CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-687

STATISTICAL REVIEW(S)

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 21-687

Drug Name: Vytorin (simvastatin / ezetimibe fixed combination tablets)

Indication(s): ———————

Applicant: MSP Singapore

Date(s): User Fee Goal date July 24, 2004

Review Priority: Standard

Biometrics Division: HFD-715

Statistical Reviewer: J. Todd Sahlroot, Ph.D.

Concurring Reviewers: S. Edward Nevius, Ph.D.

Medical Division: HFD-510

Clinical Team: Mary Parks, M.D.

Project Manager: Monika Johnson, Pharm.D.

Keywords: NDA review, clinical studies, labeling

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1. EXECUTIVE SUMMARY

Based on a prior agreement between the sponsor and FDA, the approval of Vytorin (ezetimibe + simvastatin fixed combination tablets) was to be based on pharmacokinetic data from the Definitive Bioequivalence Study 039. A number of clinical studies using the co-administered drugs ezetimibe and simvastatin were also submitted for inclusion in the product label. The reviewing Medical Officer, Mary Parks, asked Biometrics to provide a statistical review for clinical Study 021 for the purpose of evaluating point estimates in the proposed label.

Study 021 was a randomized, double-blind, multi-center, 24-week trial comparing co-administration of (simvastatin 20 mg + Ezetimibe 10 mg) to simvastatin 40 mg in patients with Type 2 diabetes mellitus (T2DM). The primary objective was to show that the addition of exetimibe 10 mg/day to ongoing simvastatin 20 mg/day would reduce LDL-C to a greater extent than doubling the dose of simvastatin to 40 mg/day. The primary endpoint was the percent change in LDL-C from baseline (Week 1) to treatment based on the average of measurements at Weeks 6 ,12 and 24.

All patients were to be on stable doses of anti-diabetic medications pioglitazone or rosiglitazone (TZDs) for 3 months prior to screening. During the 6-week screening (lipid stabilization) period, patients received open-label simvastatin 20 mg for six weeks. At the start of the double-blind period, patients were randomized to simvastatin 20mg or ezetimibe 10 mg as add-on therapy to open-label simvastatin 20 mg.

41% of the randomized patients were completers from Study 187 ("rollovers"). Study 187 was a randomized, placebo-controlled trial of simvastatin 40mg in patients with Type 2 diabetes. These patients were eligible to enter Study 021 provided they were on stable doses of a TZD. They were required only to have LDL-C > 100 mg/dL at entry for Study 187. New (i.e., non-rollover) patients in Study 021 were required to have LDL-C > 100 mg/dL at study entry.

Table 1 shows summary statistics for the primary endpoint. The % change data were not normally distributed. Mean % changes in each group were larger than the medians. The mean and median treatment differences were nevertheless similar and highly significant ($p<.001$).

Observed treatment differences for rollover patients were not statistically different than those for new patients.

Table 1. Percent change in LDL-C from baseline (ITT)

% change in LDL-C from baseline	Simva 20 + ezetimibe n=103	Simva 40 n=107	Treatment difference
Baseline mean	92.8	90.8	
Mean % change	-21.2	-0.6	-20.6
Adjusted mean (SE) [1]	-20.8 (2.2)	-0.3 (2.2)	-20.5 [2]
Median	-24.7	-4.9	-19.8
Range (min, max)	-55.4, +111.3	-30.6, +56.4	

[1] ANOVA model with fixed effects for treatment group, pooled center, TZD and TZD dose
[2] p< .001

% changes for labeled secondary endpoints total cholesterol, apo B and non-HDL cholesterol were all statistically significant (p <.001). Similar to the primary endpoint, the within-treatment data were not normally distributed (Table 2).

HDL-C and triglycerides were not statistically different between treatment groups (p ≥ .29).

