULN	8	0.7	12	0.6	4	0.3	6	0.5	32	2.4
CK>10xULN	4	0.3	4	0.2	2	0.2	1	0.1	17	1.3
Single CK elevations associated with Alt >3xULN[a]										
CK >5xULN	1	0.1	1	0.1	0	0	0	0	12	0.9
CK>10xULN	1	0.1	1	0.1	0	0	0	0	10	0.8
Single CK Elevations associated with myopathy[b]										
CK >5xULN	2	0.2	2	0.1	1	0.1	0	0	14	1.1

CK>10xULN	2	0.2	2	0.1	1	0.1	0	0	14	1.1
Rhabdo-myolysis[c]	0	0	0	0	0	0	0	0	6	0.5

[a]Data were derived from Labs.xpt data file submitted 6/26/01. The Labs.xpt data base did not include data on 4 patients with rhabdomyolysis at the time this data base was submitted. Therefore the frequency of CK elevations and CK elevations associated with Alt elevations is probably underestimated.
[b]Data was derived from Table 22 in the Pre-Approval SUR therefore it includes all patients with rhabdomyolyis during these trials
[c]These include 4 cases of rhabdomyolysis diagnosed by the treating physician, 1 case originally diagnosed as myositis and one diagnosed as myopathy and renal failure. These last two cases had peak CK's of 34,548 and 16,280 U/L with increased plasma myoglobulin. All six patients had to be hospitalized for IV hydration.

Cases of Rhabdomyolysis

Although myopathy has been observed in the NDAs of other marketed statins, rhabdomyolysis was not seen in the premarketing application of these same statins. In this NDA, all 6 patients who developed rhabdomyolysis required hospitalization for IV hydration. The peak CK levels of these patients are summarized in the following table.

Table 13. CK Elevations in 6 Rhabdoymolysis Cases

Patient ID	Peak CK Level (U/L)	fold-increase[a]
0035/0393/0002	11,123	93
0030/0317/0020	3,486	29
0025/0224/0009	2,417	20
0025/0264/0017	34,548	288
0031/0037/0001	>20,000	>167
0025/0229/0004	16,280	136

[a]The ULN for CK level at central lab was 120 U/L

Dr. Lubas reviewed all the cases of rhabdomyolysis in detail and did not find any evidence of concomitant use of drugs that are known to increase statin drug levels or increase the risk of muscle toxicity. The characteristics of the 6 patients who developed rhabdomyolysis included older age, lower creatinine clearance, and a greater incidence of concurrent heart disease or hypertension. Two-thirds of the cases occurred in women. Although these characteristics plausibly suggest that older women with diminished renal function and complicated medical problems are at greater risk for muscle toxicity (a similar association has been suggested with Baycol), the number of events are too few to make any conclusive statement regarding the characteristics predisposing to rhabdomyolysis.

Interestingly, Dr. Lubas points out that all 6 patients had prodromes including loss in appetite, fatigue, malaise, muscle soreness, muscle weakness, nausea, vomiting, and abdominal distension 3 to 28 days before hospitalization. This finding suggests that patients who develop these symptoms while on statin therapy should be evaluated with appropriate laboratory studies (e.g., CK values) and possible interruption of treatment. However, it is not known if such interventions would avert the development of serious muscle damage and renal failure.

Renal Toxicity

The finding of possible renal toxicity in this development program was unexpected and based on routine monitoring of dipstick urinalysis. In other words, the data presented below are not from prospectively designed safety monitoring measures. Despite this limitation, the ad hoc data are compelling and strongly suggest renal toxicity associated with the 40 and 80 mg dose of rosuvastatin. Furthermore, there were 2 cases of renal failure and one case of renal insufficiency not related to myopathy where drug causality could not be ruled-out.

Proteinuria

In the controlled clinical trials there was an increase in the incidence of proteinuria from baseline to end of the study in the rosuvastatin group of 20.5% to 29.5%. In contrast, the active-control statin groups and the placebo group had a decrease in incidence of proteinuria of 21% to 17.3% and 27.6% to 23.3%, respectively. As mentioned earlier this was not an expected finding nor do these rates represent findings in the same patients.

A change in the extension study protocols included an analysis for increases in grade of proteinuria from baseline. These results are summarized in the following table from Dr. Lubas's review.

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										

Grade increases in proteinuria appear dose-related and are highest at the 80 mg group, although the 40 mg dose also carries a signal for this finding.

Proteinuria with Hematuria

Dr. Lubas further evaluated the frequency of higher grade increases (>/= ++) in proteinuria with and without hematuria. The 40 and 80 mg group had a higher incidence of 2+ or greater proteinuria than the lower dose groups. Accompanying hematuria was also higher in these patients than those in the lower dose groups.

Table 15. From William Lubas, MD, PhD Medical Review of NDA 21-366

PROTEINURIA AND HEMATURIA IN PATIENTS TAKING ROSUVASTATIN WITH AT LEAST A ++ MEASUREMENT ON THEIR FINAL URINE DIPSTICK*							
Rosuvastatin (mg)	N (patients)	Proteinuria ≥ ++			Hematuria (associated with proteinuria)		
		N	%	Fold Inc	N	%	Fold Inc
5	863	7	0.8	1	2	0.2	1
10	1025	13	1.3	1.4	2	0.2	1
20	705	8	1.1	1.4	1	0.1	0.5

40	830.	24	2.9	3.6	14	1.7	8.5
80	859	94	10.9	13.6	66	7.6	38

*These data include only patients with an increase of at least one protein category above baseline in their final reading. In the few cases where no baseline values were present it was assumed the baseline value was no protein.
Patients with abnormality during dietary run in or randomization periods were excluded.
Data taken from URIN.xpt data file 6/26/01

A similar analysis was performed by Dr. Lubas in clinical trials involving atorvastatin. Patients on atorvastatin did not have a dose-related increase in proteinuria with and without hematuria.

Table 16. From William Lubas, MD, PhD FDA Medical Review of NDA 21-366

PROTEINURIA AND HEMATURIA IN PATIENTS TAKING LIPITOR WITH AT LEAST A ++ MEASUREMENT ON THEIR FINAL URINE DIPSTICK*					
Lipitor (mg)	N (pts)	Proteinuria		Hematuria (and proteinuria)	
		N	%	N	%
10	451	9	2.0	2	0.4
20	261	4	1.5	0	0
40	251	1	0.4	1	0.4
80	350	3	0.9	1	0.3
Data taken from URIN.xpt data file 6/26/01					

Elevations in Creatinine

In an analysis of patients with creatinine increases > 30% during the extension study (n=35) it was noted that more of these occurred in the 80 mg group. More striking was the finding that in those patients with 2+ or greater proteinuria, there was a corresponding increase in serum creatinine levels in the 40 and 80 mg groups but none in the 5 to 20 mg groups. It should be noted that the number of patients analyzed in the 5 to 20 mg group was small and the data were pooled for these doses.

Table 17 From William Lubas, MD, PhD FDA Medical Review of NDA 21-366 Mean Serum Creatinine (μMOL/L) increase in patients with ≥++ Proteinuria [a]					
Dose (mg)	Baseline Cr Mean ± SD	Final Cr Mean ± SD	Baseline N	Final [b] N	Mean % change in Cr
5-20	100.6 ± 19.9	101.8 ± 20.2	28	25	1
40	106.8 ± 21.8	123.6 ± 35.6	24	22	16
80	98.4 ± 16.9	114.9 ± 27.9	94	90	17
Mean Serum Creatinine increase in patients with ≥++ Proteinuria and Hematuria [a]					
5-20	95.6 ± 15.6	99.3 ± 4.5	5	4	4
40	104.2 ± 21.7	121.4 ± 31.2	14	12	17
80	96.5 ± 17.1	118.1 ± 31.7	66	63	22
[a] Data derived from Urine.xpt 6/26/01 [b] Final data was not available for all patients.					

Conclusions on Safety Results

There are several safety findings for rosuvastatin which have distinguished it from all the currently marketed statins. At its highest proposed dose for marketing, rosuvastatin 80 mg is associated with a higher incidence of myopathy and 6 cases of rhabdomyolysis were reported in the extension trial – a finding never reported in the premarketing application for the other approved statins. At the 40 and 80 mg dose, a greater incidence of proteinuria and proteinuria with hematuria was observed. In those patients with 2+ or greater proteinuria on the 40 or 80 mg dose, there was a 16-17% mean increase in serum creatinine levels suggesting a deterioration in renal function. The reversibility of these changes are not known as data are not available for patients discontinued from treatment.

Although the 20 mg dose (and lower) do not have any obvious serious safety concerns, the long-term exposures at the 20 and 40 mg dose are less than adequate with only 67 and 82 patients studied beyond 48 weeks for these two doses, respectively.

