**ABSTRACT**

Introduction. Gemcabene, a fraudulent fatty acid, induces biological properties in nonclinical models, of which many translate to clinical findings in hyperlipidemic patients. As evidence of mechanism of action includes reduction of the overall hepatic de novo triglyceride and cholesterol synthesis, inhibition of apoptosis protein (C-II), and in increase in LDL clearance. Clinical benefits in various human populations infer that other mechanisms involved that warrant evaluation. Methods and Results. We assessed the gemcabene effects in other molecular mechanisms, particularly in study inhibition of human recombinant hACL, apoptosis gene expression in Sandwich-Cultured Transporter Certified®™ Human Hepatocytes (SCHH), and expression of genes related to inflammation and cell signaling.

Gemcabene, MEDICA-16, palmitic acid and free CoA were studied in a recombinant hACL in vitro assay system. Gemcabene-CoA troxilier, but not the parent compound, inhibited recombinant hACL activity in vitro in a dose-dependent manner, in agreement with results observed with palmitic acid and palmitic acid. Unlike palmitic acid, MEDICA-16 and bempedac acid, gemcabene does not form a CoA ester when incubated in human hepatocytes; radiolabeled studies show 98.8% of the parent gemcabene remained.

Further, the gemcabene potential on the gene expression of lipoproteins and inflammation markers was assessed in a rat model of nonalcoholic steatohepatitis (NASH) and patient with liver microsomes from all species tested. Similarly in human recombinant Human ATP-citrate Lyase (hACL), gemcabene has pleiotropic effects and multiple mechanisms of action. Gemcabene has multiple mechanisms of action.

**RESULTS**

EFFECT OF GEMCABENE ON MARKERS OF INFLAMMATION IN STAM™ MICE

Hepatic gene expression indicative of inflammation are significantly reduced by gemcabene.

**RESULTS (CONTINUED)**

EFFECT OF GEMCABENE AND GEMCABENE-COENZYME-A ON RECOMBINANT HUMAN CITRATE LYASE AND IN VITRO ASSESSMENT OF GEMCABENE REDUCTION POTENTIAL IN SANDWICH-CULTURED TRANSPORTER CERTIFIED®™ HUMAN HEPATOCYTES (SCHH)

Conclusions. Gemcabene significantly decreases hepatic lipid regulating markers including Acetyl CoA Carboxylase 1, but not CoA, has a pleiotropic effect on Acetyl-CoA Carboxylase 1, ApoC-III, and ACC1. Additionally, gemcabene significantly decreases ApoC-III, TNF-β, MCP-1, and NF-kB. Gemcabene also reduces hepatic triglycerides in the chow-fed rat model.

**CONCLUSIONS AND REFERENCES**

Gemcabene has pleiotropic effects and multiple mechanisms of action.

Gemcabene significantly reduces hepatic triglycerides in the chow-fed rat model.

Gemcabene significantly reduces triglyceride levels in the chow-fed chow-fed model.

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