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Original Contribution

Efficacy and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients

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KEYWORDS:
Low-density lipoprotein cholesterol;
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C-reactive protein;
Very low-density lipoprotein;
Apolipoprotein B;
Triglycerides;
Cardiovascular disease;
Statins

BACKGROUND: Ezetimibe added to statin therapy further reduces LDL-C and clinical atherosclerotic cardiovascular disease compared to statin alone. However, the number of effective and safe oral agents for patients not at LDL-C goal is limited. In prior clinical trials, gemcabene reduced LDL-C and was generally well-tolerated in nearly 900 patients treated for up to 12 weeks.

OBJECTIVE: To evaluate the LDL-C lowering and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients.

METHODS: This was an 8-week, double-blind, placebo-controlled, randomized, phase 2 study in men and postmenopausal women ≥18 and ≤65 years of age with LDL-C ≥130 mg/dL (3.4 mmol/L) while on low-intensity to high-intensity stable statin (the majority on moderate intensity) therapy. Sixty-six patients were randomized 1:1:1 to gemcabene 300 mg, 900 mg, or placebo QD.

RESULTS: Gemcabene 300 mg and 900 mg produced a mean percent change in LDL-C of −23.4 ± 4.7% ($P = .005$) and −27.7 ± 4.3% ($P < .001$), respectively, vs −6.2 ± 4.3% for placebo. The median percent change in CRP was −26.1% ($P = .196$) and −53.9% ($P < .001$) for gemcabene 300 mg and 900 mg, respectively, vs −11.1% for placebo. Gemcabene 300 mg and 900 mg were well-tolerated with no significant difference in AEs compared to placebo.

CONCLUSIONS: Gemcabene as add-on to stable statin therapy demonstrated additional dose-dependent and statistically significant reductions in LDL-C of >20% and CRP >40% compared to placebo. The results support gemcabene-continued development for patients requiring LDL-C lowering beyond that provided by background statin therapy.

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Introduction

Low-density lipoprotein cholesterol (LDL-C) lowering is one of the most validated and modifiable of known risk factors for reducing cardiovascular events. It is also the basis of virtually all national and international guidelines for reducing the burden of clinical atherosclerotic

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Research was licensed to Gemphire, Therapeutics, Inc.

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cardiovascular disease (ASCVD).[1–5] Based on numerous cardiovascular outcome trials over the last 25 years, a robust relationship between absolute lowering in LDL-C and cardiovascular disease (CVD) has been established whereby each 1.0 mmol/L (38.7 mg/dL) lowering in LDL-C reduces the incidence of major coronary events, coronary revascularizations, and ischemic stroke by approximately 20%.[3] Although the majority of the data were derived from statin trials, the recent IMPROVE-IT trial confirmed the LDL-C/ASCVD relationship when a non-statin, ezetimibe was added to high-dose simvastatin and compared to simvastatin alone to achieve further LDL-C lowering.[6]

Most guidelines for the prevention of CVD recommend lowering of LDL-C to <100 mg/dL (<2.59 mmol/L) for patients considered at high coronary heart disease risk and <70 mg/dL (<1.81 mmol/L) in patients with established CVD.[7,8] The only major departure from these treatment-targeted guidelines is the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, which focus on individual patient risk and maximizing statin therapy while de-emphasizing LDL-C goals.[8] Guidelines from other organizations in the United States such as the National Lipid Association and the American Association of Clinical Endocrinologists continue to emphasize the NCEP-ATP III treatment goals for LDL-C levels.[9,10]

Statins, as the first line therapy, are very effective at lowering LDL-C; however, many patients do not achieve LDL-C targets with statins alone.[11,12] In addition, a small but significant percentage of patients are unable or unwilling to tolerate effective doses of statins.[13] Secondary oral agents used to achieve additional LDL-C reduction are often limited by tolerability, side effects, or efficacy; these include bile acid sequestrants, fibrates, nicotinic acid, and ezetimibe.[14–17] Other agents such as lomitapide, an oral microsomal triglyceride transfer protein inhibitor,[18] and mipomersen, an anti-sense apolipoprotein B synthesis inhibitor administered by subcutaneous injection,[19,20] are approved only for the rare patient population with homozygous familial hypercholesterolemia (HoFH). Both these lipid-altering agents carry a "boxed" warning for risk of hepatotoxicity and are administered under a risk evaluation and mitigation strategy program. The recently approved proprotein convertase subtilisin/kexin type 9 monoclonal antibody inhibitors, while being the most effective LDL-C lowering class to enter routine practice, are very expensive for broad market use and require parenteral administration every 2 or 4 weeks.[21–23] Therefore, there remains a need for more effective, well-tolerated and safe oral agents to lower LDL-C levels.