Overall, there is no additional LDL-lowering benefit at the 80 mg dose that will outweigh the risk of myopathy and rhabdomyolysis in any studied population including homozygous FH patients. At the remaining proposed doses for marketing, 10 to 40 mg, there are concerns of renal toxicity (40 mg) and inadequate safety exposure (20 and 40 mg) that the sponsor will need to address prior to approval. Although the 10 mg dose appears safe, the sponsor will need to ensure that higher doses will provide an adequate safety margin since drug exposure with the 10 mg dose may be elevated in special populations and in the presence of certain concomitant medications (see biopharm review for details of drug interaction studies and studies in hepatic and renal impaired patient populations).

TEAM LEADER'S RECOMMENDATION ON NDA 21-366

This application is approvable for the proposed doses of 10 to 40 mg pending additional studies. These studies should include long-term safety exposure for the 20 and 40 mg dose and prospective evaluation of the potential for renal toxicity associated with rosuvastatin use. Specifically, the studies should address whether these renal findings lead to progressive renal deterioration, whether these findings are reversible, and what would be sensitive and specific monitoring tools for this toxicity should doses at 40 mg and below be approved.

The 80 mg dose should not be approved for marketing since there is no additional efficacy over the 40 mg dose but there is a greater risk for myopathy and rhabdomyolysis such that the risks of treatment at this dose outweighs the benefits.

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/s/

Mary Parks
5/1/02 04:58:55 PM
MEDICAL OFFICER

David Orloff
5/1/02 05:22:16 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: July 28, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-366
Crestor (rosuvastatin sodium)
Astra Zeneca
Treatment of hypercholesterolemia

SUBJECT: NDA review issues and recommended action

Background

Crestor (rosuvastatin, RSV) is the 7th HMG-CoA reductase inhibitor (HMGRI, statin) proposed for U.S. marketing. It is synthetic (in contrast to some older statin that are fungal products) and more potent per mg than Lipitor (approximately 2-4 times). The highest proposed dose, 40 mg, effects LDL-lowering marginally greater than 80 mg Lipitor. The efficacy of RSV has been very well characterized, and the claims of efficacy are supported by the data from multiple controlled trials in a broad spectrum of dyslipidemic populations. This memorandum will not address the specific efficacy of RSV. My previous memo on this application, dated May 2, 2002, discussed efficacy in brief, and the reviews by the medical officer, statistician, and medical team leader more than adequately address this issue.

With regard to efficacy of this class of drugs, it is well established that HMG-CoA reductase inhibition as a pharmacological approach to lipid altering favorably impacts the course of ASCVD in a broad range of populations, by age, gender, concomitant risk factors, diabetes or no diabetes, in patients with high or low LDL-C, and in those with normal or low HDL-C. The controlled clinical trials experience with the class includes nearly 30,000 statin-treated patients followed in 5-year placebo-controlled trials examining hard cardiovascular outcomes as well as non-cardiovascular serious morbidity and mortality. Lowering LDL-C with HMGRIs in at-risk individuals is proven to reduce all the manifestations of ASCVD, including CV mortality, with no evidence of a treatment-associated excess of non-cardiovascular deaths relative to placebo.

With regard to specific aspects of the safety profile of these drugs, it has long been known that statin use is associated with a dose-related increased incidence of mild-to-moderate (up to 3-5 X ULN), asymptomatic, often transient and resolving on therapy, elevations in hepatic transaminases. Rare cases of serious liver injury have been reported, though in most if not all cases without definitive attribution of causality to drug. The hepatic effects of RSV are consistent with the rest of the class and will not be discussed here.

Also long known, though poorly understood, is a potentially much more serious side effect of statins, myopathy. This, indeed, is the most serious side effect of the class, potentially fatal (although extremely rarely so), and the dose-limiting toxicity. The muscle effects of statins present across a broad clinical spectrum from asymptomatic CK elevations, to marked CK elevations with symptoms, to full-blown rhabdomyolysis. From clinical trials of these drugs, we know that marked CK elevations with or without clinically evident myopathy, which we consider a surrogate for rhabdomyolysis risk, occurs with increasing frequency at increasing doses of drug and appears to be related to a number of different factors, some better understood than others. They include but are likely not limited to:

1. dose of drug
2. systemic bioavailability
3. PK interactions leading to augmented drug "exposure"
4. "affinity" of drug for muscle
5. "potency" of drug as HMGRI
6. predisposing factors: DM, renal failure, hypothyroidism, surgery, severe acute illness or injury

Rhabdomyolysis, or fulminant myopathy with frank necrosis, myoglobinemia/uria, and acute renal injury (pigment induced) occurs very rarely in the clinic in, at least retrospectively, uniquely susceptible individuals, in whom it appears that some threshold muscle exposure to drug has been exceeded. In many but not all cases, rhabdomyolysis appears precipitated by some change in the patient's medical regimen (increased dose, initiation of therapy with interacting drug) or dietary habits (e.g., ingestion of grapefruit juice) or clinical status, such that the duration of statin treatment prior to the development of rhabdomyolysis ranges from a few weeks to years. Myopathy does not, however, appear to be a cumulative-dose-related toxicity.

Finally, in the Crestor development program, a renal adverse effect, heretofore undescribed with HMG-CoA reductase inhibitors, has been observed.

The original NDA for Crestor was submitted on June 26, 2001. An AE action was taken by the agency on May 31, 2002, based on safety concerns arising out of the initial review, specifically regarding muscle and kidney. More specifically, 6 cases of severe myopathy/rhabdomyolysis occurred in patients treated with 80 mg daily, the highest dose initially proposed. There were no cases seen at 40 mg, though the patient exposures at 40 mg were far fewer and generally of lesser duration. Based on this primary safety concern and the marginal incremental LDL-lowering seen with the step from 40 to 80 mg, the Agency concluded that 80 mg should not be approved. Because the clinical trial exposures had been skewed toward the low and high ends of the proposed dosage range, further data were deemed necessary before a decision could be reached on the balance of risk and benefit vis a vis the 20 and 40 mg doses. The FDA requested that the sponsor conduct additional trials to augment the patient exposure at 40 mg, specifically as 40 mg "starts", in order to answer this important question: Is Crestor more prone to cause myopathy than currently marketed statins, or did the experience with 80 mg daily simply define the safe dosage limit for a drug not different from the other members of the class? This question was critically important in light of the experience with Baycol (cerivastatin) which conferred substantial risk of myopathy (relative to other statins) at the high end of its approved dose range,

though with those doses (0.4 and 0.8 mg) effecting comparatively modest LDL-C lowering. Thus with particular regard to muscle adverse effects, after the Baycol experience, it is clear that not all statins possess identical risk-benefit profiles. In response to the deficiencies and the required remedies put forward in the AE letter, the sponsor has studied the myopathic risk associated with Crestor use in a very large premarketing patient exposure, indeed by far the largest of any statin brought before the FDA. The data submitted in response to the AE demonstrate that the risk of myopathy with Crestor relative to LDL-lowering efficacy is at the very least no greater than that with the other marketed members of the class.

In addition, the sponsor was asked to investigate further the finding of new onset mild proteinuria, observed mostly in patients taking Crestor 80 mg. Specifically, the sponsor was charged with investigating the "nature, magnitude, and frequency" of renal adverse events observed in patients treated with RSV and to explore whether these effects were "reversible, chronic, or progressive." This is not a finding noted in other statin development programs or in long-term trials of statins. The clinical picture of Crestor-associated renal effects may include, variably, the combination of low-grade proteinuria, minor elevations in Cr, and microscopic hematuria. Using an *in vitro* model (OK cells, opossum proximal tubular epithelial cell line), sponsor generated data demonstrating that HMGRI can inhibit proximal tubular reabsorption of filtered protein in a mevalonate-dependent manner, and proposed that the propensity for the documented effect of RSV to cause mild (< 600 mg daily) "tubular" proteinuria in some patients may be a function of the high degree of renal clearance of RSV compared to other statins.

Response to the May 31, 2002, approvable letter

Drs. Lubas and Parks and Ms. Mele have reviewed the clinical safety and efficacy data in detail. The following two issues will be discussed here:

1. Clinical safety of all doses by increased exposures to the 20 mg and particularly 40 mg doses, with particular reference to myopathic risk.
2. Potential renal toxicity informed by further investigations of the nature, magnitude, and frequency of renal adverse events across the proposed dosage range.

Augmented patient exposures

First of all, the sponsor now proposes a daily dosage range from 5 mg to 40 mg. The CMC information to support the 5 mg dose has been submitted and reviewed and is acceptable. The total exposure to RSV reported to the NDA is 12,569, at least 3 times the pre-market exposure for any other statin. This includes nearly 5000 patients who have received 40 mg daily or more, with over 1000 of those receiving 40 or 80 mg for greater than one year. Some ~3700 patients are listed as 40 mg "starts" and of those, ~1200 took RSV for greater than 6 months. The total exposure at 40 mg for greater than 12 weeks (~2000) is approximately twice that of total such exposures to 80 mg. The ~1200 40 mg "starts" treated beyond 6 months should be compared to the ~1000 patients treated at 80 mg for greater than 6 months. All the rhabdomyolysis cases at 80 mg occurred within 13 months, and 3 of 6 occurred with 6.4 months of initiation of the 80 mg dose. The "sample size" at 40 mg is satisfactory and meets the requests of FDA in our AE letter and follow up meetings.

