Hepatic de novo lipogenesis (DNL) and fatty acid oxidation (FAO) are dysregulated in nonalcoholic steatohepatitis (NASH), and are implicated in disease pathogenesis. GS-0976 is an oral, liver-targeted inhibitor of acetyl-coenzyme A (CoA) carboxylase (ACC) in clinical development for the treatment of NASH.

Inhibition of ACC1 and ACC2 by GS-0976 Decreases Hepatic de Novo Lipogenesis and Increases Mitochondrial β-Oxidation of Fatty Acids, Respectively

Plasma MAI and BC were significantly increased (p <0.01), plasma BHOBC MC.

Hepatic DNL was stimulated by oral consumption of fructose 250 mg/kg body weight every 30 min for 10 h. Blood was collected at multiple time points after overnight fast beginning at Hour -1 relative to dosing and then every hour for a total of 10 postdose samples.

Hepatic DNL was assessed by 13C incorporation into new palmitate in plasma very-low-density lipoprotein particles by gas chromatography–mass spectrometry using mass isotope distribution analysis and kinetic modeling.

Biomarkers Expected to Change With GS-0976 Therapy: Malonate, Malonylcarnitine, Butyrylcarnitine, β-OH-Butyrylcarnitine.

Biomarkers in Stimulated DNL Challenge Study*

*Violet circles indicate significant change vs. PBO (all p <0.001) at 2–6 h post-dose, with the exception of MC.

Simple Biomarker Index for DNL Measurement

- We explored whether a simple index of the metabolites would improve diagnostic performance to measure DNL following fructose stimulation

Correlation Between Change in DNL and Changes in Biomarkers in Stimulated DNL Challenge Study*

- % change in index correlated well with % change in DNL (r=0.83; p <0.001)

Conclusions

- Plasma levels of MAL, BC, and BHOBC were elevated in NASH patients compared with healthy subjects
- BHOBC was a PD biomarker of GS-0976 treatment in fasted, healthy subjects (in absence of DNL stimulation)
- Plasma MAL, BC, BHOBC, and a simple index (MAL+BC+BHOBC):
  - Were significantly correlated with fructose-stimulated hepatic DNL as measured by stable isotope incorporation in very low-density lipoprotein over time; and
  - Accurately measured GS-0976 suppression of DNL
- These metabolites show promise in evaluating GS-0976-related activity

References