Efficacy and Safety of Gemcabene as Add-on to Stable Statin Therapy in Patients with Hypercholesterolemia

Michael Koren[1]*, Harold Bays[2], Evan Stein[3], Rebecca Bakker-Arkema[4], Charles Bisgaier[5]

Jacksonville Center for Clinical Research, Jacksonville, FL[1]; Louisville Metabolic & Atherosclerotic Research Center, Louisville, KY[2]; Metabolic & Atherosclerosis Research Center, Cincinnati, OH[3], Tanglewood Clinical Consulting, Ann Arbor, MI[4]; Gemphire Therapeutics Inc, Northville, MI[5]

ABSTRACT

Synopsis: More effective and well-tolerated agents are needed to treat hypercholesterolemic patients on background statins not at low-density lipoprotein cholesterol (LDL-C) goal. Gemcabene may offer a novel and complementary mechanism to statins as demonstrated by LDL-C lowering in preclinical models devoid of LDL receptors. Gemcabene has shown LDL-C reduction as monotherapy in several Phase 2 studies and with good-tolerability for up to 12 weeks in nearly 900 patients.

Objective/Purpose: Gemcabene is a novel lipid-lowering therapy with a dual mechanism of action designed to enhance the clearance of very low-density lipoproteins (VLDLs) in the plasma and inhibit the production of fatty acids and cholesterol in the liver, further lowering plasma VLDL and its metabolic product (LDL). An 8-week, double-blind, placebo-controlled, randomized, Phase 2 study was conducted to determine the utility of administering gemcabene stable statin therapy in patients whose LDL-C remained above 130 mg/dL.

Methods: Sixty-six patients with baseline LDL-C ≥130 mg/dL on stable statin (majority on moderate-intensity) therapy ≥3 months were randomized 1:1:1 to gemcabene 300 mg (N=20), 900 mg (N=22) or placebo (N=24) administered orally once daily.

Results: At 8 weeks, gemcabene 300 and 900 mg produced a mean change in LDL-C of -23.4 ± 5% (p=0.005) and -27.7 ± 4% (p<0.001), respectively, versus -6.2 ± 4% with placebo. These lipid effects resulted in a significant change in Framingham Risk Score of -1.95 (p=0.006) and -3.21 (p<0.0001), respectively, compared to -0.75 with placebo. Concomitant reductions in apolipoprotein B, non-high-density lipoprotein-C, and triglycerides (or VLDL-C) were observed. The median change in C-reactive protein (CRP) was -26.1% (p=0.196) and -53.9% (p<0.001) for 300 mg and 900 mg, respectively, versus -11.1% with placebo. Gemcabene 300 and 900 mg was well-tolerated with no significant increase in adverse events compared to placebo.

Conclusions: In patients on stable statin therapy, gemcabene demonstrated additional significant reductions in LDL-C and hsCRP. This study supports future development of gemcabene as a well-tolerated and effective oral agent for additional lipid lowering beyond background statin therapy.

INTRODUCTION

Low-density lipoprotein cholesterol (LDL-C) is a validated biomarker for reducing cardiovascular events and a cornerstone of national and international guidelines for reducing the burden of atherosclerotic cardiovascular disease (ASCVD)[1-3]. Statins are safe and effective at lowering LDL-C; however, many patients do not achieve LDL-C targets with statins alone.[4,5] and others are unable or unwilling to tolerate effective doses of statins.[6] Secondary agents used to achieve additional LDL-C reduction are often limited by tolerability, side effects or poor efficacy.[7,8,9, 10]

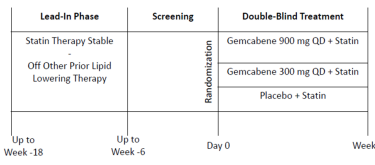
High-sensitivity C-reactive protein (hsCRP), a marker of systemic inflammation produced mainly in the liver, is independently associated with increased risk of coronary heart disease (CHD); however, causality of high levels of hsCRP and CHD have not been established.[11] In the primary prevention JUPITER trial, rosuvastatin demonstrated a incremental reduction in CHD risk in patients achieving both LDL-C < 1.8 mmol (70 mg/dl) and hsCRP < 2mg/L compared to patients achieving one or the other.[12] Increased hsCRP also predicted which patients benefited from lovastatin in the Air Force/Texas Coronary Atherosclerosis Prevention Study.[13] More recently, increased beneficial effects of achieving both LDL-C and hsCRP goals was observed in a subgroup analysis of IMPROVE-IT, in which patients with LDL-C and hsCRP below selected cut-points had fewer cardiovascular disease events compared to patients with both LDL-C and hsCRP above these cut-points.[14]

Gemcabene regulates lipids by decreasing production of apolipoprotein CIII (apoC III) resulting in the enhanced clearance of very-low density lipoprotein (VLDL) remnants and reducing the formation of LDL, while also breaking down triglycerides by lipoprotein lipase to deliver more fatty acids to muscle and adipose tissue.[15,16] The current Phase 2 study design resembles clinical practices, whereby patients on background statins with LDL-C levels above the target of 130 mg/dL received add-on gemcabene.

