Combination of fatty acid synthase (FASN) inhibitor and thyroid hormone receptor beta (THRb) 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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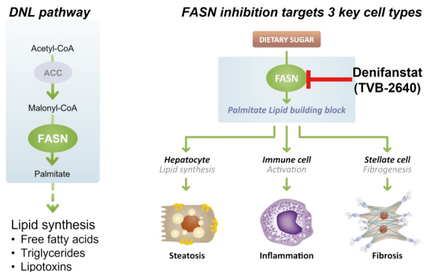
Introduction

- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor in clinical development for MASH. Denifanstat recently demonstrated significant MASH resolution and fibrosis improvement in the phase 2b MASH study, FASCINATE-2 (NCT04906421)[1]
- In preclinical models, FASN inhibitors improved 3 hallmarks of MASH: inhibited liver fat synthesis and accumulation (hepatocytes), inhibited fibrosis (hepatic stellate cells require DNL for activation) and decreased inflammation (inflammasome activation by palmitate)[2]
- THRb agonists increase lipid oxidation which decreases liver fat; resmetirom demonstrated significant MASH resolution or fibrosis improvement in phase 3[3]

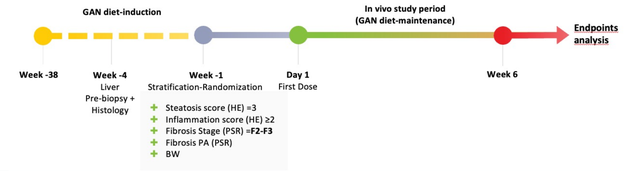


Hypothesis & Aim

- Hypothesis: Combination of a FASN inhibitor and resmetirom may increase efficacy for MASH treatment based on complementary mechanisms of liver fat reduction and the FASN inhibitor's direct anti-fibrotic effect
- To evaluate the effect of a FASN inhibitor alone and in combination with resmetirom on liver histology in biopsy-confirmed MASH 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 vehicle, TVB-3664 (a surrogate FASN inhibitor for denifanstat, 5 mg/kg, PO, QD) or resmetirom (MGL-3196, 3 mg/kg, PO, QD) individually or in combination for 6 weeks (n=10-12 for each group, Gubra, Denmark)

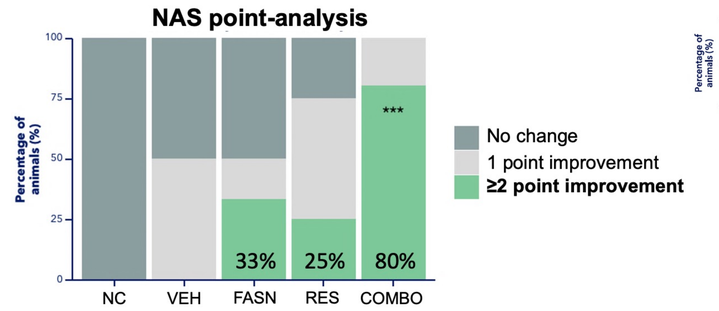


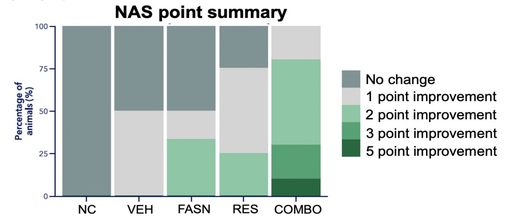
Results

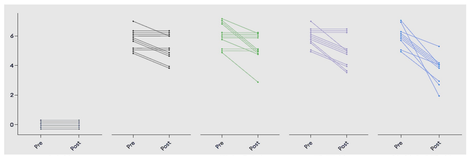
Combination of FASN inhibitor and resmetirom improved NAS in MASH mice

- *100% and 80% response rate in combo group for at least 1-point and 2-point improvement*
- *30% combo-treated mice showed ≥3-point improvement*

Treatment groups
NC: Normal chow diet control
VEH: MASH vehicle control
FASN: TVB-3664 (FASN inhibitor)
RES: Resmetirom
COMBO: TVB-3664/resmetirom combo

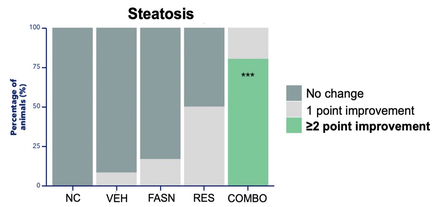


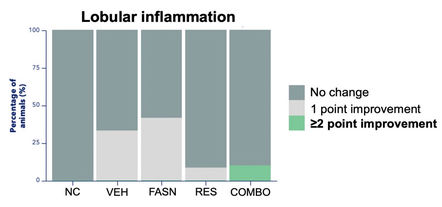


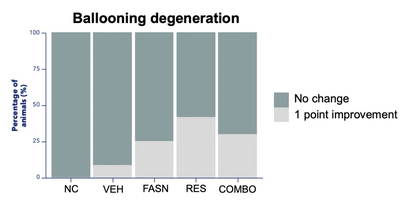


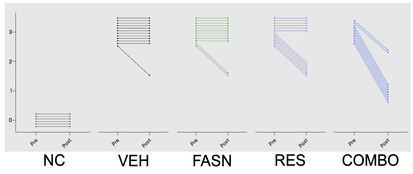
Combination of FASN inhibitor and resmetirom improved each component of NAS in MASH mice

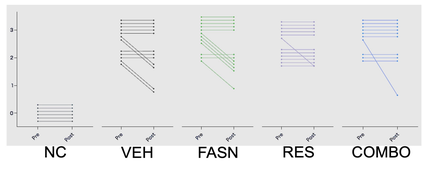
- *80% response rate in combo group for 2-point improvement in steatosis*

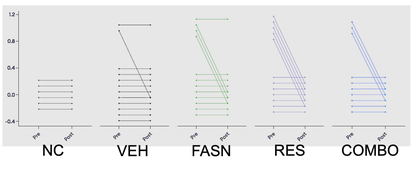












Histological analysis based on CRN definition for all groups; ** p <0.05, ** p<0.01, *** p<0.001, NC n=6; VEH, FASN, RES, COMBO n=10~12*

Conclusions

- Combination of a FASN inhibitor and a THRb agonist, resmetirom, 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 combination of complementary mechanisms of action of denifanstat (directly decreases lipid synthesis, inflammation and fibrosis) and resmetirom (increases lipid oxidation) could provide added treatment benefit, and support future clinical evaluation of this combination for the treatment of MASH

References

(1)https://ir.sagimet.com/news-releases/news-release-details/sagimet-biosciences-announces-positive-topline-results-phase-2b
(2)O'Farrell et al., 2022. Scientific Reports. doi.10.1038/s41598-022-19459-z
(3)Harrison et al., 2024. N Engl J Med 2024;390:497-509