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STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 21-654

AP

Drug Name: Omacor (omega-3-acid ethyl esters) Capsules, 1 gram

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Applicant: Abbott

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1. EXECUTIVE SUMMARY

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

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

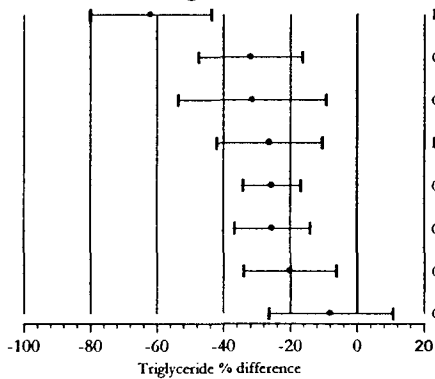
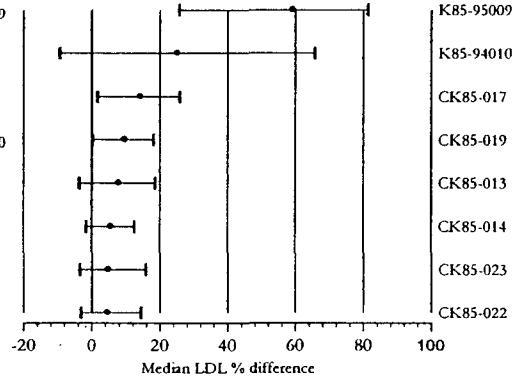


Figure 2 Median % change difference (95% C.I.)



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.

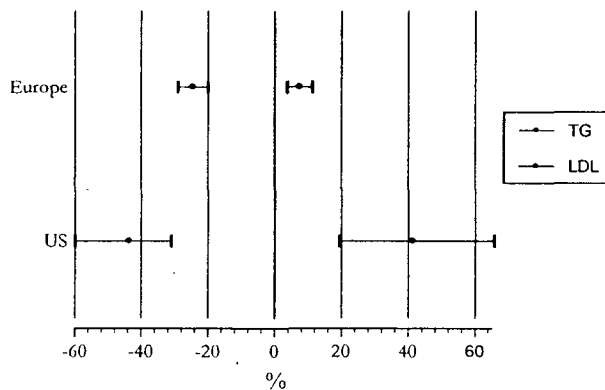
1.1 Conclusions and Recommendations

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 \geq 177 mg/dL, TG \geq 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 studies	n	Placebo			4 g K85				Median shift	95% C.I.
			BL	EP	%Chg	n	BL	EP	%Chg		
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 ($500 \text{ mg/dl} \leq \text{TG} \leq 2000 \text{ mg/dl}$). 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 $\geq 177 \text{ mg/dL}$ while the criteria for the 2 US studies was $\geq 500 \text{ mg/dL}$. 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

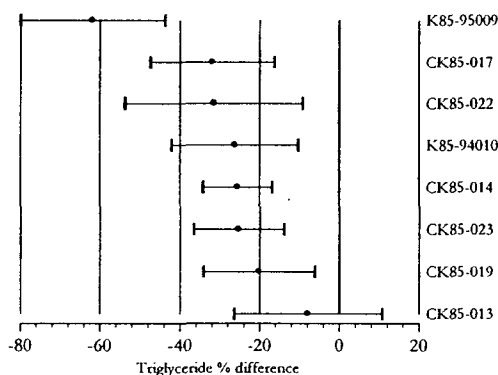
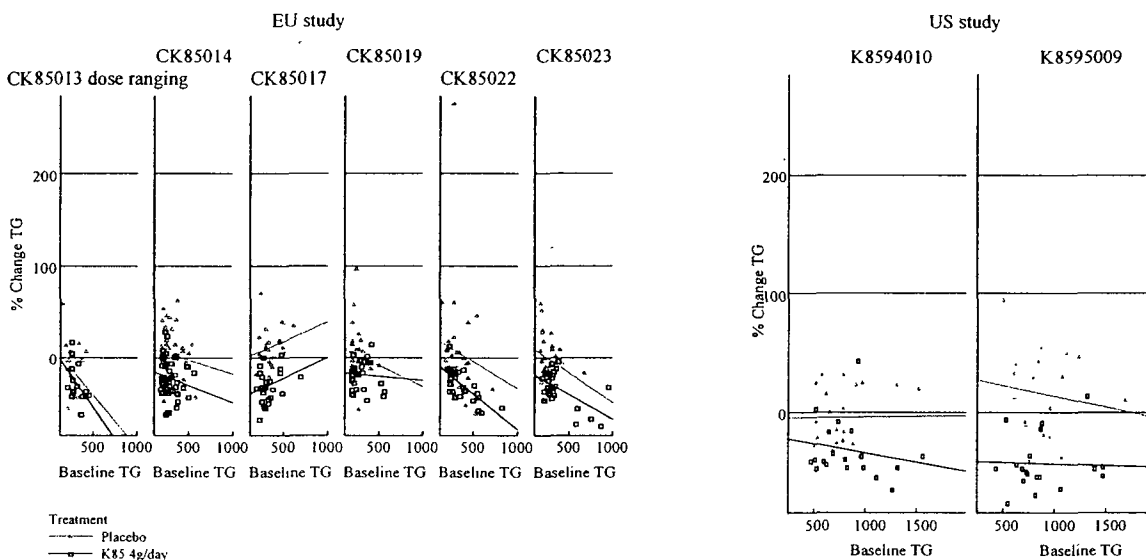


Figure 5 Triglyceride % change from baseline versus baseline – ITT

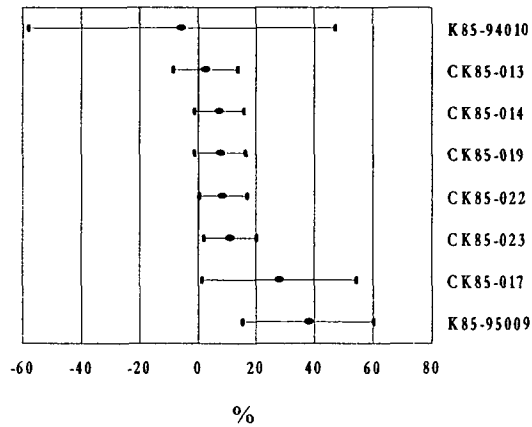


Mean percent change from baseline in LDL increased in the K85 treatment group compared to the placebo group. Table 12 displays the results of the analysis of covariance in LDL and Figure 6 displays the differences in LSM of LDL percent change from baseline with corresponding confidence intervals. Figure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

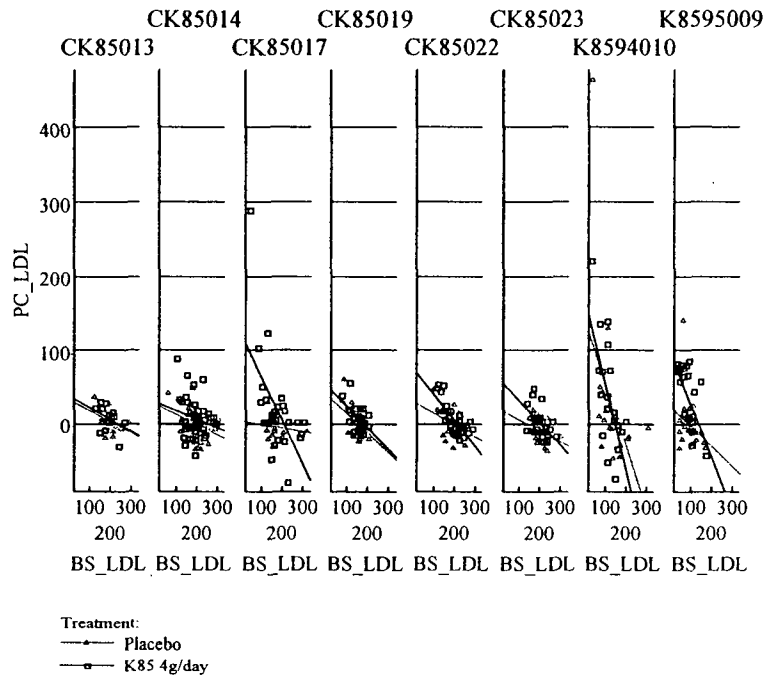


Figure 8 shows the percent change of LDL versus the percent change of triglyceride by pooled study. The correlation coefficients (r-square) were 0.0005 for the European study and 0.00023 for the US study. Hence, the triglycerides percent change is not correlated with the percent change in LDL indicating 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

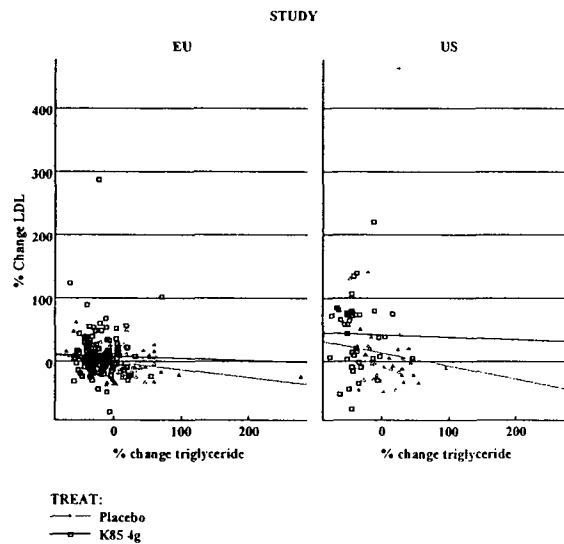
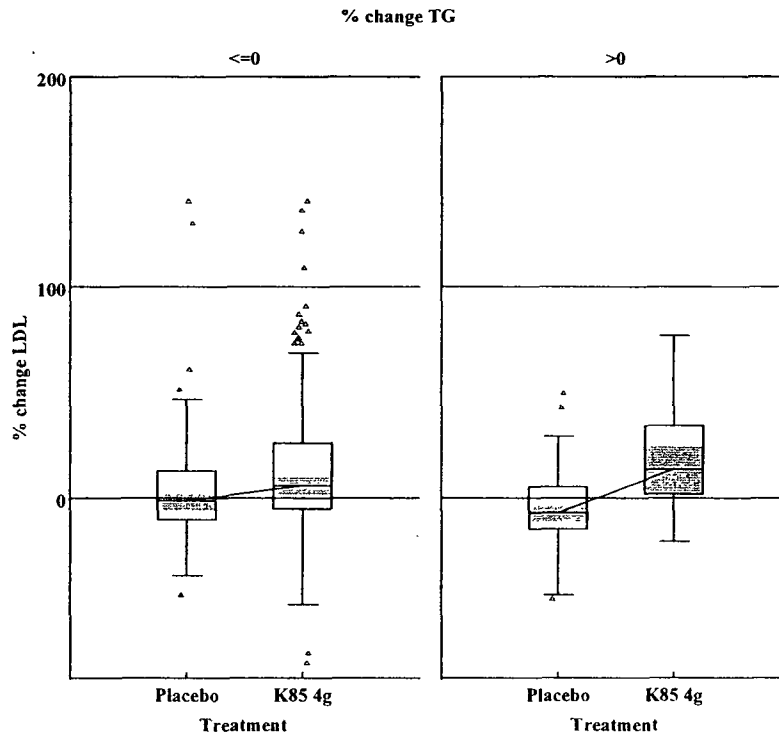


Table 13 and Figure 9 display the median percent change of LDL by percent increase or decrease of triglyceride at endpoint combining all studies. The median percent change in LDL decreased in placebo-treated patients and increased in K85-treated patients regardless of triglyceride percent increase or 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 —

The indication for TG reduction should be limited to triglyceride monotherapy ㄥ

Data concerning the increase in high-density lipoprotein cholesterol in type V hyperlipidemia should be limited to the clinical studies section, ㄥ ㄗ

**APPEARS THIS WAY
ON ORIGINAL**

6. APPENDICES
6.1 LIST OF TABLES

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

	Pooled studies	Placebo				4 g K85				Mean difference	95% C.I.
		n	BL	EP	%Chg	n	BL	EP	%Chg		
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		

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		

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				

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				

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		

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		

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		

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		

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		
Single 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		

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		

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		
Single 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		

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		

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		
Single 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		

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		

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		
Single 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		

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		

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		
Single 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		

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		

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		
Single 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		

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		

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		

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		

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		

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

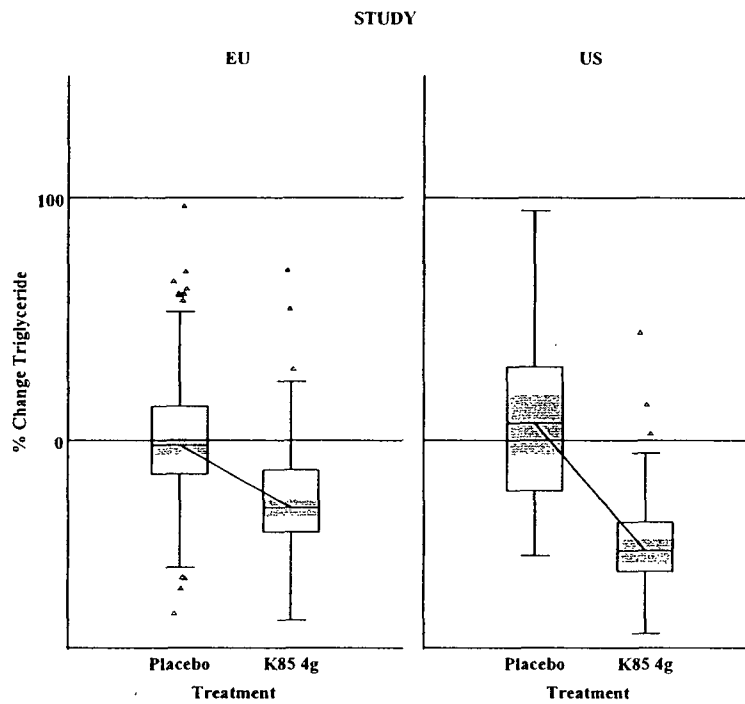
Placebo & Omacor 4g												
	Placebo					K85 4g						
	n	Mean	(SD)	Median	Min	Max	n	Mean	(SD)	Median	Min	Max
Average Baseline Triglyceride	17	263.1	(70.5)	260			15	299.6	(74)	261		
Singe Value Trig Endpoint LOCF	17	217.5	(87.5)	189			15	209.7	(53.3)	214		
Change in Triglycerides - ITT	17	-45.5	(72.6)	-28			15	-89.9	(73.3)	-94		
% Change in single value Trigs	17	-15.3	(29.8)	-13.7			5	-27.7	(20.7)	-35.3		

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

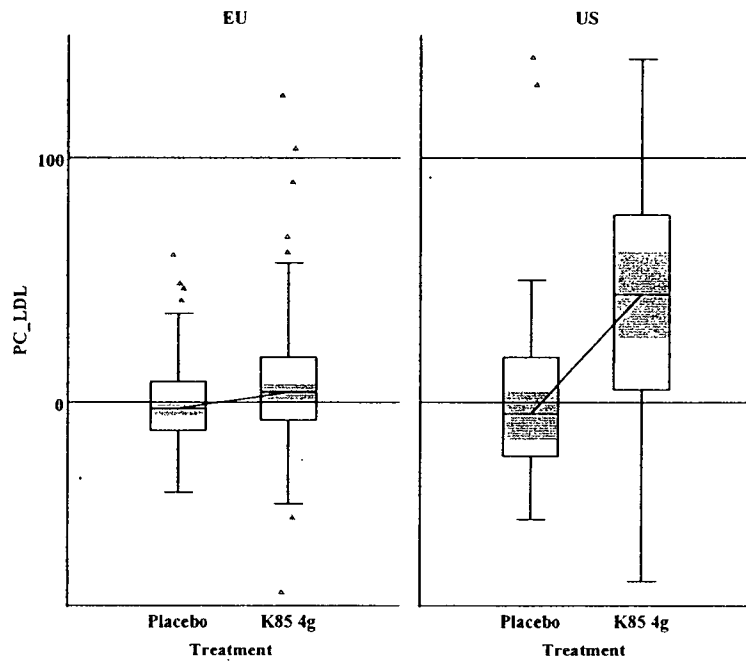
	Omacor 2 g						Omacor 8 g					
	n	Mean	(SD)	Median	Min	Max	n	Mean	(SD)	Median	Min	Max
Average Baseline Triglyceride	16	257.4	(68)	242.5			18	236.4	(88.5)	216.5		
Singe Value Trig Endpoint LOCF	16	193.6	(74.4)	190.5			18	146.1	(60.7)	131		
Change in Triglycerides - ITT	16	-63.8	(83.6)	-75.5			18	-90.3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

6.2 LIST OF FIGURES

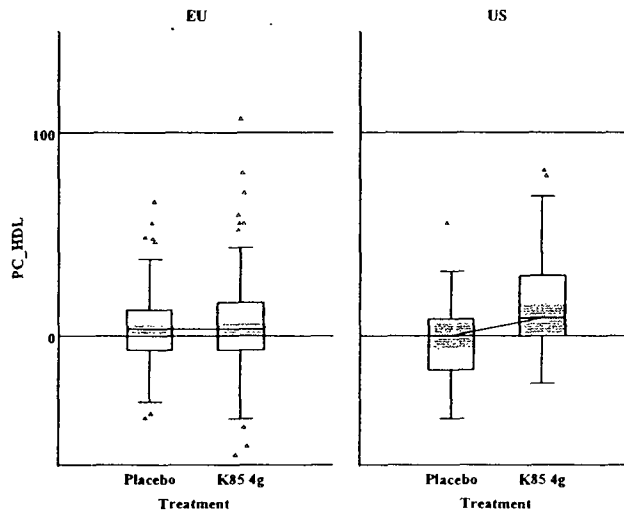
1. Box plot of pooled Category I studies - % change of TG.



