only in female patients. Male patients do not receive any additional benefit for LDL-lowering with Advicor over lovastatin alone. However, as Advicor was found to be significantly better than Niaspan alone for LDL-lowering, and was better than lovastatin alone for HDL-raising and TG-lowering (at doses 1000/20 and higher), Advicor could be considered a convenient product for patients who require combined therapy with Niaspan and lovastatin for the management of multiple dyslipidemias.

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. This Reviewer, however, included all reported AEs regardless of Investigator attribution. 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 subjects taking at least one dose of study medication as the denominator. Clinical AEs were coded using the COSTART dictionary. Adverse Events were also analyzed by subgroups (male vs female, geriatric 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 in Appendix III).

There were 156 different AE terms reported by 217 of 236 (92%) patients overall. Fewer patients in the lovastatin group (80%) reported any AE compared to the 3 niacin-exposed groups (95-97%). The incidence rates of patients reporting any AE by treatment group are summarized in the following table

Table 72: MA-06 Adverse Events Incidence by Treatment Group

		Treatment			
	All	Advi/20	Advi/40	Niaspan	Lovastatin
ITT Patients, n =	236	57	57	61	61
Patients reporting any AE, n (%)	217 (92)	55 (97)	55 (97)	58 (96)	49 (80)

(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 3 niacin-exposed groups (69-83%) than in the lovastatin group (20%). Niacin-exposed patients were also more likely than lovastatin patients to complain of nausea (5-11% vs 0%), rash (4-15% vs 3%), and pruritus (4-11% vs 2%). The most commonly reported AEs by body system (occurring in ≥5% of patients overall) are listed in the following table

Table 73: MA-06 Incidence of Most Common Adverse Events by Body System

			Treatment			
		All	**Advi/20**	**Advi/40**	**Niaspan**	**Lovastatin**
ITT Patients, n =		236	57	57	61	61
Body System		n (%)	n (%)	n (%)	n (%)	n (%)
Body as a whole	**All**	**126 (53)**	**35 (61)**	**32 (56)**	**33 (54)**	**26 (43)**
	Infection	52 (22)	17 (30)	13 (23)	10 (16)	12 (20)
	Headache	28 (12)	11 (19)	5 (9)	9 (15)	3 (5)
	Pain	23 (10)	4 (7)	8 (14)	5 (8)	6 (10)
	Flu syndrome	15 (6)	3 (5)	5 (9)	3 (5)	4 (7)
	Pain, back	15 (6)	6 (11)	0	4 (7)	5 (8)
Cardiovascular	**All**	**156 (66)**	**49 (86)**	**48 (84)**	**43 (71)**	**16 (26)**
	Flushing	148 (63)	47 (83)	47 (83)	42 (69)	12 (20)
Digestive	**All**	**51 (22)**	**14 (25)**	**14 (25)**	**13 (21)**	**10 (16)**
	Nausea	13 (6)	3 (5)	6 (11)	4 (7)	0
	Diarrhea	11 (5)	3 (5)	4 (7)	2 (3)	2 (3)
Skin and Appendages	**All**	**41 (17)**	**9 (16)**	**12 (21)**	**13 (21)**	**7 (12)**
	Rash	16 (7)	2 (4)	3 (5)	9 (15)	2 (3)
	Pruritus	12 (5)	2 (4)	6 (11)	3 (5)	1 (2)

Other AEs of particular interest in this study were myalgias, myopathy, rhabdomyolysis, and hepatitis. Sixteen patients complained of myalgias during the study. Three of the patients with myalgias had a CPK >normal at any time, which were not clinically significant. The patients reporting myalgias are:

Table 74: MA-06 Patients Reporting Myalgias

Code	Sex	Age	Treatment	Week	CPK Range	CPK during Myalgias
0109	F	68	Advi/20	16		68
0507	M	44	Advi/20	8		153
2018	F	60	Advi/20	4		41, 58 (repeat)
1014	M	62	Advi/40	4		114
1604	F	65	Advi/40	8		107
0707	F	60	Niaspan	4		82
0814	M	68	Niaspan	16		46
2201	F	51	Niaspan	4		42
2402	F	60	Niaspan	8 and 12		58 67
0513	F	51	Lovastatin	4		138
0816	M	70	Lovastatin	12		235
1019	F	42	Lovastatin	4		44
2016	F	58	Lovastatin	12		98
2019	F	70	Lovastatin	28		65
2312	F	63	Lovastatin	12		67, 78 (repeat)
2408	F	57	Lovastatin	4 and 8		65 59

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

There were no 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 (≥5% overall) AEs by subgroup 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 than the patients in the lovastatin group, and this did not differ by male vs female patients, as follows

Table 75: MA-06 Patients Reporting Any AE, Male vs Female

		Treatment			
	All	**Advi/20**	**Advi/40**	**Niaspan**	**Lovastatin**
ITT Patients, n =	236	57	57	61	61
ITT Male (M) Patients, n =	M = 130	M = 31	M = 32	M = 28	M = 39
ITT Female (F) Patients, n =	F = 106	F = 26	F = 25	F = 33	F = 22
Males Reporting Any AE, n (%)	118 (91)	30 (97)	31 (97)	27 (96)	30 (77)
Females Reporting Any AE n (%)	99 (93)	25 (96)	24 (96)	31 (94)	19 (86)

Overall, females were more likely than males to complain of flushing (68% vs 58%) and headache (21% vs 5%). Flushing was more common in the 3 niacin-exposed groups than in the lovastatin group, whereas headache was distributed relatively evenly across the treatment groups. The incidence of these selected AEs, male vs females, is summarized in the following table

Table 76: MA-06 Selected AEs, Male vs Female

				Treatment			
			All	**Advi/20**	**Advi/40**	**Niaspan**	**lovastatin**
ITT Male (M) Patients, n =			M = 130	M = 31	M = 32	M = 28	M = 39
ITT Female (F) Patients, n =			F = 106	F = 26	F = 25	F = 33	F = 22
Body System	**COSTART Term**	**M/F**	n (%)	n (%)	n (%)	n (%)	n (%)
Body as a Whole	Headache	M	6 (5)	1 (3)	2 (6)	3 (11)	0
		F	22 (21)	10 (38)	3 (12)	6 (18)	3 (14)
Cardiovascular	Flushing	M	76 (58)	25 (81)	26 (81)	18 (64)	7 (24)
		F	72 (68)	22 (85)	21 (84)	24 (73)	5 (23)

(b) Geriatric vs Non-Geriatric

Adverse Events by age (geriatric vs non-geriatric) were similar to the results overall. More patients in the niacin-exposed groups reported any AE than the patients in the lovastatin group regardless of age. The results are as follows

Table 77: MA-06 Patients Reporting Any AE, Geriatric vs Non-Geriatric

		Treatment			
	All	**Advi/20**	**Advi/40**	**Niaspan**	**Lovastatin**
ITT Patients, n =	236	57	57	61	61
ITT Geriatric (G) Patients, n =	G = 80	G = 18	G = 20	G = 17	G = 25
ITT Non-Geriatric (NG) Patients, n =	NG = 156	NG = 39	NG = 37	NG = 44	NG = 36
Geriatric Patients Reporting Any AE, n (%)	72 (90)	16 (89)	20 (100)	17 (100)	19 (76)
Non-Geriatric Patients Reporting Any AE, n (%)	145 (93)	39 (100)	35 (93)	41 (93)	30 (83)

Overall, there were no notable differences by AE term between geriatric and non-geriatric patients. Reported AEs tended to reflect treatment group assignment rather than age.

(4) Adverse Events Resulting in Drug Discontinuation

Sixty (60) of the 236 ITT patients discontinued study medication prior to study completion. Of the 60 who discontinued, 40 discontinuations were due to AEs. Discontinuations occurred more frequently in the 3 niacin-exposed groups (26-33%) than in the lovastatin group (13%). Flushing (7%), myalgia (3%), rash (3%), and pruritus (3%) were the most commonly reported AEs resulting in discontinuation. Discontinuations due to flushing were more common in the 3 niacin-exposed treatment groups. There were 2 discontinuations for laboratory abnormalities, one patient each in the Advi/20 and lovastatin groups. Both patients were discontinued for an increase in fasting blood sugar (FBS). The most commonly reported AEs resulting in drug discontinuation are summarized in the following table

Table 78: MA-06 Discontinuations Due to Adverse Events, Most Common

			Treatment			
		All	**Advi/20**	**Advi/40**	**Niaspan**	**lovastatin**
ITT Patients, n =		236	57	57	61	61
All Discontinuations, n (%)		60 (25)	17 (30)	15 (26)	20 (33)	8 (13)
Discontinued for AE*, n(%)		40 (17)	12 (21)	10 (18)	12 (20)	6 (10)
Body System	**COSTART Term**					
Cardiovascular	Flushing	16 (7)	6 (11)	6 (11)	3 (5)	1 (2)
Musculoskeletal	Myalgia	8 (3)	2 (4)	0	2 (3)	4 (7)
Skin and	Rash	6 (3)	1 (2)	1 (2)	3 (5)	1 (2)
Appendages	Pruritus	6 (3)	1 (2)	2 (4)	2 (3)	1 (2)
	Urticaria	4 (2)	0 (2)	1 (2)	2 (3)	1 (2)
Body as a Whole	Headache	4 (2)	1 (2)	1 (2)	2 (2)	0
DC for Lab abnormality		2(1)	1 (2)	0	0	1 (2)

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

A complete list of all reported AE terms resulting in drug discontinuation is 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

Discontinuations for any reason and due to AEs were almost twice as common for female patients (35% and 24% respectively) as for male patients (18 % and 12% respectively). Discontinuations for myalgias were somewhat more common for female (6%) vs male (2%) patients, although given the small number of patients, no meaningful conclusions can be made from this observation. Other common AEs resulting in discontinuation were relatively well balanced between the sexes. The results are summarized as follows (a complete list of discontinuations due to AEs can be found in Appendix VI)

Table 79: MA-06 Discontinuations Due to Adverse Events, Most Common Male vs Female

				Treatment			
			All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Patients, n =			236	57	57	61	61
All Discontinuations, n (%)			60 (25)	17 (30)	15 (26)	20 (33)	8 (13)
ITT Male (M) Patients, n =			M = 130	M = 31	M = 32	M = 28	M = 39
ITT Female (F) Patients, n =			F = 106	F = 26	F = 25	F = 33	F = 22
All Discontinuations Male, n =			23 (18)	8 (26)	6 (19)	5 (18)	4 (10)
All Discontinuations Female, n =			37 (35)	9 (35)	9 (36)	15 (45)	4 (18)
Discontinued for AE*, n(%)		**All**	40 (17)	12 (21)	10 (18)	12 (20)	6 (10)
		Male	15 (12)	6 (19)	5 (16)	2 (7)	2 (5)
		Female	25 (24)	6 (23)	5 (20)	10 (30)	4 (18)
Body System	**COSTART Term**						
Musculoskeletal	Myalgia	All	8 (3)	2 (4)	0	2 (3)	4 (7)
		Male	2 (2)	1 (3)	0	1 (4)	0
		Female	6 (6)	1 (4)	0	1 (3)	4 (18)

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

(b) Geriatric vs Non-Geriatric

Discontinuations were about as common for geriatric and non-geriatric patients overall. There were no obvious differences in discontinuations due to Adverse Events by body system or COSTART term (A complete list of discontinuations due to AEs can be found in the Appendix VI).

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Table 80: MA-06 Discontinuations Due to Adverse Events, Geriatric vs Non-Geriatric

			Treatment			
		All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Patients, n =		236	57	57	61	61
All Discontinuations, n (%)		60 (25)	17 (30)	15 (26)	20 (33)	8 (13)
ITT Geriatric (G) Patients, n =		G = 80	G = 18	G = 20	G = 17	G = 25
ITT Non-Geriatric (NG) Patients, n =		NG = 156	NG = 39	NG = 37	NG = 44	NG = 36
All Discontinuations Geriatric, n =		17 (21)	5 (28)	8 (40)	3 (18)	1 (4)
All Discontinuations Non-Geriatric, n =		43 (28)	12 (31)	7 (19)	17 (39)	7 (19)
Discontinued for AE*, n(%)	**All**	40 (17)	12 (21)	10 (18)	12 (20)	6 (10)
	G	14 (18)	5 (28)	7 (35)	2 (12)	0
	NG	26 (17)	7 (18)	3 (8)	10 (23)	6 (17)

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

(6) Serious Adverse Events

There were 11 SAEs occurring in 11 patients (5% of ITT patients). There were 2 deaths: Patient 1208 in the Advi/20 group death secondary to cardiac arrest due to an MI; and Patient 1505 in the lovastatin group death due to cardiac arrest secondary to a ruptured abdominal aortic aneurysm (AAA). The SAEs are summarized in the following table

Table 81: MA-06 Serious Adverse Events

Treatment	Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Investigator Attribution	Drug Discontinued?
Niaspan	0101	F	40	Attempted suicide	Body	14	NR	No
Niaspan	0404	M	64	Reflux esophagitis/gastritis	Dig	91	Possibly	No
Niaspan	1314	M	34	Unstable angina	CV	126	NR	No
Niaspan	1003	M	42	Rib pain/metastatic adenocarcinoma	Body	3	NR	No
Advi/20	0701	F	74	Pseudoaneurysm/post-operative bleed	CV	98	NR	No
Advi/20	1208	M	72	Myocardial Infarction/death	CV	11	NR	Yes
Advi/40	0212	M	60	Kidney stones	Uro	154	Remotely	No
Advi/40	2013	F	67	Pneumonia/possible bronchitis	Resp	154	NR	No
Advi/40	0203	F	75	Aortoiliac occlusive disease	CV	91	NR	No
Lovastatin	1505	M	58	Death/ruptured AAA/cardiac arrest	CV	196	NR	No (completed)
Lovastatin	2006	M	65	Right shoulder impingement syndrome	MS	196	NR	No

The Cardiovascular System was most commonly affected, however as the number of SAEs was small, no trends or conclusions can be generated. One patient discontinued in the study for an SAE [patient 1208 (Advi/20): myocardial infarction/death], and one SAE [patient 0404 (Niaspan): reflux esophagitis/gastritis] was assessed by the Investigator as at least possibly related to study drug.

