(2) Dropouts

Of the 164 patients randomized to a treatment group, 129 (79%) patients completed the 20 weeks of study drug treatment and 35 patients (21%) were discontinued. Most dropouts occurred by Week 12. Dropouts by week by treatment group are summarized in the following table

Table 16: MA-14 Dropouts by Week by Treatment

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**Lovastatin**
Randomized Patients, n =	164	31	34	34	32	33
Week completed						
Week 4, n (%)	153 (93)	28 (90)	32 (94)	33 (97)	29 (91)	31 (94)
Week 8, n (%)	146 (89)	27 (87)	32 (94)	30 (88)	27 (84)	30 (91)
Week 12, n (%)	135 (82)	26 (84)	31 (91)	26 (76)	23 (72)	29 (88)
Week 16, n (%)	133 (81)	25 (81)	30 (88)	26 (76)	23 (72)	29 (88)
Week 20, n (%)	129 (79)	23 (74)	30 (88)	24 (71)	23 (72)	29 (88)

Of the 35 patients who were discontinued, 28 of 35 patients discontinued due to adverse events. More patients discontinued for any reason in the Niaspan, Advi/20 and Advi/40 groups (26-29%) than in the Advi/10 and lovastatin groups (12% each). The majority of patients discontinued for adverse events, and more patients in the Niaspan, Advi/20 and Advi/40 (19-26%) groups discontinued for AEs than in the lovastatin and Advi/10 (6-9%) groups, as follows

Table 17: MA-14 Patients Discontinued

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**Lovastatin**
Randomized Patients, n =	164	31	34	34	32	33
Number of Withdrawals, n (%)	35 (21)	8 (26)	4 (12)	10 (29)	9 (28)	4 (12)
Reason for Dropout						
Adverse event	28 (17)	7 (19)	2 (6)	9 (26)	7 (22)	3 (9)
Protocol violation	4 (3)	1 (3)	2 (6)	0	1 (3)	0
Withdrew consent	1 (<1)	0	0	0	0	1 (3)
Lost to follow up	1 (<1)	0	0	1 (3)	0	0
Other	1 (<1)	0	0	0	1 (3)	0

The baseline demographics of patients who dropped out during study drug treatment differed somewhat from patients who remained in the study. However, as the number of patients in each treatment group is small, the effect of these differences is unlikely to have significantly affected the overall results of the study. Notable differences are:

1) Overall, dropouts were more likely to have been female
2) The dropouts in the lovastatin group were all female, had a higher mean age, and were all Caucasian.
3) The dropouts in the Niaspan group had a higher BMI.
4) The dropouts in the Advicor/10 group had a higher mean Lp(a).
5) The dropouts in the Advicor/40 group were mainly female (89%).

Table 18: MA-14 Baseline Demographics of Randomized Patients vs Dropouts

	Randomized	Dropouts by Treatment					
	All	All	Niaspan	Advi/10	Advi/20	Advi/40	lovastatin
Number of Patients, n =	164	35	8	4	10	9	4
Demographic Measure							
Gender, n (%)							
Male	85 (52)	14 (40)	6 (75)	2 (50)	5 (50)	1 (11)	0
Female	79 (48)	21 (60)	2 (25)	2 (50)	5 (50)	8 (89)	4 (100)
Age, years							
mean	59.3	61.5	58.4	59.3	64.8	57.7	70.0
median	61	64	55.5	58.0	67.0	59.0	70.5
min, max	28, 78	35, 77	35, 77	49, 72	45, 75	40, 70	64, 75
Patients Age $\geq$ 65 years, n (%)	63 (38)	15 (43)	3 (38)	1 (25)	7 (70)	2 (22)	3 (75)
Ethnicity, n(%)							
Caucasian	135 (82)	26 (74)	6 (75)	2 (50)	8 (80)	6 (67)	4 (100)
Black	22 (13)	8 (23)	2 (25)	2 (50)	1 (10)	3 (33)	0
Hispanic	1 (<1)	1 (3)	0	0	1 (10)	0	0
Asian	6 (4)	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
Risk Factors (RF)							
Diabetes, n (%)	15 (9)	4 (11)	2 (25)	1 (25)	0	1 (11)	0
Current smoker, n (%)	27 (16)	4 (11)	0	1 (25)	2 (20)	1 (11)	0
$\geq$2 CAD RF, n (%)	118 (72)	24 (69)	6 (75)	2 (50)	9 (90)	4 (44)	3 (75)
<2 CAD RF, n (%)	46 (28)	11 (31)	2 (25)	2 (50)	1 (10)	5 (56)	1 (25)
Mean BMI, kg/M^2	29.0	30.0	34.2	29.7	27.8	30.6	26.7
Baseline Lipid Value							
Mean LDL-C, mg/dL	-	-	193.1	208.4	183.6	206.3	201.6
Mean HDL-C, mg/dL	-	-	39.7	46.8	41.3	55.1	52.1
Median Triglycerides, mg/dL	-	-	180.3	126.5	215.3	187.0	162.3
Mean Lp(a), mg/dL	-	-	49.9	114.5	36.9	42.1	53.8

c) Concomitant Medications

Concomitant medications (conmeds) were medications that were either started prior to randomization and continued during study drug treatment, or were started during study drug treatment. Overall, >95% of study patients reported the use of any concomitant medication during the study, as follows

Table 19: MA-14 Patients Reporting any Concomitant Medication Use

		Treatment				
	All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Patients, n =	164	31	34	34	32	33
Patients Reporting Any Conmed Use, n (%)	158 (96)	26 (84)	34 (100)	34 (100)	32 (100)	31 (97)

A large number of different medications was used (over 300 different medications were reported), with the majority of these medications used by a small number of patients (used by $\leq$ 2 patients per medication, or by $\leq$1% of patients overall). The most frequently reported concomitant medication used was aspirin, which was used by 54% of study patients overall. Aspirin use in the lovastatin group (46%) was slightly lower than in the

niacin-exposed groups (50-62%). However, the differences are small and it is unclear if aspirin was used for the treatment of flushing, for prevention of flushing, or for other indications such as CHD treatment or prevention. Aspirin use by treatment group is summarized in the following table. A list of commonly used concomitant medications (use reported by ≥5% of patients overall) is reported in Appendix I.

Table 20: MA-14 Patients Reporting Concomitant Aspirin Use

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**Lovastatin**
Randomized Patients, n =	164	31	34	34	32	33
Patients Reporting Aspirin Use, n (%)	88 (54)	16 (52)	21 (62)	21 (62)	16 (50)	15 (46)

No patient was reported as having used any of the prohibited lipid-lowering medications during the treatment period of the study. One patient (0417, Advicor/40) was withdrawn for the use of prohibited medication azithromycin. Of the medications known to have minor effects on serum lipid levels that were permitted for use during the trial, such as thiazide diuretics, systemic beta-blockers or psyllium preparations, there did not appear to be any significant imbalances between treatment groups. It is therefore unlikely that the use of concomitant medications had any overall effect on the study results.

d) Patient Compliance

Compliance was assessed by pill counts at each study visit every 4 weeks. Patients were considered to be compliant with study medication if they were at least 75% compliant with study treatments. Compliance across treatment groups was similar, and was >90% for all groups at each 4-week interval.

e) Efficacy Results

Please also refer to: Mele, Joy. "Statistical Review and Evaluation: Clinical Studies NDA #21-249" for the statistical analysis. The statistical analysis will be referred to frequently in this section.

(1) Statistical Methods

The primary efficacy endpoint was the mean percent change from baseline in LDL-C for each treatment group. Comparisons were made between the Advicor treatment groups and the Niaspan and lovastatin groups at each study visit. It was stated by the Sponsor in the protocol however, that the two primary between-treatment comparisons for this study were: 1) Advicor 1500/20 to lovastatin 20 mg; and 2) Advicor 2000/40 to lovastatin 40 mg. The Advicor 1500/20:lovastatin 20 mg comparison occurred at Week 12. A comparison of Advicor 2000/40:lovastatin 40 mg however, would have involved a comparison of two different time points (Week16:Week 20 respectively). A Comparison between different time points, in the opinion of this Reviewer and per the statistical review, is not acceptable, and the Advicor 2000/40:lovastatin 40 mg comparison will therefore not be considered further.

Possible valid comparisons for Advicor vs lovastatin include (shaded and bolded below)

Table 21: MA-14 Advicor vs Lovastatin Valid Comparisons

	Week				
Treatment	**4**	**8**	**12**	**16**	**20**
Niaspan (mg)	500	1000	1500	2000	2500
Advi/10 (mg/mg)	**500/10**	**1000/10**	1500/10	2000/10	2500/10
Advi/20 (mg/mg)	500/20	1000/20	**1500/20**	**2000/20**	2500/20
Advi/40 (mg/mg)	500/40	1000/40	1500/40	2000/40	**2500/40**
Lovastatin (mg)	**10**	**10**	**20**	**20**	**40**

In addition, as stated in the protocol, the primary efficacy analysis is to be performed on the intent-to-treat (ITT) population, which is defined as all patients who received at least one dose of study medication. The primary analysis performed by the sponsor however, was performed on observed cases at each time point. As there were a large number of dropouts, an ITT with last observation carried forward (LOCF) analysis and an ETRANS analysis were also performed by the Statistical Reviewer. These analyses produced similar results to the observed cases analysis (see Statistical Review) suggesting that dropouts did not have a significant impact on the outcome. Therefore, the observed cases results will be discussed here.

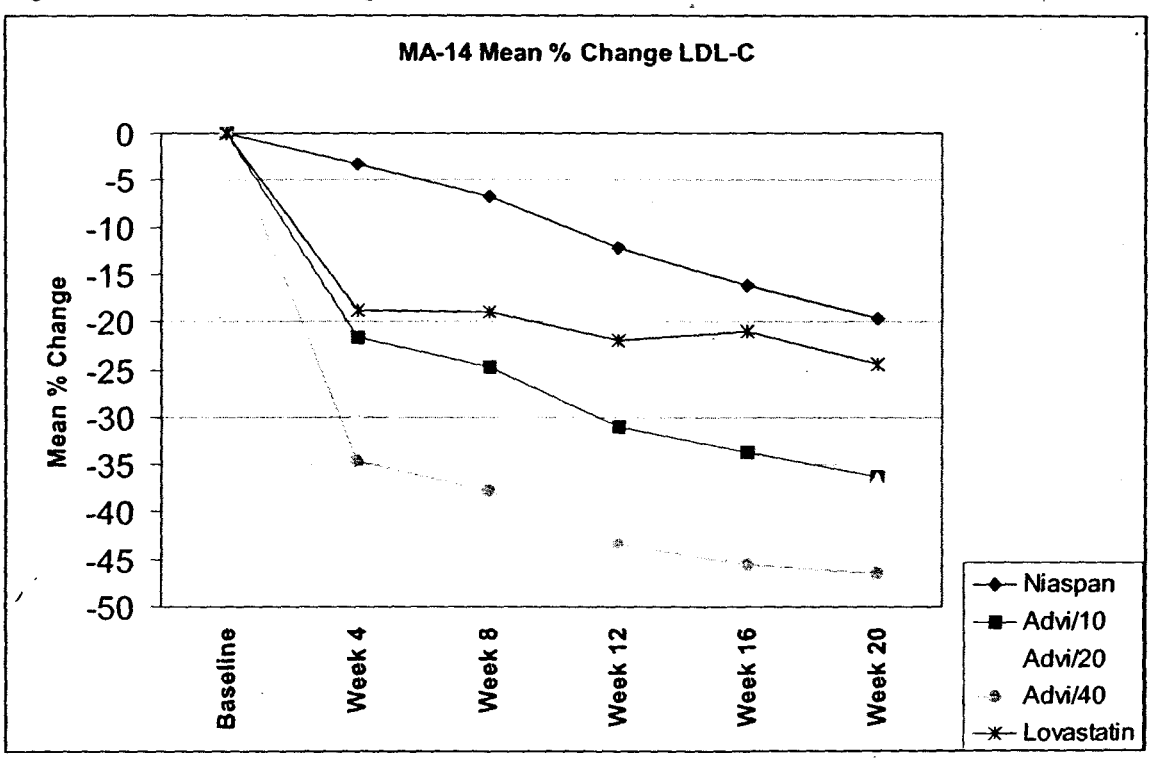
(2) Primary Efficacy Analysis: Mean Percent Change in LDL-C

The mean percent changes in LDL-C from baseline by treatment group are summarized in the following table and graph

Table 22: MA-14 Mean % Change from Baseline in LDL-C

		Week				
Treatment	**Baseline**	**4**	**8**	**12**	**16**	**20**
Niaspan: dose (mg)		**500**	**1000**	**1500**	**2000**	**2500**
n	31	28	27	26	25	23
Mean	201.6 mg/dL	-3.3%	-6.8%	-12.2%	-16.2%	-19.7%
Standard Error (SE)	6.79	1.38	1.92	2.30	2.57	3.70
Advi/10: dose (mg/mg)		**500/10**	**1000/10**	**1500/10**	**2000/10**	**2500/10**
n	34	32	32	31	30	30
Mean	199.5 mg/dL	-21.6%	-24.7%	-31.0%	-33.7%	-36.3%
SE	7.11	1.81	1.82	2.08	2.10	2.36
Advi/20: dose (mg/mg)		**500/20**	**1000/20**	**1500/20**	**2000/20**	**2500/20**
n	34	33	30	26	26	24
Mean	191.4 mg/dL	-29.4%	-31.9%	-34.9%	-38.6%	-36.4%
SE	5.43	2.07	2.55	3.58	3.42	4.39
Advi/40: dose (mg/mg)		**500/40**	**1000/40**	**1500/40**	**2000/40**	**2500/40**
n	32	29	27	23	23	23
Mean	204.9 mg/dL	-34.7%	-37.8%	-43.3%	-45.6%	-46.6%
SE	7.65	1.61	2.52	2.58	3.35	4.48
Lovastatin: dose (mg)		**10**	**10**	**20**	**20**	**40**
n	33	31	29	29	29	29
Mean	195.6 mg/dL	-18.8%	-19.0%	-21.9%	-21.0%	-24.4%
SE	4.59	2.04	1.56	2.03	2.62	2.41

Figure 1: MA-14 Mean % Change From Baseline in LDL-C



The Niaspan group shows a dose dependent reduction in LDL-C with each increase in dose from -3% at Week 4 (500 mg) to -20% at Week 20 (2500 mg). The 3 Advicor treatment groups show initial steep decreases in mean % change in LDL-C at Week 4 of Advi/10: -22%, Advi/20: -29%, and Advi/40: -35%. The differences in mean % change in LDL-C between the groups are a result of the increasing proportion of lovastatin in each treatment arm (10, 20 and 40 mg respectively). The 3 Advicor groups then show a slower progressive decrease in mean % change in LDL-C with increasing dose of the Niaspan component (500 mg to 2500 mg) from Week 8 to Week 20. The lovastatin group shows an initial steep decrease at Week 4 (10 mg dose), then a flat dose response thereafter with little mean % change in LDL-C despite doubling the lovastatin dose at Week 12 (20 mg) and Week 20 (40 mg).