Gemcabene (administered as 6, 6'-oxybis [2, 2-dimethyl-4-hexanoic acid] monocalcium salt) is a lipid-regulating compound with a novel mechanism of action that enhances the clearance of very low density lipoprotein (VLDL) via the reduction of hepatic apolipoprotein C-III (apoC-III) messenger RNA (mRNA).[24–26] In the early 2000s, seven phase 2 studies were conducted, with the results from six of these studies never being published. Integration of the data supports gemcabene as being generally well tolerated across various patient populations with significant lowering of LDL-C, apolipoprotein B (apoB), and C-reactive protein (CRP) in hypercholesterolemia patients, and significant lowering of triglycerides (TG) and increases in high-density lipoprotein cholesterol (HDL-C) in hypertriglyceridemic patients. To date, gemcabene has been administered to 895 healthy subjects and patients and has been observed to be well tolerated in doses up to 900 mg once daily (QD) for up to 12 weeks.[27,28]

In 2011 gemcabene was in-licensed by Gemphire Therapeutics Inc. for continued development. Herein, we report data from the first study assessing gemcabene when added to previously prescribed background statins; an 8-week, double-blind, placebo-controlled study evaluating the efficacy and safety of gemcabene in patients whose LDL-C remained ≥ 130 mg/dL (3.4 mmol/L) while on stable statin therapy.

Methods

The study was conducted in compliance with good clinical practices. The study protocol, amendments, and subject-informed consent documents were approved by site-specific Institutional Review Boards, and the informed consent was signed by all participants before performance of any study-related activity.

Study subjects

From August 2000 to April 2002, patients entered into a run-in phase of up to 12 weeks whereby other lipid-lowering agents (fibrates, niacin, and fish oils) were discontinued and statin doses were stabilized. Patients on stable statin monotherapy (>3 months) and who met the eligibility criteria were randomized to an 8-week treatment phase (NCT02571257). Major inclusion criteria included men and postmenopausal women 18 to 65 years old and LDL-C ≥ 130 mg/dL (3.4 mmol/L). Patients were excluded if they had TGs > 400 mg/dL, creatine kinase [CK] > 3 × the upper limit of normal (ULN); body mass index > 35 kg/m^2; uncontrolled diabetes mellitus (HbA1C > 10%); renal dysfunction (blood urea nitrogen [BUN] or creatinine > 2 × ULN); or hepatic dysfunction (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 2 × ULN); myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary bypass graft, or any other major cardiovascular event resulting in hospitalization in the previous month; or a history of gall stones or gall bladder disease.

Study design

This was an 8-week, double-blind, placebo-controlled, randomized, multicenter, phase 2 study in

hypercholesterolemic patients on stable statin therapy. Before the screening visit, patient's statin therapy was stabilized, and all other lipid-altering medications were discontinued for at least 12 weeks. Patients with LDL-C $\geq$ 130 mg/dL at the screening visit (and who continued to meet entry criteria) remained on their current background statin therapy and were randomized within 6 weeks 1:1:1 to either gemcabene 300 mg QD, gemcabene 900 mg QD or matching placebo for 8 weeks (Fig. 1).

Study procedures

Fasting serum samples for lipid efficacy and key chemistry assessments (AST, ALT, and CK) were collected at screening and weeks 0, 2, 4, and 8. More complete laboratory (hematology and chemistry) analysis was performed at screening and week 8. Elevations of ALT or AST $>$ 3 $\times$ ULN at 2 consecutive measurements 1 week apart ($\pm$3 days) or CK $>$ 10 $\times$ ULN at 2 consecutive measurements 1 week apart ($\pm$3 days) were reported as adverse events and required active management by investigators. A physical examination was performed at weeks 0 and 8. At each visit, vital signs were performed and patients were queried about adverse experiences, including specific inquiring for signs/symptoms of myalgia, muscle weakness, or production of brown urine.

Study endpoints

The primary endpoint was the mean percent change from baseline in LDL-C at week 8. Secondary and exploratory endpoints included the percent change from baseline in total cholesterol (TC), TGs, VLDL-C, HDL-C, apoB, and CRP at week 8. The calculated change from baseline in non-HDL-C (TC minus HDL-C) is also reported, as is the Framingham Risk Score. Safety and tolerability were determined by treatment emergent adverse event (AE) reporting, clinical laboratory assessments, vital signs, and physical examination. Clinically significant abnormal laboratory values or clinically significant changes in vital signs or physical examinations were recorded as adverse events.

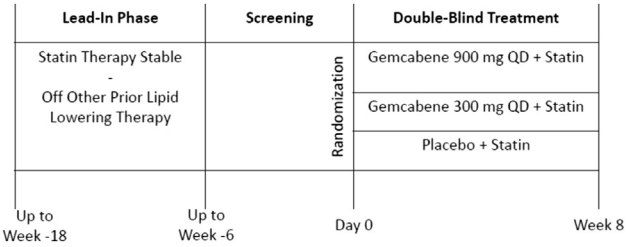

Figure 1 Study design. After patient consent, statin therapy was stabilized and all other lipid-modifying medications were discontinued during a run-in phase of up to 12 weeks. Patients were screened (over 6 weeks) and then randomized 1:1:1 to either gemcabene 300 mg QD, 900 mg QD, or matching placebo for 8 weeks. Low-density lipoprotein cholesterol (LDL-C); once daily (QD).