Myopathic effects of RSV

In the controlled trials submitted for review, there have been no cases of rhabdomyolysis at other than the 80 mg dose. (There has been one case reported from a large ongoing trial of RSV in a patient with multiple medical problems, including renal insufficiency and severe congestive heart failure, taking 10 mg daily). Among the ~800 patients whose dose was adjusted downward from 80 to 40 mg daily after the decision to halt study and development of the 80 mg dose, among whom are some of the longest users of the drug, again there are no rhabdomyolysis cases. Overall, in the controlled studies safety pool, the incidence of CK > 10 ULN with or without muscle symptoms (a surrogate for rhabdomyolysis risk, expected to occur at some very small, unknown, fraction of the rate of marked CK elevations) among RSV-treated patients, as summarized in Dr. Parks' table 4, was low (< 1%) with an apparent increase, however, at 80 mg (0.9%) relative to lower doses. Figure 4 of Dr. Parks' review, from the sponsor's AC briefing package, shows that the tendency for muscle injury with RSV as a function of dose and LDL-lowering efficacy is as low or lower than for the currently marketed statins and similarly distinguished in this aspect from the clearly more myotoxic cerivastatin. These data are from the largest safety data pool from the RSV trials, and shows an inflection to an incidence of CK > 10 X ULN of 1.9% at 80 mg.

It is important to understand that the failure to observe cases of severe myopathy or rhabdomyolysis in controlled clinical trials of RSV to date at doses below 80 mg should not suggest that such risk does not exist, or that cases will not occur going forward, particularly in open-market use. Myopathy/rhabdomyolysis occurs with all statins, and more frequently with higher doses. RSV is no different in this regard. Importantly, however, the LDL-lowering efficacy of the drug is such that only those patients at the greatest risk for coronary or cardiovascular disease because of marked high cholesterol are apt to receive the 40 mg dose. Indeed, the labeling states that RSV 40 mg is reserved for those patients not achieving goal LDL-C at 20 mg, which will be a small minority of statin-eligible patients. In such patients, it can be argued that their exaggerated high risk for ASCVD justifies a slight increased risk for myopathy, keeping in mind that though potentially very serious, it is a symptomatic, diagnosable, monitorable, and reversible condition in the vast majority of patients who develop it in the context of statin use. As for all the statins, the labeling for RSV is very clear in its discussion of safe use in light of the potential (however low) for myopathy with these drugs.

Finally, the potential for drug-drug interactions with RSV leading to marked increases in systemic exposures to active drug (and risk of myopathy) is low. In contrast to certain other statins (lovastatin, simvastatin, atorvastatin, cerivastatin), RSV is not metabolized to a clinically significant extent by cytochrome P-450 3A4. Potent inhibitors of this enzyme, including grapefruit juice, can raise systemic exposures to 3A4-metabolized statins by as much as 20-fold, and have been associated with many cases of rhabdomyolysis in patients who have tolerated statins for extended periods of time. The documented, clinically meaningful pharmacokinetic interactions of RSV with cyclosporine and with gemfibrozil are described in labeling and direct instructions to limit strictly the dose of RSV in patients receiving these drugs.

Renal effects of RSV

Dr. Parks has reviewed in depth the various analyses of the renal safety data from the review by Dr. Lubas as well as from the sponsor's submissions. Briefly, Dr. Lubas' primary analyses have

been of data collected at "any visit" during the course of trial follow up whereas the sponsor has focused on the analysis of "last visit" laboratory data. In assessing which approach is most appropriate, it is important first to note that when all is said and done, the renal abnormalities (proteinuria, microscopic hematuria, minor increases in serum creatinine) noted in RSV-treated patients in the trials to date have been transient in many instances and do not appear, given the limitations with regard to numbers and duration of therapy in the pre-market trials, to eventuate in irreversible renal dysfunction.

Having said that, it seems most appropriate to rely on the data from the "last visit" on-treatment since neither persistent nor progressive renal adverse effects are in clear evidence. Furthermore, the "last visit" dataset analysis is not biased by differences in the number of laboratory determinations over the course of follow up across patients and dose groups for a given parameter. Though clearly themselves not ideal (because they also are not "adjusted" for duration of therapy by treatment group), I believe the "last visit" analyses are more meaningful than the "any visit" analyses with regard to the clinical relevance of the renal events of interest.

Furthermore, as explained by Dr. Parks, the sponsor's sample for the purposes of assessments of the renal effects consisted of those patients with an available baseline urinalysis showing no or trace protein (and at least one follow up urinalysis). Dr. Lubas, by contrast, probed a substantially larger dataset from patients who had at least one urinalysis post-baseline and imputed a normal baseline study in those without a baseline study. This is an obviously biased investigative approach.

From tables 6-9 in Dr. Parks' review, analysis of last visit data shows the following:

1. In a dose-related pattern of increasing incidence, 0.2 to 1.1% of patients treated with 5 to 40 mg RSV from the pool with no or only trace urine protein at baseline had $\geq$ 2+ proteinuria at last visit. Of a total of 54 patients with this finding, only 2 (treated with 20 mg) had an elevation in serum creatinine of > 30% over the highest pre-treatment level on the last visit. No patients developed clinically apparent renal impairment.

   Among patients treated with 5-40 mg RSV for $\geq$ 96 weeks and with no or trace urine protein at baseline, 0.5-2% had $\geq$ 2+ proteinuria at last visit, and none had a > 30% creatinine rise. Of note, 6.3% of patients in this pool treated for this duration with 80 mg RSV for > 96 weeks had $\geq$ 2+ proteinuria on the last visit, and 7 of 37 of these had mild creatinine elevations, though still with no evidence of significant or irreversible renal functional impairment.

2. 0.1-0.2% of patients treated with 5-40 mg RSV from the pool with no or only trace urine protein and no urine blood at baseline had combined $\geq$ 2+ proteinuria and dipstick-positive hematuria (microscopic in all cases) at the last visit. Of these 8 total patients, 1 (treated with 20 mg) had an elevation in serum creatinine of > 30% on the last visit. No patient developed clinically apparent renal impairment.

   Among patients treated with 5-40 mg RSV for $\geq$ 96 weeks and with no or trace urine proteins and no urine blood at baseline, 0.1-1% had $\geq$ 2+ proteinuria combined with dipstick positive microscopic hematuria at last visit, and neither of these 2 patients had an

elevation in creatinine > 30%. Of note, 2.3% of patients from this pool treated for ≥ 96 weeks with 80 mg RSV had ≥ 2+ proteinuria combined with dipstick positive microscopic hematuria at the last visit. 5 of these 13 patients had serum creatinine at last visit > 30% elevated over the highest pre-treatment baseline level.

The nature of the proteinuria has been characterized by the sponsor and is deemed by them with concurrence by the two nephrologists present on the FDA advisory panel to be "tubular" proteinuria. This finding denotes an *in vivo* effect of RSV on the proximal tubular epithelium that mirrors the *in vitro* effect seen in the opossum kidney cell line experiments described above. If indeed microscopic hematuria and/or increased serum creatinine (suggesting decreased glomerular filtration rate) are aspects of the RSV renal effects, which is not clear from the data, they are not explained by the proximal tubular effect.

The frequency (incidence) and magnitude of the renal effects of RSV have been characterized in a large clinical database, and the reversibility of the proteinuria and the overall non-progressive nature of the renal effects, at least over the duration of exposures in the trials to date, has been documented. Not mentioned above, among patients developing proteinuria on 80 mg, reduction in dose to 40 mg resulted in reduction in the magnitude and incidence of the abnormality.

Finally, as per Dr. Parks review, 7 cases of acute renal failure of unknown etiology occurred in patients receiving RSV: 2 at 10 mg, 1 at 20 mg, 2 at 40 mg, and 2 at 80 mg in clinical trials. Just recently, we have learned of another case in open market use in Britain. The patient is an 82 year old female, on atenolol and chlorthalidone, flucloxacillin, ASA, diclofenac, and Crestor 10 mg started 5-6-03. Baseline cholesterol (?total-C) was ~ 285 mg/dL. Baseline Cr was 0.9 mg/dL. Patient was hospitalized on 7-23-03 for acute renal failure with Cr peak of 10 mg/dL. CK was 215, and Crestor, chlorthalidone, diclofenac, and flucloxacillin were discontinued. Blood pressure has 190/89 the day prior to admission. She received 3 liters of IV fluid over 24 hours and diuresed. Urinalysis showed blood and protein. Renal ultrasound was normal, and renal biopsy onf 7-25-03 showed degeneration of tubular epithelial cells with areas of regeneration. Glomeruli were generally intact. There was mild interstitial nephritis and lymphocytic and eosinophilic infiltration. Patient improving as of last information with Cr 2.1 on 8-1-03. This is clearly not myoglobinuric renal failure and it is confounded by her medical regimen and hypertension. Although she clearly was not profoundly "dry", she did respond to a substantial 24-hour fluid load with diuresis, and her Cr is returning toward her baseline. It is not, however, possible to exclude a role of Crestor in her acute renal failure.

