

Gemcabene Monotherapy and in Combination with Atorvastatin Lowers High Sensitivity C-Reactive Protein (hsCRP) in a Phase 2 Clinical Trial



Stein EA¹, Bakker-Arkema R², McShane M³, Sooch MP³, and Bisgaier CL³

Metabolic and Atherosclerosis Res. Ctr.¹, Cincinnati, OH, Tanglewood Clinical Consulting², Ann Arbor, MI and Gemphire Therapeutics Inc.³, Northville, MI

ABSTRACT

Background: Inflammation plays a key role in the progression of atherosclerosis, and serum high sensitivity c-reactive protein (hsCRP) appears to be a good marker of the degree of underlying vascular inflammation and has been recognized as a predictor of cardiovascular risk. Lipid lowering drugs such as statins also reduce hsCRP and may be more likely to reduce cardiovascular events than those that do not. Gemcabene is an inhibitor of hepatic cholesterol triglyceride and apoCIII synthesis resulting in decreased assembly of VLDL and enhanced systemic clearance of VLDL and its subsequently production of remodeled lipoproteins including LDL.

Summary of the Median Percent Change in hsCRP Across All Treatment Groups		Atorvastatin (mg)			
		0	10	40	80
Gemcabene (mg)	0	9	-27	-31	-41
	300	-26	-27	-58	-59
	600	-42	-32	-65	-70
	900	-35	-53	-61	-63

Study Design and Results: In an 8-week double blind randomized, placebo-controlled, dose-ranging, efficacy and safety Phase 2 study, gemcabene 300, 600 and 900 mg/day administered as monotherapy or in combination with atorvastatin 10, 40 and 80 mg/day resulted in a significant and dose dependent reduction of LDL-C (Study 4141001). A secondary objective of this study was to evaluate the modulation of hsCRP by gemcabene. Of 277 patients randomized, 250 (90%) completed the study. Baseline mean LDL-C was 174.7mg/dL, and median hsCRP was 2.5 mg/L. The median % reduction in hsCRP with Gemcabene 300, 600 and 900 mg monotherapy was 25.8%, 41.5% and 35.3% respectively compared with 9.4% for placebo. The rank-transformed data showed significant difference favoring gemcabene over placebo in the 600 and 900 mg groups (p=0.007 and p=0.002, respectively). Co-administration of 300, 600, and 900 mg gemcabene with atorvastatin aggregated over the dose range showed decreases in hsCRP beyond atorvastatin monotherapy (which ranged from 27-41%) by an additional 16% (p=0.024), 23% (p=0.002) and 28% (p<0.001), respectively.

Conclusions: Gemcabene significantly lowered hsCRP alone and on top of statins in hypercholesterolemic patients.

INTRODUCTION

C-reactive protein (CRP), a marker of systemic inflammation produced mainly in the liver in response to pro-inflammatory cytokines, is part of an acute phase response. Increased levels of high-sensitivity CRP (hsCRP) have been independently associated with increased risk of coronary heart disease (CHD) but causality between hsCRP and CHD has not been established (1). In the primary prevention JUPITER trial, rosuvastatin demonstrated a lower CHD risk in patients with LDL-C < 130mg/dL and hsCRP < 2mg/L compared to patients with hsCRP ≥ 2 mg/L (2). Similar findings of reduced CHD risk were observed with lovastatin in the Air Force/Texas Coronary Atherosclerosis Prevention Study in patients with LDL-C < 150mg/dL and hsCRP < 2 mg/L compared to patients with hsCRP ≥ 2 mg/L (3). Furthermore, patients during the trial who had both LDL-C < 70 mg/dL and hsCRP < 2 mg/L in a subgroup analysis of IMPROVE-IT, had fewer cardiovascular disease (CVD) events compared to patients with both LDL-C and hsCRP above these cut-points (5).