Randomization and blinding

Patients were randomized within each site to one of the three treatment groups. Study medication was shipped to the sites in fixed block sizes of six. Each patient qualifying for a treatment assignment was given the next consecutive number within a site and was dispensed the corresponding study medication. Gemcabene 300 mg tablets and matching placebo tablets were supplied by Pfizer Inc. Patients randomized to the 300-mg dose group were administered 1 $\times$ 300 mg gemcabene and 2 placebo tablets/dose QD; those randomized to the 900-mg dose group were administered 3 $\times$ 300 mg gemcabene tablets/dose QD, and those randomized to the placebo group were administered 3 placebo tablets/dose QD.

Analytical methods

Medical Research Laboratories (currently PPD Global Central Laboratories, Highland Heights, Kentucky) was the central laboratory for measurement of all laboratory procedures including lipid profile, clinical chemistries, hematology, and urinalysis. The laboratory was accredited by the College of American Pathologists and standardized by the Centers for Disease Control part III Lipid Standardization Program. LDL-C was calculated by the Friedewald equation.[29] VLDL-C was estimated from TG by using the formula TG/5. HDL-C was measured after precipitation of apoB containing lipoproteins with dextran sulfate.[30]

Statistical methods

The efficacy analyses included all patients with at least 1 baseline lipid value and at least 1 postrandomization measurement. The baseline value was calculated as the mean of the screening and week 0 measures. If one of the two baseline measurements was missing, the single available measurement was used alone. The last double-blind measurement was carried forward for patients who did not have a measurement at week 8. All tests were 2-sided and conducted at the 5% level of significance. A sample size of 69 patients (23 patients per treatment group) was expected to provide 90% power to detect an absolute difference of 20% between the placebo and gemcabene 900 mg groups in the mean percent change from baseline in LDL-C. This was based on the use of a 2-sided t test with a 5% level of significance and a standard deviation of 20%.

The mean percent change from baseline in LDL-C at week 8 was analyzed using an analysis of covariance (ANCOVA) model with the effects due to treatment, combined center, and baseline LDL-C value as a covariate. Adjusted means from the ANCOVA are presented. To adjust for multiple comparisons, a step-down approach to testing was used. Treatment-by-center and treatment-by-baseline interactions were investigated separately. The Shapiro–Wilk test determined if the residuals from the ANCOVA analysis were normally distributed. In cases

where non-normality was indicated, the parameter and its baseline value were ranked and also analyzed by Conover's nonparametric ANCOVA technique, and thus, median changes were also reported.[31]

The analysis described for LDL-C was also conducted for change from baseline in TC, TGs, non-HDL-C, HDL-C, VLDL-C, apo B, and CRP at week 8. Owing to small patient numbers, only descriptive statistics by statin-intensity subgroups was provided for changes in LDL-C.

All patients who received at least 1 dose of study medication were included in the safety analyses. Descriptive statistics by treatment group were provided for adverse event data and clinical laboratory data. The incidence of adverse events was compared by visual inspection between treatment groups. Descriptive summaries were provided for changes in vital signs.

Results

Subject disposition and baseline characteristics

Of the 211 patients screened, a total of 66 patients were randomized as follows: 24 to placebo, 20 to gemcabene 300 mg, and 22 to gemcabene 900 mg. A majority of the screen failures did not meet the inclusion criterion of LDL-C ≥ 130 mg/dL. Sixty-one patients completed the study: 3 patients (2 placebo and 1 gemcabene discontinued due to adverse events and 2 patients withdrew consent; Fig. 2). Patient demographic and other baseline characteristics are summarized in Table 1 and were generally similar across treatment groups, other than LDL-C values, which were slightly higher in the placebo group and TGs, which were higher in the 900-mg gemcabene group. The number of patients with diabetes mellitus was low with 1 (4.2%) patient in the placebo group and 4 (9.5%) patients in the gemcabene treatment groups. Approximately 10% of patients were current smokers, with most patients (approximately 50%) having never smoked. Patients entered the study on previously established stable low-intensity (n = 15, 22.7%), moderate-intensity (n = 39, 59.1%), and high-intensity (n = 12, 18.2%) statins.[32] Most patients across treatment groups were receiving moderate-intensity simvastatin and atorvastatin. Most of the patients entered in the study had low-to-moderate CVD risk.

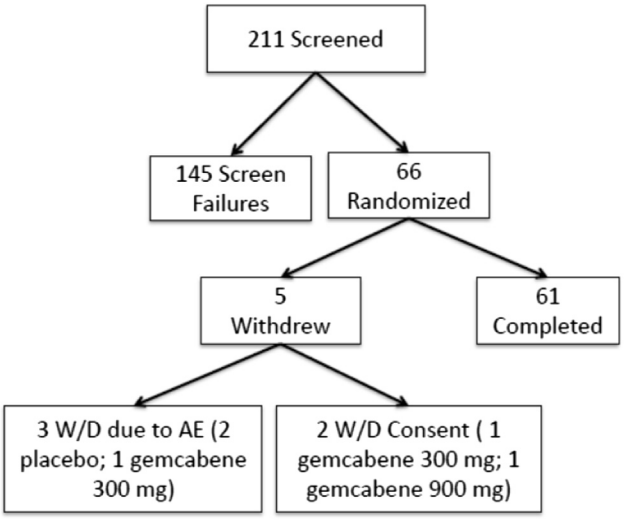

Figure 2 Patient disposition. A total of 211 patients were screened, 66 patients were randomized, and 61 patients completed the study. Withdrew (W/D); adverse event (AE).

