Denifanstat-mediated reduction of plasma glycine- and taurine-conjugated bile acids correlates with histological improvements in denifanstat-treated metabolic dysfunction-associated steatohepatitis patients in Phase 2b FASCINATE-2 study

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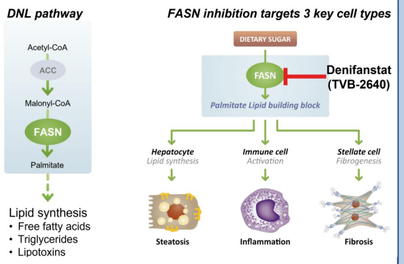
Introduction

- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor in clinical development for MASH
- FASN inhibition targets 3 hallmarks of MASH:

  - inhibits liver fat synthesis & accumulation (hepatocytes)

  - **inhibits fibrosis (hepatic stellate cells require DNL for activation)**

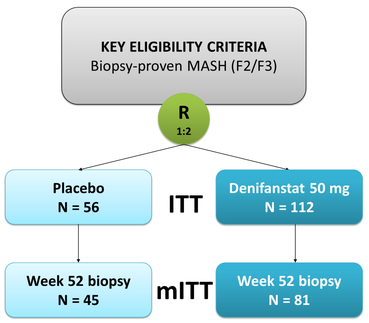
  - decreases inflammation (inflammasome activation by palmitate)[1]



Background and Aims

- The phase 2b FASCINATE-2 trial (see study design below) met its primary and multiple secondary endpoints, including fibrosis improvement without worsening of MASH, and MASH resolution without worsening of fibrosis[2]
- To identify potential biomarkers that predict histological responses, plasma lipidomic/metabolomic analyses were performed. This study evaluated the correlation between bile acid changes and histological improvements in MASH patients treated with denifanstat

Methods



ITT: *Intention-to-treat*
mITT: *Modified intention-to-treat*

FASCINATE-2 was a 52-week randomized, double-blind, placebo-controlled phase 2b trial

Primary Endpoints

- NAS ≥2 points improvement without worsening of fibrosis
- MASH resolution + NAS ≥2 improvement without worsening of fibrosis

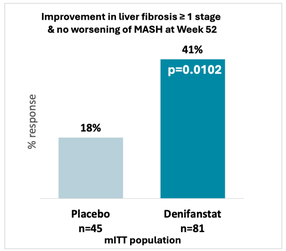
Selected Secondary Endpoints

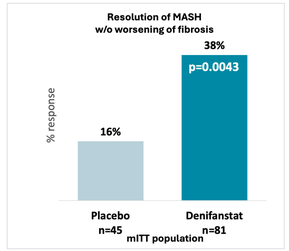
- Improvement in liver fibrosis ≥1 stage without worsening of MASH
- Digital artificial intelligence (AI) pathology

- Specific bile acid species were measured in patient plasma samples collected at baseline (BL), week 26 and week 52 using a metabolomic platform (OWL Metabolomics). Changes in bile acids were correlated with histology responses, including fibrosis regression and MASH resolution

Results

Denifanstat significantly improved fibrosis and MASH resolution



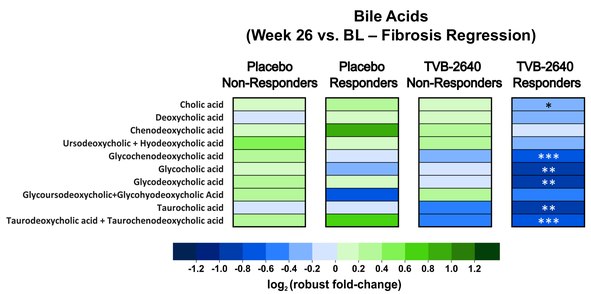


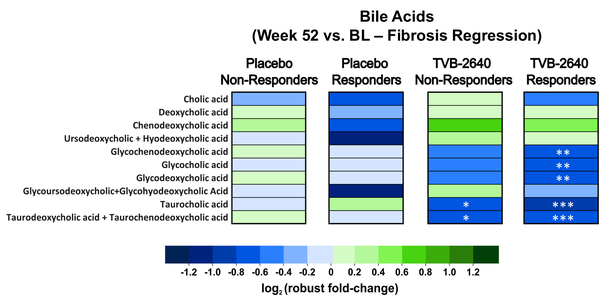
Cochran-Mantel-Haenszel Test – Two sided at the 0.05 significance level

