U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

PEDIATRIC STUDY

NDA/Serial Number:	21-445/S-020 (Zetia) and 21-687/S-023 (Vytorin)
Drug Name:	Zetia (ezetimibe)
	Vytorin (ezetimibe/simvastatin)
Indication(s):	Treatment of heterozygous familial hypercholesterolemia in adolescent patients
Applicant:	MSP Singapore Co., LLC
	Schering Corporation (Zetia)
	Merck Research Laboratories (Vytorin)
Date(s):	Submitted 12/14/07
	Review Completed 2/29/08
	UFGD 6/17/08
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Joy Mele, M.S.
Concurring Reviewers:	Todd Sahlroot, Ph.D. Deputy Division Director
Medical Division:	Division of Metabolic and Endocrine Products (HFD-510)
Clinical Team:	Eileen Craig, M.D. Clinical Reviewer
	Eric Colman, M.D. Deputy Division Director
Project Manager:	Margaret Simoneau

Keywords: Pediatric study, clinical studies, NDA

1. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Conclusions and Recommendations

The applicant has submitted the results of a single clinical trial designed to demonstrate the safety and efficacy of vytorin (ezetimibe plus simvastatin) for the treatment of adolescents diagnosed with heterozygous familial hypercholersterolemia. This trial showed statistically significant decreases in LDL, total cholesterol, apo B and non-HDL for vytorin over simvastatin alone. For LDL, a 15% treatment difference (CI -18% to -12%) was seen at Week 6.

This reviewer recommends that the Week 6 results be reported in the labeling; results from later weeks are consistent with these results and support a statement regarding maintenance of the effect up to Week 53.

2. Data Sources

A study report for Study P02579 and xpt datasets were provided in the CDER Electronic Document Room at \\CDSESUB1\NONECTD\N21445\S_020\2007-12-14. Synopses of studies previously submitted containing adolescent patients and information on post-marketing safety in adolescents were also provided.

Tables and graphs presented in this review were created by this reviewer unless otherwise noted.

3. Statistical Evaluation

3.1 Overview of Pediatric Written Request

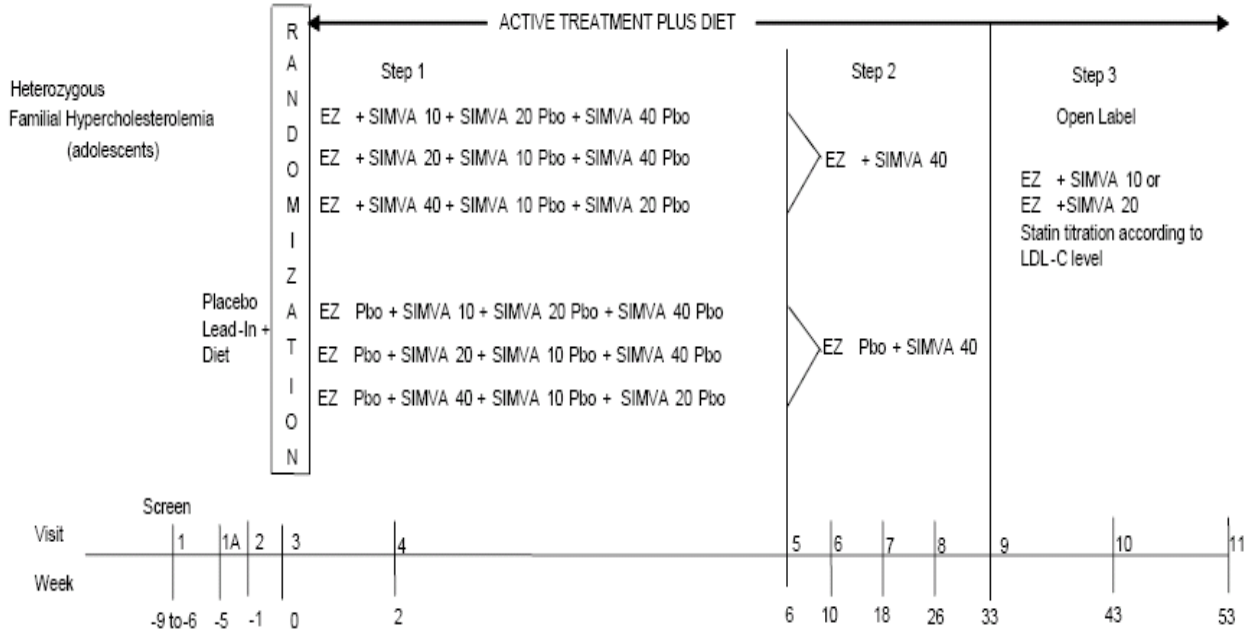
A written request for a pediatric study of Zetia was issued on April 14, 2004 and amended on November 23, 2004. MSP Singapore Company (a joint venture between Schering Corporation and Merck & Co) was asked by FDA to comply with the Zetia written request which included an evaluation of Vytorin (Zetia+simvastatin) to win pediatric exclusivity for Vytorin. The single pediatric study reviewed here (Study P02579) then was designed to address written requests for both Zetia alone and Vytorin.