Effect on LDL-C and other key parameters

The mean (±SE) percent change in LDL-C from baseline at week 8 was −23.4 ± 4.7% ($P = .009$) for gemcabene 300 mg, −27.7 ± 4.37% ($P < .001$) for gemcabene 900 mg and −6.2 ± 4.3% for placebo (Fig. 3). LDL-C effects across statin intensities were highly variable at the gemcabene 300 mg dose. At the most efficacious gemcabene dose (900 mg), LDL-C changes were (n = 5, −40.6%), (n = 12, −23.8%), and (n = 4, −23.8%) on background low, moderate, and high-intensity statins, respectively (Table 2).

Parallel reductions were seen in non-HDL-C and apoB (Fig. 3), with mean (±SE) percent change in non-HDL-C of −19.8 ± 4.3% ($P = .032$) and −23.9 ± 4.0% ($P = .004$) in the 300 mg and 900 mg treatment groups, respectively, vs −6.9 ± 3.9% with placebo. Mean (±SE) percent change in apoB was −11.9 ± 6.6% ($P = .301$) and −17.2 ± 6.0% ($P = .086$) in the 300 mg and 900 mg treatment groups, respectively, vs −2.80 ± 5.7% with placebo.

Median percent change in CRP was −26.1% ($P = .196$) and −53.9% ($P < .001$) in the 300 mg and 900 mg treatment groups, respectively, vs −11.1% with placebo (Fig. 3). In the 900-mg gemcabene treatment group, 75% (15 of 20) of patients had a CRP lowering of ≥ 50%, vs 14% (3 of 21) in the placebo group.

Mean (±SE) percent change in TC was −15.6 ± 3.5% ($P = .026$) and −19.9 ± 3.1% ($P = .001$) in the 300 mg and 900-mg treatment groups, respectively, vs −4.8 ± 3.1% with placebo. Mean changes in TG and VLDL-C trended lower in the gemcabene treatment groups but were not statistically different from placebo. There was no change in HDL-C vs placebo in this study (Table 3).

Safety

Treatment-emergent adverse events (Table 4) were experienced by 45% (9 patients) receiving gemcabene 300 mg and 72.7% (16 patients) receiving gemcabene 900 mg compared to 50% (12 patients) receiving placebo. The most frequently occurring adverse events in the gemcabene-treatment group were headache (4 patients; 9.5%) and infection (4 patients; 9.5%). The most frequently occurring adverse event in the placebo group was infection (3 patients; 12.5%).

Table 1 Baseline characteristics for all randomized patients

	Number of patients (%)			
		Gemcabene + Statin		
	Placebo + Statin	300-mg QD	900-mg QD	All doses
Characteristic	N = 24	N = 20	N = 22	N = 42
Sex, N (%)				
Men	11 (45.8)	12 (60)	7 (31.8)	19 (45.2)
Women	13 (54.2)	8 (40)	15 (68.2)	23 (54.8)
Race, N (%)				
White	20 (83.8)	15 (75)	18 (81.8)	33 (78.6)
Nonwhite	4 (16.7)	5 (25)	3 (13.5)	5 (21.4)
Age (y)				
Mean (SE)	57.5 (1.2)	51.2 (1.7)	57.3 (1.5)	54.3 (1.2)
Body mass index (kg/m^2)				
Mean (SE)	28.5 (0.9)	28.0 (0.9)	27.6 (0.7)	27.8 (0.6)
Smoking, N (%)				
Current smoker	2 (9.1)	1 (5.6)	4 (19.0)	5 (12.8)
Never smoked	11 (50.0)	10 (55.6)	9 (42.9)	19 (48.7)
Past smoker	9 (40.9)	7 (38.9)	8 (38.1)	15 (38.5)
Diabetic, N (%)				
Yes	1 (4.5)	1 (5.6)	2 (9.5)	3 (7.7)
No	21 (95.5)	17 (94.4)	19 (90.5)	36 (92.3)
Laboratory parameters (mg/dL)				
Mean (SE)				
LDL-C*,†	157.4 (5.7)	149.6 (6.8)	149.0 (6.1)	149.3 (4.5)
HDL-C*	53.2 (2.5)	51.7 (3.1)	54.5 (2.9)	53.2 (2.1)
Non-HDL-C*	190.6 (6.3)	185.2 (6.8)	185.6 (6.6)	185.4 (4.7)
TG*	168.5 (18.4)	159.5 (17.2)	189.4 (17.9)	175.2 (12.5)
TC*	244.5 (6.4)	234.5 (6.5)	241.1 (6.6)	238.0 (4.6)
Apolipoprotein B*	147 (4.2)	144.6 (4.7)	151.7 (5.5)	148.3 (3.7)
C-reactive protein (mg/L)	4.2 (1.2)	0.7 (0.07)	4.2 (1.1)	3.5 (0.7)
Systolic blood pressure (mm Hg)				
Mean (SE)	128.4 (2.4)	123.3 (2.3)	135.8 (2.7)	129.8 (2.0)
Diastolic blood pressure (mm Hg)				
Mean (SE)	80.4 (1.5)	77.6 (1.7)	81.5 (1.5)	79.6 (1.1)
Statin therapy, N(%)‡				
Low intensity	4 (17)	6 (30)	5 (23)	11 (26)
Moderate intensity	15 (62)	11 (55)	13 (59)	24 (57)
High intensity	5 (21)	3 (15)	4 (18)	7 (17)