STUDY DESIGN

The study evaluated hypercholesterolemic patients in an 8-week, double-blind, placebo-controlled, randomized, multicenter, Phase 2 trial. Statin therapy was stabilized prior to screening and all other lipid altering medications were discontinued for at least 12 weeks. Patients with LDL-C > 130 mg/dL at the screening visit who met entry criteria on background statin therapy were randomized 1:1;1 within 6 weeks, to either gemcabene 300 mg QD, gemcabene 900 mg QD or matching placebo for 8 weeks (Figure 1).

Fig 1: Study Design



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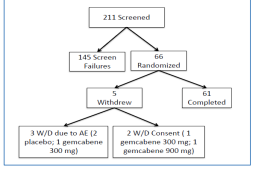
METHODS

The primary study endpoint was mean percent change in LDL-C from baseline to Week 8. The endpoint was evaluated using an analysis of covariance (ANCOVA) model with effects due to treatment arm, study sites, and baseline LDL-C value as covariates. Adjusted means are presented below. Tests were 2-sided and conducted at the 5% level of significance. To adjust for multiple comparisons, a step-down approach to testing was used. Treatment-by-site 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. The analysis described for LDL-C was also conducted for change from baseline in total cholesterol (TC), triglycerides (TGs), VLDL-C, HDL-C, non-HDL-C, apolipoprotein B (apo B) and hsCRP at Week 8. The patient's Framingham Risk Score (including age, gender, systolic blood pressure [± treatment], TC and HDL-C level, and smoking status) was calculated at baseline and at week 8. Change from baseline was calculated using the Student's paired t-test and the Wilcoxon Signed Rank test.

Descriptive statistics by treatment group were provided for adverse event (AE) data and clinical laboratory data. The incidence of AEs was compared by visual inspection between treatment groups. Descriptive summaries were provided for changes in vital signs.

PATIENT CHARACTERISTICS

Fig. 2: Patient Disposition



Sixty-one patients completed the study: 3 patients – 2 placebo and 1 gemcabene – discontinued due to adverse events and two patients withdrew consent (**Figure 2**). Table 1 summarizes patient demographic and baseline characteristics. These were matched across treatment groups, except for a slightly older age in the placebo group, slightly higher LDL-C values in the placebo group, and somewhat higher TGs in the 900 mg gemcabene group. 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. Most patients across treatment groups received moderate-intensity simvastatin and atorvastatin and had low to moderate CVD risk.

Table 1: Patient Characteristics

Baseline Characteristics for All Randomized Patients						
Characteristic	[Number of Patients (%)]					
	Placebo + Statin	Gemcabene + Statin				
		300 mg QD + Statin		900 mg QD + Statin		All Doses
	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)
Non-White	4	(16.7)	5	(25)	4 * (18.2)	9 (21.4)
Age, (yrs)						
Mean (SE)	57.5	(1.2)	51.2	(1.7)	57.3 (1.5)	54.3 (1.2)
Body Mass Index (kg/m2)						
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	(4.2)	2	(10)	2 (9.1)	4 (9.5)
No	23	(95.8)	19	(90)	20 (90.9)	39 (90.5)
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)	185.8 (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 †	4.2	(1.2)	2.7	(0.7)	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)	81.3 (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>400mg/dL, in which case ultracentrifugation was used.
¶ Low intensity statin therapy included, fluvastatin 40mg/day, cerivastatin 0.4 mg/day, lovastatin 10-20 mg/day, pravastatin 10-20 mg/day, or simvastatin 10mg/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

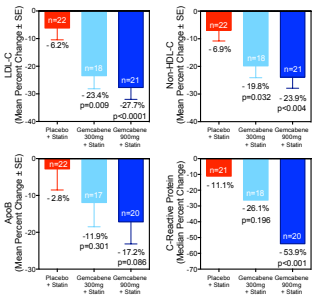
EFFECTS ON LDL-C, NON-HDL-C, APO-B, and hsCRP

