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

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Intermediate-density lipoprotein;
Antisense RNA

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]

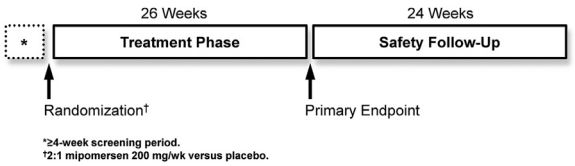

Figure 1 Study design for the 4 phase 3, randomized, double-blind, placebo-controlled trials of mipomersen in patients receiving maximally tolerated lipid-lowering therapy. * indicates ≤4-week screening period; † indicates 2:1 mipomersen 200 mg/wk versus placebo.

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.

not cholesterol.[19,22–24] As a result, several expert panels recommend the use of apo B or NMR LDL-P as a target of therapy to guide management and adjudicate response to pharmacotherapy in patients with increased cardiovascular risk.[23,25–29] The evaluation of LDL-P by either apo B or LDL-P determinations was shown to be a better discriminator of cardiovascular disease risk than LDL-C.[23] Recently, the American Association for Clinical Chemistry published a comprehensive review comparing apo B and NMR LDL-P with diverse cardiovascular outcomes.[30] Among 25 studies reviewed, both apo B and LDL-P were significantly associated with at least 1 outcome in 21 of the 25 studies (84.0%). Furthermore, apo B and LDL-P were compared in a total of 85 outcomes reported in these studies. In 50 of 85 comparisons (58.8%), both apo B and LDL-P were significantly associated with clinical outcomes. However, a substantial amount of discordance (21.2%) was noted in which one biomarker was statistically significant whereas the other was not. In these cases, LDL-P showed a significant association with a clinical outcome more often than apo B. Although limited data were available for review, the authors reasoned these findings could relate to differences in the analytical methods used to measure these biomarkers.

Four phase 3, randomized, double-blind, placebo-controlled trials have demonstrated that mipomersen significantly reduces LDL-C, apo B, total cholesterol, non–high-density lipoprotein cholesterol (non–HDL-C), and Lp(a) in patients who are already receiving maximally tolerated lipid-lowering therapy and who have HoFH, Severe-HC, heterozygous FH (HeFH) with established coronary artery disease (CAD), or hypercholesterolemia with high risk for CHD.[11–14] This article reports on the prespecified tertiary end point results of these 4 phase 3 studies, namely, the effects of mipomersen on lipoprotein particle numbers as well as subclass distribution using NMR.

Materials and methods

NMR lipoprotein analysis was a prespecified tertiary end point analysis in 4 phase 3, randomized, double-blind, placebo-controlled, multicenter trials with similar study designs (Fig. 1), for which primary analyses have been previously published.[11–13] The primary objectives of all 4 studies were to compare the additive effects of mipomersen vs placebo in patients receiving a maximally tolerated lipid-lowering regimen. Each of the 4 trials included patients with varying degrees of hypercholesterolemia (ranging from HoFH to Severe-HC): (1) HoFH; (2) Severe-HC; (3) HeFH and documented stable CAD (HeFH-CAD); and (4) hypercholesterolemia and high risk for coronary heart disease events (HC-CHD) (Table 1).[14] In the HC-CHD study, patients were included who had CHD or a CHD risk equivalent, including diabetes mellitus, or multiple risk factors that placed them at >20% risk for CHD over

Table 2 Patient demographics and baseline characteristics, lipid levels, apo B, and Lp(a)