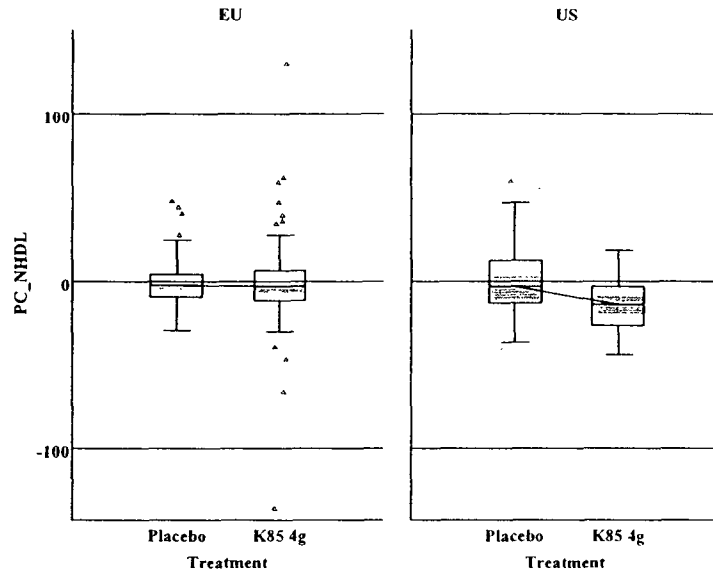
2. Box plot of pooled Category I studies -% change of LDL
STUDY



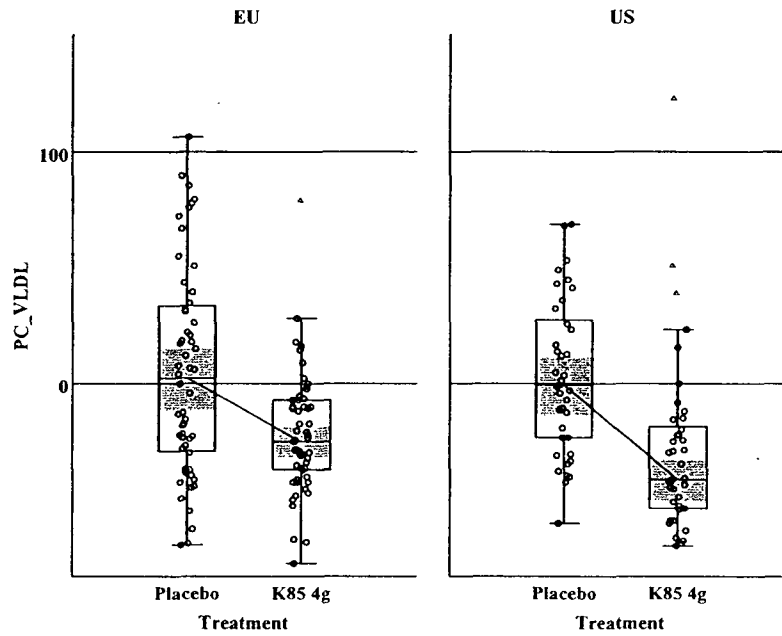
3. Box plot of pooled Category I studies -% change of HDL
STUDY



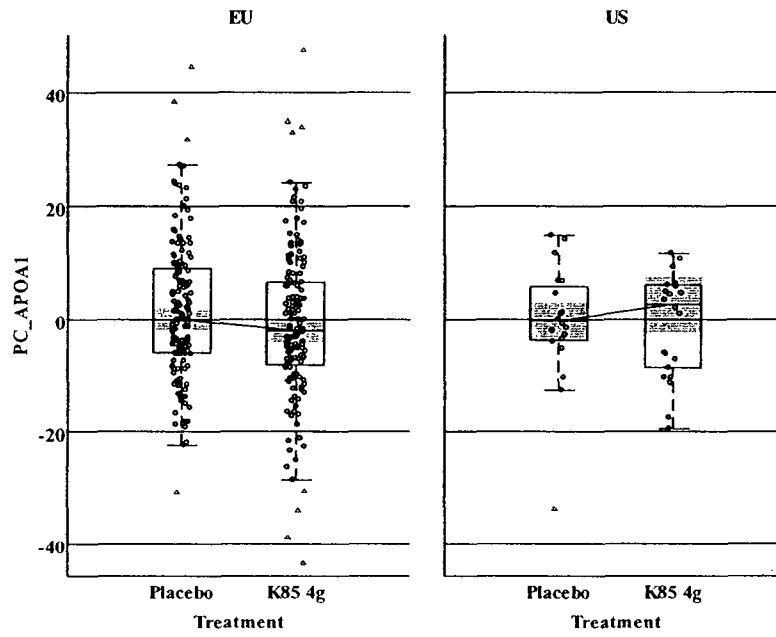
4. Box plot of pooled Category I studies -% change of NHDL



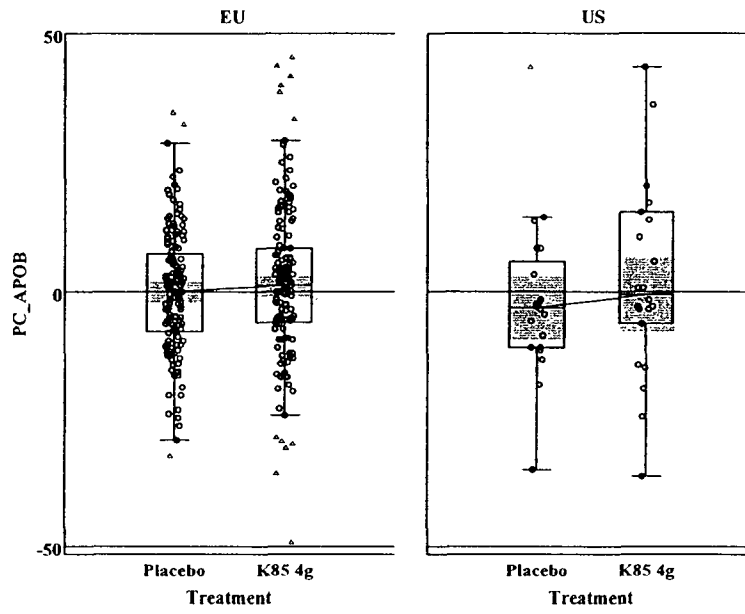
5. Box plot of pooled Category I studies -% change of VLDL



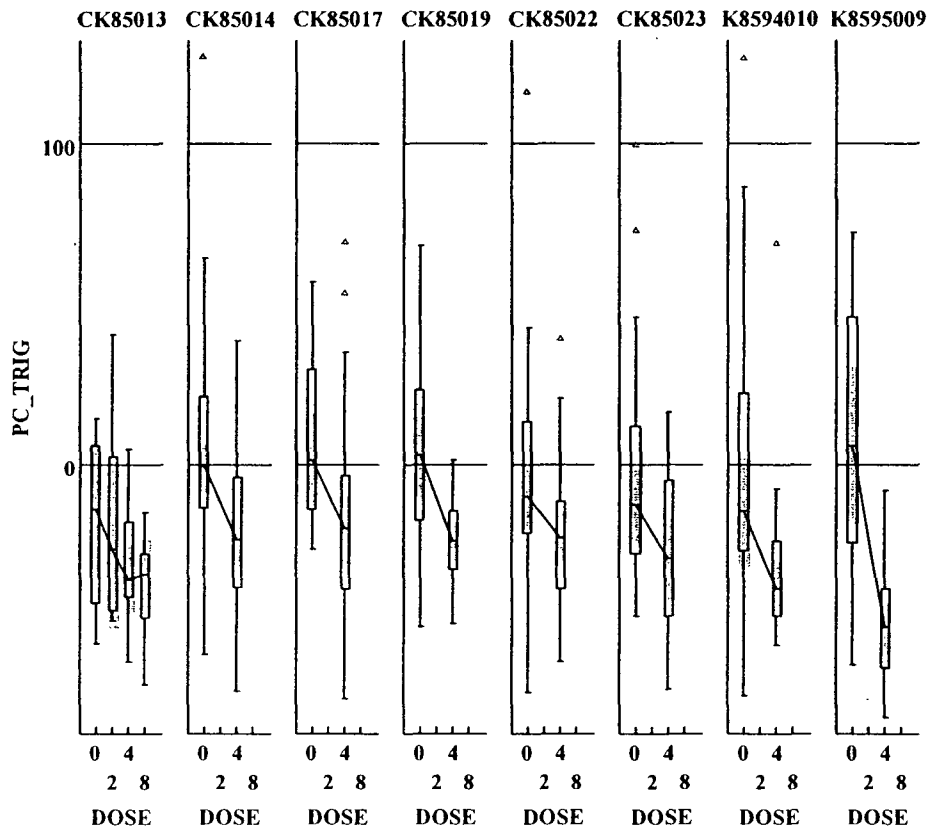
6. Box plot of pooled Category I studies -% change of APOA1



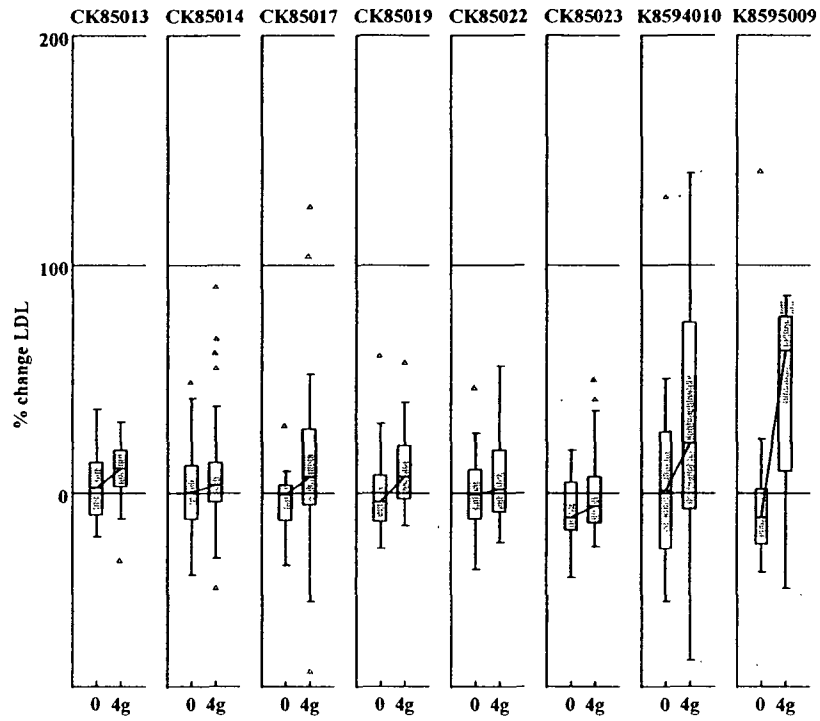
7. Box plot of pooled Category I studies -% change of APOB



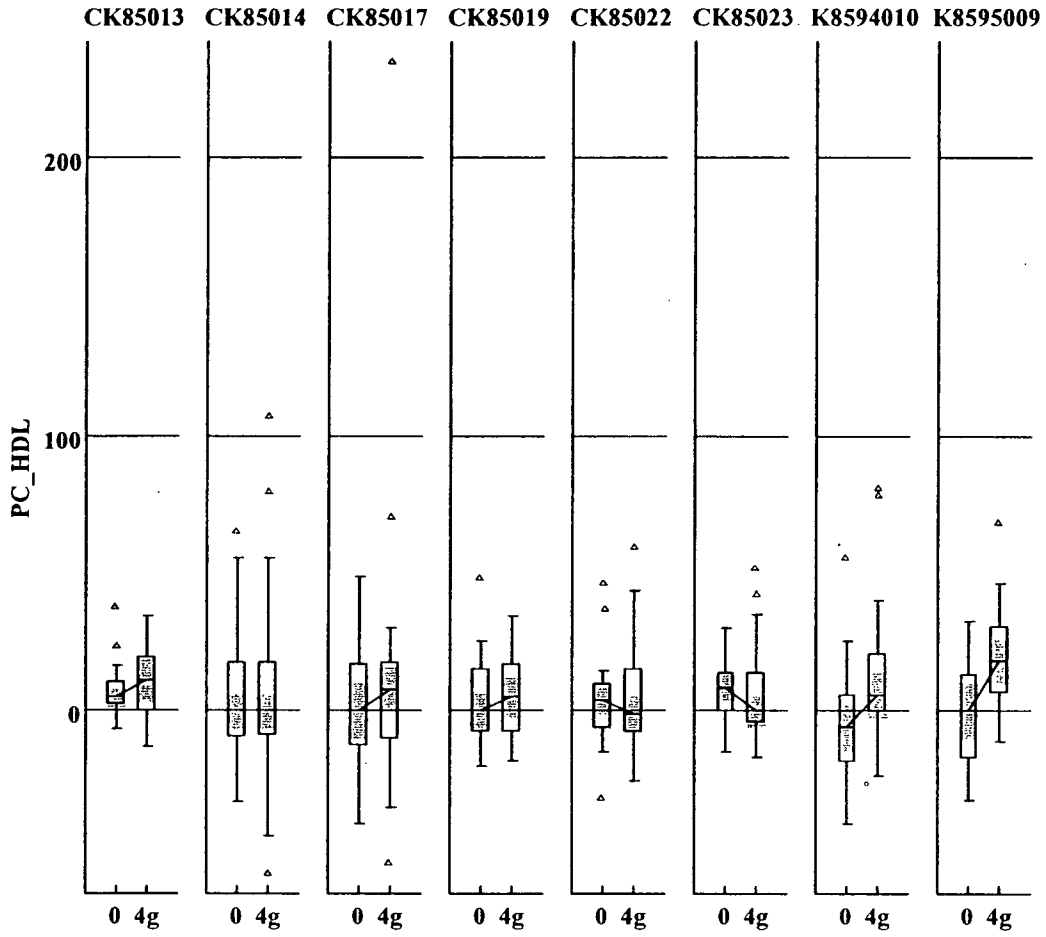
8. Box plot of individual Category I studies - % change of TG



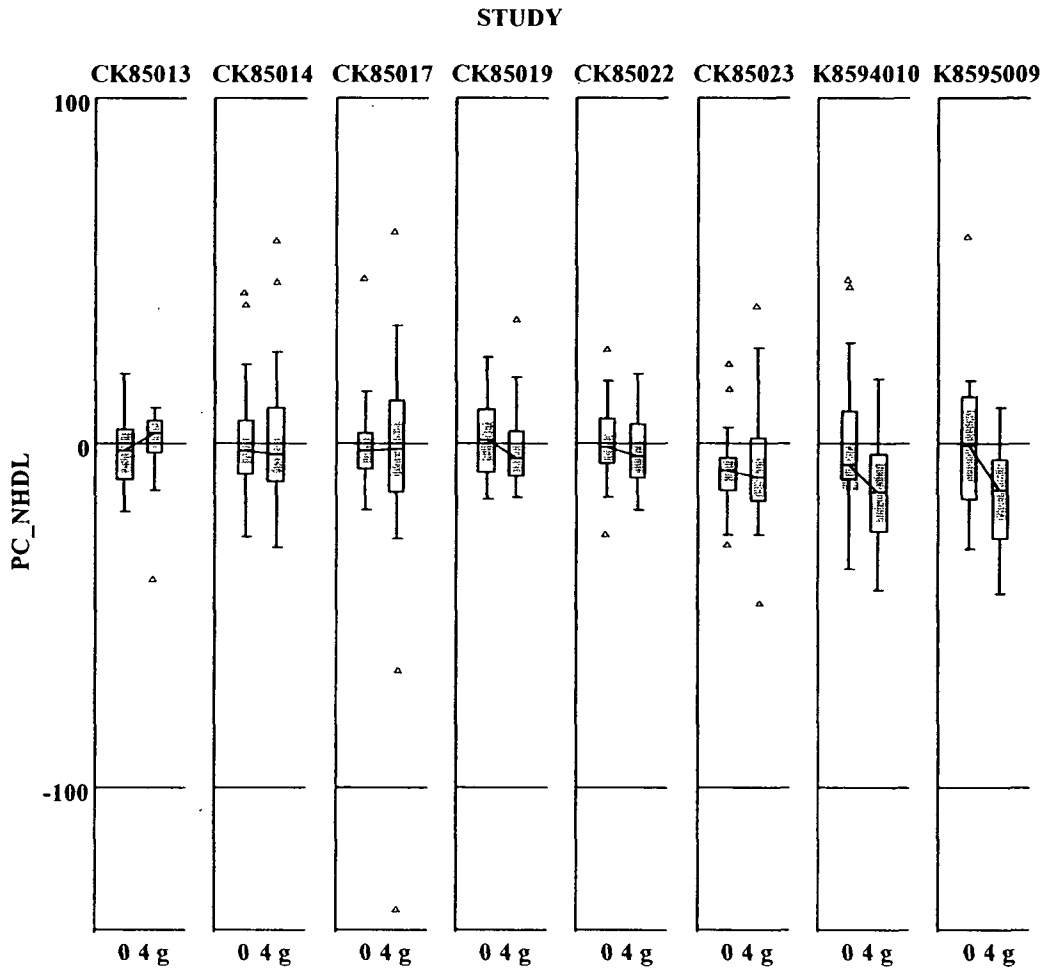
9. Box plot of individual Category I studies -% change of LDL
 STUDY



