CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-853

21654s016

STATISTICAL REVIEW(S)

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

CLINICAL STUDIES

NDA/Serial Number:	21-853 / N000; SE8-001
Drug Name:	Omacor (omega-3-acid ethyl esters) Capsules, 4 grams/day
Indication(s):	Reduce triglycerides levels in patients treated with a statin and with TG levels between 200 and 500 mg/dL
Applicant:	Reliant Pharmaceuticals, Inc.
Date(s):	Submitted 12/11/06, Review completed 5/11/07, UFGD 6/11/07
Review Priority:	Response to approvable letter; 6-month review
Biometrics Division:	Division of Biometrics 2 (HFD-715)
Statistical Reviewer:	Joy Mele, M.S.
Concurring Reviewer:	Tom Permutt, Ph.D. Biometric Division Director
Medical Division:	Division of Metabolic and Endocrine Products
Clinical Team:	Iffat Chowdhury, MD Clinical Reviewer
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	Mary Parks, MD Division Director
Project Manager:	Kati Johnson

Keywords: Clinical studies, combination drug

1. Executive Summary[1]

Omacor (omega-3-acid ethyl esters 4 gram/day) was approved as monotherapy under NDA 21-654 to reduce triglycerides in patients with triglycerides ≥ 500 mg/dL (Fredrickson Type V). The application under review here is a complete response to an approvable letter for an application seeking approval of omacor given in combination with statin therapy [ ] to treat patients with triglycerides between 200 and 500 mg/dL [ ] b(4)

Study OM6 was submitted to support approval of omacor as add-on therapy to a statin for lowering of triglycerides in patients with triglycerides between 200 and 500 mg/dL. Patients in this trial were treated with simvastatin 40 mg for 8 weeks and then randomized to add-on omacor or placebo and treated for 8 weeks.

Statistically significant treatment effects in favor of omacor over placebo were seen for non-HDL, TG, TC, VLDL, Apo-B and HDL; labeling has been proposed for all these measures. A statistically significant treatment difference between omacor and placebo of about 3-4% was seen for LDL. In the omacor plus simvastatin group, most of the increases in LDL were seen in patients with low LDL at baseline (see Table 3.2.3 and Appendix 3); in addition, 91% of the patients were at NCEP goal at endpoint with only 3 patients in each group having an increase in LDL moving them above their NCEP goal after baseline.

In conclusion, omacor significantly impacts TG in a population of patients with increased TG levels in spite of statin therapy. Regarding LDL, the trial results did not meet the criterion of ruling out a 4-6% treatment difference but it is a clinical issue as to whether the differences seen are of clinical relevance.

1 This section is identical to Section 4 of this review.

2. Introduction

2.1 Overview

Omacor (omega-3-acid ethyl esters 4 gram/day) was approved as monotherapy under NDA 21-654 to reduce triglycerides in patients with triglycerides ≥ 500 mg/dL (Fredrickson Type V). NDA 21-853 (unbundled from NDA 21-654) was submitted January 9, 2004 for approval of omacor given in combination with statin therapy [ ] to treat patients with triglycerides between 200 and 500 mg/dL [ ] An approvable letter was issued November 10, 2004. The application under review here is a complete response submitted December 11, 2006. b(4)

In the original application decreases in triglycerides (TG) were associated with increases in LDL, HDL and Apo-B in patients treated with omacor. The FDA expressed concern that these changes may increase cardiovascular risk and that these changes may attenuate the effects of a statin given in combination. As part of a complete response, the applicant has submitted the results of one clinical trial (OM6) to support an indication for combination use of omacor with a statin to reduce non-HDL, TG, TC, Apo-B and VLDL and to increase HDL in patients with TG between 200 and 500 mg/dL.

In a letter from FDA dated February 15, 2005, the Division of Metabolic and Endocrine made the following recommendations for the protocol of OM6:

- Patients treated with simvastatin 40 mg should be at NCEP AT III goal levels for LDL at randomization to placebo or omacor.
- Non-HDL should be the primary endpoint.
- The study should be adequately powered to rule out a treatment difference of 4% to 6% on LDL.
- Covariates should be pre-specified.

2.2 Summary of results from original submission

The results of the trials reviewed for the original submission are summarized in a table from Dr. Lee-Ping Pian's statistical review shown in Appendix 1 of this review. The approval of omacor for the treatment of patients with triglycerides ≥ 500 mg/dL (Frederickson Type V) was based on the results of two US studies where a median treatment difference for TG of -52% (placebo +7%, omacor -45%) and a median treatment difference for LDL of +49% (placebo -5%, omacor +44%%) for the studies pooled were observed. Note that for the latter patient population, the primary concern is lowering of TG because LDL is not usually elevated in these patients. The five trials in patients with Frederickson Type IIb or IV were considered inadequate because patients were only treated with omacor and therefore TG levels decreased while LDL levels increased in this population with abnormally high levels of LDL. The median decrease in TG seen for the latter patients treated with omacor was about 26% with an increase in LDL of about 1% in Type IIb patients and about 33% in Type IV patients. The results by Fredrickson type are summarized in the table below which was extracted from the FDA clinical review by Dr. Mary Parks. For this table, studies shown in Appendix 1 were pooled.

Table 2.2.1 Table extracted from the FDA clinical review by Dr. Mary Parks

Table 1. Median Percent Changes From Baseline by Dyslipidemic Type

	TG		TC		HDL		LDL		VLDL		nonHDL	
	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo
Type IIb	-26.3	+2.9	-2.3	-1.5	+5.5	+4.6	+1.4	-3.9	-10..9	+13.7	-3.2	-2.1
Type IV	-25.5	+4.5	+2.0	+1.1	+11.1	+2.9	+33.8	+2.2	-34.3	+6.7	+1.4	+1.0
Type V	-39.4	+2.8	-16.5	+0.5	+18.1	-4.6	+42.8	+19.9	-31.9	+2.2	-18.9	+0.7

In the original application, the results of one trial where omacor was co-administered with a statin were presented. Study K85-95014 was a 6-week study in a total of 59 Type IIb patients randomized to simvastatin+omacor or simvastatin alone. The combination resulted in a 29% decrease in TG compared to no change in the simvastatin alone group. Either no change or small increases in LDL were seen in both groups suggesting that the statin was not properly administered (dosing of the statin was at the discretion of the investigator). This trial was deemed inadequate by the FDA clinical reviewer.

Based on the original submission, it was concluded that additional data was needed to show that the increases in LDL seen in Type IIb and IV patients using omacor would not increase the risk of atherosclerosis or that the addition of omacor to a statin would not attenuate the effects of the statin while providing a clinical benefit regarding TG. The applicant has submitted the results of one study to demonstrate the latter.

2.3 Data Sources

The applicant submitted datasets to the CDER electronic document room. These datasets are stored at \\CDSESUB1\N21853\N_000\2006-12-11 and \\CDSESUB1\N21853\N_000\2007-05-03 .

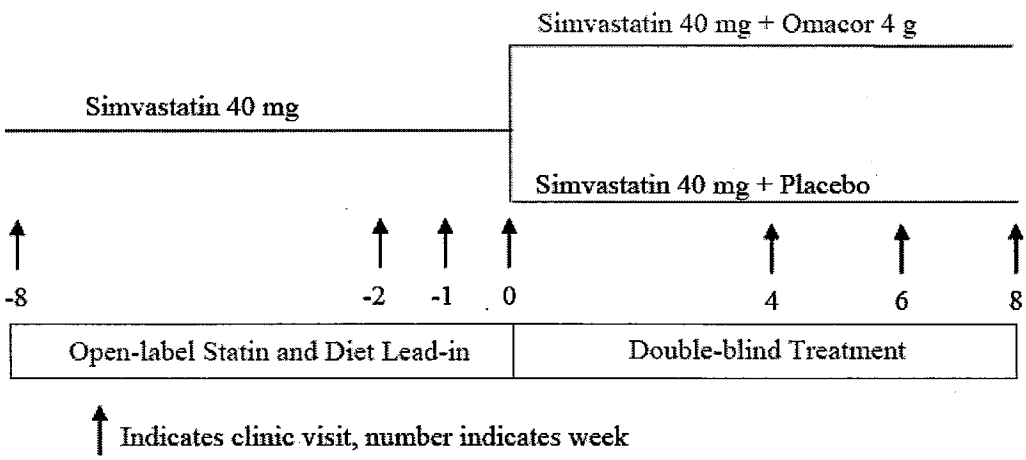
3. Statistical Evaluation

3.1 Evaluation of Efficacy

Study OM6 (conducted May, 2005 to June, 2006)

Study OM6 was a randomized, double blind, parallel study to assess the effectiveness of omacor as add-on therapy to simvastatin 40 mg for the treatment of hypertriglyceridemia. Patients were eligible for this study if they were on a stable dose of a statin for at least 8 weeks prior to the screening visit. Following an 8-week lead-in period on simvastatin 40 mg and NCEP diet, patients with 200≤TG<500 (average of weeks -2 and -1) and LDL within 10% of NCEP goal were randomized to add-on omacor or placebo (Figure 3.1.1).

Figure 3.1.1. Applicant's schematic of trial design extracted from the study report



The primary endpoint was the percent change from baseline of non-HDL (total cholesterol minus HDL) at the end of treatment where baseline was computed as the average of Weeks -2, -1 and 0 and endpoint was the average of Weeks 6 and 8. Secondary endpoints included the usual lipoprotein profile. This reviewer will focus primarily on non-HDL, TG and LDL; endpoints mentioned in labeling will be checked as well but not presented in the body of this report.

A total of 256 patients (123 on omacor+simvastatin and 133 on placebo+simvastatin) from 41 US sites were randomized to placebo or omacor; 243 (95%) patients completed the study. Seven patients on simvastatin plus omacor and 6 patients on simvastatin discontinued treatment; 3 on each therapy withdrew due to ADE. Only one patient in each group was not included in the efficacy analysis. Given the high completion rate, it is clear that missing data is not an issue in this study.

The treatment groups were well-balanced for baseline demographics. The average age of patients in this study was 60 years with ages ranging from 24 to 79 years; 37% of patients were 65 years or older. About 42% of the patients were female and almost all the patients were Caucasian. As part of the entry criteria, patients were to be on a statin for at least 8 weeks prior to screening so it is not possible to ascertain the patients' Fredrickson types based on their baseline LDL. About 12% of the patients had a screening LDL greater than 130 mg/dL and about 18% were not at NCEP goal at screening.

After a 6-week run-in on simvastatin 40 mg, the majority of patients achieved a level of LDL below 100 mg/dL (Table 3.1.1) with 71% in the omacor plus simvastatin group and 67% in the simvastatin group. According to this reviewer's analysis, there were a total of 22 patients (10 randomized to omacor plus simvastatin and 12 to simvastatin alone) who had values of LDL above target at baseline; so about 91% of the patients attained or maintained their NCEP goal during the run-in on simvastatin.

Table 3.1.1 Baseline distribution of LDL by NCEP ATPIII category (Reviewer's Analysis)

LDL mg/dL	Omacor+Simva (n=123)	Placebo+Simva (n=133)
<100	71%	67%
100-129	24%	26%
130-159	5%	7%
160+	0%	1%

Efficacy Results

According to the protocol, the percent change from baseline in non-HDL was to be analyzed by ANOVA and baseline non-HDL would be considered as a covariate. The protocol stipulated that variables imbalanced at baseline or related to outcome would be added to the model and then the model was to be reduced using a stepwise approach until, at minimum, treatment was the only factor in the model. The applicant was advised at the protocol stage that covariates should be prespecified. Secondary variables were to be analyzed using the same approach. Last-observation-carried-forward imputation was to be used for missing data.

From the applicant's study report, most results were produced by an ANOVA model with only treatment as a factor. Since lipid changes (particularly non-HDL and LDL) are usually strongly correlated with baseline, a model with baseline as a covariate is preferable. To check the applicant's results, this reviewer performed an ANCOVA for the primary variables of interest; non-HDL, TG and LDL, with baseline as a covariate.

The treatment differences and confidence intervals (Table 3.1.2) computed by this reviewer show statistically significant decreases for non-HDL (-7% treatment difference, p<0.0001) and TG (-25%, p<0.0001); these results are in agreement with the applicant's results.

Table 3.1.2 Baseline and percent change from baseline for non-HDL, TG and LDL
Least square mean differences in percent change from baseline were computed by the reviewer using an ANCOVA model with baseline as a covariate

	Omacor+Simva (n=122)	Placebo+Simva (n=132)	LS Mean Diff (95% CI)	p-value
non-HDL				
Baseline Mean (SD)	136 (25)	141 (29)		
Endpoint % change				
Mean (SD)	-8% (14)	-1.5% (11)	-6.9% (-10%, -4%)	<0.0001
Median	-9%	-2.2%		
TG				
Baseline				
Mean (SD)	282 (76)	287 (78)		
Median	268	271		
Endpoint % change				
Mean (SD)	-28% (19)	-4% (22)	-25% (-30%, -20%)	<0.0001
Median	-30%	-6%		
LDL				
Screening	96 (24)	99 (29)		
Baseline	89 (22)	92 (23)		0.6[1]
Endpoint	90 (20)	90 (24)		0.6[1]
Endpoint % change				
Mean (SD)	+3% (19)	-2% (12)	+4.7% (+1.0, +8.3)	0.01
Median	+0.7%	-3%		0.054[1]
Percent of pts with 4% increase or greater	40%	35%		0.44[2]
% of pts at NCEP LDL goal at endpoint	91%	91%		

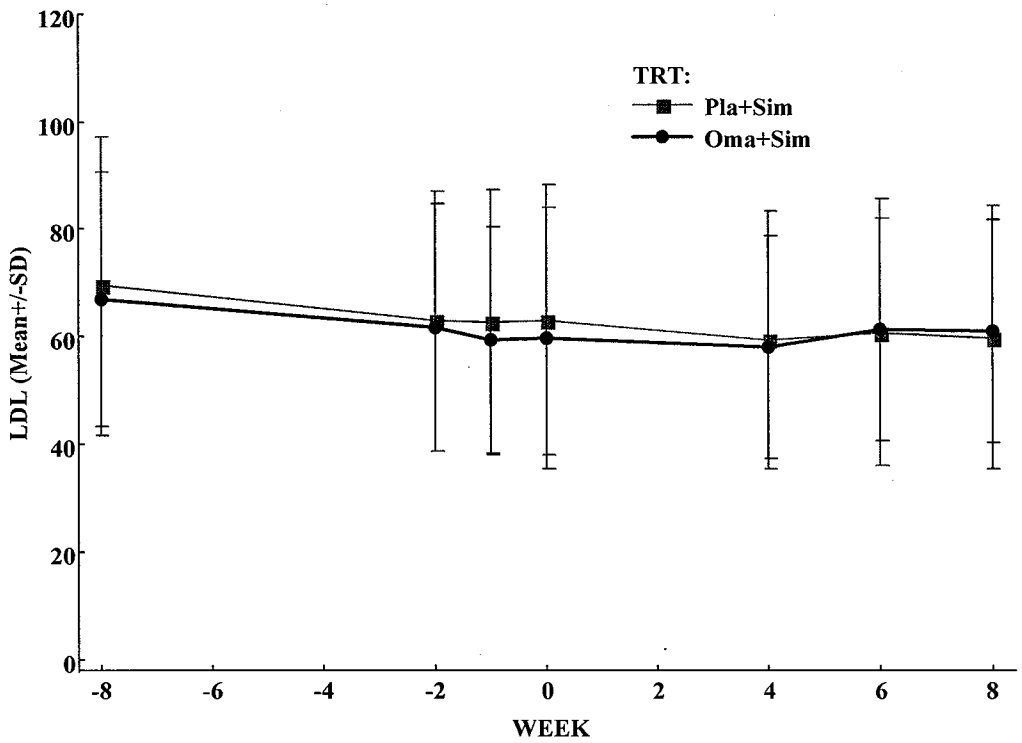
1-Wilcoxon signed rank test 2- Two-sided Fisher's exact test

For LDL, the mean treatment difference is +4.7% (median difference of approximately 4%) with a confidence interval from 1% to 8% which suggests that differences against the combination of omacor and simvastatin as large as 8% are possible. These trial results do not satisfy the goal of ruling out a treatment difference of 4% to 6%, the criterion set by the FDA medical division at the protocol stage. However, the data shows that the percentage of patients having an increase of 4% or more during double-blind treatment was not significantly different for the two treatment groups (40% of omacor+simvastatin and 35% for placebo+simvastatin, p=0.44).

At endpoint, 91% of patients in both treatment groups met their NCEP goal; there were 3 patients in each treatment group who met their NCEP goal at baseline but not at endpoint.

The primary comparisons were based on the difference of values computed by averaging several weeks. To check that averaging did not appreciably affect the results, this reviewer looked at the data by week. A plot of data from patients who completed the study (95% of randomized patients) suggests that the groups do not differ appreciably on average; these results are consistent with the comparisons of means at baseline (average of weeks -2, -1 and 0) and endpoint (average of weeks 6 and 8)[see results in Table 3.1.2 above and boxplots in Appendix 2].

Figure 3.1.2 Mean LDL (±1 SD) over time by treatment group for patients completing the study; 95% of patients were completers



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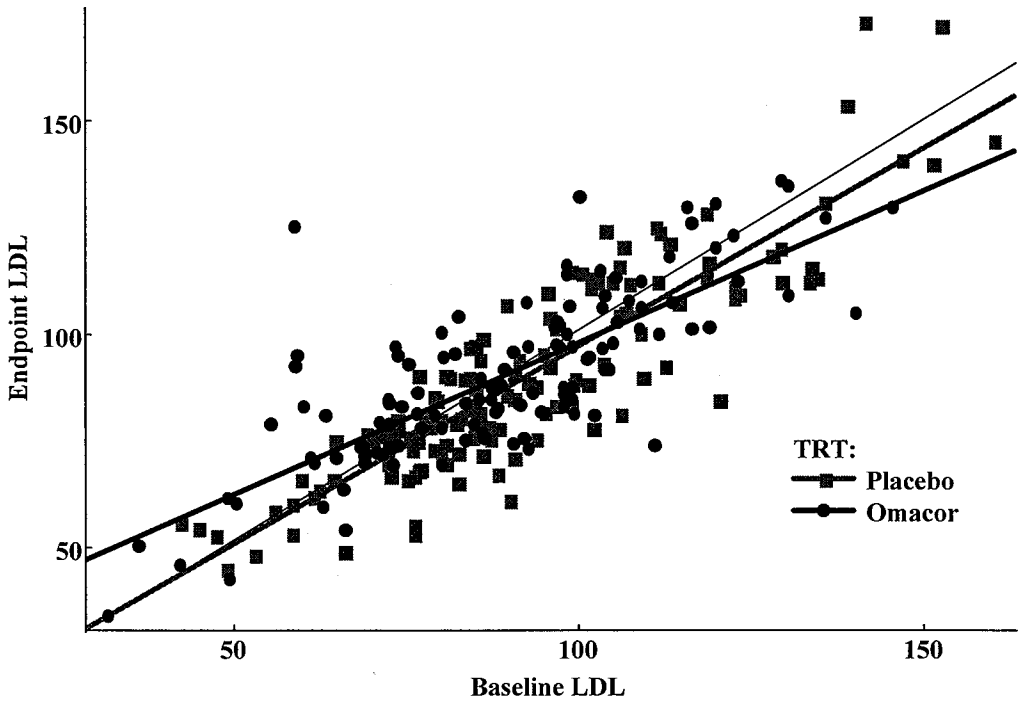
The relationship between baseline and endpoint in each treatment group is illustrated in the graph below; points below the identity line indicate a decrease from baseline in LDL.

Figure 3.1.3 Endpoint LDL versus Baseline LDL by treatment group



The table below confirms what the graph above illustrates; LDL increases are seen on average for low values of LDL (values under about 85 mg/dL) while decreases are seen on average for values above about 100 mg/dL in the both groups. These results are supportive of omacor since they suggest that clinically significant increases are most likely in patients with low LDLs (see Appendix 3 for more details).

Table 3.1.3 Median percent change from baseline for non-HDL, TG and LDL at endpoint by baseline LDL tertile (Applicant's results)

Baseline LDL tertile	Omacor+Simva (n=122)	Placebo+Simva (n=132)	Treatment Difference
LDL≤80.3 mg/dL			
non-HDL	-5%	-0.2%	-4.8%
TG	-27%	-1.5%	-25.5%
LDL	**+10%**	**+1%**	**+9%**
80.3<LDL≤98.7 mg/dL			
non-HDL	-13%	+4%	-17%
TG	-32%	-5%	-27%
LDL	-0.9%	-4%	**+3.1%**
LDL>98.7 mg/dL			
non-HDL	-11%	-2%	-9%
TG	-30%	-6%	-24%
LDL	-6%	-5%	**-1%**

4. Summary and Conclusions

Omacor (omega-3-acid ethyl esters 4 gram/day) was approved as monotherapy under NDA 21-654 to reduce triglycerides in patients with triglycerides ≥ 500 mg/dL (Fredrickson Type V). The application under review here is a complete response to an approvable letter for an application seeking approval of omacor given in combination with statin therapy [ ] to treat patients with triglycerides between 200 and 500 mg/dL [ ] b(4)

Study OM6 was submitted to support approval of omacor as add-on therapy to a statin for lowering of triglycerides in patients with triglycerides between 200 and 500 mg/dL. Patients in this trial were treated with simvastatin 40 mg for 8 weeks and then randomized to add-on omacor or placebo and treated for 8 weeks.

Statistically significant treatment effects in favor of omacor over placebo were seen for non-HDL, TG, TC, VLDL, Apo-B and HDL; labeling has been proposed for all these measures. A statistically significant treatment difference between omacor and placebo of about 3-4% was seen for LDL. In the omacor plus simvastatin group, most of the increases in LDL were seen in patients with low LDL at baseline (see Table 3.2.3 and Appendix 3); in addition, 91% of the patients were at NCEP goal at endpoint with only 3 patients in each group having an increase in LDL moving them above their NCEP goal after baseline.

In conclusion, omacor significantly impacts TG in a population of patients with increased TG levels in spite of statin therapy. Regarding LDL, the trial results did not meet the criterion of ruling out a 4-6% treatment difference but it is a clinical issue as to whether the differences seen are of clinical relevance.

5. Labeling Comments

This reviewer has checked the numbers in the first paragraph and first table proposed in the Clinical Trials section of labeling and has found no notable errors.

This reviewer does <u>not</u> agree with the following statement under Table 1: [ ]

b(4)

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Appendix 1. Summary of studies reviewed in original submission

The following table was copied from the statistical review of Dr. Lee-Ping Pian.

Table 1 Brief summary of Category I studies

Study ID # of Centers	Total Sample Size		Type of Study & Control	Duration treatment (dietary run-in)	TG (mg/dL) Median			LDL (mg/dL) Median		
					n	BL	%Chg	n	BL	%Chg
Ck85014 7 UK	corn oil K85 4g/day	57 54	hyperlipidemic patients with 177≤TG ≤885 mg/dl and TC≥201 mg/dl	12 (10) weeks	53 52	258 265	-0.5 -23.3	50 49	199 192	0.9 3.6
Ck85017 5 UK	corn oil K85 4g/day	26 29	hyperlipidemic patients with 177≤TG ≤885 mg/dl and TC≥201 mg/dl	12 (10) weeks	23 29	330 276	1.8 -19.8	22 28	152 158	-0.6 7.5
Ck85019 1 Sweden	corn oil K85 4g/day	27 26	post-myocardial infarction patients with 177≤TG ≤885 mg/dl and TC≤386 mg/dl	12 (9) weeks	26 26	238 268	3.0 -23.8	26 26	156 156	-3.5 7.2
Ck85022 1 Sweden	corn oil K85 4g/day	30 30	patients with hyperTG levels 177≤TG ≤885 mg/dl and TC≥232 mg/dl	12 (9) weeks	30 30	305 279.0	-9.6 -22.5	30 30	202 201	-0.7 1.9
Ck85023 1 Norway	corn oil K85 4g/day	29 28	hypertriglyceridemia,177≤TG ≤1526 mg/dl and TC≥232 mg/dl	12 (10) weeks	28 28	275 295	-12.2 -29.2	27 24	185 206	-10.3 -5.5
K85-94010 1 US	corn oil K85 4g/day	21 20	patients with severe hypertriglyceridemia, type IV, with 500≤TG ≤2000 mg/dl	6 (6) weeks	21 20	786 811	-14.3 -38.4	21 20	126 108	1.2 23.5
K85-95009 2 US	corn oil K85 4g/day	21 22	patients with severe hypertriglyceridemia, 500≤TG ≤2000 mg/dl	16 (4) weeks	21 22	841 818	6.4 -50.7	21 22	93 78	-10.1 62.7
Ck85-013(K85 4-g part) 2 Sweden	corn oil K85 4g/day	17 17	patients with hyperlipidemia, 1770≥TG ≥442 mg/dl and TC levels ≥250 mg/dl	8 (8) weeks	17 15	260 261	-15.6 -35.6	17 16	208 180	2.8 11.3

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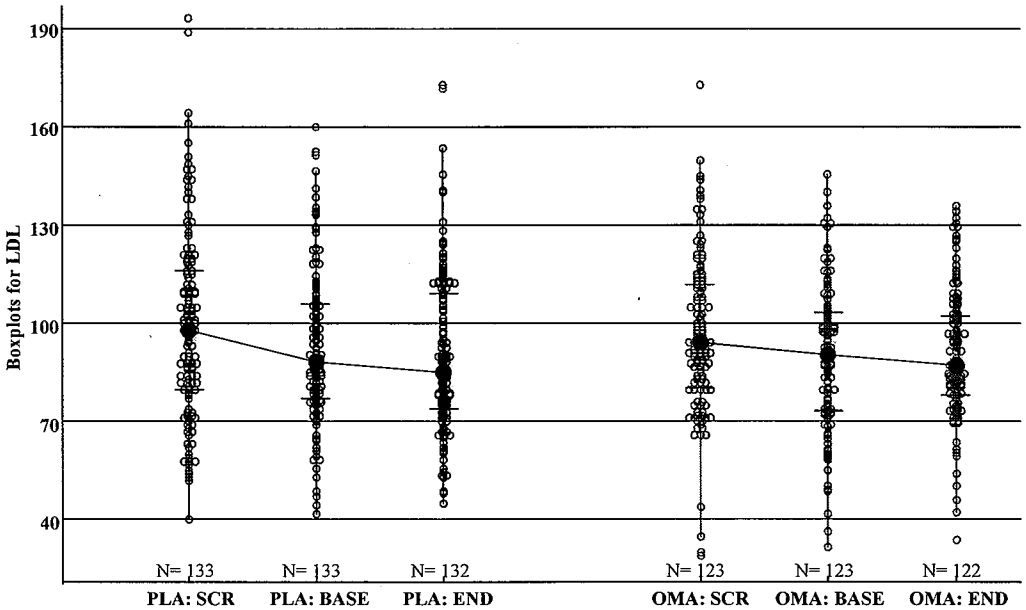
Appendix 2 Boxplots of LDL at screening, baseline and endpoint

Baseline is defined as the average of Weeks -2, -1 and 0 and endpoint is the average of Week 6 and 8.



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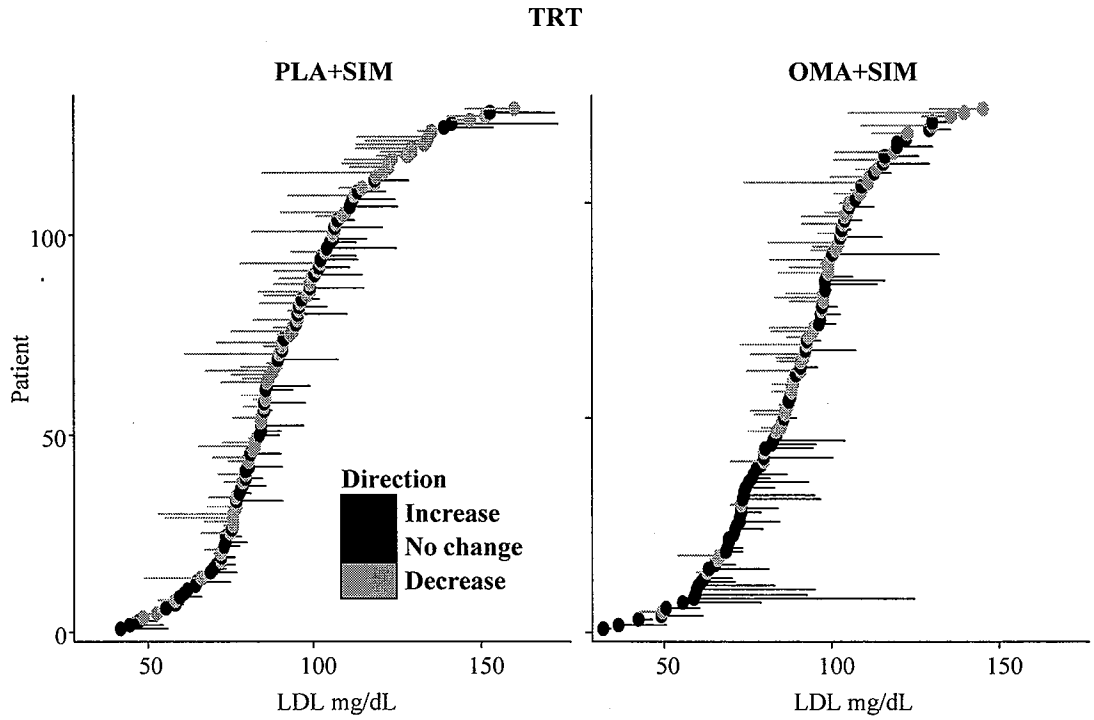
Appendix 3. LDL change from baseline for each patient

A blue line indicates an LDL decrease from baseline and a black line indicates an LDL increase. The symbol is at the baseline value.



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Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-853
Drug Name:	Omacor (omega-3-acid ethyl esters) Capsules, 1 gram
Indication(s):	as an adjunct to diet to reduce triglyceride levels
Applicant:	Abbott
Date(s):User fee goal date	November 9, 2004
Review Priority:	Standard
Biometrics Division:	DB 2 (HFD-715)
Statistical Reviewer:	Lee-Ping Pian, Ph.D.
Concurring Reviewers:	Todd Sahlroot, Ph.D.
Medical Division:	Metabolic and Endocrinologic Drug Products (HFD-510)
Clinical Team:	Mary Parks, M.D.
Project Manager:	Valerie Jimenez

Keywords: clinical study NDA review

Table of Contents

1. EXECUTIVE SUMMARY

K85 is a lipid-filled gel capsule containing 1000 mg of 84% omega-3 acid ethyl ester fish-oil concentrate of 465 mg EPA (eicosapentaenoic acid ethyl ester) and 375 mg DHA (docosahexaenoic acid ethyl ester) with 4 mg α-tocopherol added as an antioxidant. The proposed indication is as an adjunct to diet to reduce patient's elevated triglyceride level.

The efficacy of the 4 g/day K85 is based on 8 double-blind, placebo-controlled, randomized, parallel group studies or parts of study that used K85 4 mg dose per day. These Category I studies included a 8 week dose response study (85013), 5 European studies that had a dietary run-in phase (9 or 10 weeks) and a 12-week double-blind treatment phase, and 2 U.S. studies in patients with severe hypertriglyceridemia (TG≥500). Category II consisted of 11 studies that used doses other than K85 4 g per day, and/or different study designs. Table 1 displays the design and result of the 8 Category I studies. Figures 1 and 2 display the least squared mean (LSM) difference between K85 and placebo in percent change from baseline for triglyceride and median difference in percent change from baseline for LDL by studies. Table 2 and Figure 3 display the pooled 6 European studies and the pooled 2 U.S. studies. The primary efficacy comparison was between K85 and corn oil in percent change from baseline in fasting serum triglyceride. LDL increased in K85-treated patients compared to placebo-treated patients.

Table 1 Brief summary of Category I studies

Study ID # of Centers	Total Sample Size		Type of Study & Control	Duration treatment (dietary run-in)	TG (mg/dL) Median			LDL (mg/dL) Median		
					n	BL	%Chg	n	BL	%Chg
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Figure 1 LSM % change difference (95% C.I.)

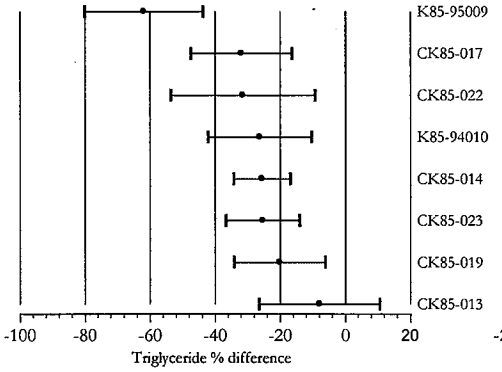
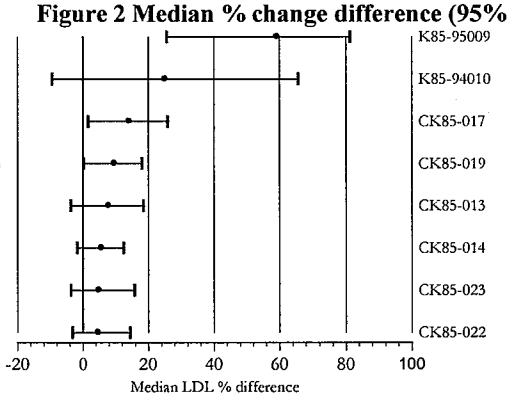


Figure 2 Median % change difference (95% C.I.)



The comparisons between K85 and placebo on the primary efficacy variable, percent change from baseline triglycerides levels were statistically significant favoring K85 in all studies but the dose ranging study (CK85-013). The median increase in LDL percent change from baseline was greater in the 2 US studies in severe hypertriglyceridemia than in the European studies. The baseline LDL levels for the U.S. studies were lower than the European studies, however.
The appendix contains additional tables and graphs for the Category I and Category II studies.

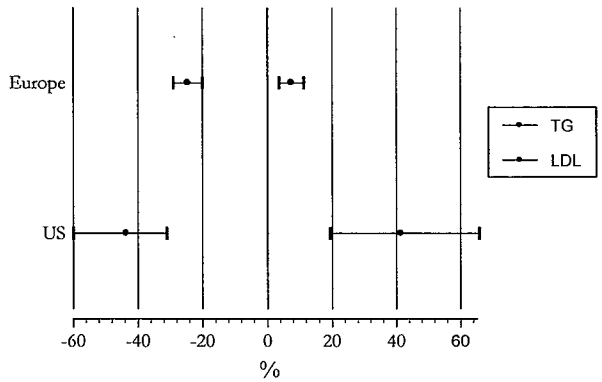
1.1 Conclusions and Recommendations

K85 was efficacious in triglycerides reduction. However, LDL increased in the K85 group compared to placebo. The 2 pooled analyses by baseline severity of hypertriglyceridemia (TG≥177 mg/dL, TG≥500 mg/dL) showed that estimates of the median shift from placebo in percent change of triglyceride were -25%, and -44%, respectively and 7.5% and 41.4% in LDL, respectively (Table 2 & Fig. 3).

Table 2 Median (95% C.I.) of % change from baseline for pooled analysis

	Pooled	Placebo				4 g K85				**Median**	95% C.I.
	studies	n	BL	EP	%Chg	n	BL	EP	%Chg	**shift**	
TG	European	173	272	264	-2.0	177	275	208	-27.1	**-24.5%**	(-29, -20)
LDL	European	171	185	174	-2.4	173	182	191	4.5	**7.5%**	(3.7, 11.3)
TG	US	42	788	762	6.7	42	816	489	-44.9	**-43.6%**	(-60, -31)
LDL	US	41	108	112	-4.8	41	89	109	44.5	**41.4%**	(19.4, 65.9)

Figure 3 Median % change from baseline difference (K85 minus placebo) and 95% CI



The correlation between TG percent change and LDL percent change was poor (r^2=0.0002 US) indicating that changes in TG and LDL with K85 treatment are not related on an individual patient basis.

1.2 Brief Overview of Clinical Studies

Category I studies included 8 double blind, placebo (corn oil) controlled, randomized, parallel group studies that were conducted in Europe (2 UK, 3 Sweden, 1 Norway), and the U.S. (2). The two US studies were in patients with severe hypertriglyceridemia (500 mg/dl ≤TG≤2000 mg/dl). Five of the European studies had a double-blind treatment phase of 12 weeks that followed a 9 or 10 week dietary run-in. Parts of the dose response study (placebo and 4 g K85) were in Category I and Parts (placebo, 2 g, 8 g K85) were in Category II. Category II included 11 controlled studies which used doses other than K85 4 g per day and/or different study designs.

1.3 Statistical Issues and Findings

This reviewer used the intent-to-treat population for the primary efficacy analysis. The ITT population was defined as patients with a baseline measurement and at least one follow up measurement for that outcome variable. In the label the sponsor presented data for individual studies and the pooled analysis of 8 Category I studies. This reviewer presented the pooled studies according to the severity of the hypertriglyceridemia. The 6 European studies were pooled which had a baseline criteria of triglyceride levels ≥ 177 mg/dL while the criteria for the 2 US studies was ≥500 mg/dL. The analysis of covariance as well as nonparametric Wilcoxon-Mann-Whitney test was used to analyze the data. The median shift and the 95% confidence interval were from the Hodges-Lehmann procedure.

2. STATISTICAL EVALUATION

2.1 Evaluation of Efficacy

The 6 European studies and the 2 US studies from Category I were pooled separately according to the baseline severity of hypertriglyceridemia. Table 3 and Table 4 display patient disposition for the pooled studies.

Table 3 Disposition of patients – EU

Reason	Placebo	K85	Total
Randomized	186	184	370
ITT	178	181	359
PP	166	167	333
Completed	171	186	357
Discontinued	15	14	29
Adverse event	4	8	12
Intercurrent disease/illness	0	1	1
Non-compliance	3	3	6
Other	8	2	10

Table 4 Disposition of patients – US

Reason	Placebo	K85	Total
Randomized	42	42	84
ITT	42	42	84
PP	38	39	77
Completed	39	41	80
Discontinued	3	1	4

Reason	Placebo	K85	Total
Adverse event	2	0	2
Non-compliance	0	1	1
Other	1	0	1

Tables 5 and Table 6 display patient demographics. 98% of the European patients were Caucasian and 75% were male. 81% of US patients were Caucasian and 64% were male.

Table 5 Demographics of patients – European

Reason	Placebo	K85	Total
ITT	178	181	359
Age			
Mean (SD)	52.8 (10.3)	53.2 (10.0)	53.0 (10.1)
Range	26, 70	26, 70	(26, 70)
Gender			
Male	134	135	269 (75%)
Female	43	46	89 (25%)
Race			
Caucasian	174	179	353 (98%)

Table 6 Disposition of patients – US

Reason	Placebo	K85	Total
ITT	42	42	84
Age			
Mean (SD)	48.1 (10.1)	48.6 (10.0)	48.4 (10.0)
Range	(31, 72)	(31, 70)	(31, 72)
Gender			
Male	26	28	54 (64%)
Female	16	14	30 (36%)
Race			
Caucasian	34	34	68 (81%)
Other	8	8	16 (19%)

Tables 7 and 8 present a summary of baseline characteristics for the ITT populations for the 2 pooled studies. Patients were similar in mean weight, BMI and height. The US patients weighed approximately 87 kg and the European patients 81 kg.

Table 7 Baseline Characteristics – European

Reason	Placebo	K85	Total
Weight (kg)	n=178	n=181	n=359
Mean (SD)	80.8 (12.2)	80.2 (13.1)	80.5 (12.7)
(Min, Max)	(51.6, 112.6)	(50.0, 125)	(50, 125)
BMI (kg/m^2)	n=177	n=181	n=357
Mean (SD)	27.0 (3.0)	27.0 (3.7)	27 (3.3)
(Min, Max)	(20.4, 35.0)	(19.3, 40.7)	(19.3, 40.7)
Height (cm)	n=177	n=180	n=357
Mean (SD)	172.9 (9.2)	172.0 (9.2)	172.5 (9.2)
(Min, Max)	(144, 195)	(147, 202)	(144, 202)

Table 8 Baseline characteristics – US

Reason	Placebo n=42	K85 n=42	Total n=84
Weight (kg)			
Mean (SD)	87.9 (17.5)	85.2 (18.2)	86.6 (17.8)
(Min, Max)	(51.7, 135.6)	(58.5, 124.3)	(51.7, 135.6)
BMI (kg/m^2)			
Mean (SD)	29.3 (4.5)	28.6, (4.3)	29.0 (4.4)
(Min, Max)	(21.5, 42.2)	(21.4, 41.3)	(21.4, 42.2)
Height (cm)			
Mean (SD)	172.6 (8.8)	171.9 (11.6)	172.3 (10.2)
(Min, Max)	(155, 193)	(150, 200)	(150, 200)

Tables 9 and 10 display a summary of baseline TG levels and other lipid levels for the ITT populations by the 2 pooled studies.

Table 9 Baseline lipid characteristics – European

	Placebo	K85	Total
Triglyceride	n=178	n=180	n=358
Mean (SD)	307.7 (159.2)	315 (131.2)	311.4 (145.6)
(Min, Max)	(136, 1858)	(178, 938)	(136, 1858)
LDL	n=173	n=173	n=346
Mean (SD)	185.5 (43.9)	183.5 (46.4)	184.5 (45.1)
(Min, Max)	(67, 320)	(45, 298)	(45, 320)
HDL	n=178	n=180	n=358
Mean (SD)	36.6 (9.4)	37.2 (10.1)	36.9 (9.7)
(Min, Max)	(20, 73)	(15, 85)	(15, 85)
TC	n=178	n=181	n=359
Mean (SD)	278.8 (45.7)	280.1 (53)	279.5 (49.5)
(Min, Max)	(178, 440)	(141, 510)	(141, 510)

Table 10 Baseline lipid characteristics – U.S.

	Placebo	K85	Total
Triglyceride	n=42	n=42	n=84
Mean (SD)	847.6 (274.2)	881 (341.9)	864.5 (308.5)
(Min, Max)	(500, 1685)	(422, 1940)	(422, 1940)
LDL	n=42	n=42	n=84
Mean (SD)	116.4 (54.2)	94.8 (42.4)	105.6 (49.6)
(Min, Max)	(41, 310)	(30, 194)	(30, 310)
HDL	n=42	n=42	n=84
Mean (SD)	24.4 (8.2)	24.2 (11.8)	24.3 (10.1)
(Min, Max)	(11, 46)	(10, 72)	(10, 72)
TC	n=42	n=42	n=84
Mean (SD)	316.6 (76.4)	299.7 (91.6)	308.1 (84.2)
(Min, Max)	(116, 452)	(163, 600)	(116, 600)

There were no significant differences between K85 4 g/day and placebo in lipids at baseline.

2.2 Analysis results – 8 studies

K85 was compared to placebo in percent change from baseline using an analysis of covariance model. The model included treatment and site as fixed effect and baseline triglyceride value as covariate. Table 11 displays the least squared mean differences (K85 minus placebo) with the 95% confidence intervals. The dose response study (85013) was the only study which did not

achieve statistical significance. The two US studies (94010, 95009) enrolled patients with severe hypertriglyceridemia. Figure 4 displays the LSM differences and the confidence intervals. Figure 5 displays the individual patient triglyceride percent changes from baseline versus baseline by study.

Table 11 Summary results of analysis of covariance – ITT

Study	Placebo			K85			K85 minus Placebo			p-value
	n	LSM	SE	n	LSM	SE	LSM	SE	95% CI	
CK85-014	53	3	3.2	52	-22	3.2	-25	4.3	-33.5, -16.5	<0.001
CK85-017	23	12	5.8	29	-19.8	5.3	-31.8	7.9	-47.6 -15.9	0.0002
CK85-019	26	1.8	4.9	26	-18.3	4.9	-20.1	7.0	-34.1, -6.1	0.006
CK85-022	30	3.4	7.8	30	-28.0	7.8	-31.4	11.1	-53.6, -9.2	0.006
CK85-023	28	-4.3	3.9	28	-29.6	3.9	-25.3	5.7	-36.6, -13.9	<0.001
K85-94010	21	-4.0	5.5	20	-30.2	5.6	-26.2	7.9	-42.1, -10.3	0.0019
K85-95009	21	158	6.8	22	-46	6.6	-61.8	9.1	-80.1, -43.5	<0.0001
CK85-013	17	-17.4	6.1	15	-25.3	6.5	-7.9	9.1	-26.4, 10.7	0.39

Figure 4 Change from baseline LSM difference (K85 minus placebo) and 95% C.I. by study – ITT

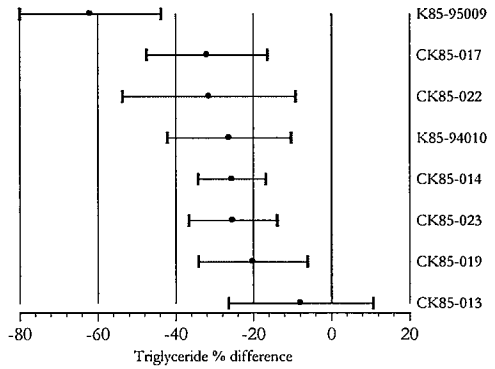
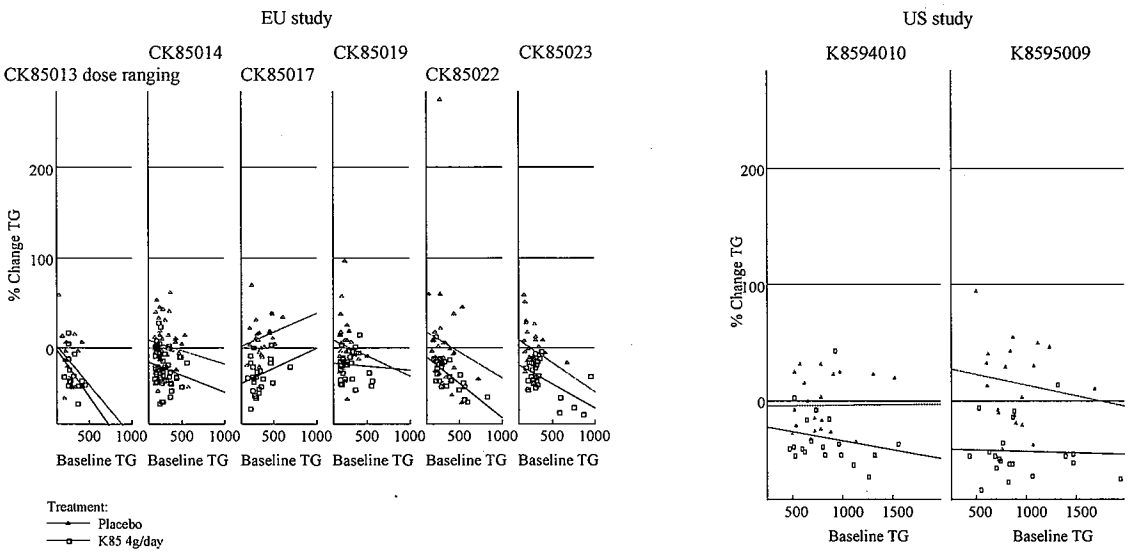


Figure 5 Triglyceride % change from baseline versus baseline – ITT



Mean percent change from baseline in LDL increased in the K85 treatment group compared to the placebo group. Table 12 displays the results of the analysis of covariance in LDL and Figure 6 displays the differences in LSM of LDL percent change from baseline with corresponding confidence intervals. Figure 7 displays individual patient percent changes from baseline versus baseline LDL.