Characteristic	HoFH (N = 51)	Severe-HC (N = 58)	HeFH-CAD (N = 124)	HC-CHD (N = 157)
Age, mean (y)	31.3	50.5	56.1	59.3
Males, n (%)	22 (43.1)	25 (43.1)	78 (62.9)	81 (51.6)
BMI, mean, kg/m^2 (SD)	26.1 (5.3)	28.9 (5.0)	29.2 (4.1)	30.4 (4.6)
Waist-to-hip ratio, mean (SD)	0.84 (0.1)	0.93 (0.1)	0.93 (0.1)	0.94 (0.1)
Metabolic syndrome, n (%)	8 (15.7)	23 (39.7)	46 (37.1)	113 (72.0)
Fasting glucose, mean, mg/dL (SD)	N/A	92.9 (19.9)	96.7 (10.3)	108.4 (22.6)
Baseline lipid levels, mean, mg/dL (SD)				
Patients with baseline triglycerides >150 mg/dL, n (%)	7 (13.7)	18 (31.0)	24 (19.4)	66 (42.0)
Triglycerides	115.9 (71.8)	141.6 (76.0)*	113.0 (44.5)†	146.0 (41.5)‡
HDL-C	39.3 (14.1)	48.6 (14.5)*	49.2 (12.8)†	45.0 (13.4)‡
LDL-C	426.0 (139.4)	267.7 (76.4)*	149.6 (49.7)†	122.6 (34.0)‡
apo B, mean, mg/dL (SD)	275.1 (80.4)	196.0 (49.3)*	130.8 (33.6)†	116.7 (26.8)‡
Lp(a), median, nmol/L (range)	2017.1 (107.1, 6283.2)	982.2 (107.1, 12,066.6)*	1642.2 (107.1, 10,549.4)†	1142.4 (107.1, 9567.6)‡

apo B, apolipoprotein B; BMI, body mass index; HC-CHD, hypercholesterolemia and high risk for coronary heart disease study; HDL-C, high-density lipoprotein cholesterol; HeFH-CAD, heterozygous familial hypercholesterolemia and documented stable coronary artery disease study; HoFH, homozygous familial hypercholesterolemia study; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); N/A, not available; SD, standard deviation; Severe-HC, severe hypercholesterolemia study.

*N = 57.

†N = 123.

‡N = 151.

Table 3 Mean percentage of low-density lipoprotein (LDL) subclasses at baseline

	Placebo (N = 129)			Mipomersen (N = 261)		
Study	Small LDL (%)	Large LDL (%)	IDL (%)	Small LDL (%)	Large LDL (%)	IDL (%)
HoFH (N = 51)	33.1	60.2	6.7	38.9	54.9	6.3
Severe-HC (N = 58)	55.2	40.2	4.5	54.7	39.8	5.6
HeFH-CAD (N = 124)	61.8	35.2	3.1	62.0	34.2	3.8
HC-CHD (N = 157)	67.5	28.8	3.8	68.1	28.6	3.3

HC-CHD, hypercholesterolemia and high risk for coronary heart disease study; HeFH-CAD, heterozygous familial hypercholesterolemia and documented stable coronary artery disease study; HoFH, homozygous familial hypercholesterolemia study; IDL, intermediate-density lipoproteins; Severe-HC, severe hypercholesterolemia study.

10 years as defined by the National Cholesterol Education Program, Adult Treatment Panel III Guidelines.[31]

All patients were receiving maximally tolerated lipid-lowering therapy at the study entry, including statins in 98.0% of patients (50 of 51) in the HoFH study, and in all patients in the Severe-HC (N = 58), HeFH-CAD (N = 124), and HC-CHD (N = 157) studies.[11–14] No 2 patients were on LDL apheresis within 8 weeks of the screening visit.[11–13]

Patients were randomized 2:1 to receive either weekly subcutaneous injections of 200 mg mipomersen or placebo for 26 weeks. All 4 protocols included measurements of lipid subclass concentrations at a minimum at weeks 1 and 28 (or at the early termination visit for those who discontinued early). All blood samples were collected before study drug administration after a fast of more than 10 hours. The primary efficacy end point was percentage reduction from baseline in LDL-C level. Secondary end points were percentage reductions from baseline in apo B total cholesterol and non–HDL-C levels. Tertiary end points included percentage changes in triglycerides, Lp(a), VLDL cholesterol, LDL-C-to-HDL ratio, apolipoprotein A-1 (apo A-1), HDL-C, and lipoprotein subclasses.

Plasma lipid and apolipoprotein determinations

Determinations of plasma lipids and apolipoproteins were done at a central laboratory (Medpace Reference Laboratories, Cincinnati, OH, USA; and Leuven, Belgium). Concentrations of total cholesterol, HDL-C, and triglycerides were measured by enzymatic colorimetry. HDL was isolated after dextran sulfate precipitation of VLDL and LDL. LDL-C concentration was calculated by the Friedewald formula (or after ultracentrifugation if triglyceride concentration was >4.5 mmol/L). Lp(a) was measured by a rate nephelometric assay standardized to Northwest Lipid Research Clinic (Seattle, WA, USA). Apo B and apo A-1 were measured by nephelometry.

