CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-366

Statistical Review(s)

MEMORANDUM
DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: July 18, 2003

From: Joy D. Mele, M.S.
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Through: Todd Sahlroot, Ph.D.
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Subject: Study 65 of the Crestor (rosuvastatin) Application

To: File (NDA 21-366)

An approvable action was taken on the original application for Crestor (rosuvastatin) (NDA 21-366 submitted June 26, 2001) because of insufficient data to assess the benefit-risk ratio of 20 and 40 mg. In February of 2003, the sponsor (Astra-Zeneca) submitted additional safety data and the results of Study 65 (STELLAR) which is briefly reviewed here.

Study 65 is a 6-week open-label study designed to compare the effects of rosuvastatin to atorvastatin, pravastatin and simvastatin over the full dose ranges. The sponsor stated "These analyses have been performed to support the 40 mg/day maximum dose of rosuvastatin planned for marketing" (from \\CDSESUB1\N21366\N_000\2003-02-12). The results of this study were shown by the sponsor and by FDA at the Metabolic and Endocrine Advisory Committee on July 9, 2003 and are included in the proposed label.

Study 65 had the following design:

- Open-label
- Conducted at 183 US centers from 4/2001 to 3/2002
- Randomized to the following treatment groups
  - Rosuvastatin 10, 20, 40, 80
  - Atorvastatin 10, 20, 40, 80
  - Simvastatin 10, 20, 40, 80
  - Pravastatin 10, 20, 40
  - Cerivastatin 0.3, 0.4, 0.8 (these arms were dropped during recruitment and the data not analyzed)
- Parallel fixed-dose groups studied for 6 weeks

Entry criteria included the following:

1. Fasting 160 mg/dL ≤LDL-C<250 mg/dL at Visit 1 for subjects not on a lipid-lowering therapy or at Visits 2 and 3 for subjects who discontinued therapy at Visit 1.
2. TG<400 mg/dL during the dietary lead-in.
3. Men and women 18 years or older.
4. Patients with uncontrolled hypertension were not enrolled

About 160 patients were randomized to each group and 90% or more of the patients in each group completed the study (Table 1). The primary reason for dropout in the rosuvastatin 80 mg group was serious adverse event (14 patients) which included 4 dropping due to myalgia (3 on simvastatin 80 mg and 3 on atorvastatin 40 mg also dropped due to myalgia) and 2 due to kidney failure.

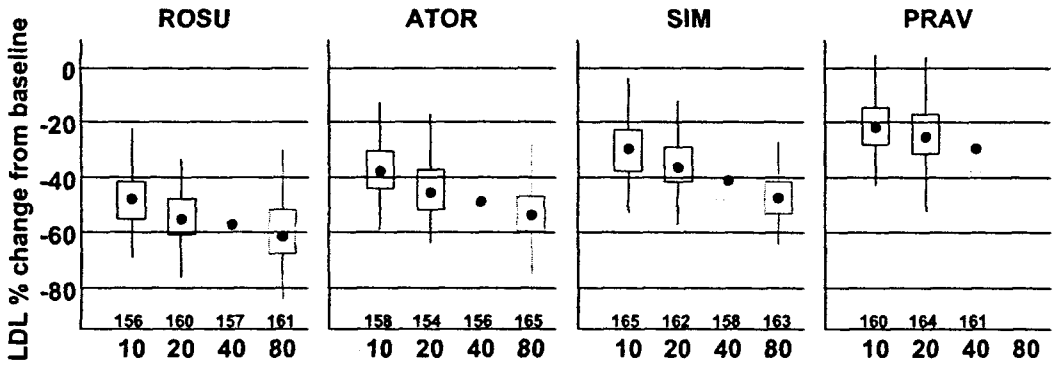
Table 1. Study 65 Patient Disposition

	ROSUVASTATIN				ATORVASTATIN				SIMVASTATIN				PRAVASTATIN		
	10	20	40	80	10	20	40	80	10	20	40	80	10	20	40
Rand	158	164	158	163	158	156	160	167	167	164	159	165	162	166	164
Compl	152	154	151	146	155	147	147	156	158	159	149	152	153	157	152
	96%	94%	96%	90%	98%	94%	92%	93%	95%	97%	94%	92%	94%	95%	93%

The treatment groups were balanced for demographic and baseline characteristics. The average age of patients was 57 years (range of 21 to 92); 29% were 65 or older. About 86% of the patients were Caucasian and 51% were females.

The primary efficacy variable was LDL-C percent change from baseline at Week 6 with the last-observation-carried-forward (LOCF). The distribution of LDL-C percent change from baseline for each treatment group is shown in the boxplots of Figure 1 below.

Figure 1. LDL % change from baseline Week 6 LOCF



Comparisons of like doses show that rosuvastatin significantly lowers LDL more than any of the statin comparators (Table 2).

Table 2. Efficacy results for comparisons of rosuvastatin against all doses of atorvastatin, simvastatin and pravastatin. ** indicates p-value<0.001 * indicates p-value<0.01 for rosuvastatin better than comparator

ROSU	ATORVASTATIN				SIMVASTATIN				PRAVASTATIN		
	10	20	40	80	10	20	40	80	10	20	40
10	**				**	**	**		**	**	**
20	**	**	**		**	**	**	**	**	**	**
40	**	**	**	p=.014	**	**	**	**	**	**	**

In this reviewer's original review of rosuvastatin, the comparison of rosuvastatin to atorvastatin was examined using 95% confidence intervals using data from Study 33; those results are shown in Table 3 on the following page. In Table 4, the results from Study 65 are depicted in the same way.

In Tables 3 and 4, negative values favor rosuvastatin and differences larger than 6% in favor of rosuvastatin are bolded. The highlighted squares show where there is a notable difference between the results of the two studies.

Table 3. Study 33 Comparison of Rosu versus Ator for LDL results (mg/dL) at Week 6 LOCF

	ATOR 10	ATOR 20	ATOR 40	ATOR 80
ROSU 5 vs. ATOR				
LS means difference	-4.3%	+4.7%	+4.1%	+14%
p-value	.13	.13	.16	.0001 A
95% CI	-10, 1	-1, 10	–1.7, 9.8	8, 20
ROSU 10 vs. ATOR				
LS means difference	**-10.9%**	-2.0%	-2.4%	+7.3%
p-value	**.0001**	.48	.38	.01 A
95% CI	**-16, -5**	-7.6, 3.6	-7.9, 3.1	1.8, 13
ROSU 20 vs. ATOR				
LS means difference	**-13%**	-4.4%	-4.8%	+4.9%
p-value	**<.0001**	.13	.10	.09
95% CI	**-19, -8**	-10.3, 1.4	-10.6, 1	-0.8, 11
ROSU 40 vs. ATOR				
LS means difference	**-21%**	**-12%**	**-12%**	-2.4%
p-value	**<.0001**	**<.0001**	**<.0001**	.39
95% CI	**-26, -15**	**-17, -6**	**-18, -7**	-8, 3

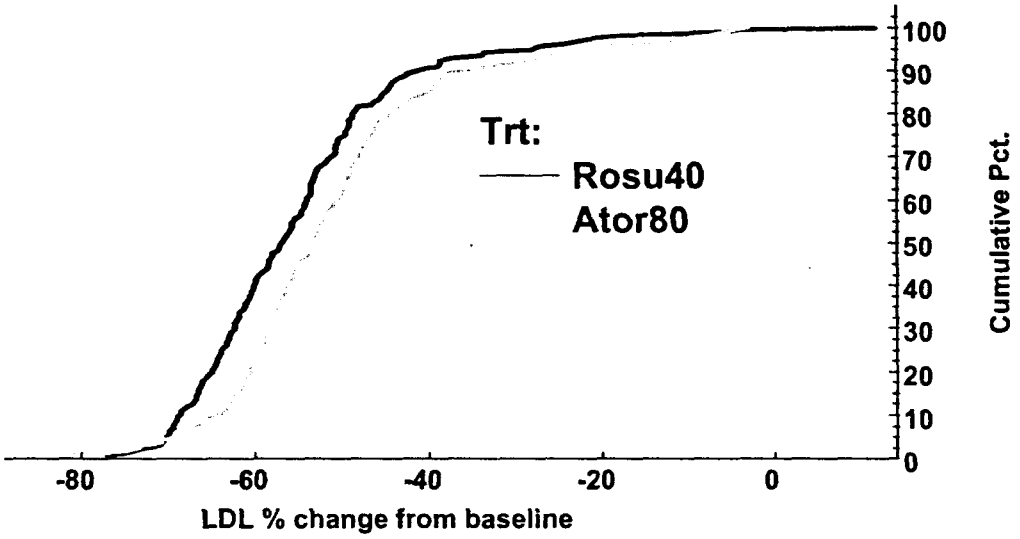
Table 4. Study 65 Comparison of Rosu versus Ator for LDL results (mg/dL) at Week 6 LOCF

	ATOR 10	ATOR 20	ATOR 40	ATOR 80
ROSU 10 vs. ATOR				
LS means difference	**-9.6%**	-3.7%	+1.5%	+5.5%
p-value	**.0001**	.01	.32	.0003 A
95% CI	**-12.5, -6.6**	-6.7, -0.7	–1.5, +4.4	+2.6, +8.4
ROSU 20 vs. ATOR				
LS means difference	**-15.7%**	**-9.9%**	-4.7%	-0.7%
p-value	**.0001**	**.0001**	.002	.65
95% CI	**-18.7, -12.8**	**-12.8, -6.9**	-7.6, -1.7	-3.6, +2.2
ROSU 40 vs. ATOR				
LS means difference	**-18.5%**	**-12.6%**	**-7.4%**	-3.4%
p-value	**<.0001**	**<.0001**	**<.0001**	.02
95% CI	**-21.4, -15.6**	**-15.6, -9.7**	**-10.4, -4.5**	-6.4, -0.5

Overall the results from Study 33 and Study 65 are similar with both studies showing that rosuvastatin is comparable to about 2-4 times the dose of atorvastatin. On a mg per mg basis, the mean response for rosuvastatin exceeds the mean response for atorvastatin by about 10% with confidence intervals showing that a difference as small as about 5% is plausible.

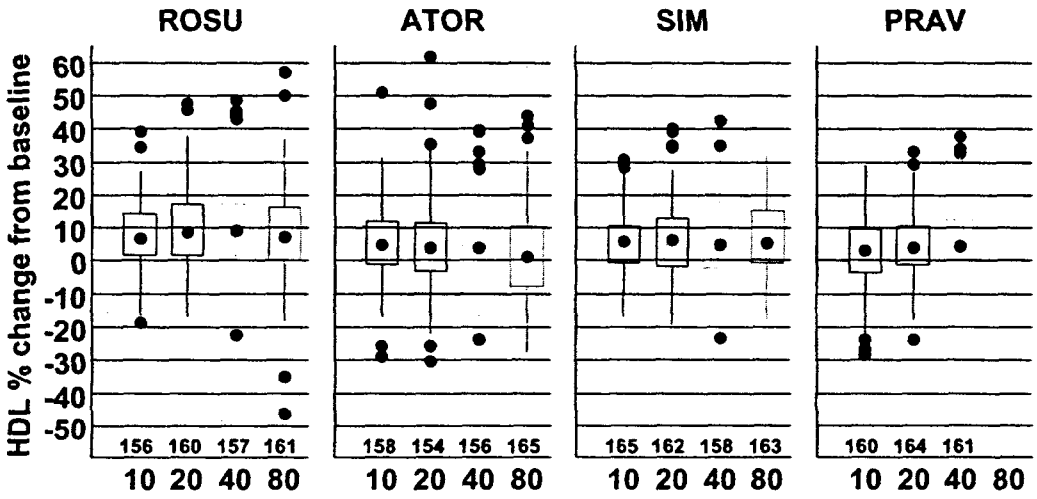
Another way to look at the comparison of rosuvastatin 40 mg and atorvastatin 80 mg is a plot of the cumulative distribution curves. These curves show for any given value on the x-axis between about –70% and –30%, there are about 20% more rosuvastatin than atorvastatin patients having that decrease or more.

Figure 2. Cumulative distribution plot of LDL % change from baseline for rosuvastatin 40 mg and atorvastatin 80 mg.



Rosuvastatin was more effective in raising HDL at doses of 20, 40 and 80 mg compared to like doses of atorvastatin. The boxplots in Figure 3 clearly illustrate no dose response relationship for rosuvastatin with only about a 2% difference between rosuvastatin 10 mg and 20 mg.

Figure 3. HDL % change from baseline Week 6 LOCF



An advisory committee member expressed concern about the rosuvastatin patients showing decreases in HDL and was interested in the LDL changes seen for those patients. This reviewer found that patients with decreases in HDL showed decreases in LDL of magnitudes similar to those seen for the rest of the group.

In conclusion, Study 65 showed that rosuvastatin is more potent on a mg per mg basis than atorvastatin, simvastatin and pravastatin for lowering LDL. The 40 mg dose of rosuvastatin, the highest proposed dose for marketing, produces marginally more mean LDL lowering (about 3%) than the highest marketed dose of atorvastatin (80 mg). About 42 % of rosuvastatin 40 mg patients had a decrease in LDL of 60% or more compared to about 23% of atorvastatin patients (Figure 2).

/S/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-366
Name of drug:	Crestor (rosuvastatin calcium)
Applicant:	AstraZeneca Pharmaceuticals
Indication:	Treatment of hyperlipidemia
Documents reviewed:	\\CDSESUB1\N21366\N_000\2001-06-26\clinstat
Dates:	Received 6/26/01; user fee due date 5/26/02
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Keywords: NDA review, clinical studies, active control, dose response

Introduction

The sponsor has submitted the results of 14 controlled clinical trials to establish the efficacy and safety of rosuvastatin for the treatment of dyslipidemia. These trials are briefly described in Tables 1, 2 and 3 below. Studies 24, 25 and 26 are reviewed in a separate document by FDA statistical reviewer Cynthia Liu. The results for those studies are included in summaries in this review. The remaining 11 trials are reviewed here.

No studies had the same overall design, therefore each study provides additional insight regarding the efficacy of rosuvastatin.

Eight trials were conducted in Type IIa and Type IIb patients (Table 1). Doses for rosuvastatin ranged from 1 mg to 80 mg in these trials; Studies 8, 23 and 33 were specifically designed to examine the dose response relationship of rosuvastatin.

Atorvastatin was an active control in five of the eight trials while pravastatin and simvastatin were active controls in two trials. In Study 33, doses from 5 to 80 mg for rosuvastatin and doses from 10 to 80 mg for atorvastatin were examined; this trial, by design, was the best comparative trial submitted since it contained a full range of doses for both active drugs.

Table 1. Clinical trials in patients with IIa/IIb dyslipidemia and LDL primary endpoint

Study #	Design	Rosuvastatin doses (mg)	Pla?	Active Control (dose)	Duration of treatment
Multiple fixed doses of Rosuvastatin compared to multiple fixed doses of Atorvastatin					
8	Fixed-dose	1, 2.5, 5, 10, 20, 40	Yes	Ator (10, 80 OL)	6 weeks
23	Fixed-dose	40, 80	Yes		6 weeks
33	Fixed-dose	5, 10, 20, 40, 80	No	Ator (10, 20,40, 80)	6 weeks
Rosuvastatin compared to Atorvastatin					
24	Fixed-dose	5, 10	Yes	Ator (10)	12 weeks
25	Forced titration	5→20→80 10→40→80	No	Ator 10→40→80	12 wks at 1st dose 6 wks at each higher dose
26	Titration to NCEP goal	5 →max 80 10 →max 80	No	Ator 10→max 80	12 wks at 1st dose 52 weeks total
Rosuvastatin compared to Pravastatin and Simvastatin					
27	Fixed-dose	5, 10	No	Prav (20), Sim (20)	12 weeks
28	Titration to NCEP goal	5 →max 80 10 →max 80	No	Prav 20→max 40 Sim 20→max 80	12 wks at 1st dose 52 weeks total

Patients with Type IIb or Type IV dyslipidemia were enrolled in Studies 35, 29 and 36 (Table 2). Study 35 was a fixed dose placebo-controlled study while the other two studies examined rosuvastatin in combination with niaspan or fenofibrate

Table 2. Clinical trials in patients with IIb/IV dyslipidemia

Study #	Design	Rosuvastatin doses (mg)	Pla?	Active Control (dose)	Duration of treatment
35	Fixed-dose (TG EP)	5, 10, 20, 40, 80	Yes	None	6 weeks
29	Forced titration (LDL EP)	10→20→40 OL	No	Niaspan alone and combined	12 wks at 1st dose 6 wks at each higher dose
36 (Type II Diabetes)	Forced titration (TG EP)	10→20→40	Yes	Fenofibrate alone and combined	6 wks at 1st dose 6 wks at each higher dose

Patients with homozygous or heterozygous familial dyslipidemia or severe hypercholesterolemia were enrolled in Studies 54, 30 and 31, respectively (Table 3). In these high risk populations, rosuvastatin doses of 20, 40 and 80 mg were used. In Study 31, the combination of rosuvastatin plus cholestyramine (Questran) was examined.

Table 3. Clinical trials in patients with other dyslipidemias

Study #	Design	Rosuvastatin doses (mg)	Active Control (dose)	Duration of treatment
54 (Homozygous Familial)	Forced titration/ crossover (LDL EP)	20→40→80	Ator 80	6 wks at each rosuvastatin dose followed by 2-period crossover (6 wks/period)
30 (Heterozygous Familial)	Forced titration (LDL EP)	20→40→80	Ator 20→40→80	6 wks at each dose
31 (Severe HC)	Combination (LDL EP)	40→80	Questran 16 mg	6 wks at rosuvastatin 40; randomized to rosuvastatin 80 or rosuvastatin 80 +Questran for 6 weeks

Reviewer's Methods

The sponsor provided datasets for each of the 11 studies reviewed here. All statistical results, tables and figures in this review were created by this reviewer unless otherwise noted.

The protocol-defined primary analysis population in all studies except Study 8 was the ITT population where all patients with baseline and at least one post-baseline measurement were included. For patients with missing data at the primary endpoint, the last observation for that patient was used (LOCF analysis).

Baseline was computed as the average of Week –2, -1 and 0 unless otherwise noted.

For most studies (exceptions are noted in the review), an analysis of variance with treatment and region as fixed effects was used to analyze the response variable. Tests for interactions of treatment with subgroup and region were performed and the results are noted when significant. [Note that the protocols specified that center would be included in the ANOVA model; however, from the sponsor's output, it was clear that country or region was included as a term instead. This is acceptable since many centers had a small number of patients overall or were missing patients in 1 or more treatment groups. It seems logical to this reviewer to group small centers based on country or US region.] In some models, baseline was included as a covariate. This reviewer generally only performed analyses of the primary efficacy variable. Few important differences between the results of the sponsor and those of the reviewer were found, though, there are many differences in interpretation and presentation of the results.

Missing data/dropouts was not an issue in these trials since generally over 90% of the patients completed treatment. Therefore, no analyses to assess bias due to missing data were performed by this reviewer.

A statistical methods section is included with those studies where additional description of the methods is needed beyond what is given here.

Clinical trials in patients with IIa/IIb dyslipidemia

Multiple fixed-dose studies of Rosuvastatin

Statistical Methods for Studies 8 and 23

For both Studies 8 and 23, the protocol stipulated as the primary analysis population patients with baseline and Week 6 data (i.e. patients completing the randomized treatment phase). The intent-to-treat analysis of all randomized patients using LOCF for missing data was proposed as a secondary analysis. Analysis of covariance of % change from baseline of LDL with baseline as a covariate and treatment group as a term in the model was performed. William's test was planned to identify the minimum effective dose and Dunnett's test was proposed to compare each rosuvastatin dose to placebo. Only the results of William's test are included in the NDA study report. A regression analysis was done to assess the dose response relationship.

The sponsor suggested that dose response could best be assessed using only patients that complete 6 weeks of therapy. Since the bulk of the response to treatment occurs during the first 2 weeks of therapy, this reviewer thinks that an ITT LOCF analysis will not unduly bias against the drug or cloud interpretation of the dose response relationship. Also, this reviewer felt that a Week 6 LOCF analysis would produce estimates consistent with estimates from the other studies in this submission. For these reasons, only ITT analyses are presented here. Note that there were very few dropouts in these studies so there are no important differences between the sponsor's results and this reviewer's results.

Both studies were multicenter studies conducted outside the USA. The sponsor did not present results by center or country or perform analyses with center or country as terms in the model. This reviewer did these analyses for the primary efficacy variable, LDL and found that inclusion of center or country as a fixed effect had no effect on assessment of efficacy and there were no positive interactions with treatment.

