AI-Based Digital Pathology Shows that Denifanstat Improves Multiple Parameters of Fibrosis and Reduces Progression to Cirrhosis in MASH patients with F2/F3

Results of the FASCINATE-2 study

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1: Division of Gastroenterology & Hepatology, University of Chicago Pritzker School of Medicine; 2: Sagimet Biosciences; 3: LiverPat; 4: HistoIndex; 5: University of California, San Diego

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Disclosures

Consulting past 24 months:

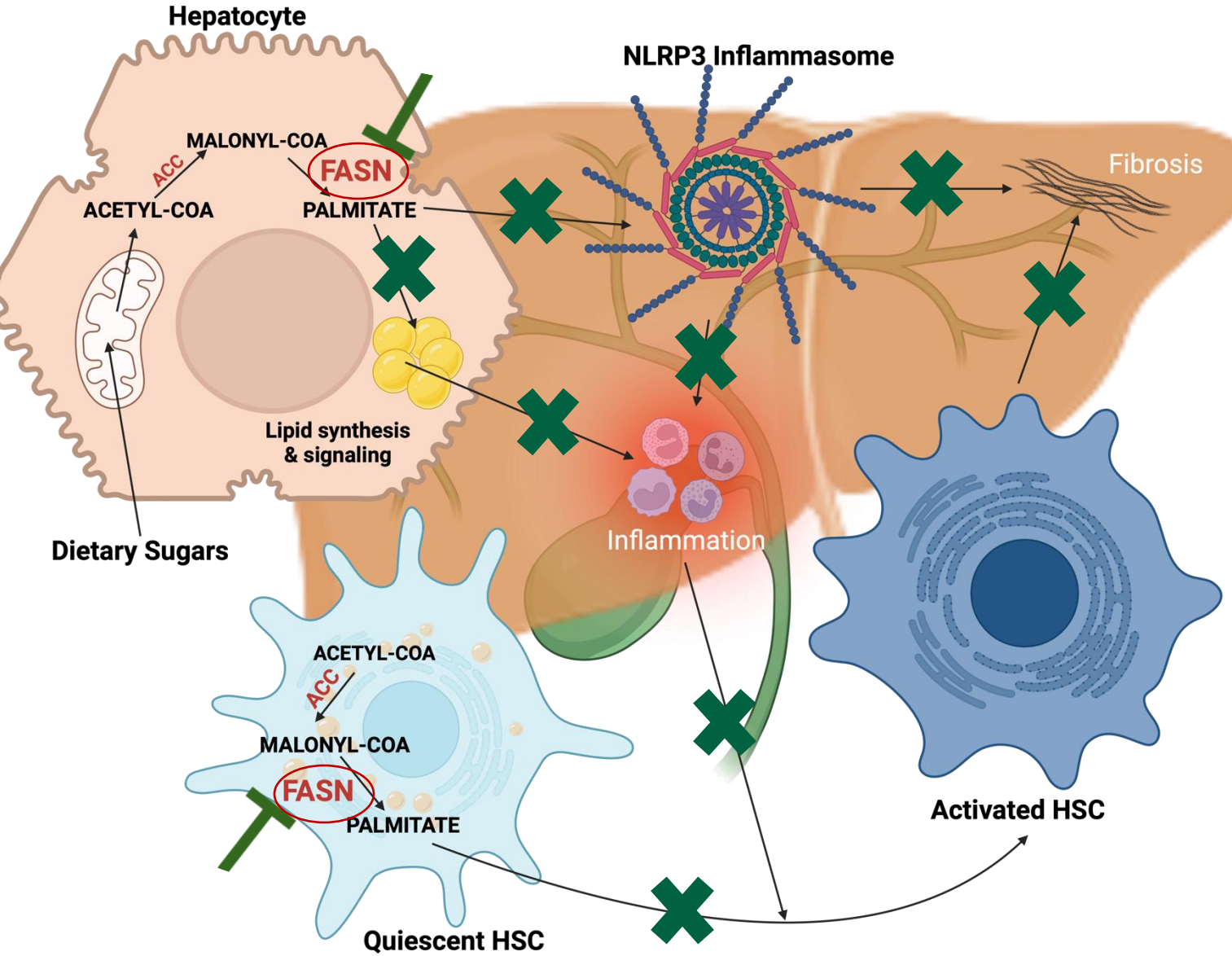
- *Scientific consulting:*

Akero, 89Bio, Boehringer Ingelheim, Intercept Pharmaceuticals, Histoindex, Madrigal, NGM Biopharmaceuticals, Novo Nordisk, Eli Lilly, Sagimet Biosciences, Sonic Incytes, Cytodyn, GSK

- *Scientific executive boards:*

Akero, Madrigal, Novo Nordisk

Denifanstat Independently Targets Three Mechanisms of MASH Pathogenesis



Main actions of denifanstat (FASN inhibitor):

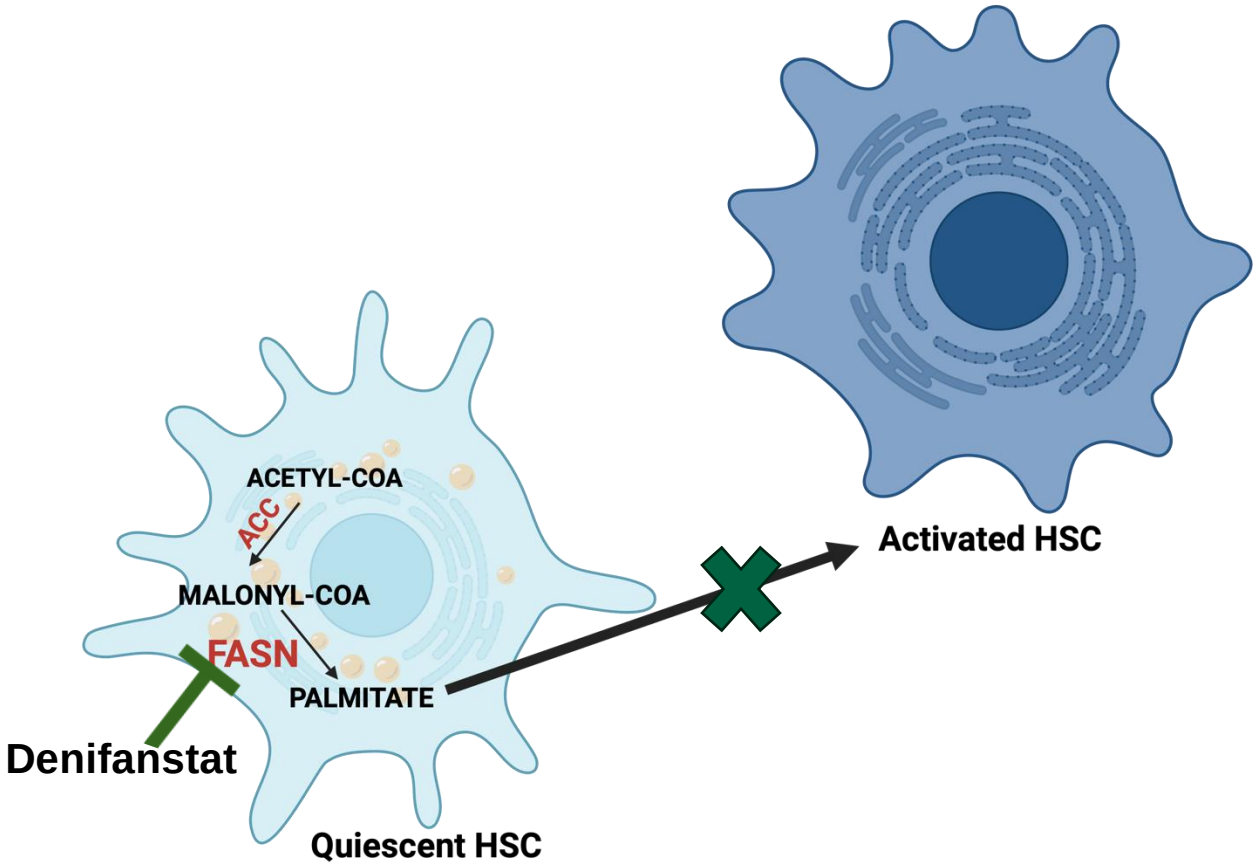
- **Reduces liver fat and lipotoxic species** by inhibition of intrahepatic DNL
- **Blocks stellate cell activation** by inhibiting cell-based DNL
- **Reduces inflammation** through decreased NLRP3 inflammasome activity

