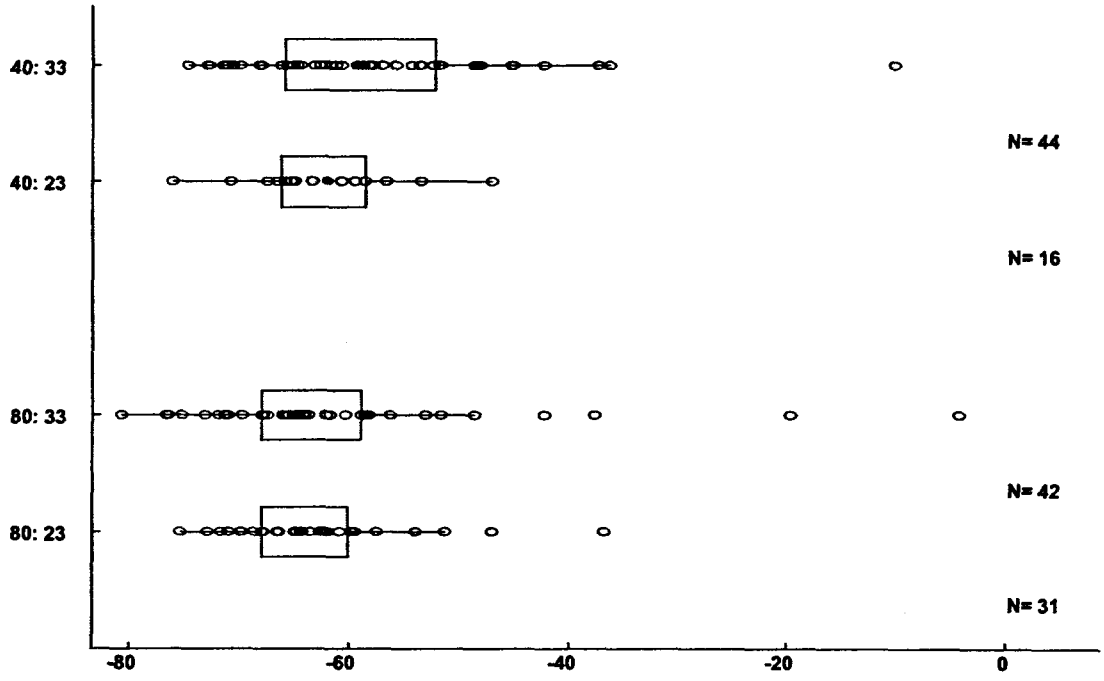
Assessment of treatment effect

In this section, the treatment effect of rosuvastatin is assessed in three ways; 1) 40 mg and 80 mg are compared 2) the full dose response relationship is described and 3) the effects of the potential starting doses (5 mg and 10 mg) are described. The goal here is to describe the responses not to present comparative statistics; see the individual study reports for the results of statistical tests.

40 mg versus 80 mg

Severe adverse events have been seen with the 80 mg dose of rosuvastatin (see Dr. Lubas's clinical review for further details) and so it is important to see if the 80 mg dose offers benefit over the 40 mg dose. From Studies 23 and 33 (see Figure 3 and Appendix 2), it could be seen that the mean responses for 40 and 80 mg were very close through Week 4 and that there was a small further decrease in LDL seen at Week 6 in the 80 mg group. The boxplots below (Figure 26) show the distribution of data at Week 6 LOCF and illustrate the similarity of response between studies and doses.

Figure 26. Boxplots of LDL % change from baseline at Week 6 LOCF for rosuvastatin doses 40 and 80 mg in Studies 23 and 33



The 80 mg dose was also administered in the titration studies (Studies 25, 26, and 28). Statistical reviewer Cynthia Liu concluded in her review of Study 25 (a force titration study with all groups forced to a dose of 80 mg) that there was essentially no benefit to increasing the dose to 80 mg from 40 mg with only an additional decrease of about 2%. It also worth noting that in

this forced titration study about 16% of the patients were not further titrated to 80 mg from 40 mg because of the large response they had on 40 mg. In Studies 26 and 28, patients were titrated to reach NCEP goals. In Study 26, Ms. Liu found that only 4 patients out of 228 rosuvastatin patients were titrated to the 80 mg dose. In Study 28, 5 patients out of 239 rosuvastatin patients were titrated to the 80 mg dose. So with only about 2% of the patients titrated to 80 mg in both studies, It is clear that most IIa/IIb patients are adequately treated with lower doses (more than 80% of the patients met goal with doses of 5 or 10 mg).

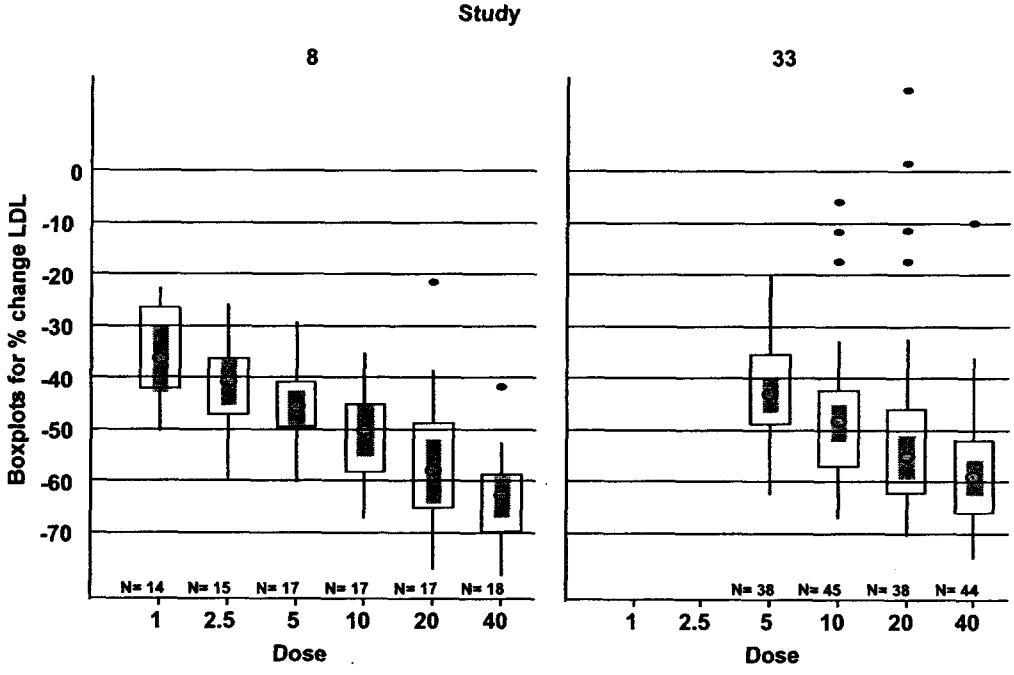
This reviewer concludes from the results of Studies 23, 33, 25, 26, and 28 that there is no significant benefit to 80 mg over 40 mg for Type IIa/IIb patients.

Doses of 40 and 80 were also studied in the other patient populations examined for this NDA. In a study of Type IIb/IV patients (Study 35), no further benefit was seen for doses above 10 mg with respect to TG lowering. In patients with severe hypercholesterolemia marked by high levels of LDL (such as, homozygous and heterozygous familial dyslipidemias), about 1/3 of the patients appear to benefit from titration to the highest dose of 80 mg with about 6% more LDL lowering though most of the effect can be attained with a dose of 20 mg.

Dose response for rosuvastatin

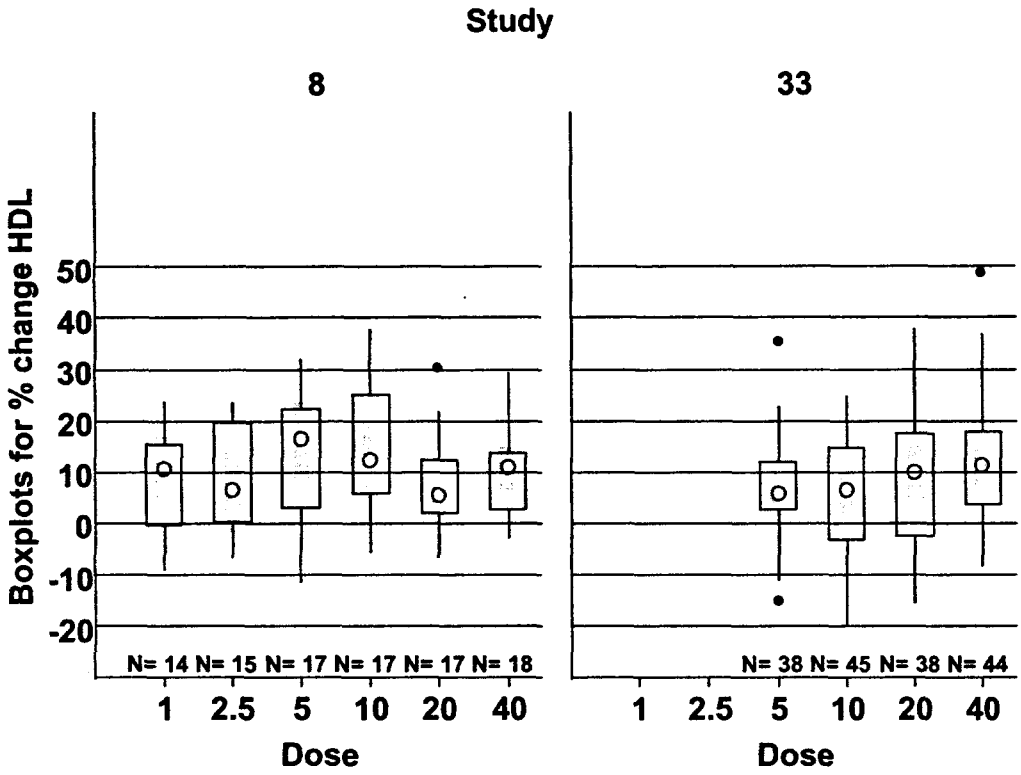
For Type IIa/IIb patients, the dose response of rosuvastatin was examined in Studies 8 (doses 1, 2.5, 5, 10, 20 and 40) and 33 (doses 5, 10, 20, 40 and 80). For Type IIb/IV patients, the dose response was examined in Study 35 (doses 5 to 80). Boxplots of the LDL % change from baseline data from Studies 8 and 33 (Figure 27) show a clear dose response for LDL and similar responses for the two studies. These results are consistent with the results in other studies of Type IIa/IIb patients in this application.

Figure 27. Boxplots of LDL % change from baseline at Week 6 LOCF by dose and study



The results for HDL and TG were not seen to be dose-related; Figure 28 illustrates this point for HDL in Studies 8 and 33. This was found to be the case for all types of patients examined in this NDA.

Figure 28 Boxplots of HDL % change from baseline at Week 6 LOCF by dose and study



For the Type IIb/IV patients in Study 35, differences in response between the 5 and 10 mg doses were evident but doses above 10 mg generally showed a magnitude of response similar to 10 mg.

The results by dyslipidemic type are examined further on pages 62 and 63 of this review.

5 and 10 mg rosuvastatin doses

The sponsor studied the 5 and 10 mg doses of rosuvastatin in 7 trials of Type IIa and IIb patients; Studies 8 and 33 had 6-week treatment periods and the other 5 studies had 12-week treatment periods. In most studies about a 7% difference in response is seen between the doses. The sponsor has proposed a starting dose of 10 mg but it is clear from this data that 5 mg also offers considerable efficacy with mean decreases of 39% or greater. The titration-to-NCEP-goal studies also show the sufficiency of effect afforded by the 5 mg dose with about 75% of the patients starting on 5 mg reaching goal without titration to higher doses.

Table 53. LDL % change from baseline at endpoint LOCF in Type IIa/IIb patients

	5 mg			10 mg		
Study	N	Baseline	% change	N	Baseline	% change
8	17	193	**-45%**	17	190	**-52%**
24	128	188	**-40%**	129	184	**-43%**
25	127	188	**-40%**	128	186	**-47%**
26	135	188	**-46%**	132	186	**-50%**
27	120	190	**-42%**	115	186	**-49%**
28	121	187	**-39%**	116	187	**-47%**
33	38	193	**-42%**	45	190	**-48%**

In Type IIb/IV patients, however, the 10 mg dose did afford significantly more lipid lowering than the 5 mg dose (see Table 34 for Study 35).

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Findings in Subgroup Populations

In this section subgroups based on dyslipidemia type, gender, age and race are examined.

Dyslipidemia Type

The sponsor studied Type IIa, IIb and IV patients. The dyslipidemia types are defined as follows:

- Type IIa LDL≥130 TG<200
- Type IIb LDL≥130 TG≥200
- Type IV LDL<130 TG≥200

The majority of the patients in the NDA were Type IIa patients (~1140); about 800 were Type IIb and about 260 were Type IV (Table 54).

Table 54. Entry criteria and number (%) of patients of each dyslipidemia type for each study

Study	Entry Criteria	Type IIa	Type IIb	Type IV
8	160 ≤LDL<220 TG<300	129/139 (93%)	10/139 (10%)	NA
23	160 ≤LDL<220 TG<300	60/64 (94%)	4/64 (6%)	NA
33	160 ≤LDL<250 TG<400	254/372 (68%)	118/372 (32%)	NA
27	160 ≤LDL<250 TG<400	383/494 (77%)	111/494 (22%)	NA
28	160 ≤LDL<250 TG<400	313/474 (66%)	161/474 (34%)	NA
35	300 ≤TG<800	NA	64/156 (41%)	92/156 (59%)
29	200 ≤TG<800 TC>200 HDL<45	NA	164/268 (61%)	104/268 (39%)
36	300 ≤TG<800	NA	151/219 (69%)	68/219 (31%)

To characterize the effect of rosuvastatin for each of these types, this reviewer combined studies. Studies were combined based roughly on entry criteria; so Studies 33, 27 and 28 were combined and Studies 35, 29 and 36 were combined. The results are in two tables on the following page.

The LDL % change from baseline for the Type IIa patients show a clear dose response for doses 5 to 40 (Table 55) which is consistent with what we saw in Study 8. For the Type IIb and Type IV patients, the LDL effect is more variable across dose. The difference in magnitude of effect (decreases from 42% to 66% for IIb and from 24% to 43% for IV) is probably related to the baseline differences between the groups.

The TG changes show no dose response relationship though the numbers in Table 56 show a clear advantage for 10 mg dose over the 5 mg dose; again the baseline levels appear to play a role.

HDL changes are not dose related for Type IV patients whom could benefit from HDL raising. (Note that no dose-related responses for HDL were seen in Type IIa or IIb patients either.) As for TG, the 10 mg dose offers about doubling of the HDL effect over the 5 mg dose.

Table 55 Rosuvastatin LDL results at endpoint by dyslipidemic type for Studies 27, 28 and 33 Combined

	5	10	20	40	80
Type IIa	n=184	n=197	n=30	n=31	n=28
LDL Mean (SD)					
Baseline	189 (19)	186 (19)	189 (24)	188 (21)	199 (22)
% change	-40% (13)	-48% (13)	-52% (17)	-57% (12)	-59% (15)
TG Median					
Baseline	143	145	150	143	138
% change	-18%	-21%	-24%	-28%	-21%
Type IIb	n=94	n=75	n=8	n=13	n=14
LDL Mean (SD)					
Baseline	190 (20)	190 (20)	183 (27)	188 (20)	195 (22)
% change	-42% (12)	-47% (17)	-44% (25)	-60% (12)	-66% (11)
TG Median					
Baseline	246	238	215	248	248.5
% change	-30%	-30%	-25%	-46%	-42%

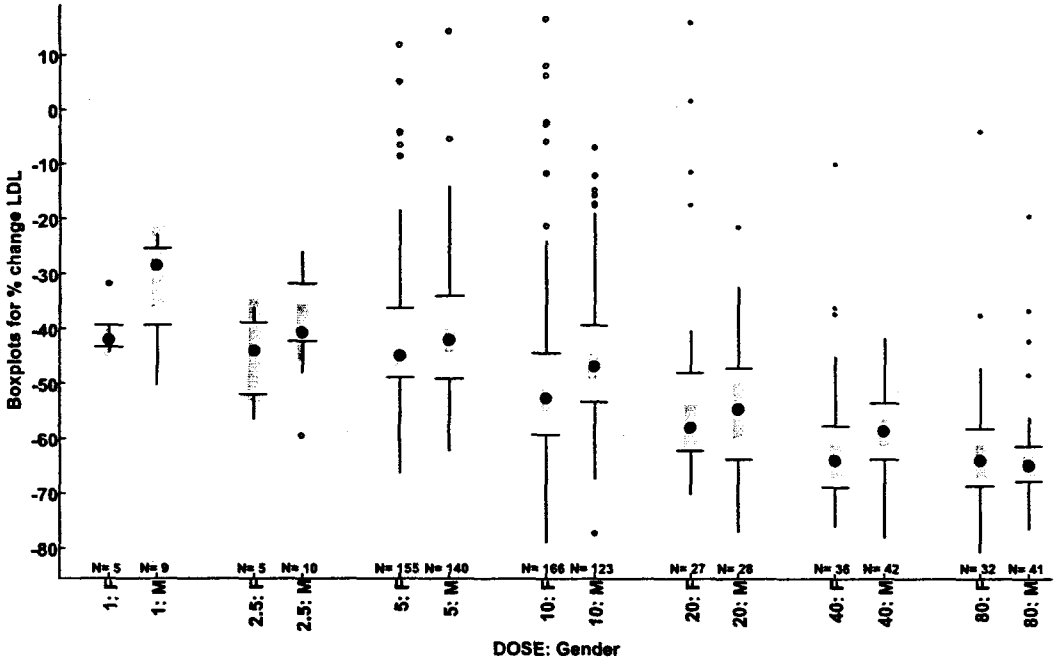
Table 56 Rosuvastatin LDL results at endpoint by dyslipidemic type for Studies 35, 29 and 36 Combined

	5	10	20	40	80
Type IIb	n=9	n=11	n=10	n=70	n=17
LDL Mean (SD)					
Baseline	157 (19)	158 (16)	175 (32)	165 (51)	164 (40)
% change	-34% (6)	-51% (5)	-44% (19)	-47% (20)	-53% (21)
TG Median					
Baseline	374	389	386	323	398
% change	-18%	-37%	-30%	-35%	-46%
Type IV	n=16	n=12	n=17	n=47	n=10
LDL Mean (SD)					
Baseline	90 (28)	97 (22)	86 (23)	101 (23)	94 (26)
% change	-24% (19)	-30% (16)	-27% (25)	-43% (16)	-32% (28)
TG Median					
Baseline	518	502	439	410	430
% change	-21%	-47%	-38%	-43%	-37%
HDL Mean (SD)					
Baseline	33 (8)	37 (7)	32 (5)	34 (6)	34 (9)
% change	+3% (19)	+8% (8)	+15% (12)	+11% (15)	+8% (10)

Gender

The results from Study 8 suggested that a larger effect was seen for females than males though a test for interaction was non-significant (p=.96). An analysis of LDL percent change from baseline for the rosuvastatin doses in Studies 8, 23, 27, 28 and 33 yielded an interaction p-value of .095; analyzing just doses 5 to 40 mg gave p=.046. An examination of the data via the boxplots below shows greater response for females (lower median) than males at all doses except the 80 mg dose. Focussing on doses 5 to 40 where the sample sizes are all greater than 30, we see approximately a 5% greater median drop in LDL in females than males (the difference between means tends to be less than 3%; not a clinically relevant difference according to the medical reviewer). [Note that in Studies 8 and 23, there was essentially no difference in the placebo responses for females and males, so placebo subtracted effects will show relationships similar to those in the graph below.] Adjustments for weight or bmi did not alter the relationship between the genders.

