ARTIFICIAL INTELLIGENCE BASED DIGITAL PATHOLOGY REVEALS FATTY ACID SYNTHASE (FASN) INHIBITOR ALONE OR IN COMBINATION WITH SEMAGLUTIDE IMPROVES FIBROSIS IN DIET-INDUCED OBESE MICE WITH BIOPSY-CONFIRMED NASH AND FIBROSIS

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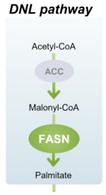
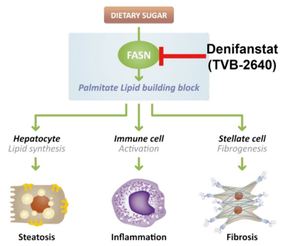
Introduction

- 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)[1]
- 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[2]

DNL pathway



FASN inhibition targets 3 key cell types

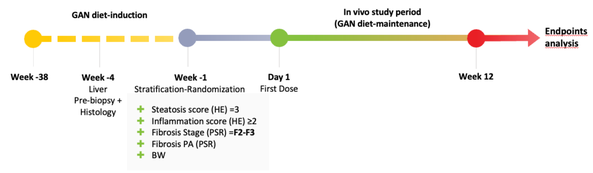


Aim

- Hypothesis: FASN inhibition shows a direct anti-fibrotic effect in hepatic stellate cells[1]. 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

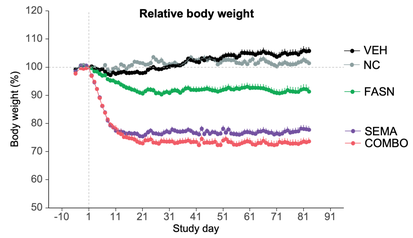
- Male C57BL/6J Gubra-Amylin-NASH (GAN) diet-induced obese mice with histologically-confirmed NAS (≥ 5) and fibrosis stage (F2-F3) were randomized and treated with either TVB-3664 (a surrogate FASN inhibitor for denifanstat, 10 mg/kg, PO, QD) or semaglutide (30 nmol/kg, SC, QD) alone or in combination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



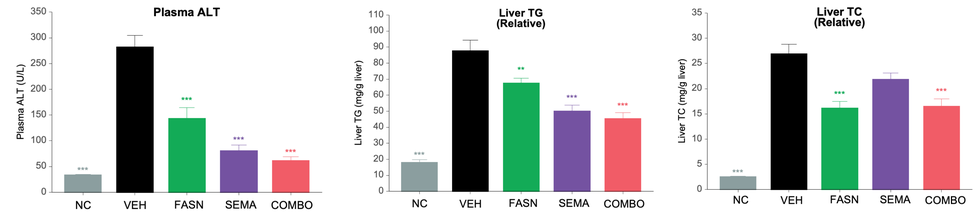
Results

Semaglutide reduced body weight by >20% in NASH mice

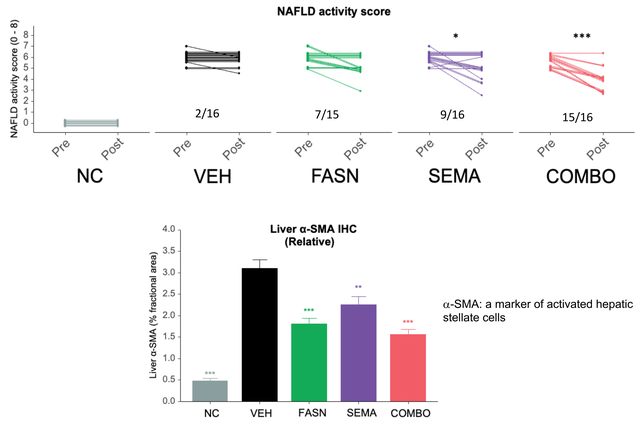
Treatment groups
NC: Normal chow diet control
VEH: NASH vehicle control
FASN: TVB-3664 (FASN inhibitor)
SEMA: Semaglutide (weight loss dose)
COMBO: TVB-3664/Semaglutide combo



Combination of FASN inhibitor and semaglutide significantly decreased ALT, liver triglycerides (TG) and cholesterol (TC) in NASH mice

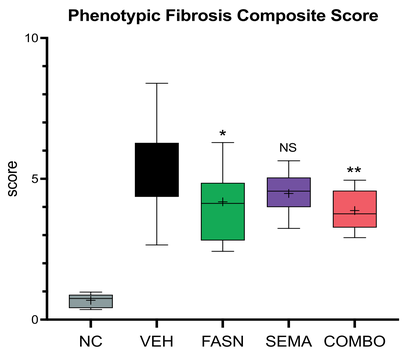


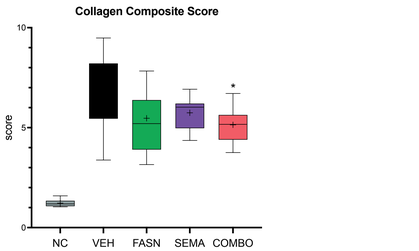
Combination of FASN inhibitor and semaglutide improved histological features in NASH mice

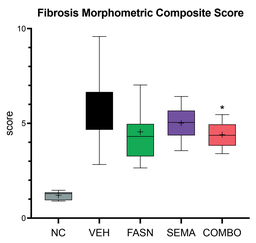


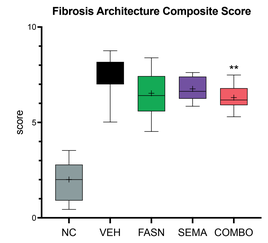
α-SMA: a marker of activated hepatic stellate cells

Fibrosis analyzed by digital pathology









PSR images were analyzed by FibroNest; no fibrosis stage change by histological analysis based on CRN definition for all groups; ** p <0.05, ** p<0.01, *** p<0.001, NS: not significant; NC n=8; VEH, FASN, SEMA, COMBO n=15~16*

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

References
(1) O'Farrell et al., 2022. Scientific Reports. doi.10.1038/s41598-022-19459-z
(2) Newsome et al., 2021. N ENGL J MED