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



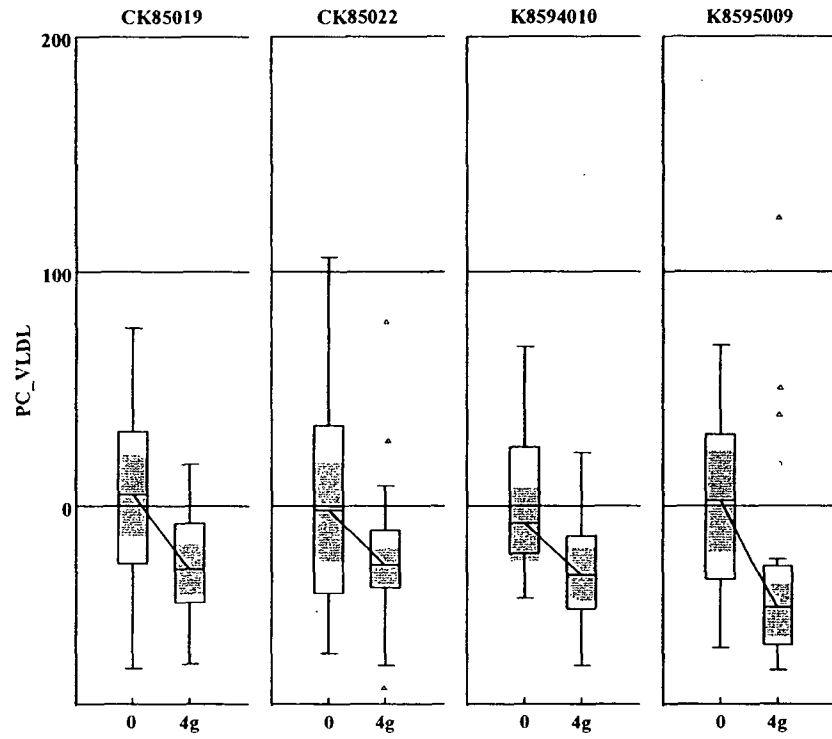
11. Box plot of individual Category I studies -% change of NHDL



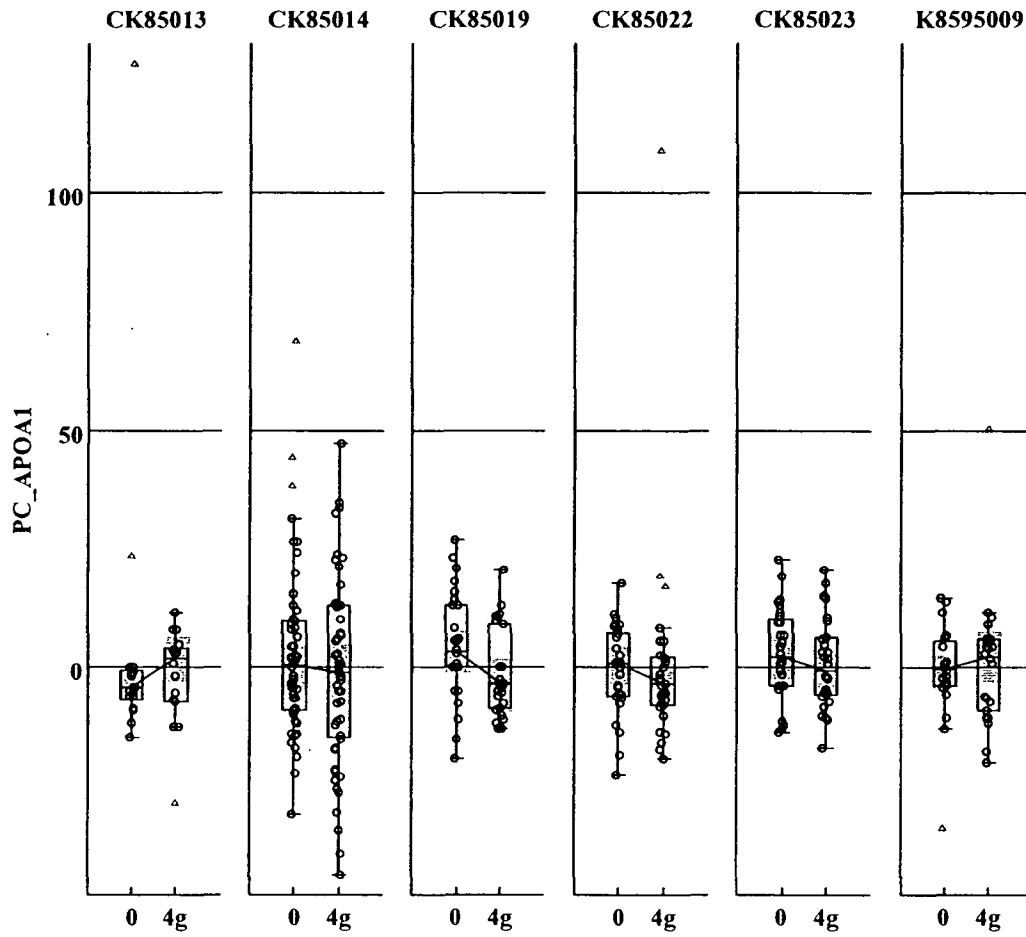
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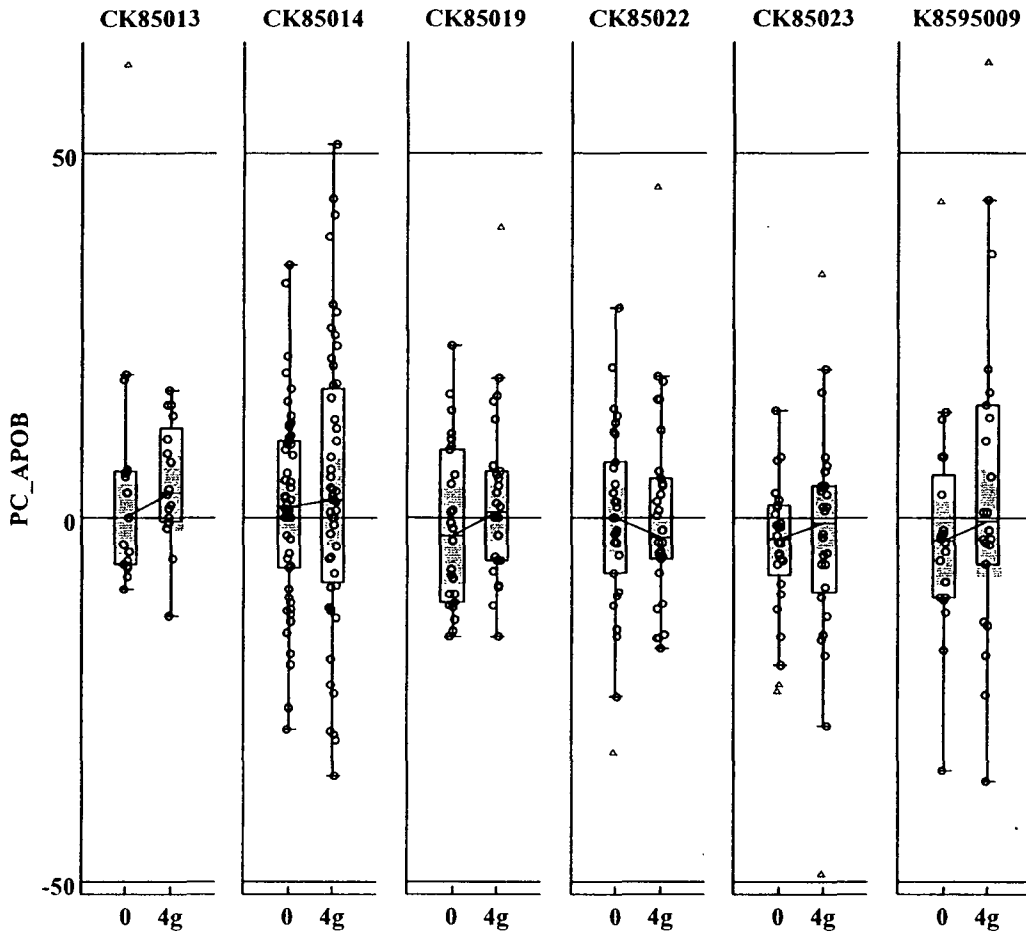
12. Box plot of individual Category I studies -% change of VLDL
STUDY



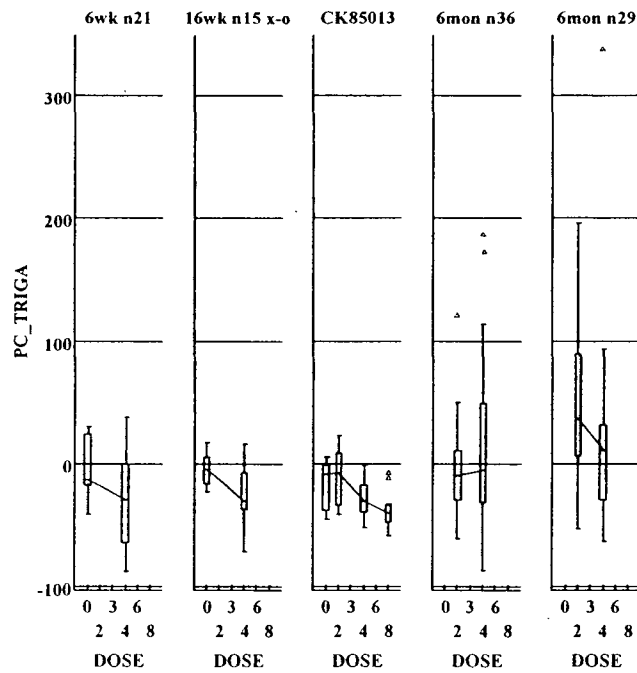
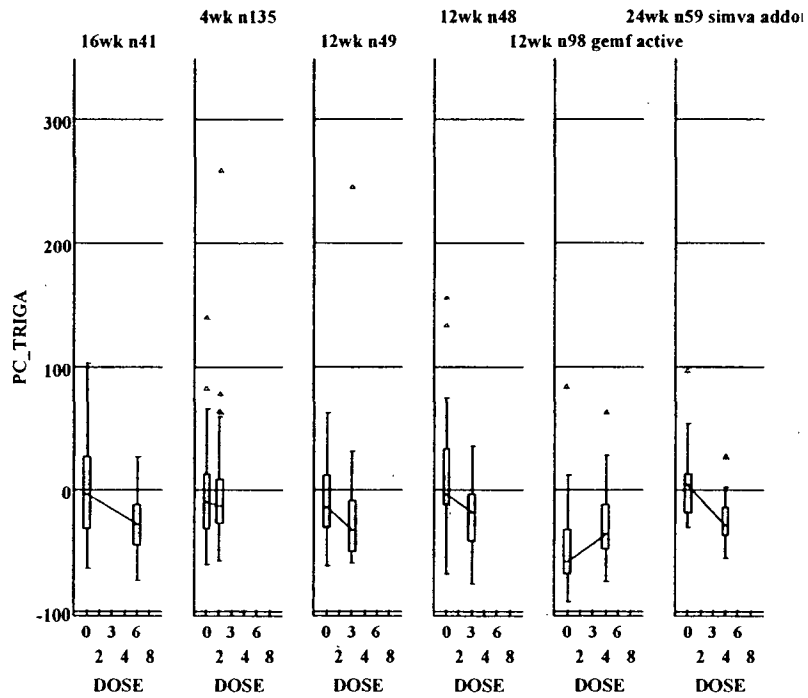
13. Box plot of individual Category I studies -% change of APOA1



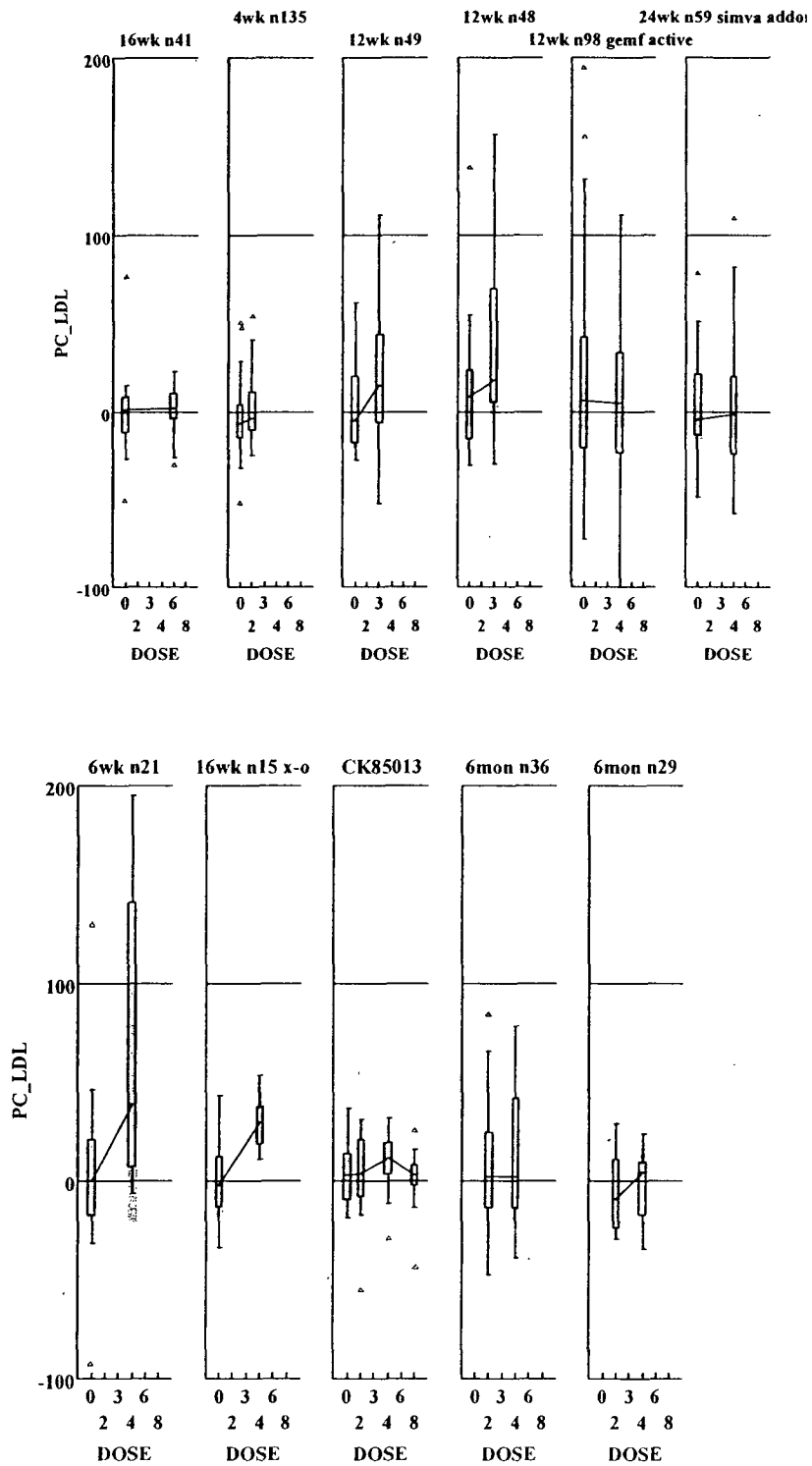
14. Box plot of individual Category I studies -% change of APOB