Table 2. Results for secondary lipid endpoints

Secondary lipid endpoint	Simva 20 + eze 10 N=103	Simva 40 N=107	Treatment difference
Total cholesterol			
Adjusted mean	-14.5	-1.5	-13.0 [1]
Median	-15.9	-5.0	-10.9
Apo B			
Adjusted mean	-14.1	-1.8	-12.4 [1]
Median	-18.9	-4.9	-14.0
Non-HDL-C			
Adjusted mean	-20.0	-1.7	-18.3 [1]
Median	-22.6	-4.5	-18.1
HDL-C			
Adjusted mean	+0.2	+0.3	-0.1 [2]
Median	-1.2	-2.3	+1.1
Triglycerides (TG)			
Adjusted mean	-2.1	+2.4	-4.5
Median	-3.6	+0.9	-4.5 [3]

1 p <.001 from ANOVA
2 p = .95 from ANOVA
3 p = .29 from nonparametric analysis

1.1 Conclusions and Recommendations

Co-administered Simvastatin 20mg and ezetimbe 10mg was superior to simvastatin 40mg in reducing LDL-C in diabetic patients taking a thiazolidineodine (TZD) to control their diabetes (p<.001). Co-administered Simvastatin 20mg and ezetimbe 10mg was also superior to simvastatin 40mg in reducing levels of secondary lipids total-C, Apo B and non-HDL-C.

The labeled effects of treatment on lipids (with the exception of triglycerides) are usually estimated by the raw or adjusted treatment means. Due to the non-normality of the distributions for LDL-C, total-C, apo B and non-HDL-C, the within-treatment % changes for all labeled lipid endpoints should be estimated by the medians.

1.2 Brief Overview of Clinical Studies

Based on a prior agreement between the sponsor and FDA, the approval of Vytorin (ezetimibe + simvastatin fixed combination tablets) was to be based on pharmacokinetic data from the Definitive Bioequivalence Study 039. A number of clinical studies using the co-administered drugs ezetimibe and simvastatin were also submitted for inclusion in the product label. The reviewing Medical Officer, Mary Parks, asked Biometrics to provide a statistical review for clinical study 021 for the purpose of evaluating point estimates in the proposed label.

1.3 Statistical Issues and Findings

Study 021 enrolled and randomized 214 patients. Of these, 128 patients were newly recruited ("new" patients) and 86 patients were completers from Study 187. Study 187 was a 24-week, double-blind, placebo controlled trial that compared simvastatin 40mg to placebo in TZD-treated T2DM patients. Patients from Study 187 ("rollovers") were eligible to enter Study 021 without further assessment of eligibility provided they were on a stable dose of TZD therapy.

Rollovers had a numerically greater mean response to (simva20 + eze10) vs simvastatin 40mg. The least-square mean treatment differences for % change from baseline in LDL-C were -26.4 and -17.5 for rollover and new patients, respectively. The treatment effects for rollover and new patients were not statistically different, however (p=0.11). There was insufficient statistical evidence to warrant presenting separate results in the label for rollover and new patients.

While non-normality is usually not an important concern in the analysis of LDL-C data, it was an issue in Study 021. The % change LDL-C values were not normally distributed. The data in each group were skewed towards higher values. Consistent with this

finding, mean % changes in each group were larger than the medians. The treatment differences were nevertheless similar with respect to the mean and median.

2. INTRODUCTION

2.1 Overview

The primary objective of Study 021 was to show that the addition of exetimibe 10 mg/day to ongoing simvastatin 20 mg/day would reduce LDL-C to a greater extent than doubling the dose of simvastatin to 40 mg/day. Table 3 shows major study characteristics.

Table 3. Study characteristics

Trial # Centers Dates	Patients	# randomized	Design Primary endpoint	Duration of double blind period
021 26 US centers 2/02 - 1/03	M and F ages 30-75 with T2DM [1] receiving TZDs [2] LDL-C > 100 mg/dL in new patients [3] HbA1c ≤ 9%	Simvastatin 20mg + ezetimibe 10mg n=104 Simvastatin 40mg n=110	Randomized double-blind active-controlled % Change from baseline in LDL-C based on mean of levels at Weeks 6, 12 and 24	6 weeks open label simva 20 mg followed by 24 weeks of rand study drug

1 T2DM = Type 2 Diabetes Mellitius
2 TZD = Thiazolidineodione anti-diabetic medication (rosiglitazone or pioglitazone)
3 Rollover patients from Study 187 had no requirements for LDL-C in Study 021

