Combination of fatty acid synthase (FASN) inhibitor and thyroid hormone receptor beta (THRβ) agonist resmetirom shows synergistic improvement of NAFLD activity score (NAS) within 6-weeks in diet-induced obese mice with biopsy-confirmed MASH

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Background and Aims: Increased de novo lipogenesis (DNL) drives the development of MASH, and FASN is the rate-limiting enzyme in the DNL pathway. In preclinical studies, denifanstat (TVB-2640) directly blocks endogenous FASN in stellate cells, immune cells and hepatocytes, thereby directly inhibiting fibrosis, inflammation and steatosis. Denifanstat, an oral FASN inhibitor, has demonstrated significant improvements in MASH resolution and fibrosis improvement in the Ph2b MASH study, FASCINATE-2, as well as decreased liver fat and biomarkers of inflammation and fibrosis. THRβ agonists increase lipid oxidation which decreases liver fat; resmetirom (RES) recently demonstrated significant MASH resolution or fibrosis improvement in Phase 3 and is FDA approved for the treatment of MASH with moderate to advanced liver fibrosis. We hypothesized that the combination of a FASN inhibitor and RES may increase efficacy for MASH treatment based on complementary mechanisms of liver fat reduction and the FASN inhibitor’s direct anti-fibrotic effect. This study was designed to evaluate a FASN inhibitor alone and in combination with RES on liver histology in biopsy-confirmed MASH mice.

Method: Male C57BL/6J GAN-diet-induced obese mice with histologically confirmed NAS ≥ 5 and fibrosis stage F1-F3 were randomized and treated with either vehicle, TVB-3664 (a surrogate FASN inhibitor for denifanstat, 5 mg/kg, PO, QD) or RES (3 mg/kg, PO, QD) individually or in combination for 6 weeks (n=10-12 for each group).

Results: After a 6-week treatment, the response rate (RR) for reduction of NAS by 2 or more points was 33% for TVB-3664, 25% for RES, 0% for vehicle and 80% for the combination. Notably, 100% of combination-treated mice showed at least 1-point reduction in NAS, and 30% had 3 or more points of NAS reduction. For steatosis, the RR for 1-point reduction was 17% for TVB-3664, 50% for RES and 100% for the combination, with a 2-point reduction in 80% of combination-treated animals. This was consistent with significant reduction of % hepatocytes with lipid droplets and % area of liver lipids in drug-treated groups. For lobular inflammation, the 1-point RR was 42% for TVB-3664, 8% for RES, and 10% for the combination although these 10% combination-treated animals all had a 2-point reduction. Some ballooning hepatocytes (ballooning score 1) were present before initiation of treatment and all treatments decreased the ballooning score to 0.

Conclusion: Combination of FASN inhibitor and THRβ agonist RES had a synergistic effect on histological improvement of NAS compared to single agents within 6-weeks in a mouse model of MASH. These results suggest that the complementary mechanisms of action of denifanstat (directly decrease lipid synthesis, inflammation and fibrosis) and RES (increase lipid oxidation) combined could provide added benefit and support future clinical evaluation of this combination for MASH.