Effect of Gemcabene on Insulin Sensitivity in Non-Diabetic, Obese Subjects

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ABSTRACT

Background: Gemcabene (GEM), an ApoC-III and CRP modulator, showed significant LDL-C, ApoB, TG and hsCRP lowering and trends of glucose lowering in dyslipidemic subjects. In preclinical studies, 3T3L1 differentiated adipocytes treated with 100µM GEM plus insulin resulted in a 25% increase in [14C] deoxyglucose uptake compared to a 70% increase with 5 µM troglitazone, suggesting possible GEM insulin sensitization. To further investigate these observations, we assessed the GEM effect on average glucose disposal rate (GDR) during the last 30 minutes of a 3-hour euglycemic hyperinsulinemic clamp in healthy, obese, non-diabetic subjects.

Methods: Fifty-three subjects with BMI 30 to 40 kg/m^2 and fasting glucose < 126 mg/dL were randomized 1:1 to GEM 900 mg or PBO orally QD for 4 weeks. A clamp study was performed prior to treatment and 1 hour following the last GEM dose. The % change from baseline in GDR was compared for GEM and PBO using a 2-sample t-test.

Results: GEM 900 mg lowered LDL-C by 40% compared to placebo ($p < 0.0001$). The point estimate of the mean difference in the % change from baseline in the GDR was in favor of GEM, but did not attain statistical significance.

GEM Mean %	PBO Mean %	GEM-PBO			95% Lower Confidence Bound	One-Sided p-value for H_0: Mean = 0
		Mean %	SE	df		
13.11	6.35	6.76	8.17	48	-6.94	0.2059
SE = Standard Error; df = Degrees of freedom for the difference between GEM and PBO						

Conclusion: GEM 900 mg QD was generally well-tolerated and associated with a 6.76% mean increase in GDR compared to placebo. Although statistical significance was not observed in this pilot study, results support further exploration of GEM on glucose and insulin sensitization in a larger study in diabetic subjects.

INTRODUCTION

The insulin resistance of obesity and Type 2 diabetes is often associated with a metabolic dyslipidemia that increases cardiovascular risk. Insulin resistance can impair the ability to metabolize glucose for fuel, prompting a switch toward fat storage that promotes free fatty acid flux, hepatic triglyceride synthesis and increased very-low density lipoprotein (VLDL) production.

Gemcabene, the monocalcium salt of a dialkyl ether dicarboxylic acid, has a dual mechanism of action that involves: (1) enhancing the clearance of VLDL; and (2) blocking the overall production of hepatic triglycerides (TGs) and cholesterol synthesis. Gemcabene decreases the expression level of apolipoprotein C-III (ApoC-III) mRNA likely resulting in decreased ApoC-III protein production. Gemcabene reduction in ApoC-III increases VLDL-remnant clearance and enhances lipoprotein lipase activity, with the overall effect of reducing VLDL particle number and production of low-density lipoprotein (LDL). In primary rat hepatocytes, gemcabene markedly blocked radiolabeled acetate incorporation into both fatty acid (TG) and cholesterol. In human hepatocytes, gemcabene increased HMGCoA synthase mRNA levels, suggesting a block in this metabolic step in de novo cholesterol synthesis. Cytoplasmic acetylCoA carboxylase (ACC1) is the rate-limiting step in de novo fatty acid synthesis that catalyzes the conversion of acetylCoA to malonylCoA. Gemcabene's inhibition of human recombinant ACC1 enzymatic activity suggests it may block this rate-limiting step of de novo fatty acid synthesis. In diabetic mice fed a high fat diet, gemcabene reduced hepatic ACC1 mRNA levels. In addition, gemcabene may have an effect on inflammation by reducing C-reactive protein (CRP) mRNA production and decreasing hsCRP.[1] Taken together, gemcabene's mechanism of action should lower several parameters (atherogenic particles [VLDL and LDL] and inflammation) associated with the pathology of metabolic syndrome.

