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Advicor:
The First Combination Antilipemic Agent

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Introduction

Hyperlipidemia significantly contributes to the development of heart disease, the leading cause of death in the United States.[1] According to the National Health and Nutrition Examination Survey and the Adult Treatment Panel III, 52 million Americans are candidates for dietary therapy and approximately 12.7 million Americans are candidates for drug therapy for their high cholesterol. Of these 12.7 million, 4 million have already been diagnosed with coronary heart disease.[2] Although dietary therapy is the recommended initial therapy, many patients require pharmacotherapy to control their lipid disorder. On December 18, 2001, the FDA approved Advicor (extended-release niacin, immediate-release lovastatin) the first dual-component medication for cholesterol modulation in the United States. Advicor is marketed by KOS Pharmaceuticals.

Advicor is indicated for the treatment of primary hypercholesterolemia and mixed dyslipidemia. It is not intended for first line therapy, but only after the patient has tried lovastatin or niacin and still needs further triglyceride-lowering and/or HDL-raising.[3] This article will address the pharmacology, clinical trials, adverse effects, costs, and prescribing considerations of Advicor.

Pharmacology/Pharmacokinetics

Lovastatin is an HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme-A) reductase inhibitor. It is a pro-drug that is hydrolyzed to the active metabolite mevinolinic acid in vivo. The mevinolinic acid competes with HMG-CoA for HMG-CoA reductase, a hepatic microsomal enzyme. This competition reduces the quantity of mevalonic acid, a cholesterol precursor, thereby reducing the production of cholesterol.[4] Lovastatin also enhances the clearance of LDL since cholesterol can be taken up from LDL by endocytosis. Lovastatin works mainly on LDL and total cholesterol, although it does have small effects on HDL and triglycerides.

Niacin, also known as nicotinic acid or 3-pyridinecarboxylic acid, reduces total cholesterol, LDLs, VLDLs, and triglycerides and increases HDLs. However, the precise mechanism of action for its antilipemic effects is unknown.[3]

Lovastatin is not completely absorbed from the gastrointestinal tract. It undergoes first-pass extraction by the liver, its main site of action. Less than 5% of the dose reaches the systemic circulation. After oral administration, lovastatin reaches its peak concentration in 2-4 hours. Food in the gastrointestinal tract will increase the oral absorption. Consumption of grapefruit juice can increase absorption 30% or more. Lovastatin is most effective when given as a single dose in the evening before bedtime due to the diurnal variation in cholesterol synthesis. Lovastatin is highly lipophillic and thus can cross the blood-brain barrier, the placental barrier, and distribute into the breast milk. Lovastatin and its beta-hydroxy acid metabolite are highly plasma protein bound (> 95%). Lovastatin is metabolized in the liver by the hepatic isoen-

Table 1. Mean percentage change from baseline at endpoint for LDL-C, HDL-C, TG by gender[4]

	Extended-release Niacin/Lovastatin 2000mg/40mg		Extended-release Niacin 2000mg		Lovastatin 40mg	
	Women (n=22)	Men (n=30)	Women (n=28)	Men (n=28)	Women (n=21)	Men (n=38)
LDL-C	-47%	-34%	-12%	-9%	-31%	-31%
HDL-C	+33%	+24%	+22%	+15%	+3%	+7%
TG	-48%	-35%	-25%	-15%	-15%	-23%

zyme, CYP3A4, to mevinolinic acid and other active metabolites. Mevinolinic acid has a plasma half-life of 1.1-1.7 hours. Eighty-three percent of the dose is excreted in the feces as both active and inactive metabolites and 10% of the drug is eliminated renally as inactive drug. In patients with CrCl = 10-30 mL/min, plasma concentrations were found to be two-fold higher than those of healthy volunteers.

Peak concentrations of niacin are reached in 5 hours. Oral nicotinic acid is well-absorbed (approximately 72% based on urinary excretion data). Presence of food in the GI tract maximizes the bioavailability of niacin and minimizes stomach upset. The sustained-release form of niacin helps to reduce the onset and severity of peripheral vasodilatation, although it has a higher incidence of hepatoxicity when compared to the immediate-release dosage form. Niacin concentrates in the spleen, liver and adipose tissue and is widely distributed throughout the body. Niacin undergoes first-pass metabolism via several pathways. One pathway is conjugation with glycine to form nicoturic acid, which is then excreted in the urine. Another pathway results in the formation of NAD (nicotinamide adenine dinucleotide) which is used in the liver and intestines for other body processes. About 12% of niacin is excreted unchanged in the urine at dosages of 1000mg/day, as larger dosages are given more nicotinic acid will be excreted unchanged in the urine. Steady state concentrations of niacin are usually higher in females, although the absorption, metabolism, and excretion of the drug appears to be the same in both men and women. There appears to be no information available about the pharmacokinetics in patients with renal impairment.