Lipoprotein particle methodology

Lipoprotein subclass concentrations were performed by Liposcience, Inc (Raleigh, NC, USA) using NMR spectroscopy.[32] Concentrations are presented as quantity per volume (nanomoles per liter) rather than by weight (grams) to best reflect particle numbers.[32] LDL particle subclasses were defined by Liposcience, Inc as follows: IDL (23–27 nm), large LDL (21.2–23 nm), and small LDL (18–21.2 nm). Diameters are consistent with data from electron microscopy, being approximately 5 nm smaller than diameters obtained with gradient gel electrophoresis. Total LDL-P was composed of the sum of IDL, small LDL, and large LDL fractions.[32]

Statistical methods

The analyses reported included all randomized patients who received at least 1 injection of the study drug unless

Table 4 Percentage change from baseline in LDL-C, apo B, and Lp(a) levels in patients given mipomersen across the 4 phase 3 trials*

	LDL-C		apo B		Lp(a)	
Patient population (N = 256)	Baseline (mg/dL)	Change (%)	Baseline (mg/dL)	Change (%)	Baseline (nmol/L)	Change (%)
HoFH (N = 34)	439	−25	283	−27	2284.8	−31
Severe-HC (N = 39)	276	−36	202	−36	2177.7	−33
HeFH-CAD (N = 82)	153	−28	133	−26	2284.8	−20
HC-CHD (N = 101)	123	−37	117	−38	1927.8	−24

apo B, apolipoprotein B; CAD, coronary artery disease; CHD, coronary heart disease; HC, hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a).

*P values for all LDL-C and Lp(a) percentage changes from baseline within the mipomersen group are <.001. LDL-C and apo B results and Lp(a) are shown as mean. Patients received mipomersen 200 mg weekly administered subcutaneously for 26 weeks.