Study 8 (conducted 8/98 to 1/99)

Design

Study 8 is a double-blind, multicenter, randomized Phase II/III trial designed to compare multiple doses of rosuvastatin to placebo. Doses of 1, 2.5, 5, 10, 20 and 40 mg of rosuvastatin were studied. In addition, atorvastatin (10 and 80 mg) was studied with the objective of only estimating the treatment effect to provide information for planning future trials. Note that atorvastatin was administered open-label to patients; the sponsor states that investigators remained blinded to atorvastatin assignment. So there were a total of 9 treatment arms. After a 6-week dietary run-in period, patients were randomized to treatment and followed for 6 weeks.

The primary outcome variable was percent change from baseline in LDL at Week 6. Secondary endpoints named in the protocol were the following:

- % change at 6 weeks for TC, HDL, TG, ApoB, ApoA-1, Apo-A-2, fibrinogen and Lp(a)

Upon advice from the medical reviewer, the following secondary endpoints are reviewed here:

- **TC, HDL, ApoB, TG** (non-HDL was not reported)

Inclusion criteria included the following:

1. 160 mg/dL≤LDL<220 mg/dL at Visits 2 (Week –2) and 3 (Week –1)
2. TG<300 mg/dL at Visits 2 (Week –1) and 3 (Week –1)

3. males 18-70 years and post-menopausal females 50-70 years

Fasting lipids were measured at Weeks –6, -2, -1, 0, 1, 2, 4, 6, 8 and 10. (Weeks 8 and 10 were follow-up after withdrawal of therapy)

Patients were to be withdrawn from the trial if CK>10xULN with pain or ALT or AST>3xULN.

Patient Disposition

A total of 142 patients completed screening and were randomized to treatment in 4 countries (Table 4).

Table 4. Study 8 Patient Disposition by Country and Treatment

Country (# centers)	Placebo	ROSU 1	ROSU 2.5	ROSU 5	ROSU 10	ROSU 20	ROSU 40	ATOR 10	ATOR 80
Norway (3)	6	7	7	7	7	7	8	7	7
Netherlands (3)	2	2	2	3	2	2	2	2	2
Finland (3)	3	3	3	3	4	4	4	3	2
Sweden (5)	2	2	3	4	4	4	4	3	2

Only 6 patients did not complete the 6-week treatment period; one patient did not continue into the follow-up period (Table 5). Three patients (2 not treated and 1 rosu 5mg patient) had no post-baseline data. The difference, then, between a completer analysis population (all patients with 6-week data; the sponsor's analysis population) and an LOCF analysis population (this reviewer's analysis population) is the data of 3 patients (1 rosu 20, 1 ator 10 and 1 ator 80).

Table 5. Study 8 Patient Disposition by Week on Study

	Placebo	ROSU 1	ROSU 2.5	ROSU 5	ROSU 10	ROSU 20	ROSU 40	ATOR 10	ATOR 80
Randomized	14	15	15	18	17	17	18	15	13
(Not treated)	(1)	(1)							
Wk 2	13	14	15	17	17	17	18	15	12
Wk 6	13	14	15	17	17	16	18	14	12
Completers	13 (93%)	14 (93%)	15 (100%)	17 (94%)	17 (100%)	16 (94%)	18 (100%)	14 (93%)	12 (92%)
ITT	13 (93%)	14 (93%)	15 (100%)	17 (94%)	17 (100%)	17 (100%)	18 (100%)	15 (100%)	13 (100%)

The reasons for trial discontinuation for the 6 dropouts were ADE (rosu 20 and ator 10), patient request and protocol violation.

Baseline Demographics

Three patients were Asian and the remainder were Caucasian. About one-third of the patients were female (Table 6). The average age was 55 years (range of 24 to 70). About 15% of the patients were 65 years or older. Treatment groups were not well-balanced regarding gender or patients 65 or older[1].

1 An imbalance in age would expect to accompany an imbalance in gender since men had to be 18-70 years at entry while women had to be 50-70 years and postmenopausal though it not always the case in each group.

Table 6. Study 8 Patient Demographics for ITT Patients

	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)	ATOR 10 (n=15)	ATOR 80 (n=13)
Age									
Mean (SD)	56 (7)	59 (7)	54 (10)	55 (7)	56 (11)	52 (11)	55 (11)	56 (10)	56 (11)
Range	45-64	48-69	31-67	42-65	24-69	29-66	38-70	30-67	36-69
%≥65years	0%	29%	13%	6%	18%	6%	28%	13%	23%
Gender									
% female	38%	36%	33%	24%	53%	24%	33%	40%	15%
Race									
% white	92%	93%	100%	100%	100%	100%	100%	100%	92%

Efficacy

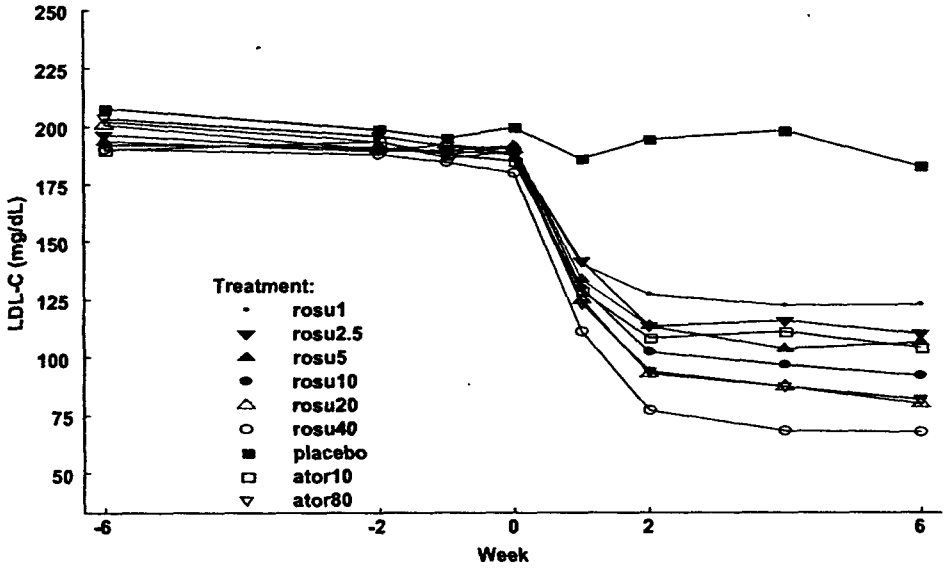
The Week 6 LOCF results for the primary endpoint LDL and four secondary endpoints are shown in Table 7 below for all nine treatment groups. All doses of rosuvastatin showed a significant decrease in LDL, total cholesterol (TC) and ApoB ($p<.001$). The rosuvastatin results for HDL and TG are variable and do not appear to be dose-related.

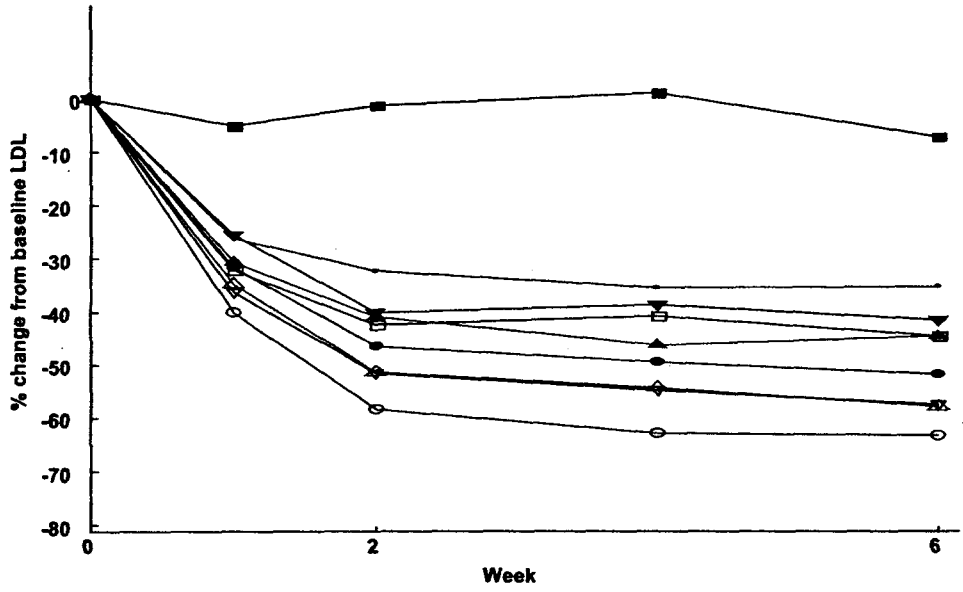
Table 7. Study 8 Lipoprotein results (mg/dL) at Week 6 LOCF

	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)	ATOR 10 (n=15)	ATOR 80 (n=13)
LDL									
Baseline	197 (14)	191 (18)	190 (15)	193 (16)	190 (16)	191 (22)	184 (19)	189 (9)	192 (18)
% change	-7% (7)	-35% (9)	-42% (9)	-45% (7)	-52% (9)	-56% (13)	-63% (9)	-44% (9)	-54% (15)
P-value vs. pla		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
TC									
Baseline	272 (12)	267 (21)	264 (24)	269 (20)	267 (16)	267 (21)	257 (27)	264 (16)	265 (16)
% change	-5% (6)	-24% (7)	-30% (8)	-33% (6)	-36% (7)	-41% (10)	-46% (8)	-32% (7)	-42% (13)
P-value vs. pla		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
HDL									
Baseline	49 (12)	55 (14)	48 (10)	52 (9)	50 (15)	50 (13)	52 (13)	50 (16)	49 (9)
% change	+3% (10)	+8.5% (10)	+8.8% (10)	+13% (13)	+14% (12)	+7.5% (9)	+9.4% (8)	+7% (10)	-3% (13)
P-value vs. pla		.4	.5	.04	.04	.4	.3	>.3	>.3
TG									
Baseline	130 (41)	116 (49)	132 (45)	123 (51)	135 (52)	134 (52)	107 (48)	126 (52)	119 (41)
% change	-3% (23)	-16% (18)	-14% (33)	-35% (16)	-12% (35)	-27% (18)	-25% (23)	-15% (17)	-25% (24)
P-value vs. pla		.2	.7	.001	.8	.07	.009	>.3	>.1
Apo-B									
Baseline	140 (16)	132 (14)	135 (12)	139 (18)	143 (18)	136 (20)	130 (15)	138 (11)	135 (12)
% change	-3% (10)	-27% (11)	-34%	-38% (9)	-42% (8)	-46% (11)	-55% (6)	-36% (11)	-46% (15)
P-value vs. pla		<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001

Statistically significant changes in LDL for rosuvastatin compared to placebo are seen as early as Week 1 with large part of the response achieved by Week 2 and essentially complete by Week 4 (Figure 1).

Figure 1. Study 8 LDL-C (mg/dL) and % change from baseline by week on study for all observed cases





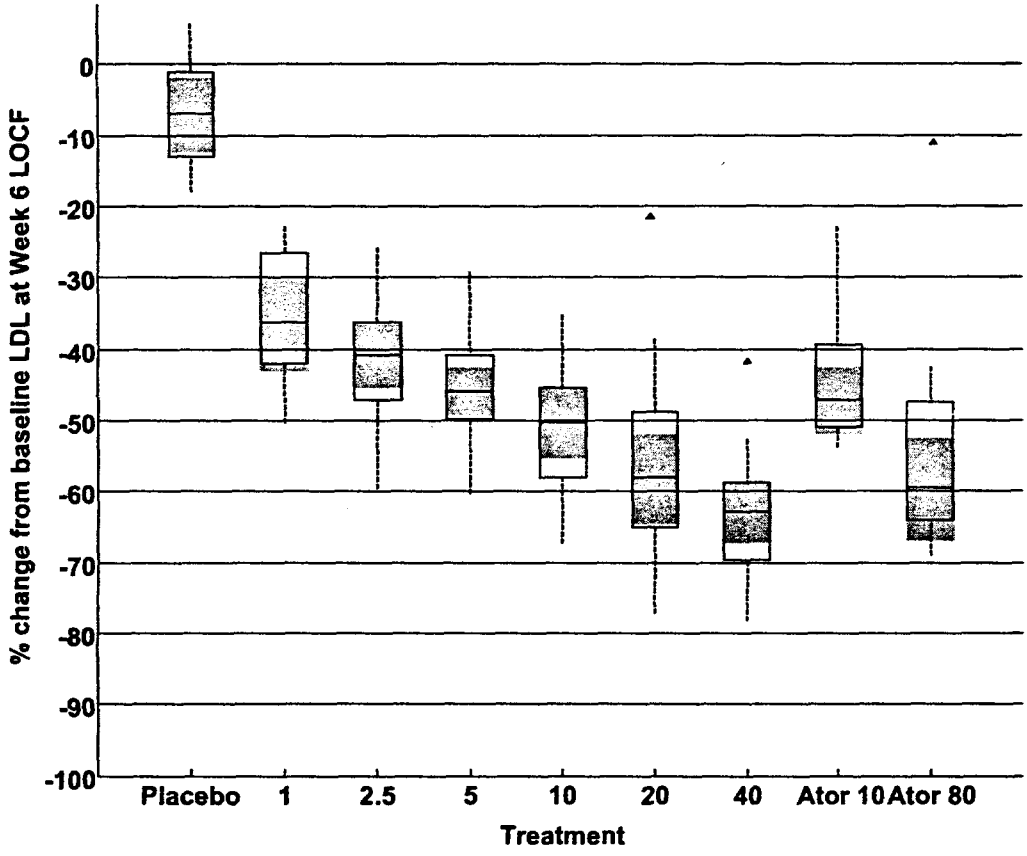
The boxplots in Figure 2 show the distribution of the LDL % change from baseline data at endpoint (Week 6 LOCF) for all treatment groups. There is a clear dose response for rosuvastatin. The overlap of the 95% confidence intervals between adjacent doses of rosuvastatin would be expected especially considering the small number of patients in each treatment group (14-18).

A regression analysis of the five rosuvastatin doses by the sponsor yielded a significant slope and the following regression equation (r^2=.49):

LDL response at Week 6= -35.1 – 7.5* Ln(dose)

According to this linear model, a doubling of the dose up to a maximum of 40 mg results in a further decrease of about 5% (Ln2*7.5). See Appendix 1 for a graph of the dose response and the fitted line.

Figure 2 Study 8 Boxplots[1] of LDL % change from baseline at Week 6 LOCF



1 The top line of the box of the boxplot represents the 25th percentile and the bottom line, the 75th percentile. The middle line marks the median. The whiskers are defined by 75th percentile + (1.5 IQR) and 25th percentile - (1.5 IQR). Points beyond the whiskers are outliers as defined by Tukey. The gray area is the 95% confidence interval on the median.

According to the protocol, the sponsor did not intend to compare the atorvastatin responses to the rosuvastatin responses. For a subsequent Phase 3 trial, Study 33, this comparison was made. This reviewer thinks that it is useful to examine the relationship between atorvastatin and rosuvastatin in this study for further comparison to Study 33. The boxplots suggest that the response for atorvastatin 10 is similar to rosuvastatin 5 and atorvastatin 80 to rosuvastatin 20. Also from Figure 1 we saw that the lines for rosuvastatin 20 mg and atorvastatin 80 mg are superimposed. Confidence intervals on the treatment differences were computed by this reviewer and are shown in Table 8 below. Since no standards for comparability were named in this trial and also atorvastatin was administered open-label, one cannot draw any definitive conclusions from this data. Nevertheless we can use the clinical standard of 6% as a clinically significant difference as a guide for interpreting the limits of the confidence intervals. In doing so, we can not draw any conclusions regarding the comparability of Rosu 5 to Ator 10; the confidence interval for Rosu 20/Ator 80 suggests comparability with an upper limit of 5%. The data does show that Rosu 40 is statistically better than Ator 80.

Table 8. 95% confidence intervals on the treatment difference between atorvastatin and rosuvastatin for LDL % change from baseline at the primary endpoint (Week 6 LOCF)

	95% confidence interval (neg. favors rosuvastatin)
ATOR10 versus	
ROSU 2.5	-5%, 9.5%
ROSU 5.0	-8%, 6%
ATOR 80 versus	
ROSU 10	-6%, 9%
ROSU 20	-10%, 5%
ROSU 40	-17%, -2%

Reviewer's Comments on Study 8

In conclusion, Study 8 shows that rosuvastatin significantly decreases LDL in a dose-related manner for doses from 1 mg to 40 mg. Doubling the dose results in an additional mean decrease of about 5%. Similar dose-related responses are seen for total cholesterol and Apo-B but not for HDL and TG. For HDL, only the 5 mg and 10 mg doses showed significant increases compared to placebo. For TG, only the 5 mg and 40 mg doses showed significant decreases compared to placebo. Also, for atorvastatin, neither dose showed significantly different changes in HDL or TG compared to placebo. The lack of effects seen for HDL and TG in this study is most likely due to the fact that 93% of the patients had Type IIa dyslipidemia, a population characterized by high LDL; the mean HDL at baseline was about 50 mg/dL and the mean TG about 125 mg/dL. Comparisons of rosuvastatin to atorvastatin suggest that at most half of the dose of rosuvastatin is needed to get a response similar to atorvastatin; however, due to sample size and design (open-label administration of limited doses of atorvastatin), these comparisons are inconclusive.

Study 23 (conducted 4/99 to 12/99)

Study 23 is a double-blind, multicenter, randomized trial designed to compare the 40 mg and 80 mg doses of rosuvastatin to placebo. After a 6-week dietary run-in period, patients were randomized in a 1:1:2 ratio to placebo, Rosu 40 mg and Rosu 80 mg and followed for 6 weeks.

The primary outcome variable was percent change from baseline in LDL at Week 6. Secondary endpoints named in the protocol were the following:

- % change at 6 weeks for TC, HDL, TG, ApoB, ApoA-1, Apo-A-2, fibrinogen and Lp(a)

Upon advice from the medical reviewer, the following secondary endpoints are reviewed here:

- **TC, HDL, ApoB, TG** (non-HDL was not reported)

Inclusion criteria included the following:

1. 160 mg/dL≤LDL<220 mg/dL at Visits 2 (Week –2) and 3 (Week –1)
2. TG<300 mg/dL at Visits 2 (Week –1) and 3 (Week –1)
3. males 18-70 years and post-menopausal females 50-70 years

Fasting lipids were measured at Weeks –6, -2, -1, 0, 1, 2, 4, 6, 8 and 10. (Weeks 8 and 10 were follow-up after withdrawal of therapy).

Patients should have been withdrawn from the trial if CK>10xULN with pain or ALT or AST>3xULN.

Design

A total of 65 patients (Table 9) were randomized to treatment at 9 centers (all 9 centers were used in Study 8 also). Only one patient (rosu 40 mg) discontinued treatment; this patient is included in this reviewer's analyses.

Table 9. Study 23 ITT Patient Disposition

	Placebo	ROSU 40	ROSU 80
Randomized	17	16	31
Dropouts	0	1 at Week 5	0
ITT	17	16	31

Baseline Demographics

The average age of patients was about 58 years with about ¼ of the patients 65 or older (Table 10). About half of the patients were female and all patients were Caucasian.

Table 10. Study 23 ITT Patient Disposition

	Placebo (n=17)	ROSU 40 (n=16)	ROSU 80 (n=31)
Age			
Mean (SD)	57 (7)	59 (9)	57 (8)
Range	43-69	41-69	39-69
%≥65years	24%	31%	16%
Gender			
% female	47%	50%	42%
Race			
% white	100%	100%	100%

Efficacy

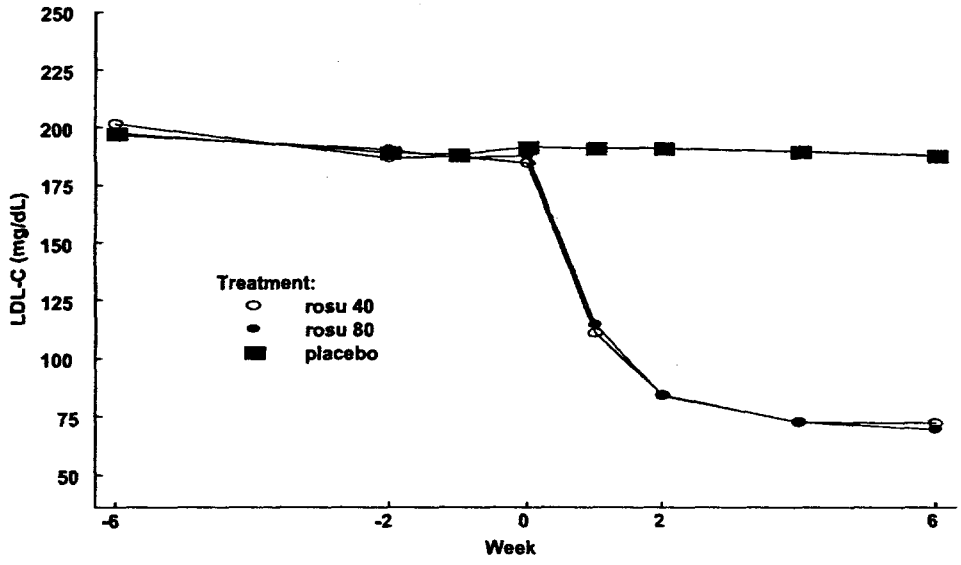
Both doses (40 and 80 mg) of rosuvastatin show significant decreases in LDL, TC and ApoB (Table 11). Results for HDL and TG are borderline significant. Overall the results show small differences between the 40 and 80 mg rosuvastatin doses suggesting no important advantages to increasing the dose from 40 to 80 mg.