The renal effects of RSV continue to be investigated by the sponsor in patients enrolled in ongoing controlled trials. The labeling will describe the renal function and urinalysis findings in Precautions, Laboratory Tests as well as in Adverse Reactions, Laboratory Abnormalities as occurring predominantly in patients treated with 80 mg (above the recommended dosage range) but more frequently in patients taking RSV 40 mg compared to lower doses of RSV or comparator statins. Additionally, while the finding is described as generally transient and not associated with worsening renal function, dose reduction is to be considered in patients on RSV 40 mg who have persistent unexplained proteinuria on routine urinalysis.

Labeling

NDA #
Drug:
Proposal:
08/12/03

Labeling, as described in more detail in Dr. Parks' memo emphasizes, with respect to safety, the muscle effects and does include the available information on the renal effects of Crestor.

Another area of discussion has been that of recommendations regarding starting dose. The 5 mg dose is available and the sponsor intends to market it. Indeed, 5 mg is the dose limitation for concomitant use with cyclosporine. A 20 mg start dose is proposed by the sponsor for people with severe hypercholesterolemia. Given the unknowns about the renal effects of this drug, its potency as an LDL-lowering agent, and its absolute efficacy at even the 5 mg dose, I believe it is prudent to recommend the lowest available dose as the usual start dose. Those requiring more LDL lowering will simply need to be up-titrated to 10, 20, or 40 mg, as needed, with appropriate clinical surveillance and laboratory monitoring.

Biopharmaceutics
The sponsor submitted results of interaction studies with gemfibrozil (inhibitor of statin glucuronidation) and cyclosporine (p-glycoprotein inhibitor). Labeling recommends RSV dose limitation to 5 mg daily with cyclosporine and to 10 mg daily when RSV is used in combination with gemfibrozil. One incompletely resolved issue relates to systemic drug exposures in certain Asian populations. Small PK studies in Japanese residing in Japan and Chinese residents of Singapore show a doubling of systemic exposure to RSV relative to Caucasians. No such data are available for Asians living in the U.S. Labeling will convey these results without specific dosing recommendations for Asians, as the clinical significance of these data particularly as regards U.S. patients of Asian descent is not known. Further studies are ongoing in U.S. Asians and the sponsor will investigate potential differences in PK relative to Caucasians as a phase 4 commitment.

Pharmacology/Toxicology
Nothing outstanding.

Chemistry/ Microbiology
Nothing outstanding.

DSI/Data Integrity
No issues.

Financial disclosure
Information complete.

ODS
The name Crestor is acceptable.

Recommendation
Approve

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

/s/

Mary Parks
8/12/03 02:55:14 PM
MEDICAL OFFICER
Submitted into DFS and signed off for Dr. Orloff

Robert Meyer
8/12/03 03:30:22 PM
MEDICAL OFFICER

MEDICAL TEAM LEADER MEMO

NDA #:	21-366
Drug:	Crestor® (rosuvastatin)
Sponsor:	Astra-Zeneca
Date of submission:	February 12, 2003
Indication:	lipid-altering drug
Primary Medical Reviewer	William Lubas, MD, PhD
Statistical Reviewers	Joy Mele, MS and Cynthia Liu, MA
Date Memo Completed	July 30, 2003

BACKGROUND

Summary of Original NDA Review

The marketing application for Crestor® (rosuvastatin) was submitted to the FDA in June 2001 to support an indication for the treatment of hypercholesterolemia in Fredrickson Types IIa/IIb dyslipidemia, hypertriglyceridemia in Type IV dyslipidemia, and treatment of homozygous familial hypercholesterolemia. This was the 7th new drug application (NDA) reviewed by the Agency for the HMG-CoA reductase inhibitors, a class of lipid-altering drugs also referred to as statins. The original application had proposed to market the 10, 20, 40, and 80 mg doses.

The efficacy review of this application revealed that rosuvastatin was a more potent LDL-lowering drug, on a mg-to-mg basis, than the currently marketed statins: lovastatin, pravastatin, simvastatin, fluvastatin, and atorvastatin. The mean LDL-C change observed with rosuvastatin ranged from -33% (1 mg) to -65% (80 mg). These reductions were dose-related; however, the range of response observed at the 80 mg dose overlapped markedly with that of the 40 mg dose. The additional 2 to 4% mean reduction in LDL-C at the 80 mg dose was counterbalanced by the findings of severe myopathy and rhabdomyolysis at the same dose in the open-label extension studies.

In addition to muscle toxicity, proteinuria with or without microscopic hematuria was observed primarily at the 80 mg dose. Some of these cases were associated with an increase in serum creatinine and two subjects developed renal failure of unknown etiology at the 80 mg dose. These adverse events have never before been described in this drug class and therefore raised the bar of approvability for this drug. In the original NDA, fewer than 100 patients were exposed beyond 48 weeks to the 20 and 40 mg doses each. As a result, it was not possible to exclude a similar risk of muscle and renal toxicity observed at the 80 mg dose in these lower doses.

Clinical Deficiencies Summarized in Approvable Letter

On May 31, 2002, the Agency issued an approvable (AE) letter for the 10, 20, and 40 mg doses. The 80 mg dose was deemed 'not approvable', stating little added benefit over the 40 mg dose in view of the apparent risks of myopathy and renal toxicity at the higher dose. In a June 7, 2002 letter to the Agency, the sponsor stated that they were withdrawing the 80 mg dose from NDA 21-366. Patients treated at the 80 mg dose in clinical trials had their dose reduced to the 40 mg dose.

Deficiencies summarized in this action letter involved clinical, biopharmaceutics, and CMC issues. Within the clinical category, three issues needed to be addressed; these issues are summarized as follows:

1. Increase patient exposure at the 20 and 40 mg doses.
   The sponsor had to establish that the risk of myopathy, normalized for LDL-lowering efficacy, was similar to other marketed statins. Furthermore, the sponsor was asked to study a more diverse ethnic population in subsequent studies.
2. Evaluate further the signals of renal adverse events.
   The sponsor had to perform additional studies across the full range of proposed doses and in relevant clinical subgroups (e.g., diabetics and hypertensives) and demonstrate that the risk of nephrotoxicity did not outweigh the benefit of the drug given other alternative products available.
3. Address the potential for increase myotoxicity risk in rosuvastatin-gemfibrozil combined use in clinical trials.

Overview of NDA Resubsmission

In response to the AE letter, the sponsor has submitted an application for the marketing of **rosuvastatin 5, 10, 20, and 40 mg** in primary hypercholesterolemia, mixed dyslipidemia, isolated hypertriglyceridemia, and homozygous familial hypercholesterolemia (HoFH). The sponsor is also proposing special dosing instructions for patients with severe familial hypercholesterolemia (LDL ≥ 190 mg/dL) and HoFH.

This submission includes an integrated safety database comprised of data from 27 Phase 2/3 clinical studies. Nineteen of these trials were completed; eight were ongoing; and real time laboratory data (RTLD) were collected from a central lab from current ongoing studies to further bolster the database for laboratory tests of interests (i.e., transaminases, CK levels, and renal studies). The following datapools were generated to analyze specific areas of safety[1]:

Table 1. Safety Data Pool*

Safety Data Pool	N
All controlled Phase 2/3 studies	5721
Combined All Controlled and RTLD studies	8135
Fixed-dose controlled Phase 2/3 studies	4239
All controlled and uncontrolled Phase 2/3 studies w/ RTLD studies	12,569

*from sponsor's AC briefing document submitted 6-6-03

In accordance with the recommendation made by the Agency in the AE letter, the sponsor has increased the patient exposure for the 20 and 40 mg dose. These updated numbers fulfill the ICH requirements for drugs being developed for chronic use in non-life-threatening illnesses. The following table presents the number of patients and duration of exposure for all proposed doses in the all controlled and uncontrolled Phase 2/3 studies w/ RTLD pool (n=12,569).