2.2 Data Sources

Raw Data from Study 021 were obtained from

Derived data were found in

The final study report was located in

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Design

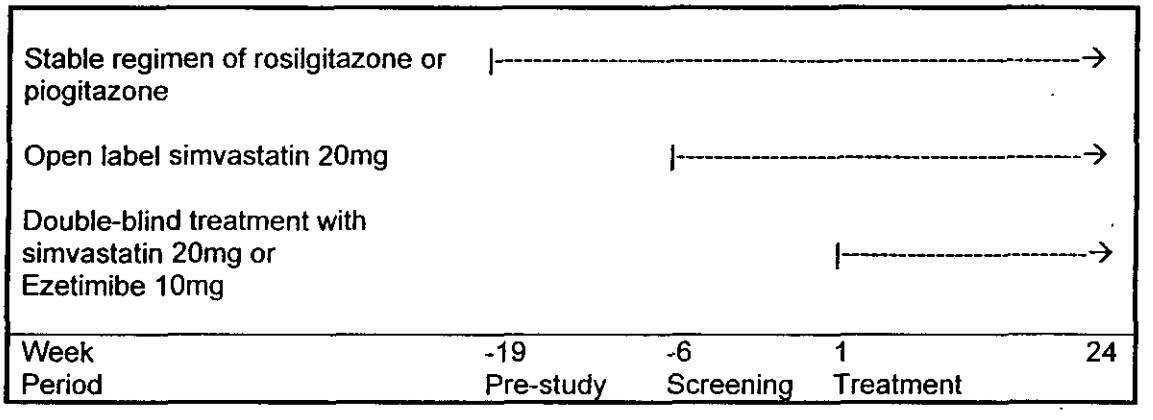
Study 021 was a randomized, double-blind multicenter 24-week trial comparing co-administration of simvastatin 20 mg and Ezetimibe 10 mg to simvastatin 40 mg in patients with Type 2 diabetes mellitus. The primary endpoint was the percent change in LDL-C from baseline (Week 1) to treatment based on the average of measurements at Weeks 6, 12 and 24.

All patients were to be on stable doses of anti-diabetic medications pioglitazone or rosiglitazone (TZDs) for 3 months prior to screening. During the 6-week screening (lipid stabilization) period, patients received open-label simvastatin 20 mg for six weeks. At the start of the double-blind period, patients were randomized to simvastatin 20mg or ezetimibe 10 mg as add-on therapy to simvastatin 20 mg. Randomization was stratified by TZD and TZD dose (low, high)

41% of randomized patients were completers from Study 187 ("rollovers"). Study 187 was a randomized, placebo-controlled trial of simvastatin 40mg in patients with Type 2 diabetes. These patients were eligible to enter Study 021 provided they were on stable doses of a TZD. They were required only to have LDL-C > 100 mg/dL at entry for Study 187. New (i.e., non-rollover) patients in Study 021 were required to have LDL-C > 100 mg/dL at study entry.

Clinic visits were scheduled for Weeks -6, 1, 6, 12 and 24.

Below is a schematic of the trial design:



The protocol was amended to change the primary endpoint from % change from baseline to treatment based on the average of Week 6 and 12 measurements to the average of levels at Weeks 6, 12 and 24.

Statistical methods

Per protocol, the primary statistical model was an ANOVA with factors for treatment, pooled study center, TZD (pioglitazone or rosiglitazone) and TZD dose (high or low).

Demographics and selected baseline characteristics

Table 4 shows selected demographics and baseline characteristics for all randomized patients. There were no obvious imbalances between groups for age, race and sex. TZD stratum, LDL-C and HbA1c values were comparable between groups. 54% of patients were white, 57% were male.

