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Mipomersen preferentially reduces small low-density lipoprotein particle number in patients with hypercholesterolemia

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BACKGROUND: Because of variability in lipoprotein cholesterol content, low-density lipoprotein (LDL) cholesterol frequently underrepresents or overrepresents the number of LDL particles. Mipomersen is an antisense oligonucleotide that reduces hepatic production of apolipoprotein B–100, the sole apolipoprotein of LDL.

OBJECTIVE: To characterize the effects of mipomersen on lipoprotein particle numbers as well as subclass distribution using nuclear magnetic resonance (NMR) spectroscopy.

METHODS: We compared the tertiary results for the direct measurement of LDL particle numbers by NMR among 4 placebo-controlled, phase 3 studies of mipomersen that had similar study designs but different patient populations: homozygous familial hypercholesterolemia (HoFH), severe hypercholesterolemia, heterozygous familial hypercholesterolemia with established coronary artery disease, or hypercholesterolemia with high risk for coronary heart disease (HC-CHD).

RESULTS: HoFH patients had the highest median total LDL particles at baseline compared with HC-CHD patients, who had the lowest. At baseline, the HoFH population uniquely had a greater mean percentage of large LDL particles (placebo, 60.2%; mipomersen, 54.9%) compared with small LDL particles (placebo, 33.1%; mipomersen, 38.9%). In all 4 studies, mipomersen was associated with greater reductions from baseline in the concentrations of small LDL particles compared with those of large LDL particles, and both total LDL particles and small LDL particles were statistically significantly reduced.

CONCLUSIONS: Mipomersen consistently reduced all LDL particle numbers and preferentially reduced the concentration of small LDL particles in all 4 phase 3 studies.

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The treatment of hypercholesterolemia has been greatly advanced by the use of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, which became widely available in the 1990s.[1] However, in individuals with severe hypercholesterolemia (Severe-HC),

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particularly those with familial hypercholesterolemia (FH), even high-dose statin therapy and adjuvant treatments (such as ezetimibe, resins, and niacin) may not be sufficient to achieve target low-density lipoprotein (LDL) levels in a significant number of patients.[2,3]

Statins act by reducing the production of cholesterol through inhibition of the rate-limiting enzyme HMG-CoA reductase in cholesterol synthesis.[4] The result is an upregulation of LDL receptors (LDLRs) in peripheral tissues and a subsequent increase in LDL particle clearance from the circulation.[5] However, individuals with FH have both increased production of LDL particles[6,7] and, because they have dysfunctional LDLR, markedly decreased LDLR-mediated clearance of LDL particles.[5,6] In patients with homozygous FH (HoFH) who have a near-complete or a complete loss of LDLR functionality, this pattern is even more pronounced.[5]

Statin therapy does offer benefit to patients with HoFH. A recent retrospective study of 149 patients demonstrated that statins were associated with delayed cardiovascular events and prolonged survival in patients with HoFH, whereas patients who go untreated rarely survive beyond the second decade of life.[1] However, a substantial number of patients with HoFH have persistently high plasma levels of LDL despite receiving maximally tolerated lipid-lowering therapy.[3,8]

Mipomersen, a therapeutic option with a unique mode of action that differs from that of statins, is approved for the treatment of HoFH in the United States.[9] Mipomersen is a 20-nucleotide, second-generation, antisense oligonucleotide that inhibits human apolipoprotein B (apo B)–100 production by sequence-specific binding to its messenger RNA (mRNA), causing degradation of the mRNA through enzyme-mediated pathways or disruption of mRNA function through binding alone.[9,10] Because apo B–100 is an essential structural component of very low–density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL, and lipoprotein(a) [Lp(a)], its decreased production by mipomersen leads to reduced circulating levels of these atherogenic lipoprotein particles.[11–14]

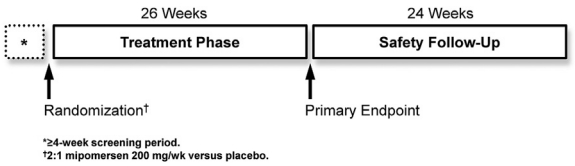

Figure 1 Study design for the 4 phase 3, randomized, double-blind, placebo-controlled trials of mipomersen in patients receiving maximally tolerated lipid-lowering therapy. * indicates ≤4-week screening period; † indicates 2:1 mipomersen 200 mg/wk versus placebo.

Traditionally, the concentration of circulating LDL has been estimated by measuring cholesterol contained in LDL particles (LDL-C). Alternatively, the number of LDL particles (LDL-P) can be quantified directly by nuclear magnetic resonance (NMR) spectroscopy, as well as estimated by measurement of apo B. Because of a variety of metabolic abnormalities (eg, insulin resistance, metabolic syndrome, type 2 diabetes mellitus), as well as use of pharmacologic therapy, the cholesterol content of lipoprotein particles varies widely among individuals.[15–19] Consequently, frequent discordance is noted between cholesterol (LDL-C) and particle number (NMR LDL-P, apo B) measures of LDL quantity in which LDL-C frequently underrepresents or overrepresents the LDL-P.[15,16,20–22]

When cholesterol (LDL-C) and particle number measures (apo B or NMR LDL-P) of LDL quantity are discordant, cardiovascular risk tracks with particle number,

Table 1 Patient population and key inclusion criteria

Patient population	Inclusion criteria*
HoFH	• Age ≥12 y • Genetic confirmation of HoFH or history of untreated LDL-C level >500 mg/dL • Xanthoma before age 10 y or evidence of HeFH in both parents • LDL-C level ≥130 mg/dL and triglyceride level <350 mg/dL
Severe-HC	• Age ≥18 y • Diagnosis of severe hypercholesterolemia: LDL-C level ≥300 mg/dL or ≥200 mg/dL with CHD • Triglyceride level <350 mg/dL
HeFH-CAD	• Age ≥18 y • Diagnosis of HeFH • LDL-C level ≥100 mg/dL with triglyceride level <200 mg/dL • Presence of CAD
HC-CHD	• Age ≥18 y • Documented history of CHD or CHD risk equivalents • LDL-C level ≥100 mg/dL with triglyceride level <200 mg/dL

CAD, coronary artery disease; CHD, coronary heart disease; HC-CHD, hypercholesterolemia and high risk for coronary heart disease study subjects; HeFH, heterozygous familial hypercholesterolemia; HeFH-CAD, heterozygous familial hypercholesterolemia and documented stable coronary artery disease study subjects; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Severe-HC, severe hypercholesterolemia study subjects.

*Patients in all studies were required to be taking maximally tolerated doses of lipid-lowering medications.