Clinical Trials

In a clinical trial organized by the manufacturer, the extended-release niacin/lovastatin product was compared to each of its individual components (extended-release niacin and lovastatin) in a multicenter, randomized, double-blind, parallel, 28-week, active comparator study in patients with Type IIa or IIb hyperlipidemia. Each patient received each dose for at least 4 weeks, using a forced dose-escalation study design. Patients who were randomly assigned to the extended-release niacin/lovastatin treatment group initially received 500mg/20mg. Then half of these patients were titrated up to 1000mg/20mg at 4 week intervals, while the other half were titrated up to 2000mg/40mg. The extended-release niacin-only group started at 500mg and were titrated at 4 week intervals to 2000mg. The lovastatin-only group received 20mg for 12 weeks titrated up to 40mg for up to 16 weeks. In this study, extended-release niacin/lovastatin decreased LDL-C, TG, Lp(a), and increased HDL-C in a dose-dependent manner. Furthermore, the extended-release niacin/lovastatin lowered LDL-C significantly greater ($p<0.0001$) than lovastatin 40mg, extended-release niacin 2000mg and extended-release niacin/lovastatin at doses of 1000mg/20mg after 28 weeks of titration to 2000mg/40mg (Table 1). Also, extended-release niacin/lovastatin was better at raising HDL and reducing TG at doses of 1000mg/20mg or greater when compared to lovastatin or extended-release niacin individually. Finally, the Lp(a) lowering effects of extended-release niacin were superior to extended-release niacin/lovastatin and both were superior to lovastatin alone.

In a separate study, Kashyap et al investigated the long-term safety and efficacy of extended-release niacin/lovastatin in 818 enrolled patients over 52 weeks in a multi-center, open-label study.[5] The researchers used 4 escalating doses of

Table 2: Mean % Change in Lipids with Extended-release Niacin/Lovastatin[5]

Week	N*	Dose (mg/mg)	LDL	HDL	TG
Baseline	814	-	195 +/- 1.4	48 +/- 0.4	199 +/- 3.3
4	753	500/10	-25%	11%	-16%
8	705	1000/20	-34%	18%	-27%
12	676	1500/30	-41%	26%	-34%
16	655	2000/40	-47%	30%	-41%
28	604	2000/40	-46%	35%	-40%
52	226	2000/40	-45%	41%	-42%

N* = number of patients remaining in the trial at each time point. Observed values (mean +/- SE) in milligrams per deciliter

extended-release niacin/lovastatin: 500/10 for the first 4 weeks, 1000/20 for weeks 5-8, 1500/30 for weeks 9-12, and 2000/40 for week 13-52. They found that dose-dependent effects were seen for all of the lipid parameters (Table 2). At week 16, the medication reached its maximum effect on LDLs (47%) and triglycerides (41%). Also, HDLs were increased by 30% at week 16 with the effects persisting as HDLs were increased to 41% by week 52 (all $p < 0.001$).

Dosing

Extended-release niacin/lovastatin is not indicated for first-line therapy of hyperlipidemia. Before initiation of this combination therapy, each of the individual products (extended-release niacin and lovastatin) should first be titrated up. The manufacturer recommends titration with the niacin supplement, Niaspan, as this is bioequivalent to the extended-release niacin in Advicor. For patients already titrated with Niaspan, they can be immediately switched over to Advicor, otherwise begin with Niaspan 500mg once daily at bedtime and then titrate upward in increments of 500mg every 4 weeks up to a maximum of 2000mg/day as tolerated to achieve the target NCEP-ATP III goals. Advicor is available in three strengths 500/20, 750/20, and 1000/20, each containing 20mg of lovastatin with varying amounts of extended-release niacin.

The tablet should be taken once daily at bedtime as cholesterol production is highest in the early morning hours. It should be taken with a small low-fat snack to limit GI side effects, flushing, and increase the bioavailability of lovastatin. The patient should avoid drinking grapefruit juice with their dose to avoid drastic increases in the lovastatin concentration. The tablet should not be crushed or broken, nor taken with hot beverages or alcohol. If the niacin-induced flushing is bothersome the patient may take 325mg of aspirin (if appropriate) or another non-steroidal anti-inflammatory 30 minutes before their dose to lessen this side effect.