Table 4. Selected demographic and baseline characteristics
All randomized patients

	Simva 20 + ezetimibe n=104	Simva 40 n=110	Total n=214
Females	42 (40%)	49 (45%)	91 (43%)
Males	62 (60%)	61 (55%)	123 (57%)
Age (yrs)			
Mean (SD)	58 (10)	59 (10)	58 (10)
Range	(35, 80)	(37, 78)	(35, 80)
Race			
White	55 (53%)	61 (56%)	116 (54%)
Black	16 (15%)	13 (12%)	29 (14%)
Hispanic	25 (24%)	30 (27%)	55 (26%)
Other	8 (8%)	6 (6%)	14 (7%)
TZD stratum			
Pioglitazone 15 to 30mg	28 (27%)	36 (33%)	64 (30%)
Pioglitazone 45mg	21 (20%)	24 (22%)	45 (21%)
Rosiglitazone 2 to 4mg	23 (22%)	14 (13%)	37 (17%)
Rosiglitazone 8mg	32 (31%)	36 (33%)	68 (32%)
LDL-C (mg/dL)			
Mean (SD)	93.7 (28.5)	91.4 (24.3)	92.5 (26.4)
Range (min, max)			
HbA1c (%)			
Mean (SD)	7.3 (1.3)	7.4 (1.1)	7.3 (1.2)
Range (min, max)			

Table 5 shows these same characteristics stratified by rollover status. Rollover patients randomized to (simva 20mg + eze 10mg) had the highest LDL-C (95.4 mg/dL) and HbA1c (7.7%) values.

Table 5. Selected demographic and baseline characteristics for All randomized patients by rollover status

	Rollover patients from Study 187		New patients	
	Simva 20 + eze 10 n=48	Simva 40 n=38	Simva 20 + eze 10 n=56	Simva 40 n=72
Females	20 (42%)	20 (53%)	22 (39%)	29 (40%)
Males	28 (58%)	18 (47%)	34 (61%)	43 (60%)
Age (yrs)				
Mean (SD)	56 (10)	57 (11)	60 (9)	59 (9)
Range	(35, 78)	(37, 75)	(37, 80)	(38, 78)
Race				
White	14 (29%)	16 (42%)	14 (25%)	20 (28%)
Black	9 (19%)	6 (16%)	12 (21%)	18 (25%)
Hispanic	9 (19%)	4 (11%)	14 (25%)	10 (14%)
Other	16 (55%)	12 (32%)	16 (29%)	24 (33%)
TZD stratum				
Pio 15 to 30mg	18 (38%)	15 (39%)	37 (66%)	46 (64%)
Pio 45mg	5 (10%)	1 (3%)	11 (20%)	12 (17%)
Rosi 2 to 4mg	19 (40%)	20 (53%)	6 (11%)	10 (14%)
Rosi 8mg	6 (13%)	2 (5%)	2 (4%)	4 (3%)
LDL-C (mg/dL)				
Mean (SD)	95.4 (32.5)	87.6 (25.2)	92.2 (24.8)	93.5 (23.7)
Range (min, max)				
HbA1c (%)				
Mean (SD)	7.7 (1.5)	7.4 (1.3)	6.9 (0.9)	7.3 (0.9)
Range (min, max)				

Disposition

Table 6 shows the number of patients with LDL-C values by Study Week. 98% of patients contributed to the ITT population.

Thirty-two (32, 15%) patients discontinued from the trial. About 2/3 of the 32 discontinuations were in the simvastatin 40mg group. No single reason for discontinuation predominated.

Table 6. Disposition

	Simva 20 + eze 10	Simva 40	Total
Randomized	104 (100%)	110 (100%	214 (100%)
Baseline	104 (100%)	110 (100%)	214 (100%)
Week 6	100 (96%)	107 (97%)	207 (97%)
Week 12	98 (94%)	102 (93%)	200 (93%)
Week 24	96 (92%)	90 (82%)	187 (86%)
Completers	93 (89%)	89 (81%)	182 (85%)
ITT	103 (99%)	107 (97%)	210 (98%)

Primary endpoint

Table 7 shows summary measures for LDL-C % change from baseline for the ITT population. The least squares mean treatment difference (-20.5) was statistically significant (p<.001).

