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Mipomersen, an Apolipoprotein B Synthesis Inhibitor, Reduces Atherogenic Lipoproteins in Patients With Severe Hypercholesterolemia at High Cardiovascular Risk

A Randomized, Double-Blind, Placebo-Controlled Trial

Gregory S. Thomas, MD, MPH,*† William C. Cromwell, MD,‡ Shariq Ali, PHD,§ Wai Chin, PHD,§ JoAnn D. Flaim, PHD,‖ Michael Davidson, MD¶

Irvine, Long Beach, and Carlsbad, California; Raleigh, North Carolina; Cambridge, Massachusetts; and Chicago, Illinois

Objectives This study sought to examine the efficacy and safety of mipomersen for reducing atherogenic lipids and lipoproteins in patients with hypercholesterolemia.

Background Many patients on lipid-lowering therapies remain unable to achieve target low-density lipoprotein (LDL) cholesterol levels. Mipomersen, an antisense oligonucleotide inhibitor of apolipoprotein B, reduces LDL cholesterol and atherogenic lipoproteins.

Methods This randomized, double-blind, multicenter study enrolled 158 patients with baseline LDL cholesterol levels ≥100 mg/dl with, or at high risk for, coronary heart disease who were receiving maximally tolerated lipid-lowering therapy. Patients received weekly subcutaneous mipomersen 200 mg (n = 105) or placebo (n = 52) for 26 weeks, with a 24-week follow-up period. Randomization was stratified by type 2 diabetes status.

Results Sixty mipomersen and 44 placebo patients completed treatment. Mean baseline LDL cholesterol levels were 122.7 and 122.6 mg/dl in the placebo and mipomersen patients, respectively. Mipomersen reduced LDL cholesterol by −36.9% compared with placebo at −4.5% ($p < 0.001$). Target LDL cholesterol <100 mg/dl was attained in 76% of mipomersen and 38% of placebo patients. Mipomersen also significantly reduced apolipoprotein B (−38%) and lipoprotein(a) (−24%) ($p < 0.001$). Common adverse events included injection site reactions (78% with mipomersen, 31% with placebo) and flu-like symptoms (34% with mipomersen, 21% with placebo). Elevations in transaminases and liver fat also occurred in some patients, and these levels returned toward baseline after treatment cessation.

Conclusions Mipomersen significantly reduced LDL cholesterol, apolipoprotein B, and lipoprotein(a) in patients with hypercholesterolemia with, or at risk for, coronary heart disease not controlled by existing therapies. (Safety and Efficacy of Mipomersen [ISIS 301012] as Add-On Therapy in High Risk Hypercholesterolemic Patients; NCT00770146) (J Am Coll Cardiol 2013;62:2178–84) © 2013 by the American College of Cardiology Foundation

Low-density lipoprotein (LDL) is key in the pathogenesis of coronary heart disease (CHD). LDL particles enter the arterial wall through a gradient-driven process. Once inside the intima, LDL particles that bind to arterial wall proteoglycans are retained, oxidized, and subsequently taken up by macrophages to form foam cells (1). LDL particle–lowering agents such as statins significantly reduce CHD risk (2,3). National Cholesterol Education Program Adult Treatment Panel guidelines emphasize the importance of LDL

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From the *Long Beach Memorial Medical Center, Long Beach, California; †University of California, Irvine, Irvine, California; ‡Lipoprotein & Metabolic Disorders Institute, Raleigh, North Carolina; §Genzyme Corporation, Cambridge, Massachusetts; ‖Isis Pharmaceuticals, Carlsbad, California; and the ¶University of Chicago, Chicago, Illinois. This study was sponsored by Isis Pharmaceuticals and Genzyme Corporation, a sanofi-aventis company. Dr. Thomas is a consultant for Genzyme, a sanofi-aventis company; and has received research grant support from Genzyme, Regeneron, and sanofi-aventis. Dr. Cromwell is a consultant for Genzyme/Isis, LabCorp, and Health Diagnostic Laboratory; has received research grant support from Isis Pharmaceuticals; and is a speaker for Abbott, Kowa, Merck, and LipoScience. Drs. Ali and Chin are Genzyme employees. Dr. Flaim is an Isis Pharmaceuticals employee. Dr. Davidson is a consultant for Genzyme and Sanofi; and has received research grants from Isis Pharmaceuticals, Genzyme, sanofi-aventis, Regeneron, and Amgen.

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management to reduce CHD risk. Among high-risk patients with known CHD, the guidelines recommend an LDL cholesterol level of <100 mg/dl (3). However, conventional lipid-lowering therapies often result in insufficient LDL cholesterol reductions, even when administered at maximally tolerated doses (4).