There is no correlation between lowering of LDL-C and lowering of hsCRP, as indicated by several categories of lipid-lowering therapies including statins, fibrates and the recently approved proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibody inhibitors (6-8). Thus, it is not possible to predict in advance which lipid-lowering drugs will also lower hsCRP. Gemcabene is a novel lipid-lowering therapy with structural features similar to known molecules that inhibit both fatty acid and cholesterol synthesis, reducing both hepatic cholesterol and triglyceride (TG) synthesis and lowering very-low-density lipoprotein (VLDL) and its metabolic product (LDL) in the plasma (9, 10). In this Phase 2 study of gemcabene combined with atorvastatin, gemcabene showed significant effects on LDL-C levels. Unexpectedly, gemcabene also showed statistically significant reductions in hsCRP as both monotherapy and in combination with atorvastatin. The results of gemcabene on hsCRP and the proposed mechanism for this lowering is described further below.

STUDY DESIGN

We conducted a 8-week double blind randomized, placebo-controlled, dose-ranging, efficacy and safety Phase 2 study, gemcabene 300, 600 and 900 mg/day administered as monotherapy or in combination with atorvastatin 10, 40 and 80 mg/day (Figure 1; Table 1). Patients had to be men or naturally menopausal or surgically sterile women 18 to 70 years of age. Patients without overt coronary heart disease (CHD) had to have a mean LDL-C of ≥130 mg/dL if National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III CHD risk ≥10%, or ≥160 mg/dL if NCEP ATP III CHD risk <10% and mean LDL-C <250 mg/dL.

Fig 1: Study Design

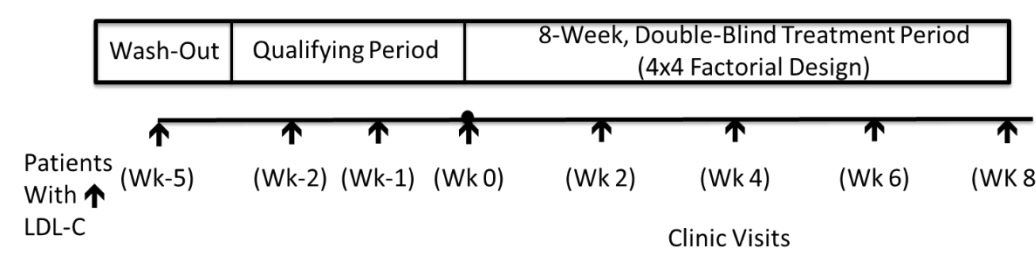


Table 1: Drug and Dose Matrix

4 x 4 Factorial Design Used in 8-Week, Double Blind Treatment Period				
	Gem 300 mg	Gem 600 mg	Gem 900 mg	
Placebo	N = 17	N = 18	N = 17	
Ator 10 mg	Gem 300 mg/Ator 10 mg	Gem 600 mg/Ator 10 mg	Gem 900 mg/Ator 10 mg	
N = 17	N = 18	N = 18		
Ator 40 mg	Gem 300 mg/Ator 40 mg	Gem 600 mg/Ator 40 mg	Gem 900 mg/Ator 40 mg	
N = 18	N = 18	N = 16		
Ator 80 mg	Gem 300 mg/Ator 80 mg	Gem 600 mg/Ator 80 mg	Gem 900 mg/Ator 80 mg	
N = 17	N = 18	N = 18		

METHODS

Statistical analysis: Analysis of variance (ANOVA) was used to evaluate the treatment effects on hsCRP. The model included the effects of 16 treatment groups with aggregate treatment groups and comparisons, and the baseline value as a covariate. Changes in LDL-C and other lipid parameters were calculated as described for hsCRP.