This drug is not recommended for children or adolescents, patients with elevated hepatic enzymes or hepatic disease, and should be used with caution in patients with renal disease. For patients with CrCl ≥ 30mL/min no dosage adjustment is needed, below CrCl < 30mL/min, doses of lovastatin ≥ 20mg per day should be carefully considered. As of yet, the dialyzability of niacin and lovastatin are unknown.

Patients on extended-release niacin/lovastatin will require monitoring. The patient's lipid levels should be evaluated at baseline and then at intervals no less than 4 weeks after initiation of drug therapy or dosage change.[4] Once the patient has reached their NCEP-ATP III goals for lipids then monitor their lipids every 4 to 6 months thereafter.[2] Liver function tests and serum transaminase levels, including AST and ALT (SGOT and SGPT), should be performed on all patients treated with extended-release niacin/lovastatin. Levels should be evaluated at baseline, then every 6-12 weeks for the first 6 months and every 6 months thereafter. If levels elevate to 3 times the upper limit of normal the drug should be discontinued.[4] Occasional creatine kinase (CK) levels may be considered in at risk patients. If the level is 10 times the upper limit

Table 3. Treatment-emergent adverse effects in ³ 5% of patients[4,5]

Adverse Event	ER Niacin/ Lovastatin[a]	ER Niacin/ Lovastatin[b]	ER Niacin[a]	Lovastatin[a]
Total no. of patients	214	814	92	94
Cardiovascular	**163 (76%)**	--	**66 (72%)**	**24 (26%)**
Flushing	152 (71%)	--	60 (65%)	17 (18%)
Body as a whole	**104 (49%)**	--	**50 (54%)**	**42 (45%)**
Asthenia	10 (5%)	--	6 (7%)	5 (5%)
Flu syndrome	12 (6%)	--	7 (8%)	4 (4%)
Headache	20 (9%)	57 (7%)	12 (13%)	5 (5%)
Infection	43 (20%)	--	14 (15%)	19 (20%)
Pain	18 (8%)	--	3 (3%)	9 (10%)
Pain, abdominal	9 (4%)	--	1 (1%)	6 (6%)
Pain, back	10 (5%)	--	5 (5%)	5 (5%)
Digestive system	**51 (24%)**	**195 (24%)**	**26 (28%)**	**16 (17%)**
Diarrhea	13 (6%)	65 (8%)	8 (9%)	2 (2%)
Dyspepsia	6 (3%)	65 (8%)	5 (5%)	4 (4%)
Nausea	14 (7%)	65 (8%)	11 (12%)	2 (2%)
Vomiting	7 (3%)	--	5 (5%)	0
Metabolic and nutrition system	**37 (17%)**	--	**18 (20%)**	**13 (14%)**
Hyperglycemia	8 (4%)	41 (5%)	6 (7%)	6 (6%)
Musculoskeletal system	**19 (9%)**	--	**9 (10%)**	**17 (18%)**
Myalgia	6 (3%)	--	5 (5%)	8 (9%)
Skin and appendages	**3 (2%)**	--	**19 (21%)**	**11 (12%)**
Pruritus	14 (7%)	130 (16%)	7 (8%)	3 (3%)
Rash	11 (5%)	73 (9%)	11 (12%)	3 (3%)

[a] Adverse events as reported by manufacturer[4]; [b] Adverse events as reported by Kashyap et al study[5]; -- Not reported

of normal and the patient is experiencing unexplained muscle pain, myopathy is likely. The patient should stop the medication immediately if myopathy, rhabdomyolysis, or elevations in creatine kinase are present.[3] Niacin may cause a dose-related elevation in fasting blood glucose. Close monitoring of blood glucose in patients with diabetes is advised and adjustment of hypoglycemic medication may be necessary.

Adverse Effects

Flushing episodes (warmth, redness, itching, and/or tingling) due to niacin were the most common adverse effects in controlled clinical studies occurring in up to 71% of patients. Flushing caused 8% of patients to discontinue the KOS study and 10% to discontinue the Kashyap et al study.[4,5] Table 3 lists the adverse effects that occurred in greater than 5% of patients.