Table 12 Summary results of analysis of covariance in LDL

Study	Placebo			K85			K85 minus Placebo			p-value
	n	LSM	SE	n	LSM	SE	LSM	SE	95% CI	
CK85-014	50	0.9	3.1	49	7.9	3.2	6.9	4.3	-1.6, 15.4	0.11
CK85-017	21	-4.9	9.9	28	22.9	8.7	27.8	13.0	1.5, 54.1	0.039
CK85-019	26	0.9	3.0	26	8.4	3.0	7.5	4.3	-1.1, -16.0	0.088
CK85-022	30	-0.7	2.8	30	7.6	2.8	8.3	4.0	0.3, 16.4	0.043
CK85-023	27	-8.8	3.0	24	2.0	3.2	10.9	4.5	1.9, 19.8	0.019
K85-94010	21	35.8	17.7	19	29.8	18.6	-6.0	26	-58.6, 46.7	0.82
K85-95009	20	4.5	8.2	22	42.1	7.8	37.6	11.1	15.2, 60.0	0.0016
CK85-013	17	4.8	3.7	16	7.3	3.8	2.5	5.3	-8.5, 13.4	0.65

Figure 6 LSM difference of LDL % change from baseline (K85 minus placebo)

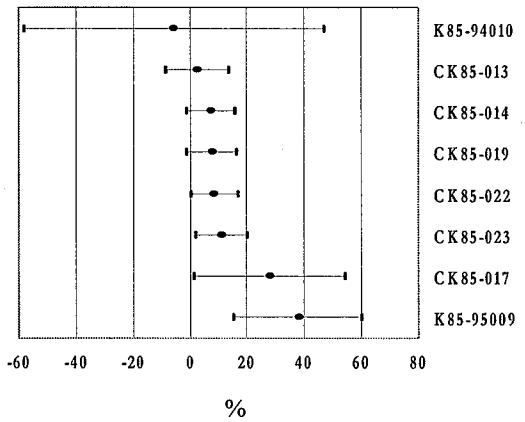


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Figure 7 Regression of LDL % change from baseline by baseline LDL

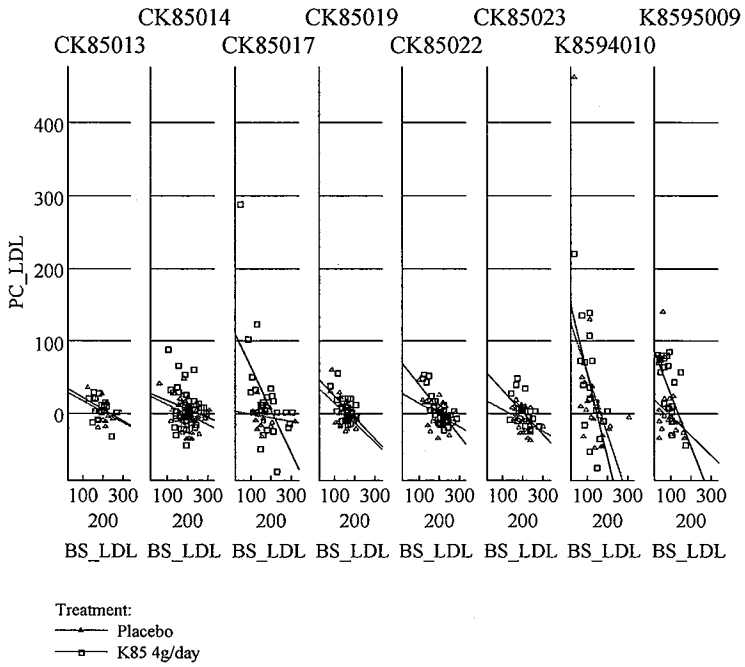


Figure 8 shows the percent change of LDL versus the percent change of triglyceride by pooled study. The correlation coefficients (r-square) were 0.0005 for the European study and 0.00023 for the US study. Hence, the triglycerides percent change is not correlated with the percent change in LDL indicating that changes in these 2 variables are not related on an individual patient basis.

Figure 8 Regressing of % change LDL by % change of TG - pooled

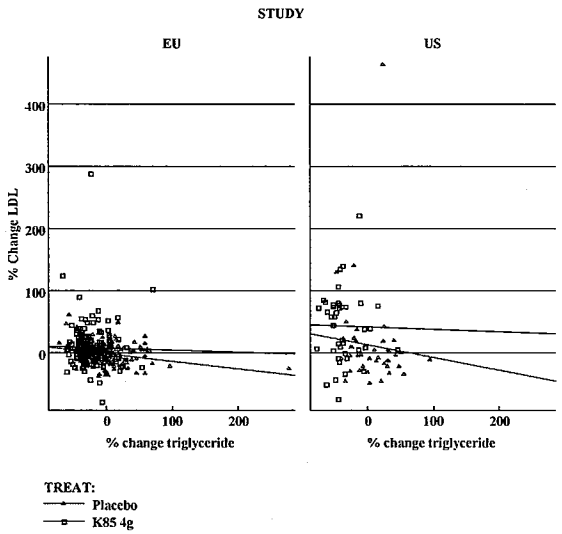
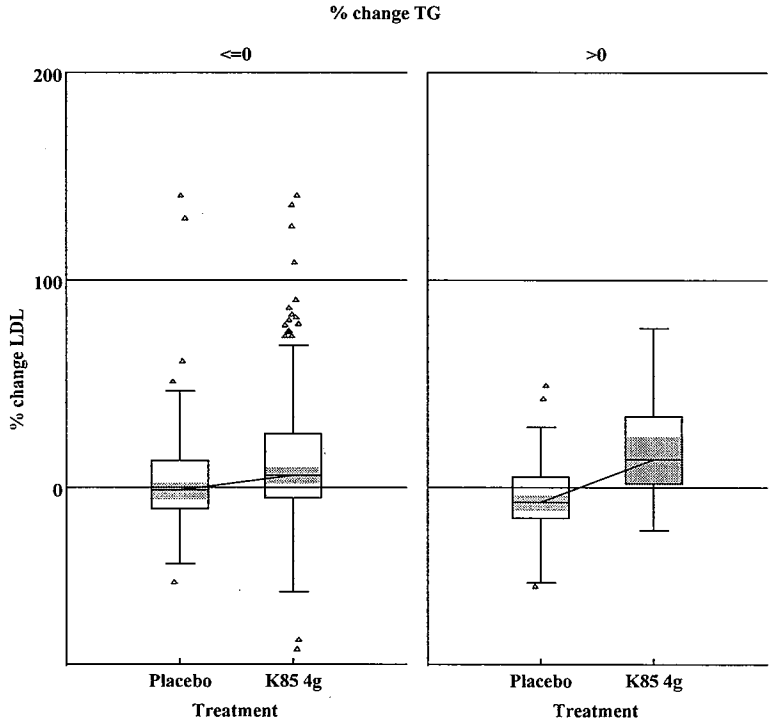


Table 13 and Figure 9 display the median percent change of LDL by percent increase or decrease of triglyceride at endpoint combining all studies. The median percent change in LDL decreased in placebo-treated patients and increased in K85-treated patients regardless of triglyceride percent increase or decrease. This finding is consistent with the data shown in Figure 8.

Table 13 Percent change of LDL by % increase or decrease of TG

	Placebo	K85
TG % change>0	n=97 -7%	n=20 13%
TG % change≤0	n=107 -2%	n=182 6%

Figure 9 Median % change of LDL by % increase or decrease of TG



3. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Gender, Race and Age

Results for these subgroups were consistent with the results for the entire population in terms of percent change from baseline in triglyceride.

4. SUMMARY AND CONCLUSIONS

The efficacy of K85 in triglyceride reduction was consistently better than placebo in the 8 Category I studies. The significance of the small increase in LDL requires clinical judgment. With only one small study of K85 as add-on therapy to simvastatin, the evidence is insufficient to warrant labeling for combination therapy of K85 and the statins.

5. LABELING COMMENTS:

The sponsor presented 8 clinical studies in Table 2 individually and corporately (pooled) and in Table 3 by severity. The presentation by severity is sufficient. The table should include the number of patients in each treatment group. The sponsor should present the 8 studies with graphs to depict the median treatment difference and corresponding confidence intervals for the 8 studies in percent change from baseline triglyceride. The ITT population should be presented instead of the Per Protocol population.

The inference from the published literature is not sufficient evidence to support the claim in [ ] b(4)

The indication for TG reduction should be limited to triglyceride monotherapy [ ] b(4)

Data concerning the increase in high-density lipoprotein cholesterol in type V hyperlipidemia should be limited to the clinical studies section, [ ] b(4)

6. APPENDICES
6.1 LIST OF TABLES

Table 1 Mean (95% C.I.) of % change from baseline for pooled analysis

	Pooled studies	Placebo n	BL	EP	%Chg	4 g K85 n	BL	EP	%Chg	**Mean difference**	95% C.I.
TG	European	173	309	303	1.5	177	316	230	-24.4	**-25.9**	(-31.7, -20.1)
	US	42	848	899	6.5	42	881	538	-38.1	**-44.4%**	(-56.9, 32)
LDL	European	171	186	181	-1.3	173	184	193	9.2	**9.9**	(4.8, 14.9)
	US	41	117	118	14.4	41	96	123	43.0	**15.8%**	(-12.1, 43.6)

Sponsor's descriptive statistics on lipids for the per protocol and intent-to-treat population

Table 1 Descriptive statistics of triglyceride levels (PP) – Study 85014

	Placebo (n=46)					K85 4g (n=49)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	296.8	(104.4)	255.0			284.2	(92.0)	258.0		
Average Endpoint Triglyceride	302.7	(118.9)	269.0			218.8	(83.3)	205.0		
Change in Average Value Trig -PP	5.8	(78.1)	1.0			-65.4	(62.6)	-60.0		
% Change in averaged value Trigs	3.0	(23.7)	0.5			-21.9	(20.4)	-25.4		

b(4)

Table 14 Descriptive statistics of triglyceride levels (ITT) – Study 85014

	Placebo (n=53)					K85 4g (n=52)				
	Mean	(S.D.)	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	305	(110.5)	258			294.5	(104.9)	264.5		
Singe Value Trig Endpoint LOCF	313.9	(140.4)	281			225.9	(104.8)	216.5		
Change in Triglycerides - ITT	8.9	(112.2)	-1			-68.6	(77.8)	-70.5		
% Change in single value Trigs	4.2	(31.7)	-0.5			-22.1	(25.6)	-23.3		

b(4)

Table 15 Descriptive statistics of total cholesterol levels (ITT)

	Placebo (n=53)				K85 4g (n=52)			
	Mean (Median)	S.D.	Min	Max	Mean	S.D.	Min	Max
Baseline Cholesterol	299.9 (301)	45.4			291.4 (282)	53.2		
Endpoint Cholesterol	300.5 (293)	60.8			292.8 (284)	59.8		
Change in Cholesterol	0.7 (0.0)	41.1			1.4 (-4.0)	39.3		
Percent Change in Cholesterol	0.4 (0.0)	12.4			0.9 (-1.2)	14.2		

b(4)

Table 16 Descriptive statistics of HDL (ITT)

	Placebo (n=53)				K85 4g (n=51)			
	Mean (Median)	S.D.	Min	Max	Mean (Median)	S.D.	Min	Max
Baseline HDL	40.0 (39.0)	11.3			41.3 (42.0)	12.2		
Endpoint HDL	41.3 (39.0)	10.9			42.8 (42.0)	11.5		
Change in HDL	1.3 (0.0)	7.9			1.3 (0.0)	10.8		
Percent Change in HDL	5.5 (0.0)	19.9			7.5 (0.0)	28.5		

b(4)

Table 17 Descriptive statistics of LDL (PP)

	Placebo					K85 4g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Baseline Derived LDL	43	202.8 (200.0)	41.2			47	192.5 (192.0)	41.8		
Protocol-defined Endpoint LDL	40	200.9 (202.5)	42.4			47	207.0 (204.0)	56.0		
Change in Last (PP) LDL	39	-1.8 (2.0)	35.5			46	14.7 (9.0)	40.4		
Percent Change in Last (PP) LDL	39	0.2 (0.9)	18.0			46	8.8 (4.8)	24.9		

b(4)

Table 18 Descriptive statistics of LDL (ITT)

	Placebo					K85 4g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Baseline Collected/Derived LDL	50	199.2 (199)	43.7			49	192.1 (192)	42.1		
Endpoint Collected/Derived LDL	53	198.1 (203)	47.3			51	203.4 (202)	56.3		
Change in Analysis LDL	50	-2.9 (2.0)	33.6			49	12.9 (8.0)	40.0		
Percent Change in Analysis LDL	50	-0.2 (0.9)	17.8			49	7.8 (3.6)	24.4		

b(4)

Table 19 Descriptive statistics of LDL (ITT)

	Placebo					K85 4g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Baseline APO_A1	50	1.21 (1.15)	0.30			51	1.23 (1.21)	0.23		
Endpoint APO_A1	53	1.23 (1.19)	0.30			52	1.20 (1.21)	0.21		
Change in APO_A1	50	0.02 (0.01)	0.23			51	-0.04 (-0.01)	0.27		
Percent Change in APO_A1	50	2.96 (0.49)	18.04			51	-0.95 (-0.95)	19.79		

b(4)

Table 20 Descriptive statistics of triglyceride levels (PP) – Study 85017

	Placebo (n=23)					K85 4g (n=24)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	356.4	(110.1)	330			314.3	(114)	278		
Average Endpoint Triglyceride	403.3	(161.2)	353			223.5	(115.9)	189.5		
Change in Average Value Trig -PP	46.9	(75.4)	30			-90.8	(52.6)	-84		
% Change in averaged value Trigs	11.8	(20.7)	10.5			-30.6	(17.7)	-32.4		

b(4)

Table 21 Descriptive statistics of triglyceride levels (ITT) – Study 85017

	Placebo (n=24)					K85 4g (n=29)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	358.5	(108.2)	340.0			305.8	(106.5)	276		
Singe Value Trig Endpoint LOCF	394.8	(183.2)	338.0			256.8	(138.1)	212		
Change in Triglycerides - ITT	38.4	(105.8)	6.0			-49	(94.9)	-65		
% Change in single value Trigs	8.7	(25.1)	1.8			-16.6	(32.1)	-19.8		

b(4)

Table 22 Descriptive statistics of triglyceride levels (PP) – Study 85019

	Placebo (n=26)					K85 4g (n=26)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	251	(76.7)	238			295.6	(113.4)	267.5		
Average Endpoint Triglyceride	253.9	(96.6)	233			239	(97.4)	208		
Change in Average Value Trig -PP	3	(74.1)	-10			-56.5	(64.8)	-43		
% Change in averaged value Trigs	2.2	(30.3)	-4.4			-18.8	(16.2)	-17.3		

b(4)

Table 23 Descriptive statistics of triglyceride levels (ITT) – Study 85019

	Placebo (n=26)					K85 4g (n=26)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	251	(76.7)	238			295.6	(113.4)	267.5		
Singe Value Trig Endpoint LOCF	263.8	(111.3)	251.5			223.7	(83)	201		
Change in Triglycerides - ITT	12.8	(83.6)	6			-71.9	(60.6)	-52.5		
% Change in single value Trigs	4.9	(33.1)	3			-23.3	(14.1)	-23.8		

b(4)

Table 24 Descriptive statistics of triglyceride levels (PP) – Study 85022

	Placebo (n=30)					K85 4g (n=28)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	374.1	(306.5)	305			350.2	(152.5)	286		
Average Endpoint Triglyceride	331.3	(197.2)	250.5			234.3	(63)	232		
Change in Average Value Trig -PP	-42.7	(303.5)	-23.5			-115.9	(109.9)	-69.5		
% Change in averaged value Trigs	2.5	(60.9)	-6.5			-28.1	(16.5)	-28.7		

b(4)

Table 25 Descriptive statistics of triglyceride levels (ITT) – Study 85022

	Placebo (n=30)					K85 4g (n=30)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	374.1	(306.5)	305			343.5	(149.3)	279		
Singe Value Trig Endpoint LOCF	310.9	(151.3)	267			242.5	(66.7)	235.5		
Change in Triglycerides - ITT	-63.1	(266.8)	-23			-101	(115)	-71.5		
% Change in single value Trigs	-5.6	(37)	-9.6			-23.4	(22.2)	-22.5		

b(4)

Table 26 Descriptive statistics of triglyceride levels (PP) – Study 85023

	Placebo (n=28)				K85 4g (n=28)				
	Mean	(S.D.)	Median	Min	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	278.2	(104)	274.5		358.3	196.6	-294.5		
Average Endpoint Triglyceride	265.7	(96.9)	253		224.2	98.3	-201.5		
Change in Average Value Trig -PP	-12.5	(61.9)	-24.5		-134.1	153.4	-84		
% Change in averaged value Trigs	-2	(25.4)	-7.3		-31.8	18.4	-31.3		

b(4)

Table 27 Descriptive statistics of triglyceride levels (ITT) – Study 85023

	Placebo (n=26)					K85 4g (n=26)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	278.2	(104)	274.5			358.3	(196.6)	294.5		
Singe Value Trig Endpoint LOCF	259	(122.2)	239			245.6	(154.8)	216.5		
Change in Triglycerides - ITT	-19.3	(84.8)	-29			-112.7	(156.4)	-70.5		
% Change in single value Trigs	-4.4	(35)	-12.2			-27.6	(25.2)	-29.2		

b(4)

Table 28 Descriptive statistics of triglyceride levels (PP) – Study K85-94010

	Placebo (n=19)					K85 4g (n=19)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	771.1	248.3	725			836.1	(305.3)	801		
Average Endpoint Triglyceride	753.6	344.7	656			559.6	(259.9)	512		
Change in Average Value Trig -PP	-17.5	198.1	-40			-276.5	(267.9)	-241		
% Change in averaged value Trigs	-3.1	23.9	-7.6			-31.4	(24.5)	-38.8		

b(4)

Table 29 Descriptive statistics of triglyceride levels (ITT) – Study K85-94010

	Placebo (n=21)					K85 4g (n=20)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	823	(286.9)	786			840.1	(297.7)	810.5		
Singe Value Trig Endpoint LOCF	824.6	(436.2)	663			584.3	(310.1)	522.5		
Change in Triglycerides - ITT	1.7	(406.6)	-102			-255.8	(280.1)	-254		
% Change in single value Trigs	2.9	(45.9)	-14.3			-30.8	(27.7)	-38.4		

b(4)

Table 30 Descriptive statistics of triglyceride levels (PP) – Study K85-95009

	Placebo (n=19)					K85 4g (n=20)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	887.9	(274.7)	863			926.1	(391)	817.5		
Average Endpoint Triglyceride	1013	(418.5)	859			523.9	(306.5)	390.5		
Change in Average Value Trig -PP	125.1	(293.7)	171			-402.3	(315.6)	-381.5		
% Change in averaged value Trigs	15.6	(35.5)	12.4			-43.1	(23.2)	-47.7		

b(4)

Table 31 Descriptive statistics of triglyceride levels (ITT) – Study K85-95009

	Placebo (n=21)					K85 4g (n=20)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	872.2	(265.6)	841			919	(380.8)	817.5		
Singe Value Trig Endpoint LOCF	967.3	(476.2)	828			459.9	(224.3)	406		
Change in Triglycerides - ITT	95.1	(366.1)	107			-459	(247.4)	-443		
% Change in single value Trigs	11.1	(39.6)	6.4			-49.5	(17)	-50.7		

b(4)

Table 32 Descriptive statistics of triglyceride levels (PP) – Study CK85-013

Placebo & Omacor 4 g

	Placebo (n=13)					K85 4g (n=12)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	270.2	(68.9)	260			307.8	(71.7)	280		
Singe Value Trig Endpoint LOCF	227.8	(90.3)	212			216.8	(48.7)	212		
Change in Triglycerides - ITT	-42.4	(53.7)	-15			-91	(58.7)	-87		
% Change in single value Trigs	-16.4	(19.7)	-8.2			-28.1	(15.3)	-30		

b(4)

Table 33 Descriptive statistics of triglyceride levels (PP) – Study CK85-013

Omacor 2g & Omacor 8 g

	K58 2 g (n=7)					K85 8 g (n=8)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	252	(77.2)	212			242.8	(73.1)	219.5		
Singe Value Trig Endpoint LOCF	219	(54)	224			138.9	(25.4)	136		
Change in Triglycerides - ITT	-33	(73.7)	-17			-103.9	(65)	-92		
% Change in single value Trigs	-9.7	(24.4)	-8.2			-40.4	(14.4)	-40.9		

b(4)

Table 34 Descriptive statistics of triglyceride (ITT) – Study CK85013

Placebo & Omacor 4g

	Placebo					K85 4g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Average Baseline Triglyceride	13	270.2 (260.0)	68.9			13	308.2 (299.0)	68.7		
Singe Value Trig Endpoint LOCF	17	217.5 (189.0)	87.5			15	209.7 (214.0)	53.3		
Change in Triglycerides - ITT	13	-44.6 (-27.0)	66.3			12	-98.1 (-94.0)	68.9		
% Change in single value Trigs	13	-17.1 (-13.6)	24.6			12	-30.0 (-35.6)	18.3		

b(4)

Omacor 2 g & Omacor 8g

	K85 2 g					K85 8g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Average Baseline Triglyceride	7	252.0 (212.0)	77.2			11	232.1 (218.0)	66.5		
Singe Value Trig Endpoint LOCF	14	201.6 (199.0)	75.9			20	145.2 (131.0)	57.9		
Change in Triglycerides - ITT	7	-52.1 (-66.0)	95.5			11	-94.9 (-75.0)	70.4		
% Change in single value Trigs	7	-14.7 (-26.4)	34.2			11	-37.5 (-33.9)	15.7		

b(4)

Amendment 7 included patients with single baseline value as well as average of 2 baseline values of triglycerides in the ITT population. Table 36 displays the descriptive statistics.

Table 35 Descriptive statistics of triglyceride (ITT) – Study CK85013

Placebo & Omacor 4g

	Placebo						K85 4g					
	n	Mean	(SD)	Median	Min	Max	n	Mean	(SD)	Median	Min	Max
Average Baseline Triglyceride	17	263.1	(70.5)	260			15	299.6	(74)	261		
Singe Value Trig Endpoint LOCF	17	217.5	(87.5)	189			15	209.7	(53.3)	214		
Change in Triglycerides - ITT	17	-45.5	(72.6)	-28			15	-89.9	(73.3)	-94		
% Change in single value Trigs	17	-15.3	(29.8)	-13.7			15	-27.7	(20.7)	-35.3		

b(4)

Table 36 Descriptive statistics of triglyceride (ITT) – Study CK85013

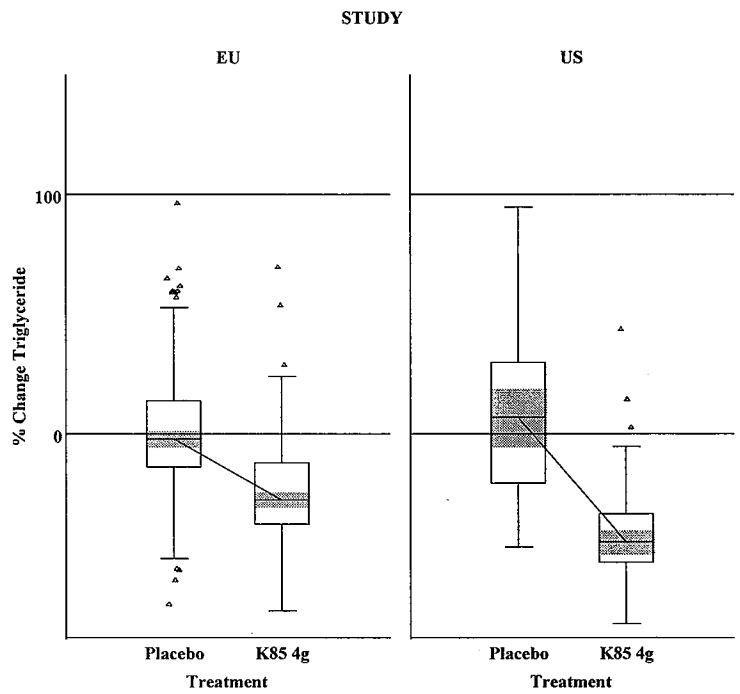
Omacor 2 g & Omacor 8g

	Omacor 2 g						Omacor 8 g					
	n	Mean	(SD)	Median	Min	Max	n	Mean	(SD)	Median	Min	Max
Average Baseline Triglyceride	16	257.4	(68)	242.5			18	236.4	(88.5)	216.5		
Singe Value Trig Endpoint LOCF	16	193.6	(74.4)	190.5			18	146.1	(60.7)	131		
Change in Triglycerides - ITT	16	-63.8	(83.6)	-75.5			18	-90.3	(65.1)	-76.5		
% Change in single value Trigs	16	-21.9	(31)	-29.6			18	-36.7	(17.2)	-34.4		

b(4)

6.2 LIST OF FIGURES

1. Box plot of pooled Category I studies - % change of TG



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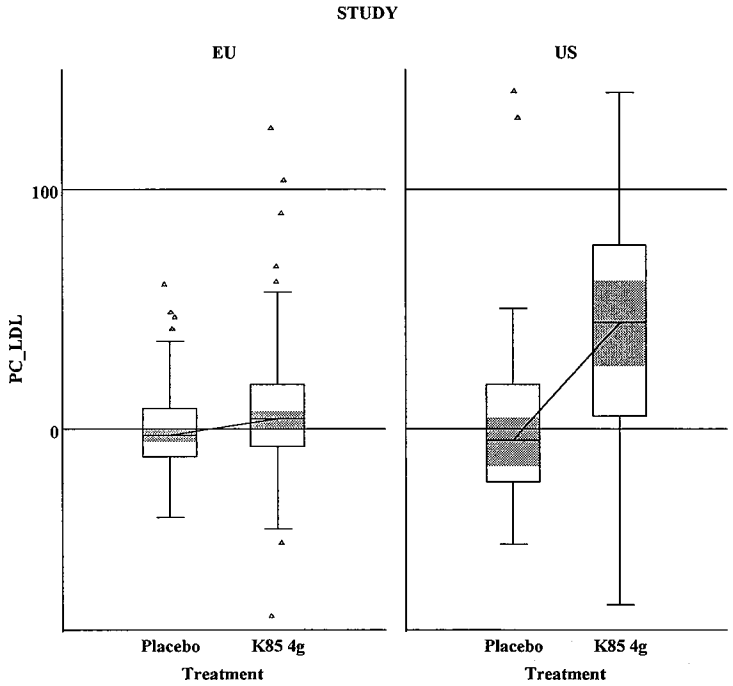
2. Box plot of pooled Category I studies -% change of LDL



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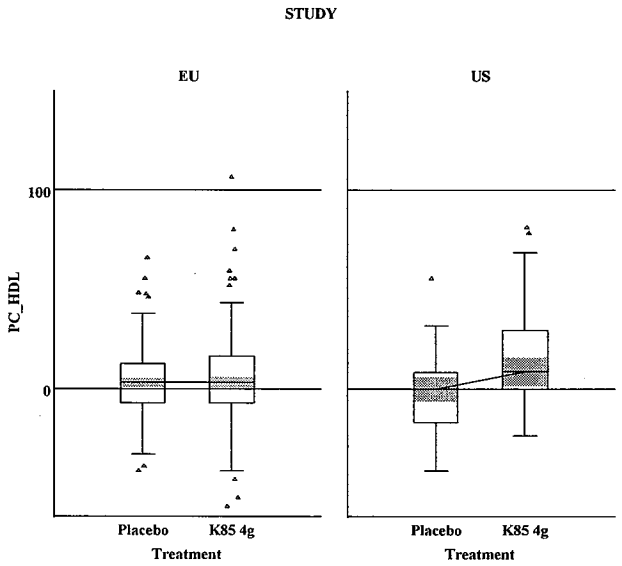
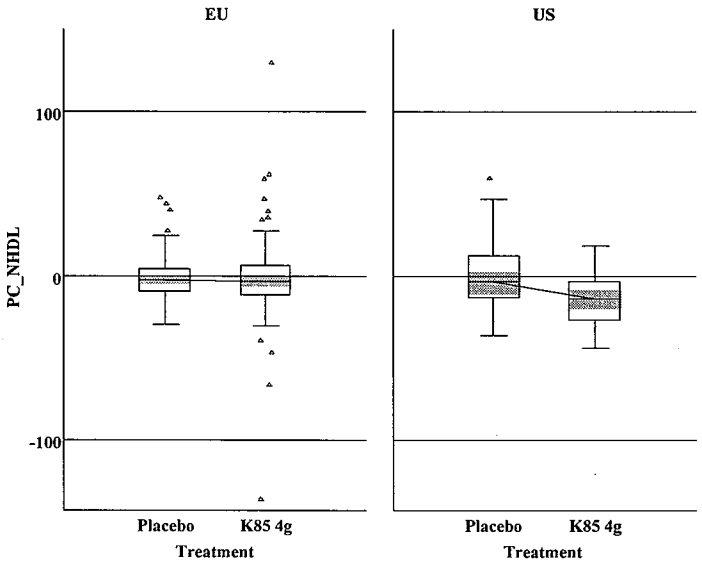
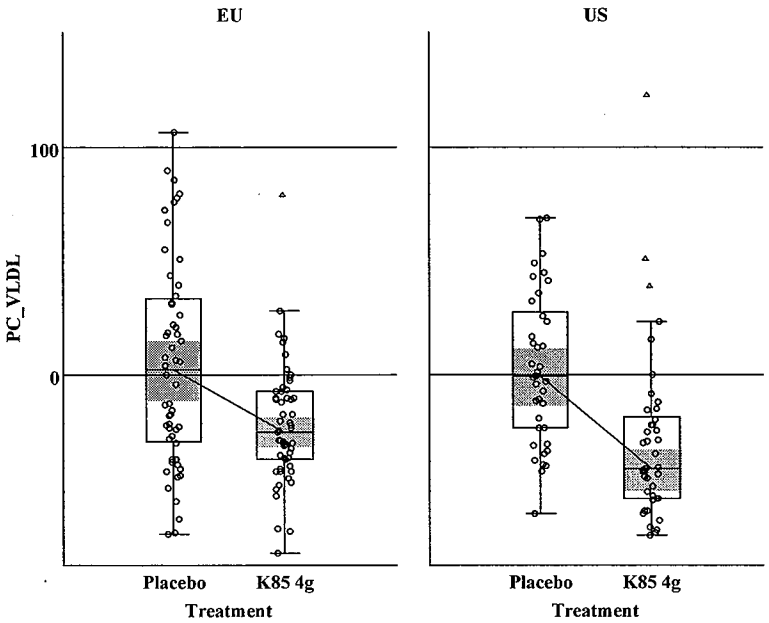
3. Box plot of pooled Category I studies -% change of HDL



4. Box plot of pooled Category I studies -% change of NHDL



5. Box plot of pooled Category I studies -% change of VLDL



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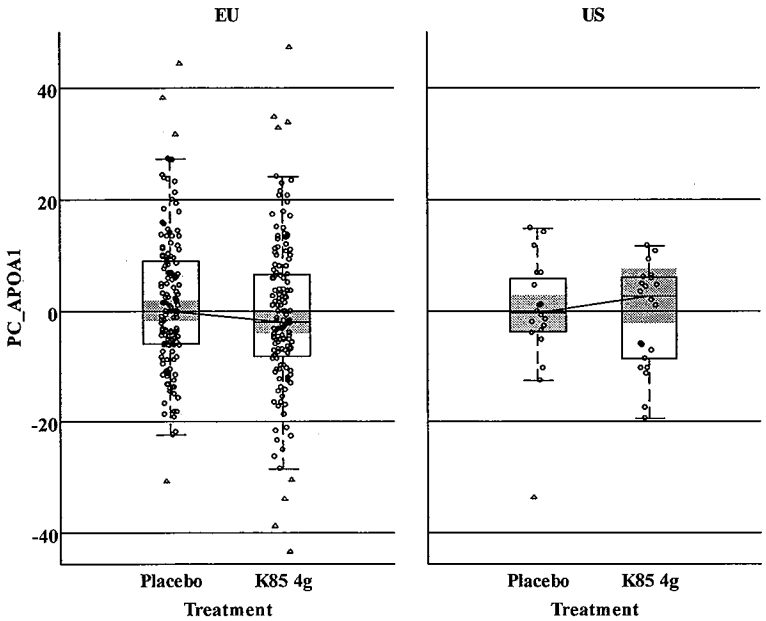
6. Box plot of pooled Category I studies -% change of APOA1



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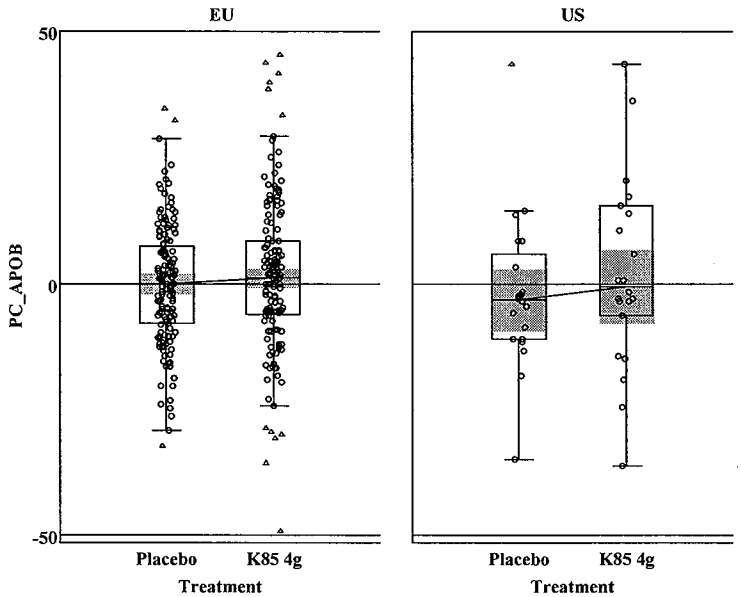
7. Box plot of pooled Category I studies -% change of APOB



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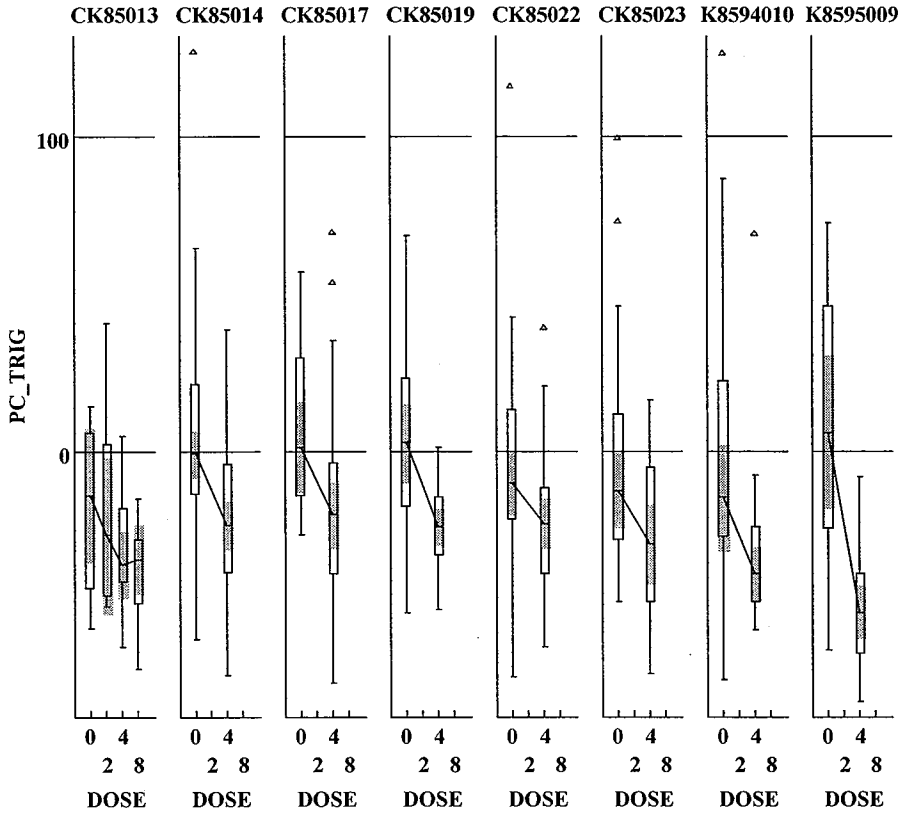
8. Box plot of individual Category I studies - % change of TG



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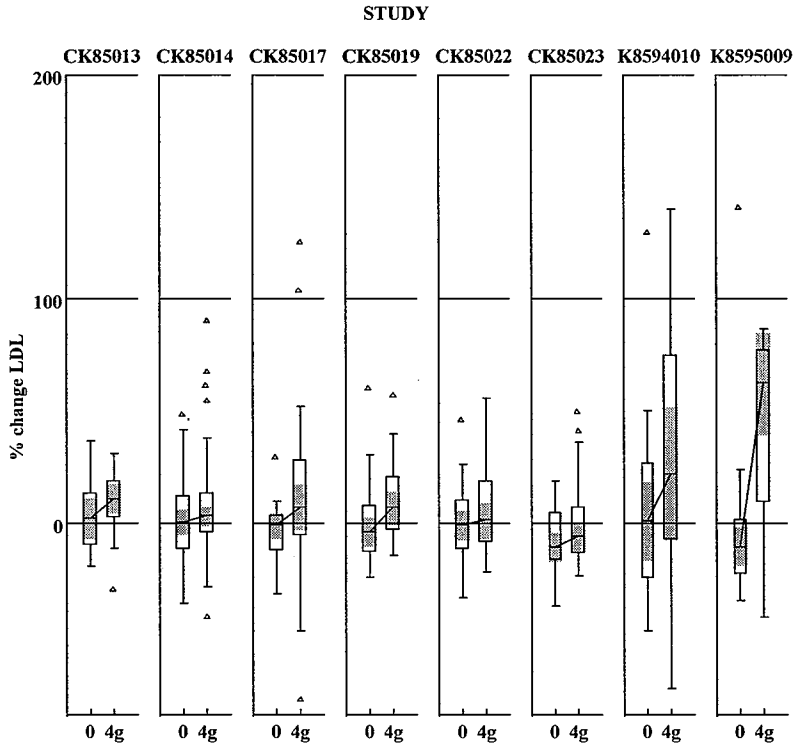
9. Box plot of individual Category I studies -% change of LDL



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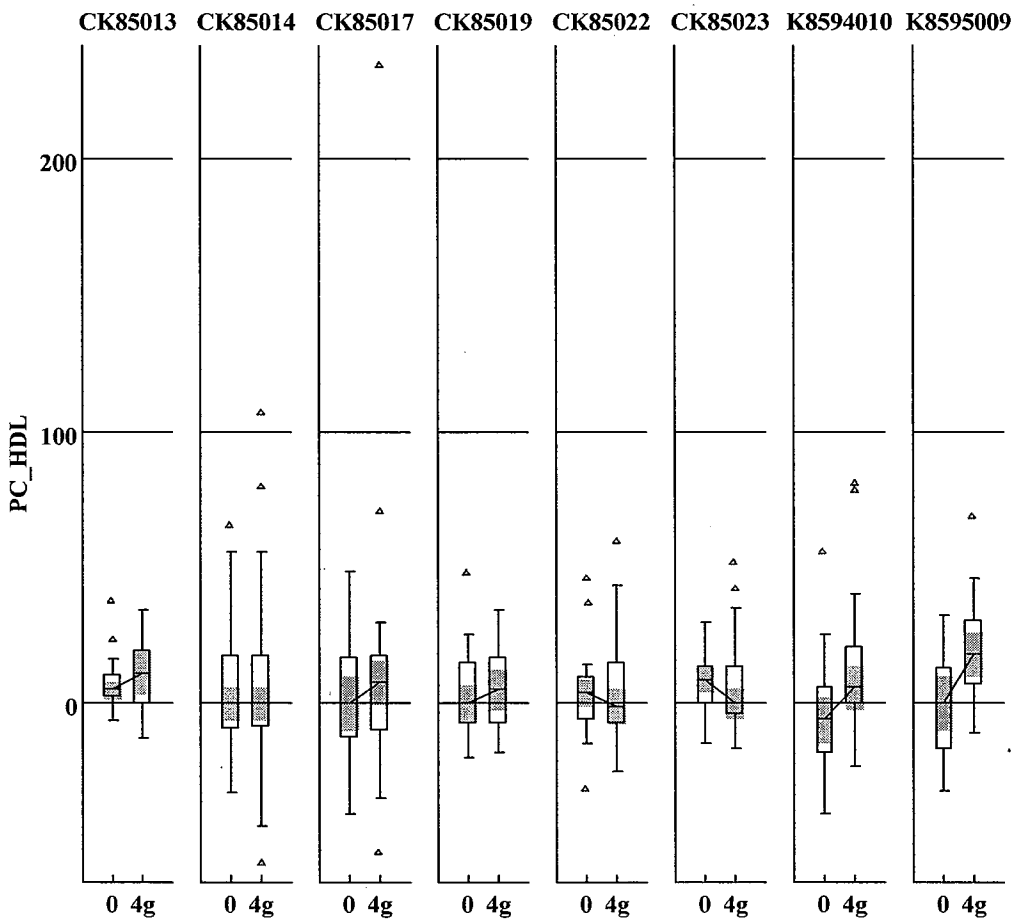
10. Box plot of individual Category I studies -% change of HDL



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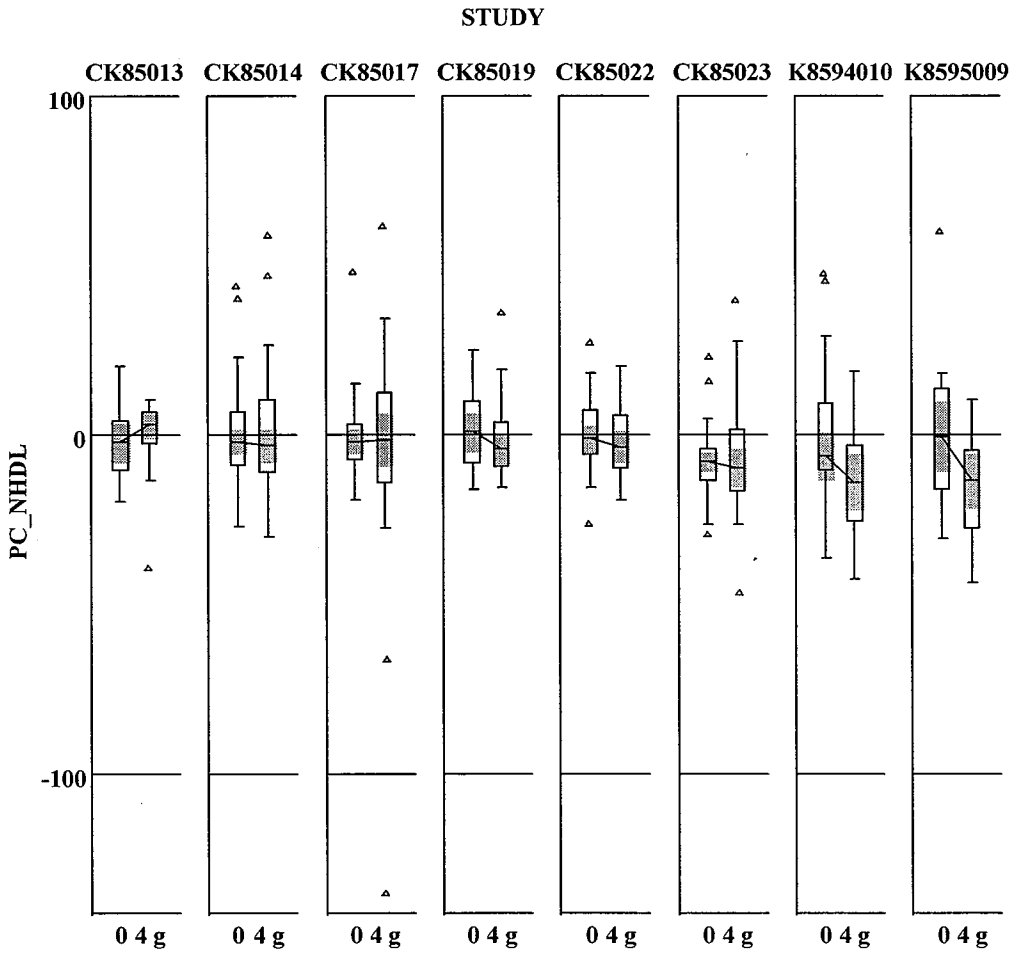
11. Box plot of individual Category I studies -% change of NHDL



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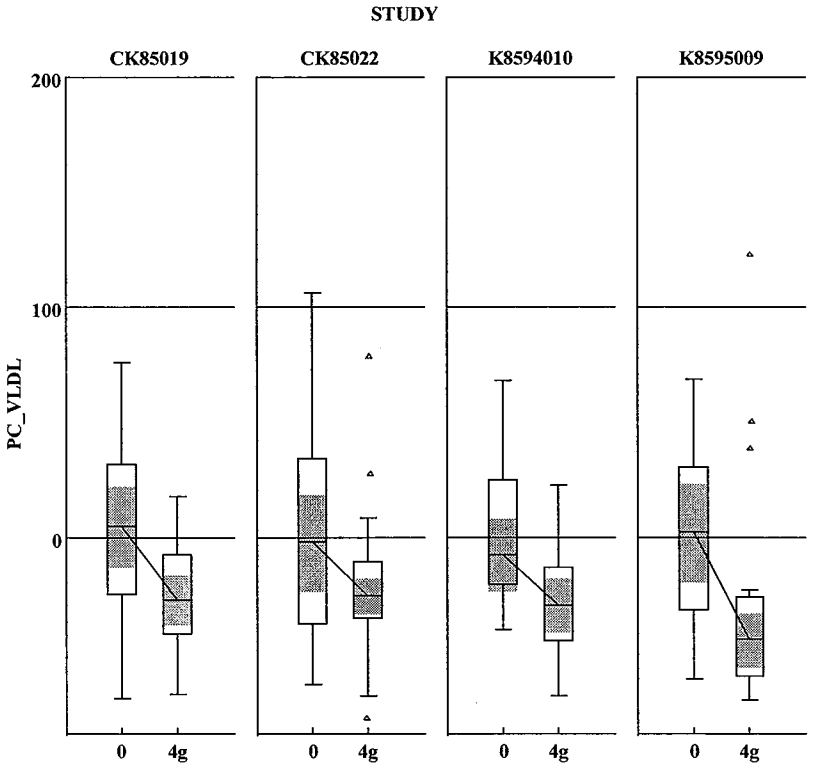
12. Box plot of individual Category I studies -% change of VLDL