PATIENT CHARACTERISTICS

Fig. 2: Patient Disposition

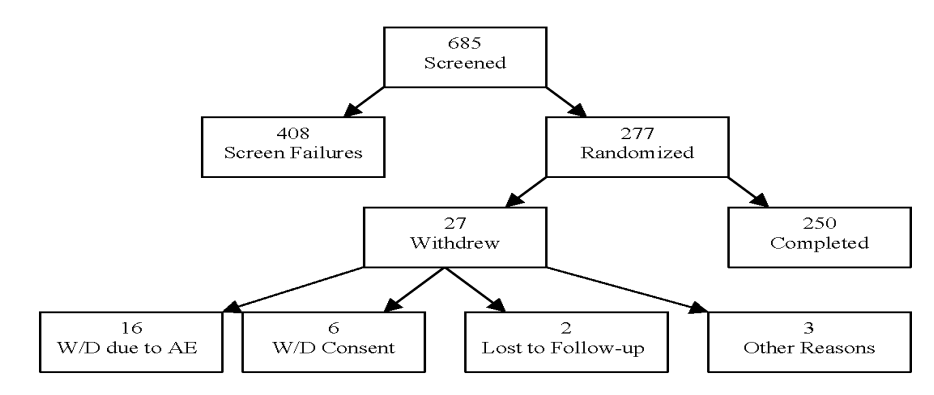


Table 2: Patient Characteristics

Baseline Characteristics (All Patients)		Smoking n(%)	
Gender n(%)		Current	50 (18.1)
Male	151 (54.5)	Never	148 (53.4)
Female	126 (45.5)	Past	79 (28.5)
Race n(%)		LDL-C mg/dL	
White	234 (84.5)	mean (min, max)	174.7 (114, 258.5)
Black	23 (8.3)	hsCRP mg/L	
Other	20 (7.2)	mean (min, max)	2.9 (0.2, 9.8)
Age (years)		hsCRP mg/L (95% CI)	
mean (min, max)	54.8 (32, 70)	mean (min, max)	3.8 (0.2, 33.6)
BMI		HDL-C mg/dL	
mean (min, max)	28.9 (20, 38.3)	mean (min, max)	49.3 (29, 86.5)
Diabetes Mellitus n(%)		Triglycerides mg/dL	
no	227 (82.8)	mean (min, max)	170.1 (49, 407)
yes	20 (7.2)	hsCRP mg/L	
Hypertension n(%)		mean (min, max)	159.5 (102, 229)
no	194 (70)	hsCRP mg/L (95% CI)	
yes	83 (30)	mean (min, max)	159.5 (102, 229)
Family History Premature CHD n(%)			
no	203 (73.3)		
yes	74 (26.7)		

LDL-C EFFECTS

Gemcabene 300, 600, and 900 mg monotherapy significantly lowered mean LDL-C from baseline by 17% (p=0.001), 26% (p<0.001), and 29% (p<0.001), respectively, compared with a decrease of 4% for placebo. Co-administration of 300, 600, and 900 mg gemcabene with atorvastatin aggregated over the dose range showed decreases in mean LDL-C beyond atorvastatin. LDL-C mean change and value at the end of the study are shown in Table 3.

Table 3: Mean LDL-C Change and Mean at End of Study (mg/dL)

Atorvastatin (mg/day)	Mean LDL-C Change (mg/dL) / Mean LDL-C at End of Study (mg/dL)	Gemcabene (mg/day)			
		0	300	600	900
10	-6.8/165	-31.2/147	-42.7/125	-53.3/127	
40	-69/111	-81/102	-85/85	-82/90	
80	-84/93	-90/82	-90/79	-100/83	
		-93/79	-97/82	-83/78	
				-108/74	

hsCRP

Gemcabene 300, 600, and 900 mg monotherapy decreased median hsCRP from baseline by 26% (p=0.161), 42% (p=0.007), and 35% (p=0.002) compared with a 9% elevation for placebo (Table 4). Co-administration of 300, 600, and 900 mg gemcabene with atorvastatin aggregated over the dose range showed decreases in median hsCRP beyond atorvastatin monotherapy by 16% (p=0.023), 23% (p=0.002), and 28% (p<0.001), respectively (Fig. 3). The relationship between the natural log (ln) of the change from baseline in hsCRP and dose was well described by a linear model for gemcabene and a sigmoid Emax model for atorvastatin (Fig.4). The interaction term describing the nature of the interaction suggested an additive (on log scale) effect of gemcabene and atorvastatin on hsCRP.