SE, Standard error; TG, Triglyceride; TC, total cholesterol.
*Baseline was the mean of screening and week 0.
†Friedewald method unless TG > 400 mg/dL, in which case ultracentrifugation was used.
‡Low-intensity statin therapy included, fluvastatin 40 mg/day, cerivastatin 0.4 mg/day, lovastatin 10-20 mg/day, pravastatin 10-20 mg/day, or simvastatin 10 mg/day. Moderate intensity statin therapy included, atorvastatin < 40 mg/day, pravastatin 40 mg/day, or simvastatin 20-40 mg/day. High intensity statin therapy included, atorvastatin ≥ 40 mg/day, simvastatin 80 mg/day. QD, once daily.

Associated treatment-emergent adverse events (Table 5) were experienced by 21.4% (300 mg: 4 patients; 900 mg: 5 patients) receiving gemcabene and by 29.2% (7 patients) receiving placebo. The most common treatment-associated adverse events in the gemcabene-treatment group were asthenia, headache, and dizziness (2 patients each; 4.8%). For the placebo group, the most common adverse event was vasodilatation (2 patients; 8.3%).

One patient receiving gemcabene 900 mg had a serious adverse event of iliac occlusive disease requiring hospitalization that was considered unrelated to treatment. Three patients (2 placebo and 1 gemcabene 300 mg) withdrew due to adverse events, all of which were considered possibly related to treatment. There were no deaths in this study.

Laboratory adverse events

Changes in clinical laboratory assessments (Table 4) were small, nonsignificant, and generally similar across

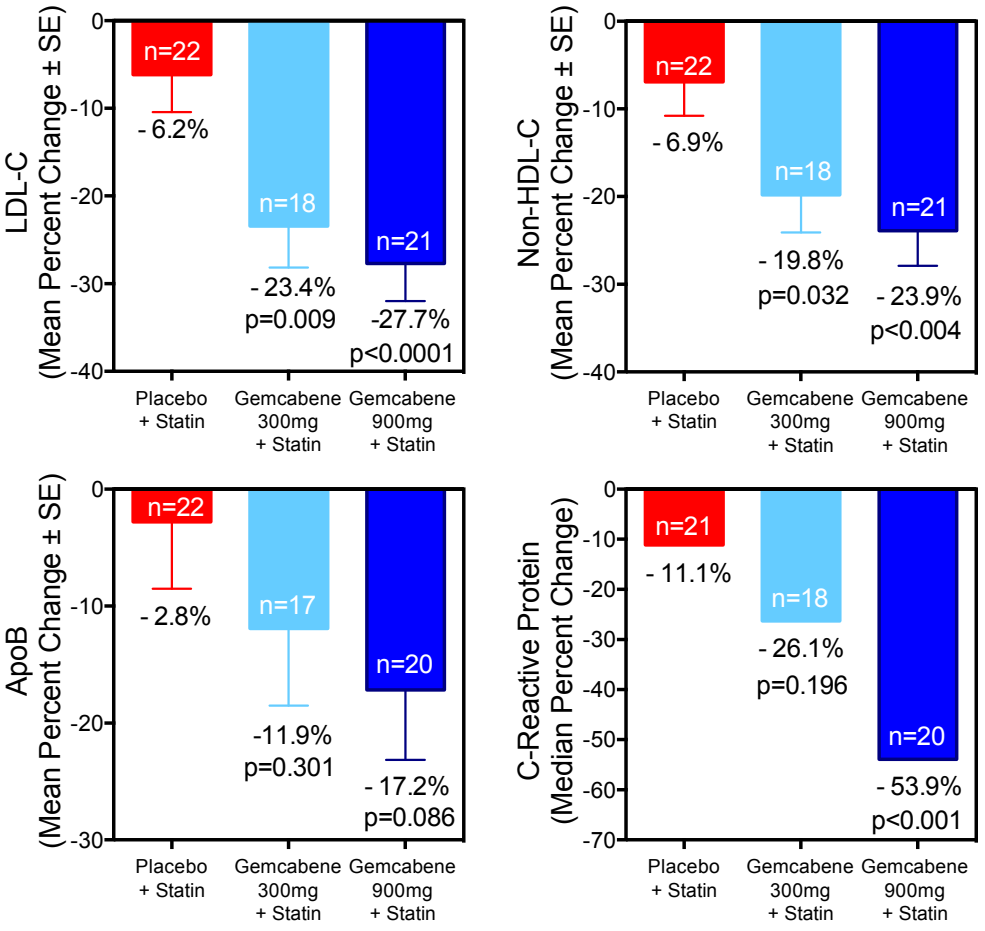

Figure 3 Gemcabene effects on mean percent change in LDL-C, non-HDL-C, ApoB, and median percent change in CRP. LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; apoB, apolipoprotein B; non-HDL-C, non-high-density lipoprotein cholesterol.