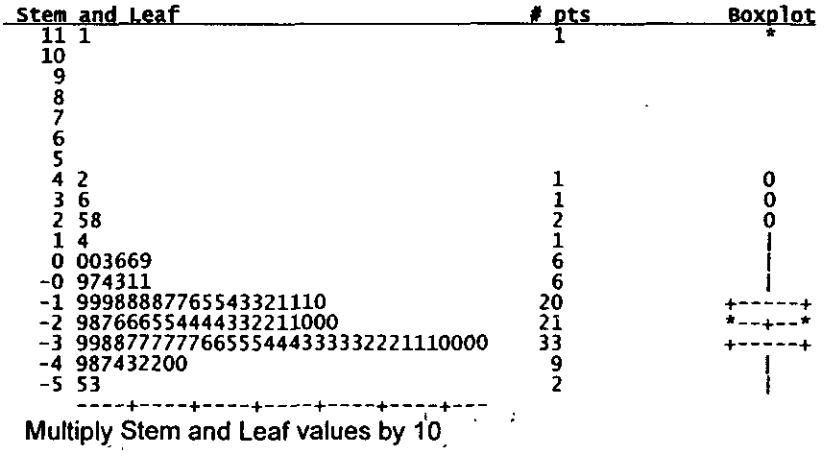
Table 7. % change in LDL-C from baseline (ITT)

% change in LDL-C from baseline	Simva 20 + ezetimibe n=103	Simva 40 n=107	Treatment difference
Baseline mean	92.8	90.8	
Mean % change	-21.2	-0.6	-20.6
Adjusted mean (SE) [1]	-20.8 (2.2)	-0.3 (2.2)	-20.5 [2]
Median	-24.7	-4.9	-19.8
Range (min, max)	-55.4, +111.3	-30.6, +56.4	

[1] ANOVA model with fixed effects for treatment, pooled center, TZD and TZD dose
[2] p< .001

Figures 1 (simva 20 + exe 10) and 2 (simva 40) show stem and leaf plots and boxplots of individual patient data for LDL-C % change. The % change data were not normally distributed. The data in each group were skewed towards higher values. Consistent with this finding, mean % changes in each group were larger than the medians. The treatment differences were nevertheless similar with respect to the mean and median.

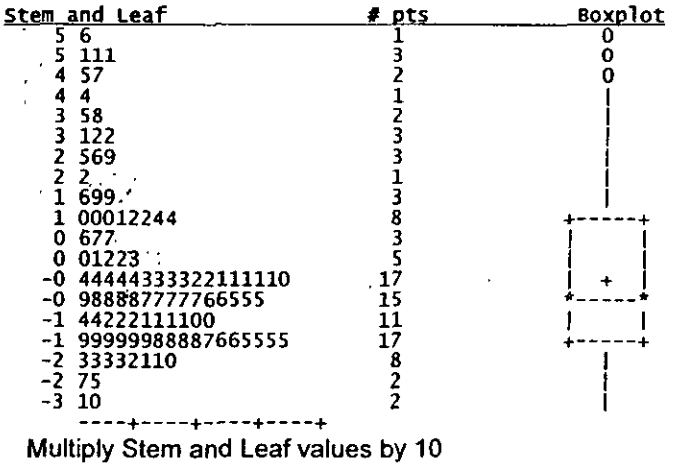
Figure 1. Simvastatin 20mg + ezetimibe 10mg
LDL-C % change from baseline



Stem and Leaf	# pts	Boxplot
11 1	1	*
10		
9		
8		
7		
6		
5		
4 2	1	0
3 6	1	0
2 58	2	0
1 4	1	|
0 003669	6	|
-0 974311	6	|
-1 99988887765543321110	20	+-----+
-2 987666554444332211000	21	*--+--*
-3 998877777766555444333332221110000	33	+-----+
-4 987432200	9	|
-5 53	2	|

Multiply Stem and Leaf values by 10

Figure 2. Simvastatin 40mg
LDL-C % change from baseline



Stem and Leaf	# pts	Boxplot
5 6	1	0
5 111	3	0
4 57	2	0
4 4	1	|
3 58	2	|
3 122	3	|
2 569	3	|
2 2	1	|
1 699	3	|
1 00012244	8	+-----+
0 677	3	| |
0 01223	5	| |
-0 44444333322111110	17	| + |
-0 988887777766555	15	*-----*
-1 44222111100	11	| |
-1 99999988887665555	17	+-----+
-2 33332110	8	|
-2 75	2	|
-3 10	2	|

Multiply Stem and Leaf values by 10

Secondary endpoints

Percent changes from baseline for labeled secondary endpoints total cholesterol, apo B and non-HDL cholesterol were statistically significant (Table 8, $p < .001$). Similar to the primary endpoint, within-treatment % changes were not normally distributed.