The statistical comparisons between Advicor (Advi) and lovastatin (lova) for the mean % change in LDL-C (from the Statistical Review) for the possible between-group comparisons are as follows

Table 23: MA-14 Statistical Comparison Advi vs Lova, Mean % Change LDL-C

	Advi	lova	Advi vs lova p-value
Week 4			
Dose	500/10	10	
Mean % change LDL-C	-22	-19	.29
Week 8			
Dose	1000/10	10	
Mean % change LDL-C	-25	-20	.10
Week 12			
Dose	1500/20	20	
Mean % change LDL-C	-34	-23	.001
Week 16			
Dose	2000/20	20	
Mean % change LDL-C	-37	-22	.0001
Week 20			
Dose	2500/40	40	
Mean % change LDL-C	-43	-25	.0001

The results show that Advicor 1500/20 (Week 12), Advicor 2000/20 (Week 16), and Advicor 2500/40 (Week 20) were statistically significantly better at producing a mean % decrease from baseline in LDL-C than lovastatin at doses of 20, 20, and 40 mg respectively. However, there are several concerns with these results.

First of all, per the Sponsor's NDA summary and the proposed labeling, the sponsor is planning to market 500/20, 750/20, and 1000/20 mg tablet strengths of Advicor. These formulations will allow for the following Advicor combinations: 500/20, 750/20, 1000/40, 1500/40, and 2000/40. Thus, none of the valid Advicor vs lovastatin comparisons made in MA-14 study (see Table 12) are possible dose combinations with the proposed tablet strengths. As such, the efficacy results in the MA-14 study are not supportive of the proposed labeling for Advicor.

Second of all, the lovastatin group's response to treatment was lower than expected, and is not consistent with Mevacor labeling or other clinical studies using Mevacor. Typically, a doubling of the lovastatin dose would result in a further mean % decrease in LDL-C of about 6%. In contrast, the LDL-lowering observed at Week 4 in the 3 Advicor treatment groups were reflective of a doubling of the lovastatin component of Advicor. As Niaspan 500 mg has little effect on LDL-C lowering (about -3%), and as the Niaspan component remained constant at Week 4 in all three Advicor treatment arms, then the differences in the decreases in LDL-C between the 3 Advicor groups at Week 4 should be due to the increasing dose of lovastatin. This finding is not surprising as the sponsor demonstrated bioequivalence between the lovastatin component of Advicor to Mevacor.

The inconsistent results of LDL-lowering in MA-14 compared to the Mevacor labeling and two other studies using Mevacor are summarized as follows

Table 24: MA-14 Mean % Change LDL, Comparisons of MA-14 vs Mevacor

	Mean % Change LDL			
Lovastatin Dose	Mevacor Label	*EXCEL[19]	**Lova-Prava Study[29]	Lovastatin Control Group
10 mg	-21 %	NA	NA	-19%
20 mg	-27%	-24%	-28%	-22%
40 mg	-31%	-30%	-33%	-24%

* The Expanded Clinical Evaluation of Lovastatin (EXCEL) Study was a multicenter, double-blind, placebo-controlled study that evaluated the efficacy and safety of lovastatin in 8245 patients with hypercholesterolemia. Patients were randomly assigned to placebo or lovastatin (20 mg qD, 40 mg qD, or 40 mg BID X 48 weeks). Study medication remained at a fixed dose, and was not titrated to an endpoint (e.g. LDL-C) during the study.

**A Multicenter Comparative Trial of Lovastatin and Pravastatin in the Treatment of Hypercholesterolemia was a multicenter, double-blind, active-comparator study that evaluated the efficacy and safety of lovastatin and pravastatin in 672 patients with hypercholesterolemia. Patients were randomly assigned to lovastatin (20– 80 mg) or pravastatin (10-40 mg). All patients received escalating doses of study medication on a forced-titration schedule.

One of the objectives of this trial was to demonstrate a greater LDL-lowering observed with the combined Advicor product to its individual components (i.e., Niaspan and lovastatin). The lower than expected LDL response observed with the lovastatin comparator arm in this study raises concerns of internal validity in this trial thereby making the results of this trial uninterpretable.

Comparisons of Advicor to Niaspan (Nia) for these same doses were also performed. Advicor showed statistically significantly better mean % decreases in LDL-C (p-value .0001) for all comparisons as follows

Table 25: MA-14 Statistical Comparison Advi vs Nia, Mean % Change LDL-C

	Advi	Nia	Advi vs Nia p-value
Week 4			
Dose	500/10	500	
Mean % change LDL-C	-22	-3	.0001
Week 8			
Dose	1000/10	1000	
Mean % change LDL-C	-25	-7	.0001
Week 12			
Dose	1500/20	1500	
Mean % change LDL-C	-34	-11	.0001
Week 16			
Dose	2000/20	2000	
Mean % change LDL-C	-37	-14	.0001
Week 20			
Dose	2500/40	2500	
Mean % change LDL-C	-43	-17	.0001

(a) Subgroup Analysis

Subgroup analysis was performed by the Statistical Reviewer for age (≥65 years vs <65 years), baseline LDL, and gender. No significant interaction by treatment for any of these subgroups was found.

(3) Secondary Efficacy Measures

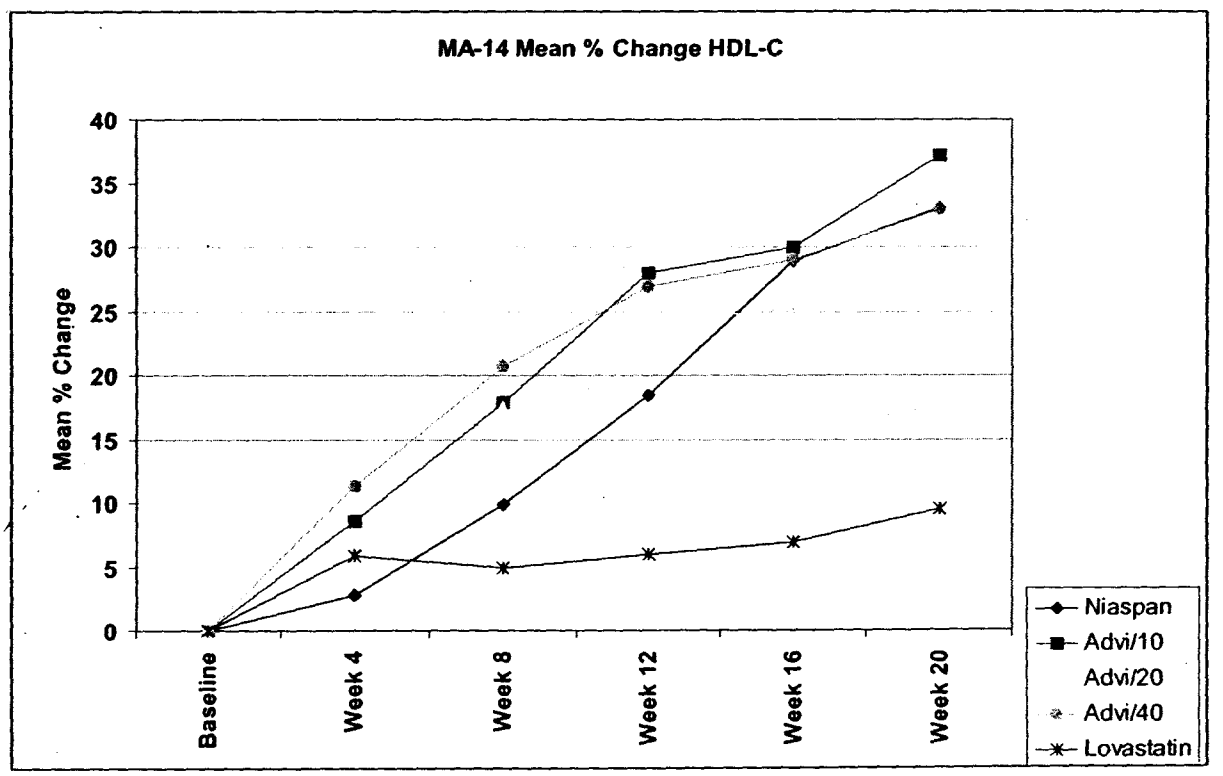
(a) Mean Percent Change from Baseline in HDL-C

The mean percent changes from baseline in HDL-C by treatment group are summarized in the following table and graph

Table 26: MA-14 Mean % Change from Baseline in HDL-C

		Week				
Treatment	**Baseline**	**4**	**8**	**12**	**16**	**20**
Niaspan: dose (mg)		**500**	**1000**	**1500**	**2000**	**2500**
n	31	28	27	26	25	23
Mean	41.8 mg/dL	+2.8%	+9.9%	+18.5%	+28.9%	+33.1%
SE	1.73	1.39	2.16	3.60	3.95	3.60
Advi/10: dose (mg/mg)		**500/10**	**1000/10**	**1500/10**	**2000/10**	**2500/10**
n	34	32	32	31	30	30
Mean	45.3 mg/dL	+8.6%	+17.9%	+28.0%	+30.0%	+37.2%
SE	2.25	1.90	3.10	3.25	3.66	3.55
Advi/20: dose (mg/mg)		**500/20**	**1000/20**	**1500/20**	**2000/20**	**2500/20**
n	34	33	30	26	26	24
Mean	43.2 mg/dL	+6.6%	+17.5%	+24.1%	+25.3%	+28.2%
SE	1.66	1.74	1.99	3.22	4.16	4.74
Advi/40: dose (mg/mg)		**500/40**	**1000/40**	**1500/40**	**2000/40**	**2500/40**
n	32	29	27	23	23	23
Mean	45.4 mg/dL	+11.3%	+20.7%	+26.9%	+29.1%	+32.9%
SE	2.22	2.17	3.09	4.46	4.58	4.28
Lovastatin: dose (mg)		**10**	**10**	**20**	**20**	**40**
n	33	31	29	29	29	29
Mean	45.3 mg/dL	+5.9%	+4.9%	+6.0%	+7.0%	+9.5%
SE	2.00	1.47	2.88	2.48	2.37	2.07

Figure 2: MA-14 Mean % Change From Baseline HDL-C



Statistical comparisons were made between treatment groups at the same time points and for the same dose comparisons as for LDL-C (see Table 21). Advicor was statistically superior to lovastatin for mean % increase in HDL-C at doses of 1000/10 or greater at Weeks 8, 12, 16, and 20. The results are summarized in the following table

Table 27: MA-14 Statistical Comparison Advi vs Lova, Mean % Change HDL-C

	Advi	lova	Advi vs lova p-value
Week 4			
Dose	500/10	10	
Mean % change HDL-C	+9	+6	.20
Week 8			
Dose	1000/10	10	
Mean % change HDL-C	+18	+5	.0001
Week 12			
Dose	1500/20	20	
Mean % change HDL-C	+23	+6	.0001
Week 16			
Dose	2000/20	20	
Mean % change HDL-C	+24	+7	.0001
Week 20			
Dose	2500/40	40	
Mean % change HDL-C	+29	+9	.0001

Advicor was not found to be statistically significantly superior to Niaspan at any dose for mean % change in HDL-C. Results are summarized in the following table

Table 28: MA-14 Statistical Comparison Advi vs Nia, Mean % Change HDL-C

	Advi	Nia	Advi vs Nia p-value
Week 4			
Dose	500/10	500	
Mean % change HDL-C	+9	+3	.04
Week 8			
Dose	1000/10	1000	
Mean % change HDL-C	+18	+9	.02
Week 12			
Dose	1500/20	1500	
Mean % change HDL-C	+23	+18	.28
Week 16			
Dose	2000/20	2000	
Mean % change HDL-C	+24	+27	.62
Week 20			
Dose	2500/40	2500	
Mean % change HDL-C	+29	+30	.49

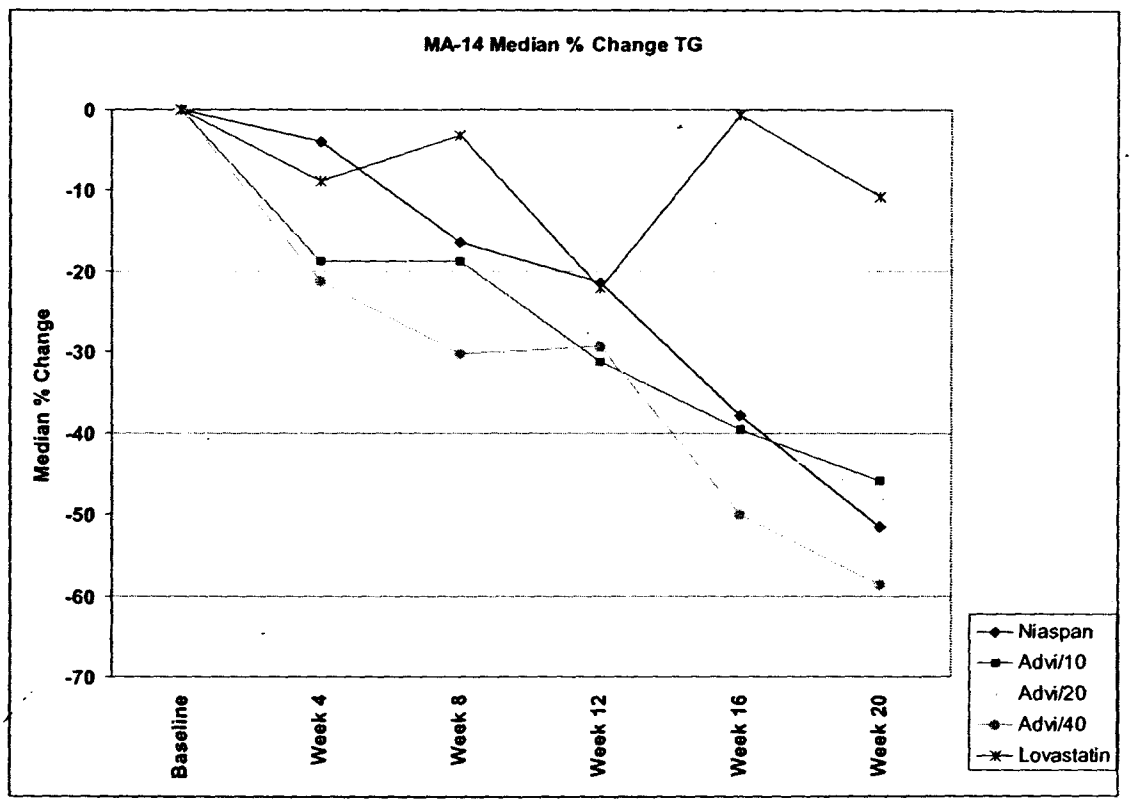
(b) Median % Change from Baseline in Triglyceride

