Effectiveness and Tolerability of a New Lipid-Altering Agent, *Gemcabene*, in Patients With Low Levels of High-Density Lipoprotein Cholesterol

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This study evaluated the efficacy and tolerability of gemcabene, a new lipid-altering agent, in a double-blind, randomized, dose-response study of 161 patients with high-density lipoprotein (HDL) cholesterol of <35 mg/dl and serum triglyceride (TG) levels of either ≥200 (n = 94) or <200 mg/dl (n = 67). After a 6-week, placebo, dietary lead-in period, patients were administered either 150, 300, 600, or 900 mg of gemcabene or placebo once daily for 12 weeks. In the TG ≥200 mg/dl stratum, gemcabene significantly increased serum HDL cholesterol by 18% with corresponding significant increases of 6% in both apolipoprotein A-I and A-II levels at the 150-mg dose. HDL cholesterol levels also increased 12% at the 300-mg dose; however, this did not reach statistical significance. Also, in the TG ≥200 mg/dl stratum, serum TG levels were significantly reduced by 27% and 39% at the 150- and 300-mg doses of gemcabene, respectively. No significant differences were found in serum HDL cholesterol or TG levels in the TG ≥200 mg/dl groups that received 600 or 900 mg of gemcabene, or in TG <200 mg/dl groups administered any dose of gemcabene. However, at these higher 600- and 900-mg doses, gemcabene significantly reduced serum low-density lipoprotein (LDL) cholesterol levels by 15% to 25%, respectively, in both TG strata, with proportionate decreases in the levels of apolipoprotein B. Gemcabene was well tolerated with a frequency of adverse events similar to that of placebo. In conclusion, at the lower doses, gemcabene significantly increased HDL cholesterol and reduced TG serum levels in patients with low HDL cholesterol and TG ≥200 mg/dl. At the higher doses, gemcabene significantly reduced LDL cholesterol levels in all patients with low HDL cholesterol. ©2003 by Excerpta Medica, Inc.

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Gemcabene, a dialkyl ether (dicarboxylic acid), is a novel lipid-altering agent whose mechanism of action has yet to be completely established. In chow-fed male rats, gemcabene (PD 72953) increased high-density lipoprotein (HDL) cholesterol levels and increased HDL particle size. Low-density lipoprotein (LDL) cholesterol, trigylcerides (TG), and apolipoprotein C-III levels were decreased as well.[1] In human studies of single-dose tolerance up to 1,500 mg/day and multiple dose tolerance up to 900 mg/day involving >70 subjects, no adverse clinical effects were observed, and the drug was well tolerated (data on file). The purpose of this 12-week, double-blind, placebo-controlled study was to determine the efficacy and tolerability of gemcabene over a broad dose range administered to patients with low HDL cholesterol and TG serum levels of either <200 or ≥200 mg/dl.

METHODS

Study design: This was a randomized, double-blind, placebo-controlled, parallel group, dose-response multicenter study. The study was conducted at 11 centers in the United States and 1 center in Canada. Institutional review board approval was obtained at each center and every patient was informed of the study, freely consented to participate, and signed an informed consent document. After a 6-week, single-blind placebo, dietary lead-in period conducted according to the National Cholesterol Education Program Step 1 Diet,[2] eligible patients with HDL cholesterol levels of <35 mg/dl (0.9 mmol/L) were stratified according to whether mean serum TG levels, calculated from measurements at 2 and 4 weeks before randomization, were <200 (2.3 mmol/L) or ≥200 mg/dl (2.3 mmol/L). Within each TG stratum, patients were randomized to receive either 150, 300, 600, or 900 mg of gemcabene, or placebo, once daily for 12 weeks (Table 1).