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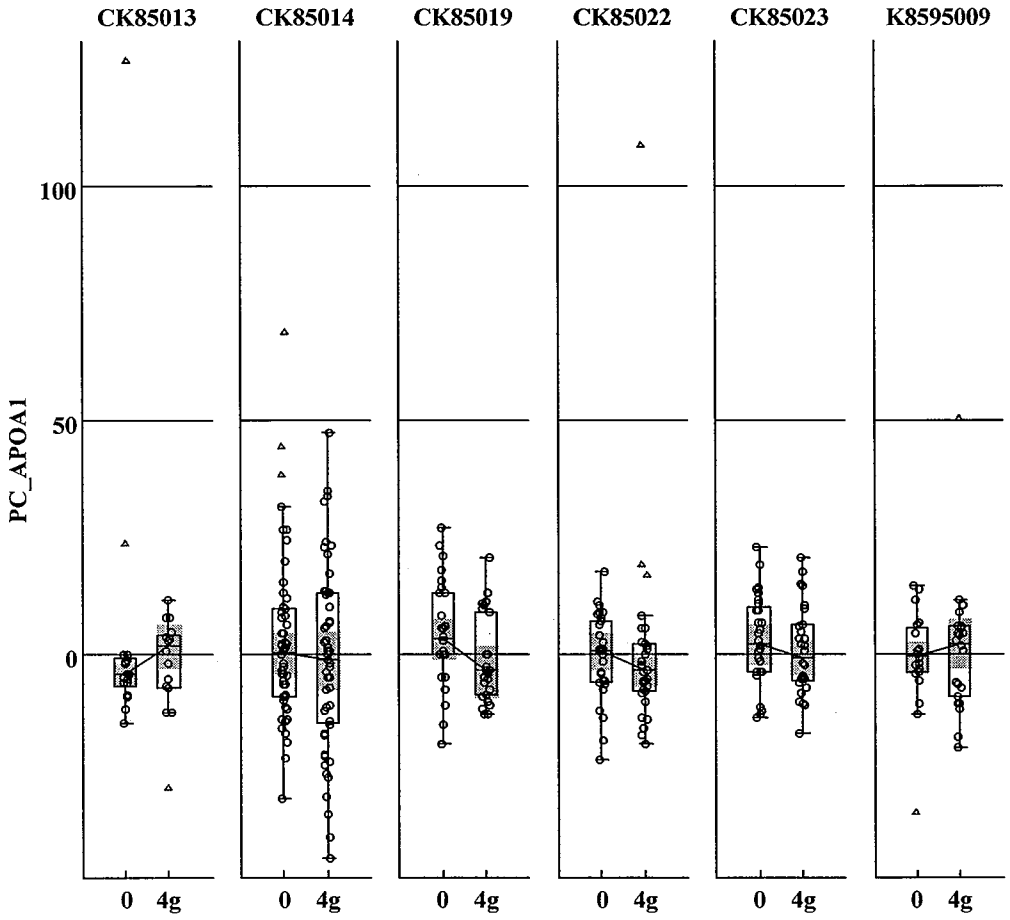
13. Box plot of individual Category I studies -% change of APOA1



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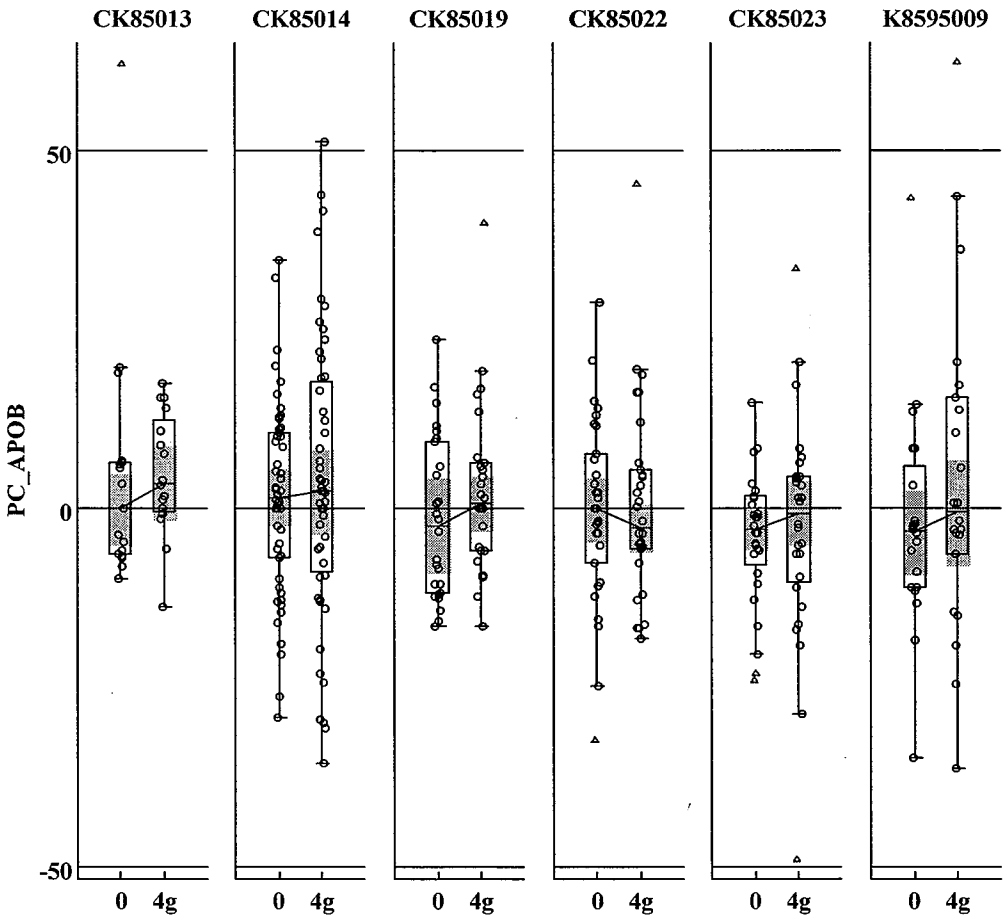
14. Box plot of individual Category I studies -% change of APOB



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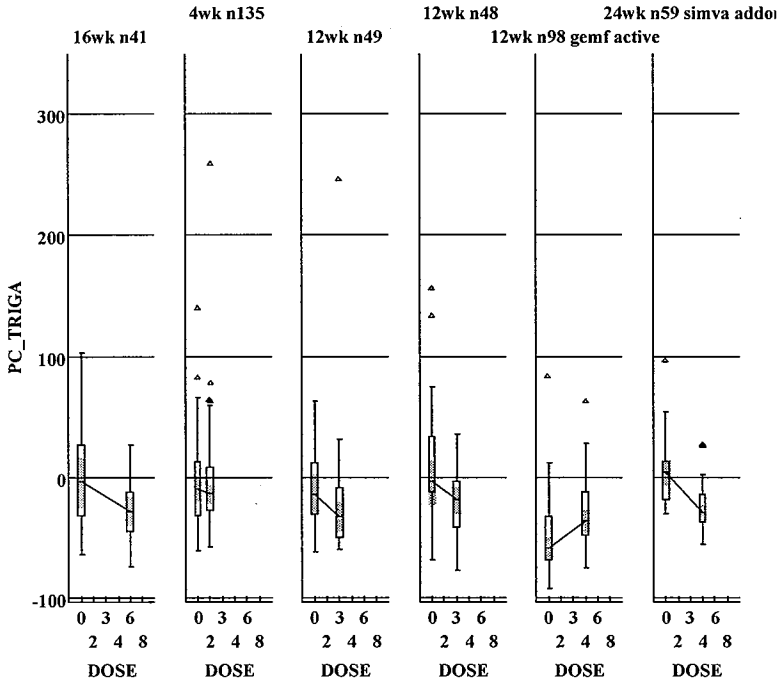
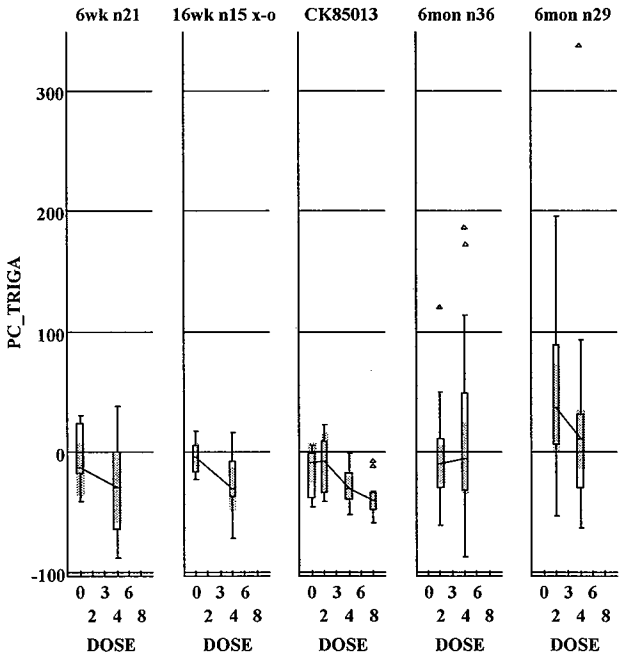
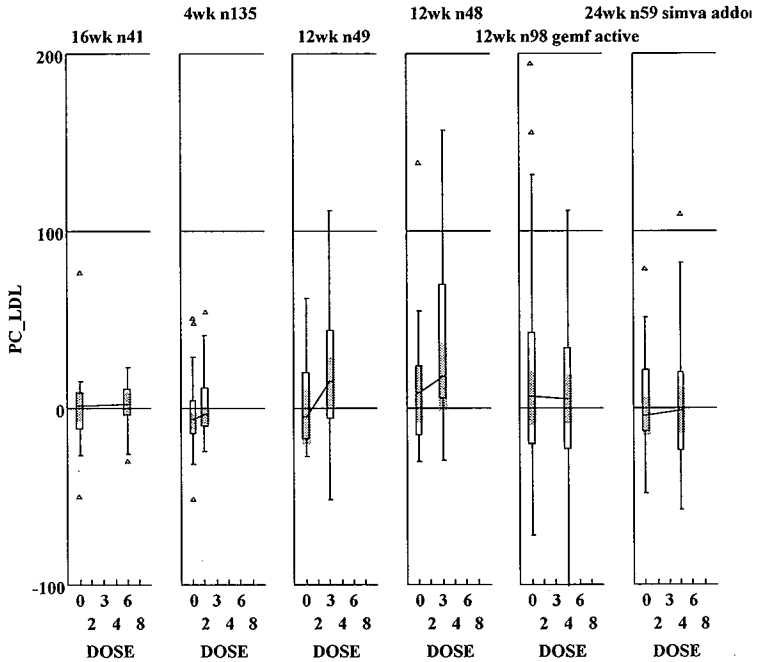
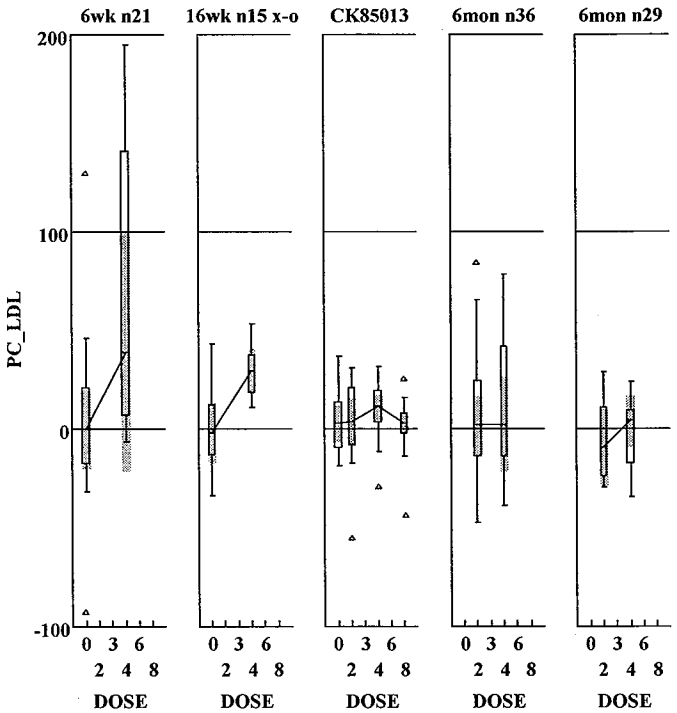
15. Median % change from baseline triglyceride - Category 2 Study



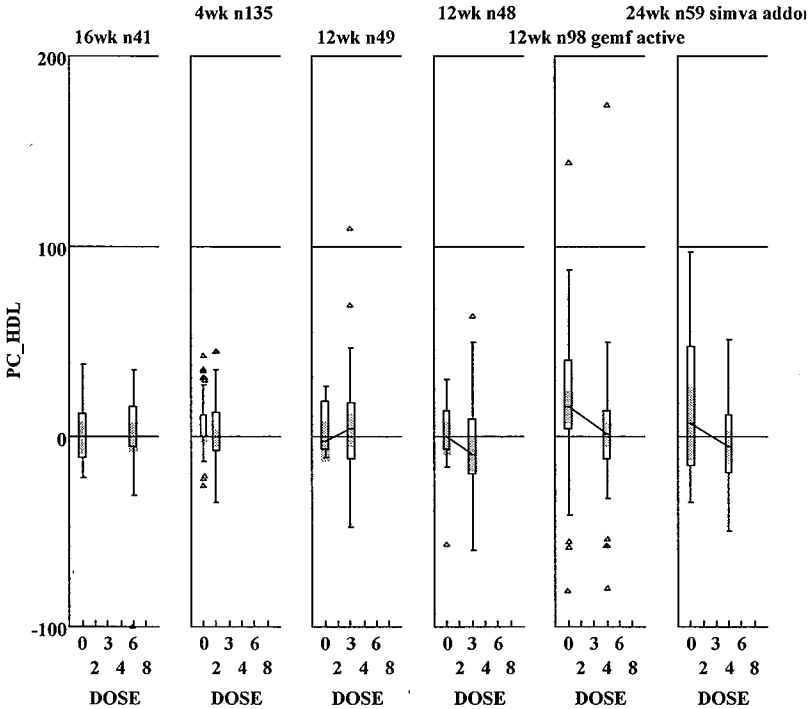


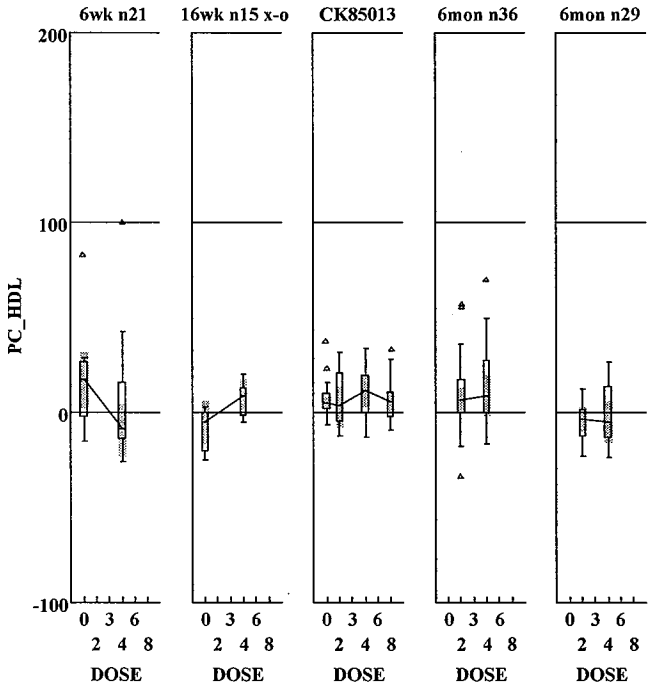
16. Median % change from baseline LDL - Category 2 Study



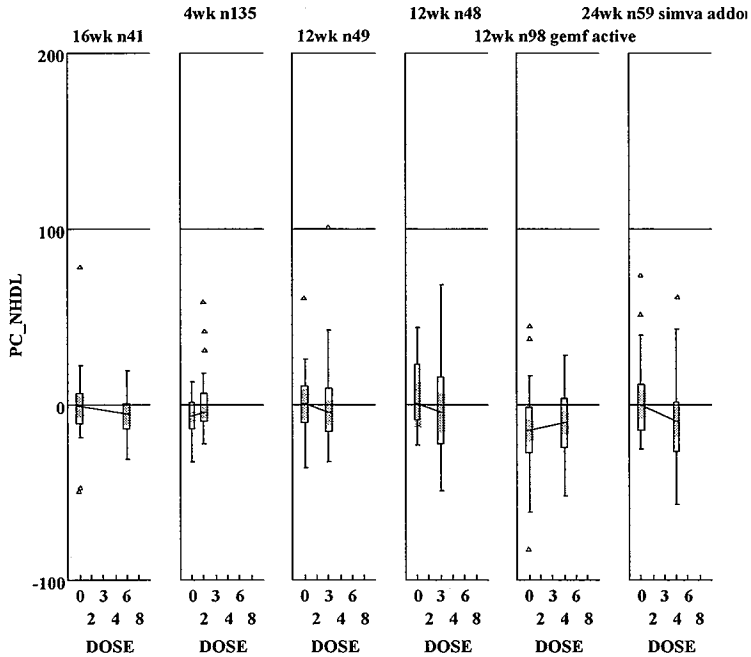


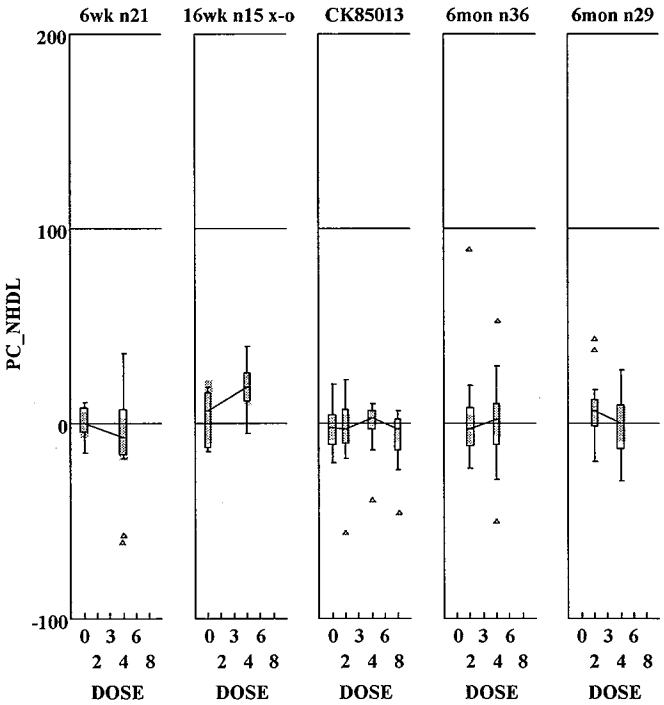
17. Median % change from baseline HDL - Category 2 Study



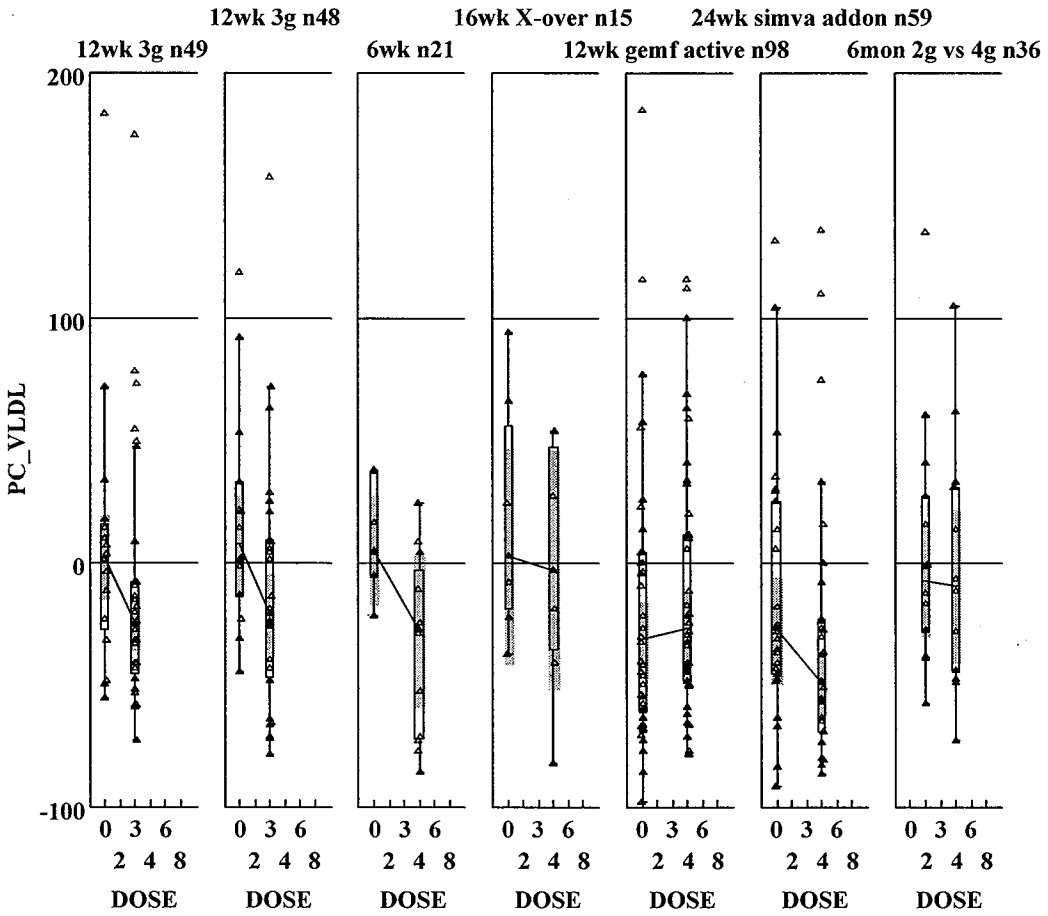


18. Median % change from baseline NHDL - Category 2 Study





19. Median % change from baseline VLDL - Category 2 Study



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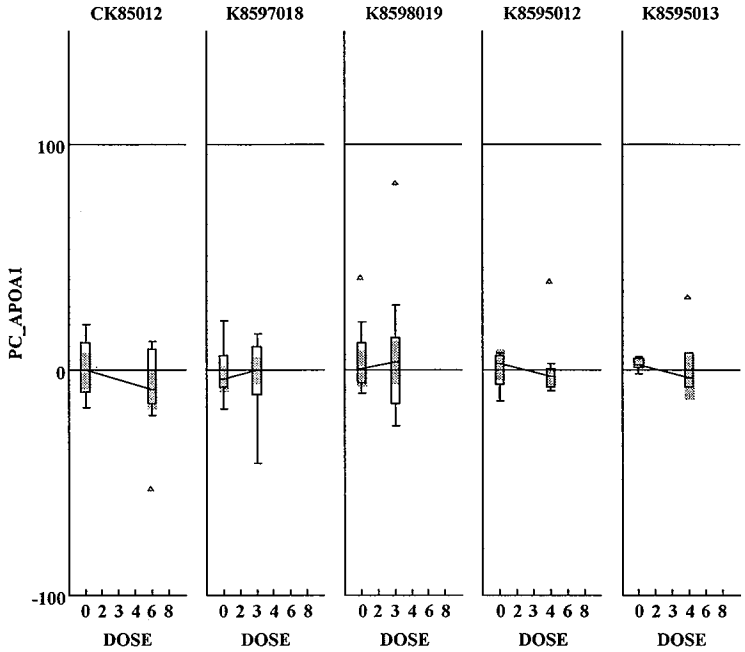
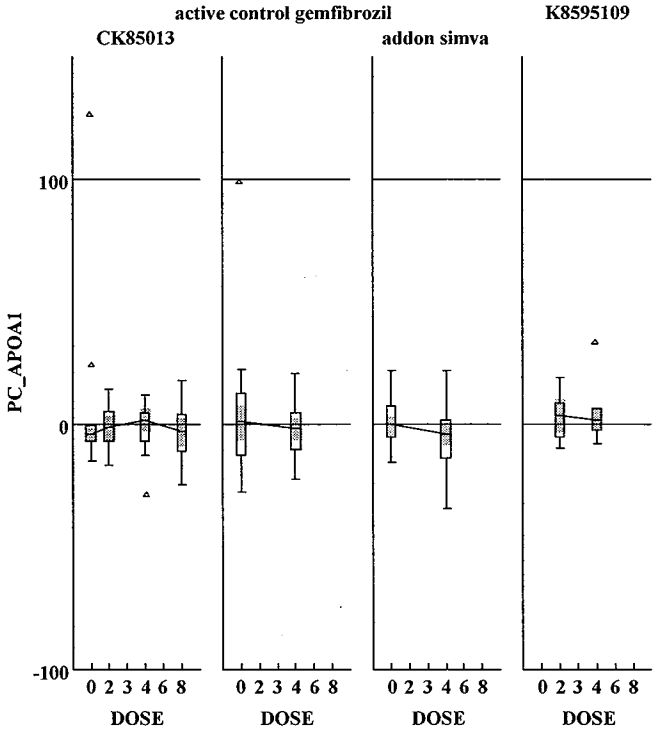
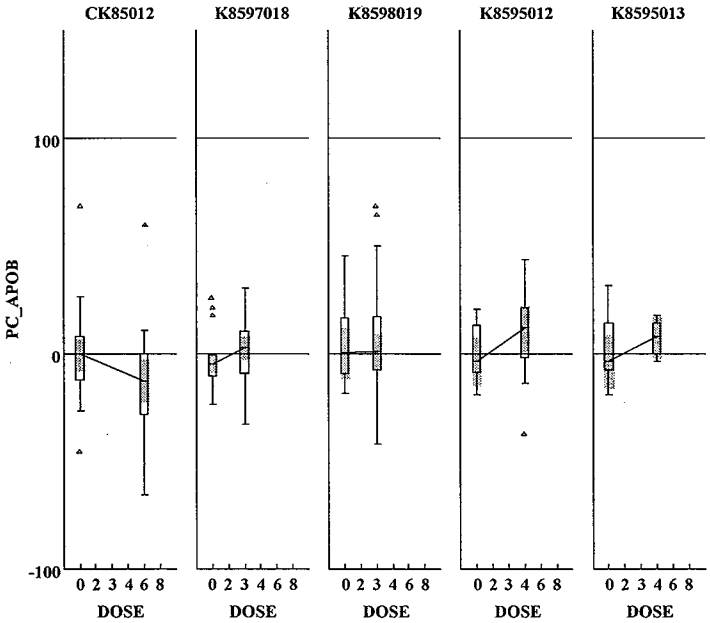
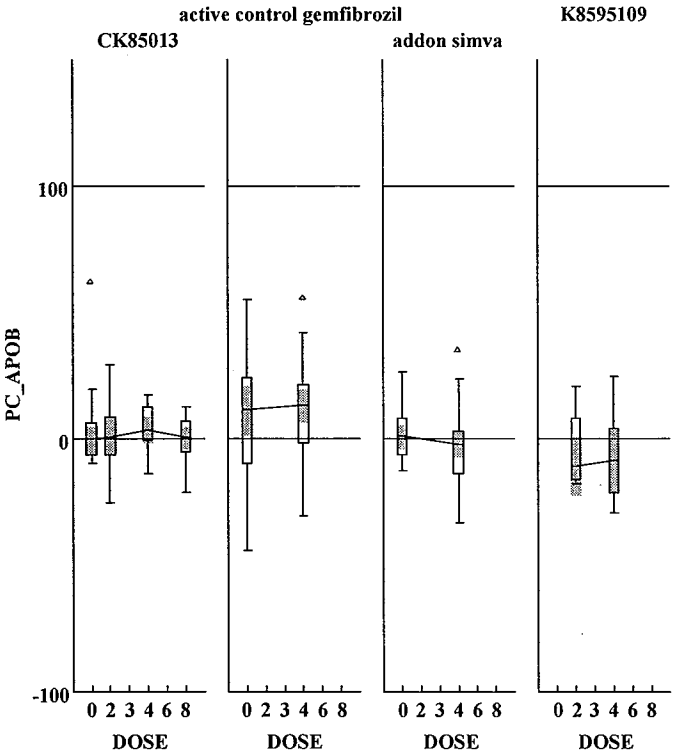
20. Median % change from baseline ApoA1 - Category 2 Study





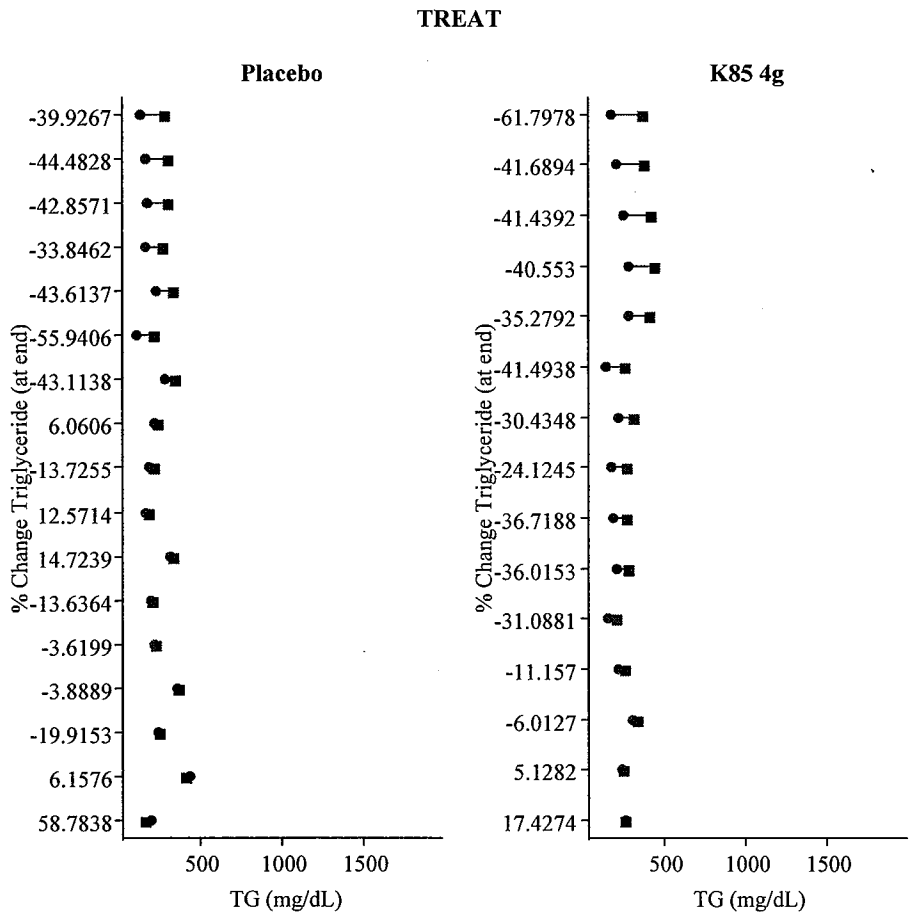
21. Median % change from baseline ApoA1 - Category 2 Study





22. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85013

STUDY
CK85013



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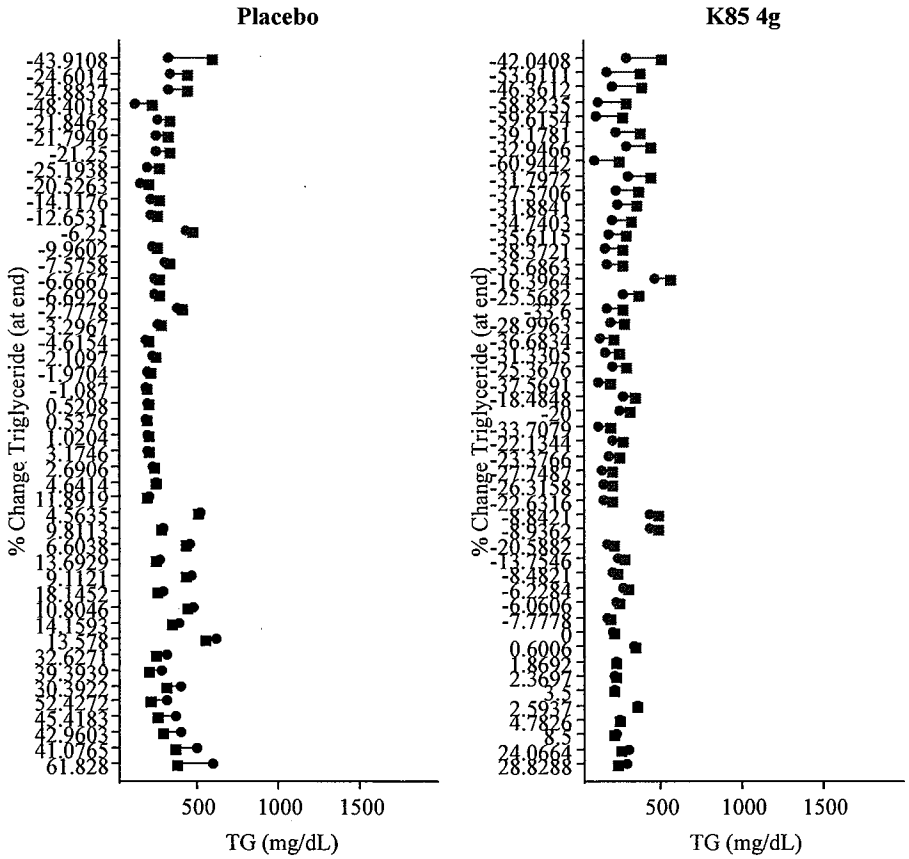
23. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85014

STUDY
CK85014

TREAT



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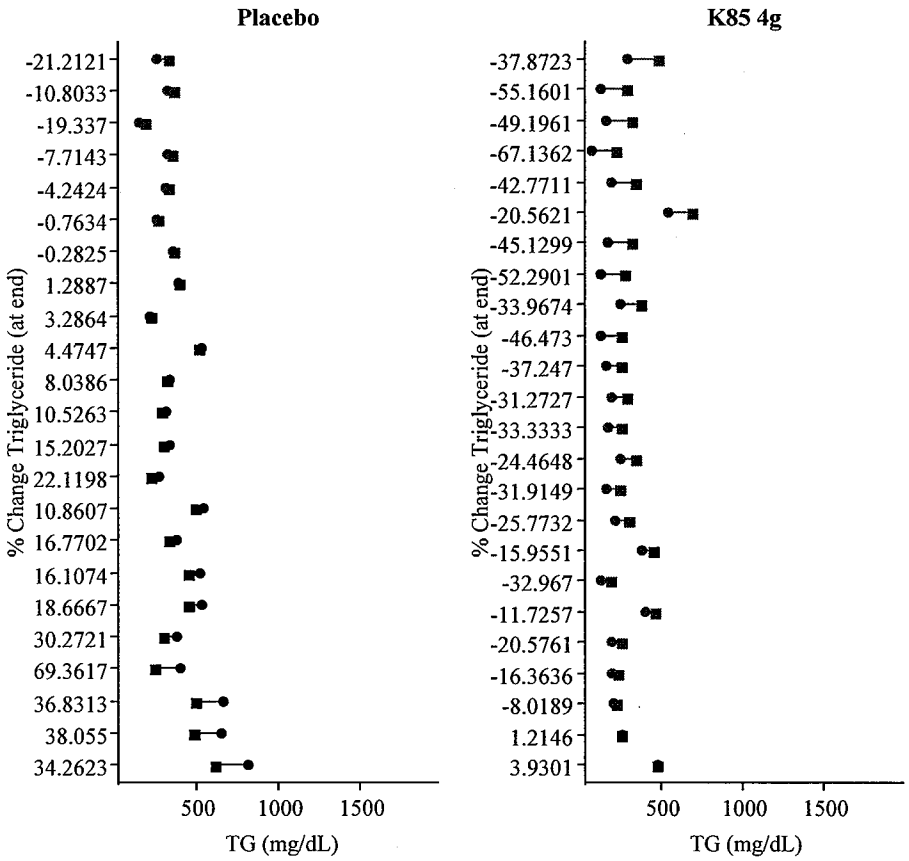
24. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85017

STUDY
CK85017

TREAT



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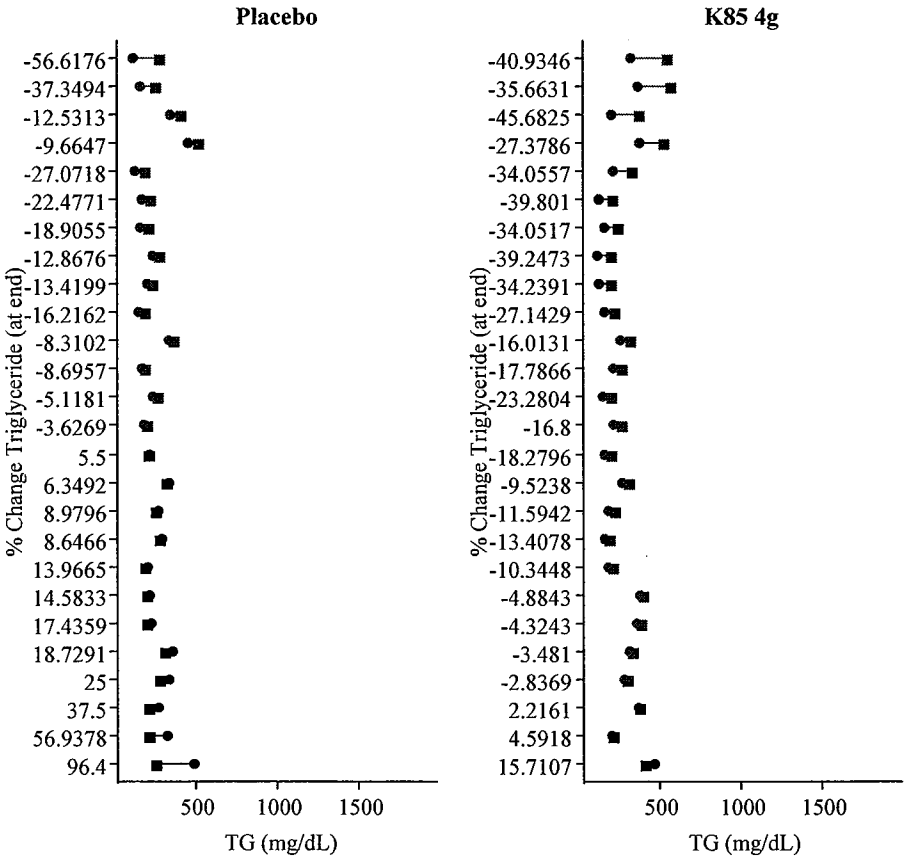
25. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG - 85019

STUDY
CK85019

TREAT



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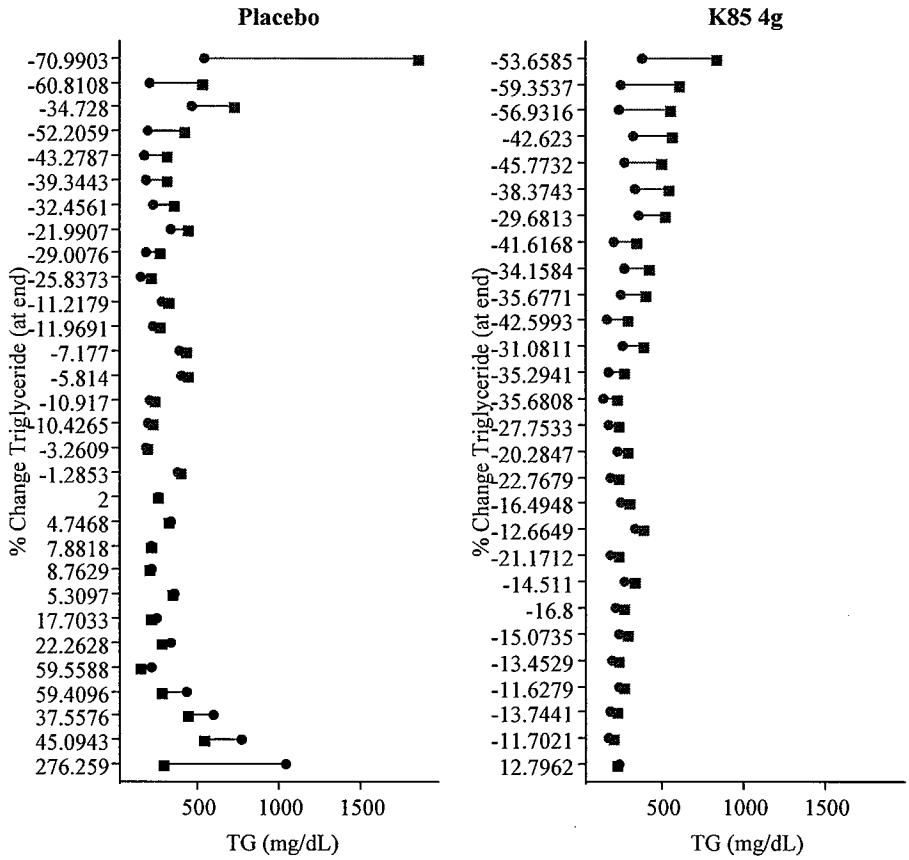
26. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG - 85020

STUDY
CK85022

TREAT



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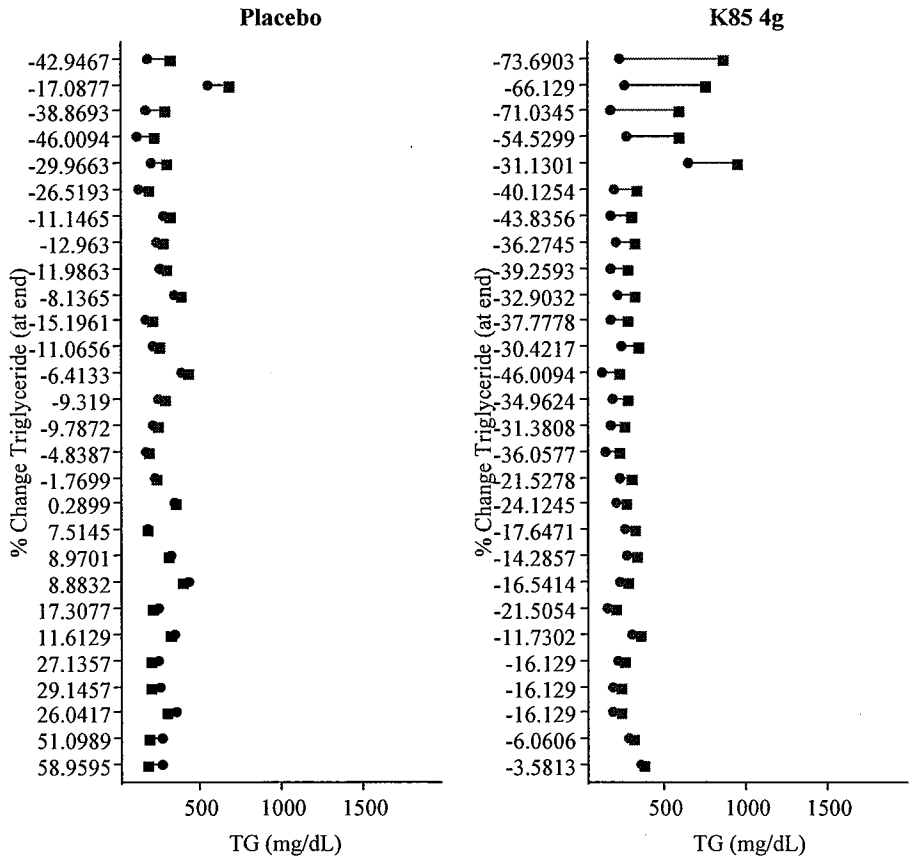
27. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85023

STUDY
CK85023

TREAT



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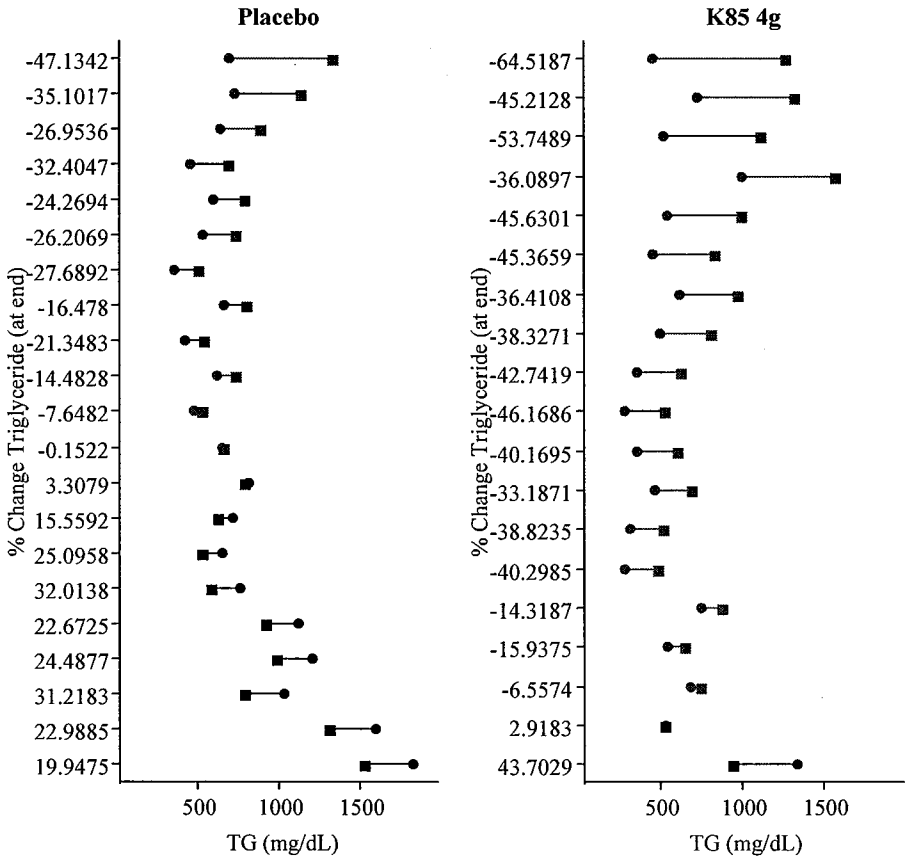
28. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 94010