=> Both direct and indirect antifibrotic effect

Denifanstat Directly Blocks Human Stellate Cell Function

Stellate cells require DNL for fibrogenesis

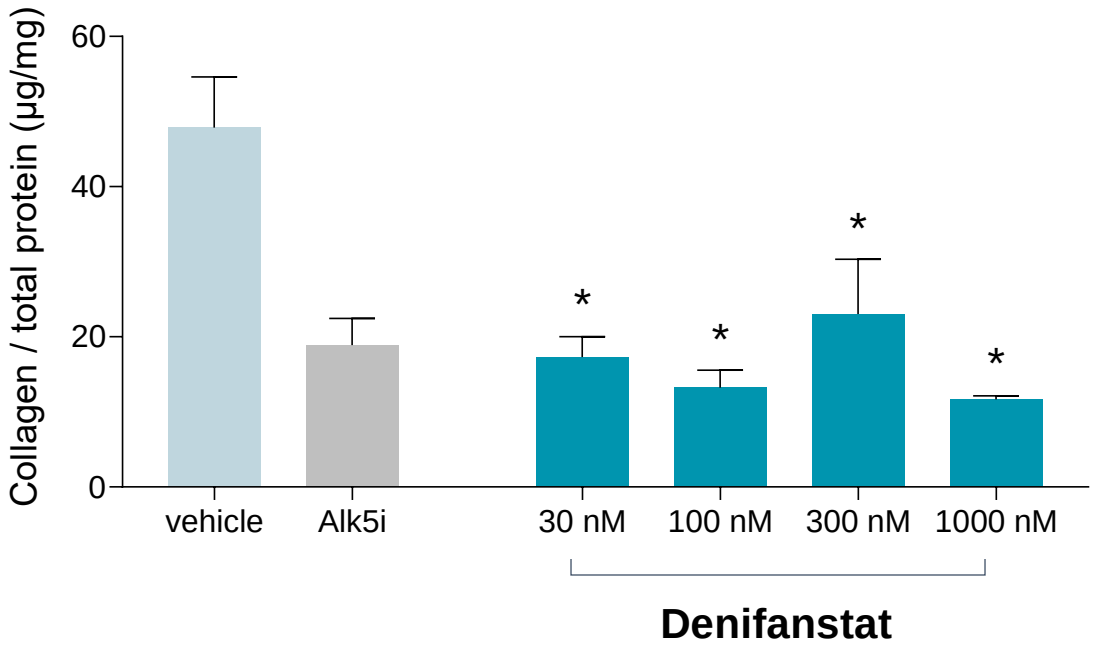
Denifanstat blocks stellate cell activation



Primary human stellate cell assay

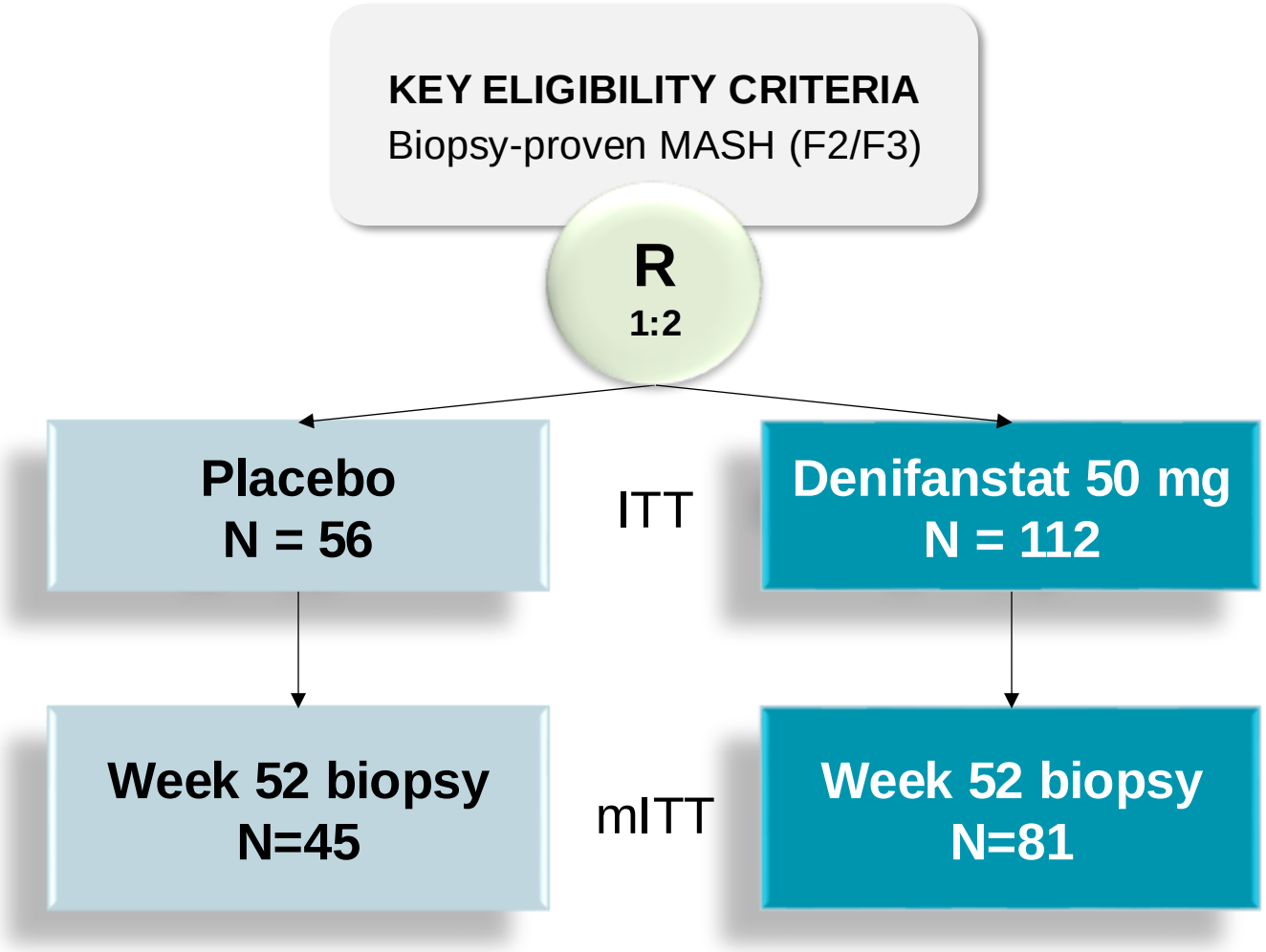
Denifanstat directly inhibits fibrogenic activity

- Stimulated by TGF-beta to activate fibrogenesis



*p<0.05. FASNi directly inhibits fibrosis published in O'Farrell et al.,2022. Scientific Reports. 12:15661

FASCINATE-2 – Study Design & Population



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
- Digital AI pathology (HistoIndex Platform)

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

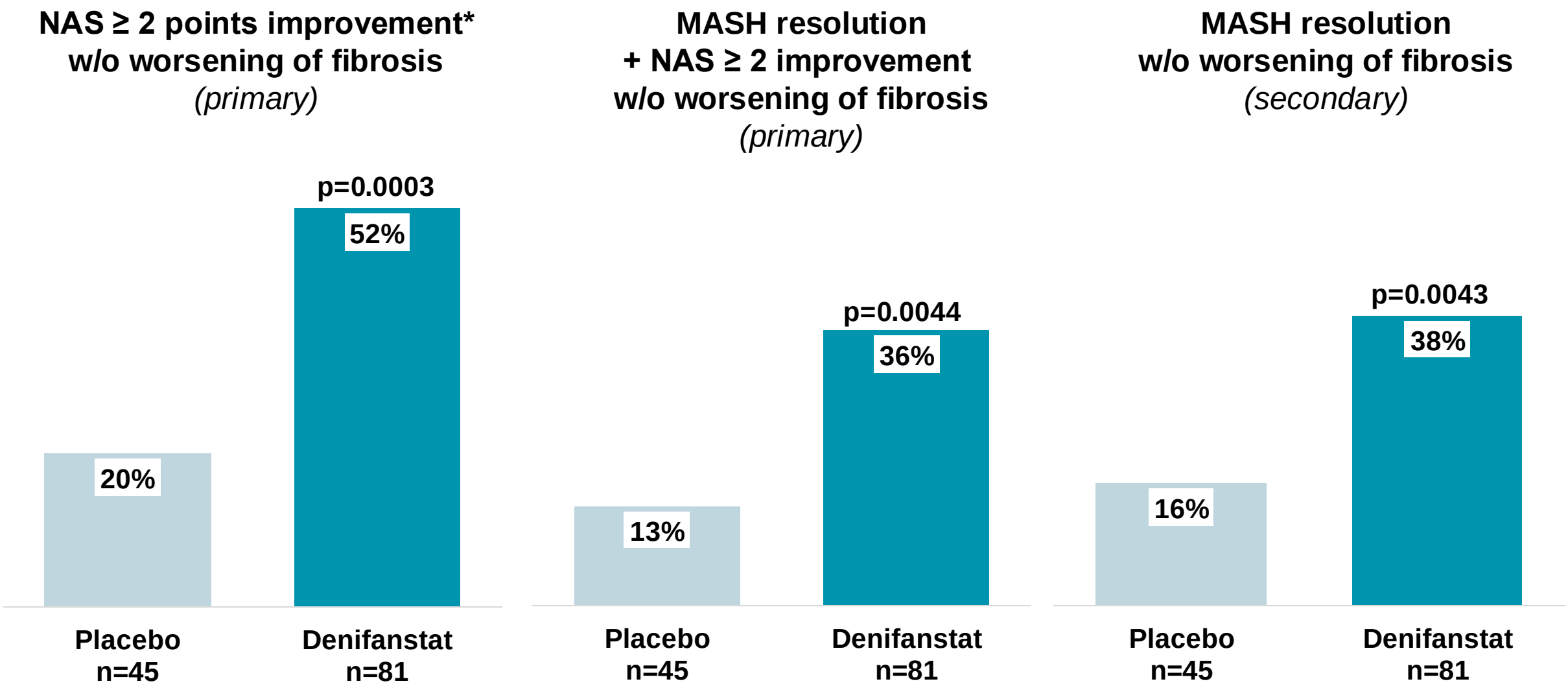
FASCINATE-2 – Study Design & Population

Baseline characteristics of mITT population

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** **F3**	 22 (49%) 23 (51%)	 34 (42%) 47 (58%)