The median percent changes from baseline in Triglyceride (TG) by treatment group are summarized in the following table and graph

Table 29: MA-14 Median % Change From Baseline in TG

		Week				
Treatment	**Baseline**	**4**	**8**	**12**	**16**	**20**
Niaspan: dose (mg)		**500**	**1000**	**1500**	**2000**	**2500**
n	31 mg/dL	28	27	26	25	23
Median	181.9	-4.0%	-16.4%	-21.5%	-37.8%	-51.6%
Advi/10: dose (mg/mg)		**500/10**	**1000/10**	**1500/10**	**2000/10**	**2500/10**
n	34 mg/dL	32	32	31	30	30
Median	187.0	-18.7%	-18.8%	-31.2%	-39.6%	-45.8%
Advi/20: dose (mg/mg)		**500/20**	**1000/20**	**1500/20**	**2000/20**	**2500/20**
n	34 mg/dL	33	30	26	26	24
Median	177.3	-10.9%	-23.5%	-42.1%	-40.7%	-47.6%
Advi/40: dose (mg/mg)		**500/40**	**1000/40**	**1500/40**	**2000/40**	**2500/40**
n	32 mg/dL	29	27	23	23	23
Median	189.5	-21.3%	-30.2%	-29.4%	-50.0%	-58.7%
Lovastatin: dose (mg)		**10**	**10**	**20**	**20**	**40**
n	33 mg/dL	31	29	29	29	29
Median	177.6	-8.9%	-3.1%	-22.0%	-0.7%	-10.7%

Figure 3: MA-14 Median % Change From Baseline TG



Statistical comparisons were made between treatment groups at the same time points and for the same doses as for LDL-C and HDL-C. Advicor was statistically superior to lovastatin for median % decrease in TG at doses of Advicor 1000/10 (at Week 8) and higher. Results are summarized as follows

Table 30: MA-14 Statistical Comparison Advi vs Lova, Median % Change TG

	Advi	lova	Advi vs lova p-value
Week 4			
Dose	500/10	10	
Median % change TG	-10	-2	.89
Week 8			
Dose	1000/10	10	
Median % change in TG	-14	+2	.03
Week 12			
Dose	1500/20	20	
Median % change in TG	-31	-16	.03
Week 16			
Dose	2000/20	20	
Median % change in TG	-33	+2	.0001
Week 20			
Dose	2500/40	40	
Median % change in TG	-44	-9	.0001

Advicor was found to be statistically significantly superior to Niaspan for median % decrease in TG only at the Advicor 2000/20 vs Niaspan 2000 mg dose at Week 16. Results are summarized as follows

Table 31: MA-14 Statistical Comparison Advi vs Nia, Median % Change TG

	Advi	Nia	Advi vs Nia p-value
Week 4			
Dose	500/10	500	
Median % change TG	-10	-2	.15
Week 8			
Dose	1000/10	1000	
Median % change in TG	-14	-10	.76
Week 12			
Dose	1500/20	1500	
Median % change in TG	-31	-16	.15
Week 16			
Dose	2000/20	2000	
Median % change in TG	-33	-26	.0001
Week 20			
Dose	2500/40	2500	
Median % change in TG	-44	-41	.73

(4) Conclusions on Efficacy Results

The review of MA-14 raised several problems with the trial that made the study results uninterpretable and non-supportive of the proposed label. The poor LDL-lowering response in the lovastatin group compared to historical data raised concerns regarding the internal validity of the efficacy results. More importantly however, the study design did not provide for valid comparisons between the to-be-marketed Advicor doses and lovastatin. In conclusion, the efficacy results of MA-14 are inconclusive and will not be considered in the approval process of Advicor.

f) Safety Results

(1) Adverse Events

The Sponsor defined a Treatment Emergent Adverse Event as any Adverse Event (AE) whose onset occurred after the initiation of study medication or increased in intensity or frequency after study medication was initiated, and was at least remotely related to study medication (See NDA #21-249, Integrated Summary of Safety, Volume 9, page 45). This Reviewer however, included all reported AEs regardless of Investigator attribution as this was felt to be a more objective evaluation of the data. Adverse Events in the data set included those occurring in randomized patients who took at least one dose of study medication through study completion/discontinuation. Recurrent or continuing AEs were counted only once. Adverse Event incidence rates were calculated using all randomized patients as the denominator. Clinical AEs were coded using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) dictionary. Adverse Events were also analyzed by subgroups [male vs female, geriatric (age ≥65 years) vs non-geriatric]. There were too few non-Caucasians to evaluate by race. Common AEs were defined as having an incidence of ≥2% (A complete list of common AEs is contained in Appendix III).

There were 122 different AE terms reported by 142 of 164 (87%) patients overall. Fewer patients in the lovastatin group (73%) reported any AE compared to the 4 niacin-exposed groups (84-97%). The incidence rates of patients reporting any AE by treatment group are summarized in the following table

Table 32: MA-14 Adverse Events Incidence by Treatment Group

		Treatment				
	All	**Niaspan**	**Advi /10**	**Advi/20**	**Advi/40**	**Lovastatin**
Randomized Patients, n =	164	31	34	34	32	33
Patients Reporting Any AE, n (%)	142 (87)	30 (97)	30 (88)	31 (91)	27 (84)	24 (73)

(2) Adverse Events by Body System

Adverse Events occurring in the Cardiovascular system were the most commonly reported, followed by Body as a Whole, the Digestive system, and Skin and Appendages. Flushing accounted for almost all of the Cardiovascular AEs and was much more common in the 4 niacin-exposed groups (52-66%) than in the lovastatin group (15%). Digestive system complaints were more common in the Niaspan, Advi/20 and Advi/40 groups, than in the lovastatin and Advi/10 groups. Body as a Whole and Skin and Appendage complaints were relatively evenly distributed across the treatment groups. The most commonly reported AEs by body system (occurring in ≥5% of patients overall) are listed in the following table

Table 33: MA-14 Incidence of Most Common Adverse Events by Body System

			Treatment				
		All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Patients, n =		164	31	34	34	32	33
Body System		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Body as a whole	**All**	**70 (43)**	**17 (55)**	**9 (27)**	**16 (47)**	**12 (38)**	**16 (49)**
	Infection	24 (15)	4 (12)	4 (12)	4 (12)	5 (16)	7 (21)
	Asthenia	12 (7)	3 (10)	3 (9)	1 (3)	2 (6)	3 (9)
	Pain	12 (7)	3 (10)	3 (9)	2 (6)	1 (3)	3 (9)
	Headache	9 (6)	3 (10)	1 (3)	2 (6)	1 (3)	2 (6)
	Flu syndrome	8 (5)	4 (12)	1 (3)	3 (9)	0	0
	Pain, abdominal	8 (5)	1 (3)	0	3 (9)	2 (6)	2 (6)
Cardiovascular	**All**	**97 (59)**	**23 (74)**	**22 (65)**	**22 (65)**	**22 (69)**	**8 (24)**
	Flushing	86 (52)	20 (65)	18 (53)	22 (65)	21 (66)	5 (15)
Digestive	**All**	**42 (26)**	**13 (42)**	**3 (9)**	**13 (38)**	**7 (22)**	**6 (18)**
	Nausea	14 (9)	7 (23)	1 (3)	2 (6)	2 (6)	2 (6)
	Diarrhea	12 (7)	6 (19)	0	4 (12)	2 (6)	0
	Vomiting	8 (5)	4 (12)	0	2 (6)	2 (6)	0
Skin and Appendages	**All**	**27 (17)**	**6 (19)**	**4 (12)**	**7 (21)**	**6 (19)**	**4 (12)**
	Pruritus	12 (7)	4 (12)	1 (3)	3 (9)	2 (6)	2 (6)
	Rash	9 (6)	2 (6)	1 (3)	3 (9)	2 (6)	1 (3)

Other AEs of particular interest in this study were myalgias, myopathy, rhabdomyolysis, and hepatitis. Three patients reported myalgias during the trial, one each in the Niaspan, Advi/10 and lovastatin groups. Myalgias were associated with a CPK elevation >normal in patient 1604, but no CPK elevations occurred in patients 1417 and 1805. Myalgias did not result in an interruption or discontinuation of study drug treatment in any patient. The patients reporting myalgias are:

Table 34: MA-14 Patients Reporting Myalgias

Code	Sex	Age (yrs)	Treatment	Week	CPK Range (IU/L)	CPK during Myalgias
1604	F	54	Niaspan	12	[redacted]	229
1417	F	58	Advi/10	8		80
1805	F	78	Lovastatin	4	[redacted]	97

CPK upper limit of normal: Female 164 U/L, Male 207 U/L

There were no reported cases of myopathy, rhabdomyolysis, or hepatitis.

(3) Adverse Events by Subgroup

Adverse Events were further analyzed by sex, and geriatric vs non-geriatric patients. A listing of the most common AEs by subgroups (≥5% overall) is in Appendix IV.

(a) Male vs Female

Adverse Events by sex were similar to the results overall. More patients in the niacin-exposed groups reported any AE compared to the patients in the lovastatin group. This did not differ when analyzed by male vs female patients, as follows

Table 35: MA-14 Patients Reporting Any AE, Male vs Female

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**lovastatin**
Randomized Patients All, n =	164	31	34	34	32	33
Randomized Male (M) Patients, n =	M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =	F=79	F=14	F=17	F=16	F=17	F=15
Males Reporting Any AE, n (%)	73 (86)	17 (100)	15 (88)	16 (89)	12 (80)	13 (72)
Female Reporting Any AE, n (%)	69 (87)	13 (93)	15 (88)	15 (94)	15 (88)	11 (73)

Overall, females were more likely than males to report flushing (62% vs 47% respectively), nausea (15% vs 2%), pruritus (11% vs 4%), and rash (10% vs 1%). However, similar to the results overall, reported AEs tended to reflect treatment assignment. This is especially true for flushing which was more common in the niacin-exposed groups than the lovastatin group regardless of gender. Additionally, as the numbers of patients per treatment group was small when divided into subgroups, small differences between the subgroups should be interpreted with caution. The incidence of selected AEs, male vs female, are summarized in the following table

Table 36: MA-14 Selected AEs, Male vs Female

				Treatment				
			All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**Lovastatin**
Randomized Male (M) Patients, n =			M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =			F=79	F=14	F=17	F=16	F=17	F=15
Body System	**COSTART Term**	**M/F**	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiovascular	Flushing	M	40 (47)	11 (65)	7 (41)	10 (56)	10 (67)	2 (11)
		F	46 (62)	9 (64)	11 (65)	12 (75)	11 (65)	3 (20)
Digestive	Nausea	M	2 (2)	1 (6)	0	1 (6)	0	0
		F	12 (15)	6 (43)	1 (6)	1 (6)	2 (13)	2 (13)
Skin and	Pruritis	M	3 (4)	0	0	2 (11)	0	1 (6)
Appendages		F	9 (11)	4 (29)	1 (6)	1 (6)	2 (13)	1 (7)
	Rash	M	1 (1)	0	0	1 (6)	0	0
		F	8 (10)	2 (14)	1 (6)	2 (13)	2 (13)	1 (7)

(b) Geriatric vs Non-Geriatric

Patients reporting any AE geriatric vs non-geriatric were similar to the results overall, with the incidence of AEs depending more on treatment assignment rather than age. More patients in the niacin-exposed groups in general reported any AE than the patients in the lovastatin group. The results are as follows

Table 37: MA-14 Patients Reporting any AE, Geriatric vs Non-Geriatric

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**lovastatin**
Randomized Patients All, n =	164	31	34	34	32	33
Randomized Geriatric (G) Patients, n =	G = 63	G=8	G=14	G=15	G=13	G=13
Randomized Non-Geriatric (NG) Patients, n =	NG = 101	NG=23	NG=20	NG=19	NG=19	NG=20
Geriatric Patients Reporting any AE, n (%)	55 (87)	8 (100)	14 (100)	13 (87)	10 (77)	10 (77)
Non-Geriatric Reporting any AE, n (%)	87 (86)	22 (96)	16 (80)	18 (95)	17 (89)	14 (70)

Overall, non-geriatric patients were more likely than geriatric patients to complain of flushing (58% vs 43%) and infection (18% vs 10%). Geriatric patients were more likely than non-geriatric patients to complain of rash (10% vs 3%). Infection was evenly distributed across treatment groups, but flushing and rash tended to reflect treatment group assignment rather than age. The incidence of selected AEs, geriatric vs non-geriatric, are summarized in the following table

Table 38: MA-14 Selected AEs, Geriatric vs Non-Geriatric

				Treatment				
			All	Niaspan	Advi/10	Advi/20	Advi/40	Lovastatin
Randomized Geriatric (G) Patients, n =			G = 63	G=8	G=14	G=15	G=13	G=13
Randomized Non-Geriatric (NG) Patients, n =			NG = 101	NG=23	NG=20	NG=19	NG=19	NG=20
Body System	**COSTART Term**	G\NG	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Body as a	Infection	G	6 (10)	1 (13)	1 (7)	0	2 (15)	2 (15)
Whole		NG	18 (18)	3 (13)	3 (15)	4 (21)	3 (16)	5 (25)
Cardiovascular	Flushing	G	27 (43)	4 (50)	6 (43)	9 (60)	7 (54)	1 (8)
		NG	59 (58)	16 (70)	12 (60)	13 (68)	14 (74)	4 (20)
Skin and	Rash	G	6 (10)	2 (25)	0	2 (13)	2 (15)	0
Appendages		NG	3 (3)	0	1 (5)	1 (5)	0	1 (5)

(4) Adverse Events Resulting in Drug Discontinuation

Thirty-five (35) of the 164 (21%) randomized patients discontinued study medication prior to study completion. Of the 35 patients who discontinued, 28 discontinuations (DCs) were due to AEs. Discontinuations occurred more frequently in the Niaspan, Advi/20 and Advi/40 groups (26-29%) than in the lovastatin and Advi/10 groups (12% each). Flushing (5%) and rash (4%) were the most commonly reported AEs resulting in discontinuation, all of which occurred in the 4 niacin-exposed groups. It is interesting to note that there were no discontinuations in the Advi/10 group for flushing. As the number of patients in each group is small however, this variability between the treatment groups is not unexpected. There were no discontinuations for laboratory abnormalities. The most commonly reported AEs resulting in drug discontinuation are summarized in the following table

Table 39: MA-14 Discontinuations Due to Adverse Events, Most Common

		Treatment					
		All	Niaspan	Advi/10	Advi/20	Advi/40	lovastatin
Randomized Patients, n =		164	31	34	34	32	33
All Discontinuations, n (%)		35(21)	8(26)	4(12)	10(29)	9(28)	4(12)
Discontinued for AE*, n (%)		28(17)	7(23)	2(6)	9 (26)	7 (22)	3 (9)
Body System	**COSTART Term**						
Cardiovascular	Flushing	9 (5)	3 (10)	0	4 (12)	2 (6)	0
Skin and	Rash	7 (4)	1 (3)	1 (3)	3 (9)	2 (6)	0
Appendages	Pruritis	3 (2)	0	0	1 (3)	2 (6)	0
	Urticaria	3 (2)	0	0	3 (9)	0	0
Body as a Whole	Asthenia	3 (2)	1 (3)	0	0	1 (3)	1 (3)
Digestive	Nausea	3 (2)	1 (3)	0	0	1 (3)	1 (3)
DCs for Lab Abnormality		0	0	0	0	0	0

*Patients may have reported more than one AE term per discontinuation

A complete list of all reported AEs resulting in drug discontinuation is listed in Appendix V.