Contraindications

Advicor is absolutely contraindicated in children and adolescents, patients with a hypersensitivity to niacin or lovastatin, active peptic ulcer disease, active hepatic disease (including cholestasis, hepatic encephalopathy, hepatitis, jaundice, elevations in liver enzymes, etc), rhabdomyolysis, arterial bleeding, and patients who are pregnant or breast feeding. Extended-release niacin/lovastatin should be used with caution in patients with renal disease or renal failure.

Retail Cost of Therapy

Three different pharmacies (one supermarket pharmacy, one discount pharmacy, and one major chain pharmacy) were asked for their prices for Advicor # 30 in three different strengths. Table 4 lists the prices charged. The average prices for 30 tablets were $49.87 for 500/20, $58.63 for 750/20, and $63.45 for 1000/20.

Summary

Table 4. Prices for Advicor #30 at assorted pharmacies

Strength	Pharmacy A	Pharmacy B	Pharmacy C	Average
500/20	$52.95	$45.99	$50.68	$49.87
750/20	$62.95	$55.59	$57.34	$58.63
1000/20	$66.95	$59.49	$63.92	$63.45

Advicor, marketed by KOS pharmaceuticals, is the first combination oral antilipemic agent to be introduced in the United States. It is indicated for the treatment of primary hypercholesterolemia and mixed dyslipidemia for patients who have not effectively responded to lovastatin or niacin alone. This combination product is available to practitioners as another option in treating hyperlipidemia for the purposes of preventing coronary heart disease.

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Promising New Products for the Administration of Insulin

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Introduction

Based on the 58th annual American Diabetes Association Scientific Session there are 3.5 million users of injected insulin in the United States. It is estimated that 16 million Americans would benefit from exogenous insulin but refuse to do so because of painful injections. These patients run a high risk of developing complications caused by diabetes since they are not optimizing therapy to control their glycemic levels.[1]

Since the first insulin injection was given in 1922, researchers have sought to develop a less invasive route of administration. With recent advances in the development of administration devices and the manipulation of the insulin molecule, insulin-dependent diabetics may finally have a less invasive alternate route of administration. This article will focus on three such products that have shown promise in clinical trials.

Many types of dosage forms have been considered, however, because of the size of the insulin molecule, it is nearly impossible to attach it to a carrier system. Dermal insulin application is not possible. An oral tablet is not feasible because the molecule would be denatured in the stomach and there is not a specific peptide carrier in the stomach for insulin.[2] As far back as 1935, the idea of intranasal administered insulin was considered. However, low bioavailability and variability in absorption made this route less practical for insulin administration.[3]

These inhalation insulin products have advantages and disadvantages. Advantages include a completely painless delivery of insulin, delivery is uncomplicated and well tolerated by patients, less hypoglycemic events occurred in trials than with subcutaneous (subcutaneous) insulin, and the lung is capable of absorbing insulin in a reproducible, dose-dependent manner.[4] This is in contrast with insulin injections, which are affected by factors such as the site of injection, the depth of injection, the temperature and vascularity of the tissue, and

Table 1. Hb_{A1c} comparisons between trials for Inhance System

Author	# patients	Patient type	SC insulin dose	Inhalation insulin dose	HbA1c (pre-trial)	HbA1c (post-trial)
Skyler[6]	35	Type 1	--	12.2 mg	8.5%	7.9%
Skyler[6]	36	Type 1	24.8 U	--	8.5%	7.7%
Cefalu[7]	26	Type 2	35.7 U	14.6 mg	8.7%	8.0%

Milligram and Units are given as average daily dose during the trials

whether the underlying muscle is exercising or not. Disadvantages and concerns stem from the fact that, if approved, the drugs are new and thus, extensive and long-term studies have not been conducted. Clinicians point out that the growth-promoting properties of insulin and the effect of patients that smoke and/or have pulmonary diseases has not been studied. Furthermore, since inhalable insulin requires larger doses than subcutaneous insulin, cost may be a factor as well.[5]

Exubera

Exubera is an inhaled insulin product co-developed by Aventis and Pfizer. The delivery of insulin is via the Inhance System by Inhale Therapeutic Systems. Dry-powdered insulin is blister packed into different dosages. A special delivery system generates a pulse of compressed air and the insulin forms a white fog in a 210 milliliter transparent chamber that can be inhaled by deep breathing.[4] This enables patients to view the aerosol before inhalation to ensure proper dosing. This method also eliminates the need for coordination between inhalation and actuation. The insulin particles produced are small (1-3 micrograms) and reach the alveoli in the lungs, which is the site of action.

