

Utilizing AI-Based Digital Pathology to Evaluate Denifanstat's Anti-Fibrotic Effect in MASH Patients with Advanced Fibrosis

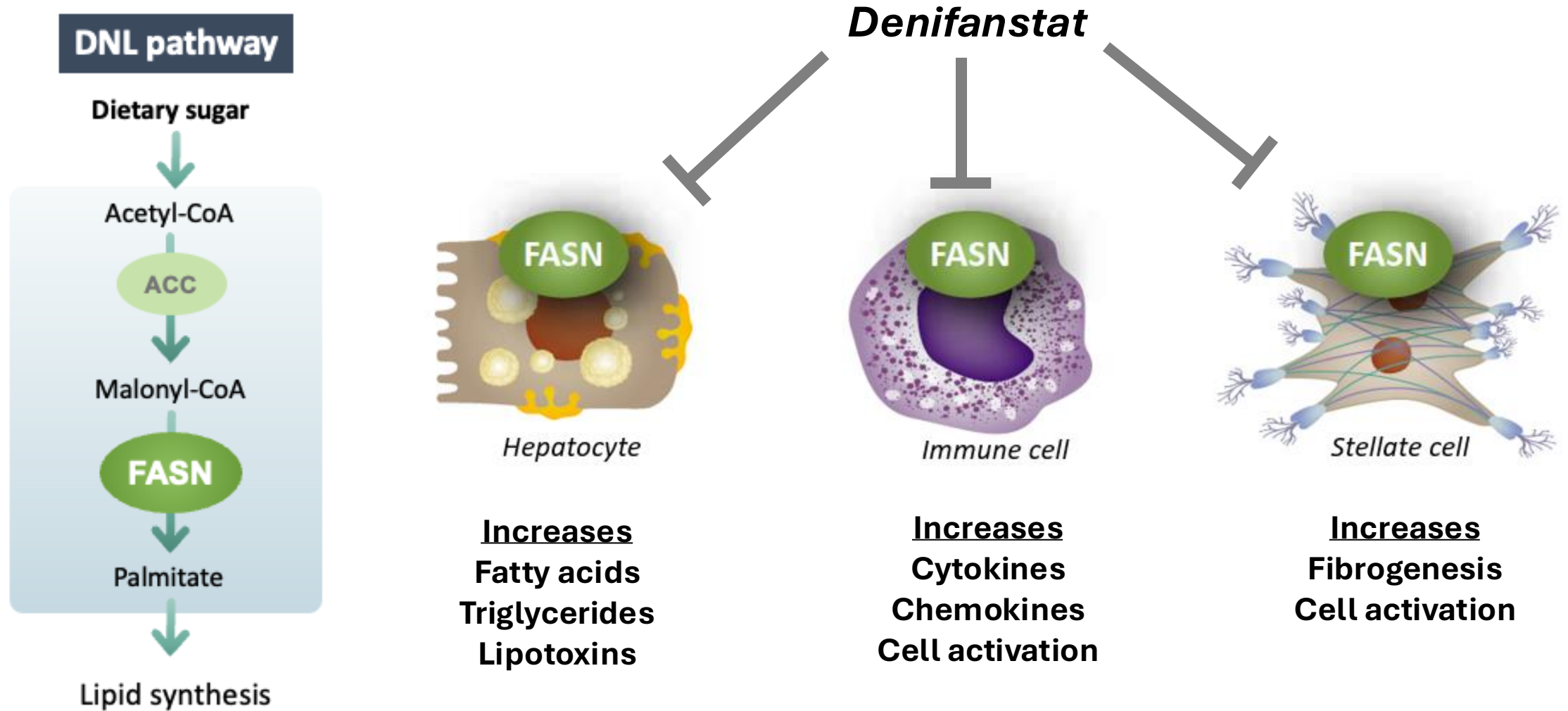
Wen-Wei Tsai, Ph.D.

September 30, 2025

Outline

- Introduction of fatty acid synthase (FASN) and denifanstat MOA
- Denifanstat Phase 2b FASCINATE-2 study results in F2/F3 MASH
 - Histological endpoints
 - Applying AI digital pathology to assess the anti-fibrotic effect
 - Utilizing zonal analysis to explore denifanstat's potential to offer long-term clinical benefit

FASN Plays a Key Role in Three Major Cell Types in MASH

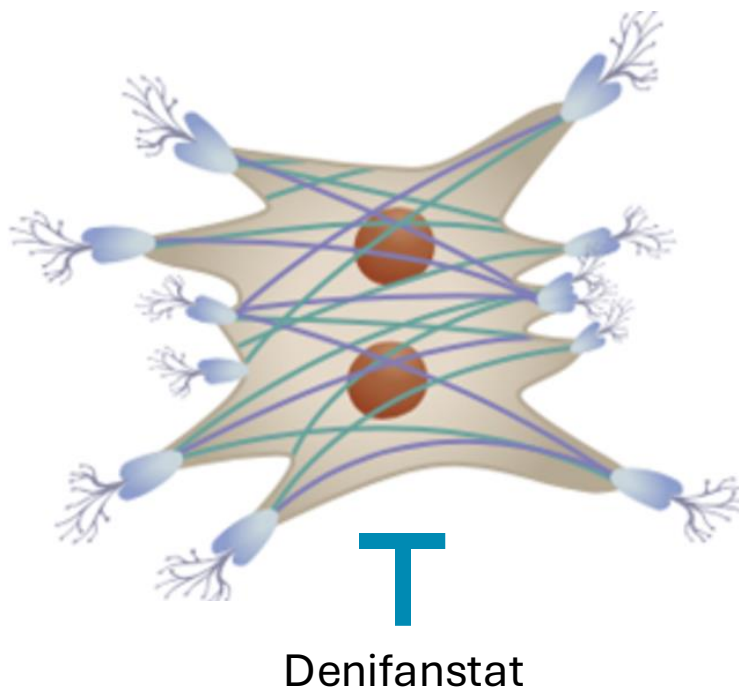


DNL: *de novo* lipogenesis

FASN Inhibition Directly Blocks Human Liver Stellate Cell Function

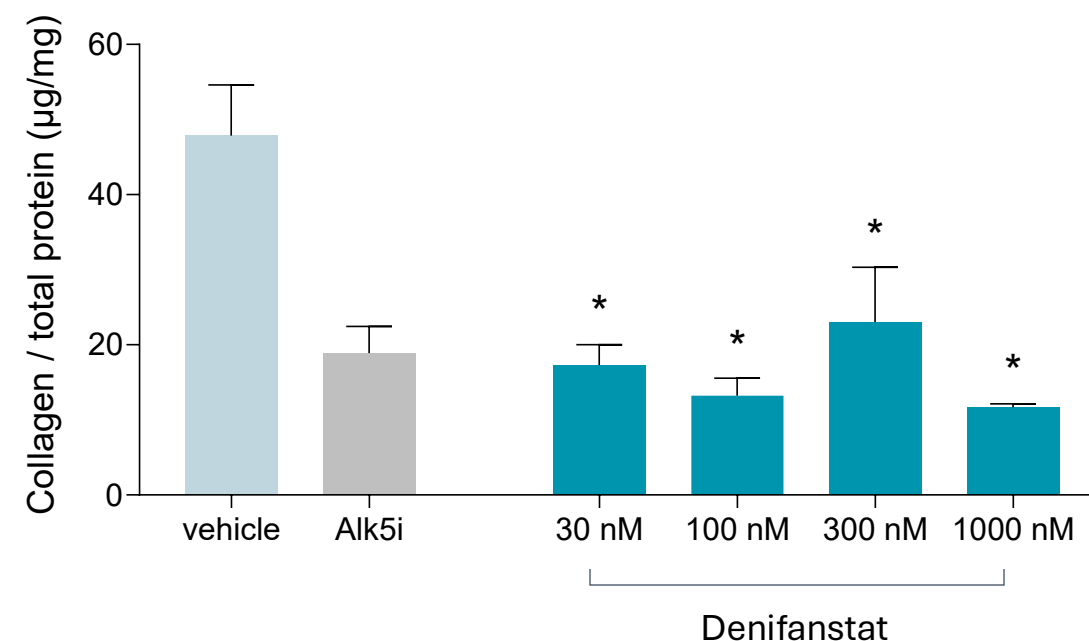
Stellate cells require DNL for fibrogenesis

Denifanstat blocks stellate cell activation



Denifanstat directly inhibits fibrogenic activity¹

Primary human stellate cell assay

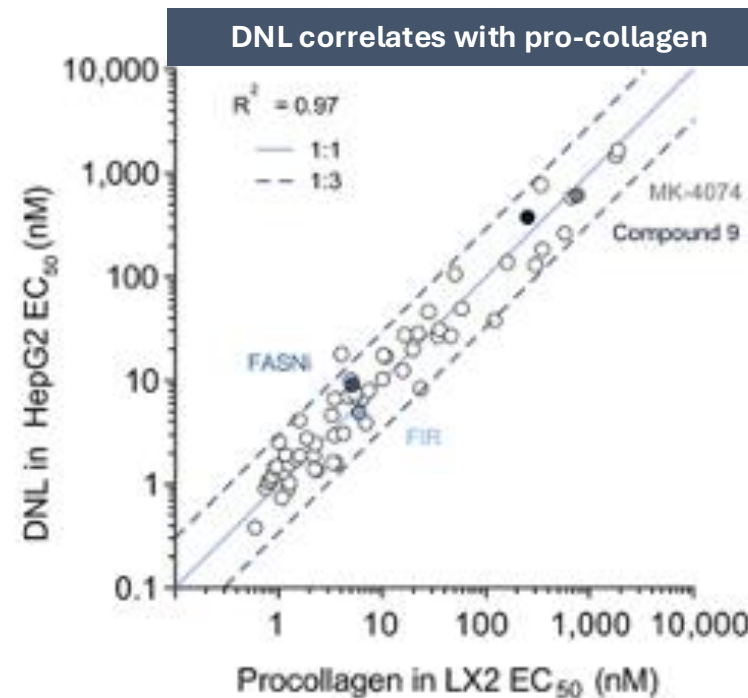
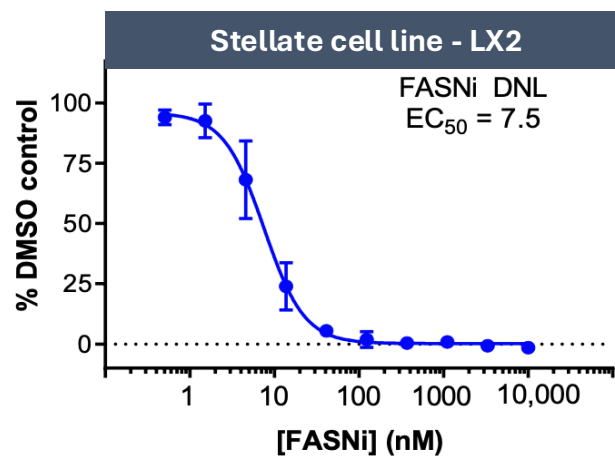
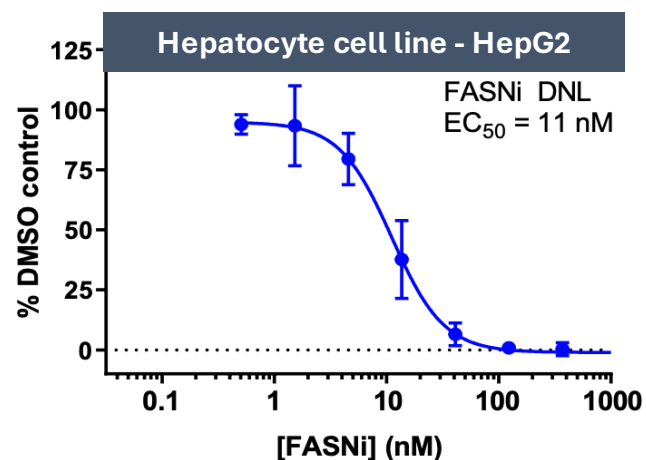