Data are mean ± standard deviation, or n (%)

Denifanstat Met Histological Primary Endpoints

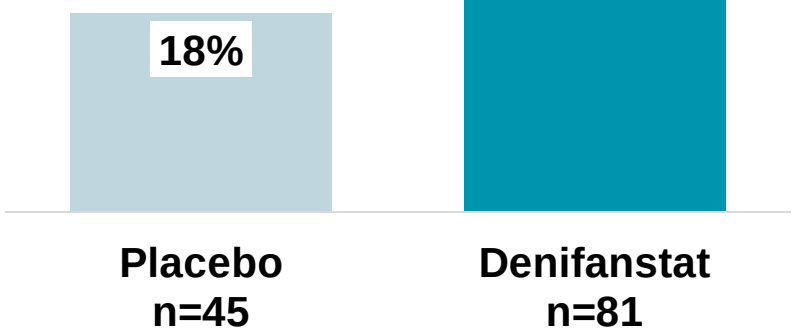


mITT population. Cochran-Mantel-Haenszel Test – two sided at the 0.05 significance level, * ≥1-point improvement in ballooning or inflammation.

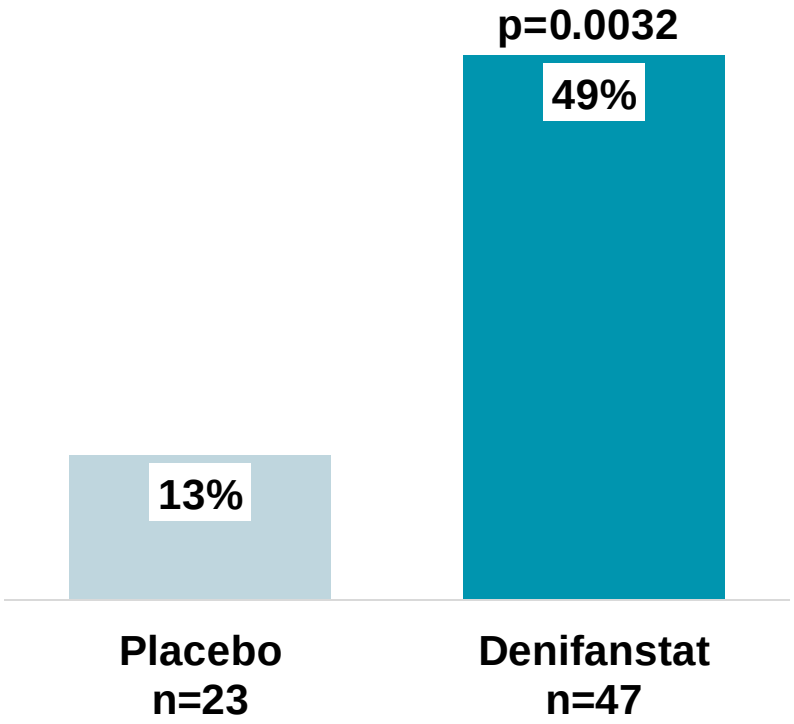
Loomba R et al. Lancet Gastroenterol Hepatol. 2024 Dec;9(12):1090-1100

Denifanstat Showed Strong Effect on Fibrosis

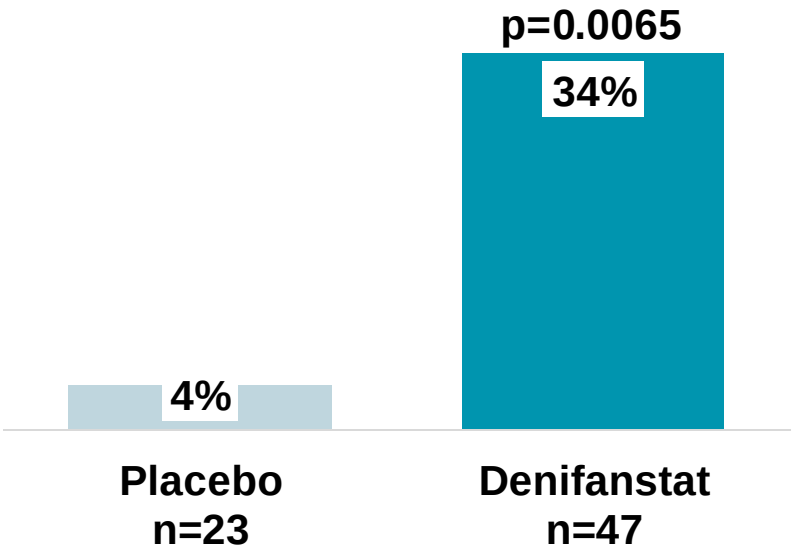
≥ 1 stage improvement in fibrosis w/o worsening of MASH



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



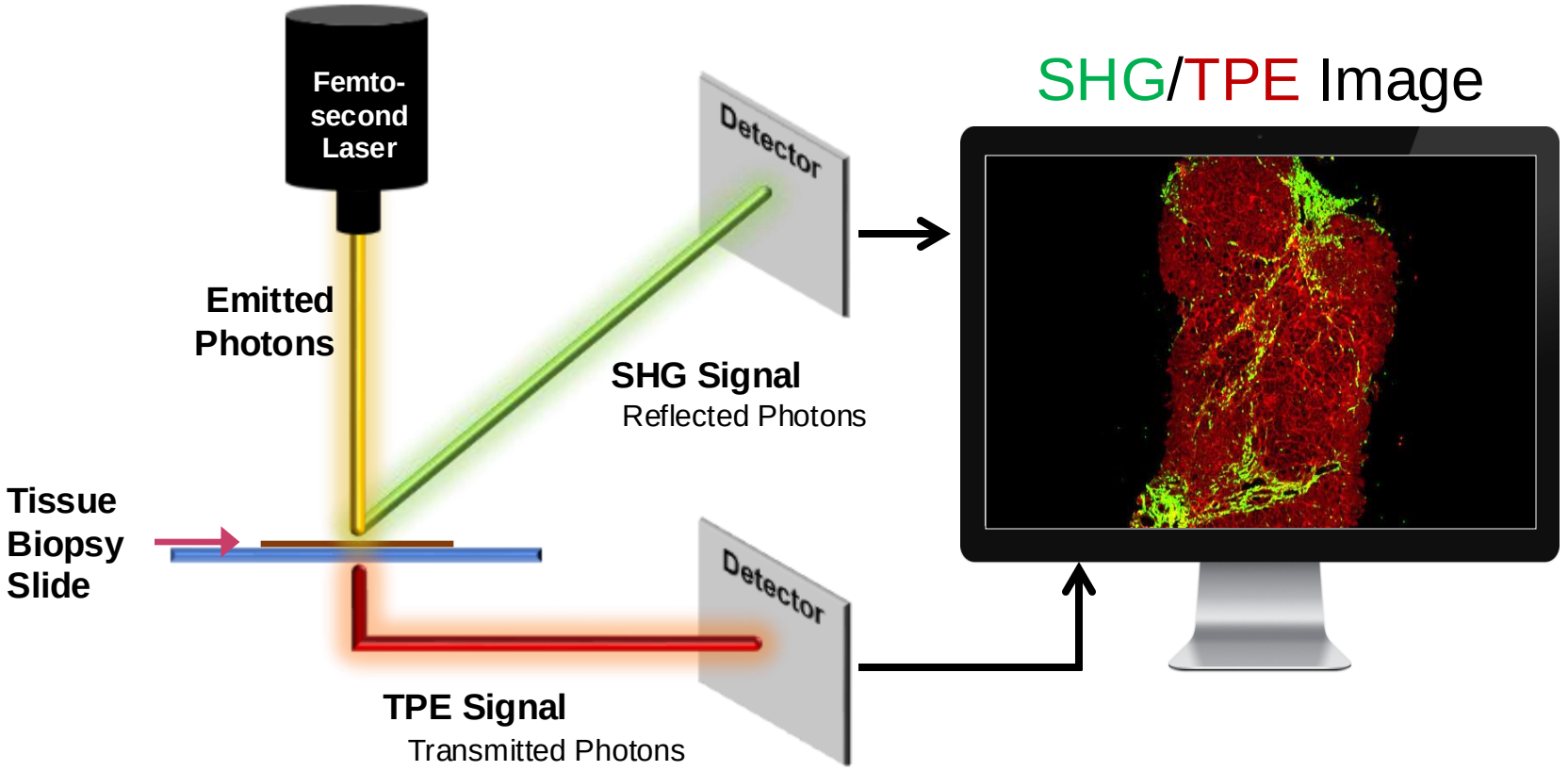
≥ 2 stage improvement in fibrosis w/o worsening of MASH
F3 population