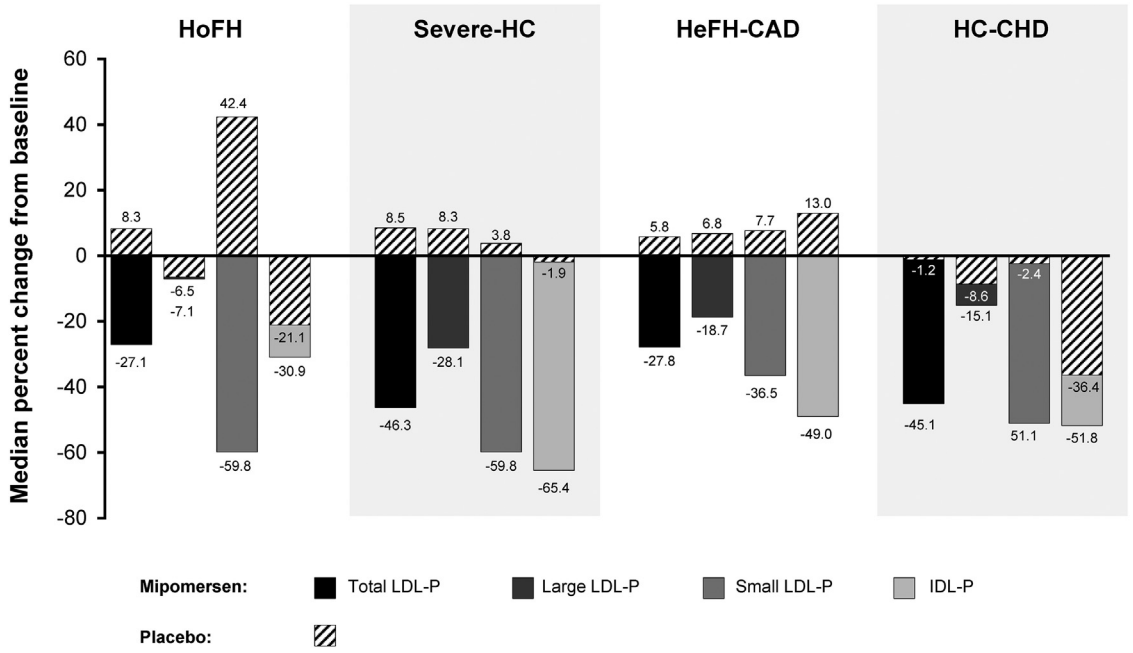

Figure 2 Median percentage change from baseline in total and subclasses of low-density lipoprotein particle (LDL-P) and intermediate-density lipoprotein particle (IDL-P) numbers for the mipomersen and placebo groups of all 4 phase 3 trials. HC-CHD, hypercholesterolemia and high risk for coronary heart disease study subjects; HeFH-CAD, heterozygous hypercholesterolemia and documented stable coronary artery disease study subjects; HoFH, homozygous familial hypercholesterolemia study subjects; Severe-HC, severe hypercholesterolemia study subjects.

otherwise specified. The baseline value for levels of lipids and/or lipoproteins was defined as the average of the sample taken at screening (<4 weeks before study day 1) and the sample taken on day 1 (pretreatment). If the difference between the 2 measurements was greater than 12%, then the day 1 value was used. The end point was week 28. Data were presented as nominal change from baseline. Determination of *P* values was performed only for comparisons of the efficacy parameters between treatment groups, with a conclusion of statistical significance if $P < .05$. *P* values for the between-group comparisons of absolute change from baseline to end point for total LDL-P, subclasses, and mean LDL-P size were based on the Wilcoxon rank sum test.

Results

Patient demographics and baseline characteristics are presented in Table 2. The mean age of patients in the HoFH study at baseline was 31.3 years (median, 31 years; range, 22–53 years), which was noticeably lower than that of the other 3 studies. The studies recruiting subjects at risk for or having CAD (ie, the HeFH-CAD study and the HC-CHD study) had a greater percentage of males than the HoFH study and the Severe-HC study. Metabolic syndrome was the most prevalent in the HC-CHD study (72% of patients) compared with the other studies: HoFH (15.7%), HeFH-CAD (37.1%), and Severe-HC (39.7%). Baseline triglyceride levels were higher in the HC-CHD and Severe-HC studies than in the HoFH and HeFH studies, and baseline LDL was the highest in the HoFH study.

Data for LDL subclasses were available for most patients. In the HoFH study, data were missing at end point for 1 of 17 patients and 3 of 34 patients in the placebo and mipomersen groups, respectively. In the Severe-HC study, end point data were missing for 1 of 19 patients and 3 of 39 patients in the placebo and mipomersen groups, respectively. In the HeFH-CAD study, baseline data were missing for 1 of 41 patients in the placebo group, and baseline and end point data were missing for 2 of 83 patients in the mipomersen group. In the HC-CHD study, data were not available at end point for 3 of 52 patients and 10 of 105 patients in the placebo and mipomersen groups, respectively. Across the 4 studies, injection-site reactions and flu-like symptoms were among the most common adverse events leading to study discontinuation for patients treated with mipomersen.

Baseline lipoprotein analysis

Patients with HoFH had the highest median total LDL-P at baseline compared with patients with HC-CHD, who had the lowest. When the concentrations of LDL subclasses were compared relative to each other (Table 3), the population with HoFH given placebo or mipomersen, respectively, had a greater mean percentage of large LDL particles (60.2% or 54.9%) than small LDL particles (33.1% or 38.9%). This result contrasted with results of the 3 other study populations (Severe-HC, HeFH-CAD, and HC-

Table 5 Median particle concentrations and change from baseline in LDL-P in patients given mipomersen or placebo in the 4 phase 3 trials