Apolipoprotein B (apoB) is an essential component of very-low-density lipoprotein (VLDL), intermediate-density lipoprotein, LDL, and lipoprotein(a) (Lp[a]), with 1 molecule of apoB present in each lipoprotein particle. ApoB is constitutively expressed in the liver. The consequences of pharmacologic inhibition of apoB synthesis are unknown and include the potential of hepatic compensation via increased beta oxidation of hepatic lipid, as well as steatosis. Mipomersen, an antisense oligonucleotide, decreases apoB synthesis by inhibition of messenger ribonucleic acid translation (Fig. 1) (5–7). Mipomersen has significantly reduced LDL, apoB, and Lp(a) in patients with homozygous familial hypercholesterolemia (FH) and moderate or severe heterozygous FH (8–10). We evaluated the safety and efficacy of mipomersen compared with placebo in patients with hypercholesterolemia with, or at high risk for, CHD already receiving a maximally tolerated lipid-lowering regimen. This is the first phase 3 evaluation of mipomersen in patients without FH.

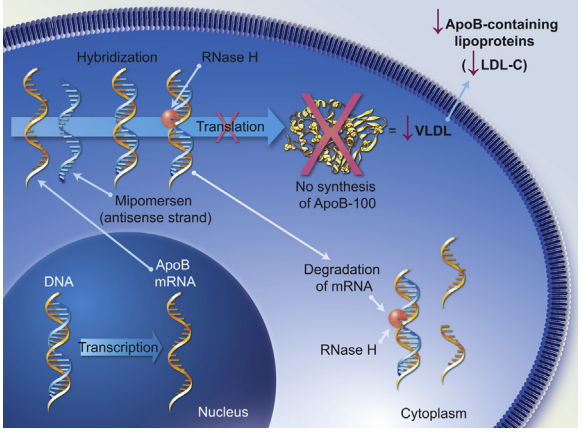

Figure 1 **Mipomersen Mechanism of Action**

Mipomersen is a second-generation antisense oligonucleotide (ASO) that inhibits the synthesis of apolipoprotein B-100 (apoB-100) by binding to the cognate apoB messenger ribonucleic acid (mRNA) through Watson-Crick base pairs to form a substrate for ribonuclease H (RNase H), a ubiquitously expressed nuclease, which preferentially hydrolyzes the ribonucleic acid (RNA) strand of a RNA:deoxyribonucleic acid (DNA) duplex. Second-generation ASOs are synthetic phosphorothioate-modified oligodeoxynucleotides with 2′-O-(2-methoxyelthyl)-D-ribose (2′-MOE) modified nucleotides incorporated into a portion of the ASO for increased affinity toward the target RNA and greater resistance to exonuclease and endonuclease activity, while maintaining a 2′-deoxy domain to support RNase H activity. The net result from incorporation of the 2′-MOE modification is an increase in antisense drug potency and durability and an associated attenuation of off-target class effects. Inhibition of apoB mRNA translation takes place in the cytoplasm. Binding of mipomersen to apoB mRNA and RNase H activit, can occur either in the nucleus or cytoplasm. LDL-C = low-density lipoprotein cholesterol; VLDL = very-low-density lipoprotein.

Abbreviations and Acronyms

AE = adverse event(s)
ALT = alanine aminotransferase
apoB = apolipoprotein B
CHD = coronary heart disease
FH = familial hypercholesterolemia
FLS = flu-like symptoms
HDL = high-density lipoprotein
ISR = injection site reaction
LDL = low-density lipoprotein
Lp(a) = lipoprotein(a)
T2DM = type 2 diabetes mellitus
VLDL = very-low-density lipoprotein

Methods

This prospective, randomized, double-blind, placebo-controlled study was conducted at 62 U.S. centers between November 2008 and October 2010. After providing informed consent and undergoing screening, eligible patients were randomized (2:1) to mipomersen 200 mg or placebo. Randomization was stratified so that a minimum number of patients (40%) would have type 2 diabetes mellitus (T2DM). Medication was administered as a single, subcutaneous injection once weekly for 26 weeks, allowing assessment at steady-state levels of mipomersen given its half-life of approximately 31 days (7). Patients then entered a 24-week safety follow-up. This trial (NCT00770146) was approved by all ethics boards and conducted according to Good Clinical Practice and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines.

Men and nonpregnant, nonlactating women age ≥18 years with hypercholesterolemia (fasting LDL cholesterol ≥100 mg/dl, triglyceride <200 mg/dl) with, or at high risk for, CHD (per National Cholesterol Education Program Adult Treatment Panel III guidelines) were eligible (3). At screening, all patients were at stable weights, on low-fat diets, and receiving lipid-lowering regimens that included a maximally tolerated statin dose. Major exclusion criteria included significant cardiovascular or cerebrovascular events within 24 weeks of screening, congestive heart failure, type 1 diabetes, uncontrolled hypertension, any disorder known to predispose to secondary hyperlipidemia, or a history of renal or hepatic disease. Patients were not permitted to alter their lipid-lowering regimens for 28 weeks.