Table 2. Duration of Exposure (from Sponsor's AC Briefing Document 6-6-03)

[1] See sponsor's AC briefing document (6-6-03) pages 56 and 57 for explanation of each safety data pool and how these data were utilized

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

Duration of Tx	5 mg N=1325	10 mg N=7819	20 mg N=3939	not down-titrated to 40 mg N=3742	down-titrated to 40 mg N=825	total at 40 mg N=4007	80 mg N=1583	total rosuvastatin N=12,569
≥ 6 wks	1234	7467	3582	3381	820	3705	1417	12049
≥ 12 wks	995	6219	2143	2001	803	2758	1055	10603
≥ 24 wks	647	5041	1353	1227	686	1893	971	8860
≥ 48 wks	542	4055	**545**	276	0	**276**	891	6646
≥ 72 wks	324	1546	235	159	0	159	783	3423
≥ 96 wks	283	903	120	110	0	110	642	2356
Mean duration of treatment (days)	362.8	348.6	167.8	142.9	211.8	169.5	450.5	413.6
Pt-yrs of tx	1315	7458	1800	1461	477	1857	1944	14231

Patients treated at the 40 mg dose included those who were initiated on or up-titrated to this dose (yellow column). In addition, there were patients who were previously on the 80 mg dose but had their dose reduced as a result of protocol amendments (grey column). There were 545 patients in the 20 mg dose group and 276 patients in the 40 mg dose group who received treatment for at least 1 year or more.

Fourteen of the controlled trials and part of the open-label extension trial (Study 34) were reviewed in the original submission. Many of the new studies were long-term extension studies intended to provide additional safety data; however, the sponsor also submitted the results of a 6-week, open-label study evaluating the efficacy and safety of rosuvastatin 10, 20, and 40 mg compared to atorvastatin 10, 20, 40, and 80 mg, pravastatin 10, 20, and 40 mg, and simvastatin 10, 20, 40, and 80 mg.

The patient population studied included patients with hypertension (52%), diabetes (16.5%), CVD (36%), and mild renal impairment (44%). The mean age was 58.1 years with 31% being 65 years or older. There were approximately equal numbers of males and females studied; two-thirds of the female patients were post-menopausal. The majority of the patients was Caucasian (88%) followed by Blacks (6.5%), Hispanics (2.4%), and Asians (1.9%).

REVIEW OF NDA RESUBMISSION

Efficacy

The effectiveness of rosuvastatin 5 to 40 mg in the treatment of hypercholesterolemia (Types IIa and IIb) and isolated hypertriglyceridemia (Types IV) and rosuvastatin 20 to 40 mg in patients with heterozygous and homozygous familial hypercholesterolemia has been reviewed in the original NDA submission. Please see the medical team leader memo and statistical reviews for NDA 21-366, submission date 26-Jun-2001.

Comparative Efficacy to Other Marketed Statins

Study 65 was not submitted with the original NDA. The sponsor is proposing to incorporate the study findings into the label for rosuvastatin under the CLINICAL PHARMACOLOGY: Clinical Studies section. The FDA statistical reviewer, Joy Mele, MS has also reviewed this trial and discussed these results in her memo.

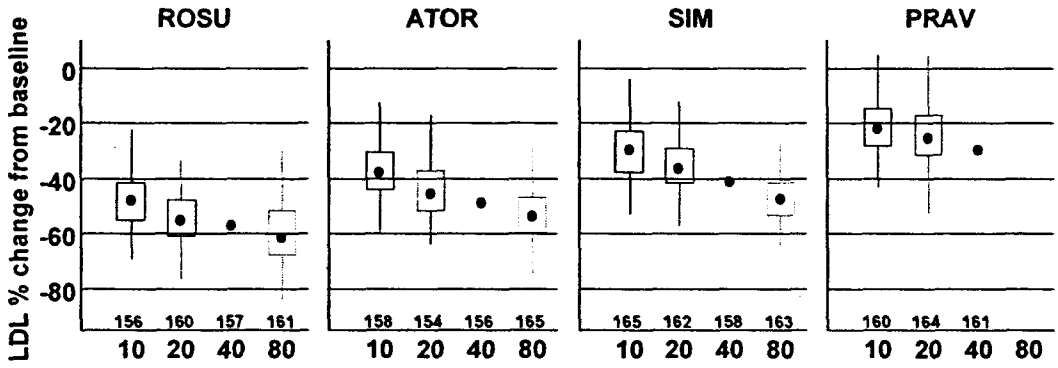
Briefly, this was a 6-week, open-label study which compared the efficacy of rosuvastatin 10 to 80 mg with that of atorvastatin 10 to 80 mg, pravastatin 10 to 40 mg, and simvastatin 10 to 80 mg. The full dose ranges of all the comparator statins are studied in this trial except for pravastatin 80 mg as this dose was not approved until December 2001, after study initiation. After a 6-wk dietary lead-in period, 2,431 patients with primary hypercholesterolemia (LDL-C ≥ 160 mg/dL and < 250 mg/dL off lipid-lowering therapy) were randomized to the following treatment groups:

Table 3. Randomization Scheme of Study 65

Rosuvastatin N=643				**Atorvastatin N=641**				**Pravastatin N=492**			**Simvastatin N=655**			
10	20	40	80	10	20	40	80	10	20	40	10	20	40	80
n=158	n=164	n=158	n=163	n=158	n=156	n=160	n=167	n=162	n=166	n=164	n=167	n=164	n=159	n=165

The LDL-C percent change from baseline at Week 6 based on a LOCF analysis showed a dose-response for all 4 statins. The distribution of LDL-C change from baseline for each treatment group is shown in the following figure obtained from Joy Mele's review.

Figure 1. LDL % Change from Baseline, LOCF (from Joy Mele's statistical review of NDA 21-366)

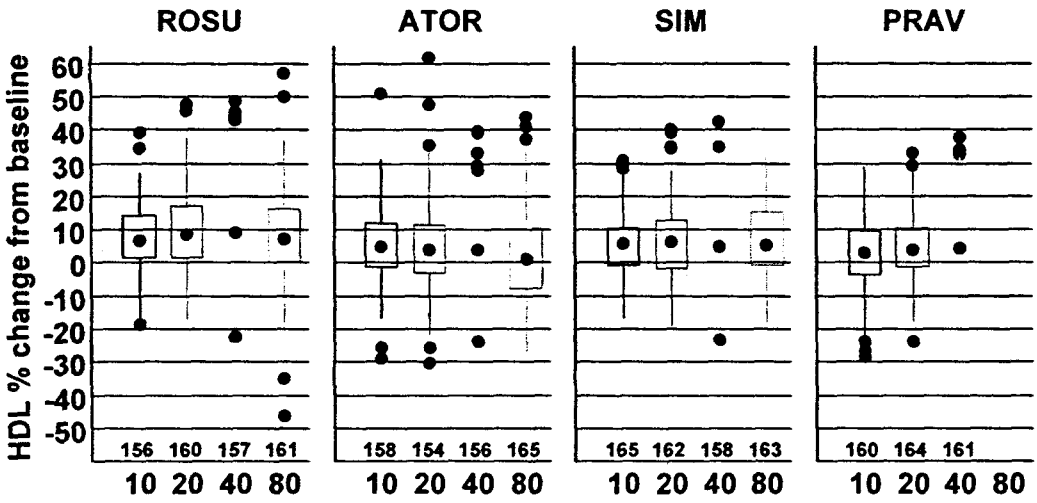


This study is consistent with the studies reviewed in the original NDA submission. Rosuvastatin is more potent on a mg per mg basis than the comparator statins: atorvastatin, pravastatin, and simvastatin. Although the highest approved dose of pravastatin is not included in this trial, the average LDL-C reduction observed with pravastatin 80 mg (as summarized in the package insert) after 6 weeks of therapy is only 37%. Rosuvastatin 10 mg achieves a greater mean reduction (46%) after a similar duration of therapy. Figure 1 reveals that > 75% of patients treated with rosuvastatin 10 mg achieved a ≥ 40% reduction in LDL-C levels.

The effect of rosuvastatin therapy on HDL is also similar to previously reviewed studies. Rosuvastatin, at all doses, raised HDL-C levels from baseline; however, the response is not dose-related. Figure 2 from Joy Mele's review shows slightly higher mean increases achieved with rosuvasatin over several doses of comparator statins. The distribution of

response is, however, broad with marked overlap across doses within a statin group and across the statin groups.

Figure 2. % HDL change from baseline, LOCF (from Joy Mele's statistical review of NDA 21-366)



The primary conclusion from Study 65 is that rosuvastatin achieves greater mean reductions in LDL-C levels across its dosage range compared to other statins, across their dosage ranges. Rosuvastatin therapy also increases HDL-C; however, the distribution of response does not support a claim that this effect is of any greater magnitude than that seen with other statins.

The inclusion of Study 65 into the product labeling should include a graph summarizing the distribution of LDL-response by dose and treatment group similar to the graph produced by Ms. Mele (Figure 1).