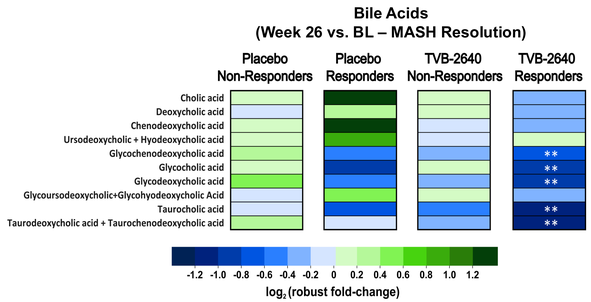
Denifanstat decreased glycine and taurine-conjugated bile acid pools

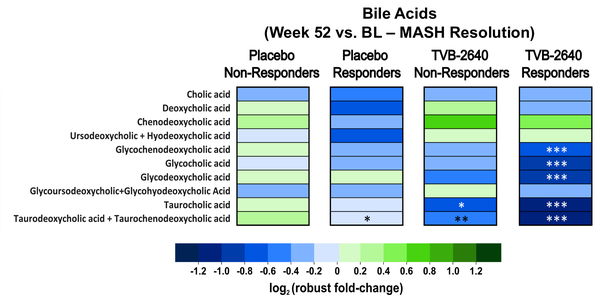
	Change from baseline to week 52			
	Placebo		Denifanstat	
	% change	p values	% change	p values
Bile Acids	**0**	0.95	**-5**	0.136
Free bile acids	**7**	0.80	**10**	0.803
Glycine-conjugated bile acids	**5**	0.89	**-27**	0.002
Taurine-conjugated bile acids	**7**	0.82	**-45**	<0.001

Reduction of glycine- and taurine-conjugated bile acids correlated with histological responses



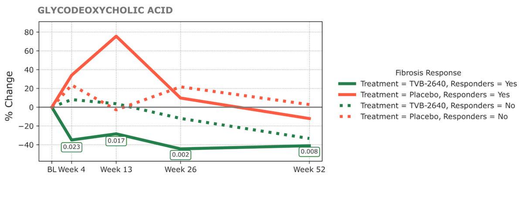


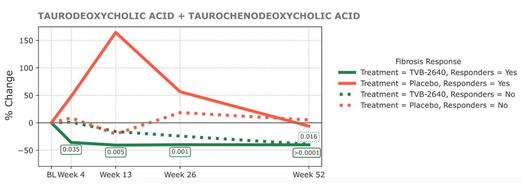




mITT population. * p < 0.05, ** p < 0.01, *** p< 0.001; BL: baseline

Glycodeoxycholic and taurodeoxycholic/taurochenodeoxycholic acids showed rapid reductions in fibrosis responders with denifanstat treatment





Lines represent median of the % change in different weeks; p-values are only shown if <0.05, Wilcoxon signed-rank test

Conclusions

- Denifanstat demonstrated a statistically significant improvement in liver fibrosis and MASH resolution in the Phase 2b study FASCINATE-2
- In MASH patients treated with denifanstat, glycine- and taurine-conjugated bile acids were significantly reduced at 26 weeks in histological responders for both fibrosis regression and MASH resolution, suggesting that the reduction in these bile acids could potentially be leveraged as a response biomarker in patients treated with denifanstat

References
(1) O'Farrell et al., 2022. Scientific Reports. doi:10.1038/s41598-022-19459-z
(2) Loomba et al., 2024. The Lancet Gastroenterology & Hepatology. doi:10.1016/S2468-1253(24)00246-2

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