Patients were evaluated at baseline and every other week for the first 9 weeks, every 4 to 5 weeks for the remainder of treatment, and 4 times during follow-up. Laboratory assessments and statistical analysis were similar to a previously published trial (8), as described in Online Appendix A. The primary outcome was percent reduction in LDL cholesterol from baseline to the primary efficacy timepoint, defined as the post-baseline visit closest to 14 days after the last dose of medication (week 28). Additional efficacy outcomes included percent changes in apoB, total cholesterol, non–high-density lipoprotein (HDL) cholesterol, triglyceride, Lp(a), VLDL cholesterol, LDL/HDL ratio,

apolipoprotein A-I, and HDL cholesterol. An exploratory analysis of lipoprotein particles occurred.

Results

Online Figure 1 displays patient flow. At baseline, among patients who received the study treatment (n = 157), 72% had metabolic syndrome (11), 56% had T2DM, and 52% had CHD or other atherosclerotic disease. All patients were receiving lipid-lowering medications, including statins; 43% were receiving the maximal U.S. Food and Drug Administration–approved statin dose. Patients were typically middle aged, white, and overweight, with a mean body mass index of 30.4 ± 4.6 kg/m^2 (Table 1). Groups were well balanced in demographics and baseline characteristics; there were no clear differences between patients with and without T2DM.

Mean LDL cholesterol was elevated at baseline: 122.6 ± 31.7 mg/dl in the mipomersen group and 122.7 ± 38.6 mg/dl in the placebo group (Table 2). At the primary efficacy timepoint, mipomersen-treated patients experienced significantly greater reductions from baseline in mean LDL cholesterol (−36.9%) than placebo-treated patients (−4.5%) ($p < 0.001$) (Fig. 2). Moreover, 76% of mipomersen versus 38% of placebo patients attained LDL cholesterol <100 mg/dl at the primary efficacy timepoint, while 51% of mipomersen versus 8% of placebo attained LDL cholesterol <70 mg/dl. Substantial reductions in mean LDL cholesterol (−17%) were seen by week 5, with near maximal effects observed by week 17, consistent with a half-life of approximately 31 days (7); after treatment completion (week 26), LDL cholesterol gradually increased and returned to baseline by week 50 (Fig. 3).

Table 1 Demographics and Baseline Characteristics

Parameter*	Placebo (n = 52)	Mipomersen (n = 105)
Age (yrs)	59.3 ± 9.5	59.3 ± 10.0
Men/women	29 (55.8%)/23 (44.2%)	52 (49.5%)/53 (50.5%)
Race/ethnicity		
White	40 (76.9%)	83 (79.0%)
Black	11 (21.2%)	20 (19.0%)
Hispanic or Latino	9 (17.3%)	16 (15.2%)
American Indian or Alaskan Native	1 (1.9%)	1 (1.0%)
Other	0 (0.0%)	1 (1.0%)
BMI (kg/m^2)	30.0 ± 4.4	30.7 ± 4.6
Metabolic syndrome†	40 (76.9%)	73 (69.5%)
Current smoker	11 (21.2%)	18 (17.1%)
T2DM	30 (57.7%)	58 (55.2%)
Cardiovascular history		
Angina	5 (9.6%)	9 (8.6%)
CHD‡	21 (40.4%)	52 (49.5%)
Other clinical atherosclerotic disease§	3 (5.8%)	11 (10.5%)
Lipid-lowering regimen		
Any statin	52 (100.0%)	105 (100.0%)
Maximal FDA-approved statin dose	20 (38.5%)	43 (41.0%)
Statin plus other	32 (61.5%)	58 (55.2%)

Values are mean ± SD or n (%). †Metabolic syndrome was determined according to the American Heart Association and the National Heart, Lung, and Blood Institute definition (11). ‡Includes myocardial infarction, coronary artery bypass graft surgery, percutaneous coronary intervention, and coronary artery disease without event. §Includes peripheral artery disease, abdominal aortic aneurysm, and carotid artery disease.

BMI = body mass index; CHD = coronary heart disease; FDA = U.S. Food and Drug Administration; T2DM = type 2 diabetes mellitus.

The effect of mipomersen was greater in women and patients older than 59 years (mean/median age) compared with men and patients younger than 59 years, whose lipid lowering was still clinically meaningful and statistically significant. The mean percent changes in LDL cholesterol were −32.7 ± 25% and −41.2 ± 28.3% for male and female mipomersen patients, respectively, compared with placebo at −8.6 ± 26.6% and −1.1 ± 19.7%. The mean percent changes in LDL cholesterol were −29.8 ± 30.3% and −41.8 ± 23.3% for mipomersen patients younger and older than 59 years, respectively, compared with −7.4 ± −25.2% and −1.9 ± 23.5% for placebo. Baseline LDL cholesterol and race did not influence treatment effect.