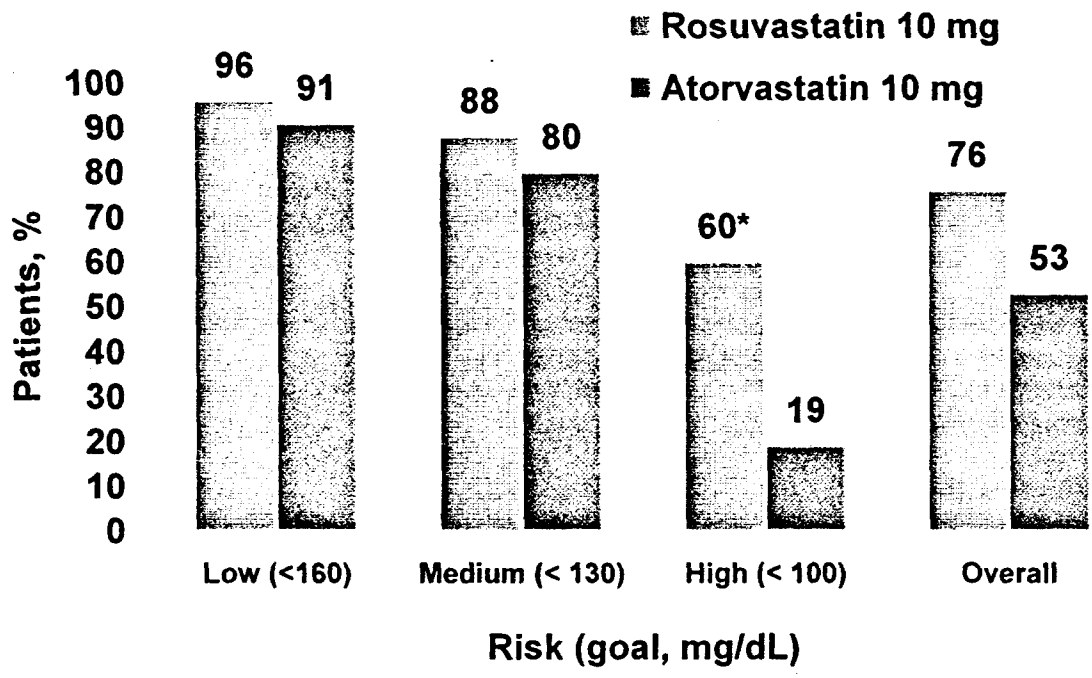
Recommended Start Doses

The sponsor is recommending the 10 mg dose as the start dose for the general population while the 20 mg dose is reserved for patients with marked hypercholesterolemia (LDL-C > 190 mg/dL) or patients with HoFH. The 5 mg dose is reserved only for patients treated with cyclosporine based on a pK interaction that results in a 7-fold increase in rosuvastatin AUC levels.

The sponsor presented in their Advisory Committee (AC) briefing document several analyses in which the 10 mg dose of rosuvastatin allows more patients to reach NCEP ATP III targets than the lowest recommended start doses of comparator statins (atorvastatin 10 mg, simvastatin 20 mg, and pravastatin 20 mg). This is a predictable finding as Figure 1 already demonstrates a greater mean percent reduction for rosuvastatin 10 mg over several doses of the comparator agents. The sponsor argues that initiation of patients at the 10 mg dose will allow more patients to achieve NCEP target goals without the need to titrate therapy to goal. However, atorvastatin, simvastatin, and pravastatin have a range of start doses, hence therapy with these agents can be initiated at a higher dose that will achieve treatment goals based on baseline LDL-C levels and CHD risks. Indeed, the sponsor presented the following slide

comparing the percentage of patients reaching ATP-III LDL goals with atorvastatin 10 mg dose versus rosuvastatin 10 mg. This slide shows comparable efficacy between the 10 mg doses of the two statins for reaching LDL goals in the low and medium CHD risk groups. In the high CHD risk group, a significantly greater percentage of patients achieved their LDL goals with rosuvastatin 10 mg than atorvastatin 10 mg. However, the patients in the high risk category could alternatively be initiated at atorvastatin 20 or 40 mg doses (approved start doses) with a greater likelihood of achieving treatment goals.

Figure 3. Percentage of Patients Achieving ATP-III Goals at Wk 12, Rosuvastatin v. Atorvastatin (Trials 24-26, pooled data analysis; presented by Astra-Zeneca at July 9, 2003 AC Meeting)



P<0.05 vs atorvastatin

While it is apparent that a 10 mg start dose of rosuvastatin will allow a greater number of patients to achieve LDL targets, the 5 mg dose of rosuvastatin is also an effective dose achieving a mean LDL reduction of 42% after 6 weeks of therapy (Study 008, reviewed in original NDA submission). As stated in Dr. Lubas' review, this dose of rosuvastatin allows approximately 67% of patients in a clinical study to achieve their NCEP target goals. This dose should also be recommended as an optional start dose in the general population for patients who may require LDL-C reductions within the range observed with rosuvastatin 5 mg. The 5 mg dose should not be limited only to patients taking cyclosporine.

Safety

Liver Safety

Transaminase elevations have been reported with all statins. These laboratory abnormalities are rarely associated with hepatitis or serious liver injury in the clinical trials and many resolve spontaneously or with discontinuation or dose-reduction of drug. Similar to currently marketed statins, elevations in ALT values were observed with rosuvastatin therapy. From Table 6 in Dr. Lubas' review, the frequency of single and multiple ALT elevations is higher at the 80 mg dose than at the lower doses. The incidence of multiple ALT elevations range from 0.1 to 0.4% in the 5 to 40 mg dose range for rosuvastatin.

There were no cases of liver failure. Two patients developed jaundice at the 10 mg dose and resolved with drug discontinuation. Relationship to drug therapy could not be established in these two cases. One case had a normal liver biopsy and the other involved a patient with a remote history of hepatitis B. These cases are summarized in Dr. Lubas' review.

This reviewer concurs with Dr. Lubas regarding baseline and periodic monitoring of transaminase levels for rosuvastatin.

Muscle Safety

Myopathy and rare cases of rhabdomyolysis remain the most serious safety concerns associated with statin use. The recent withdrawal of Baycol (cerivastatin) secondary to a large number of post-marketing reports of rhabdomyolysis observed primarily at the higher doses or in combination with gemfibrozil raised concerns regarding the safety of rosuvastatin as rhabdomyolysis cases were observed pre-marketing at 80 mg. These cases have been discussed in the initial review of this NDA.

In this resubmission, the sponsor has increased patient exposures in the 20 and 40 mg doses to better evaluate the risk of muscle toxicity at doses lower than 80 mg. Approximately 4,000 patients were exposed and more than 200 were treated at each of the 20 and 40 mg doses. These numbers and that of the entire cohort exposed to rosuvastatin across the 5 to 80 mg dose range exceed exposures from any other statin pre-marketing application (Table 2).

Muscle toxicity has been reported as either asymptomatic elevations in CK levels (> 10xULN), > 10xULN CK elevations with muscle symptoms (myopathy), or clinical diagnoses of rhabdomyolysis. There were no cases of rhabdomyolysis observed at rosuvastatin doses of 40 mg or lower.

The following table summarizes the incidence of CK elevations across the dosage range of rosuvastatin and 4 other comparator statins.

Table 4. CK > 10x ULN in All Controlled Study Pools

	N	CK > 10x ULN
Rosuvastatin		
5 mg	833	0.4%
10 mg	3193	0.1%
20 mg	2113	0.1%
40 mg	2804	0.4%
80 mg	988	0.9%
Atorvastatin		
10 mg	1573	0.1%
20 mg	1772	0.1%
40 mg	522	0
80 mg	555	0
Simvastatin		
10 mg	163	1.2%
20 mg	127	0.1%
40 mg	532	0
80 mg	501	0.4%
Pravastatin		
10 mg	161	0
20 mg	416	0
40 mg	751	0
Cerivastatin		
0.3 mg	64	0
0.4 mg	54	0
0.8 mg	45	0