Table 11. Study 23 Lipoprotein responses at Week 6 LOCF

	Placebo (n=17)	ROSU 40 (n=16)	ROSU 80 (n=31)
LDL			
Baseline	190 (15)	186 (16)	188 (13)
% change	-0.8% (11)	-61% (7)	-63% (8)
p vs. PLA		<.001	<.001
TC			
Baseline	269 (21)	264 (24)	263 (20)
% change	-0.2% (7)	-44% (8)	-45% (6)
p vs. PLA		<.001	<.001
HDL			
Baseline	56 (9)	53 (13)	51 (14)
% change	+2.6% (11)	+11% (13)	+15% (15)
p vs. PLA		.10	.04
TG			
Baseline	114 (47)	127 (60)	119 (46)
% change	-0.1% (39)	-27% (35)	-23% (25)
p vs. PLA		.05	.06
Apo-B			
Baseline	139 (16)	138 (21)	139 (14)
% change	-1.8% (11)	-52% (8)	-54% (6)
p vs. PLA		<.001	<.001

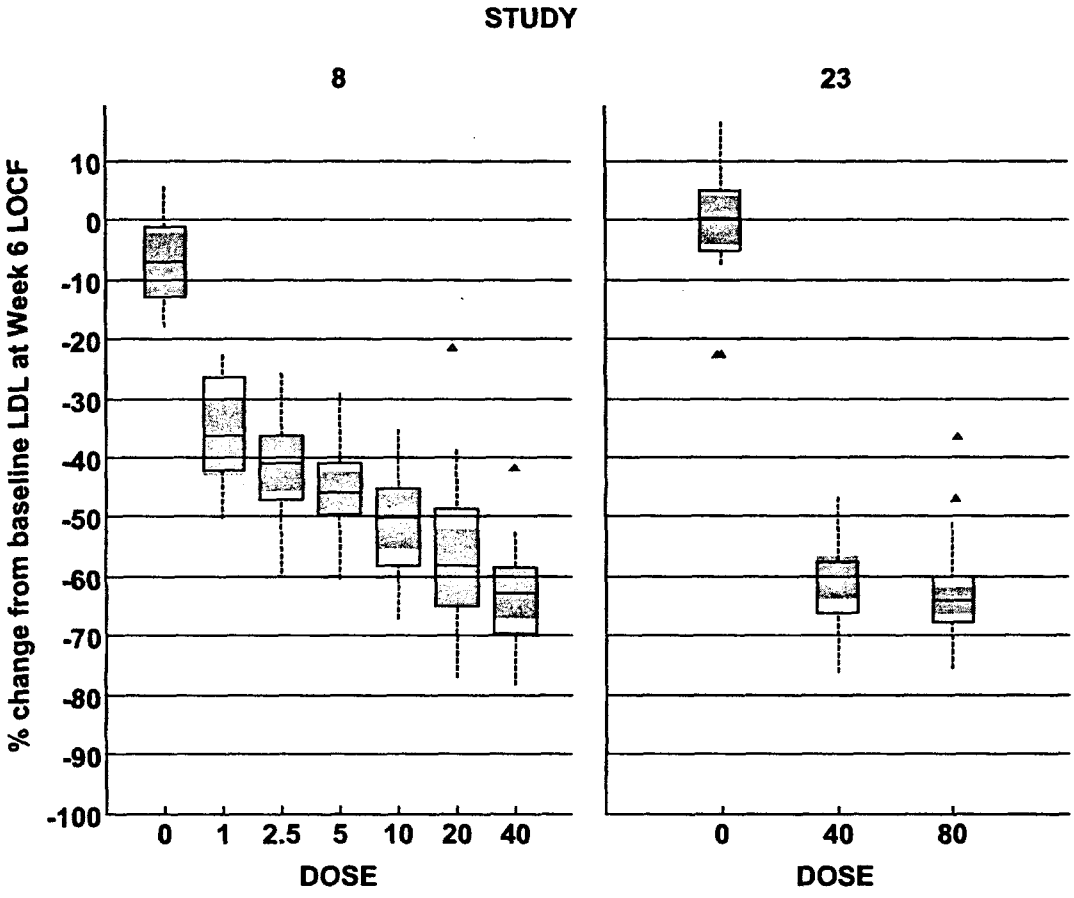
The lack of a difference between 40 and 80 is further illustrated by a graph of LDL overtime.

Figure 3. Study 23 LDL-C (mg/dL) by week on study for all observed cases



The boxplots below (Figure 4) show the range of % change in LDL seen in both Study 8 and 23 at Week 6. The overlap of the confidence intervals (the gray area) for the 40 mg doses demonstrate the consistency of response across the studies. The 40 mg placebo-subtracted effects are –56% and –60% for Studies 8 and 23, respectively.

Figure 4. LDL % change from baseline at Week 6 LOCF for Studies 8 and 23



Reviewer's Comments on Study 23

One of the objectives of Study 23 was to further characterize the dose response of rosuvastatin to 80mg. The intention was to combine the results of Study 8 and Study 23 if the 40 mg doses showed similar responses. Though similarity of response was seen, there appears to be little utility to combining the studies since it seems clear that the 80 mg dose offers no clinically significant advantage over 40 mg (this was also seen in Study 33 which is reviewed in the following section).

Statistical Methods for Study 33

The sponsor's initial model was an analysis of covariance model defined as follows:

$$y = \beta_0+\beta_1 \text{ Baseline}+\beta_2 \text{ Tx}+\beta_3 \text{ log(Dose)}+\beta_4 \text{ Tx*log(Dose)}+\beta_5 \text{ Center}+\beta_6 \text{ Tx* Center}$$

The treatment by center interaction term (β_6) was dropped if it was found to be non-significant . (In the sponsor's analysis, region instead of centers was used in the model with region defined as shown in Table 12.) The treatment by log(dose)[1] interaction tested whether the slopes for atorvastatin and rosuvastatin were parallel; if they were found to be parallel (non-significant β_4) then this interaction term was dropped from the model and the remaining terms re-estimated. The results of this model and an alternative model defined by this reviewer are discussed with the LDL results.

Study 33 (conducted 10/99 to 6/00)

Design

Study 33 was a double-blind, multicenter, randomized trial designed to compare multiple doses of rosuvastatin (5, 10, 20, 40 and 80 mg) to multiple doses of atorvastatin (10, 20, 40 and 80 mg). After a 6-week dietary run-in period, patients were randomized to treatment and followed for 6 weeks.

The primary outcome variable was percent change from baseline in LDL at Week 6. In addition to LDL, the following lipoprotein data was collected:

- TC, HDL, TG, ApoB, ApoA-1 and non-HDL

Upon advice from the medical reviewer, the following secondary endpoints are reviewed here:

- **TC, HDL, ApoB, TG, non-HDL**

Inclusion criteria included the following (differences from Studies 8 and 23 are bolded):

4. 160 mg/dL≤LDL<**250** mg/dL at Visits 2 (Week –2) and 3 (Week –1)
5. TG<**400** mg/dL at Visits 2 (Week –1) and 3 (Week –1)
6. males and **females 18 years or older**

Fasting lipids were measured at Weeks –6, -2, -1, 0, 1, 2, 4, and 6.

Patients may be withdrawn from the trial if CK>10xULN with pain or ALT or AST>3xULN.

Patient Disposition

A total of 374 patients were randomized to treatment at 35 centers in the USA and 4 centers in Canada (Table 12). For analysis purposes, centers were pooled into regions as

1 For Study 8, the sponsor modeled ln(dose) while for this study the sponsor modeled log(dose); this reviewer found that for the range of doses studied here that both transformations were appropriate. Though, given the range of doses and response, neither transformation greatly improves characterization of the dose response curve over using the studied doses (see Appendix 1 and Appendix 3 for plots of the dose responses in Studies 8 and 33).

shown in the table below.

Table 12. Study 33 Patient Disposition by Region and Treatment

Region (# centers)	ROSU 5	ROSU 10	ROSU 20	ROSU 40	ROSU 80	ATOR 10	ATOR 20	ATOR 40	ATOR 80
Northeast (9)	9	12	8	11	10	10	9	11	9
Southeast (7)	6	8	8	9	6	9	9	7	10
Central (12)	15	16	14	16	15	18	16	13	15
West (7) Canada (4)	8	9	7	9	11	6	7	8	10

Over 95% of the randomized patients completed the study (Table 13); only 2 patients did not have data on study and are excluded from the ITT analysis.

Table 13. Study 33 Patient Disposition by Week on Study

	ROSU 5	ROSU 10	ROSU 20	ROSU 40	ROSU 80	ATOR 10	ATOR 20	ATOR 40	ATOR 80
Randomized	38	45	39	45	42	43	39	42	41
(Not treated)			(1)	(1)					
Wk 2	38	45	38	44	42	43	39	41	40
Wk 6	38	42	37	43	41	41	37	41	40
Completers	38 (100%)	42 (93%)	37 (95%)	43 (96%)	41 (98%)	41 (95%)	37 (95%)	39 (93%)	39 (95%)
ITT	38 (100%)	45 (100%)	38 (97%)	44 (98%)	42 (100%)	43 (100%)	39 (100%)	42 (100%)	41 (100%)

Note that some patients dropped during Week 6 and had Week 6 data but were not completers.

The reasons for trial discontinuation show that ADE is the most common reason for trial discontinuation for both rosuvastatin and atorvastatin patients (Table 14).

Table 14. Study 33 Reasons for treatment discontinuation

	ROSU 5	ROSU 10	ROSU 20	ROSU 40	ROSU 80	ATOR 10	ATOR 20	ATOR 40	ATOR 80
Randomized	38	45	39	45	42	43	39	42	41
ADE	0	2	1	1	1	1	0	1	2
Pt request	0	0	1	0	0	1	2	0	0
Prot. Viol.	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	2	0
Lost-to-FU	0	1	0	1	0	0	0	0	0

Baseline Demographics

The treatment groups were fairly well-balanced regarding age, gender and race (Table 15 on following page). About 88% of the patients were Caucasian; another 8% were Black. About half of the patients were female. The average age was 57 years (range of 25 to 81). About 25% of the patients were 65 years or older.

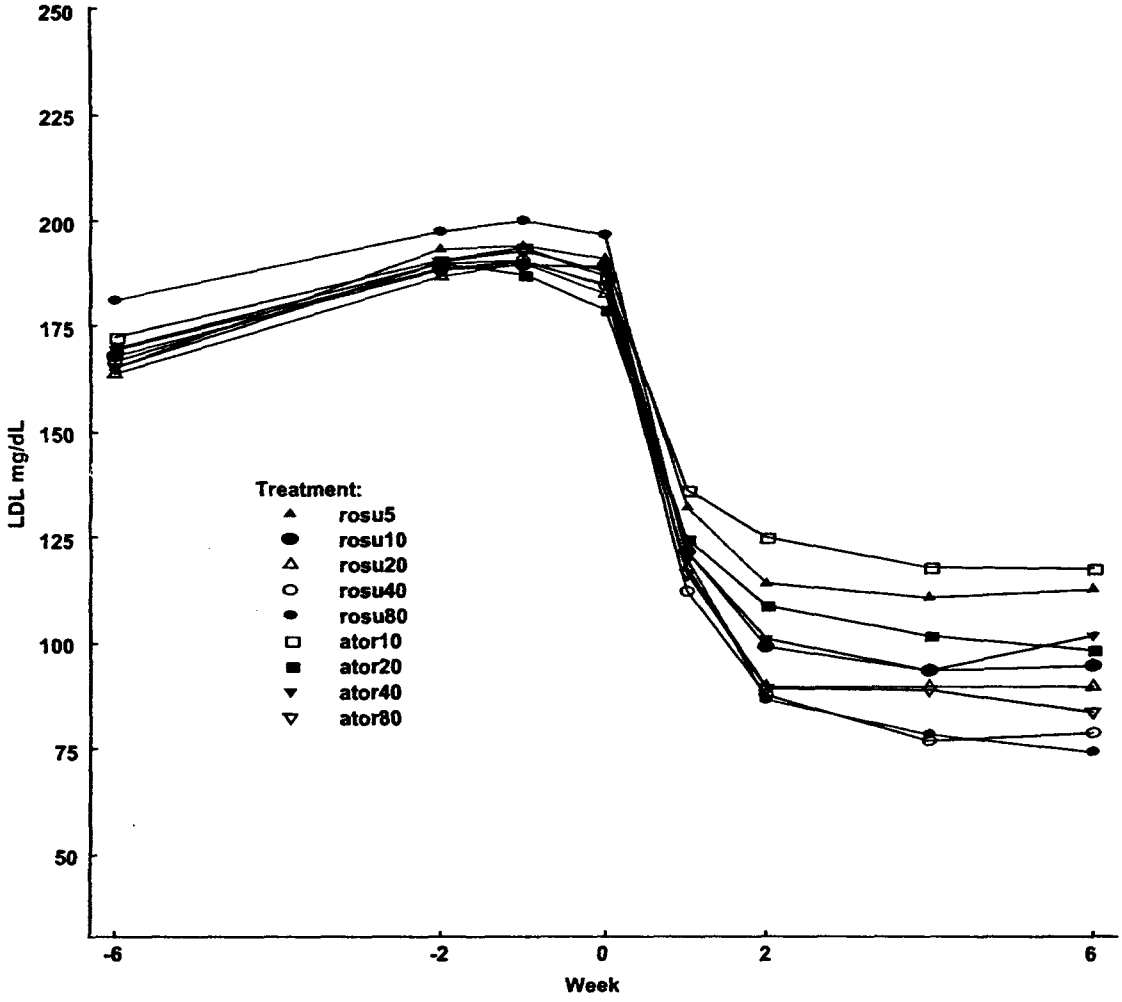
Table 15. Study 33 Patient Demographics for ITT Patients

	ROSU 5 (n=38)	ROSU 10 (n=45)	ROSU 20 (n=38)	ROSU 40 (n=44)	ROSU 80 (n=42)	ATOR 10 (n=43)	ATOR 20 (n=39)	ATOR 40 (n=42)	ATOR 80 (n=41)
Age									
Mean (SD)	55 (12)	58 (10)	56 (12)	57 (9)	57 (9)	59 (11)	56 (12)	57 (11)	54 (12)
Range	30-78	36-79	33-81	38-80	39-75	38-80	25-78	34-74	27-74
%≥65years	21%	29%	26%	18%	26%	33%	21%	26%	22%
Gender									
% female	53%	49%	61%	50%	45%	53%	49%	43%	32%
Race									
% white	82%	82%	89%	89%	88%	88%	90%	88%	95%

Efficacy

The LDL (Figure 5) overtime shows a pattern of response akin to what was seen in Study 8; the bulk of response occurs by Week 2 with some further lowering observed primarily in the higher doses.

Figure 5. Study 33 LDL (mg/dL) by week on study and treatment group



The Week 6 LOCF results for the primary endpoint LDL are shown in Table 16 below for

all nine treatment groups. (See Appendix 2 for a plot of the LDL % change from baseline data for the duration of the trial.)

Table 16. Study 33 LDL results (mg/dL) at Week 6 LOCF

	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

This reviewer considered two models to analyze this data. The first model is the sponsor's model:

$$y = \beta_0+\beta_1 \text{ Baseline}+\beta_2 \text{ Tx}+\beta_3 \log(\text{Dose})+\beta_4 \text{Tx*log(Dose)}+\beta_5 \text{ Center}+\beta_6 \text{ Tx* Center}$$

The treatment by region and treatment by dose interactions were non-significant. The latter indicates that the difference between the slopes for the two treatment groups is not statistically significant indicating parallel slopes for the two treatment groups. The sponsor then dropped both terms from the model. In their final model, then, response was regressed on both baseline LDL[1] and dose. This is essentially akin to separate regressions for each treatment group (see Appendix 3 for a plot of the regression lines). The fit of these lines is not good with an $r^2 \leq .2$. The sponsor's model, then, does not well-characterize the dose response for each treatment group. Comparisons between like doses based on this model and the linearity of the dose response are not acceptable to this reviewer.

Instead of regressing on dose, dose may be treated as a classification variable. This second alternative model yields the results shown at the bottom of Table 16. Using the sponsor's model, rosuvastatin is significantly different from atorvastatin at each dose (recall that the differences will all be the same since the comparisons are based on regressing on dose) while this reviewer's model shows no statistically significant difference between the 20 mg doses. Given the mean results by dose (particularly the similarity of the responses for the atorvastatin 20 and 40 mg doses) it is not surprising that the results of the two models would differ.

In addition to being interested in how the two treatment groups compare at like doses, we are also interested in seeing which rosuvastatin doses and atorvastatin doses are comparable. The results in Table 17 on the following page are from this reviewer's model described above (rosuvastatin 80 mg beats all doses of atorvastatin and is not included in the table, $p<.03$). The bolded numbers are for the doses where rosuvastatin is either better or comparable to

1 This reviewer found that the addition of baseline to the model did not improve the model and the correlation of baseline with % change was very low, nevertheless the high baseline seen for Rosu 80 (significantly higher than some) suggests adjustment for baseline is warranted.

atorvastatin, using an upper limit of the CI of +6% as the acceptable margin. According to these LDL results, rosuvastatin is as good as twice the dose of atorvastatin

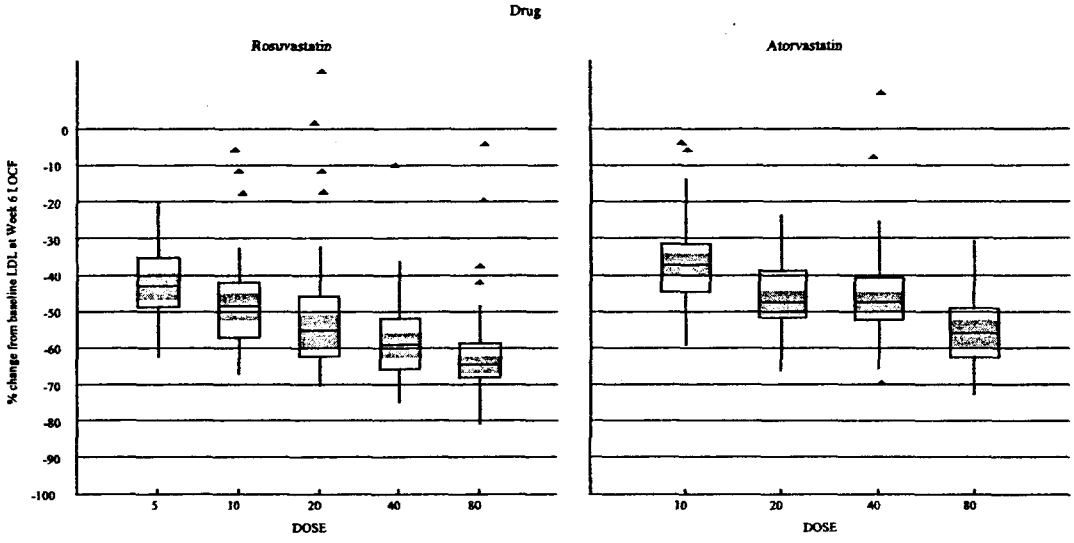
Table 17. Study 33 Comparison of Rosu versus Ator for LDL results (mg/dL) at Week 6 LOCF

	ATOR 10	ATOR 20	ATOR 40	ATOR 80
ROSU 5 vs. ATOR				
LS means difference	**-4.3%**	+4.7%	+4.1%	+14%
p-value	**.13**	.13	.16	.0001
95% CI	**-10, 1**	-1, 10	–1.7, 9.8	8, 20
ROSU 10 vs. ATOR				
LS means difference	**-10.9%**	**-2.0%**	**-2.4%**	+7.3%
p-value	**.0001**	**.48**	**.38**	.01
95% CI	**-16, -5**	**-7.6, 3.6**	**-7.9, 3.1**	1.8, 13
ROSU 20 vs. ATOR				
LS means difference	**-13%**	**-4.4%**	**-4.8%**	+4.9%
p-value	**<.0001**	**.13**	**.10**	.09
95% CI	**-19, -8**	**-10.3, 1.4**	**-10.6, 1**	-0.8, 11
ROSU 40 vs. ATOR				
LS means difference	**-21%**	**-12%**	**-12%**	**-2.4%**
p-value	**<.0001**	**<.0001**	**<.0001**	**.39**
95% CI	**-26, -15**	**-17, -6**	**-18, -7**	**-8, 3**

Note that negative values favor rosuvastatin.

