Combination of fatty acid synthase (FASN) inhibitor and thyroid hormone receptor beta (THRb) agonist, resmetirom, improved markers of NASH and cardiovascular health in LDL receptor knockout NASH mice

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Background and Aims: Increased de novo lipogenesis (DNL) drives the development of NASH and FASN is the key enzyme in the DNL pathway. FASN inhibition not only reduces liver fat but also acts directly on immune and hepatic stellate cells (HSCs) reducing inflammation and fibrosis. Denifanstat (TVB-2640), an oral FASN inhibitor, has demonstrated improvements in liver fat and biomarkers associated with inflammation and fibrosis in NASH trials. THRb agonists increase lipid oxidation which decreases liver fat and resmetirom recently demonstrated significant NASH resolution and fibrosis improvement in the phase 3 trial. We hypothesized that the combination of FASN inhibitor and resmetirom may increase efficacy for NASH treatment based on complementary mechanisms of liver fat reduction and the direct anti-fibrotic effect of FASN inhibitor. This study was designed to evaluate FASN inhibitor alone and in combination with resmetirom on plasma biomarkers and liver histology in LDL receptor knockout (Ldlr⁻⁻⁻) NASH mice. Denifanstat and resmetirom were also evaluated in vitro in HSCs for direct anti-fibrotic effects

Method: Male Ldlr⁻⁻⁻ mice were fed with fast-food diet (FFD) for 18 weeks to induce NASH features and treated with either TVB-3664 (a surrogate FASN inhibitor for denifanstat, 5 mg/kg, PO, QD) or THRb agonist resmetirom (MGL-3196, 3 mg/kg, PO, QD) alone or in combination for 10 weeks. Endpoints included liver enzymes, lipids and liver histology (pending). Primary human HSCs were stimulated by TGF-b1 and treated with denifanstat or resmetirom at various concentrations.

Results: FFD feeding significantly increased plasma ALT/AST, total cholesterols and triglycerides in Ldlr⁻⁻⁻ mice. TVB-3664 or resmetirom alone rapidly reduced plasma ALT/AST, total cholesterols and triglycerides with 4 weeks treatment and these reductions were sustained until end of the study (10 weeks); importantly, combination of TVB-3664/resmetirom showed further additive improvements compared to either agent alone. Lipoprotein analysis showed that LDL-C and VLDL-C were highly induced by FFD and both were strongly reduced by TVB-3664 or resmetirom alone and further reduced by the combination. In primary human HSCs, TGF-b1-stimulated collagen production and plasminogen activator inhibitor 1 secretion were decreased by denifanstat, but not resmetirom, in a dose-dependent manner.

Conclusion: Combination of FASN inhibitor and THRb agonist resmetirom showed further ALT/AST improvement and lipid lowering compared to either agent alone in a mouse model of dyslipidaemia and NASH. In vitro, denifanstat, but not resmetirom, directly reduced collagen production. These results suggest that complementary MOAs of denifanstat (DNL inhibition and direct anti-fibrotic effect) and resmetirom (lipid burning) combined could provide added benefit and support future clinical evaluation of this combination for NASH.