(7) Other Significant Adverse Events

Three patients were diagnosed with cancer during the study, or in the case of patient 1003, presented with symptoms that were later diagnosed as cancer after study completion. These patients were:

Table 82: MA-06 Other Significant Adverse Events

Treatment	Patient	M/F	Age (yrs)	Diagnosis	Onset (days)	Investigator Attribution	Drug Discontinued?
Niaspan	1003	M	42	Metastatic Adenocarcinoma (rib pain)	3	NR	No
Lovastatin	2006	M	65	Bowen's disease (intraepithelial squamous cancer – skin)	77	NR	No
Lovastatin	2019	F	71	Non-Hodgkins lymphoma	84	NR	No

(8) 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." This Reviewer defined a TELA as any laboratory abnormality that worsened during study drug treatment regardless of the baseline value.

(a) ALT and AST Elevations

ALT and AST elevations were somewhat less common in the Advi/20 group (5% and 19% respectively), with little differences between the other three groups. Elevations in AST and ALT tended to be mild, with clinically significant elevations (>3 X ULN) occurring in only 2 patients (one patient each in the Advi/40 and lovastatin groups). The incidence of treatment emergent AST and ALT elevations by treatment group are as follows

Table 83: MA-06 Incidence of Treatment Emergent ALT and AST Elevations

		Treatment			
	All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Patients, n =	236	57	57	61	61
ALT >normal	28 (12)	3 (5)	9 (16)	9 (15)	7 (11)
ALT >2 X ULN	4 (2)	0	1 (2)	1 (2)	2 (3)
ALT >3 X ULN	1 (<1)	0	0	0	1 (2)
AST > normal	65 (28)	11 (19)	19 (33)	14 (23)	21 (34)
AST > 2 X ULN	6 (3)	0	2 (4)	2 (3)	2 (3)
AST > 3 X ULN	2 (1)	0	1 (2)	0	1 (2)

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

The 2 patients who experienced clinically significant elevations in ALT, AST, or AST and ALT are described in the following table

Table 84: MA-06 Patients Experiencing Clinically Significant ALT, AST, or ALT and AST Elevations

Week	AST	ALT	Dose	Contributing history
Patient 0203 (Advi/40):				
Baseline	28	22	None	75 year old female, history of hypertension (HTN), CHD, angioplasty, duodenal ulcer, left and right femoral-popliteal bypass surgeries, hysterectomy, rectocoele, cataracts, and tinnitus. No other relevant history.
Week 4	25	22	500/20 X 4 weeks	
Week 8	25	21	750/20 X 4 weeks	
Week 12	25	21	1000/20 X 4 weeks	
Week 16	25	18	1000/40 X 4 weeks	
Week 20	27	21	1500/40 X 4 weeks	
Week 20 retest	34	39	2000/40 X 3 weeks	
Week 24	124	100	2000/40 X 4 weeks	
Week 24 retest	40	60	2000/40 X 5 weeks	
Week 28	34	43	2000/40 X 8 weeks	
Patient 0106 (lovastatin):				
Baseline	32	28	None	47 year old female, history of tubal ligation. No other relevant history.
Week 4	102	118	20 X 4 weeks	
Week 4 retest	69	89	20 X 5 weeks	
Week 8	76	60	20 X 9 weeks	
Week 8 retest	156	207	20 X 10 weeks	
Week 8 retest	74	120	20 X 11 weeks	
Week 12	55	69	20 X 13 weeks	
Week 16	49	77	40 X 4 weeks	
Week 20	35	44	40 X 8 weeks	
Week 24	33	47	40 X 12 weeks	
Week 28	45	53	40 X 16 weeks	

(b) Fasting Blood Sugar

Mild elevations in FBS were common, and somewhat more common in the Advi/20 group (63%) as compared to the other 3 groups (41-46%). Elevations in FBS >1.3 X ULN or higher were less common (14% overall), and 6 patients had clinically significant elevations in blood sugar. The incidence of treatment emergent FBS elevations by treatment group are as follows

Table 85: MA-06 Incidence of Treatment Emergent FBS Elevations

		Treatment			
	All	**Advi/20**	**Advi/40**	**Niaspan**	**lovastatin**
ITT Patients, n =	236	57	57	61	61
FBS >normal	113 (48)	36 (63)	26 (46)	26 (43)	25 (41)
FBS > 1.3 X ULN	34 (14)	12 (21)	8 (14)	6 (10)	8 (13)
FBS > 2 X ULN	4 (2)	1 (2)	2 (4)	0	1 (2)

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

Of the 6 patients who experienced clinically significant changes in FBS during the study, 2 patients terminated early from the study secondary to FBS elevations, 4 patients had FBS > 2 X ULN (including one patient who terminated early), and one patient received a new diagnosis of type 2 DM. The treatment assignments for these 6 patients were: 2 patients in the Advi/20 treatment group, 2 in the Advi/40 group, 1 in the Niaspan group and 1 in the lovastatin group. These patients are summarized as follows

Table 86: MA-06 Patients With Clinically Significant FBS Elevations

Week	FBS	Elevation	Dose	Contributing history
Patient 0705 (Advi/20):				60 year old female, history of type 2 DM, uterine cancer, hysterectomy, and hypothyroidism. HgA1C baseline: 6.6, Week 4:6.9, Week 12: 7.7, ET: 7.5. At Week 8, the patient's Amaryl was increased. At Week 12, the patient was discontinued secondary to increased FBS. One week after DC of study medication, the Amaryl dose was decreased to the baseline dose. The patient was also on a stable dose of glucophage throughout the study.
Baseline	158	>1.3 X ULN	None	
Week 4	190	>1.3 X ULN	500/20 X 4 weeks	
Week 8	180	>1.3 X ULN	750/20 X 4 weeks	
Week 12	186	>1.3 X ULN	1000/20 X 4 weeks	
ET	155	>1.3 X ULN	Off study medication X 10 days	
Patient 0210 (Advi/20):				53 year old male, history hypertension, type 2 DM, hemorrhoids, and hayfever. HgA1C baseline: 7.3, Week 16: 7.5, Week 28: 7.6. The patient experienced an upper respiratory infection (URI) 10 days before Week 24. No other relevant history
Baseline	169	>1.3 X ULN	None	
Week 4	195	>1.3 X ULN	500/20 X 4 weeks	
Week 8	202	>1.3 X ULN	750/20 X 4 weeks	
Week 12	194	>1.3 X ULN	1000/20 X 4 weeks	
Week 16	204	>1.3 X ULN	1000/20 X 8 weeks	
Week 20	227	>2 X ULN	1000/20 X 12 weeks	
Week 24	227	>2 X ULN	1000/20 X 16 weeks	
Week 28	227	>2 X ULN	1000/20 X 20 weeks	
Patient 0706 (Advi/40):				52 year old male, history of hypertension, tonsillectomy, appendectomy, and type 2 DM. HgA1C baseline: 7.1, Week 28: 7.0. The patient reported increased stress at Week 16. At Week 28, the patient's Glucophage was increased from 1000 mg qD to 1000 mg BID. The patient was also on a stable dose of Glynase throughout the study.
Baseline	178	>1.3 X ULN	None	
Week 4	178	>1.3 X ULN	500/20 X 4 weeks	
Week 8	196	>1.3 X ULN	750/20 X 4 weeks	
Week 12	166	>1.3 X ULN	1000/20 X 4 weeks	
Week 16	224	>2 X ULN	1000/40 X 4 weeks	
Week 20	186	>1.3 X ULN	1500/40 X 4 weeks	
Week 24	230	>2 X ULN	2000/40 X 4 weeks	
Week 24 retest	189	>1.3 X ULN	2000/40 X 5 weeks	
Week 28	197	>1.3 X ULN	2000/40 X 8 weeks	
Patient 0801 (Advi/40):				70 year old male, history of peripheral neuropathy; myocardial infarction, bleeding ulcer, bilateral carpal tunnel syndrome, type 2 DM, angioplasty, HTN, colon polyps, CAD, arthritis, and alcohol use. HgA1C baseline: 6.9, Week 4: 7.0, Week 8: 6.7, Week 16 retest: 7.1, Week 20: 7.2, Week 28: 7.1. The patient reported he was noncompliant with DM medication at Week 4. The patient reported eating candy prior to Week 16 blood draw. The patient was taking Glucophage and Glyburide.
Baseline	182	>1.3 X ULN	None	
Week 4	234	>2 X ULN	500/20 X 4 weeks	
Week 8	201	>1.3 X ULN	750/20 X 4 weeks	
Week 12	176	>1.3 X ULN	1000/20 X 4 weeks	
Week 16	196	>1.3 X ULN	1000/40 X 4 weeks	
Week 16 retest	ND		1500/40 X 2 weeks	
Week 20	206	>1.3 X ULN	1500/40 X 4 weeks	
Week 24	228	>2 X ULN	2000/40 X 4 weeks	
Week 28	232	>2 X ULN	2000/40 X 8 weeks	
Patient 2404 (Niaspan):				60 year old female, history of hypertension, tonsillectomy, bilateral carpal tunnel, vitiligo, and hysterectomy, . HgA1C baseline:5.7, Week 16:6.0. Two weeks prior to Week 16, the patient had a sore throat and was treated with Ceftin. One week prior to Week 28 the patient experienced a URI, treated with Biaxin. The patient was diagnosed with new onset Type 2 DM at Week 28.
Baseline	133	>normal	None	
Baseline retest	119	>normal	None	
Week 4	114	>normal	500 X 4 weeks	
Week 8	111	>normal	750 X 4 weeks	
Week 12	140	>normal	1000 X 4 weeks	
Week 16	143	>normal	1000 X 4 weeks	
Week 20	123	>normal	1500 X 4 weeks	
Week 24	103	>normal	2000 X 4 weeks	
Week 28	143	>normal	2000 X 8 weeks	

Week	FBS	Elevation	Dose	Contributing history
Patient 1201 (lovastatin):				
Baseline	175	>1.3 X ULN	None	70 year old male, history of hypertension, memory loss, glaucoma, sick sinus syndrome, cardiac pacemaker, and mild stroke. HgA1C baseline: 8.1, retest: 7.9, Week 8: 7.7, Week 16 retest: 8.7, ET: 8.7, Physician's visit: 8.8. The patient discontinued study drug at after Week 16 secondary to increased FBS. The patient was referred to his primary care physician, but was non-compliant with follow up.
Baseline retest	not done		None	
Week 4	174	>1.3 X ULN	20 X 4 weeks	
Week 8	207	>1.3 X ULN	20 X 8 weeks	
Week 12	195	>1.3 X ULN	20 X 12 weeks	
Week 16	246	>2 X ULN	40 X 4 weeks	
Week 16 retest	not done		40 X 5 weeks	
ET	231	>1.3 X ULN	off study medication X 1 day	
Physician's visits	218	>1.3 X ULN	off study medication X 3 weeks	

(c) Phosphorous

Decreases in serum phosphorous were more common in the 3 niacin-exposed groups (21-26%) than in the lovastatin group (10%). Five patients overall (2%), all in the 3 niacin-exposed groups had phosphorous < 2 X LLN. 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 treatment emergent phosphorous decreases by treatment group is as follows

Table 87: MA-06 Incidence of Treatment Emergent Phosphorous Decreases

		Treatment			
	All	**Advi/20**	**Advi/40**	**Niaspan**	**lovastatin**
ITT Patients, n =	236	57	57	61	61
Phosphorous <normal, n (%)	48 (20)	15 (26)	14 (25)	13 (21)	6 (10)
Phosphorous <2 X LLN, n (%)	5 (2)	3 (5)	1 (2)	1 (2)	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 1 patient [patient 0807 (Niaspan)]. There were no cases of CPK elevation >10 X ULN, and no patient was discontinued due to CPK abnormalities. The incidence of CPK elevations by treatment group is as follows

Table 88: MA-06 Incidence of Treatment Emergent CPK Elevations

		Treatment			
	All	**Advi/20**	**Advi/40**	**Niaspan**	**lovastatin**
ITT Patients, n =	236	57	57	61	61
CPK > normal	75 (32)	18 (32)	22 (39)	13 (21)	22 (36)
CPK >5 X ULN	1 (<1)	0	0	1 (2)	0

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

The CPK values for the patient experiencing the CPK elevation >5 X ULN are:

Table 89: MA-14 Patients With CPK Elevations > 5 X ULN

Patient	Week	CPK	Elevation
0807 (Niaspan)	Baseline	158	
	Week 4	86	
	Week 8	286	>normal
	Week 12	115	
	Week 16	136	
	Week 20	150	
	Week 24	1085	>5 X ULN
	Week 24 retest	156	
	Week 28	111	

(e) Other Laboratory Values

There were no instances of elevations >2 X ULN in alkaline phosphatase, LDH, total bilirubin or uric acid. Three patients had amylase elevations >2 X ULN, all of which were asymptomatic and resolved. Two patients experienced platelet counts <100,000 during the study as follows

Table 90: MA-06 Patients With Platelet Counts <100,000

Treatment	Patient	Week	Platelet Count
Advi/40	1308	Baseline	91,000
		Week 28	64,000
		Week 28 retest	126,000
Niaspan	2307	Baseline	Not done
		Week 16	53,000
		Week 16 retest	108,000
		Week 20	70,000
		Week 20 retest	70,000
		Week 28	81,000
		Week 28 retest	111,000

Three patients experienced PT elevations >2 X ULN: 1 patient in the Advi/40 group, and 2 patients in the lovastatin group. There were no clinical signs reported with these PT elevations. There were no clinically significant decreases in WBC. There were no other clinically significant laboratory abnormalities reported during the study.