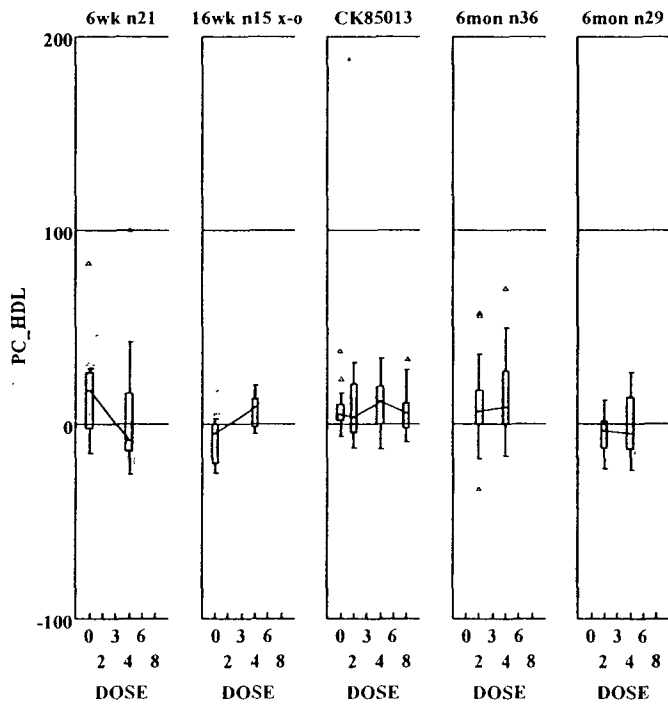
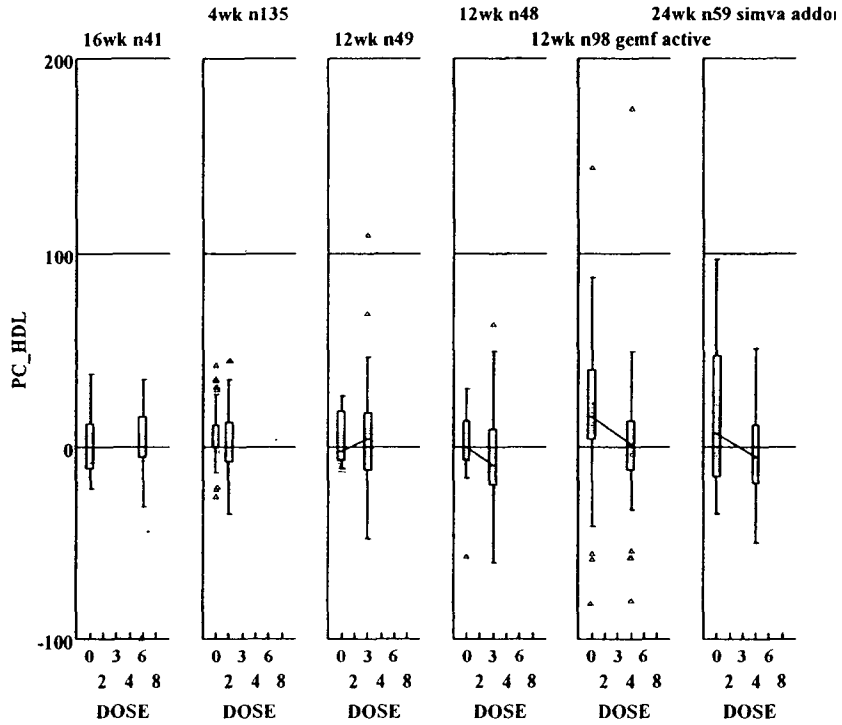
15. Median % change from baseline triglyceride - Category 2 Study



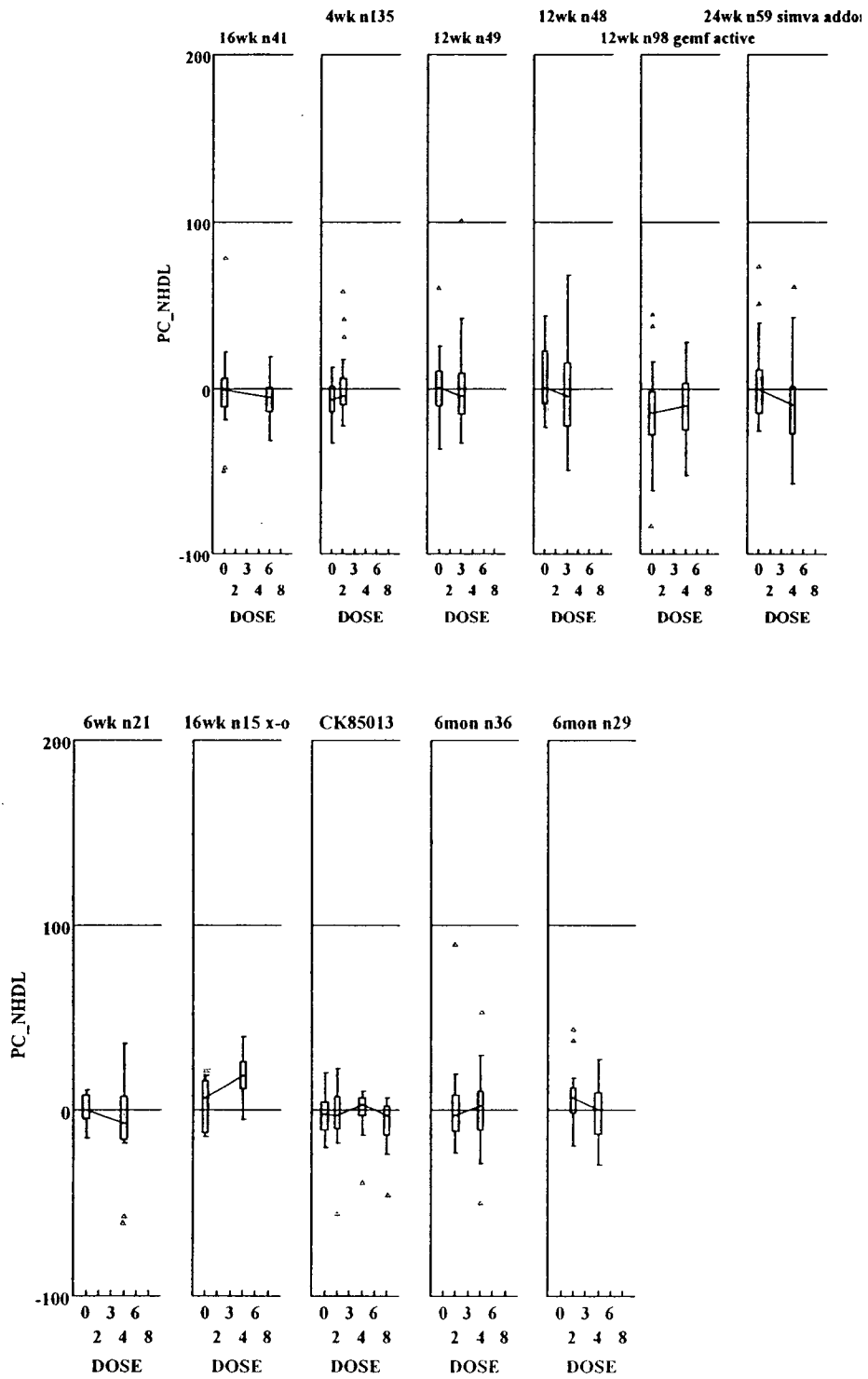
16. Median % change from baseline LDL - Category 2 Study



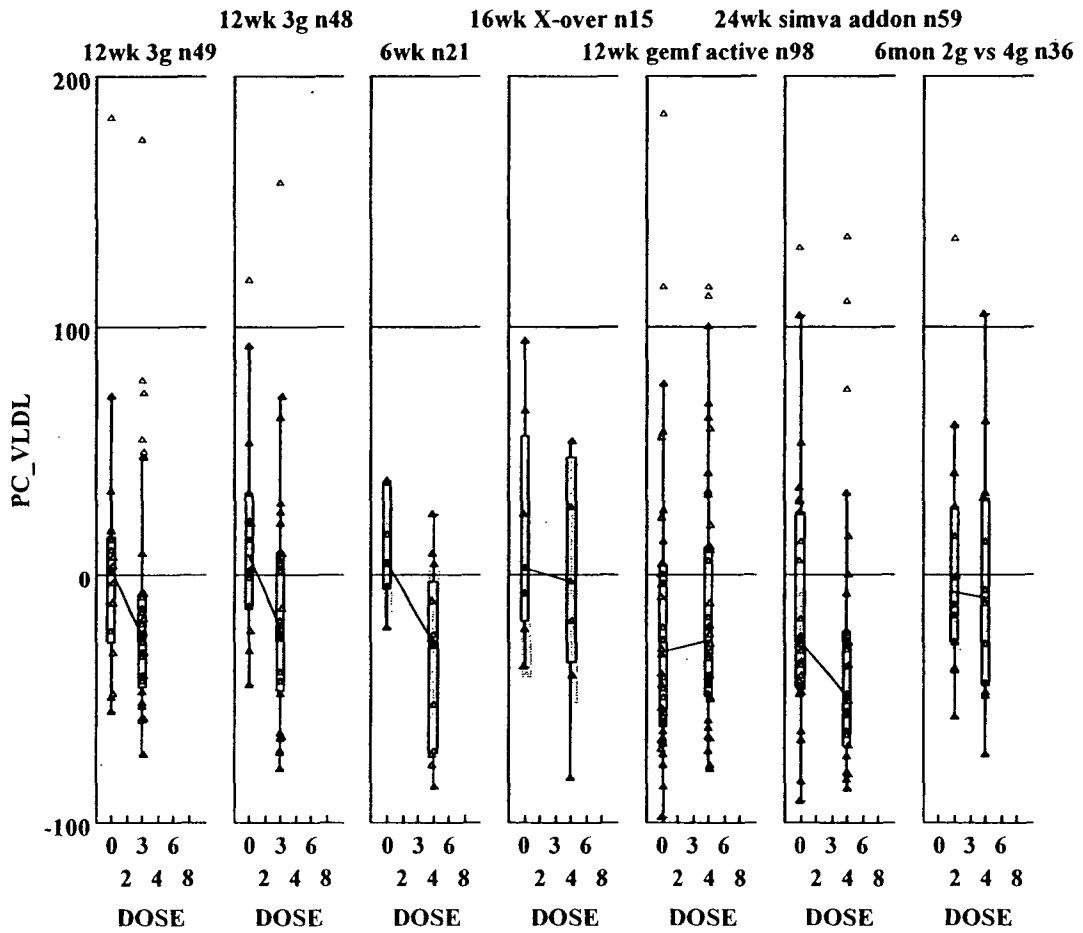
17. Median % change from baseline HDL - Category 2 Study



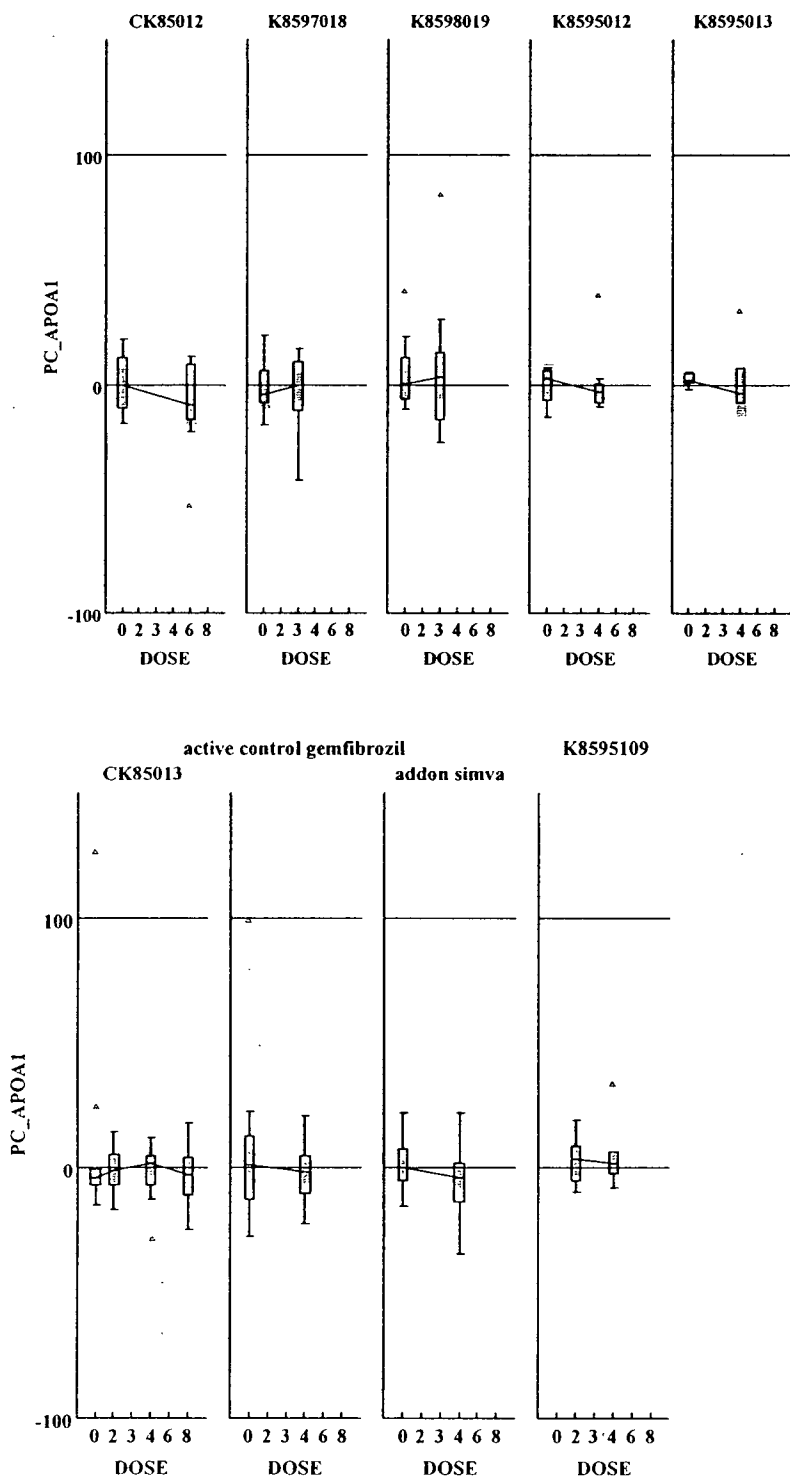
18. Median % change from baseline NHDL - Category 2 Study



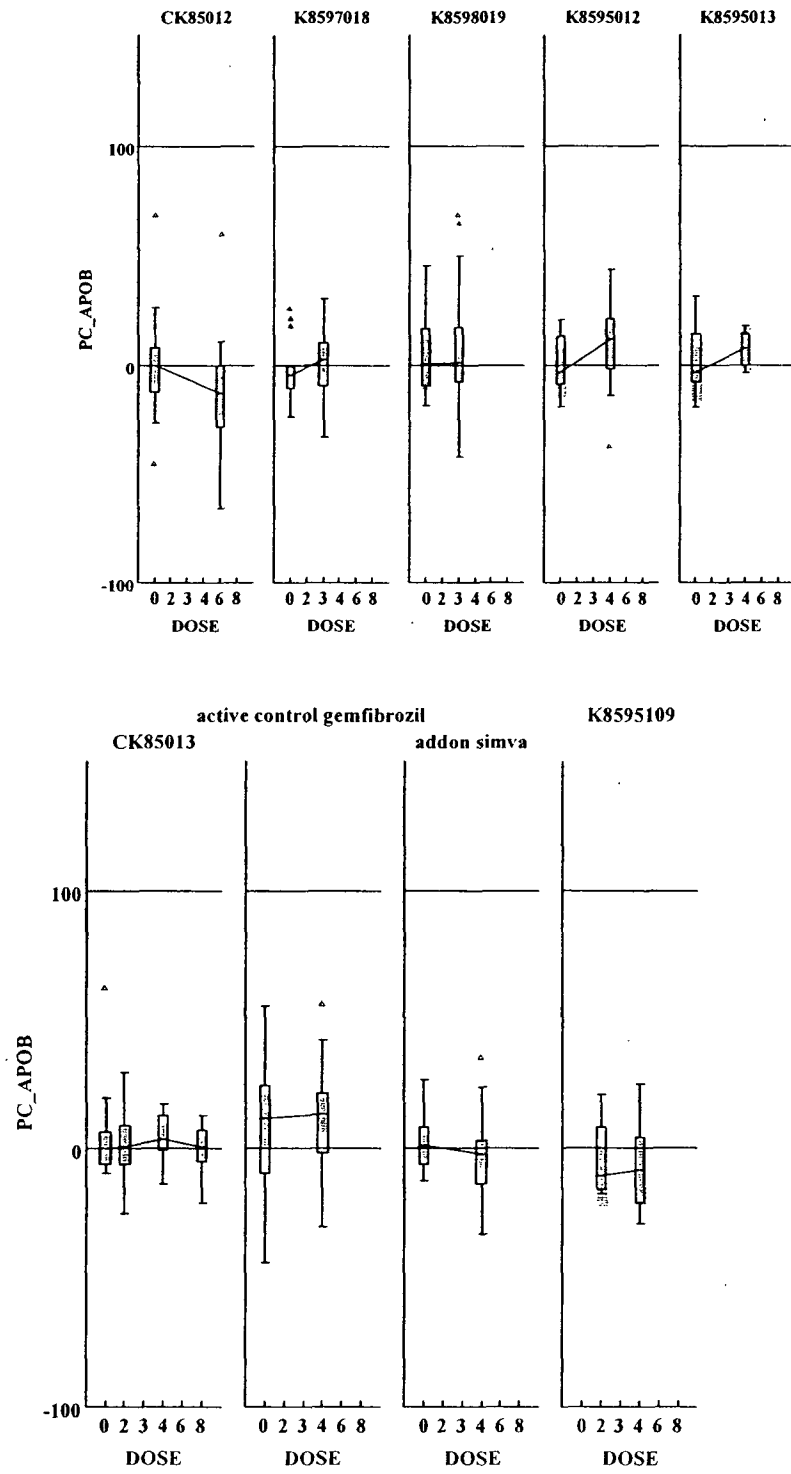
19. Median % change from baseline VLDL - Category 2 Study



