Denifanstat improved multiple qFibrosis-based collagen features linked to major adverse liver outcomes in patients with metabolic dysfunction-associated steatohepatitis patients and high polygenic risk

Mary E. Rinella[1], Philip Newsome[2], Vlad Ratziu[3], Brent Neuschwander-Tetri[4], Shipra Vinod Gupta[5], Wen-Wei Tsai[5], Marie O'Farrell[5], Katharine Grimmer[5], George Kemble[5], Eduardo Bruno Martins[5], Jean-Marie Grouin[6], Dean Tai[7], Elaine Chng[7], Julie Dubourg[5], Joern Schattenberg[8], Arun Sanyal[9], Rohit Loomba[10]

1. University of Chicago, Chicago, IL, USA, 2. King's College London, London, UK, 3. University of Sorbonne, Paris, France, 4. Saint Louis University, Saint Louis, USA, 5. Sagimet Biosciences Inc., San Mateo, CA, USA, 6. University of Rouen, Rouen, France, 7. Histoindex, Singapore, Singapore, 8. University of the Saarland, Homburg, Germany, 9.Virginia Commonwealth University, Richmond, United States, 10. UC San Diego School of Medicine, San Diego, CA, USA.

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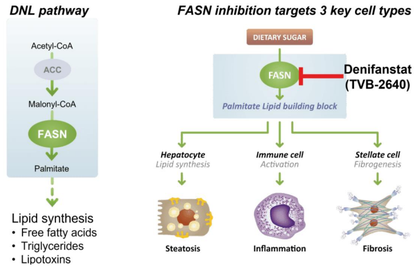
Introduction

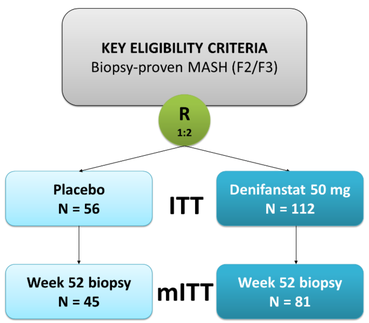
- Denifanstat (TVB-2640) is an oral, once daily, selective FASN inhibitor in clinical development for MASH
- FASN inhibition targets 3 hallmarks of MASH:
  - inhibits liver fat synthesis & accumulation (hepatocytes)
  - **inhibits fibrosis (hepatic stellate cells require DNL for activation)**
  - decreases 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]
- This study analyzed specific patterns of collagen deposition that predict major adverse liver outcomes (MALO)[3] by quantifying changes in portal and periportal fibrosis architecture in FASCINATE-2
- This study also evaluated the anti-fibrotic effect across different genetic risk profiles by analysing the changes in qFibrosis-based key collagen parameters linked to MALO

Methods



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

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

Histology endpoints analyzed by:

- Single pathology reader
- AI digital pathology (HistoIndex): relative changes from baseline in qFibrosis parameters were calculated with steatosis correction for the following features that are associated with MALO: IntersectionPT, LongStrPeriPortalAgg, ThinStrPeriPortal, ThinStrPeriPortalDis, and StrLengthPeriPortal

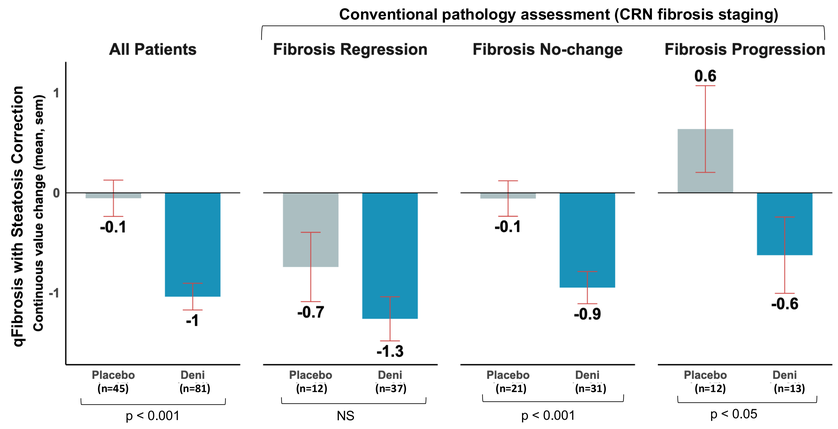
Genotyping

- Genetic variants: *PNPLA3* rs738409, *MBOAT7* rs641738, and *TM6SF2* rs58542926 were characterized in consenting patients (Health in Code)