(5) Adverse Events Resulting in Drug Discontinuation by Subgroup

Adverse Events resulting in drug discontinuation were further analyzed by sex, and by geriatric vs non-geriatric patients.

(a) Male vs Female

Female patients were more likely to be discontinued from the study for any reason and for an AE (27% and 20 % respectively) than were male patients (16% and 14% respectively). Discontinuations for flushing were also somewhat more common for female (8%) than male (4%) patients. The number of patients per treatment group was small however, so no valid conclusion can be made from this. No other differences between the subgroups were found. The results are summarized as follows (a complete list of discontinuations for AEs by sex can be found in Appendix VI)

Table 40: MA-14 Discontinuations Due to Adverse Events, Most Common Male vs Female

		Treatment					
		All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**lovastatin**
Randomized Patients, All, n =		164	31	34	34	32	33
All Discontinuations, n (%)		35(21)	8(26)	4(12)	10(29)	9(28)	4(12)
Randomized Male (M) Patients, n =		M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =		F=79	F=14	F=17	F=16	F=17	F=15
All Discontinuations, Male, n =		14 (16)	6 (35)	2 (12)	5 (28)	1 (7)	0
All Discontinuations, Female, n =		21 (27)	2 (14)	2 (12)	5 (31)	8 (47)	4 (27)
Discontinued for AE*, n (%)	**All**	28(17)	7(23)	2 (6)	9 (26)	7 (22)	3 (9)
	Male	12 (14)	5 (29)	2 (12)	5 (28)	0	0
	Female	16 (20)	2 (14)	0	4 (25)	7 (41)	3 (20)
Cardiovascular Flushing	**All**	9 (5)	3 (10)	0	4 (12)	2 (6)	0
	Male	3 (4)	2 (12)	0	1 (6)	0	0
	Female	6 (8)	1 (7)	0	3 (19)	2 (12)	0

*Patients may have reported more than one AE term per discontinuation

(b) Geriatric vs Non-Geriatric

Discontinuations overall and due to AEs were more common for geriatric (25% and 22% respectively) than for non-geriatric (19% and 14% respectively) patients overall, however the number of patients, particularly in the geriatric patient group was small. All discontinuations for rash (7/7) and urticaria (3/3) were in geriatric patients, and all discontinuations for asthenia were in non-geriatric patients (3/3). No other differences were found. The results are summarized as follows (a complete list of discontinuations for AEs, geriatric vs non-geriatric, can be found in Appendix VI)

Table 41: MA-14 Discontinuations Due to Adverse Events, Most Common Geriatric vs Non-Geriatric

			Treatment					
			All	Niaspan	Advi/10	Advi/20	Advi/40	lovastatin
Randomized Patients, All, n =			164	31	34	34	32	33
Randomized Geriatric (G) Patients, n =			G = 63	G=8	G=14	G=15	G=13	G=13
Randomized Non-Geriatric (NG) Patients, n =			NG = 101	NG=23	NG=20	NG=19	NG=19	NG=20
All Discontinuations, n (%)			35(21)	8(26)	4(12)	10(29)	9(28)	4(12)
All Discontinuations, Geriatric Patients, n =			16 (25)	3 (38)	1 (7)	7 (47)	2 (15)	3 (23)
All Discontinuations, Non-Geriatric patients, n =			19 (19)	5 (22)	3 (15)	3 (16)	7 (37)	1 (5)
Discontinued for AE*, n (%)		**All**	28(17)	7(23)	2 (6)	9 (26)	7 (22)	3 (9)
		G	14 (22)	2 (25)	1 (7)	7 (47)	2 (15)	2 (15)
		NG	14 (14)	5 (22)	1 (5)	2 (11)	5 (26)	1 (5)
Skin and Appendages	**Rash**	**All**	7 (4)	1 (3)	1 (3)	3 (9)	2 (6)	0
		G	7 (11)	1 (2)	1 (7)	3 (20)	2 (15)	0
		NG	0	0	0	0	0	0
	Urticaria	**All**	3 (2)	0	0	3 (9)	0	0
		G	3 (5)	0	0	3 (20)	0	0
		NG	0	0	0	0	0	0
Body as a Whole	**Asthenia**	**All**	3 (2)	1 (3)	0	0	1 (3)	1 (3)
		G	0	0	0	0	0	0
		NG	3 (3)	1 (4)	0	0	1 (5)	1 (5)

*Patients may have reported more than one AE term per discontinuation

(6) Serious Adverse Events

There were 8 Serious Adverse Events (SAEs) occurring in 8 patients (5% of randomized patients). There were no deaths. All of the SAEs were in the Cardiovascular and Digestive systems, however given the small number of SAEs no trends or conclusions can be generated. One patient was discontinued in the study for an SAE [patient 1715 (Niaspan): nausea and vomiting], and one SAE [patient 1203 (Advi/20): cholelithiasis/cholecystitis] was assessed by the Investigator as at least possibly related to study drug. The SAEs are summarized in the following table

Table 42: MA-14 Serious Adverse Events

Treatment	Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Investigator Attribution	Drug Discontinued?
Niaspan	1715	M	77	Nausea, vomiting	Dig	14	NR	Yes
Niaspan	1803	F	78	Urosepsis	CV	14	NR	No
Advi/10	0805	F	73	Possible syncope	CV	3	NR	No
Advi/10	1402	M	67	CVA/HTN	CV	140	NR	No (completed)
Advi/20	1203	F	51	Cholecystitis/cholelithiasis	Dig	21	Probable	No
Advi/20	1406	M	73	Coronary occlusion/ASHD	CV	7	NR	No
Advi/40	0711	F	71	Esophageal stricture/hiatal hernia	Dig	4	NR	No
Lovastatin	0107	M	67	Chest pain/dyspnea/sweating	CV	14	NR	No

(7) Treatment Emergent Laboratory Abnormalities

Treatment Emergent Laboratory Abnormalities (TELA) were defined by the Sponsor as any laboratory abnormality "...commencing after initiation of study medication for which the baseline value was within normal limits."(See NDA #21-249, Integrated Summary of Safety, Vol.9, page 70). This reviewer defined a TELA as any laboratory abnormality that worsened during study drug treatment regardless of baseline value. This is consistent with the ICH definition of an Adverse Event as "...any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product" (from ICH Good Clinical Practice guidelines, Section II. Definitions and Terminology Associated with Clinical Safety Experience, Sept. 1997).

There were no discontinuations due to laboratory abnormalities.

(a) ALT and AST Elevations

Elevations from baseline in ALT and AST were more common in the Advi/20, Advi/40, and Niaspan groups than in the Advi/10 and lovastatin groups. Elevations in both AST and ALT tended to be mild, with clinically significant elevations [>3 X the upper limit of normal (ULN)] occurring in only 4 patients. The incidence of treatment emergent AST and ALT elevations by treatment group are as follows

Table 43: MA-14 Incidence of Treatment Emergent ALT and AST Elevations

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**lovastatin**
Randomized Patients, n =	164	31	34	34	32	33
ALT >normal, n (%)	34 (21)	6 (19)	5 (15)	13 (38)	7 (22)	3 (9)
ALT > 2 X ULN, n (%)	6 (4)	1 (3)	1 (3)	3 (9)	1 (3)	0
ALT > 3 X ULN, n (%)	2 (1)	0	0	2 (6)	0	0
AST >normal, n (%)	78 (48)	17 (55)	9 (27)	23 (68)	21 (66)	8 (24)
AST >2 X ULN, n (%)	11 (7)	2 (7)	1 (3)	5 (15)	3 (9)	0
AST >3 X ULN, n (%)	4 (2)	0	0	3 (9)	1 (3)	0

ALT normal range: 6-53 IU/L
AST normal range: 3-34 IU/L

The 4 patients who experienced clinically significant elevations (>3 X ULN) in ALT, AST, or ALT and AST were in the Advi/20 (3 patients) and Advi/40 (1 patient) treatment groups. These patients are described in the following table

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Table 44: MA-14 Patients Experiencing Clinically Significant ALT, AST, or ALT and AST Elevations

Week	AST	ALT	Advicor dose	Contributing history
Patient 0414 (Advi/20):				
Baseline	25	33	None	55 year old male, history of colitis, benign prostatic hypertrophy (BPH), gout, and type 2 Diabetes Mellitus (DM). Experienced prostatitis at Week 16. Treated with Cipro X 17 days. Developed severe nausea and vomiting 4 days prior to Week 20, and therapy changed to Floxin. Completed study Week 20, and entered open-label, extension study (MA-09). Study medication was not restarted and patient was discontinued in MA-09.
Week 4	27	34	500/20 X 4 weeks	
Week 8	25	33	1000/20 X 4 weeks	
Week 12	25	31	1500/20 X 4 weeks	
Week 16	27	32	2000/20 X 4 weeks	
Week 20	218	306	2500/20 X 4 weeks (completed)	
Week 20 retest	58	173	3 days off study medication	
Week 20 retest	30	65	9 days off study medication	
Open-label	20	28	Approx. 1 month off study med	
Patient 1203 (Advi/20):				51 year old female, history of type 2 DM, suspected cholelithiasis, appendectomy, and tonsillectomy. Developed abdominal pain and was diagnosed with cholelithiasis/cholecystitis after 3 weeks on study medication. Treated with Cipro, Asic, Darvocet and Compazine. Study medication interrupted X 2 days, then resumed. Patient completed the study. The patient had clinically significant elevations in AST and ALT (Week 20) after cholelithiasis/cholecystitis diagnosed.
Baseline	25	35	None	
Week 4	25	29	500/20 X 4 weeks	
Week 8	37	41	1000/20 X 4 weeks	
Week 12	24	28	1500/20 X 4 weeks	
Week 16	25	34	2000/20 X 4 weeks	
Week 20	163	161	2500/20 X 4 weeks (completed)	
Week 20 retest	42	64	16 days off study medication	
Week 20 retest	27	32	5 weeks off study medication	
Patient 1614 (Advi/20):				69 year old female, history of edema, hysterectomy, arthritis, depression, and cataract surgery. Patient reported an increased alcohol intake at Week 16 visit.
Baseline	19	31	None	
Week 4	24	24	500/20 X 4 weeks	
Week 8	23	20	1000/20 X 4 weeks	
Week 12	28	28	1500/20 X 4 weeks	
Week 16	126	107	2000/20 X 4 weeks	
Week 16 retest	42	64	2500/20 X 5 days, off drug X 8 days	
Week 20	53	51	2500/20 X 4 weeks (completed)	
Week 20 retest	20	not done	2 weeks off study medication	
Patient 0708 (Advi/40):				75 year old male, history arteriosclerosis, coronary artery bypass grafting (CABG), hypertension, and appendectomy. Patient completed the study and entered MA-09. Advicor was resumed after being off medication for 8 days in MA-09.
Baseline	30	32	None	
Week 4	52	76	500/40 X 4 weeks	
Week 8	71	125	1000/40 X 4 weeks	
Week 12	76	120	1500/40 X 4 weeks	
Week 16	84	98	2000/40 X 4 weeks	
Week 20	111	143	2500/40 X 4 weeks (completed)	
Week 20 retest	40	68	8 days off study medication	

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(b) Fasting Blood Sugar

Mild elevations in FBS (>111) were common, and were more common in the 4 niacin-exposed groups (53-65%) than in the lovastatin group (24%). Elevations in FBS > 1.3 X ULN or higher were less common (9% of patients overall). Incidences of FBS elevations are as follows

Table 45: MA-14 Incidence of Treatment Emergent FBS Elevations

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**lovastatin**
Randomized Patients, n =	164	31	34	34	32	33
FBS >normal	86 (52)	18 (58)	21 (62)	22 (65)	17 (53)	8 (24)
FBS >1.3 X ULN	15 (9)	2 (7)	2 (6)	4 (12)	5 (16)	2 (6)
FBS >2 X ULN	1 (<1)	0	0	1 (3)	0	0

FBS > normal: >111 mg/dL, FBS > 1.3 X ULN: >145 mg/dL, and FBS > 2 X ULN: >220 mg/dL

The clinical significance of the FBS increases >normal are not known, however it is established that even mild increases in blood sugar are associated with accelerated atherosclerosis[30, 31]. Three patients experienced clinically significant elevations in FBS. One patient with a history of type 2 DM in the Advi/20 group (0414) had an elevation in FBS >2 X ULN during an acute illness. Another patient in the Advi/20 group (0919) had a worsening of diabetes during the study requiring a change in diabetic medication, and one patient in the Niaspan group (1803) developed diabetes during the study. These three patients are described in the following table