(f) Subgroup Analysis

Subgroup analyses by sex and geriatric vs non-geriatric patients were also performed. Overall, mild FBS elevations were more common in male patients than female patients (54% vs 31%), however, this varied considerably by treatment group (see Table 91). For example, in the Advi/20 group, FBS >normal occurred in 58% of males and 69% of females, and in the Advi/40 group, FBS >normal occurred in 59% of males and 28% of females. CPK elevations were also more common in males than females overall (44% vs 17%), and were consistent across all treatment groups (see Table 92). There were no other notable differences in TELAs between male vs female, or geriatric vs non-geriatric patients. The incidence of FBS elevations and CPK elevations, males vs females are summarized in the following tables

Table 91: MA-06 FBS Elevations from Baseline, Male vs Female

			Treatment			
		All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Male (M) Patients, n =		M = 130	M = 31	M = 32	M = 28	M = 39
ITT Female (F) Patients, n =		F = 106	F = 26	F = 25	F = 33	F = 22
FBS >normal	M	70 (54)	18 (58)	19 (59)	13 (46)	20 (51)
FBS >normal	F	33 (31)	18 (69)	7 (28)	13 (39)	5 (23)
FBS >1.3 X ULN	M	22 (17)	5 (16)	8 (25)	3 (11)	6 (15)
FBS >1.3 X ULN	F	12 (11)	7 (27)	0	3 (9)	2 (9)
FBS >2 X ULN	M	4 (3)	1 (3)	2 (6)	0	1 (3)
FBS >2 X ULN	F	0	0	0	0	0

Table 92: MA-06 CPK Elevations from Baseline, Male vs Female

			Treatment			
		All	Advi/20	Advi/40	Niaspan	lovastatin
ITT Male (M) Patients, n =		M = 130	M = 31	M = 32	M = 28	M = 39
ITT Female (F) Patients, n =		F = 106	F = 26	F = 25	F = 33	F = 22
CPK >normal	M	57 (44)	13 (42)	17 (53)	8 (29)	19 (49)
CPK >normal	F	18 (17)	5 (19)	5 (20)	5 (15)	3 (14)
CPK >5 X ULN	M	0	0	0	0	0
CPK >5 X ULN	F	1 (1)	0	0	1 (3)	0

(9) Overall Safety Conclusions

Advicor and Niaspan were not well tolerated. More patients in the niacin-exposed groups reported any AE during study drug treatment than patients in the lovastatin group. Niacin-exposed patients were much more likely to report a Cardiovascular system AE, especially flushing, and were somewhat more likely to complain of Digestive system (nausea), and Skin and Appendage (rash and pruritus) AEs. The niacin-exposed patients were also more likely to discontinue from the study for any reason, mainly due to AEs. Flushing, rash, pruritus and myalgia were the most commonly reported reasons for discontinuation, with only myalgia being more common in the lovastatin group. Female patients were about twice as likely as male patients to discontinue from the study for any reason, mainly due to AEs. Clinically significant TELAs were uncommon. Two (2) patients were discontinued for laboratory abnormalities, both of which were FBS elevations. Mild elevations in AST, ALT, FBS, and CPK, and mild to moderate decreases in phosphorous were common, but only the phosphorous decreases were more common in the niacin-exposed groups.

3. Conclusions on Review of Protocol MA-06

Study MA-06 does not support Advicor as a first-line drug treatment for LDL-lowering. Treatment with Advicor produced dose-dependent decreases in LDL-C; however, the LDL-lowering was significantly better than lovastatin 40 mg monotherapy only at Weeks 24 and 28 after dose-titration to 2000/40. On subgroup analysis, the greater LDL-lowering efficacy of Advicor over lovastatin was confined only to female patients; there was no advantage with the addition of Niaspan to lovastatin for LDL-lowering in males. Advicor was significantly better at LDL-lowering than Niaspan alone, and at TG-lowering and HDL-raising than either Niaspan alone or lovastatin alone. Advicor therefore could be considered as a convenient product in patients who would benefit from combination therapy with niacin and lovastatin for the management of multiple dyslipidemias. The safety findings for MA-06 were similar to the MA-14 study. Advicor was poorly tolerated, and there were high dropout rates in the niacin-exposed groups, mainly due to AEs. Flushing, rash, and pruritus were the most commonly reported reasons for discontinuation in the niacin-exposed groups. The side-effect profile of Advicor closely resembled that of Niaspan. Most AEs were not serious and were reversible with discontinuation of study medication. The majority of the niacin-exposed patients complained of flushing during the study, and other complaints seen more frequently in the niacin-exposed groups were nausea, rash, and pruritus. Mild laboratory abnormalities were frequently seen in AST, ALT, FBS, CPK, and phosphorous, but only mild decreases in phosphorous were more common in the niacin-exposed groups. Clinically significant laboratory abnormalities were uncommon and two patients discontinued for laboratory abnormalities.

C. Protocol MA-98-010407

(Protocol MA-98-010407 will be referred to as MA-07 from this point forward)

1. Study Design for MA-07

a) Study Design

Protocol MA-98-010407 (MA-07) "A Long-term, open-label, multi-center trial of the safety and efficacy of Advicor in patients with dyslipidemia" was a 52-week, open-label, uncontrolled study of Advicor (a combination tablet of niacin extended-release/lovastatin immediate-release) conducted at 41 sites nationally. The study evaluated the safety and efficacy of Advicor in 814 patients with Type IIa and IIb hyperlipidemia and LDL-C levels warranting treatment per NCEP II guidelines.

b) Study Objectives

The purpose of the study was to determine the long-term safety and efficacy of Advicor. The primary efficacy endpoint was mean percent change from baseline in LDL-C. Secondary endpoints were mean percent changes from baseline in TC, HDL-C, TG, TC/HDL-C ratio, LDL-C/HDL-C ratio, Lp(a), and the number of risk factors pre- and post-treatment. Safety endpoints included changes from baseline in chemistry, hematology, and urinalysis tests, and adverse events.

c) Eligibility Criteria

(1) Inclusion Criteria

1) Men and women 21 years of age or older
2) Patient was willing to participate and sign Informed Consent
3) Women must not have been pregnant or breast-feeding. Women of childbearing potential must have used an acceptable form of contraception for at least 3 months prior to enrollment, including: an oral contraceptive, an IUD, or a double barrier method of contraception
4) Patient had not taken lipid-altering medications for at least 6 weeks prior to randomization, or at least 4 weeks prior to qualification visits, and for the duration of the study.
5) Patient must have demonstrated a stable low density lipoprotein cholesterol (LDL-C) by two samples drawn about 1 week apart. Stable was defined as an LDL lower value $\leq$12% of the higher value, calculated by

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

6) LDL-C after diet and drug washout must have been (based on NCEP II guidelines):
   d) For patients with diabetes or a history of CHD: mean LDL $\geq$130 mg/dL
   e) For patients with 2 or more CAD risk factors: mean LDL $\geq$160 mg/dL
   f) For patients with fewer than 2 CAD risk factors: mean LDL $\geq$190 mg/dL
7) Mean baseline TG was $\leq$800 mg/dL

(2) Exclusion Criteria

1) Patient had an allergy or hypersensitivity to niacin, lovastatin, or their derivatives
2) Patient had a previous history (within 6 months of screening) of substance abuse or dependency
3) Patient had untreated or unsuccessfully treated psychiatric disease
4) Patient had type 1 diabetes or poorly controlled type 2 diabetes
5) Patient had:
    - Active gallbladder disease
    - Recent acute arterial hemorrhaging
    - Severe hypertension
    - Clinically significant cardiac arrhythmia or serious cardiac abnormalities
    - Significant renal disease
    - Any other clinically significant abnormality except for dyslipidemia
    - Current moderate to severe hepatic dysfunction or a baseline AST and/or ALT >1.3 X ULN
    - Active peptic ulcer disease
    - Recent acute gouty attack
    - Myocardial infarction, stroke, or coronary artery bypass grafting within the preceding 6 months
    - Secondary hyperlipoproteinemia due to an uncontrolled, underlying disease. Hypothyroid patients receiving thyroid replacement therapy must have been on a stable dosage for at least 3 months prior to entry (TSH must have been in an acceptable range prior to entry)
    - Any clinically significant laboratory value obtained during the Qualification Phase, other than lipid levels
6) Patient had used an investigational study medication within 30 days of screening
7) Patient had any condition which, in the opinion of the Investigator, may have adversely affected the study conclusions
8) Patient had any health condition which, in the opinion of the Investigator, may have been adversely affected by the procedures or medications in the study
9) Patient had been treated with Lorelco (probucol) within 1 year prior to screening
10) Concomitant therapy with any of the following medications:
    - 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

d) Study Visits and Procedures

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

Table 93: MA-07 Study Visits and Procedures

Week	Qualification Visits	Treatment Visits 0	4	8	12	16	28	40	52/ET
Procedure Sign Informed Consent	X								
Medical History		X							
Physical Exam		X							X
Vital Signs		X	X	X	X	X	X	X	X
ECG		X							X
3-Day Diet Log Collected	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	X	X	X
Urinalysis	X								X
HgA1C(diabetics only)	X								X
PT/PTT	X								X
TSH (thyroid replacement only)	X								
Pregnancy Test (if applicable)	X								
Reference Sample Collected	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

Study patients were recruited at 41 study sites. Each site could enroll up to 20 patients. Patients were screened for eligibility including inclusion/exclusion criteria, lipid, chemistry and hematology profiles, urinalysis, PT/PTT, fibrinogen, TSH (patients on thyroid replacement only), HgA1C (diabetics only), and pregnancy test (females age <60 years only). All patients were queried as to diet, and were required to have followed the NCEP Step 1 diet for at least 4 weeks prior to obtaining the qualifying lipid profile. Patients using lipid-lowering medications were required to provide informed consent, and then discontinue medication use for at least 4 weeks prior to obtaining qualification labs.

For qualification, 2 fasting lipid profiles within about 1 week of each other were obtained. The mean of 2 lipid profiles (see formula, inclusion criterion #5) was used for qualification. Patients must also have had TG ≤800 mg/dL, and have had no clinically significant laboratory abnormalities as determined by the Investigator.

Up to 2 additional qualification visits could be conducted to evaluate the patient's LDL-C level.

(2) Open-Label Phase (Weeks 0, 4, 8, 12, 16, 28, and 40)

Qualifying patients returned to the study center (Week 0) and underwent a medical history, physical examination including vital signs, and an ECG. Study medication was

dispensed for 4 weeks. Patients returned to the study center at Weeks 4, 8, 12, 16, 28 and 40, and underwent vital signs and laboratory assessment [lipid profile, chemistry profile, hematology profile (Weeks 16, 28, and 40 only), and reference sample (Weeks 4, 8, and 12 only)]. Adverse events and concomitant medications were reviewed, and compliance with study medication and diet were assessed. Study medication was collected, and medication for the subsequent weeks was dispensed.

(3) Final Visit (Week 52) or Early Termination

Patients underwent physical examination, vital sign measurement, laboratory assessment [lipid, chemistry, and hematology profiles, urinalysis, PT/PTT, fibrinogen, reference sample, and HgA1C (diabetics only)], ECG, and assessment of diet and medication compliance. Adverse events and concomitant medications were reviewed. All study medication was collected.

All patients completing 52 weeks of study drug treatment were eligible to immediately roll-over into a 48-week extension of this study.

e) Study Medication Dispensing and Compliance

All patients received Advicor tablets once daily at bedtime after a low-fat snack. Medication was administered in a forced dose-escalation as follows

Table 94: MA-07 Dose Titration Schedule

	Week					
	0-4	5-8	9-12	13-16	17-28	29-52
Advicor dose (mg/mg)	500/10	1000/20	1500/30	2000/40	2000/40	2000/40
Tablet strength	500/10	500/10	500/10	500/10	1000/20	1000/20
Number of tablets	1	2	3	4	2	2

The Investigator could decrease the dose of study medication for patient tolerability or safety after the patient had completed the dose-escalation phase of the study. Interruption of study medication >7 days required re-titration of study medication.

Unused study medication was collected at the following study visit, and patient compliance with study medication was determined by a tablet count.

f) Efficacy and Endpoint Measures

Primary: The primary efficacy analysis is the mean percent change from baseline in LDL-C.

Secondary: Secondary efficacy measures are mean percent change from baseline in:

1) Total cholesterol [TC]
2) High density lipoprotein cholesterol [HDL-C]
3) Triglycerides [TG]
4) TC/HDL-C ratio
5) LDL-C/HDL-C ratio
6) Lipoprotein a [Lp(a)]

7) Number of risk factors pre- and post-treatment

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

2. Results

One thousand five hundred eighty (1580) patients were screened at 41 sites. Eight hundred eighteen (818) patients (52% of total screened) were enrolled between 27-Jul-1998 and 28-Apr-1999. Four patients who enrolled never took study medication, so the Intent-To-Treat (ITT) population consisted of 814 patients.

a) Baseline Demographics and Characteristics

Overall, 62% of the ITT population was male, and 88% was Caucasian. Patients ranged in age from 25-84 years, with a mean age of 59.3 years. Demographic data were not supplied for the non-enrolled (screen failure) patients, but 464/762 (61% of screen failures) were not eligible due to failure to qualify by lipid inclusion criteria. Baseline characteristics and demographics for the ITT patients are summarized as follows

Table 95: MA-07 Baseline Demographics

ITT Patients, n =	814
Demographic Measure	
Gender, n (%)	
Male	518 (62)
Female	296 (38)
Age, years	
mean	59.3
median	60
min, max	25, 84
Age ≥ 65 years, n (%)	296 (36)
Ethnicity, n(%)	
Caucasian	716 (88)
Black	47 (6)
Hispanic	34 (4)
Asian	13 (2)
Other	4 (<1)
Risk Factors (RF)	
Diabetes, n (%)	88 (11)
Current smoker, n (%)	127 (16)
≥2 CAD RF, n (%)	529 (65)
<2 CAD RF, n (%)	285 (35)
Mean BMI, kg/M^2	28.9
Baseline Lipid Value	
Mean LDL-C, mg/dL	195.3
Mean HDL-C, mg/dL	47.6
Median Triglycerides, mg/dL	199.4
Mean Lp(a), mg/dL	42.8

b) Patient Disposition

(1) Screening

Of the 1580 patients screened, 762 (48% of total screened) did not meet the eligibility criteria during the qualification phase. The most common reason for not qualifying was a failure to meet lipid inclusion criteria. The next most common reason for not enrolling was withdrawal of consent by the patient. Patients failing to meet eligibility criteria are summarized in the following table

Table 96: MA-07 Patients Failing to Meet Eligibility Criteria

Eligibility criteria not met, n = 762	n (%)
Failure to have appropriate lipid levels per inclusion criteria	464 (61)
Withdrawal of consent	159 (21)
Lost to follow up	52 (7)
Abnormal laboratory value	38 (5)
Other medical	29 (4)
Other non-medical	16 (2)