HDL-C and triglycerides (TG) were not statistically significant ($p \geq .29$).

Table 8. Results for secondary lipid endpoints

Secondary lipid endpoint	Simva 20 + eze 10 N=103	Simva 40 N=107	Treatment difference
Total cholesterol			
Adjusted mean	-14.5	-1.5	-13.0 [1]
Median	-15.9	-5.0	-10.9
Apo B			
Adjusted mean	-14.1	-1.8	-12.4 [1]
Median	-18.9	-4.9	-14.0
Non-HDL-C			
Adjusted mean	-20.0	-1.7	-18.3 [1]
Median	-22.6	-4.5	-18.1
HDL-C			
Adjusted mean	+0.2	+0.3	-0.1 [2]
Median	-1.2	-2.3	+1.1
Triglycerides (TG)			
Adjusted mean	-2.1	+2.4	-4.5
Median	-3.6	+0.9	-4.5 [3]

1 p <.001 from ANOVA
2 p = .95 from ANOVA
3 p = .29 from nonparametric analysis

3.2 Evaluation of Safety

This reviewer did not perform any statistical evaluations of safety endpoints.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Descriptive statistics by subgroup are shown in Table 9. Median responses within treatment groups for each subgroup were generally lower than mean responses, similar to the results in Table 5 for all patients. Treatment differences were consistent across all age, gender and race subgroups.

Table 9. LDL-C % change from baseline by gender, age and race

Subgroup	Simva 20 + eze 10 N=103			Simva 40 N=107			Treatment difference	
	N	mean	median	N	mean	median	mean	Median
Gender								
Males	61	-25	-28	59	-4	-7	-21	-21
Females	42	-15	-22	48	+3	-3	-18	-19
Age group								
< 65	77	-22	-23	76	0	-5	-22	-18
≥ 65	26	-19	-31	31	-3	-7	-16	-24

Race								
White	55	-21	-27	63	-1	-6	-20	-21
Black	16	-16	-16	12	-1	-5	-15	-11
Hispanic	24	-22	-22	28	+3	-3	-25	-19
Asian	8	-28	-29	4	-12	-15	-16	-14

4.2 Other Special/Subgroup Populations

TZD status

Table 10 shows descriptive statistics by TZD status (rosiglitazone, pioglitazone). The observed treatment effects in the two strata were not statistically different (p=0.23). The p-value was obtained from the interaction term in a model with terms for treatment, TZD (pioglitazone or rosiglitazone) and the interaction.

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Table 10. % change in LDL-C from baseline by TZD subgroup

TZD subgroup	Simva 20 + Ezetimibe 10	Simva 40	Treatment difference
Rosiglitazone (n=103)	N=55	N=48	
Baseline mean	96.9	95.7	
Mean % change	-20.0	-3.1	-16.9
Adjusted Mean (SE)	-20.8	-3.2	-17.6
Median	-26.2	-7.1	-19.1
Range (min, max)	(-55.2, +111.3)	(-30.4, +47.4)	

Pioglitazone (n=107)	N=48	N=59	
Baseline mean	88.1	86.7	
Mean % change	-22.5	+1.4	-21.1
Adjusted mean (SE)	-17.8	+5.2	-23.0
Median	-21.9	-3.8	-18.1
Range	(-55.4, +35.9)	(-30.6, +56.4)	

Note: p = .23 for the treatment-by-TZD interaction

Rollover vs new patients

Table 11 shows descriptive statistics by rollover status [1]. The observed treatment effects for rollover and new patients were not statistically different (p=0.11). The p-value was obtained from the interaction term in a model with terms for treatment, rollover status and the interaction.