Table 46: MA-14 Patients With Clinically Significant FBS Elevations

Week	FBS	Elevation	Advicor dose	Contributing history
Patient 0414 (Advi/20):				
Baseline	127	>normal	None	55 year old male, history of colitis, BPH, gout, and type 2 (DM). Experienced prostatitis Week 16. Treated with Cipro X 17 days. Developed severe nausea and vomiting 4 days prior to Week 20, and therapy changed to Floxin. Completed study Week 20, and entered MA-09. Study medication was not restarted and patient discontinued in MA-09.
Week 4	137	>normal	500/20 X 4 weeks	
Week 8	153	>1.3 X ULN	1000/20 X 4 weeks	
Week 12	140	>normal	1500/20 X 4 weeks	
Week 16	166	>1.3 X ULN	2000/20 X 4 weeks	
Week 20	283	>2 X ULN	2500/20 X 4 weeks (completed)	
Week 20 retest	162	>1.3 X ULN	3 days off study medication	
Week 20 retest	133	>1.3 X ULN	9 days off study medication	
Patient 0919 (Advi/20):				59 year old female, history of type 2 DM, headache, diverticulitis, anemia, back pain, and sinusitis. Baseline: HgA1C 6.9, and Week 12: HgA1C 7.9 Patient's Glucophage was increased from 500 mg TID to 850 mg TID, and started on Avandia 40 mg qD. The patient also experienced a UTI 5 days prior to Week 12 treated with Achromycin.
Baseline	108	WNL	None	
Week 4	102	WNL	500/20 X 4 weeks	
Week 8	117	>normal	1000/20 X 4 weeks	
Week 12	175	>1.3 X ULN	1500/20 X 4 weeks	
Week 16	104	WNL	2000/20 X 4 weeks	
Week 20	127	>normal	2500/20 X 4 weeks	
Patient 1803 (Niaspan):				78 year old female, history of CVA, Parkinson's disease, PVD, hypertension, CHF, and CAD. Patient was hospitalized for syncope at approx. Week 10, and found to have pyelonephritis. An elevated glucose of 228 was also noted during hospitalization. The patient was diagnosed with DM and treated with Glucophage 500 mg qD. At approximately Week 18, the Glucophage was discontinued.
Baseline	118	>normal	None	
Week 4	122	>normal	500 X 4 weeks	
Week 8	136	>normal	1000 X 4 weeks	
Hospitalization	228	>2 X ULN	1500 X 3 weeks	
Week 12	126	>normal	1500 X 4 weeks	
Week 16	136	>normal	2000 X 4 weeks	
Week 20	135	>normal	2500 X 4 weeks	

(c) Phosphorous

Decreases in serum phosphorous were common in the 4 niacin-exposed groups. Low serum phosphorous was seen in only one patient in the lovastatin group (3%) and in 31-71% of the niacin-exposed patients. Fourteen (14) patients overall (9%) had phosphorous levels <2 X LLN, all of whom were in the 4 niacin-exposed groups. No clinically significant changes in serum calcium were noted. No clinical findings were attributed to the low phosphorous values, and the clinical significance of mild to moderate hypophosphatemia in this group of patients is unknown. The incidence of phosphorous decreases is summarized in the following table

Table 47: MA-14 Incidence of Treatment Emergent Phosphorous Decreases

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**lovastatin**
Randomized Patients, n =	164	31	34	34	32	33
Phosphorus <normal, n (%)	70 (43)	17 (55)	24 (71)	18 (53)	10 (31)	1 (3)
Phosphorous <2 X LLN, n (%)	14 (9)	4 (13)	5 (15)	3 (9)	2 (6)	0

Phosphorous normal range: 2.4-4.3 mg/dL

(d) CPK Elevations

Mild CPK elevations were common, but elevations >5 X ULN occurred in only 3 patients [patient 0105 (Niaspan), patient 0701 (Niaspan), and patient 0106 (Advi/20)]. There were no cases of CPK elevation >10 X ULN. No patient was discontinued due to CPK abnormalities and there were no reported cases of myopathy. The incidence of CPK elevations is as follows

Table 48: MA-14 Incidence of Treatment Emergent CPK Elevations

		Treatment				
	All	**Niaspan**	**Advi/10**	**Advi/20**	**Advi/40**	**lovastatin**
Randomized Patients, n =	164	31	34	34	32	33
CPK >normal	65 (40)	10 (32)	15 (44)	14 (41)	13 (41)	13 (39)
CPK >5 X ULN	3 (2)	2 (7)	0	1 (3)	0	0

CPK upper limit of normal: Female 164 U/L, Male 207 U/L

The CPK values for the 3 patients experiencing CPK elevations >5 X ULN are summarized in the following table

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Table 49: MA-14 Patients With CPK Elevations > 5 X ULN

Patient	Week	CPK	Elevation
0105 (Niaspan)	Baseline	576	>normal
	Week 4	709	>3 X ULN
	Week 8	784	>3 X ULN
	Week 12	1810	>5 X ULN
	Week 12 retest	963	>3 X ULN
	Week 16	430	>normal
	Termination	438	>normal
0701 (Niaspan)	Baseline	180	WNL
	Week 4	104	WNL
	Week 8	861	>5 X ULN
	Week 8 retest	115	WNL
	Week 12	66	WNL
	Week 16	138	WNL
	Week 20	135	WNL
0106 (Advi/20)	Baseline	283	>normal
	Week 4	387	>normal
	Week 8	1293	>5 X ULN
	Week 8 retest	285	>normal
	Week 12	328	>normal
	Week 16	307	>normal
	Termination	273	>normal

(e) Other Laboratory Values

There were no instances of elevations > 2 X ULN in alkaline phosphatase, total bilirubin, LDH, or uric acid. Two patients had amylase >2 X ULN [Patient 1002 (Advi/20) and Patient 0704 (Advi/40)] which resolved. No patient had a platelet count <100,000, and there were no clinically significant decreases in WBC. Two patients had PT > 1.3 X ULN without any accompanying clinical signs. There were no other clinically significant laboratory abnormalities reported during the study.

(f) Subgroup Analysis

Subgroup analyses by sex, and by geriatric vs non-geriatric patients were also performed (Tables of TELAs by subgroup, by laboratory value are listed in Appendix VIII). In general, TELAs by subgroup were similar to the overall results. The only notable difference seen was that decreases in phosphorous were more common in male than female patients (61% vs 23% respectively, overall). As the numbers of patients per treatment group when divided into subgroups was small, any findings should be interpreted with caution.

The serum phosphorous results by sex are as follows

Table 50: MA-14 Incidence of Treatment Emergent Phosphorous Decreases, Male vs Female

			Treatment				
		All	Niaspan	Advi/10	Advi/20	Advi/40	lovastatin
Randomized Male (M) Patients, n =		M=85	M=17	M=17	M=18	M=15	M=18
Randomized Female (F) Patients, n =		F=79	F=14	F=17	F=16	F=17	F=15
Phosphorous <normal, n (%)	M	52 (61)	13 (76)	16 (94)	13 (72)	9 (60)	1 (6)
Phosphorous <normal, n (%)	F	18 (23)	4 (29)	8 (47)	5 (31)	1 (6)	0
Phosphorous <2 X LLN, n (%)	M	12 (14)	4 (24)	4 (24)	2 (11)	2 (13)	0
Phosphorous <2 X LLN, n (%)	F	2 (3)	0	1 (6)	1 (6)	0	0

(8) Overall Safety Conclusions

Advicor and Niaspan, in general, were not well tolerated. More patients in the 4 niacin-exposed groups reported any AE during study drug treatment than patients in the lovastatin group. The niacin-exposed patients were much more likely to report a Cardiovascular system AE, especially flushing, and were more likely to complain of Digestive system AEs (diarrhea and vomiting). With the exception of the Advi/10 group, patients in the niacin-exposed groups were also more likely to discontinue from the study for any reason, mainly due to AEs. Flushing and rash were the most commonly reported reasons for discontinuation, and occurred exclusively in the 4 niacin-exposed groups. Female and geriatric patients were somewhat more likely to be discontinued from the study than male and non-geriatric patients, most commonly due to AEs. Female patients were more likely than male patients to discontinue due to flushing. Geriatric patients were more likely than non-geriatric patients to discontinue due to rash and urticaria, and non-geriatric patients were more likely to discontinue due to asthenia. Clinically significant TELAs were uncommon, and no patient discontinued for a laboratory abnormality. However, mild elevations in AST, ALT, FBS, and CPK, and mild to moderate decreases in phosphorous were common during study drug treatment. FBS increases were the most common TELA, occurring in >50% of patients, and were more common in the 4 niacin-exposed groups. The long-term clinical significance of these laboratory findings is unknown.

3. Conclusions on Review of Protocol MA-14

Study MA-14 does not support the Sponsor's proposed labeling indications for Advicor. The study design did not include any of the treatment doses proposed for marketing based on the planned tablet strengths. In addition, inconsistencies in the lovastatin comparator arm rendered the efficacy findings uninterpretable. The safety data are consistent with historical data with niacin use and with the other Advicor clinical studies submitted to the NDA, and the side-effect profile for Advicor closely resembled that of Niaspan. Advicor was not well tolerated. The dropout rate in this study was high, particularly in the niacin-exposed patients, and AEs were the most frequently cited reason for study discontinuation. However, the majority of AEs were not serious, and were reversible with discontinuation of (or a decrease in) study medication. Flushing was experienced by the majority of niacin-exposed patients, and was the most frequent reason given for study discontinuation. Discontinuations due to rash, pruritus, and urticaria were also more frequent in the niacin-exposed patients. Other side-effects seen more frequently in the niacin-exposed patients were vomiting and diarrhea. Laboratory abnormalities seen more frequently in the niacin-exposed patients included mild elevations in AST, ALT, and FBS, and mild decreases in phosphorous. The clinical significance of these laboratory findings is unknown, and there were no discontinuations due to laboratory abnormalities.

B. Protocol Study MA-0-98-010406

(Protocol MA-98-010406 will be referred to as MA-06 from this point forward)

1. Study Design for MA-06

a) Study Design

Protocol MA-98-010406 (MA-06) "Evaluation of the Safety and Efficacy of Advicor (a combination tablet of niacin extended-release/lovastatin immediate-release): A Dose-Ranging Study" was a 28-week, double-blind, randomized, controlled, dose-escalation study conducted at 23 clinical sites nationally. The study evaluated the efficacy and safety of Advicor vs Niaspan vs lovastatin in 236 patients with Type IIa and IIb hyperlipidemia and LDL-C levels warranting treatment per NCEP II guidelines.

b) Study Objectives

The objective of the study was to evaluate the dose-response relationships and safety of a range of Advicor doses in patients with dyslipidemia, and to evaluate the efficacy of various fixed combination doses of Advicor compared to each of the individual components (niacin and lovastatin).

c) Eligibility Criteria

(1) Inclusion Criteria

1) Men and women 18 years of age or older
2) Patient was willing to participate and sign Informed Consent
3) Patient had primary hypercholesterolemia Frederickson Type IIa or IIb
4) Patient had not taken lipid-altering or other prohibited medications for at least 6 weeks prior to randomization, or 4 weeks prior to qualification visits, and for the duration of the study
5) Female patients must not have been pregnant or breast-feeding. Women of childbearing potential must have used an oral contraceptive, an IUD, or a double barrier method of contraception

(2) Exclusion Criteria

1) Patient had an allergy or hypersensitivity to niacin, lovastatin, or their derivatives
2) Patient had a previous history (within 12 months of screening) of substance abuse or dependency
3) Patient had untreated or unsuccessfully treated psychiatric disease
4) Patient had used an investigational study medication or participated in an investigational study within 30 days of screening
5) Patient had taken a prohibited medication within 4 weeks of obtaining qualification labs. Prohibited medications were:
   - 3-isotretinoin (Accutane)
   - cyclosporin (Sandimmune)
   - troglitazone (Rezulin)
   - oral erythromycin and/or any other oral macrolide antibiotic

- oral itraconazole and/or any other oral azole-type antifungal agent
- any HMG-CoA reductase inhibitor [atorvastatin (Lipitor), fluvastatin (Lescol), lovastatin (Mevacor), pravastatin (Pravachol), simvastatin (Zocor), cerivastatin (Baycol)]
- any fibric acid derivative [gemfibrozil (Lopid), fenofibrate (TriCor), clofibrate (Atromid-S)]
- bile acid sequestrants [cholestyramine (Questran, Questran Lite), colestipol (Colestid), etc.]
- any product containing over 30 mg of niacin

Concomitant medications known to have minor effects on serum lipid levels were permitted if the dose had been stable for 1 month prior to randomization and remained stable throughout study participation, e.g., thiazide diuretics, systemic beta-blockers, systemic corticosteroids, and psyllium products. Estrogen replacement and thyroid replacement therapy were allowed if the doses had been stable for at least three months prior to randomization and throughout the study. Thyroid Stimulating Hormone (TSH) must have been within normal limits (WNL) for patients on thyroid replacement.

6) Patient had a history of:
   - Active gallbladder disease within one year (cholecystectomy was allowed)
   - Persistent treated or untreated severe hypertension
   - Unstable angina
   - Myocardial infarction, coronary artery surgery, angioplasty, or stroke within the preceding six months
   - Significant renal disease (serum creatinine $\geq$1.5 mg/dL)
   - Significant hepatic disease (AST or ALT >1.3 X ULN)
   - Congestive heart failure (NYHA class III or IV)
   - Active gout symptoms and/or uric acid levels >1.3 X ULN
   - Active peptic ulcer disease
   - Arterial bleeding
   - Type 1 diabetes or uncontrolled type 2 diabetes (HgA1C >8%)
   - Active cancer or a diagnosis of cancer within the last 5 years (excluding basal cell carcinoma)
7) Patient had any health condition or laboratory abnormality which, in the opinion of the Investigator, may have been adversely affected by the procedures or medications in this study
8) Patient had been treated with Lorelco (probucol) within 1 year prior to screening

d) Study Visits and Procedures

The study visits and procedures are summarized below and in the following table.

Table 51: MA-06 Study Visits and Procedures

	Qualification Visits	Treatment Visits							
Week	**-8 to -1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28/ET**
Procedure Sign Informed Consent	X								
Medical History	X	X							
Physical Exam		X							X
Vital Signs	X	X	X	X	X	X	X	X	X
ECG	X								
Dietary Instruction/Evaluation	X								
3-Day Diet Log Collected		X			X				X
Serum Chemistries	X		X	X	X	X	X	X	X
Fasting Lipid Panel	X		X	X	X	X	X	X	X
Hematology	X								X
Urinalysis	X								X
HgA1C(diabetics only)	X				X				X
PT/PTT	X								X
TSH (thyroid replacement only)	X								
Pregnancy Test (if applicable)	X								
Flushing Logs Dispensed		X	X	X	X	X	X	X	
Adverse Events Query			X	X	X	X	X	X	X
Dispense Study Medication		X	X	X	X	X	X	X	
Collect Study Medication			X	X	X	X	X	X	X

(1) Screening and Qualification Visits (Weeks –8 to –1)

All participants were recruited at 23 study sites, and screened for eligibility including medical history, ECG, laboratory assessment [including serum chemistry, hematology PT/PTT, HCG (females age <60), TSH (patients on thyroid replacement), HgA1C (type 2 diabetics), and urinalysis], and vital signs. All patients underwent diet assessment and teaching, and were required to follow a NCEP Step 1 diet for at least 4 weeks prior to obtaining qualification laboratories. A 3-day diet log was dispensed during qualification, and was to be completed prior to the randomization visit. Patients using lipid-lowering medications were required to discontinue their use for at least 4 weeks prior to obtaining qualification labs.