treatment groups. Small nonstatistically significant reductions in mean fasting glucose of −9.8 and −3.0 mg/dL were seen for gemcabene 300 mg and 900 mg, respectively, vs −0.7 mg/dL for placebo. No meaningful changes were observed in liver transaminases (ALT and AST) in patients administered gemcabene as compared

Table 2 Mean change in LDL-C by statin intensity*

Treatment/statin intensity (32)	N	Mean baseline LDL	Mean final LDL	Mean % change baseline LDL	Mean absolute change baseline LDL
Placebo	22	158.6	147.1	−6.7	−11.5
Low-intensity statin	4	150.4	162.0	4.4	11.6
Moderate-intensity statin	14	156.1	142.0	−8.2	−14.1
High-intensity statin	4	175.8	150.0	−12.3	−25.8
Gemcabene 300 mg	18	149.1	112.7	−24.3	−36.4
Low-intensity statin	5	157.4	124.8	−19.9	−32.6
Moderate-intensity statin	10	144.5	92.8	−35.0	−51.7
High-intensity statin	3	150.5	158.7	4.3	8.2
Gemcabene 900 mg	21	149.0	108.0	−27.7	−41.0
Low-intensity statin	5	145.1	85.4	−40.6	−59.7
Moderate-intensity statin	12	141.0	107.3	−23.6	−33.8
High-intensity statin	4	178.0	138.5	−23.8	−39.5

*Low-intensity statin therapy included, fluvastatin 40 mg/day, cerivastatin 0.4 mg/day, lovastatin 10-20 mg/day, pravastatin 10-20 mg/day, or simvastatin 10 mg/day. Moderate intensity statin therapy included, atorvastatin < 40 mg/day, pravastatin 40 mg/day, or simvastatin 20-40 mg/day. High intensity statin therapy included, atorvastatin ≥ 40 mg/day, simvastatin 80 mg/day.

Table 3 Mean percent change in lipids from baseline to last assessment (week 8)*

	Placebo + Statin	Gemcabene + Statin	
		300-mg QD	900-mg QD
Lipid parameter	N = 22	N = 18	N = 21
TC			
N	22	18	21
Mean baseline (SE)	243.3 (6.2)	234.5 (6.5)	241.1 (6.6)
Mean week 8 (SE)	231.5 (8.5)	201.4 (11.4)	195.1 (7.2)
Adj. mean % change (SE)	−4.8 (3.1)	−15.6 (3.5)	−19.9 (3.1)
P value		0.026	0.001
HDL-C			
N	22	18	21
Mean baseline (SE)	53.6 (2.6)	52.1 (3.3)	54.6 (3.0)
Mean week 8 (SE)	53.7 (2.8)	52.2 (2.9)	52.9 (3.5)
Adj. mean change (SE)	0.1 (1.7)	0.2 (1.9)	−4.2 (2.9)
P value	N/A	0.656	0.265
VLDL-C			
N	22	18	21
Mean, baseline (SE)	34.5 (3.8)	32.1 (3.6)	37.9 (3.6)
Mean week 8 (SE)	33.0 (3.6)	29.1 (4.0)	31.9 (3.6)
Adj. mean % change (SE)	−2.0 (5.2)	−10.1 (5.9)	−14.6 (5.3)
P value	N/A	0.3	0.093
TG			
N	22	18	21
Mean baseline (SE)	172.4 (18.8)	160.7 (18.1)	189.4 (17.9)
Mean week 8 (SE)	165.0 (18.1)	145.3 (20.2)	159.5 (17.8)
Adj. mean % change (SE)	−2.0 (5.2)	−10.1 (5.9)	−14.6 (5.3)
P value	N/A	0.3	0.093

SE, standard error; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; VLDL-C, very low-density lipoprotein-cholesterol; TG, triglyceride.

*Week 8 of double-blind treatment or last observation carried forward (LOCF) if Week 8 is missing.

to placebo. One patient receiving 300-mg gemcabene had a single transient elevation of CK 5 × ULN (661 U/L [ULN = 120 U/L]), which was not present on repeat testing. No clinically meaningful changes in physical examinations or vital signs from baseline to the end of the study were observed.