STUDY
K8594010

TREAT



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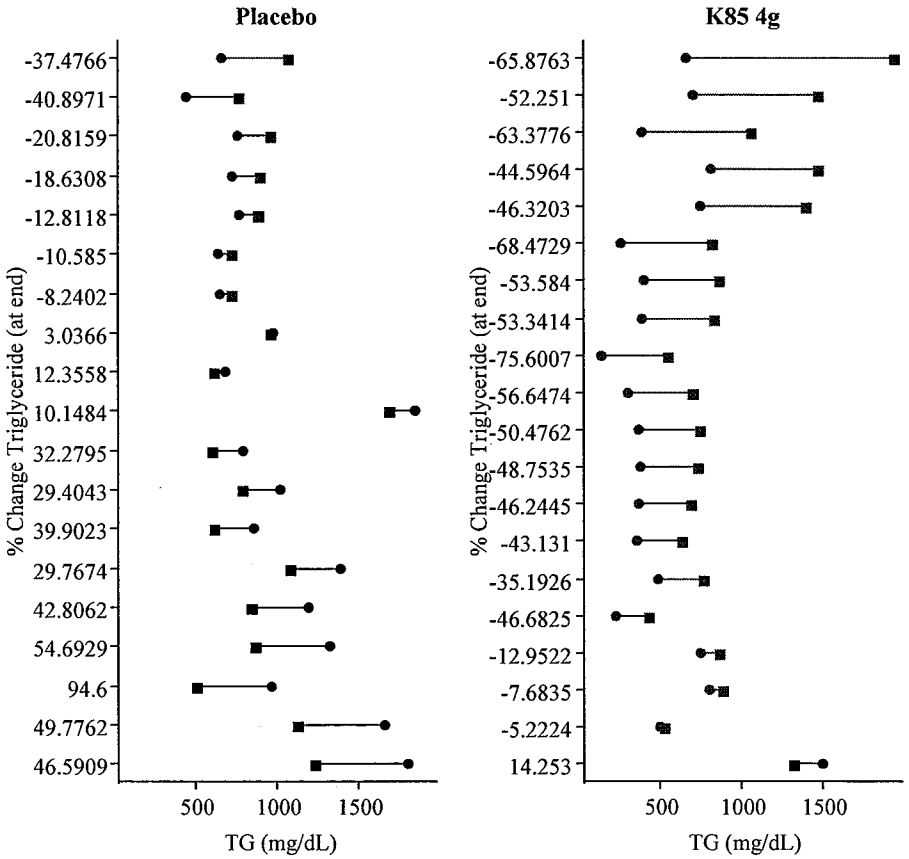
29. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 95009

STUDY
K8595009

TREAT



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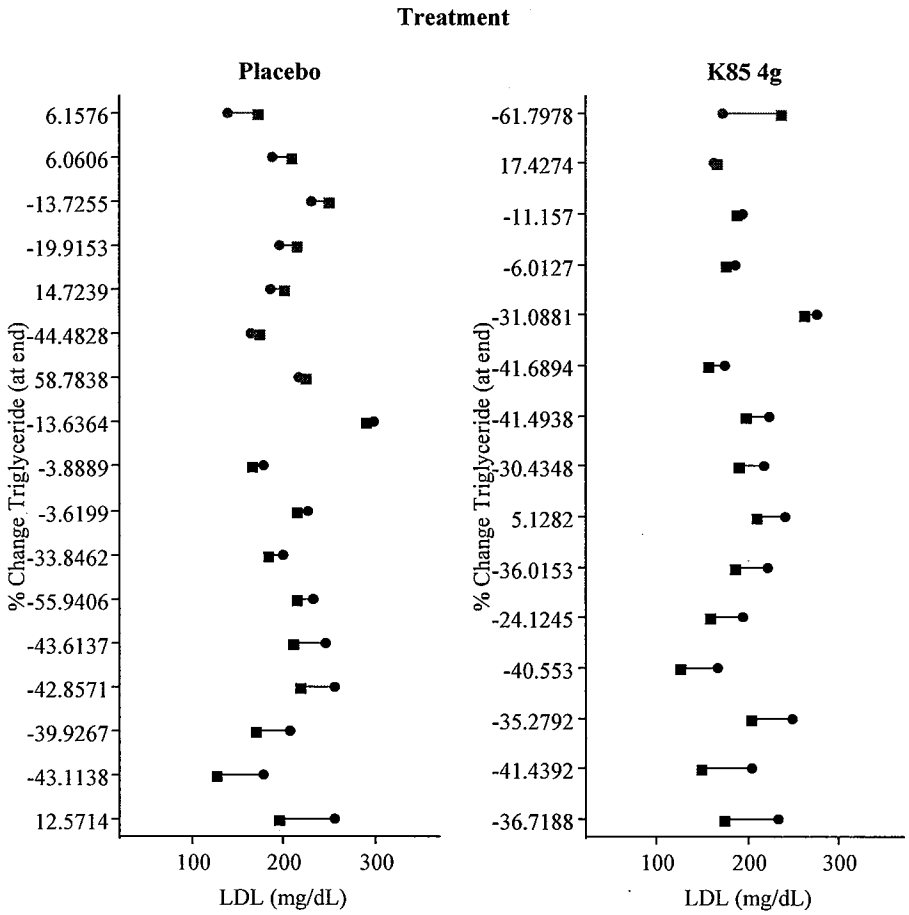
STUDY
CK85013



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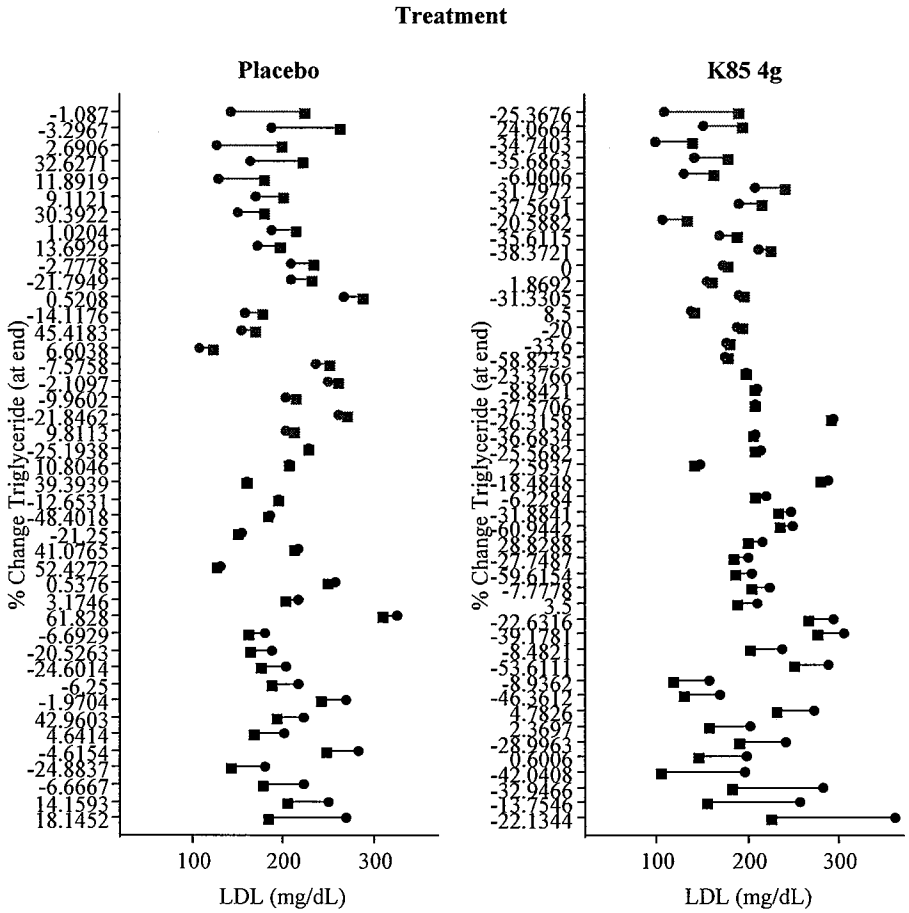
STUDY
CK85014



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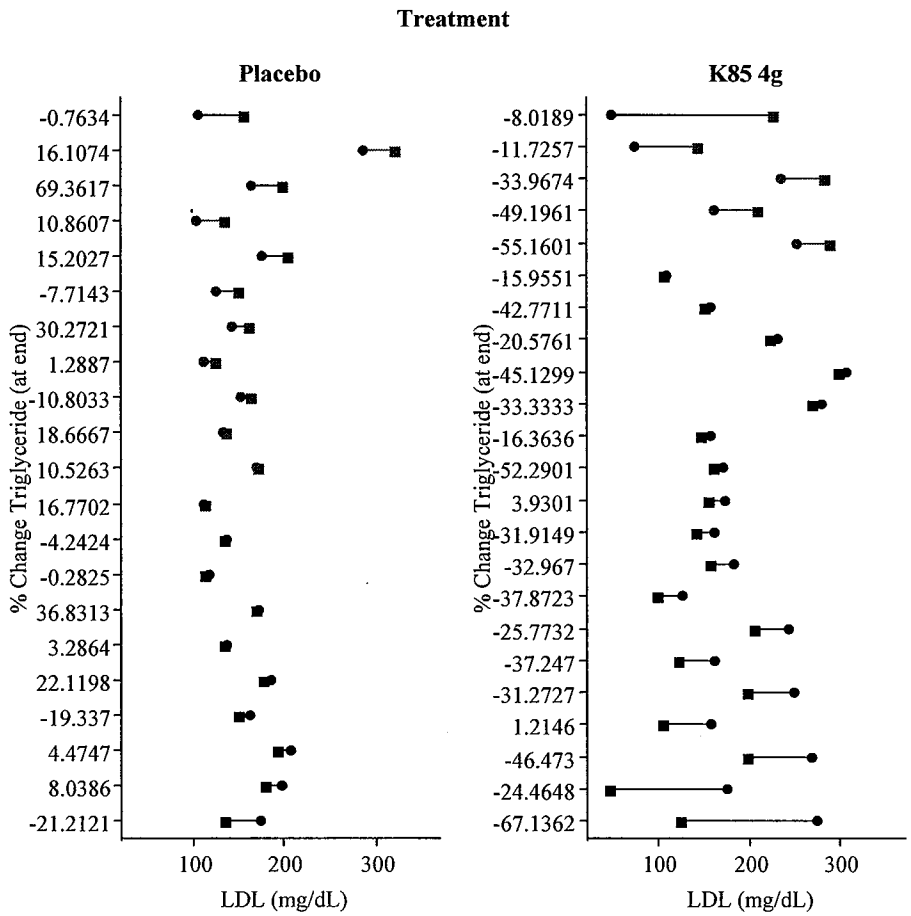
STUDY
CK85017



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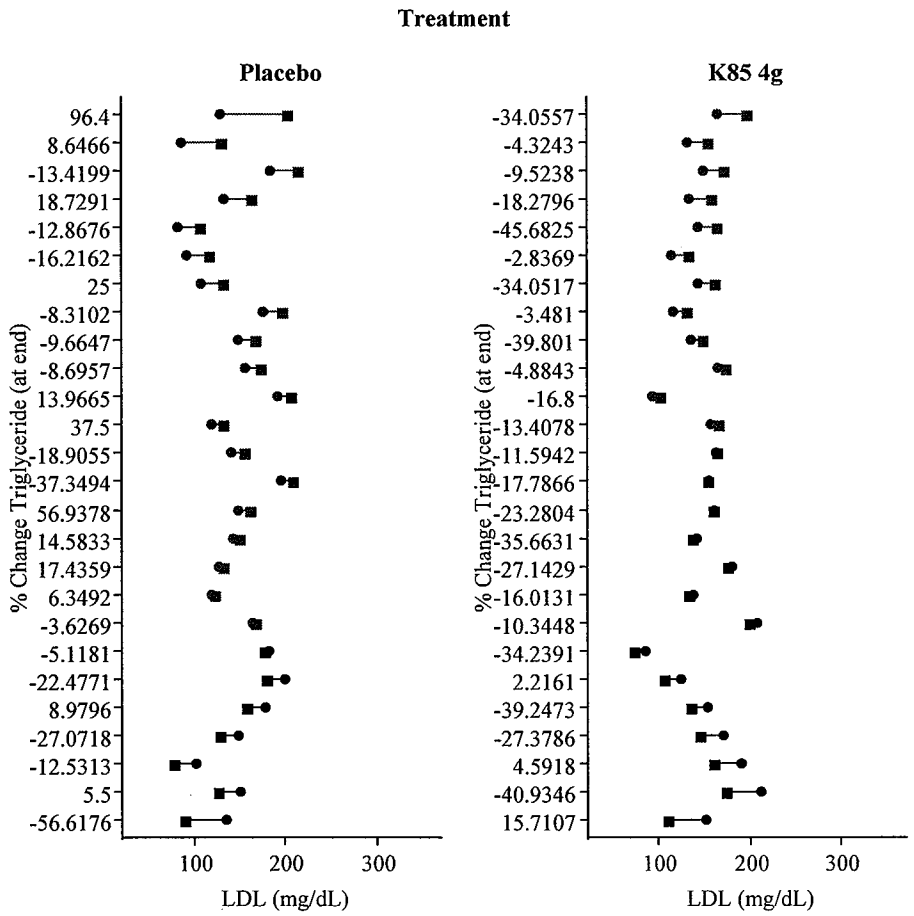
STUDY
CK85019



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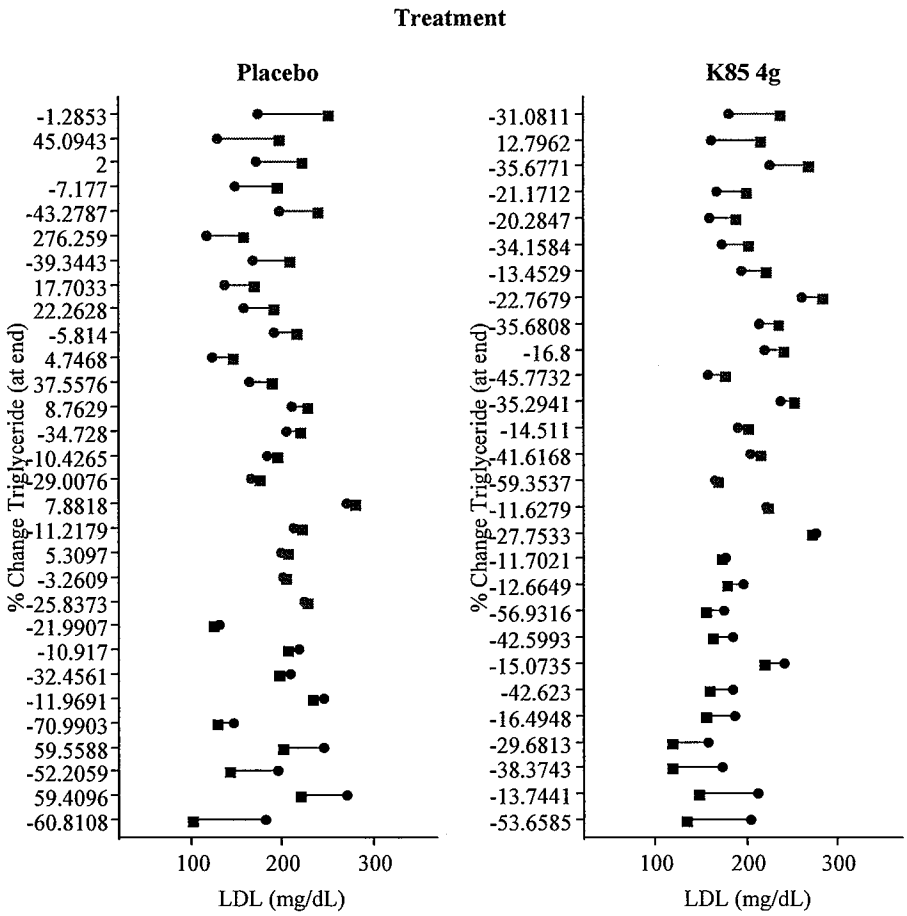
STUDY
CK85022



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STUDY
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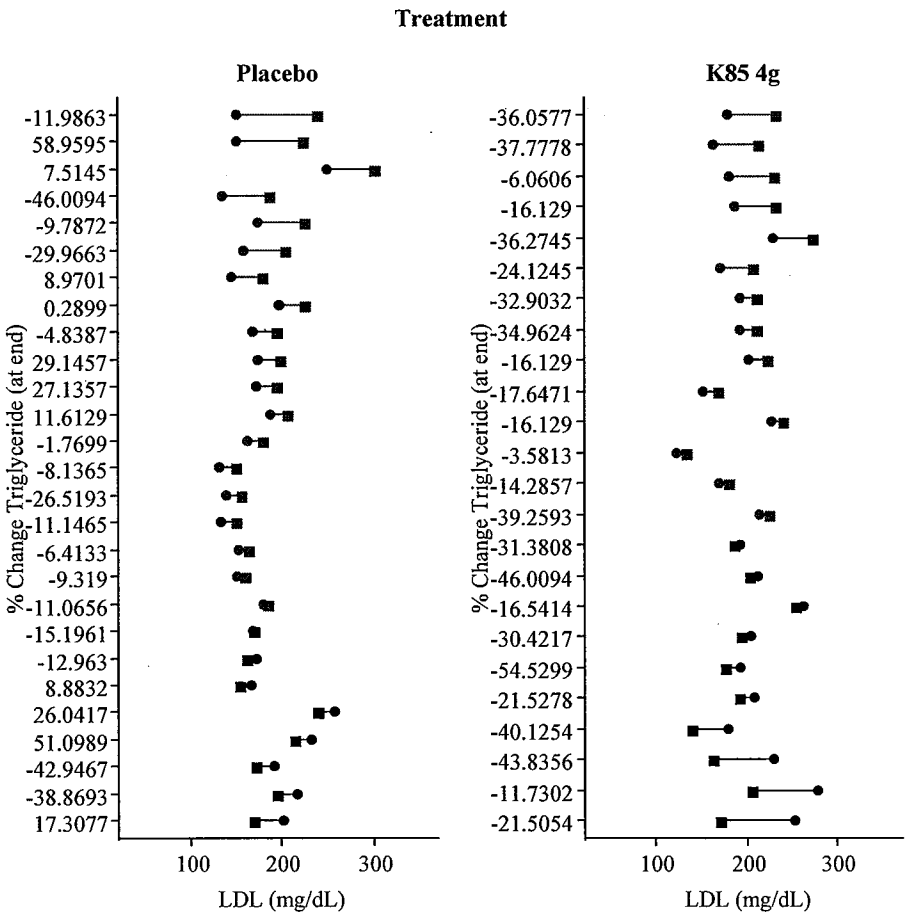

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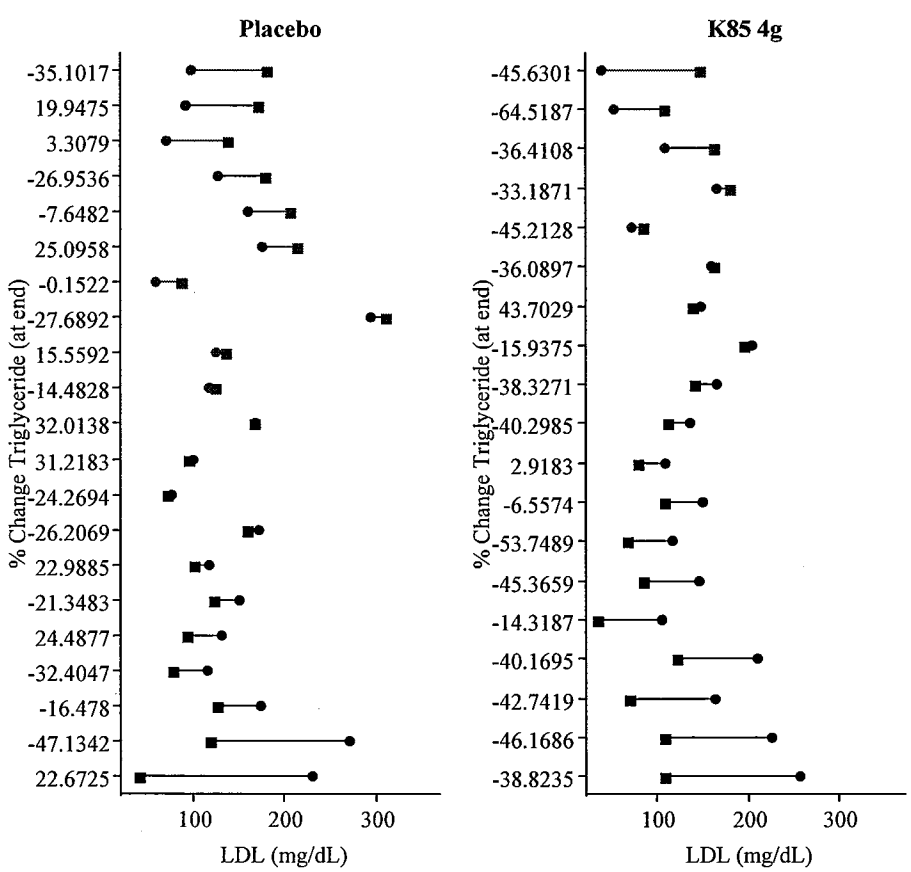
STUDY
K8594010



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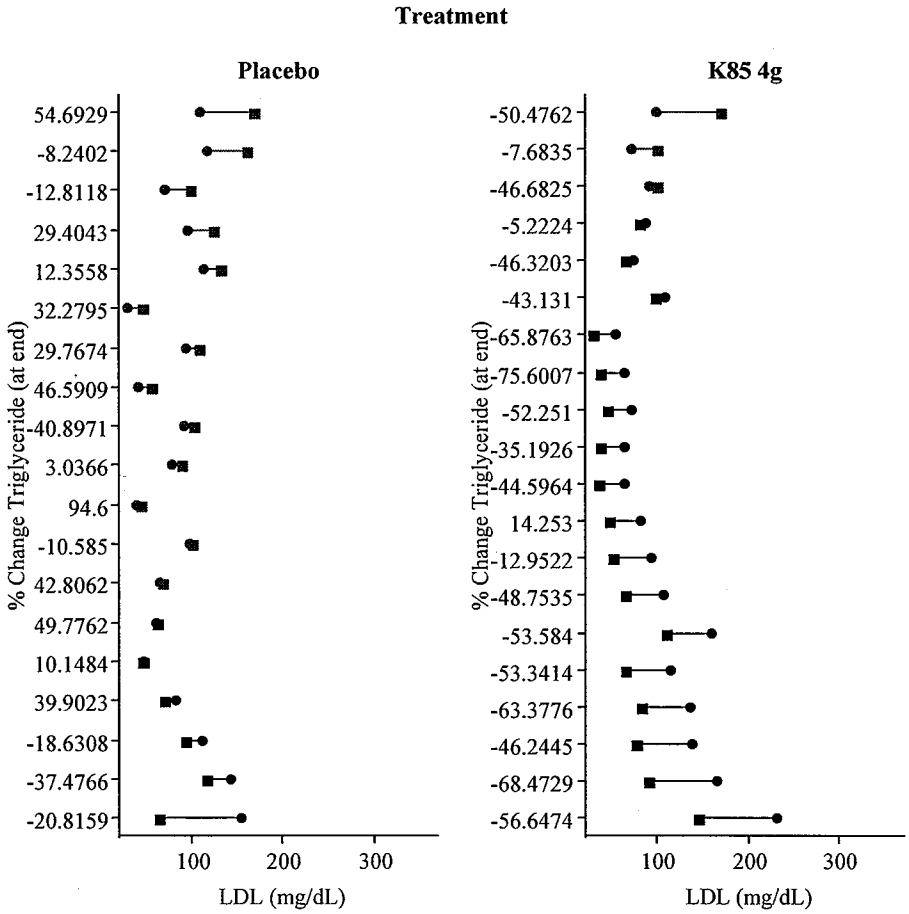
STUDY
K8595009



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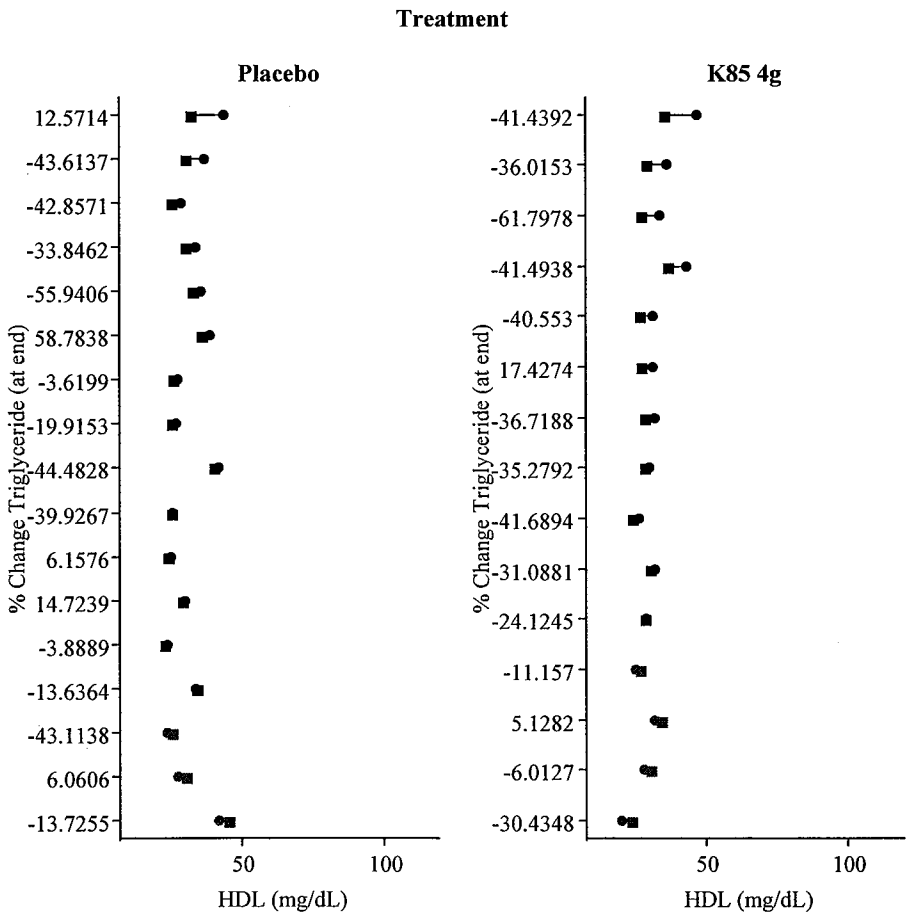
STUDY
CK85013



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STUDY
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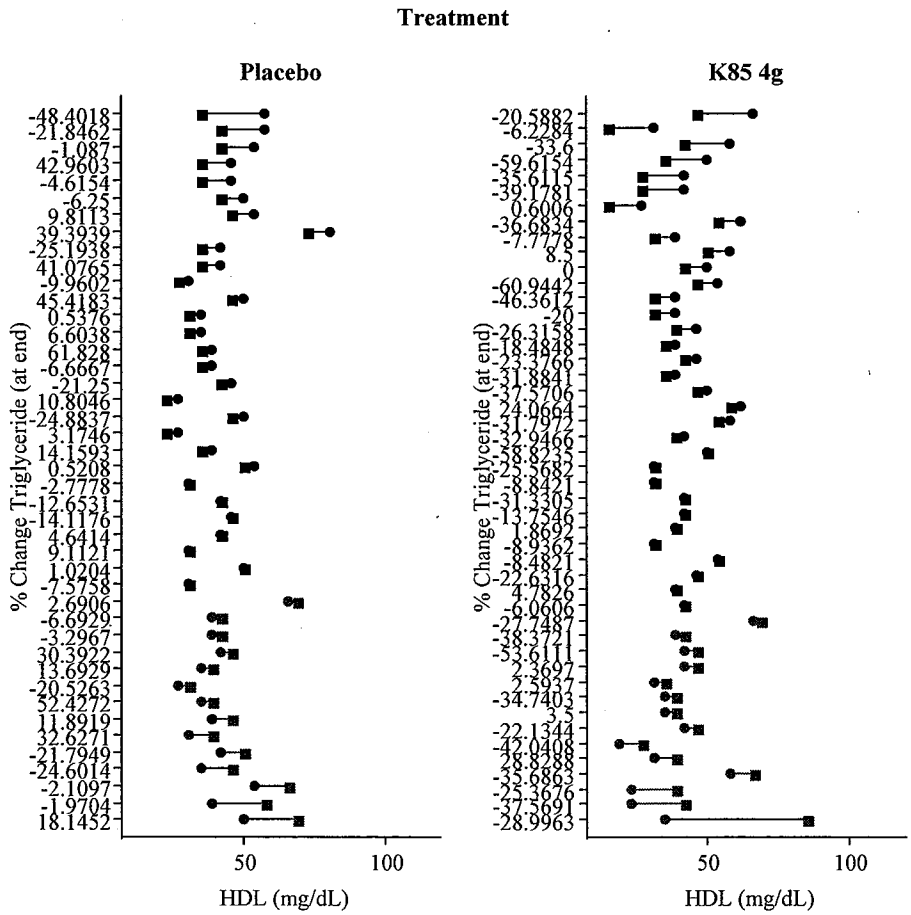

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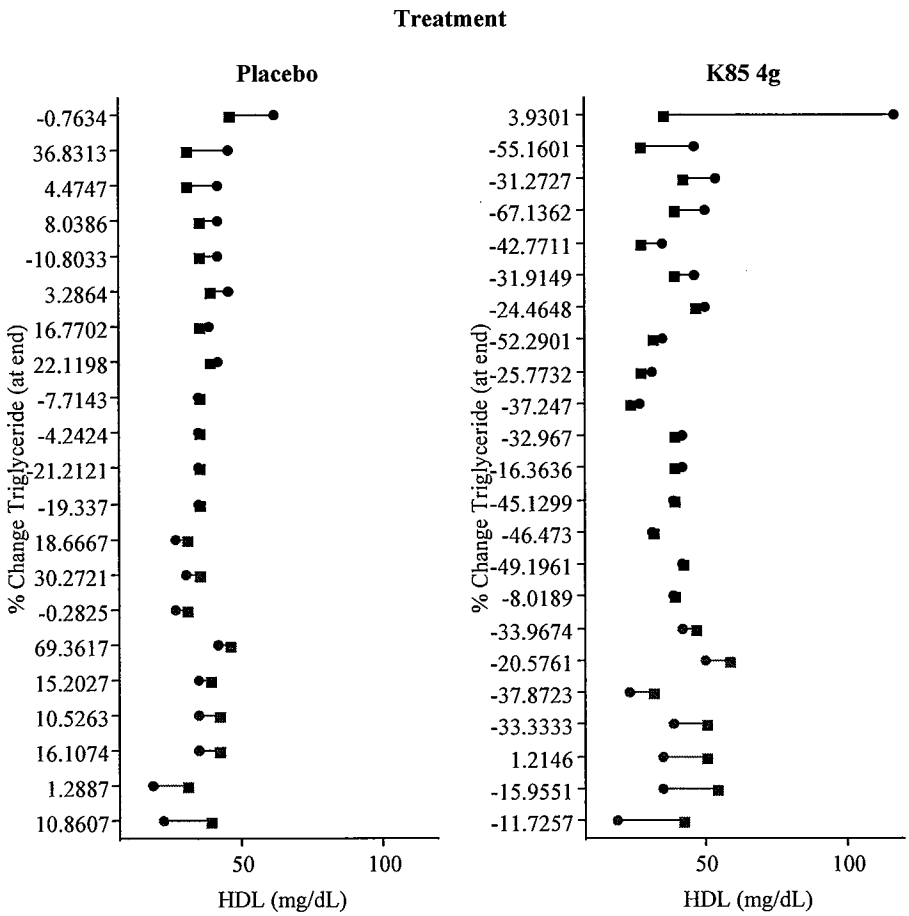
STUDY
CK85017



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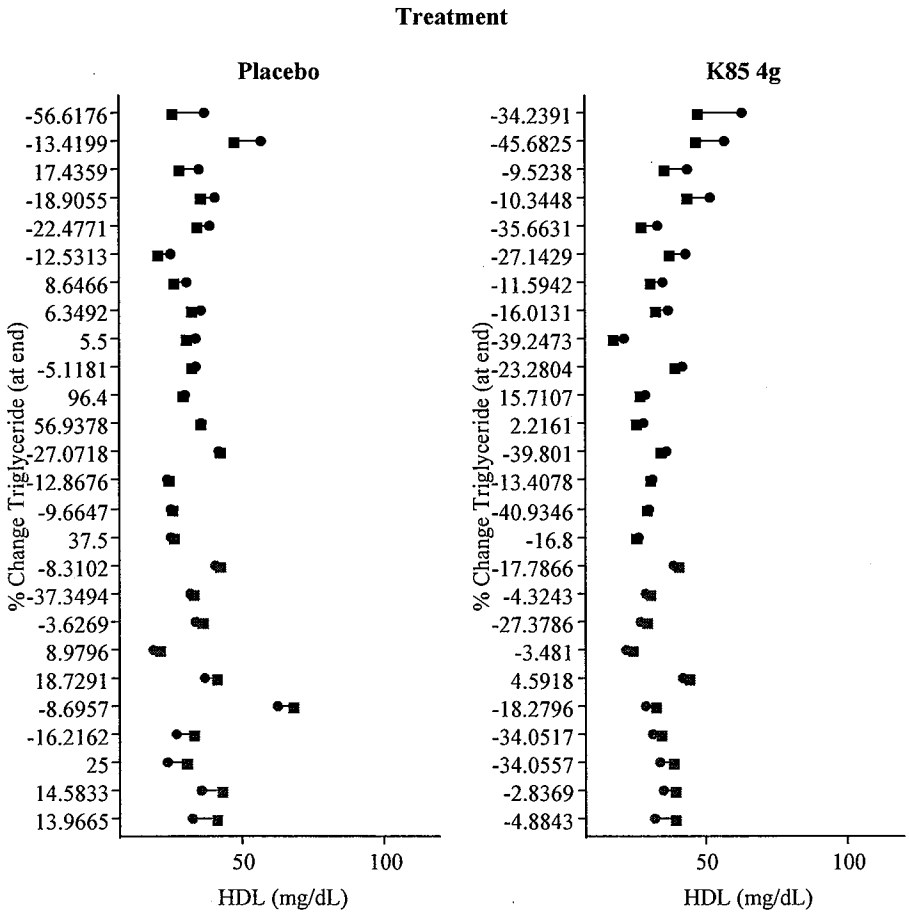
STUDY
CK85019



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42. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85022

STUDY
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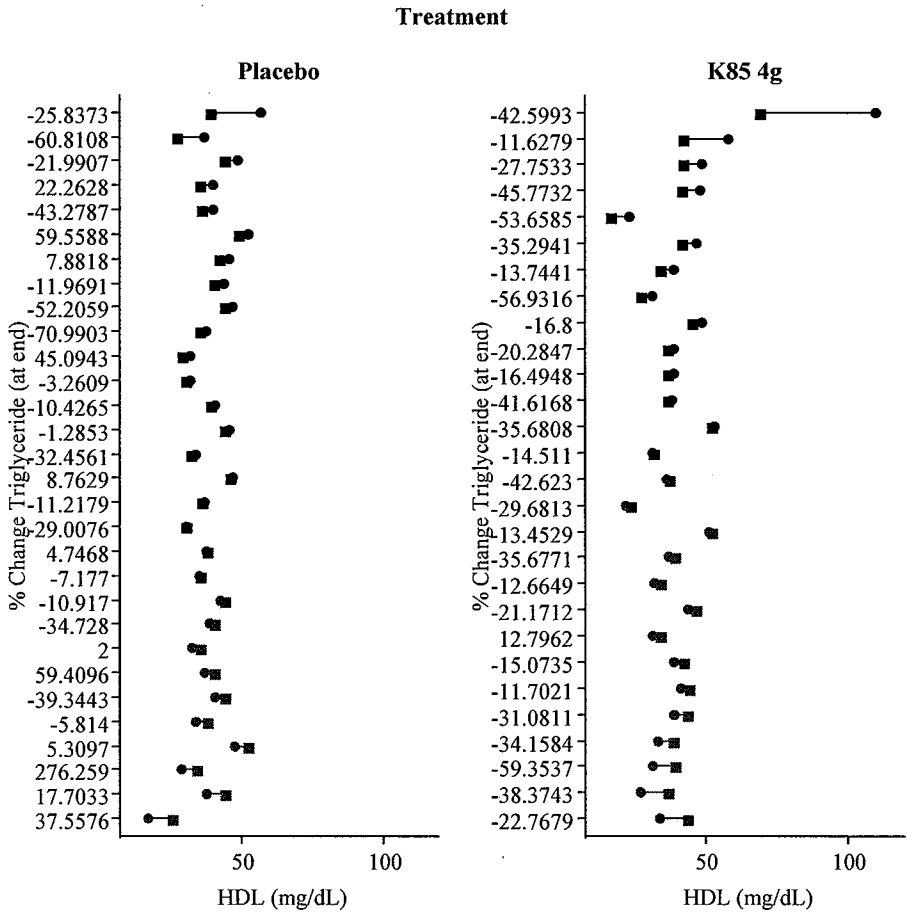

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STUDY
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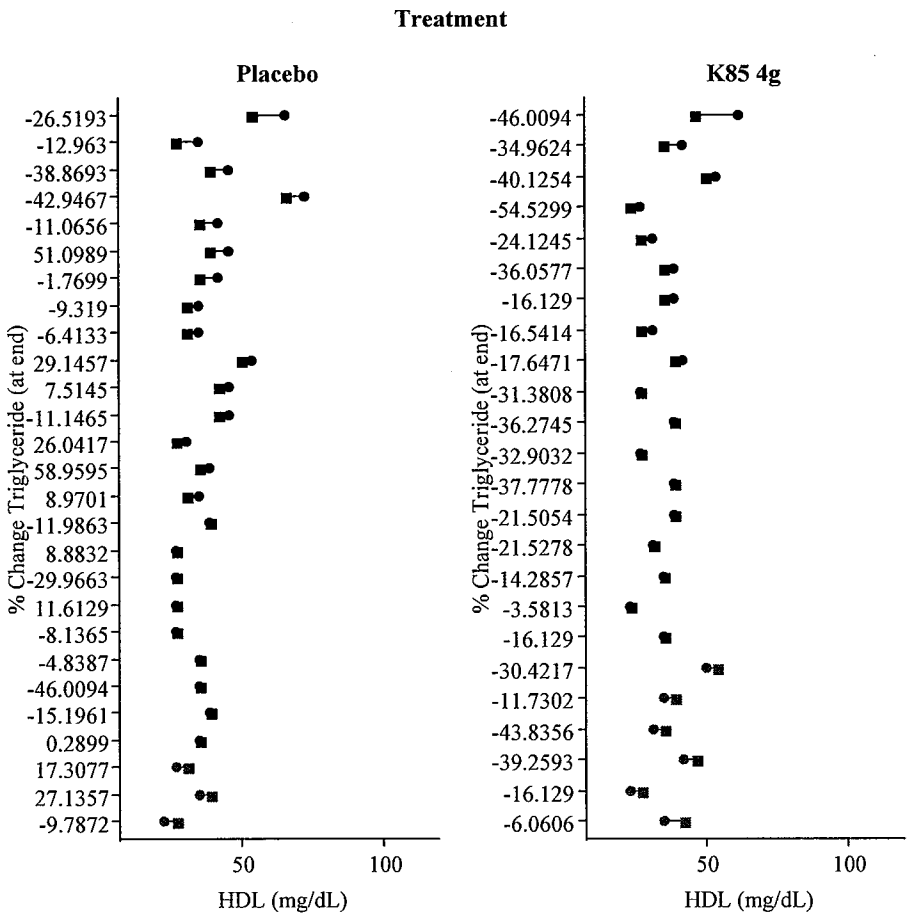

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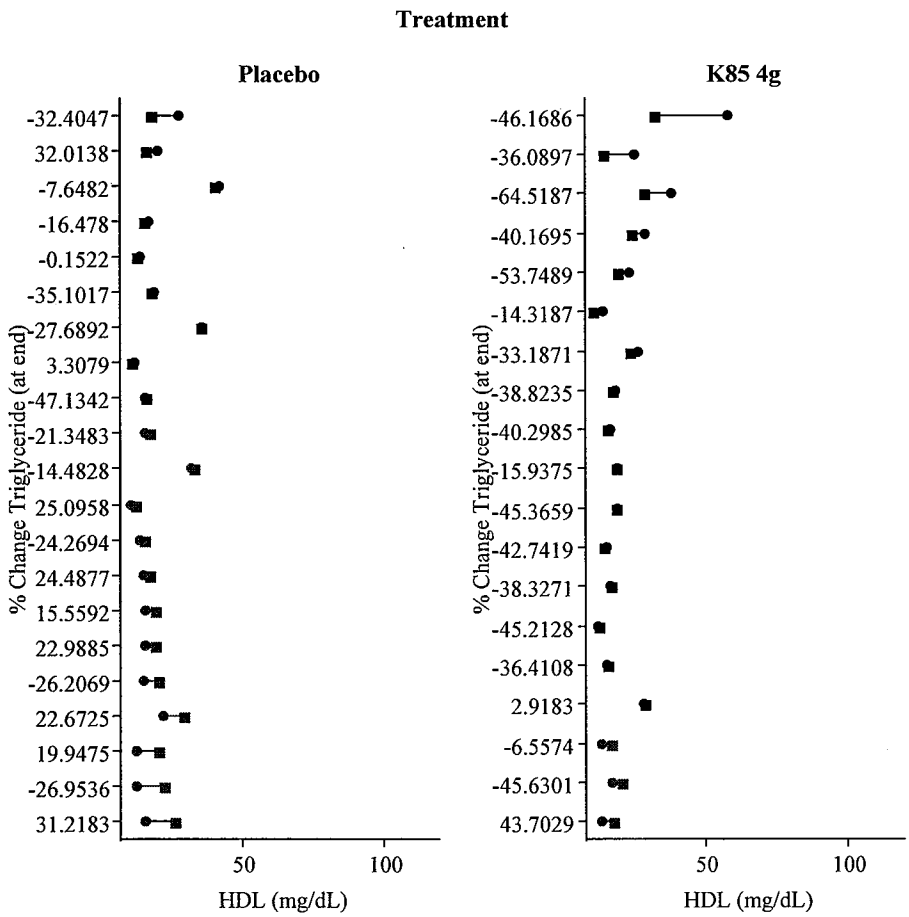
STUDY
K8594010



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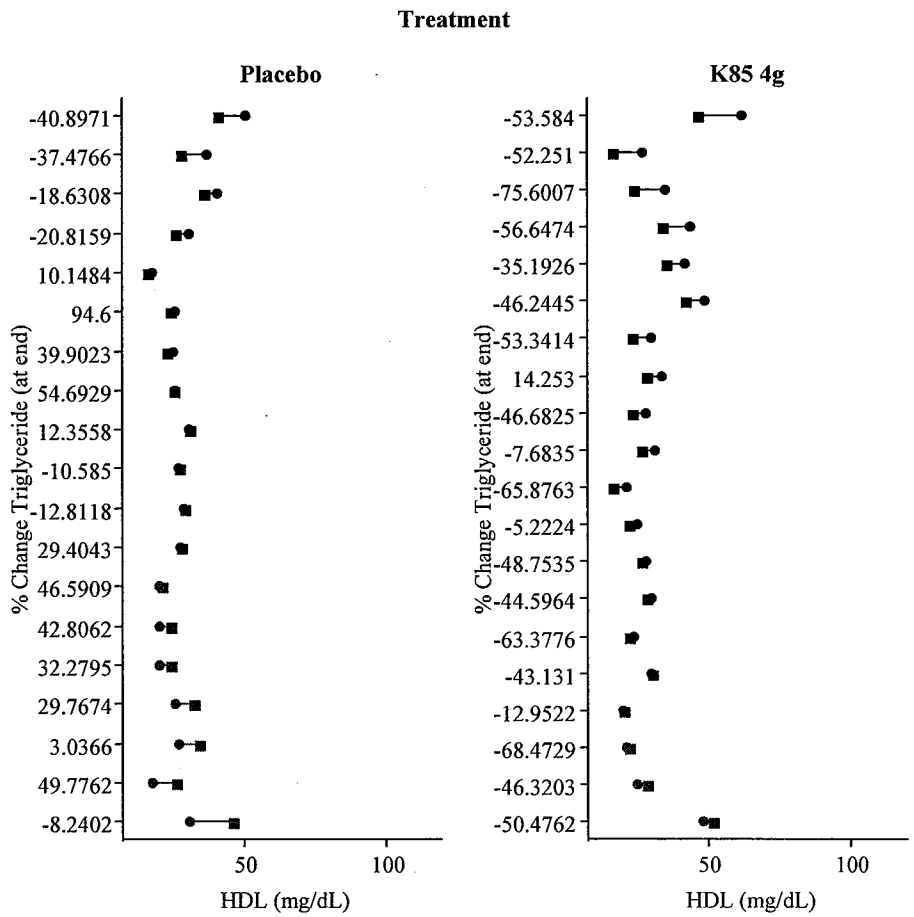
45. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 95009

STUDY
K8595009



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Lee-Ping Pian
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Todd Sahlroot
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S. Edward Nevius
10/28/04 01:29:41 PM
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Concur with review.

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:	21-654
Drug Name:	Omacor (omega-3-acid ethyl esters) Capsules, 1 gram
Indication(s):	as an adjunct to diet to reduce triglyceride levels
Applicant:	Abbott
Date(s):User fee goal date	November 9, 2004
Review Priority:	Standard
Biometrics Division:	DB 2 (HFD-715)
Statistical Reviewer:	Lee-Ping Pian, Ph.D.
Concurring Reviewers:	Todd Sahlroot, Ph.D.
Medical Division:	Metabolic and Endocrinologic Drug Products (HFD-510)
Clinical Team:	Mary Parks, M.D.
Project Manager:	Valerie Jimenez

Keywords: clinical study NDA review

Table of Contents

1. EXECUTIVE SUMMARY

K85 is a lipid-filled gel capsule containing 1000 mg of 84% omega-3 acid ethyl ester fish-oil concentrate of 465 mg EPA (eicosapentaenoic acid ethyl ester) and 375 mg DHA (docosahexaenoic acid ethyl ester) with 4 mg α-tocopherol added as an antioxidant. The proposed indication is as an adjunct to diet to reduce patient's elevated triglyceride level.

