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

Gemcabene, the monocarboxylate 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-II (ApoC-II) and microsomal triglyceride transfer protein (MTP). Gemcabene reduces apolipoprotein A-I levels in human subjects, and decreases plasma cholesterol and triglycerides levels.

However, gemcabene markedly blocked red blood cell incorporation into both fatty acid (TG) and cholesterol. In human hepatocytes, gemcabene increased the secretion of apolipoprotein A-I and the production of low-density lipoprotein (LDL). In primary rat hepatocytes, gemcabene blocked the production of triglycerides and cholesterol.

The primary efficacy parameter was insulin sensitivity defined as average GDR (mg/kg per min) during the last 30 minutes of a 5-hour euglycemic hyperinsulinemic clamp. The percent change in baseline from the result was calculated for the placebo and gemcabene 100 mg/kg 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 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 analyzed using a paired t-test, considering an appropriate analysis for this small pilot study.

**Clinical Experimental Design and Analyses**

**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 temporarily, a transition period is sustained wherein increases in 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 different suppliers. Gemcabene produced a significant decrease in lipogenic fatty liver (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 with VLDL-C. At 100 mg/kg gemcabene produced a small decrease in blood glucose and a significant decrease in insulin levels thereby improving the insulin ratio to make the Zucker rat less insulin resistant (Figure 3).