Reductions from baseline to the primary efficacy timepoint in apoB, non-HDL cholesterol, and LDL/HDL ratio were similar (about 37%) to those in LDL cholesterol; reductions in total cholesterol, triglyceride, and VLDL cholesterol were slightly smaller (about 25%) (Table 2, Fig. 3). Lp(a), not typically affected by statins, ezetimibe, or bile acid sequestrants (12), was also reduced (26% with mipomersen, 0% with placebo). A small decrease in apolipoprotein A-I was observed with mipomersen. No significant difference was noted between treatment groups in HDL cholesterol or high-sensitivity C-reactive protein. As with LDL cholesterol, all lipids and lipoproteins gradually returned to baseline after treatment cessation. Baseline levels of lipids and lipoproteins and changes in lipids and lipoproteins associated with mipomersen treatment were similar regardless of diabetic status (Table 3).

In an exploratory analysis, lipoprotein particle concentrations were determined using nuclear magnetic resonance spectroscopy. As in previous studies (13,14) greater reductions were noted in the number of small (−542.5 nmol/l) versus large LDL particles (−79.7 nmol/l) in the mipomersen group; no meaningful changes occurred in the placebo group (small, −54.1 nmol/l; large, −22.6 nmol/l).

The most common adverse events (AEs) related to tolerability were injection site reactions (ISRs) and flu-like symptoms (FLS). The incidence of ISRs was greater with mipomersen (78.1%) compared with placebo (30.8%), as was the incidence of FLS (34.3% vs. 21.2%) (Table 4). The most common AEs related to safety were elevated liver enzyme levels and increased liver fat. Alanine aminotransferase (ALT) increased in more mipomersen patients compared with placebo but trended toward baseline after week 26 (Fig. 4). Ten mipomersen patients had ALT levels ≥3 times the upper limit of normal on 2

Table 2 Effect of Treatment on Lipid Parameters

Parameter	Placebo (n = 50)			Mipomersen (n = 101)		
	Baseline	PET	% Change, Baseline to PET	Baseline	PET	% Change, Baseline to PET*
LDL cholesterol (mg/dl)	122.7 ± 38.6	113.3 ± 35.1	−4.5 ± 24.22	122.6 ± 31.7	75.3 ± 32.4	−36.9 ± 26.85
ApoB (mg/dl)	115.7 ± 30.1	109.1 ± 27.2	−4.1 ± 18.09	117.1 ± 25.2	72.8 ± 30.7	−37.5 ± 23.59
Lp(a) (mg/dl)	31 (11, 76)	33 (10, 78)	0.0 (−16.0, 17.6)	36 (10, 85)	21 (6, 54)	−25.6 (−40.0, −7.8)
TC (mg/dl)	200.0 (42.1)	192.2 (38.3)	−2.7 ± 14.58	202.6 ± 36.8	147.4 ± 39.9	−26.4 ± 18.65
Non-HDL cholesterol (mg/dl)	151.6 ± 44.4	143.2 ± 38.7	−3.1 ± 20.43	151.8 ± 35.1	96.3 ± 38.3	−35.7 ± 23.75
HDL cholesterol (mg/dl)	48.4 ± 15.9	48.9 ± 16.1	2.2 ± 16.44	50.8 ± 12.0	51.1 ± 12.3	2.2 ± 17.99
TG (mg/dl)	144.6 ± 66.1	152.9 ± 97.5	11.3 ± 53.26	146.7 ± 65.3	105.0 ± 55.7	−25.2 ± 29.21
VLDL cholesterol (mg/dl)	28.9 ± 13.2	29.9 ± 16.3	10.7 ± 53.83	29.2 ± 12.1	21.0 ± 11.1	−25.3 ± 28.75
ApoA1 (mg/dl)	150.8 ± 30.5	147.8 ± 27.3	−1.0 ± 11.16	156.8 ± 25.4	146.8 ± 24.5	−5.6 ± 12.56
LDL/HDL ratio	2.8 ± 1.4	2.5 ± 1.1	−5.27 ± 25.31	2.5 ± 0.9	1.5 ± 0.8	−37.36 ± 27.2

Values are mean ± SD or median (25th percentile, 75th percentile). *$p < 0.001$, mipomersen versus placebo, except HDL cholesterol ($p = 0.977$) and apoA1 ($p = 0.032$). P values were calculated for the between-group comparisons of percent changes from baseline to PET, which were obtained using Student *t* tests for all parameters except LDL cholesterol, apoB, non-HDL cholesterol, TG, and VLDL cholesterol, for which the Wilcoxon rank sum test was used because of deviations from normality.

ApoA1 = apolipoprotein A1; apoB = apolipoprotein B; HDL = high-density lipoprotein; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); PET = primary efficacy timepoint; TC = total cholesterol; TG = triglycerides; VLDL = very-low-density lipoprotein.

consecutive measures at least 7 days apart; no concomitant increases in bilirubin or changes in liver synthetic function occurred.

