Denifanstat elicited a significant ≥ 2-stage improvement in fibrosis in F3 MASH patients, and improved liver fibrosis and biomarkers in qFibrosis stage 4 MASH patients: secondary analysis of phase 2b FASCINATE-2 trial

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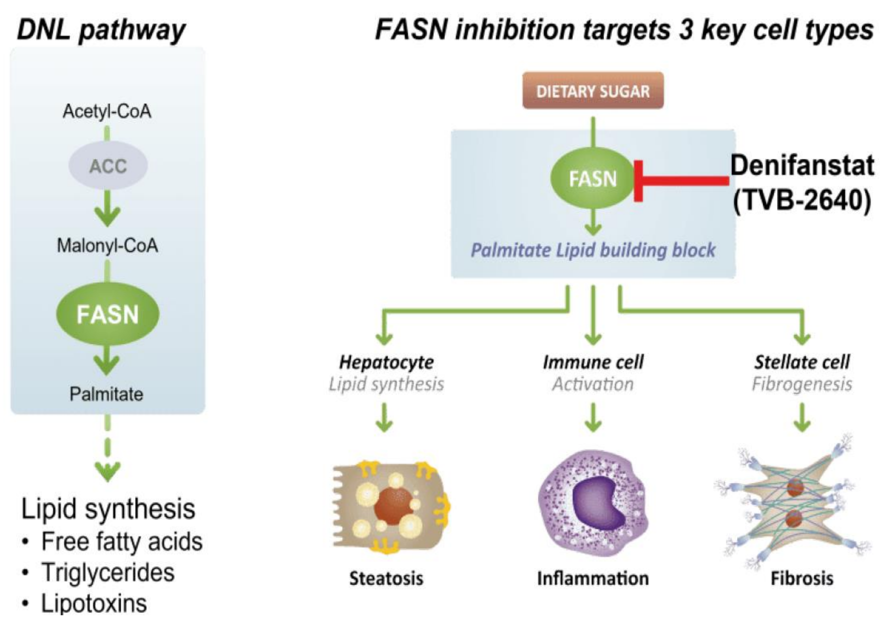
Introduction

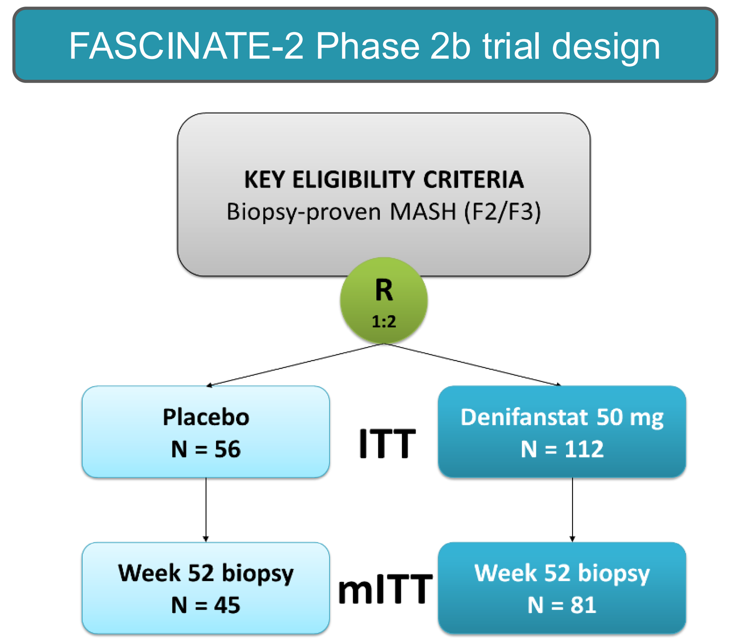
- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor in clinical development for MASH
- FASN inhibition targets 3 hallmarks of MASH: inhibits liver fat synthesis & accumulation (hepatocytes), inhibits fibrosis (hepatic stellate cells require DNL for activation) and decreases inflammation (inflammasome activation by palmitate)[1]
- Denifanstat has recently demonstrated statistically significant MASH resolution and fibrosis improvement in the Phase 2b MASH trial, FASCINATE-2 (NCT04906421)[2]