For qualification, 2 fasting lipid profiles within 7-10 days of each other were obtained. Lipid profiles could be repeated twice if needed for qualification, and the mean of 2 consecutive lipid profiles was used for qualification. In order to be randomized, patients must have met all of the following qualification criteria:

1) Low density lipoprotein cholesterol (LDL-C) based on NCEP II guidelines must have been:

a) For patients with diabetes or a history of CHD: mean LDL $\geq$130 mg/dL
b) For patients with 2 or more CAD risk factors: mean LDL $\geq$160 mg/dL

c) For patients with fewer than 2 CAD risk factors: mean LDL ≥190 mg/dL

2) LDL lower value within 12% of the greater value, calculated as

$$\frac{[\text{LDL(higher)} - \text{LDL(lower)}]}{\text{LDL(higher)} \times 100}$$

5) Mean triglycerides ≤800 mg/dL
6) ALT and AST ≤1.3 X ULN

(2) Randomization Visit (Week 0)

Qualifying patients returned to the study center within 7-14 days of the last qualification visit. Three-day diet logs were returned and evaluated prior to randomization. Qualifying patients were randomized to one of 4 blinded treatment groups. Patients then underwent physical examination including medical history update and vital signs (blood pressure, pulse, height and weight), and randomization. Flushing logs and study medication were dispensed.

(3) Post-Randomization Visits (Weeks 4, 8, 12, 16, 20 and 24)

Patients underwent vital sign measurements and laboratory assessment [fasting lipid profile, and serum chemistry]. Adverse events and concomitant medications were reviewed. Flushing logs and study medication were collected, and medication for the next 4 weeks was dispensed. At Week 12 only, a 3-day diet log was collected and HgA1C (diabetics only) laboratory testing was performed.

(4) End of Study (Week 28) or Early Termination

Patients underwent a physical exam including vital signs, and laboratory assessment [fasting lipid profile, serum chemistry, hematology, HbA1C (diabetics only), PT/PTT, and urinalysis]. Adverse events and concomitant medications were reviewed. Three-day diet logs and all study medication were collected.

e) Study Medication Dispensing and Compliance

Study patients were randomly assigned to one of four treatment groups as follows
Group A: Advicor 1000/20 (Advi/20) [mg Niaspan/mg lovastatin]
Group B: Advicor 2000/40 (Advi/40) [mg Niaspan/mg lovastatin]
Group C: Niaspan [mg]
Group D: lovastatin [mg]
Randomization occurred at the study sites using blocks of four dispensed sequentially by blinded study personnel.

All four study treatments were administered in a forced dose-escalation fashion at 4-week intervals for a total of 28 weeks. Study treatments were dosed once daily at bedtime with a low fat snack. Patients took 1 tablet a day during Weeks 1-12, three tablets a day during Weeks 13-20, and 2 tablets a day during Weeks 21-28. The dose titration schedule by treatment group is as follows

Table 52: MA-06 Dose Titration Schedule

	Weeks						
Treatment	**1-4**	**5-8**	**9-12**	**13-16**	**17-20**	**21-24**	**25-28**
Advi/20 (mg/mg)	500/20	750/20	1000/20	1000/20	1000/20	1000/20	1000/20
Advi/40(mg/mg)	500/20	750/20	1000/20	1000/40	1500/40	2000/40	2000/40
Niaspan (mg)	500	750	1000	1000	1500	2000	2000
Lovastatin (mg)	20	20	20	40	40	40	40
Number of tablets	1	1	1	3	3	2	2

Study medications were visually identical, supplied in blister cards, and dispensed for a 4-week period + 7 days extra medication. Unused medication was collected at the following study visit, and compliance was determined by a tablet count.

The study medication tablet consisted of:
Advicor - Niacin extended-release (ER) — lovastatin 20 mg
Niaspan - Niacin ER
Lovastatin - placebo — lovastatin 20 mg
Placebo - placebo
Tablet content varied by visit and by treatment group. Tablets given by week by treatment group are as follows

Table 53: MA-06 Tablet Content

	Weeks						
Treatment	**1-4**	**5-8**	**9-12**	**13-16**	**17-20**	**21-24**	**25-28**
Advicor dose (mg/mg)	**500/20**	**750/20**	**1000/20**	**1000/20**	**1000/20**	**1000/20**	**1000/20**
Advicor 500/20 tablets	1	0	0	0	0	0	0
Advicor 750/20 tablets	0	1	0	0	0	0	0
Advicor 1000/20 tablets	0	0	1	1	1	1	1
Placebo tablets	0	0	0	2	2	1	1
Advicor dose (mg/mg)	**500/20**	**750/20**	**1000/20**	**1000/40**	**1500/40**	**2000/40**	**2000/40**
Advicor 500/20 tablets	1	0	0	2	0	0	0
Advicor 750/20 tablets	0	1	0	0	2	0	0
Advicor 1000/20 tablets	0	0	1	0	0	2	2
Placebo tablets	0	0	0	1	1	0	0
Niaspan dose (mg)	**500**	**750**	**1000**	**1000**	**1500**	**2000**	**2000**
Niacin ER 500 mg tablets	1	0	0	2	0	0	0
Niacin ER 750 mg tablets	0	1	0	0	2	0	0
Niacin ER 1000 mg tablets	0	0	1	0	0	2	2
Placebo tablets	0	0	0	1	1	0	0
Lovastatin dose (mg)	**20**	**20**	**20**	**40**	**40**	**40**	**40**
Lovastatin 500p*/20 tablets	1	0	0	2	0	0	0
Lovastatin 750p/20 tablets	0	1	0	0	2	0	0
Lovastatin 1000p/20 tablets	0	0	1	0	0	2	2
Placebo tablets	0	0	0	1	1	0	0

*p = placebo

f) Efficacy and Endpoint Measures

Primary: The primary efficacy analysis is the mean percent change from baseline in LDL-C for each dose compared among the Advicor, lovastatin, and Niaspan treatment groups.

Secondary: Secondary efficacy measures are mean percent change from baseline in:
1) Apoprotein B [Apo B]
2) Total Cholesterol [TC]
3) High density lipoprotein cholesterol [HDL-C]
4) Triglycerides [TG]
5) Lipoprotein a [Lp(a)]
6) TC:HDL-C ratio
7) LDL-C:HDL-C ratio

Safety: Safety was assessed by measuring serum transaminases, chemistry and hematology profiles, urinalysis, physical examination including vital signs, and adverse events.

2. Results

Four hundred ninety-nine (499) patients were screened at 23 study sites. Two hundred thirty-seven (237) patients were randomized between 01-Apr-1999 and 23-Jun-1999. One randomized patient never took any study medication, so the Intent-To-Treat (ITT) population consisted of 236 patients. Intent-to treat patients were randomized into treatment groups as follows

Table 54: MA-06 ITT Patients by Treatment Group

		Treatment			
	All	**Advi/20**	**Advi/40**	**Niaspan**	**Lovastatin**
ITT patients, n =	236	57	57	61	61

a) Baseline Demographics and Patient Characteristics

Overall, 55% of the ITT population was male and >85% was Caucasian. Patients ranged in age from 32-86 years, with a mean age of 59.2 years. Demographic data were not supplied for the non-randomized (screen failure) patients, but 159/262 (61%) were not eligible due to failure to qualify by lipid inclusion criteria. Baseline characteristics and demographics for the treatment groups are summarized as follows

Table 55: MA-06 Baseline Demographics

	ITT	Treatment			
	All	Advi/20	Advi/40	Niaspan	Lovastatin
Number of Patients, n =	236	57	57	61	61
Demographic Measure					
Gender, n (%)					
Male	130 (55)	31(54)	32(56)	28(46)	39(64)
Female	106 (45)	26(46)	25(44)	33(54)	22(36)
Age, years					
mean	59.2	59.1	59.5	57.9	60.6
median	60	59.0	58.0	59.0	63.0
min, max	32, 86	32, 86	35, 84	33, 84	33, 81
Age ≥65 years, n (%)	80 (34)	18 (32)	20 (35)	17 (28)	25 (41)
Ethnicity, n(%)					
Caucasian	205 (87)	50(88)	49(86)	55(90)	51(84)
Black	12 (5)	2(4)	4(7)	3(5)	3(5)
Hispanic	14 (6)	5(9)	3(5)	2(3)	4(7)
Asian	5 (2)	0	1(2)	1(2)	3(5)
Other	0	0	0	0	0
Risk Factors (RF)					
Diabetes, n (%)	34 (14)	13 (22)	6 (11)	8 (13)	7 (11)
Current smoker, n (%)	35 (15)	12 (21)	6 (11)	11 (18)	6 (10)
≥2 CAD RF, n (%)	163 (69)	39 (68)	40 (66)	44 (72)	40 (66)
<2 CAD RF, n (%)	73 (31)	18 (32)	17 (28)	17 (28)	21 (34)
Mean BMI, kg/M^2	29.1	29.9	28.6	29.2	29.0
Baseline Lipid Value					
Mean LDL-C, mg/dL	-	192.1	190.9	189.7	185.6
Mean HDL-C, mg/dL	-	44.8	45.4	46.8	43.5
Median Triglycerides, mg/dL	-	224.4	212.6	195.6	181.5
Mean Lp(a), mg/dL	-	32.4	34.3	41.0	42.3

b) Patient Disposition

(1) Screening and Randomization

Of the 499 screened patients, 262 (53% of total screened) were not randomized. Of the 262 non-randomized patients, 159 (61% of screen failures) were not eligible for randomization due to failure to qualify by lipid inclusion criteria. Patients failing to meet eligibility criteria are summarized in the following table

Table 56: MA-06 Patients Failing to Meet Eligibility Criteria

Eligibility criteria not met, n = 262	n (%)
Failure to have appropriate lipid levels per inclusion criteria	159 (61)
Withdrawal of consent	56 (21)
Abnormal laboratory value	21 (8)
Other medical	11 (4)
Lost to Follow-up	10 (4)
Other non-medical	4 (2)
Unstable lipid parameter	1 (<1)

(2) Dropouts

Of the 237 patients randomized to a treatment group, 1 patient never received study medication. Two hundred thirty-six (236) patients comprised the ITT population. Of these 236 patients, 176 (75%) completed the 28 weeks of study drug treatment and 60 patients (25%) were discontinued. Most dropouts occurred by Week 16. Dropouts by week by treatment group are summarized in the following table

Table 57: MA-06 Dropouts by Week by Treatment

		Treatment			
	All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Patients, n =	236	57	57	61	61
Week completed					
Week 4, n (%)	222 (94)	55 (96)	52 (91)	56 (92)	59 (97)
Week 8, n (%)	206 (87)	49 (86)	48 (84)	51 (84)	58 (95)
Week 12, n (%)	198 (84)	48 (84)	47 (82)	47 (77)	56 (92)
Week 16, n (%)	188 (80)	43 (75)	45 (79)	44 (72)	56 (92)
Week 20, n (%)	181 (77)	42 (74)	42 (74)	43 (70)	54 (89)
Week 24, n (%)	179 (76)	42 (74)	42 (74)	42 (69)	53 (87)
Week 28, n (%)	176 (75)	40 (70)	42 (74)	41 (67)	53 (87)

Of the 60 patients who were discontinued, 40 of 60 patients discontinued due to adverse events and 2 were discontinued for abnormal laboratory values. More patients discontinued for any reason in the 3 niacin-exposed groups (26-33%) than in the lovastatin group (13%). More patients also discontinued for AEs in the 3 niacin-exposed groups (18-21%) than in the lovastatin group (10%), as follows

Table 58: MA-06 Patients Discontinued

		Treatment			
	All	**Advi/20**	**Advi/40**	**Niaspan**	**Lovastatin**
ITT Patients, n =	236	57	57	61	61
Number of Withdrawals, n (%)	60 (25)	17 (30)	15 (26)	20 (33)	8 (13)
Reason for Dropout					
Adverse event	40 (17)	12 (21)	10 (18)	12 (20)	6 (10)
Protocol violation	7 (3)	2 (4)	2 (4)	2 (3)	1 (2)
Other (noncompliance)	5 (2)	1 (2)	2 (4)	2 (3)	0
Withdrew consent	4 (2)	1 (2)	1 (2)	2 (3)	0
Lost to follow up	3 (1)	1 (2)	0	2 (3)	0
Abnormal labs	2 (1)	1	0	0	1 (2)

One patient (1401, Advi/40) was unblinded at the site after a protocol violation. No other patients were unblinded during the study.

The baseline demographics of patients who dropped out during study drug treatment differed somewhat from the ITT patients at baseline. However, as the number of patients in each treatment group was small, the effects of these differences are unlikely to have significantly affected the overall results of the study. Notable differences are:

1) The dropouts in all groups had fewer CAD risk factors (<2) than the ITT patients as a group.
2) The dropouts in the Advi/40 group had a higher number of geriatric patients (age ≥65 years).
3) The dropouts in the lovastatin group had a lower baseline mean LDL-C.