(2) Dropouts

Of the 818 patients who entered the study, 4 patients never received study medication. Eight hundred fourteen (814) patients comprised the ITT population. At the time of the original NDA submission, data had been collected on study patients up to September 2000 (interim analysis). The mean duration of treatment as of Sept-2000 was 31 weeks. The number of patients experiencing 52 weeks of study drug exposure by Sept-2000 was 226, and 247 patients had been discontinued from the study for any reason. Of the 247 patients discontinued, 176 patients were discontinued for AEs and 15 patients were discontinued for laboratory abnormalities. Patients completing each scheduled study visit as of Sept-2000 are:

Table 97: MA-07 Patient Status as of Sept-2000

ITT Patients, n =	814
Week Completed	
Week 4, n (%)	756 (93)
Week 8, n (%)	707 (87)
Week 12, n (%)	680 (84)
Week 16, n (%)	656 (81)
Week 28, n (%)	605 (74)
Week 40, n (%)	238 (29)
Week 52, n (%)	226 (28)

A 4-month safety update as of January 2001 was later submitted during the NDA review. The mean duration of treatment as of the Jan-2001 update was 40.9 weeks. The number of patients experiencing 52 weeks of study drug exposure by Jan-2001 was 550. From Sept-2000 to Jan-2001, 17 additional patients discontinued from the study, most of whom (12 of 17 patients) were discontinued due to AEs. As of Jan-2001, 264 patients had been discontinued prior to study completion. One hundred eight-eight (188) of the 264

patients were discontinued due to AEs, and 15 patients were discontinued due to laboratory abnormalities. The reasons for the discontinuations of these 264 patients as of Jan-2001 are summarized in the following table (discontinuations as of Sept-2000 are presented for comparison)

Table 98: MA-07 Patients Discontinued

As of:	**Sept-2000**	**Jan-2001**
ITT Patients, n =	814	814
Number of Withdrawals, n (%)	247 (30)	264 (32)
Reason for Dropout, n (%)		
Adverse Event	176 (22)	188 (23)
Withdrew Consent	21 (3)	23 (3)
Lost to Follow Up	17 (2)	19 (2)
Abnormal Laboratory Value	15 (2)	15 (2)
Other Non-Medical	8 (<1)	9 (<1)
Protocol Violation	5 (<1)	5 (<1)
Other Medical	5 (<1)	5 (<1)

The baseline demographics of patients who discontinued (as of Jan-2001) differ somewhat from the baseline demographics of the ITT population overall. Notable differences are:

1) More females dropped out compared to the ITT population overall (females comprised 47% of dropouts vs 36% of ITT population)

2) Dropouts were more likely to be ≥65 years of age (42% of dropouts vs 36% of ITT population)

There were no other notable differences. The baseline demographics of the ITT population vs the dropouts is as follows

Table 99: MA-07 Baseline Demographics of ITT Patients vs Dropouts

	ITT Patients	Dropouts
Number of Patients, n =	814	264
Demographic Measure		
Gender, n (%)		
Male	518 (62)	140 (53)
Female	296 (38)	124 (47)
Age, years		
mean	59.3	60.5
median	60	63
min, max	25, 84	25, 84
Age ≥ 65 years, n (%)	296 (36)	111 (42)
Ethnicity, n(%)		
Caucasian	716 (88)	225 (85)
Black	47 (6)	18 (7)
Hispanic	34 (4)	19 (7)
Asian	13 (2)	2 (1)
Other	4 (<1)	0
Risk Factors (RF)		
Diabetes, n (%)	88 (11)	17 (6)
Current smoker, n (%)	127 (16)	42 (16)
≥2 CAD RF, n (%)	529 (65)	173 (66)
<2 CAD RF, n (%)	285 (35)	91 (34)
Mean BMI, kg/M^2	28.9	28.7

c) Concomitant Medications

Concomitant medications were medications that were either started prior to study entry and continued during study drug treatment, or were started during study drug treatment. Overall, 100% of patients reported using any concomitant medication at anytime during the study. A large number of different medications (over 700 different medications) were reported, with the majority of medications having been used by a small number of patients (used by ≤4 patients per medication, or by ≤1% of patients overall). The most frequently reported concomitant medication used was aspirin, which was used by 78% of study patients. No patient was reported as having used any prohibited lipid-lowering medications during the treatment period. Medications known to have minor effects on the lipid profile, such as thiazide diuretics, systemic beta blockers, and psyllium preparations, were used by a relatively small percentage of the study population. Concomitant medication use was therefore, unlikely to have substantially affected the results of the study. A list of commonly used concomitant medications (use reported by ≥5% of patients) is reported in Appendix I.

d) Patient Compliance

Compliance was assessed by pill counts at each study visit. Patients were considered to have been compliant if they were at least 75% compliant with study treatment. The sponsor states that the majority of patients followed the protocol defined dosing schedule. At the interim analysis (Sept-2000), overall compliance was about 94%, however compliance for many patients was not available secondary to patients having been lost to

follow up, not having returned study medication, or for other reasons. Individual compliance was not provided and will be provided with the final study report.

At the Division's request, the Sponsor submitted a listing of the number of patients receiving each dosage of study medication by week of treatment, on 03-July-2001. At Week 52:

- 264 patients (32% of the ITT population) had discontinued study medication
- 453 patients (56%) were receiving the maximum dose (2000/40) of Advicor
- 97 patients (12%) were receiving from 500/10 to 1500/30 of Advicor

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e) Efficacy Results

The efficacy results reported are based on the interim analysis with data available as of Sept-2000.

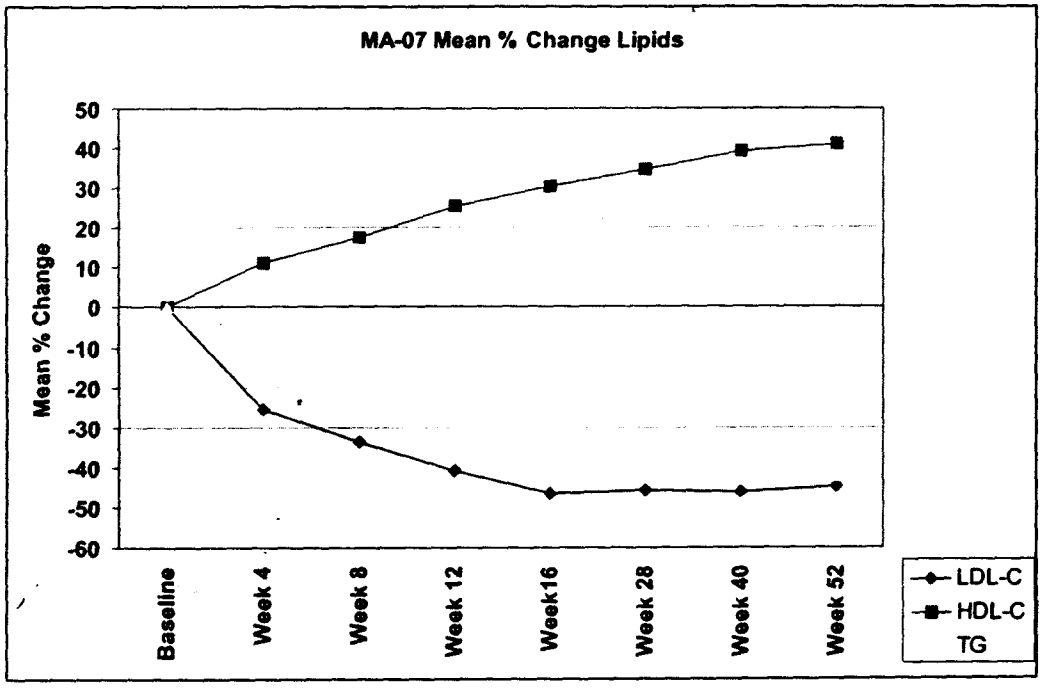
(1) Interim Efficacy Results: Overall

The primary efficacy endpoint was the mean percent change from baseline in LDL-C. The primary analysis performed by the sponsor was on observed cases at each time point. Secondary efficacy analyses were performed on HDL-C and TG. Lp(a) results were incomplete and are summarized in Appendix II only. The results for LDL-C, HDL-C and TG are as follows

Table 100: MA-07 Interim Mean % Change from Baseline in Lipid Parameters

			Week						
		Baseline	4	8	12	16	28	40	52
Advicor dose (mg/mg)			500/10	1000/20	1500/30	2000/40	2000/40	2000/40	2000/40
Observed Cases, n =		814	753	705	676	655	604	236	226
LDL-C	Mean	195.3	-25.3	-33.8	-40.8	-46.6	-45.9	-46.0	-44.8
	SE	1.38	0.45	0.54	0.61	0.62	0.70	1.05	1.07
HDL-C	Mean	47.6	+11.1	+17.7	+25.6	+30.3	+34.7	+39.4	+41.2
	SE	0.4	0.52	0.67	0.79	0.82	0.86	1.54	1.80
TG	Mean	199.4	-15.6	-26.0	-34.4	-41.2	-39.5	-39.7	-42.3
	SE	3.26	1.01	1.01	0.91	0.97	1.00	2.75	1.79

Figure 8: MA-07 Interim Mean % Change Lipids



The efficacy results show that:

1) Advicor produces dose-dependent decreases in LDL-C and TG, and increases in HDL-C
2) Lipid-altering effects are durable and remain consistent throughout 52 weeks of treatment

As MA-06 was an open-label trial with no active comparator, no comparative efficacy assumptions can be made. It should also be noted that as the results are for interim data, the number of observed cases was smaller for the later weeks of the study, particularly after Week 28.

(2) Subgroup Analysis:

(a) Male vs Female

Efficacy results for male vs female patients are consistent with results previously obtained for both Niaspan and Advicor (MA-06). Females tended to have better LDL-C and TG-lowering and HDL-C raising compared to males. The lipid-altering effects of Advicor were maintained in both groups throughout the 52 weeks of treatment. The results for male vs female patients are summarized in the following tables and figures

Table 101: MA-07 Mean % Change from Baseline for LDL-C and TG, Male vs Female

			Week						
		Baseline	4	8	12	16	28	40	52
Advicor dose (mg/mg)			500/10	1000/20	1500/30	2000/40	2000/40	2000/40	2000/40
LDL-C	Male, n =	518	489	465	448	438	411	149	144
	Mean change	190.7 mg/dL	-23.7 %	-31.7 %	-38.1 %	-44.2 %	-44.4 %	-43.5 %	-42.9 %
LDL-C	Female, n =	296	264	240	228	217	193	87	82
	Mean change	203.2 mg/dL	-28.3 %	-37.8 %	-46.1 %	-51.4 %	-49.2 %	-50.1 %	-48.0 %
TG	Male, n =	518	489	466	448	438	411	150	144
	Mean Change	199.9 mg/dL	-14.7 %	-23.5 %	-31.7 %	-38.6 %	-37.7 %	-38.6 %	-40.2 %
TG	Female, n =	296	264	240	228	217	193	87	82
	Mean Change	198.5 mg/dL	-17.2 %	-30.7 %	-39.8 %	-46.2 %	-43.3 %	-41.7 %	-46.1 %

Figure 9: MA-07 Mean % Change LDL-C and TG, Male vs Female

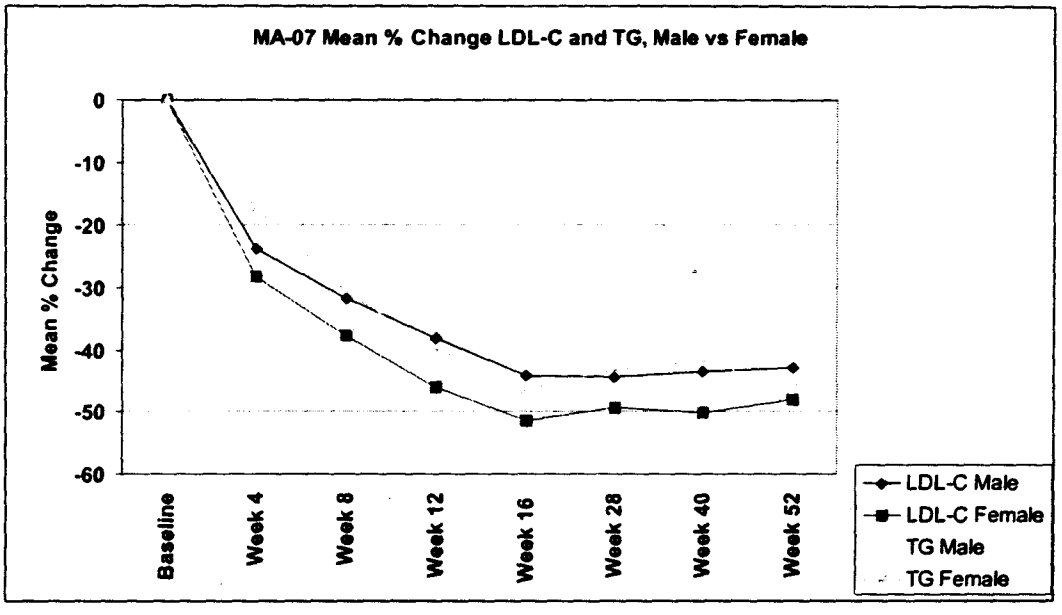


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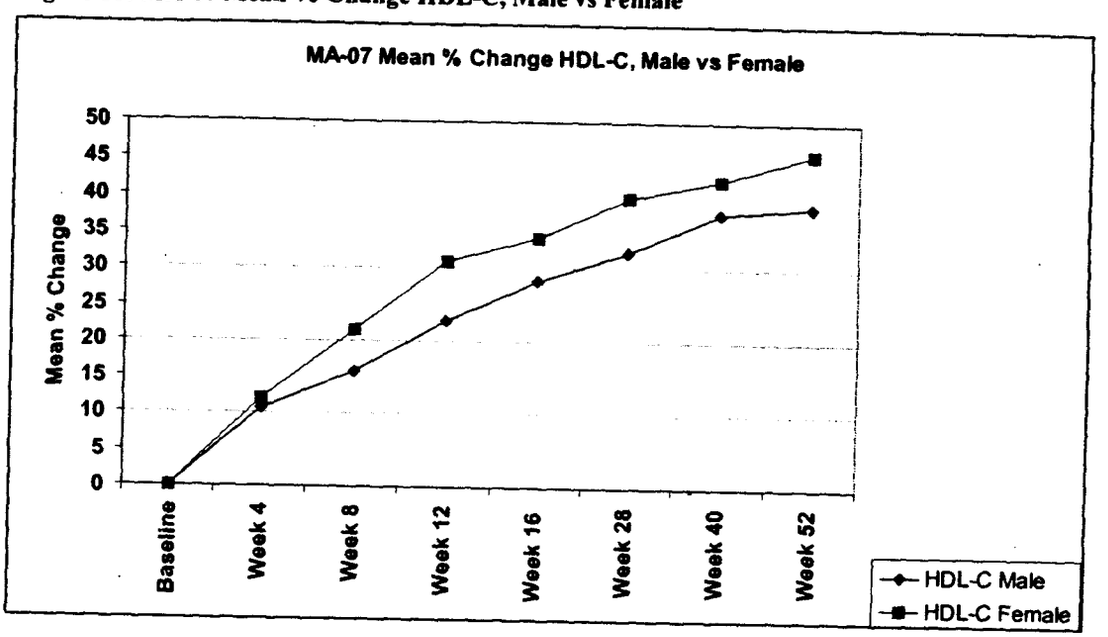
Table 102: MA-07 Mean % Change from Baseline for HDL-C, Male vs Female