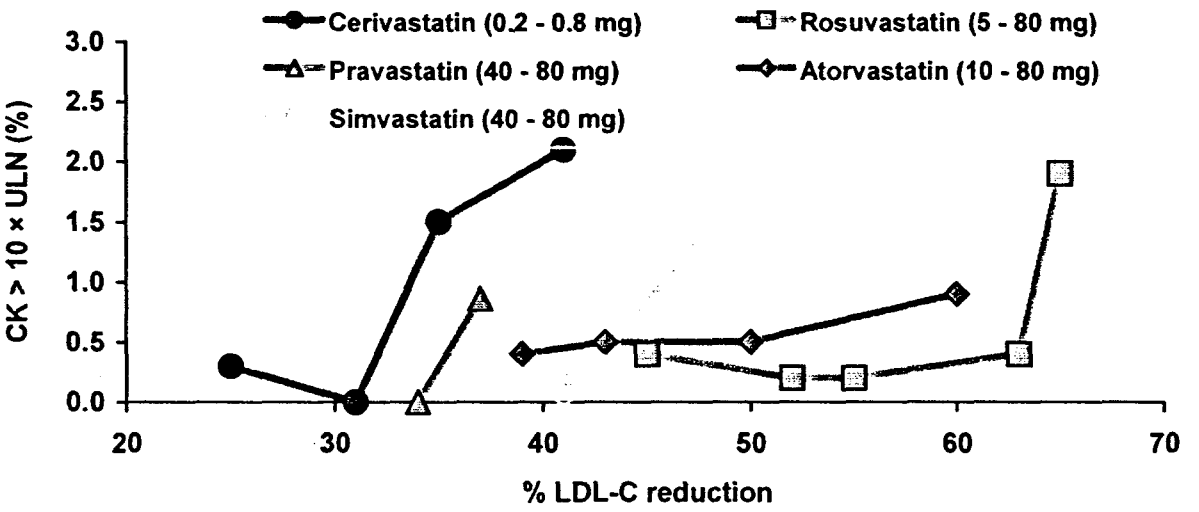
The number of patients exposed to rosuvastatin in this database far exceeds that of the comparator statins. The frequency of CK elevations reported in Table 4 for cerivastatin is not reliable because of the small sample sizes (cerivastatin treatment groups discontinued during clinical development program with the withdrawal of the drug). Despite the differences in sample sizes, the incidence of CK elevations greater than 10x ULN for the 40 mg doses and lower of rosuvastatin ranged from 0.1 to 0.4%, and was similar to other marketed statins. The 80 mg dose had at least a 2-fold higher incidence of CK elevations compared to the lower doses.

The incidence of myopathy for the 5, 10, 20, and 40 mg doses of rosuvastatin was 0.2%, 0.1%, 0.1%, and 0.2%, respectively. These rates are similar to rates reported with the currently marketed statins (0 to 0.5%). Rosuvastatin 80 mg had a rate of myopathy that was at least 4-fold higher (1.0%) and was closer to the range observed with cerivastatin 0.4 to 0.8 mg doses (0.9% to 1.6%).

The sponsor charted the incidence of > 10x ULN CK elevations as a function of mean % LDL reduction by dose of statin. In this figure, presented by the sponsor in the AC briefing document and at the Advisory Committee meeting, it is evident that the 80 mg

dose of rosuvastatin is associated with a higher incidence of CK elevations while providing only a 3-4% greater reduction in LDL-C from the 40 mg dose. At doses of 40 mg and below, the rate of CK elevations observed with rosuvastatin is well within the range observed with the remaining marketed statins (atorvastatin, pravastatin, simvastatin shown here) while providing a greater mean % reduction in LDL-C (further right shift on x-axis). In contrast, cerivastatin 0.4 and 0.8 mg doses had a rate of CK elevation that exceeded the other statins while providing mean LDL reductions of only 35 to 40%.

Figure 4. Frequency of CK >10xULN elevations of Different Statins (across dose range) Normalized for LDL-lowering (Presented by Astra-Zeneca at 7-9-03 AC Meeting)



The sponsor has provided sufficient data to support the conclusion that rosuvastatin at daily doses of 5 to 40 mg has a similar risk of myopathy compared to the currently marketed statins. Special circumstances (e.g., drug-drug interactions, special populations) which may increase the rosuvastatin drug levels will require specific dosing instructions. These cases are addressed later in this memo.

Renal Safety

The finding of proteinuria with and without hematuria primarily at the 80 mg dose in the original application resulted in the sponsor conducting additional clinical studies at the lower doses and preclinical studies to investigate the effects of rosuvastatin as well as other statins on renal protein excretion. Quantitative analyses of urinary proteins from patients treated with rosuvastatin 80 mg who were subsequently down-titrated to 40 mg, revealed elevations in proteins of tubular origin (beta-2-microglobulins, N-acetyl-beta-D-glucosaminidase (NAG), and albumin). Gel electrophoresis evaluation also confirmed a tubular pattern of urinary protein excretion.

The sponsor hypothesized that this proteinuria was the result of a pharmacologic effect of rosuvastatin and other statins. The inhibition of HMG-CoA reductase in the proximal tubular cells reduces the tubular reabsorption of these proteins. Using an experimental system involving cultured cell lines from opossum renal tubular cells to test this hypothesis, rosuvastatin and 3 other statins (simvastatin, fluvastatin, and pravastatin) were shown to inhibit the uptake of albumin in a dose-dependent fashion. Furthermore, the addition of mevalonate, the immediate downstream product of HMG-CoA reductase, blocked the inhibitory effects of these statins on tubular reabsorption of albumin. Based on these experiments, the sponsor concluded that proteinuria was a class of effect of statins.

The clinical safety database was further analyzed for renal laboratory abnormalities and clinical adverse events.

Renal Laboratory Data - Proteinuria

The sponsor and Dr. Lubas have both presented data from the Controlled/Uncontrolled and RTLD pools showing the incidence of ≥ 2+ proteinuria, ≥ 2+ proteinuria and hematuria, and ≥ 2+ proteinuria/hematuria associated with a ≥ 30% in serum creatinine. This is the largest safety data pool including data from 12,569 patients exposed to rosuvastatin of varying durations and doses (see Tables 1 and 2). However, it should be noted that renal safety data are not presented for every single patient in this database as not all patients had urinalyses performed at baseline or other times in the trial. Serum creatinine levels, although not available in all subjects, were performed more frequently than urinalyses.

Although analyses were performed on the same safety datapool, there were marked differences in sample sizes and methods of evaluation between the sponsor and the FDA reviewer.

Table 5. Incidence of Proteinuria at Any Visit as Analyzed by Sponsor and FDA reviewer (Data from Combined All Controlled/Uncontrolled and RTLD Pools)

Rosuvastatin Dose	Sponsor's Analysis of Proteinuria at Any Visit (Table 25 of AC briefing document)		Rosuvastatin Dose	FDA Reviewer's Analysis of Proteinuria at Any Visit (Table 15 of AC briefing document)*	
	N	% ≥ 2+ proteinuria		N	% ≥ 2+ proteinuria
5 mg	906	1.0%	5 mg	653	1.1%
			5 mg OLE	438	4.1%
10 mg	2279	1.4%	10 mg	1202	2.2%
			10 mg OLE	5011	2.7%
20 mg	1992	1.6%	20 mg	1460	2.1%
			20 mg OLE	1894	4.2%
40 mg	3172	3.5%	40 mg	2384	3.8%
not down-titrated	2860	3.1%	40 mg OLE	1684	5.0%
down-titrated	724	3.2%			
80 mg	1157	16.2%	80 mg	804	11.8%
			80 mg OLE	959	17.2%

*incidence rates estimated to nearest 10th whereas briefing document rounded rates to nearest whole digit

Table 5 summarizes the analysis of proteinuria at any time performed by the sponsor (left 3 columns) and the FDA reviewer (right 3 columns). The following points need to be considered in interpreting the results of both analyses:

1. The sponsor selected patients (denominator/N) if a baseline urinalysis was available which had 'none or trace' protein to minimize the inclusion of patients who may have baseline renal abnormalities. In contrast, Dr. Lubas' selected patients who had any urinalysis post-baseline. Patients with no baseline urinalysis were included in the denominator and assumed to have a normal urine study at baseline. This difference accounts for the discrepant numbers of patients summarized in the 2nd and 5th columns in Table 5.

2. Patients were categorized as having proteinuria (numerator) if there was evidence of ≥ 2+ proteinuria in a urinalysis performed post-baseline. In the sponsor's analysis, a patient could be tallied more than once if proteinuria was observed at different doses. For example, a patient who developed proteinuria with rosuvastatin 20 mg which disappeared after being titrated to 40 mg but then developed proteinuria again at the 80 mg dose in an open-label extension study, would be included in the incidence rate column for both the 20 and 80 mg doses but not the 40 mg dose. Dr. Lubas analyzed the database by controlled study periods and uncontrolled (OLE = open label extension) periods. Patients in the OLE period could have been exposed previously to other statins or rosuvastatin at lower doses during the controlled study periods. The controlled studies were from 6 to 24 weeks duration, therefore the rates observed in the OLE period would not necessarily reflect continuous exposure to rosuvastatin at one dose nor would it reflect rosuvastatin treatment for a prolong period of time as patients could have been previously treated with another statin.

Despite the differences in analyzing this database, a similar conclusion can be made regarding the 80 mg dose: the incidence of ≥ 2+ proteinuria increases 3 to 5-fold from the 40 mg dose to 80 mg. In patients who had their 80 mg dose lowered to 40 mg, the incidence was lower (3.2%). In a subgroup of patients with at least 2+ proteinuria while on 80 mg, dose reduction to 40 mg resulted in a decrease in the rate of proteinuria from 7.4% to 1.9%, suggesting that proteinuria was reversible.