The efficacy of the 4 g/day K85 is based on 8 double-blind, placebo-controlled, randomized, parallel group studies or parts of study that used K85 4 mg dose per day. These Category I studies included a 8 week dose response study (85013), 5 European studies that had a dietary run-in phase (9 or 10 weeks) and a 12-week double-blind treatment phase, and 2 U.S. studies in patients with severe hypertriglyceridemia (TG≥500). Category II consisted of 11 studies that used doses other than K85 4 g per day, and/or different study designs. Table 1 displays the design and result of the 8 Category I studies. Figures 1 and 2 display the least squared mean (LSM) difference between K85 and placebo in percent change from baseline for triglyceride and median difference in percent change from baseline for LDL by studies. Table 2 and Figure 3 display the pooled 6 European studies and the pooled 2 U.S. studies. The primary efficacy comparison was between K85 and corn oil in percent change from baseline in fasting serum triglyceride. LDL increased in K85-treated patients compared to placebo-treated patients.

Table 1 Brief summary of Category I studies

Study ID # of Centers	Total Sample Size		Type of Study & Control	Duration treatment (dietary run-in)	TG (mg/dL) Median			LDL (mg/dL) Median		
					n	BL	%Chg	n	BL	%Chg
Ck85014 7 UK	corn oil K85 4g/day	57 54	hyperlipidemic patients with 177≤TG ≤885 mg/dl and TC≥201 mg/dl	12 (10) weeks	53 52	258 265	-0.5 -23.3	50 49	199 192	0.9 3.6
Ck85017 5 UK	corn oil K85 4g/day	26 29	hyperlipidemic patients with 177≤TG ≤885 mg/dl and TC≥201 mg/dl	12 (10) weeks	23 29	330 276	1.8 -19.8	22 28	152 158	-0.6 7.5
Ck85019 1 Sweden	corn oil K85 4g/day	27 26	post-myocardial infarction patients with 177≤TG ≤885 mg/dl and TC≤386 mg/dl	12 (9) weeks	26 26	238 268	3.0 -23.8	26 26	156 156	-3.5 7.2
Ck85022 1 Sweden	corn oil K85 4g/day	30 30	patients with hyperTG levels 177≤TG ≤885 mg/dl and TC≥232 mg/dl	12 (9) weeks	30 30	305 279.0	-9.6 -22.5	30 30	202 201	-0.7 1.9
Ck85023 1 Norway	corn oil K85 4g/day	29 28	hypertriglyceridemia,177≤TG ≤1326 mg/dl and TC≥232 mg/dl	12 (10) weeks	28 28	275 295	-12.2 -29.2	27 24	185 206	-10.3 -5.5
K85-94010 1 US	corn oil K85 4g/day	21 20	patients with severe hypertriglyceridemia, type IV, with 500≤TG ≤2000 mg/dl	6 (6) weeks	21 20	786 811	-14.3 -38.4	21 20	126 108	1.2 22.5
K85-95009 2 US	corn oil K85 4g/day	21 22	patients with severe hypertriglyceridemia, 500≤TG ≤2000 mg/dl	16 (4) weeks	21 22	841 818	6.4 -50.7	21 22	93 78	-10.1 62.7
Ck85-013(K85 4-g part) 2 Sweden	corn oil K85 4g/day	17 17	patients with hyperlipidemia, 1770≥TG ≥442 mg/dl and TC levels ≥250 mg/dl	8 (8) weeks	17 15	260 261	-13.6 -35.6	17 16	208 180	2.8 11.3

Figure 1 LSM % change difference (95% C.I.)

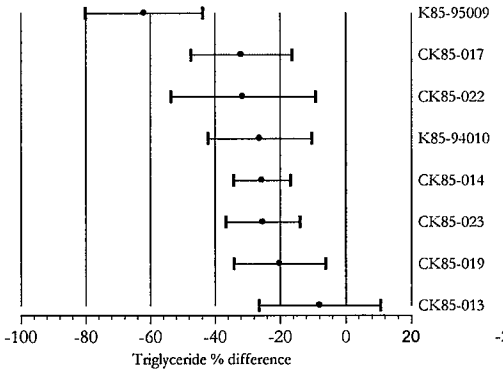
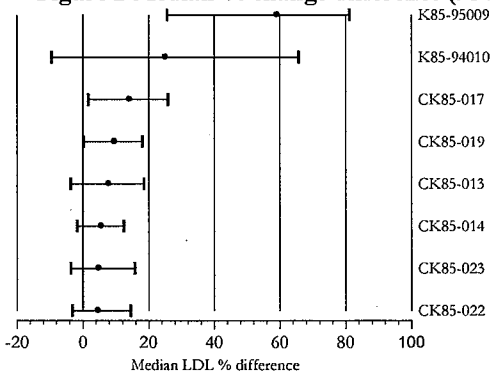


Figure 2 Median % change difference (95% C.I.)



The comparisons between K85 and placebo on the primary efficacy variable, percent change from baseline triglycerides levels were statistically significant favoring K85 in all studies but the dose ranging study (CK85-013). The median increase in LDL percent change from baseline was greater in the 2 US studies in severe hypertriglyceridemia than in the European studies. The baseline LDL levels for the U.S. studies were lower than the European studies, however.
The appendix contains additional tables and graphs for the Category I and Category II studies.

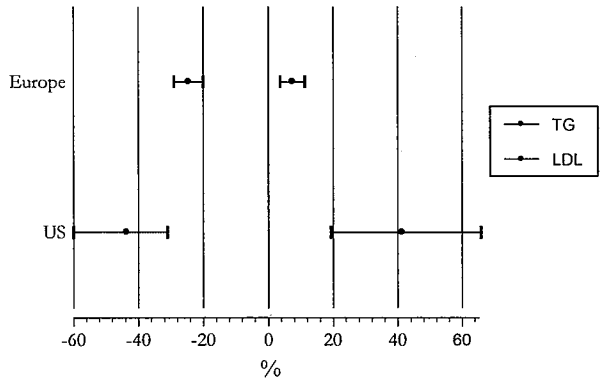
1.1 Conclusions and Recommendations

K85 was efficacious in triglycerides reduction. However, LDL increased in the K85 group compared to placebo. The 2 pooled analyses by baseline severity of hypertriglyceridemia (TG≥177 mg/dL, TG≥500 mg/dL) showed that estimates of the median shift from placebo in percent change of triglyceride were -25%, and -44%, respectively and 7.5% and 41.4% in LDL, respectively (Table 2 & Fig. 3).

Table 2 Median (95% C.I.) of % change from baseline for pooled analysis

	Pooled	Placebo				4 g K85				**Median**	95% C.I.
	studies	n	BL	EP	%Chg	n	BL	EP	%Chg	**shift**	
TG	European	173	272	264	-2.0	177	275	208	-27.1	**-24.5%**	(-29, -20)
LDL	European	171	185	174	-2.4	173	182	191	4.5	**7.5%**	(3.7, 11.3)
TG	US	42	788	762	6.7	42	816	489	-44.9	**-43.6%**	(-60, -31)
LDL	US	41	108	112	-4.8	41	89	109	44.5	**41.4%**	(19.4, 65.9)

Figure 3 Median % change from baseline difference (K85 minus placebo) and 95% CI



The correlation between TG percent change and LDL percent change was poor (r^2=0.0002 US) indicating that changes in TG and LDL with K85 treatment are not related on an individual patient basis.

1.2 Brief Overview of Clinical Studies

Category I studies included 8 double blind, placebo (corn oil) controlled, randomized, parallel group studies that were conducted in Europe (2 UK, 3 Sweden, 1 Norway), and the U.S. (2). The two US studies were in patients with severe hypertriglyceridemia (500 mg/dl ≤TG≤2000 mg/dl). Five of the European studies had a double-blind treatment phase of 12 weeks that followed a 9 or 10 week dietary run-in. Parts of the dose response study (placebo and 4 g K85) were in Category I and Parts (placebo, 2 g, 8 g K85) were in Category II. Category II included 11 controlled studies which used doses other than K85 4 g per day and/or different study designs.

1.3 Statistical Issues and Findings

This reviewer used the intent-to-treat population for the primary efficacy analysis. The ITT population was defined as patients with a baseline measurement and at least one follow up measurement for that outcome variable. In the label the sponsor presented data for individual studies and the pooled analysis of 8 Category I studies. This reviewer presented the pooled studies according to the severity of the hypertriglyceridemia. The 6 European studies were pooled which had a baseline criteria of triglyceride levels ≥ 177 mg/dL while the criteria for the 2 US studies was ≥500 mg/dL. The analysis of covariance as well as nonparametric Wilcoxon-Mann-Whitney test was used to analyze the data. The median shift and the 95% confidence interval were from the Hodges-Lehmann procedure.

2. STATISTICAL EVALUATION

2.1 Evaluation of Efficacy

The 6 European studies and the 2 US studies from Category I were pooled separately according to the baseline severity of hypertriglyceridemia. Table 3 and Table 4 display patient disposition for the pooled studies.

Table 3 Disposition of patients – EU

Reason	Placebo	K85	Total
Randomized	186	184	370
ITT	178	181	359
PP	166	167	333
Completed	171	186	357
Discontinued	15	14	29
Adverse event	4	8	12
Intercurrent disease/illness	0	1	1
Non-compliance	3	3	6
Other	8	2	10

Table 4 Disposition of patients – US

Reason	Placebo	K85	Total
Randomized	42	42	84
ITT	42	42	84
PP	38	39	77
Completed	39	41	80
Discontinued	3	1	4

Reason	Placebo	K85	Total
Adverse event	2	0	2
Non-compliance	0	1	1
Other	1	0	1

Tables 5 and Table 6 display patient demographics. 98% of the European patients were Caucasian and 75% were male. 81% of US patients were Caucasian and 64% were male.

Table 5 Demographics of patients – European

Reason	Placebo	K85	Total
ITT	178	181	359
Age			
Mean (SD)	52.8 (10.3)	53.2 (10.0)	53.0 (10.1)
Range	26, 70	26, 70	(26, 70)
Gender			
Male	134	135	269 (75%)
Female	43	46	89 (25%)
Race			
Caucasian	174	179	353 (98%)

Table 6 Disposition of patients – US

Reason	Placebo	K85	Total
ITT	42	42	84
Age			
Mean (SD)	48.1 (10.1)	48.6 (10.0)	48.4 (10.0)
Range	(31, 72)	(31, 70)	(31, 72)
Gender			
Male	26	28	54 (64%)
Female	16	14	30 (36%)
Race			
Caucasian	34	34	68 (81%)
Other	8	8	16 (19%)

Tables 7 and 8 present a summary of baseline characteristics for the ITT populations for the 2 pooled studies. Patients were similar in mean weight, BMI and height. The US patients weighed approximately 87 kg and the European patients 81 kg.

Table 7 Baseline Characteristics – European

Reason	Placebo	K85	Total
Weight (kg)	n=178	n=181	n=359
Mean (SD)	80.8 (12.2)	80.2 (13.1)	80.5 (12.7)
(Min, Max)	(51.6, 112.6)	(50.0, 125)	(50, 125)
BMI (kg/m^2)	n=177	n=181	n=357
Mean (SD)	27.0 (3.0)	27.0 (3.7)	27 (3.3)
(Min, Max)	(20.4, 35.0)	(19.3, 40.7)	(19.3, 40.7)
Height (cm)	n=177	n=180	n=357
Mean (SD)	172.9 (9.2)	172.0 (9.2)	172.5 (9.2)
(Min, Max)	(144, 195)	(147, 202)	(144, 202)

Table 8 Baseline characteristics – US

Reason	Placebo n=42	K85 n=42	Total n=84
Weight (kg)			
Mean (SD)	87.9 (17.5)	85.2 (18.2)	86.6 (17.8)
(Min, Max)	(51.7, 135.6)	(58.5, 124.3)	(51.7, 135.6)
BMI (kg/m^2)			
Mean (SD)	29.3 (4.5)	28.6, (4.3)	29.0 (4.4)
(Min, Max)	(21.5, 42.2)	(21.4, 41.3)	(21.4, 42.2)
Height (cm)			
Mean (SD)	172.6 (8.8)	171.9 (11.6)	172.3 (10.2)
(Min, Max)	(155, 193)	(150, 200)	(150, 200)

Tables 9 and 10 display a summary of baseline TG levels and other lipid levels for the ITT populations by the 2 pooled studies.

Table 9 Baseline lipid characteristics – European

	Placebo	K85	Total
Triglyceride	n=178	n=180	n=358
Mean (SD)	307.7 (159.2)	315 (131.2)	311.4 (145.6)
(Min, Max)	(136, 1858)	(178, 938)	(136, 1858)
LDL	n=173	n=173	n=346
Mean (SD)	185.5 (43.9)	183.5 (46.4)	184.5 (45.1)
(Min, Max)	(67, 320)	(45, 298)	(45, 320)
HDL	n=178	n=180	n=358
Mean (SD)	36.6 (9.4)	37.2 (10.1)	36.9 (9.7)
(Min, Max)	(20, 73)	(15, 85)	(15, 85)
TC	n=178	n=181	n=359
Mean (SD)	278.8 (45.7)	280.1 (53)	279.5 (49.5)
(Min, Max)	(178, 440)	(141, 510)	(141, 510)

Table 10 Baseline lipid characteristics – U.S.

	Placebo	K85	Total
Triglyceride	n=42	n=42	n=84
Mean (SD)	847.6 (274.2)	881 (341.9)	864.5 (308.5)
(Min, Max)	(500, 1685)	(422, 1940)	(422, 1940)
LDL	n=42	n=42	n=84
Mean (SD)	116.4 (54.2)	94.8 (42.4)	105.6 (49.6)
(Min, Max)	(41, 310)	(30, 194)	(30, 310)
HDL	n=42	n=42	n=84
Mean (SD)	24.4 (8.2)	24.2 (11.8)	24.3 (10.1)
(Min, Max)	(11, 46)	(10, 72)	(10, 72)
TC	n=42	n=42	n=84
Mean (SD)	316.6 (76.4)	299.7 (91.6)	308.1 (84.2)
(Min, Max)	(116, 452)	(163, 600)	(116, 600)

There were no significant differences between K85 4 g/day and placebo in lipids at baseline.

2.2 Analysis results – 8 studies

K85 was compared to placebo in percent change from baseline using an analysis of covariance model. The model included treatment and site as fixed effect and baseline triglyceride value as covariate. Table 11 displays the least squared mean differences (K85 minus placebo) with the 95% confidence intervals. The dose response study (85013) was the only study which did not

achieve statistical significance. The two US studies (94010, 95009) enrolled patients with severe hypertriglyceridemia. Figure 4 displays the LSM differences and the confidence intervals. Figure 5 displays the individual patient triglyceride percent changes from baseline versus baseline by study.

Table 11 Summary results of analysis of covariance – ITT

Study	Placebo			K85			K85 minus Placebo			p-value
	n	LSM	SE	n	LSM	SE	LSM	SE	95% CI	
CK85-014	53	3	3.2	52	-22	3.2	-25	4.3	-33.5, -16.5	<0.001
CK85-017	23	12	5.8	29	-19.8	5.3	-31.8	7.9	-47.6 -15.9	0.0002
CK85-019	26	1.8	4.9	26	-18.3	4.9	-20.1	7.0	-34.1, -6.1	0.006
CK85-022	30	3.4	7.8	30	-28.0	7.8	-31.4	11.1	-53.6, -9.2	0.006
CK85-023	28	-4.3	3.9	28	-29.6	3.9	-25.3	5.7	-36.6, -13.9	<0.001
K85-94010	21	-4.0	5.5	20	-30.2	5.6	-26.2	7.9	-42.1, -10.3	0.0019
K85-95009	21	158	6.8	22	-46	6.6	-61.8	9.1	-80.1, -43.5	<0.0001
CK85-013	17	-17.4	6.1	15	-25.3	6.5	-7.9	9.1	-26.4, 10.7	0.39

Figure 4 Change from baseline LSM difference (K85 minus placebo) and 95% C.I. by study – ITT

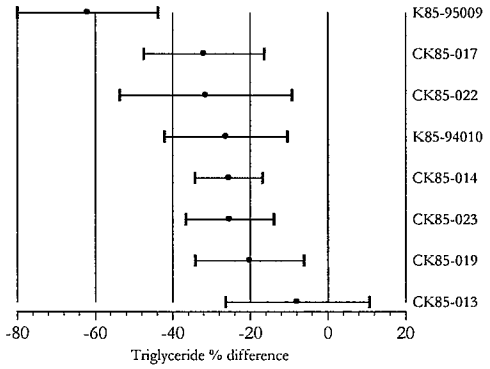
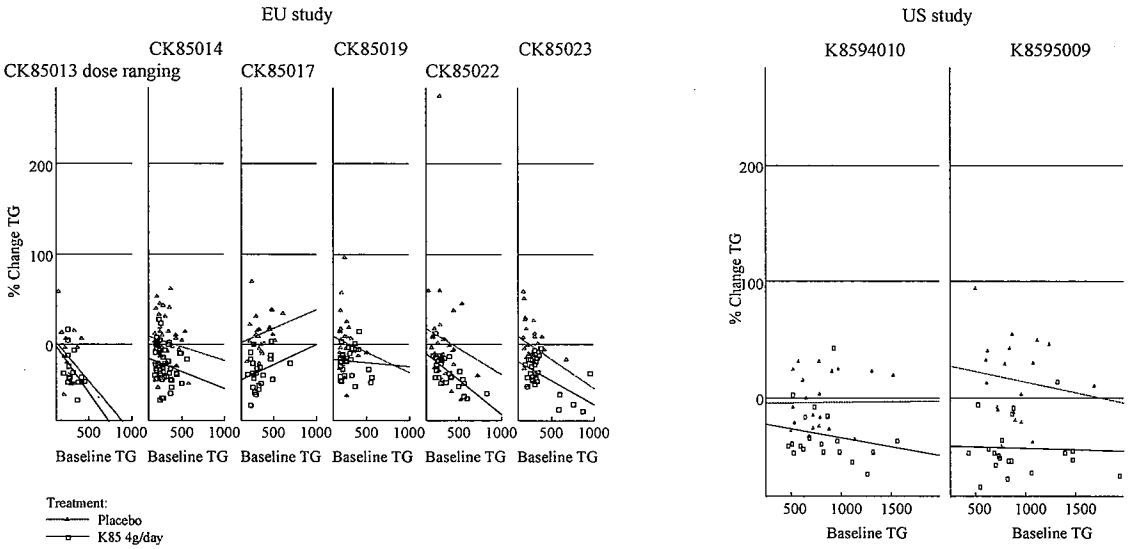


Figure 5 Triglyceride % change from baseline versus baseline – ITT



Mean percent change from baseline in LDL increased in the K85 treatment group compared to the placebo group. Table 12 displays the results of the analysis of covariance in LDL and Figure 6 displays the differences in LSM of LDL percent change from baseline with corresponding confidence intervals. Figure 7 displays individual patient percent changes from baseline versus baseline LDL.

Table 12 Summary results of analysis of covariance in LDL

Study	Placebo			K85			K85 minus Placebo			p-value
	n	LSM	SE	n	LSM	SE	LSM	SE	95% CI	
CK85-014	50	0.9	3.1	49	7.9	3.2	6.9	4.3	-1.6, 15.4	0.11
CK85-017	21	-4.9	9.9	28	22.9	8.7	27.8	13.0	1.5, 54.1	0.039
CK85-019	26	0.9	3.0	26	8.4	3.0	7.5	4.3	-1.1, -16.0	0.088
CK85-022	30	-0.7	2.8	30	7.6	2.8	8.3	4.0	0.3, 16.4	0.043
CK85-023	27	-8.8	3.0	24	2.0	3.2	10.9	4.5	1.9, 19.8	0.019
K85-94010	21	35.8	17.7	19	29.8	18.6	-6.0	26	-58.6, 46.7	0.82
K85-95009	20	4.5	8.2	22	42.1	7.8	37.6	11.1	15.2, 60.0	0.0016
CK85-013	17	4.8	3.7	16	7.3	3.8	2.5	5.3	-8.5, 13.4	0.65

Figure 6 LSM difference of LDL % change from baseline (K85 minus placebo)

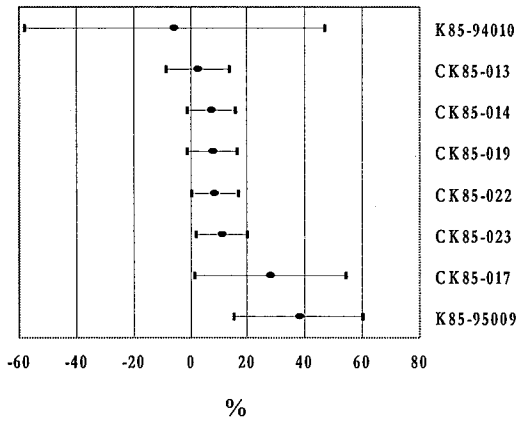


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Figure 7 Regression of LDL % change from baseline by baseline LDL

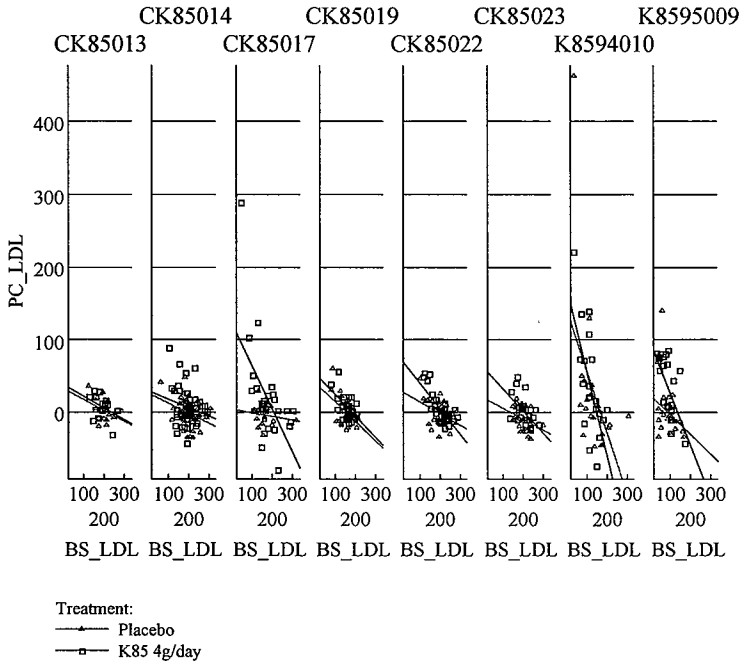


Figure 8 shows the percent change of LDL versus the percent change of triglyceride by pooled study. The correlation coefficients (r-square) were 0.0005 for the European study and 0.00023 for the US study. Hence, the triglycerides percent change is not correlated with the percent change in LDL indicating that changes in these 2 variables are not related on an individual patient basis.

Figure 8 Regressing of % change LDL by % change of TG - pooled

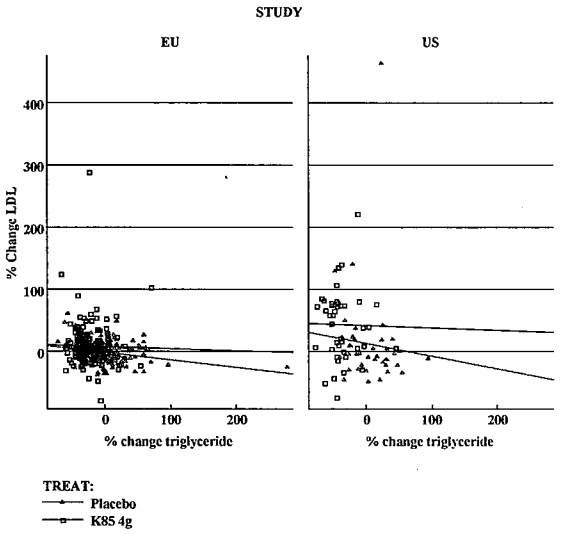
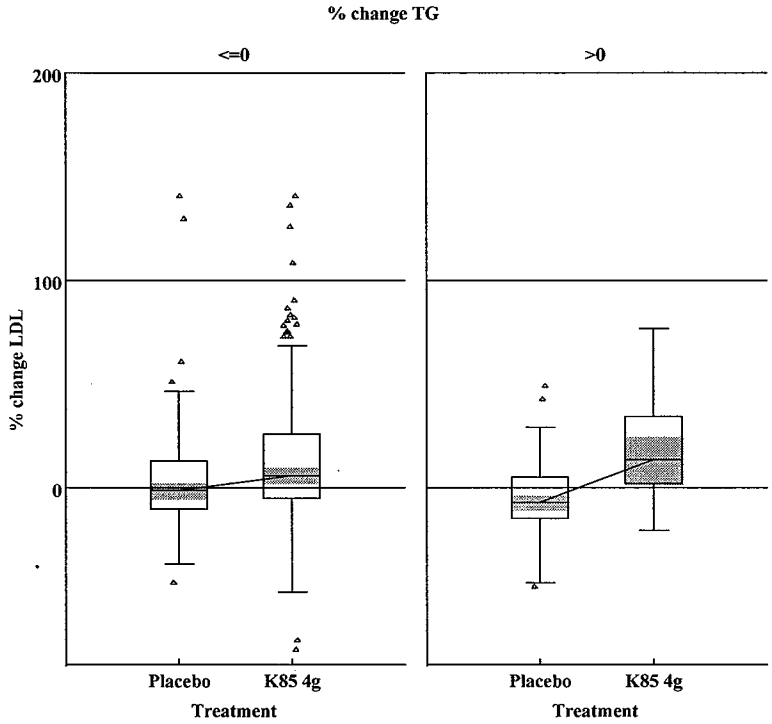


Table 13 and Figure 9 display the median percent change of LDL by percent increase or decrease of triglyceride at endpoint combining all studies. The median percent change in LDL decreased in placebo-treated patients and increased in K85-treated patients regardless of triglyceride percent increase or decrease. This finding is consistent with the data shown in Figure 8.

Table 13 Percent change of LDL by % increase or decrease of TG

	Placebo	K85
TG % change>0	n=97 -7%	n=20 13%
TG % change≤0	n=107 -2%	n=182 6%

Figure 9 Median % change of LDL by % increase or decrease of TG



3. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Gender, Race and Age

Results for these subgroups were consistent with the results for the entire population in terms of percent change from baseline in triglyceride.

4. SUMMARY AND CONCLUSIONS

The efficacy of K85 in triglyceride reduction was consistently better than placebo in the 8 Category I studies. The significance of the small increase in LDL requires clinical judgment. With only one small study of K85 as add-on therapy to simvastatin, the evidence is insufficient to warrant labeling for combination therapy of K85 and the statins.

5. LABELING COMMENTS:

The sponsor presented 8 clinical studies in Table 2 individually and corporately (pooled) and in Table 3 by severity. The presentation by severity is sufficient. The table should include the number of patients in each treatment group. The sponsor should present the 8 studies with graphs to depict the median treatment difference and corresponding confidence intervals for the 8 studies in percent change from baseline triglyceride. The ITT population should be presented instead of the Per Protocol population.

The inference from the published literature is not sufficient evidence to support the claim in [ ] b(4)

The indication for TG reduction should be limited to triglyceride monotherapy [ ] b(4)

Data concerning the increase in high-density lipoprotein cholesterol in type V hyperlipidemia should be limited to the clinical studies section, [ ] b(4)

6. APPENDICES
6.1 LIST OF TABLES

Table 1 Mean (95% C.I.) of % change from baseline for pooled analysis

	Pooled studies	Placebo n	Placebo BL	Placebo EP	Placebo %Chg	4 g K85 n	4 g K85 BL	4 g K85 EP	4 g K85 %Chg	**Mean difference**	95% C.I.
TG	European	173	309	303	1.5	177	316	230	-24.4	**-25.9**	(-31.7, -20.1)
	US	42	848	899	6.5	42	881	538	-38.1	**-44.4%**	(-56.9, 32)
LDL	European	171	186	181	-1.3	173	184	193	9.2	**9.9**	(4.8, 14.9)
	US	41	117	118	14.4	41	96	123	43.0	**15.8%**	(-12.1, 43.6)

Sponsor's descriptive statistics on lipids for the per protocol and intent-to-treat population

Table 1 Descriptive statistics of triglyceride levels (PP) – Study 85014

	Placebo (n=46)					K85 4g (n=49)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	296.8	(104.4)	255.0			284.2	(92.0)	258.0		
Average Endpoint Triglyceride	302.7	(118.9)	269.0			218.8	(83.3)	205.0		
Change in Average Value Trig -PP	5.8	(78.1)	1.0			-65.4	(62.6)	-60.0		
% Change in averaged value Trigs	3.0	(23.7)	0.5			-21.9	(20.4)	-25.4		

b(4)

Table 14 Descriptive statistics of triglyceride levels (ITT) – Study 85014

	Placebo (n=53)					K85 4g (n=52)				
	Mean	(S.D.)	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	305	(110.5)	258			294.5	(104.9)	264.5		
Singe Value Trig Endpoint LOCF	313.9	(140.4)	281			225.9	(104.8)	216.5		
Change in Triglycerides - ITT	8.9	(112.2)	-1			-68.6	(77.8)	-70.5		
% Change in single value Trigs	4.2	(31.7)	-0.5			-22.1	(25.6)	-23.3		

b(4)

Table 15 Descriptive statistics of total cholesterol levels (ITT)

	Placebo (n=53)				K85 4g (n=52)			
	Mean (Median)	S.D.	Min	Max	Mean	S.D.	Min	Max
Baseline Cholesterol	299.9 (301)	45.4			291.4 (282)	53.2		
Endpoint Cholesterol	300.5 (293)	60.8			292.8 (284)	59.8		
Change in Cholesterol	0.7 (0.0)	41.1			1.4 (-4.0)	39.3		
Percent Change in Cholesterol	0.4 (0.0)	12.4			0.9 (-1.2)	14.2		

b(4)

Table 16 Descriptive statistics of HDL (ITT)

	Placebo (n=53)				K85 4g (n=51)			
	Mean (Median)	S.D.	Min	Max	Mean (Median)	S.D.	Min	Max
Baseline HDL	40.0 (39.0)	11.3			41.3 (42.0)	12.2		
Endpoint HDL	41.3 (39.0)	10.9			42.8 (42.0)	11.5		
Change in HDL	1.3 (0.0)	7.9			1.3 (0.0)	10.8		
Percent Change in HDL	5.5 (0.0)	19.9			7.5 (0.0)	28.5		

b(4)

Table 17 Descriptive statistics of LDL (PP)

	Placebo					K85 4g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Baseline Derived LDL	43	202.8 (200.0)	41.2			47	192.5 (192.0)	41.8		
Protocol-defined Endpoint LDL	40	200.9 (202.5)	42.4			47	207.0 (204.0)	56.0		
Change in Last (PP) LDL	39	-1.8 (2.0)	35.5			46	14.7 (9.0)	40.4		
Percent Change in Last (PP) LDL	39	0.2 (0.9)	18.0			46	8.8 (4.8)	24.9		

b(4)

Table 18 Descriptive statistics of LDL (ITT)

	Placebo					K85 4g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Baseline Collected/Derived LDL	50	199.2 (199)	43.7			49	192.1 (192)	42.1		
Endpoint Collected/Derived LDL	53	198.1 (203)	47.3			51	203.4 (202)	56.3		
Change in Analysis LDL	50	-2.9 (2.0)	33.6			49	12.9 (8.0)	40.0		
Percent Change in Analysis LDL	50	-0.2 (0.9)	17.8			49	7.8 (3.6)	24.4		

b(4)

Table 19 Descriptive statistics of LDL (ITT)

	Placebo					K85 4g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Baseline APO_A1	50	1.21 (1.15)	0.30			51	1.23 (1.21)	0.23		
Endpoint APO_A1	53	1.23 (1.19)	0.30			52	1.20 (1.21)	0.21		
Change in APO_A1	50	0.02 (0.01)	0.23			51	-0.04 (-0.01)	0.27		
Percent Change in APO_A1	50	2.96 (0.49)	18.04			51	-0.95 (-0.95)	19.79		

b(4)

Table 20 Descriptive statistics of triglyceride levels (PP) – Study 85017

	Placebo (n=23)					K85 4g (n=24)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	356.4	(110.1)	330			314.3	(114)	278		
Average Endpoint Triglyceride	403.3	(161.2)	353			223.5	(115.9)	189.5		
Change in Average Value Trig -PP	46.9	(75.4)	30			-90.8	(52.6)	-84		
% Change in averaged value Trigs	11.8	(20.7)	10.5			-30.6	(17.7)	-32.4		

b(4)

Table 21 Descriptive statistics of triglyceride levels (ITT) – Study 85017

	Placebo (n=24)					K85 4g (n=29)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	358.5	(108.2)	340.0			305.8	(106.5)	276		
Singe Value Trig Endpoint LOCF	394.8	(183.2)	338.0			256.8	(138.1)	212		
Change in Triglycerides - ITT	38.4	(105.8)	6.0			-49	(94.9)	-65		
% Change in single value Trigs	8.7	(25.1)	1.8			-16.6	(32.1)	-19.8		

b(4)

Table 22 Descriptive statistics of triglyceride levels (PP) – Study 85019

	Placebo (n=26)					K85 4g (n=26)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	251	(76.7)	238			295.6	(113.4)	267.5		
Average Endpoint Triglyceride	253.9	(96.6)	233			239	(97.4)	208		
Change in Average Value Trig -PP	3	(74.1)	-10			-56.5	(64.8)	-43		
% Change in averaged value Trigs	2.2	(30.3)	-4.4			-18.8	(16.2)	-17.3		

b(4)

Table 23 Descriptive statistics of triglyceride levels (ITT) – Study 85019

	Placebo (n=26)					K85 4g (n=26)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	251	(76.7)	238			295.6	(113.4)	267.5		
Singe Value Trig Endpoint LOCF	263.8	(111.3)	251.5			223.7	(83)	201		
Change in Triglycerides - ITT	12.8	(83.6)	6			-71.9	(60.6)	-52.5		
% Change in single value Trigs	4.9	(33.1)	3			-23.3	(14.1)	-23.8		

b(4)

Table 24 Descriptive statistics of triglyceride levels (PP) – Study 85022

	Placebo (n=30)					K85 4g (n=28)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	374.1	(306.5)	305			350.2	(152.5)	286		
Average Endpoint Triglyceride	331.3	(197.2)	250.5			234.3	(63)	232		
Change in Average Value Trig -PP	-42.7	(303.5)	-23.5			-115.9	(109.9)	-69.5		
% Change in averaged value Trigs	2.5	(60.9)	-6.5			-28.1	(16.5)	-28.7		

b(4)

Table 25 Descriptive statistics of triglyceride levels (ITT) – Study 85022

	Placebo (n=30)					K85 4g (n=30)				
	Mean	(S.D.)	Median	Min	Max	Mean	(S.D.)	Median	Min	Max
Average Baseline Triglyceride	374.1	(306.5)	305			343.5	(149.3)	279		
Singe Value Trig Endpoint LOCF	310.9	(151.3)	267			242.5	(66.7)	235.5		
Change in Triglycerides - ITT	-63.1	(266.8)	-23			-101	(115)	-71.5		
% Change in single value Trigs	-5.6	(37)	-9.6			-23.4	(22.2)	-22.5		

b(4)

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Table 26 Descriptive statistics of triglyceride levels (PP) – Study 85023

	Placebo (n=28)				K85 4g (n=28)				
	Mean	(S.D.)	Median	Min	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	278.2	(104)	274.5		358.3	196.6	-294.5		
Average Endpoint Triglyceride	265.7	(96.9)	253		224.2	98.3	-201.5		
Change in Average Value Trig -PP	-12.5	(61.9)	-24.5		-134.1	153.4	-84		
% Change in averaged value Trigs	-2	(25.4)	-7.3		-31.8	18.4	-31.3		

b(4)

Table 27 Descriptive statistics of triglyceride levels (ITT) – Study 85023

	Placebo (n=26)					K85 4g (n=26)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	278.2	(104)	274.5			358.3	(196.6)	294.5		
Singe Value Trig Endpoint LOCF	259	(122.2)	239			245.6	(154.8)	216.5		
Change in Triglycerides - ITT	-19.3	(84.8)	-29			-112.7	(156.4)	-70.5		
% Change in single value Trigs	-4.4	(35)	-12.2			-27.6	(25.2)	-29.2		

b(4)

Table 28 Descriptive statistics of triglyceride levels (PP) – Study K85-94010

	Placebo (n=19)					K85 4g (n=19)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	771.1	248.3	725			836.1	(305.3)	801		
Average Endpoint Triglyceride	753.6	344.7	656			559.6	(259.9)	512		
Change in Average Value Trig -PP	-17.5	198.1	-40			-276.5	(267.9)	-241		
% Change in averaged value Trigs	-3.1	23.9	-7.6			-31.4	(24.5)	-38.8		

b(4)

Table 29 Descriptive statistics of triglyceride levels (ITT) – Study K85-94010

	Placebo (n=21)					K85 4g (n=20)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	823	(286.9)	786			840.1	(297.7)	810.5		
Singe Value Trig Endpoint LOCF	824.6	(436.2)	663			584.3	(310.1)	522.5		
Change in Triglycerides - ITT	1.7	(406.6)	-102			-255.8	(280.1)	-254		
% Change in single value Trigs	2.9	(45.9)	-14.3			-30.8	(27.7)	-38.4		

b(4)

Table 30 Descriptive statistics of triglyceride levels (PP) – Study K85-95009

	Placebo (n=19)					K85 4g (n=20)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	887.9	(274.7)	863			926.1	(391)	817.5		
Average Endpoint Triglyceride	1013	(418.5)	859			523.9	(306.5)	390.5		
Change in Average Value Trig -PP	125.1	(293.7)	171			-402.3	(315.6)	-381.5		
% Change in averaged value Trigs	15.6	(35.5)	12.4			-43.1	(23.2)	-47.7		

b(4)

Table 31 Descriptive statistics of triglyceride levels (ITT) – Study K85-95009

	Placebo (n=21)					K85 4g (n=20)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	872.2	(265.6)	841			919	(380.8)	817.5		
Singe Value Trig Endpoint LOCF	967.3	(476.2)	828			459.9	(224.3)	406		
Change in Triglycerides - ITT	95.1	(366.1)	107			-459	(247.4)	-443		
% Change in single value Trigs	11.1	(39.6)	6.4			-49.5	(17)	-50.7		

b(4)

Table 32 Descriptive statistics of triglyceride levels (PP) – Study CK85-013

Placebo & Omacor 4 g

	Placebo (n=13)					K85 4g (n=12)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	270.2	(68.9)	260			307.8	(71.7)	280		
Singe Value Trig Endpoint LOCF	227.8	(90.3)	212			216.8	(48.7)	212		
Change in Triglycerides - ITT	-42.4	(53.7)	-15			-91	(58.7)	-87		
% Change in single value Trigs	-16.4	(19.7)	-8.2			-28.1	(15.3)	-30		

b(4)

Table 33 Descriptive statistics of triglyceride levels (PP) – Study CK85-013

Omacor 2g & Omacor 8 g

	K58 2 g (n=7)					K85 8 g (n=8)				
	Mean	S.D.	Median	Min	Max	Mean	S.D.	Median	Min	Max
Average Baseline Triglyceride	252	(77.2)	212			242.8	(73.1)	219.5		
Singe Value Trig Endpoint LOCF	219	(54)	224			138.9	(25.4)	136		
Change in Triglycerides - ITT	-33	(73.7)	-17			-103.9	(65)	-92		
% Change in single value Trigs	-9.7	(24.4)	-8.2			-40.4	(14.4)	-40.9		

b(4)

Table 34 Descriptive statistics of triglyceride (ITT) – Study CK85013

Placebo & Omacor 4g

	Placebo					K85 4g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Average Baseline Triglyceride	13	270.2 (260.0)	68.9			13	308.2 (299.0)	68.7		
Singe Value Trig Endpoint LOCF	17	217.5 (189.0)	87.5			15	209.7 (214.0)	53.3		
Change in Triglycerides - ITT	13	-44.6 (-27.0)	66.3			12	-98.1 (-94.0)	68.9		
% Change in single value Trigs	13	-17.1 (-13.6)	24.6			12	-30.0 (-35.6)	18.3		

b(4)

Omacor 2 g & Omacor 8g

	K85 2 g					K85 8g				
	n	Mean (Median)	S.D.	Min	Max	n	Mean (Median)	S.D.	Min	Max
Average Baseline Triglyceride	7	252.0 (212.0)	77.2			11	232.1 (218.0)	66.5		
Singe Value Trig Endpoint LOCF	14	201.6 (199.0)	75.9			20	145.2 (131.0)	57.9		
Change in Triglycerides - ITT	7	-52.1 (-66.0)	95.5			11	-94.9 (-75.0)	70.4		
% Change in single value Trigs	7	-14.7 (-26.4)	34.2			11	-37.5 (-33.9)	15.7		

b(4)

Amendment 7 included patients with single baseline value as well as average of 2 baseline values of triglycerides in the ITT population. Table 36 displays the descriptive statistics.