*p<0.05. DNL: de novo lipogenesis

1. O'Farrell M, et al. *Sci Rep*. 2022;12(1):15661. Sagimet Biosciences data on file.

- Stimulated by TGF-beta to activate fibrogenesis
- Denifanstat showed similar inhibition to positive control ALK5 inhibitor

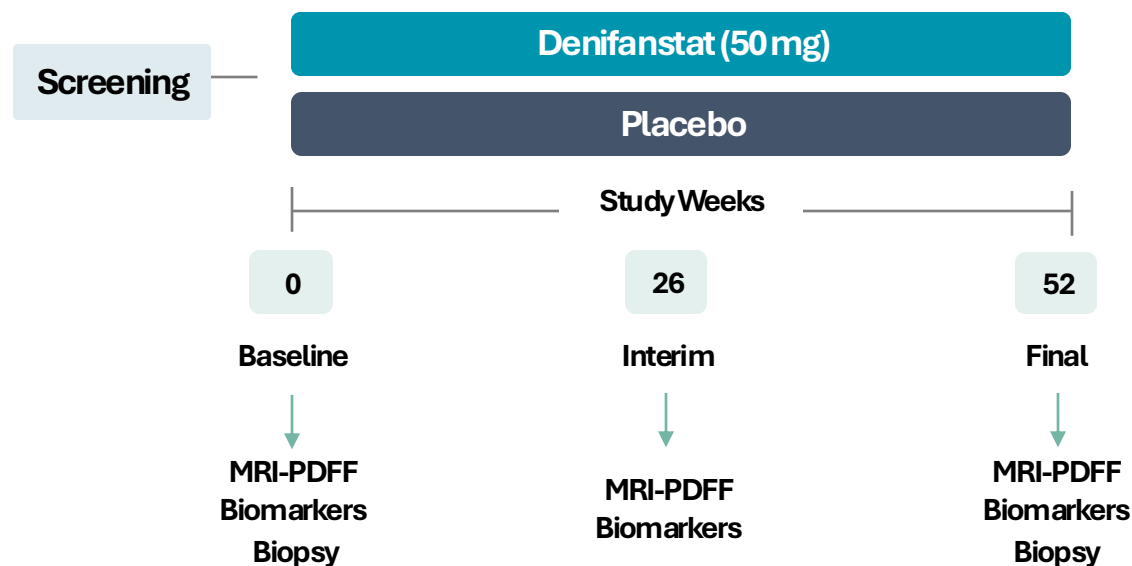
DNL Inhibition Correlates with Collagen Inhibition Across DNL Inhibitors



Adapted from Bates et al., 2020, Hepatology, 20: 30281-6

FASCINATE-2: Biopsy Trial Design Focused on Histological Endpoints

FASCINATE-2 Phase 2b trial design



- Biopsy confirmed F2-F3 MASH patients (n=168)
- 52 weeks, 2:1 randomization to 50mg or placebo, double-blind
- Single pathology reader: Dr. Pierre Bedossa
- AI digital pathology: HistoIndex

Primary endpoints

- NAS ≥ 2 points improvement w/o worsening of fibrosis
- MASH resolution + NAS ≥ 2 improvement w/o worsening of fibrosis

Selected secondary endpoints

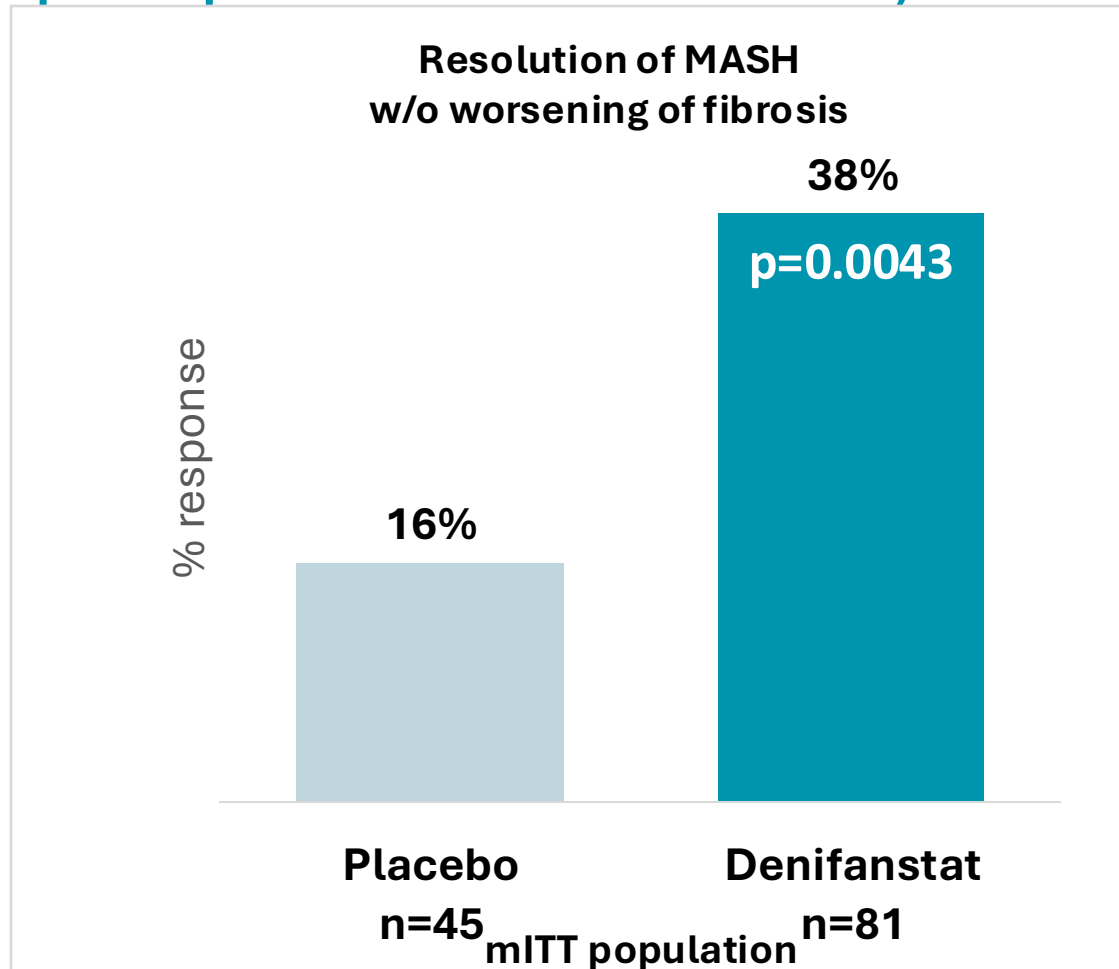
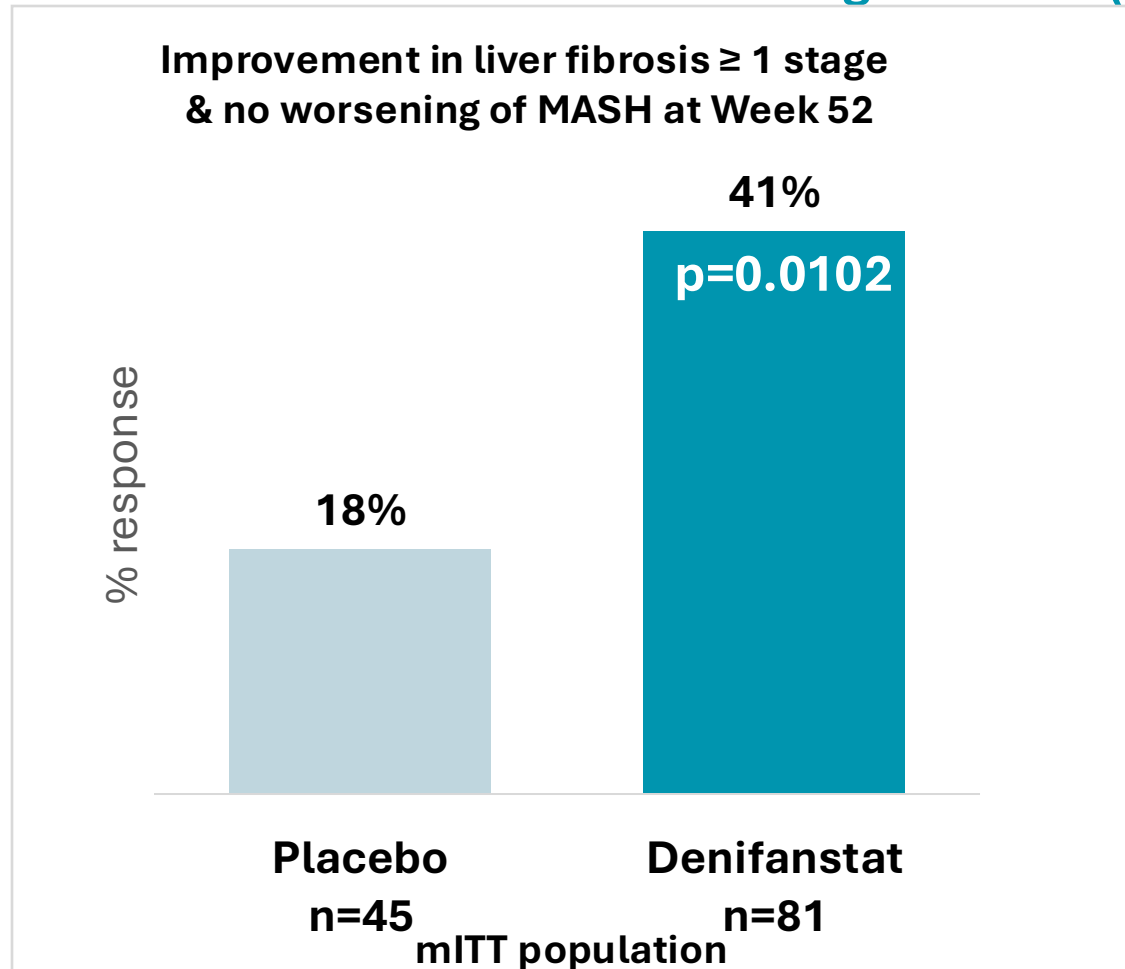
- Improvement in liver fibrosis ≥ 1 stage without worsening of MASH as assessed by biopsy
- Digital AI pathology
- MRI-PDFF: absolute decrease, % change from baseline, % pts $\geq 30\%$ reduction from baseline (responders)

AI: Artificial Intelligence, MRI-PDFF; magnetic resonance imaging derived proton density fat fraction, NAS; NAFLD Activity Score.