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

Artificial Intelligence (AI) Pathology Reading
Second Harmonic Generation Microscopy

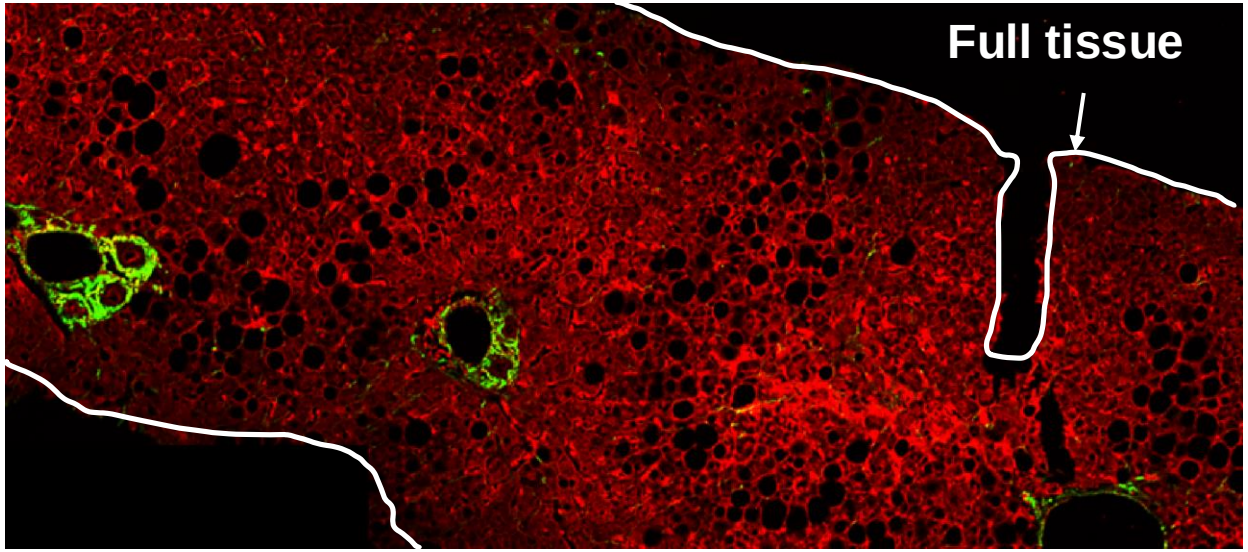
SHG permits measurement of quantifiable collagen fibrillar properties