		Week						
	Baseline	4	8	12	16	28	40	52
Advicor dose (mg/mg)		500/10	1000/20	1500/30	2000/40	2000/40	2000/40	2000/40
HDL-C Male, n =	518	489	466	448	438	411	150	144
Mean Change	44.3 mg/dL	+10.6 %	+15.7 %	+22.8 %	+28.3 %	+32.3 %	+37.7 %	+38.6 %
HDL-C Female, n =	296	264	240	228	217	193	87	82
Mean Change	53.3 mg/dL	+11.9 %	+21.4 %	+31.0 %	+34.3 %	+39.8 %	+42.2 %	+45.8 %

Figure 10: MA-07 Mean % Change HDL-C, Male vs Female



(b) Efficacy Geriatric vs Non-Geriatric

Efficacy results for geriatric vs non-Geriatric patients show that geriatric patients have at least as great a response to LDL-C and TG-lowering, and HDL-C raising as do non-geriatric patients. The lipid-altering responses were maintained in both groups throughout the 52 weeks of study drug treatment.

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Table 103: MA-07 Mean % Change from Baseline in LDL-C and TG, Geriatric vs Non-Geriatric

			Week						
		Baseline	4	8	12	16	28	40	52
Advicor dose (mg/mg)			500/10	1000/20	1500/30	2000/40	2000/40	2000/40	2000/40
LDL-C	Geriatric, n =	295	275	257	241	232	209	75	69
	Mean change	188.4 mg/dL	-26.8 %	-36.2 %	-45.1 %	-49.6 %	-49.0 %	-51.2 %	-50.4 %
LDL-C	Non-Geriatric, n =	518	478	448	435	423	395	161	157
	Mean change	199.1 mg/dL	-24.4 %	-32.3 %	-38.4 %	-44.9 %	-44.3 %	-43.5 %	-42.3 %
TG	Geriatric, n =	295	275	257	241	232	209	75	69
	Mean Change	184.6 mg/dL	-16.4 %	-27.8 %	-34.7 %	-42.1 %	-40.9 %	-43.2 %	-44.3 %
TG	Non-Geriatric, n =	518	478	449	435	423	395	162	157
	Mean Change	208.0 mg/dL	-15.1 %	-24.9 %	-34.3 %	-40.7 %	-38.8 %	-38.1 %	-41.5 %

Figure 11: MA-07 Mean % Change LDL-C and TG, Geriatric vs Non-Geriatric

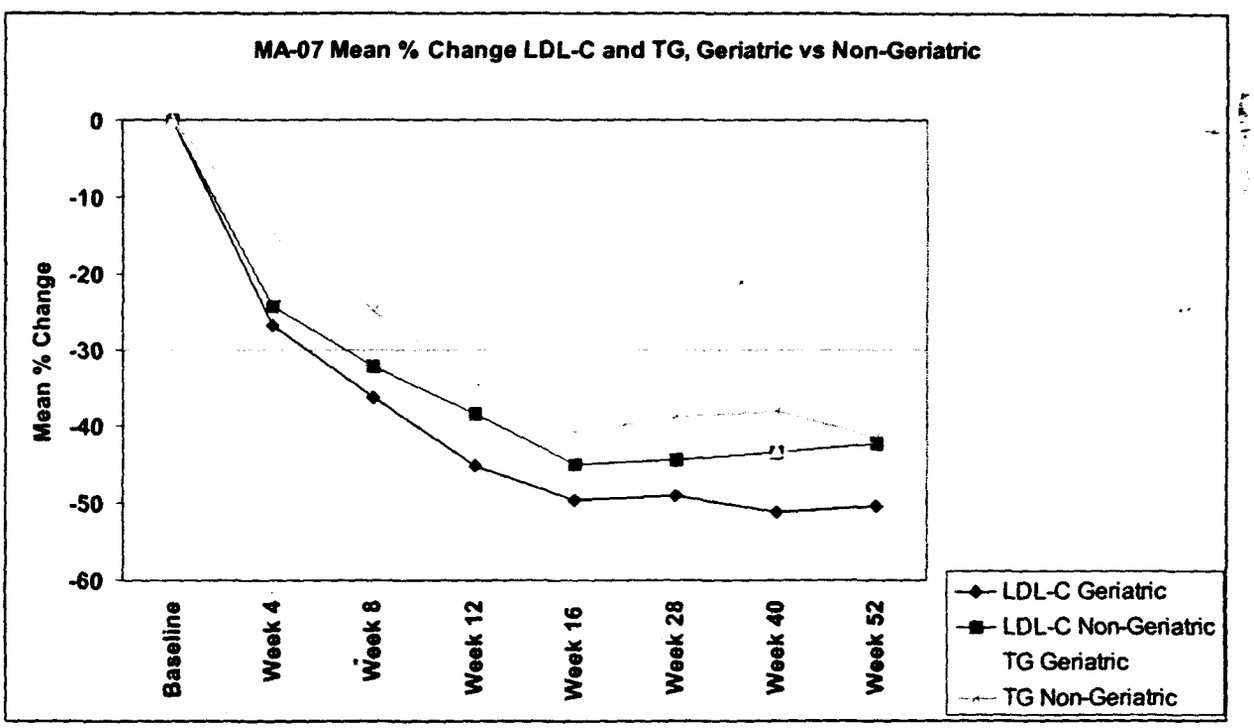

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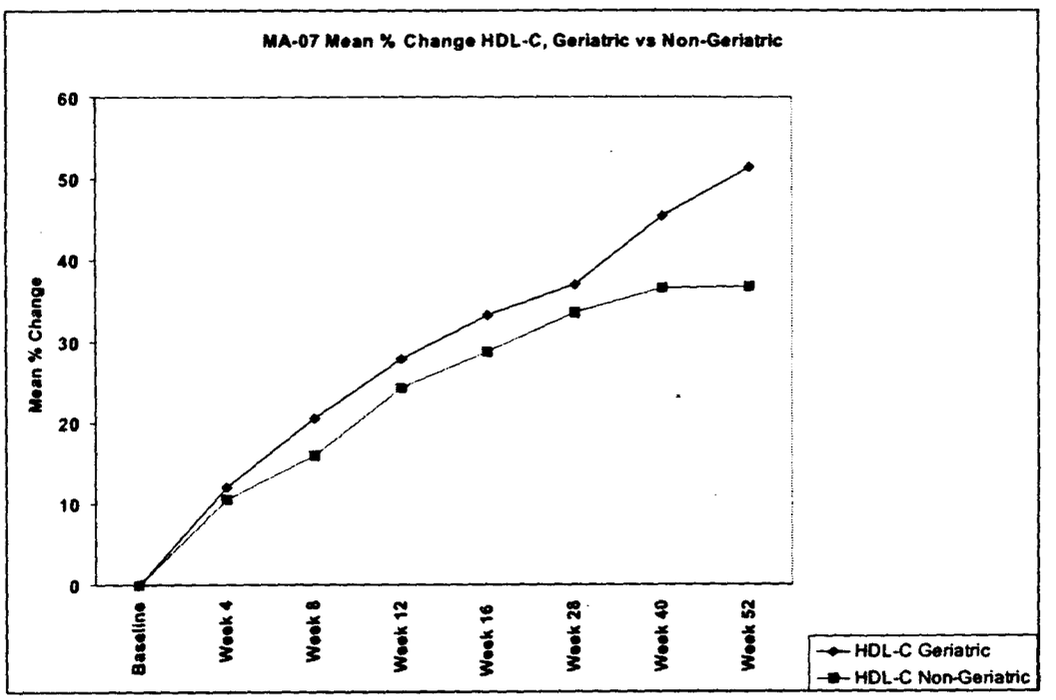
Table 104: MA-07 Mean % Change from Baseline in HDL-C, Geriatric vs Non-Geriatric

		Week						
	Baseline	**4**	**8**	**12**	**16**	**28**	**40**	**52**
Advicor dose (mg/mg)		**500/10**	**1000/20**	**1500/30**	**2000/40**	**2000/40**	**2000/40**	**2000/40**
HDL-C Geriatric, n =	295	275	257	241	232	209	75	69
Mean Change	49.8 mg/dL	+12.1 %	+20.5 %	+27.9 %	+33.2 %	+37.0 %	+45.4 %	+51.4 %
HDL-C Non-Geriatric, n =	518	478	449	435	423	395	162	157
Mean Change	46.3 mg/dL	+10.5 %	+16.0 %	+24.3 %	+28.7 %	+33.5 %	+36.6 %	+36.7 %

Figure 12: MA-07 Mean % Change HDL-C, Geriatric vs Non-Geriatric



(3) Final Efficacy Results

Final efficacy results were submitted at the Division's request on 03-Jul-2001. The final results included mean percent changes from baseline in LDL-C, HDL-C, TG, and TC for observed-cases throughout the 52 weeks of the study. Final data were not available by subgroup. Findings for the final efficacy data were similar to the interim results, and did not change the overall efficacy conclusion that the observed lipid-altering effects of Advicor were durable throughout the 52 weeks of the study. For completeness, the final efficacy results are shown in Appendix IX.

(4) Conclusions on Efficacy Results

The efficacy results for MA-07 show that Advicor produced dose-dependent LDL-C and TG-lowering, and HDL-C raising that were durable throughout the 52 weeks of the study. As expected from previous experience with Niaspan and from the Advicor results in the MA-06 study, there were greater responses seen for LDL-C and TG-lowering, and HDL-C raising in female patients compared to male patients. Geriatric patients appeared to have at least as great a response to the lipid-altering effects of Advicor as non-geriatric patients. As MA-06 was an open-label trial with no active comparator, no comparative efficacy assumptions can be made.

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. This Reviewer however, included all reported AEs regardless of Investigator attribution. 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 COSTART dictionary. Adverse Events were also analyzed by subgroups (male vs female, geriatric 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 the Appendix).

(a) Interim Analysis

At the interim analysis (Sept-2000), there were 288 different AE terms reported by 762 of 814 (94%) patients overall. The incidence rates for any AE reported by subgroup (male vs female, geriatric vs non-geriatric) were similar and are summarized as follows

Table 105: MA-07 Incidence of Adverse Events, Overall and by Subgroup, by Sept-2000

		Subgroup			
	ITT, All	**Male**	**Female**	**Geriatric**	**Non-Geriatric**
Number of Patients, n =	814	518	296	296	518
Patients Reporting Any AE, n (%)	762 (94)	481 (93)	281 (95)	280 (95)	482 (93)

(b) 4-Month Safety Update

Results at the 4-month safety update (Jan-2001) were similar to the interim analysis (Sept-2000) results. There were 318 different AE terms reported by 781 of 814 (96%) patients overall. The incidence rates for any AE reported by subgroup were also similar and are summarized as follows

Table 106: MA-07 Incidence of Adverse Events, Overall and by Subgroup, by Jan-2001

		Subgroup			
	ITT, All	**Male**	**Female**	**Geriatric**	**Non-Geriatric**
Number of Patients, n =	814	518	296	296	518
Patients Reporting Any AE, n (%)	781 (96)	494 (95)	287 (97)	286 (97)	495 (96)

As the results at the Sept-2000 and Jan-2001 timepoints are similar, and as the 4-month update is more complete due to a larger number of patients having had longer study medication exposure, only the results from the 4-month update results will be summarized from this point forward.

