Introduction

- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor in clinical development for NASH
- In preclinical models, FASN inhibitors improved 3 hallmarks of NASH: inhibited liver fat accumulation (hepatocytes), inhibited fibrosis (hepatic stellate cells require DNL for activation) and decreased inflammation (inflammasome activation by palmitate)
- Semaglutide, a GLP-1 analog, reduced body weight and demonstrated NASH resolution in a recent NASH trial; however, it did not improve fibrosis compared to placebo

Aim

- Hypothesis: FASN inhibition shows a direct anti-fibrotic effect in hepatic stellate cells. We hypothesize that FASN inhibitor alone or in combination with GLP-1 analog will decrease liver fibrosis in NASH
- To evaluate the effect of FASN inhibitor alone and in combination with semaglutide on liver pathology, including NAFLD activity score (NAS) and fibrosis, in biopsy-confirmed NASH mice

Methods

- Male C57BL/6J Guba-Amyln-NASH (GAN) diet-induced obese mice with histologically-confirmed NAS (≥ 5) and fibrosis stage (F2/F3) were randomized and treated with either TVB-3664 (a surrogate FASN inhibitor for denifanstat, 10 mg/kg, PO, QD) or semaglutide (30 mg/kg, SC, QD) alone or in combination for 12 weeks (Gubra, Denmark)
- Artificial intelligence (AI) based digital pathology, phenotypic FibroNest analysis (PharmaNest, NJ), was used to evaluate changes in fibrosis

Results

- Semaglutide reduced body weight by >20% in NASH mice
- Combination of FASN inhibitor and semaglutide significantly decreased ALT, liver triglycerides (TG) and cholesterol (TC) in NASH mice
- Combination of FASN inhibitor and semaglutide improved histological features in NASH mice

Conclusions

- Single treatment of FASN inhibitor (TVB-3664) or semaglutide improved NAS and decreased several biomarkers associated with NASH. However, only the FASN inhibitor, but not semaglutide, showed significant reduction of liver fibrosis by digital AI pathology assessment in a mouse model of NASH
- Combination treatment of FASN inhibitor and semaglutide showed further histological improvement of NAS and liver fibrosis compared to single agent treatment. This supports future clinical evaluation of denifanstat/GLP-1 combination therapy.
- A FASCINATE-2 Ph2b biopsy study is ongoing with denifanstat in NASH patients with F2/F3 fibrosis; results expected in Q1 2024