Figure 29. LDL % change from baseline by dose and gender for Studies 8, 23, 27, 28 and 33 combined



Age, Race and Baseline LDL

An examination of the treatment effects for patients 65 and older showed results consistent with younger patients (interaction p=.27). There were insufficient patients in the database to assess race with over 90% of the patients Caucasian. LDL response was not strongly correlated with baseline LDL and so results based on subgroups defined by baseline LDL are similar.

Rosuvastatin versus other statins

In 7 of the 8 clinical trials of Type IIa/IIb patients, a marketed statin was used as a comparator. For Studies 8, 33, 24, 25, and 26, atorvastatin was a comparator; for Studies 27 and 28, pravastatin and simvastatin were comparators. The data for LDL, TC, non-HDL and Apo-B clearly showed that at like doses, rosuvastatin consistently beats atorvastatin and the doses of 5 and 10 mg of rosuvastatin beat the 20 mg dose of pravastatin and simvastatin.

FDA pharmacometrics reviewer Dr. He Sun concluded from his analyses of the data from Study 33 that rosuvastatin doses are comparable to four times the dose of atorvastatin. Results in this review and Ms. Liu's statistical review suggest that comparability is seen when doubling the dose of atorvastatin though some results showed rosuvastatin significantly more effective than twice the atorvastatin dose.

To summarize the comparability of the two drugs from several trials, this reviewer computed 95% confidence intervals for the treatment difference rosuvastatin-atorvastatin (so negative values favor rosuvastatin). The focus here is on comparing rosuvastatin to two times and four times the atorvastatin dose using LDL at endpoint (the primary endpoint in these trials).

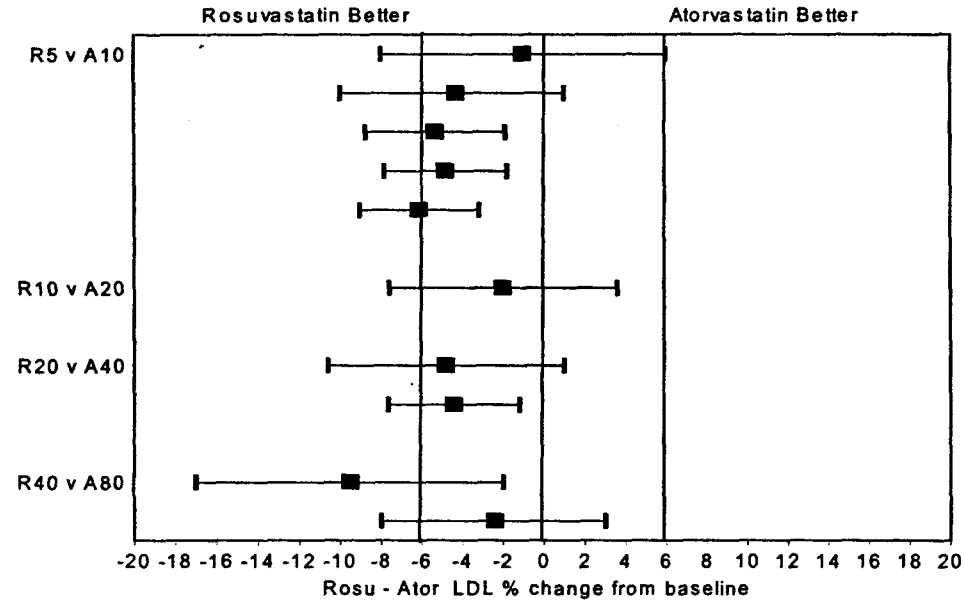
The table below shows which studies provide data for which comparisons:

	Ator 10	Ator 20	Ator 40	Ator 80
Rosu 2.5	8			
Rosu 5	8, 33, 24, 25, 26	33		
Rosu 10		33	33	
Rosu 20			33, 25	8, 33
Rosu 40				8, 33

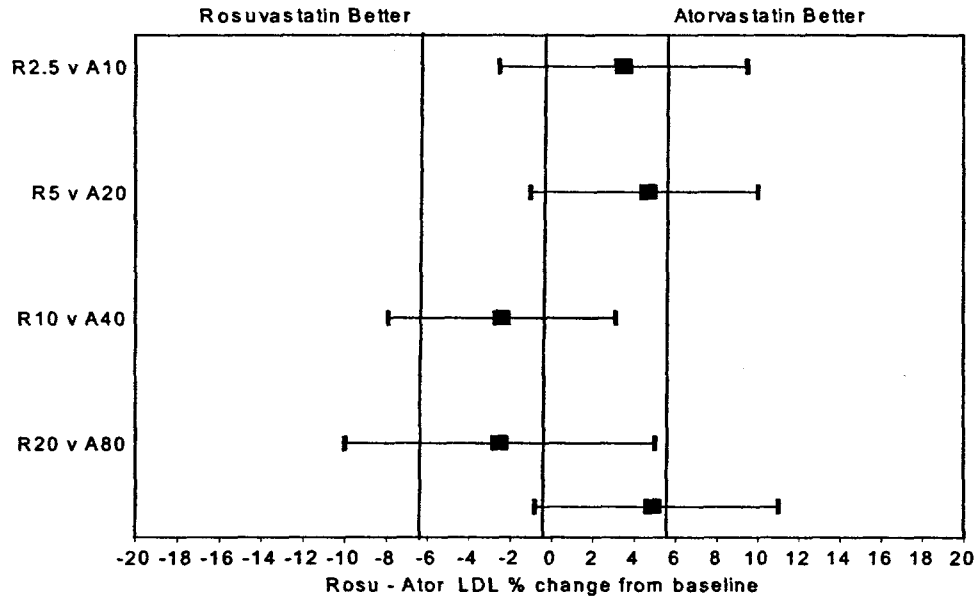
Two graphs on the following page show the mean treatment differences and 95% confidence intervals for these comparisons; the first graph depicts the relationship between rosuvastatin and two times the atorvastatin dose and the second graph depicts the relationship between rosuvastatin and four times the atorvastatin dose. There was no pooling of data for this summary; each datapoint represents a single study. Each graph contains three reference lines; one at 0, one at –6 and one at +6. The –6 and +6 lines represent clinically important differences so a value of +6 or above would suggest that atorvastatin could be better than rosuvastatin by a clinically important amount. To show that rosuvastatin is significantly better than atorvastatin, the confidence interval would be to the left of the 0 reference line. To show rosuvastatin is as good as atorvastatin, the upper limit of the confidence interval should be less than 6%, i.e., left of the +6 reference line.

Figure 30. Rosuvastatin LS mean minus atorvastatin LS mean and 95% CI by comparison and study

Rosuvastatin compared to 2x the atorvastatin dose



Rosuvastatin compared to 4x the atorvastatin dose



The results for the comparison of rosuvastatin to twice the dose of atorvastatin (top graph) are clearly more favorable to rosuvastatin and, with the exception of rosuvastatin 10 vs. atorvastatin 20, the treatment differences are statistically significant for every comparison in at least one study. The results for the comparison of rosuvastatin to four times the dose of

atorvastatin, however, are more ambiguous with some comparisons suggesting that rosuvastatin is as good as 4x the dose of atorvastatin (e.g. R10 vs. A40) while other results are borderline significant in favor of atorvastatin with the lower bound of the confidence interval close to zero (e.g. R5 vs. A20). One should be reminded here that the atorvastatin 40 mg dose in Study 33 had a smaller mean effect than the atorvastatin 20 mg dose so the magnitude of the atorvastatin 40 mg response is not consistent with the dose response seen in other atorvastatin studies. This reviewer would conclude from this data that rosuvastatin is better or at least as good as twice the dose of atorvastatin.

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Summary and Conclusions

The sponsor's phase III clinical program consists of 14 clinical trials (see Tables 1, 2 and 3 on pages 3 and 4); 11 of the trials are reviewed here and 3 are reviewed in a separate document by FDA statistical reviewer Cynthia Liu. All trials were multicenter and most were multinational. These trials included three dose response studies (doses ranging from 1 mg to 80 mg); two in Type IIa/IIb patients and one in Type IIb/IV patients. Three combination drug studies assessed the effect of rosuvastatin in combination with fenofibrate, cholestyramine and niaspan. Twelve out of the 14 trials had an active control; for 7 trials, atorvastatin was the active control. In addition to fixed dose studies, several studies included a titration period where either patients were force titrated to 80 mg or titrated to NCEP goal. In most trials the treatment period was 6 weeks. In addition to Types IIa, IIb and IV, familial homozygous and heterozygous patients and patients with severe hypercholesterolemia were studied. These trials provided a wealth of information on the efficacy of rosuvastatin in lowering lipids in a variety of patient populations and against several active comparators.

The population of Type IIa, IIb and IV patients consisted primarily of Caucasians (>95%) with an average age of about 58 years (range of 19 to 86); about ¼ of the patients were 65 or older. In most studies, there are approximately equal numbers of males and females. Diabetic patients were included in two studies.

The primary endpoint in most of the trials was LDL percent change from baseline at endpoint. For a couple of trials in Type IV patients, the primary endpoint was triglycerides.

This reviewer's conclusions are given below along with the location in the review of supporting evidence.

- Rosuvastatin doses of 1, 2.5, 5, 10, 20, 40 and 80 mg significantly decreased LDL, TC, Apo-B and non-HDL compared to placebo in Type IIa or Type IIb patients. The decreases were dose-related (Table 7, Table 18, Figure 27, and Appendix 1).

- Statistically significant decreases in LDL are seen as early as the end of Week 1 (Figure 1 and Figure 5) with most of the effect achieved by Week 2 and essentially complete by Week 4. The mean dose responses for LDL % change from baseline ranged from –35% for the 1 mg dose to about –60% for the 40 mg dose of rosuvastatin.

- Lipid changes for the 40 mg and 80 mg doses of rosuvastatin in Type IIa or IIb patients were similar, suggesting no significant benefit to increasing the dose to 80 mg (Table 11, Figure 3 and Figure 26).

- Female patients consistently showed a larger decrease in LDL (mean about 3%) than male patients (treatment by gender interaction p<.10) (Figure 29).

- The HDL and TG effects of rosuvastatin were not dose related (Table 7 and Table 18) and, for Type IIa/IIb patients, not different from placebo for most doses (Table 7).

- Rosuvastatin LDL effects are as good as or significantly better than the effects of two times the dose of atorvastatin (Table 17 and Figure 30).

- Doses of 5 and 10 mg of rosuvastatin were significantly more effective in lowering LDL than the 20 mg dose of pravastatin and simvastatin (Table 23 and Table 29).

- The addition of fenofibrate to rosuvastatin was more effective in lowering TG than increasing the dose of rosuvastatin in Type IIb/IV diabetic patients (Table 41).

- The addition of niacin to rosuvastatin was more effective in increasing HDL than increasing the dose of rosuvastatin in Type IIb/IV patients (Table 37).

- In two studies of patients with homozygous and heterozygous familial dyslipidemia, patients force-titrated from 20 to 40 to 80 mg of rosuvastatin showed significant decreases in LDL at all three doses. At 20 mg, homozygous patients had about a 20% drop while heterozygous patients had about a 47% drop (Table 44 and Table 49). About 1/3 of patients benefited from the higher doses with additional lowering of 6% or more.

- In patients with severe hypercholesterolemia characterized by 190≤LDL-C<400 mg/dL and TG<400 mg/dL, no significant benefit was seen from increasing the rosuvastatin dose from 40 mg to 80 mg or from adding cholestyramine to rosuvastatin 40 mg (Figure 24 and Table 51).

- Rosuvastatin significantly lowered triglycerides in Type IV and IIb patients with the effect strongest in patients with baseline HDL under 40 mg/dL (Figure 13). 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 (Table 34 and Figure 12).

Overall, all doses of rosuvastatin (1 to 80 mg) were shown to significantly decrease LDL. In special populations (familial hypercholesterolemia and Type IV), doses above 10-20 mg did not offer significant further benefit. Given the potential risks with the 80 mg dose and the lack of a sufficient safety database for the 20 and 40 mg dose from which to assess the safety margin, the medical reviewer has recommended approval of 5 mg and lower. Doses of 5 mg or lower show significant efficacy only in Type IIa and IIb patients; data on these doses is limited in other patient populations. From a statistical viewpoint, the 10 mg dose, if deemed safe, offers more significant and broader benefit over the 5 mg dose.

This review contains no comments on labeling since labeling is not being considered at this time by the review staff.

/S/

Joy Mele, M.S.
Mathematical Statistician

Concur:

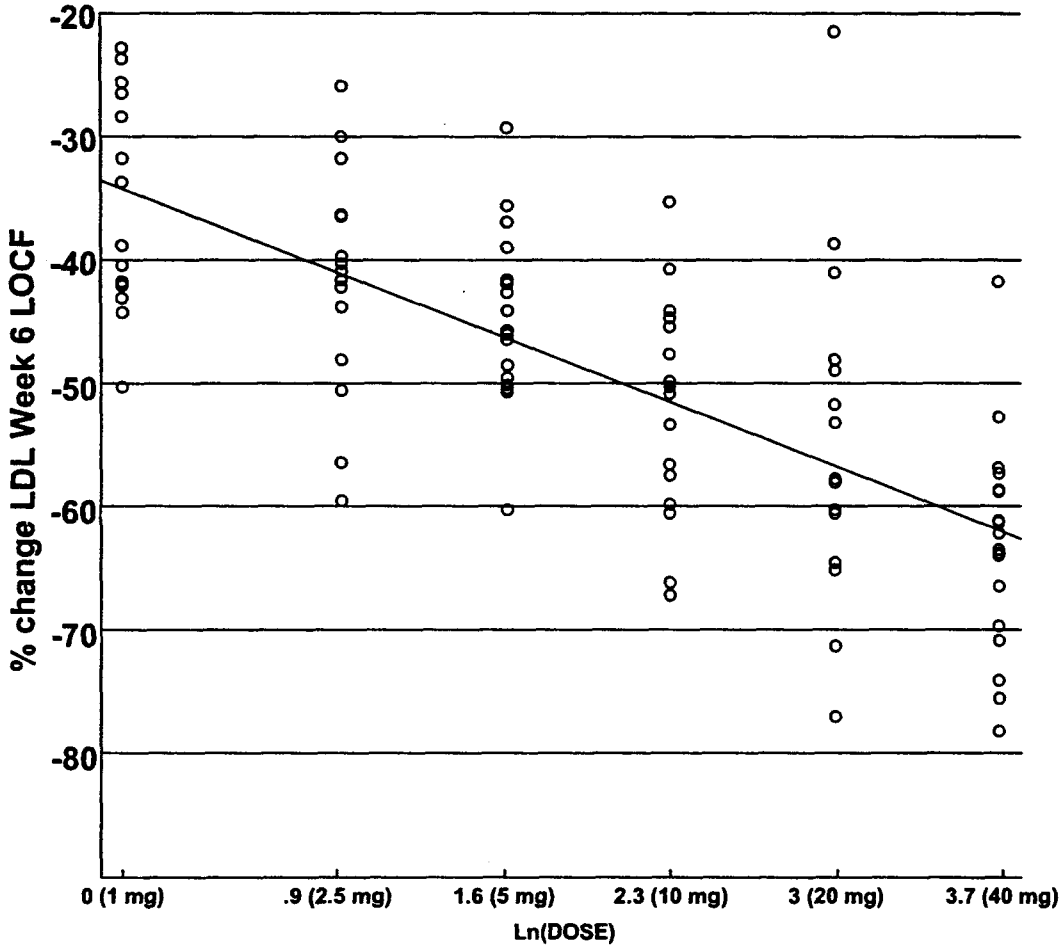
Todd Sahlroot, Ph.D.
Team Leader

Ed Nevius, Ph.D.
Director of DOB2

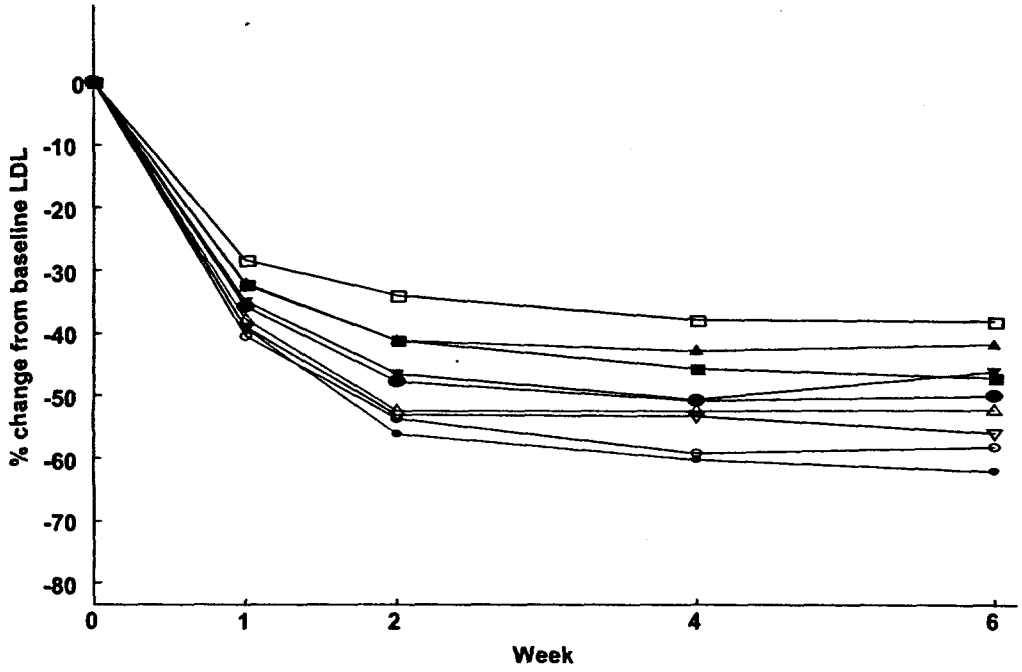
cc:
Archival NDA
HFD-510
HFD-510/WKoch, MParks, DOrloff
HFD-715/JMele, TSahlroot, ENevius, CAnello
Mele/x76376/DOB2/Word-rev.doc/March 27, 2002

Appendix 1. Study 8 Dose Response for rosuvastatin

Total sample size=98
Linear Model % change LDL = -34 – 7.5 (Ln dose)
R^2 = 0.49



Appendix 2. Study 33 LDL-C (mg/dL) % change from baseline by week on study for all treatment groups



