Denifanstat significantly improves liver fibrosis in difficult-to-treat MASH patients – Results from conventional and AI-based pathology from the phase 2b FASCINATE-2, a 52-week randomized, double-blind, placebo-controlled trial

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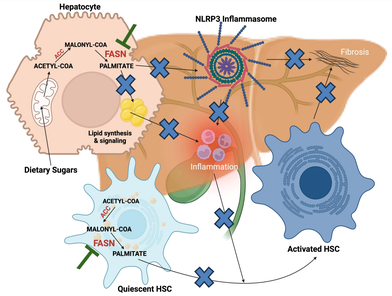
1. University of California, San Diego, US, 2. Sagimet Biosciences, San Mateo, US, 3. Liverpat, Paris, France, 4. Global Research Associates, Homestead, US, 5. The Texas liver Institute, San Antonio, US, 6. Pinnacle Clinical Research, San Antonio, US, 7. University of Oxford, Oxford, UK, 8. In Memoriam

Introduction

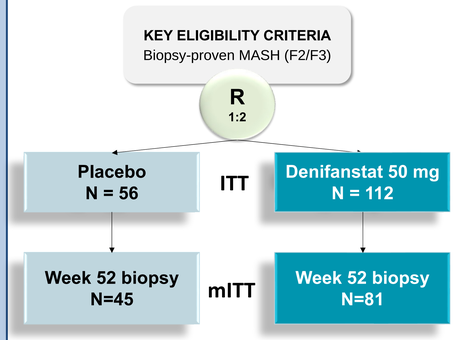
- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor in clinical development for MASH
- FASN inhibition targets 3 hallmarks of MASH:
  - inhibits liver fat synthesis & accumulation (hepatocytes)
  - **inhibits fibrosis (hepatic stellate cells require DNL for activation)**
  - decreases inflammation (inflammasome activation by palmitate)[1]



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]
- The objective of the analyses described herein was to assess the effect of denifanstat on fibrosis in the overall study population and difficult-to-treat subsets by conventional histopathology and second harmonic generation (SHG) AI-based digital pathology (HistoIndex)

Methods



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

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

- 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 artificial intelligence (AI) pathology

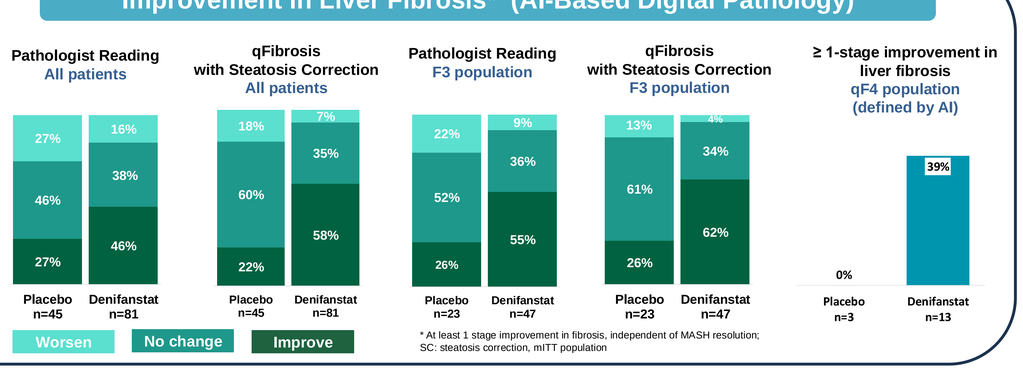
Results

Baseline Characteristics – Population with Paired Liver Biopsies

Parameter	Placebo, n=45	Denifanstat, n=81
Age, years	59.6 (+/- 10.9)	56.1 (+/- 10.8)
Sex, female	27 (60%)	48 (59%)
Ethnicity, Hispanic or Latino	15 (33%)	27 (33%)
BMI, kg/m^2	36.5 (+/- 6.7)	34.6 (+/- 6.1)
Type 2 diabetes	27 (60%)	55 (68%)
ALT, U/L	67 (+/- 33)	57 (+/- 29)
AST, U/L	52 (+/- 27)	48 (+/- 29)
ELF (Enhanced Liver Fibrosis) Score	9.8 (+/- 0.8)	9.6 (+/- 0.8)
Liver Fat Content (MRI-PDFF), %	19.0 (+/- 7.0)	16.6 (+/- 7.1)
Baseline liver biopsy NAS ≥ 5	34 (76%)	63 (78%)
Baseline Fibrosis		
F2	22 (49%)	34 (42%)
F3	23 (51%)	47 (58%)
qFibrosis Continuous Value	2.5 (0.64)	2.6 (0.75)

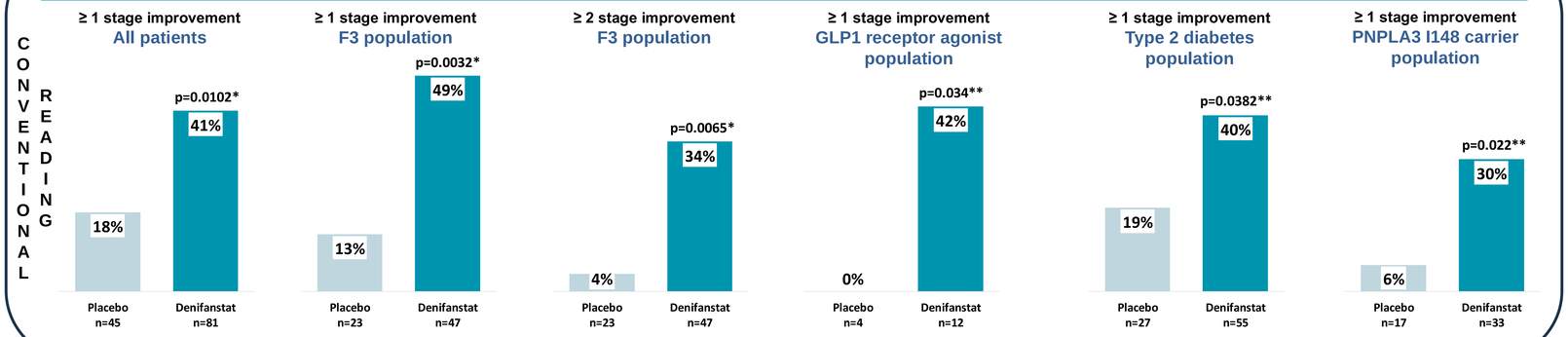
Data are mean (SD), or n (%)

Improvement in Liver Fibrosis* (AI-Based Digital Pathology)



* At least 1 stage improvement in fibrosis, independent of MASH resolution; SC: steatosis correction, mITT population

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



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

Conclusions

- Denifanstat demonstrated a statistically significant improvement in liver fibrosis without worsening of MASH, including in difficult-to-treat subpopulations.
- The fibrosis improvement was independently demonstrated by conventional reading and AI-based pathology, and denifanstat had a strong anti-fibrotic effect in the F3 population.
- These data demonstrate the unique mechanism of action of denifanstat 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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