Table 35 Descriptive statistics of triglyceride (ITT) – Study CK85013

Placebo & Omacor 4g

	Placebo						K85 4g					
	n	Mean	(SD)	Median	Min	Max	n	Mean	(SD)	Median	Min	Max
Average Baseline Triglyceride	17	263.1	(70.5)	260			15	299.6	(74)	261		
Singe Value Trig Endpoint LOCF	17	217.5	(87.5)	189			15	209.7	(53.3)	214		
Change in Triglycerides - ITT	17	-45.5	(72.6)	-28			15	-89.9	(73.3)	-94		
% Change in single value Trigs	17	-15.3	(29.8)	-13.7			15	-27.7	(20.7)	-35.3		

b(4)

Table 36 Descriptive statistics of triglyceride (ITT) – Study CK85013

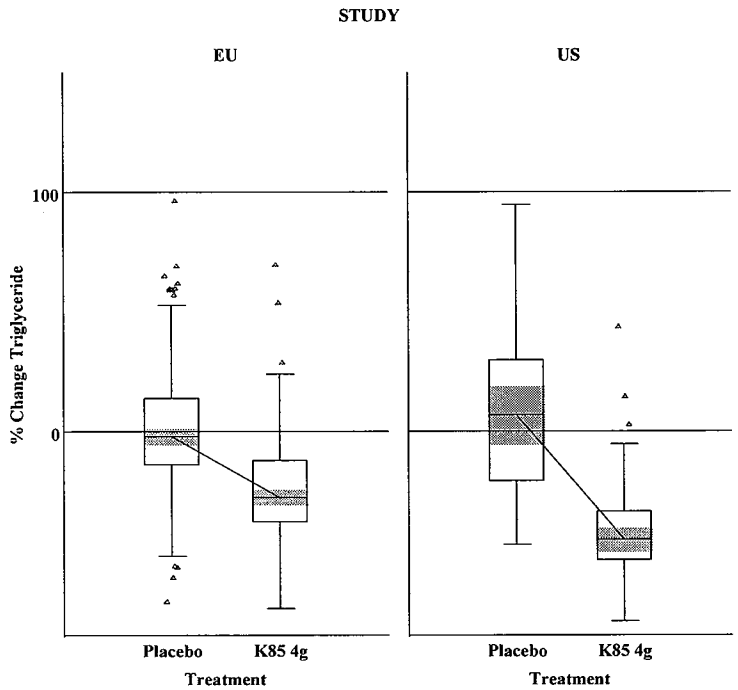
Omacor 2 g & Omacor 8g

	Omacor 2 g						Omacor 8 g					
	n	Mean	(SD)	Median	Min	Max	n	Mean	(SD)	Median	Min	Max
Average Baseline Triglyceride	16	257.4	(68)	242.5			18	236.4	(88.5)	216.5		
Singe Value Trig Endpoint LOCF	16	193.6	(74.4)	190.5			18	146.1	(60.7)	131		
Change in Triglycerides - ITT	16	-63.8	(83.6)	-75.5			18	-90.3	(65.1)	-76.5		
% Change in single value Trigs	16	-21.9	(31)	-29.6			18	-36.7	(17.2)	-34.4		

b(4)

6.2 LIST OF FIGURES

1. Box plot of pooled Category I studies - % change of TG



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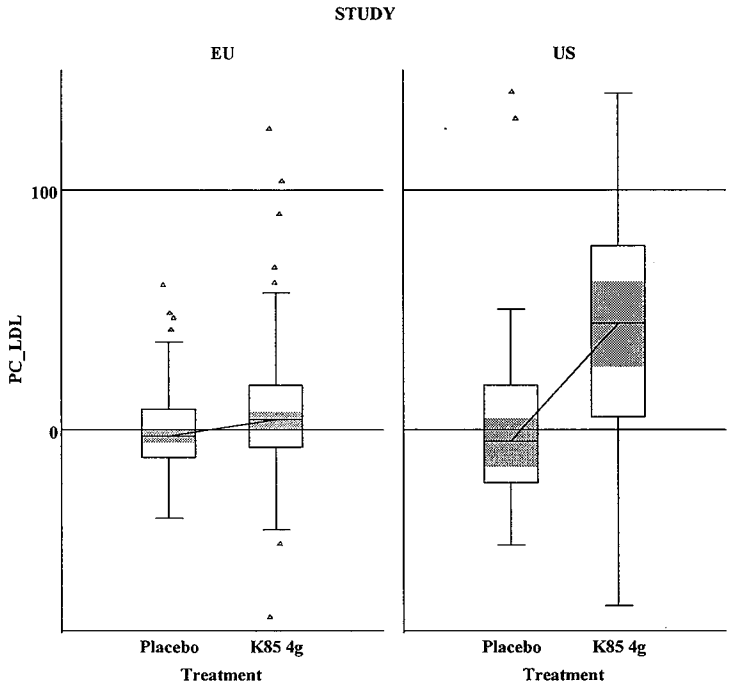
2. Box plot of pooled Category I studies -% change of LDL



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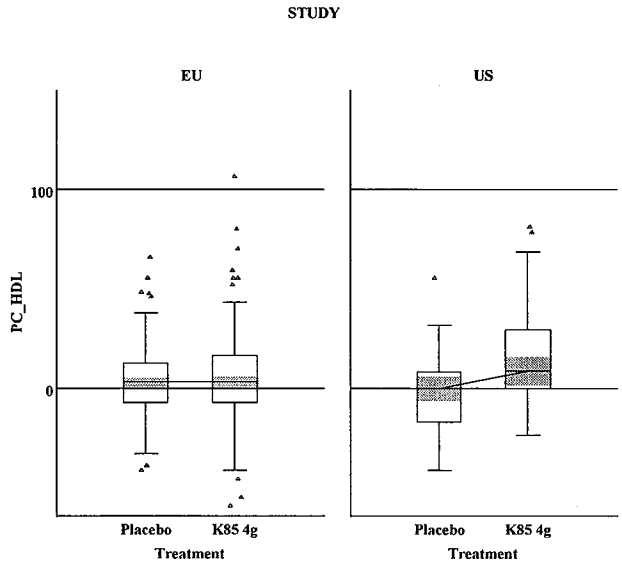
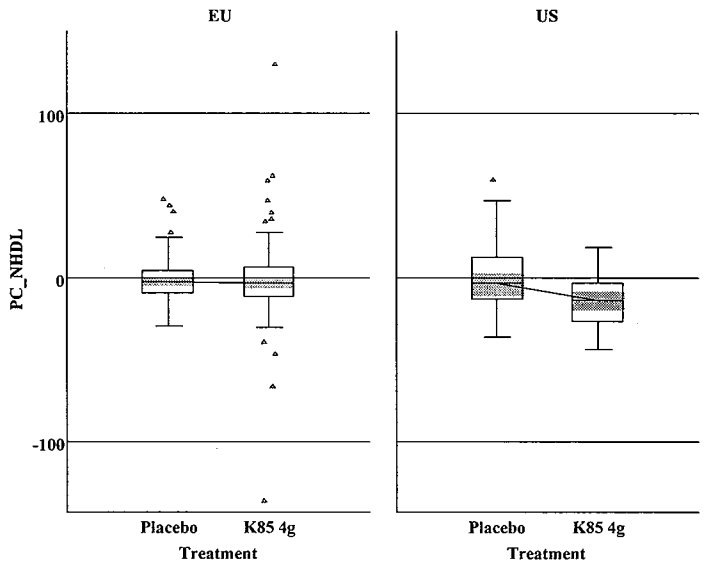
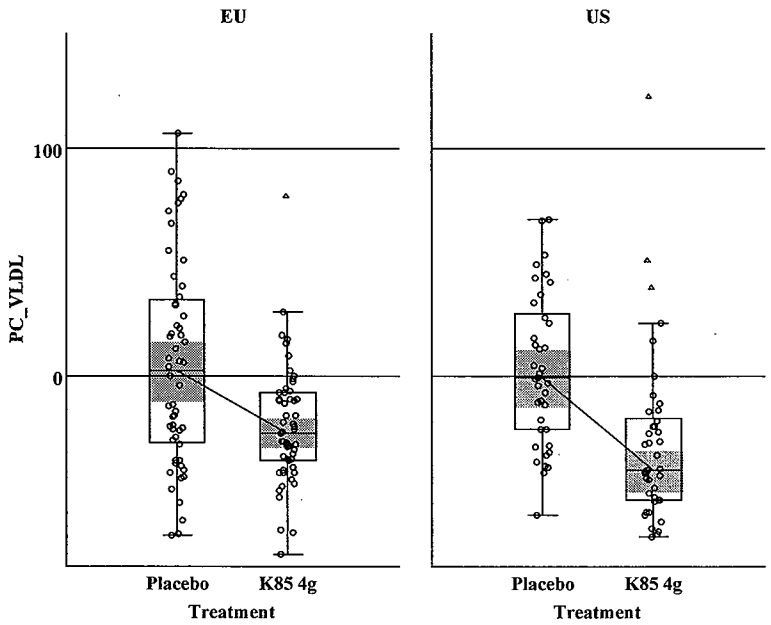
3. Box plot of pooled Category I studies -% change of HDL



4. Box plot of pooled Category I studies -% change of NHDL



5. Box plot of pooled Category I studies -% change of VLDL



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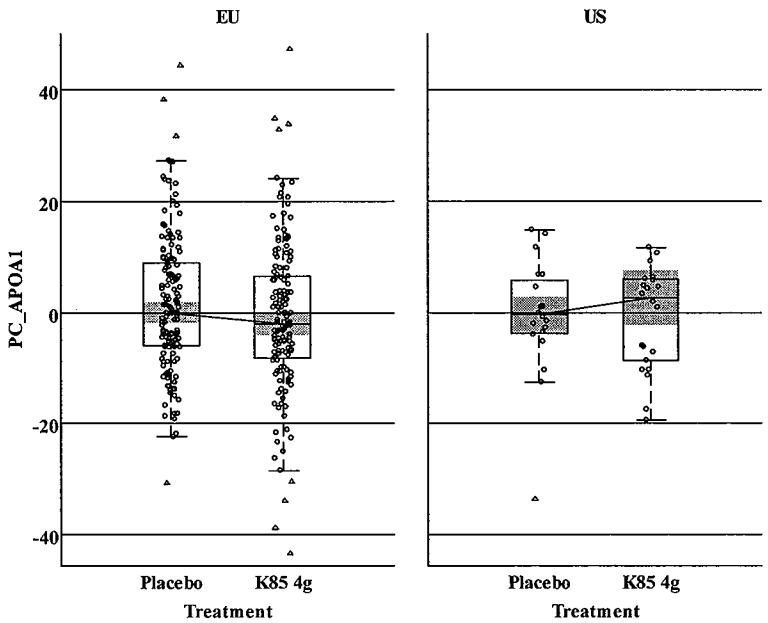
6. Box plot of pooled Category I studies -% change of APOA1



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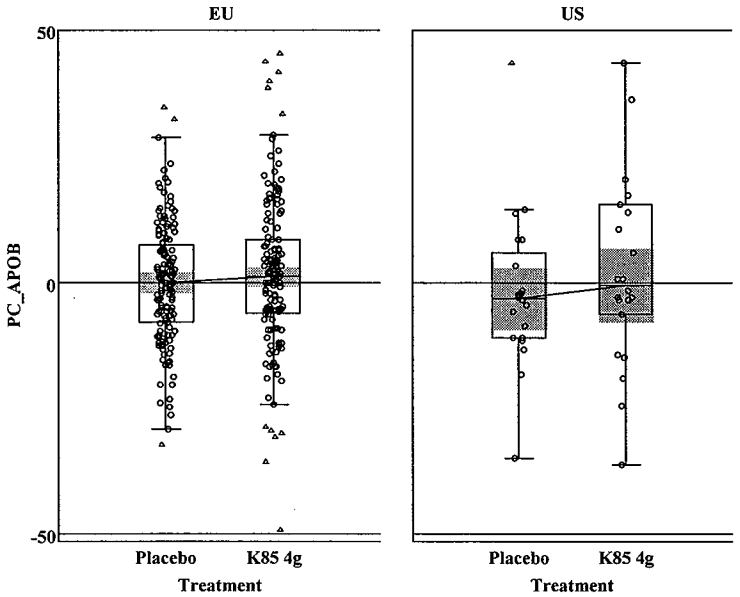
7. Box plot of pooled Category I studies -% change of APOB



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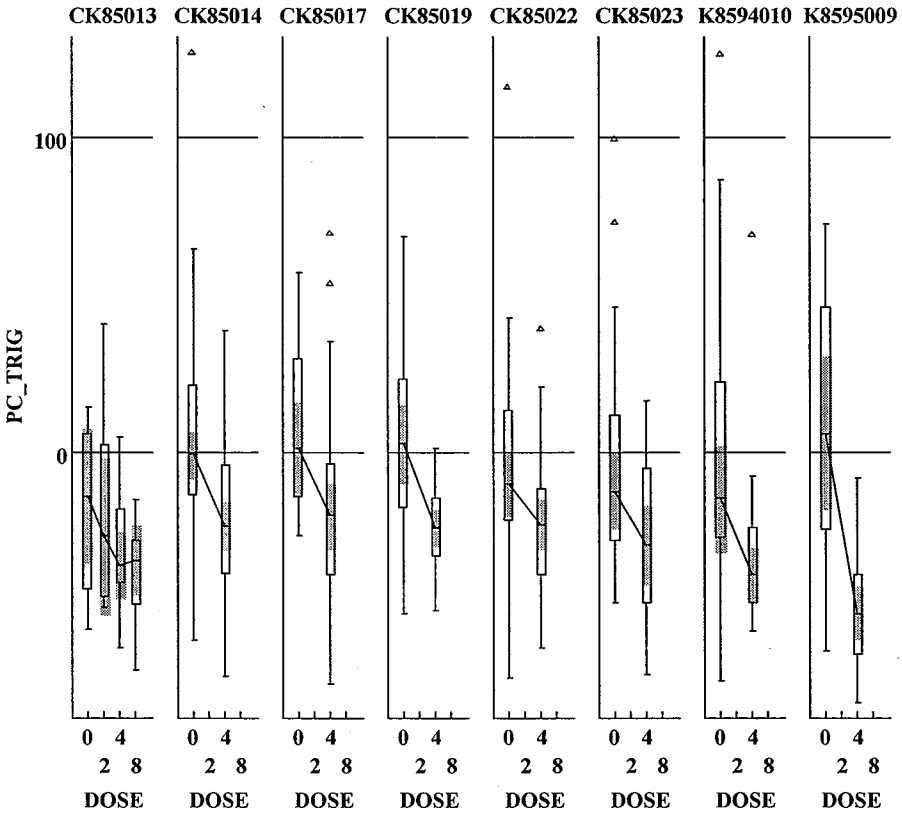
8. Box plot of individual Category I studies - % change of TG



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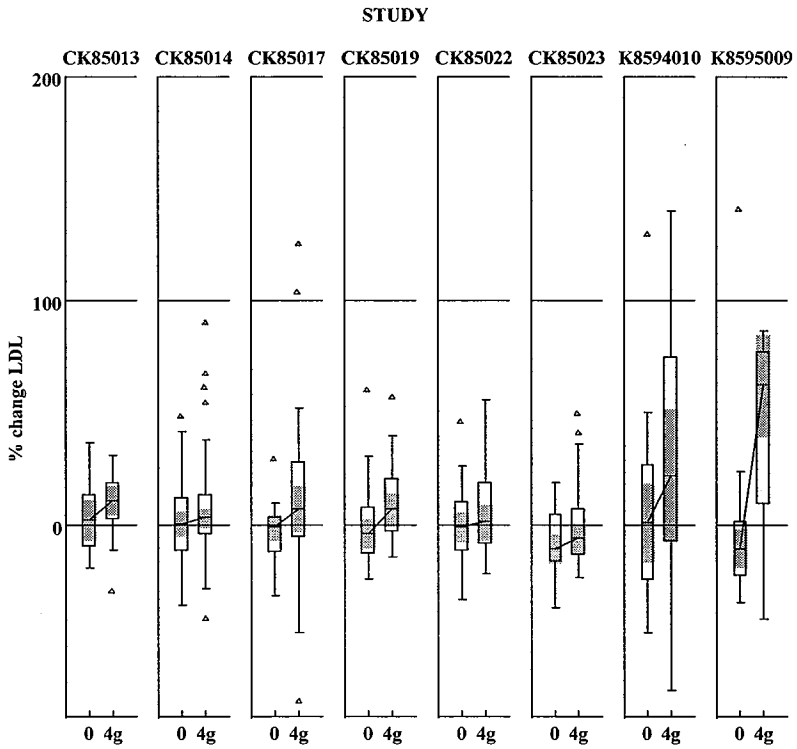
9. Box plot of individual Category I studies -% change of LDL



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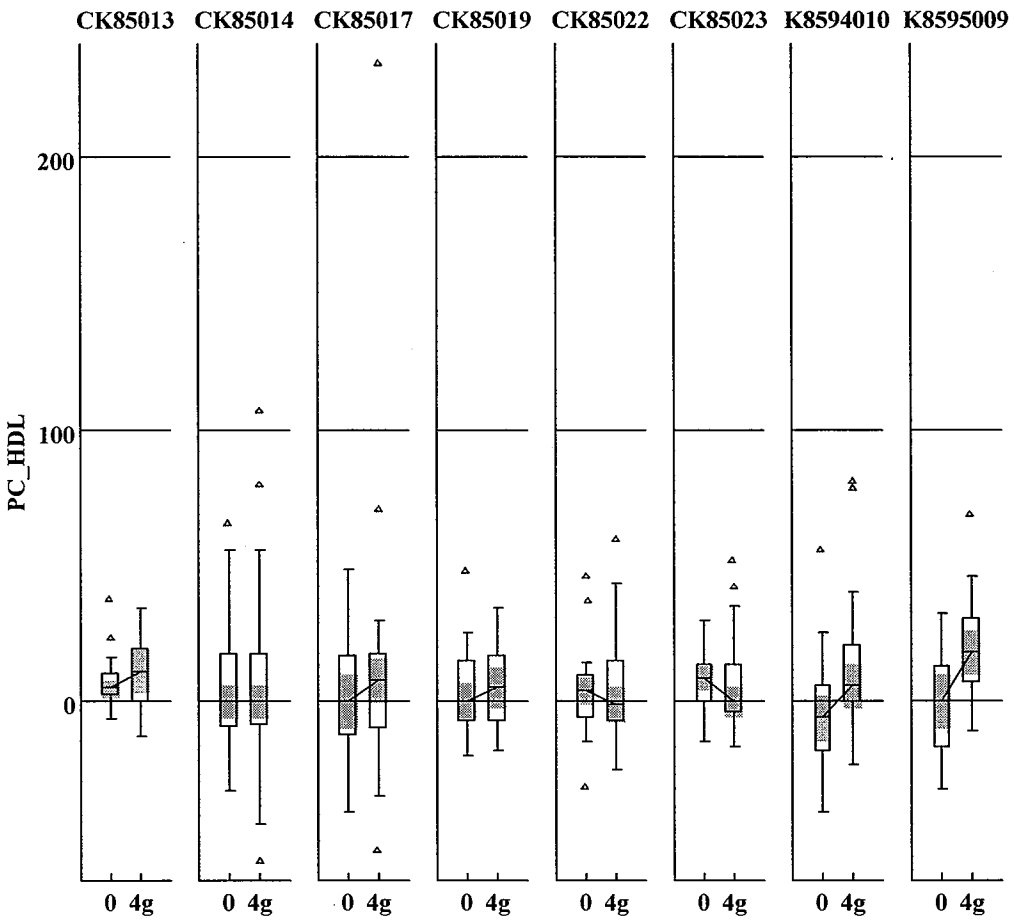
10. Box plot of individual Category I studies -% change of HDL



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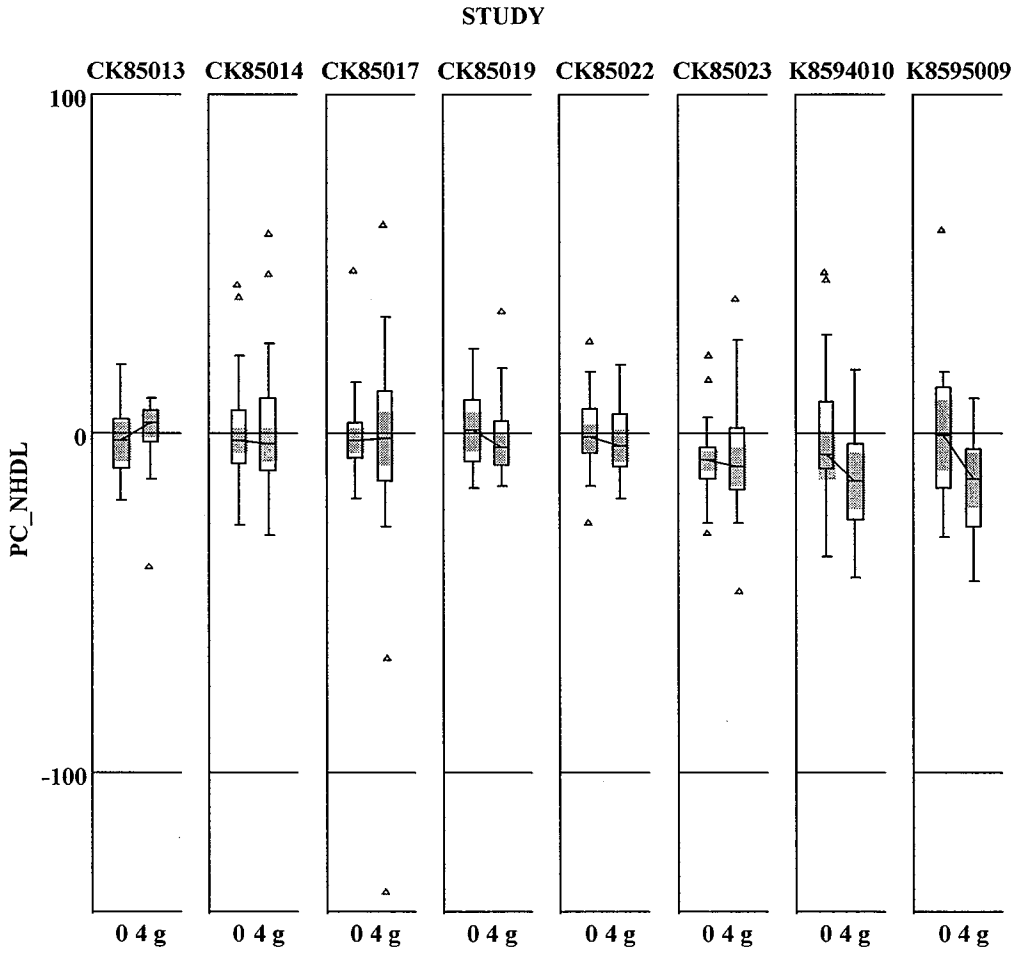
11. Box plot of individual Category I studies -% change of NHDL



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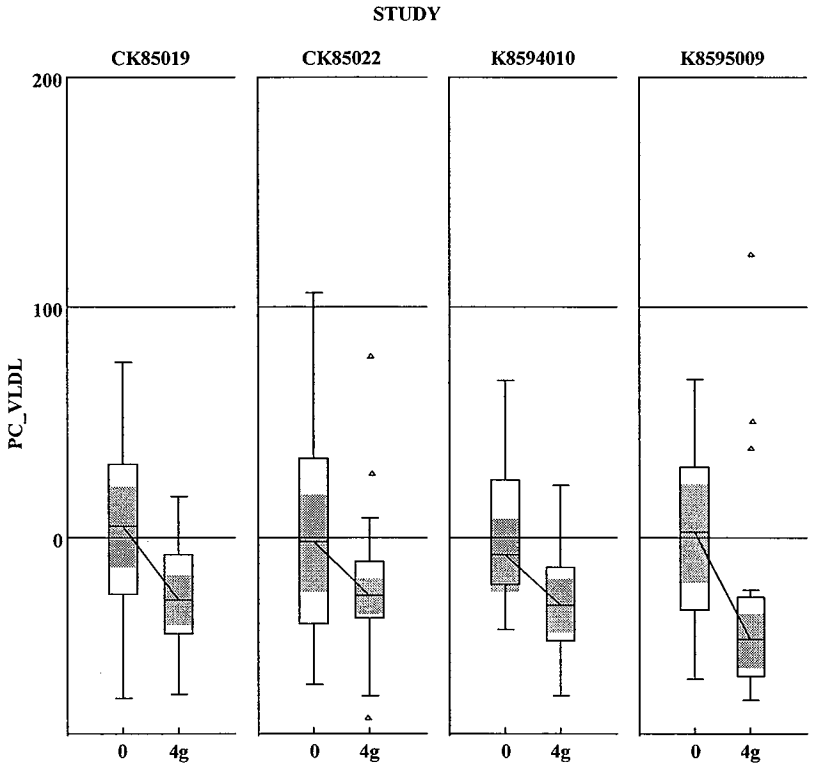
12. Box plot of individual Category I studies -% change of VLDL



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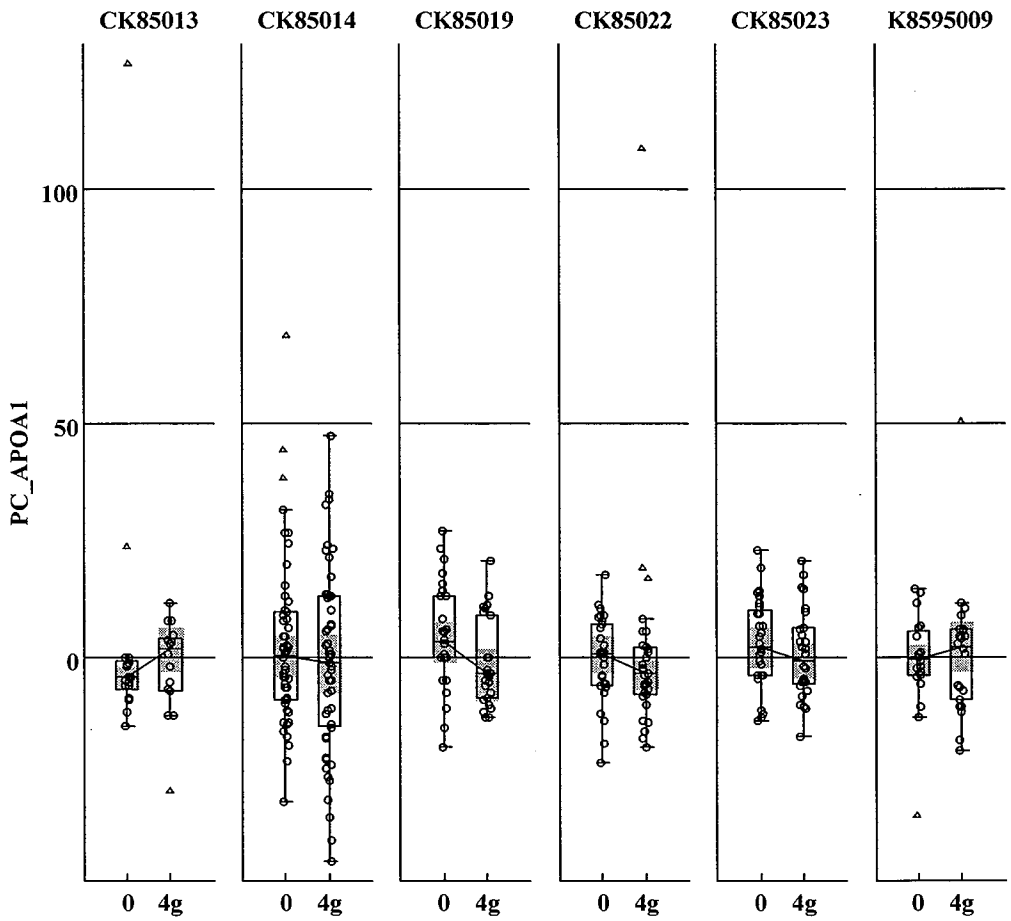
13. Box plot of individual Category I studies -% change of APOA1



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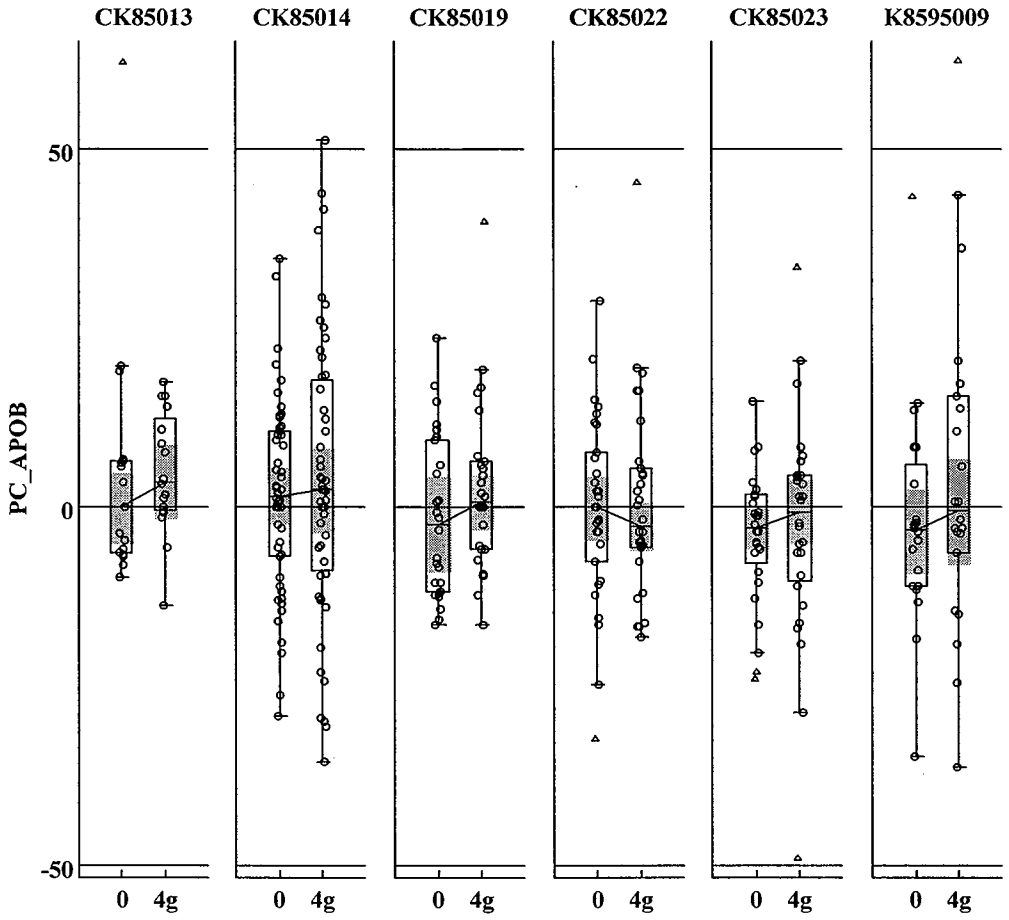
14. Box plot of individual Category I studies -% change of APOB



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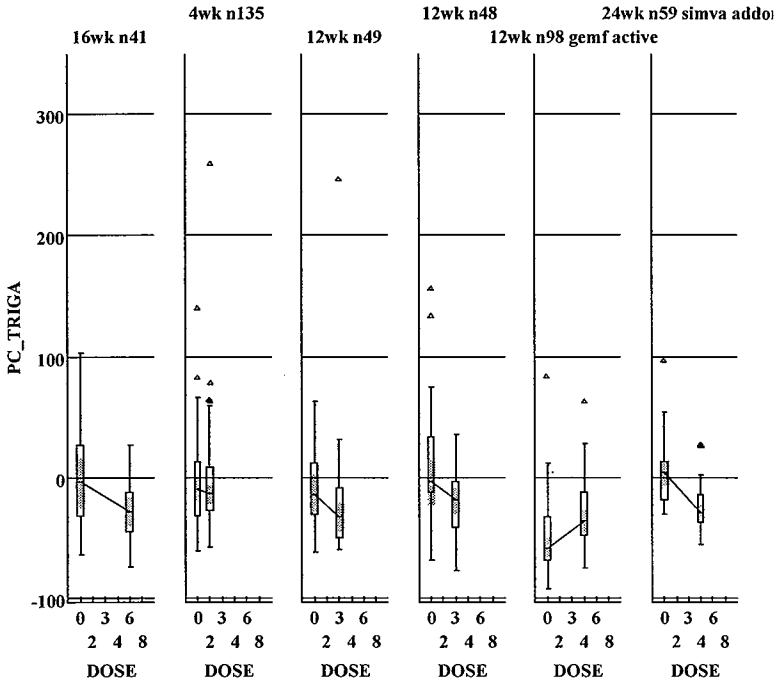
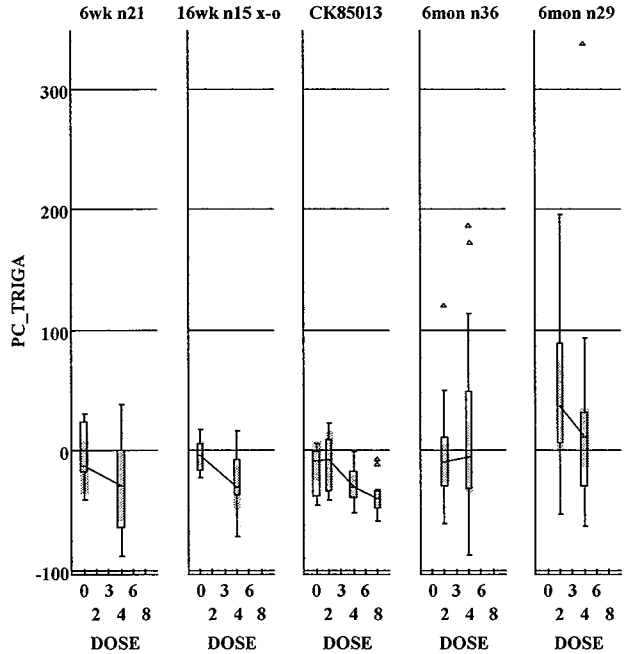
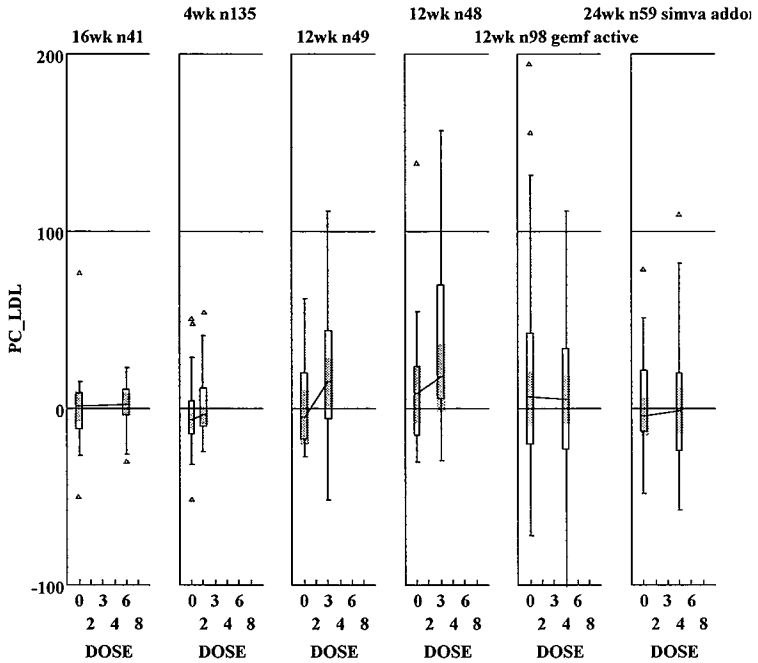
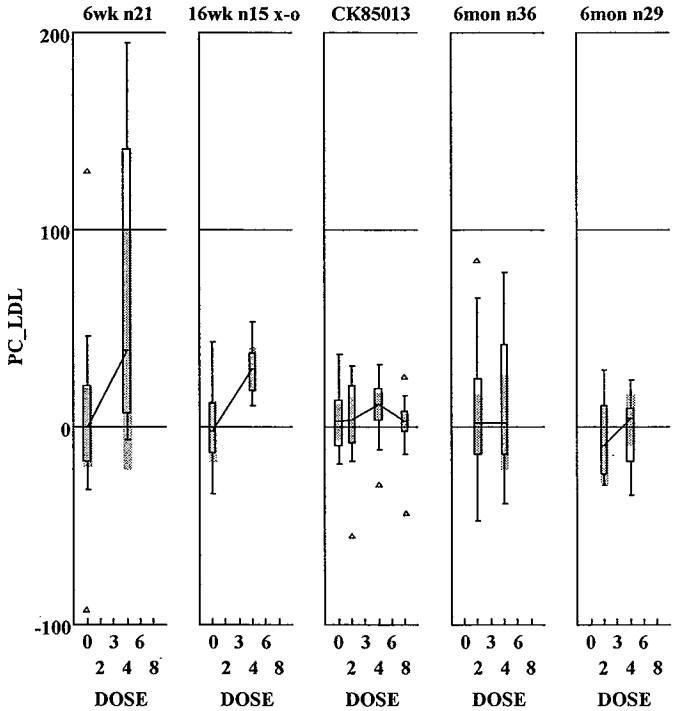
15. Median % change from baseline triglyceride - Category 2 Study



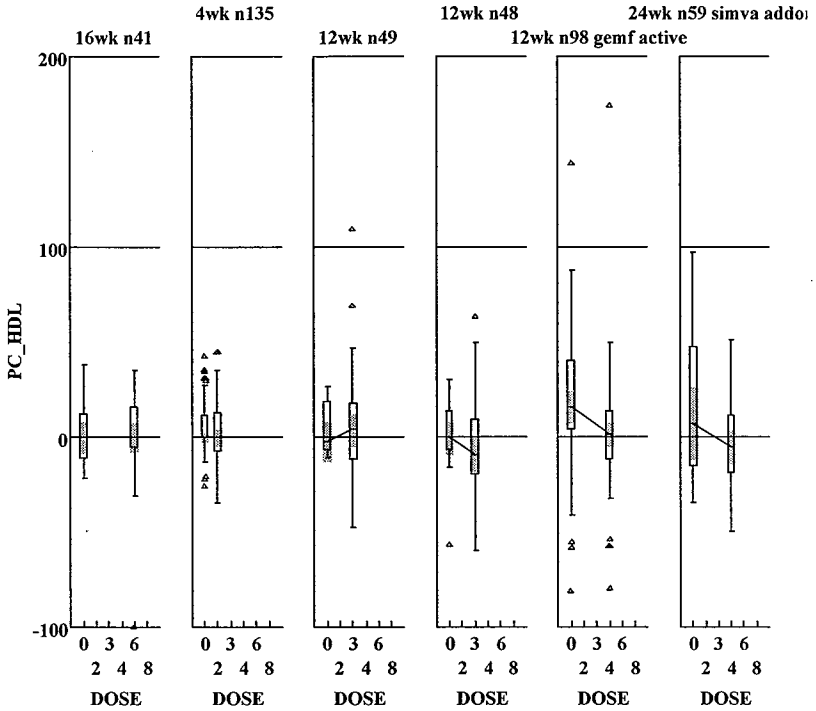


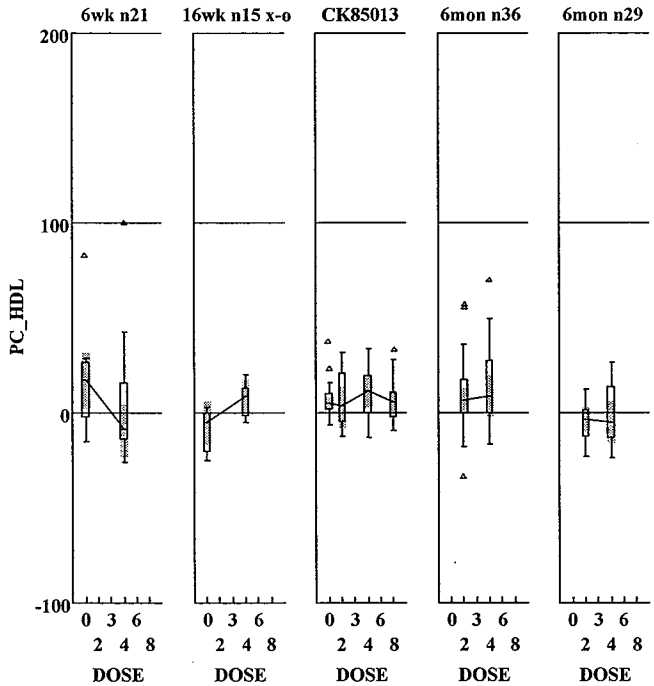
16. Median % change from baseline LDL - Category 2 Study



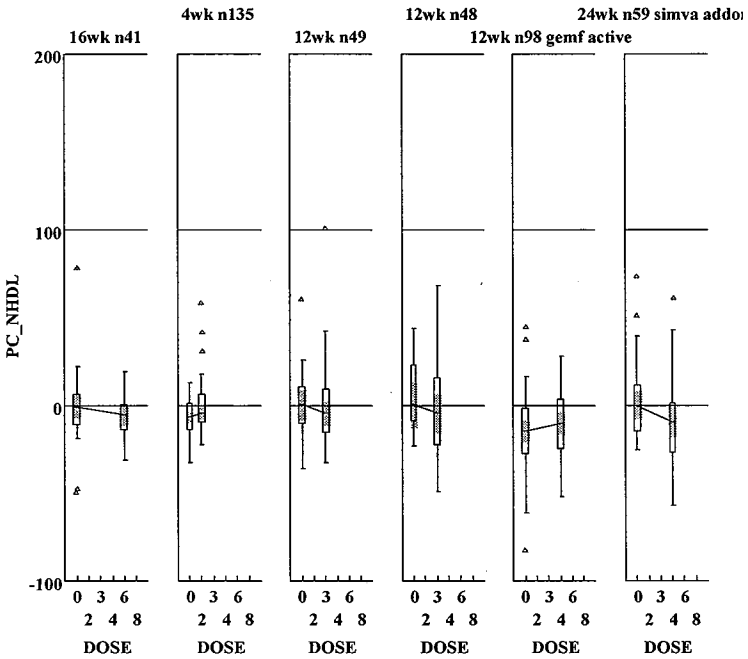


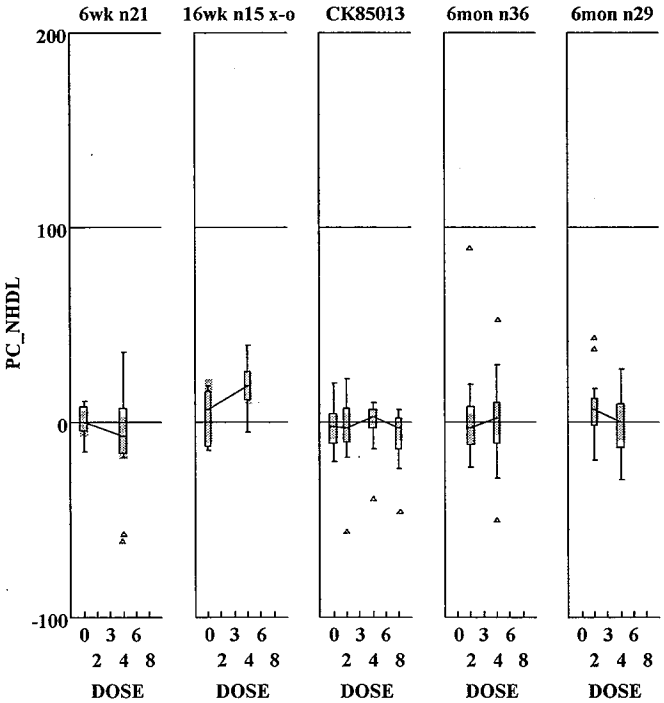
17. Median % change from baseline HDL - Category 2 Study



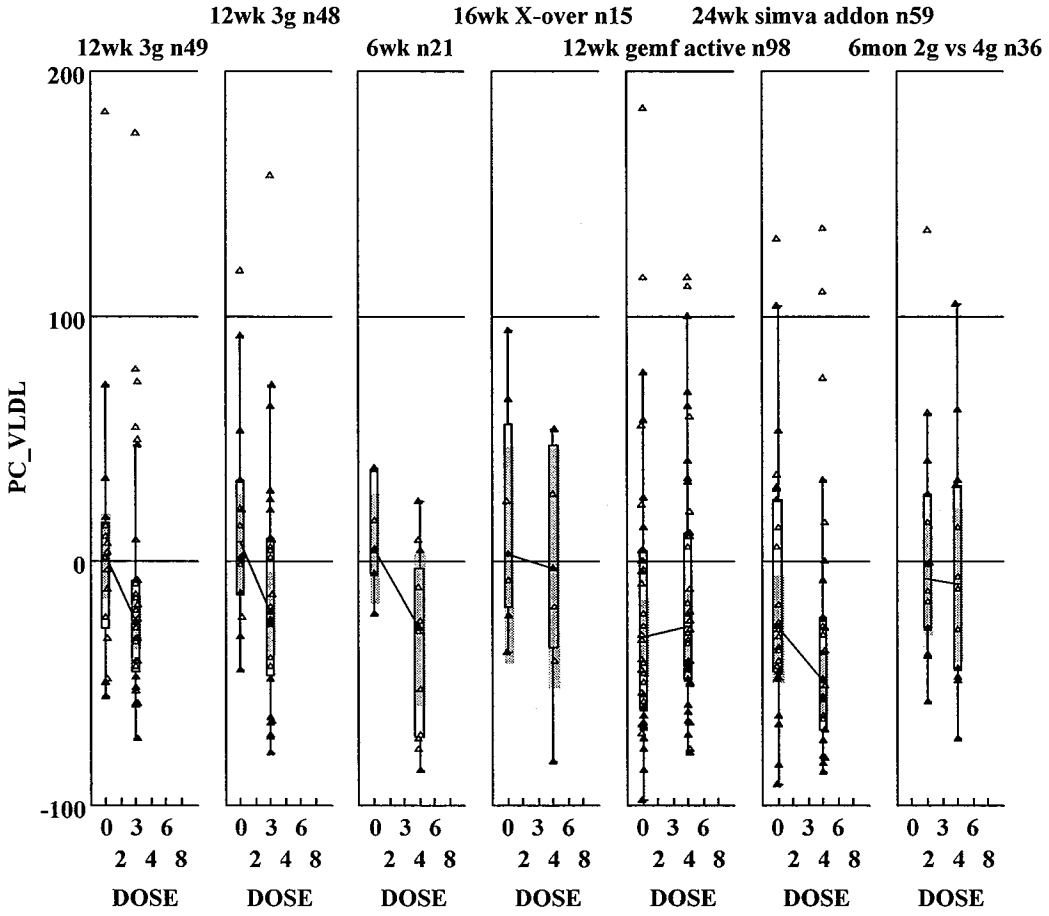


18. Median % change from baseline NHDL - Category 2 Study





19. Median % change from baseline VLDL - Category 2 Study



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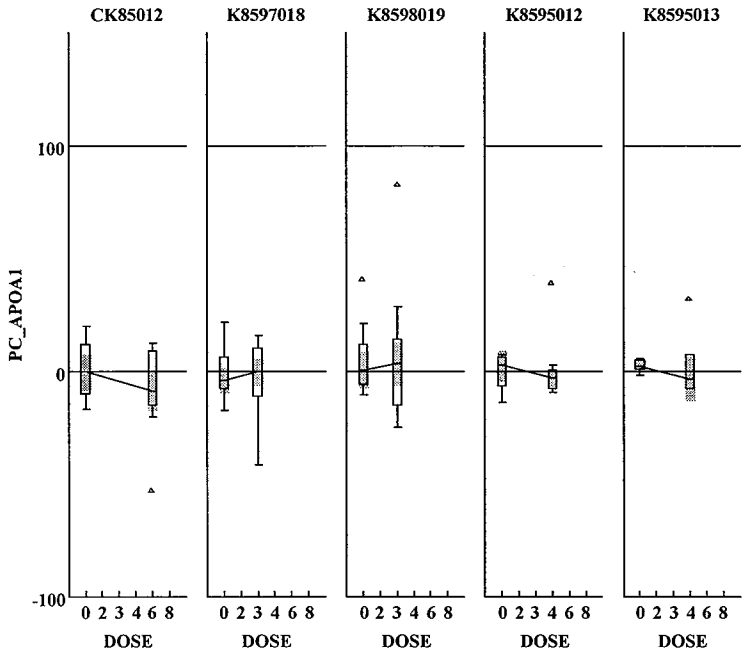
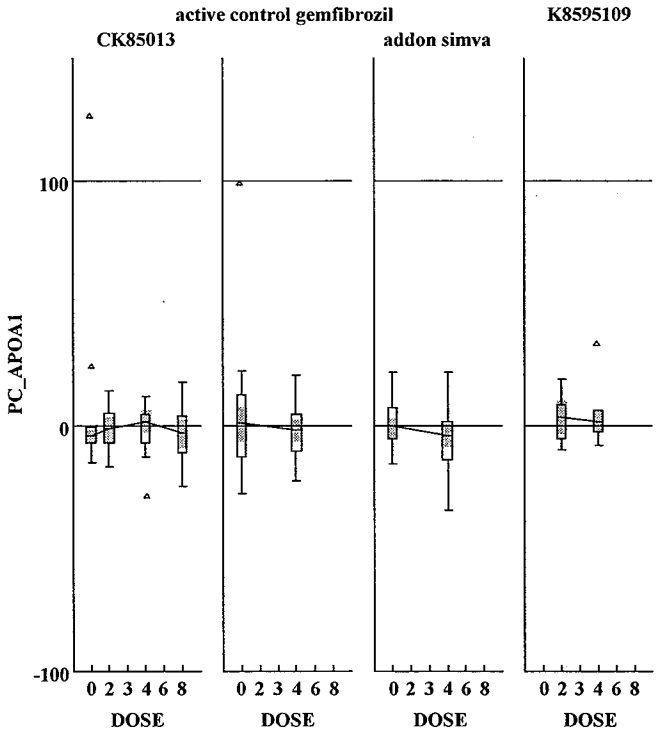
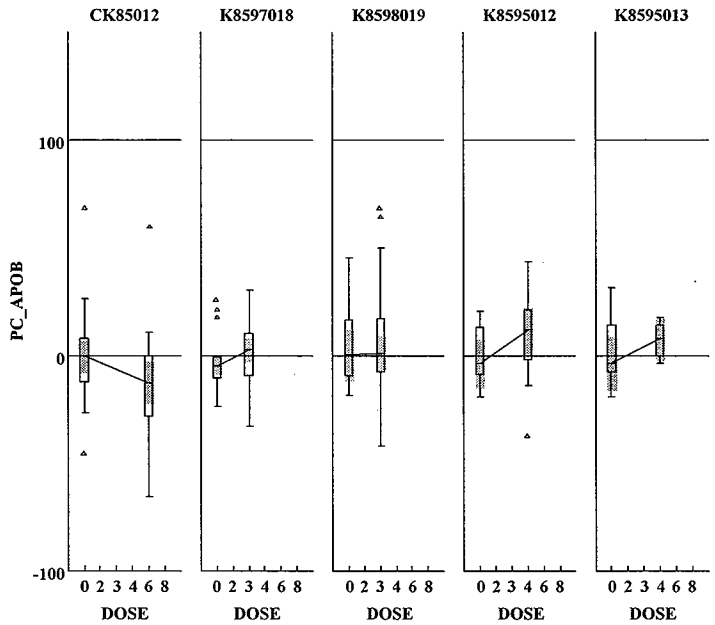
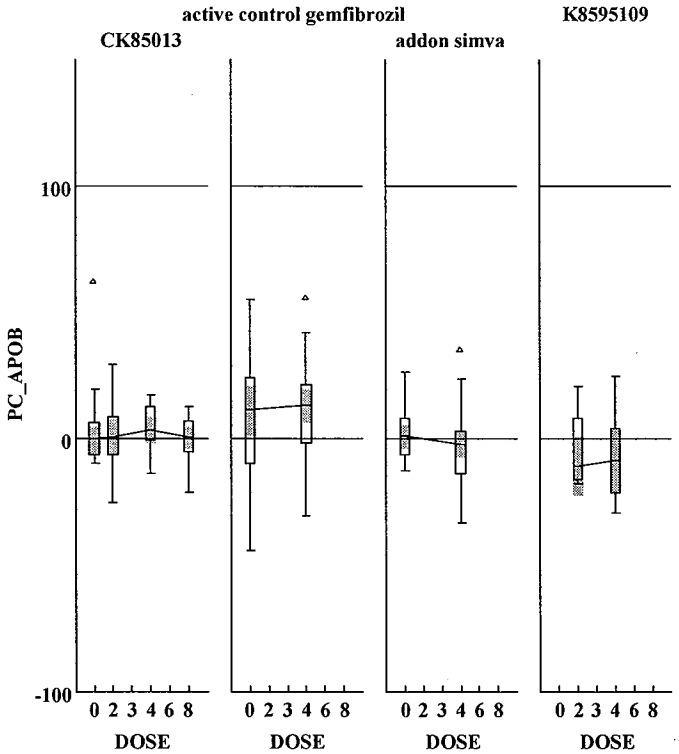
20. Median % change from baseline ApoA1 - Category 2 Study