The mean of absolute changes in average liver fat fraction from baseline to end of treatment was 15.9 ± 11.2% for mipomersen (n = 48) versus 0.6 ± 7.1% for placebo (n = 33) (Table 5). The mean liver fat fraction remained unchanged at the end of the week 24 follow-up in the placebo group (1.3 ± 7.7%) and decreased in the mipomersen group (5.1 ± 7.5%). Results were similar when summarized by diabetes status. Post-hoc analyses were performed to explore correlations in liver parameters (Online Figs. 2A to 2D). As expected, in the mipomersen group, there was a strong correlation between the percent changes in apoB and LDL cholesterol levels from baseline to the primary efficacy timepoint (r = 0.95). Weaker associations were observed between percentage change in apoB and change in liver fat fraction (r = −0.52), percent change in apoB and maximal ALT level (r = −0.44), and change in liver fat fraction and maximal ALT level (r = 0.52). Except for the close association of LDL cholesterol versus apoB (r = 0.80), there was no correlation in the placebo group.

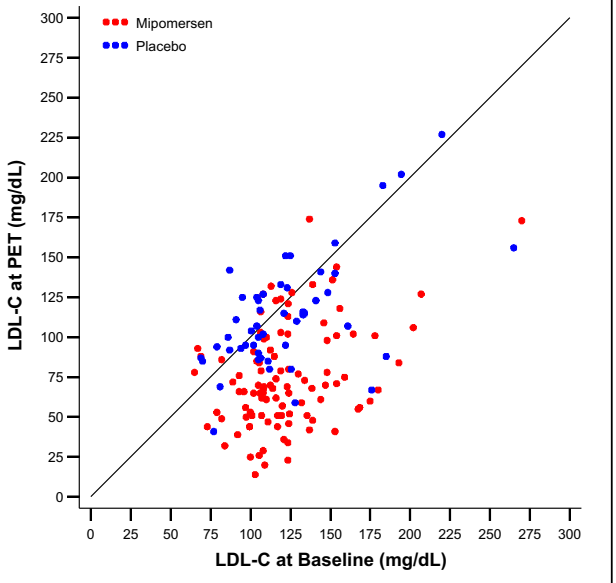

Figure 2 Change in LDL-C by Patient

LDL-C = low-density lipoprotein cholesterol; PET = primary efficacy timepoint.

Of the 54 patients who discontinued, 45 were in the mipomersen group and 9 in the placebo group. AEs were responsible for 28 (18%) of the discontinuations: 26 (25%) in the mipomersen group (7 because of liver enzyme elevations and other AEs and 7 because of ISRs) and 2 (4%) in the placebo group (Online Appendix B). Discontinuation was approximately 11% of patients in both groups secondary to withdrawal of consent. Serious AEs occurred in 7 (7%) mipomersen and 4 (8%) placebo patients. One death occurred in each group. The placebo patient died during the treatment period from acute myocardial infarction and cardiogenic shock. The mipomersen patient was admitted to the hospital with acute myocardial infarction and pneumonia 149 days after completing treatment with mipomersen; the patient died the following day from acute liver failure. The case was adjudicated by 2 independent hepatologists, who concluded that the cause of death was hepatic failure due to acetaminophen toxicity and was unrelated to mipomersen.

Mipomersen had no adverse effect on renal function (serum creatinine, estimated glomerular filtration rate, blood urea nitrogen), muscle (creatinine kinase), hematology, glucose, or blood pressure, nor were any clinically meaningful safety findings or trends in weight, vital signs, or electrocardiographic parameters noted. T2DM status did not alter the safety profile in these parameters or in

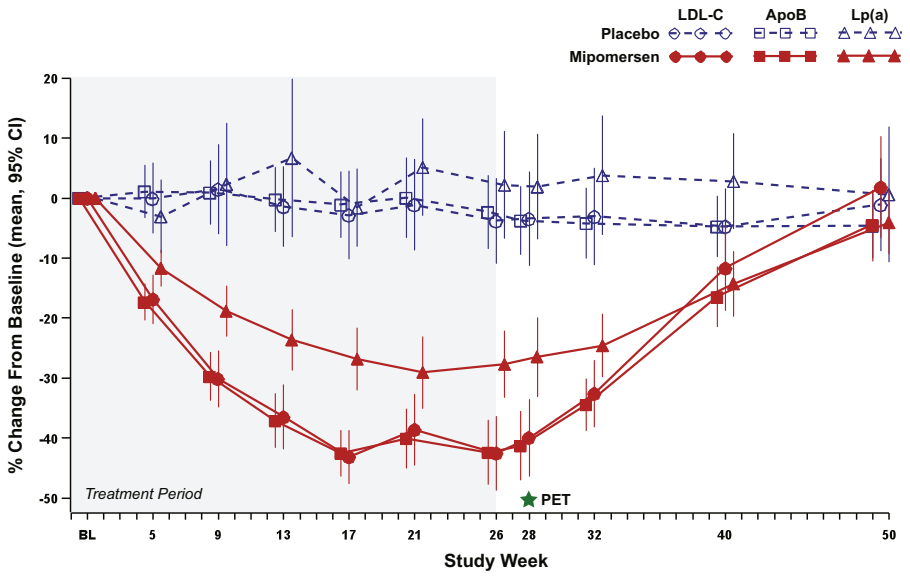

Figure 3 Changes in Lipoproteins

Changes in low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), and lipoprotein(a) (Lp[a]) over time. CI = confidence interval; PET = primary efficacy timepoint or 2 weeks from end of treatment for completers.

relation to ISRs, FLS, or hepatic transaminase elevation or steatosis.