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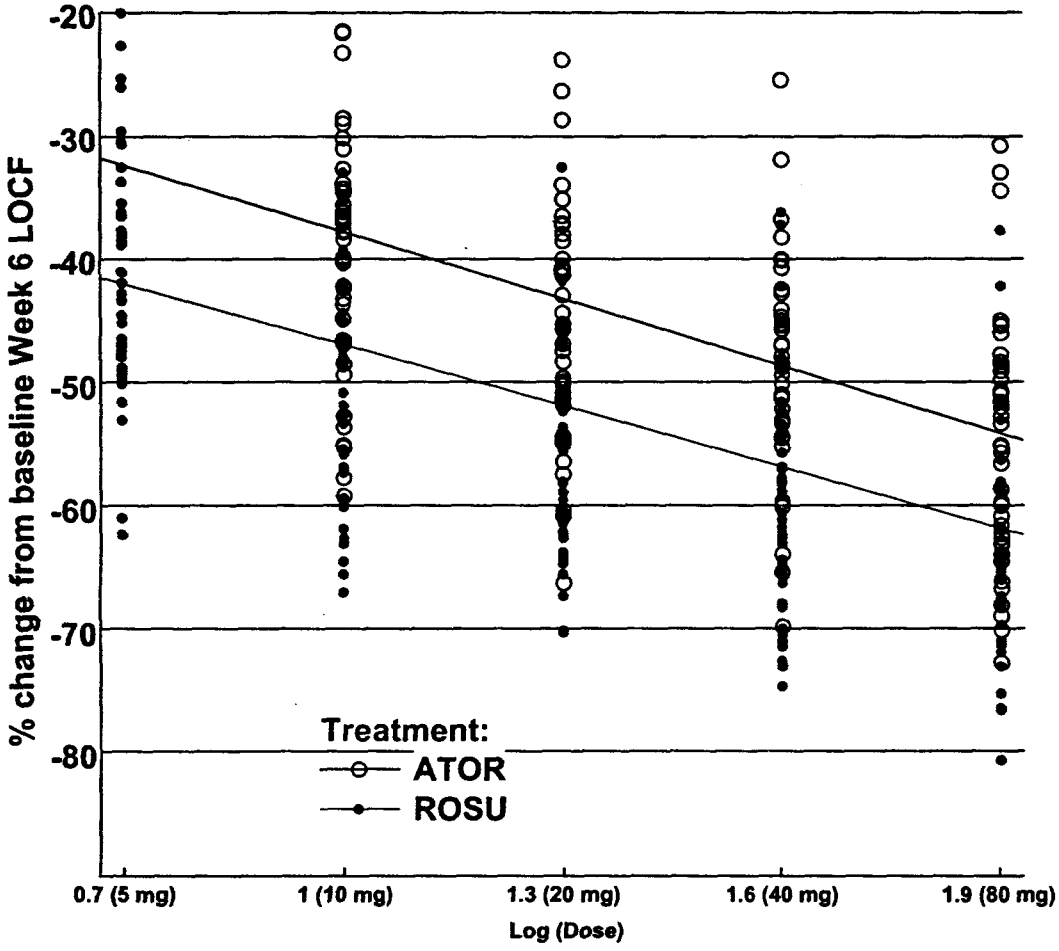
Appendix 3. Study 33 Linear regression of dose versus LDL % change at endpoint for atorvastatin and rosuvastatin

Total sample size=374
R^2 <.2



Appendix 4. Study 29 Sponsor's summary of secondary endpoints

Table 42 Summary of key efficacy findings

Efficacy endpoint	Lsmean of % change from baseline at Week 24			
	ZD4522 10/20/40 mg	Niacin 0.5/1/1.5/2 g	ZD4522 10/20/40 mg with niacin 0.5/1 g	ZD4522 10 mg with niacin 0.5/1/1.5/2 g
Lipids and lipid ratios[a]				
LDL-C	-47.5	-0.1[b]	-42.4	-35.5[b]
TC	-40.7	-7.2[b]	-37.5	-29.1[b]
HDL-C	10.6	12.3	16.7	23.7[b]
HDL-TG	-11.1	-4.9	-8.9	-15.1
HDL2	9.3	14.9	20.3	40.6[b]
HDL3	22.2	15.5	24.0	21.4
TG	-32.6	-20.9	-38.6	-33.9
LDL-TG	-23.4	36.7[b]	-30.2	-7.8
VLDL-TG	-43.5	-23.1	-43.6	-35.4
VLDL-C	-51.0	-22.0[b]	-46.6	-38.4
LDL-C/HDL-C	-52.5	-11.7[b]	-49.1	-45.5
TC/HDL-C	-45.3	-16.1[b]	-45.3	-39.2
Non-HDL-C/HDL-C	-52.4	-18.8[b]	-52.9	-45.8
ApoB	-42.4	-8.9[b]	-41.7	-33.7[b]
LDL-ApoB	-32.9	0.4[b]	-34.2	-27.4
VLDL-ApoB	-62.2	-48.1	-36.0	-19.4
ApoA-I	4.7	7.0	6.2	10.6[b]
ApoA-II	-2.4	-4.2	-5.7	0.5
ApoB/ApoA-I	-44.5	-14.5[b]	-44.3	-38.9
ApoC-III	-19.8	-6.4	-20.5	-18.4
ApoC-III:B	-25.9	-9.2	-23.6	-20.4
ApoC-III:Non-B	13.8	17.7	-9.7	2.7
Lp(a)	6.5	-19.8[b]	-17.5[b]	-20.2[b]
Activated factor XII[c]				
Activated factor XII	2.7	-2.5	3.6	1.0

[a] Main analysis of LOCF from the ITT population.
[b] $p<0.017$ versus ZD4522 40 mg.
[c] Observed data from the ITT population. Hypothesis testing not performed for activated factor XII.

In patients with Fredrickson type IIb or IV hyperlipidemia, ZD4522 40 mg produced a 47.5% reduction from baseline in LDL-C by Week 24 versus 0.1% with niacin 2 g and 42.4% and 35.5% with combination therapy with ZD4522 40 mg + niacin 1 g and with ZD4522 10 mg + niacin 2 g, respectively. For patients randomized to ZD4522, either as

Appendix 5. Study 36 Sponsor's summary of secondary endpoints

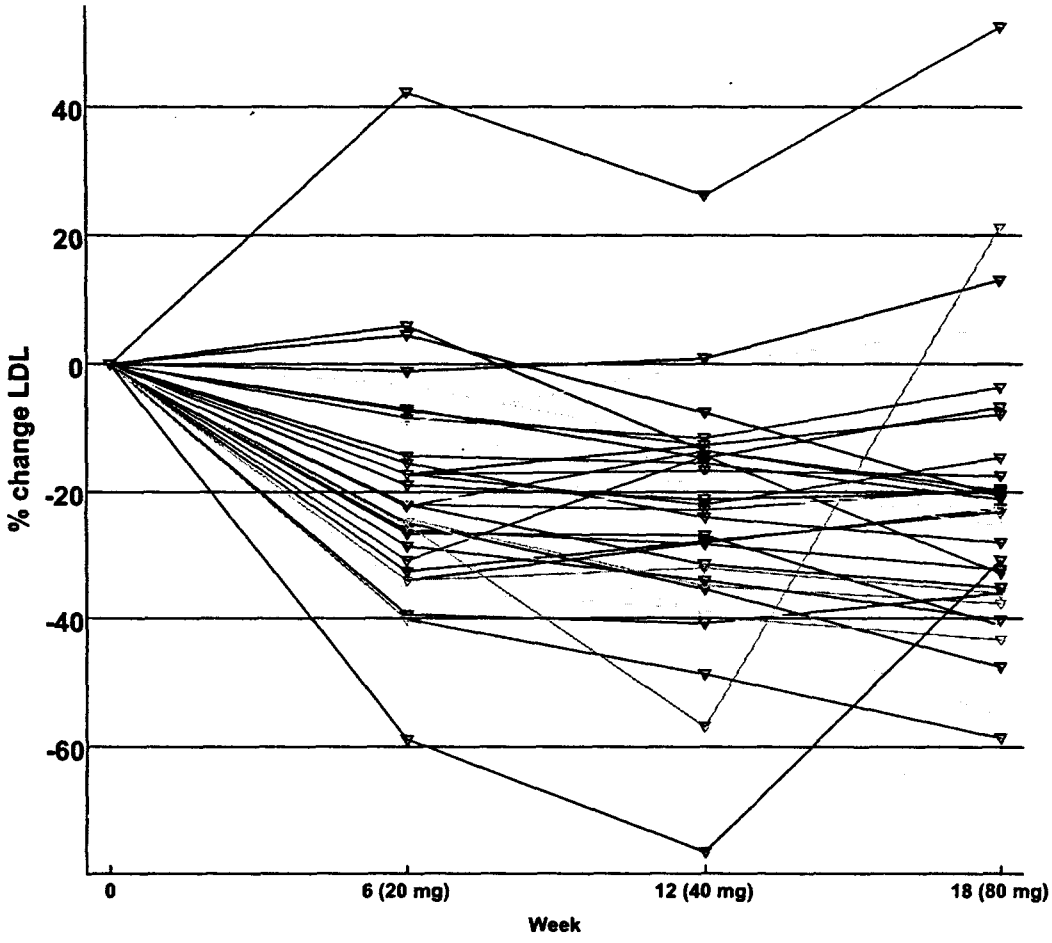
Table I Summary of key efficacy findings (LOCF on ITT population)

Efficacy end-point	Placebo/ZD4522 10/20/40 mg	Placebo/Feno od/bd/tds	ZD4522 5 mg + Feno od/bd/tds	ZD4522 10 mg + Feno od/bd/tds
lsmean of % change from baseline to Week 24 in key lipids and lipid ratios				
TG	-30.25	-33.55	-40.88	-47.11[a]
LDL-C	-46.69	0.70[a]	-34.06[a]	-42.16
TC	-36.58	-7.49[a]	-30.97	-36.26
HDL-C	6.42	9.24	10.79	11.72
LDL-C/HDL-C	-48.86	-6.30[a]	-38.76[a]	-46.80
TC/HDL-C	-39.22	-13.90[a]	-36.20	-41.89
non-HDL-C/HDL-C	-47.33	-16.64[a]	-43.51	-50.39
VLDL-C	-43.56	-30.09	-46.81	-44.16
VLDL-TG	-31.93	-14.68	-32.46	-41.53
ApoA-I	2.71	5.02	4.72	5.41
ApoB	-41.38	-7.55[a]	-34.98	-40.21
ApoB/ApoA-I	-41.89	-11.26[a]	-37.15	-42.70
Lp(a)	67.30	41.50	22.86	39.22

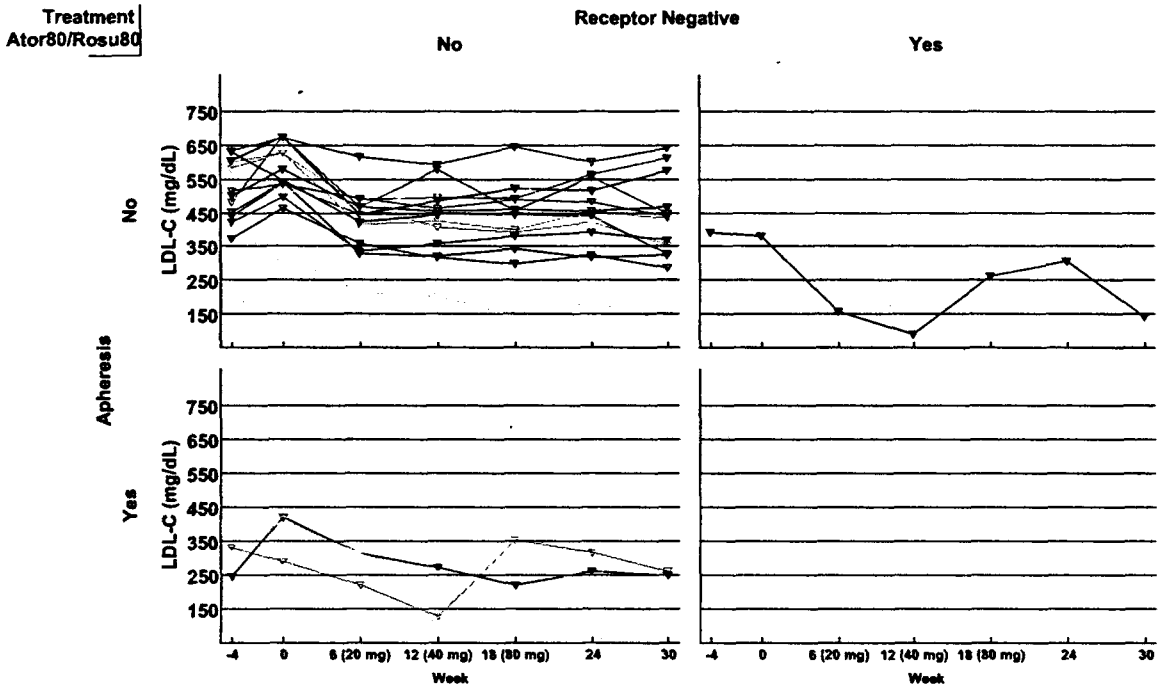
[a] $p \leq 0.017$ versus ZD4522 10/20/40 mg. A threshold for statistical significance of $p \leq 0.017$ was used at Weeks 12, 18 and 24 in order to control for multiple comparisons

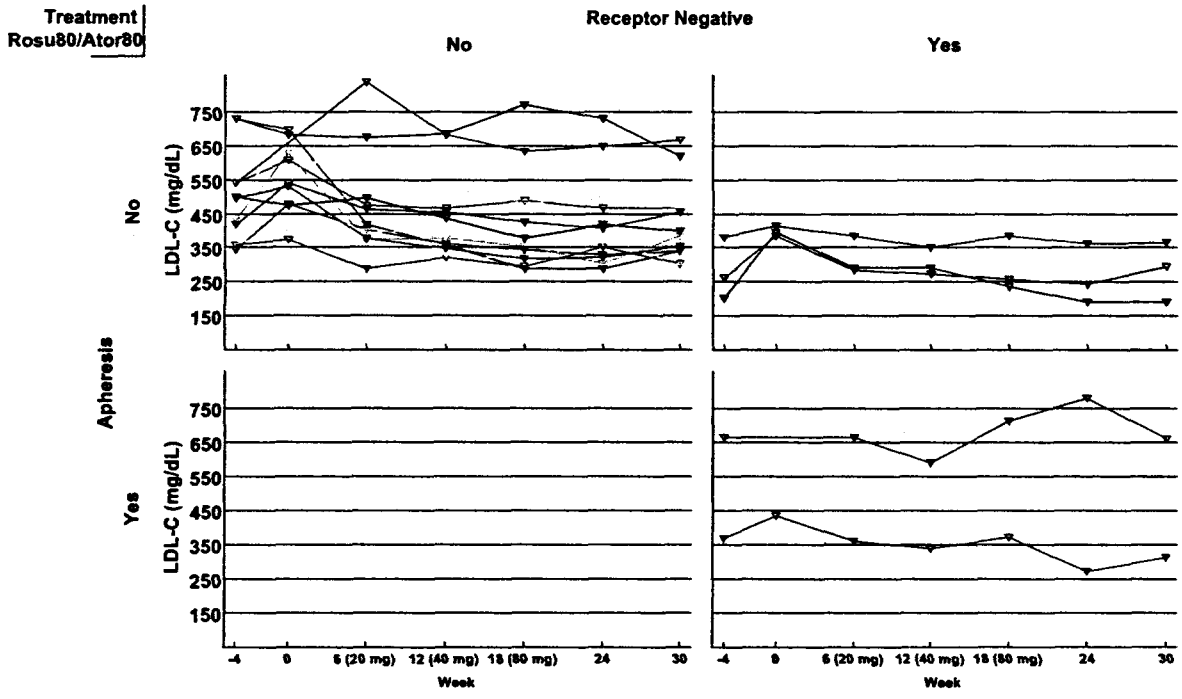
Feno = fenofibrate; lsmean = Least squares mean; NA = results not available due to inadequate samples

Appendix 6. Study 54 LDL-C % change from baseline by patient



Appendix 7. Study 54 LDL-C by patient , receptor type and aphresis





Appendix 8. Sponsor's Table of Study 30 Secondary Efficacy Results

Table 38 **Summary of changes of efficacy parameters at Week 18 (ITT population)**

Efficacy endpoint	ZD4522 20/40/80 mg	Atorvastatin 20/40/80 mg
lsmean of percentage change from baseline to Week 18		
TC	-46.35[a]	-42.13
HDL-C	12.36[a]	2.91
TG	-27.82[ns]	-31.60
LDL-C/HDL-C	-61.69[a]	-51.16
TC/HDL-C	-51.44[a]	-43.17
Non-HDL-C/HDL-C	-59.40[a]	-49.86
ApoB	-50.21[a]	-44.44
ApoA-I	5.86[a]	-2.33
ApoB/ApoA-I	-52.03[a]	-42.46
% subjects reaching NCEP or EAS targets for LDL-C Week 18		
NCEP, overall	60.5	46.0
NCEP, high-risk	23.9	3.2
EAS, overall	47.4	24.1
EAS, high-risk	47.5	24.2
Median percentage change from baseline to Week 18 in inflammatory marker (Observed data)		
CRP	-34.00	-33.33

[a] $p<0.001$ in favor of ZD4522 20/40/80 mg

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/s/

Joy Mele
4/23/02 02:40:57 PM
BIOMETRICS

Todd Sahlroot
4/24/02 10:44:48 AM
BIOMETRICS

S. Edward Nevius
4/24/02 01:32:49 PM
BIOMETRICS
Concur with review.

4/12/02

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) Tablets
Applicant:	AstraZeneca Pharmaceuticals LP
Indication:	Dyslipidemia
Documents reviewed:	\\CDSESUB1\N21366\N_000\2001-06-26\clinstat\dyslipid\IL0024\IL0024.pdf, IL0024a.pdf \\CDSESUB1\N21366\N_000\2001-06-26\clinstat\dyslipid\IL0025\IL0025.pdf, IL0025a.pdf \\CDSESUB1\N21366\N_000\2001-06-26\clinstat\dyslipid\IL0026.pdf
Project manager:	Bill Koch, R.Ph. (HFD-510)
Clinical reviewer:	Bill Lubas, M.D. (HDF-510)
Dates:	Received 6/26/01; user fee (10 months) 4/26/02
Statistical reviewer:	Cynthia Liu, MA (HFD-715)
Statistics team leader:	Todd Sahlroot, Ph.D. (HFD-715)
Biometrics division director:	Ed Nevius, Ph.D. (HFD-715)

Keywords: NDA review, clinical studies, LDL-C, analysis of variance, closed testing procedure

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1. SUMMARY OF STATISTICAL REVIEW

AstraZeneca has conducted a clinical program for CRESTOR™ (rosuvastatin calcium, ZD4522) for treating patients with dyslipidemias (Fredrickson Type IIa, IIb, IV, heterozygous, or homozygous familial hypercholesterolemia) under NDA 21-366. Among 4497 subjects given rosuvastatin in 50 clinical trials, 3747 subjects with dyslipidemias in 15 Phase II/III trials (including one on-going open-label extension trial) were evaluated for the efficacy and safety of rosuvastatin.

Three Phase III, randomized, double-blind, active-controlled, multi-center trials, in subjects with Fredrickson Type IIa (LDL-C ≥130, TG <200) and IIb (LDL-C ≥130, TG ≥200) dyslipidemia, were reviewed in this report (Trials 24, 25, and 26). Another FDA statistician, Joy Mele, reviewed the other 11 clinical trials. Trial 24 was also placebo-controlled. CRESTOR™ 5 mg and 10 mg were the two starting doses in those 3 trials, while Lipitor® (atorvastatin) was the active comparator starting at the 10-mg dose. Both Trials 24 and 25 were conducted in USA/Canada; Trial 26 was in Europe. Trial 25 recruited high-risk subjects defined as not only having Type IIa/IIb dyslipidemia, but also having documented atherosclerosis or Type II diabetes mellitus. The total numbers of randomized subjects were 519, 383, and 412 for Trials 24, 25, and 26, respectively. The principal findings and conclusions based on those three trials are summarized as follows.

- This reviewer's results generally agree with the sponsor's results.

- Data from ZD4522 5-, 10-, 20-, 40-, 80-mg doses show that rosuvastatin reduced LDL-C levels by more than 15% from baseline, a clinically meaningful reduction based on FDA 1990 Guidelines, in adult subjects with Type IIa/IIb dyslipidemia, regardless of gender, age, race, weight, atherosclerotic disease, and diabetes.

- Significant reductions in LDL-C were seen by Week 2, the first post-baseline time point that LDL-C was measured and statistically analyzed. Efficacy was sustained beyond Week 6. The ZD4522 5- and 10-mg doses reduced LDL-C by at least 40% after 12 weeks of treatment.

- Data from Trial 24 (placebo- and active-controlled trial) demonstrate that rosuvastatin 5- and 10-mg doses were highly effective in improving LDL-C, TC, HDL-C, non-HDL-C, TG, and ApoB levels, in a dose-related fashion (except HDL-C), when compared with the placebo group.