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Table 11. % change in LDL-C from baseline by rollover subgroup

Rollover subgroup	Simva 20 + Ezetimibe 10	Simva 40	Treatment difference
Rollovers from Study 187	N=47	N=37	
Baseline mean	93.5	88.8	
Mean % change	-25.1	+0.9	-26.0
Adjusted Mean (SE)	-22.8 (3.4)	+3.5 (4.0)	-26.4
Median	-26.0	-4.8	-21.2
Range	-53.2, +41.7	-26.6, +50.9	

[1] The sponsor did not include analysis results by rollover status in the Final Study Report

New patients	N=56	N=70	
Baseline mean	92.2	91.8	
Mean % change	-18.0	-1.4	-16.6
Adjusted mean (SE)	-18.0 (3.5)	-0.4 (3.4)	-17.5
Median	-24.2	-5.3	-18.9
Range	-55.4, +111.3	-30.6, +56.4	

Note: p = .11 for the treatment-by-rollover status interaction

Figures 3 and 4 show patient-level LDL-C % changes form baseline by baseline LDL-C for new and rollover patients, respectively. The Figures confirm the data in Table 6 showing numerically larger treatment effects in rollover patients.

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Figure 3
LDL-C % change by baseline LDL-C
New (non-rollover) patients

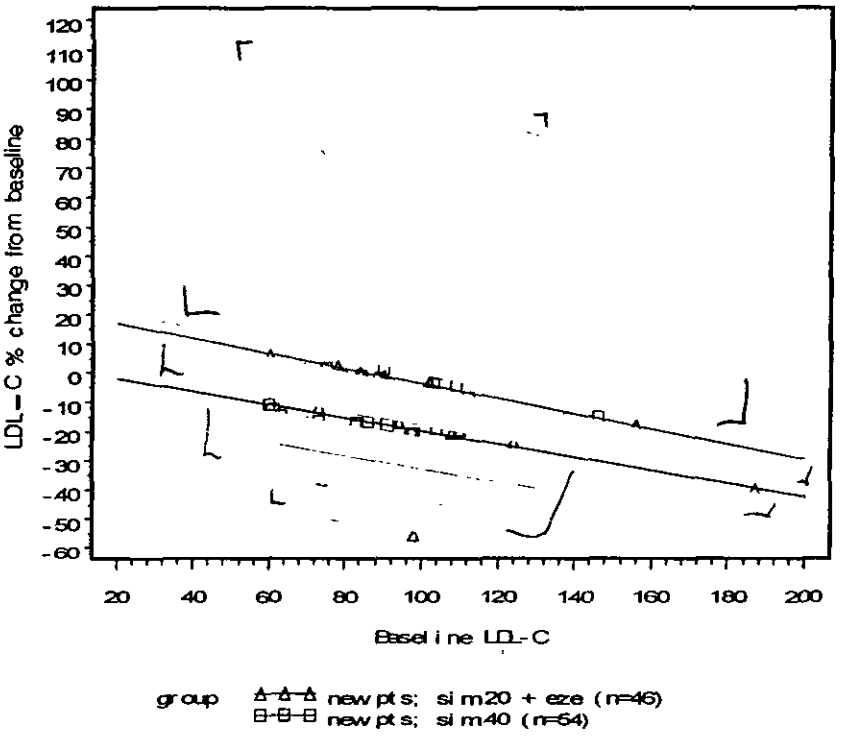

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Figure 4
LDL-C x change by baseline LDL-C
Rollover patients