The overlap of boxes in Figure 6 illustrates the variation in response which was also reflected in the low r^2 's observed in the regression analyses.

Figure 6. Boxplots for LDL % change from baseline at endpoint by dose and treatment group



The rosuvastatin results for TC, non-HDL and ApoB show a clear dose response (Table 18). The comparisons to atorvastatin look similar to those seen for LDL (note due to time constraints, analyses comparing rosuvastatin and atorvastatin were not done on secondary endpoints by this reviewer). As in Study 8, no dose response is seen for TG and HDL.

Table 18. Study 33 Lipoprotein results (mg/dL) at Week 6 LOCF

	ROSU 5 (n=38)	ROSU 10 (n=45)	ROSU 20 (n=38)	ROSU 40 (n=44)	ROSU 80 (n=42)	ATOR 10 (n=43)	ATOR 20 (n=39)	ATOR 40 (n=42)	ATOR 80 (n=41)
TC									
Baseline	281 (27)	276 (25)	270 (25)	276 (27)	286 (27)	280 (29)	271 (23)	274 (24)	278 (23)
% change	-30% (8)	-35% (10)	-36% (14)	-41% (9)	-44% (11)	-27% (11)	-34% (7)	-35% (11)	-43% (8)
HDL									
Baseline	53 (14)	51 (15)	50 (10)	53 (14)	52 (10)	54 (15)	49 (11)	49 (10)	48 (11)
% change	+7% (10)	+6% (11)	+9% (13)	+12% (11)	+10% (14)	+4% (11)	+7% (12)	+4% (9)	+2% (10)
non-HDL									
Baseline	228 (29)	225 (23)	221 (27)	223 (24)	233 (26)	226 (9)	222 (23)	225 (25)	229 (25)
% change	-39% (9)	-44% (11)	-46% (17)	-53% (11)	-56% (14)	-34% (13)	-43% (8)	-43% (14)	-52% (9)
TG									
Baseline	180 (89)	180 (62)	164 (52)	176 (67)	177 (72)	179 (71)	188 (90)	181 (66)	193 (68)
% change	-23% (15)	-22% (24)	-18% (29)	-26% (18)	-20% (44)	-17% (28)	-25% (26)	-27% (22)	-34% (29)
Apo-B									
Baseline	183 (24)	182 (19)	181 (21)	178 (21)	189 (19)	184 (24)	181 (20)	183 (20)	184 (22)
% change	-35% (9)	-41% (10)	-43% (17)	-48% (10)	-51% (12)	-32% (11)	-38% (10)	-39% (13)	-48% (9)

Reviewer's Comments on Study 33

The results for Study 33 show a rosuvastatin dose-response relationship for LDL, TC, non-HDL and Apo-B. As in Study 8 no dose–response is seen for HDL or TG. Comparisons to atorvastatin show that comparable responses are seen when the dose of atorvastatin is double the dose of rosuvastatin.

Rosuvastatin 5 mg and 10 mg compared to pravastatin and simvastatin

Statistical Methods for Studies 27 and 28

The sponsor planned to perform pairwise t-tests to compare each dose of rosuvastatin to each comparator using the following steps:

1. Test each dose of rosuvastatin to pravastatin and simvastatin for non-inferiority using a 6% margin. If the rosuvastatin is found to be non-inferior to simvastatin or pravastatin, then a test of superiority will be performed.
2. Tests of superiority will be performed for the 10 mg dose of rosuvastatin versus each comparator. If the results of a test are significant at the .05 level, then a test of the 5 mg dose will be performed.

Study 27 (conducted 6/99 to 4/00)

Design

Study 27 is a double-blind, multicenter, randomized trial designed to compare two low doses of rosuvastatin (5 mg and 10 mg) to the 20 mg dose of pravastatin and simvastatin. After a 6-week dietary run-in period, patients were randomized to one of 4 treatment arms and followed for 12 weeks.

The primary outcome variable was percent change from baseline in LDL at Week 12. Secondary endpoints named in the protocol were the following:

- % change at 12 weeks for TC, HDL, LDL/HDL, TC/HDL, non-HDL/HDL, TG, ApoB, ApoB/ApoA-1, ApoA-1 and Lp(a)
- % change at 2, 6, and 10 weeks for LDL, TC, HDL, LDL/HDL, TC/HDL, non-HDL/HDL, and TG
- % of patients within NCEP and EAS guidelines at 12 weeks

Upon advice from the medical reviewer, the following secondary endpoints are reviewed here:

- **TC, HDL, non-HDL, ApoB, TG**

Inclusion criteria included the following:

1. 160 mg/dL≤LDL<250 mg/dL at Visits 2 (Week –1) and 3 (Week –1)
2. TG<400 mg/dL at Visits 2 (Week –1) and 3 (Week –1)
3. Men and women≥18 years

Fasting lipids were measured at Weeks –6, -2, -1, 0, 2, 6, 10 and 12.

Patients could be withdrawn from the trial if CK>10xULN with pain or ALT or AST>3xULN.

Patient Disposition

A total of 502 patients were randomized to treatment at 63 centers in 7 countries (Table 19 on following page). About ⅓ of the patients were from the United Kingdom.

Table 19. Study 27 Distribution of centers and patients by country

Country	# centers	ROS 5	ROS 10	PRAV 20	SIM 20
France	10	15	13	21	19
Germany	7	6	6	9	9
Holland	4	5	6	6	6
Italy	9	12	15	18	17
Poland	7	22	20	20	20
Spain	7	14	15	14	16
United Kingdom	19	46	40	49	42

Table 20 shows the number of patients on study by study week; overall only 6% of the patients did not complete the 12 weeks of the study. Dropout rates were similar across treatment groups. Seven patients were not included in the ITT analysis due to missing data at baseline or on study.

Table 20. Study 27 Patient Disposition by Week on Study

	ROSU 5	ROSU 10	PRAV 20	SIM 20
Randomized	120	115	137	130
Wk 2	120	114	137	129
Wk 6	117	109	133	126
Wk 10	114	108	132	122
Wk 12	114	106	131	122
Completers	114 (95%)	106 (92%)	131 (96%)	122 (94%)
ITT	119 (99%)	111 (97%)	136 (99%)	129 (99%)

In the rosuvastatin groups and the pravastatin group, the major reason for dropout was adverse event (ADE) while in the simvastatin group the major reason was patient request (Table 21).

Table 21. Study 27 Reasons for discontinuation

	ROSU 5 (n=120)	ROSU 10 (n=115)	PRAV 20 (n=137)	SIM 20 (n=130)
ADE	2 (1.7%)	6 (5.2%)	3 (2.2%)	1 (0.8%)
Pt request	0 (0%)	1 (0.9%)	2 (1.5%)	3 (2.3%)
Prot. Viol.	2 (1.7%)	1 (0.9%)	0 (0%)	2 (1.5%)
Other	2 (1.7%)	1 (0.9%)	0 (0%)	0 (0%)
Lost-to-FU	0 (0%)	0 (0%)	1 (0.7%)	1 (0.8%)

Baseline Demographics

The treatment groups were well-balanced regarding baseline demographics (Table 22) and medical history including CHD risk factors. The average age of patients in this study was 58 years with about ⅓ of the patients 65 years or older. Except for 2 patients, all patients were Caucasian.

Table 22. Study 27 Patient Demographics for All Randomized Patients

	ROSU 5 (n=120)	ROSU 10 (n=115)	PRAV 20 (n=137)	SIM 20 (n=130)
Age				
Mean (SD)	57 (12)	60 (10)	59 (11)	59 (11)
Range	28-79	28-84	20-78	22-81
%≥65years	30%	32%	37%	32%
Gender				
% female	49%	57%	54%	50%
Race				
% white	100%	100%	99%	100%

Efficacy Results

Primary Endpoint LDL-C

The primary endpoint in this trial is LDL-C measured at Week 12 with the last observation carried forward for missing data. Results of an ANOVA of LDL-C for the ITT population (Table 23) clearly show that each dose of rosuvastatin is superior to pravastatin and simvastatin at the doses tested. The p-values and 95% confidence intervals clearly show that the results meet the standards for both non-inferiority and superiority set in the protocol.

Table 23. Study 27 LDL-C Week 12 LOCF ITT Results (mg/dL)

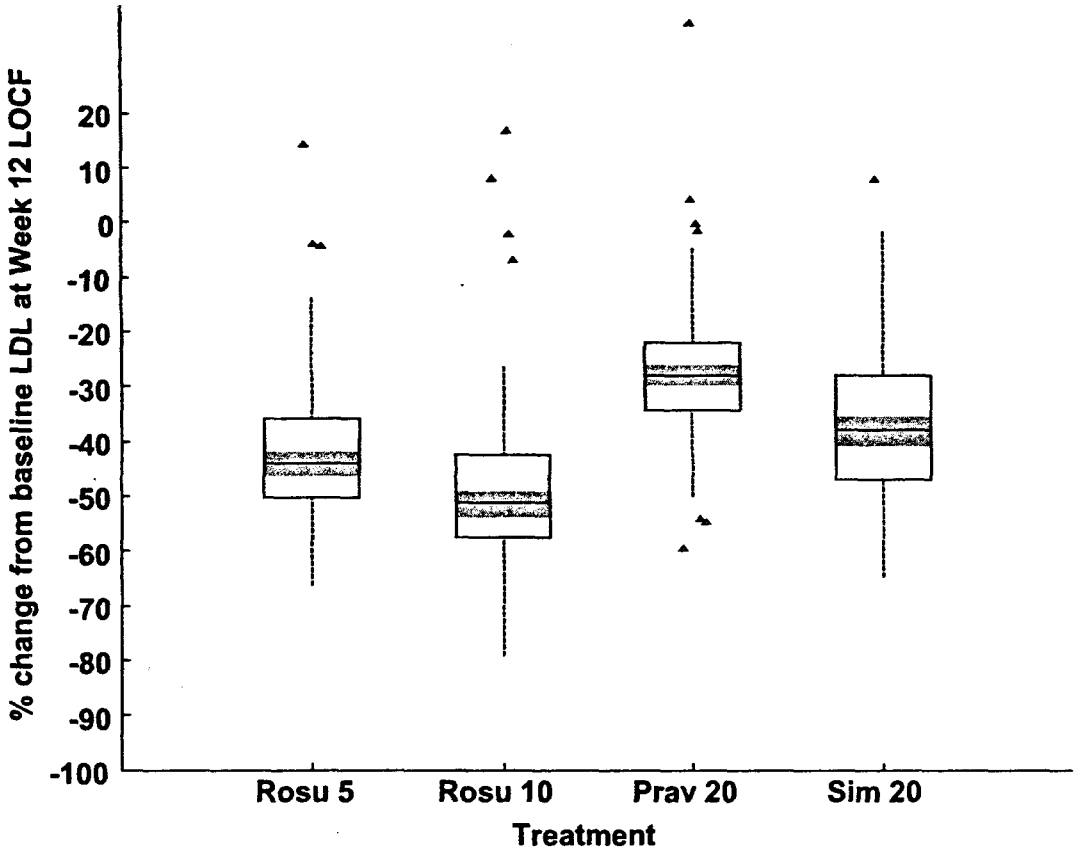
	ROSU 5 (n=120) Mean (SD)	ROSU 10 (n=115) Mean (SD)	PRAV 20 (n=137) Mean (SD)	SIM 20 (n=130) Mean (SD)
Baseline	190 (20)	186 (19)	189 (19)	188 (22)
% Change from Baseline	-42% (12)	-49% (15)	-28% (12)	-37% (13)
Results vs. Prav 20				
p-value	.0001	.0001		
95% Confidence Interval	-17.5%, -11.2%	-24.3%, -17.8%		
Results vs. Sim 20				
p-value	.03	.0001		
95% Confidence Interval	-8.2%, -1.8%	-15.0%, -8.5%		

For the 95% confidence intervals, negative values favor rosuvastatin.

In addition to testing for treatment effect, the protocol stated that a test for interaction would be done; these results are not included in the sponsor's report. This reviewer's test of treatment by country interaction yielded a p-value of .057 suggesting that further examination of the country results is warranted. This reviewer found that removing Poland from the analysis increased the interaction p-value to .42. A comparison of the results for each country showed that the interaction was quantitative not qualitative with the relationship between doses for each

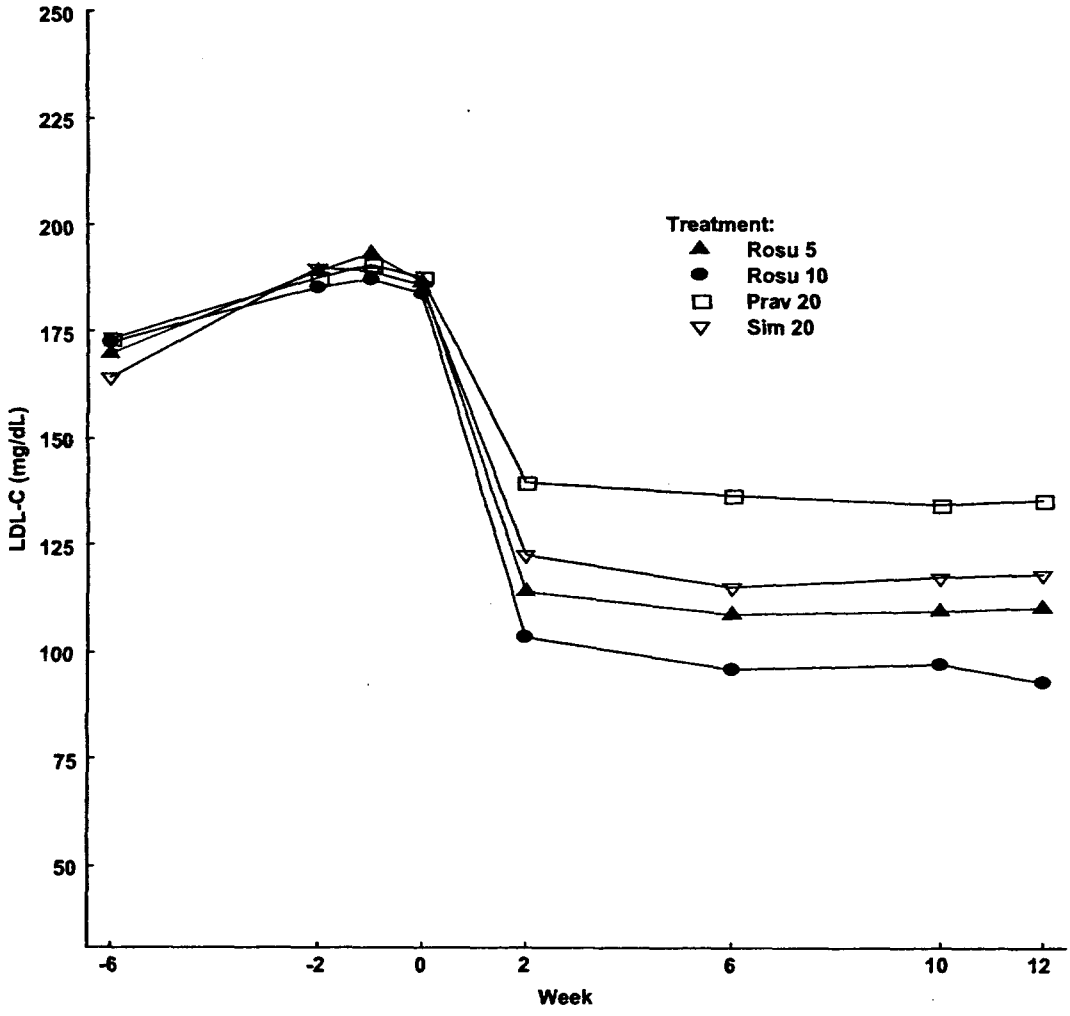
country similar to what is illustrated in the boxplots below (Figure 7).

Figure 7. Study 27 Boxplots of % change from baseline for LDL-C at Week 12 LOCF



A graph of LDL over the duration of the trial (Figure 8) illustrates two points; 1) the response is quite stable from Week –2 to 0 so averaging of these three values to obtain a baseline is acceptable and 2) it appears that most of the response occurs during the first 2 weeks of treatment. Further examination of the latter point by this reviewer showed that in the rosu 5 mg group, the average additional decrease from Week 2 to endpoint was about 2% and in the rosu 10 mg group, about 4%. About 56% of the rosu 5 mg patients and 70% of rosu 10 mg patients had a smaller LDL at endpoint than at Week 2 but the bulk of their response occurred by Week 2.

Figure 8. Study 27 LDL-C by week on study (observed cases)



Secondary Endpoints

The results for five secondary endpoints (selected by the medical reviewer from the 10 named by the sponsor) are shown in Table 24 below. Significantly larger decreases in TC, non-HDL, and Apo-B were seen for both doses of rosuvastatin compared to pravastatin and simvastatin. Similar changes in HDL and TG were seen in all groups. No criteria for non-inferiority were named in the protocol for secondary endpoints.

Table 24. Study 27 LDL-C Results at Week 12 LOCF (mg/dL)
Sponsor's Results

	ROSU 5 (n=120) Mean (SD[1])	ROSU 10 (n=115) Mean (SD)	PRAV 20 (n=137) Mean (SD)	SIM 20 (n=130) Mean (SD)
TC				
Baseline	274 (24)	271 (23)	275 (23)	274 (25)
% Change	-30% (1)	-34% (1)	-20% (1)	-26% (1)
Results vs. Prav 20				
p-value (95% CI)	.001 (-12%, -8%)	.001 (-17%, -12%)		
Results vs. Sim 20				
p-value (95% CI)	.004 (-6%, -1%)	.001 (-10%, -5%)		
non-HDL				
Baseline	224 (24)	218 (24)	221 (23)	219 (25)
% Change	-38% (1)	-44% (1)	-26% (1)	-34% (1)
Results vs. Prav 20				
p-value (95% CI)	.0001 (-16%, -10%)	.0001 (-22%, -16%)		
Results vs. Sim 20				
p-value (95% CI)	.004 (-7%, -1%)	.0001 (-14%, -8%)		
HDL				
Baseline	51 (13)	53 (12)	54 (13)	55 (14)
% Change	+6.2% (1.2)	+6.8% (1.3)	+4.4% (1.2)	+3.9% (1.2)
Results vs. Prav 20				
p-value (95% CI)	.26 (-1%, +5%)	.14 (-1%, +6%)		
Results vs. Sim 20				
p-value (95% CI)	.15 (-1%, +5.5%)	.07 (-0.2%, +6%)		
TG				
Baseline	168 (62)	160 (59)	161 (64)	156 (62)
% Change	-12% (3)	-18% (3)	-13% (3)	-14% (3%)
Results vs. Prav 20				
p-value (95% CI)	.80 (-6%, +8%)	.15 (-13%, +2%)		
Results vs. Sim 20				
p-value (95% CI)	.62 (-6%, +9%)	.23 (-12%, +3%)		
Apo-B				
Baseline	183 (24)	177 (22)	178 (24)	178 (24)
% Change	-34% (1)	-39% (1)	-21% (1)	-29% (1)
Results vs. Prav 20				
p-value (95% CI)	.001 (-15%, -9%)	.001 (-21%, -14%)		
Results vs. Sim 20				
p-value (95% CI)	.011 (-7%, -1%)	.001 (-12%, -6%)		

1 For the % change from baseline estimates, the least squares mean and the standard error are reported.

Study 28 (conducted 4/99 to 10/00)

Design

Study 28 was a double-blind, multicenter, randomized trial designed to compare rosuvastatin to pravastatin and simvastatin. The primary objective was to compare doses of 5 mg and 10 mg of rosuvastatin to the 20 mg dose of pravastatin and simvastatin after 12 weeks of treatment. After the 12-week fixed dose period, patients were followed for an additional 40 weeks during which the dose could be titrated to achieve NCEP target LDL-C.

The primary outcome variable was percent change from baseline in LDL at Week 12. Secondary endpoints were the following:

- % change at 52 weeks for LDL
- % change for TC, HDL, LDL/HDL, TC/HDL, non-HDL/HDL, TG, ApoB, ApoB/ApoA-1, ApoA-1 and Lp(a) at 12 weeks and 52 weeks
- % of patients within NCEP and EAS guidelines at 12 weeks and 52 weeks
- number of titration steps
- % of patients on each titrated dose at 52 weeks

Upon advice from the medical reviewer, the following secondary endpoints are reviewed here:

- **TC, HDL, non-HDL, ApoB, TG**

The Eating Pattern Assessment Tool was administered during the 6-week dietary lead-in period at Weeks –6 and –2 and during double-blind treatment at Weeks 12, 20, 28, 36, 44 and 52. The results of this test were analyzed by the sponsor to assess adherence to the NCEP Step-I diet and they are not included here.