(2) Adverse Events by Body System

Adverse Events in the Cardiovascular system were the most commonly reported (reported by 70% of patients), followed by Body as a Whole (59%), the Digestive system (35%), and Skin and Appendages (33%). Flushing was the most commonly reported AE term (63% of patients), and accounted for almost all of the Cardiovascular system complaints. The most commonly reported AEs by body system (occurring in ≥5% of patients overall) are listed in the following table [A list of common (≥2%) AEs by body system is in Appendix III]

Table 107: MA-07 Incidence of Most Common Adverse Events by Body System

ITT Patients, n =		814
Body System	**COSTART Term**	n (%)
Body as a Whole	**All**	**484 (59)**
	Infection	191 (23)
	Pain	134 (16)
	Headache	90 (11)
	Injury, Accidental	58 (7)
	Flu Syndrome	59 (7)
	Asthenia	50 (6)
	Pain, Abdominal	47 (6)
	Pain, Back	43 (5)
Cardiovascular	**All**	**572 (70)**
	Flushing	513 (63)
Digestive	**All**	**286 (35)**
	Nausea	83 (10)
	Diarrhea	82 (10)
	Dyspepsia	62 (8)
Metabolic and Nutritional	**All**	**175 (21)**
	Hyperglycemia	45 (6)
	Edema, Peripheral	41 (5)
Nervous	**All**	**208 (26)**
	Dizziness	54 (7)
Respiratory	**All**	**171 (21)**
	Sinusitis	46 (6)
	Rhinitis	42 (5)
Skin and Appendages	**All**	**271 (33)**
	Pruritus	148 (18)
	Rash	96 (12)

Other AEs of particular interest in this study were myalgias, myopathy, rhabdomyolysis and hepatitis. Thirty-one (31) patients complained of myalgias at any time during the study. Of these 31 patients with myalgia, 1 patient (23-014) had her dosage of study medication adjusted, 5 patients (08-003, 15-002, 26-011, 35-014, 39-007) had their study medication interrupted, and 2 patients (07-009, 11-003) had their study medication discontinued. One patient (19-005) was diagnosed with myopathy, although she did not have a significant elevation in her CPK. Another patient (08-005) had CPK elevations 10 X ULN and was discontinued secondary to "fibromyalgia". As myopathy was defined in the protocol as "...myalgia with CPK levels >10 X ULN...", patient 08-005 will be considered by this Reviewer as a case of myopathy and patient 19-005 will not. These two patients are summarized as follows (these two patients are also included in the CPK section)

Table 108: MA-07 Patients With Myopathy

Week	CPK	Elevation	Dose	Contributing history
Patient 19-005				59 year old female was dropped due to a diagnosis of myopathy by her primary care physician. The patient complained of feeling weak and achy, and refused a blood draw. The patient later informed the investigator that she was asymptomatic and was told to stop Advicor by her primary care physician due to a 10-15% increase in CPK. No CPK >10 X ULN was confirmed.
Baseline	144	>normal	None	
Week 4	122	>normal	500/10 X 4 weeks	
ET	N/A		1000/20 X 3 weeks	
Patient 08-005				52 year old male with an extensive medical history, which includes arthromyalgia and muscular aches. At Week 52 the patient was diagnosed with "fibromyalgia". Also at Week 52 the patient was entered in the study extension and Advicor 2000/40 was continued. Approximafely 1 week into the study extension the patient was discontinued due to an elevated CPK. The patient reported heavy yard work prior to the Week 52 retest, and complained of chest heaviness. An EKG, thallium stress test, and CPK isoenzymes were all normal. The patient's symptoms improved on Ultram, and CPK decreased on retesting.
Baseline	82		None	
Week 4	233	>normal	500/10 X 4 weeks	
Week 8	178		1000/20 X 4 weeks	
Week 8 retest	453	>normal	1500/30 X 2 weeks	
Week 12	149		2000/40 X 1 day	
Week 16	97		2000/40 X 4 weeks	
Week 28	151		2000/40 X 17 weeks	
Week 40	87		2000/40 X 28 weeks	
Week 52	796	>normal	2000/40 X 41 weeks	
Week 52 retest	6700	>10 X ULN	off study drug X 8 days	
Week 52 retest	94		off study drug X 2 weeks	
ET (extension)	108		off study drug X 6 weeks	

Three patients (24-015, 34-005 and 45-012) were diagnosed with hepatitis (hepatitis C, hepatitis A, and hepatitis A respectively) during the study. No cases of study drug-induced hepatitis were reported. There were no reported cases of rhabdomyolysis.

(3) Adverse Events by Subgroup

Adverse Events were further analyzed by sex and by age. Females were more likely than males to complain of headaches (15% vs 9% respectively), nausea (18% vs 6%), and diarrhea (13% vs 8%). Geriatric patients were more likely than non-geriatric patients to complain of pruritus (24% vs 15%) and dizziness (10% vs 5%). Non-geriatric patients were more likely than geriatric patients to complain of flu syndrome (10% vs 2%) and infection (25% vs 21%). These differences between the subgroups are small however, and no definite conclusions will be drawn from them. The most common ($\geq$5% incidence) AEs overall and by subgroup are summarized as follows

Table 109: MA-07 Incidence of Most Common Adverse Events, Overall and by Subgroup

			Subgroup			
		ITT, All	Male	Female	Geriatric	Non-Geriatric
ITT Patients, n =		814	518	296	296	518
Body System	**COSTART Term**	n (%)	n (%)	n (%)	n (%)	n (%)
Body as a Whole	Infection	191 (23)	120 (23)	71 (24)	62 (21)	129 (25)
	Pain	134 (16)	84 (16)	50 (17)	53 (18)	81 (16)
	Headache	90 (11)	45 (9)	45 (15)	31 (10)	59 (11)
	Flu Syndrome	59 (7)	45 (9)	14 (5)	7 (2)	52 (10)
	Injury, Accidental	58 (7)	40 (8)	18 (6)	21 (7)	37 (7)
	Asthenia	50 (6)	33 (6)	17 (6)	17 (6)	33 (6)
	Pain, Abdominal	47 (6)	24 (5)	23 (8)	19 (6)	28 (5)
	Pain, Back	43 (5)	28 (5)	15 (5)	16 (5)	27 (5)
Cardiovascular	Flushing	513 (63)	324 (63)	189 (64)	179 (60)	334 (64)
Digestive	Nausea	83 (10)	31 (6)	52 (18)	34 (11)	49 (9)
	Diarrhea	82 (10)	44 (8)	38 (13)	38 (13)	44 (8)
	Dyspepsia	62 (8)	36 (7)	26 (9)	24 (8)	38 (7)
Metabolic and Nutritional	Hyperglycemia	45 (6)	27 (5)	18 (6)	14 (5)	31 (6)
	Edema, Peripheral	41 (5)	17 (3)	24 (8)	19 (6)	22 (4)
Nervous	Dizziness	54 (7)	35 (7)	19 (6)	30 (10)	24 (5)
Respiratory	Sinusitis	46 (6)	25 (5)	21 (7)	11 (4)	35 (7)
	Rhinitis	42 (5)	27 (5)	15 (5)	15 (5)	27 (5)
Skin and Appendages	Pruritus	148 (18)	89 (17)	59 (20)	70 (24)	78 (15)
	Rash	96 (12)	57 (11)	39 (13)	37 (13)	59 (11)

(4) Adverse Events Resulting in Drug Discontinuation

By Jan-2001, 264 of the 814 (32%) ITT patients had discontinued study medication prior to study completion. Of the 264 patients who discontinued, 188 patients discontinued due to AEs, and 15 discontinued due to laboratory abnormalities. The most commonly reported AEs resulting in drug discontinuation were flushing (10%), pruritus (4%) and rash (2%).

(5) Adverse Events Resulting Drug Discontinuation by Subgroup

Adverse Events resulting in study drug discontinuation were further analyzed by subgroups. Female patients were more likely than male patients to discontinue from the study for any reason (42% vs 27% respectively), and to discontinue for an AE (33% vs 18%). Female patients were more likely to discontinue for flushing (14%) than male patients (8%). Geriatric patients were also more likely than non-geriatric patients to discontinue from the study for any reason (38% vs 30%), and were more likely to discontinue due to an AE (30% vs 19%). Geriatric patients were somewhat more likely than non-geriatric patients to discontinue secondary to pruritus (7% vs 3%) or rash (4% vs 2%), however, as the differences are small, no conclusions will be made from these results. Discontinuations due to the most common AEs are summarized in the following table (A complete list of discontinuations due to AEs, overall and by subgroup, is in the Appendix V)

Table 110: MA-07 Discontinuations Due to Adverse Events, Most Common Overall and by Subgroup

			Subgroup			
		ITT, All	Male	Female	Geriatric	Non-Geriatric
ITT Patients, n =		814	518	296	296	518
All Discontinuations, n (%)		264 (32)	140 (27)	124 (42)	111 (38)	153 (30)
Discontinued for AE*, n (%)		188 (23)	91 (18)	97 (33)	90 (30)	98 (19)
Body System	COSTART Term	n (%)	n (%)	n (%)	n (%)	n (%)
Body as a Whole	Headache	10 (1)	4 (1)	6 (2)	4 (1)	6 (1)
Cardiovascular	Flushing	79 (10)	39 (8)	40 (14)	29 (10)	50 (10)
Digestive	Diarrhea	12 (1)	3 (1)	9 (3)	7 (2)	5 (1)
	Nausea	11 (1)	1 (<1)	10 (3)	3 (1)	8 (2)
Skin and Appendages	Pruritis	33 (4)	18 (3)	15 (5)	20 (7)	13 (3)
	Rash	20 (2)	8 (2)	12 (4)	12 (4)	8 (2)
Discontinued for Lab Abnormality		15 (2)	12 (2)	3 (1)	4 (1)	11 (2)

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

(6) Serious Adverse Events

There were 70 Serious Adverse Events (SAEs) occurring in 52 patients. Serious Adverse Events were as common in male as in female patients, and not surprisingly, were somewhat higher in geriatric (9%) vs non-geriatric (5%) patients. The incidence rates for SAEs overall and by subgroup are summarized as follows

Table 111: MA-07 Incidence of Serious Adverse Events, Overall and by Subgroup

		Subgroup			
	ITT, All	Male	Female	Geriatric	Non-Geriatric
ITT Patients, n =	814	518	296	296	518
Patients Reporting Any SAE, n (%)	52 (6)	36 (6)	16 (5)	27 (9)	25 (5)

There were 4 deaths during the study: Patient 02-007 due to MI/Cardiac arrest; patient 06-008 due to MI/Cardiac Arrest; patient 06-011 due to Cardiac Arrest; and patient 22-015 due to perforated duodenal/stomach ulcers.

The Cardiovascular system (47%) was the body system most commonly affected, and this is not unexpected in this high-risk group of patients. The body systems next most commonly affected were the Gastrointestinal system (19%), and the Musculoskeletal system (9%). Nine (9) of the 52 patients who experienced an SAE discontinued study medication due to the SAE. Three (3) SAEs were attributed by the Investigator as being at least possibly related to study drug: Hematemesis/hiatal hernia/esophagitis/Mallory Weis tear (patient 07-021); non-cardiac chest pain/ulcerated antritis/hiatal hernia/ulcerative esophagitis (patient 30-020); and diabetes mellitus (patient 34-004).

A complete list of SAEs is reported in Appendix VII.

(7) Other Significant Adverse Events

Eleven patients were diagnosed with cancer during the study. These patients were:

Table 112: MA-07 Other Significant Adverse Events

Patient	M/F	Age (yrs)	Diagnosis	Onset (days)	Investigator Attribution	Drug Discontinued?
			Skin Cancers			
01-009	M	72	Basal cell skin cancer	84	NR	N
16-003	F	58	Skin cancer	70	NR	N
29-015	M	79	Squamous cell skin cancer	28	NR	N
34-009	M	62	Basal cell skin cancer	28	Remotely	N
			Other Cancers			
02-015	M	64	Lung cancer	154	NR	Y
02-036	M	64	Bladder cancer	119	Remotely	N
17-015	M	73	Kidney cancer	42	NR	Y
31-018	M	72	Prostate cancer	49	NR	Y
35-007	M	78	Bladder cancer	273	NR	Y
35-015	M	54	Lung cancer	196	NR	N
40-007	M	64	Gastrointestinal cancer	280	NR	N

(8) 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." This Reviewer defined a TELA as any laboratory abnormality that worsened during study drug treatment regardless of the baseline value.

(a) ALT and AST

Mild elevations from baseline in ALT and AST occurred in 11% and 9% of patients respectively. Clinically significant (>3 X ULN) elevations in ALT, AST, or ALT and AST occurred in five patients. The incidence of ALT and AST elevations overall and by subgroup is as follows

Table 113: MA-07 Incidence of Treatment Emergent ALT and AST Elevations

		Subgroup			
	All	Male	Female	Geriatric	Non-Geriatric
ITT Patients, n =	814	518	296	296	518
ALT >normal, n (%)	92 (11)	67 (13)	25 (8)	26 (9)	66 (13)
ALT >2 X ULN, n (%)	13 (2)	7 (1)	6 (2)	7 (2)	6 (1)
ALT >3 X ULN, n (%)	4 (<1)	2 (<1)	2 (1)	2 (1)	2 (<1)
AST >normal, n (%)	75 (9)	41 (8)	34 (11)	25 (8)	50 (10)
AST >2 X ULN, n (%)	18 (2)	10 (2)	8 (3)	7 (2)	11 (2)
AST >3 X ULN, n (%)	5 (1)	2 (<1)	3 (1)	3 (1)	2 (<1)

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

The five patients with clinically significant ALT, AST or ALT and AST are summarized in the following table

Table 114: MA-07 Patients Experiencing Clinically Significant ALT, AST, or ALT and AST Elevations

Week	ALT	AST	Dose	Contributing history
Patient 10-004				
Baseline	22	21	None	58 year old female, with no contributing history. Patient was also receiving concomitant medications Daypro and Biaxin. Three days after Week 12 visit, Advicor and Daypro were discontinued.
Week 4	16	21	500/10 X 4 weeks	
Week 8	21	31	1000/20 X 4 weeks	
Week 12	148	181	1500/30 X 4 weeks	
Week 12 retest	157	140	Off study drug X 1 week	
Week 12 retest	32	31	Off study drug X 3 weeks	
ET	21	25	Off study drug X 5 weeks	
Patient 16-005				
Baseline	19	23	None	65 year old female, history of fatigue, osteoarthritis, and hypothyroidism. The patient was taking a large number of concomitant medications, one of which was Ultram.
Week 4	21	22	500/10 X 4 weeks	
Week 8	21	25	1000/20 X 4 weeks	
Week 12	66	50	1500/30 X 4 weeks	
Week 16	270	239	2000/40 X 4 ½ weeks	
Week 16 retest	274	98	Off study drug X 4 days	
ET	60	88	Off study drug X 2 ½ weeks	
ET retest	25	22	Off study drug X 6 ½ weeks	
Patient 16-021				
Baseline	12	22	None	74 year old female, history of hypertension (HTN). Patient was diagnosed with a UTI a few days after Week 12 visit, and treated with Cipro. A few days later, the patient complained of swelling in her legs and ankles treated with K-Dur and Maxzide, and Cardizem was discontinued. The symptoms resolved.
Week 4	24	39	500/10 X 4 weeks	
Week 8	33	46	1000/20 X 4 weeks	
Week 12	135	187	1500/30 X 4 weeks	
Week 12 retest	63	82	2000/40 X 3 weeks	
Week 16	45	70	2000/40 X 4 weeks	
Week 16 retest	23	36	2000/40 X 8 weeks	
Week 28	23	35	2000/40 X 16 weeks	
Week 40	21	21	2000/40 X 28 weeks	
Week 52	35	59	2000/40 X 40 weeks	
Patients 24-015				
Baseline	30	33	None	62 year old male, history of HTN and MI. The patient was also taking concomitant herbal medication saw palmetto for a prostate disorder at Week 23. The patient discontinued both Advicor and saw palmetto one week after the Week 28 visit. The patient's hepatitis profile was positive for hepatitis C, and the patients was discontinued from the study.
Week 8	32	30	1000/20 X 4 weeks	
Week 16	35	34	2000/40 X 4 weeks	
Week 28	169	114	2000/40 X 15 weeks	
Week 28 retest	218	152	2000/40 X 17 weeks	
Week 28 retest	398	247	Off study drug X 1 week	
Week 28 retest	280	135	Off study drug X 2 weeks	
ET	132	70	Off study drug X 4 ½ weeks	
Patient 34-005				
Baseline	12	11	500/10 X 4 weeks	70 year old male, history of PVD, CAD, CABG, HTN and a blood transfusion. After Week 52, the patient continued in the extension study. The patient was discontinued from study medication 2 days later for elevated AST and ALT. Alk phos, LDH, and total and direct bilirubin were also increased. The patient complained of abdominal pain, anorexia, fatigue and dark urine, and a hepatitis panel was positive for hepatitis A. The patient was discontinued from the study.
Week 4	20	14	1000/20 X 4 weeks	
Week 8	22	20	1500/30 X 4 weeks	
Week 12	25	24	2000/40 X 4 weeks	
Week 16	21	13	2000/40 X 8 weeks	
Week 28	24	16	2000/40 X 20 weeks	
Week 40	28	18	2000/40 X 32 weeks	
Week 52	330	365	2000/40 X 44 weeks	
ET/extension	24	17	Off study drug X 3 weeks	