Patients: Eligible patients were women of non-childbearing potential (naturally postmenopausal or surgically sterilized) or men 18 to 80 years of age with baseline

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TABLE 1 Study Design Summary

Patients with HDL Cholesterol <35 mg/dl		
Visit 1	Visit 2 to 4	Visit 5 to 9
		Placebo Gemcabene 150 mg once daily Gemcabene 300 mg once daily Gemcabene 600 mg once daily Gemcabene 900 mg once daily
	Triglycerides ≥200 mg/dl ↗	
	Triglycerides <200 mg/dl ↘	Placebo Gemcabene 150 mg once daily Gemcabene 300 mg once daily Gemcabene 600 mg once daily Gemcabene 900 mg once daily
Screening	6-week placebo dietary baseline	12-week treatment period

serum HDL cholesterol levels of <35 mg/dl. Patients were excluded if they had creatine kinase serum levels >3 times the upper limit of normal; a body mass index >35 kg/m^2; uncontrolled hypertension (defined as sitting diastolic blood pressure >95 mm Hg, whether taking an acceptable antihypertensive medication or not); uncontrolled diabetes mellitus (hemoglobin A_{1C} >10%); hepatic dysfunction, including asparate aminotransferase or alanine aminotransferase levels >2 times the upper limits of normal; renal dysfunction as defined by blood urea nitrogen or creatinine levels >2 times the upper limit of normal; or uncontrolled hypothyroidism (thyroid stimulating hormone >1.5 times the upper limit of normal). Patients were also excluded if they had a history of known gallbladder disease or pancreatitis, a history of consuming >14 alcoholic drinks per week, or a known hypersensitivity to lipid-altering drugs. Patients who had myocardial infarction, severe or unstable angina pectoris, coronary artery bypass graft, or any other cardiovascular event requiring hospitalization within the last 3 months were also excluded. Patients were not permitted any other lipid-altering drugs during the study, and if on prestudy lipid-altering drug therapy, were required to undergo an additional 4-week wash-out period. Use of isotretinoin, insulin, warfarin, immunosuppressive agents, and intermittent systemic steroids were also prohibited. Alpha blockers, β blockers, hormone replacement therapy, and oral hypoglycemic agents were permitted, provided that their use was stable for ≥3 months before the study.

Efficacy parameters: The primary efficacy parameter was the percent change from baseline in serum HDL cholesterol levels at the study subject's last visit. Other efficacy parameters included the percent change from baseline in serum LDL cholesterol, TG, apolipoproteins A-I, A-II, B, C-III, and E, and non-HDL cholesterol levels. For HDL cholesterol, non-HDL cholesterol, LDL cholesterol, and TG levels, the baseline value was the mean plasma value of 2 measurements: 1 obtained 2 weeks before randomization and 1 obtained at randomization. For all other parameters, the baseline value was defined as the single measurement obtained at randomization.

Clinical and laboratory data: All blood samples were collected after a 12-hour fast and analyzed by Medical Research Laboratories (Highland Heights, Kentucky). Blood samples for routine chemistry and hematologic profiles were measured at screening, at randomization, and at 4, 8, and 12 weeks after the start of study medication. Basic lipid profiles (HDL cholesterol, LDL cholesterol, and TG) were measured at screening, at 2 and 4 weeks before starting study medication (during the baseline phase), at randomization, and at weeks 2, 4, 8, and 12 of the treatment phase. Other efficacy parameters were measured at randomization and study completion. Serum concentrations of cholesterol and TG were measured using an enzymatic, colorimetric assay on the Hitachi 747 analyzer (Roche Diagnostics, Indianapolis, Indiana). HDL cholesterol samples were obtained from the supernatant after precipitation of the non-HDL lipoproteins using heparin and manganese chloride. Concentrations of LDL cholesterol were measured by β quantification, using a preparative ultracentrifuge fraction density of >1.006 kg/L − HDL cholesterol, when TG was >400 mg/dl. LDL cholesterol levels were calculated using the Freidewald formula when TG was ≤400 mg/dl.[3] Concentrations of apolipoproteins A-I, A-II, B, and E were measured using immunonephelometry on the Dade Behring nephelometer. Concentration of apolipoprotein C-III was measured by electroimmunodiffusion using Hydragel LP CIII kits (Serbia, Issy-les-Moulineaux, France). Non-HDL cholesterol was calculated by subtracting the measured HDL cholesterol from the measured total cholesterol. Patients were observed and queried in a nonspecific fashion at each visit during the study for any new or continuing symptoms. Adverse events were recorded at each clinic visit and up to 15 days after treatment cessation.

Statistical analyses: A sample size of 15 patients per treatment group was planned, to provide >90% power to detect a 30% difference in the percent change in HDL cholesterol from baseline to week 12 between the placebo group and ≥1 gemcabene dose group in each triglyceridemic stratum. This calculation assumed a Dunnett-adjusted 2-sided α of 0.05 and a common SD of 18%.