Loomba R, et al. Lancet Gastroenterol Hepatol. 2024;9(12):1090-1100

Histology Endpoints of MASH Resolution and Liver Fibrosis at Week 52

Denifanstat Achieved Statistical Significance (Endpoints per FDA Draft Guidance 2020)



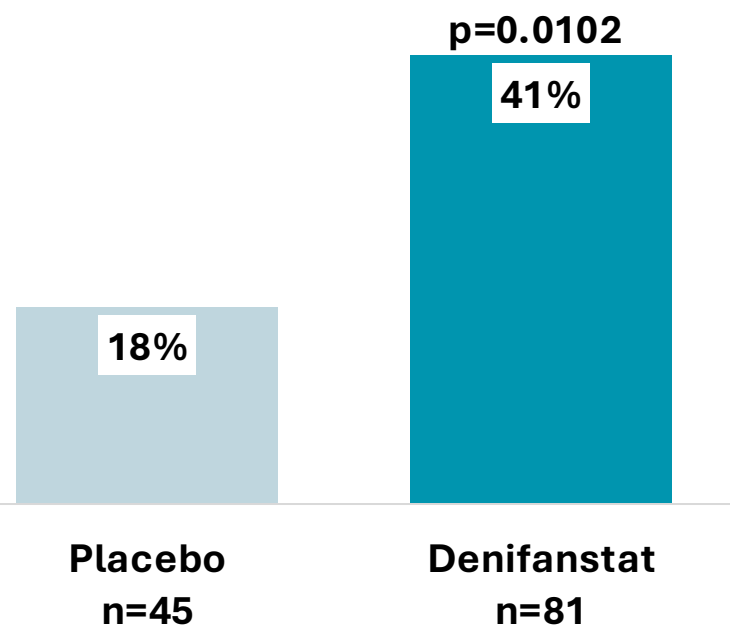
Cochran-Mantel-Haenszel Test – Two sided at the 0.05 significance level

Loomba R, et al. Lancet Gastroenterol Hepatol. 2024;9(12):1090-1100

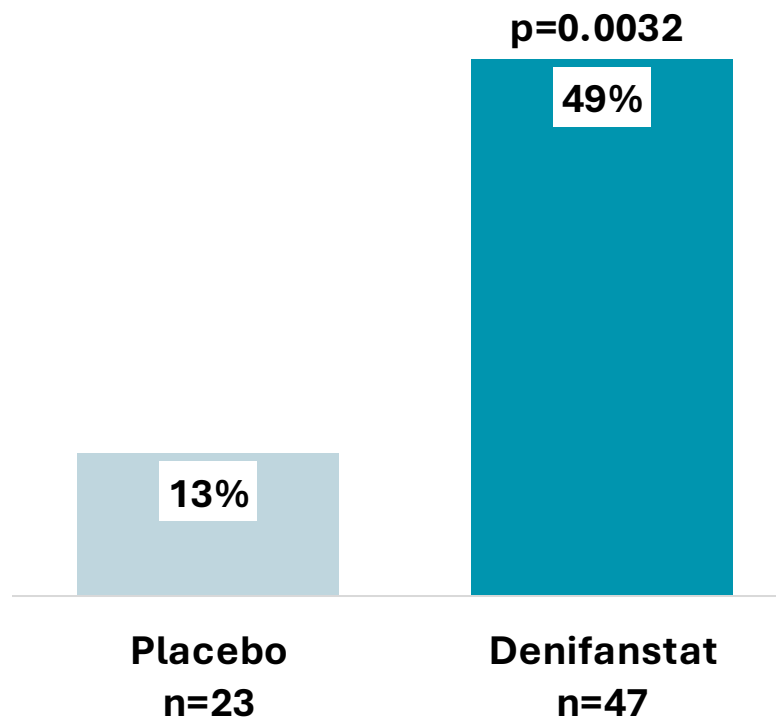
Secondary Endpoints: Liver Fibrosis at 52 week

Denifanstat Achieved Statistically Significant Improvement of Fibrosis

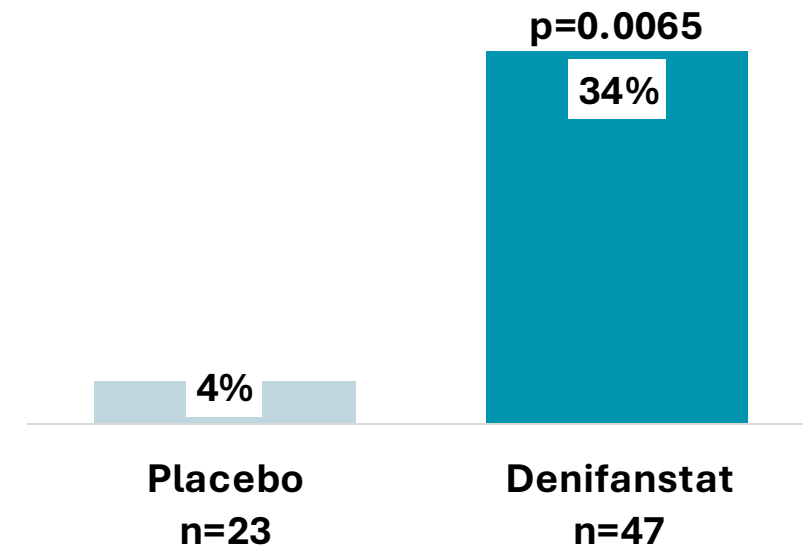
≥ 1 stage improvement in fibrosis
w/o worsening of MASH



≥ 1 stage improvement in fibrosis
w/o worsening of MASH
F3 population



≥ 2 stage improvement in fibrosis
w/o worsening of MASH
F3 population



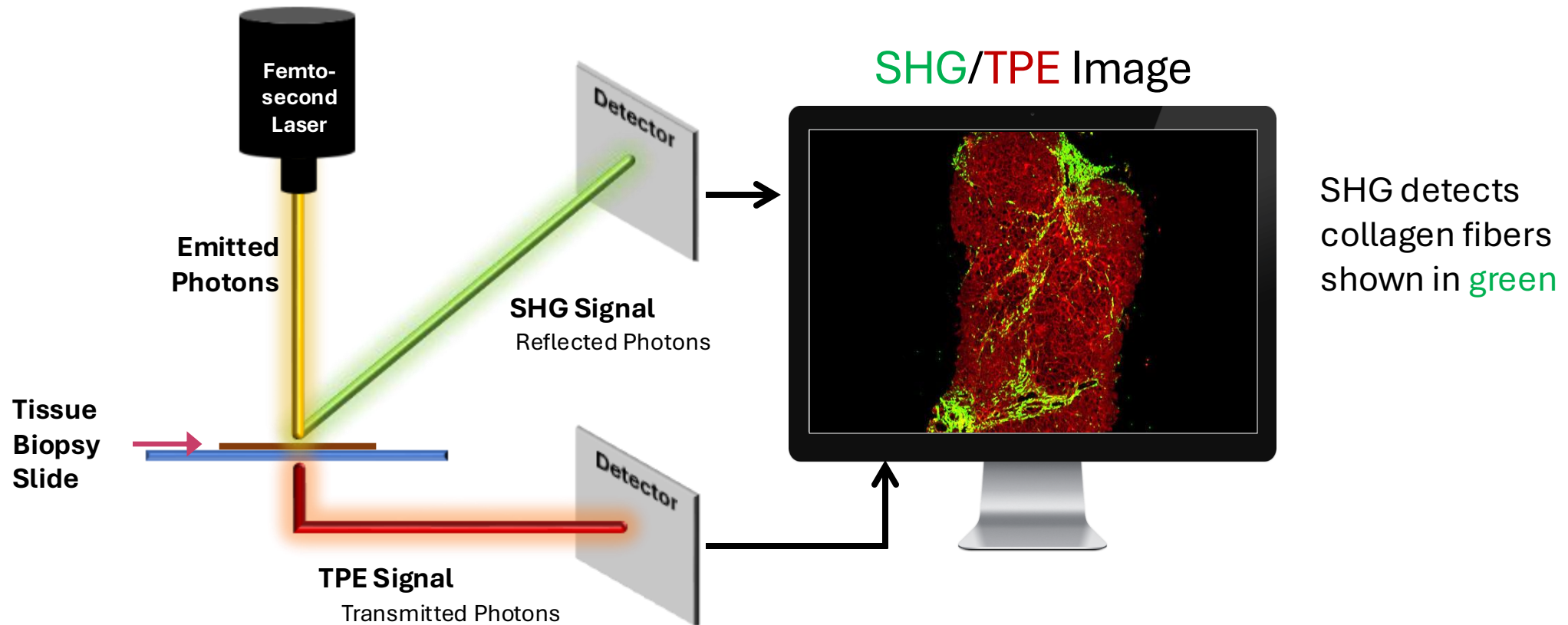
Cochran-Mantel-Haenszel Test – Two sided at the 0.05 significance level; mITT population

Loomba R, et al. Lancet Gastroenterol Hepatol. 2024;9(12):1090-1100

Artificial Intelligence (AI) Digital Pathology Analysis

Second Harmonic Generation Microscopy

SHG permits measurement of quantifiable collagen fibrillar properties



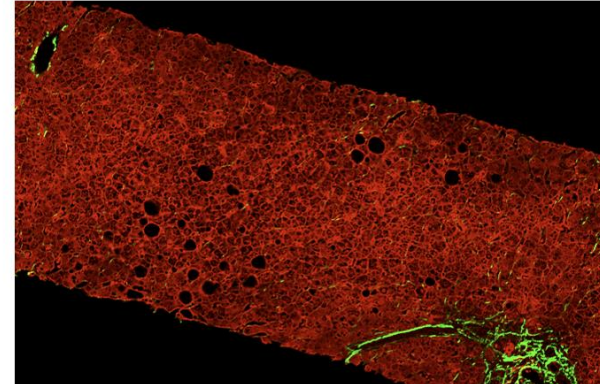
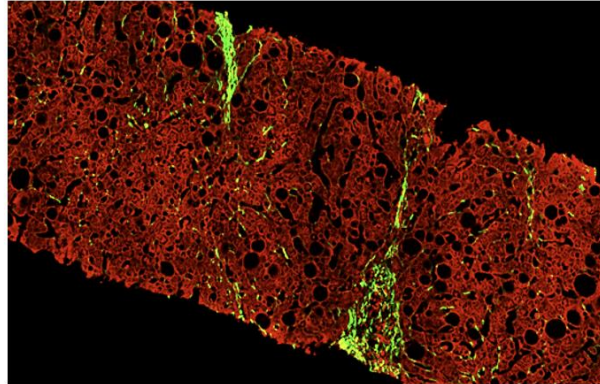
Xu S, et al. J Hepatol. 2014;61(2):260-269

qFibrosis with Steatosis Correction (SC): Methodology

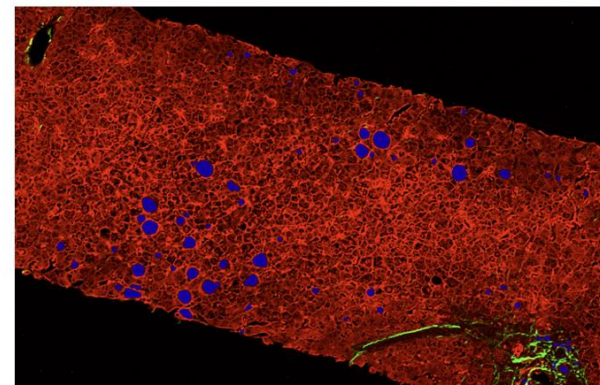
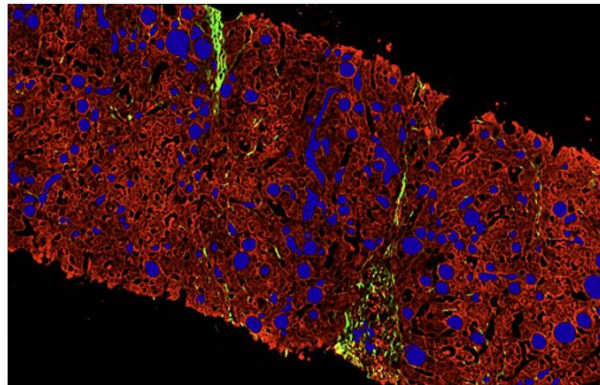
Baseline