	Placebo			Mipomersen			
Patient population	Baseline, nmol/L (P25, P75)	End point nmol/L (P25, P75)	Nominal change nmol/L (P25, P75)	Baseline nmol/L (P25, P75)	End point nmol/L (P25, P75)	Nominal change nmol/L (P25, P75)	*P* value*
HoFH							
Total LDL-P	2212 (1802, 3502)	2771 (1765, 3637)	237 (−235, 539)	2917 (2127, 3624)	1925 (1538, 2685)	−882 (−1263, −351)	<.001
IDL	148 (67, 258)	117 (29, 266)	−12 (−115, 26)	198 (88, 257)	84 (0, 230)	−45 (−180, 0)	.317
Large LDL	1542 (1228, 2036)	1786 (1098, 2208)	−138 (−233, 253)	1619 (1318, 2047)	1378 (1101, 1894)	−119 (−477, 94)	.356
Small LDL	505 (384, 1208)	505 (289, 1823)	143 (−122, 481)	849 (195, 1848)	199 (47, 723)	−559 (−1090, −90)	<.001
Mean LDL particle size, nm (SD)	21.9 (0.7)	21.8 (0.8)	−0.1 (0.5)	21.7 (0.9)	22.1 (0.8)	0.5 (0.6)	.002
Severe-HC							
Total LDL-P	2210 (1619, 2881)	2381 (1725, 2634)	162 (−17, 573)	2470 (1860, 2978)	1216 (1012, 2003)	−931 (−1670, −389)	<.001
IDL	115 (53, 156)	101 (57, 186)	15 (−56, 64)	157 (44, 215)	36 (16, 94)	−100 (−129, −1)	.004
Large LDL	967 (466, 1165)	1009 (595, 1169)	65 (−214, 162)	972 (771, 1263)	634 (525, 1008)	−274 (−517, 37)	.018
Small LDL	1115 (662, 1618)	1355 (817, 1570)	43 (−125, 596)	1173 (588, 1984)	507 (181, 696)	−484 (−1210, −164)	<.001
Mean LDL particle size, nm (SD)	21.1 (0.7)	21.1 (0.6)	−0.1 (0.5)	21.2 (0.9)	21.7 (0.7)	0.51 (0.7)	.002
HeFH-CAD							
Total LDL-P	1490 (1316, 1829)	1664 (1390, 2044)	82 (−66, 381)	1651 (1337, 2000)	1173 (881, 1416)	−457 (−787, −82)	<.001
IDL	21 (5, 75)	26 (5, 90)	4 (−21, 31)	48 (8, 91)	25 (4, 55)	−19 (−54, 6)	.010
Large LDL	526 (379, 662)	513 (371, 691)	42 (−73, 104)	561 (380, 733)	488 (360, 574)	−121 (−285, 56)	.001
Small LDL	916 (762, 1186)	988 (726, 1372)	87 (−118, 365)	989 (670, 1469)	664 (284, 953)	−268 (−593, −65)	<.001
Mean LDL particle size, nm (SD)	21 (0.6)	21 (0.7)	−0.1 (0.5)	21 (0.8)	21 (0.9)	0.3 (0.6)	.001
HC-CHD							
Total LDL-P	1400 (1150, 1593)	1356 (1118, 1671)	−20 (−219, 106)	1462 (1231, 1718)	796 (558, 1141)	−590 (−956, −292)	<.001
IDL	33 (14, 89)	37 (8, 70)	−9 (−33, 16)	37 (9, 87)	16 (3, 45)	−12 (−48, 11)	.363
Large LDL	390 (269, 576)	363 (253, 445)	−15 (−102, 80)	446 (248, 550)	317 (225, 425)	−64 (−220, 52)	<.001
Small LDL	978 (649, 1209)	883 (678, 1257)	−17 (−275, 98)	994 (741, 1246)	451 (234, 723)	−478 (−784, −287)	<.001
Mean LDL particle size, nm (SD)	20.7 (0.8)	20.7 (0.8)	0.01 (0.54)	20.7 (0.7)	21.3 (0.8)	0.58 (0.76)	<.001

HC-CHD, hypercholesterolemia and high risk for coronary heart disease study subjects; HeFH-CAD, heterozygous familial hypercholesterolemia and documented stable coronary artery disease study subjects; HoFH, homozygous familial hypercholesterolemia study subjects; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDL-P, low-density lipoprotein particle number; P, percentile; SD, standard deviation; Severe-HC, severe hypercholesterolemia study subjects.

**P* value is for the between-group comparison of absolute change from baseline to end point via Wilcoxon rank sum test.

CHD), all of which had a larger mean percentage of small LDL particles than large LDL particles.

Within each study, baseline values for total LDL-P and subclasses were not statistically different between treatment groups.