Discussion

Gemcabene is a lipid-lowering therapy with a novel mechanism of action. Chow-fed Sprague–Dawley rats orally administered gemcabene showed a dose-dependent reduction in hepatic apoC-III mRNA levels, which correlated with the reduction in plasma TG.[26] In the same study, gemcabene also showed a markedly enhanced clearance in ^{125}I-labeled VLDL.[26] This is consistent with known effects of lowering apoCIII including the enhanced clearance of VLDL remnants, the reduced formation of LDL, and enhanced TG lipolysis by lipoprotein lipase.[33,34] In mice devoid of LDL receptors treatment with gemcabene 60 mg/kg/day for 14 days lowered LDL-C 55%, supporting a mechanism independent of the hepatic LDL receptor to reduce plasma LDL levels.[25,35] A study assessing the effects of gemcebene in HoFH patients is currently underway. Finally, gemcabene showed cytokine-induced inhibition of CRP promoter activity in PLC/PR5/human hepatocytes. Site-directed mutagenesis of the C/EBP, Nf-kB, and STAT sites of human CRP promoter together with gel-shift assay suggested C/EBP-δ as a major player and C/EBP-β and Nf-kB binding protein as minor players in gemcabene-mediated down-regulation of CRP transcription.[36] Taken together, gemcabene's mechanism of action should lower the full range of atherogenic particles (VLDL, IDL, and LDL) resulting in decreases in atherogenic particle number (apoB), particle cholesterol (non-HDL-C), and TGs (when elevated); with concomitant lowering of hsCRP.

Table 4 Overview of adverse events and clinical laboratory changes

Adverse events	Placebo + Statin	Gemcabene + Statin 300-mg QD	Gemcabene + Statin 900-mg QD	Gemcabene + Statin All doses
N (% of patients)	N = 24	N = 20	N = 22	N = 42
All AEs				
Mild	6 (25.0)	6 (30.0)	9 (40.9)	15 (35.7)
Moderate	6 (25.0)	3 (15.0)	6 (27.3)	9 (21.4)
Severe	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.4)
Associated AEs by max intensity				
Mild	2 (8.3)	2 (10.0)	5 (22.7)	7 (16.7)
Moderate	5 (20.8)	2 (10.0)	0 (0.0)	2 (4.8)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Withdrawals due to AEs				
All AEs	2 (8.3)	1 (5.0)	0 (0.0)	1 (2.4)
Associated AEs	2 (8.3)	1 (5.0)	0 (0.0)	1 (2.4)
Serious AEs (not associated)	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.4)
Number of patients who died	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Clinical laboratory changes for all randomized patients	Placebo + Stain	Gemcabene + Statin 300-mg QD	Gemcabene + Statin 900-mg QD	Gemcabene + Statin All doses
Mean ± (SE) or frequency (n)	N = 24	N = 19	N = 21	N = 40
Laboratory parameter (units)				
ALT (U/L)	−0.6 (0.8)	0.8 (2.7)	−1.4 (1.8)	−0.4 (1.6)
AST (U/L)	−0.2 (0.6)	1.3 (1.3)	0.5 (1.3)	0.9 (0.9)
CK (mg/dL)	11.3 (8.5)	−0.3 (5.5)	−2.0 (4.8)	−1.2 (3.6)
Creatinine (mg/dL)	0.0 (0.0)	0 (0.0)	0.1 (0.0)	0.1 (0.0)
BUN total (mg/dL)	0.5 (0.5)	1.6 (0.7)	2.9 (0.7)	2.3 (0.5)
Glucose—fasting (mg/dL)	−0.7 (1.5)	−9.8 (11.2)	−3.0 (4.2)	−6.3 (5.7)
ALT (>3 × ULN) (n)	0	0	0	0
AST (>3 × ULN) (n)	0	0	0	0
CK (>5 × ULN) (n)	0	1	0	1

ALT, alanine aminotransferease; AST, aspartate aminotransferase; CK, creatine kinase; BUN, blood urea nitrogen; ULN, upper limit of normal.

The above effects were observed in this phase 2 study in patients on background statin therapy and with an average baseline LDL-C of approximately 150 mg/dL. Gemcabene 300 mg and 900 mg significantly lowered LDL-C 23.4% and 27.7%, respectively, vs a lowering of 6.2% for placebo. This resulted in nearly 48% of patients achieving an LDL-C of < 100 mg/dL. At the most efficacious gemcabene dose (900 mg), LDL-C reductions were (n = 5, 40.6%), (n = 12, 23.6%), and (n = 4, 23.8%) on background low, moderate, and high-intensity statins, respectively. Consistent with the LDL-C lowering, gemcabene showed reductions in non-HDL-C and TC and a significant lowering of CRP at gemcabene 900 mg. As the majority of patients presented with mild to moderate hypertriglyceridemia, only moderate and nonstatistically significant lowering of TGs was observed. However, in a study in hypertriglyceridemic patients (mean baseline TGs ≥ 200 mg/dL), gemcabene produced a correlative and significant decrease in apoCIII and triglycerides, consistent with gemcabene's mechanism.[27]

Although statins are the most widely used efficacious oral LDL-C lowering agents, they reduce LDL-C by only another 6% to 7% when the dose is doubled and are ultimately limited by toxicity.[37–39] Additional LDL-C lowering via a mechanism complementary to that of statins thus provides greater LDL-C reducing potential and has recently shown ASCVD beneficial effects. The reduction in LDL-C with ezetimibe added to simvastatin vs simvastatin alone in the IMPROVE-IT trial resulted in a significant decrease in cardiovascular events.[6] In an analysis of subgroups from IMPROVE-IT, it was noted that patients with on-treatment LDL-C and hs-CRP below selected cut-points had fewer ASCVD events compared to patients with both LDL-C and hs-CRP above these cut-points.[40] The LDL-C reductions seen with gemcabene are similar to those reported for ezetimibe,[41] as well as bempedoic acid (ETC-1002) at doses of 120 mg and 180 mg,[42] added to similar stable statin background therapy. Importantly, gemcabene has also shown a significant lowering of CRP of up to 53.9%.