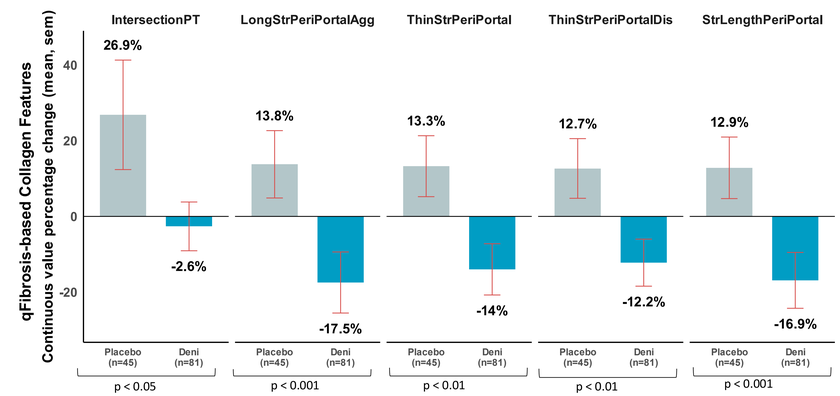
- Treatment effects were assessed across polygenic risk strata defined by the number of risk variant genes (**<u>non-carrier as '0'</u>**, **<u>carrier with single risk variant gene as '1'</u>**, and **<u>carriers with two or more risk variant genes as '≥2'</u>**) on the above 5 qFibrosis collagen features

Results

Denifanstat decreased qFibrosis including patients with no change or progression of fibrosis by conventional pathology

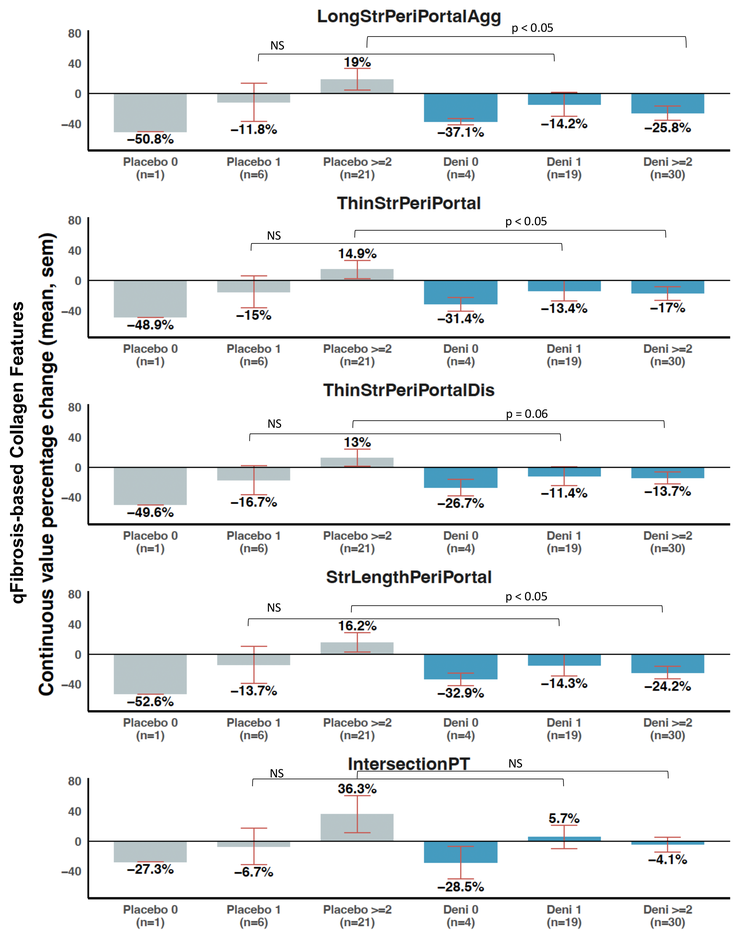


Denifanstat decreased five collagen features (CODI-F)[3] that are associated with liver decompensation



Two-sided t-test at the 0.05 significance level.

Denifanstat significantly decreased qFibrosis collagen features compared to placebo in patients <u>carrying two or more risk variant genes</u>



Two-sided t-test at the 0.05 significance level.

Conclusions

- Digital pathology demonstrated denifanstat achieved significant anti-fibrotic benefit compared to placebo, including patients who showed no change or progression of fibrosis by conventional pathology assessment
- Denifanstat decreased qFibrosis-based collagen features previously associated with major adverse liver outcomes, such as liver decompensation
- Denifanstat showed substantial reduction of collagen features in patients carrying several risk variants associated with fast fibrosis progression, including PNPLA3, MBOAT7 and TM6SF2 genes

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
(3) Akbari et al., 2023. JHEP Reports. doi: 10.1016/j.jhepr.2023.100915

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Contact information
eduardo.martins@sagimet.com