The written request asked for a 3-period trial as follows:

- Period 1: 6 weeks, double-blind, randomized, comparison of each dose level of simvastatin to Vytorin at same simvastatin dose-level, ~30 patients in each group
- Period 2: 27 weeks, double-blind, comparison of maximum dose level of simvastatin to Vytorin at maximum simvastatin dose-level, all patients on Vytorin will continue on Vytorin 40 mg simvastatin/10 mg ezetimibe and all patients on simvastatin alone will continue on simvastatin 40 mg
- Period 3: 20 weeks, open-label, all patients on Vytorin with statin dose titrated to reach NCEP goals

The trial was conducted, as shown in Figure 3.1.1, with three periods (or steps) as requested.

Figure 3.1.1 Trial design (Figure 1 of applicant's study report)



A total of 342 patients were screened for the study with 248 patients randomized. More than 30 patients in each of the 6 treatment groups were randomized (Table 3.1.1) and completed the first step of the study, thereby meeting the sample size set by the written request. About 90% of the randomized patients completed all three steps of the trial. The 26 patients who dropped out of the study did so for a number of reasons with no reason predominating and no notable differences between treatment groups.

Table 3.1.1 Patient disposition

	EZ/SIM 10/10	EZ/SIM 10/20	EZ/SIM 10/40	SIM 10	SIM 20	SIM 40
Randomized	43	40	43	40	40	42
Completed Step 1	43 (100%)	39 (98%)	41 (95%)	39 (98%)	39 (98%)	40 (95%)
Completed Step 2	114/126 (90%)			113/122 (93%)		
Completed Step 3	222/248 (90%)					

According to the written request the trial was to include adolescents (boys and post-menarchal girls with at least 30% in each gender), Tanner Stage II or higher, ages 10 to 17 years diagnosed with heterozygous familial hypercholesterolemia (FH) and failing improvement with dietary intervention.

Additional entry criteria not specified in the written request included:

- Body weight of at least 40 kg and above the 10th percentile
- TG $\leq$ 350
- Liver function tests $\leq$ 1.5 times ULN
- No cardiac disorder that may limit trial participation
- No evidence of homozygous FH

