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

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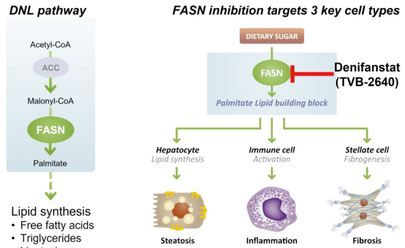
Introduction

- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor in clinical development for MASH. Denifanstat has 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 & 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]

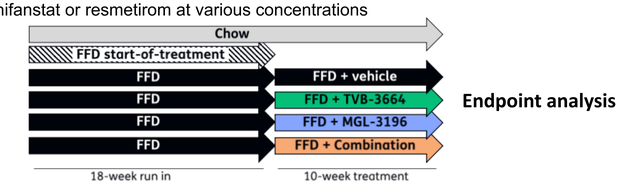


Hypothesis & Aims

- Hypothesis: Based on complementary mechanisms of resmetirom and FASN inhibitors, including the FASN inhibitor's direct anti-fibrotic effect, combination of these two drugs may have increased efficacy for MASH treatment
- To evaluate the effect of a FASN inhibitor alone and in combination with resmetirom on plasma biomarkers and liver histology in LDL receptor knockout MASH mice
- Denifanstat and resmetirom were also evaluated *in vitro* in human hepatic stellate cells (HSCs) for direct anti-fibrotic effects

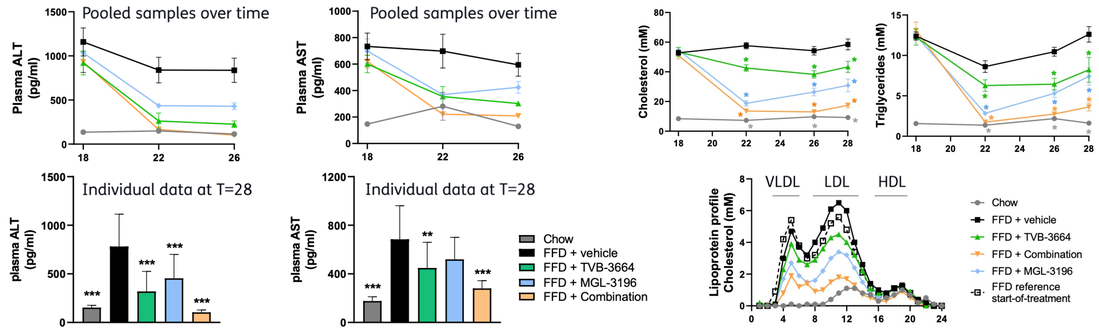
Methods

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

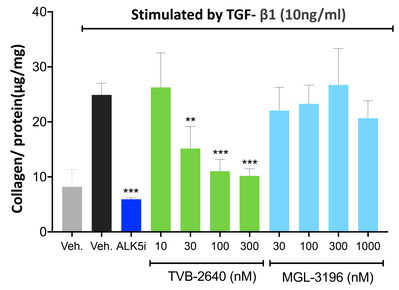


Results

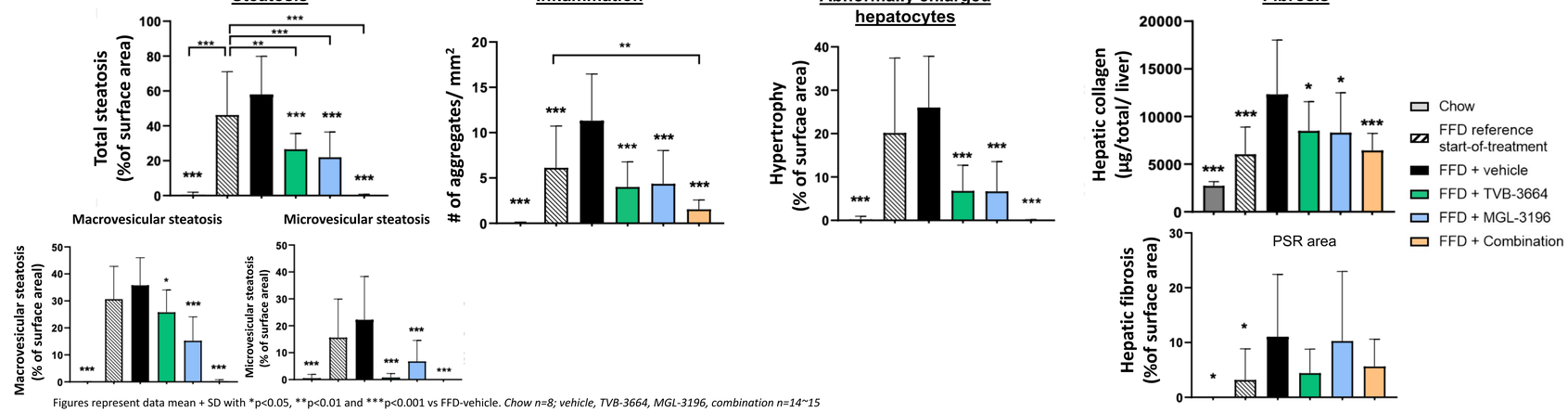
Combination of FASN inhibitor and resmetirom improved ALT/AST and circulating lipids in Ldlr-/- MASH mice



Denifanstat, but not resmetirom, reduced collagen in primary human hepatic stellate cells



Combination of FASN inhibitor and resmetirom improved liver histology in Ldlr-/- MASH mice



Figures represent data mean + SD with *p<0.05, **p<0.01 and ***p<0.001 vs FFD-vehicle. *Chow n=8; vehicle, TVB-3664, MGL-3196, combination n=14~15*

Conclusions

- Denifanstat, but not resmetirom, directly reduced collagen production in primary human hepatic stellate cells *in vitro*
- Combination of a FASN inhibitor and a THRb agonist, resmetirom, showed further ALT/AST decreases, lipid lowering, and histological improvements compared to either agent alone in a mouse model of dyslipidemia and 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 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