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

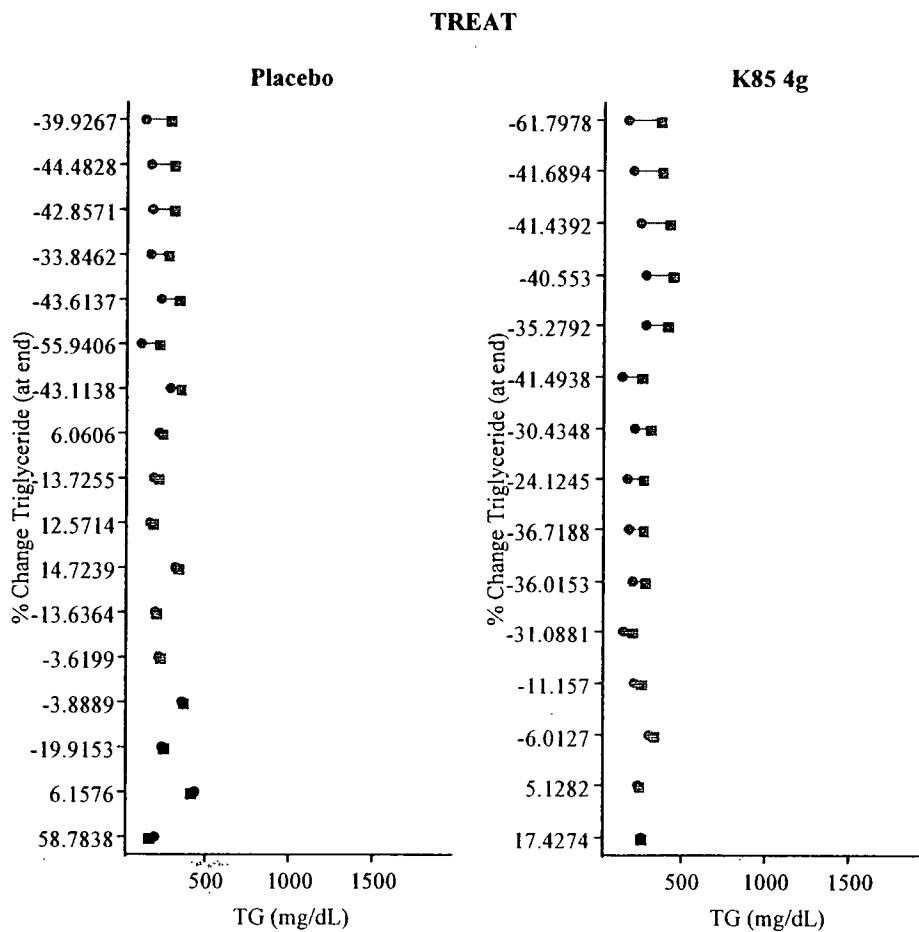


21. Median % change from baseline ApoA1 - Category 2 Study



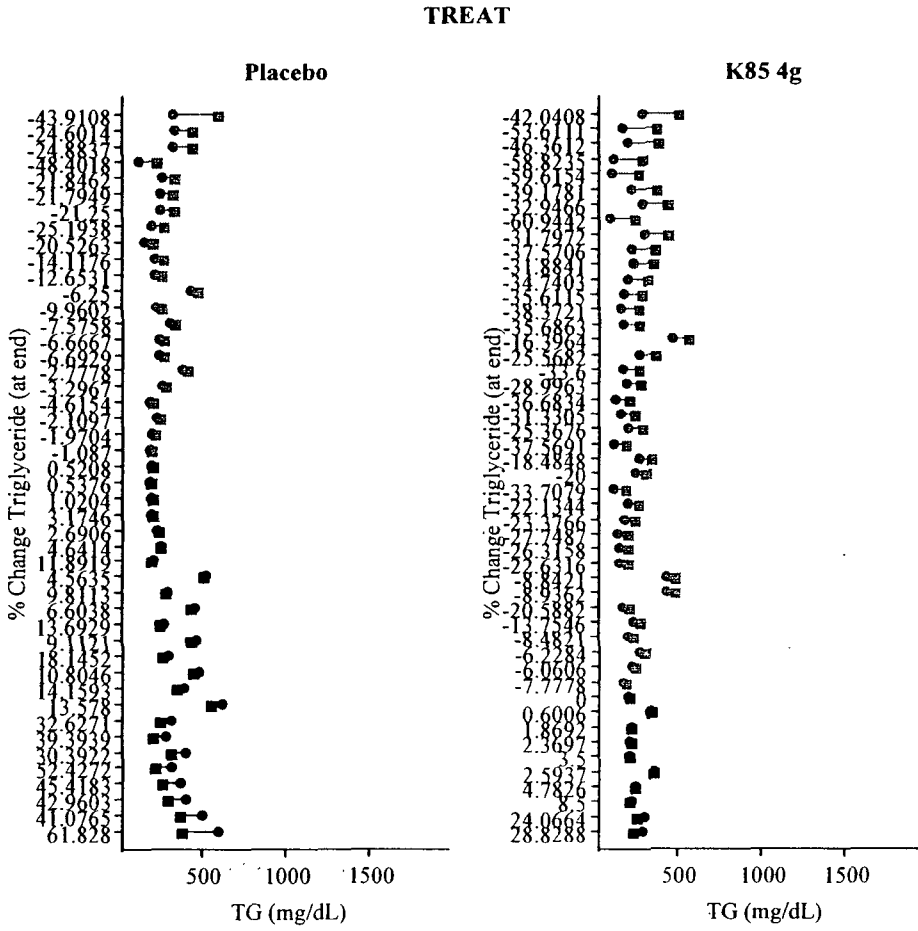
22. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85013

**STUDY
CK85013**



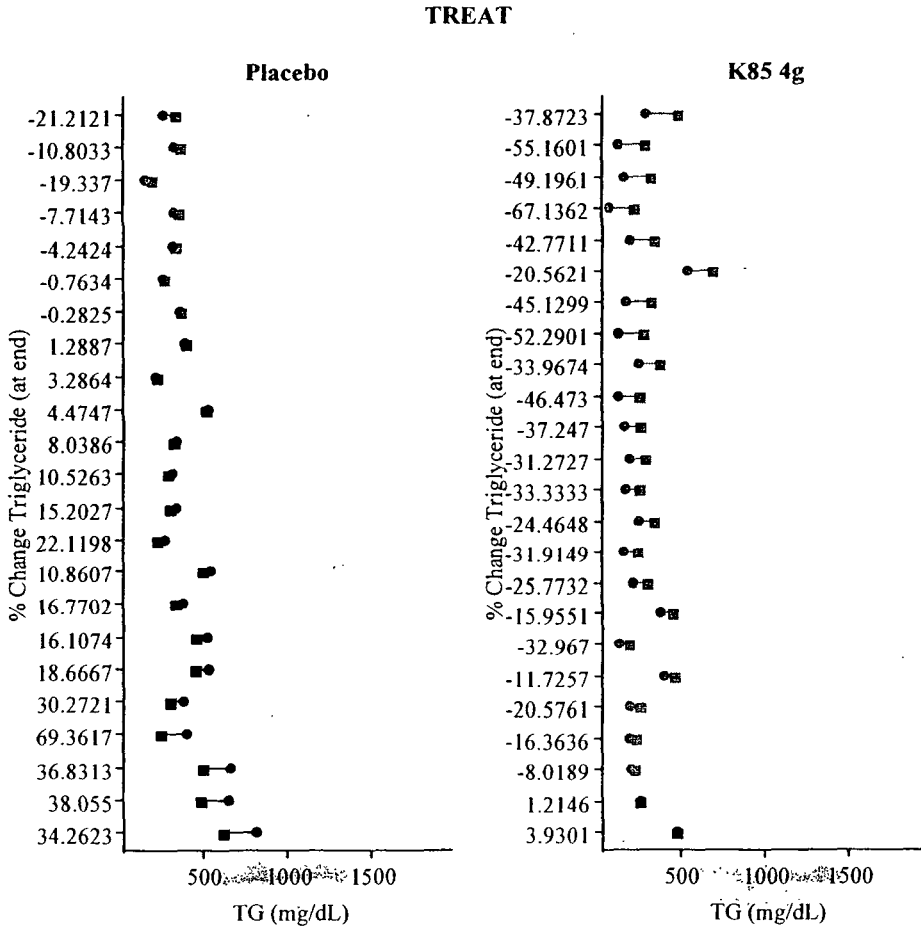
23. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85014

STUDY
CK85014



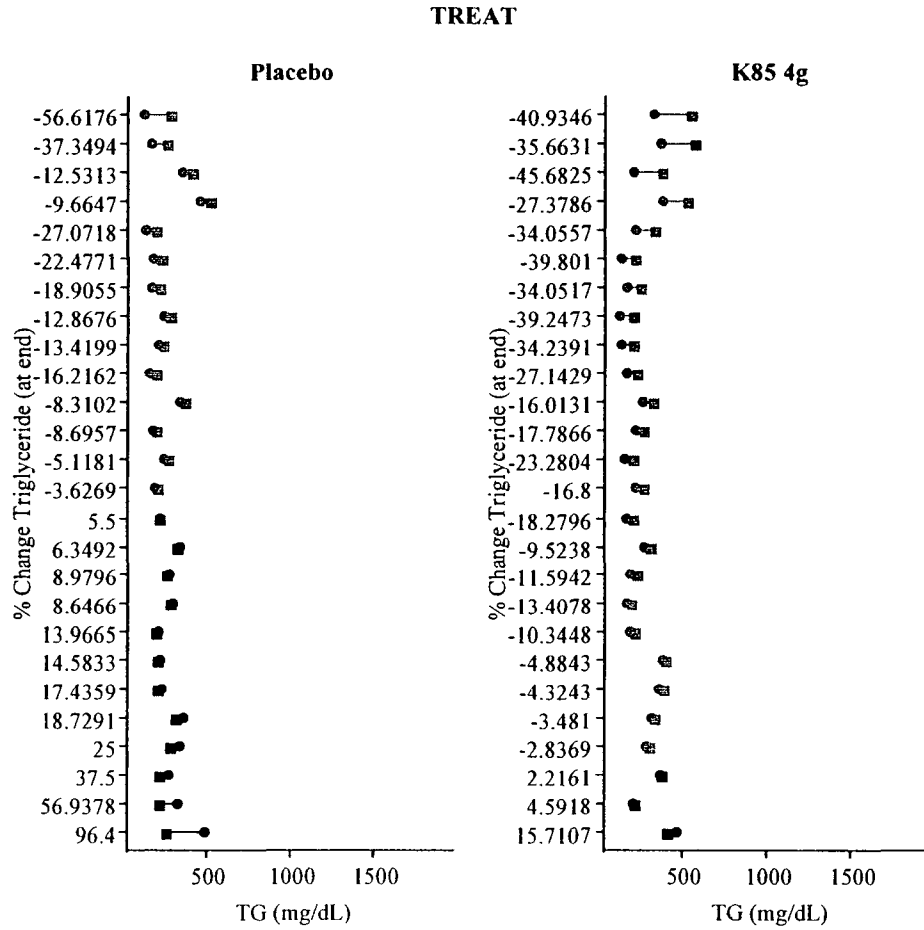
24. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85017

**STUDY
CK85017**



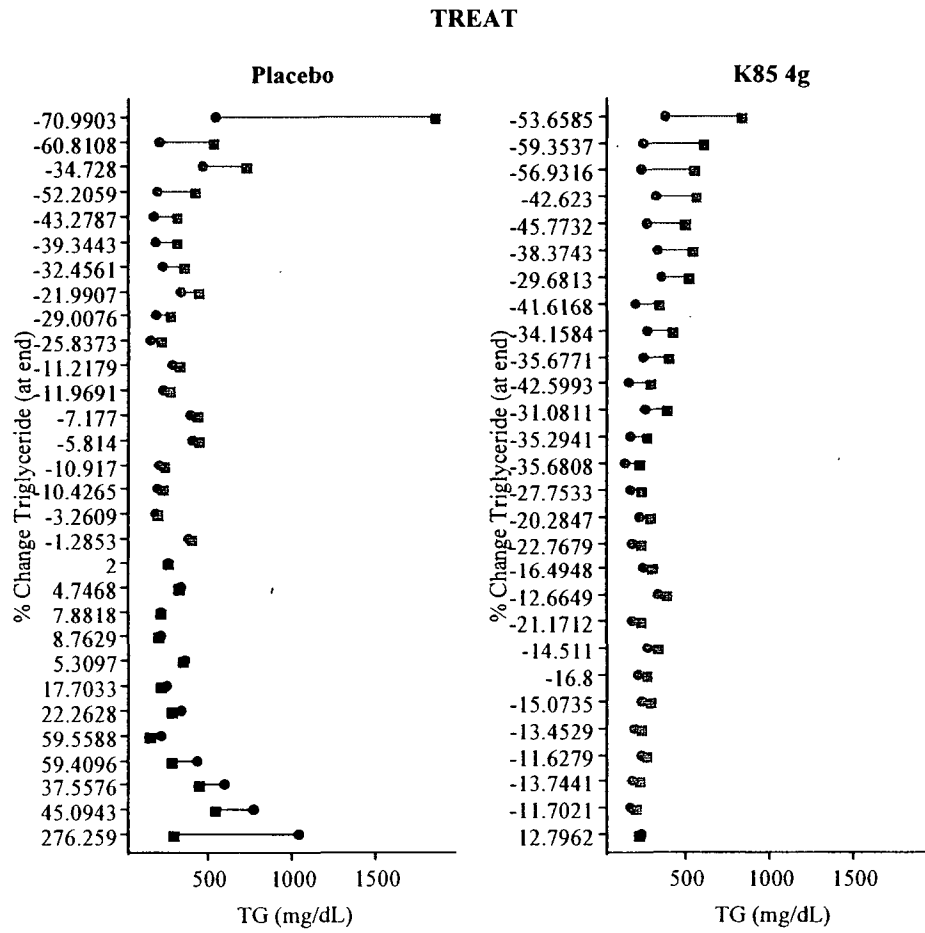
25. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG - 85019

STUDY
CK85019



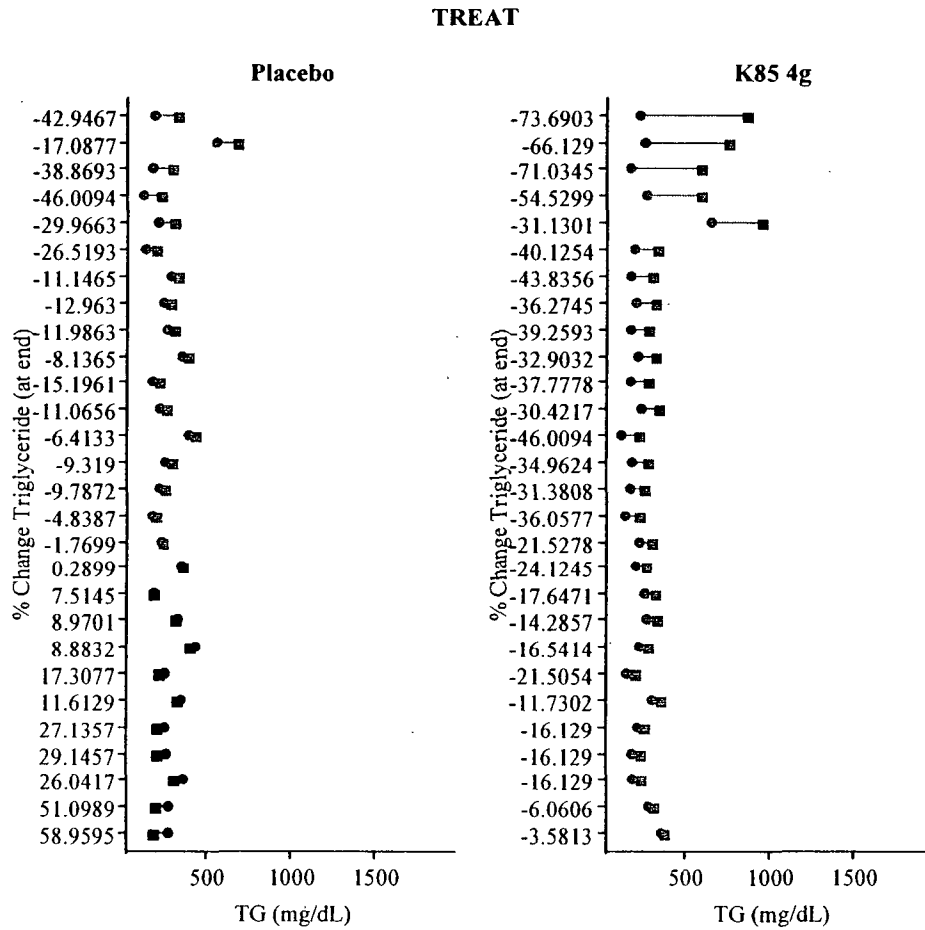
26. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG - 85020