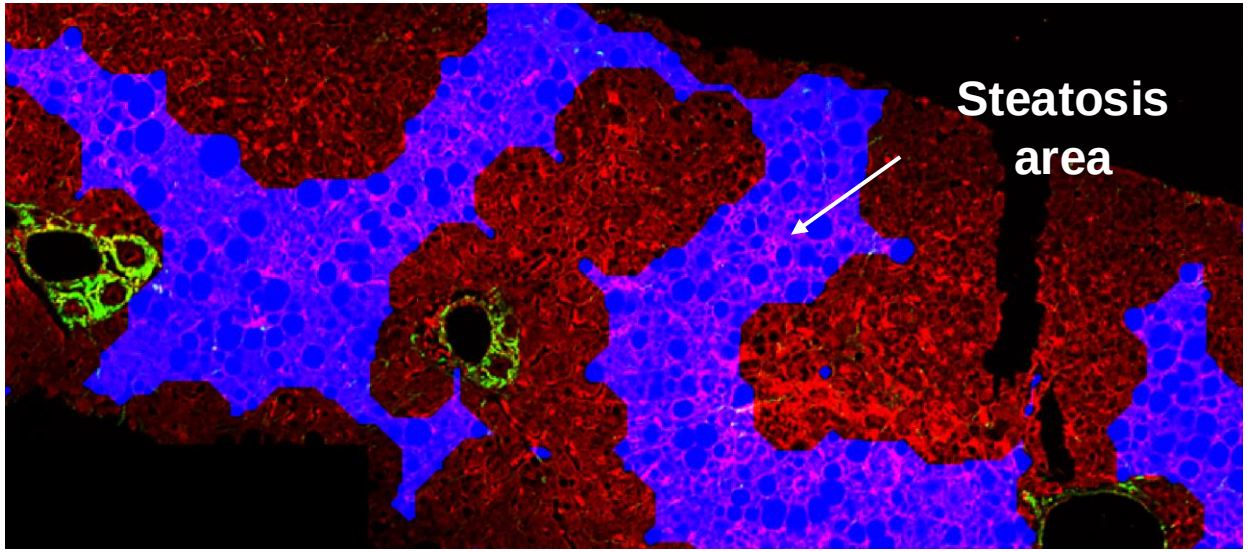


SHG detects collagen fibers shown in green

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

qFibrosis with Steatosis Correction: Methodology

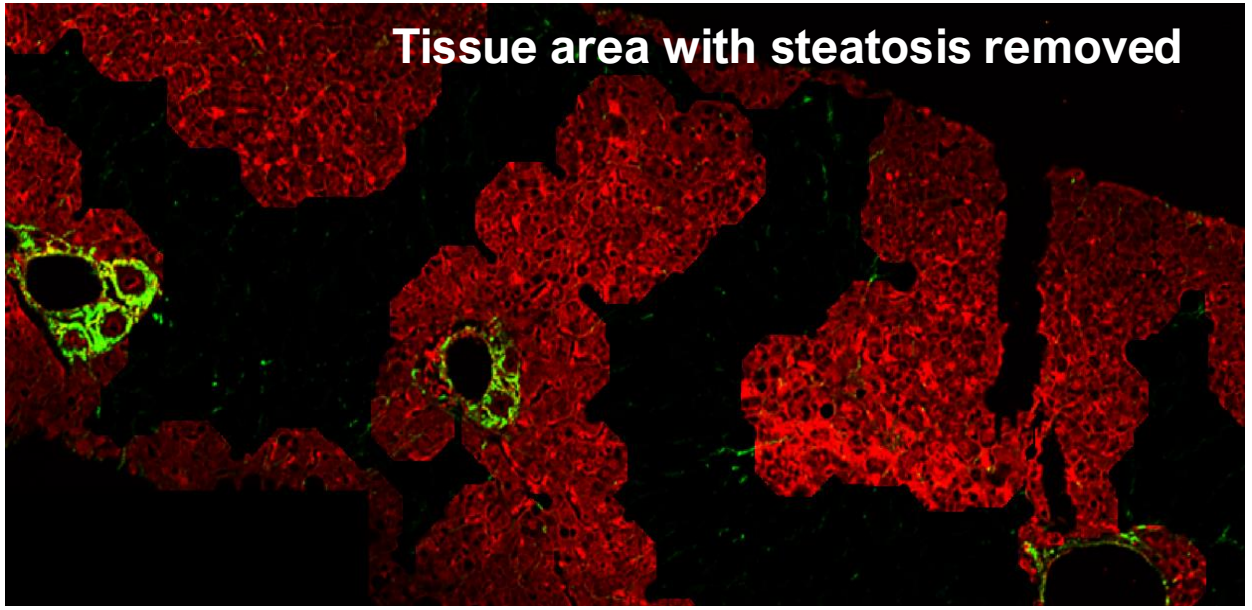




Steatosis corrected qFibrosis

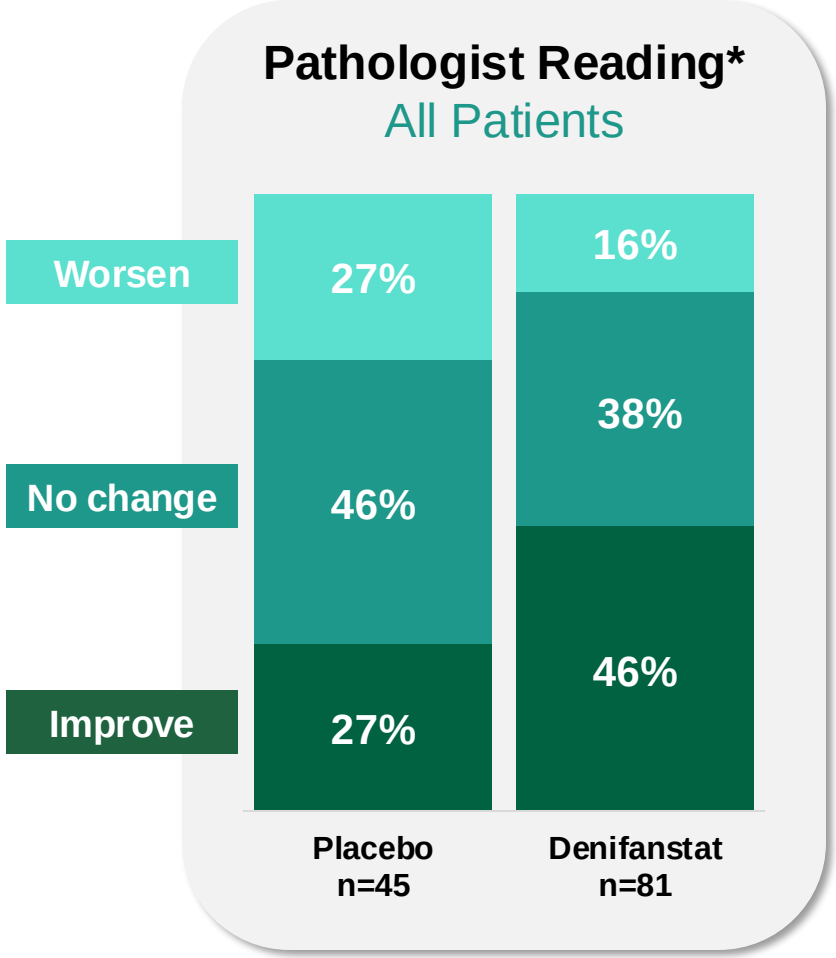
= raw parameter normalized by

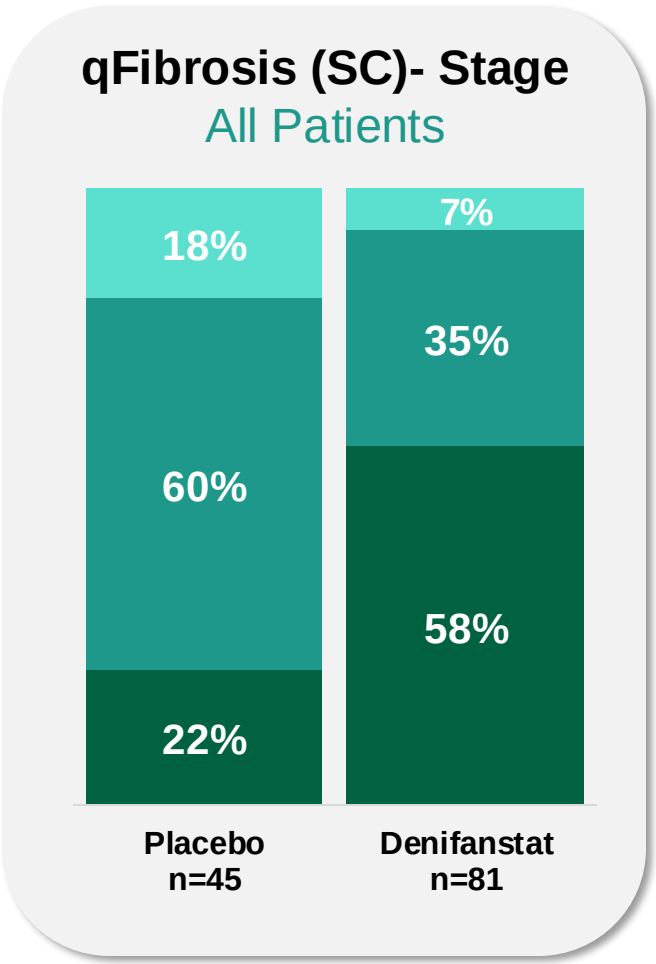
(Tissue area – Steatosis area)

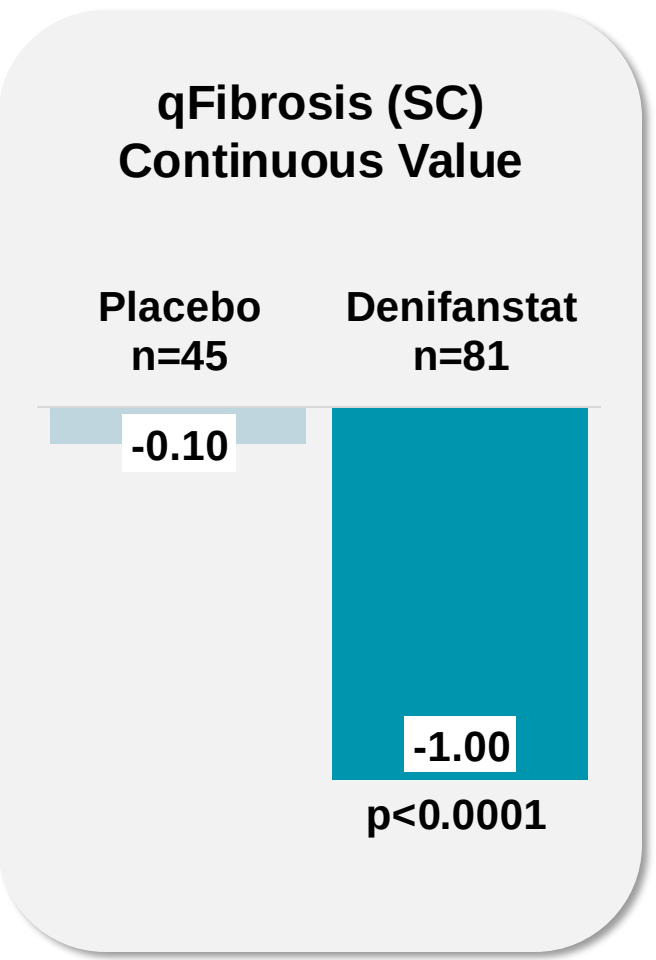


Sanyal et. al. Nature Review G&H 2023

qFibrosis Data Demonstrate Strong Antifibrotic Effect of Denifanstat

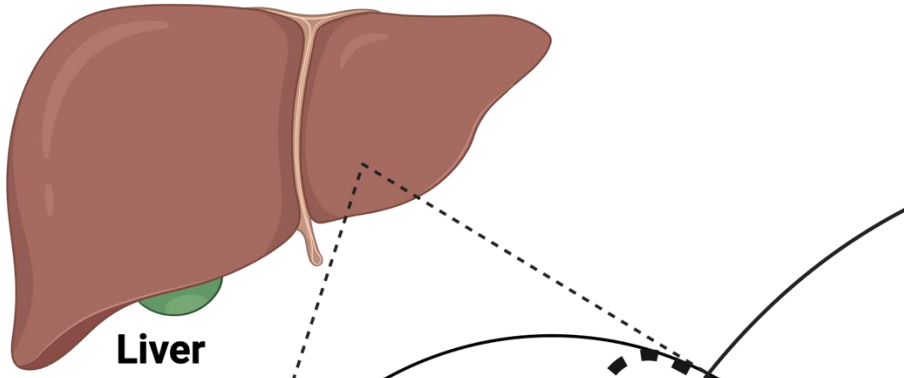


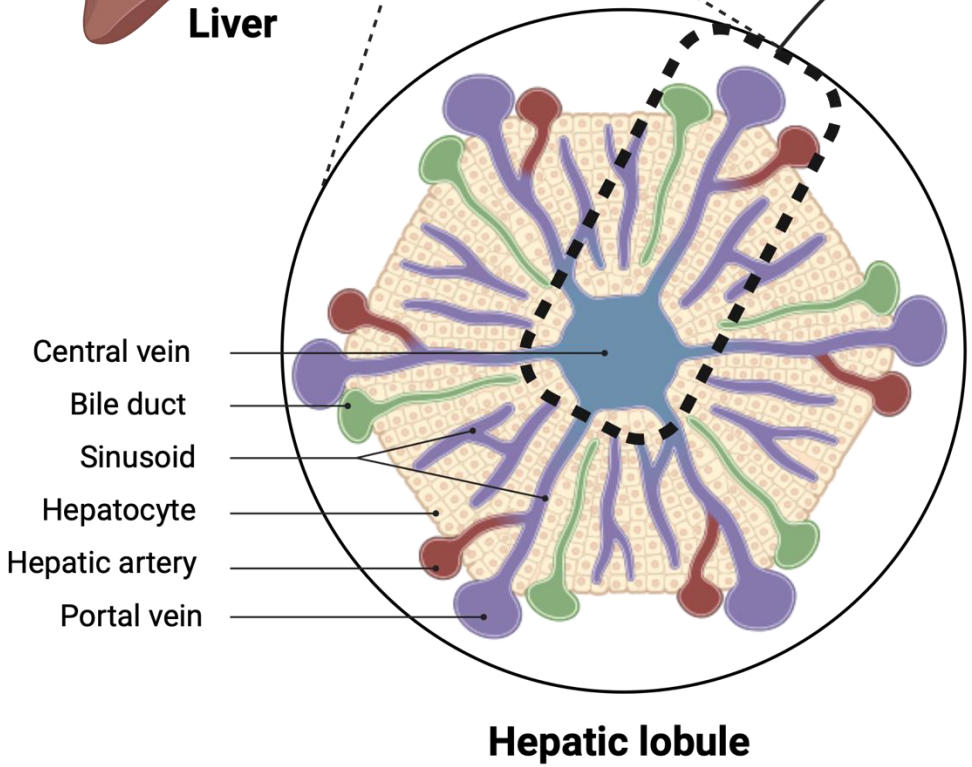


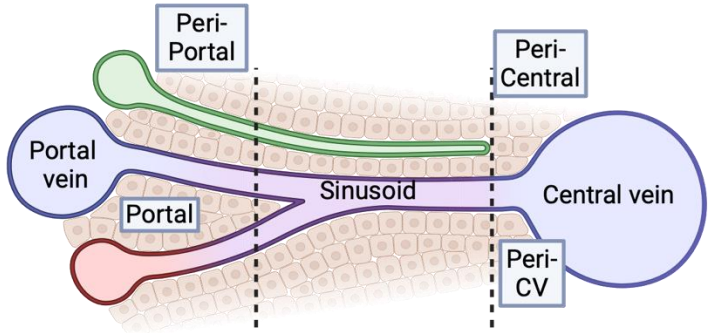


* At least 1-stage improvement in fibrosis, independent of MASH resolution; SC: steatosis correction, mITT population