Table 59: MA-06 Baseline Demographics of ITT Patients vs Dropouts

	ITT	Dropouts by Treatment				
	All	All	Advi/20	Advi/40	Niaspan	lovastatin
Number of Patients, n =	236	60	17	15	20	8
Demographic Measure						
Gender, n (%)						
Male	130 (55)	24 (40)	8 (47)	7 (47)	5 (25)	4 (50)
Female	106 (45)	36 (60)	9 (53)	8 (53)	15 (75)	4 (50)
Age, years						
mean	59.2	57.5	57.7	61.4	54.4	57.5
median	60	58.5	60	66	54	57.5
min, max	32, 86	33, 84	33, 79	35, 84	40, 74	42, 70
Patients Age ≥ 65 years, n (%)	80 (34)	17 (28)	5 (29)	8 (53)	3 (15)	1 (13)
Ethnicity, n(%)						
Caucasian	205 (87)	51 (85)	14 (82)	12 (80)	18 (90)	7 (88)
Black	12 (5)	4 (7)	1 (7)	2 (13)	1 (5)	0
Hispanic	14 (6)	5 (8)	2 (12)	1 (7)	1 (5)	1 (13)
Asian	5 (2)	0	0	0	0	0
Other	0	0	0	0	0	0
Risk factors (RF)						
Diabetes, n (%)	34 (14)	6 (10)	4 (24)	0	2 (10)	0
Current smoker, n (%)	35 (15)	13 (22)	3 (18)	3 (20)	6(30)	1 (13)
≥2 CAD RF, n (%)	163 (69)	14 (23)	8 (47)	2 (13)	2 (10)	2 (25)
<2 CAD RF, n (%)	73 (31)	46 (77)	9 (53)	13 (87)	18 (90)	6 (75)
Mean BMI, kg/M^2	29.1	29.5	29.9	28.3	29.3	31.6
Baseline Lipid Value						
Mean LDL-C, mg/dL	-	-	190.7	186.3	189.9	171.9
Mean HDL-C, mg/dL	-	-	43.4	43.7	46.6	43.1
Median Triglycerides, mg/dL	-	-	203.5	209.5	208.3	232.5
Mean Lp(a), mg/dL	-	-	51.4	32.1	42.4	39.6

c) Concomitant Medications

Concomitant medications (conmeds) were medications that were either started prior to randomization and continued during study drug treatment, or were started during study drug treatment. Overall, 99% of study patients reported the use of any concomitant medication during the study, as follows

Table 60: MA-06 Patients Reporting Any Concomitant Medication Use

	Treatment				
	All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Patients, n =	236	57	57	61	61
Patients Reporting Any Conmed Use, n (%)	234 (99)	55 (96)	57 (100)	61 (100)	61 (100)

A large number of different medications was used (over 350 different medications were reported), with the majority used by a small number of patients (used by ≤3 patients per medication, or by ≤1% of patients overall). The most frequently reported concomitant medication used was aspirin, which was used by 61% of study patients overall. Aspirin

use was similar across all treatment groups; however, it is unclear if its use was for the treatment of flushing, prevention of flushing, or for other indications such as CHD prevention or treatment. Aspirin use by treatment group is summarized in the following table. A list of commonly used concomitant medications (use reported by ≥5% of patients overall) is reported in Appendix I.

Table 61: MA-06 Patients Reporting Concomitant Aspirin Use

		Treatment			
	All	**Advi/20**	**Advi/40**	**Niaspan**	**lovastatin**
ITT Patients, n =	236	57	57	61	61
Patients Reporting Aspirin Use, n (%)	144 (61)	37 (65)	32 (56)	37 (61)	38 (62)

No patient was reported as having used a lipid-lowering medication during study drug treatment. Of the medications known to have minor effects on serum lipid levels that were permitted for use during the trial, such as thiazide diuretics, systemic beta blockers or psyllium preparations, there did not appear to be any significant imbalances between treatment groups. It is therefore unlikely that the use of concomitant medications had any overall effect on the study results.

d) Patient Compliance

Compliance was assessed by pill counts at each study visit every 4 weeks. Patients were considered to be compliant with study medication if they were at least 75% compliant with study treatments. Compliance across treatment groups was similar, and was >90% for all groups at each 4-week interval.

e) Efficacy Results

Please also refer to: Mele, Joy. "Statistical Review and Evaluation: Clinical Studies NDA #21-249" for the statistical analysis. The statistical analysis will be referred to frequently in this section.

(1) Statistical Method

The primary efficacy endpoint was the mean percent change from baseline in LDL-C for each treatment group. Comparisons were made between the Advicor treatment groups and the Niaspan and lovastatin groups at each study visit. It was stated by the Sponsor in the protocol however, that the two primary comparisons for this study were: 1) Advicor 1000/20 vs lovastatin 20 mg LDL-C response at Week 12; and 2) Advicor 2000/40 vs Advicor 1000/20 LDL-C response at Week 28. In addition, other valid comparisons between the Advicor and lovastatin treatment groups were also performed by the Statistical Reviewer and are shaded and bolded below

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Table 62: MA-06 Advicor vs Lovastatin Valid Comparisons

	Weeks						
Treatment	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Advi/20 (mg/mg)	**500/20**	**750/20**	**1000/20**	1000/20	1000/20	1000/20	1000/20
Advi/40(mg/mg)	**500/20**	**750/20**	**1000/20**	**1000/40**	**1500/40**	**2000/40**	**2000/40**
Niaspan (mg)	500	750	1000	1000	1500	2000	2000
Lovastatin (mg)	**20**	**20**	**20**	**40**	**40**	**40**	**40**

In addition, as stated in the protocol, the primary efficacy analysis is to be performed on the intent-to-treat (ITT) population, which is defined as all patients who received at least one dose of study medication. The primary analysis performed by the sponsor however, was performed on observed cases at each time point. As there were a large number of dropouts, an ITT with last observation carried forward (LOCF) analysis and an ETRANS analysis were also performed by the Statistical Reviewer. These analyses produced similar results to the observed cases analysis (see Statistical Review) suggesting that dropouts did not have a significant impact on the outcome. Therefore, the observed cases results will be discussed here.

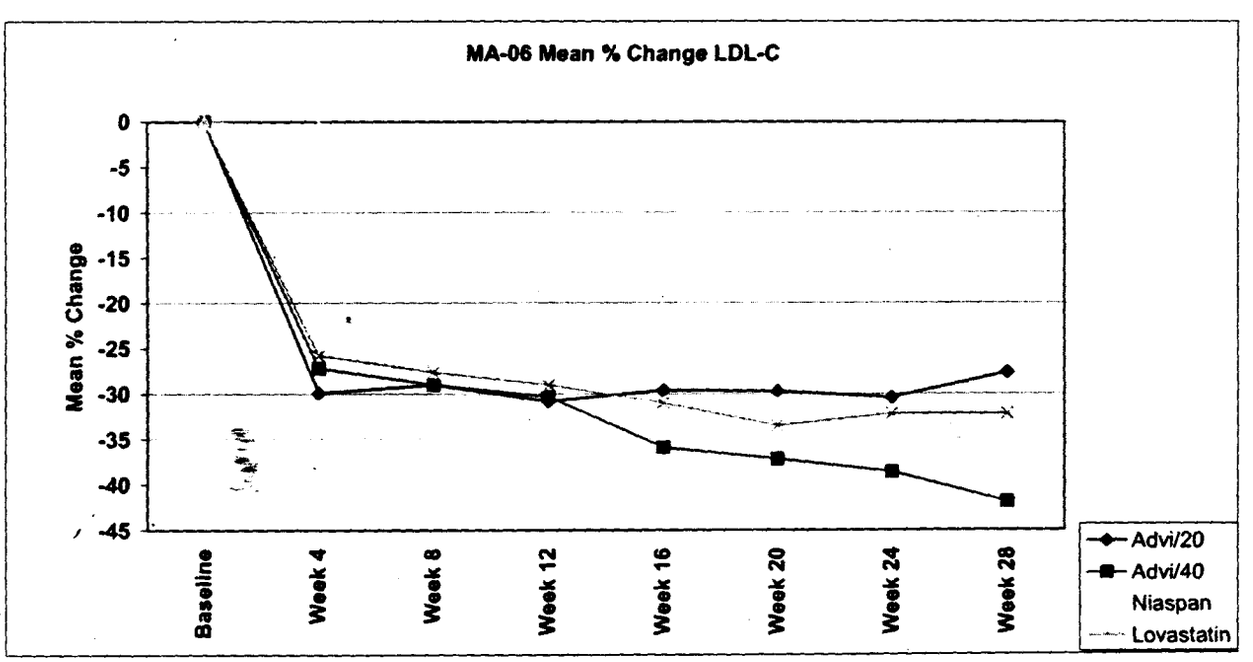
(2) Primary Efficacy Analysis: Mean Percent Change in LDL-C

The mean percent changes in LDL-C from baseline by treatment group are summarized in the following table and graph

Table 63: MA-06 Mean % Change in LDL-C

		Week						
Treatment	**Baseline**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Advi/20: dose (mg/mg)		**500/20**	**750/20**	**1000/20**	**1000/20**	**1000/20**	**1000/20**	**1000/20**
n	57	54	49	48	43	42	42	40
Mean	192.1 mg/dL	-29.9%	-29.0%	-30.8%	-29.6%	-29.7%	-30.4%	-27.6%
SE	6.03	1.24	1.67	1.89	2.46	2.24	2.34	2.34
Advi/40: dose (mg/mg)		**500/20**	**750/20**	**1000/20**	**1000/40**	**1500/40**	**2000/40**	**2000/40**
n	57	52	48	47	45	42	42	42
Mean	190.9 mg/dL	-27.2%	-29.0%	-30.3%	-35.9%	-37.2%	-38.6%	-41.9%
SE	4.47	1.64	1.92	1.88	1.85	2.45	2.79	2.11
Niaspan : dose (mg)		**500**	**750**	**1000**	**1000**	**1500**	**2000**	**2000**
n	61	56	51	46	44	43	42	41
Mean	189.7 mg/dL	-0.5%	-1.2%	-3.2%	-5.7%	-11.9%	-13.6%	-13.5%
SE	4.07	1.50	1.68	1.74	1.91	1.98	2.28	2.45
Lovastatin: dose (mg)		**20**	**20**	**20**	**40**	**40**	**40**	**40**
n	61	59	58	56	56	54	53	53
Mean	185.6 mg/dL	-25.8%	-27.6%	-29.0%	-31.0%	-33.5%	-32.2%	-32.2%
SE	4.66	1.34	1.33	1.16	1.28	1.32	1.34	1.50

Figure 4: MA-06 Mean % Change in LDL-C



The Niaspan group shows dose-related reduction in LDL-C with increasing dose from –0.5% at Week 4 (500 mg) to –14% at Week 28 (2000 mg). The lovastatin, Advi/20 and Advi/40 groups all show similar initial steep decreases in mean % change in LDL-C at Week 4 (27-30%). The Advi/20 group then has a flat response until Week 28 with little change in mean % change in LDL-C despite increasing niacin dose (-30% at Week 4 and –28% at Week 28). The lovastatin group also has a flat response curve with only a 3-4% further decrease in mean % change in LDL-C despite a doubling of the lovastatin dose from 20 to 40 from Week 12 to Week 16. The Advi/40 group shows a progressive decrease in mean % change in LDL-C from Week 4 to Week 28, with increasing doses of the niacin and lovastatin components.

The statistical comparisons between Advicor (Advi) and lovastatin (lova) for the mean % change in LDL-C (from the Statistician's Review) for the possible between-group comparisons are as follows

Table 64: MA-06 Statistical Comparison Advi vs Lova, Mean % Change LDL-C

	Advi	lova	Advi vs lova p-value
Week 4			
Dose	500/20	20	
Mean % change LDL-C	-29	-26	.13
Week 8			
Dose	750/20	20	
Mean % change LDL-C	-29	-27	.52
Week 12			
Dose	1000/20	20	
Mean % change LDL-C	-30	-29	.49
Week 16			
Dose	1000/40	40	
Mean % change LDL-C	-35	-31	.06
Week 20			
Dose	1500/40	40	
Mean % change LDL-C	-36	-32.5	.20
Week 24			
Dose	2000/40	40	
Mean % change LDL-C	-37	-31	.04
Week 28			
Dose	2000/40	40	
Mean % change LDL-C	-40	-31	.002

The results show a statistically significant difference between Advicor and lovastatin only at the dose comparisons of Advicor 2000/40 to lovastatin 40 mg at Weeks 24 and 28.

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Statistical comparisons between Advicor (Advicor) and Niaspan (Nia) are as follows

Table 65: MA-06 Statistical Comparison Advi vs Nia, Mean % Change LDL-C

	Advi	Nia	Advi vs Nia p-value
Week 4			
Dose	500/20	500	
Mean % change LDL-C	-29	-0.5	.0001
Week 8			
Dose	750/20	750	
Mean % change LDL-C	-29	-1	.0001
Week 12			
Dose	1000/20	1000	
Mean % change LDL-C	-30	-3	.0001
Week 16			
Dose	1000/40	1000	
Mean % change LDL-C	-35	-5	.0001
Week 20			
Dose	1500/40	1500	
Mean % change LDL-C	-36	-10	.0001
Week 24			
Dose	2000/40	2000	
Mean % change LDL-C	-37	-11	.0001
Week 28			
Dose	2000/40	2000	
Mean % change LDL-C	-40	-10	.0001

Advicor was significantly better than Niaspan at all dose comparisons for mean % change in LDL-C.

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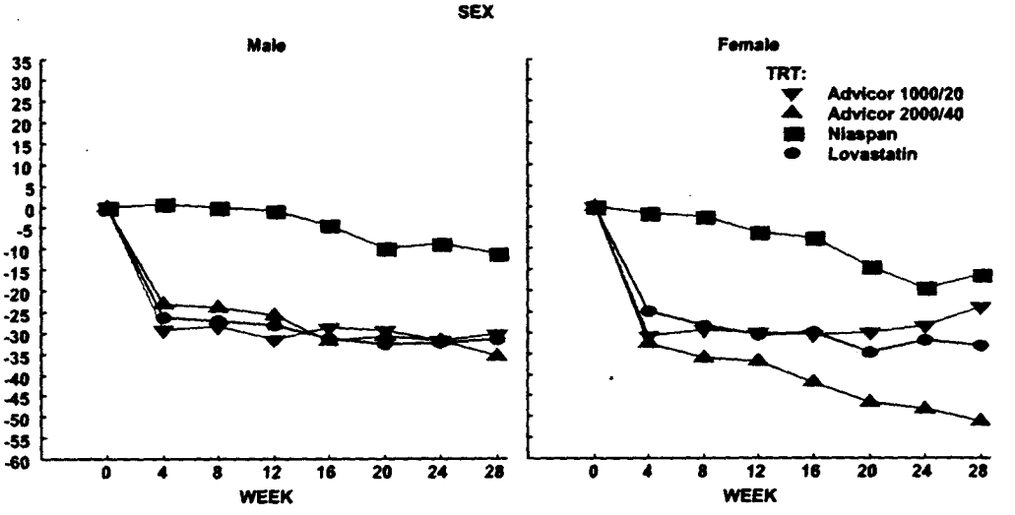
(a) Subgroup Analysis

Subgroup analysis was performed by the Statistical Reviewer for age (≥65 years vs <65 years), baseline LDL-C, and gender. A significant interaction for gender by treatment was seen ($p<.02$), which shows a statistically significant LDL-lowering for female patients only. There is no statistically significant difference for LDL-lowering between Advicor and lovastatin for males. The results are shown graphically as follows (from the statistical review; prepared by Joy D. Mele, M.S.)