End of treatment

SHG/TPE image



Steatosis labeled SHG/TPE image

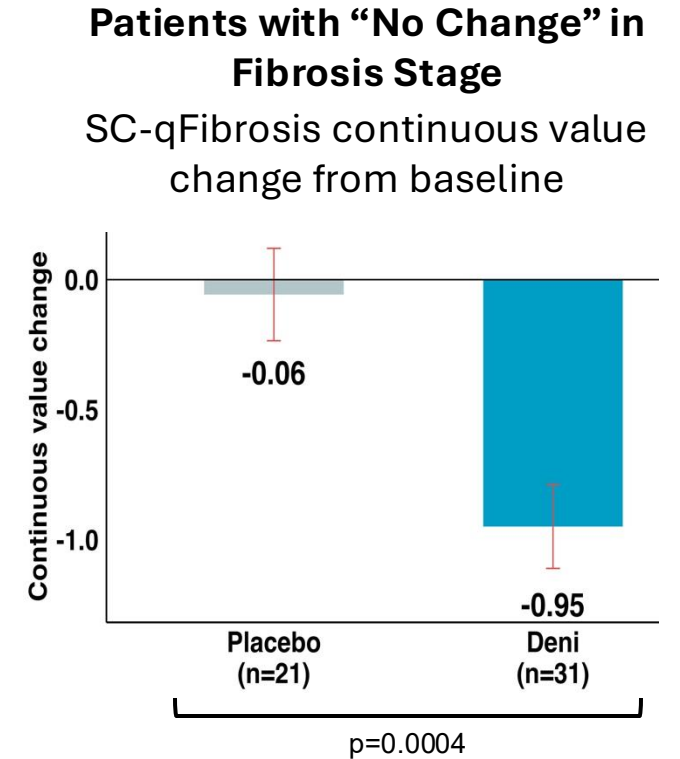
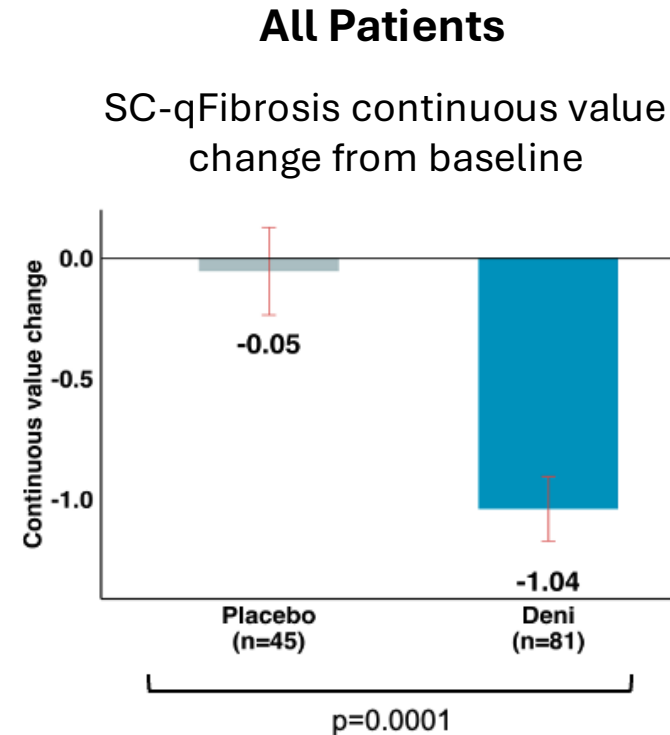
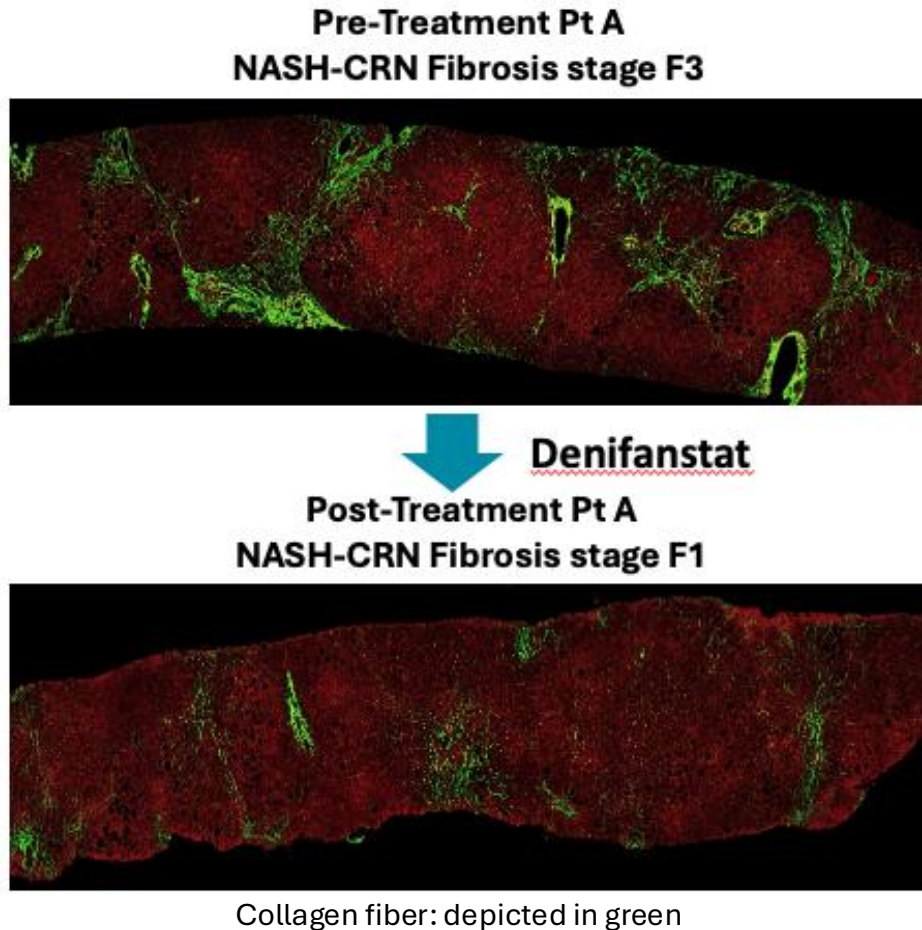


- Steatosis area: depicted in blue
- Tissue area: depicted in red
- Collagen fiber: depicted in green

Steatosis corrected qFibrosis
= raw parameter normalized by
(Tissue area – Steatosis area)

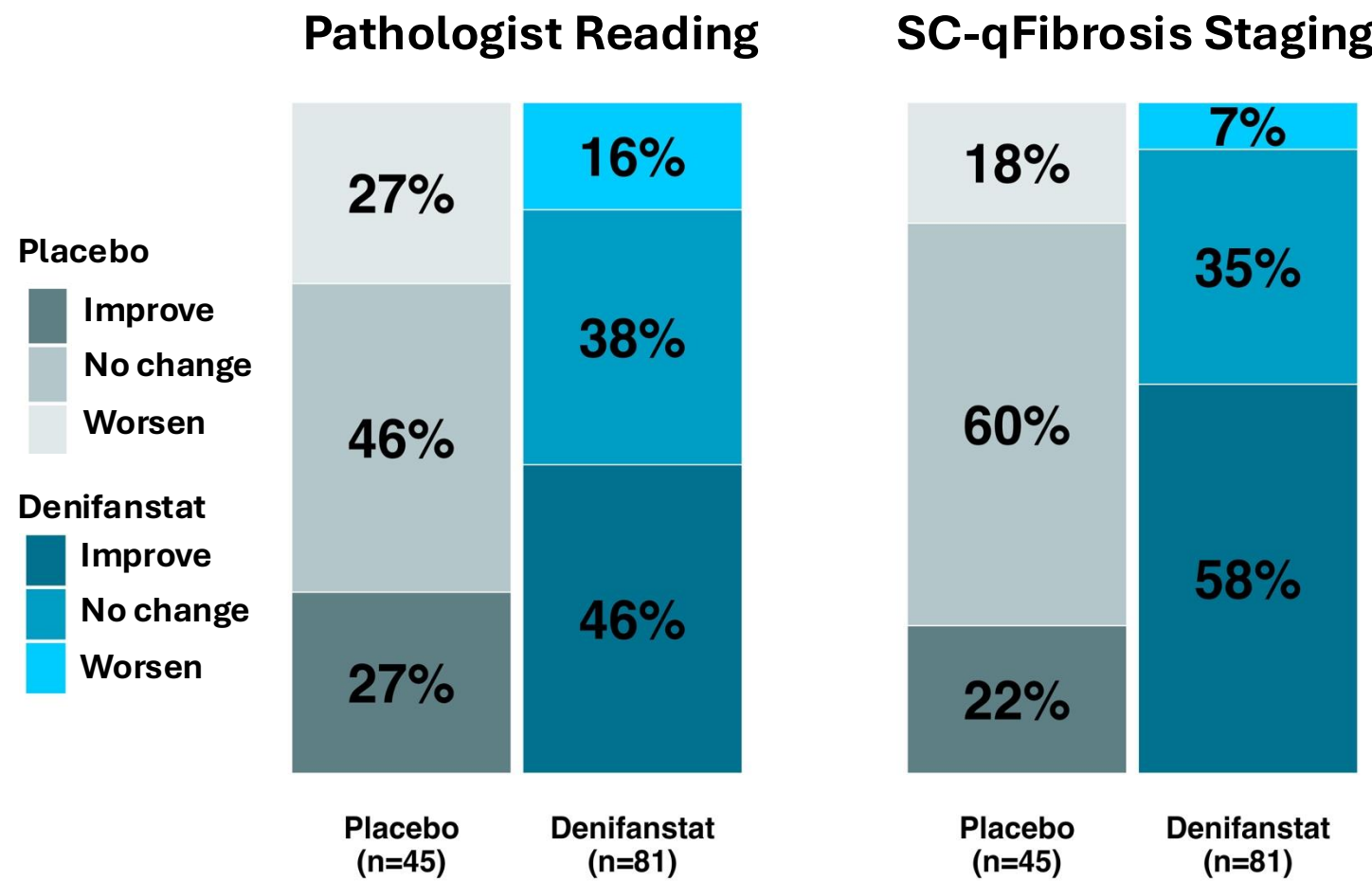
Digital Imaging Showed that Denifanstat Significantly Reduced Fibrosis

Separate Approach Performed Prospectively



SC: steatosis-corrected; Wilcoxon test; mITT population; Rinella M, et al. Presented at: EASL 2025; May 7-10 2025; Amsterdam, the Netherlands