In preclinical studies, 3T3L1 differentiated adipocytes treated with gemcabene 100µM plus insulin resulted in a 25% increase in [14C] deoxyglucose uptake compared to a 70% increase with 5 µM troglitazone, suggesting possible insulin sensitization by gemcabene. Subsequently, gemcabene has shown dose-dependent reductions in insulin levels in obese female Zucker rats, supporting the evaluation of the effects of gemcabene on insulin sensitivity in a clinical trial. Euglycemic hyperinsulinemic clamp studies in obese nondiabetic subjects has demonstrated improvements during treatment with agents that increase insulin sensitivity.[2] This multiple dose study in obese subjects was designed to determine the effect of gemcabene on insulin sensitivity (average glucose disposal rate [GDR]) using the euglycemic hyperinsulinemic clamp technique.

PRECLINICAL EVIDENCE

Female Obese Zucker Rats

The metabolic syndrome associated with Type 2 diabetes includes low HDL, elevated VLDL-C and TGs, insulin resistance and elevated glucose. As the metabolic syndrome condition develops temporally, a transition period is sustained whereby increasing amounts of insulin are produced to maintain baseline glucose levels. Animals were studied during this period.

The effects of gemcabene (lipids, glucose and insulin) were evaluated at 10 mg/kg, 30 mg/kg, and 100 mg/kg in two separate strains of female obese Zucker rat obtained from separate vendors. Gemcabene produced a significant increase in high-density lipoprotein (HDL-C) and a decrease in TGs throughout the dose range (Figures 1 and 2). There was a decrease in LDL-C at the lower doses and no consistent response on VLDL-C. At 100 mg/kg gemcabene produced a small decrease in blood glucose and a significant decrease in plasma insulin levels thereby improving the glucose to insulin ratio making the Zucker rats less insulin resistant (Figure 3).[3]

PRECLINICAL EVIDENCE (CONTINUED)

Figure 1: HDL Cholesterol

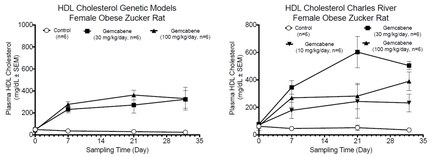


Figure 2: Triglycerides

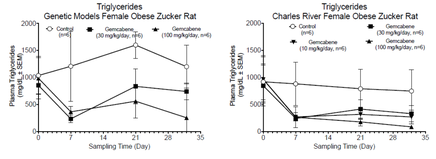
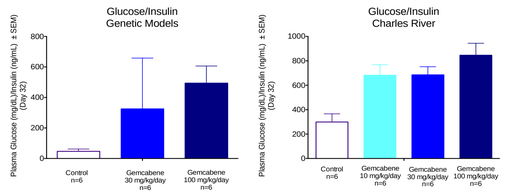


Figure 3: Glucose/Insulin



CLINICAL EXPERIMENTAL DESIGN AND ANALYSES

Following a 2-week screening phase, subjects entered a double-blind, placebo-controlled, multiple-dose, multicenter study (1027-014). Subjects were randomized to receive either 900 mg gemcabene or placebo on Day 2 through Week 4. A clamp study was performed on Day 1 and 1 hour following the last dose of gemcabene at the end of the fourth week of treatment.

Subjects of any race and either gender (female subjects were required to be of nonreproductive potential) were required to meet the following criteria in order to be eligible to participate in the study: Age ≥ 18 years; body mass index between 30 and 40 kg/m^2 (weight [kg]/height [meters]^2); fasting glucose < 126 mg/dL; and be in good health as determine by medical history, physical examination, vital signs, electrocardiography (ECG), and clinical laboratory measurements.

The primary efficacy parameter was insulin sensitivity as defined by average GDR (mg/kg per min) during the last 30 minutes of a 3-hour euglycemic hyperinsulinemic clamp study. The percent change in from baseline in the GDR was compared for the placebo and 900 mg gemcabene group using a 2-sample t-test. The 95% lower confidence bound on the mean effect of gemcabene minus placebo, and the 1-sided p-value for H_0: mean treatment difference = 0 have been reported.

A post-hoc analysis was performed on mean percent change in total cholesterol (TC), LDL-C and TGs using a paired t-test. In addition, GDR was re-analyzed using a paired t-test, considered an appropriate analysis for this small pilot study.