Inclusion criteria included the following:

- 160 mg/dL≤LDL<250 mg/dL at Visits 2 (Week –1) and 3 (Week –1)
- TG<400 mg/dL at Visits 2 (Week –1) and 3 (Week –1)
- men and women ≥18 years

Fasting lipids were measured at Weeks –6, -2, -1, 0, 2, 6, 10, 12, 20, 28, 36, 44, 50 and 52. The dose could be increased to the next dose level at Weeks 12, 20, 28, 36, 44 or 50 based on whether the NCEP target LDL had been met and at the discretion of the investigator.

Patients should have been withdrawn from the trial if CK>10xULN with pain or ALT or AST>3xULN on 2 or more occasions.

Patient Disposition

A total of 477 patients were randomized to treatment at 44 centers in the United States (Table 25). About 40% of the patients were from Central United States. The number of patients in each center ranged from 1 to 36 patients; 3 centers were missing patients in 1 or more treatment groups.

Table 25. Study 28 Distribution of centers and patients by USA region

	# centers	ROS 5	ROS 10	PRAV 20	SIM 20
Northeast	11	27	28	28	28
Southeast	10	30	27	28	30
Central	14	50	45	48	48
West	8	14	16	13	14

Table 26 shows the number of patients on study by study week. At Week 12 about 95% of the patients on rosuvastatin 10 mg, pravastatin 20 mg or simvastatin 20mg remained on study while 89% remained on study in the rosuvastatin 5 mg group. At the end of the study, over 80% of the patients were still on study. Only 3 patients were not included in the ITT analysis due to missing data at baseline or on study.

Table 26. Study 27 ITT Patient Disposition by Week on Study

	ROSU 5	ROSU 10	PRAV 20	SIM 20
Randomized	123	116	118	120
Wk 2	121	116	117	120
Wk 6	117	114	114	120
Wk 10	113	112	113	116
Wk 12	109 (89%)	109 (94%)	112 (95%)	115 (96%)
Wk 20	109	107	109	114
Wk 28	107	104	108	110
Wk 36	105	101	105	107
Wk 44	105	100	100	105
Wk 50	102	98	97	103
Wk 52	101	98	95	102
Completers	101 (82%)	98 (84%)	95 (81%)	102 (85%)
ITT	121 (98%)	116 (100%)	117(99%)	120 (100%)

The major reason for dropout was adverse event (ADE) in all treatment groups; patient request was the second most frequent reason (Table 27).

Table 27. Study 27 Reasons for discontinuation

	ROSU 5 (n=123)	ROSU 10 (n=116)	PRAV 20 (n=118)	SIM 20 (n=120)
ADE	12 (9.8%)	10 (8.6%)	11 (9.3%)	9 (7.5%)
Pt request	4 (3.3%)	3 (2.6%)	5 (4.2%)	5 (4.2%)
Prot. Viol.	1 (0.8%)	1 (0.9%)	3 (2.5%)	3 (2.5%)
Other	3 (2.4%)	1 (0.9%)	3 (2.5%)	0 (0%)
Lost-to-FU	2 (1.6%)	3 (2.6%)	1 (0.8%)	1 (0.8%)

Baseline Demographics

The treatment groups were well-balanced regarding baseline demographics (Table 28) and medical history including CHD risk factors. The average age of patients in this study was about 58 years with about ⅓ of the patients 65 years or older. More elderly patients were seen in the pravastatin group than each of the other groups. Majority of the patients were Caucasian with fewer than 10% in each of the other racial groups.

Table 28. Study 28 Patient Demographics for All Randomized Patients

	ROSU 5 (n=123)	ROSU 10 (n=116)	PRAV 20 (n=118)	SIM 20 (n=120)
Age				
Mean (SD)	57 (10)	58 (10)	60 (11)	59 (12)
Range	30-79	34-81	28-82	19-86
%≥65years	24%	33%	40%	38%
Gender				
% female	60%	63%	58%	63%
Race				
% white	81%	84%	86%	85%
% black	11%	5%	7%	8%
% Hispanic	4%	7%	4%	3%
% Asian	3%	3%	3%	3%

Efficacy Results

Primary Endpoint LDL-C

The primary endpoint in this trial was percent change from baseline in LDL at Week 12 when all patients were still on their starting doses. The results (Table 29) are consistent with what was observed in Study 27 (Table 23); each dose of rosuvastatin was found to be superior to pravastatin and simvastatin.

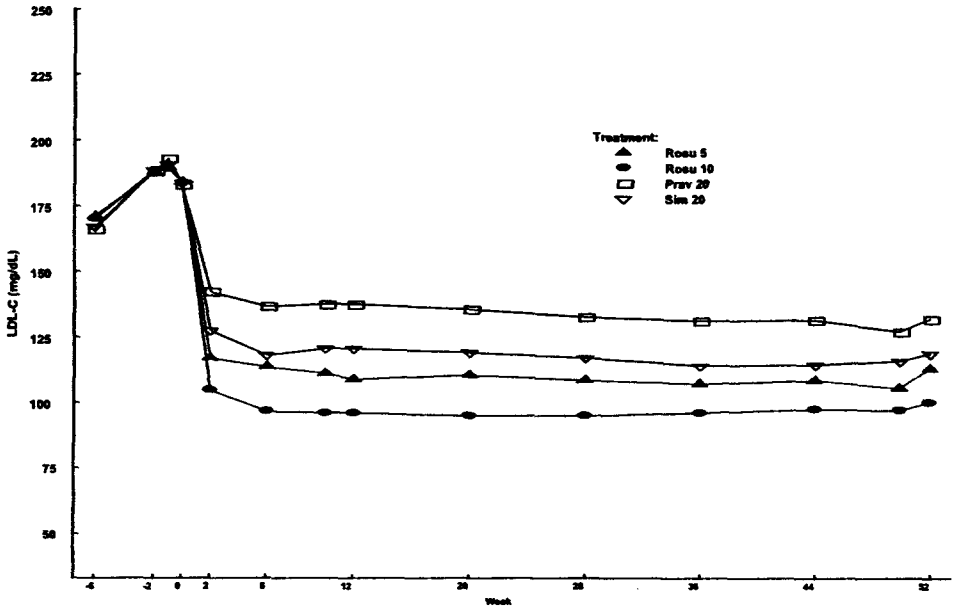
Table 29. Study 28 LDL-C Week 12 LOCF ITT Results

	ROSU 5 (n=121) Mean (SD)	ROSU 10 (n=116) Mean (SD)	PRAV 20 (n=117) Mean (SD)	SIM 20 (n=120) Mean (SD)
Baseline (mg/dL)	187 (18)	187 (21)	189 (19)	188 (19)
% Change from Baseline	-39% (14)	-47% (15)	-27% (10)	-35% (16)
Results vs. Prav 20				
p-value	.0001	.0001		
95% Confidence Interval	-16%, -8.8%	-23.8%, -16.5%		
Results vs. Sim 20				
p-value	.01	.0001		
95% Confidence Interval	-8.1%, -1%	-16.0%, -8.7%		

For the 95% confidence intervals, negative values favor rosuvastatin.

LDL was also measured from Week 12 to Week 52. During this time period the dose could be titrated to meet NCEP goals. The LDL response for the full duration of the trial (Figure 9) shows no important changes in LDL after Week 12 in any of the treatment groups (a graph of just completers looks the same).

Figure 9. LDL-C (mg/dL) by week on study for all observed case



As for Study 27, most of the response is seen after 2 weeks of treatment. Small additional decreases averaging from 1-4% between Week 2 and Week 12 were seen in all treatment groups.

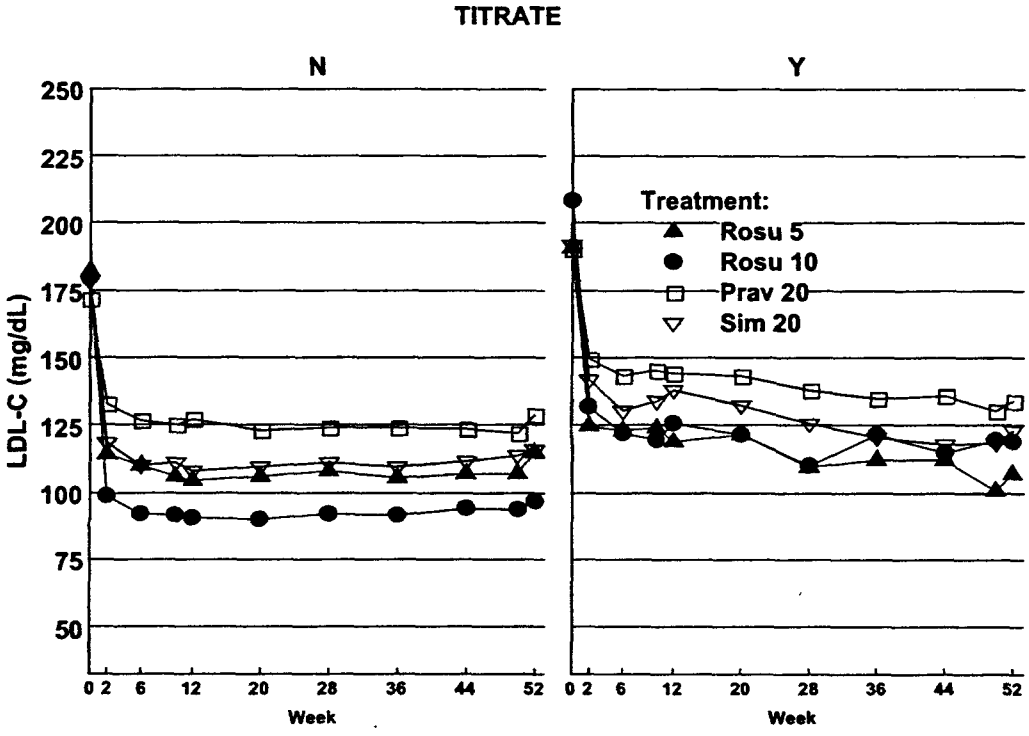
After 12 weeks of the therapy at the randomized dose, patients could be titrated to a higher dose to achieve NCEP goals. In the rosuvastatin groups, 26% of the rosuvastatin 5 mg patients and 15% of rosuvastatin 10 mg patients were titrated to a higher dose (Table 30). About 59% of pravastatin patients were titrated to 40 mg and 40% of simvastatin patients were titrated to either 40 mg or 80 mg.

Table 30. Study 28 Percentage of patients by highest dose received during the trial

Highest Dose	ROSU 5 (n=123)	ROSU 10 (n=116)	PRAV 20 (n=118)	SIM 20 (n=120)
5	74%	NA	NA	NA
10	16%	85%	NA	NA
20	5%	10%	41%	60%
40	3%	2%	59%	21%
80	2%	3%	NA	19%

From Figure 10 it can be seen that the LDL continues to decrease in patients titrated to a higher dose (right graph) while for patients maintained on the same dose, on average, the response is largely unchanged.

Figure 10. Study 28 LDL by week on study for patients remaining on the same dose throughout the trial (left graph) and for patients titrated after Week 12 (right graph)



Secondary Endpoints

The results for five secondary endpoints (selected by the medical reviewer from the 10 named by the sponsor) are shown in Table 31 below. Significantly larger decreases in TC, non-HDL, and Apo-B were seen for both doses of rosuvastatin compared to pravastatin and simvastatin. Significant TG results for rosuvastatin 10 mg compared to pravastatin and simvastatin were observed with borderline results for the 5 mg dose. Similar changes in HDL were seen for rosuvastatin 5 and the comparators; significantly greater increases were seen for rosuvastatin 10 mg. No criteria for non-inferiority were named in the protocol for secondary endpoints.

Table 31. Study 28 LDL-C Results at Week 12 LOCF (mg/dL)
Sponsor's Results

	ROSU 5 (n=120) Mean (SD[1])	ROSU 10 (n=115) Mean (SD)	PRAV 20 (n=137) Mean (SD)	SIM 20 (n=130) Mean (SD)
TC				
Baseline	276 (24)	273 (23)	274 (24)	274 (25)
% Change	-28% (1)	-33% (1)	-19% (1)	-24% (1)
Results vs. Prav 20 p-value (95% CI)	.001 (-12%, -7%)	.001 (-17%, -12%)		
Results vs. Sim 20 p-value (95% CI)	.002 (-7%, -1.5%)	.001 (-12%, -7%)		
non-HDL				
Baseline	226 (22)	223 (22)	224 (24)	223 (23)
% Change	-36% (1)	-43% (1)	-25% (1)	-31% (1)
Results vs. Prav 20 p-value (95% CI)	.0001 (-14%, -8%)	.0001 (-22%, -15%)		
Results vs. Sim 20 p-value (95% CI)	.005 (-8%, -1%)	.0001 (-15%, -9%)		
HDL				
Baseline	51 (11)	50 (11)	50 (11)	51 (11)
% Change	+8.2% (1.2)	+12% (1.2)	+8.3% (1.2)	+8.8% (1.2)
Results vs. Prav 20 p-value (95% CI)	.95 (-3%, +3%)	.03 (+0.4%, +6.8%)		
Results vs. Sim 20 p-value (95% CI)	.69 (-4%, +2.5%)	.06 (-0.1%, +6%)		
TG				
Baseline	193 (72)	180 (62)	178 (67)	176 (63)
% Change	-18% (3)	-22% (3)	-11% (3)	-10% (2.5%)
Results vs. Prav 20 p-value (95% CI)	.07 (-13%, +0.6%)	.004 (-17%, -3%)		
Results vs. Sim 20 p-value (95% CI)	.03 (-14%, -0.7%)	.001 (-18%, -5%)		
Apo-B				
Baseline	178 (20)	174 (21)	175 (21)	175 (21)
% Change	-31% (1)	-37% (1)	-20% (1)	-27% (1)
Results vs. Prav 20 p-value (95% CI)	.001 (-14%, -8%)	.001 (-20%, -14%)		
Results vs. Sim 20 p-value (95% CI)	.006 (-8%, -1%)	.001 (-14%, -7%)		

1 For the % change from baseline estimates, the least squares mean and the standard error are reported.

Reviewer's comments on Studies 27 and 28

Both the 5 mg and 10 mg doses of rosuvastatin showed significantly larger drops in LDL than the 20 mg dose of pravastatin and simvastatin in Studies 27 and 28. The magnitude of the LDL % change from baseline for both doses of rosuvastatin was consistent with what was observed in Studies 8 and 33 even though the duration of treatment was twice as long in Studies 27 and 28. In Study 28, patients were treated up to 52 weeks with no further lowering of LDL observed.

In Study 28, patients were titrated after 12 weeks of therapy to achieve NCEP goals. About 87% of the rosuvastatin patients achieved goal with 5 or 10 mg of rosuvastatin. Only 5% of the patients were titrated to the high doses of 40 or 80 mg. It appears that for most patients doses of 10 mg or less are sufficient to reach LDL goals.

The HDL results show favorable results (not always significant) for rosuvastatin 10 mg over pravastatin and simvastatin in both studies; the comparisons to rosuvastatin 5 mg were non-significant but comparable.

The TG results for rosuvastatin show no difference from pravastatin and simvastatin in Study 27 but favor rosuvastatin significantly in Study 28.

Clinical trials in patients with IIb/IV dyslipidemia

Study 35 (conducted 12/99 to 8/00)

Design

Study 35 is a double-blind, multicenter, randomized Phase III trial designed to compare multiple doses of rosuvastatin to placebo in Type IIb or IV patients. Doses of 5, 10, 20, 40 and 80 mg of rosuvastatin were studied. After a 6-week dietary run-in period, patients were randomized to treatment and followed for 6 weeks.

The primary outcome variable was percent change from baseline in triglycerides at Week 6. The sponsor measured about 25 secondary endpoints. Upon advice from the medical reviewer, the following secondary endpoints are reviewed here:

- **TC, HDL-C, ApoB, LDL-C, LDL-TG, VLDL-C, VLDL-TG**

Inclusion criteria included the following:

- 300≤TG<800 mg/dL Visits 2 (Week –2) and 3 (Week –1)
- males and females >18 years

Fasting lipids were measured at Weeks –6, -2, -1, 0, 2, 4, and 6.

Patients were to be withdrawn from the trial if CK>10xULN with pain or ALT or AST>3xULN.

Patient Disposition

A total of 156 patients completed screening and were randomized to treatment at 31 centers in the USA (Table 32).

Only 7 randomized patients did not complete the 6-week treatment period; only 2 patients are excluded from the ITT analysis due to missing data.

Table 32. Study 35 Patient Disposition by Week on Study

	Placebo	ROSU 5	ROSU 10	ROSU 20	ROSU 40	ROSU 80
Randomized	26	26	23	28	26	27
(Not treated)		(1)				
Wk 2	26	26	23	28	26	27
Wk 4	25	25	23	27	24	27
Completers	24 (92%)	25 (96%)	23 (100%)	27 (96%)	24 (92%)	26 (96%)
ITT	26 (100%)	25 (96%)	23 (100%)	27 (100%)	25 (96%)	27 (100%)

The primary reasons for trial discontinuation for the 7 dropouts were ADE and patient request.

Baseline Demographics

More than 90% of the patients were Caucasian. About 40% of the patients were female (Table 33). The average age was about 56 years (range of 28 to 82). About 20% of the patients were 65 years or older. About 59% of the patients had Type IV dyslipidemia and 41% had Type IIb.

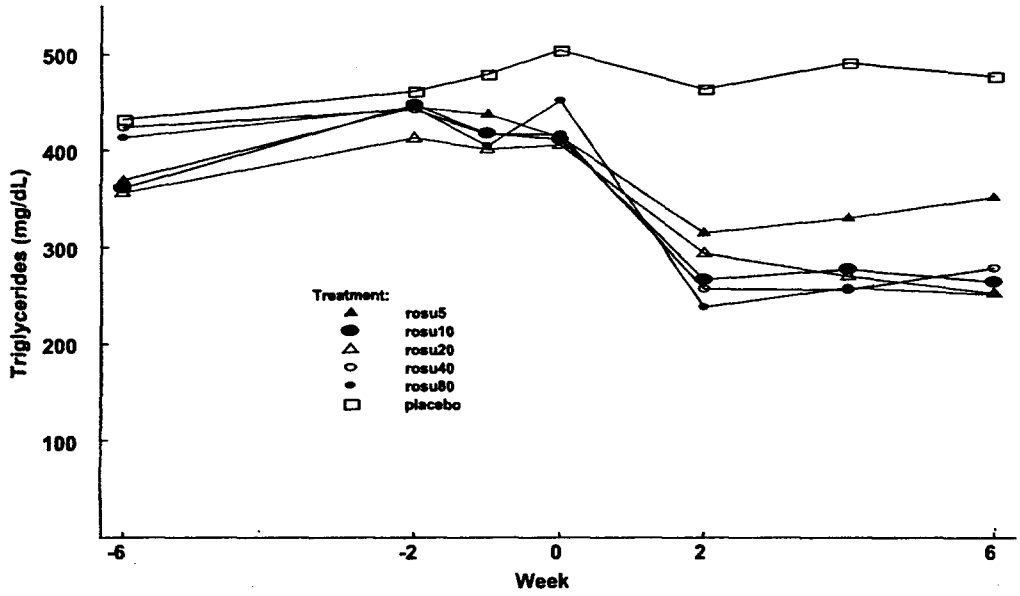
Table 33. Study 35 Patient Demographics for ITT Patients
(Extracted from sponsor's Table 11)

	Placebo (n=26)	ROSU 5 (n=26)	ROSU 10 (n=23)	ROSU 20 (n=28)	ROSU 40 (n=26)	ROSU 80 (n=27)
Age						
Mean (SD)	56 (12)	57 (10)	58 (9)	55 (10)	53 (12)	58 (11)
Range	28-74	40-74	39-73	30-72	32-82	34-76
%≥65years	27%	19%	30%	14%	15%	30%
Gender						
% female	46%	35%	35%	29%	42%	52%
Race						
% white	100%	81%	87%	96%	92%	93%

Efficacy Results

The primary efficacy variable in this trial was triglycerides at Week 6 LOCF. The data over the duration of the trial (Figure 11) illustrates the similarity of response for all rosuvastatin doses except the 5 mg dose and the difference from placebo both at baseline and endpoint. Note that since values at Weeks –2, -1 and 0 were averaged to compute baseline, the baseline difference from placebo is not as large as illustrated at Week 0. Nevertheless this reviewer performed analyses adjusting for baseline and looked at the results by subgroups defined by baseline and found that the highly significant changes for all doses held-up.

Figure 11. Study 35 Median triglycerides (mg/dL) by week on study and treatment group.



Significant decreases in triglycerides were seen for all doses compared to placebo

(Dunnett's test, p<.001). Doubling the rosuvastatin dose from 5 mg to 10 mg resulted in nearly doubling of the response. No notable differences in response were seen among the 10, 20, 40 and 80 doses for triglycerides or the secondary endpoints (Table 34), with the exception of HDL. For HDL, significantly greater responses were seen for the 20 and 40 doses compared to 10 but 80 was seen not to be different from 10; these results speak to the inconsistency of the HDL response to rosuvastatin.