(b) Fasting Blood Sugar

Mild elevations in FBS were common during the study, occurring in 64% of patients overall. FBS elevations >1.3 X ULN occurred in 20% of patients overall. Mild elevations in FBS were more common in males (70%) than females (55%). The incidence of treatment emergent FBS elevations overall and by subgroups are as follows

Table 115: MA-07 Incidence of Treatment Emergent FBS Elevations

		Subgroup			
	All	**Male**	**Female**	**Geriatric**	**Non-Geriatric**
Number of Patients, n =	814	518	296	296	518
FBS > normal	525 (64)	362 (70)	163 (55)	194 (66)	331 (64)
FBS >1.3 X ULN	165 (20)	109 (21)	56 (19)	63 (21)	102 (20)
FBS >2 X ULN	33 (4)	24 (5)	9 (3)	10 (3)	23 (4)
FBS >3 X ULN	6 (1)	5 (1)	1 (<1)	1 (<1)	5 (1)

FBS >normal: >111 mg/dL, FBS >1.3 X ULN: >145 mg/dL, FBS >2 X ULN: >221 mg/dL, FBS >3 X ULN: >330 mg/dL

Twelve (12) patients were discontinued due to blood sugar abnormalities:

1) Nine (9) patients were discontinued for worsening hyperglycemia or an elevated HgA1C (patients 06-014, 20-001, 21-019, 23-022, 27-001, 28-012, 33-003, 36-002, 45-006)
2) Two (2) patients were discontinued for worsening diabetes mellitus (DM) (23-013, 38-026)
3) One (1) patient was discontinued for a new diagnosis of DM type 2 (34-004)

(c) Phosphorous

Mild to moderate treatment emergent decreases in serum phosphorous were common, occurring in 26% of patients. Serum phosphorous <normal was more common in males (33%) than in females (14%). No clinically significant findings and no discontinuations were attributed to low serum phosphorous, and no clinically significant changes in serum calcium were noted. The clinical significance of mild to moderate hypophosphatemia in this group of patients is unknown. The incidence of phosphorous decreases overall and by subgroup is as follows

Table 116: MA-07 Incidence of Treatment Emergent Phosphorous Decreases

		Subgroup			
	All	**Male**	**Female**	**Geriatric**	**Non-Geriatric**
Number of Patients, n =	814	518	296	296	518
Phosphorous <normal	212 (26)	171 (33)	41 (14)	62 (21)	150 (29)
Phosphorous <2 X LLN	19 (2)	17 (3)	2 (1)	4 (1)	15 (3)

Phosphorous normal range: 2.4-4.3 mg/dL

(d) CPK

Mild CPK elevations were common, occurring in 50% of patients overall. Elevations > 5 X ULN occurred in 10 patients, and elevations >10 X ULN occurred in 4 patients.

Eleven (11) patients were discontinued from the study due to CPK elevations. The incidence of CPK elevations is as follows

Table 117: MA-07 Incidence of Treatment Emergent CPK Elevations

		Subgroup			
	All	**Male**	**Female**	**Geriatric**	**Non-Geriatric**
Number of Patients, n =	814	518	296	296	518
CPK >normal	411 (50)	268 (52)	143 (48)	131 (44)	280 (54)
CPK > 5 X ULN	10 (1)	10 (2)	0	2 (1)	8 (2)
CPK > 10 X ULN	4 (<1)	4 (1)	0	0	4 (1)

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

The 11 patients experiencing clinically significant CPK elevations (>10 X ULN or CPK elevations resulting in treatment discontinuation) are summarized in the following table

Table 118: MA-07 Patients With Clinically Significant CPK Elevations

Week	CPK	Elevation	Dose	Contributing history
Patient 08-005				
Baseline	82		None	52 year old male with an extensive medical history which includes arthromyalgia and muscular aches. At Week 52 the patient was diagnosed with "fibromyalgia". Also at Week 52 the patient was entered in the study extension and Advicor 2000/40 was continued. Approximately 1 week into the study extension the patient was discontinued due to an elevated CPK. The patient reported heavy yard work prior to the Week 52 retest, and complained of chest heaviness. An EKG, thallium stress test, and CPK isoenzymes were all normal. The patient's symptoms improved on Ultram, and CPK decreased on retesting.
Week 4	233	>normal	500/10 X 4 weeks	
Week 8	178		1000/20 X 4 weeks	
Week 8 retest	453	>normal	1500/30 X 2 weeks	
Week 12	149		2000/40 X 1 day	
Week 16	97		2000/40 X 4 weeks	
Week 28	151		2000/40 X 17 weeks	
Week 40	87		2000/40 X 28 weeks	
Week 52	796	>3 X ULN	2000/40 X 41 weeks	
Week 52 retest	6700	>10 X ULN	off study drug X 8 days	
Week 52 retest	94		off study drug X 2 weeks	
ET (extension)	108		off study drug X 6 weeks	
Patient 14-010				
Baseline	58		500/10 X 4 weeks	68 year old male who exercised strenuously with a trainer prior to Week 52. The patient was asymptomatic, and continued in the extension study.
Week 4	44		1000/20 X 4 weeks	
Week 8	48		1500/30 X 4 weeks	
Week 12	71		2000/40 X 4 weeks	
Week 16	62		2000/40 X 8 weeks	
Week 28	54		2000/40 X 20 weeks	
Week 40	86		2000/40 X 32 weeks	
Week 52	2665	>10 X ULN	2000/40 X 44 weeks	
Week 52 retest	320	>normal	2000/40 X 50 weeks	
Week 64	81		2000/40 X 52 weeks	
Patient 15-004				
Baseline	180		None	55 year old male, complained of joint pain in both hands at Week 16. The patient was discontinued 1 day after the Week 16 visit secondary to elevated CPK and FBS levels. Both resolved at follow-up, after being off study drug X 5 weeks.
Week 4	189	>normal	500/10 X 4 weeks	
Week 8	179		1000/20 X 4 weeks	
Week 12	236	>normal	1500/30 X 4 weeks	
Week 16	324	>normal	2000/40 X 4 weeks	
ET	215	>normal	Off drug X 5 weeks	

Week	CPK	Elevation	Dose	Contributing history
Patient 17-020				
Baseline	180		None	36 year old male, who reported heavy exercise the day before the Week 4 visit. The patient was asymptomatic at Week 4. On retesting, the elevated CPK resolved and the patient completed the study.
Week 4	3280	>10 X ULN	500/10 X 4 weeks	
Week 4 retest	625	>3 X ULN	1000/20 X 1 week	
Week 4 retest	101		1000/20 X 2 ½ weeks	
Week 8	263	>normal	1000/20 X 4 weeks	
Week 12	148		1500/30 X 4 weeks	
Week 16	172		2000/40 X 4 weeks	
Week 28	178		2000/40 X 12 weeks	
Week 40	160		2000/40 X 24 weeks	
Week 52	472	>normal	2000/20 X 36 weeks	
Patient 19-005				59 year old female was discontinued due to a diagnosis of myopathy by her primary care physician. The patient complained of feeling weak and achy, and refused a blood draw. The patient later informed the investigator that she was asymptomatic and was told to stop Advicor by her primary care physician due to a 10-15% increase in CPK. No CPK >10 X ULN was confirmed.
Baseline	144	>normal	None	
Week 4	122	>normal	500/10 X 4 weeks	
ET	N/A		1000/20 X 3 weeks	
Patient 22-003				
Baseline	135		None	71 year old male, history of angina, HTN, and CAD. The patient reported hard physical exercise around Week 8. The patient experienced a cold at Week 12. At Week 28 the patient reported arm aches that resolved. The patient injured her finger prior to the Week 40 retest. The patient was dropped from the study 9 days after the second Week 40 retest secondary to high CPK levels.
Week 4	214	>normal	500/10 X 4 weeks	
Week 8	580	>3 X ULN	1000/20 X 4 weeks	
Week 8 retest	291	>normal	1500/30 X 1 week	
Week 8 retest	WNL		1500/30 X 2 weeks	
Week 12	235	>normal	1500/30 X 4 weeks	
Week 16	171		2000/40 X 4 weeks	
Week 28	370	>normal	2000/40 X 16 weeks	
Week 28 retest	285	>normal	2000/40 X 22 weeks	
Week 40	333	>normal	2000/40 X 28 weeks	
Week 40 retest	201	>normal	2000/40 X 29 ½ weeks	
Week 40 retest	395	>normal	2000/40 X 34 weeks	
ET	315	>normal	Off study drug X 1 week	
ET retest	246	>normal	Off study drug X 4 weeks	
Patient 26-002				63 year old male. Advicor was discontinued 1 week after the Week 4 retest due to an elevated CPK. The patient complained of bilateral leg and foot cramps, and decreased strength to both hands. The patient's symptoms had not resolved by the ET visit.
Baseline	218	>normal	None	
Week 4	313	>normal	500/10 X 4 weeks	
Week 4 retest	423	>normal	1000/20 X 2 weeks	
ET	122		Off study drug X 11 days	
Patient 27-003				59 year old male, history of HTN. Patients sustained injuries in a hiking accident 1 week prior to study entry. CPK at Week 4 was 100% MM. Patients was discontinued from the study due to the elevated CPK.
Baseline	95		None	
Week 4	4320	>10 X ULN	500/10 X 4 weeks	
ET	111		Off study drug X 2 weeks	
Patient 34-012				
Baseline	152		None	51 year old male who sustained elbow bone chips 1 week prior to Week 4 visit. Patient was discontinued from the study at Week 8 secondary to the elevated CPK.
Week 4	197	>normal	500/10 X 4 weeks	
Week 4 retest	268	>normal	1000/20 X 2 weeks	
Week 4 retest	120		1000/20 X 3 weeks	
Week 8	521	>normal	1000/20 X 4 weeks	
ET	374	>normal	Off study drug X 10 days	
Patient 38-014				
Baseline	249	>normal	None	60 year old male, history of CAD, HTN, osteoarthritis. The patient underwent a hip replacement at Week 4. At Week 16, the patient was diagnosed with hyperbilirubinemia (peak total bilirubin 1.6; ULN 1.2). Four days after Week 16, the patient was discontinued secondary to increased CPK and bilirubin levels.
Week 4	238	>normal	Unknown	
Week 8	117		Unknown	
Week 12	224	>normal	Unknown	
Week 16	398	>normal	1500/30 X 4 weeks	
Week 16 retest	407	>normal	2000/40 X 2 weeks	
ET	323	>normal	Off study drug X 3 ½ weeks	
ET retest	433	>normal	Off study drug X 5 ½ weeks	
ET retest	343	>normal	Off study drug X 9 weeks	

Week	CPK	Elevation	Dose	Contributing history
Patient 45-012				
Baseline	166		None	68 year old male, history of CAD. At Week 4, patient complained of back pain, and 2 weeks later complained of aches all over, redness and itching. Study medication was interrupted for 11 days, then resumed at a lower dose of 500/10. At the Week 8 visit, the patient had a continued increase in CPK, and the patient was discontinued from the study.
Week 4	219	>normal	500/10 X 4 weeks	
Week 8	362	>normal	500/10 X 8 weeks	
ET	283	>normal	Off study drug	
ET retest	341	>normal	Off study drug	
ET retest	455	>normal	Off study drug	

(9) Other Laboratory Values

Treatment emergent decreases in platelets <100,000 occurred in 13 patients. Four patients were discontinued for decreased platelets. One patient (38-017) was reported as having prolonged bleeding after a tooth extraction. Patients with treatment emergent platelet counts <100,000 are summarized in the following table

Table 119 :MA-07 Treatment Emergent Platelet Counts <100,000

Patient	Week	Platelet Count (X 1,000)	Contributing History
01-022	Baseline	267	63 year old female. Patient was discontinued from the study due to fatigue and irritability. The decreased platelet count was attributed to artifact.
	Week 16	286	
	ET	79	
	ET retest	256	
03-018	Baseline	173	75 year old female. Platelet decrease at Week 28 and retest were felt to be due to clumping.
	Week 16	142	
	Week 28	83	
	Week 28 retest	97	
	Week 40	145	
	Week 52	155	
15-001	Baseline	145	84 year old male. Decreased platelet count was felt to be secondary to lab error. The patient discontinued at Week 24 due to flushing and itching.
	Week 16	145	
	Week 16 retest	92	
	Week 16 retest	110	
	ET	148	
16-029	Baseline	144	76 year old male. At Week 16 patient complained of dizziness X 1 day.
	Week 16	91	
	Week 28	140	
	Week 40	141	
	Week 52	139	
18-007	Baseline	138	No history provided
	Week 16	99	
	Week 28	107	
	Week 40	104	
	Week 52	106	
18-017	Baseline	153	75 year old male. No contributing history was reported until the extension study (see MA-07 48-week extension section).
	Week 16	110	
	Week 28	74	
	Week 28 retest	73	
	Week 28 retest	74	
	Week 28 retest	83	
	Week 40	78	
	Week 52	76	