- The ZD4522 10-mg, 40-mg, and 80-mg doses were statistically and clinically more effective than the atorvastatin 10-mg, 40-mg, and 80-mg doses, respectively, in lowering LDL-C levels. As a result, it is concluded that at the doses tested, a mg dose of rosuvastatin was more efficacious than a mg dose of atorvastatin. The trials were powered based on a clinically meaningful difference of 6% change in LDL-C.

- The ZD4522 5-mg and 20-mg doses were statistically, but not clinically, more effective than the atorvastatin 10-mg and 40-mg doses, respectively, in lowering LDL-C levels. As a result, it is concluded that the 5- and 20-mg doses of ZD4522 were as effective as the 10- and 40-mg doses of atorvastatin, respectively.

- The benefits seen in the higher doses of ZD4522 (e.g., 20-, 40-, and 80-mg) were based on only 6 weeks of titration data of high-risk subjects in Trial 25. Therefore, any safety concerns (e.g., liver toxicity and muscle adverse event) or results from the dose-ranging study (Trial 33) should be accounted for in the determination of the efficacy of the higher doses of ZD4522.

- Data from Trial 25 suggest that the clinical benefit of ZD4522 80-mg dose with regard to LDL-C lowering was similar to its own 40-mg dose.

- In general, both rosuvastatin and atorvastatin showed greater LDL-C reductions in females than in males, and in older subjects compared to younger ones.

- Rosuvastatin consistently showed numerically greater reductions in TC, non-HDL-C, and ApoB, when compared with the atorvastatin. However, the differences were not always statistically significant.

- Rosuvastatin did not significantly increase HDL-C consistently across the three trials reviewed here, when compared with the atorvastatin. The changes in the TG levels were similar between rosuvastatin and atorvastatin.

2. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

The sponsor has submitted the results of 15 Phase II/III clinical trials (including one on-going open-label extension trial) conducted on subjects with dyslipidemias, for the new drug application (NDA 21-366) for CRESTOR™ (rosuvastatin calcium, ZD4522). Rosuvastatin is a new member of the statin class of lipid-regulating agents. The intended indications are as follows:

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

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

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

One purpose of rosuvastatin development program was to identify a starting dose (*a priori*) that would provide a clinically significantly increased efficacy, with no increased risk, over the starting doses of other HMG-CoA reductase inhibitors such as atorvastatin, simvastatin, and pravastatin. Doses up to 80 mg for these statins were studied in this program. Efficacy and safety profiles of rosuvastatin were also compared with and in combination with non-statin lipid-regulating agents such as fenofibrate, extended-release niacin, and cholestyramine.

Among those 15 Phase II/III clinical trials, Trials 34 (extension trial) and 54 were uncontrolled trials and still ongoing at the time of the submission. The key elements and designs of the other 13 controlled clinical trials are summarized below (Text Table 1). This review presents the results and conclusions based on Trials 24, 25, and 26.

Text Table 1 – Summary of Key Design of Rosuvastatin Controlled Clinical Trials

Trial No./Design/Location	N	Mean Age Gender	Rosuvastatin dose (mg/day)	Comparator or combination dose (mg/day)	Baseline (mg/dL)	Primary endpoint % Δ
Treatment in subjects with Type IIa/IIb dyslipidemia						
8 Randomized, DB, placebo controlled, dose-ranging; Europe	142	55 y 94 m 48 f	1/2.5/5/10/ 20/40	Placebo Atorvastatin 10/80 (open-label)	LDL-C: 160-<220	LDL-C at 6 w
23 Randomized, DB, placebo controlled, dose-ranging; Europe	64	58 y 35 m 29 f	40/80	Placebo	LDL-C: 160-<220	LDL-C at 6 w
24 Randomized, DB, placebo controlled, active controlled; USA/Canada	519	57 y 240 m 279 f	5/10	Placebo Atorvastatin 10	LDL-C: 160-<250	LDL-C at 12 w
25 Randomized, DB, active controlled, force-titration; USA/Canada	383	62 y 232 m 151 f	5/10/20/40/80	Atorvastatin 10/40/80	LDL-C: 160-<250	LDL-C at 24 w
26 Randomized, DB, active controlled, titration to NCEP II goals up to 52 weeks; Europe	412	57 y 233 m 179 f	5/10/20/40/80	Atorvastatin 10/20/40/80	LDL-C: 160-<250	LDL-C at 12 w[a]
27 Randomized, DB, active controlled; Europe	502	59 y 238 m 264 f	5/10	Pravastatin 20 Simvastatin 20	LDL-C: 160-<250	LDL-C at 12 w
28 Randomized, DB, active controlled, titration to NCEP II goals up to 52 weeks; USA/Canada	477	59 y 186 m 291 f	5/10/20/40/80	Pravastatin 20/40 Simvastatin 20/40/80	LDL-C: 160-<250	LDL-C at 12 w[a]
33 Randomized, DB, active controlled, dose-ranging; USA/Canada	374	57 y 194 m 180 f	5/10/20/40/80	Atorvastatin 10/20/40/80	160-<250	LDL-C at 6 w

The sponsor's ISE Tables 3, 32, and 40 modified
N = total number of subjects randomized to treatment
% Δ = percent change from baseline
DB = double-blind; y = years; m = male; f = female; w = weeks
[a] The primary endpoint measurement was at the time of trial completion, except for Trials 26, 28, and 31, where the duration of the trials lasted 52, 52, and 12 weeks, respectively.

Text Table 1 – Summary of Key Design of Rosuvastatin Controlled Clinical Trials (Contd.)

Trial No./Design/Location	N	Mean Age Gender	Rosuvastatin dose (mg/day)	Comparator or combination dose (mg/day)	Baseline (mg/dL)	Primary endpoint % Δ
Treatment in subjects with familial and nonfamilial hypercholesterolemia (heterozygous and homozygous)						
30 Randomized, DB, active controlled, force-titration in subjects with heterozygous FH; Europe, USA, S Africa, Australia	623	48 y 342 m 281 f	20/40/80	Atorvastatin 20/40/80	LDL-C: 220-<500	LDL-C at 18 w
31 Randomized, open-label combination in subjects with heterozygous FH or nonfamilial hypercholesterolemia; USA	153	55 y 85 m 68 f	40/80	Combination with cholestyramine 16 g is in ISE Section 6.2.	LDL-C: 190-≤400	LDL-C at 6 w[a]
Treatment in subjects with Type IIb or IV dyslipidemia						
29 Randomized, force-titration in subjects with Type IIb or IV dyslipidemia in comparison and combination; USA	270 162 IIb 101 IV	56 y 194 m 76 f	10/20/40	Niacin (extended-release) 0.5/1.0/1.5/2.0 g (the combination data are in ISE Section 6.1)	TG: 200-800 TC: ≥200 HDL-C: <45 ApoB ≥110	LDL-C at 24 w
35 Randomized, DB, placebo-controlled, dose ranging in subjects with Type IIb or IV dyslipidemia; USA, Canada	156 65 IIb 88 IV	56 y 94 m 62 f	5/10/20/40/80	Placebo	TG: 300-<800	TG at 6 w
36 Randomized, 6 week DB, placebo-controlled; subsequent 18-week open-label force-titration, comparison and combination, in Type 2 diabetes mellitus subjects with Type IIb or IV dyslipidemia; Europe	216 144 IIb 62 IV	60 y 110 m 106 f	DB: 5/10 OL: 5/10/20/40	DB: Placebo OL: Fenofibrate 67 mg qd/bid/tid (the combination data are in ISE Section 6.3)	TG: 200-<800 TC: ≥200	TG at 24 w

The sponsor's ISE Tables 3, 32, and 40 modified
N = total number of subjects randomized to treatment
% Δ = percent change from baseline; DB = double-blind; y = years; m = male; f = female; w = weeks
FH = familial hypercholesterolemia; OL = open label; qd/bid/tid = once/twice/three times daily
The number of IIb + IV subjects were those in the ITT population.
[a] The primary endpoint measurement was at the time of trial completion, except for Trials 26, 28, and 31, where the trial duration periods were 52, 52, and 12 weeks, respectively.

2.2 Data Analyzed and Sources

The sponsor has provided extensive electronic data sets for this submission. The data files this reviewer used to do her own independent analyses for efficacy were LIPIDS.XPT in \\CDSESUB1\N21366\N_000\2001-06-26\crt\datasets\il0024, \il0025, and \il0026. In those files, the sponsor has flagged the data points that would be carried forward. Therefore, this reviewer was able to extract the last-observation-carried-forward (LOCF) data sets easily by using those flags. According to the statistical analysis plans, in case of repeated values collected at a post-baseline visit, the first value (scheduled visit value) should be used for the observed data, while the last repeated value (collected after the scheduled visit) should be used for the LOCF data. However, for a few patients, the first values of the last scheduled visit were flagged as the LOCF data points. Since they occurred sporadically among the treatment groups, this reviewer felt that the impact should not pose any major problem on the overall efficacy conclusion.

2.3 Statistical Evaluation of Evidence on Efficacy

There were at least 10 secondary lipid variables investigated in this clinical program as well as other secondary measures (e.g., percentage of subjects achieving NCEP guidelines). Based on consultation with the medical officers, ApoA-I, ApoB/ApoA-I, Lp(a), lipid ratios using HDL-C as the denominator, and any other secondary measures described in the individual protocols would not be the focus of the review. In other words, only LDL-C (primary variable) and TC, TG, HDL-C, and ApoB (secondary variables) were evaluated for Trials 24, 25, and 26. Non-HDL-C, an additional secondary variable, was also reviewed according to the medical officers' request.

Basically, the designs of Trials 24 (12-week), 25 (24-week), and 26 (52-week) were similar in terms of entry criteria, visit structures, and dosing regimens for the first 12 weeks fixed-dose period following randomization at Week 0. Trial 25 went on for an additional 12 weeks consisting of two 6-week forced-titration periods to compare the doses at 80 mg, while Trial 26 went on for an additional 40 weeks of titration period to achieve NCEP II goals (see the design details under each trial). Atorvastatin (Lipitor®) is the common active comparator for the three clinical trials. According to the protocols, the subjects were randomized to treatment in balanced blocks at each center.

Throughout this review report, ZD5, ZD10, and AT10 are used as the abbreviations for ZD4522 5 mg, ZD4522 10 mg, and atorvastatin 10 mg, respectively. Likewise, ZD20, ZD40, ZD80, AT20, AT40, and AT80 are used for 20-, 40-, and 80-mg of ZD4522, and 20-, 40-, and 80-mg of atorvastatin, respectively.

2.3.1 Sponsor's Results and Conclusions

In general, this reviewer and sponsor's results (Text Table 2) for Trials 24, 25, and 26 are in concurrence.

Text Table 2– Abstract of Sponsor's Results for Trials 24, 25, and 26 for ITT Population

Efficacy Endpoint	Placebo	ZD5	ZD10	AT10	ZD80	AT80
Trial 24: least-squares mean % change from baseline at Week 12 (LOCF)						
LDL-C	0.03	–40.43 [c, e]	–42.85 [c, f]	–35.12		
TC	0.23	–27.91 [c, d]	–29.70 [c, f]	–25.31		
HDL-C	3.84	12.51 [c, e]	11.65 [c, e]	7.99		
TG	–1.00	–16.56 [c, nss]	–18.57 [c, nss]	–18.75		
ApoB	4.39	–31.25 [c, e]	–32.99 [c, f]	–26.48		
Trial 25: least-squares mean % change from baseline at Weeks 12 and 24 (LOCF)						
LDL-C		-39.84 [e]	-47.13 [f]	-35.03	-59.56 [f]	-52.03
TC		-29.14 [d]	-33.92 [f]	-26.76	-43.24 [e]	-39.51
HDL-C		6.61 [e]	7.69 [f]	2.66	8.05 [f]	0.94
TG		-17.44 [nss]	-19.75 [nss]	-17.80	-24.59 [nss]	-27.05
ApoB		-31.52 [d]	-36.38 [f]	-28.28	-47.21 [e]	-42.82
Trial 26: least-squares mean % change from baseline at Week 12 (LOCF)						
LDL-C		-45.58 [f]	-50.08 [f]	-39.48		
TC		-31.89 [f]	-35.25 [f]	-28.10		
HDL-C		6.21 [nss]	8.04 [nss]	6.23		
TG		-15.06 [nss]	-19.11 [nss]	-16.21		
ApoB		-35.23 [d]	-39.72 [f]	-32.18		
Trial 26: least-squares mean % change from baseline at Week 52 (observed)						
LDL-C		-47.12 [d]	-53.20 [f]	-44.34		
TC		-34.42 [nss]	-38.32 [f]	-32.83		
HDL-C		1.88 [nss]	3.48 [d]	-0.58		
TG		-19.62 [nss]	-21.39 [nss]	-18.69		
ApoB		-38.68 [nss]	-43.39 [f]	-37.56		

[a] = $p \le 0.05$, [b] = $p \le 0.01$, [c] = $p \le 0.001$, [ns] = not significant, compared with placebo

[d] = $p \le 0.05$, [e] = $p \le 0.01$, [f] = $p \le 0.001$, [nss] = not significant, compared with atorvastatin

The sponsor's Tables 47, 48, and 49 in Clinical Data Summary and Results of Statistical Analysis modified

In the sponsor's Trials 24 and 25 clinical reports, although center was mentioned as being one of the factors in the analysis of variance (ANOVA) model, region was actually used in the model, where centers were pooled according to the geographic locations (e.g., east, west,

central, etc.). In Trial 26, centers were pooled by country. This reviewer noted that in those 3 trials, some centers had only 1 eligible patient, while others had as high as 42 patients (see the details under subject disposition of each trial), even though the protocols called for a minimum of 10 completed subjects from each center. To avoid the sparseness problem, this reviewer did not oppose using region or country, instead of center, as one of the factors in the ANOVA model.

Overall, the sponsor's conclusions for Trials 24, 25, and 26 are summarized below.

- Both ZD4522 5 mg and 10 mg showed highly significant decreases in LDL-C, TC, TG, and ApoB, and increases in HDL-C, over that of the placebo at Week 12.
- Both ZD4522 5 mg and 10 mg showed significantly more reductions in LDL-C than that of atorvastatin 10 mg at the end of the fixed-dose period (Week 12). The difference in the reductions between ZD4522 10 mg and atorvastatin 10 mg was at least 6% consistently across the three trials. The significant finding in favoring ZD4522 lowering LDL-C was also seen during the titration periods in Trials 25 and 26.
- Significantly greater reductions in TC and ApoB were also observed in both ZD4522 5-mg and 10-mg groups when compared with the atorvastatin 10-mg group at Week 12 in those three trials. The ZD4522 10-mg group also consistently showed significantly greater reductions in TC and ApoB during the titration periods, but the ZD4522 5-mg group did not, when compared with the atorvastatin group.
- The reduction levels in TG were similar among the ZD4522 5-mg, ZD4522 10-mg, and atorvastatin 10-mg groups at Week 12, and even during the titration periods, in those three trials.
- The ZD4522 5-mg and 10-mg groups responses to HDL-C were not consistently significantly better than the atorvastatin 10-mg group during the fixed-dose or titration period across the three trials.
- The results of Trial 25 suggest that lower doses of ZD4522 can be as effective as higher doses of atorvastatin.

2.3.2 Statistical Methodologies

This reviewer basically employed the same statistical model and testing techniques as the sponsor did to analyze the lipid variables of interest in Trials 24-26. Specifically, analysis of variance (ANOVA) and linear contrast techniques were used as described below.

The initial ANOVA model including treatment, region, and treatment by region interaction terms was tested on the percentage change from baseline in LDL-C. Since there was no significant treatment by region interaction at $p < 0.05$ (specified in the protocols) suggesting

similar response patterns across regions or treatments, the model consisting of only treatment and region main effects was then used as the main statistical model for all the analyses.

Linear contrasts were implemented to compare the efficacy of ZD4522 group (either individual or combined group) with that of atorvastatin group. Comparisons with placebo group were also made for Trial 24. To compare the combined ZD4522 80-mg group with atorvastatin 80-mg group (maximum titrated doses) in Trial 25, the sponsor simply pooled the two ZD4522 groups together and compared with atorvastatin group. This reviewer did an additional analysis by keeping the 3 groups in the ANOVA model and using contrast coefficients 0.5, 0.5, -1 for ZD5/20/80, ZD10/40/80, AT10/40/80, respectively, to estimate the treatment difference, to account for variations due to randomization and different titration histories in those 3 treatment groups.

The sponsor claimed that an additional 5-7% reduction from baseline in LDL-C with dose doubling was observed based on the data from previous studies of ZD4522 and other statins. Therefore, they proposed a 6% difference in percentage change from baseline in LDL-C between active treatment groups be considered as clinically significant. This figure was agreed to by the medical officers and statisticians, as noted in the sponsor's communication log with FDA.

No multiple-comparison adjustment to the false positive rate was needed due to the fact that (1) sequential testing techniques were applied to the comparisons between treatment groups; (2) combined tests of superiority and non-inferiority with a 6% non-inferiority margin were conducted based on closed testing procedure.

For the primary variable (LDL-C), the LOCF data of percentage change from baseline at Week 12 (the end of the fixed-dose period) and the observed (OBS) data at all post-baseline time points were analyzed. Only the results from the LOCF data are tabulated. The least-squares means of percentage change from baseline for the OBS data are plotted along with statistical significance. For Trial 25, the LOCF data at Weeks 18 and 24 (forced-titration periods) were also analyzed.

For the secondary variables of interest (TC, HDL-C, non-HDL-C, TG, and ApoB), the stated endpoints in the protocols were analyzed for the LOCF data. The least-squares means over time for the OBS data are graphically presented in the Appendix, except for ApoB since data were not collected at the intermediate time points.

All data analyzed by this reviewer were based on the intention-to-treat (ITT) population that consisted of all the randomized subjects who had a baseline and at least 1 post-baseline lipid

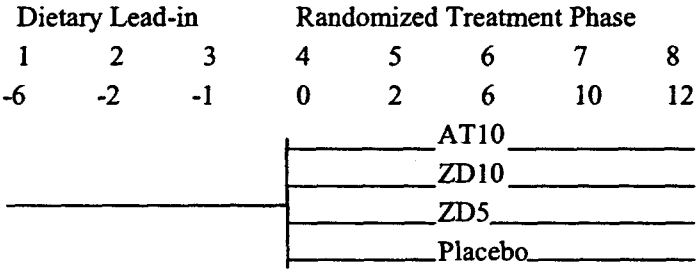
reading, as defined by the sponsor. The baseline value used in the calculation of percentage change from baseline was an average of 3 consecutive scheduled visit values immediately prior to treatment, where applicable.

2.3.3 Detailed Review of Individual Studies

2.3.3.1 Trial 4522IL/0024 (from 4/19/1999 to 2/17/2000)

Trial Design and Objectives

Trial 24 was a 12-week, randomized, double-blind, placebo- and active-controlled, 4-parallel-group, multicenter (in USA/Canada) trial, conducted in adult subjects ≥18 years old with hypercholesterolemia (Fredrickson Type IIa/IIb dyslipidemia). A 6-week dietary lead-in period was followed by a 12-week randomized treatment period (see the diagram below).



The primary objective of this trial was to compare the efficacy of ZD4522 5 mg and 10 mg with that of atorvastatin 10 mg and placebo in the reduction of LDL-C levels. The associated primary endpoint was percentage change from baseline in LDL-C at Week 12.

The stated secondary objective of interest in this review was to compare the efficacy of the aforementioned treatment groups in modifying other lipids and lipoproteins. The associated secondary endpoints were percentage change from baseline in TC, HDL-C, TG, and ApoB at Week 12, and in LDL-C, TC, HDL-C, and TG at Weeks 2, 6, and 10.