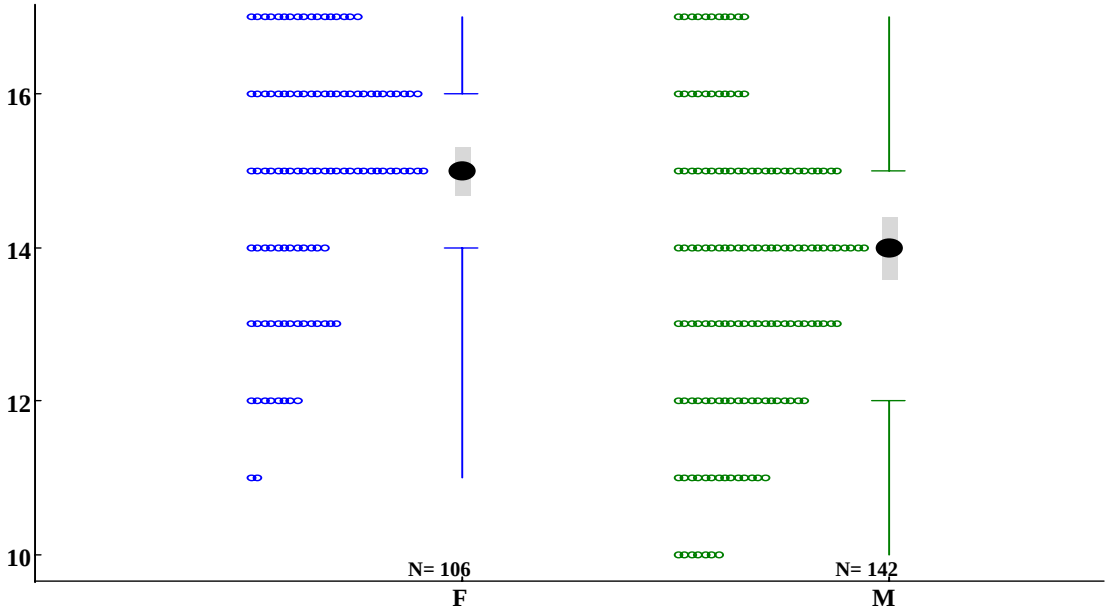
The baseline demographics (Table 3.1.2) show that the entry criteria specified by the written request were met. About 43% of the patients were female, the ages ranged from 10 to 17 and all patients had lipid values consistent with heterozygous FH. All females were of Tanner stage 3 or above and all males were of Tanner stage 2 or above.

Table 3.1.2 Baseline demographics

	EZ/SIM 10/10 (n=43)	EZ/SIM 10/20 (n=40)	EZ/SIM 10/40 (n=43)	SIM 10 (n=40)	SIM 20 (n=40)	SIM 40 (n=42)
Female (%)	42%	43%	42%	43%	45%	43%
Male (%)	58%	57%	58%	57%	55%	57%
Age (yrs) Mean (SD)	14.1 (1.8)	14.0 (2.0)	14.0 (2.0)	14.5 (1.8)	14.1 (2.1)	14.4 (1.5)
White	86%	80%	84%	85%	80%	76%
Multiracial	12%	13%	7%	10%	13%	24%
Weight (kg) Mean (SD)	59 (13)	56 (11)	59 (14)	64 (15)	56 (14)	64 (17)
Baseline Lipids Mean(SD) mg/dL						
LDL-C	226 (44)	213 (38)	236 (41)	230 (48)	212 (45)	214 (38)
HDL-C	44 (8)	49 (11)	46 (9)	46 (9)	46 (9)	45 (9)
TG (median)	89	86	95	87	88	91

The age distribution for girls was older than for boys with a median of 14 for boys (M in graph) and a median of 15 for girls (F in graph) (Figure 3.1.2). This distribution suggests that analyses by age should also be stratified on gender.

Figure 3.1.2 Boxplots and histograms for age by gender



A discussion of the statistical methods used in the trial and consistency of these methods with the written request is covered in the following section of this review along with a presentation of the efficacy results.

3.2 Evaluation of Efficacy

The primary endpoint for Study P02579 was LDL percent change from baseline at Week 6 comparing the pooled vytorin arms against the pooled simvastatin arms as specified in the written request.

Secondary endpoints specified in the written request included the following:

- LDL % change from baseline at Week 6 comparing each vytorin arm to simvastatin at the matching simvastatin dose level
- Treatment comparisons for % change from baseline for LDL, total cholesterol (TC) and apolipoprotein B (apo B) at 33 weeks
- Proportion of patients reaching LDL goal by Week 33

An ANOVA model with terms for statin dose, treatment, statin dose X treatment interaction and covariates was proposed in the written request as the analytical model. Gender was named as a covariate in the protocol. Significance on the primary analysis is required to do further analyses of secondary endpoints. The proposed model was used for the analyses conducted by the applicant.

An ANOVA model was used for all secondary endpoints except triglycerides (TG) where a non-parametric model was used. Multiplicity with regard to the multiple secondary endpoints was addressed using Hochberg's procedure which is described in detail in Section VI D of the applicant's data analysis plan.

The intent-to-treat population consisted of 246 of the 248 randomized patients. Missing data is not an important issue for this study since the completion rates at each step of the trial were over 90%.