STUDY
CK85022



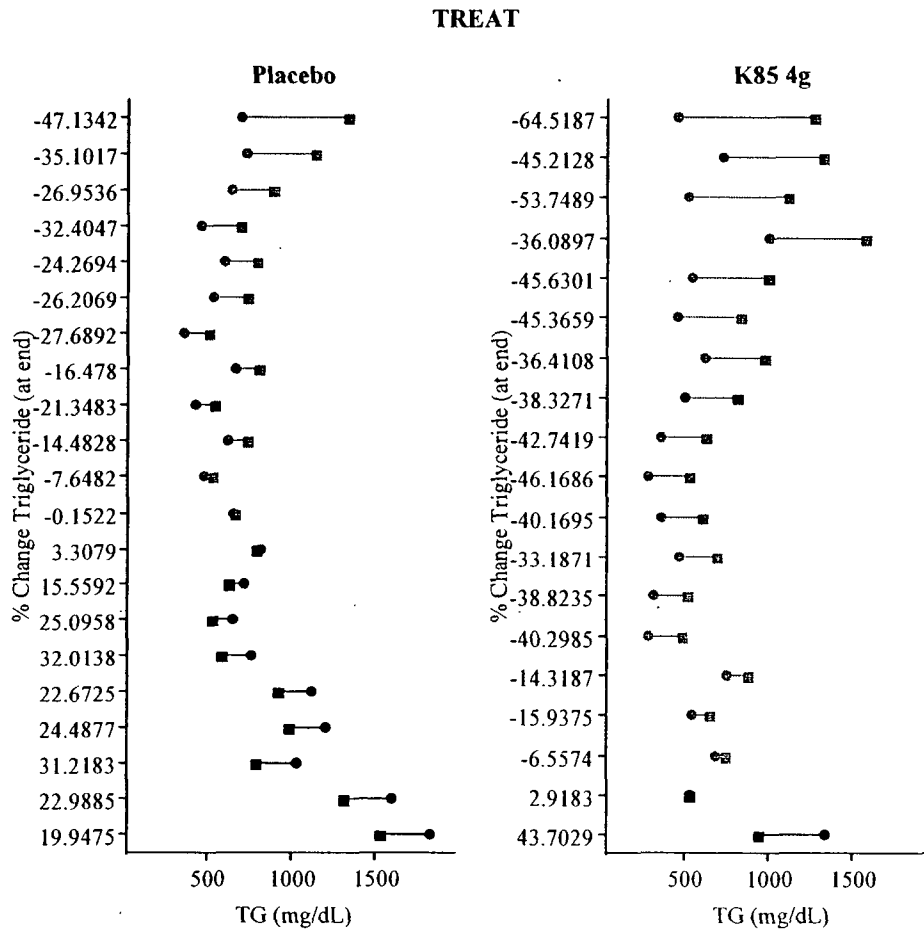
27. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 85023

STUDY
CK85023



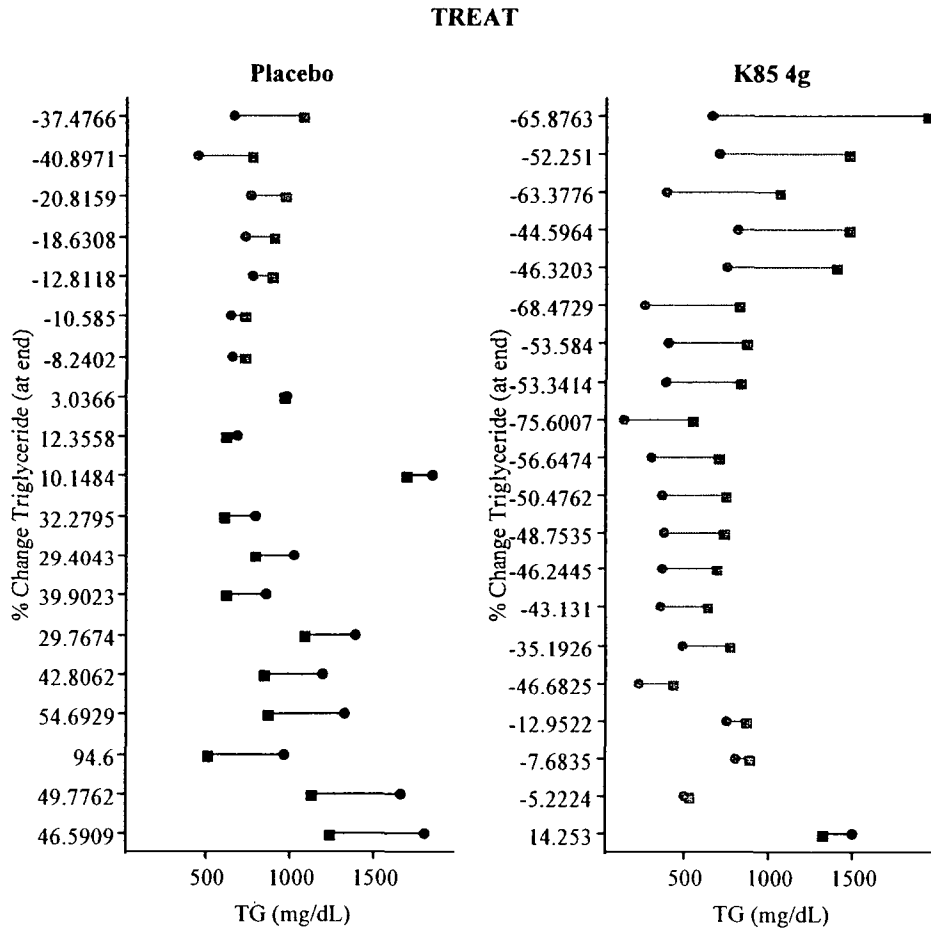
28. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 94010

STUDY
K8594010



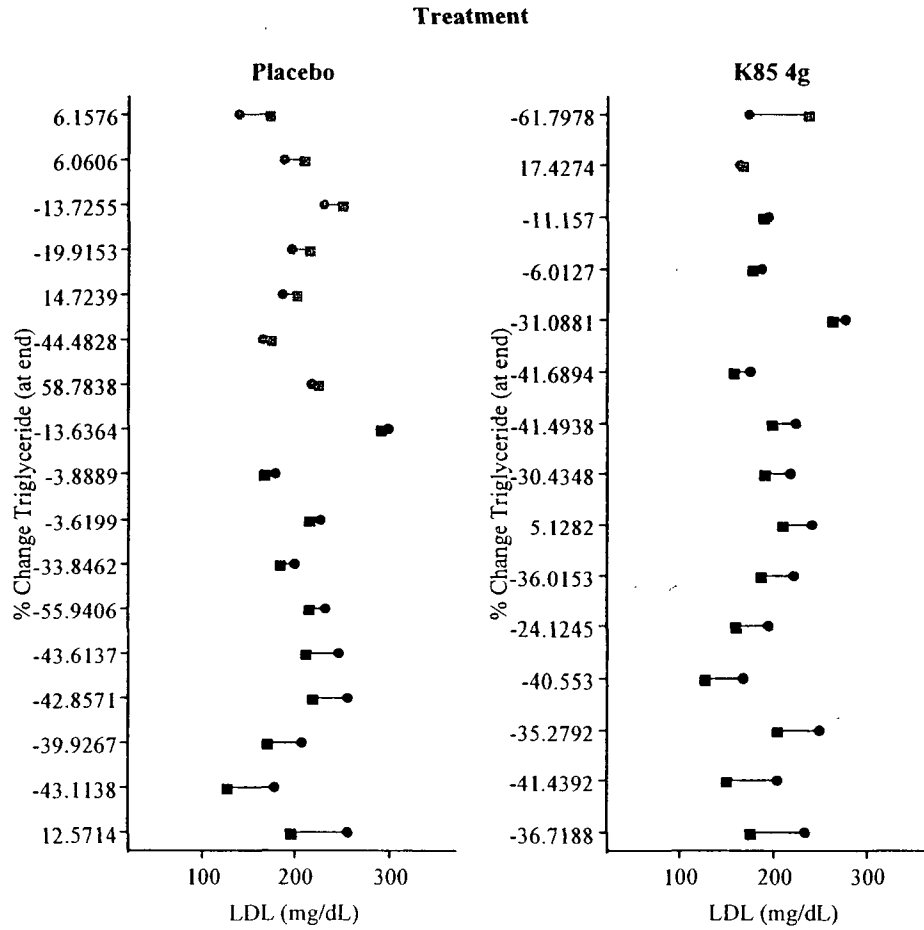
29. Change from baseline (square) to endpoint (circle) of TG by patient labeled by % change of TG – Study 95009

STUDY
K8595009



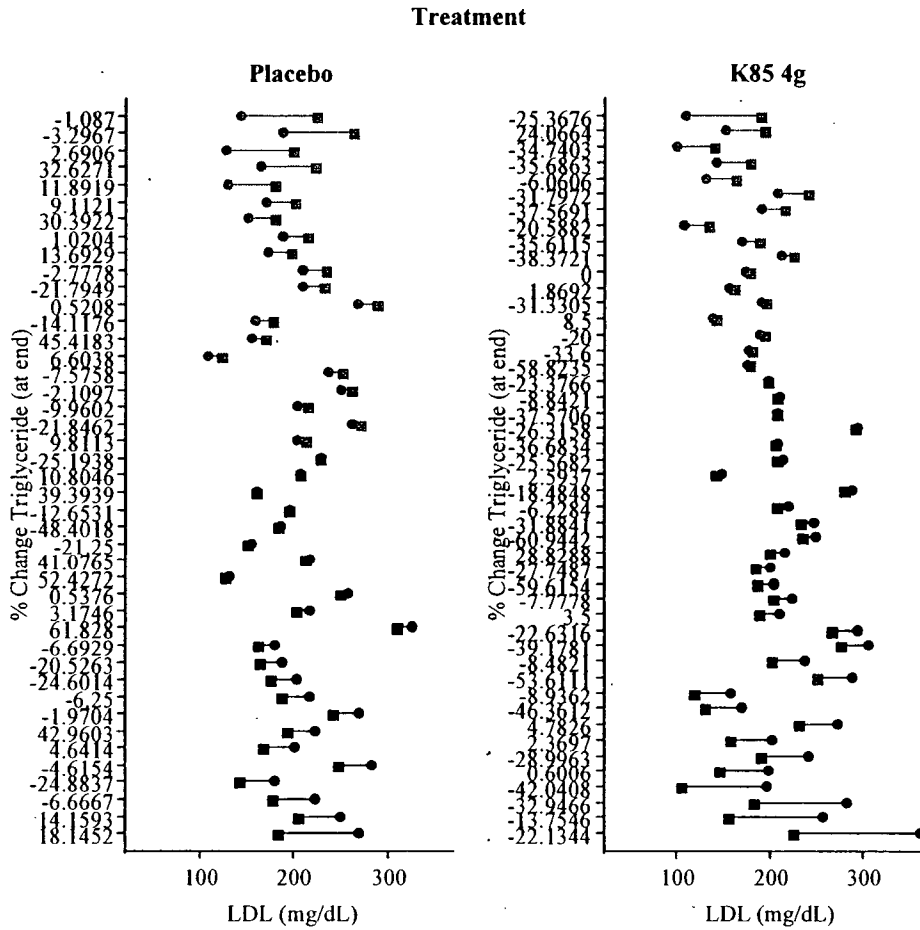
30. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85013

**STUDY
CK85013**



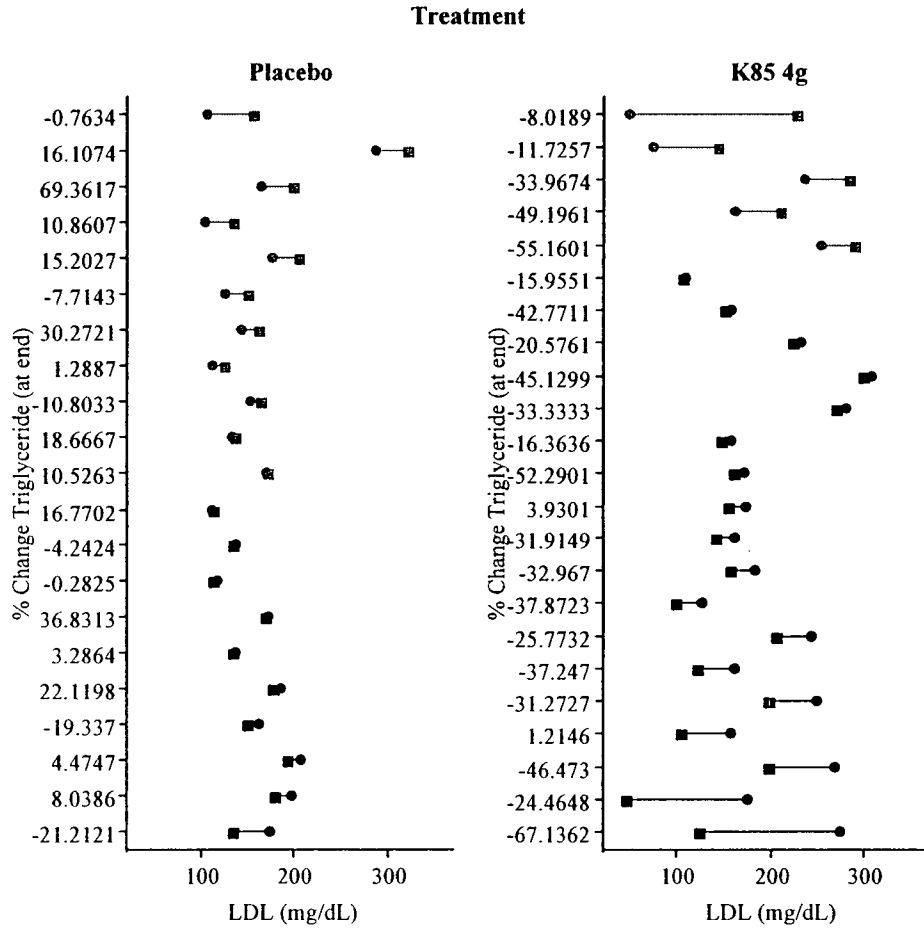
31. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85014

STUDY
CK85014



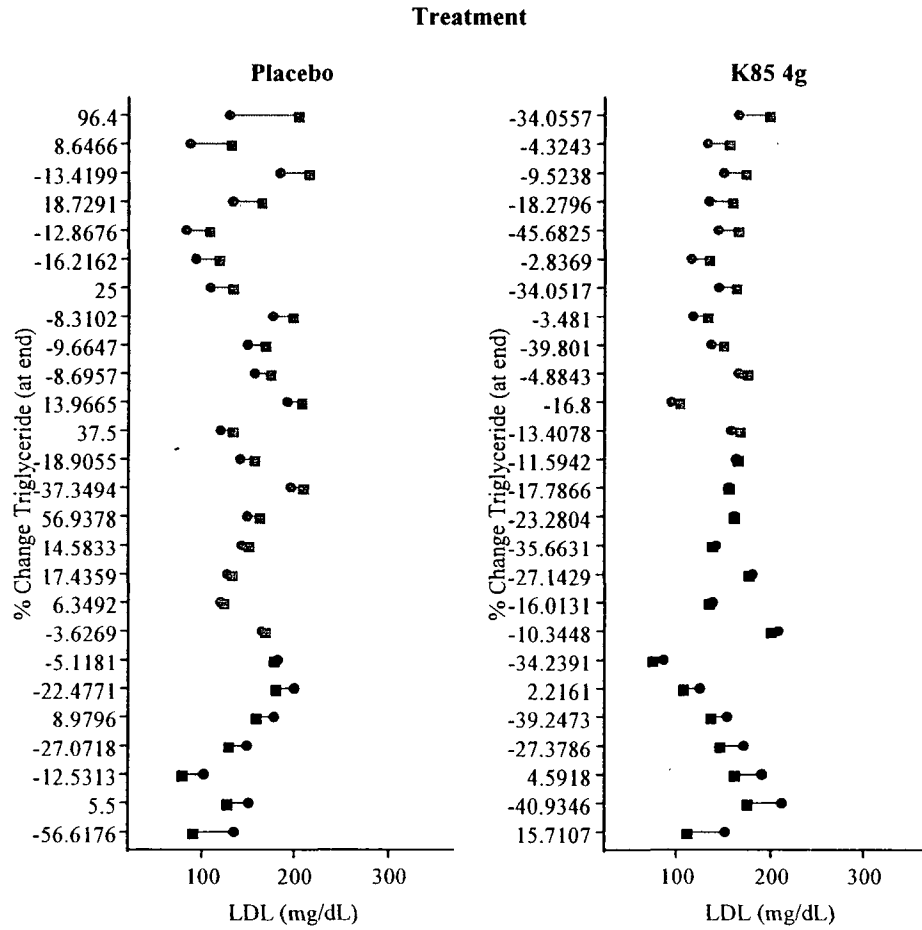
32. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85017