Background & Aims

- Denifanstat improved liver fibrosis in MASH patients with F2/F3 fibrosis as assessed by both conventional histopathology and AI-based digital pathology[2]
- We aimed to identify a subpopulation of MASH patients with advanced fibrosis (qFibrosis stage 4) using AI-based digital pathology to explore liver pathology and biomarker improvements with denifanstat treatment in this subset of patients

Methods

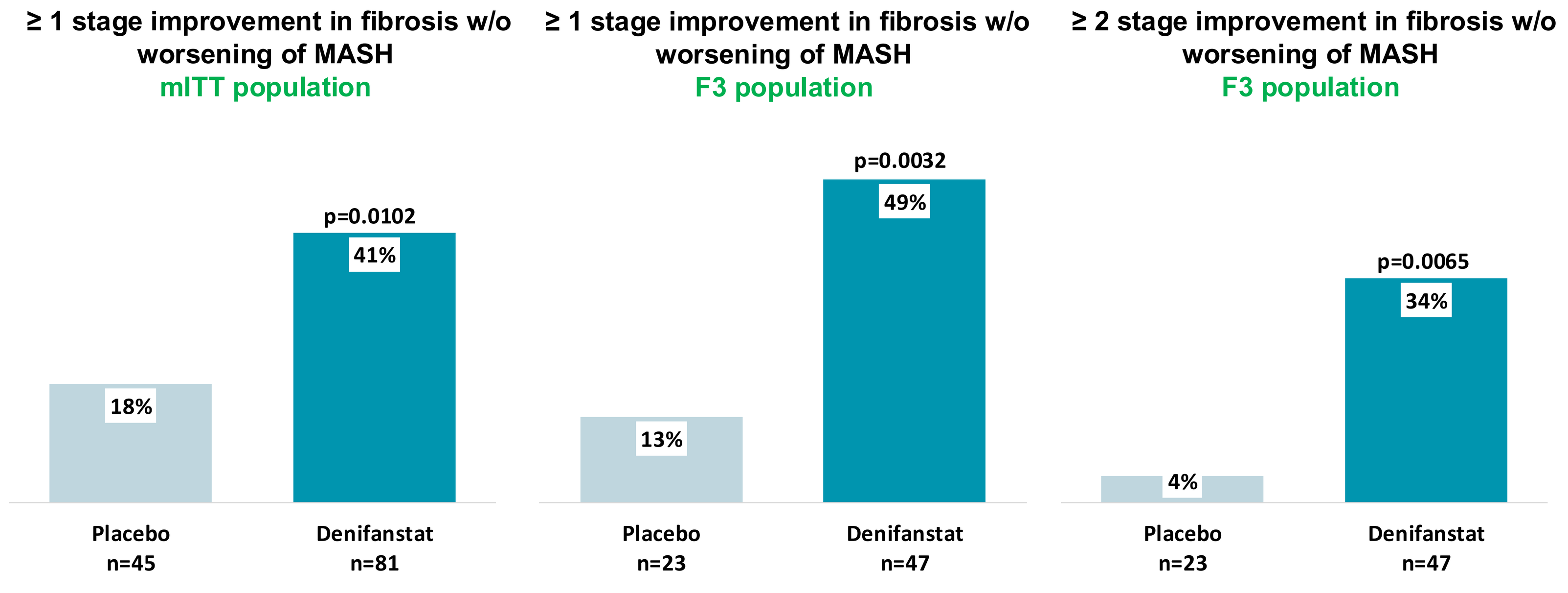


ITT: Intention-to-treat
mITT: Modified intention-to-treat

- FASCINATE-2: A total of 168 patients with biopsy-confirmed MASH and F2/F3 fibrosis were randomized 2:1 to once daily oral denifanstat 50 mg or placebo for 52 weeks
- Biopsy evaluation: Liver biopsies pre- and post-treatment were read by a central pathologist using MASH CRN criteria
- Digital pathology: An unstained biopsy slide was evaluated by second harmonic generation (SHG) AI digital pathology (HistoIndex) to identify patients with baseline qFibrosis stage 4 (qF4)
- All analyses involving qF4 patients were conducted post-hoc