qFibrosis Zonal Analysis: Methodology



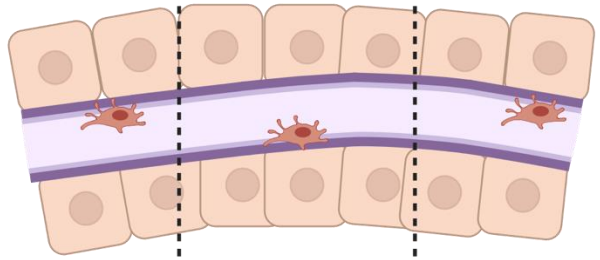




Zone 1
Periportal cells

Zone 2
Mid-lobular cells

Zone 3
Pericentral cells

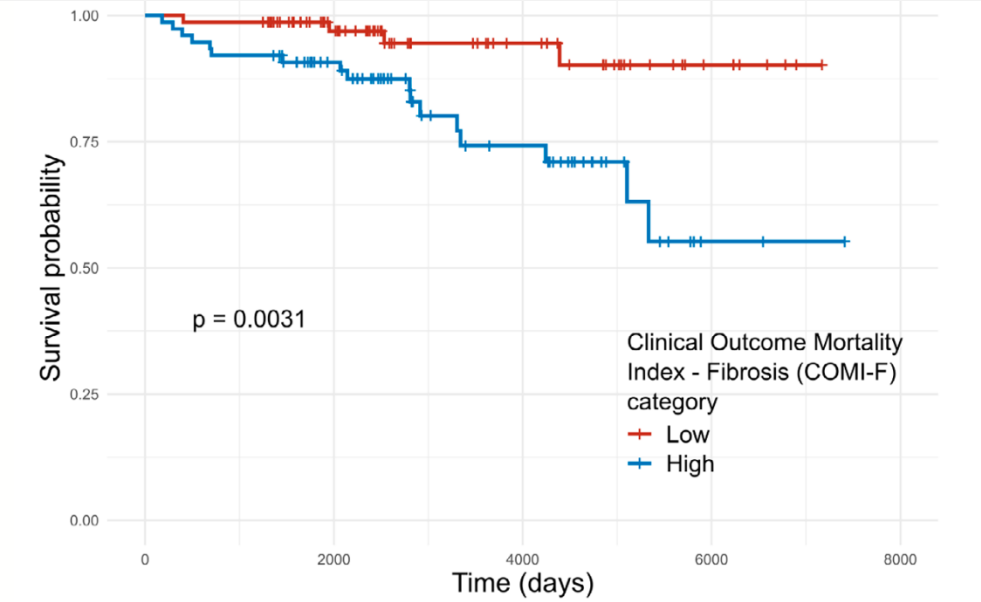


- 5 zones
- 28 parameters per zone
- Selected parameters linked to liver outcomes

Zonal Parameters have been Linked to Clinical Outcomes

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

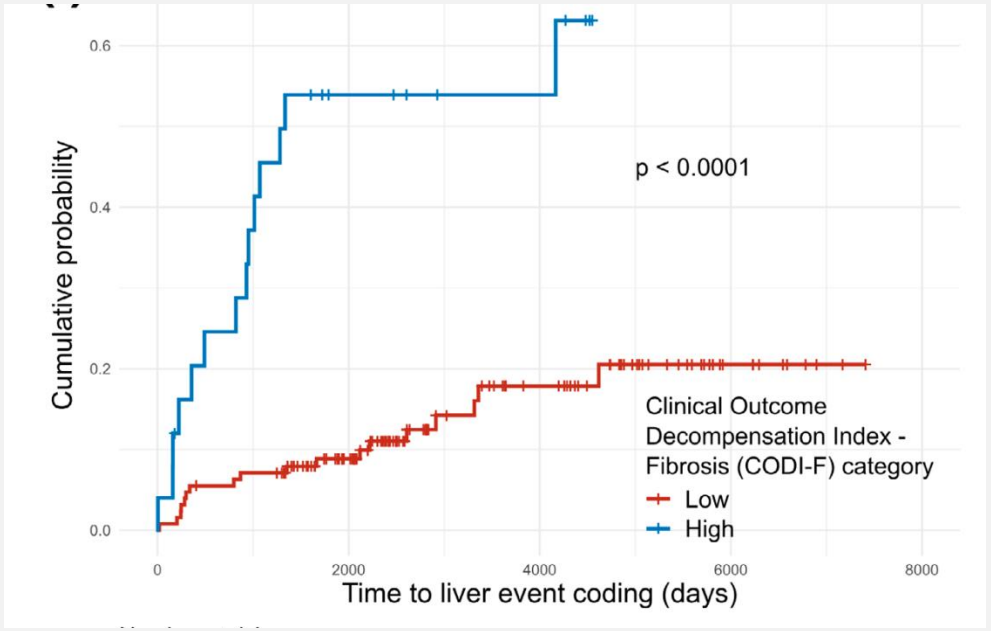
Clinical Outcome Mortality Index-Fibrosis (COMI-F) predicts mortality



COMI-F is composed of 5 individual zonal parameters:

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

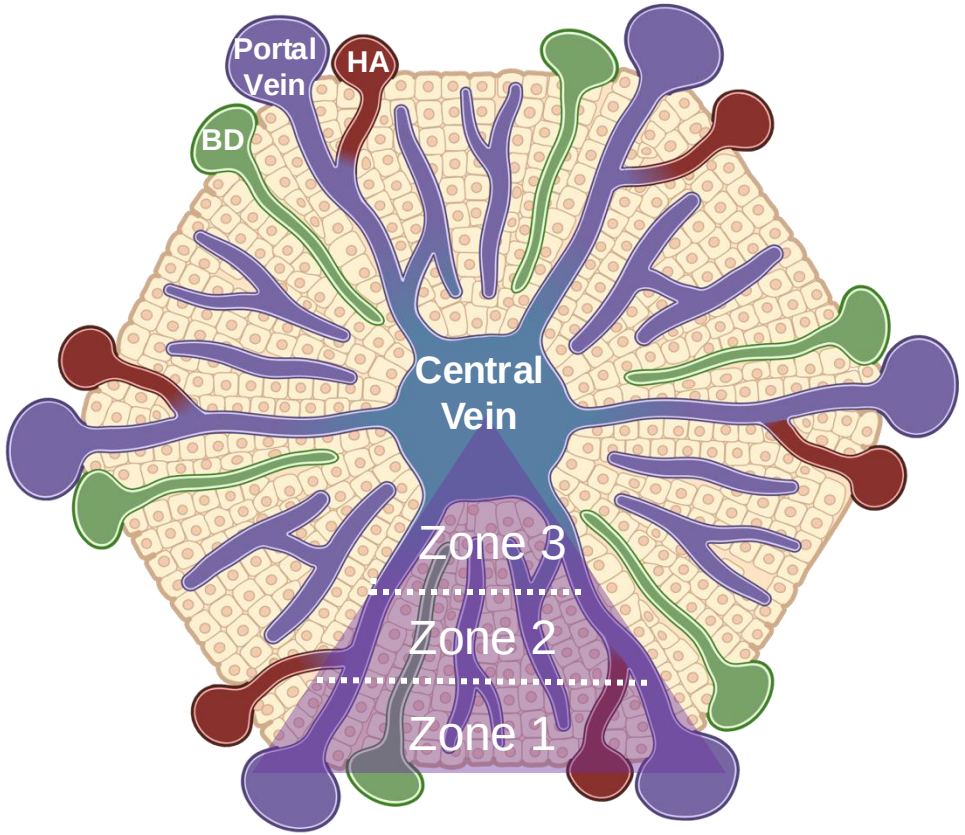
Clinical Outcomes Decompensation Index-Fibrosis (CODI-F) predicts liver decompensation