LDL subclass analysis

Previously published efficacy results from the 4 phase 3 studies demonstrated that mipomersen effectively lowered all the atherogenic lipid levels: LDL-C, apo B, and Lp(a) (Table 4).[11–14] This analysis shows that mipomersen treatment was associated with a reduction from baseline in the number of all LDL subclasses (Fig. 2). In all 4 studies, greater reductions from baseline were seen in the concentrations of small LDL particles than those of large LDL particles. In the mipomersen groups, median percentage changes from baseline in concentrations of small LDL vs large LDL, respectively, were as follows: HoFH, –59.8% vs –7.1%; Severe-HC, –59.8% vs –28.1%; HeFH-CAD, –36.5% vs –18.7%; and HC-CHD, –51.1% vs –15.1% (Fig. 2).

When the 2 treatment groups were compared, mipomersen treatment was associated with a statistically significant reduction in total LDL-P and number of small LDL in all 4 studies (Table 5). The median large LDL and IDL concentrations were significantly reduced with mipomersen treatment in the Severe-HC and HeFH-CAD study subjects; however, reductions for large LDL and IDL in HoFH and IDL in HC-CHD study subjects did not reach statistical significance. Because of mean changes in the concentrations of LDL subclasses, mean LDL particle size increased significantly in all 4 studies by an average of 0.5 nm ($P \leq .002$).

Discussion

Results from 4 previously published phase 3 studies demonstrated that mipomersen effectively lowered apo B–containing lipoproteins.[11–14] In this tertiary end point analysis, we show that mipomersen reduces the LDL-P within all subclasses; however, mipomersen preferentially reduces the concentrations of small LDL particles and has less effect on the concentrations of large LDL particles.

The NMR lipoprotein analysis showed that the trial populations had distinct LDL particle profiles at baseline. Patients in the HoFH study had a greater percentage of large vs small LDL particles. Patients in the Severe-HC study had elevated levels of both large and small LDL particles, whereas patients in the HeFH-CAD and HC-CHD studies had greater amounts of small LDL particles. These observations are not unexpected because individuals with HoFH generally are not insulin resistant[33]; only 15.7% in the HoFH study were found to have metabolic syndrome, a condition usually associated with increased small LDL-Ps. In contrast, 37% to 72% of individuals in the other 3 studies had metabolic syndrome. A number of studies support an inverse association between insulin sensitivity and increased preponderance of smaller LDL particles.[16,17,34–38] Previously published works report similar observations of larger, more buoyant LDL particles being associated with FH.[39–41]

Moreover, in HoFH, there is a total or a near-total lack of LDLR function.[42] One plausible explanation for the association of mipomersen with a preferential reduction in small LDL particles may relate to decreased VLDL production, which drives the production of small LDL. Mipomersen acts by reducing the production of apo B and subsequently the production of apo B–containing lipoproteins. Large triglyceride-rich VLDL may undergo slow metabolism and have a greater chance of remodeling via cholesterol ester transfer protein to lose cholesterol ester and gain triacylglycerol, thus priming it for conversion to small, dense LDL by hepatic lipase.[43] A reduction in triacylglycerol-rich VLDL would therefore reduce the amount of small LDL.

Another possible mechanism for the preferential reduction of small LDL subclasses by mipomersen may be related to its selective effect on apolipoprotein C-III (apo C-III) compared with apolipoprotein E (apo E) and the activity of hepatic lipase.[44] Apo E–containing triglyceride-rich lipoproteins generally undergo clearance by the liver and have a low tendency to continue the lipolytic process to form LDL.[45] Apo C-III antagonizes the action of apo E and channels particles to lipolysis and LDL formation.[45] By reducing apo C-III, mipomersen may be associated with increased clearance of VLDL and IDL particles, which would result in fewer particles processing through lipolytic cascade and reduce the small LDL-P.[18,23,43,45]

A recent systematic literature review of 36 published studies supports our observations of differential reduction in small LDL-P. The review focused on variations in effect on LDL markers (including LDL-P and LDL-C) by several common pharmacotherapies (statins, fibrates, niacin, resins, and anti–apo B oligonucleotides [ie, mipomersen]).[46] The amount of cholesterol per LDL particle varies among patients, such as those with metabolic syndrome, resulting in variation in reductions of LDL-C and LDL-P levels by different classes of pharmacotherapy.[46]

In conclusion, mipomersen, which has demonstrated an acceptable safety and tolerability profile in the target patient population in previous studies,[11–14] consistently reduced all LDL-Ps and preferentially reduced the concentration of small LDL particles in all 4 phase 3 studies. Prospective clinical trials are warranted to further explore the clinical significance of these findings.

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