Discussion

This is the first phase 3 study of mipomersen in non-FH patients with high cardiovascular risk due to prior CHD events and/or concurrent T2DM. Mipomersen 200 mg weekly significantly reduced LDL cholesterol (by 36.9%) compared with placebo (by 4.5%); the onset of action was as early as 5 weeks. Consistent with its mechanism of action, reductions in total cholesterol, non-HDL cholesterol, LDL/HDL ratio, triglyceride, VLDL cholesterol, and Lp(a) were also sizable; these effects were similar in patients with diabetes and greater in women and older patients. The mipomersen dropout rate was 43%; AEs accounted for 25% and included ISRs, FLS, and ALT increases. The placebo dropout rate was 17%; AEs accounted for 4%. AEs affecting tolerability included ISRs and FLS. ISRs did not occur at every injection site or in all patients; 20% of mipomersen patients had no ISRs. Anecdotally, ISRs lessened with pre-dose oral diphenhydramine, icing, or topical lidocaine, and FLS decreased with pre-dose nonsteroidal anti-inflammatory drugs.

Either altering cholesterol secretion from the liver, as would be expected by lowering the synthesis of apoB, or another unspecified effect resulted in a mean change of 40.9 ± 51.4 U/l in ALT from baseline to treatment end. Mean ALT decreased to near baseline at the end of the 24-week treatment follow-up. Hepatic fat content and ALT

Table 3 Effect of Treatment on Lipid Parameters in Patients With and Without Diabetes

	Placebo (Diabetic, n = 29; Nondiabetic, n = 21)			Mipomersen (Diabetic, n = 56; Nondiabetic, n = 45)		
Subgroup Parameter	**Baseline**	**PET**	**% Change, Baseline to PET**	**Baseline**	**PET**	**% Change, Baseline to PET***
Diabetic						
LDL cholesterol (mg/dl)	118.7 ± 31.8	109.8 ± 28.5	−4.89 ± 19.4	115.5 ± 22.2	67.0 ± 28.3	−40.53 ± 26.51
ApoB (mg/dl)	113.4 ± 25.8	107.6 ± 23.1	−3.56 ± 14.86	113.4 ± 18.9	67.1 ± 28.2	−40.89 ± 22.26
Lp(a) (mg/dl)	49 (12, 98)	41 (15, 105)	0.0 (−16.0, 13.8)	45 (14, 90)	34 (10, 61)	−27.9 (−43.7, −8.0)
Nondiabetic						
LDL cholesterol (mg/dl)	128.1 ± 46.8	118.1 ± 42.9	−4.04 ± 30.15	131.5 ± 38.9	85.6 ± 34.5	−32.44 ± 26.88
ApoB (mg/dl)	119.0 ± 35.7	111.1 ± 32.5	−4.83 ± 22.17	121.7 ± 31.0	80.0 ± 32.6	−33.33 ± 24.76
Lp(a) (mg/dl)	22 (11, 66)	24 (10, 69)	7.1 (−14.6, 18.8)	22 (6, 71)	13 (5, 39)	−25.0 (−37.6, 0.0)

Values are mean ± SD or median (25th percentile, 75th percentile). *$p < 0.001$, mipomersen versus placebo. P values were obtained using Student *t* tests for LDL cholesterol and apoB in both subgroups and Lp(a) in the nondiabetic subgroup. P values were obtained by the Wilcoxon rank sum test for Lp(a) in the diabetic subgroup because of deviations from normality.

Abbreviations as in Table 2.

Table 4 Adverse Events Reported and Laboratory Abnormalities of Interest

Adverse Event	Placebo (n = 52)	Mipomersen (n = 105)
On-treatment adverse events		
All events	42 (80.8%)	97 (92.4%)
Injection site reaction*	16 (30.8%)	82 (78.1%)
Flu-like symptoms†	11 (21.2%)	36 (34.3%)
ALT increased; LFT abnormality	7 (13.5%)	32 (30.5%)
Hepatic steatosis	2 (3.8%)	11 (10.5%)
ALT elevations on treatment‡		
≥3 × ULN and <5 × ULN	0 (0.0%)	10 (9.5%)
≥5 × ULN and <10 × ULN	0 (0.0%)	4 (3.8%)
≥10 × ULN	0 (0.0%)	1 (1.0%)
ALT ≥3 × ULN, 2 consecutive results ≥7days apart	0 (0.0%)	10 (9.5%)
≥3 × ULN in presence of bilirubin > ULN	0 (0.0%)	0 (0.0%)