Subject Disposition

There were 1888 outpatients recruited from 52 centers (mostly in USA) and 519 of them were eligible for randomization at Week 0 (72.5% screen failure rate): 132, 129, 130, and 128 subjects for placebo, ZD5, ZD10, and AT10, respectively (Text Table 3). Three patients did not take any trial medication and were excluded from the ITT population. The overall withdrawal rate during the randomized treatment period was 6.9% (= 36/519) with no group having a withdrawal rate greater than 10%. The reasons for withdrawal were similar across treatment groups (Text Table 4). Adverse events were apparently the most common recorded reason for withdrawal in this trial.

Text Table 3 – Trial 24: Subject Disposition during Randomized Treatment Phase

	Placebo		ZD5		ZD10		AT10		Total
Randomized	**132**		**129**		**130**		**128**		**519**
No medication taken	(0)		(1)		(1)		(1)		(3)
ITT population	**132**		**128**		**129**		**127**		**516**
Withdrawals	11 (8.3%)		9 (7.0%)		8 (6.2%)		8 (6.25%)		36 (6.9%)
	A	B	A	B	A	B	A	B	
Week 0	132	0	129	0	130	0	128	0	
Week 2	132	3	129[a]	6[a]	130[a]	2[a]	128[a]	1[a]	
Week 6	129	4	123	2	128[b]	4[b]	127	6	
Week 10	125	1	121	1	124	1	121	0	
Week 12	124	3	120	0	123	1	121	1	
Completers	121 (91.7%)		120 (93.0%)		122 (93.8%)		120 (93.75%)		483 (93.1%)

[a] = Including 1 subject not taking any trial medication

[b] = Including 1 subject having no recorded date of withdrawal

A = Total number of subjects completed at the scheduled week

B = Total number of subjects withdrew at the end or after the scheduled week

Text Table 4 – Trial 24: Number (%) of Subjects Withdrawal during Randomized Treatment Period

Reason for withdrawal	Placebo	ZD5	ZD10	AT10
Number of randomized subjects	132	129	130	128
Adverse event	7 (5.3)	6 (4.7)	4 (3.1)	4 (3.1)
Informed consent withdrawn	0	2 (1.6)	1 (0.8)	4 (3.1)
Subject lost to follow-up	3 (2.3)	1 (0.8)	2 (1.5)	0
Protocol non-compliance	1 (0.8)	0	0	0
Not recorded[a]	0	0	1 (0.8)	0
Total	**11 (8.3)**	**9 (7.0)**	**8 (6.2)**	**8 (6.3)**

The sponsor's Table 14 modified

[a] = After the database was closed, this subject's (47/08) withdrawal was identified as "informed consent withdrawn".

The 516 ITT subjects came from 51 centers, where 27 centers had <10 randomized patients each (as low as 2 patients) and 24 centers had ≥10 each (as high as 38 patients). The sponsor grouped those centers into 5 regions: Northeast, Southeast, Central, West, and Canada. Within each region, the numbers of subjects were similar across treatment groups (Text Table 5) implying to this reviewer that balanced randomizations within each center, and consequently, within pooled centers, were obtained.

Text Table 5 – Trial 24: Number of Subjects in Each Region per Treatment Group

	Region 1 Northeast	Region 2 Southeast	Region 3 Central	Region 4 West	Region 5 Canada	Total
Placebo	24	33	41	21	13	132
ZD5	23	30	42	22	11	128
ZD10	24	32	38	22	13	129
AT10	23	34	39	19	12	127
Total Subjects	94	129	160	84	49	516
Total Centers Pooled	10	15	11	11	4	51

Demographics

Based on this reviewer's analyses, demographic characteristics such as age, sex, race, weight, and BMI were generally homogeneous across the treatment groups (Text Table 6). The overall mean age was 57 years ranging from 24 to 82, with 27.4% of 519 subjects ≥65 years old. Almost 85% and 8% of 519 subjects were Caucasian and black, respectively. The mean BMI was 29 kg/m^2 ranging from 18 to 60, with 35.2% of 517 subjects having BMI >30.

Text Table 6 – Trial 24: Demographic Characteristics of All Randomized Subjects

Characteristic	Placebo	ZD5	ZD10	AT10
Number of randomized subjects	132	129	130	128
Age (years):				
Mean ± SD	56.6 ± 11.2	57.9 ± 10.8	57.2 ± 10.4	56.4 ± 12.7
Range	30 – 82	32 – 79	30 – 80	24 – 82
18 to 64 (%)	97 (73.5)	87 (67.4)	98 (75.4)	95 (74.2)
≥65 (%)	35 (26.5)	42 (32.6)	32 (24.6)	33 (25.8)
Sex:				
Male (%)	68 (51.5)	53 (41.1)	59 (45.4)	60 (46.9)
Female (%)	64 (48.5)	76 (58.9)	71 (54.6)	68 (53.1)
Race:				
Caucasian (%)	107 (81.1)	113 (87.6)	115 (88.5)	105 (82.0)
Black (%)	12 (9.1)	8 (6.2)	8 (6.2)	12 (9.4)
Other[a] (%)	13 (9.8)	8 (6.2)	7 (5.4)	11 (8.6)
Weight (kg): Mean ± SD	82.93 ± 17.40	79.50 ± 14.71	81.46 ± 15.02	83.86 ± 17.94
BMI (kg/m^2):				
Mean ± SD	29.25 ± 5.56	28.30 ± 4.84[b]	28.61 ± 4.59	29.62 ± 6.40
<20 kg/m^2 (%)	2 (1.5)	3 (2.4)	0	1 (0.8)
20 – 30 kg/m^2 (%)	81 (61.4)	82 (64.6)	84 (64.6)	82 (64.1)
>30 kg/m^2 (%)	49 (37.1)	42 (33.1)	46 (35.4)	45 (35.2)

[a] = Including Hispanic of Latino origin, Asian, native Hawaiian or Pacific Islander, or other unspecified
[b] = No BMI collected for 2 subjects; The sponsor's Table 12 modified

Note that although the treatment distributions were similar in each sex, there were actually slightly more females than males in each of the 3 active treatment groups.

Efficacy Results and Discussion

Primary Variable: LDL-C. Based on this reviewer's analyses, the baseline LDL-C values were comparable among the 4 study groups. The mean LDL-C changes from baseline at Week 12 in the ZD5, ZD10, and AT10 groups were -40.43%, -42.85%, and -35.12%, respectively, while the placebo group showed a slightly increased mean LDL-C from baseline, +0.03% (Text Table 7). It is apparent that the reductions in both ZD4522 5- and 10-mg groups were significantly greater than that of the atorvastatin 10-mg group at Week 12 (Text Table 8). The observed treatment differences in the mean percentage change from baseline in LDL-C between ZD5 and AT10 were –5.31%, and –7.73% between ZD10 and AT10, in favor of the two ZD4522 5- and 10-mg doses based on the LOCF data at Week 12. However, the data also suggest that the ZD4522 5- and 10-mg doses could be better than the atorvastatin 10-mg dose in lowering LDL-C by only 1.87% and 4.30%, respectively, according to the 95% upper confidence limit.

Text Table 7 – Trial 24: Descriptive Statistics for LDL-C Using LOCF Data at Week 12

ITT Population	Placebo	ZD5	ZD10	AT10
Raw mean LDL-C ± standard deviation (sample size)				
Baseline	186.6 ± 21.0 (132)	188.4 ± 19.2 (128)	184.5 ± 17.1 (129)	185.5 ± 19.6 (127)
Week 12	186.7 ± 31.7 (132)	112.6 ± 26.2 (128)	105.9 ± 32.9 (129)	120.7 ± 28.1 (127)
Least-squares mean % change from baseline ± standard error (sample size)				
Week 12	0.03 ± 1.24 (132)	-40.43 ± 1.27 (128)	-42.85 ± 1.25 (129)	-35.12 ± 1.27 (127)

Text Table 8 – Trial 24: Results for % Change from Baseline in LDL-C Using LOCF Data at Week 12

ITT Population	Comparison	Treatment Difference	p-value	(LCL, UCL)
Week 12	ZD5 vs. Placebo	-40.46	<.0001 **	(-43.87, -37.06)
	ZD10 vs. Placebo	-42.88	<.0001 **	(-46.28, -39.48)
Week 12	ZD5 vs. AT10	-5.31	0.0025 **	(-8.75, -1.87)
	ZD10 vs. AT10	-7.73	<.0001 **	(-11.16, -4.30)

LCL = 95% lower confidence limit; UCL = 95% upper confidence limit

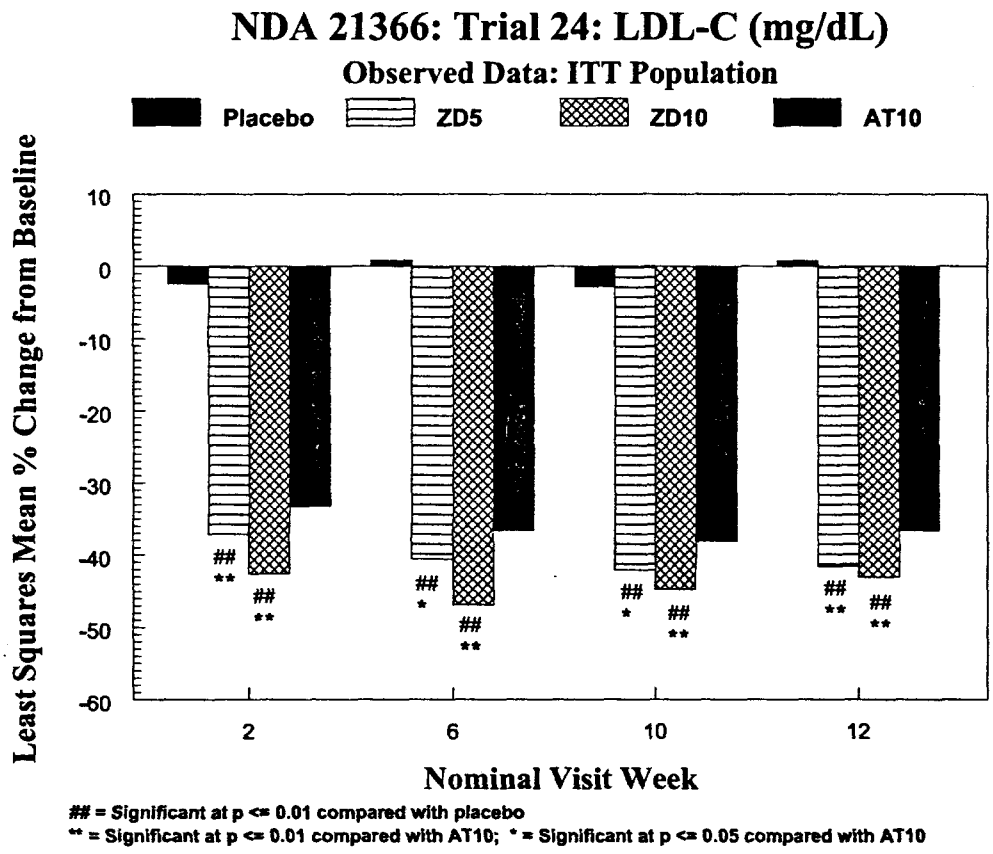
Treatment difference in negative direction favors ZD4522.

** = Significant at $p \leq 0.01$

It is also evident that both ZD4522 groups were superior to the placebo group in reducing LDL-C at Week 12.

The least-squares means of percentage change from baseline in LDL-C at Weeks 2, 6, 10, and 12 for the 4 treatment groups are shown in Text Figure 1 below based on the observed data. The LDL-C levels in the 3 active treatment groups (ZD5, ZD10, and AT10) were all decreased by at least 30% from baseline at Week 2, and decreased further at Week 6, then were maintained (or slightly increased) throughout the rest of the trial. The % reductions in both ZD4522 groups were significantly larger than those of the placebo and atorvastatin 10-mg groups at all time points. The placebo group did not show much decrease or increase in LDL-C during the 12-week course of the trial.

Text Figure 1



Secondary Variables: TC, HDL-C, non-HDL-C, TG, and ApoB. This reviewer's results for the secondary variables of interest for Trial 24 (TC, HDL-C, TG, and ApoB) generally concur with the sponsor's (see Text Table 2). For non-HDL-C, the mean changes from

baseline at Week 12 were –37.08% and –38.97% for the ZD5 and ZD10 groups, respectively, and –0.47% and –32.85% for the placebo and AT10 groups, respectively.

In summary, the ZD4522 5- and 10-mg groups were superior to the placebo group in reducing TC, non-HDL-C, TG, and ApoB levels, and in increasing HDL-C at Week 12 based on the LOCF data. Similar significant findings were also noted for TC, HDL-C, non-HDL-C, and TG at Weeks 2, 6, and 10 based on the observed data.

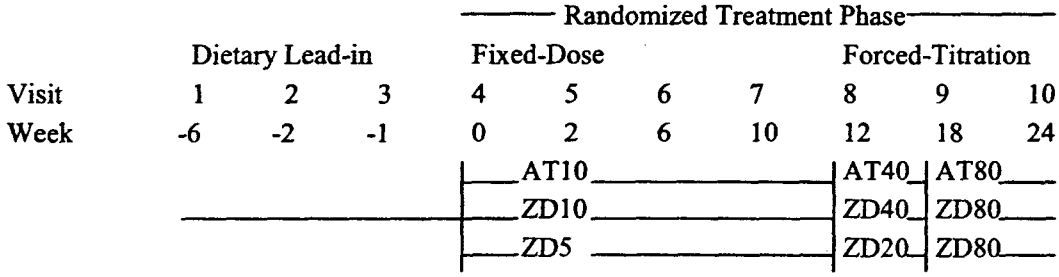
Both ZD4522 groups showed significantly greater reductions in TC, non-HDL-C, and ApoB, and significantly greater elevations in HDL-C, when compared with the atorvastatin 10-mg group at Week 12. However, the % reductions in TG at Week 12 in both ZD4522 groups were similar to that of the atorvastatin 10-mg group. At Weeks 2, 6, and 10 (observed data), the ZD10 group was consistently superior to the AT10 group in lowering TC, but the ZD5 group was only numerically better (not statistically significant) in this case. Both ZD4522 groups significantly reduced non-HDL-C and significantly increased HDL-C when compared with the atorvastatin group at all intermediate time points. The % reductions in TG at Weeks 2, 6, and 10 were similar among the 3 active treatment groups.

Figures 1-4 in the Appendix presents the graphs of means % change from baseline over time for TC, HDL-C, non-HDL-C, and TG for Trial 24.

2.3.3.2 Trial 4522IL/0025 (from 7/28/1999 to 11/16/2000)

Trial Design and Objectives

Trial 25 was a 24-week, randomized, double-blind, active-controlled, 3-parallel-group, force-titration, multicenter (in USA/Canada) trial, conducted in adult subjects ≥18 years old with not only hypercholesterolemia (Fredrickson Type IIa/IIb dyslipidemia), but also documented atherosclerosis or Type II diabetes mellitus (high-risk subjects). A 6-week dietary lead-in period was followed by a 12-week randomized treatment period; then the subjects were given the intermediate doses at Week 12 for 6 weeks and the maximum doses at Week 18 for another 6 weeks (see the diagram below), if their most recent LDL-C levels were >50 mg/dL at the time of determination for titration. Otherwise, they remained on their current doses.



The primary objective of this trial was to compare the efficacy of ZD4522 80 mg with that of atorvastatin 80 mg in the reduction of LDL-C levels. The associated primary endpoint was percentage change from baseline in LDL-C at Week 24 (the end of the titration period).

The stated secondary objectives of interest in this review were to compare the efficacy of the aforementioned treatment groups in the reduction of LDL-C after 12 and 18 weeks of treatment, and in modifying other lipids and lipoproteins after 12, 18, and 24 weeks of treatment. The associated secondary endpoints were percentage change from baseline in LDL-C at Weeks 12 and 18, and in TC, HDL-C, TG, and ApoB at Weeks 12, 18, and 24.

Subject Disposition

There were 1233 outpatients recruited from 68 centers (mostly in USA) and 383 of them were eligible for randomization at Week 0 (68.9% screen failure rate): 127, 128, and 128 subjects for ZD5/20/80, ZD10/40/80, and AT10/40/80, respectively (Text Table 9). One patient did not take any trial medication and was excluded from the ITT population.

Text Table 9 – Trial 25: Subject Disposition during Randomized Treatment Phase

	ZD5/20/80		ZD10/40/80		AT10/40/80		Total
Randomized	**127**		**128**		**128**		**383**
No medication taken	(0)		(0)		(1)		(1)
ITT population	**127**		**128**		**127**		**382**
Withdrawals	12 (9.4%)		11 (8.6%)		15 (11.7%)		38 (9.9%)
	A	B	A	B	A	B	
Week 0	127	0	128	0	128	0	
Week 2	127	1	128	0	128[a]	1[a]	
Week 6	126	1	128	3	127	4	
Week 10	125	3	125	1	123	1	
Week 12	122	0	124	1	122	2	
Week 18	122	3	123	4	120	4	
Week 24	119	4	119	2	116	3	
Completers	115 (90.6%)		117 (91.4%)		113 (88.3%)		345 (90.1%)

[a] = Including 1 subject not taking any trial medication

A = Total number of subjects completed at the scheduled week

B = Total number of subjects withdrew at the end or after the scheduled week

One subject was randomized to AT10, but given ZD5 at Week 0 for about a week.

The overall withdrawal rate during the randomized treatment period was 9.9% (= 38/383), where AT10/40/80 group showed a slightly higher withdrawal rate (11.7%) than each of the two ZD4522 groups (both <10%). The withdrawal rates at the end of the fixed-dose period (Week 12) were 3.9%, 3.9%, and 6.3% for ZD5, ZD10, and AT10, respectively.

Informed consent withdrawn and adverse events were the most common recorded reasons for withdrawal in this trial (Text Table 10). Most of the adverse events were reported at Weeks 18 and 24 during the titration period, especially in the ZD10/40/80 and AT10/40/80 groups (see the sponsor's Table G5.2).

Text Table 10 – Trial 25: Number (%) of Subjects Withdrawal during Randomized Treatment Period

Reason for withdrawal	ZD5/20/80	ZD10/40/80	AT10/40/80
Number of randomized subjects	127	128	128
Informed consent withdrawn	8 (6.3)	4 (3.1)	6 (4.7)
Adverse event	4 (3.1)	6 (4.7)	8 (6.3)
Investigator's discretion	0	1 (0.8)	0
Subject unable to make visit	0	0	1 (0.8)
Total	**12 (9.4)**	**11 (8.6)**	**15 (11.7)**

The sponsor's Table 13 modified

The 382 ITT subjects came from 57 centers, where 43 centers had <10 randomized patients each (as low as 1 patient) and 14 centers had ≥10 each (as high as 34 patients). The sponsor grouped those centers into 4 regions: Northeast, Southeast, Central, and West/Canada. Within each region, the numbers of subjects were similar across treatment groups (Text Table 11) implying to this reviewer that balanced randomizations within each center, and consequently, within pooled centers, were obtained.

Text Table 11 – Trial 25: Number of Subjects in Each Region per Treatment Group

	Region 1 Northeast	Region 2 Southeast	Region 3 Central	Region 4 West/Canada	Total
ZD5	33	29	46	19	127
ZD10	37	25	43	23	128
AT10	34	29	42	22	127
Total Subjects	104	83	131	64	382
Total Centers Pooled	13	17	19	8	57

Demographics

Based on this reviewer's analyses, demographic characteristics such as age, sex, race, weight, and BMI were generally homogeneous across the treatment groups (Text Table 12). The

overall mean age was 62 years ranging from 23 to 88, with 42.8% of 383 subjects ≥65 years old which might be related to the fact that only high-risk patients were recruited for this trial. Almost 91% and 6% of 383 subjects were Caucasian and black, respectively. The mean BMI was about 29 kg/m^2 ranging from 18 to 52, with 31.7% of 382 subjects having BMI >30.