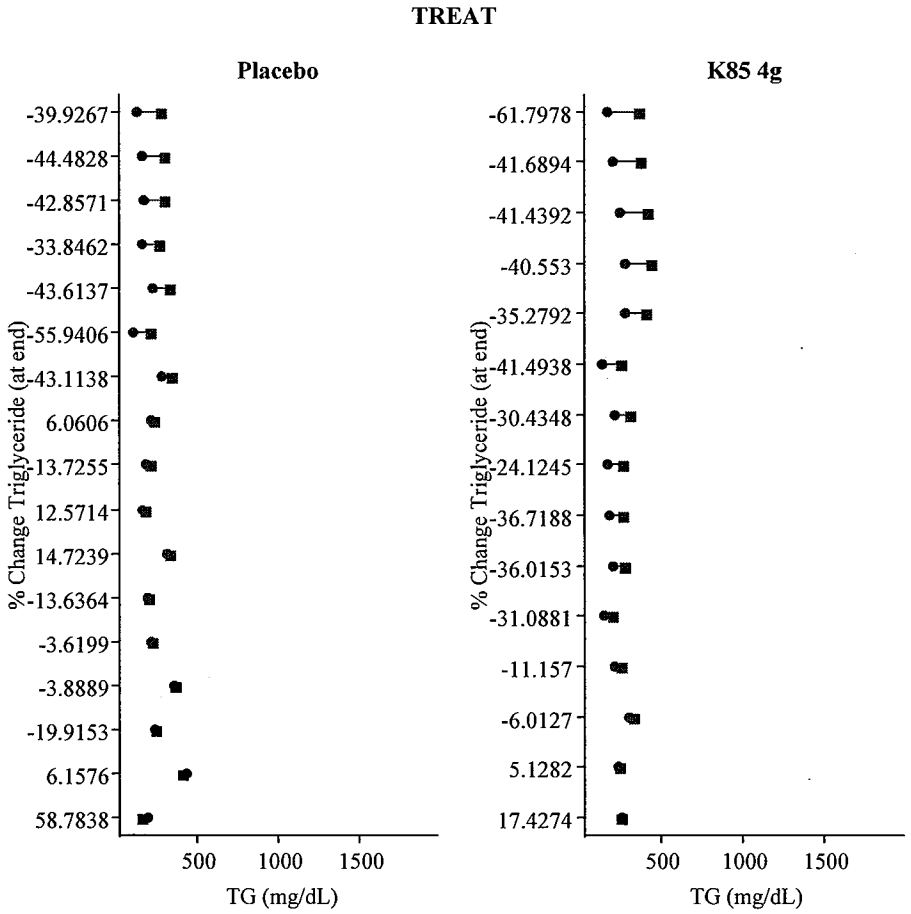
21. Median % change from baseline ApoA1 - Category 2 Study





22. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85013

STUDY
CK85013



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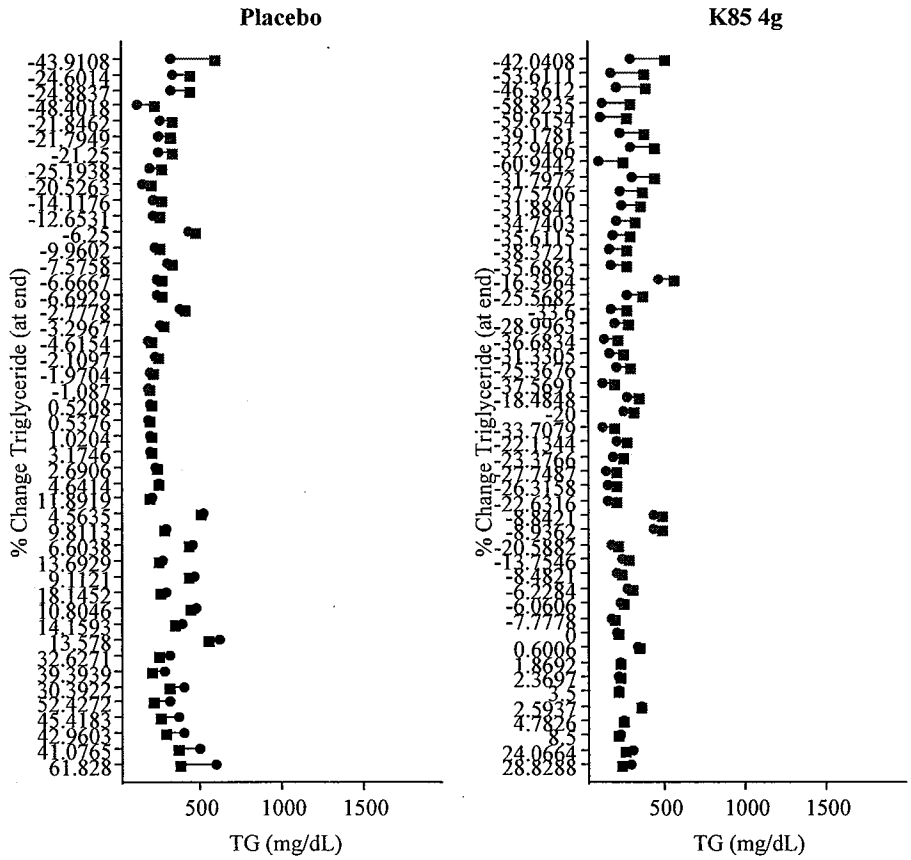
23. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85014

STUDY
CK85014

TREAT



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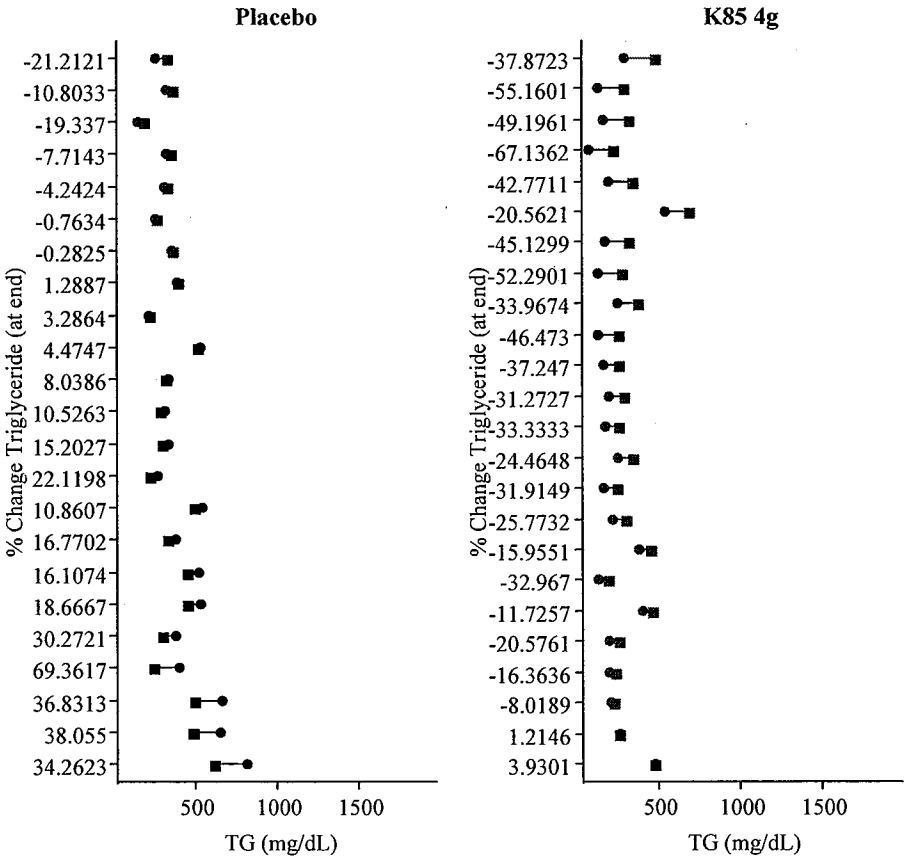
24. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85017

STUDY
CK85017

TREAT



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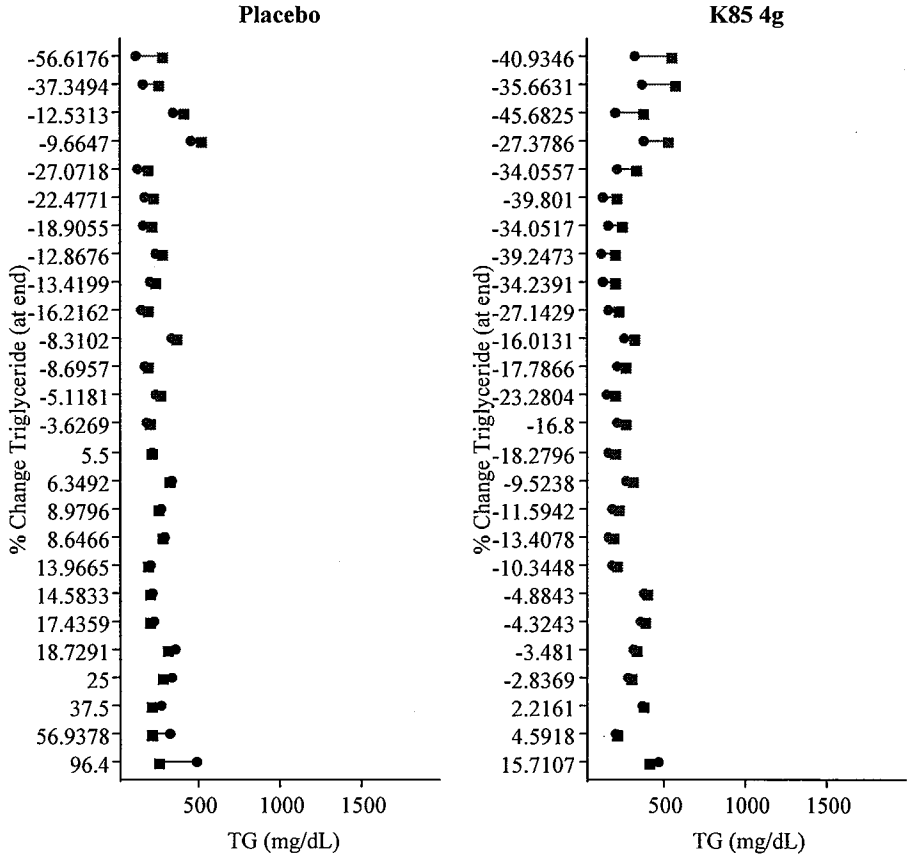
25. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG - 85019

STUDY
CK85019

TREAT



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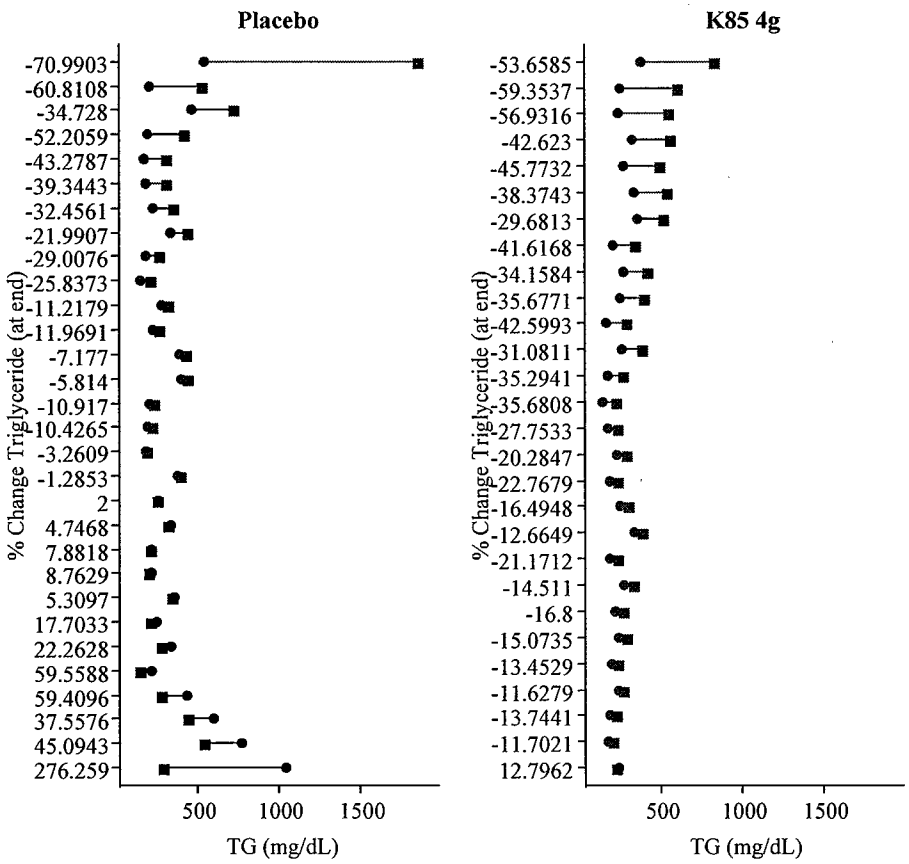
26. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG - 85020

STUDY
CK85022

TREAT



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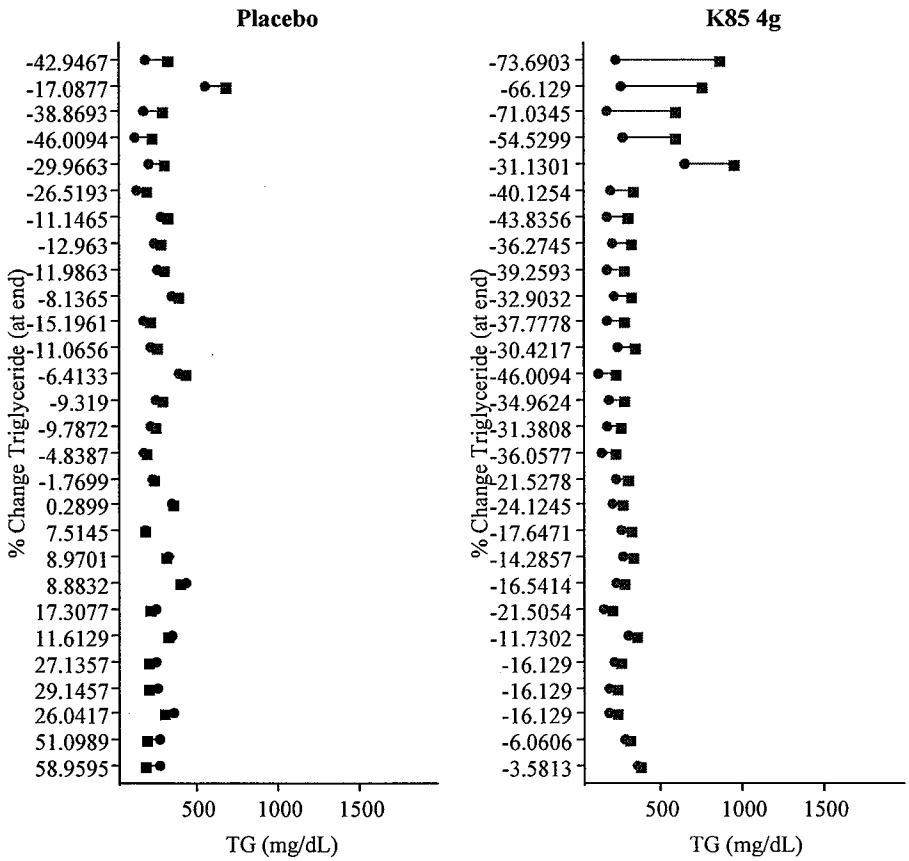
27. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85023

STUDY
CK85023

TREAT



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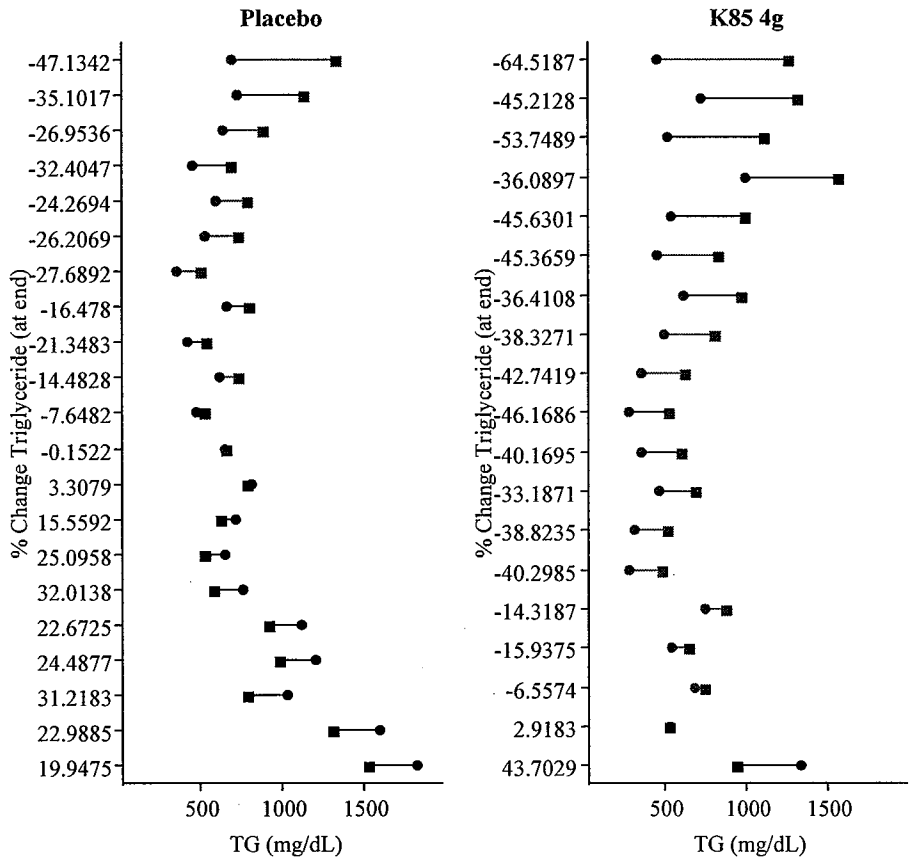
28. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 94010

STUDY
K8594010

TREAT



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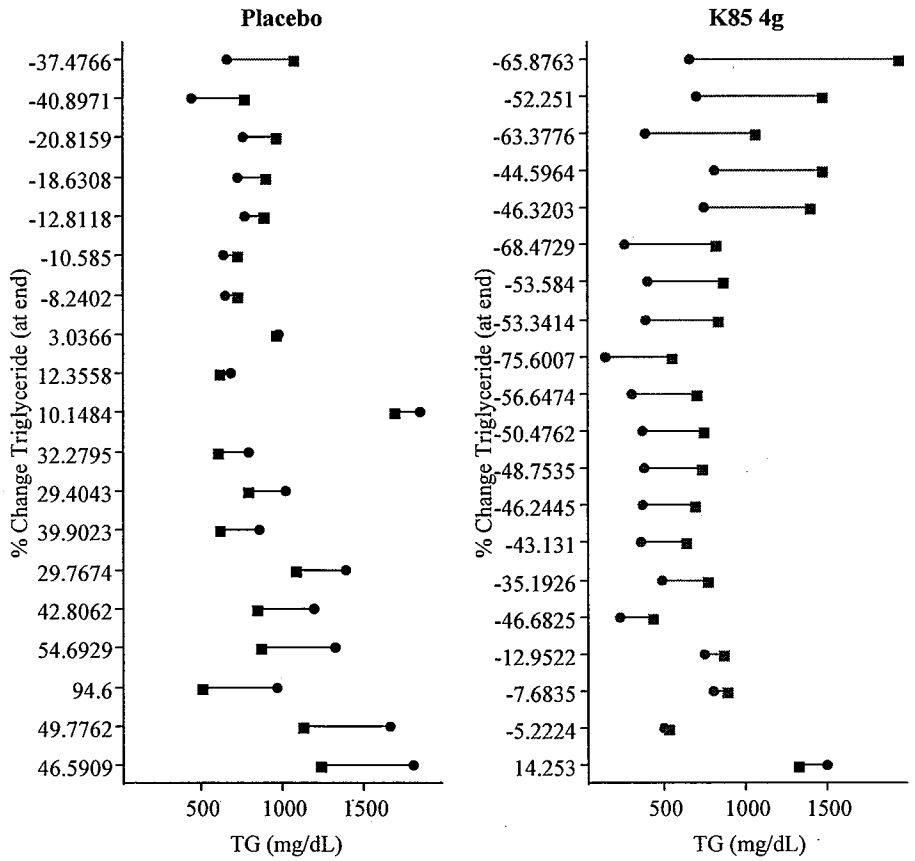
29. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 95009

STUDY
K8595009

TREAT



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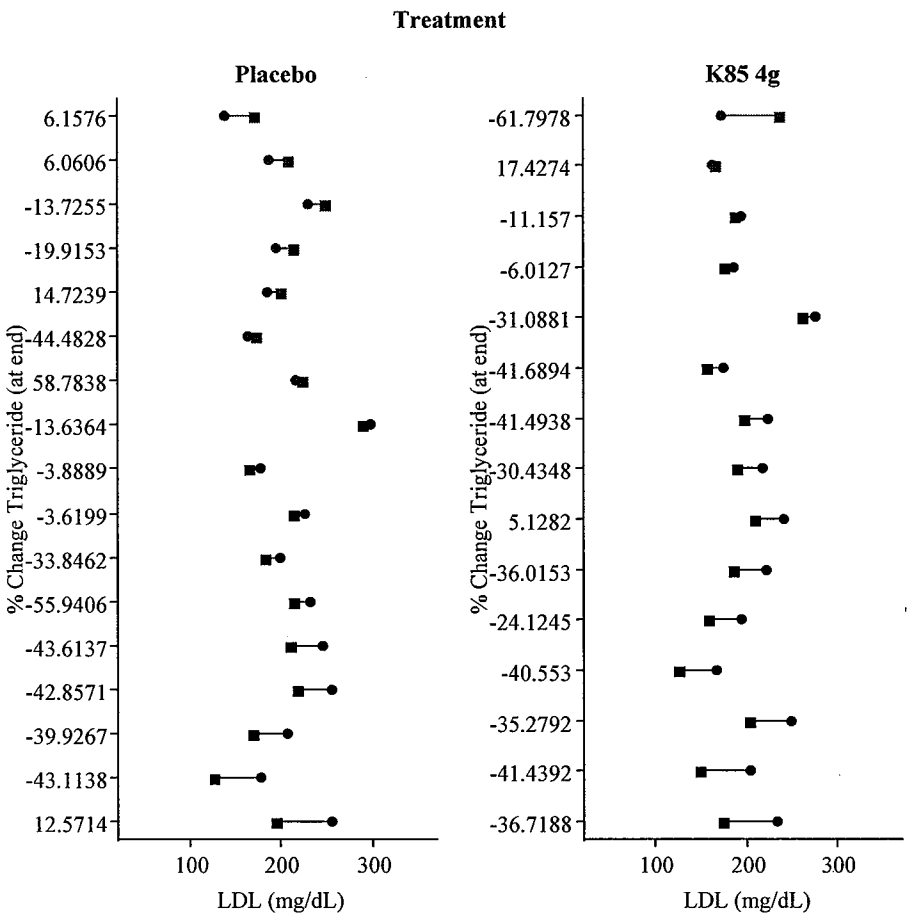
30. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85013

STUDY
CK85013



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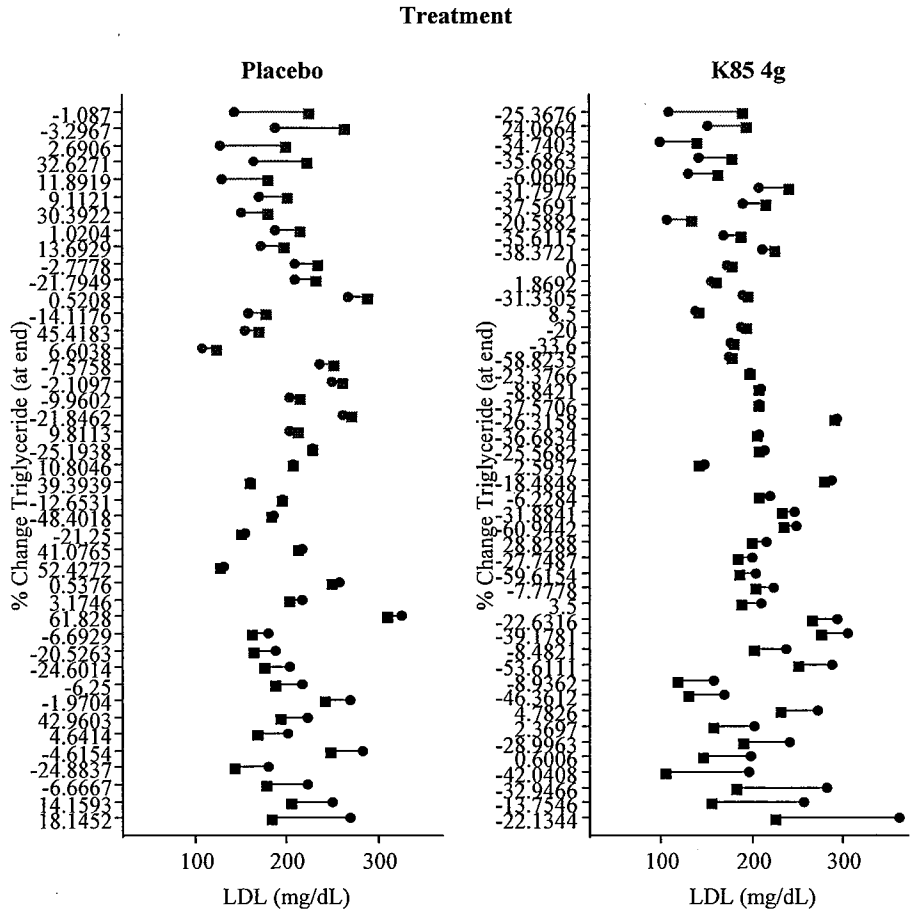
31. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85014

STUDY
CK85014



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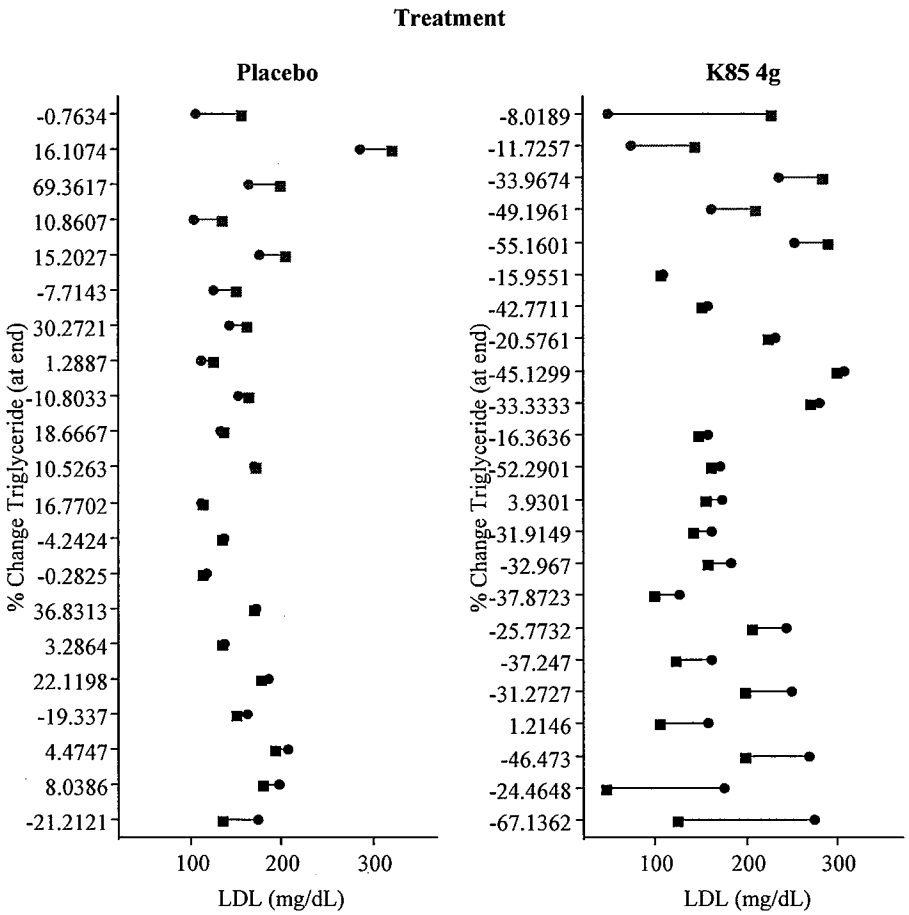
32. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85017

STUDY
CK85017



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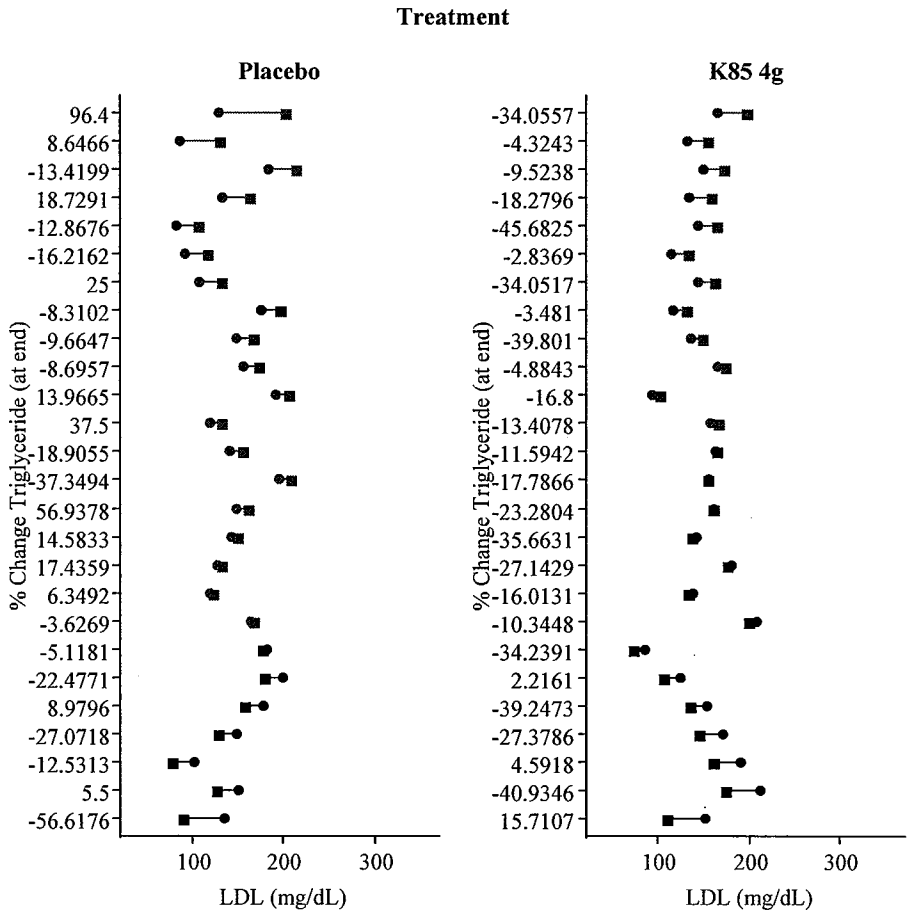
33. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85019

STUDY
CK85019



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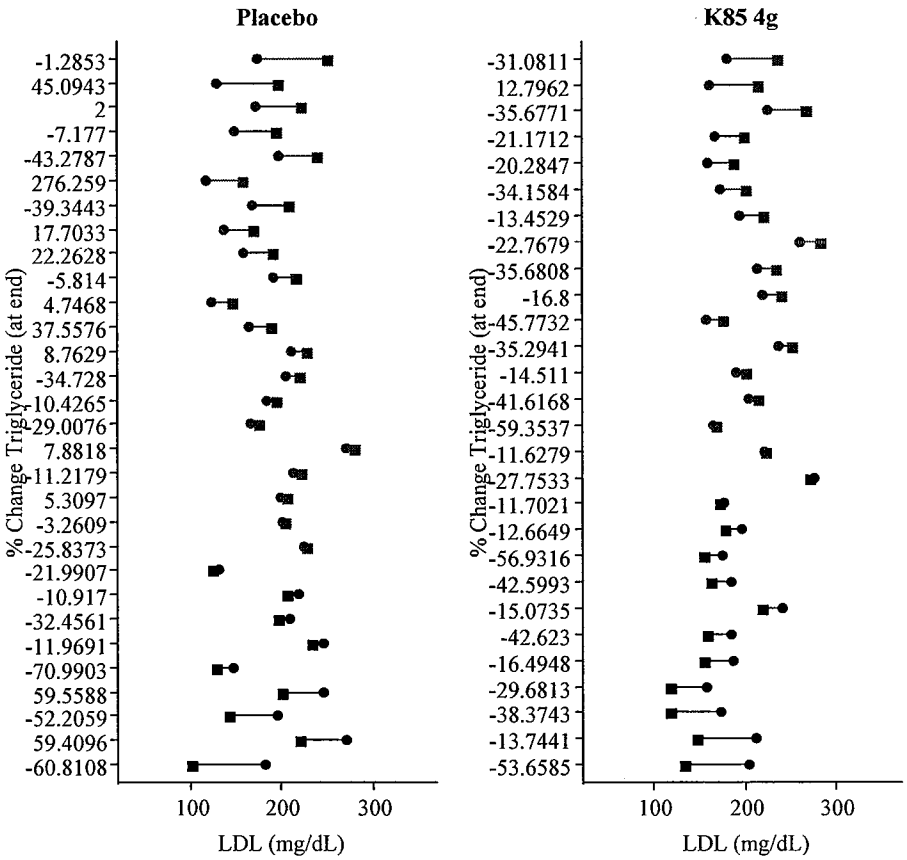
34. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85022

STUDY
CK85022



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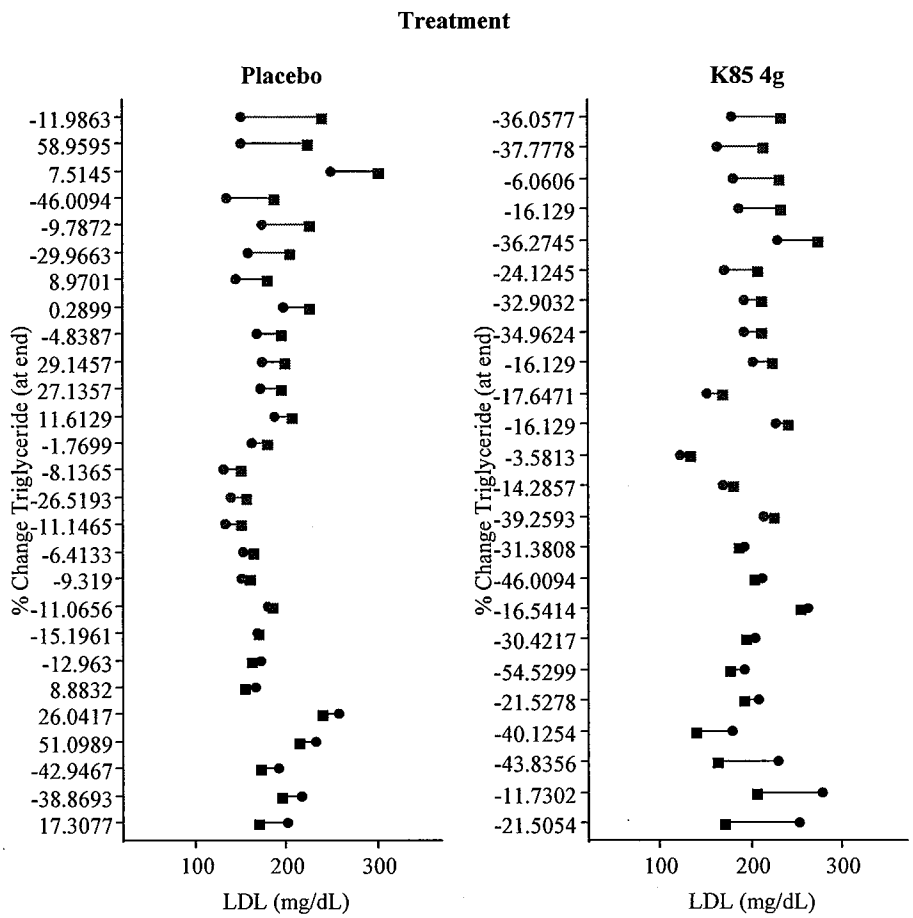
35. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85023

STUDY
CK85023



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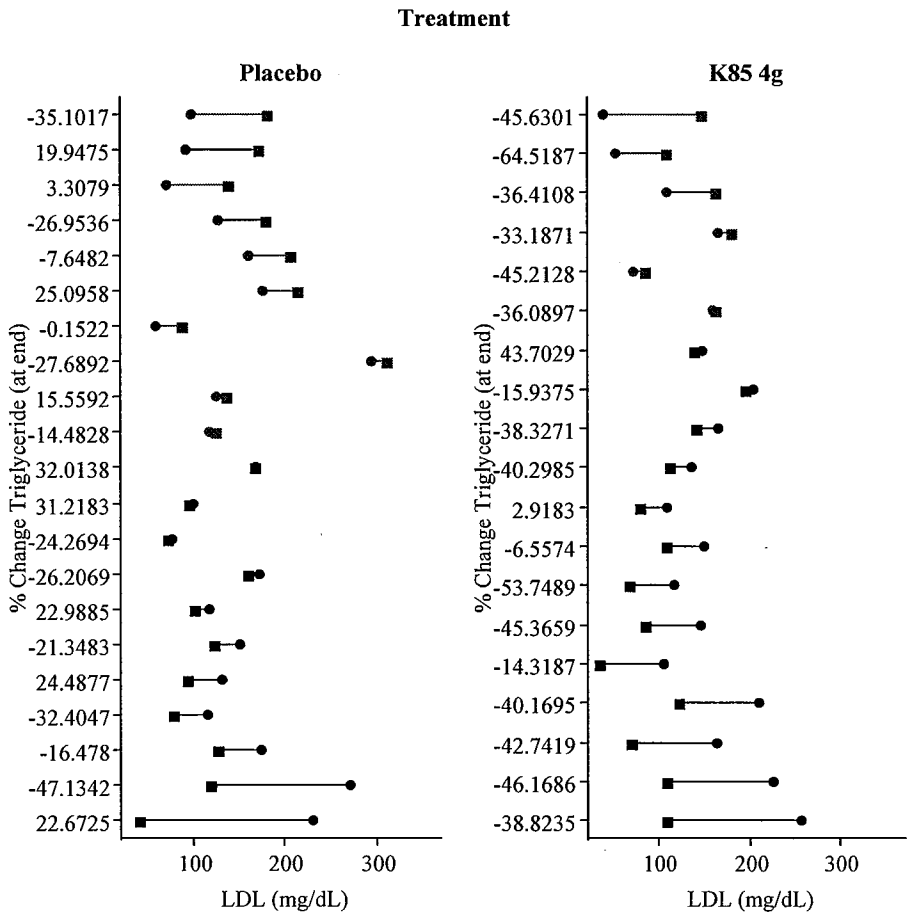
36. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 94010

STUDY
K8594010



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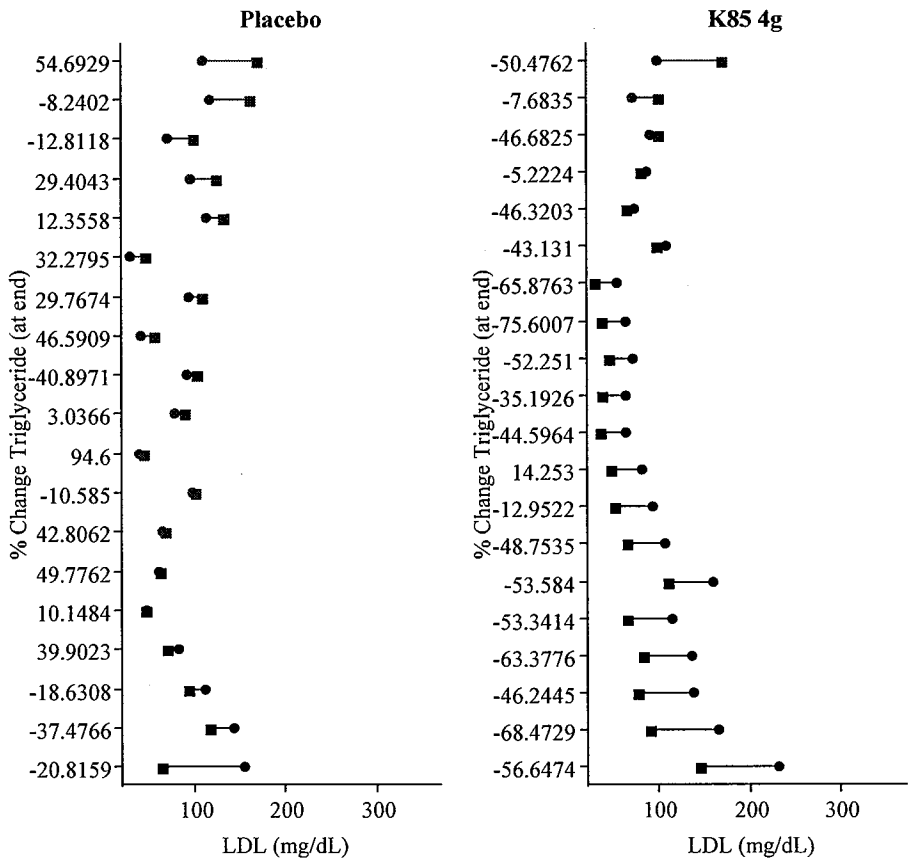
37. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 95009

STUDY
K8595009



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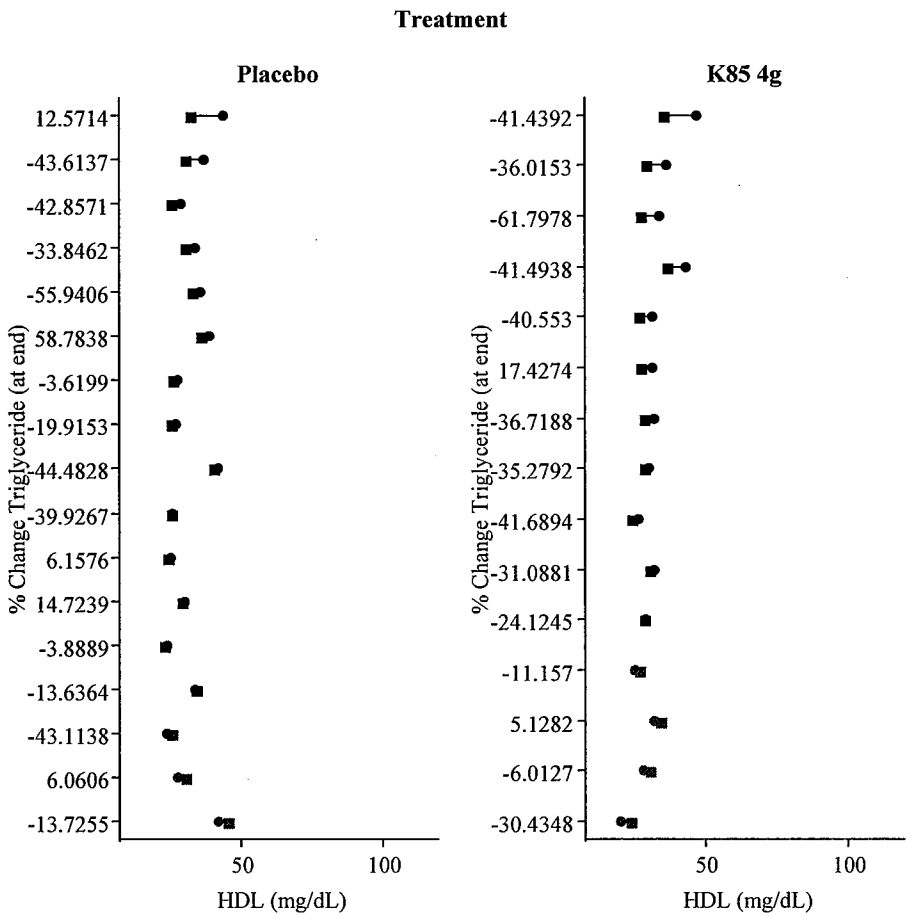
38. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85013

STUDY
CK85013



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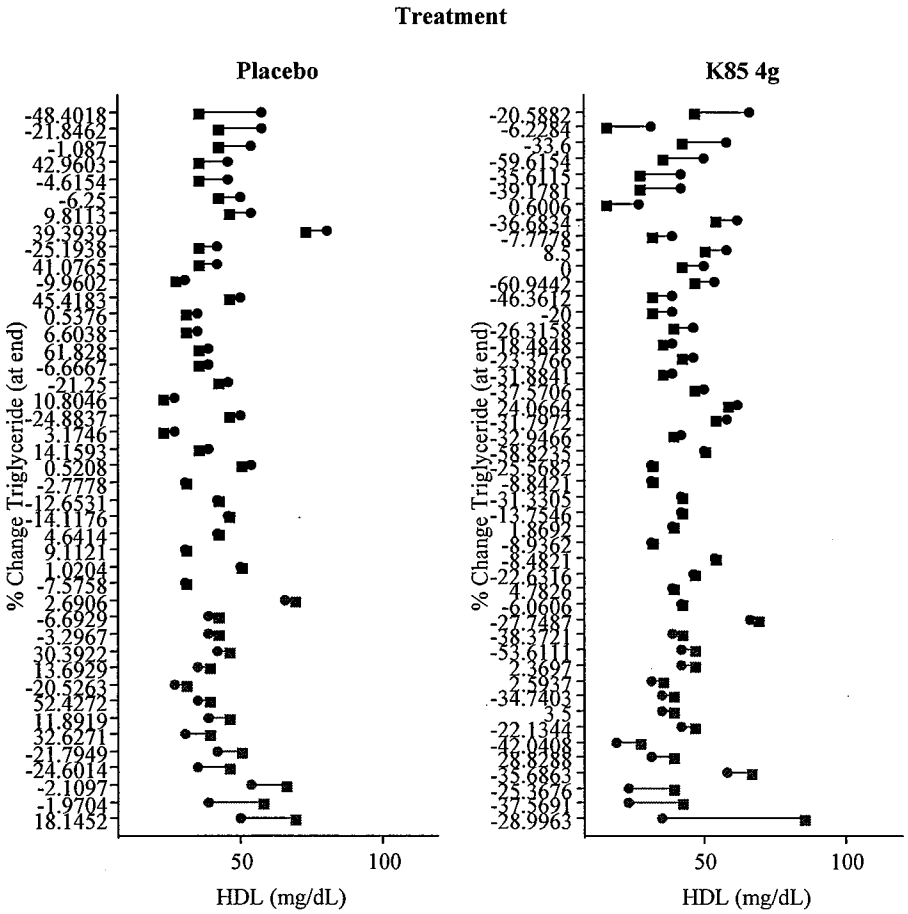
39. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85014

