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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

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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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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.

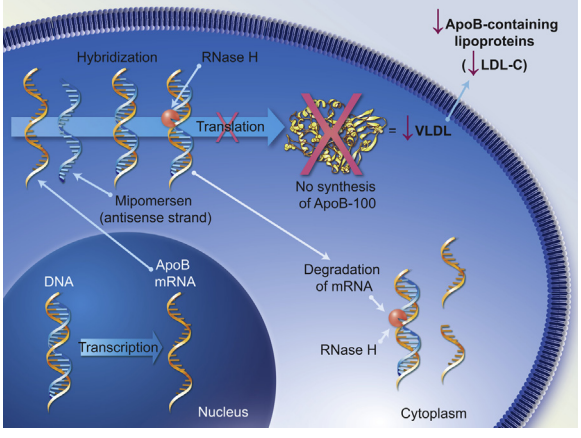

Figure 1 **Mipomersen Mechanism of Action**

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,