Text Table 12 – Trial 25: Demographic Characteristics of All Randomized Subjects

Characteristic	ZD5/20/80	ZD10/40/80	AT10/40/80
Number of randomized subjects	127	128	128
Age (year):			
Mean ± SD	62.3 ± 10.2	61.9 ± 10.2	61.9 ± 11.0
Range	36 – 84	24 – 88	23 – 86
18 to 64 (%)	67 (52.8)	77 (60.2)	75 (58.6)
≥65 (%)	60 (47.2)	51 (39.8)	53 (41.4)
Sex:			
Male (%)	80 (63.0)	81 (63.3)	71 (55.5)
Female (%)	47 (37.0)	47 (36.7)	57 (44.5)
Race:			
Caucasian (%)	114 (89.8)	117 (91.4)	117 (91.4)
Black (%)	10 (7.9)	5 (3.9)	7 (5.5)
Hispanic of Latino origin (%)	1 (0.8)	4 (3.1)	2 (1.6)
Other[a] (%)	2 (1.6)	2 (1.6)	2 (1.6)
Weight (kg): Mean ± SD	84.52 ± 15.45	82.79 ± 15.37	82.32 ± 15.49
BMI (kg/m^2):			
Mean ± SD	29.02 ± 4.53	28.22 ± 4.04[b]	29.01 ± 5.10
<20 kg/m^2 (%)	0	2 (1.6)	3 (2.3)
20 – 30 kg/m^2 (%)	85 (66.9)	92 (72.4)	79 (61.7)
>30 kg/m^2 (%)	42 (33.1)	33 (26.0)	46 (35.9)
Diabetes alone (%)	6 (4.7)	2 (1.6)	6 (4.7)
Atherosclerosis alone (%)	110 (86.6)	114 (89.1)	103 (80.5)
Diabetes and atherosclerosis (%)	11 (8.7)	12 (9.4)	19 (14.8)
Diabetes mellitus (%)[c]	17 (13.4)	14 (10.9)	25 (19.5)
Documented atherosclerosis (%)[d]	121 (95.3)	126 (98.4)	122 (95.3)

The sponsor's Table 12 modified
[a] = Including Asian, American Indian or Alaska native, or other unspecified
[b] = No BMI collected for 1 subject
[c] = With or without atherosclerosis
[d] = With or without diabetes mellitus; from the sponsor's Table G2.1.1

As Text Table 12 shows, 3.7% of 383 subjects had Type II diabetes mellitus (without atherosclerosis), 85.4% of the subjects had documented atherosclerosis (without diabetes), and 11% of the subjects had both diseases. The percentage of subjects with diabetes (with or

without atherosclerosis) was higher in the atorvastatin group (19.5%) than in either of the two ZD4522 groups (both <13.5%).

Note that although the gender distributions were similar across the 3 treatment groups, there were actually more males than females in each treatment group (60.6% males and 39.4% females overall).

Efficacy Results and Discussion

Primary Variable: LDL-C. Based on this reviewer's analyses, the baseline LDL-C values were comparable among the 3 study groups. The mean LDL-C changes from baseline at Week 24 (primary endpoint) in the ZD5/20/80, ZD10/40/80, and AT10/40/80 groups were -58.41%, -60.69%, and -52.02%, respectively (Text Table 13). It is apparent that the reductions in each of the two ZD4522 groups, and consequently the combined ZD4522 80-mg group, were all significantly greater than that of the atorvastatin 80-mg group at Week 24 (Text Table 14). The observed treatment difference in the mean percentage change from baseline in LDL-C between the combined ZD4522 and atorvastatin 80-mg groups was -7.52% in favor of the ZD4522 80-mg dose based on the LOCF data at Week 24 (the end of the second forced-titration period). However, the data also suggest that the ZD4522 80-mg dose could be better than the atorvastatin 80-mg dose in lowering LDL-C by only 4.16%, according to the 95% upper confidence limit.

Text Table 13 – Trial 25: Descriptive Statistics for LDL-C Using LOCF Data at Weeks 12, 18, and 24

ITT	ZD5/20/80		ZD10/40/80		ZD Combined	AT10/40/80	
Raw mean LDL-C ± standard deviation (sample size)							
Baseline		188.3 ± 19.2 (127)		186.0 ± 19.5 (128)	187.2 ± 19.4 (255)		187.9 ± 22.8 (127)
Week 12	5	113.3 ± 27.6 (127)	10	98.2 ± 25.8 (128)	NA	10	121.9 ± 25.0 (127)
Week 18	20	91.3 ± 27.4 (127)	40	76.7 ± 26.2 (128)	NA	40	99.6 ± 28.1 (127)
Week 24	80	78.8 ± 34.8 (127)	80	73.6 ± 31.2 (128)	76.2 ± 33.1 (255)	80	90.8 ± 28.5 (127)
Least-squares mean % change from baseline ± standard error (sample size)							
Week 12	5	-39.81 ± 1.10 (127)	10	-47.13 ± 1.09 (128)	NA	10	-35.03 ± 1.10 (127)
Week 18	20	-51.60 ± 1.18 (127)	40	-58.76 ± 1.17 (128)	NA	40	-47.18 ± 1.17 (127)
Week 24[a]	80	-58.41 ± 1.42 (127)	80	-60.69 ± 1.41 (128)	NA	80	-52.02 ± 1.41 (127)
Week 24	80	NA	80	NA	-59.56 ± 1.01 (255)	80	-52.03 ± 1.41 (127)

[a] = Based on 3 groups in this reviewer's analysis, instead of 2 groups in the sponsor's

NA = Not applicable

Note that at Week 18, the dose levels were actually ZD5/20, ZD10/40, and AT10/40. At Week 24, the dose levels were actually ZD5/20/80, ZD10/40/80, and AT10/40/80.

Text Table 14 – Trial 25: Statistical Results for LDL-C Using LOCF Data at Weeks 12, 18, and 24

ITT Population	Comparison	Treatment Difference	p-value	(LCL, UCL)
Week 24[a]	ZD5/20/80 vs. AT10/40/80	-6.38	0.0014 **	(-10.27, -2.49)
	ZD10/40/80 vs. AT10/40/80	-8.66	<.0001 **	(-12.55, -4.78)
	ZD Combined vs. AT10/40/80	-7.52	<.0001 **	(-10.89, -4.16)
Week 24	ZD Combined vs. AT10/40/80	-7.53	<.0001 **	(-10.90, -4.16)
Week 12	ZD5 vs. AT10	-4.81	0.0019 **	(-7.83, -1.79)
	ZD10 vs. AT10	-12.11	<.0001 **	(-15.12, -9.09)
Week 18	ZD5/20 vs. AT10/40	-4.42	0.0074 **	(-7.65, -1.19)
	ZD10/40 vs. AT10/40	-11.58	<.0001 **	(-14.80, -8.36)

[a] = Based on 3 groups in this reviewer's analysis, instead of 2 groups in the sponsor's
Treatment difference in negative direction favors ZD4522.
** = Significant at $p \leq 0.01$; LCL = 95% lower confidence limit; UCL = 95% upper confidence limit

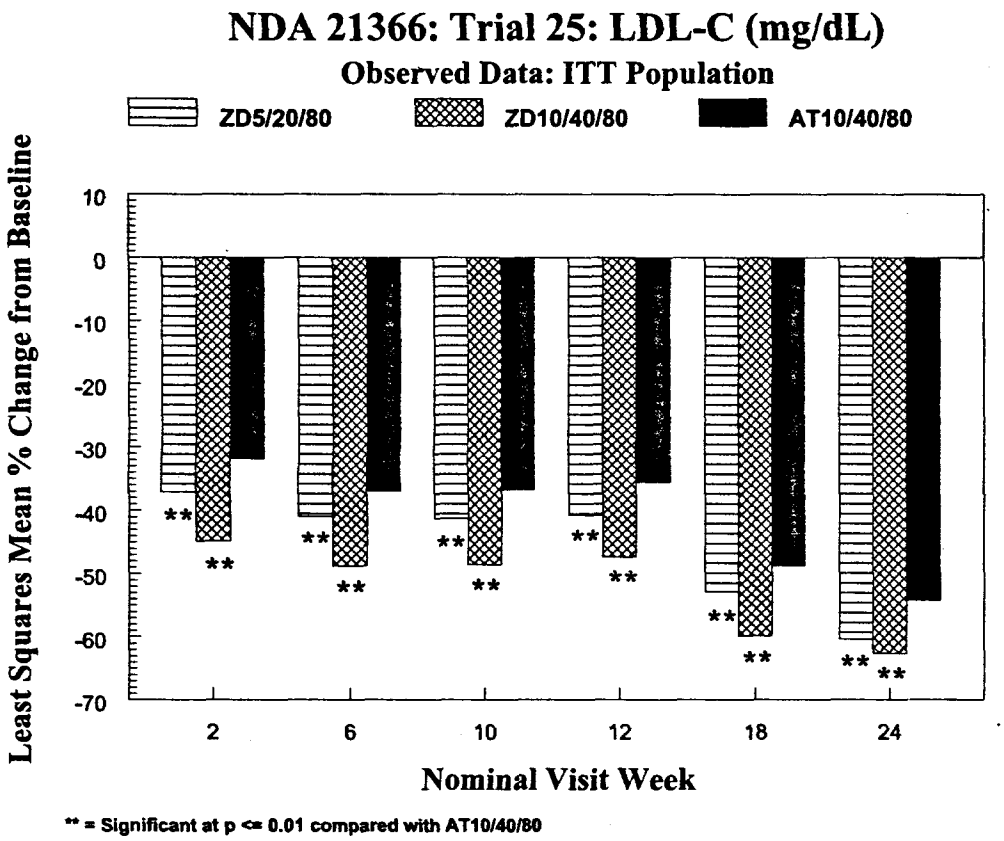
The 39.81% and 47.13% reductions in LDL-C in ZD5 and ZD10, respectively, at Week 12 (secondary endpoint), were both significantly larger than the 35.03% reduction in AT10 at the end of the fixed-dose period. The treatment difference in the reduction of LDL-C between ZD5 and AT10 was –4.81%, and –12.11% between ZD10 and AT10, in favor of the two ZD4522 5- and 10-mg starting doses based on the LOCF data at Week 12. Similar significant findings were also observed in the analyses for the intermediate doses (ZD5/20, ZD10/40, and AT10/40) at Week 18, the end of the first forced-titration period.

Significantly greater percentage reductions in LDL-C in both ZD5/20/80 and ZD10/40/80 groups were also observed at Weeks 2, 6, 10, 12, 18, and 24 using the observed data, when compared with that of the AT10/40/80 group (Text Figure 2). The LDL-C levels in the 3 treatment groups were all decreased by at least 30% from baseline at Week 2, and decreased further at Week 6, then were maintained (or slightly increased) throughout the rest of the 12-week fixed-dose period.

As seen in Text Figure 2, an additional approximately 12-13% reduction in each group was achieved at Week 18 when the subjects in the ZD5, ZD10, and AT10 groups had their doses forced-titrated to the intermediate doses (ZD5/20, ZD10/40, and AT10/40, respectively). This implies to this reviewer that additional clinically meaningful benefit in terms of efficacy might be achieved with 20- or 40-mg doses. However, when the subjects in the ZD5/20, ZD10/40, and AT10/40 groups had their doses forced-titrated again to the 80-mg maximum

doses, only another 7%, 3%, and 5% reductions were observed. In fact, the 7% reduction resulting from increasing the rosuvastatin dose (ZD20 to ZD80) would have likely been only 3-4% if the subjects had received a doubled dose as the other groups, rather than a 4-fold increased dose. It suggests to this reviewer that not much additional benefit was gained when either ZD4522 40-mg or atorvastatin 40-mg dose was increased to the 80-mg dose.

Text Figure 2



Approximately 5%, 7%, and 3% of the subjects completing 12 weeks of treatment in the ZD5, ZD10, and AT10 groups, respectively, were not titrated to receive their intermediate doses (Text Table 15), although they should have been since their LDL-C levels were all >50 mg/dL at the time of determination for titration. Approximately 7%, 20%, and 3% of the subjects in the ZD5/20, ZD10/40, and AT10/40 groups, respectively, at Week 18 did not receive the maximum doses, due to either not being titrated correctly as scheduled or their LDL-C levels being ≤50 mg/dL after exposed to the intermediate doses for 6 weeks. In fact, more subjects with LDL-C ≤50 mg/dL were observed in the ZD10/40/80 group than in the other groups after 18 weeks of treatment.

Text Table 15 – Trial 25: Doses Given during Titration Period Using OBS data

Titration Week		ZD4522 5/20/80 mg (127 randomized subjects)			ZD4522 10/40/80 mg (128 randomized subjects)			Atorvastatin 10/40/80 mg (128 randomized subjects)		
		5 mg	20 mg	80 mg	10 mg	40 mg	80 mg	10 mg	40 mg	80 mg
Week 12	N	6	116	---	9	114	---	3	117	---
	%	(4.9%)	(95.1%)		(7.3%)	(92.7%)		(2.5%)	(97.5%)	
Week 18	N	3	5	111	5	19	95	0	4	112
	%	(2.5%)	(4.2%)	(93.3%)	(4.2%)	(16.0%)	(79.8%)	0	(3.4%)	(96.6%)

The subjects were up-titrated if their LDL-C levels were >50 mg/dL at the time of determination for titration.
7 subjects in ZD5/20/80, 9 in ZD10/40/80, and 4 in AT10/40/80 were not up-titrated as scheduled at Week 12 and/or Week 18.
N = Number of subjects receiving the dose; The sponsor's Table 41 modified

Among the subjects who were up-titrated as scheduled, the subjects in the ZD10/40 group generally showed much lower LDL-C levels by Week 18 than the subjects in the other groups (Text Table 16). Similar LDL-C levels at Week 24 were observed between the two ZD4522 groups of the subjects taking the same 80-mg dose. Their mean LDL-C levels were evidently lower than that of the atorvastatin 80-mg group. Not much additional reduction in LDL-C was seen for the subjects titrated from the ZD4522 40-mg dose to the ZD4522 80-mg dose. Basically, the findings from the titration groups were similar to the ones from the whole ITT population.

Text Table 16 – Trial 25: Information for Various Dose Levels during Titration Period Using OBS data

Titration Period		ZD4522 5/20/80 mg (127 randomized subjects)			ZD4522 10/40/80 mg (128 randomized subjects)			Atorvastatin 10/40/80 mg (128 randomized subjects)		
		5 mg	20 mg	80 mg	10 mg	40 mg	80 mg	10 mg	40 mg	80 mg
1st	Baseline	190.94	188.34	---	183.02	185.82	---	168.78	187.57	---
	Mean_18	101.67	88.32	---	69.11	74.69	---	85.67	95.99	---
	% Change	-45.72	-53.26	---	-62.24	-59.80	---	-49.74	-48.77	---
2nd	Baseline	191.00	181.13	188.77	178.13	177.32	187.00	NA	175.75	186.73
	Mean_24	129.33	74.00	73.72	60.80	53.39	72.27	NA	87.00	85.21
	% Change	-30.04	-58.63	-61.02	-66.05	-70.07	-61.25	NA	-51.31	-54.23

Mean_18 (Mean_24) = Raw mean LDL-C at Week 18 (or 24); NA = Not applicable
A few subjects were excluded from the mean calculation at Weeks 18 and 24 due to missing LDL-C values.

Secondary Variables: TC, HDL-C, non-HDL-C, TG, and ApoB. This reviewer's results for the secondary variables of interest for Trial 25 (TC, HDL-C, TG, and ApoB) generally concur with the sponsor's (see Text Table 2). For non-HDL-C, the mean changes from baseline were -36.30%, -42.61%, and -32.65% for the ZD5, ZD10, and AT10 groups,

respectively, at Week 12; -46.59%, -52.86%, and -43.00% for the corresponding groups at Week 18; and -52.84%, -54.64%, and -47.66% for the corresponding groups at Week 24.

In summary, each of the two ZD4522 groups, and consequently the combined ZD4522 80-mg group, showed significantly greater reductions in TC, non-HDL-C, and ApoB, and significantly greater elevations in HDL-C, when compared with the atorvastatin 80-mg group at Week 24 using the LOCF data.

Similar superior findings in favor of either ZD5 or ZD10 were also observed in the cases of TC, HDL-C, non-HDL-C, and ApoB when compared with AT10 at Week 12 (the end of the fixed-dose period) using the LOCF data.

The same significant findings observed at Weeks 12 and 24 were also seen at Week 18 for TC, HDL-C, non-HDL-C, and ApoB when ZD5/20 or ZD10/40 was compared with AT10/40, except for the case where the % reduction in TC in ZD5/20 was only numerically greater (not statistically significant) than AT10/40.

The reduction levels in TG in both ZD4522 groups were similar to that of the atorvastatin group at Weeks 12, 18, and 24 using the LOCF data.

Figures 5-8 in the Appendix presents the graphs of means % change from baseline over time for TC, HDL-C, non-HDL-C, and TG for Trial 25.

2.3.3.3 Trial 4522IL/0026 (from 4/28/1999 to 10/31/2000)

Trial Design and Objectives

Trial 26 was a 52-week, randomized, double-blind, active-controlled, 3-parallel-group, titration to NCEP II goals, multicenter, multinational (in Europe) trial, conducted in adult subjects ≥18 years old with hypercholesterolemia (Fredrickson Type IIa/IIb dyslipidemia). A 6-week dietary lead-in period was followed by a 12-week randomized treatment period; then the subjects were given the titrated doses in a sequential manner during Visits 8 to 12 (see the diagram below), if their LDL-C levels did not meet the NCEP II targets. Otherwise, they stayed on their current doses.

				Randomized Treatment Phase										
	Dietary Lead-in			Fixed-Dose				Titrated-Dose						
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Week	-6	-2	-1	0	2	6	10	12	20	28	36	44	50	52
				AT10					AT20, AT40, AT80					
				ZD10					ZD20, ZD40, ZD80					
				ZD5					ZD10, ZD20, ZD40, ZD80					

The primary objective of this trial was to compare the efficacy of ZD4522 5 mg and 10 mg with that of atorvastatin 10 mg in the reduction of LDL-C levels. The associated primary endpoint was percentage change from baseline in LDL-C at Week 12 (the end of the fixed-dose period).

The stated secondary objectives of interest in this review were to compare the efficacy of the aforementioned treatment groups in the reduction of LDL-C after 52 weeks of treatment, and in modifying other lipids and lipoproteins. The associated secondary endpoints were percentage change from baseline in LDL-C at Week 52; in TC, HDL-C, TG, and ApoB at Weeks 12 and 52; and in LDL-C, TC, HDL-C, and TG at Weeks 2, 6, and 10.

Subject Disposition

There were 1521 outpatients recruited from 45 centers (all in Europe) and 412 of them were eligible for randomization at Week 0 (72.9% screen failure rate): 138, 134, and 140 subjects for ZD5, ZD10, and AT10, respectively (Text Table 17). Six (6) patients were excluded from the ITT population due to either no medication taken or no post-baseline value collected.

The overall withdrawal rate during the randomized treatment period was 16.7% (= 69/412) with ZD10 showing the highest rate (20.1%), but similar to that of AT10 (17.9%). Among the 69 withdrawals, 58% (= 40/69) of them withdrew at the end of the fixed-dose period, where 8.0%, 10.4%, and 10.7% withdrawal rates were observed for ZD5, ZD10, and AT10, respectively.

Adverse events were the most common recorded reasons for withdrawal in this trial (Text Table 18). In the category Other, 2, 4, and 5 subjects in ZD5, ZD10, and AT10, respectively, ranging in age from 51 to 79 years old, withdrew due to eye examination failures which were mostly reported during the fixed-dose period (see the sponsor's Table G5.2). In the sponsor's clinical trial report, under section 2.1, it was noted that pre-clinical studies with statins (including ZD4522) have shown that this class of drug can cause cataracts in dogs.