Within each TG stratum, an analysis of covariance model with the effects of baseline lipid values, treatment, and sites was used to analyze the percent change from baseline at the last visit for each of the efficacy parameters by producing least-squares means and p values. Dunnett's multiple comparison procedure was used to adjust the p values in the analysis of the primary end point of percent change in HDL cholesterol. All other end point p values were unadjusted for multiplicity.

The Shapiro-Wilk Test for Normality[4] and visual analysis of the residuals was used to determine if the assumption of normality was reasonable. Because

TABLE 2 Summary of Baseline Characteristics by Triglyceride Stratum

Characteristic	TG <200 mg/dl					TG ≥200 mg/dL				
		Gemcabene					Gemcabene			
	Placebo (n = 14)	150 mg (n = 14)	300 mg (n = 11)	600 mg (n = 14)	900 mg (n = 14)	Placebo (n = 18)	150 mg (n = 20)	300 mg (n = 21)	600 mg (n = 17)	900 mg (n = 18)
Men	100%	100%	91%	86%	100%	94%	90%	91%	82%	94%
Age (yrs)	50 ± 3	55 ± 3	64 ± 3	51 ± 4	50 ± 3.0	53 ± 3	53 ± 2	54 ± 2	56 ± 3	58 ± 2
Caucasian	93%	64%	100%	71%	71%	100%	85%	91%	84%	94%
Waist circumference (cm)	100 ± 3	99 ± 3	108 ± 3	98 ± 4	100 ± 2	103 ± 3	103 ± 2	100 ± 3	98 ± 3	102 ± 2
Body mass index (kg/m^2)	28 ± 1	29 ± 1	31 ± 1	28 ± 1	29 ± 1	30 ± 1	30 ± 1	28 ± 1	30 ± 1	29 ± 1
Diabetes	7%	14%	18%	14%	21%	28%	15%	10%	24%	22%
Diastolic blood pressure (mm Hg)	77 ± 2	77 ± 2	75 ± 2	78 ± 2	76 ± 2	78 ± 2	79 ± 1	77 ± 2	80 ± 1	82 ± 2
Systolic blood pressure (mm Hg)	119 ± 5	119 ± 3	123 ± 3	116 ± 3	119 ± 4	122 ± 3	125 ± 3	122 ± 2	124 ± 3	132 ± 2

Data are presented as mean ± SE or percentages.

TABLE 3 Summary of Baseline Lipid and Lipoprotein Parameters by Triglyceride Stratum

Characteristic	Triglycerides <200 mg/dl					Triglycerides ≥200 mg/dl				
		Gemcabene					Gemcabene			
	Placebo (n = 14)	150 mg (n = 14)	300 mg (n = 11)	600 mg (n = 14)	900 mg (n = 14)	Placebo (n = 18)	150 mg (n = 20)	300 mg (n = 21)	600 mg (n = 17)	900 mg (n = 18)
LDL cholesterol	116 ± 10	107 ± 10	139 ± 11	108 ± 8	127 ± 9	101 ± 8	120 ± 9	108 ± 8	102 ± 9	110 ± 9
Non-HDL cholesterol	163 ± 11	154 ± 9	181 ± 11	141 ± 7	169 ± 10	183 ± 12	205 ± 9	201 ± 11	208 ± 16	201 ± 11
Apo B	127 ± 7	114 ± 9	143 ± 10	113 ± 8	131 ± 7	130 ± 6	149 ± 7	147 ± 8	142 ± 8	131 ± 6
HDL-cholesterol	31 ± 1	32 ± 1	33 ± 1	33 ± 1	31 ± 1	29 ± 1	30 ± 1	28 ± 1	29 ± 1	29 ± 1
TG	181 ± 12	170 ± 13	183 ± 13	151 ± 10	166 ± 17	367 ± 32	368 ± 40	428 ± 47	580 ± 133	382 ± 31
Apo A1	114 ± 3	108 ± 4	112 ± 3	106 ± 4	105 ± 5	113 ± 3	116 ± 3	114 ± 4	118 ± 4	113 ± 3
Apo A11	28 ± 1	28 ± 1	27 ± 1	27 ± 1	26 ± 1	28 ± 1	29 ± 1	30 ± 1	31 ± 2	29 ± 1
Apo CIII	31 ± 2	28 ± 2	31 ± 2	26 ± 2	28 ± 3	56 ± 9	52 ± 5	61 ± 7	87 ± 21	62 ± 7
Apo E	4.4 ± 0.3	4.2 ± 0.3	3.8 ± 0.3	3.8 ± 0.2	3.9 ± 0.2	6.4 ± 0.9	6.4 ± 0.6	7.1 ± 0.7	8.3 ± 1.1	6.8 ± 0.7