A number of phase II studies were performed evaluating the efficacy of the insulin-Inhance system. The first study consisted of 71 patients with type 1 diabetes and was conducted over three months. The study was an open-label, parallel group trial. One group continued a conventional insulin regimen with subcutaneous injections of ultralente and regular insulin while the other group was treated with ultralente subcutaneous injections and inhaled insulin.[6] The second study consisted of 26 patients with type 2 diabetes. Patients were treated with inhaled insulin before each meal and a bedtime subcutaneous dose of ultralente insulin. Prior to being treated, the patients were on stable insulin schedules of two or three injections a day.[7] Evaluation of Hb_{A1c} levels demonstrated that for both studies the inhaled insulin was equivalent, if not superior, to subcutaneous insulin (see Table 1). Preliminary data found that the inhaled insulin was well tolerated, caused no increase in hypoglycemic events or changes in pulmonary function tests.

Exubera has completed phase III testing and submission for regulatory approval is expected at the end of 2002.

AERx iDMS

AERx iDMS inhaled insulin was developed by Aradigm and NovoNordisk. This product uses the AERx System designed by Aradigm to deliver insulin from single-use dosage forms by extruding the pre-packaged solution through hundreds of precisely laser-drilled holes in a single use nozzle. This system emits a controlled, aerosolized release of insulin. The drug is delivered to the lungs at the correct flow rate as the patient breathes. The AERx senses the inspiratory flow rate, notifies the patient when to deliver the drug, the patient activates the device, then a small piston drives the insulin through the tiny holes. The aerosol particles are between two to three microns. Like Exubera, the site of action is the alveoli.

Pharmacokinetic trials were performed using AERx iDMS. A total of 18 type 1 diabetics participated in the trial. The study was a randomized, open-label, 5-period crossover trial.[8] Human regular insulin was administered subcutaneous or inhaled by AERx iDMS at different doses. Results of the study showed that inhaled insulin provided a dose-response relation that was close to linear for

Table 2. Comparisons of Products

	Exubera	AERx iDMS	Oralin
Dosage form	Dry insulin powder converted to a fog	Aerosolized liquid insulin	Dry insulin powder
Site of action	Alveoli	Alveoli	Buccal cavity
Portability/convenience	Moderate	Moderate	High
Cost	$$	$$$	$

$ = least expensive, $$$ = most expensive

insulin (AUC, Cmax) and glucose infusion rate (AUC, Cmax). The researchers also found that inhaled insulin had a more rapid onset and shorter duration of action than subcutaneous administered insulin. The authors concluded that AERx iDMS is feasible, provides a clear dose-response, and may work best for patients who need short-acting insulin to cover prandial requirements.

NovoNordisk and Aradigm have completed phase II trials. Phase III trials should commence in late 2002.

Oralin

Oralin is being developed by Generex Biotechnology based in Toronto, Canada. This product is administered by RapidMist, a metered dose inhaler (MDI), which is also developed by Generex and uses a dry insulin powder. Unlike the previous two examples, this device's site of action is the buccal cavity. The RapidMist System propels the aerosolized particles much faster than conventional MDIs, allowing deposition in the buccal cavity where it is absorbed into the bloodstream within 10 minutes. Attributes of this system over subcutaneous insulin include: rapid absorption, simple administration, precise dosing control, and bolus delivery of insulin. The insulin itself is combined with absorption enhancers, which encapsulate and protect the insulin molecule.

There have been numerous studies on Oralin at the University of Toronto and the National Research Institute in Los Angeles.[9] These studies have focused on both patients with type 1 and type 2 diabetes. The type 1 study was a double-blind, crossover study consisting of ten subjects given subcutaneous regular insulin, Oralin, or a placebo. Glucose levels were higher in the placebo group while glucose levels were comparable between the regular insulin and Oralin groups. The researchers also found that Oralin plasma concentrations increased faster than did subcutaneous regular insulin injections. However, after four hours, glucose levels were higher for subjects on Oralin due to rapid clearance from plasma when compared to subcutaneous insulin.

The type 2 study was a double-blind, crossover study that involved 16 subjects. Oralin was given in place of regular mealtime insulin injections. It concluded that Oralin can be used safely in place of insulin injections in subjects with type 2 diabetes to control postprandial hyperglycemia.