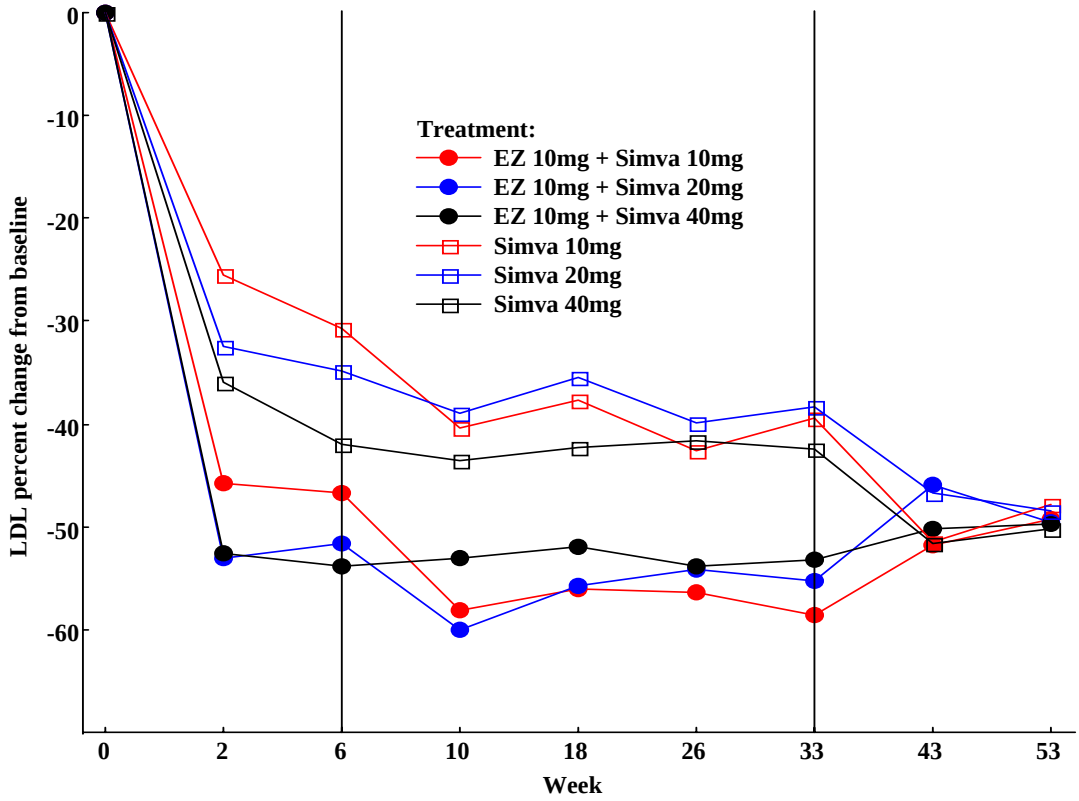
A test for interaction for treatment by simvastatin dose yielded a non-significant $p>0.7$ suggesting that pooling across dose is acceptable; the results for the pooled groups at Week 6 are shown in Table 3.2.1 for the primary efficacy variable and for the secondary variables. All pairwise comparisons (with like doses of simvastatin) were statistically significant for all measures except HDL and TG which were also not significant comparing the pooled arms (see Figure 3.2.1 for the LDL comparisons and Appendix 6.1).

Table 3.2.1 Lipid percent change from baseline (least squares mean and SE) at Week 6 (Step 1 endpoint)

	EZ/SIM pooled (n=126)	SIM pooled (n=120)	Trt Diff (95%CI)	p-value
LDL	-49% (1)	-34% (1)	-15% (-18%, -12%)	<0.01
Total Cholesterol	-38% (1)	-26% (1)	-12% (-15%, -9%)	<0.01
HDL	+6.6% (1)	+6.5% (1)	+0.1% (-3%, +3%)	0.95
Apo B	-39% (1)	-27% (1)	-12% (-15%, -9%)	<0.01
TG (median+SD)	-17% (30)	-12% (31)	-2% (-9%, +4%)	0.5
Non-HDL	-47% (1)	-33% (1)	-14% (-17%, -11%)	<0.01

Negative values for treatment difference favor vytorin over simvastatin alone except for HDL

Figure 3.2.1 LDL percent change from baseline by week and randomized treatment group for patients who completed 53 weeks on study



Week 0 to 6: randomized trt; Week 6 to Week 33: Vytorin pts on Vytorin 10/40 & SIM pts on SIM 40; Week 33 to Week 53: all pts on open-label Vytorin 10/10 with titration to goal

The Week 6 results best represent the results that can be expected at each of the recommended doses. The results for LDL at Week 6 are summarized in the table below.