Values are n (%). *Injection site reactions included injection site pain, erythema, pruritus, discoloration, hematoma, nodule, swelling, warmth, hemorrhage, edema, rash, induration, reaction, vesicles, discomfort, inflammation, recall reaction, urticaria, dryness, exfoliation, pallor, and papule. †Flu-like symptoms included influenza-like illness, influenza, pyrexia, chills, myalgia, arthralgia, malaise, and fatigue. ‡Not all laboratory abnormalities were reported as adverse events.
ALT = alanine aminotransferase; LFT = liver function test; ULN = upper limit of normal.

were correlated (r = 0.52) with decreasing apoB, which was strongly correlated with decreasing LDL (r = 0.95). Mean hepatic fat content decreased to near normal by 24 weeks after treatment. It is not known if liver adaptation with the potential to normalize hepatic fat would occur if mipomersen had been continued longer. Adaptation has been observed in mice receiving murine apoB antisense oligonucleotide, whereby compensatory changes occur in pathways of hepatic lipogenesis and fatty acid oxidation (15). Further to this observation, an interim analysis of the 2-year mipomersen open-label extension trial found hepatic fat content to increase during the first year in some patients but to stabilize or decrease with continued treatment (16).

In the present study, which included patients with diabetes, there was no indication of clinical sequelae associated with increases in ALT levels and/or liver fat content. Liver biopsies obtained from mipomersen-treated subjects in other studies have confirmed steatosis and found minimal inflammation with little to no fibrosis (17). By extension, some but not all patients with familial hypobetalipoproteinemia, a lifelong condition of reduced apoB levels, have steatotic livers. This secondary condition is not associated with insulin resistance (18,19).

In this study, fewer patients completed treatment compared with phase 3 trials of similar designs enrolling patients with FH (8–10). One theory may be a reduced sense of treatment urgency by physicians treating patients without known genetic diseases and with lower baseline LDL cholesterol levels. Additional safety studies in this population and others will be necessary to fully explain high dropout rates and potential opportunities to mitigate the occurrence of AEs. A gradual increase in the dose of mipomersen is being evaluated, for example, in the Study of the Safety and Efficacy of Two Different Regimens of Mipomersen in Patients With Familial Hypercholesterolemia and Inadequately Controlled Low-Density Lipoprotein Cholesterol in patients with heterozygous FH (NCT01475825). At this time, mipomersen is approved for the treatment of homozygous FH. The clinical development plan remains focused on patients with genetically derived hypercholesterolemia, with the greatest therapeutic potential in patients with refractory FH.

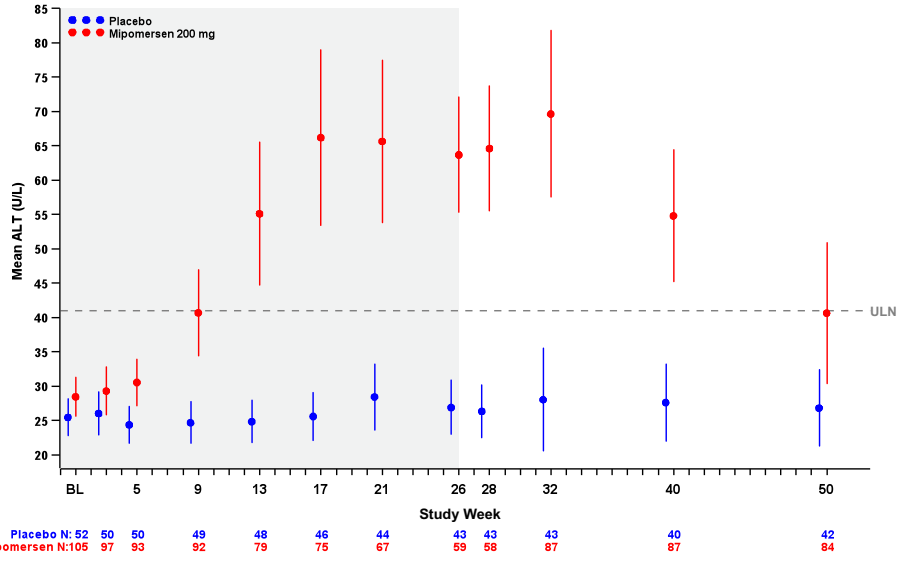

Figure 4 Change in ALT

Change in mean alanine aminotransferase (ALT) over time. BL = baseline; ULN = upper limit of normal.

Table 5 Change From Baseline in Liver Fat Fraction by Diabetes Status and Treatment Cohort

	Placebo		Mipomersen	
	Diabetic (n = 30)	Nondiabetic (n = 22)	Diabetic (n = 58)	Nondiabetic (n = 47)
Baseline	2.7 ± 7.4 (n = 26)	3.4 ± 6.9 (n = 18)	3.9 ± 7.4 (n = 45)	0.8 ± 6.0 (n = 41)
Change from baseline to end of treatment	1.3 ± 8.7 (n = 18)	-0.2 ± 8.6 (n = 15)	17.5 ± 13.5 (n = 24)	14.3 ± 8.3 (n = 24)
Change from baseline to end of off-treatment follow-up	0.5 ± 7.5 (n = 16)	2.4 ± 8.1 (n = 11)	5.7 ± 9.0 (n = 31)	4.4 ± 5.3 (n = 27)

Values for baseline liver fat fraction are mean ± SD. Changes in liver fat fraction are mean nominal change ± SD in percentage points. Liver MRI was not available for all patients for reasons such as unreadable discs, inappropriate MRI settings, metal implants, and claustrophobia.

