Denifanstat showed anti-fibrotic effect both on conventional and digital pathology in a metabolic dysfunction-associated steatohepatitis (MASH) Phase 2b trial (FASCINATE-2)

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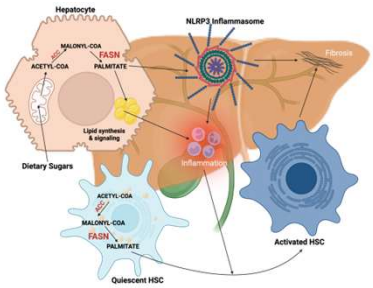
Introduction

- Denifanstat (TVB-2640) is an oral, once daily, selective fatty acid synthase (FASN) inhibitor in clinical development for MASH
- The *de novo* lipogenesis (DNL) pathway is elevated in MASH patients and converts dietary sugars to palmitate, which drives the development and progression of MASH
- **FASN inhibition targets 3 hallmarks of MASH, with both direct and indirect antifibrotic effect (1):**
  - Reduction of liver fat and lipotoxic species by inhibition of intrahepatic DNL
  - Blockage of stellate cell activation by inhibition of cell-based DNL
  - Reduction of inflammation through decreased NLRP3 inflammasome activity



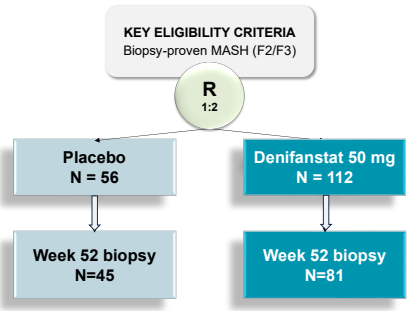
- Digital pathology complements conventional pathology by providing more sensitive and quantitative analysis of histologic changes

Aims

- To describe the fibrosis response to denifanstat using both conventional pathology and qFibrosis features

Methods

- **FASCINATE-2**
  - A 52-week randomized, double-blind, placebo-controlled phase 2b trial. Results were previously published (2)
  - Liver histology analyses by two approaches
    - Single pathology reader
    - AI digital pathology (HistoIndex)
- **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 pathology: an unstained slide was evaluated by second harmonic generation/two-photon excitation incorporating steatosis correction for qFibrosis

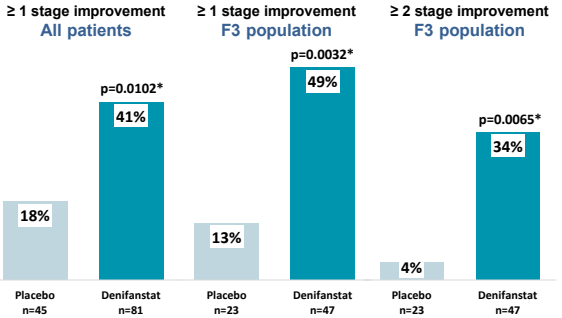


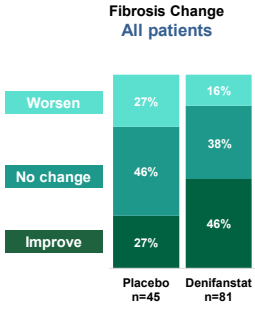
Results – Conventional Pathology

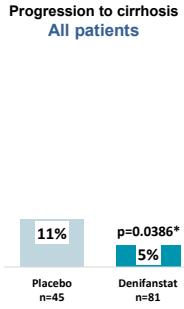
Baseline Characteristics

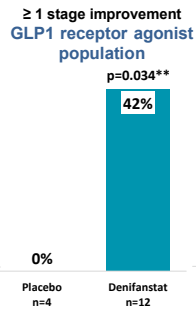
Parameter	Placebo n=45	Denifanstat n=81
Age, years	59.6 (+/- 10.9)	56.1 (+/- 10.8)
Sex, female	27 (60%)	48 (59%)
Type 2 diabetes	27 (60%)	55 (68%)
AST, U/L	52 (+/- 27)	48 (+/- 29)
ELF	9.8 (+/- 0.8)	9.6 (+/- 0.8)
MRI-PDFF, %	19.0 (+/- 7.0)	16.6 (+/- 7.1)
NAS ≥ 5	34 (76%)	63 (78%)
Baseline Fibrosis F3	23 (51%)	47 (58%)
qFibrosis Continuous Value	2.5 (0.64)	2.6 (0.75)

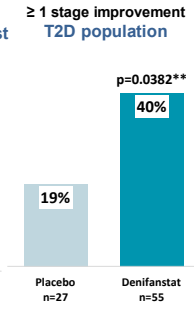
Data are mean (SD), or n (%)

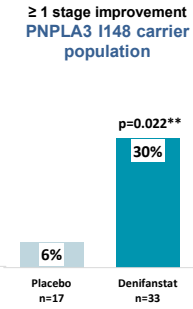






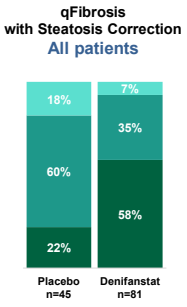


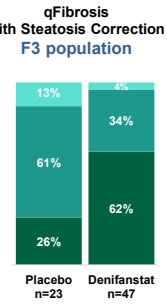


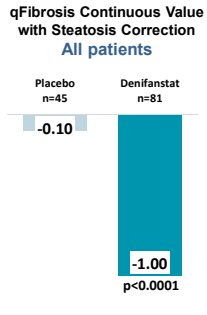


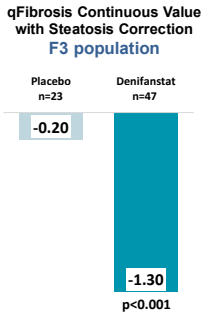
mITT population. Cochran-Mantel-Haenszel Test – *two-sided and **one-sided at the 0.05 significance level

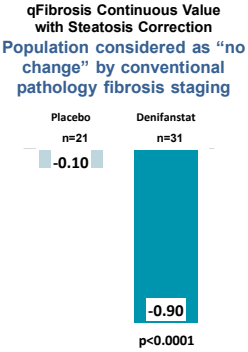
Results – Digital Pathology

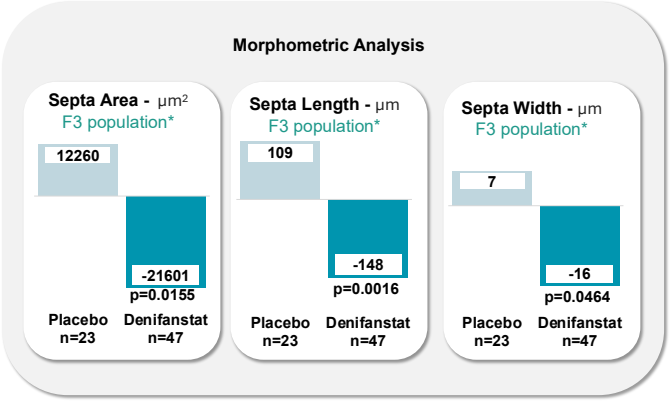












Conclusions

- **Denifanstat showed statistically significant antifibrotic effects as measured by both conventional and digital pathology, including in difficult-to-treat MASH populations**
- **Digital pathology also revealed fibrosis improvement in denifanstat-treated patients classified as "no change" by conventional pathology fibrosis staging, suggesting that longer treatment duration with denifanstat may potentially increase the proportion of responders**
- **These data demonstrate denifanstat's mechanism of action and support the initiation of phase 3 trials for denifanstat in MASH**

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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