The 406 ITT subjects came from 41 centers, where 27 centers had <10 randomized patients each (as low as 1 patient) and 14 centers had ≥10 each (as high as 42 patients). The sponsor grouped those centers into 5 regions (countries): Denmark/Holland, Finland, Norway, Sweden, and United Kingdom. Within each region, the numbers of subjects were similar across treatment groups (Text Table 19) implying to this reviewer that balanced randomizations within each center, and consequently, within pooled centers, were obtained.

Text Table 17 – Trial 26: Subject Disposition during Randomized Treatment Phase

	ZD5		ZD10		AT10		Total
Randomized	**138**		**134**		**140**		**412**
No medication taken	(2)		(2)		(0)		(4)
No post-baseline	(1)		(0)		(1)		(2)
ITT population	**135**		**132**		**139**		**406**
Withdrawals	17 (12.3%)		27 (20.1%)		25 (17.9%)		69 (16.7%)
	A	B	A	B	A	B	
Week 0	138[a]	2[a]	134[b]	1[b]	140	0	
Week 2	136[c]	1[c]	133[b]	4[b]	140[c]	5[c]	
Week 6	135	2	129	6	135	3	
Week 10	133	4	123	3	132	6	
Week 12	129	2	120	0	126	1	
Week 20	127	3	120	4	125	4	
Week 28	124	1	116	2	121	2	
Week 36	123	2	114	5	119	2	
Week 44	121	0	109	1	117	1	
Week 50	121	0	108	1	116	0	
Week 52	121	0	107	0	116	1	
Completers	121 (87.7%)		107 (79.9%)		115 (82.1%)		343 (83.3%)

[a] = Including 2 subjects not taking any trial medication

[b] = Including 1 subject not taking any trial medication

[c] = Including 1 subject having no post-baseline value collected

A = Total number of subjects completed at the scheduled week

B = Total number of subjects withdrew at the end or after the scheduled week

Text Table 18 – Trial 26: Number (%) of Subjects Withdrawal during Randomized Treatment Period

Reason for withdrawal	ZD5	ZD10	AT10
Number of randomized subjects	138	134	140
Adverse event	8 (5.8)	8 (6.0)	12 (8.6)
Other[a]	5 (3.6)	6 (4.5)	7 (5.0)
Protocol non-compliance	3 (2.2)	9 (6.7)	3 (2.1)
Informed consent withdrawn	0	3 (2.2)	2 (1.4)
Subject lost to follow-up	1 (0.7)	1 (0.7)	1 (0.7)
Total	**17 (12.3)**	**27 (20.1)**	**25 (17.9)**

The sponsor's Table 14 modified

[a] = Including reasons such as eye examination failure, no medication available for the subject, subject not able to swallow the trial medication, subject randomized in error, subject moving away from the area, LDL outside inclusion range, subject having bypass operation, and subject treated with excluded medication

Text Table 19 – Trial 26: Number of Subjects in Each Region per Treatment Group

	Region 1 Denmark + Holland	Region 2 Finland	Region 3 Norway	Region 4 Sweden	Region 5 United Kingdom	Total
ZD5	24	36	38	34	3	135
ZD10	17	36	42	34	3	132
AT10	22	37	41	34	5	139
Total Subjects	63	109	121	102	11	406
Total Centers Pooled	8	6	10	15	2	41

Demographics

Based on this reviewer's analyses, demographic characteristics such as age, sex, race, weight, and BMI were generally homogeneous across the treatment groups (Text Table 20). The overall mean age was 57 years ranging from 26 to 79, with 30.3% of 412 subjects ≥65 years old. Except 1 Hispanic of Latino origin, all 411 subjects were Caucasian. The mean BMI was about 26 kg/m^2 ranging from 18 to 45, with 11.2% of 410 subjects having body mass index >30.

Text Table 20 – Trial 26: Demographic Characteristics of All Randomized Subjects

Characteristic	ZD5	ZD10	AT10
Number of randomized subjects	138	134	140
Age (year):			
Mean ± SD	56.3 ± 10.1	57.8 ± 10.0	58.2 ± 10.6
Range	28 – 76	26 – 78	29 – 79
18 to 64 (%)	101 (73.2)	93 (69.4)	93 (66.4)
≥65 (%)	37 (26.8)	41 (30.6)	47 (33.6)
Sex:			
Male (%)	72 (52.2)	81 (60.4)	80 (57.1)
Female (%)	66 (47.8)	53 (39.6)	60 (42.9)
Race:			
Caucasian (%)	138 (100.0)	134 (100.0)	139 (99.3)
Hispanic of Latino origin (%)	0	0	1 (0.7)
Weight (kg): Mean ± SD	77.53 ± 14.06	78.25 ± 13.64	77.26 ± 12.11
BMI (kg/m^2):			
Mean ± SD	26.73 ± 3.94	26.23 ± 3.08[a]	26.48 ± 3.48[a]
<20 kg/m^2 (%)	3 (2.2)	1 (0.8)	4 (2.9)
20 – 30 kg/m^2 (%)	117 (84.8)	120 (90.2)	119 (85.6)
>30 kg/m^2 (%)	18 (13.0)	12 (9.0)	16 (11.5)

The sponsor's Table 13 modified; [a] = No BMI collected for 1 subject

Note that although the gender distributions were similar across the 3 treatment groups, there were actually more males than females in each treatment group (56.6% males and 43.4% females overall).

Efficacy Results and Discussion

Primary Variable: LDL-C. Based on this reviewer's analyses, the baseline LDL-C values were comparable among the 3 study groups. The mean LDL-C changes from baseline at Week 12 in the ZD5, ZD10, and AT10 groups were -45.58%, -50.08%, and -39.48%, respectively (Text Table 21). It is apparent that the reductions in both ZD4522 5- and 10-mg groups were significantly greater than that of the atorvastatin 10-mg group at Week 12 using the LOCF data (Text Table 22). The observed treatment differences in the mean percentage change from baseline in LDL-C between ZD5 and AT10 were –6.11%, and –10.60% between ZD10 and AT10, in favor of the two ZD4522 5- and 10-mg doses based on the LOCF data at Week 12 (the end of the fixed-dose period). However, the data also suggest that the ZD4522 5- and 10-mg doses could be better than the atorvastatin 10-mg dose in lowering LDL-C by only 3.17% and 7.65%, respectively, according to the 95% upper confidence limit.

At the end of the titration to NCEP II goals period, the ZD4522 10-mg group still showed a significantly greater reduction in LDL-C at Week 52 (secondary endpoint), 53.20%, when compared with the atorvastatin 10-mg group, 44.34%. The 47.12% reduction in the ZD4522 5-mg group was also significantly larger than that of the atorvastatin 10-mg group, but the difference was marginal (only 2.78% more in the ZD5 group).

Text Table 21 – Trial 26: Descriptive Statistics for LDL-C at Weeks 12 and 52

ITT Population	ZD5	ZD10	AT10
Raw mean LDL-C ± standard deviation (sample size)			
Baseline	188.0 ± 19.3 (135)	185.9 ± 18.1 (132)	188.1 ± 18.1 (139)
Week 12 (LOCF)	102.4 ± 23.2 (135)	92.5 ± 27.5 (132)	113.8 ± 21.5 (139)
Week 52 (observed)	101.5 ± 23.2 (121)	89.5 ± 18.3 (106)	105.7 ± 18.8 (116)
Least-squares mean % change from baseline ± standard error (sample size)			
Week 12 (LOCF)	-45.58 ± 1.26 (135)	-50.08 ± 1.28 (132)	-39.48 ± 1.22 (139)
Week 52 (observed)[a]	-47.12 ± 1.15 (121)	-53.20 ± 1.23 (106)	-44.34 ± 1.14 (116)

[a] = Due to titration, subjects at Week 52 could receive various doses up to 80 mg (see study design).

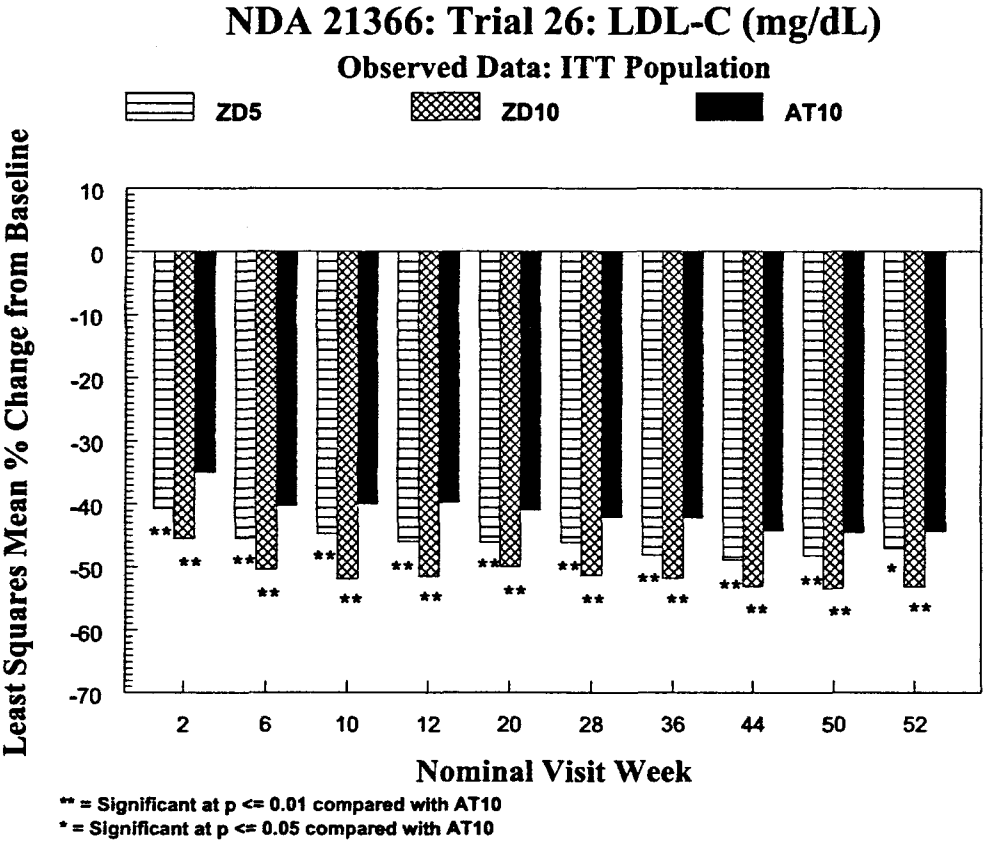
Text Table 22 – Trial 26: Statistical Results for LDL-C at Weeks 12 and 52

ITT Population	Comparison	Treatment Difference	p-value	(LCL, UCL)
Week 12 (LOCF)	ZD5 vs. AT10	-6.11	<.0001 **	(-9.04, -3.17)
	ZD10 vs. AT10	-10.60	<.0001 **	(-13.55, -7.65)
Week 52 (observed)[a]	ZD5 vs. AT10	-2.78	0.0472 *	(-5.53, -0.04)
	ZD10 vs. AT10	-8.86	<.0001 **	(-11.69, -6.02)

[a] = Due to titration, subjects at Week 52 could receive various doses up to 80 mg (see study design).
Treatment difference in negative direction favors ZD4522.
* = Significant at $p \leq 0.05$; ** = Significant at $p \leq 0.01$
LCL = 95% lower confidence limit; UCL = 95% upper confidence limit

Significantly greater percentage reductions in LDL-C in both ZD5 and ZD10 groups were also observed at all time points including the titration period, using the observed data, when compared with that of the AT10 group (Text Figure 3).

Text Figure 3



The LDL-C levels in the 3 treatment groups were all decreased by at least 30% from baseline at Week 2, and decreased further at Week 6, then were maintained (without marked increases or decreases) throughout the rest of the trial. Note that the dose levels at each nominal week of the titration period (from Week 12 to Week 52) varied from patient to patient.

At the end of the titration to goals period (Week 52), 76.0% and 82.2% of the subjects in the ZD5 and ZD10 groups, respectively, stayed with their original randomized doses, while the corresponding percentage for the AT10 group was 62.9% (Text Table 23). This implies that more subjects in the ZD4522 groups achieved NCEP II goals at lower doses (with fewer titration steps) than in the atorvastatin group.

Text Table 23 – Trial 26: Titration Information for Subjects at Week 52

Number of Titration Steps	ZD 5→10→20→40→80 mg			ZD 10→20→40→80 mg			AT 10→20→40→80 mg		
	No. of Subjects	A	B	No. of Subjects	A	B	No. of Subjects	A	B
0	92 (76.0%)	83	9	88 (82.2%)	87	1	73 (62.9%)	68	5
1	19 (15.7%)	18	1	13 (12.1%)	12	1	24 (20.7%)	21	3
2	4 (3.3%)	3	1	4[a] (3.7%)	3	0	8 (6.9%)	6	2
3	2 (1.7%)	0	2	2 (1.9%)	2	0	11 (9.5%)	6	5
4	4 (3.3%)	3	1	---	---	---	---	---	---
Total	121	107	14	107[a]	104	2	116	101	15

The sponsor's Tables 47 and 48 modified; [a] = Including 1 subject with no LDL-C value collected at Week 52
A = Number of subjects achieving target; B = Number of subjects not achieving target and not titrated after that

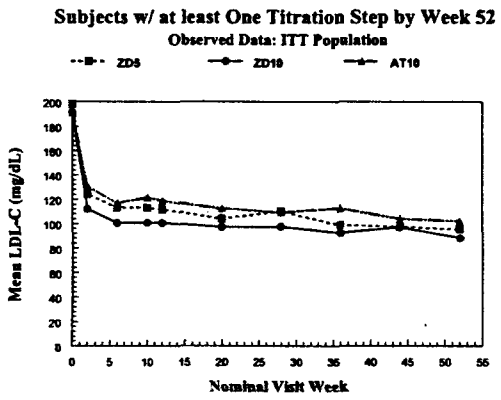
Text Table 24 – Trial 26: Mean LDL-C ± Standard Deviation for the Subjects at Week 52

Treatment	Titration	Sample Size	Baseline	Week 52	% Change
ZD5	No	92	185.59 ± 16.16	103.33 ± 24.45	-44.32%
	Yes	29	198.13 ± 23.56	95.76 ± 17.81	-51.67%
ZD10	No	88	186.31 ± 17.81	89.78 ± 19.45	-51.81%
	Yes	18	191.59 ± 20.01	88.33 ± 11.57	-53.90%
AT10	No	73	184.61 ± 15.97	107.70 ± 16.85	-41.66%
	Yes	43	191.64 ± 17.83	102.42 ± 21.47	-46.56%

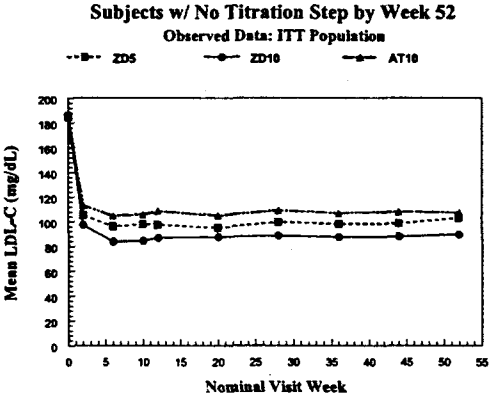
Across the 3 treatment groups, the Week 52 LDL-C levels of the subjects having at least one titration step (with higher baselines) were generally slightly smaller than that of the subjects having no titration step (with lower baselines), as shown in Text Table 24 and Text Figures 4

and 5. However, it is not clear that the greater % reductions observed in the non-responders (requiring titration) were due to the higher baselines or the actual effects of the titrated doses.

Text Figure 4 – Trial 26



Text Figure 5 – Trial 26



Secondary Variables: TC, HDL-C, non-HDL-C, TG, and ApoB. This reviewer's results for the secondary variables of interest for Trial 26 (TC, HDL-C, TG, and ApoB) generally concur with the sponsor's (see Text Table 2). For non-HDL-C, the mean changes from baseline were -41.50%, -46.29%, and -36.55% for the ZD5, ZD10, and AT10 groups, respectively, at Week 12 (LOCF), and -43.50%, -48.67%, and -40.65% for the corresponding groups at Week 52 (OBS).

In summary, both ZD4522 5- and 10-mg groups showed significantly greater reductions in TC, non-HDL-C, and ApoB, when compared with the atorvastatin 10-mg group at Week 12 (the end of the fixed-dose period) using the LOCF data. However, no significant differences in HDL-C were observed among the 3 treatment groups at Week 12.

The ZD4522 10-mg group consistently showed superiority to the atorvastatin 10-mg group in the cases of TC, HDL-C, non-HDL-C, and ApoB at Week 52. However, the ZD4522 5-mg group did not show such consistency.

Both ZD4522 5- and 10-mg groups were significantly better than the atorvastatin 10-mg group in reducing TC and non-HDL-C, but not in increasing HDL-C, at Weeks 2, 6, and 10.

The reduction levels in TG in both ZD4522 groups were similar to that of the atorvastatin group at all time points.

Figures 9-12 in the Appendix presents the graphs of means % change from baseline over time for TC, HDL-C, non-HDL-C, and TG for Trial 26.

2.4 Findings in Special/Subgroup Populations

Almost 43% of the subjects in Trial 25 (high-risk subjects trial) were ≥65 years old, compared with around 30% in Trials 24 and 26. There were more females than males in Trial 24, but more males than females in Trials 25 and 26. The subjects were generally slimmer in Trial 26 (in Europe) than in Trials 24 and 25 (in USA/Canada): 11% of the Trial 26 subjects had a BMI >30, compared with more than 31% in Trials 24 and 25. The majority of the subjects in Trials 24, 25, and 26 were Caucasian (85%, 91%, and ~100%, respectively). Approximately 19% of the Trial 26 subjects were Fredrickson Type IIb patients (with baseline TG between 200 and 400), compared with 36% and 45% in Trials 24 and 25, respectively.

Treatment effects on % change from baseline in LDL-C in subgroups of sex, age, BMI, Fredrickson hypercholesterolemia type, and region were investigated for each of the three clinical trials and the 3 trials combined, using their first initial 12-week fixed-dose LOCF data. No subgroup analysis for race was performed since the majority of the subjects were Caucasian.

The response patterns of the two sexes were similar across the treatment groups in each of the 3 trials as well as the combined trial (no significant treatment by sex interaction at $p \leq 0.10$). However, the response magnitudes of the two sexes at each treatment group were different: female subjects generally showed larger % changes from baseline in LDL-C than males (Text Table 25). This difference was even more evident in Trial 26.

Text Table 25 – Least-Squares Mean % Change from Baseline in LDL-C for Sex and Age Subgroups

		Sex				Age		
Treatment		Trial 24	Trial 25	Trial 26		Trial 24	Trial 25	Trial 26
Placebo	F	-0.4229			<65	-0.3116		
Placebo	M	0.7360			≥65	1.5201		
ZD5	F	-40.0997	-40.5821	-48.2267	<65	-40.4303	-38.0632	-43.4033
ZD5	M	-40.7121	-39.3992	-42.8511	≥65	-40.1954	-41.8176	-50.8893
ZD10	F	-43.9383	-50.0376	-54.1737	<65	-40.3289	-45.9563	-48.9345
ZD10	M	-41.3183	-45.6092	-47.3887	≥65	-50.0488	-49.1662	-52.6538
AT10	F	-36.0329	-36.4511	-42.3095	<65	-34.6599	-34.8348	-38.1010
AT10	M	-33.6901	-33.9434	-37.2182	≥65	-35.6841	-35.3583	-41.9636

The response patterns of age <65 and ≥65 subjects were also similar across the treatment groups in each of the 3 trials as well as the combined trial, except for the cases in Trial 24 where the response patterns of the two age groups in the placebo and ZD5 were different from ZD10 and AT10. In general, older subjects (≥65 years old) showed larger % changes from baseline in LDL-C than younger subjects (<65 years old) (Text Table 25). The difference was also even more evident in Trial 26.