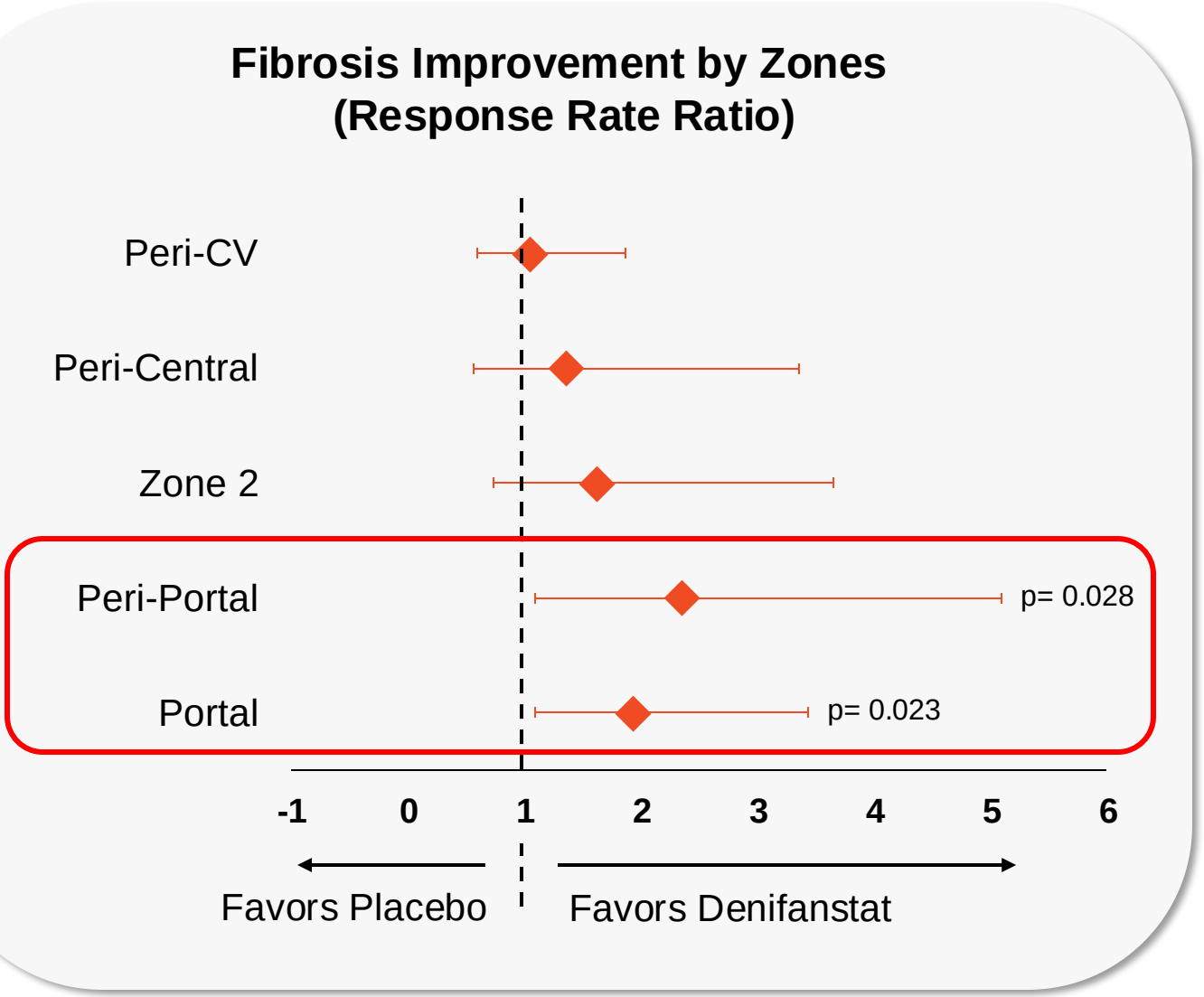
CODI-F is composed of 5 individual zonal parameters from the **peri-portal/portal** zones

Kendall TJ et al. Liver Int. 2024;44:2511-2516

qFibrosis Zonal Analysis Demonstrated that Denifanstat Improves Parameters Previously Linked to Liver Outcomes



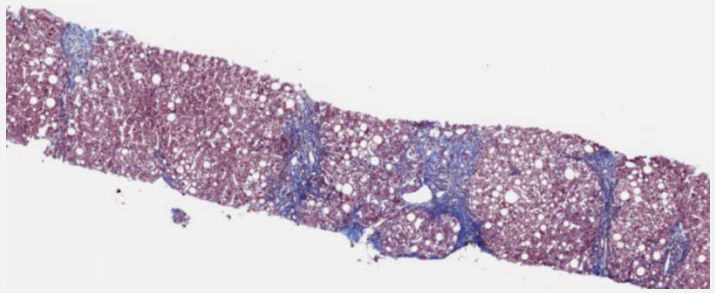
Changes in periportal and portal zones have been previously correlated with liver outcomes and mortality



Response at the individual zonal parameter level was defined as ”at least” 30% relative decrease from baseline

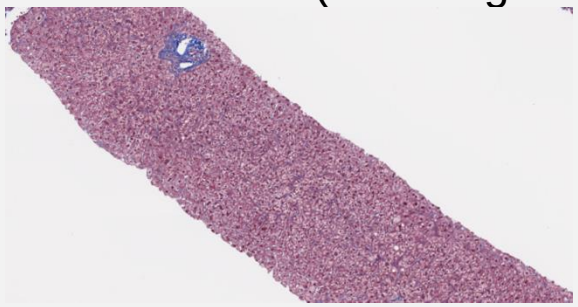
Denifanstat Reduced Number of Peri-Portal Long Strings (PPLS) in Patients with at least 1-stage Fibrosis Improvement

Baseline = F3 (Pathologist Read)



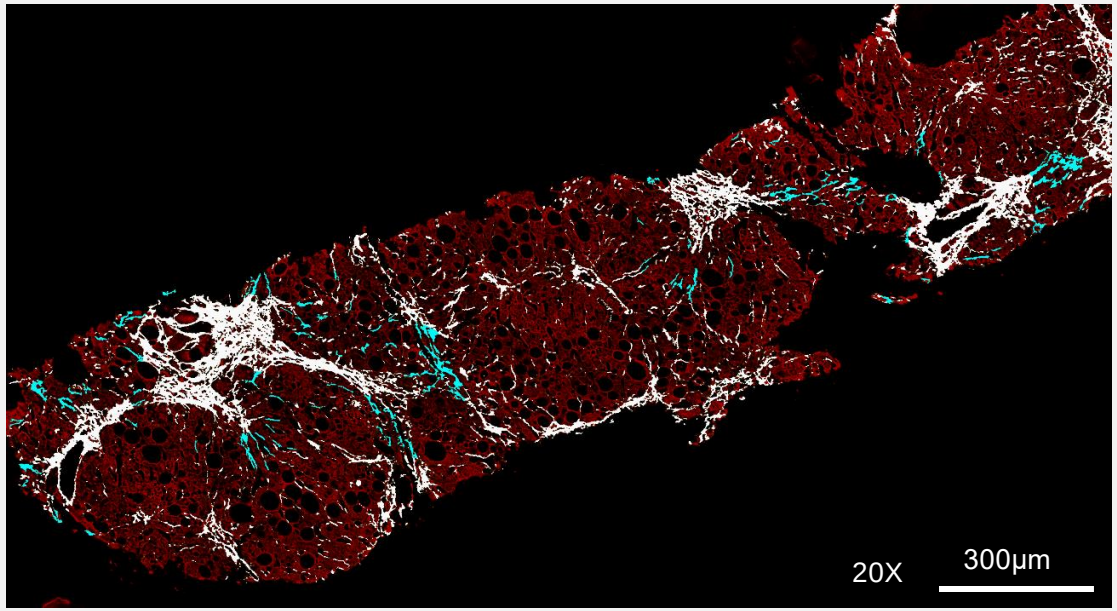
Denifanstat

End of Treatment = F1 (Pathologist Read)

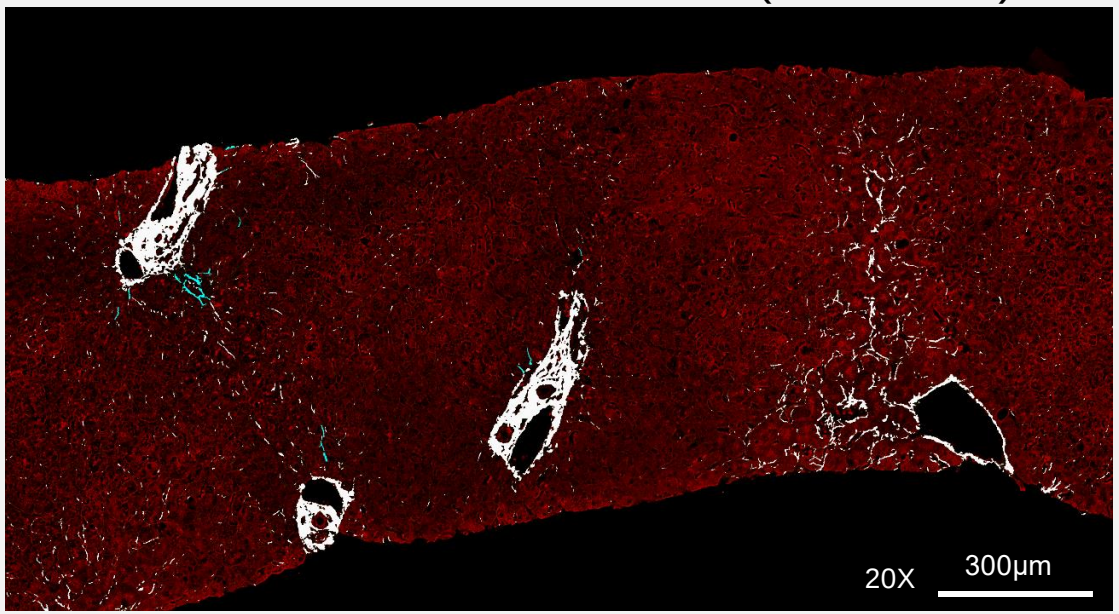


Baseline = 101 PPLS (HistoIndex)