Table 3.2.2 LDL percent change from baseline (LSM and SE) at Week 6 for all treatment groups

Simvastatin Dose	EZ/SIM	SIM	Trt Diff (95%CI)	p-value
10 mg	-47% (2)	-30% (2)	-16% (-22%, -11%)	<0.01
20 mg	-50% (2)	-34% (2)	-15% (-21%, -9%)	<0.01
40 mg	-52% (2)	-39% (2)	-14% (-19%, -8%)	<0.01

Negative values for treatment difference favor vytorin over simvastatin alone

3.3 Evaluation of Safety

According to the pediatric written request, safety evaluations at Weeks 33 and 53 of linear growth, Tanner stage, menstrual cycle monitoring and steroid hormone levels were planned. The applicant's analyses showed no differences between groups with regard to any of these safety measures.

The applicant summarized linear growth changes as percent change from baseline and showed no differences between the groups. This reviewer looked at height by age and gender and also found no treatment differences for change in height. However, it should be noted that to assess the impact of either treatment on normal growth, the changes in height should be standardized for age and gender against an untreated population. If there is any serious clinical concerns regarding growth, the applicant should re-analyze the data using standardized scores.

For more details regarding safety, please see the FDA clinical review.

4. Findings in Special/Subgroup Populations

Analyses based on gender and race and baseline TG, LDL and HDL were planned and conducted by the applicant. The results of these analyses are shown in Appendix 6.2 of this review. The results show consistency of the treatment effect across these predefined subgroups with a greater drop in LDL for Vytorin over simvastatin alone. Additional analyses by this reviewer showed consistency of effect across age and by subgroups defined both by age and gender as well.

5. Summary and Conclusions

The applicant has submitted the results of a single clinical trial designed to demonstrate the safety and efficacy of vytorin (ezetimibe plus simvastatin) for the treatment of adolescents diagnosed with heterozygous familial hypercholersterolemia. This trial showed statistically significant decreases in LDL, total cholesterol, apo B and non-HDL for vytorin over simvastatin alone. For LDL, a 15% treatment difference (CI -18% to -12%) was seen at Week 6.