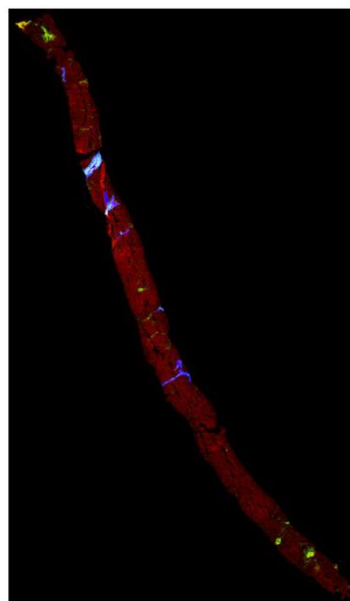
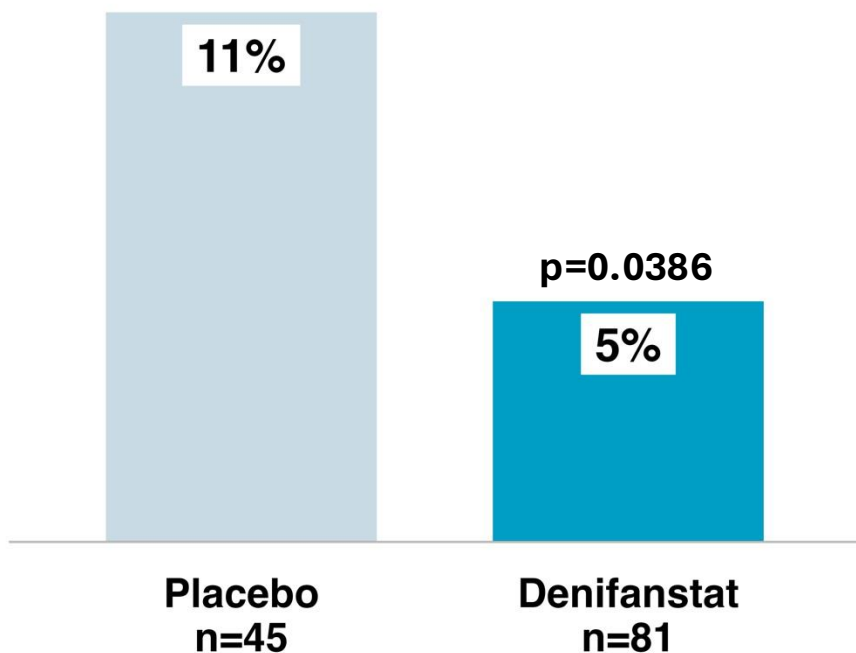
SC-qFibrosis Staging Correlated with Pathologist Reading



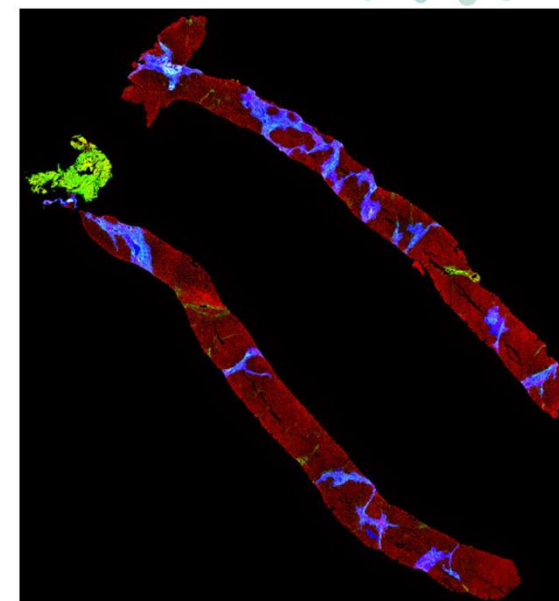
SC: steatosis-corrected; At least 1-stage improvement in fibrosis, independent of MASH resolution; mITT population
Rinella M, et al. Presented at: AASLD 2024; Nov 15-19 2024; San Diego, USA

Denifanstat Showed a Statistically Significant Difference in Progression to Cirrhosis Compared to Placebo

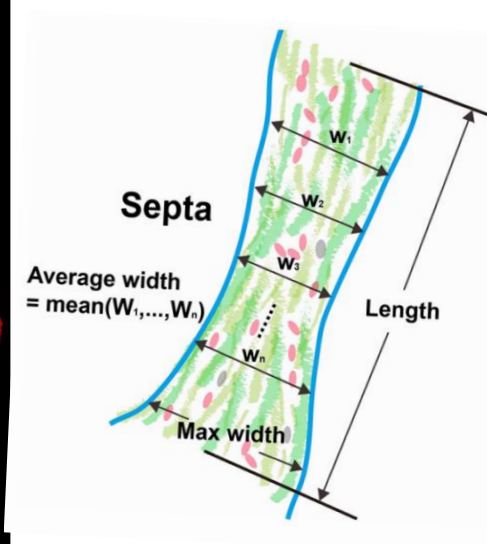
Progression to F4 (All Patients)



BL Stage F3
Septa annotations (in blue)

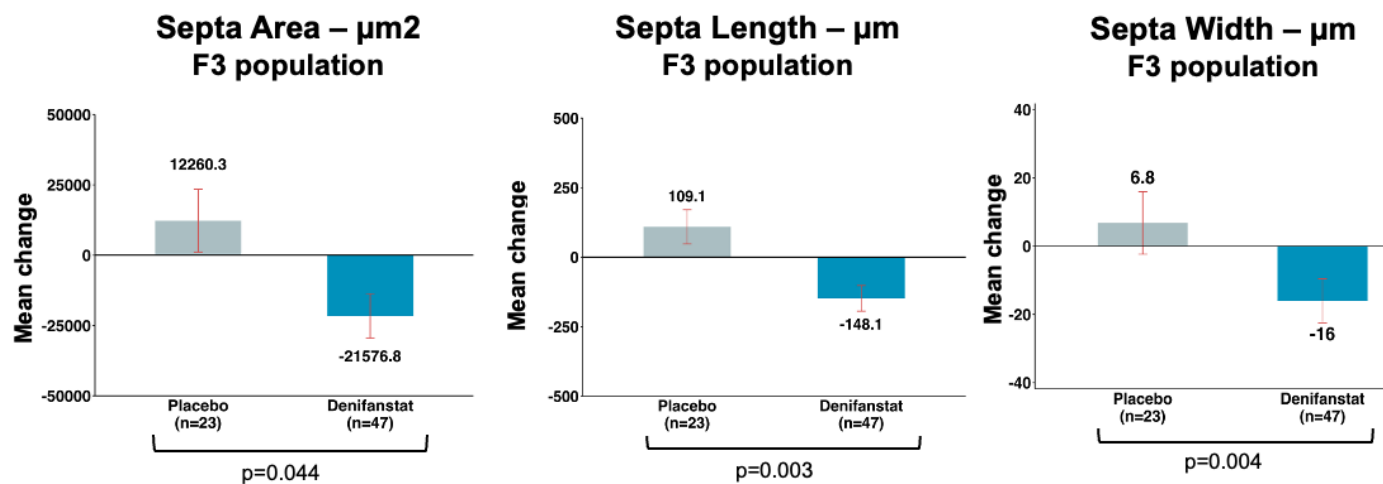


EOT Stage F4
Septa annotations (in blue)

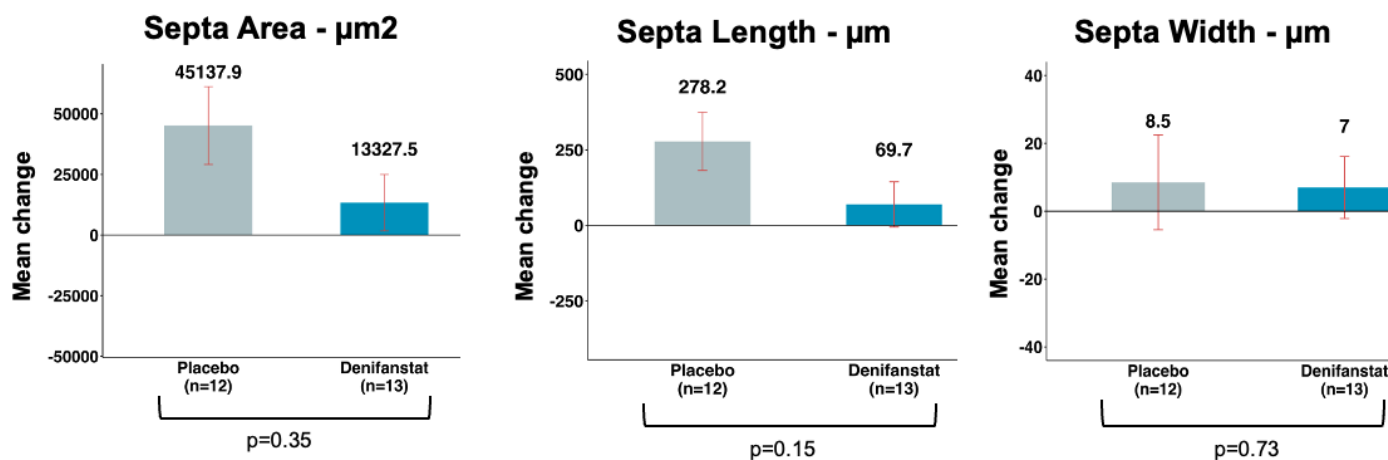


mITT population. Cochran-Mantel-Haenszel Test – one sided at the 0.05 significance level
Rinella M, et al. Presented at: AASLD 2024; Nov 15-19 2024; San Diego, USA

Denifanstat Showed a Decrease in Septa in F3 MASH Patients

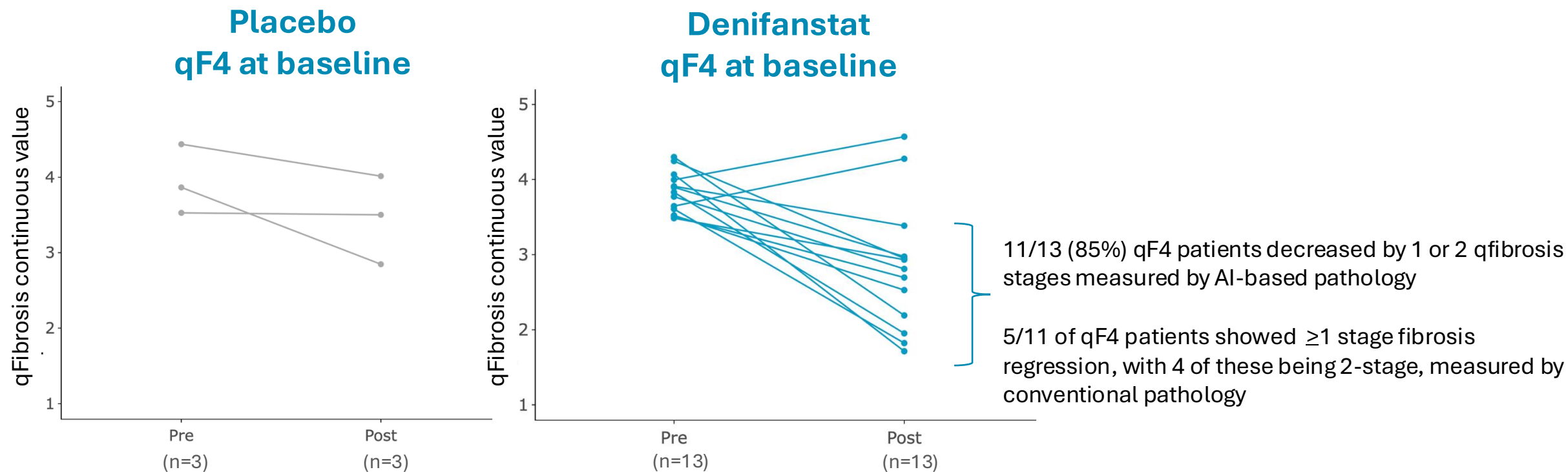


Fibrosis ≥ 1 stage progression patients



F3 population defined as per pathologist reading; Wilcoxon test; mITT population; Rinella M, et al. Presented at: AASLD 2024; Nov 15-19 2024; San Diego, USA