Treatment effects on % change in LDL-C were consistent across the subgroups defined by BMI, Fredrickson hypercholesterolemia type, and region in each of the 3 trials as well as the combined trial. The effects were also consistent between the diabetics and non-diabetics in Trial 25.

2.5 Statistical and Technical Issues

There were some operational issues noted in the sponsor's clinical Trial 26 report, section 2.5.3.4 (C). It occurred during the titration to NCEP II goals period (Weeks 12 to 52) and therefore, was not a major concern to this reviewer. No serious statistical and technical issues were noted for Trials 24 and 25.

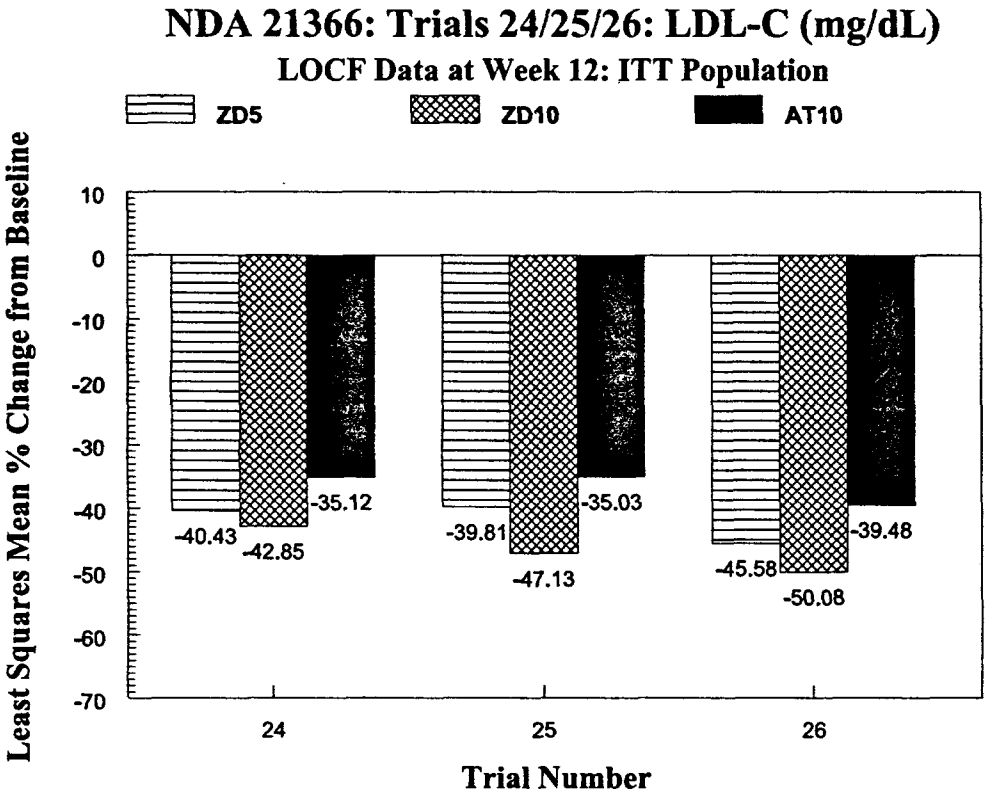
2.6 Statistical Evaluation of Collective Evidence

In Trials 24, 25, and 26, the overall withdrawal rates at the end of the 12-week fixed-dose period were 6.9%, 4.7%, and 9.7%, respectively. As mentioned previously, some baseline demographic characteristics were different among the 3 trials. The mean baseline LDL-C values were, however, comparable among all the treatment groups from the 3 clinical trials (ranging from 185 to 188 mg/dL), irrespective of atherosclerotic disease or trial location.

Based on Trial 24, both ZD4522 5- and 10-mg doses were superior to the placebo in improving LDL-C, TC, HDL-C, non-HDL-C, TG, and ApoB levels. Except HDL-C, the response degrees of those measures were in a dose-dependent fashion (see Text Table 2).

Across Trials 24, 25, and 26, all the active treatment groups showed at least 30% reductions in LDL-C by Week 2 and slightly more lowering by Week 6. During the courses of those trials, the ZD4522 10-mg group consistently exhibited the greatest reduction in LDL-C, while the atorvastatin 10-mg group showed the least. As seen at Week 12 (the end of the fixed-dose period), the % reductions in both ZD4522 5- and 10-mg groups across the 3 trials (Text Figure 6) were all statistically significantly larger than that of the atorvastatin 10-mg group (Text Table 26).

Text Figure 6



Text Table 26 – Summary of Efficacy for Trials 24, 25, and 26 Using LOCF Data at Week 12

	ZD5 vs. AT10		ZD10 vs. AT10	
Trial	LSMEAN Difference	(LCL, UCL)	LSMEAN Difference	(LCL, UCL)
24	-5.31 **	(-8.75, **-1.87**)	-7.73 **	(-11.16, **-4.30**)
25	-4.81 **	(-7.83, **-1.79**)	-12.11 **	(-15.12, **-9.09**)
26	-6.11 **	(-9.04, **-3.17**)	-10.60 **	(-13.55, **-7.65**)

LSMEAN = Least-squares mean % change from baseline in LDL-C; ** = Significant at $p \leq 0.01$
Treatment difference in negative direction favors ZD4522.
LCL = 95% lower confidence limit; UCL = 95% upper confidence limit

Clearly, both ZD4522 5- and 10-mg doses in those 3 trials were statistically superior to the atorvastatin 10-mg dose in lowering LDL-C levels based on the fact that all the 95% upper confidence limits were below 0. The ZD4522 10-mg group consistently demonstrated at least 7% more reduction in LDL-C than the atorvastatin 10-mg group, which exceeded the clinically meaningful difference (6%) that the trials were powered on. However, the ZD4522

5-mg group did not always show a 6% more reduction in LDL-C, when compared with the atorvastatin 10-mg group (e.g., only 4.81% more in Trial 25).

Based on Trial 25, the ZD4522 20- and 40-mg doses were also statistically superior to the atorvastatin 40-mg dose in reducing LDL-C levels. However, the duration of those dose levels for the majority of the subjects were only about 6 weeks and most of the adverse events were reported during the titration period. Therefore, the superiority of the ZD4522 20- and 40-mg doses should be weighed along with the amount of the data and long-term safety concerns, if any.

Although the ZD4522 80-mg dose also showed a superiority over the atorvastatin 80-mg dose in lowering LDL-C levels according to Trial 25, the extra LDL-C reduction within each treatment group did not show much of a clinical benefit when the dose levels were doubled.

In the long-term efficacy trial (Trial 26), more subjects reached NCEP II goals at lower doses of ZD4522 than that of atorvastatin (with similar baselines), indicating that fewer titration steps were needed for the subjects treated with ZD4522 than the subjects treated with the atorvastatin to reach NCEP II goals.

In general, the ZD4522 10-mg group always reduced significantly more TC, non-HDL-C, and ApoB levels than the atorvastatin 10-mg group during the courses of the 3 trials. The ZD4522 5-mg group, however, did not consistently show statistical significance in these cases. Both ZD4522 5- and 10-mg groups showed significantly greater % elevations in HDL-C than the atorvastatin 10-mg group in Trials 24 and 25, but not in Trial 26. The % changes in TG were similar among the treatment groups in those 3 trials.

2.7 Conclusions and Recommendations

Based on Trials 24, 25, and 26, ZD4522 itself was efficacious in lowering LDL-C levels by more than 15% from baseline, a clinically meaningful reduction as stated in the FDA Guidelines (1990), during the courses of the trials. The sustainability of the change in either ZD4522 or atorvastatin groups was seen after Week 6. In addition, the ZD4522 5- and 10-mg doses were clearly more effective than placebo in improving LDL-C, HDL-C, non-HDL-C, TG, and ApoB, in a dose-dependent fashion (except for the case where the 5-mg group showed a slightly higher HDL-C than the 10-mg group).

The 10-mg dose of ZD4522 was statistically and clinically superior to the same dose level of atorvastatin in improving the aforementioned lipid variables of interest based on the following findings. First, the difference in the % reduction in LDL-C between the ZD4522 10-mg and atorvastatin 10-mg doses was consistently more than 7%, exceeding the clinically

meaningful difference, 6%, claimed by the sponsor and the trials being powered on. Second, consistently significantly greater % reductions in TC, non-HDL-C, and ApoB were observed in the ZD4522 10-mg group than in the atorvastatin 10-mg group. Third, more subjects achieved NCEP II target at the ZD4522 10-mg than at the atorvastatin 10-mg (with similar LDL-C baselines).

The 5-mg dose of ZD4522 was concluded to be as effective as the 10-mg of atorvastatin by this reviewer since the difference in the % reduction in LDL-C was only indicative of statistical, but not clinical, superiority over the atorvastatin.

The 40- and 80-mg doses of ZD4522 were also superior to the same doses of atorvastatin, with a more than 6% clinically meaningful difference in the reduction of LDL-C. However, the clinical benefit of ZD4522 80-mg dose was not much different from its own 40-mg dose. The 20-mg dose of ZD4522 was comparable to the 40-mg dose of atorvastatin due to the fact that the observed difference in the reduction of LDL-C did not exceed the 6% criterion. Note that the efficacy of the higher doses of ZD4522, for example, 20-, 40-, and 80-mg doses, were only based on 6 weeks of titration data from high-risk subjects (Trial 25). The findings from the dose-ranging study (Trial 33) and any safety issues should also be accounted for in the determination of the efficacy for those higher doses.

ZD4522 did not consistently significantly increase HDL-C levels when compared with the atorvastatin. In addition, the reduction levels in TG were similar between ZD4522 and the atorvastatin.

One interesting finding to this reviewer is that an additional 5-7% reduction in LDL-C with dose doubling was not consistently seen between the 5-mg and 10-mg doses of ZD4522 across the 3 trials. For example, at the end of the fixed-dose period (Week 12), the 10-mg group in Trials 24 and 26 showed only 2.42% and 4.50% more reductions, respectively, when compared with the 5-mg group, while 7.32% was observed in Trial 25.

2.8 Labeling Comments

In the proposed labeling, the sponsor combined Trials 24, 25, and 26 to compare the 10-mg dose of rosuvastatin and atorvastatin, which was not appropriate to this reviewer due to some differences seen in the baseline demographic characteristics among the three trials.

/S/

Cynthia Liu, MA Date
Statistical Reviewer

Concur: /S/

Todd Sahlroot, Ph.D. Date
Team Leader

/S/

Ed Nevius, Ph.D. Date
Director of Division of Biometrics II

CC: HFD-510/WKoch, MParks, WLubas
HFD-715/ENevius, TSahlroot, CLiu
HFD-700/CAnello

2.9 Appendix

Figure 1

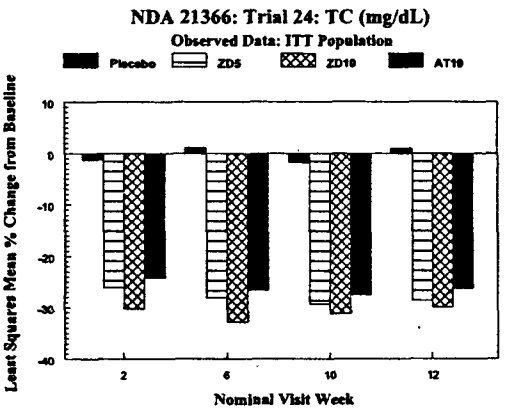
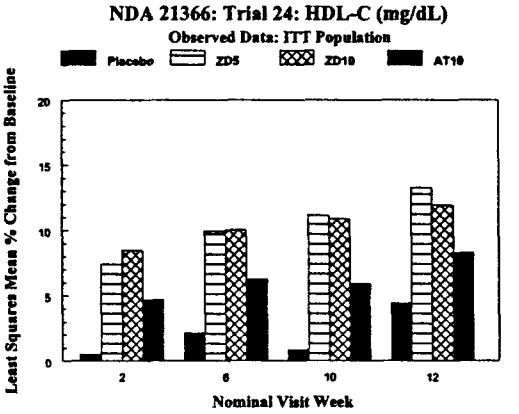


Figure 2



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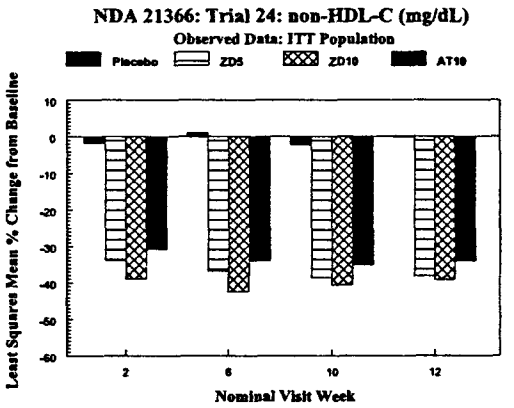

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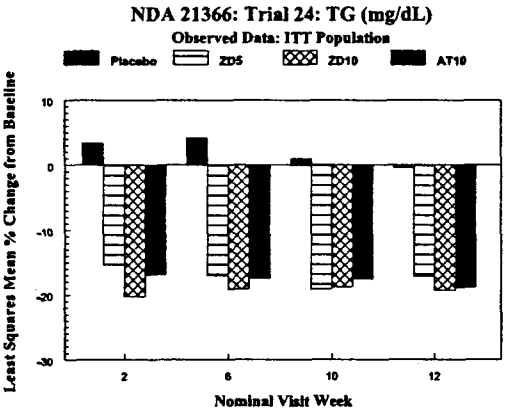
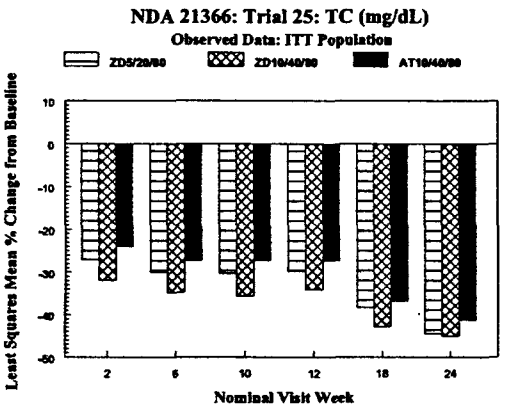


Figure 5



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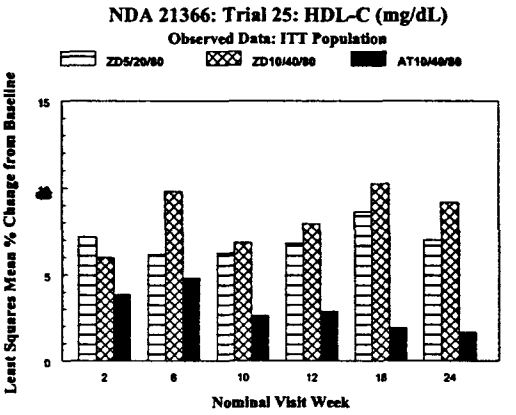

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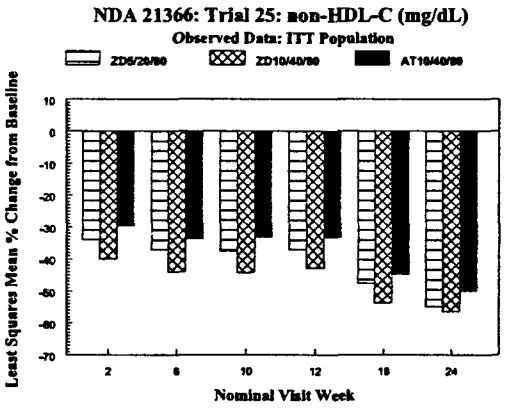

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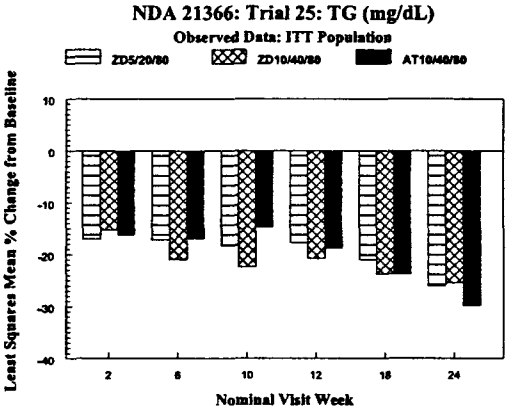

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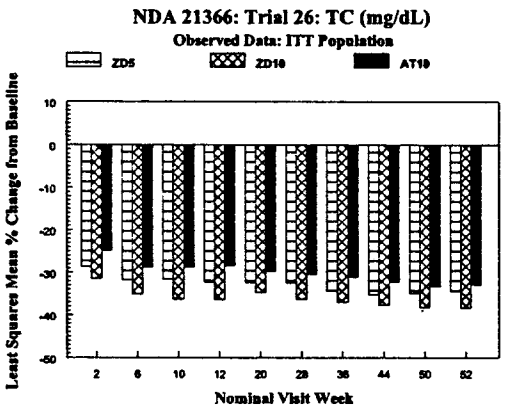
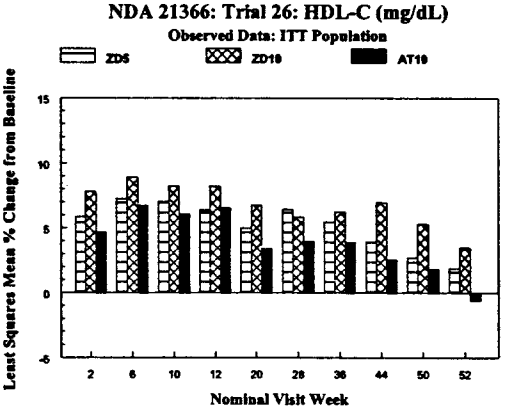


Figure 10



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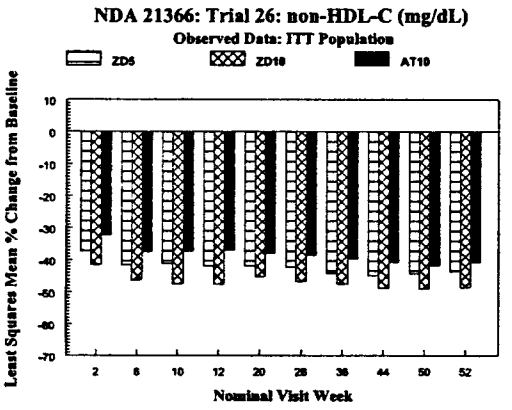
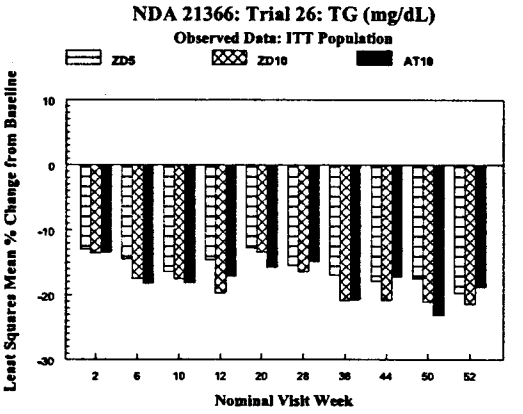


Figure 12



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/s/

Cynthia Liu
4/11/02 10:36:56 AM
BIOMETRICS

S. Edward Nevius
4/11/02 10:41:32 AM
BIOMETRICS
Concur with review.

Todd Sahlroot
4/12/02 08:27:03 AM
BIOMETRICS