Conclusions

Mipomersen represents a first-in-class injectable antisense therapy and provides the opportunity to use novel antisense technology to modulate messenger ribonucleic acid translation without altering deoxyribonucleic acid. Mipomersen, when added to lipid-lowering therapy, significantly decreased LDL cholesterol, apoB, Lp(a), and other atherogenic lipoproteins, potentially providing a new treatment option for patients. The relatively high discontinuation rate attributed to ISRs and FLS should encourage clinicians to focus on managing patient expectations.

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Reprint requests and correspondence: Dr. Gregory S. Thomas, MemorialCare Heart & Vascular Institute, Long Beach Memorial Medical Center, 2801 Atlantic Avenue, Long Beach, California 90806. E-mail: gthomas1@memorialcare.org.

REFERENCES

1. Nielsen L. Transfer of low density lipoprotein into the arterial wall and risk of atherosclerosis. Atherosclerosis 1996;123:1–15.
2. Tabas I, Williams KJ, Boren J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. Circulation 2007;116:1832–44.
3. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110:227–9.
4. Grigore L, Norata GD, Catapano AL. Combination therapy in cholesterol reduction: focus on ezetimibe and statins. Vasc Health Risk Manag 2008;4:267–8.
5. Tavridou A, Ragia G, Manolopoulos VG. Emerging targets for the treatment of dyslipidemia. Curr Med Chem 2011;18:909–12.
6. Ricotta DN, Frishman W. Mipomersen: a safe and effective antisense therapy adjunct to statins in patients with hypercholesterolemia. Cardiol Rev 2012;20:90–5.
7. Kastelein JJ, Wedel MK, Baker BF, et al. Potent reduction of apolipoprotein B and low-density lipoprotein cholesterol by short-term administration of an antisense inhibitor of apolipoprotein B. Circulation 2006;114:1729–35.
8. Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet 2010;375:998–1006.
9. Stein EA, Dufor R, Gagne C, et al. Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease. Circulation 2012;126:2283–92.
10. McGowan M, Tardif JC, Ceska R, et al. Randomized, placebo-controlled trial of mipomersen in patients with severe hypercholesterolemia receiving maximally tolerated lipid-lowering therapy. PLoS ONE 2012;7:e49006.
11. Grundy SM, Cleeman JI, Daniels SR, et al. American Heart Association; National Heart, Lung, and Blood Institute. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735–52.
12. McKenney JM, Jones PH, Bays HE, et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). Atherosclerosis 2007;192:432–7.
13. Cromwell W, Dufour R, Gagne C, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, reduces small LDL particle number and increases LDL particle size in patients with heterozygous familial hypercholesterolemia and coronary artery disease. Circulation 2010;122:A19931.
14. Cromwell WC, Santos RD, Blom DJ, et al. Mipomersen, an apoB synthesis inhibitor, preferentially reduces small LDL particle number and increases LDL particle size in HoFH patients. Atheroscler Suppl 2010;11:107–8.
15. Lee RG, Fu W, Graham MJ, et al. Comparison of the pharmacological profiles of murine antisense oligonucleotides targeting apolipoprotein B and microsomal triglyceride transfer protein. J Lipid Res 2013;54:602–14.
16. Duell PB, Santos RD, East C, et al. Long-term safety and efficacy of mipomersen in patients with familial hypercholesterolemia uncontrolled by maximally tolerated lipid lowering therapy. J Clin Lipidol 2012;6:291.
17. Visser ME, Wagener G, Baker BF, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, lowers LDL cholesterol in high risk-statin intolerant patients: a randomized, double-blind, placebo-controlled trial. Eur Heart J 2012;33:1142–9.
18. Amaro A, Fabbrini E, Kars M, et al. Dissociation between intrahepatic triglyceride content and insulin resistance in familial hypobetalipoproteinemia. Gastroenterol 2010;139:149–53.
19. Visser ME, Lammers NM, Nederveen AJ, et al. Hepatic steatosis does not cause insulin resistance in people with familial hypobetalipoproteinaemia. Diabetologia 2011;54:2113–21.

Key Words: antisense oligonucleotides ■ apolipoprotein B ■ cholesterol inhibitors ■ hypolipidemic agents ■ lipid-regulating agents.

APPENDIX

For a description of laboratory assessments and statistical analysis, a list of patients discontinuing because of adverse events, and a list of study investigators, please see the online version of this article.