Data are presented as means ± SE.
All of characteristics are measured in milligrams per deciliter.
Apo = apolipoprotein.

LDL cholesterol levels in patients with TG ≥200 mg/dl, apolipoprotein A-I levels in patients with TG <200 mg/dl, and TG and apolipoproteins B and E levels in all patients were not normally distributed, median percent changes are presented; Conover's nonparametric analysis of covariance was used to analyze the ranked data for these parameters.

RESULTS

Baseline demographics: A total of 161 patients were randomized. Of these patients, 67 had TG levels <200 mg/dl (14 randomized to placebo and 53 to active treatment) and 94 had TG levels ≥200 mg/dl (18 randomized to placebo and 76 to active treatment). Patient characteristics were generally similar across the TG strata (Table 2), with the obvious exception of the lipid parameters (Table 3). The study was completed by 152 patients. Six withdrew due to adverse events and 3 failed to complete the study for administrative or personal reasons. Compliance to study medication regimen was assessed at clinic visits by tablet count and found to be similar among the treatment groups. At the end of the study, 97% of those on placebo and 96% of the active treatment patients were ≥80% compliant.

Efficacy parameters: Percent change from baseline in HDL cholesterol, LDL cholesterol, TG, and other efficacy parameters due to the administration of 150, 300, 600, or 900 mg of gemcabene or placebo are shown in Figure 1. In patients with mean baseline TG ≥200 mg/dl, gemcabene significantly increased serum HDL cholesterol levels by 18% at the 150-mg dose, with a corresponding increase of 6% in the levels of both apolipoproteins A-I and A-II and a decrease of 24% in apolipoprotein C-III. Gemcabene 300 mg/day increased serum HDL cholesterol levels by 12%, although this did