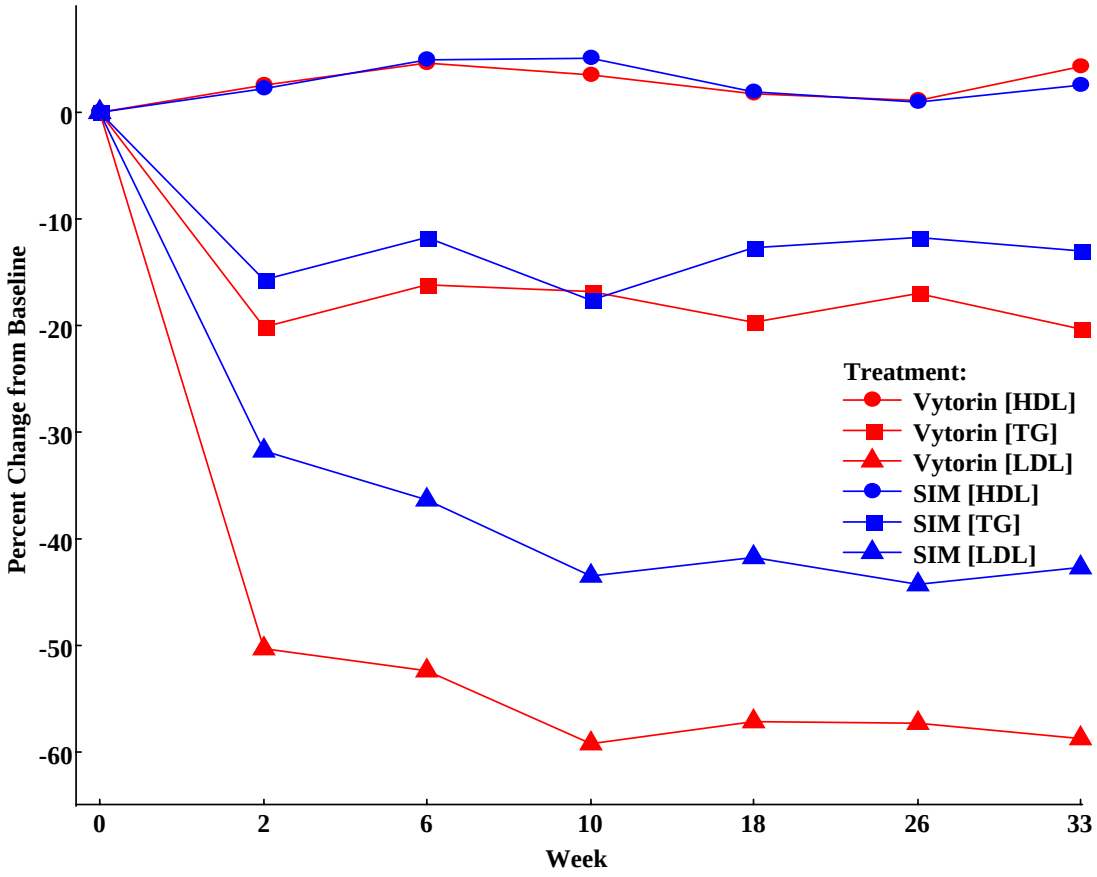
5.1 Labeling comments

This reviewer thinks only the Week 6 results should be explicitly presented in Section 14.2 of the applicant's proposed labeling. The Week 6 results best describe the results for the three available doses and also the results at later weeks are consistent with these results and add no additional information that cannot be summarized in a sentence. The text should also contain the LDL treatment differences and confidence intervals; since the results are consistent across the simvastatin doses, the pooled treatment difference and confidence interval could be reported.

The formatting of the table should be similar to Table 9 of the labeling where the results are presented by lovastatin dose; this would allow more readily for a comparison of vytorin to the appropriate dose of simvastatin.

6 Appendices

6.1 Graph of LDL, HDL and TG for pooled groups and for patients who completed 33 weeks



6.2 Graph of LDL percent change from baseline treatment difference by subgroups

Figure 3 extracted from page 111 of the study report.