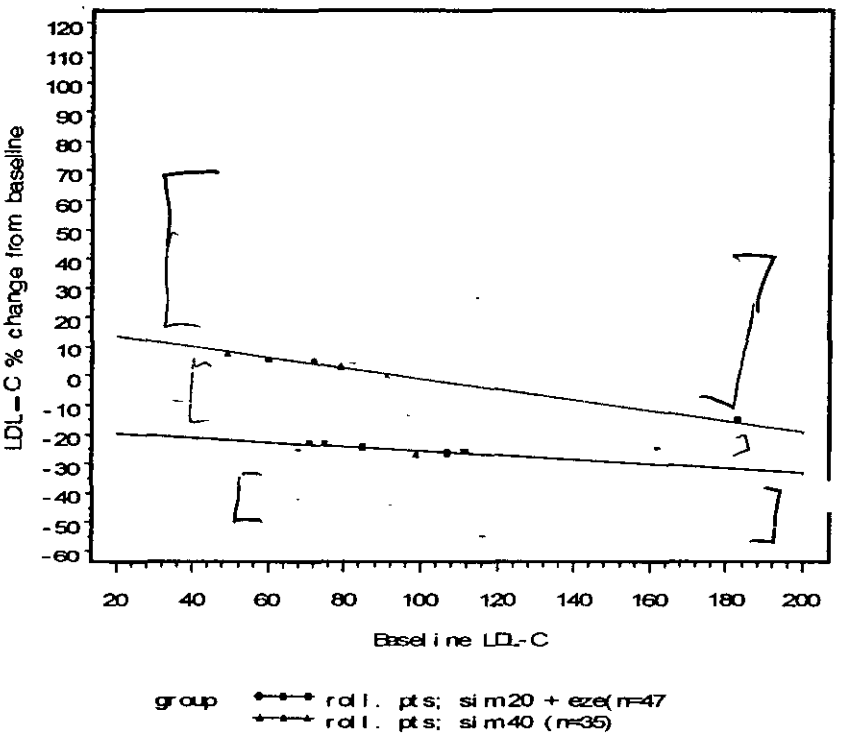

Figure 5 shows mean LDL-C values over time for completers by rollover status. (Solid lines show rollover patients, dashed lines are new patients.) Rollover patients in both groups, particularly those randomized to simvastatin 40 mg, showed increases over time after Week 6. This may represent a regression to the mean following lower values at Week 6.

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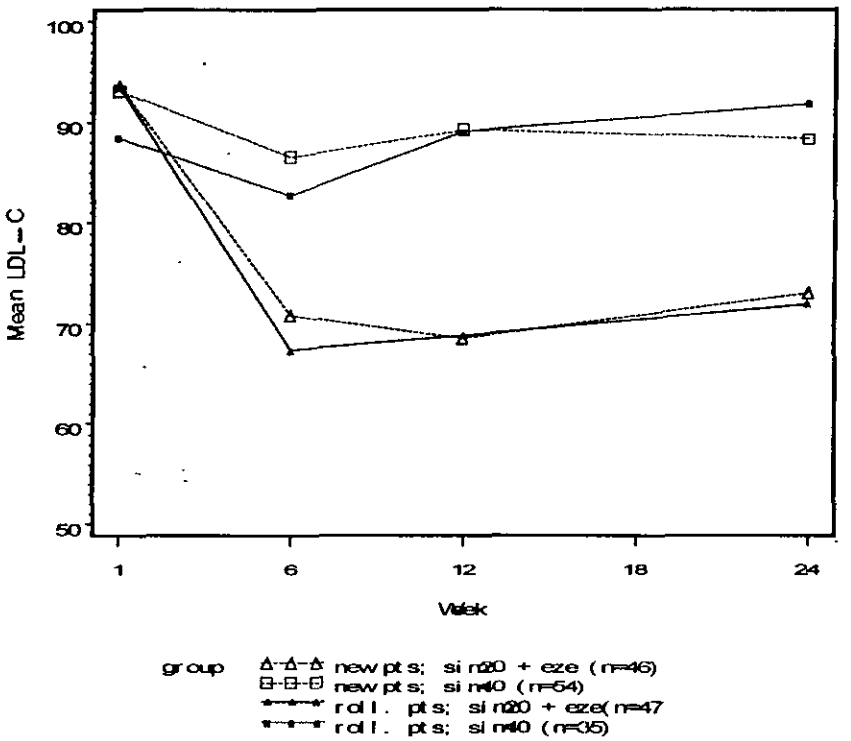
Figure 5
Mean LDL-C for completers
by rollover subgroup and treatment group



Despite some numerical differences in responses between rollover and new patients, there was insufficient statistical evidence to warrant presenting results separately by rollover status in the label.

5. Labelling considerations