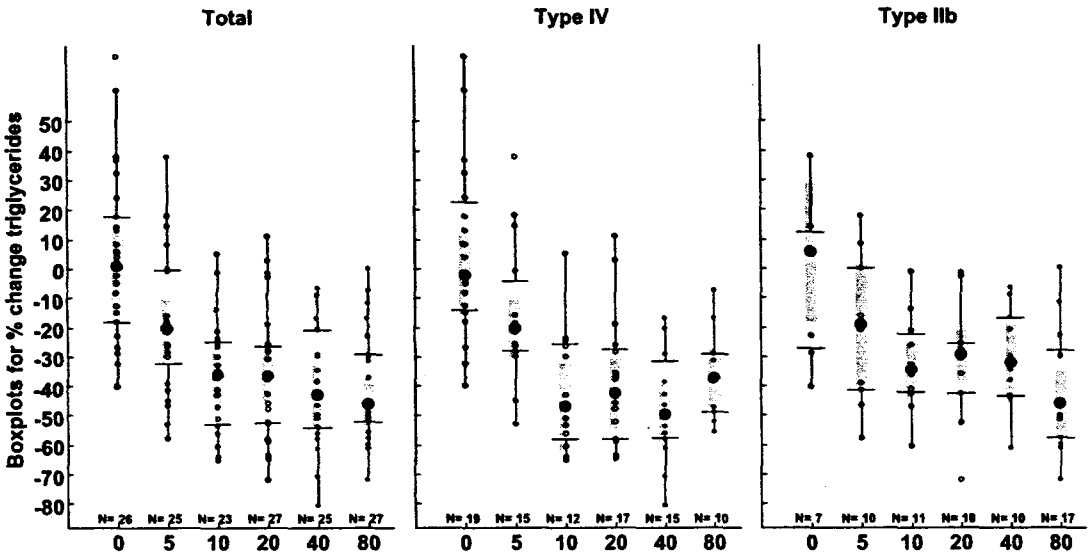
Table 34. Study 35 Mean baseline and LS Means (SE) for % change from baseline at Week 6 LOCF (Extracted from several of the sponsor's tables in the study report.)

	Placebo	5	10	20	40	80
TRIG						
Baseline	511 (138)	462 (104)	447 (96)	446 (119)	471 (142)	448 (138)
% change						
LS Mean	+3% (4)	-21% (6)	-40% (6)	-40% (6)	-43% (6)	-40% (4)
Median	+1%	-21%	-37%	-37%	-43%	-46%
TC						
Baseline	256 (61)	244 (51)	258 (49)	251 (54)	248 (75)	272 (76)
% change	+3% (2)	-23% (2)	-38% (2)	-34% (2)	-38% (2)	-42% (2)
LDL-C						
Baseline	115 (51)	114 (41)	126 (37)	119 (51)	125 (76)	139 (49)
% change	+6% (4)	-28% (4)	-40% (4)	-34% (4)	-39% (4)	-45% (4)
Type IIb	+10%	-34%	-50%	-47%	-40%	-53%
Type IV	+6%	-25%	-32%	-25%	-39%	-38%
HDL-C						
Baseline	35 (7)	36 (9)	38 (6)	34 (7)	35 (7)	36 (9)
% change	-2% (2)	+4% (3)	+6% (3)	+18% (2)	+15% (2)	+10% (2)
APO-B						
Baseline	163 (49)	152 (36)	155 (30)	151 (43)	158 (56)	166 (44)
% change	+2% (3)	-21% (3)	-36% (3)	-33% (3)	-37% (3)	-44% (3)
VLDL-C						
Baseline	114 (44)	100 (49)	93 (29)	111 (42)	98 (36)	99 (61)
% change	+6% (5)	-23% (5)	-45% (5)	-47% (5)	-52% (5)	-54 (5)
LDL-TG						
Baseline	76 (43)	80 (27)	66 (35)	66 (32)	72 (31)	76 (38)
% change	+24% (14)	-6% (15)	-15% (15)	-5% (14)	-11% (14)	-17% (14)
VLDL-TG						
Baseline	420 (220)	358 (167)	305 (111)	378 (210)	388 (271)	330 (160)
% change	+6% (7)	-11% (8)	-35% (8)	-40% (7)	-43% (7)	-49% (7)

The results for LDL were computed by this reviewer.

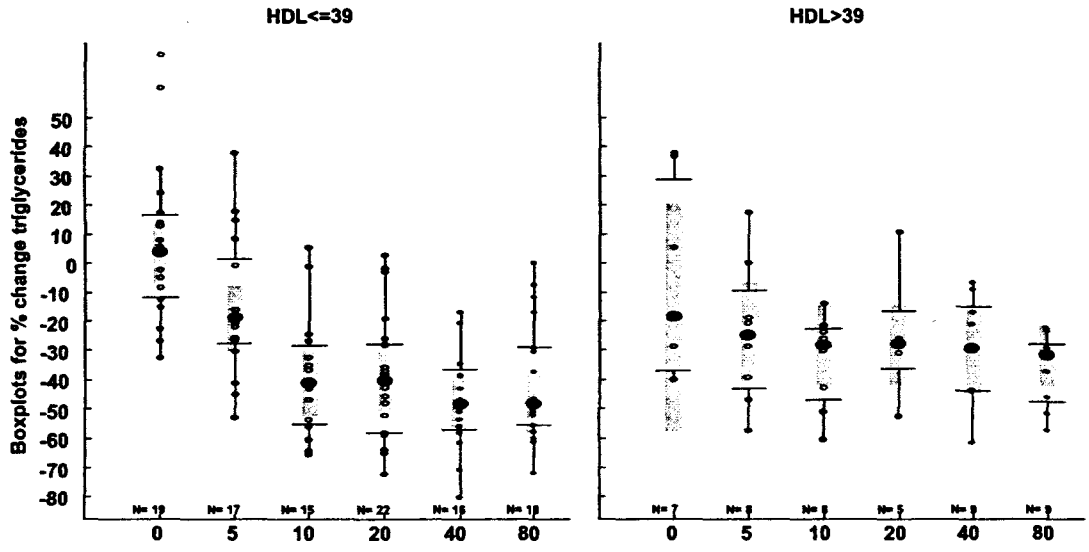
The boxplots in Figure 12 illustrate the lack of a dose response relationship for triglycerides for the overall population and for Type IV and IIb patients separately for the higher doses.

Figure 12. Study 35 Boxplots of % change from baseline for triglycerides at Week 6 LOCF for all patients and by dyslipidemia type



About 2/3 of the patients had HDL<40 at baseline; this is an important subset that could benefit from lowering of triglycerides. Figure 13 shows that patients with low HDL at baseline do show a greater benefit from treatment than patients with HDL's of 40 or greater.

Figure 13. Study 35 Boxplots of % change from baseline for triglycerides at Week 6 LOCF by baseline HDL



Reviewer's comments on Study 35

Overall Study 35 showed that rosuvastatin significantly lowered triglycerides in Type IV and IIb patients with the effect strongest in patients with HDL under 40 at baseline (about 2/3 of the patients in this study). A dose of 10 mg was significantly more effective than 5 mg but no significant benefit was seen by increasing the dose above 10 mg in this population.

Study 29 (conducted 10/99 to 10/00)

Design

Study 29 was a 24-week, randomized, open-label, multicenter trial designed to compare rosuvastatin 40 mg to extended-release niacin 2 g and to the combination rosuvastatin 40 mg with extended-release niacin 1 g and the combination of rosuvastatin 10 mg plus extended-release niacin 2 g in patients with Type IIb or IV dyslipidemia.

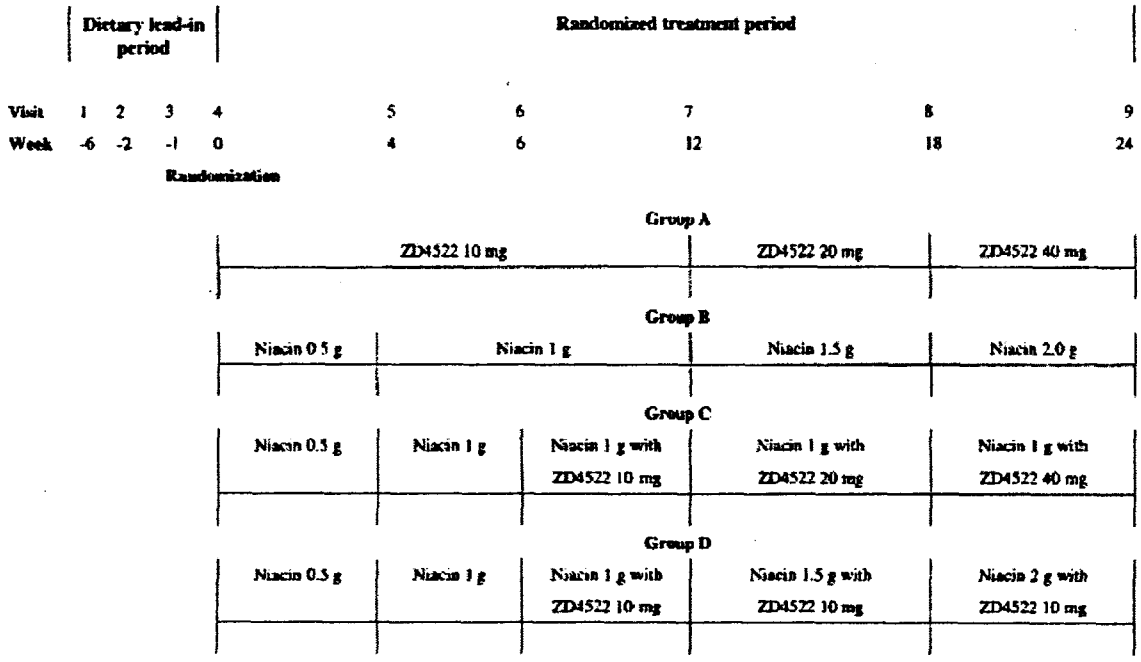
Patients were randomized to one of four treatment groups shown in the schematic (Figure 14) in a 2:3:3:3 ratio;

- Group A (ROSU) is rosuvastatin titrated from 10 mg → 20 mg → 40 mg;
- Group B (NIAC) is niacin titrated from 0.5 g → 1 g → 1.5 g →2 g;
- Group C (R40+N1) is a combination of niacin titrated from 0.5 g → 1 g and rosuvastatin titrated from 10 mg → 20 mg → 40 mg
- Group D (R10+N2) is a combination of niacin titrated from 0.5 g → 1 g → 1.5 g → 2 g and rosuvastatin 10 mg.

Both rosuvastatin and niacin were force titrated during this 24-week trial. For all groups, the titration was complete by Week 18.

Figure 14. Sponsor's schematic of the design of Study 29

Figure 1 Trial design



The inclusion criteria included the following:

- Men or women aged ≥18 years with Fredrickson type IIb or IV hyperlipidemia
- Fasting TC ≥200 mg/dL
- Fasting 200 ≤TG <800 mg/dL
- Fasting HDL-C <45 mg/dL
- ApoB ≥110 mg/dL

Though high LDL was not an entry criteria, LDL was chosen as the primary end point. The sponsor's rationale for using LDL as the primary endpoint in this trial was that patients satisfying the entry criteria are at risk for CHD and the principal approach to reducing coronary risk with lipid-altering therapies in these patients is to reduce LDL-C levels.

Patient Disposition

A total of 270 patients (Table 35) were randomized at 39 centers in USA (centers were divided into 4 regions for analysis purposes) with about 42% of patients from central USA. The completion rates show a significantly greater completion rate in the rosuvastatin group than in the niacin treated group. Note that most dropouts occur after Week 6.

Table 35. Study 29 Patient Disposition

	ROSU	NIACIN	R40+N1	R10+N2
Randomized	46 (100%)	72 (100%)	72 (100%)	80 (100%)
Week 4	46 (100%)	72 (100%)	72 (100%)	79 (99%)
Week 6	45 (98%)	66 (92%)	68 (94%)	70 (88%)
Week 12	44 (96%)	62 (86%)	62 (86%)	66 (83%)
Week 18	43 (93%)	59 (82%)	60 (83%)	63 (79%)
Week 24	43 (93%)	53 (74%)	60 (83%)	60 (75%)

The primary reason for dropout in the niacin groups was ADE with patient request as the second most frequent reason (Table 36a). Flushing was the most common ADE.

Table 36a. Study 29 Reasons for discontinuation

	ROSU (n=46)	NIACIN (n=72)	R40+N1 (n=72)	R10+N2 (n=80)
ADE	1 (2%)	10 (14%)	7 (10%)	13 (16%)
Pt request	2 (4%)	8 (8%)	5 (7%)	5 (6%)
Prot. Viol.	0	1 (1%)	0	1 (1%)
Other	0	0	0	0
Lost-to-FU	0	2 (3%)	0	1 (1%)

The average age of patients was about 56 years with about 1/5 of the patients 65 or older (Table 36b). Less than 1/3 of the patients were female. About 95% of the patients were Caucasian.

Table 36b. Study 29 Baseline demographics

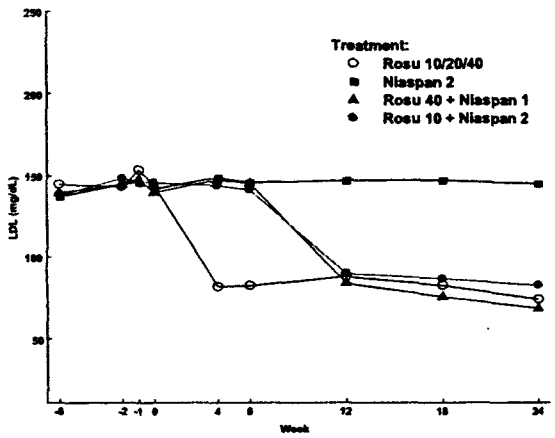
	ROSU (n=46)	NIACIN (n=72)	R40+N1 (n=72)	R10+N2 (n=80)
Age				
Mean (SD)	59 (11)	56 (10)	56 (11)	54 (12)
Range	32-84	28-73	26-78	26-77
%≥65years	26%	15%	22%	18%
Gender				
% female	30%	28%	24%	31%
Race				
% white	91%	99%	96%	96%

Efficacy Results

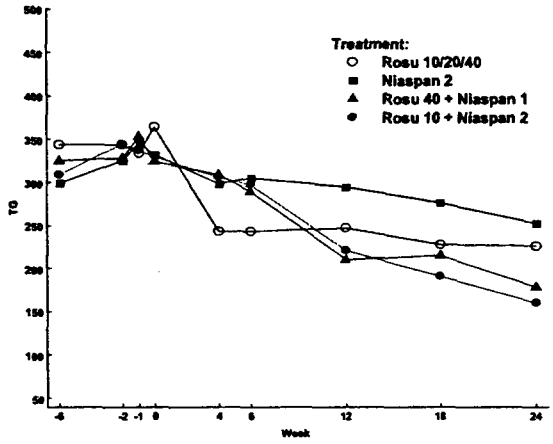
Though it is not explicitly stated as an objective, it appears from the sponsor's introduction that the objective is to see if combination therapy of niacin with rosuvastatin is effective in modifying lipids in Type IIb and IV patients, a population the sponsor characterizes as "difficult-to-treat". It would seem then that one would test the combination therapy against each component to see if each component contributes significantly to the combination therapy. However, from the sponsor's planned comparisons and from the sponsor's efficacy conclusions, it appears the sponsor's real objective was to show that rosuvastatin at 40 mg is sufficient to treat LDL, TG and HDL; i.e. that niacin did not add significantly to the effect of rosuvastatin alone. Regardless of the objective, the appropriate comparisons to the combination should be made in order to draw any conclusions regarding the efficacy of the combination therapy. So the combination should be compared to each component. For the combination studied here, one expects the statin to be more effective in lowering LDL and the niacin more effective in increasing HDL and lowering TG. So to see if niacin adds significantly to the effect of rosuvastatin, one should compare the combination to a like dose of rosuvastatin. Note that the contribution of rosuvastatin is very clear just from the LDL figure on the following page; a highly significant drop in LDL is seen in the rosuvastatin alone arm and the combination arms when rosuvastatin is added, essentially no change is seen in the niacin alone arm. Since the contribution of rosuvastatin is clear, the focus here is on whether the addition of niacin can improve efficacy for HDL or TG.

Figure 15. Study 37 Lipid responses over time by treatment group

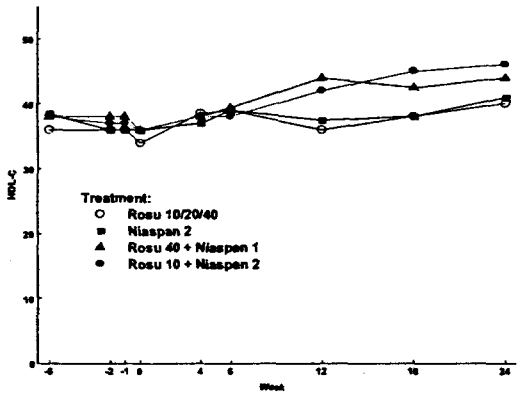
LDL



Median TG



HDL



Dosing by Week

Week	4	6	12	18	24
Rosu	10	10	10	20	40
Niaspan	0.5	1	1	1.5	2
Rosu 40+ Niaspan 1	R 0 N 0.5	R 0 N 1	R 10 N 1	R 20 N 1	R 40 N 1
Rosu 10+ Niaspan 2	R 0 N 0.5	R 0 N 1	R 10 N 1	R 10 N 1.5	R 10 N 2

The plots of HDL and TG (Figure 15 above) suggest that the combination of rosuvastatin and niaspan is beneficial in raising HDL and lowering TG compared to either component alone; this is examined further with statistical analyses on the following page.

Given the sponsor's design, we can only investigate the contribution of the 1 g dose of niacin. The results for the appropriate comparisons are given below (Table 37). The addition of niacin does not significantly improve LDL or TG lowering over rosuvastatin alone. The addition of 1 g of niacin to 10 mg of rosuvastatin increases HDL raising by about 7% (p=.005); adding 1 g to 20 or 40 mg of rosuvastatin shows results trending in favor of the combination but non-significant.

Table 37. Study 29 LS Means for LDL, TG and HDL % change from baseline

	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%

Negative values favor the combination for LDL and TG; positive values favor the combination for HDL.

Though no direct comparisons of the combination of rosuvastatin 10 mg plus niacin 2 g can be made due to the design limitations, the results for HDL strongly suggest that the addition of 2 g of niacin to rosuvastatin notably increases HDL (combination 10+2 at Week 24: HDL change of +25% and rosuvastatin 10 mg at Week 12: HDL change of +10%).

The sponsor's results for the secondary endpoints at Week 24 are presented in Appendix 4 of this review.

Reviewer's comments on Study 29

The results of Study 29 showed that the addition of niacin 1 g to rosuvastatin 10 mg significantly increases HDL. Due to the fact that changes in HDL for rosuvastatin are not dose related (see Studies 8 and 33), the results of this study suggest that the addition of niacin to raise HDL is more beneficial than increasing the dose of rosuvastatin.

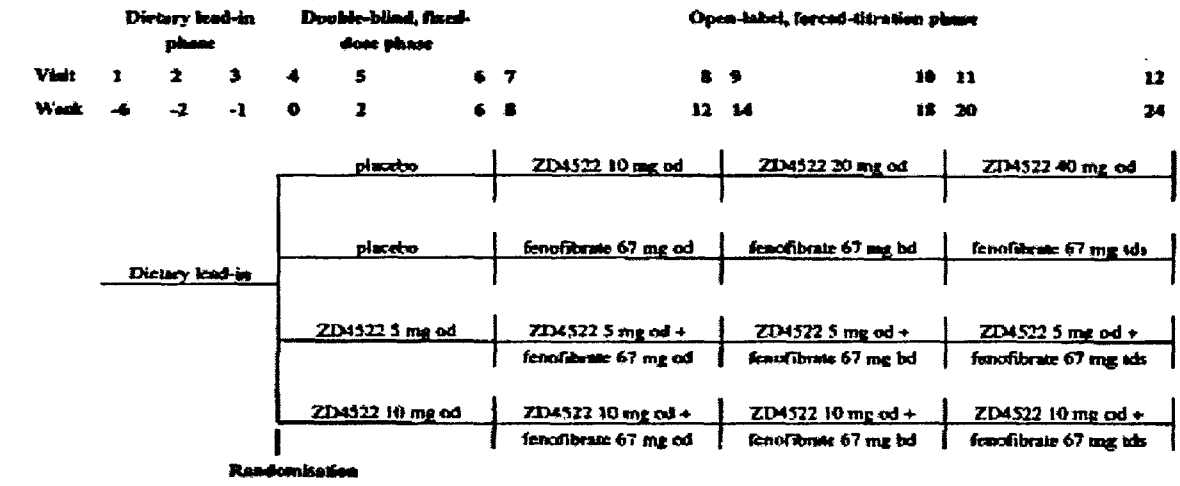
The primary efficacy variable in Study 29 was LDL though it seems to this reviewer that the results of this endpoint are not of paramount interest. Clearly a potent statin drug such as rosuvastatin will easily be superior to niacin alone and so the contribution of rosuvastatin to the combination is quite evident.