Table 4: Gemcabene hsCRP Effects by Dose

Gemcabene Monotherapy Versus Pbo - Percent Change in hsCRP From Baseline to Endpoint (MFT Population - Excluding Values >10)				
	Pbo	Gemcabene Monotherapy		
	N = 15	300 mg	600 mg	900 mg
Baseline Median	1.1	2.1	2.8	2.0
Percent Change		-25.8	-41.5	-35.3
Min, Max	(-34.6, 222.7)	(-49.0, 118.4)	(-75.7, 62.5)	(-78.1, 245.5)
Difference in Medians		-35.2	-50.9	-44.7
p-Value*		0.1612	0.007	0.0018

Pbo = Placebo; Difference in Medians = Gem-Pbo.
* Based on rank-transformed ANCOVA

hsCRP EFFECTS

Fig 3: Gemcabene hsCRP Effects as Monotherapy and in Combination with Atorvastatin

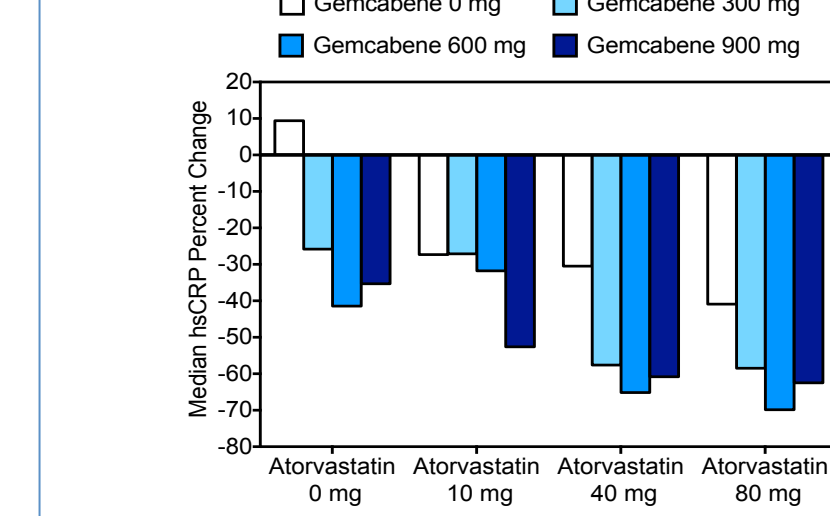
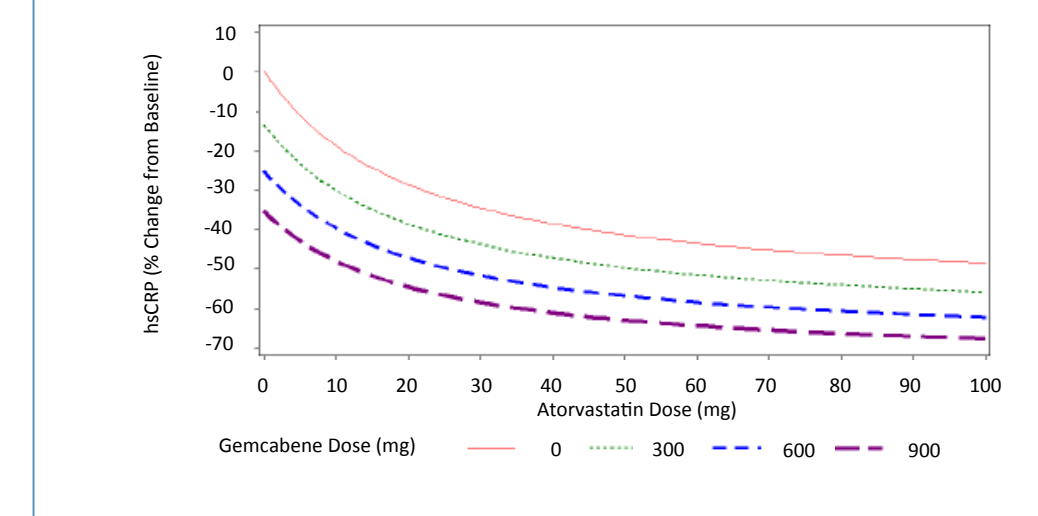