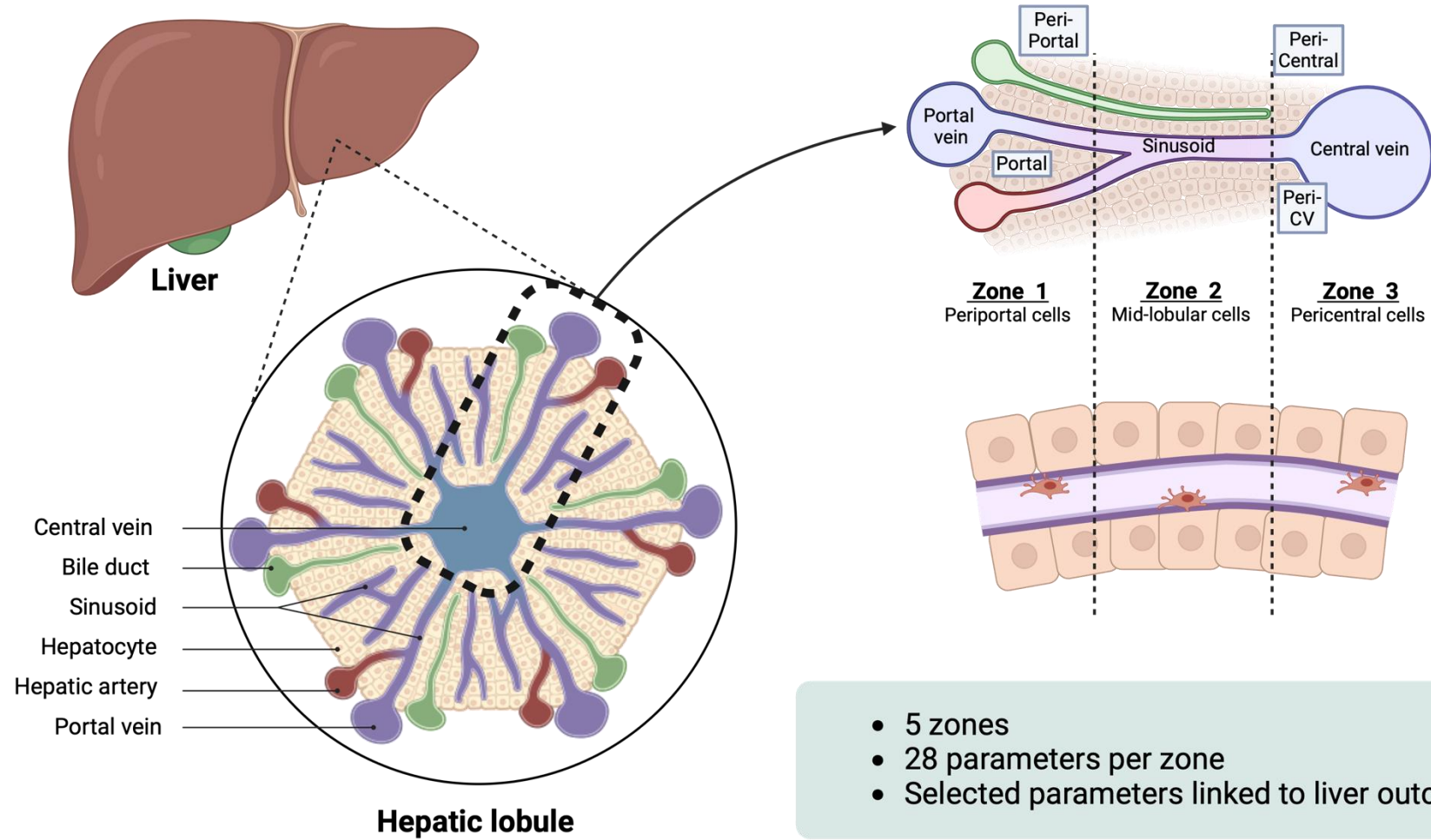
85% of qF4 Patients on Denifanstat Showed 1 to 2-Stage Reductions in Fibrosis



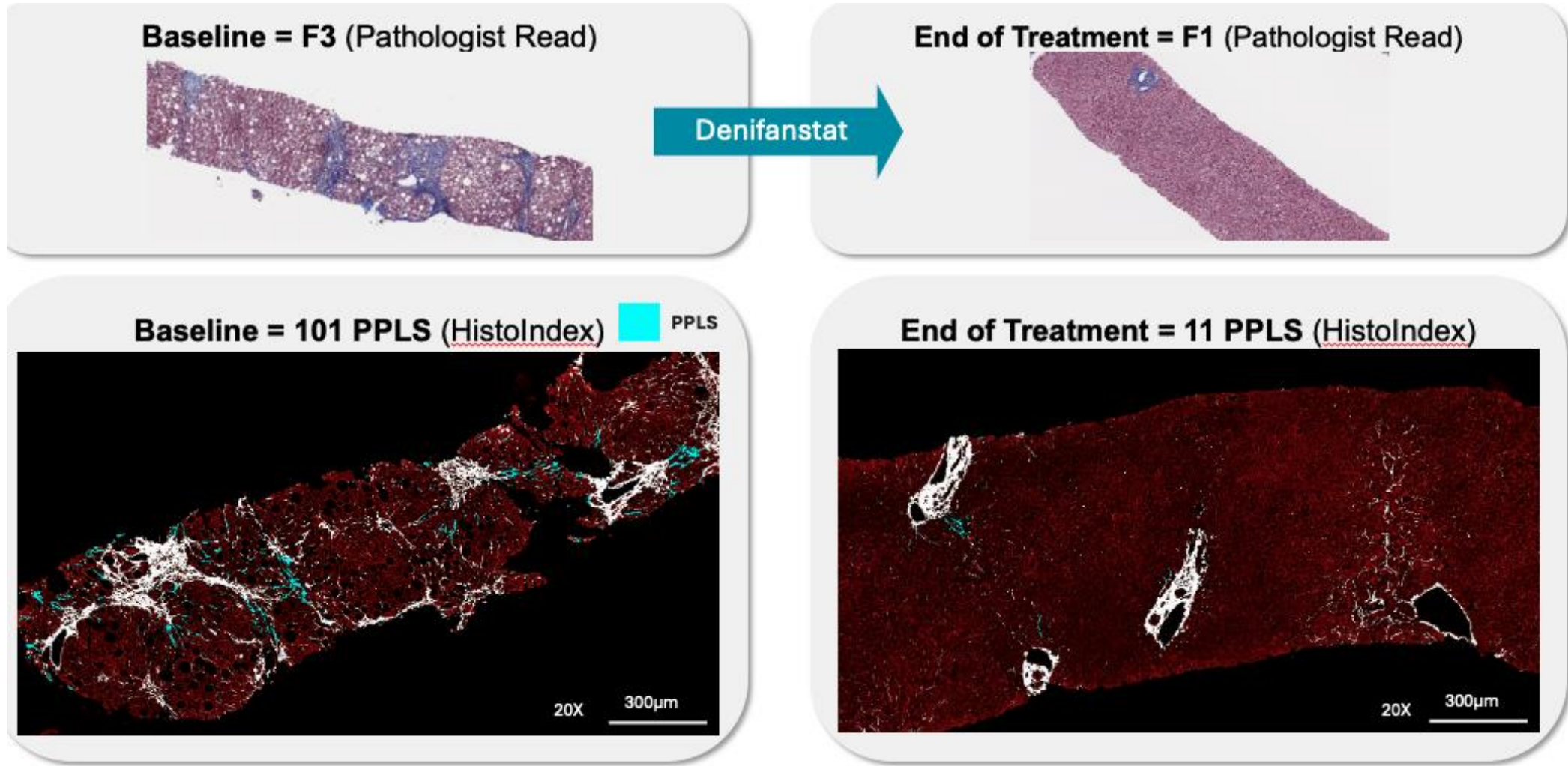
- AI may detect fibrosis regression at an earlier point in time, compared to conventional pathology
- qF4 population (defined on AI platform by HistoIndex) are likely the most advanced subgroup of F3 patients in Phase 2b study

Sagimet Biosciences data on file. FASCINATE-2 HistoIndex.

qFibrosis Zonal Analysis



Denifanstat Reduced Number of Peri-Portal Long Strings (PPLS) in a Patient with Fibrosis Improvement



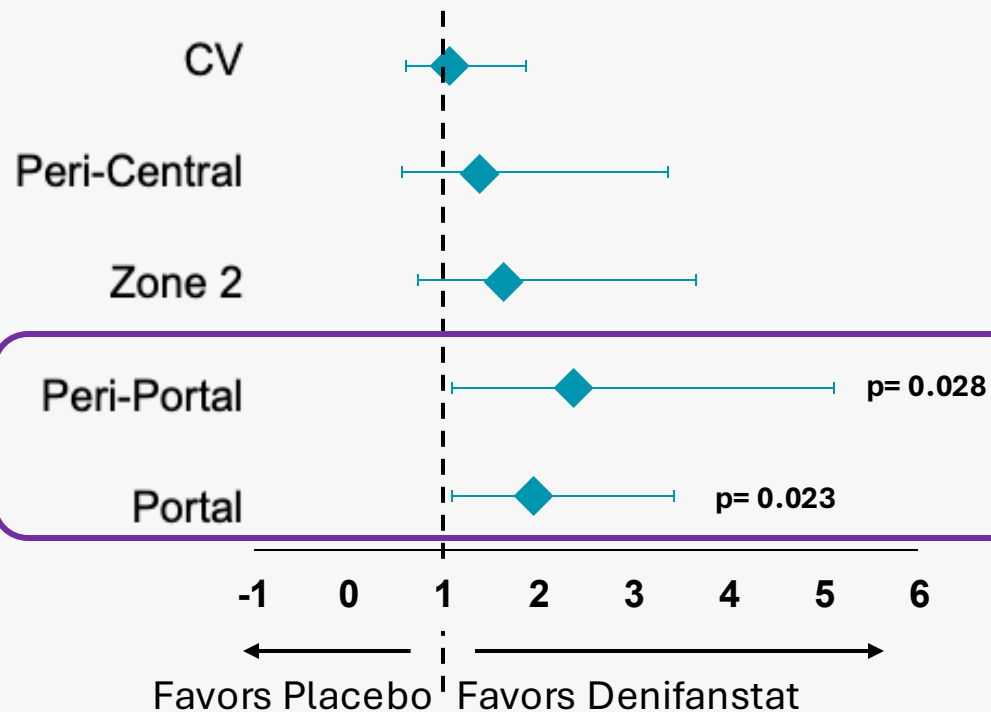
Rinella M, et al. Presented at: AASLD 2024; Nov 15-19 2024; San Diego, USA

Denifanstat Showed Statistically Significant Liver Fibrosis Regression in the Portal, Periportal and Zone 2 Regions