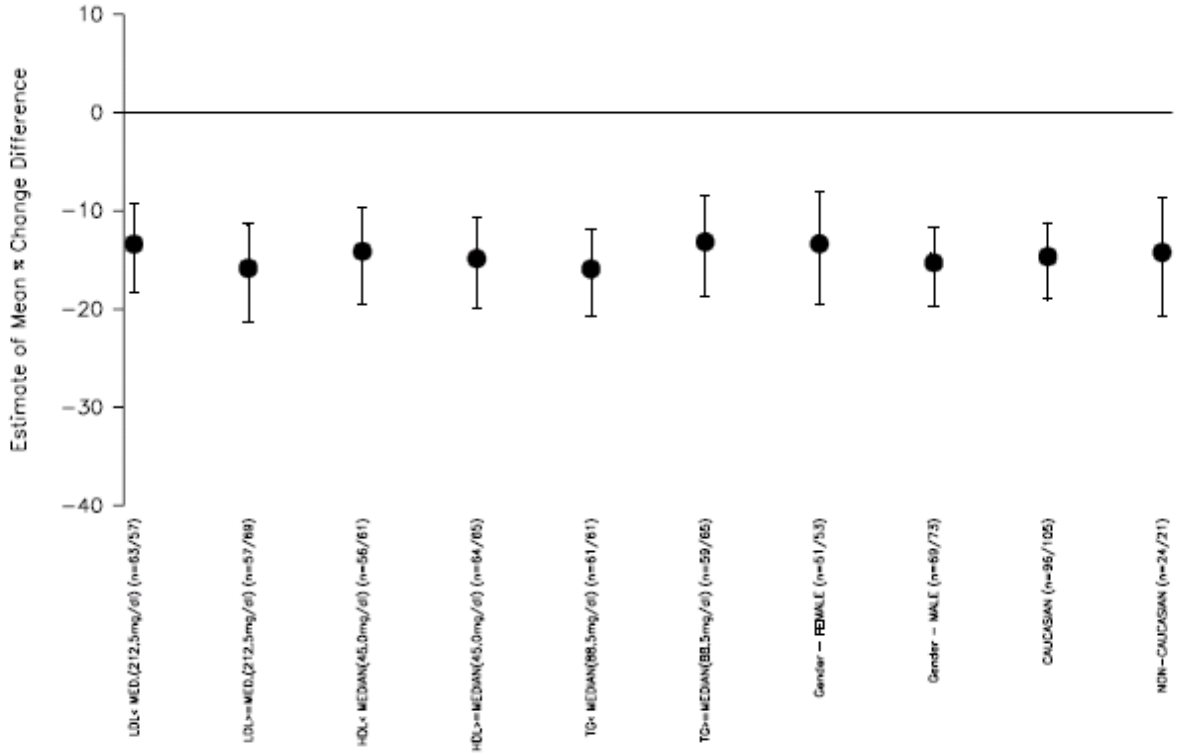
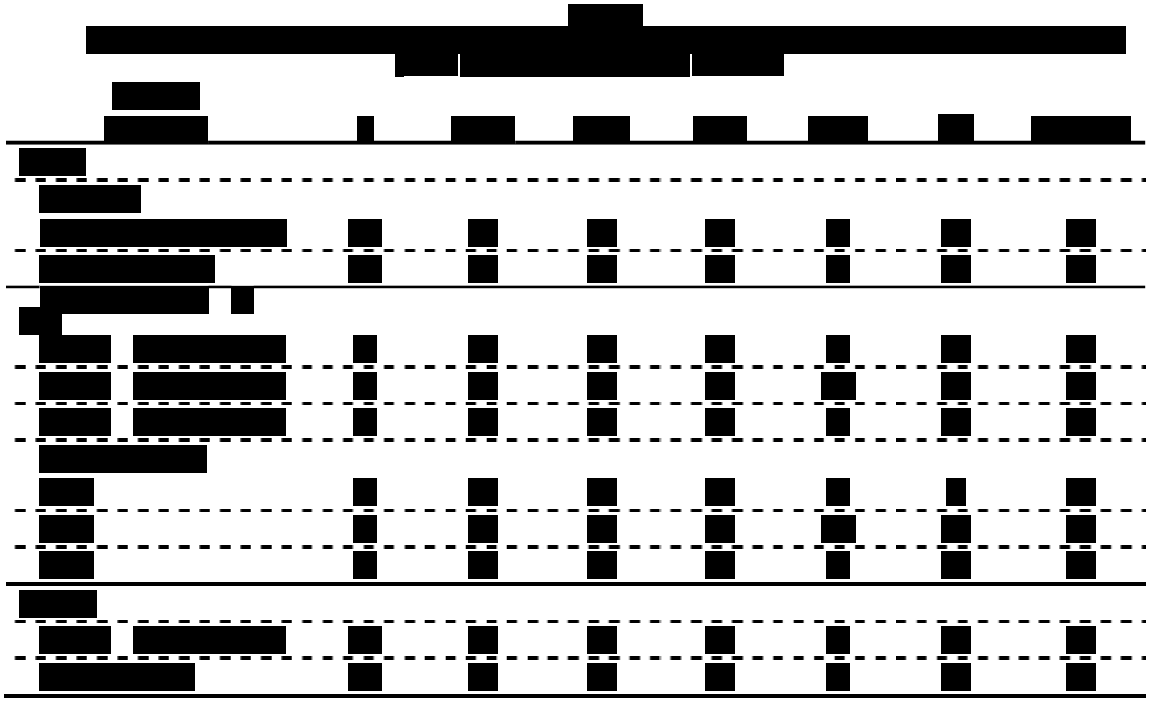


Figure 3 Point estimate and 95% confidence interval of the difference between mean percent change from Baseline of Pooled EZ/simva compared with Pooled Simva in LDL-C at Step 1 Endpoint in various subgroups of the population defined by baseline characteristics: Intent-to-Treat Data Set

6.3 Applicant's Proposed Labeling

[redacted]



[redacted]

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

/s/

Joy Mele
2/29/2008 03:17:18 PM
BIOMETRICS

Todd Sahlroot
2/29/2008 03:20:14 PM
BIOMETRICS