Study 36 (conducted 9/99 to 10/00)

Design

Study 36 is a randomized, multicenter, 24-week trial in patients with Type IIb or Type IV hyperlipidemia associated with Type 2 diabetes. After a dietary lead-in phase, patients were randomized to either placebo/rosuvastatin, placebo/fenofibrate, rosuvastatin 5 mg or rosuvastatin 10 mg and treated double-blind for 6 weeks (Figure 16). At Week 6, patients entered the open-label forced-titration phase of the study. During this 18-week phase, patients received additional treatment and were titrated as shown in the design schematic below.

Figure 16. Sponsor's schematic of the trial design for Study 36



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

The primary outcome variable was percent change from baseline in triglycerides at Week 24. Two primary comparisons were named; rosuvastatin 10/20/40 versus fenofibrate and rosuvastatin 10/20/40 versus rosuvastatin 10 mg + fenofibrate. The comparison of rosuvastatin versus rosuvastatin 5 mg + fenofibrate was considered a secondary comparison.

The primary comparisons named by the sponsor do not address the efficacy of the combination therapy. To assess the contribution of rosuvastatin to the combination, one should compare the combination therapies to fenofibrate alone; given the design, this can be done at Weeks 12, 18 and 24. To assess the contribution of fenofibrate to the combination, one should compare the combination therapies to rosuvastatin 5 mg or 10 mg alone (not 40 mg) which cannot be done given the trial's design. Nevertheless, if it can be assumed that if the combination beats rosuvastatin 40 mg, it will also beat rosuvastatin at lower doses, then the comparison to 40 mg will provide information on the contribution of fenofibrate.

Inclusion criteria included the following:

- 300≤TG<800 mg/dL Visits 2 (Week –2) and 3 (Week –1)
- TC>200 mg/dL
- Glycated hemoglobin<10% at Visit 1
- males and females >18 years
- patients with Type IIb or IV hyperlipidemia and Type 2 diabetes mellitus

Patient Disposition

A total of 219 patients completed screening and were randomized to treatment (Table 38) at 47 centers in Europe (United Kingdom, Germany, Ireland, Finland, and France).

Three patients are excluded from the ITT analysis due to missing data. The completion rates varied across treatment groups from a low of 81% in the rosuvastatin 40 mg group to a high of 94% in the fenofibrate group.

Table 38. Study 36 Patient Disposition by Week on Study

	Rosu 40	Feno	Rosu 5+Feno	Rosu 10 +Feno
Randomized	53	49	60	54
Week 6	50 (94%)	49 (100%)	60 (100%)	53 (98%)
Week 12	49 (92%)	47 (96%)	53 (88%)	52 (96%)
Week 18	44 (83%)	47 (96%)	52 (87%)	50 (93%)
Week 24	43 (81%)	46 (94%)	51 (85%)	49 (91%)
ITT	51 (96%)	49 (100%)	60 (100%)	53 (98%)

The primary reasons for trial discontinuation were ADE's (Table 39).

Table 39. Study 36 Reasons for discontinuation

	Rosu 40 n=53	Feno n=49	Rosu 5+Feno n=60	Rosu 10 +Feno n=54
ADE	6%	2%	7%	2%
Patient request	4%	1%	1%	3%
Prot. Viol.	2%	1%	0	4%
Lost-to-FU	2%	0	0	0
Other	5%	0	7%	0

Baseline Demographics

More than 94% of the patients were Caucasian. About half of the patients were female (Table 40). The average age was about 59 years (range of 26 to 79). About 10% more patients were 65 years or older in the rosu 40 group and rosu10+feno group than in the other two groups. About 69% of the patients had Type IIb dyslipidemia and 31% had Type IV; a similar ratio was seen in each treatment group.

Table 40. Study 36 Patient Demographics for ITT Patients (Extracted from sponsor's Table 12)

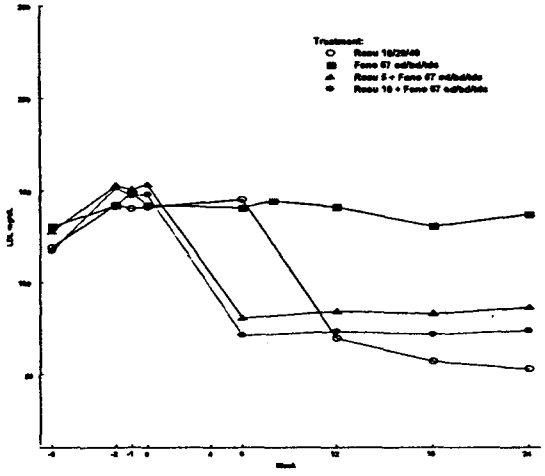
	Rosu 40 n=53	Feno n=49	Rosu 5+Feno n=60	Rosu 10 +Feno n=54
Age				
Mean (SD)	61 (10)	58 (9)	59 (9)	60 (10)
Range	26-75	35-76	35-79	39-78
%≥65years	43%	29%	28%	39%
Gender				
% female	49%	41%	53%	52%
Race				
% white	94%	94%	98%	100%

Efficacy Results

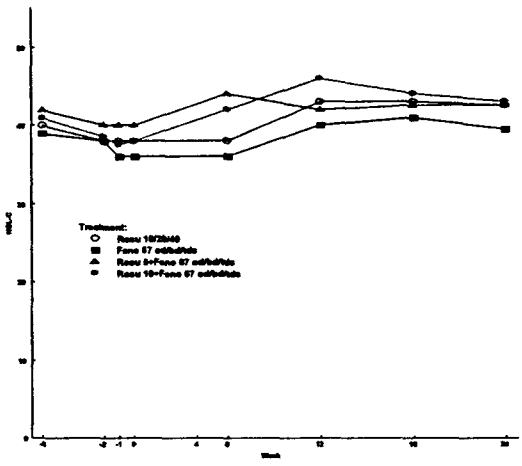
The results for the three variables examined here are shown graphically in Figure 17.

Figure 17. Study 36 Lipid results by treatment group and week on study

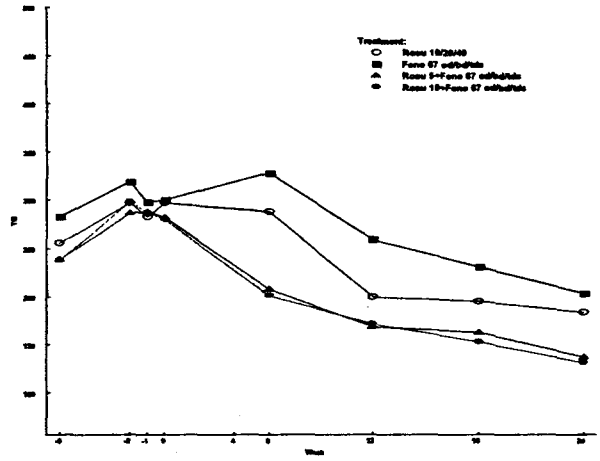
LDL



HDL



TG



Dosing by Week

Week	6	12	18	24
Rosu	placebo	10	20	40
Feno	placebo	67 od	67 bid	67 tds
Rosu 5+ Feno	R 5	R 5 F 67 od	R 5 F 67 bid	R 5 F 67 tds
Rosu 10+ Feno	R 10	R 10 F 67 od	R 10 F 67 bid	R 10 F 67 tds

It is clear from the graphs that adding rosuvastatin to fenofibrate significantly improves the LDL lowering over fenofibrate alone. Also the HDL graph shows that increasing either the rosuvastatin dose or the fenofibrate dose alone or in combination does not result in further notable increases in HDL. Two questions need to be addressed with analyses:

1. Does adding fenofibrate to rosuvastatin significantly decrease triglycerides compared to rosuvastatin alone?
2. Does the combination of rosuvastatin and fenofibrate significantly increase HDL compared to either fenofibrate alone or rosuvastatin alone at any of the dose combinations?

The efficacy results at Weeks 12, 18 and 24 are summarized in Table 41 and support the comments in the preceding paragraph.

Table 41. Study 36 Efficacy Results
Sponsor's LS Means

	Combination Rosu+Feno	Combination Rosu+Feno	Fenofibrate	Rosuvastatin
Week 12	10 mg + 67 od (n=52)	5 mg + 67 od (n=53)	67 mg od (n=47)	10 mg (n=45)
LDL	-47%	-38%	0%	-45%
TG	-42%	-32%	-20%	-33%
HDL	+13%	+7%	+6%	+10%
Week 18	10 mg + 67 bd (n=70)	5 mg + 67 bd (n=52)	67 mg bd (n=47)	20 mg (n=44)
LDL	-42%	-36%	0%	-49%
TG	-46%	-34%	-32%	-35%
HDL	+15%	+7%	+8%	+11%
Week 24 LOCF	10 mg + 67 tds (n=53)	5 mg + 67 tds (n=60)	67 mg tds (n=49)	40 mg (n=51)
LDL	-42%	-34%	+1%	-47%
TG	-47%	-41%	-34%	-30%
HDL	+12%	+11%	+9%	+6%

From other studies we have seen no clear rosuvastatin dose response for HDL and TG. If we assume then that the responses for 10, 20 and 40 are similar, we can assess the contribution of the different dose levels of fenofibrate to rosuvastatin at Week 18 and 24 by comparing the 10 mg combinations to 20 or 40 rosuvastatin alone.

Table 42 Results of Analyses of TG and HDL by week and comparison

	Combo vs. Rosu	Combo vs. Feno
Week 12	10 mg + 67 od vs. 10 mg	10 mg + 67 od vs. 67 od
TG	.05*	<.001*
HDL	.17	.008*
Week 18	10 mg + 67 bd vs. 20 mg	10 mg + 67 bd vs. 67 bd
TG	.06*	.006*
HDL	.10	.005*
Week 24[1]	10 mg + 67 tds vs. 40 mg	10 mg + 67 tds vs. 67 tds
TG	.002*	.002*
HDL	.06*	.28

* indicates the results favor the combination

1 At Week 24, both LOCF and observed cases analyses yielded essentially the same analyses.

The results in Table 42 and the graphs show that adding rosuvastatin to fenofibrate significantly improves both the TG and HDL responses in addition to the LDL response, with the exception of HDL at Week 24. In question then is the contribution of fenofibrate to the combination. Clearly for LDL, fenofibrate makes no contribution. For TG and HDL (column 2 of Table 42), the improvements in response due to the addition of fenofibrate 67 mg once or twice a day are marginal; three times a day dosing though appears to add significantly to the rosuvastatin effect on TG.

The sponsor's results for secondary endpoints is presented in Appendix 5 of this review.

Reviewer's comments on Study 36

The results of Study 36 suggest that the combination of a high dose (67 mg tds) of fenofibrate with rosuvastatin can offer additional TG lowering above that achieved by increasing the dose of rosuvastatin alone.

APPEARS THIS WAY
ON ORIGINAL

Clinical trials in patients with other dyslipidemias

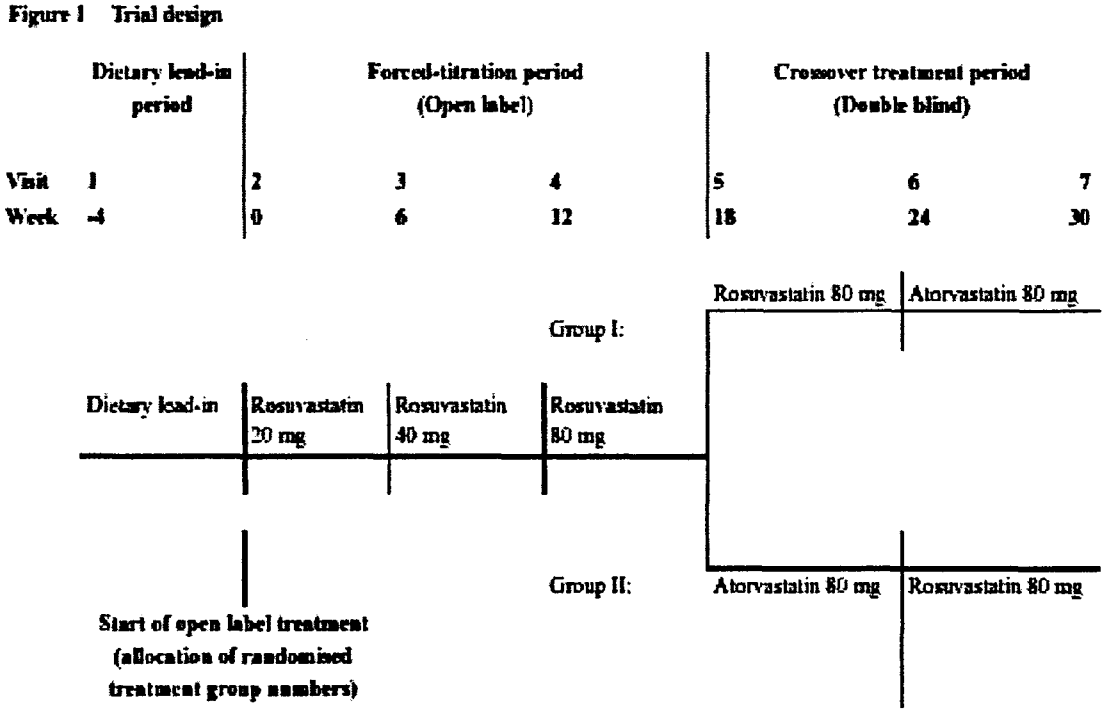
Study 54 (conducted 4/00 to 2/01)

Study 54 was a randomized, multicenter trial designed to assess the efficacy of rosuvastatin to reduce LDL-C in subjects with homozygous familial hypercholesterolaemia. During an 18-week open label phase, all patients were initially treated with 20 mg of rosuvastatin for 6 weeks (Figure 18) . The rosuvastatin dose was increased to 40 mg at Week 6 and to 80 mg at Week 12. The primary objective of the trial was to assess efficacy at Week 18.

At Week 18, patients entered the crossover phase of the trial (Figure 18). During the 12-week crossover phase, patients were treated with 80 mg of atorvastatin and 80 mg of rosuvastatin. The comparison of atorvastatin to rosuvastatin was considered a secondary objective.

At the time of the submission of this NDA, only the results through Week 18 were included in the study report. An amendment to the NDA was submitted on 10/22/01 that included the results from the crossover period and the updated study report.

Figure 18. Study 54 Sponsor's schematic of the trial design



The inclusion criteria included the following;

- Man or woman aged ≥10 years and weighing >32 kg known to have homozygous familial hypercholesterolaemia, based on clinical, genetic, or functional criteria
- Fasting LDL-C levels >500 mg/dL
- Fasting TG levels <600 mg/dL

Patients with regular apheresis were permitted to enter the trial, but all data collected within 7 days after apheresis were excluded from the analyses.

Patient Disposition

Patients were recruited at 4 centers; two in South Africa (36 patients) and two in the USA (10 patients). A total of 44 patients were treated in the forced-titration period; 2 of those patients did not have on-treatment data. Six patients withdrew before the crossover segment of the trial; the primary reason for withdrawal was protocol non-compliance (no patients withdrew due to an ADE). Thirty-eight (38) patients entered and completed the crossover period. The data presented here is for those 38 patients.

Baseline Demographics

The average age of patients in Study 35 was 28 years (range of 8 to 63); 6 patients were 18 or younger. About 42% of the patients were female. The majority of the patients were Caucasian. The randomized groups were well-balanced on demographics variables (Table 43).

Table 43. Study 54 Patient Demographics for ITT Patients (Extracted from sponsor's Table 11)

	Rosu 80/Ator 80 (n=19)	Ator 80/Rosu 80 (n=19)
Age		
Mean (SD)	26 (12)	30 (8)
Median	25	32
Range	8-63	15-45
Gender		
% female	37%	47%
Race		
% white	79%	79%
Regular Apheresis	11%	16%
Receptor Negative	26%	5%

More than 75% of the patients had genetically confirmed familial hypercholesterolemia. Five patients received apheresis regularly during the trial and are included in the database. Six patients who completed the study were receptor negative.

Efficacy Results

For this trial, values at Week 0 were used as baseline [note this is unlike the rest of the studies in this submission where 3 pre-randomization values were averaged to compute baseline). No analyses were planned of the open-label data; the crossover data was analyzed by the sponsor using a mixed effects model with terms for subject (random effect), period,

treatment, center, and.center-by-treatment interaction.

The data from the force-titration open-label phase showed a mean decrease of about 20% in LDL (Table 44). (See Appendix 6 and Appendix 7 for the individual patient data.)

Table 44. Study 54 LDL % change from baseline by dose during the forced titration phase

	LDL % change from baseline Mean (SD) / Median n=38
Baseline LDL	521 (115) / 516
Rosu 20 mg (Wk 6)	-20% (17) / -22%
Rosu 40 mg (Wk 12)	-24% (17) / -22%
Rosu 80 mg (Wk 18)	-22% (21) / -23%

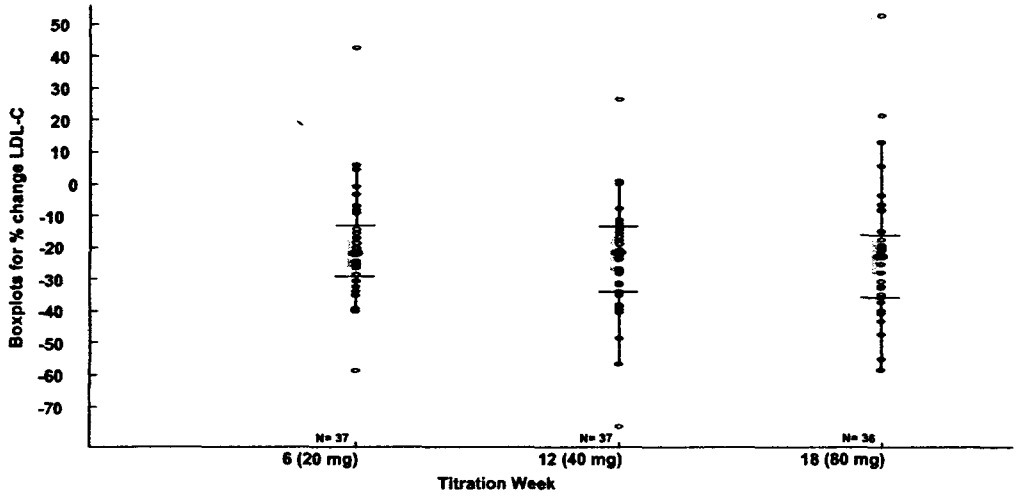
The means and medians suggest minimal benefit from titrating the dose. This reviewer, though, examined this data further to ascertain how many of these high risk patients might benefit from the 40 and 80 mg doses. A paired comparison of 20 to 40 (Table 45) shows a median 2% further decrease in LDL (p=.01, Wilcoxon signed rank test) with about 35% of the patients showing an additional decrease greater than 6%. So about 1/3 of the patients appear to benefit significantly from increasing the dose from 20 to 40 mg. A paired comparison of 40 to 80 (Table 45) shows again a further median decrease of 2% in LDL, though the decrease was not consistently seen and was not statistically significant (p=.70, Wilcoxon signed rank test).

Table 45. Study 54 Distribution of paired differences
Negative values favor the larger dose

	Mean (SD) Median	% of patients with >6% additional decrease	% of patients with 3-6% additional decrease	% of patients with >0 to <3% additional decrease	% of patients with no additional decrease
40 - 20	-3.9% (9) -2.3%	35%	10%	20%	35%
80 - 40	+2.0% (18) -2.4%	19%	28%	11%	42%

Boxplots (Figure 19) of the open-label data illustrates the similarity of response for the three doses and the increased response for a few patients at 40 mg and 80 mg.