From the sponsor's analysis, the incidence of proteinuria is slightly increased in the 40 mg dose groups (3.5% at 40 mg overall vs. 1.0 to 1.6% in the 5-20 mg doses). Similarly, in the FDA review the incidence of proteinuria in the controlled study periods suggest a slight increase at the 40 mg dose [1.1% (5 mg), 2.2 and 2.1% (10 and 20 mg); 3.8% (40 mg)]. As the sponsor is no longer proposing to market the 80 mg dose, this memo will now focus primarily on the 40 mg and lower doses to determine if an adequate safety profile can be established with respect to these doses – in particular, the 40 mg dose.

Renal Laboratory Abnormalities – Proteinuria ± hematuria w/ >30% Cr increases
Changes in serum creatinine from baseline were evaluated in patients with proteinuria and patients with combined proteinuria/hematuria to determine if there was a signal for renal function deterioration. Increases in serum creatinine of >30% from baseline were defined as changes of clinical interest by both the sponsor and FDA reviewer. The following tables summarizes the results of both analyses.

Table 6. Frequency of > 30% Creatinine Elevations in Patients with Proteinuria from Combined All Controlled/Uncontrolled and RTLD Pools

Sponsor's Analysis Based on **Last Visit** Data (Slide CS-33 from AC Meeting)				FDA Analysis Based on **Any Visit** Data			
	N	Proteinuria n (%)	Cr >30% rise n (%)		N	Proteinuria (%)	Cr >30% rise n (%)
5 mg	549	1 (0.2%)	0	5 mg	653	1.1%	0
				5 mg OLE	438	4.1%	2 (0.5%)
10 mg	1822	10 (0.5%)	0	10 mg	1202	2.2%	0
				10 mg OLE	5011	2.7%	6 (0.1%)
20 mg	1253	11 (0.9%)	2 (0.16%)	20 mg	1460	2.1%	0
				20 mg OLE	1894	4.2%	6 (0.3%)
40 mg	2824	32 (1.1%)	0	40 mg	2384	3.8%	9 (0.4%)
				40 mg OLE	1684	5.0%	6 (0.4%)

Table 7. Frequency of > 30% Creatinine Elevations in Patients with Combined Proteinuria/Hematuria from Combined All Controlled/Uncontrolled and RTLD Pools

Sponsor's Analysis Based on **Last Visit** Data (Slide CS-34 from AC Meeting)				FDA Analysis Based on **Any Visit** Data			
	N	Proteinuria/hematuria n (%)	Cr >30% rise n (%)		N	Proteinuria/hematuria n (%)	Cr >30% rise n (%)
5 mg	493	0	0	5 mg	653	0	0
				5 mg OLE	438	7 (1.6%)	0
10 mg	1707	1 (0.1%)	0	10 mg	1202	4 (0.3%)	0
				10 mg OLE	5011	39 (0.8%)	4 (0.1%)
20 mg	1194	1 (0.1%)	1 (0.08%)	20 mg	1460	5 (0.3%)	0
				20 mg OLE	1894	13 (0.7%)	3 (0.2%)
40 mg	2679	6 (0.2%)	0	40 mg	2384	30 (1.3%)	6 (0.3%)
				40 mg OLE	1684	25 (1.5%)	4 (0.2%)

In these tables it should be noted that the sponsor's analysis focuses on the last visit detection of a renal laboratory abnormality whereas the FDA analysis includes any visit data. The frequency of >30% creatinine elevations is, not surprisingly, greater in an analysis evaluating this laboratory abnormality observed at any visit. The sponsor states that the last visit is a more appropriate analysis given the variability of this laboratory value including improvements in some cases. Evaluating the last visit data provides information in patients exposed to drug over a longer duration than the 'any visit' analysis. Consequently, the sponsor evaluated a subgroup of patients within the Combined All Controlled/Uncontrolled and RTLD Pool who received treatment for ≥ 96 weeks. Tables 8 and 9 summarize these results.

Table 8. Creatinine Increases > 30% in Patients w/ ≥ 2+ Proteinuria treated for ≥ 96 weeks (Slide CS-35 from Sponsor's AC presentation)

	N	Any time n (%)	Last visit n (%)	Cr >30% n
5mg	261	3 (1.1%)	0	0
10 mg	838	17 (2.0%)	4 (0.5%)	0
20 mg	112	5 (4.5%)	1 (0.9%)	0
40 mg	100	4 (4.0%)	2 (2.0%)	0
80 mg	590	99 (16.8%)	37 (6.3%)	7
≥40 mg*	807	136 (16.9%)	10 (1.2%)	0

*includes patients who were back-titrated from the 80 mg dose

Table 9. Creatinine Increases > 30% in Patients w/ Combined Proteinuria (≥2+)/Hematuria (≥ 1+) treated for ≥ 96 weeks

	N	Last visit proteinuria/hematuria n (%)	Cr >30% n
5mg	229	0	0
10 mg	781	1 (0.1%)	0
20 mg	103	0	0
40 mg	98	1 (1.0%)	0
80 mg	562	13 (2.3%)	5
≥40 mg*	761	2 (0.3%)	0

*includes patients who were back-titrated from the 80 mg dose

The incidence of ≥ 2+ proteinuria or combined ≥ 2+ proteinuria/≥ 1+ hematuria in patients treated with rosuvastatin 80 mg for approximately 2 years is 2 to 4-fold higher than the 40 mg dose. While a slight increase in rate of proteinuria and proteinuria/hematuria is still observed at the 40 mg dose over the 5, 10, and 20 mg doses, there were no patients who developed a >30% increase in serum creatinine at the rosuvastatin 40 mg dose or lower.

Dr. Lubas' analysis of any time combined proteinuria/hematuria and >30% increase in serum creatinine resulted in a higher rate of laboratory abnormalities than the sponsor's analysis, especially at the 40 mg dose. In table 7, the sponsor's rate of ≥2+ proteinuria/hematuria at the 40 mg dose was 0.2% compared to 1.3% (controlled) and 1.5% (OLE) in the FDA review. It is unclear which analysis yields more clinically relevant information; however, similar to the sponsor's evaluation of renal safety in patients exposed to drug for ≥ 96 weeks, it is important to evaluate whether the patients in Dr. Lubas' analysis had persistent laboratory abnormalities. The following table

summarizes 9 patients (6 in controlled period, 3 in OLE) treated with rosuvastatin 40 mg who had combined proteinuria/hematuria and a >30% increase in creatinine at any visit.[2]

Table 10. Individual Profiles of Patients with Combined Proteinuria/Hematuria and > 30% Cr Increases

	Creatinine (mg/dL)	Urine Protein	Urine Blood
Pt 0029/0229/0011			
Baseline	1.3	trace	none
Wk 24 (40 mg)	2.0	++	+
Wk 120 (OLE, 10 mg)	1.3	none	+
Pt 0030/0001/0251			
Baseline	1.2	none	none
Wk 132 (40 mg)	1.8	+++	+
Wk 144 (40 mg)	1.3	++	trace
Pt 0030/0254/0019			
Baseline	0.9	none	none
Wk 84 (80 mg)	1.4	++	+
Wk 144 (40 mg)	1.1	none	none
Pt 0036/0171/0002			
Baseline	1.5	++	none
Wk 18 (fenofibrate)	1.7	++	trace
Wk 20 (fenofibrate)	2.1		
Wk 120 (OLE, 40 mg)	2.3	+++	trace
Pt 0055/076/0038			
Baseline	0.9	trace	none
Wk 6 (40 mg)	1.2	++	++
Wk 10 (off treatment)	0.9	none	none
Pt 0091/1005/0002			
Baseline	0.9	+	+
Wk 12 (40 mg)	1.2	++	++
Wk 24 (40 mg)	0.9	none	+
Pt 0091/1049/0014			
Baseline	1.0	none	+++
Wk 12 (40 mg)	1.3	++	+
F/U (40 mg)	1.0	trace	none
Pt 0091/1077/0054			
Baseline	1.2	none	none
Wk 12 (40 mg)	2.0	++	++
Wk 12 (F/U, 20 mg)	1.3	+	++
Pt 0091/3005/0038			
Baseline	1.1	+	++
Wk 12 (40 mg)	1.7	++	++
F/U (40 mg)	1.3	++	++

In the 4 patients who remained on the 40 mg dose (grey rows), one patient had persistent ++ proteinuria and hematuria while the serum creatinine decreased from 1.7 to 1.3 mg/dL. In the remaining three subjects, the renal laboratory abnormalities improved. Three patients had their dose reduced or went off treatment. In these 3 cases, serum creatinine and urine abnormalities improved or remained stable. There was one patient who developed renal laboratory abnormalities at the 80 mg dose and

[2] One patient in the 40 mg OLE phase had proteinuria/hematuria and a serum creatinine of 2.4 (Wk 108) and 8.1 (Wk 147). This 66-year old woman had a history of hypertension, diabetes mellitus, and GI bleeding. She was diagnosed with metastatic liver cancer, urinary tract infection, and hyperglycemia (glu 507 mg/dL) around Week 147. She received oral chemotherapy, IV fluids and was discharged to hospice care where she expired during week 151 (Pt 0025/0232/0002).