Figure 5: MA-06 Mean % Change LDL-C, Males vs Females



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(3) Secondary Efficacy Measures

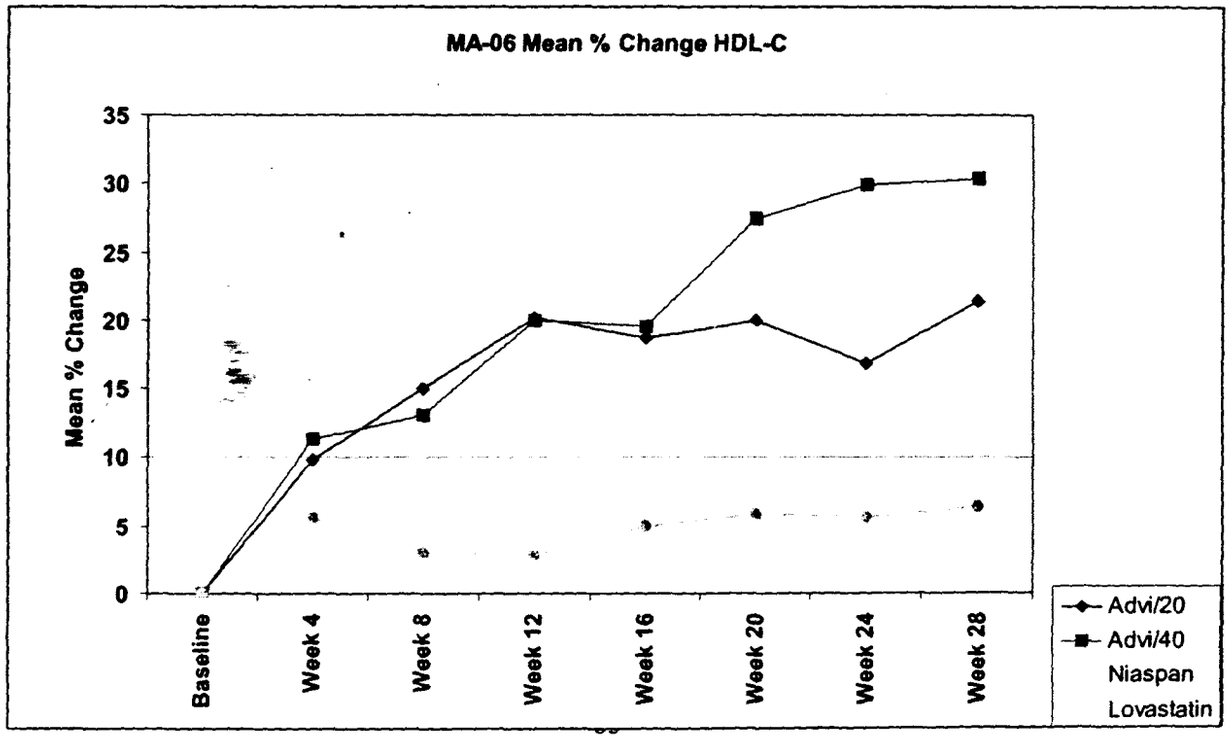
(a) Mean Percent Change from Baseline HDL-C

The mean percent changes from baseline in HDL-C by treatment group are summarized in the following table and graph

Table 66: MA-06 Mean % Change HDL-C

		Week						
Treatment	**Baseline**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Advi/20: dose (mg/mg)		**500/20**	**750/20**	**1000/20**	**1000/20**	**1000/20**	**1000/20**	**1000/20**
n	57	54	49	48	43	42	42	40
Mean	44.8 mg/dL	+9.8%	+15.0%	+20.2%	+18.7%	+20.0%	+16.9%	+21.4%
SE	1.50	1.57	2.02	2.41	2.68	2.65	2.87	2.87
Advi/40: dose (mg/mg)		**500/20**	**750/20**	**1000/20**	**1000/40**	**1500/40**	**2000/40**	**2000/40**
n	57	52	48	47	45	42	42	42
Mean	45.4 mg/dL	+11.3%	+13.1%	+20.0%	+19.5%	+27.4%	+29.9%	+30.4%
SE	1.63	1.55	2.08	2.03	2.21	2.47	2.86	2.63
Niaspan : dose (mg)		**500**	**750**	**1000**	**1000**	**1500**	**2000**	**2000**
n	61	56	51	46	44	+43	+42	+41
Mean	46.8 mg/dL	+5.3%	+7.6%	+14.3%	+14.8%	22.4%	24.4%	23.5%
SE	1.34	1.47	1.95	1.85	2.26	2.81	2.37	3.28
Lovastatin: dose (mg)		**20**	**20**	**20**	**40**	**40**	**40**	**40**
N	61	59	58	56	56	54	53	53
Mean	43.5 mg/dL	+5.6%	+3.0%	+2.8%	+5.0%	+5.8%	+5.6%	+6.4%
SE	1.38	1.30	1.59	1.30	1.44	1.64	1.70	2.09

Figure 6: MA-06 Mean % Change in HDL-C



Statistical comparisons were made between treatment groups at the same time points and for the same dose comparisons as for LDL-C. Advicor was statistically superior to lovastatin for mean % increase in HDL-C at all doses. Advicor was also statistically significantly better than Niaspan for HDL-raising at all doses, as follows

Table 67: MA-06 Statistical Comparison Advi vs Lova, Mean % Change HDL-C

	Advi	lova	Advi vs lova p-value
Week 4			
Dose	500/20	20	
Mean % change HDL-C	+11	+6	.005
Week 8			
Dose	750/20	20	
Mean % change HDL-C	+14	+3	.0001
Week 12			
Dose	1000/20	20	
Mean % change HDL-C	+19	+3	.0001
Week 16			
Dose	1000/40	40	
Mean % change HDL-C	+19	+5	.0001
Week 20			
Dose	1500/40	40	
Mean % change HDL-C	+26	+5	.0001
Week 24			
Dose	2000/40	40	
Mean % change HDL-C	+28	+5	.0001
Week 28			
Dose	2000/40	40	
Mean % change HDL-C	+28	+6	.0001

Table 68: MA-06 Statistical Comparison Advi vs Nia, Mean % Change HDL-C

	Advi	Nia	Advi vs Nia p-value
Week 4			
Dose	500/20	500	
Mean % change HDL-C	+11	+5	.007
Week 8			
Dose	750/20	750	
Mean % change HDL-C	+14	+6	.002
Week 12			
Dose	1000/20	1000	
Mean % change HDL-C	+19	+12	.001
Week 16			
Dose	1000/40	1000	
Mean % change HDL-C	+19	+12	.02
Week 20			
Dose	1500/40	1500	
Mean % change HDL-C	+26	+18	.007
Week 24			
Dose	2000/40	2000	
Mean % change HDL-C	+28	+20	.006
Week 28			
Dose	2000/40	2000	
Mean % change HDL-C	+28	+19	.0008

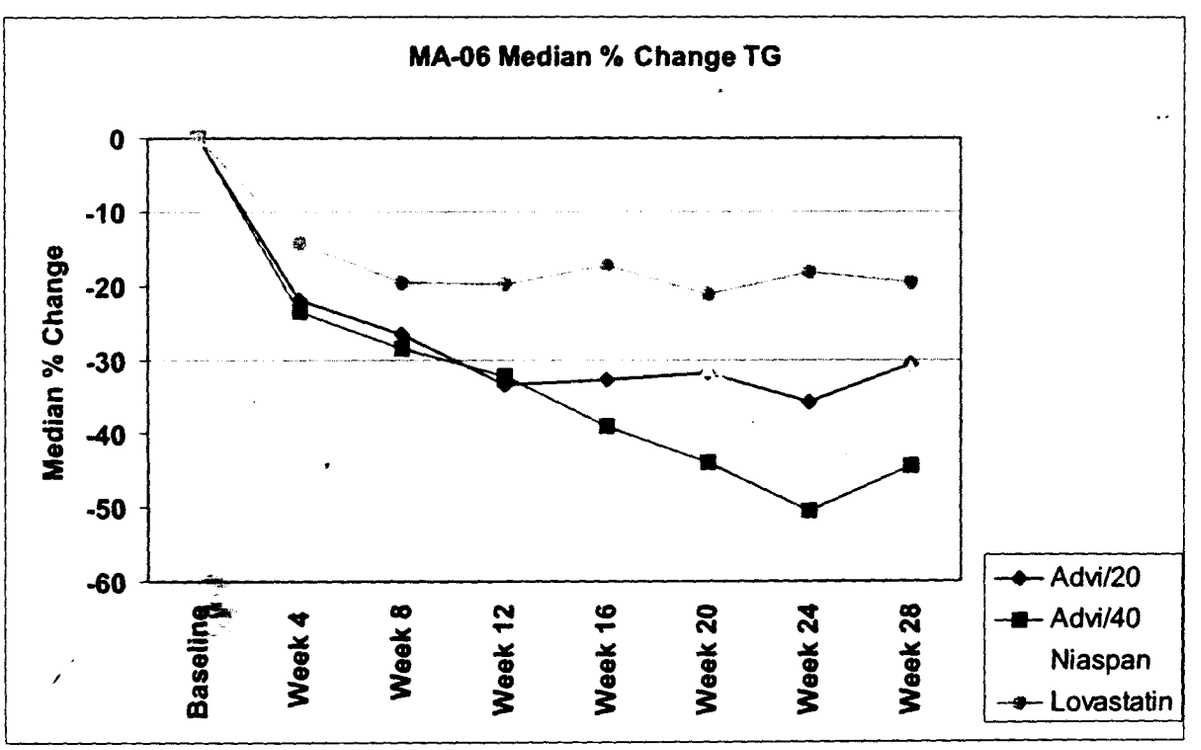
(b) Median % Change from Baseline in Triglyceride

The median percent changes from baseline in Triglyceride (TG) by treatment group are summarized in the following table and graph

Table 69: MA-06 Median % Change TG

		Week						
Treatment	**Baseline**	**4**	**8**	**12**	**16**	**20**	**24**	**28**
Advi/20: dose (mg/mg)		500/20	750/20	1000/20	1000/20	1000/20	1000/20	1000/20
N	57	54	49	48	43	42	42	40
Median	189.5 mg/dL	-22.0%	-26.6%	-33.5%	-32.7%	-31.8%	-35.8%	-30.7%
Advi/40: dose (mg/mg)		500/20	750/20	1000/20	1000/40	1500/40	2000/40	2000/40
N	57	52	48	47	45	42	42	42
Median	174.0 mg/dL	-23.5%	-28.5%	-32.3%	-39.0%	-44.0%	-50.4%	-44.3%
Niaspan: dose (mg)		500	750	1000	1000	1500	2000	2000
N	61	56	51	46	44	43	42	41
Median	185.5 mg/dL	-12.5%	-12.7%	-21.9%	-23.1%	-31.4%	-39.3%	-31.0%
Lovastatin: dose (mg)		20	20	20	40	40	40	40
N	61	59	58	56	56	54	53	53
Median	170.5 mg/dL	-14.2%	-19.5%	-19.9%	-17.2%	-21.2%	-18.2%	-19.5%

Figure 7: MA-06 Median % Change in TG



Statistical comparisons were made between treatment groups at the same time points and for the same doses as for LDL-C and HDL-C. Advicor was statistically superior to lovastatin for median % decrease in TG at Advicor doses of 1000/20 or greater, and to Niaspan at doses of 750/20 or greater as follows

Table 70: MA-06 Statistical Comparison Advi vs Lova, Median % Change TG

	Advi	lova	Advi vs lova p-value
Week 4			
Dose	500/20	20	
Median % change TG	-16	-16	.89
Week 8			
Dose	750/20	20	
Median % change TG	-21	-16	.26
Week 12			
Dose	1000/20	20	
Median % change TG	-26	-15	.01
Week 16			
Dose	1000/40	40	
Median % change TG	-32	-15	.01
Week 20			
Dose	1500/40	40	
Median % change TG	-37	-18	.0006
Week 24			
Dose	2000/40	40	
Median % change TG	-43	-16	.0007
Week 28			
Dose	2000/40	40	
Median % change TG	-40	-20	.0002

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Table 71: MA-06 Statistical Comparison Advi vs Nia, Median % Change TG

	Advi	Nia	Advi vs Nia p-value
Week 4			
Dose	500/20	500	
Median % change TG	-16	-8	.15
Week 8			
Dose	750/20	750	
Median % change TG	-21	-5	.002
Week 12			
Dose	1000/20	1000	
Median % change TG	-26	-13	.01
Week 16			
Dose	1000/40	1000	
Median % change TG	-32	-18	.04
Week 20			
Dose	1500/40	1500	
Median % change TG	-37	-22	.01
Week 24			
Dose	2000/40	2000	
Median % change TG	-43	-30	.11
Week 28			
Dose	2000/40	2000	
Median % change TG	-40	-20	.004

(4) Conclusions on Efficacy Results

The efficacy results for MA-06 show that:

1) Advicor was statistically significantly better than lovastatin alone in producing a mean % decrease from baseline in LDL-C; however, this difference was only seen after 24 weeks of treatment with Advicor at a dose of 2000/40 vs lovastatin 40 mg. Additionally, as stated in the protocol, one of the primary comparisons for this study was Advicor 1000/20 vs lovastatin 20 mg at Week 12. There was no statistically significant difference between the Advicor 1000/20 (-30%) and the lovastatin 20 mg (-29%) mean % change from baseline in LDL-C for this comparison (p-value .49).
2) On subgroup analysis, a significantly better result for LDL-lowering was seen only in female patients. There was no difference in LDL-lowering seen for male patients with Advicor compared to lovastatin at any dose and for any time point.
3) Advicor was statistically significantly better than Niaspan for LDL-lowering at all dosage comparisons.
4) For the secondary endpoints, Advicor was significantly better than Niaspan alone and lovastatin alone for HDL-raising at all doses. Advicor was also better than lovastatin for TG-lowering at doses of 1000/20 or higher, and was better than Niaspan for TG-lowering at doses of 750/20 or higher.

These findings do not support the use of Advicor as a first-line treatment for LDL-lowering. Advicor had no LDL-lowering benefit over lovastatin monotherapy at doses lower than 2000/40. Furthermore, Advicor was found to be beneficial for LDL-lowering