RESULTS

Patient Characteristics

Fifty-three subjects (37 male, 16 female) ranging in age from 26 to 63 years (mean 44.9 years) entered the study. Fifty subjects completed the study (Table 1).

Safety

Gemcabene 900 mg QD for 4 weeks was generally well-tolerated in healthy obese non-diabetic subjects. Thirteen of the 26 subjects treated with gemcabene reported a total of 20 adverse events (AEs). Five subjects reported 9 AEs that were considered related to gemcabene. Of these 9 AEs, 8 were mild and 1 (headache) was severe. Eight of the 27 subjects who received placebo reported 13 AEs. Five of these AEs were considered related to treatment; all were mild to moderate. There were no deaths, serious AEs, or withdrawals due to AEs during the study. There were no clinically significant changes in physical examinations, vital signs, ECGs or laboratory measurements.

Table 1: Baseline Characteristics

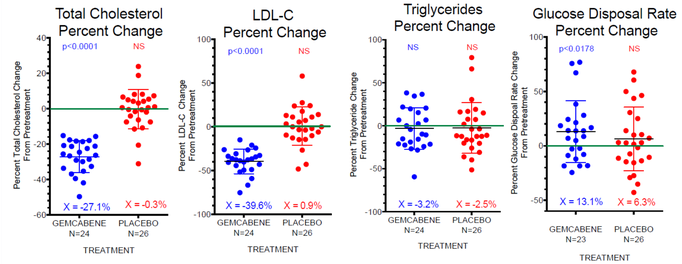
Baseline Characteristics	Gemcabene	Placebo
N	24	26
Mean Age in years	44.5	43.9
Sex –Male (%)	17 (81%)	17 (65%)
Race – Caucasian (%)	20 (83%)	19 (73%)
TC (mg/dL)	198.4	182.5
LDL-C (mg/dL)	119.1	106.3
TG (mg/dL)	171.4	161.8
Fasting glucose (mg/dL)	97.5	102.3

RESULTS (CONTINUED)

Table 2: Glucose Disposal Rate

Gemcabene Mean % Change	Placebo Mean % Change	Gemcabene -Placebo			95% Lower Confidence Bound	One-Sided P-Value For H_0: Mean = 0
		Mean	SE	df		
13.11	6.35	6.76	8.17	48	-6.94	0.2059
SE = Standard error; df = Degrees of freedom for the difference between gemcabene and placebo						

Figure 4: Post-Hoc Analysis - Lipid and Glucose Disposal Rate Scatterplots



In a post-hoc analysis gemcabene 900 mg lowered mean TC, LDL-C and TGs by 27% ($p < 0.0001$), 40% ($p < 0.0001$), and 3.2% (NS), respectively. In a re-analysis of GDR using the paired t-test gemcabene 900 mg increased mean GDR by 13% ($p < 0.0178$).

CONCLUSIONS

- Gemcabene has shown beneficial effects on lipids and indicators of glucose metabolism in a rat model of the metabolic syndrome of Type 2 diabetes.
- Gemcabene was subsequently tested in a Phase 2 pilot study (1027-014) in healthy obese subjects with lipids and glucose indicative of metabolic syndrome.
- Gemcabene 900 mg lowered TC by 27% and LDL-C by 40% with a modest effect on TGs, consistent with past results of this dose in hypercholesterolemic subjects.
- Gemcabene was associated with a 13% mean increase or a doubling in GDR compared to placebo. Although statistical significance was not observed in the prespecified analysis, a post-hoc analysis more applicable to the size of this pilot study showed a statistically significant change from baseline to Day 29 in GDR for gemcabene 900 mg versus a NS effect for placebo.
- Gemcabene 900 mg QD in non-diabetic, obese subjects was generally well-tolerated.
- The results from this study support further exploration of gemcabene on glucose and insulin sensitization in a larger study in diabetic/obese subjects.
- Gemcabene is currently being evaluated in 3 Phase 2b trials in HoFH, HeFH/ASCVD, and SHTG subjects.

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DISCLOSURE

Rebecca Bakker-Arkema MS, RPh: SALARY – Gemphire Therapeutics Inc.
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