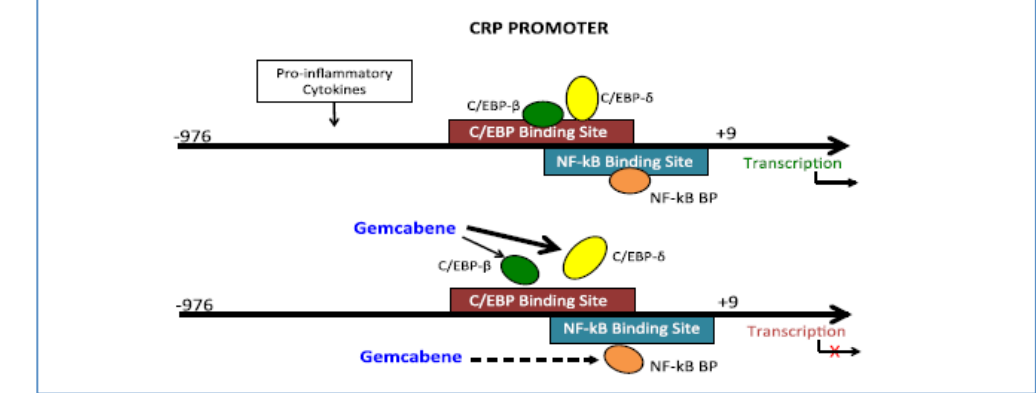
Fig 4: Gemcabene hsCRP Effects are Additive Across Atorvastatin Dose Range



PROPOSED MECHANISM OF hsCRP EFFECTS

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-α as a major player and C/EBP-β and NF-kB binding proteins as minor players in gemcabene-mediated down-regulation of CRP transcription (Fig. 5).

Fig. 5: Mechanism of Gemcabene Lowering of hsCRP



SAFETY

Patients across all treatment groups had a relatively similar safety profile. The most frequently occurring adverse events (AEs) were pain, headache, and infection throughout all treatment groups. Three patients experienced a serious AE (Gem 300 mg/Ator 80 mg, Gem 600 mg/Ator 40 mg, and Gem 600 mg/80 mg), none of which was related to treatment. Sixteen patients withdrew due to AEs; 9 (7 gemcabene) patients had events that were considered possibly related to treatment. Of the 277 patients randomized one patient receiving Gem 600mg/80 mg had an alanine aminotransferase elevation > 3 x ULN. The patient recovered and remained in the study. There were no deaths in the study (Table 5).

Table 5: Summary of Adverse Events

AE Category	Overview of Adverse Events (AEs) for Patients Across Aggregate Treatment Groups (Number (%) of Patients)*					All
	Ator 10/40/80 mg	Gem 300/600/900 mg	Gem 300 mg/Ator 10/40/80 mg	Gem 600 mg/Ator 40/80 mg	Gem 900 mg/Ator 80 mg	
All AEs	26 (50)	27 (53)	28 (53)	32 (62)	33 (64)	154 (66)
Associated AEs	7 (14)	9 (18)	9 (17)	9 (17)	8 (15)	45 (16)
Withdrawal Due to AE†						
All AEs	2 (4)	6 (12)	0 (0)	3 (6)	4 (8)	16 (6)
Associated AEs‡	2 (4)	4 (8)	0 (0)	1 (2)	2 (4)	9 (3)
Serious AEs§						
All AEs	0 (0)	0 (0)	1 (2)	2 (4)	0 (0)	3 (1)
Associated AEs‡	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Deaths¶	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

* Percent based on total number of patients in treatment group unless otherwise indicated.
† TSS scores only.
‡ Based on TSS and non-TSS events.
§ Considered possibly, probably, or definitely related to study medication, insufficient information, or no answer.
¶ Based on rank-transformed ANCOVA

CONCLUSIONS

- Increased levels of hsCRP have been independently associated with increased risk of CHD.
- Gemcabene 300, 600, and 900 mg monotherapy decreased median hsCRP from baseline by 26% (p=0.161), 42% (p=0.007), and 35% (p=0.002) compared with a 9% elevation for placebo. Co-administration of 300, 600, and 900 mg gemcabene with atorvastatin aggregated over the dose range showed decreases in median hsCRP beyond atorvastatin monotherapy by 16% (p=0.023), 23% (p=0.002), and 28% (p<0.001), respectively.
- Gemcabene, a novel lipid-lowering therapy, decreases hsCRP as monotherapy produces an additive decrease in hsCRP in combination with atorvastatin, supporting its development for patients with increased risk of CHD.

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