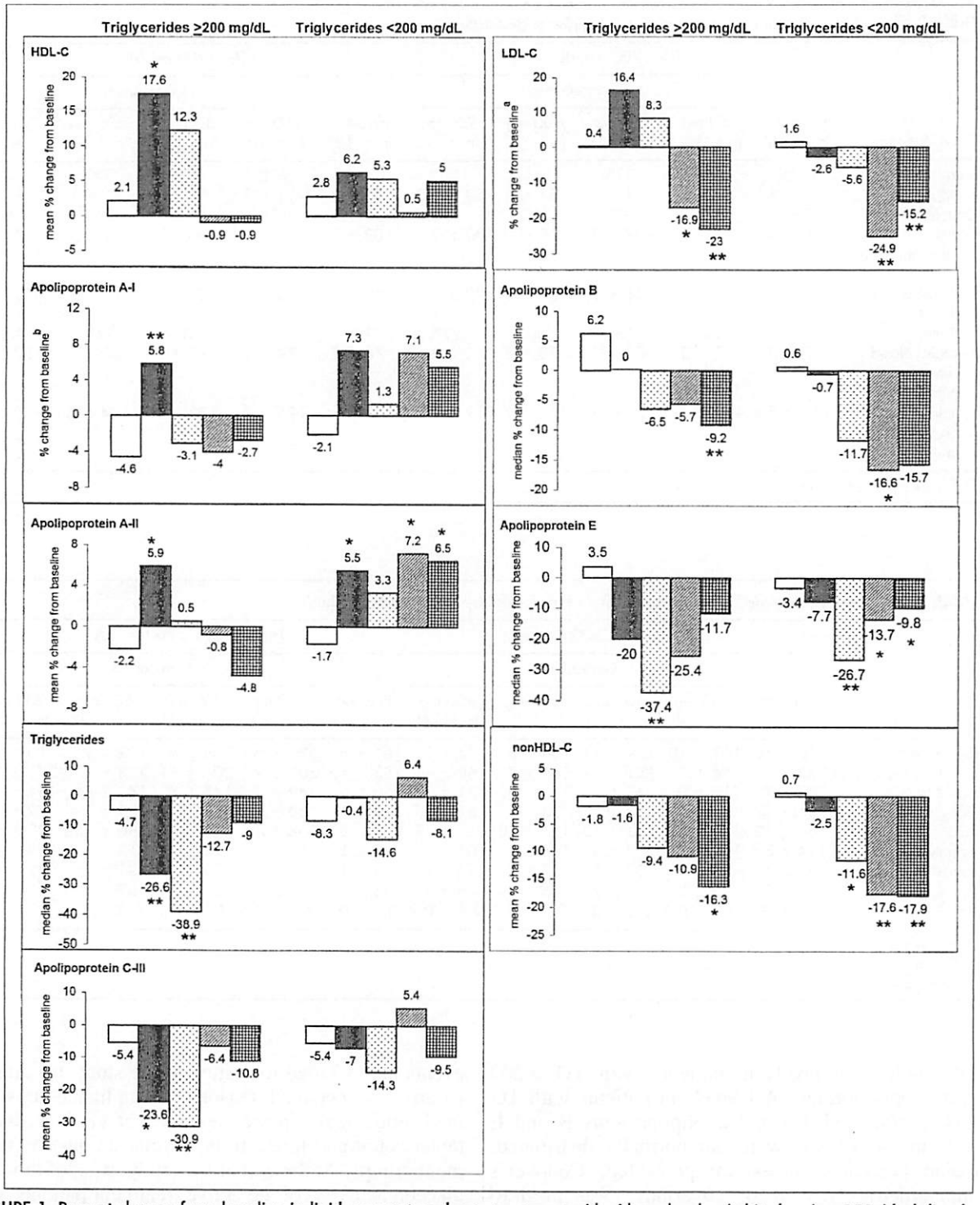

FIGURE 1. Percent change from baseline in lipid parameters due to treatment with either placebo *(white bars)* or 150 *(dark-lined bars)*, 300 *(dotted bars)*, 600 *(cross-hatched bars)*, or 900 *(plaid bars)* mg gemcabene in patients with TG ≥200 or <200 mg/dl. *p <0.05 versus placebo; **p <0.01 versus placebo. [a]For low-density lipoprotein cholesterol (LDL-C), percent change from baseline data are medians for TG strata ≥200 mg/dl and means for TG strata <200 mg/dl. [b]For apolipoprotein AI, percent change from baseline data are means for TG strata ≥200 mg/dl and medians for TG strata <200 mg/dl.

not reach statistical significance. TG serum levels were significantly reduced by 27% and 39% at the 150- and 300-mg doses, respectively. No significant differences were found in serum HDL cholesterol or TG levels at the 600- or 900-mg doses versus placebo.

In patients with mean baseline TG <200 mg/dl, no significant differences were seen in serum HDL cholesterol or TG levels in groups administered any dose of gemcabene versus placebo.

In both TG strata, gemcabene significantly reduced serum LDL cholesterol levels by 15% to 25% at the 600- and 900-mg doses, respectively, with corre-

sponding decreases in the levels of apolipoprotein B. Also, in both TG strata, gemcabene significantly reduced non-HDL cholesterol levels by up to 18% at the higher doses.

All dose regimens of gemcabene were well tolerated and had adverse event profiles similar to placebo. Adverse events occurred in ≥5% of patients in the placebo group, including infection (16%), accidental injury (6%), back pain (6%), dyspepsia (6%), sinusitis (6%), and headache (6%). Adverse events occurred in ≥5% of patients in the gemcabene treatment groups, including infection (12%), headache (7%), and asthenia (5%).

Six of 161 patients withdrew due to adverse events. Two patients had adverse events that were not related to treatment (as judged by the investigator). This included 1 patient who received placebo who withdrew due to sinusitis, and another patient who received 600-mg gemcabene who withdrew due to a maculopapular rash.