STUDY
CK85017



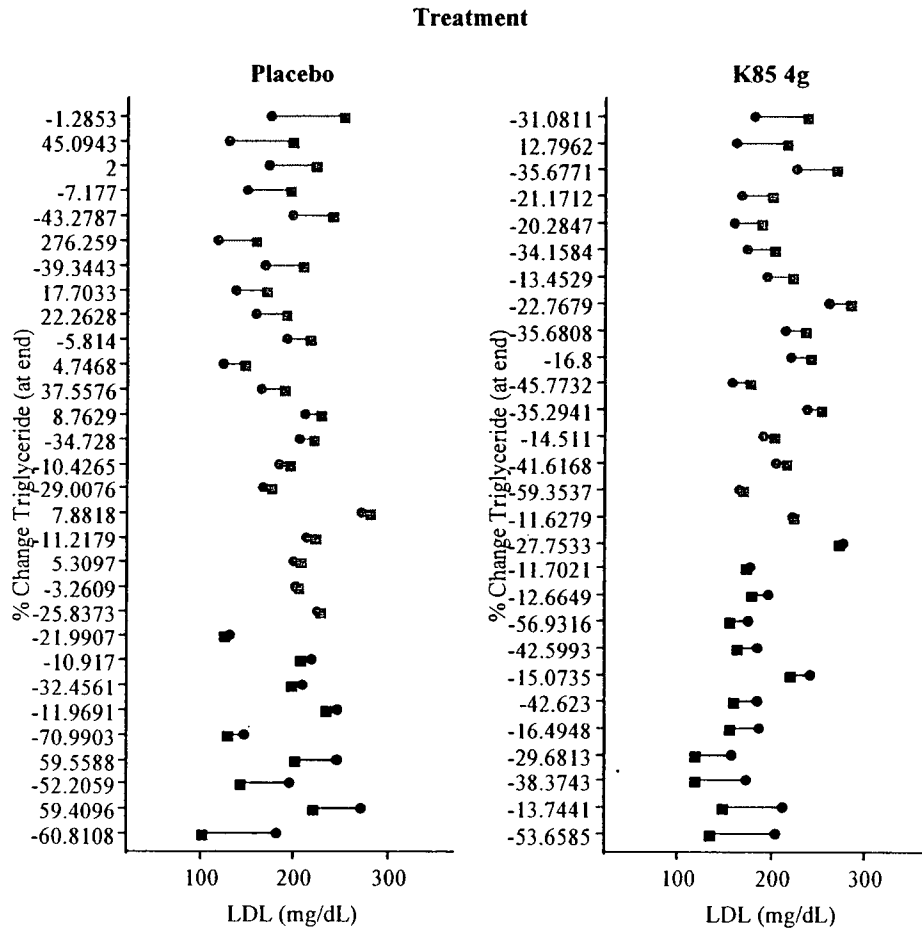
33. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85019

STUDY
CK85019



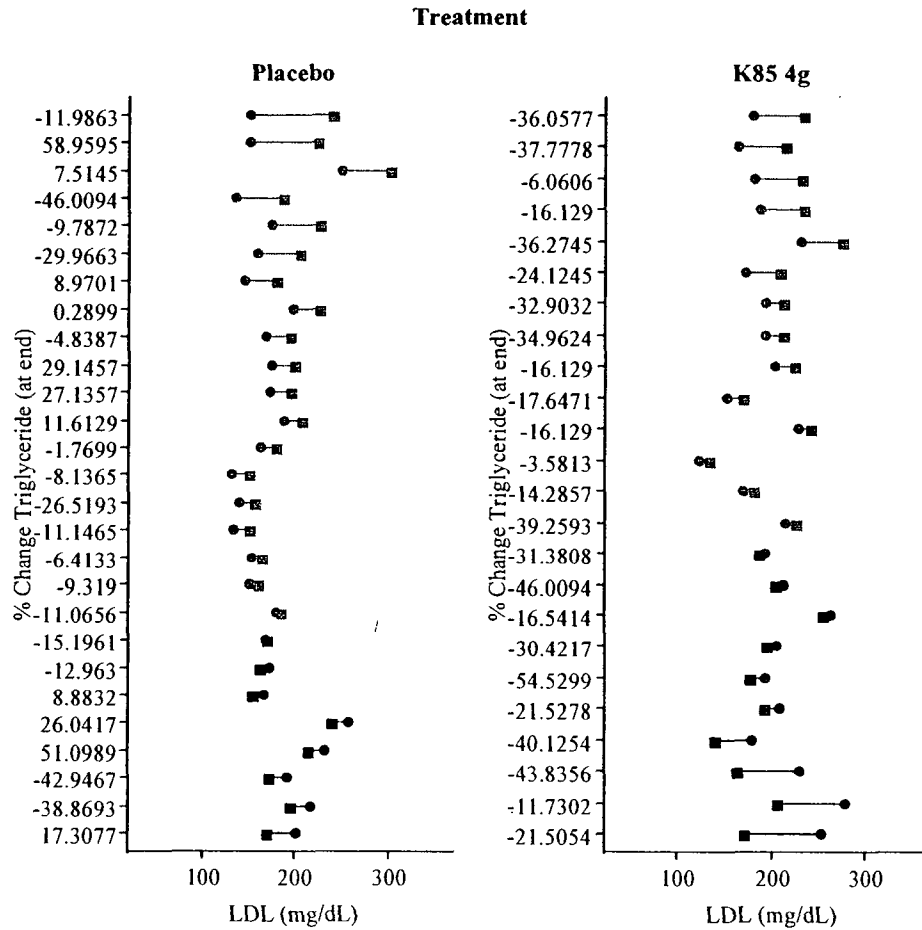
34. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85022

STUDY
CK85022



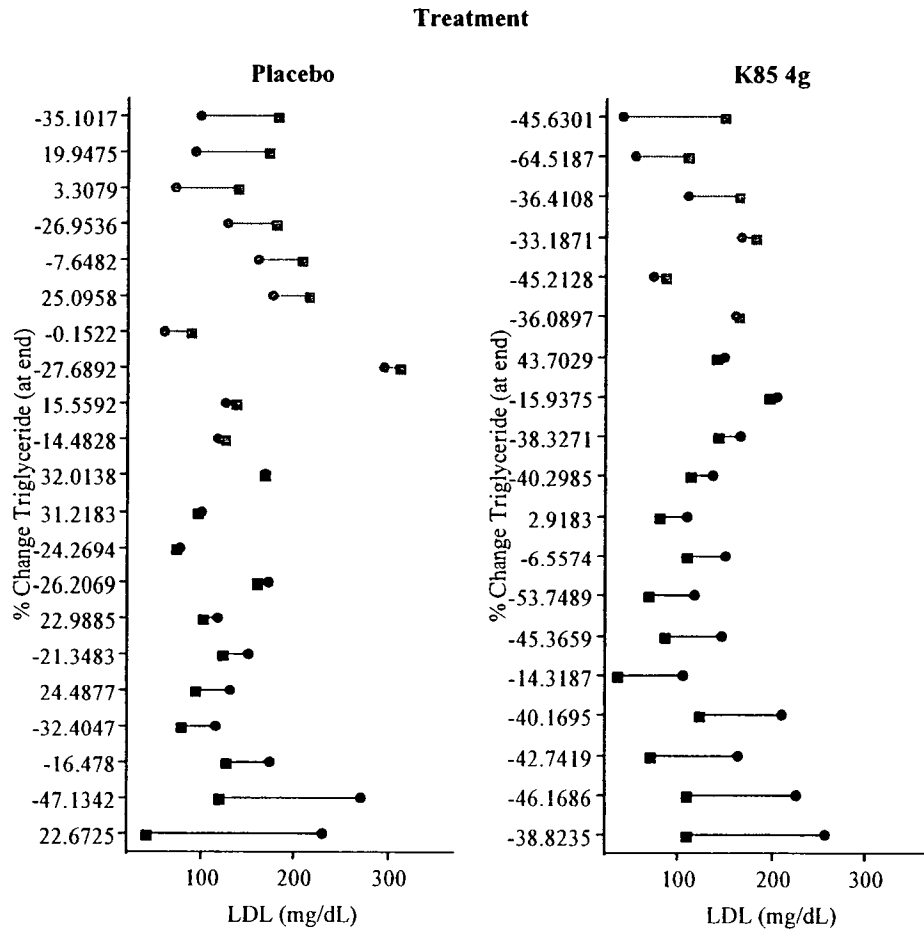
35. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 85023

STUDY
CK85023



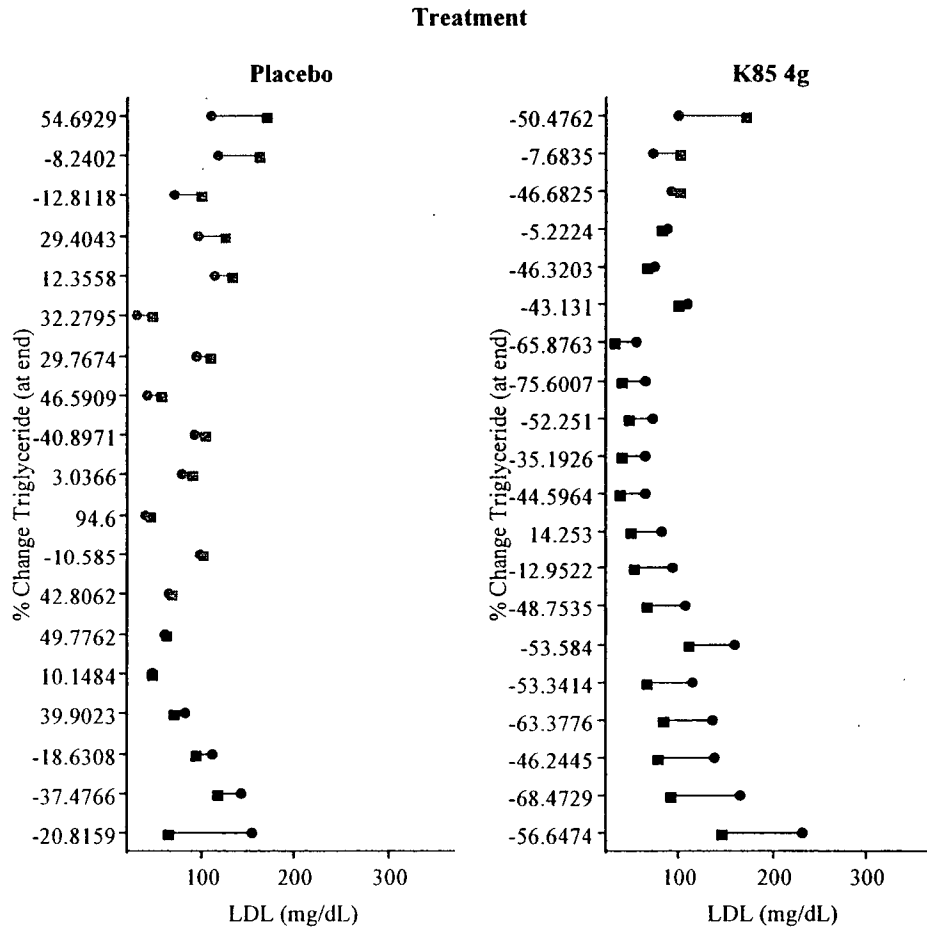
36. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 94010

STUDY
K8594010



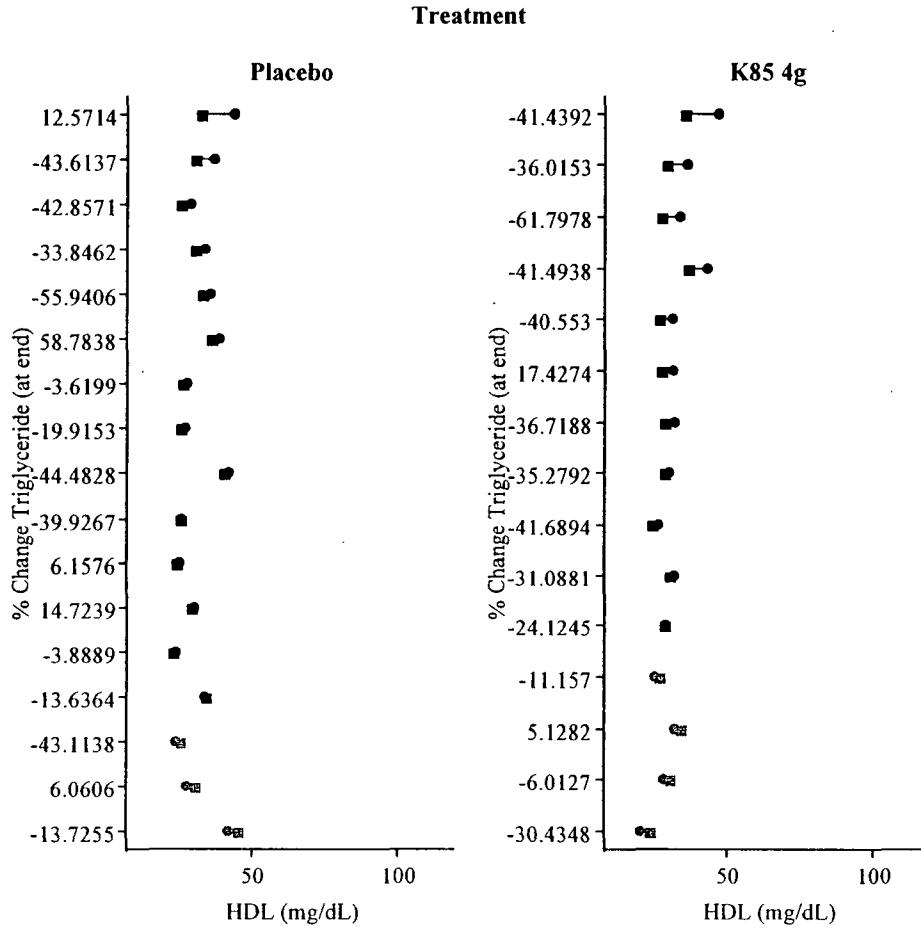
37. Change from baseline (square) to endpoint (circle) of LDL by patient labeled by % change of TG – Study 95009

STUDY
K8595009



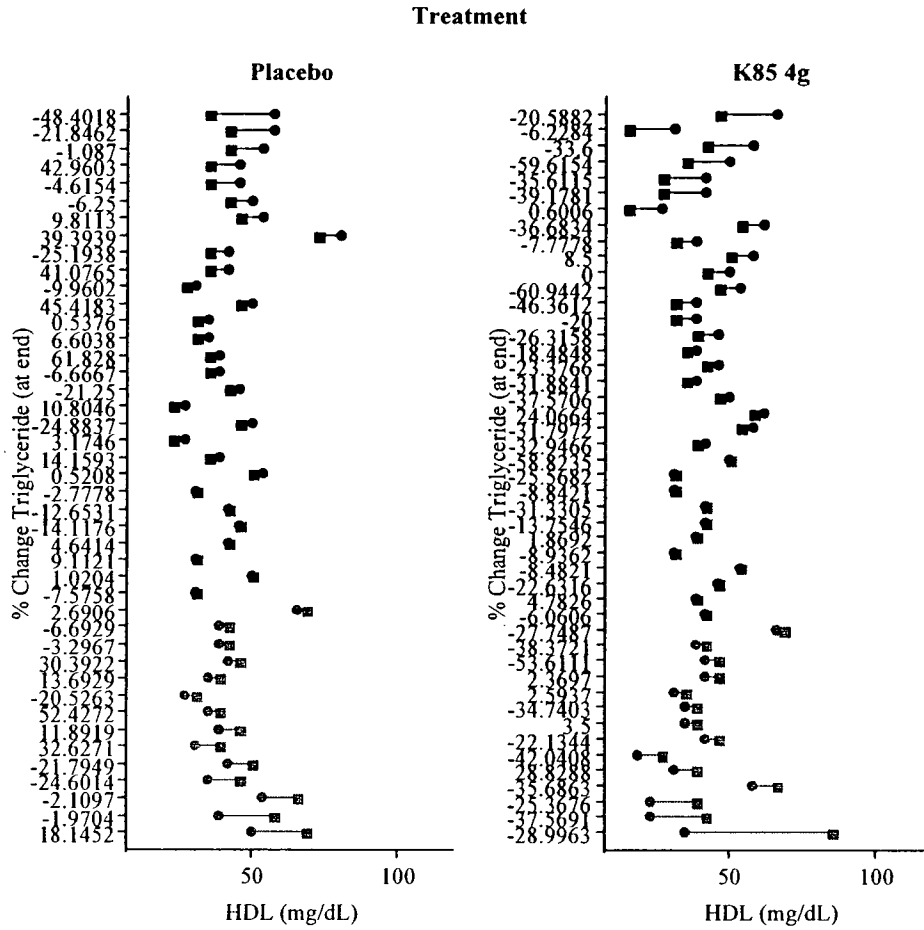
38. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85013