The mean (±SE) percent change in LDL-C from baseline at Week 8 was -23.4 ± 5% (p=0.009) for gemcabene 300 mg, -27.7 ± 4% (p< 0.001) for gemcabene 900 mg and -6.2 ± 4% for placebo (**Figure 3, Panel 1**). Parallel reductions were seen in non-HDL-C and apoB (**Figure 3, Panels 2 and 3**), with mean (±SE) percent change in non-HDL-C of -19.8 ± 4% (p=0.032) and -23.9 ± 4% (p=0.004) in the 300 mg and 900 mg treatment groups, respectively, versus -6.9 ± 4% with placebo. Mean (±SE) percent change in apoB was -11.9 ± 7% (p=0.301) and -17.2 ± 6% (p=0.086) in the 300 mg and 900 mg treatment groups, respectively, versus -2.8 ± 6% with placebo. Median percent change in CRP was -26.1% (p=0.196) and -53.9% (p<0.001) in the 300 mg and 900 mg treatment groups, respectively, versus -11.1% with placebo (**Figure 3, Panel 4**). In the 900 mg gemcabene treatment group, 75% (15/20) of patients had a CRP lowering of ≥ 50%, versus 14% (3/21) in the placebo group. Mean (±SE) percent change in TC was -15.6 ± 4% (p=0.026) and -19.9 ± 3% (p=0.001) in the 300 mg and 900 mg treatment groups, respectively, versus -4.8 ± 3% 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 versus placebo in this study.

Patients treated with gemcabene 300 mg and 900 mg had significant reductions of 1.95 (p=0.007, p=0.006) and 3.21 (P<0.001, p<0.0001) in their Framingham Risk Score, compared to 0.75 (p=0.128, p=0.152) with placebo.

EFFECTS ON LDL-C, NON-HDL-C, APO-B, and CRP

Fig 3. Gemcabene Effects on Mean Percent Change in LDL-C (Panel 1), non-HDL-C (Panel 2), ApoB (Panel 3); and Median Percent Change in CRP (Panel 4)



SAFETY

The most frequently occurring adverse events (AEs) were headache (4 patients; 9.5%) and infection (4 patients; 9.5%) in the gemcabene-treatment group and infection (3 patients; 12.5%) in the placebo group. The most common treatment-associated AEs were asthenia, headache and dizziness (2 patients each; 4.8%) in the gemcabene-treatment group and vasodilatation (2 patients; 8.3%) in the placebo group. One patient receiving gemcabene 900 mg had a serious AE event of iliac occlusive disease requiring hospitalization considered unrelated to treatment. Three patients (2 placebo and 1 gemcabene 300 mg) withdrew due to AEs, all of which were considered possibly related to treatment. There were no deaths in this study. Changes in clinical laboratory assessments were small, nonsignificant and generally similar across treatment groups with the possible exception of somewhat lower glucose levels in gemcabene treated patients. One patient receiving 300 mg gemcabene had a single transient elevation of CK 5 x ULN (661 U/L [ULN = 120 U/L]) which was not present on repeat testing. No clinically meaningful changes in physical exams or vital signs from baseline to the end of the study were observed.

Table 2: Summary of Adverse Events (AEs)

[Number (%) of Patients]	Statin	300 mg QD + Statin	900 mg QD + Statin	All Doses
	N = 24	N = 20	N = 22	N = 42
All AEs				
Mild	6 (25.0)	6 (30.0)	8 (40.9)	15 (36.7)
Moderate	6 (25.0)	5 (15.0)	8 (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 + Statin	Gemcabene + Statin		
Mean ± (SE) or Frequency (n)		300 mg QD + Statin	900 mg QD + Statin	All Doses
	N = 24	N = 19	N = 21	N = 40
Lab 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 x ULN (n)	0	0	0	0
AST ≥3 x ULN (n)	0	0	0	0
CK ≥5 x ULN (n)	0	1	0	1

ALT = alanine aminotransferase, AST= aspartate aminotransferase,CK = creatinine kinase, BUN =Blood Urea Nitrogen, ULN =Upper Limit of Normal

CONCLUSIONS

- Mean percent change in LDL-C from baseline at Week 8 was significantly lower for gemcabene 300 and 900 mg/ day compared to placebo. Parallel reductions occurred in non-HDL-C and apo B.
- Median percent change in CRP was significant in the gemcabene 900 mg treatment groups versus placebo.
- Gemcabene was generally safe and well-tolerated.
- In light of limited options for oral add-on therapies, gemcabene may offer an alternative secondary therapy using a novel and complementary mechanism to statins to help patients achieve LDL-C goals.

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