The LDL-C results in this add-on to statin study differ substantially from those seen in another study where gemcabene and atorvastatin therapy was administered concurrently.[28] Differences in LDL-C lowering results

Table 5 Summary of all associated treatment emergent adverse events, N (% of patients)

		Gemcabene + Statin		
	Placebo+ Statin	300-mg QD	900-mg QD	All doses
Preferred term	N = 24	N = 20	N = 22	N = 42
Abdominal pain	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	1 (5.0)	1 (4.5)	2 (4.8)
Chest pain	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.4)
Face edema	0 (0.0)	1 (5.0)	0 (0.0)	1 (2.4)
Headache	1 (4.2)	2 (10.0)	0 (0.0)	2 (4.8)
Infection	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vasodilatation	2 (8.3)	0 (0.0)	1 (4.5)	1 (2.4)
Constipation	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (4.2)	1 (5.0)	0 (0.0)	1 (2.4)
Thirst	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.4)
Leukopenia	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.4)
Myalgia	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Myasthenia	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	1 (4.2)	1 (5.0)	1 (4.5)	2 (4.8)
Hypesthesia	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Polyuria	0 (0.0)	0 (0.0)	1 (4.5)	1 (2.4)
Prostatic Disorder	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Number of patients with AEs	7 (29.2)	4 (20)	5 (22.7)	9 (21.4)

between the two studies are likely due to the study design and patient populations, which underestimates the LDL-C lowering potential as add-on therapy. This has been observed with ezetimibe, whereby ezetimibe administered concurrently with atorvastatin 80 mg resulted in a 6% additional lowering of LDL-C, whereas ezetimibe administered on background atorvastatin 80 mg resulted in an additional 17%–21% lowering in LDL-C.[41,43]

Limitations to the present study are as follows: (1) low patient numbers limit the ability to make certain conclusions, including the ability to summarize data by entry TG levels; (2) patients were not on the highest doses of what today are considered the most efficacious statins, atorvastatin 80 mg, or rosuvastatin 40 mg, which may affect both the efficacy and safety of gemcabene; (3) we only tested gemcabene in patients with LDL-C ≥130 mg/dL, and it is unknown if the efficacy is the same at lower LDL-C levels (and levels still not at goal) on stable statin therapy; and (4) whereas it is highly probably that many of the patients had heterozygous familial hypercholesterolemia given their LDL-C ≥130 mg/dL on moderate dose statin, it is important to conduct similar studies specifically in such subjects. Based on the results of IMPROVE-IT and the likelihood that ezetimibe added to statin will become the standard of care, it is also important to evaluate the LDL-C efficacy of gemcabene when added to not only moderate statin (as in this trial) but also high-dose statin alone and/or statin/ezetimibe-treated patients who fail to achieve optimal LDL-C. A study is planned in patients needing further LDL-C lowering on stable high-intensity statin therapy, which will address the utility of gemcabene over intensive standard of care as well as further explore the mechanism of effect.

Gemcabene and a series of other carboxyalkylethers were patented in 1995.[24] The first preclinical data on gemcabene (PD72953) and select compounds of the series were reported in 1998.[26] Gemcabene was selected for further development as a clinical candidate in 1998. The current phase 2 study (NCT02571257) was conducted between August 10, 2000 and April 15, 2002. The Investigational New Drug (IND) application for the program was withdrawn without prejudice in 2005. The gemcabene program was licensed from Pfizer Inc. by Michigan Life Therapeutics, LLC (currently Gemphire Therapeutics Inc.) in 2011, and a new IND application for gemcabene was filed in 2015.

To date, gemcabene has been administered for up to 12 weeks to 895 healthy subjects and patients and has been observed to be generally well tolerated to 900-mg QD.[27,28] The present study confirmed that treatment with gemcabene in patients on stable statin therapy was well-tolerated with a safety profile similar to statin therapy alone. The results from this study support the continued development of gemcabene as an adjunctive therapy to lower LDL-C in patients with CVD unable to reach goal with existing statin therapy and in patients without CVD but severe hypercholesterolemia including HoFH or heterozygous FH.

Conclusions

In this phase 2 study, gemcabene 300 mg and 900 mg showed placebo-corrected significant lowering of LDL-C (17 and 22%) and CRP (15 and 43%) in hypercholesterolemic patients on stable statin therapy. Importantly, gemcabene (up to 900 mg for 8 weeks) was well-tolerated with a safety profile similar to statin therapy alone and supports the further development of gemcabene as an adjunctive therapy to reduce LDL-C in patients unable to reach goal with existing statin therapy.

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