STUDY
CK85014



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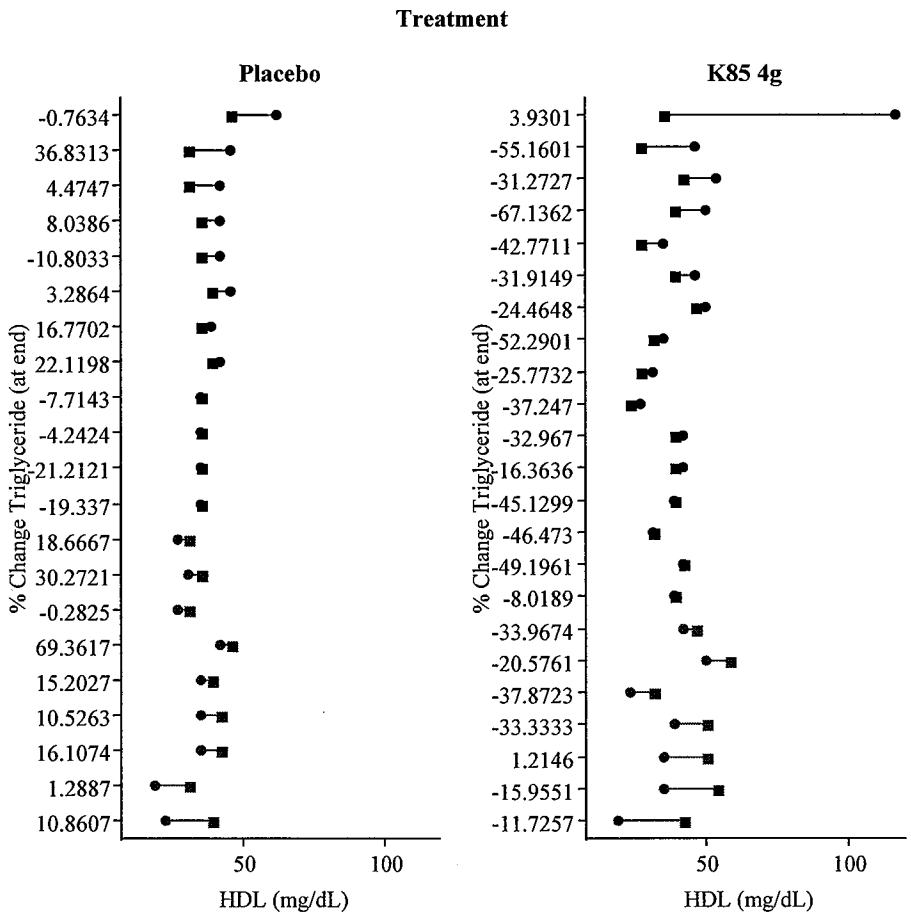
40. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85017

STUDY
CK85017



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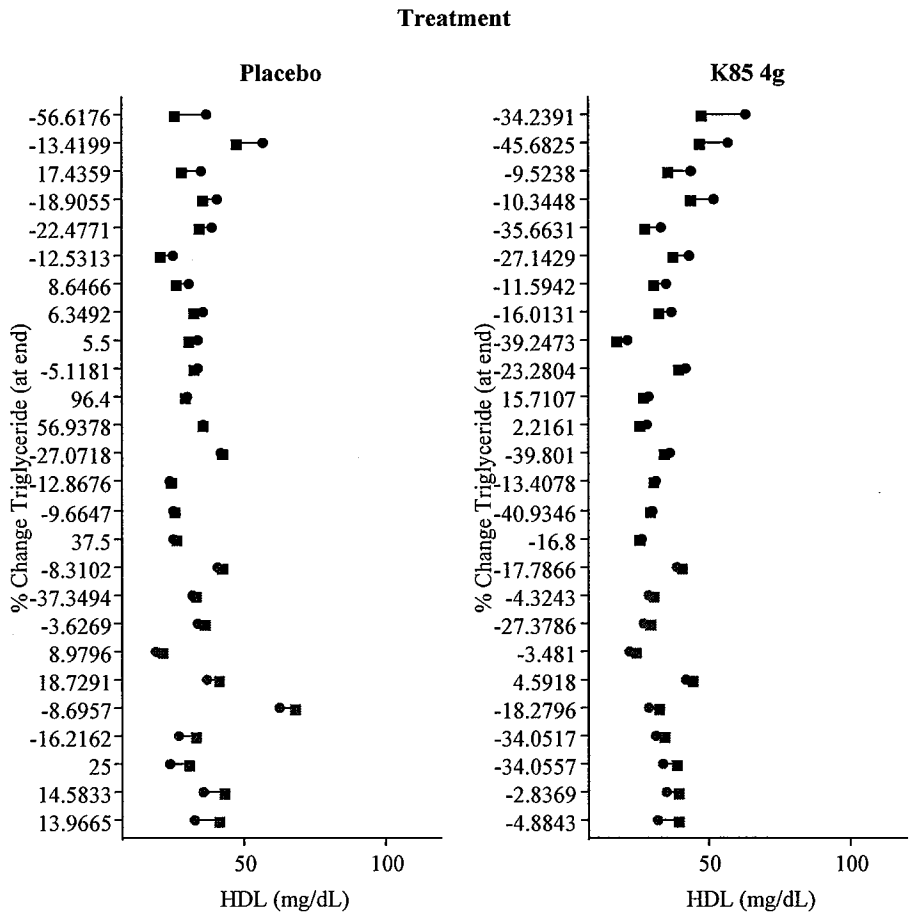
41. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85019

STUDY
CK85019



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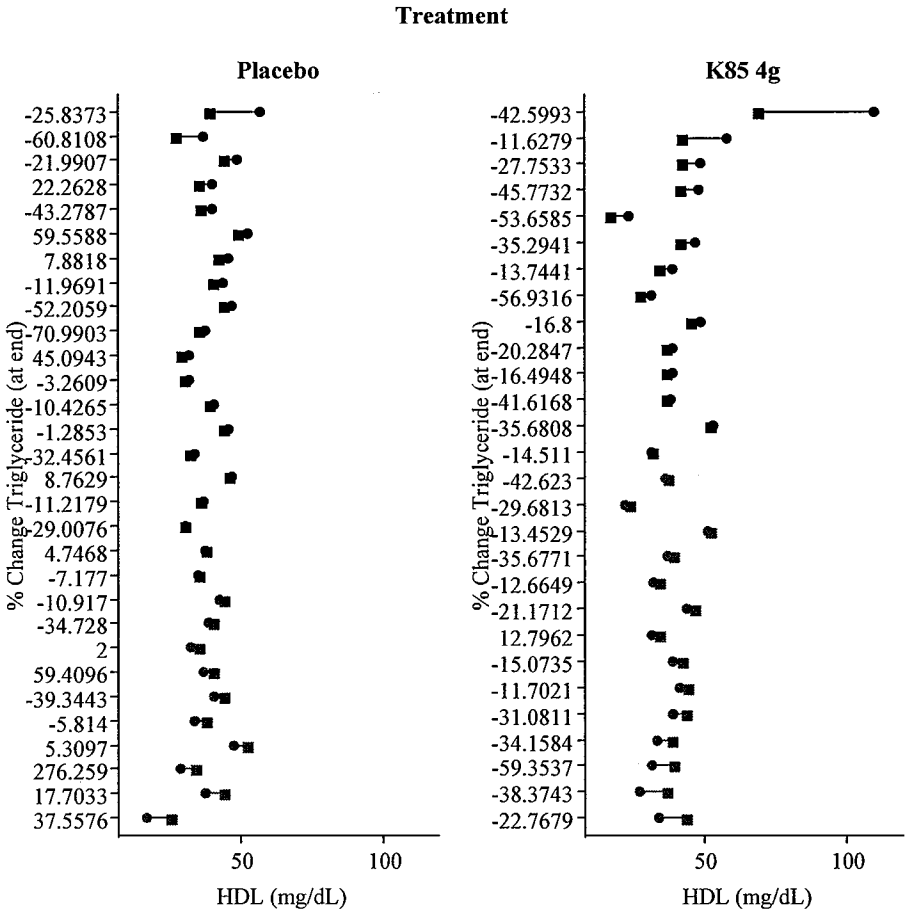
42. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85022

STUDY
CK85022



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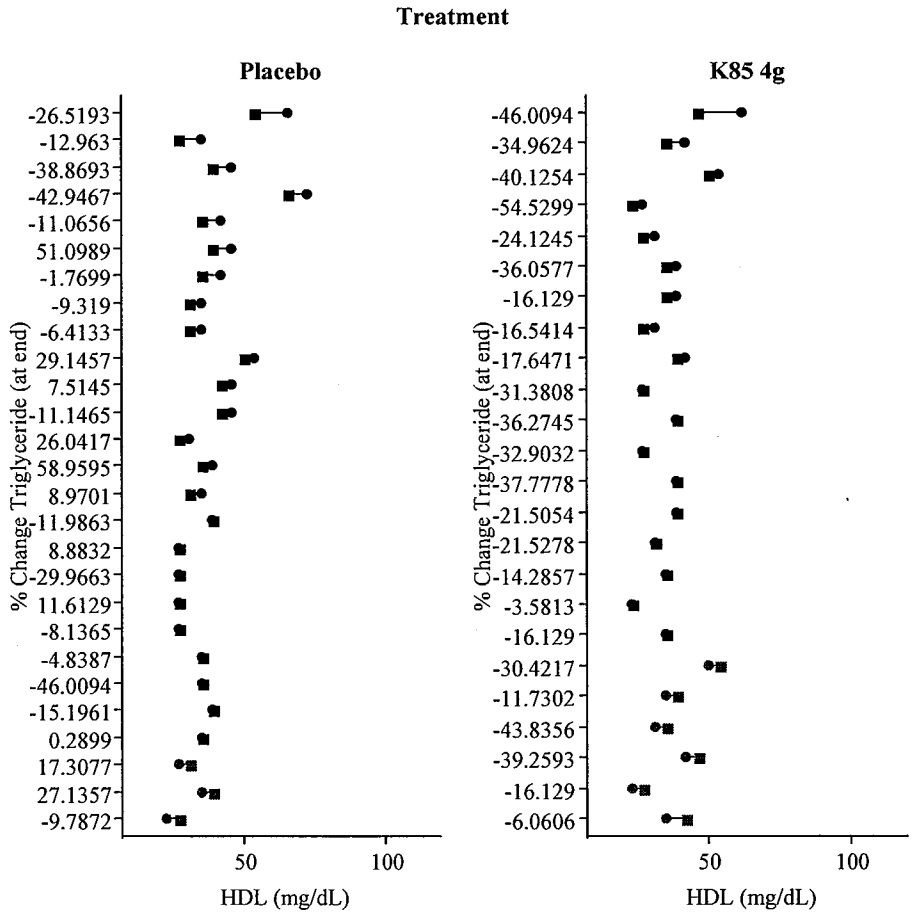
43. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85023

STUDY
CK85023



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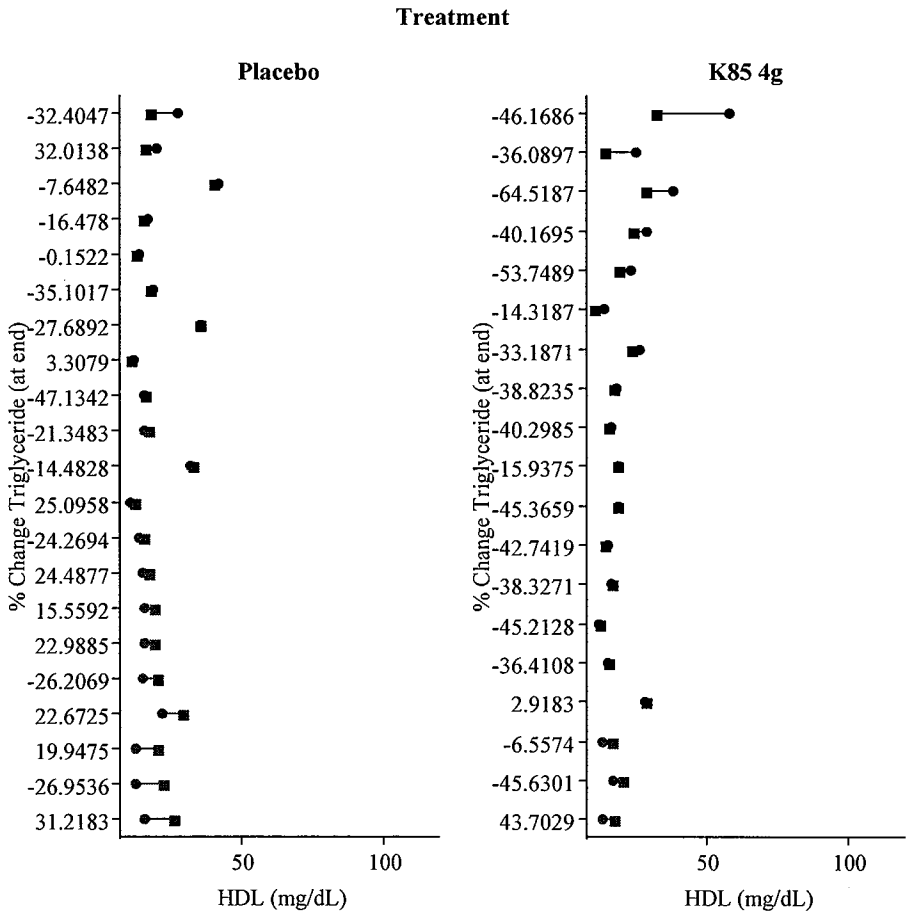
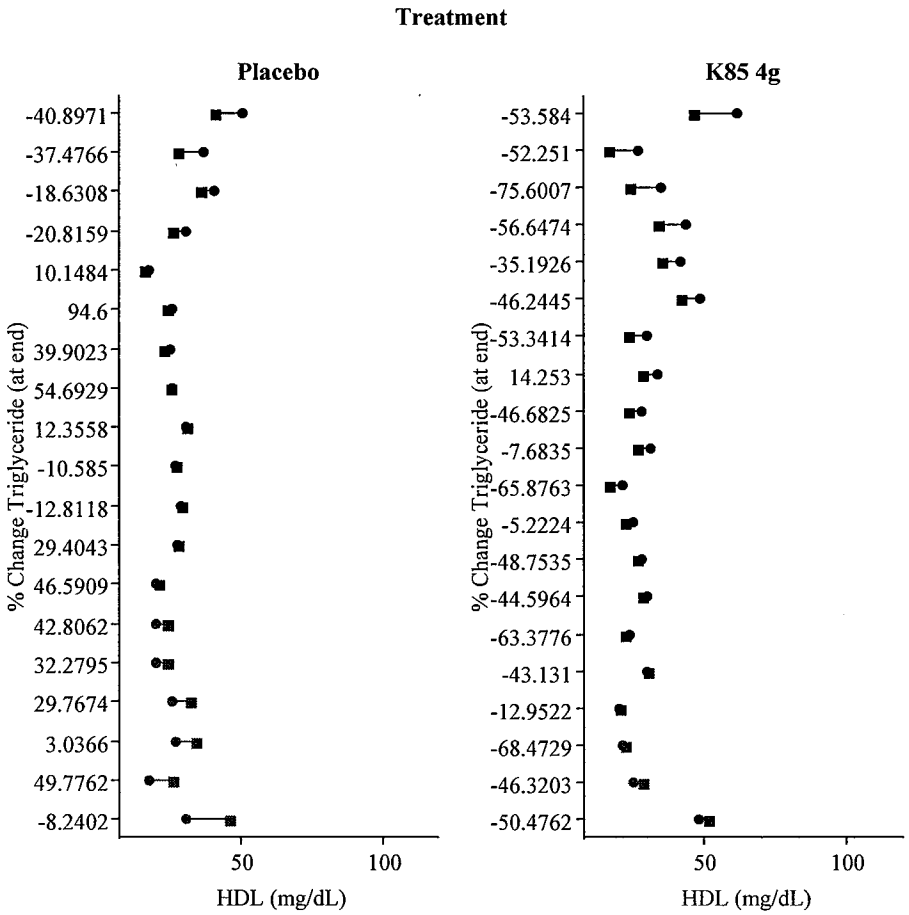
44. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 94010

STUDY
K8594010



45. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 95009

STUDY
K8595009



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Lee-Ping Pian
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Todd Sahlroot
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S. Edward Nevius
10/18/04 05:06:25 PM
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Concur with review.

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

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/Serial Number:	21-654/N-000
Drug Name:	Omacor® (omega-3-acid ethyl esters)
Indication(s):	Hypertriglyceridemia
Applicant:	Ross Products Division, Abbott Laboratories
Date(s):	Received 01/09/04; user fee (10 months) 11/09/04
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Cynthia Liu, MA
Concurring Reviewer(s):	Karl K. Lin, Ph.D., Expert Mathematical Statistician (Applications in Pharmacology and Toxicology)
Medical Division:	Div. of Metabolic and Endocrine Drug Products (HFD-510)
Pharmacology Team:	Indra Antonipillai, Ph.D., Pharmacological Reviewer
	Karen Davis-Bruno, Ph.D., Team Leader
Project Manager:	Valerie Jimenez
Keywords:	NDA review, carcinogenicity studies, survival, neoplastic lesions

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Summary of Statistical Review

- Documents of two carcinogenicity studies (rat and mouse) with two sexes each, submitted by the sponsor along with electronic data sets, were reviewed.

- Dose levels were 0, 100, 600, and 2000 mg/kg/day for both species. There were 2 identical controls in those studies. Route of administration was oral gavage.

- The rat and mouse studies were designed to be of 104 and 80 weeks, respectively. According to the sponsor, because of lower than expected survival, the male and female rats were killed after 101 and 89 weeks of treatment, respectively. However, due to good survival, the female mouse study was extended to the 50% survival point and terminated at Week 88.

- The number of animals with adequate treatment exposure was generally sufficient with respect to the duration of each study.

- In both the rat and mouse studies, there were no significant positive trends or group comparisons in mortality in either sex, nor were there significant increases in the high dose tumor incidences when compared to the combined control.

- There were no analyses of combining tumors, tissues, and/or related hyperplastic lesions requested by the reviewing pharmacologist.

- This reviewer's findings of the survival and tumor analyses for both the rat and mouse studies agree with the sponsor's.

Introduction

The sponsor has submitted two carcinogenicity studies (rat and mouse) with two sexes each, for the new drug application (NDA 21-654) for Omacor® (omega-3-acid ethyl esters). The purpose of these studies was to evaluate the effect of the test article, Etylester K85, on the incidence and morphology of tumors following oral (gavage) administration once daily to the rats and mice for at least 104 and 80 weeks, respectively.

[ ] conducted the rat study during Years 1990-1992 and the mouse study during Years 1992-1993. According to the review report (dated 11/1/2000 [ ] of Dr. Albert DeFelice (previous reviewing pharmacologist), the data had been submitted to the agency before, but the formats were not in compliance. Therefore, no analysis or verification on the data or results was conducted by the agency at that time. b(4)

The sponsor finally reformatted the tumorigenicity data and this reviewer was able to perform her own independent statistical analyses on survival and neoplastic lesions, using the electronic data sets submitted by the sponsor on 1/9/2004. The data files are located in \\Cdsesub1\n21654\N_000\2004-01-09\Tox. However, no electronic study reports were submitted. The paper volumes this reviewer used as references are Vols. 14 (mouse) and 18-19 (rat).

Study Design

The group designation, dose level, and number of animals per group for the rat and mouse studies are provided below. The strains of rats and mice were — CD(SD)BR and — CD-1(ICR)BR, respectively. Note that the two controls were identical. b(4)

Group Number	Group Description	Rat			Mouse		
		Dose Level mg/kg/day	Animals/group		Dose Level mg/kg/day	Animals/group	
			Male	Female		Male	Female
1	Control I	0	50	50	0	51	51
2	Low	100	50	50	100	51	51
3	Intermediate	600	50	50	600	51	51
4	High	2000	50	50	2000	51	51
5	Control II	0	50	50	0	51	51

According to the sponsor, because of lower than expected survival, the male and female rats were killed after 101 and 89 weeks of treatment, respectively. However, due to good survival, the female mouse study was extended to the 50% survival point. In other words, for the rat study, the males were treated for a minimum of 101 weeks and the females for a

minimum of 89 weeks; for the mouse study, the males were treated for a minimum of 80 weeks and the females for a minimum of 88 weeks.

Reviewer's Analysis Methods

Survival. Evaluations of dose-response trend in mortality and group comparisons were conducted using Cox-Tarone binary regression (parametric) and Gehan-Breslow (nonparametric) tests. The former method is weighted more heavily toward late incidences and the latter method is weighted more heavily toward early incidences due to treatment. As a result, both are valuable tools for incidence data with onset times. Kaplan-Meier product limit survival curves were a supplementary tool to examine the survival distribution patterns among the study groups. Two-sided tail probabilities for trend and group comparisons are evaluated at the 5% significance level.

Neoplastic Lesions. The occult tumors (incidental and/or fatal) were analyzed by interval-based exact permutation test incorporating cause of death information. The cut-off points used for the intervals were Weeks 0-52, 53-78, 79-92, 93-before terminal sacrifice (T_{sac}), and T_{sac} for the male rats, which are based on the suggestions from National Toxicology Program (NTP). Since the durations of the other studies were shorter than 104 weeks, this reviewer used Weeks 0-50, 51-75, 76-before T_{sac}, and T_{sac} for the 89-week female rat and 88-week female mouse studies, and Weeks 0-50, 51-70, 71-before T_{sac}, and T_{sac} for the 80-week male mouse study. The palpable (superficial) tumors were also analyzed by interval-based exact permutation test as in the case of fatal tumors, using the first palpation time (provided in the sponsor's electronic data files) as the tumor onset time. SAS PROC MULTTEST (1999) was used to implement the interval-based exact permutation test. Since the low and intermediate dose groups did not have all the animals examined microscopically for the protocolled tissues (unless noted otherwise), they were excluded from the statistical analyses.

The benign and malignant neoplastic lesions were evaluated individually as well as combined. In the cases of multiple-organ findings (e.g., hemangioma and hemangiosarcoma), the incidences were counted and evaluated by animal as well as by tissue type. The statistical results for these cases may be biased because not all the animals were examined for every tissue. This reviewer has selected combined tumor types and/or combined organ types, where appropriate, for the analyses based on the work of McConnell et al. (1986) and her past experience. There were no combining cases requested by the reviewing pharmacologist.

Since whether tumor incidence rates increase as doses increase is the main concern of the FDA/CDER pre-clinical review team regardless of the real direction indicated by the data,

upper-tailed probabilities (p-values) were, therefore, always computed in testing for positive trend and group comparisons in tumor incidences. The following table provides the criterion for determining the statistical significance according to the FDA's Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals (May 2001).

	Test for Positive Trend	Control-High Pairwise Comparisons
Standard 2-Year Studies with 2 Species and 2 Sexes	Common and rare tumors are tested at 0.005 and 0.025 significance levels, respectively.	Common and rare tumors are tested at 0.01 and 0.05 significance levels, respectively.

Common tumor is defined as a tumor type with background (control) rate >1% and rare tumor with background (control) rate ≤1%. The concurrent controls and historical control (where applicable) were taken into consideration in determining commonality of a tumor.

Based on this reviewer's initial analyses at 0.05 significance level (2-sided), there were no striking differences between the two controls in the mortality and tumor incidence rates. Therefore, this reviewer used combined control (Groups 1+5) in all the statistical analyses.

There are some minor differences between the sponsor and reviewer's analysis methods. For example, the cut-off points used by the sponsor were Weeks 1-50, 51-80, 81-before terminal sacrifice, and terminal sacrifice, which are based on the suggestions from FDA. Whether the onset-rate method or onset times were used in the sponsor's analyses for palpable tumors is unknown. Interval-based methods were applied to both incidental and fatal tumors in this reviewer's analyses, while only incidental tumors were analyzed by the interval-based method in the sponsor's analyses.

Results and Discussion

In Tables 1-4, p-value under Group 1 is for trend analysis and p-values under Groups 2, 3, and 4 are for group comparisons.

The Rat Study

Survival. As shown in Tables 1 (male) and 2 (female), there were no significant positive trends or group comparisons in mortality in either of the two sexes in the rat study. The non-monotonic dose-response curve in each sex was mainly caused by the high dose group (2000 mg/kg/day), where the mortality was smaller than that of the combined control. In fact,

based on the Kaplan-Meier estimates, a monotonic positive trend in mortality was observed up to the intermediate dose group (600 mg/kg/day) in both sexes.

In the males, there were at least 50% of the animals in each group still surviving at the beginning of Week 90, indicating that a sufficient number of the male rats were exposed to the treatment adequately, even though the study was terminated at Week 101. In the females, there were at least 50% of the animals in each group still surviving at the beginning of Week 80. However, the Control-I, low-dose, and intermediate-dose groups survival rates were down to below 50% around the middle of Week 80, which was probably the reason for the sponsor to terminate the study at Week 89. The Kaplan-Meier product limit survival curves for the males and females are presented in Figures 1 and 2, respectively.

Neoplastic Lesions. In either sex of the rat study, there were no significant increases in the incidences of any tumors in the high-dose group when compared to the combined control. The summary incidences can be found in Volume 19, Table 8.6 of Reference 44.

The Mouse Study

Survival. As shown in Tables 3 (male) and 4 (female), there were no significant positive trends or group comparisons in mortality in either of the two sexes in the mouse study. In the males, there were at least 68% of the animals in each group still surviving at the beginning of Week 70 and more than 50% of animals were alive when the study was terminated at Week 80. In the females, by Week 80 (the original planned study termination week), there were at least 67% of the animals in each group still surviving, which was probably the reason for the sponsor to extend the study to Week 88. With respect to the duration of the mouse study, there were a sufficient number of animals exposed to the treatment adequately.

Neoplastic Lesions. The sponsor noted a statistically significant increase in uterine smooth muscle tumors (leiomyoma and leiomyosarcoma) in the high-dose group compared with controls. Since the concurrent combined control rates for the leiomyoma and consequently the combined leiomyoma and/or leiomyosarcoma were >1%, they were considered to be common tumor types. As a result, both the sponsor and this reviewer's analyses showed that the increased incidences of those tumors in the high dose group over the combined control were judged not to be significant at 0.01 significance level according to the FDA's guidance.

Uterus	Combined Control	High Dose	Reviewer's p	Sponsor's p
Leiomyoma	7/102 (= 5/51 + 2/51)	7/51	0.0752	NA
Leiomyosarcoma	1/102 (= 0/51 + 1/51)	2/51	0.2139	NA
Combined tumors	8/102 (= 5/51 + 3/51)	9/51	0.0295	0.019

In summary, there were no significant positive tumor findings in either sex of the mouse study. The summary incidences can be found in Volume 14, Table 9.3 of Reference 39.

Conclusion

In both the rat and mouse studies, no significant positive findings in mortality or tumor incidence rates were observed in either sex. Based on examination of the validity of the study designs, the majority of the rats and mice were exposed to treatment adequately.

In general, this reviewer's conclusions for survival and tumor analyses for the rat and mouse studies agree with the sponsor's.

Labeling Comments

The sponsor might be interested in adding [redacted] to the text where it says [redacted] b(4)

Prepared by: Cynthia Liu, MA, Statistical Reviewer

Concurred by: Karl K. Lin, Ph.D., Expert Mathematical Statistician (Applications in Pharmacology and Toxicology)

CC: HFD-510/VJimenez, KDavisbruno, IAntonipillai
HFD-715/ENevius, KLin, TSahlroot, CLiu
HFD-700/CAnello

Table 1 – Results of Statistical Analyses of Mortality Data for Male Rats

Group	1	2	3	4	5
Dose (mg/kg/day)	0	100	600	2000	0
Number of Deaths ([a] = Including 1 animal with accidental death)					
Weeks 0-52	1[a]	2[a]	4[a]	5[aaa]	2
Weeks 53-78	5	4	9[a]	6	6
Weeks 79-92	14	14[a]	10	8	9
Weeks 93-before term sac	7	8	7	6	11[a]
Terminal Sacrifice Weeks	23	22	20	25	22
Unadjusted Mortality	26/50	26/50	28/50	22/50	27/50
Kaplan-Meier Estimate (Final)	0.531	0.540	0.582	0.468	0.542
Cox-Tarone Test (two-sided p)	0.6025 –	0.9680 –	0.4453 +	0.6583 –	
Gehan-Breslow Test (two-sided p)	0.8143 –	0.8996 –	0.2164 +	0.7426 –	

Figure 1 – Kaplan-Meier Product Limit Survival Curves for Male Rats

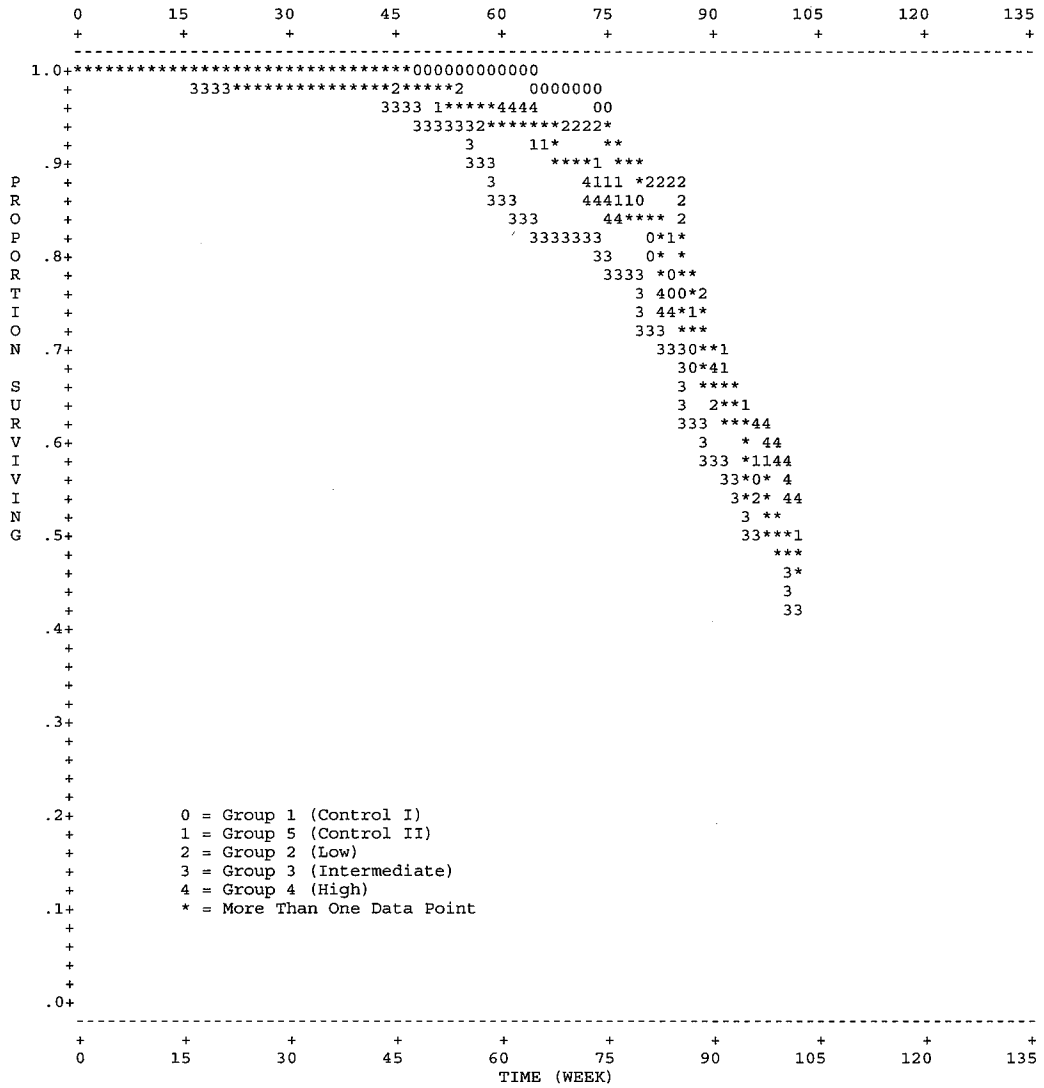


Table 2 – Results of Statistical Analyses of Mortality Data for Female Rats

Group	1	2	3	4	5
Dose (mg/kg/day)	0	100	600	20000	0
Number of Deaths ([a] = Including 1 animal with accidental death)					
Weeks 0-50	1[a]	2[a]	3	5[a]	4[a]
Weeks 51-75	13[a]	12	11[a]	5	10
Weeks 76-before term sac	14	14	18	12	11
Terminal Sacrifice Weeks	22	22	18	28	25
Unadjusted Mortality	26/50	27/50	31/50	21/50	24/50
Kaplan-Meier Estimate (Final)	0.542	0.551	0.632	0.428	0.489
Cox-Tarone Test (two-sided p)	0.2689 –	0.8691 +	0.3400 +	0.3806 –	
Gehan-Breslow Test (two-sided p)	0.2869 –	0.9001 +	0.4305 +	0.3289 –	

Figure 2 – Kaplan-Meier Product Limit Survival Curves for Female Rats

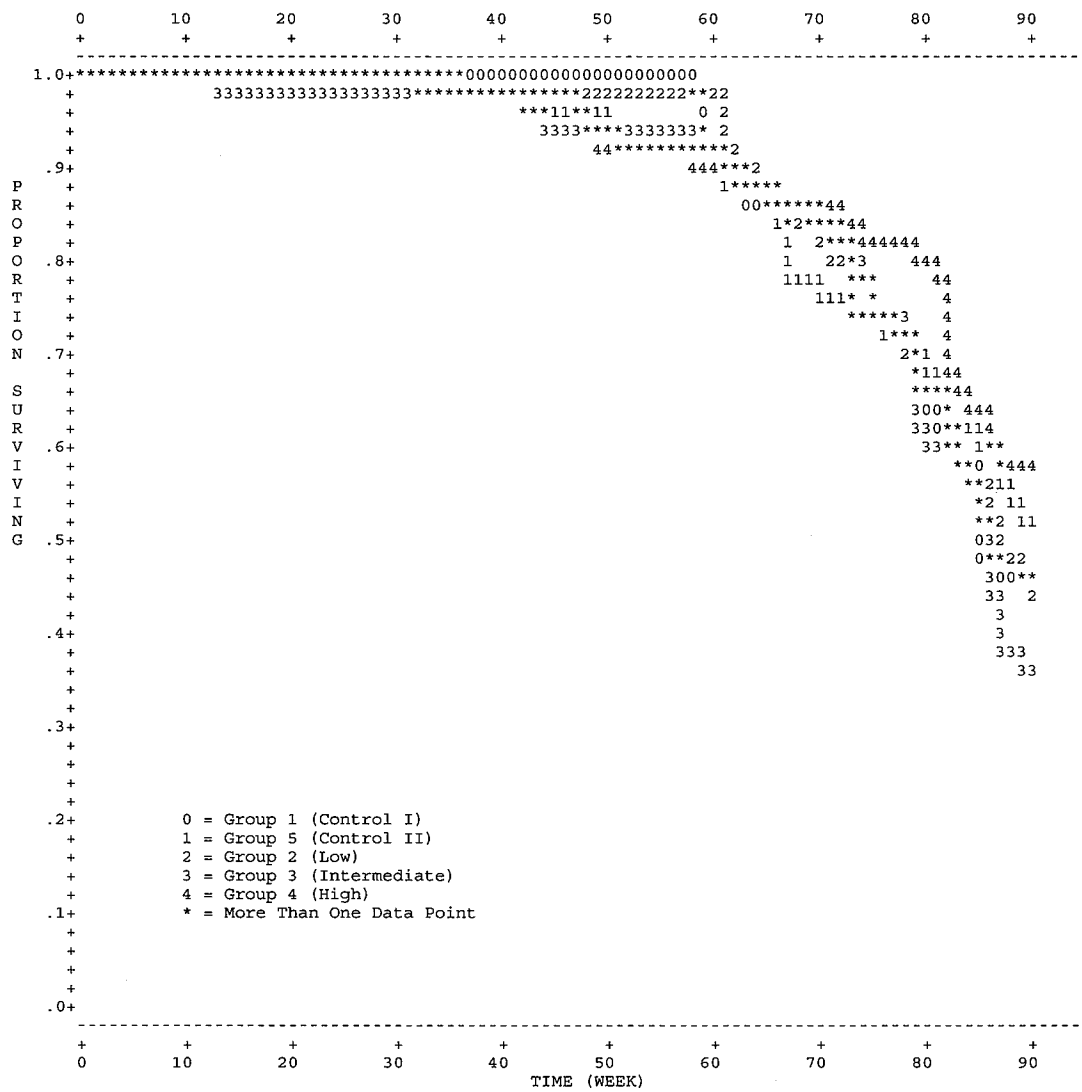


Table 3 – Results of Statistical Analyses of Mortality Data for Male Mice

Group	1	2	3	4	5
Dose (mg/kg/day)	0	100	600	2000	0
Number of Deaths ([a] = Including 1 animal with accidental death)					
Weeks 0-50	4[aa]	3	4[a]	6	7
Weeks 51-70	8	13[aa]	6[a]	5	10[a]
Weeks 71-before term sac	10[a]	9[a]	10[a]	6	8[a]
Terminal Sacrifice Weeks	29	26	31	34	26
Unadjusted Mortality	19/51	22/51	17/51	17/51	23/51
Kaplan-Meier Estimate (Final)	0.388	0.448	0.349	0.333	0.458
Cox-Tarone Test (two-sided p)	0.2717 –	0.9398 +	0.3753 –	0.4359 –	
Gehan-Breslow Test (two-sided p)	0.3598 –	0.8944 +	0.2531 –	0.4581 –	

Figure 3 – Kaplan-Meier Product Limit Survival Curves for Male Mice

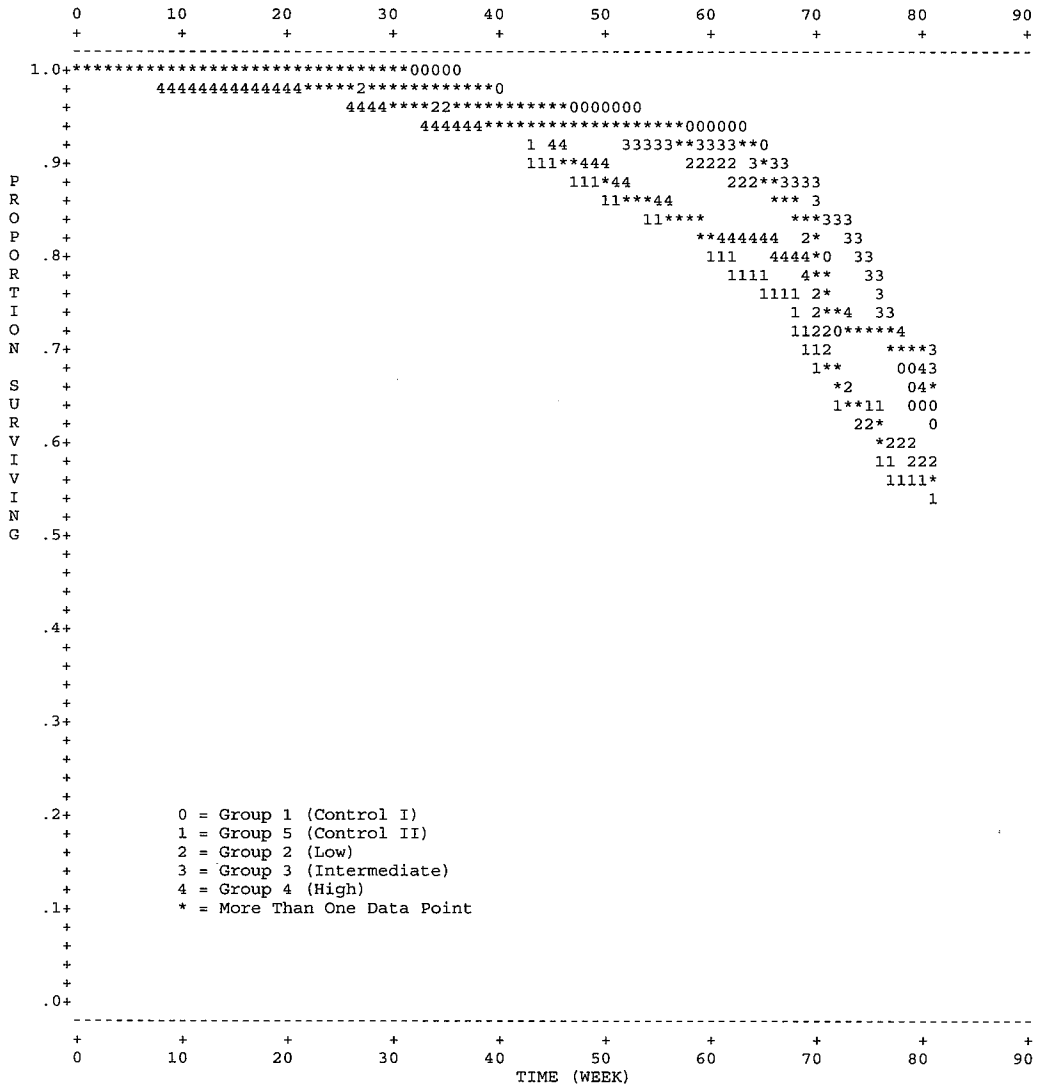
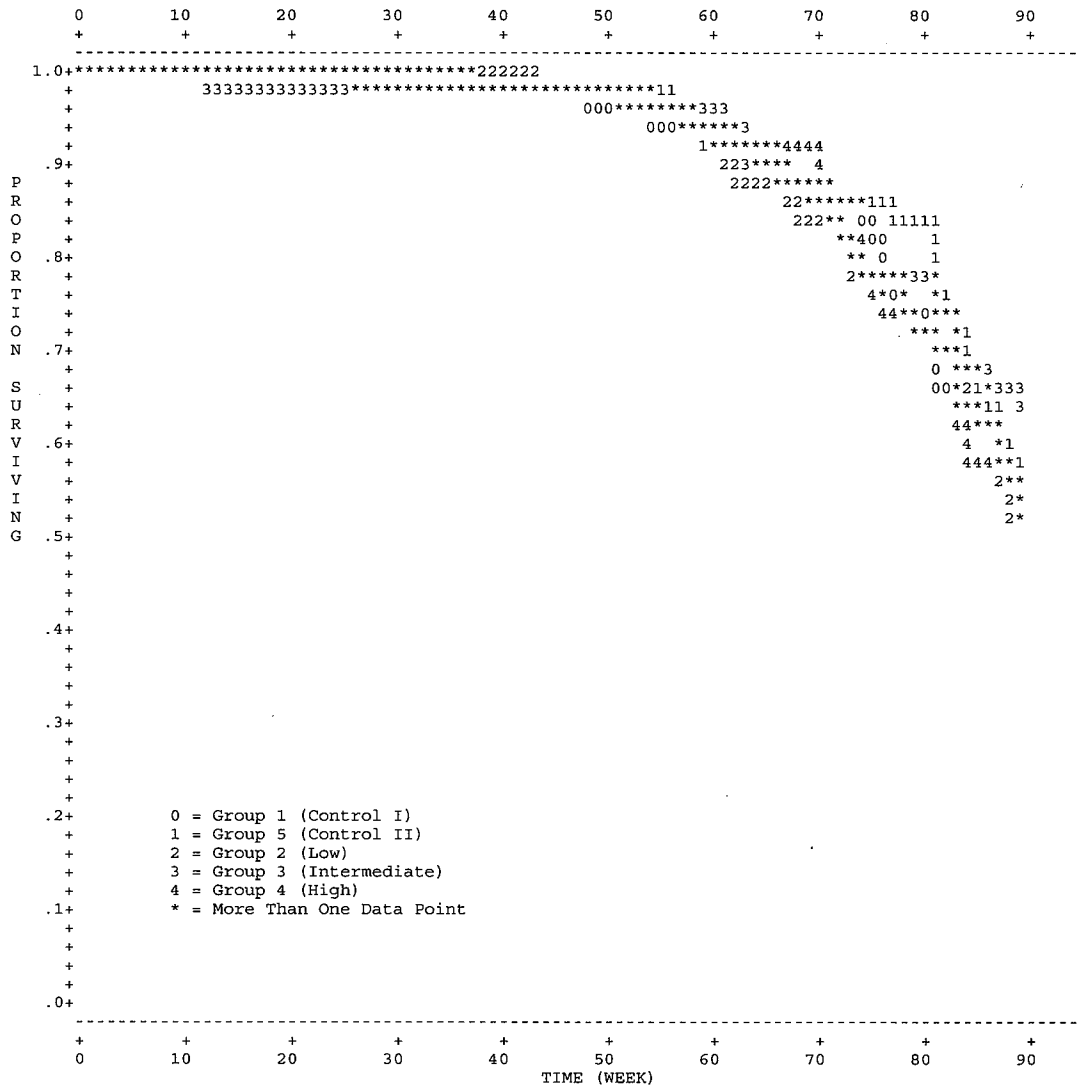


Table 4 – Results of Statistical Analyses of Mortality Data for Female Mice

Group	1	2	3	4	5
Dose (mg/kg/day)	0	100	600	2000	0
Number of Deaths ([a] = Including 1 animal with accidental death)					
Weeks 0-50	2	1	1	1	1
Weeks 51-75	7	10	13[aaa]	14[aaa]	6
Weeks 76-before term sac	14	13	6	11	14
Terminal Sacrifice Weeks	28	27	31	25	30
Unadjusted Mortality	23/51	24/51	17/51	23/51	21/51
Kaplan-Meier Estimate (Final)	0.451	0.471	0.353	0.475	0.412
Cox-Tarone Test (two-sided p)	0.7110 +	0.7302 +	0.5608 –	0.6702 +	
Gehan-Breslow Test (two-sided p)	0.7104 +	0.6377 +	0.5889 –	0.5700 +	

Figure 4 – Kaplan-Meier Product Limit Survival Curves for Female Mice



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Cynthia Liu
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