Response at the individual zonal parameter level was defined as $\geq 30\%$ relative decrease from baseline

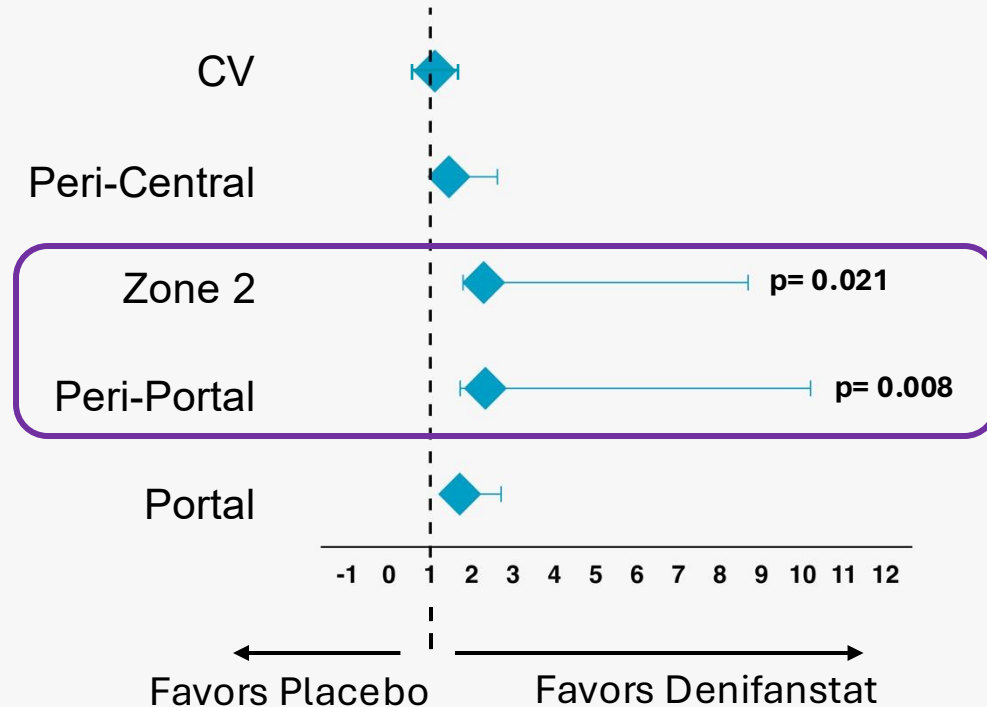
All Patients

Fibrosis Improvement by Zones
(Response Rate Ratio)¹



Patients with “No Change” in Fibrosis Stage

Fibrosis Improvement by Zones
(Response Rate Ratio)

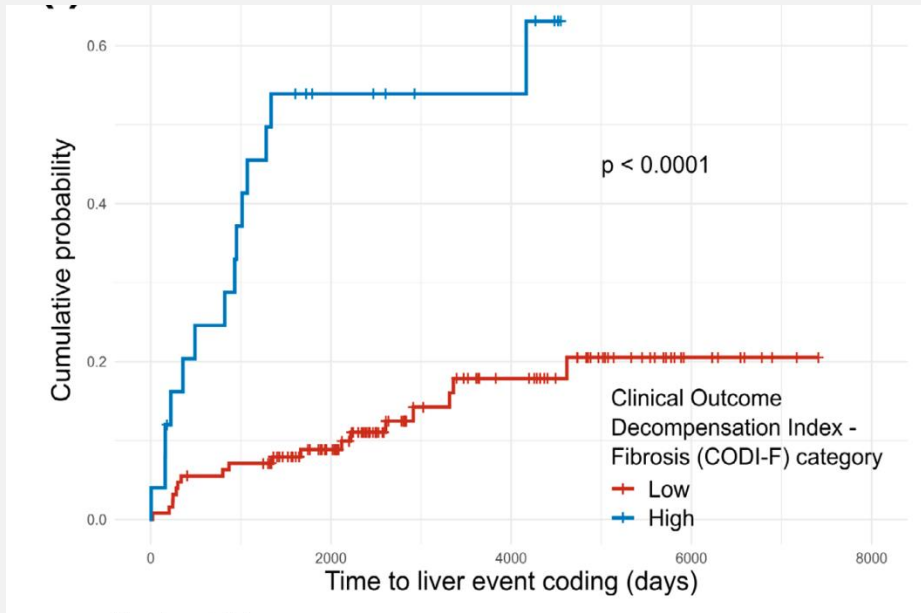


CV: central vein; PT: portal ; 1. Rinella M, et al. Presented at: AASLD 2024; Nov 15-19 2024; San Diego, USA; mITT population

Zonal Parameters have been Linked to Clinical Outcomes

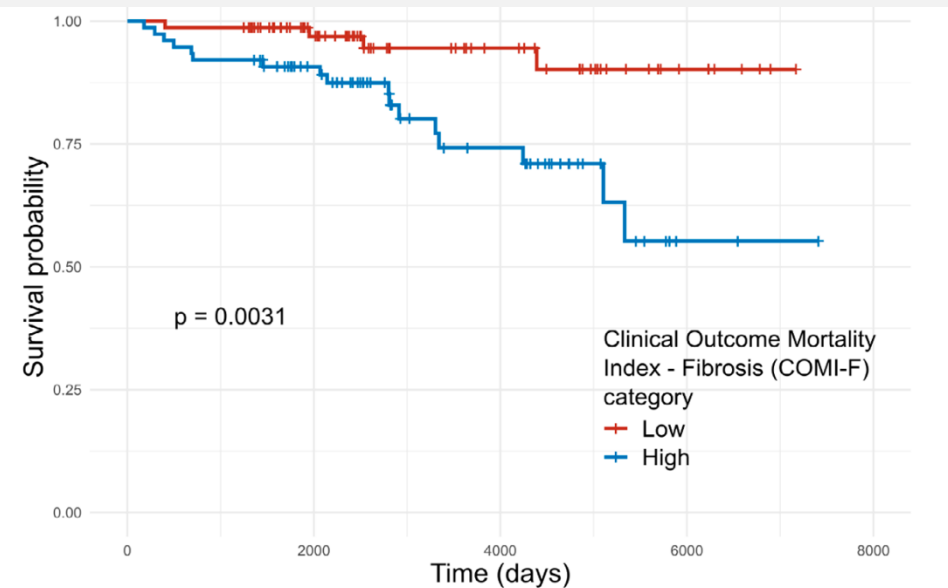
SteatoSITE: well phenotyped retrospective UK cohort of patients across MASLD spectrum (N=452 liver biopsy)

Clinical Outcomes Decompensation Index-Fibrosis (CODI-F) predicts liver decompensation



CODI-F is composed of 5 individual zonal parameters from the **peri-portal/portal** zones

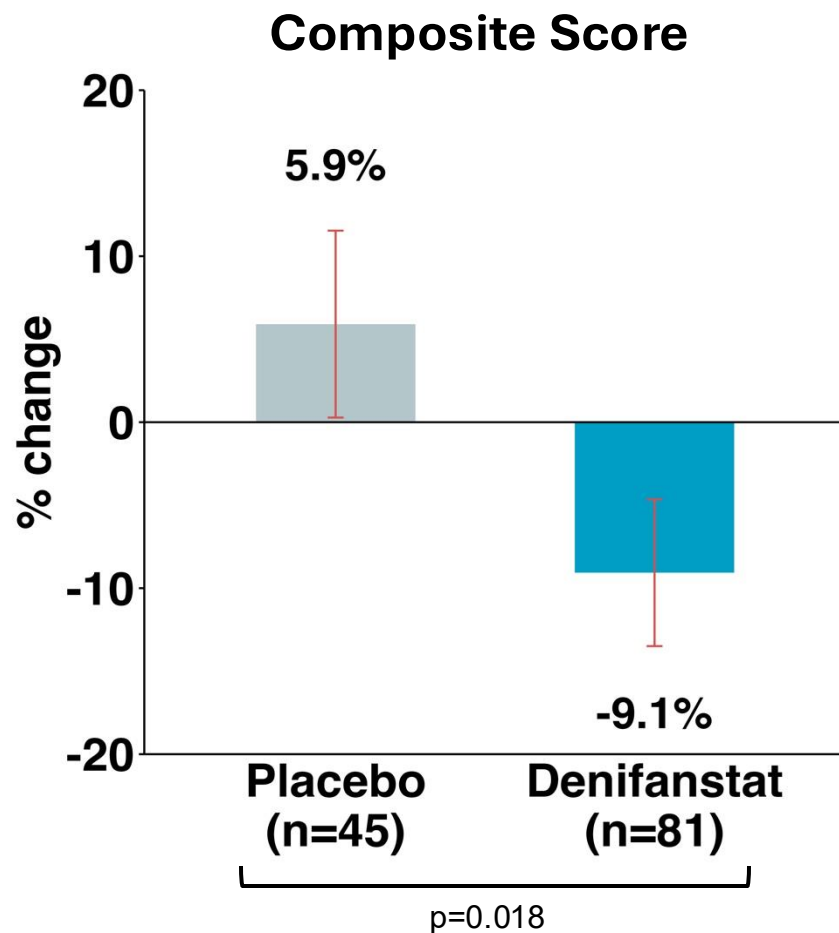
Clinical Outcome Mortality Index-Fibrosis (COMI-F) predicts mortality



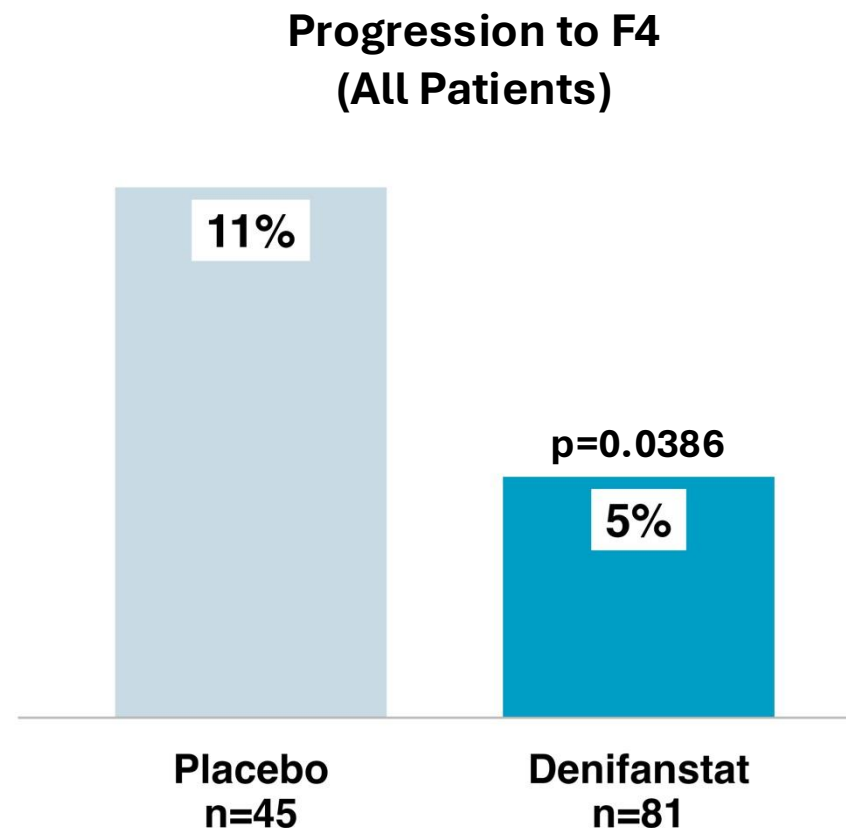
COMI-F is composed of 5 individual zonal parameters:

- 3 from the **peri-portal/portal** zones
- 2 from **zone 2**

Denifanstat Showed Reduction in Composite Score of Collagen Parameters Linked to Liver Decompensation



Wilcoxon test; collagen parameters with steatosis correction; mITT population

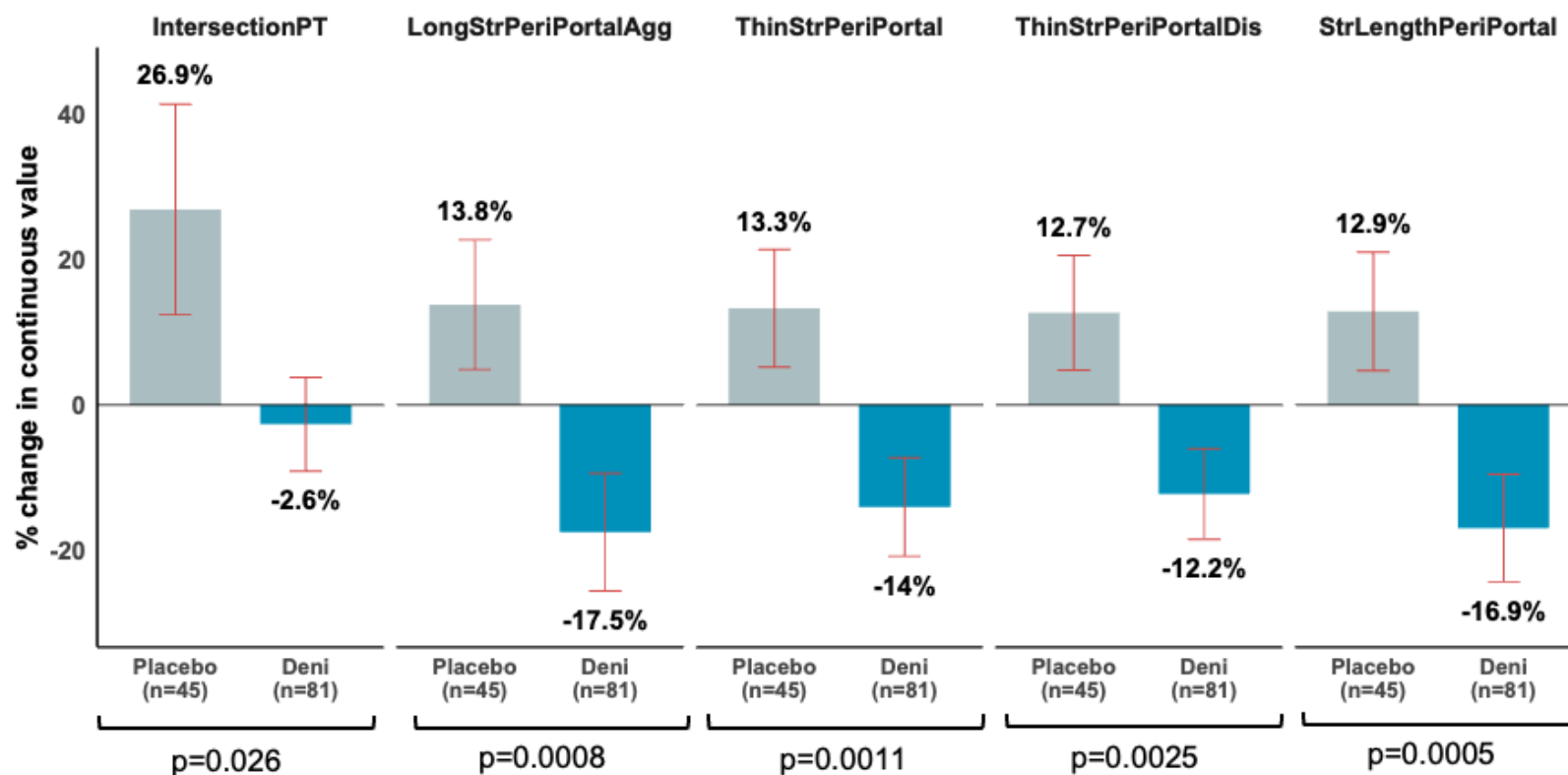


mITT population. Cochran-Mantel-Haenszel Test – one sided at the 0.05 significance level
Rinella M, et al. Presented at: AASLD 2024; Nov 15-19 2024; San Diego, USA

Denifanstat Showed Reduction in Individual Collagen Parameters Linked to Liver Decompensation

4 periportal and 1 portal zonal parameters

Collagen Parameters Associated with Liver Decompensation

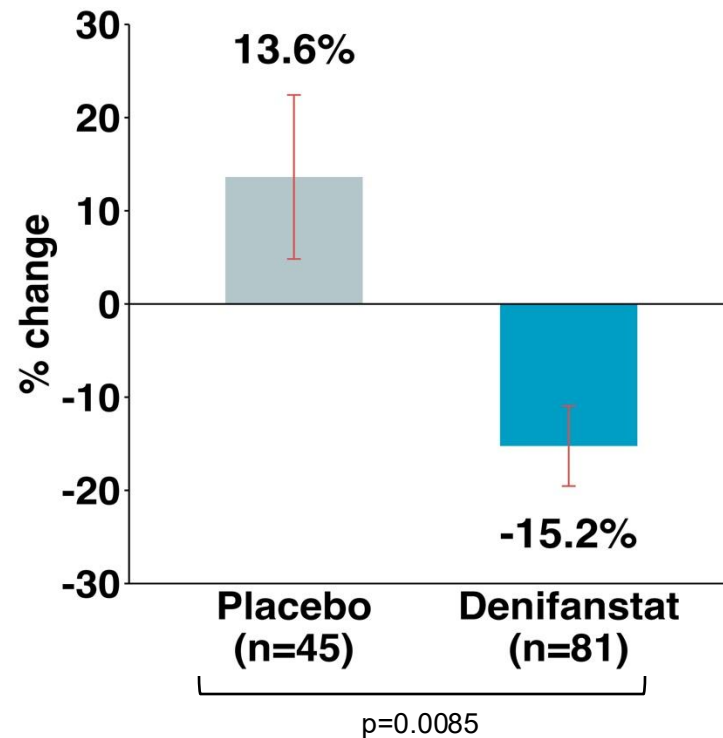


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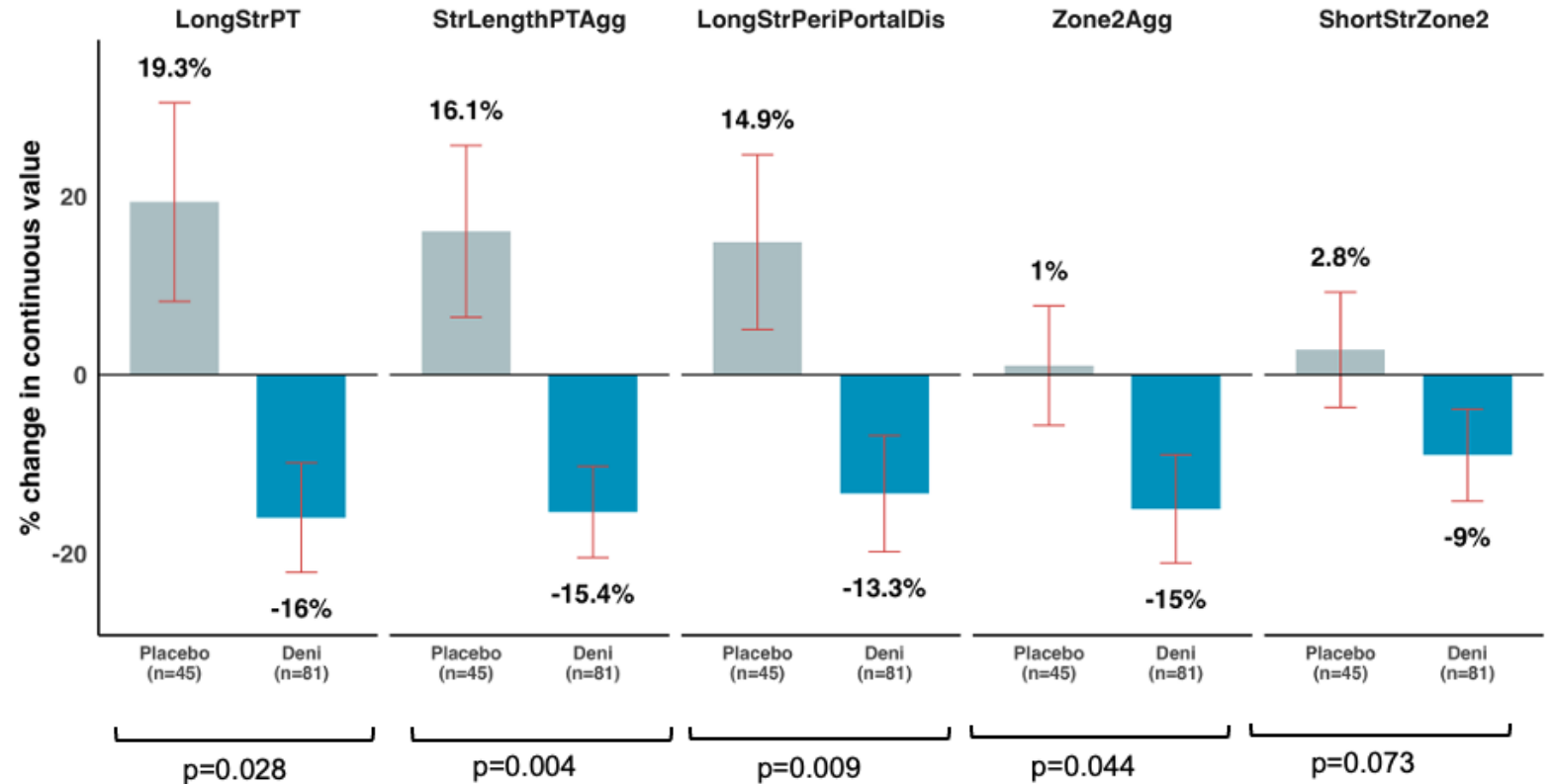
Denifanstat Showed Reduction in Collagen Parameters Linked to Mortality

2 portal, 2 zone 2 and 1 periportal zonal parameters

Composite Score



Collagen Parameters Associated with Mortality



Wilcoxon test; collagen parameters with steatosis correction; mITT population

Denifanstat Provides a Differentiated Mechanism of Action in MASH

- Denifanstat is not only a liver fat blocker, but acts directly on stellate cells -> tackles both “initiating” (liver fat synthesis) and “progressing” (fibrosis) events
- Denifanstat showed significant improvement in fibrosis and MASH resolution in Phase 2b FASCINATE-2 study
- AI-based digital pathology demonstrated that denifanstat:
 - Showed a decrease in fibrosis in patients with no “stage” change in fibrosis
 - Showed a statistically significant difference in progression to cirrhosis by decreasing septa progression

Acknowledgements

- Investigators, sites and patients involved in FASCINATE-2 studies
- Sagimet Team
- Sagimet Advisors
- HistoIndex Team