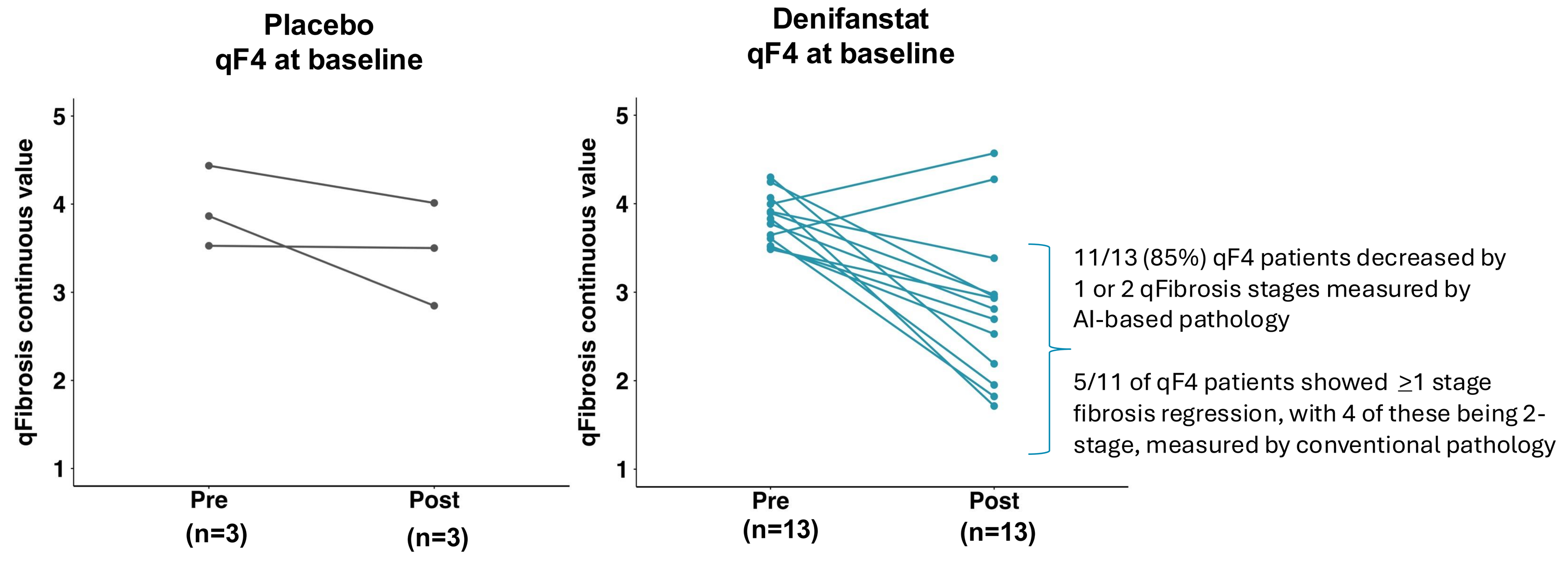
Results

Improvement in Liver Fibrosis Without Worsening of MASH (Conventional Pathology)