Four patients withdrew from the study due to adverse events, as judged by the investigator, as possibly, probably or definitely related to study drug. One patient who received placebo withdrew due to dyspepsia. Another withdrew due to tremulousness after 22 days of receiving 300-mg gemcabene, which resolved after discontinuation of study medication. One patient administered 600-mg gemcabene for 29 days experienced a worsening of creatinine. The baseline creatinine value was elevated at 1.6 mg/dl (upper limit of normal 1.4 mg/dl) and increased to 2.0 mg/dl. Creatinine returned to baseline (1.6 mg/dl) after discontinuing the study drug. Similarly, this same patient's blood urea nitrogen level also increased from a baseline level of 18 mg/dl to 28 mg/dl and then returned to 21 mg/dl (upper limit of normal 20 mg/dl) after discontinuing study drug. Finally, 1 patient who received 600-mg gemcabene for 29 days withdrew due to reported "gallbladder pain" and a worsening of elevated baseline alanine aminotransferase serum level that increased from 41 mU/ml at baseline to a peak of 93 mU/ml. After withdrawal of study drug, the alanine aminotransferase serum level of 43 mU/ml approximated the elevated baseline level (upper limit of normal 25 mU/ml).

No patient had a persistent creatine kinase elevation (defined as >10 times the upper limit of normal occurring on ≥2 separate occasions) or a persistent aspartate aminotransferase elevation (>3 times the upper limit of normal occurring on ≥2 separate occasions). As detailed previously, 1 patient reporting "gallbladder pain" did have a persistent alanine aminotransferase serum level >3 times the upper limit of normal that occurred on ≥2 separate occasions.

Only 2 patients experienced treatment emergent adverse events that were serious during the study. Both were judged by the investigator as unrelated to treatment, and neither resulted in patient withdrawal. One patient was hospitalized due to a perirectal abscess on day 43 of placebo administration. Another patient with a history of coronary heart disease was hospitalized for dizziness and chest pain on day 68 of administration of 150-mg gemcabene; this patient recovered while continuing study medication. No deaths occurred during the study.

DISCUSSION

This study was conducted to determine the effectiveness and tolerability of a new lipid-altering compound, gemcabene, in a dose-response study, and represents the first published report of the use of gemcabene in human test subjects. The primary efficacy parameter evaluated was the percent change from baseline in serum HDL cholesterol levels, because clinical improvement in HDL cholesterol levels may further reduce coronary heart disease risk above that achieved with LDL cholesterol lowering.[5]

The effect of gemcabene on serum HDL cholesterol and TG levels was shown to be dependent upon baseline TG levels and gemcabene dose. In patients with TG <200 mg/dl, gemcabene did not significantly alter these lipid parameters. In patients with TG ≥200 mg/dl, gemcabene increased HDL cholesterol levels in a manner in which the greatest elevation (18%, $p = 0.011$) was observed at the lowest dose studied in this trial. Also, in patients with TG ≥200 mg/dl, TG was significantly reduced by up to 38% at lower doses.

At the higher 600- and 900-mg doses, LDL cholesterol was reduced by 15% to 25%, regardless of the baseline TG level. This change was accompanied by a reduction in apolipoprotein B. Baseline LDL cholesterol levels in this study were quite low, with mean values ranging from 101 to 139 mg/dl in the various groups studied. Further study will determine whether greater LDL cholesterol lowering occurs in patients with hypercholesterolemia.

Gemcabene was generally well tolerated when administered in doses up to 900 mg/day for 12 weeks.

An intriguing result of this trial is the potential benefit that gemcabene may have in patients with elevated non-HDL cholesterol. Non-HDL cholesterol comprises the cholesterol found in the potentially atherogenic lipoprotein particles LDL, very LDL and its remnants, intermediate density lipoprotein, and lipoprotein(a). Due to the inclusion of more atherogenic particles, some studies have suggested that non-HDL cholesterol may be a better predictor of coronary heart disease risk than LDL cholesterol alone.[6,7] Although there were inconsistent effects on individual lipid and lipoprotein measurements with increasing doses of gemcabene, there was a consistently favorable effect on atherogenic serum non-HDL cholesterol levels with increasing doses of gemcabene in patients with higher and lower TG levels. Not surprisingly, this same benefit with increasing dose of gemcabene was seen in apolipoprotein B measurements as well.

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APPENDIX

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