Additional sub-studies were conducted with Oralin. One study compared pre-prandial Oralin plus metformin 850 milligrams (mg) vs. placebo and metformin 850 mg. The researchers found that Oralin in combination with metformin was useful in subjects with secondary sulfonylurea failure. Another study compared 15 subjects, failing diet and exercise, with Oralin or placebo. Results suggest that Oralin can be introduced early in the treatment of recently diagnosed patients failing diet and exercise regimens. The diet and exercise study also concluded that exogenous administered Oralin can be used safely in type 2 diabetics without inducing the pancreas to produce more insulin and create down-regulation of insulin receptors. The authors hypothesized that the early introduction of Oralin may actually help preserve beta-cell function and avoid future diabetic complications.

Oralin is currently in phase III trials in Canada. Generex Biotechnology has submitted an Investigational New Drug Application (IND) to the FDA in the United States.

Oralin is the most portable and convenient of the three products discussed. The insulin is de-

livered through an MDI-styled device. The cost should not be much more than other new drugs using MDIs in the market. Exubera uses a slightly larger and more complicated device than an MDI, which might increase its cost over Oralin. AERx iDMS predictably would have the highest cost associated with their product because of the sophistication of the delivery device which is about the size of a camera. Table 2 provides a comparison of the three products.

Summary

Within the next couple of years, healthcare providers and patients can expect to see new products offering alternatives to subcutaneous insulin injections. Clinical trials have demonstrated that alternate forms of administering insulin are feasible. Patient satisfaction surveys indicate that subjects were pleased with the convenience, ease of use, and lack of social stigma of the products.[10] These products are short-acting only and should eliminate the total number of injections a day but not eliminate the need for long-acting insulin injections.

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Table 2. LDL-C mean percent change from baseline[4]

Week	Extended-release Niacin/Lovastatin N*	Dose (mg/mg)	LDL	Extended-release Niacin N*	Dose (mg)	LDL	Lovastatin N*	Dose (mg)	LDL
Baseline	57	-	190.9 mg/dL	61	-	189.7 mg/dL	61	-	185.6 mg/dL
12	47	1000/20	-30%	46	1000	-3%	56	20	-29%
16	45	1000/40	-36%	44	1000	-6%	56	40	-31%
20	42	1000/40	-37%	43	1500	-12%	54	40	-34%
28	42	2000/40	-42%	41	2000	-14%	53	40	-32%

N* = number of patients remaining in the trial at each time point.

Table 3. HDL-C mean percent change from baseline[4]

Week	Extended-release Niacin/Lovastatin N*	Dose (mg/mg)	HDL	Extended-release Niacin N*	Dose (mg)	HDL	Lovastatin N*	Dose (mg)	HDL
Baseline	57	-	45 mg/dL	61	-	47 mg/dL	61	-	43 mg/dL
12	47	1000/20	+20%	46	1000	+14%	56	20	+3%
16	45	1000/40	+20%	44	1000	+15%	56	40	+5%
20	42	1000/40	+27%	43	1500	+22%	54	40	+6%
28	42	2000/40	+30%	41	2000	+24%	53	40	+6%

N* = number of patients remaining in the trial at each time point.

Table 4. TG median percent change from baseline[4]

Week	Extended-release Niacin/Lovastatin N*	Dose (mg/mg)	TG	Extended-release Niacin N*	Dose (mg)	TG	Lovastatin N*	Dose (mg)	TG
Baseline	57	-	174 mg/dL	61	-	186 mg/dL	61	-	171 mg/dL
12	47	1000/20	-32%	46	1000	-22%	56	20	-20%
16	45	1000/40	-39%	44	1000	-23%	56	40	-17%
20	42	1000/40	-44%	43	1500	-31%	54	40	-21%
28	42	2000/40	-44%	41	2000	-31%	53	40	-20%

N* = number of patients remaining in the trial at each time point.

Table 5. Lp(a) median percent change from baseline[4]

Week	Extended-release Niacin/Lovastatin N*	Dose (mg/mg)	Lp(a)	Extended-release Niacin N*	Dose (mg)	Lp(a)	Lovastatin N*	Dose (mg)	Lp(a)
Baseline	57	-	34 mg/dL	61	-	41 mg/dL	61	-	42 mg/dL
12	47	1000/20	-9%	46	1000	-8%	56	20	+8%
16	45	1000/40	-9%	44	1000	-12%	56	40	+8%
20	42	1000/40	-17%	43	1500	-22%	54	40	+6%
28	42	2000/40	-22%	41	2000	-32%	53	40	0%

N* = number of patients remaining in the trial at each time point.