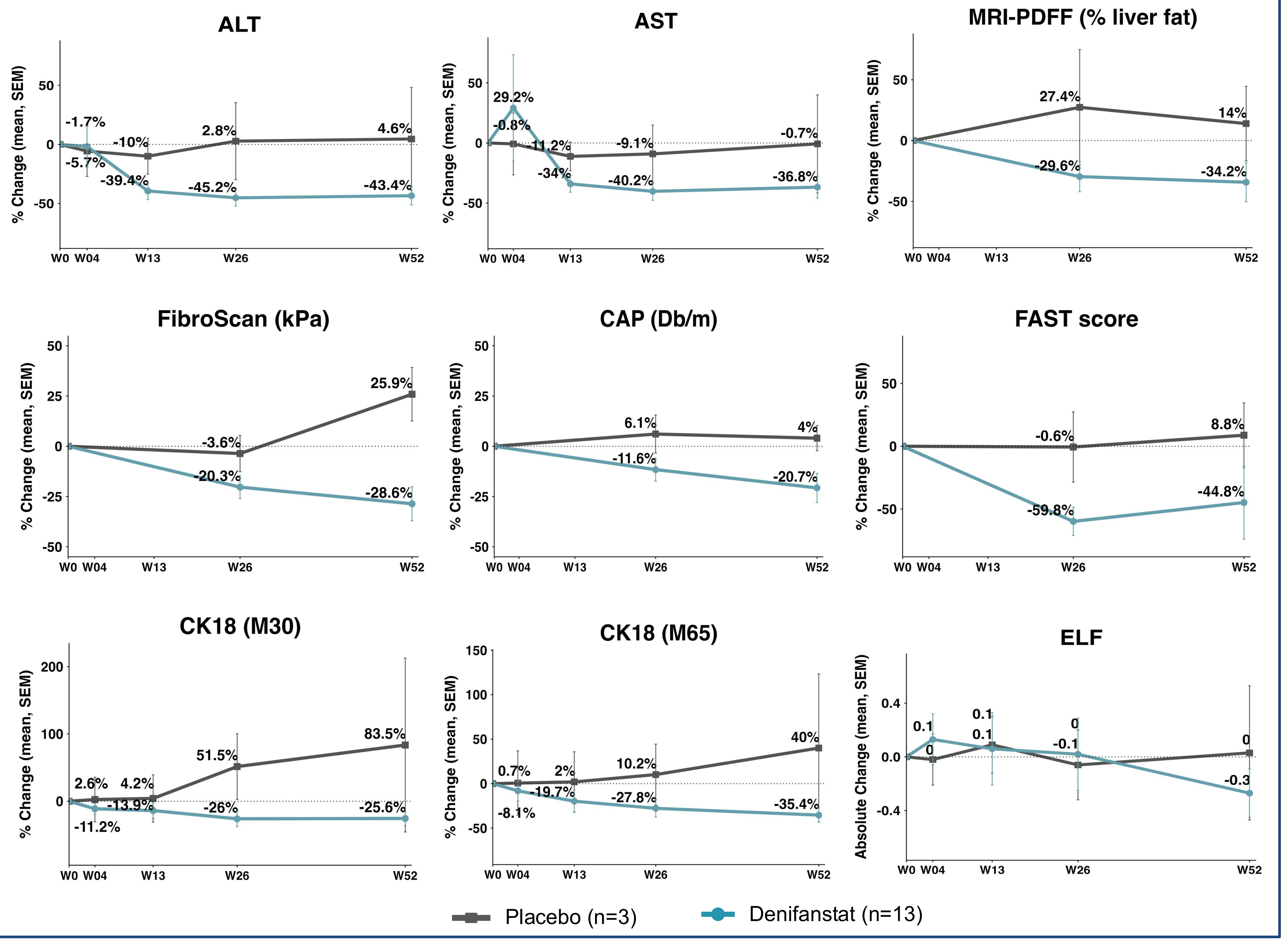
Cochran-Mantel-Haenszel Test – Two sided at the 0.05 significance level; mITT population[2]

85% of qF4 Patients on Denifanstat Showed 1 to 2-Stage Reductions in qFibrosis Stage



qF4 patients were identified using AI-based digital pathology by HistoIndex

Denifanstat Reduced Multiple Non-Invasive Test Biomarkers in qF4 patients



Conclusions

- Denifanstat demonstrated a robust anti-fibrotic effect as measured by both conventional pathology and AI-based digital pathology
- Denifanstat reduced fibrosis and multiple non-invasive biomarkers associated with histological improvements in steatosis and inflammation in patients with advanced fibrosis defined as qF4 by AI-based digital pathology
- These findings support the continued clinical evaluation of denifanstat in MASH patients with advanced fibrosis, including compensated liver cirrhosis

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