**STUDY
CK85013**



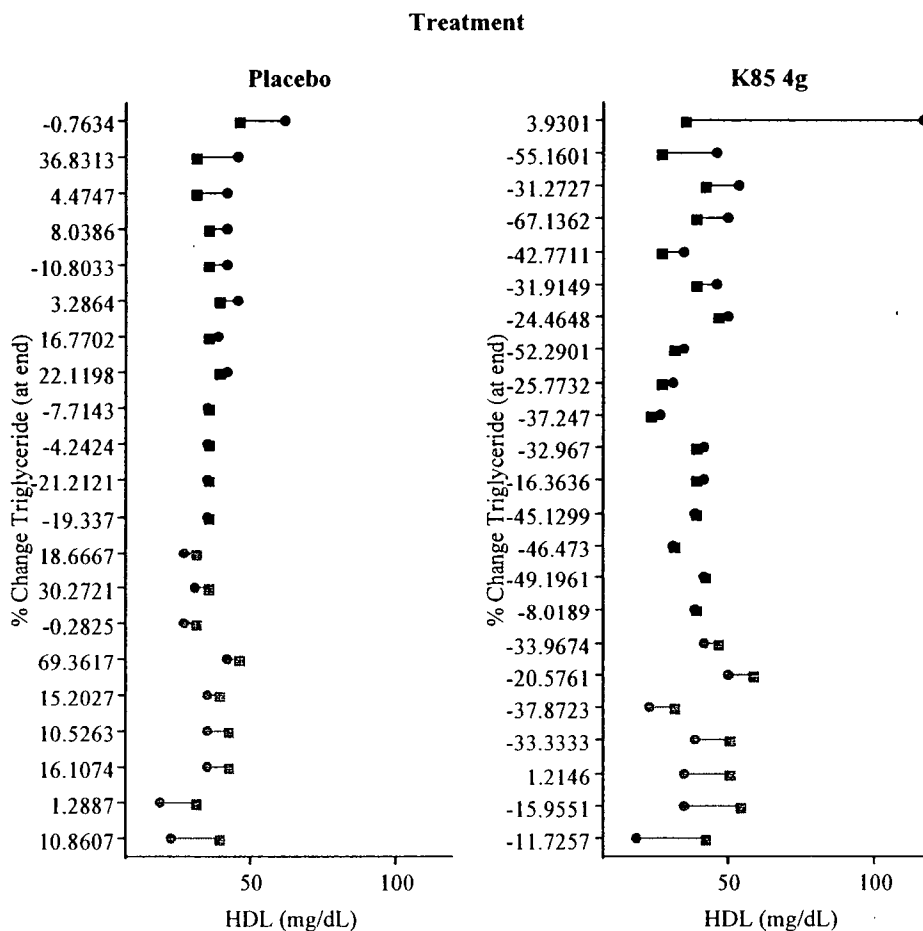
39. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85014

STUDY
CK85014



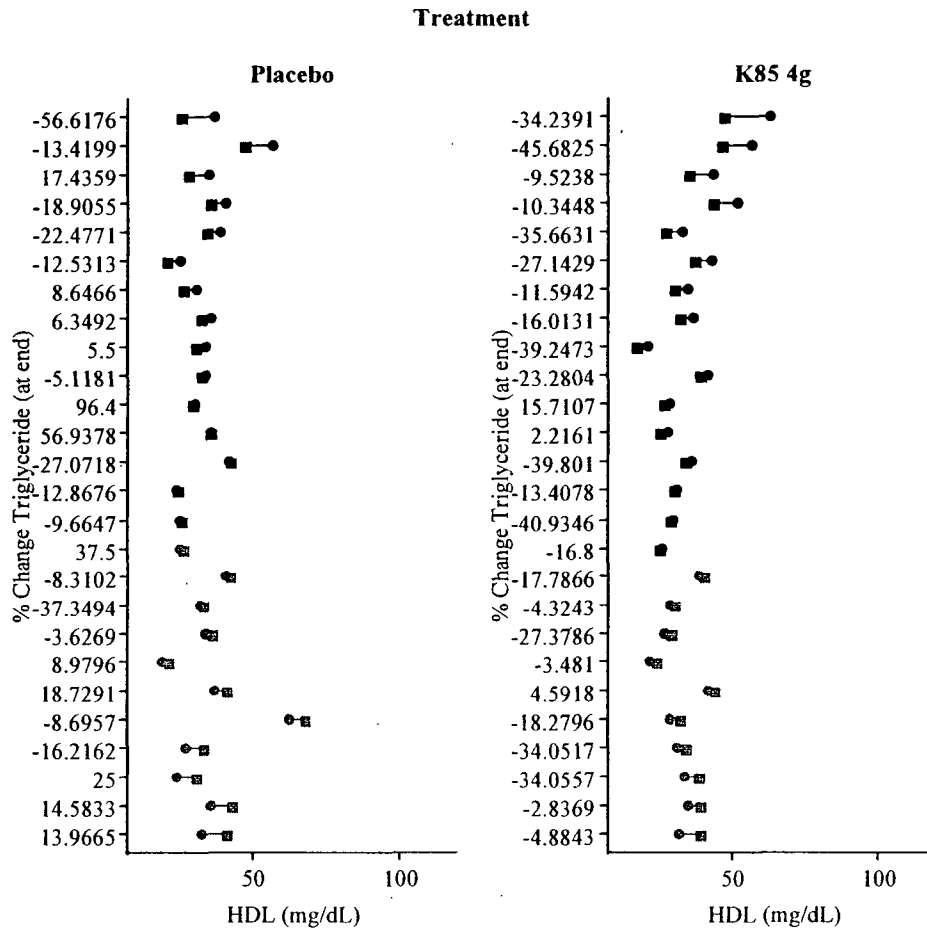
40. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85017

STUDY
CK85017



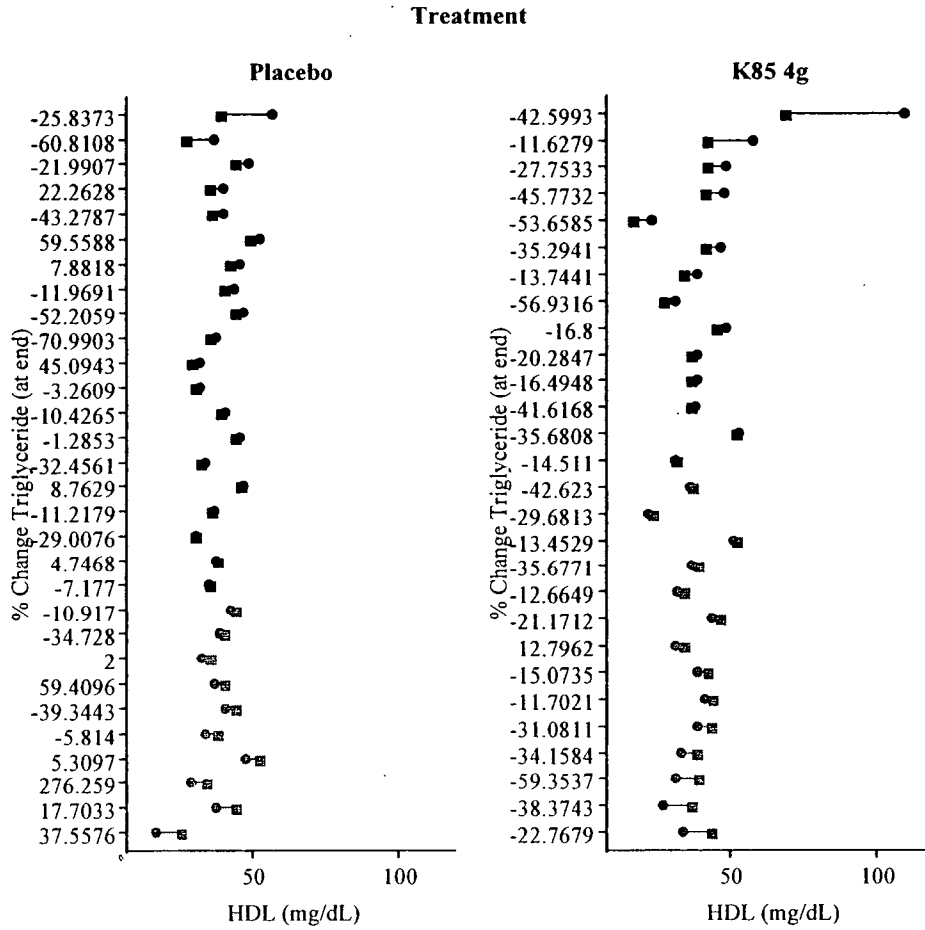
41. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85019

**STUDY
CK85019**



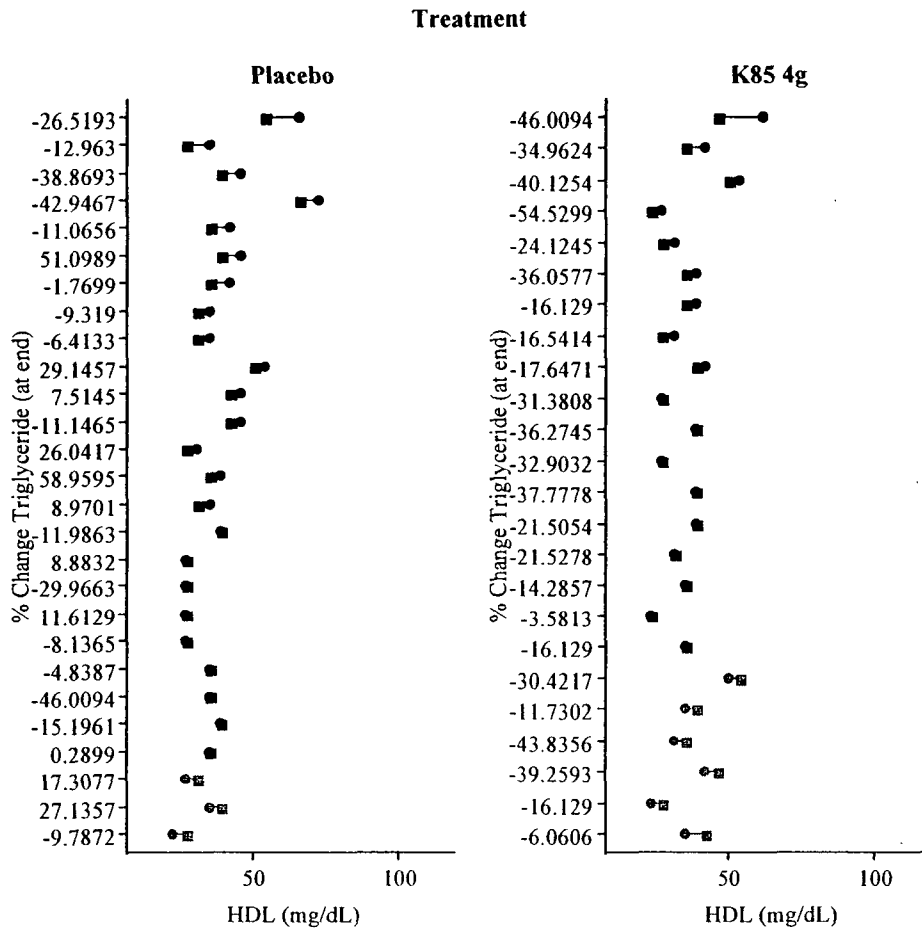
42. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85022

STUDY
CK85022



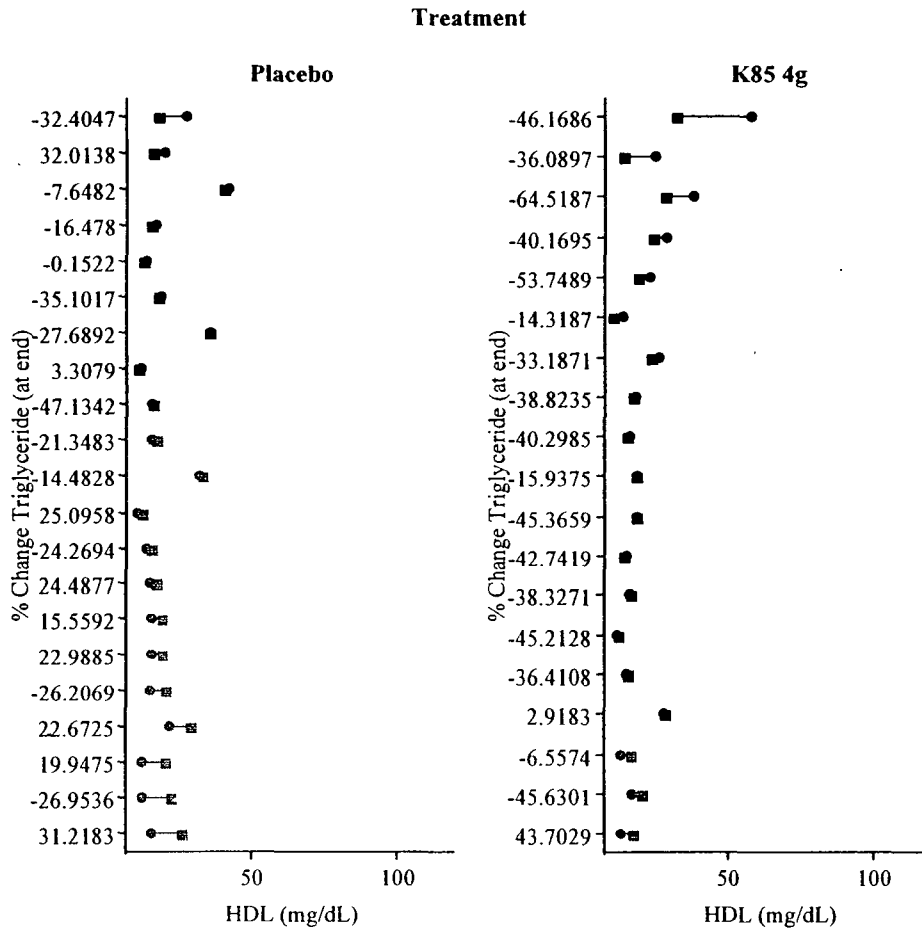
43. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 85023

STUDY
CK85023



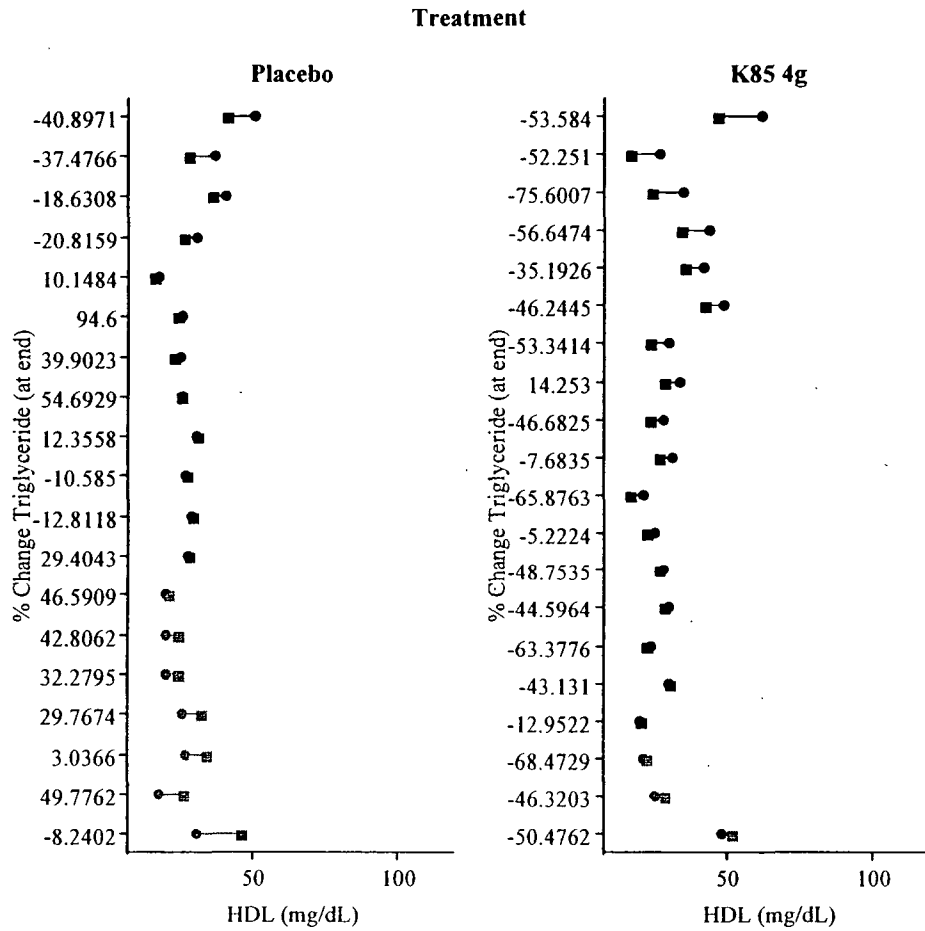
44. Change from baseline (square) to endpoint (circle) of HDL by patient labeled by % change of TG – Study 94010

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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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/s/

Lee-Ping Pian
10/5/04 02:50:16 PM
BIOMETRICS

Todd Sahlroot
10/6/04 11:02:09 AM
BIOMETRICS

S. Edward Nevius
10/17/04 08:38:03 PM
BIOMETRICS
Concur with review.