Patient	Week	Platelet Count (X 1,000)	Contributing History
20-015	Baseline	254	69 year old male. Decreased platelets at Week 52 attributed to clumping.
	Week 16	213	
	Week 28	203	
	Week 40	225	
	Week 52	7	
	Week 52 retest	232	
20-016	Baseline	91	No history provided
	Week 16	61	
	Week 16 retest	61	
	Week 16 retest	104	
	Week 16 retest	68	
	Week 28	66	
	Week 28 retest	70	
	Week 40	72	
	Week 40 retest	79	
	Week 52	79	
29-005	Baseline	129	55 year old male, history of epistaxis, thrombocytopenia, and HTN. Study drug was interrupted for 21 days, 6 days after Week 28 due to a low platelet count. Study drug was resumed and titrated to 2000/40, and 2 ½ weeks later the platelet count was again noted to have decreased. The patient was discontinued from the study.
	Week 16	129	
	Week 28	90	
	Week 28 retest	122	
	Week 28 retest	98	
	ET	141	
32-008	Baseline	125	63 year old male. Patient was discontinued from the study at Week 48 due to decreased platelets.
	Week 16	142	
	Week 28	103	
	Week 40	94	
	ET	143	
35-007	Baseline	173	77 year old male. Decreased platelets noted at Week 16. Patient had fatigue and an irregular heartbeat at Week 40. At Week 42, the patient was hospitalized for bilateral hydroureteronephrosis, and study drug was interrupted for 1 month. The patient was retitrated on study drug, and approximately 10 weeks later was rehospitalized for bladder cancer. The patient was discontinued from the study
	Week 16	83	
	Week 16 retest	90	
	Week 28	109	
	Week 40	116	
	Week 40 retest	176	
	ET	285	
35-016	Baseline	106	No history provided.
	Week 4	111	
	Week 8	104	
	Week 16	114	
	Week 28	97	
	Week 40	101	
	Week 52	100	
38-017	Baseline	185	79 year old male. The patient had an abscessed tooth extracted between Weeks 28 and 40 and experienced continuous bleeding post-extraction, which was treated with subcutaneous epinephrine, lidocaine, and vitamin K, with eventual resolution. At Week 40 the patient was noted to have a platelet count <100,000. The patient was discontinued from the study.
	Week 16	168	
	Week 28	118	
	Week 40	99	
	Week 40 retest	143	
	ET	173	

Additional notable laboratory abnormalities include:

1) One patient (38-022) was discontinued for an elevated bilirubin (peak total bilirubin: 1.8, ULN 1.2).
2) Six patients had amylase elevations >2 X ULN, which resolved.
3) Thirteen (13) patients had PT elevations >2 X ULN (09-003, 18-009, 18-017, 20-002, 24-013, 26-011, 32-003, 32-016, 38-001, 38-017, 39-003, 45-014, and 45-016), 5 of whom had PT elevations >3 X ULN. There were no clinical sequelae reported with these elevations.

No other significant laboratory abnormalities were reported.

(10) Overall Safety Conclusions

Advicor was not well tolerated. Adverse Events were reported by 96% of study patients overall. Adverse Events in the Cardiovascular system were the most commonly reported, almost all which were complaints of flushing. Adverse Events in the Body as a Whole, the Digestive system, and Skin and Appendages body systems were the next most commonly reported. Overall, 32% of patients discontinued prior to study completion, and the majority of patients discontinued due to AEs. Female and geriatric patients were more likely than male and non-geriatric patients to discontinue from the study for any reason and for an AE. The most commonly reported reasons for discontinuation due to an AE were flushing (10%), pruritus (4%), and rash (2%). Clinically significant TELAs were uncommon, and only 15 (2%) patients discontinued due to lab abnormalities. Discontinuations for lab abnormalities resulted from elevations in ALT, AST, FBS, CPK, and bilirubin, and from decreases in platelet counts. Mild abnormalities were commonly seen in ALT, AST, FBS, phosphorous, and CPK. Mild FBS elevations were the most commonly observed laboratory abnormalities, and occurred in 64% of patients overall. Serious Adverse Events occurred in 6% of study patients, most commonly in the Cardiovascular and Gastrointestinal systems.

3. Conclusions on Review of Protocol MA-07

MA-07 was a single-arm, open-label study and therefore no comparative efficacy assumptions can be made. Advicor was found to produce dose-dependent LDL-C and TG-lowering, and HDL-raising, and these results were durable over the 52 weeks of the study. As in the MA-06 study, female patients had greater LDL and TG-lowering and HDL-raising than male patients. Geriatric patients had at least as great a response to the lipid-altering effects of Advicor as non-geriatric patients. The safety results were similar to what has been reported previously in the MA-14 and MA-06 studies. Advicor was poorly tolerated, and about one-third of patients discontinued prior to study completion, mainly due to AEs. Adverse Events most frequently cited as the reason for discontinuation were flushing, pruritus, and rash. Flushing was reported by the majority of patients during the study, and other frequently reported AEs were infection, pruritus, pain, rash, headache, nausea, and diarrhea. Most AEs were not serious, and reversible with discontinuation of study medication. Six percent of patients experienced an SAE during the study, mainly cardiovascular events, which was not unexpected in this high-risk group of patients. Mild laboratory abnormalities were frequently seen in AST, ALT, FBS, CPK, and phosphorous. Glucose abnormalities were particularly common, with the majority of patients reporting an elevation in FBS at any time during the study. Laboratory abnormalities resulting in study discontinuation occurred in 15 patients (2%), 12 of which were due to glucose abnormalities.

D. Protocol MA-98-010407 48-Week Extension Safety Update

(The 48-week extension to MA-07 will be referred to as the extension study from this point forward)

1. Study Design for MA-07 Extension Study

a) Study Design

Patients completing the 52-week MA-07 study were offered enrollment in the 48-week extension of MA-07. As the extension study was a continuation of MA-07, the study design was the same as for the initial 52 weeks of the study.

b) Study Medication

All patients received Advicor once daily at bedtime. Patients were continued on the same dose of Advicor as they were receiving in the 52-week study. In most cases, this was Advicor 2000/40, however the dose could be adjusted down by the Investigator for safety and tolerability. There was no comparator arm.

2. Results

Three-hundred (300) patients from the original 52-week MA-07 study were rolled over (enrolled) into the extension study.

a) Baseline Demographics

The patients entering the 48-week extension had similar baseline demographics as the patients in the original 52-week study. Sixty-eight (68) percent of patients were male and 92 % were Caucasian. Patients ranged in age from 29-83, with a mean age of 59.6. Demographic data are summarized in the following table

Table 120: MA-07 Baseline Demographics, 52-Week and 48-Week Extension Patients

	52-Week	48-Week Extension
Patients, n =	814	300
Demographic Measure		
Gender, n (%)		
Male	518 (62)	205 (68)
Female	296 (38)	95 (32)
Age, years		
mean	59.3	59.6
median	60	60
min, max	25, 84	29, 83
Age ≥ 65 years, n (%)	296 (36)	110 (37)
Ethnicity, n(%)		
Caucasian	716 (88)	276 (92)
Black	47 (6)	9 (3)
Hispanic	34 (4)	7 (2)
Asian	13 (2)	8 (3)
Other	4 (<1)	0

b) Patient Disposition

As of the database cut-off date (Mar-2001), the mean duration of treatment with study medication was 96.1 weeks, and 253 of the 300 patients (84%) received at least 100 weeks of study medication. Forty-seven (47) of the 300 patients (16%) had withdrawn, and 30 of the 47 dropouts were due to AEs. The reasons for patient discontinuations are summarized in the following table (patients discontinued from the original 52-week study are presented for comparison purposes)

Table 121: 48-Week Extension Study Patients Discontinued

	52-Week	48-Week Extension
Patients, n =	814	300
Number of Withdrawals, n (%)	264 (32)	47 (16)
Reason for Dropout		
Adverse Event	188 (23)	30 (10)
Withdrew Consent	23 (3)	5 (2)
Lost to Follow Up	19 (2)	4 (1)
Other	34 (4)	5 (2)

c) Safety Results

The original NDA submission contained interim safety information for the original 52-week MA-07 study up to the database cut-off of Sept-2000. A 4-month safety update was subsequently submitted with a database cut-off of Jan-2001. At the Jan-2001 update, 550 of the 814 patients had completed 52-weeks of study drug treatment and 264 patients had been discontinued (see MA-07 Study Section). An additional 8-month safety update was submitted with a database cut-off of Mar-2001. This updated safety information includes the safety information on the original 814 ITT patients (who completed the initial 52 weeks of the MA-07 study) from the Jan-2001 update combined with the new safety information on the 300 patients who continued in the 48-week extension study. The Adverse Event and Treatment Emergent Laboratory Abnormality sections presented below include combined safety information for MA-07 for the 814 ITT patients from study initiation through the 8-month safety update cut-off date of Mar-2001 (safety information as of the Jan-2001 cut-off date is also presented for comparison purposes).

(1) Adverse Events

Adverse Events reported during the extension phase were similar to those reported during the initial 52-week study. Flushing continued to be the most commonly reported AE, reported by 64% of patients at any time during the study. Other frequently reported AEs were infection (27%), pain (20%), pruritus (19%), rash (13%), headache (12%), and nausea (12%). There did not appear to be a substantial change in the types or frequencies of AEs reported during the extension study. The most commonly reported AEs ($\geq$5%) are listed in the following table [A list of common ($\geq$2%) AEs is in Appendix III]

Table 122: MA-07 Incidence of Most Common Adverse Events at Jan-2001 and Mar-2001 Updates

Patients, n =		Jan-2001 814	Mar-2001 814
Body System	**COSTART Term**		
Body as a Whole	Infection	191 (23)	220 (27)
	Pain	134 (16)	159 (20)
	Headache	90 (11)	99 (12)
	Injury, Accidental	58 (7)	72 (9)
	Flu Syndrome	59 (7)	70 (9)
	Asthenia	50 (6)	57 (7)
	Pain, Abdominal	47 (6)	53 (7)
	Pain, Back	43 (5)	57 (7)
	Pain, Chest	34 (4)	39 (5)
Cardiovascular	Flushing	513 (63)	525 (64)
Digestive	Nausea	83 (10)	98 (12)
	Diarrhea	82 (10)	89 (11)
	Dyspepsia	62 (8)	68 (9)
	Flatulence	35 (4)	37 (5)
	Vomiting	36 (4)	51 (6)
	Constipation	32 (4)	38 (5)
Metabolic and Nutritional	Hyperglycemia	45 (6)	50 (6)
	Edema, Peripheral	41 (5)	52 (6)
	CPK Increase	31 (4)	38 (5)
Musculoskeletal	Myalgia	31 (4)	37 (5)
Nervous	Dizziness	54 (7)	59 (7)
	Paresthesia	32 (4)	37 (5)
	Insomnia	33 (4)	38 (5)
Respiratory	Sinusitis	46 (6)	55 (7)
	Rhinitis	42 (5)	50 (6)
Skin and Appendages	Pruritis	148 (18)	154 (19)
	Rash	96 (12)	105 (13)

Other AEs of particular interest in this study were myalgias, myopathy, rhabdomyolysis, and hepatitis. There were 6 patients who reported myalgias during the extension study. One patient had study medication interrupted due to myalgias (patient 03-011), and one patient had study medication adjusted due to myalgias (patient 07-009). No patient was discontinued due to myalgias in the extension study. There were no reported cases of myopathy, rhabdomyolysis or hepatitis.

(2) Adverse Events Resulting in Study Drug Discontinuation

Thirty (30) of the 300 patients in the extension study (10%) discontinued due to an AE. The most commonly reported AE resulting in study drug discontinuation during the extension phase was flushing, which resulted in discontinuation in 8 of the 300 patients (3%). Nausea was the next most commonly reported AE resulting in discontinuation, with 4 of 300 patients (1%) discontinuing. During the initial 52-week study, 23% of patients discontinued from the study due to AEs. Flushing was also the most commonly reported AE resulting in study drug discontinuation during the initial 52-weeks of the study, resulting in 10% of patients discontinuing. Pruritus (4%) and rash (2%) were the next most commonly reported reasons for discontinuation during the 52-week study. The

number of discontinuations during the 48-week extension study is small relative to the 52-week study, which is not unexpected as the patients continuing in the extension had demonstrated compliance and tolerance to study medication prior to enrolling in the extension phase. The most common AEs resulting in study drug discontinuation for the 48-week extension (see Table 124) and the 52-week study (see Table 123) are as follows (A complete list of AEs resulting in study drug discontinuation for the extension study is in Appendix V)

Table 123: 52-Week Study Discontinuations Due to Adverse Events, Most Common

		52-Week Study
ITT Patients, n =		814
All Discontinuations, n (%)		264 (32)
Discontinued for AE*, n (%)		188 (23)
Body System	**COSTART Term**	n (%)
Body as a Whole	Headache	10 (1)
Cardiovascular	Flushing	79 (10)
Digestive	Diarrhea	12 (1)
	Nausea	11 (1)
Skin and Appendages	Pruritis	33 (4)
	Rash	20 (2)
Discontinued for Lab Abnormality		15 (2)

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

Table 124: 48-Week Extension Study Discontinuations Due to Adverse Events, Most Common

		48-Week Extension
Patients, n =		300
All Discontinuations, n (%)		47 (16)
Discontinued for AE*, n (%)		30 (10)
Body System	**COSTART Term**	n (%)
Cardiovascular	Flushing	8 (3)
	Heart Arrest	2 (1)
Digestive	Nausea	4 (1)
	Colitis	2 (1)
	Vomiting	2 (1)
Metabolic and Nutritional	CPK increased	2 (1)
	Glucose tolerance decreased	2 (1)
Skin and Appendages	Pruritis	2 (1)
Discontinued for Lab Abnormality		3 (1)

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

(3) Serious Adverse Events

There were 30 Serious Adverse Events in 25 patients in the 48-week extension study. There were no deaths. The Cardiovascular system was most commonly affected (16 of the 30 events, or 53%), which is not unexpected in this group of high-risk patients. The Musculoskeletal system was the next most commonly affected with 5 events. Male patients (7%) were about as likely as female patients (11%) to experience an SAE. Also as expected, geriatric patients (18%) were more likely to experience an SAE than non-