Figure 19 Boxplots of LDL-C % change from baseline



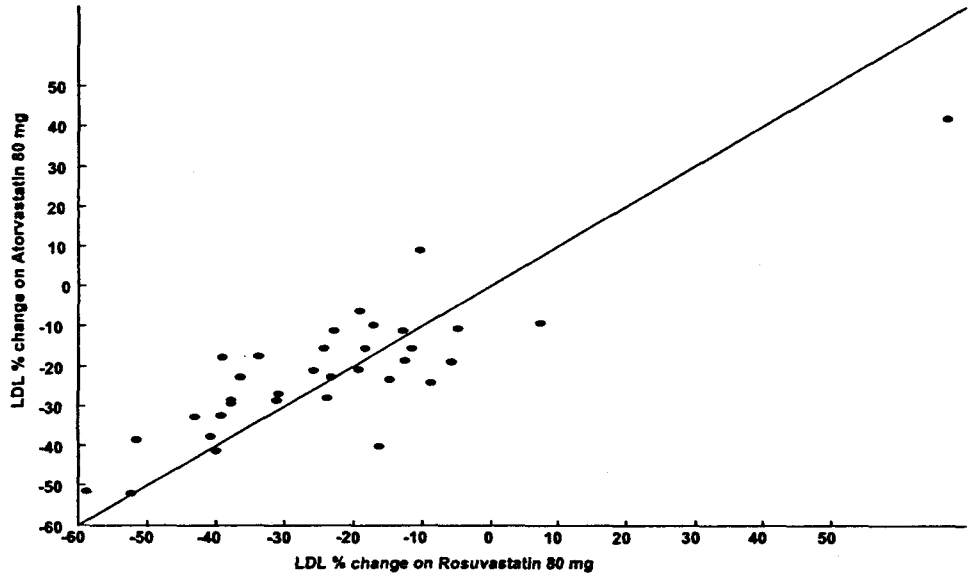
All 36 patients who entered the crossover phase completed both treatment periods. The mean decease on rosuvastatin was about 25% and the mean decrease on atorvastatin was about 22% (Table 46). The mean paired difference of about 3% was not statistically significant (p=.10, Wilcoxon signed rank test).

Table 46. Study 54 LDL % change from baseline during the crossover phase

	LDL % change from baseline Mean (SD) / Median n=36
Crossover (6 wk each period)	
Rosu 80 mg	-25% (23) / -24%
Ator 80 mg	-22% (17) / -22%

A plot of atorvastatin 80 mg versus rosuvastatin 80 mg (Figure 20) illustrates there are more patients with a greater rosuvastatin response than atorvastatin response (points above the identity line).

Figure 20. Study 54 LDL% change for rosuvastatin 80 mg versus atorvastatin 80 mg after 6 weeks of treatment



Reviewer's comments on Study 54

The similar mean LDL decreases (~22%) for the 20, 40 and 80 doses of rosuvastatin suggest no additional benefit from titrating up the dose (see Table 44), however, further analyses by this reviewer suggests that ~20-30% of patients benefited significantly (6% or greater further decrease) from increasing the dose.

A comparison of rosuvastatin 80 mg to atorvastatin 80 mg showed no significant difference (p=.10) though the results favor rosuvastatin.

Study 30 (conducted 7/99 to 6/00)

Study 30 is a multicenter trial designed to compare the efficacy of rosuvastatin (titrated to 80 mg) with that of atorvastatin (titrated to 80 mg) in reducing LDL-C in subjects with heterozygous familial hypercholesterolemia after 18 weeks of treatment. In a 3:1 ratio patients were randomized to rosuvastatin or atorvastatin; the objective was to obtain additional safety data for rosuvastatin 80.mg.

After a 6 week diet lead-in, patients were force-titrated at 6-week intervals from 20 mg to 40 mg and to 80 mg in each treatment group.

The inclusion criteria included the following:

- Men and women ≥18 years known to have heterozygous FH, based on clinical or genetic criteria
- 500<LDL-C≤220 mg/dL (mean of Visits 2 and 3)
- TG levels ≤400 mg/dL

The primary endpoint was % change from baseline for LDL-C at Week 18 LOCF.

Patient Disposition

Study 30 was a multinational study with patients recruited at a total of 57 centers in 15 countries; USA (15 centers), Australia (6) South Africa (3) Israel (1) Europe (10 countries, 28 centers) and Canada (4). Three large sites [Canada (49 pts) 1 USA (63) and 1 Norway (56)] had about ¼ of the patients; the rest of the sites enrolled 1-34 patients with most less than 15.

A total of 436 patients were randomized to rosuvastatin and 187 to atorvastatin (Table 47); only one rosuvastatin patient was not included in the ITT population for analysis. About 97% completed the study; the primary reason for dropout in both groups was ADE.

Table 47. Study 30 Patients on study by week

	Rosuvastatin	Atorvastatin
Week 0	436 (100%)	187 (100%)
Week 6	435 (99%)	187 (100%)
Week 12	429 (98%)	185 (99%)
Week 18	421 (97%)	183 (98%)
ITT	435 (99%)	187 (100%)

Baseline Demographics

Patients ranged in age from 19 to 79 with a mean of 47 years (Table 48). The majority of the patients were Caucasian (95%) and male (~55%).

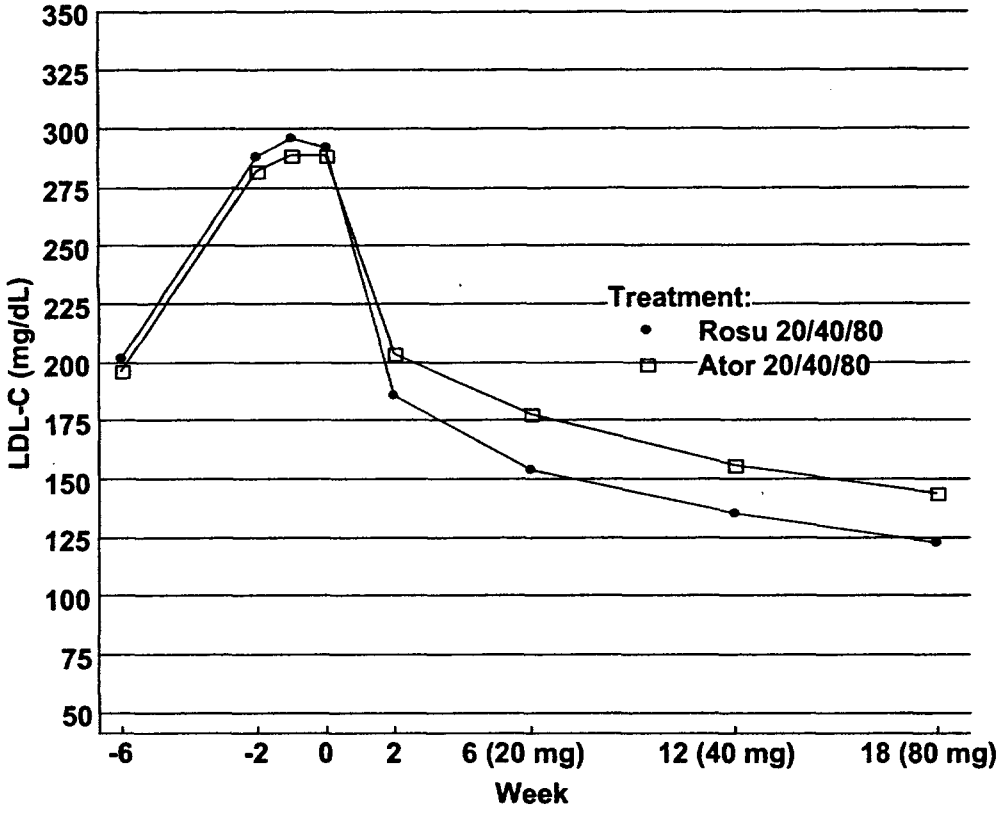
Table 48. Study 30 Patient Demographics for ITT Patients
(Extracted from sponsor's Table 12)

	Rosu 20/40/80 (n=436)	Ator 20/40/80 (n=187)
Age Mean (SD) Range ≥65	 48 (14) 19-79 14%	 47 (13) 20-78 9%
Gender % female	 46%	 43%
Race % white	 96%	 94%

Efficacy Results

The LDL results over time show essentially no difference between the treatments at baseline. Differences between the treatment groups are seen as early as Week 2 and remain through titration to Week 18 (Figure 21).

Figure 21 Study 30 LDL (mg/dL) by week and treatment group



Treatment comparisons at Week 6, 12, 18 and 18 LOCF show statistically significant effects for rosuvastatin over atorvastatin (p<.0001, ANOVA) with differences from 7-9% (Table 49).

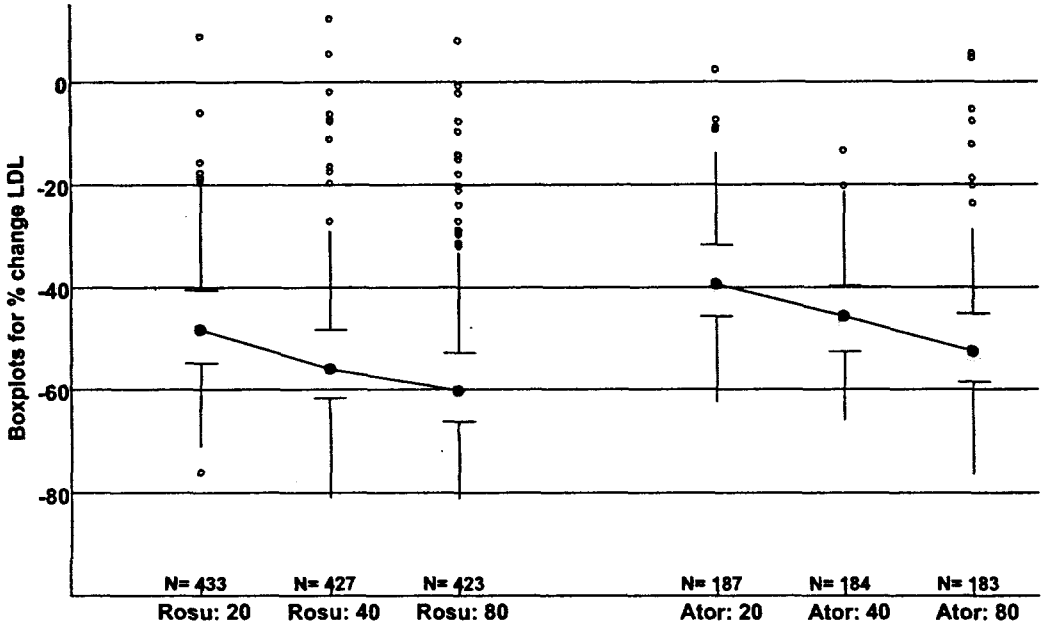
Table 49. LDL % change from baseline by week and dose

	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

Boxplots (Figure 22) show a clear dose response for each treatment and show that the

distribution of data for rosuvastatin 40 is similar to atorvastatin 80 and rosuvastatin 20 is similar to atorvastatin 40 (comparable to results seen in other studies in this submission).

Figure 22. Study 30 LDL % change from baseline at Week 6 (20 mg), Week 12 (40 mg) and Week 18 (80 mg) (responses are for a group of patients titrated from 20 to 40 to 80)



Fifty-seven percent of rosuvastatin patients had a further decrease of 6% of greater when increasing the dose from 20 to 40; while 38% of patients had a further decrease of 6% of greater when increasing the dose from 40 to 80. About 15% of the rosuvastatin patients had 6% decrease or greater with both dose escalations.

For a listing of the sponsor's results for secondary endpoints, see Appendix 8 .

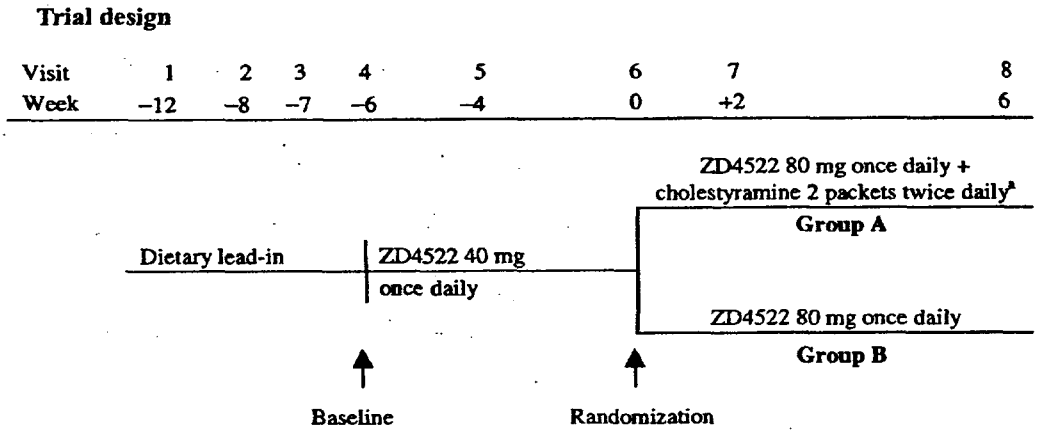
Reviewer's comments on Study 30

This large, multinational study showed that in patients with heterozygous familial hyperlipidemia (LDL of 220 or greater) titrating rosuvastatin from 20 to 40 to 80 mg results in significant additional LDL lowering in the majority of patients. Direct comparisons to atorvastatin showed that at like doses, rosuvastatin gives about 7% more lowering of LDL than atorvastatin. As seen in other studies, it appears that twice the dose of atorvastatin is needed to give similar effects to rosuvastatin.

Study 31 (conducted 10//99 to 9/00)

Study 31 was an open-label trial to assess the efficacy of the combination of rosuvastatin 80 mg once daily and cholestyramine 2 packets twice daily (16 g total) in reducing LDL-C in a population of patients with severe hypercholesterolemia. After a 6-week dietary lead-in, baseline was measured and then all patients were placed on rosuvastatin 40 mg for 6 weeks. At the end of the 6-week treatment period, patients were randomized to rosuvastatin 80 mg or rosuvastatin 80 mg plus cholestyramine (Figure 23).

Figure 23. Sponsor's schematic of Study 31 trial design



[a] Subjects who did not tolerate cholestyramine 2 packets twice daily may have had their dose of cholestyramine reduced to no fewer than 1 packet twice daily, and once reduced could not be increased.

Inclusion criteria included the following:

- Man or woman ≥18 years with severe hypercholesterolemia
- 190≤Fasting LDL-C <400 mg/dL
- Fasting TG<400 mg/dL

Patient Disposition

A total of 153 patients were enrolled and treated with Rosu 40 mg in the 6-week pre-randomization period; 6 patients did not complete this first period (3 due to ADE's). So 147 patients were randomized to rosuvastatin 80 mg (71 patients) or to rosuvastatin 80 mg plus cholestyramine (76 patients); 3 patients in each group did not complete the randomized treatment period.

Baseline Demographics

The treatment groups were well-balanced regarding baseline demographics (Table 50 on the following page). The mean age of patients was 54 years with about 1/3 of patients 65 or older. The majority of patients were Caucasian and male.

Table 50. Study 31 Patient Demographics for ITT Patients

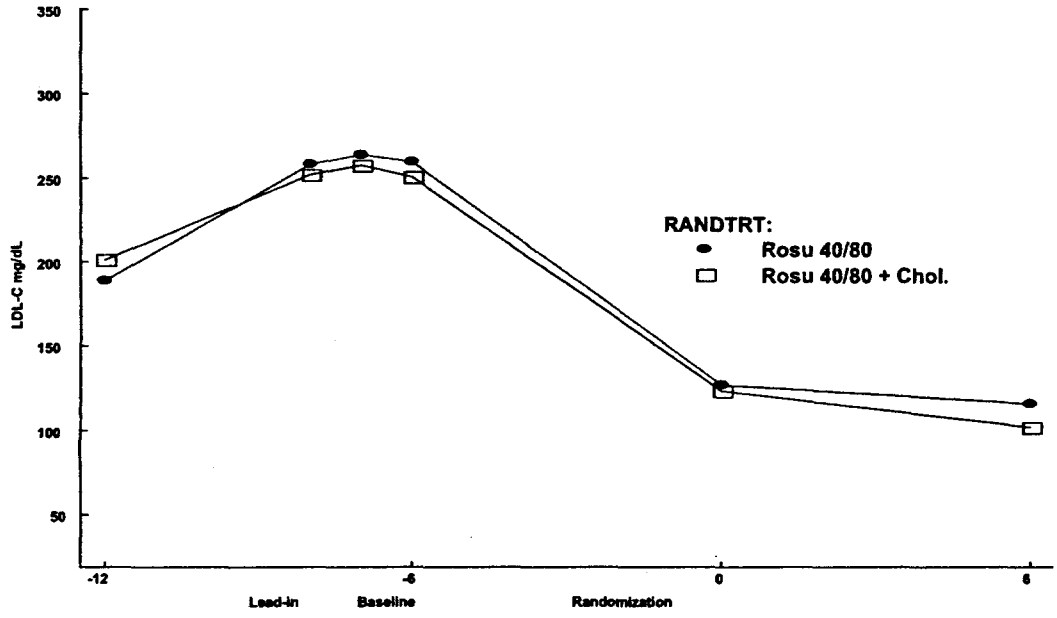
(Extracted from sponsor's Tables 11 and 12)

	Rosuvastatin 80 (n=71)	Rosu 80 + cholestyramine (n=76)
Age Mean (SD) Range ≥65	 54 (13) 31-78 27%	 55 (13) 21-84 33%
Gender % female	 39%	 47%
Race % white	 93%	 92%
Atherosclerotic disease	28%	25%
Family Hx premature vascular disease	47%	49%
Hypertension	32%	33%

Efficacy Results

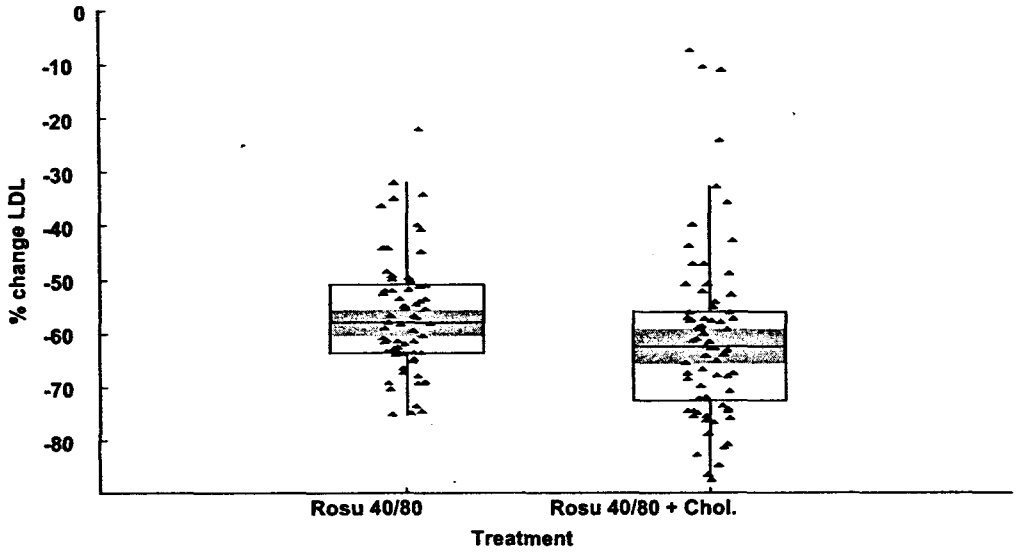
Figure 24 illustrates the comparability of the randomized groups during the run-in and during treatment with rosuvastatin 40 mg. The addition of cholestyramine results in a small drop in LDL while little change is seen for the rosuvastatin only group in spite of doubling the dose.

Figure 24. Study 31 Mean LDL (mg/dL) by week on study and treatment



Boxplots of percent change from baseline of LDL at Week 6 LOCF (Figure 25 on the next page) illustrate the shift in the distribution towards larger decreases for patients treated with rosuvastatin 80 with cholestyramine, although the difference between the groups is not statistically significant (Table 51).

Figure 25. Study 31 Boxplots of LDL % change from baseline at Week 6 LOCF



The LDL, HDL and TG results show no significant difference between rosuvastatin 80 mg plus cholestyramine and rosuvastatin 80 mg alone (Table 51) though the LDL results are borderline. It is clear from the data by week that most of the effect takes place during the open-label period when all patients were treated for 6 weeks with rosuvastatin 40 mg (Week –6 to Week 0).

Table 51. Study 31 Efficacy results at endpoint
(LDL and % change from baseline extracted from sponsor's tables and computed by reviewer)

	Rosu 40/80 (n=69)	Rosu 40/80 + cholestyramine (n=75)	p-value
LDL			
Baseline (Wk –6)	263	256	
Randomization (Wk 0)	126	124	
Final (Wk 6)	116	104	
% change from baseline	-56%	-61%	.08
HDL			
Baseline (Wk –6)	48	48	
Randomization (Wk 0)	54	53	
Final (Wk 6)	53	52	
% change from baseline	+11%	+10%	.71
TG			
Baseline (Wk –6)	186	192	
Randomization (Wk 0)	122	124	
Final (Wk 6)	126	130	
% change from baseline	-23%	-26%	.47

Reviewer's comments on Study 31

Study 31 showed that the addition of cholestyramine to rosuvastatin did not improve lipids significantly and also that increasing the rosuvastatin dose to 80 mg from 40 mg did not afford any greater benefit for patients.