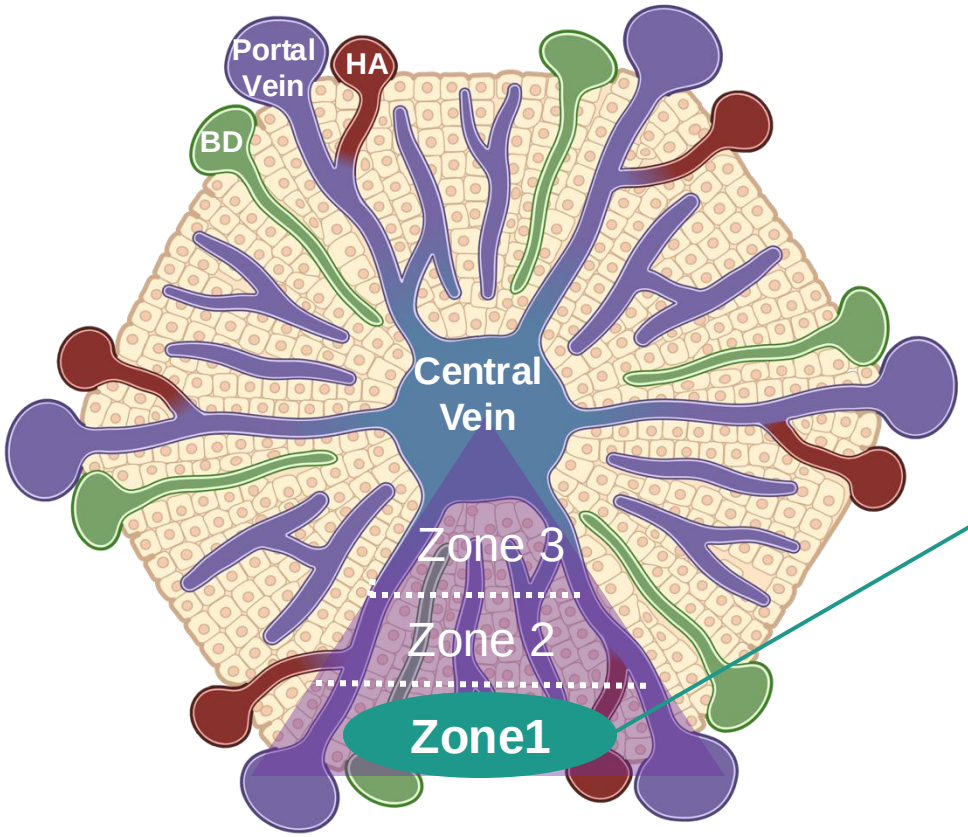
PPLS



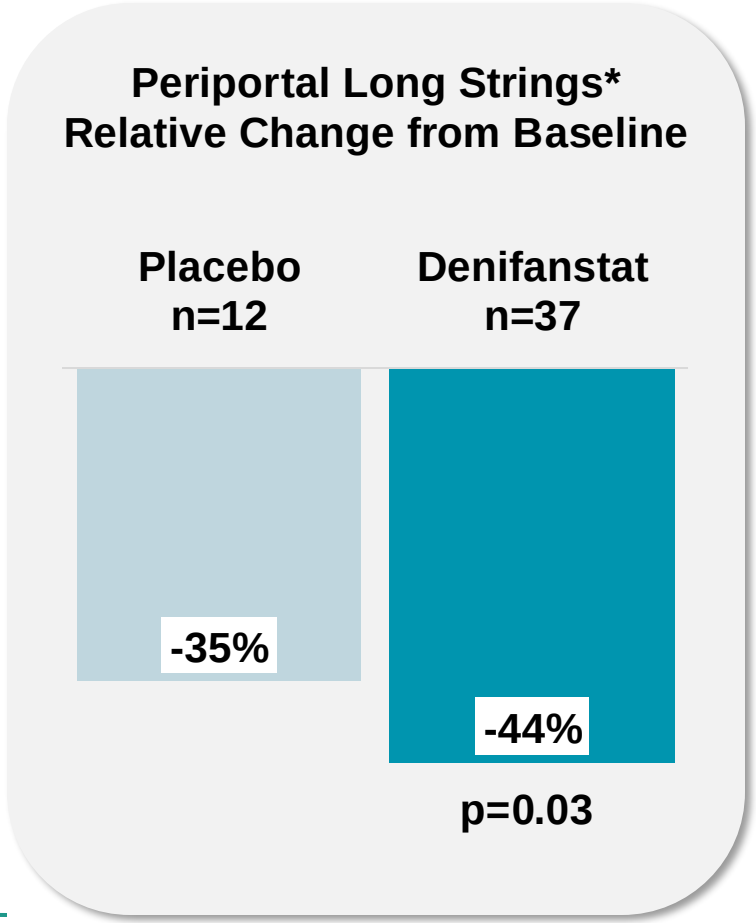
End of Treatment = 11 PPLS (HistoIndex)



Denifanstat Reduced Number of Peri-Portal Long Strings* (PPLS) in Patients with at least 1-stage Fibrosis Improvement



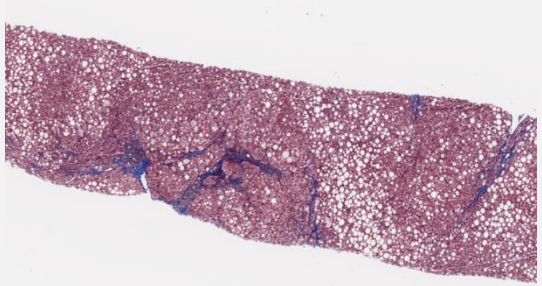
Fibrosis Improvement
(pathologist read)



* Peri-Portal Long Strings are not impacted by steatosis correction, mITT population

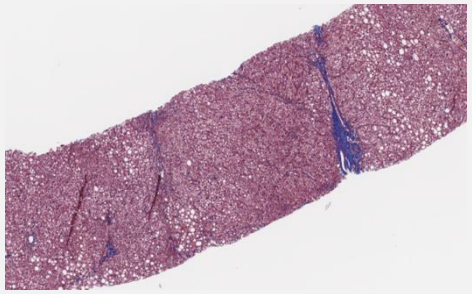
Denifanstat Reduced Number of Peri-Portal Long Strings (PPLS) even in Patients with ”No Change” in Fibrosis Stage

Baseline = F3 (Pathologist Read)



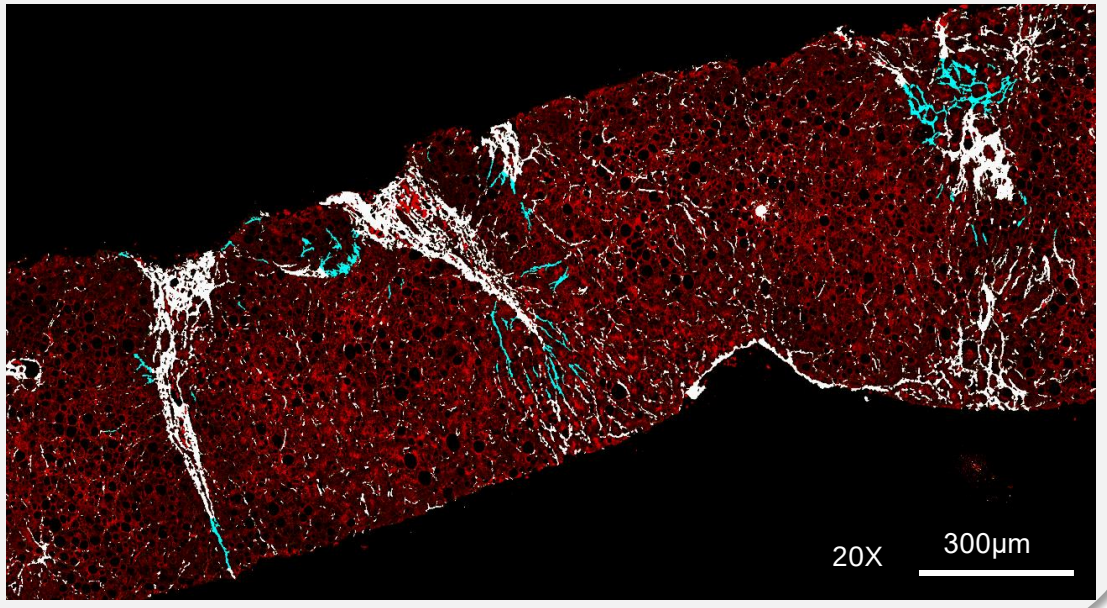
Denifanstat

End of Treatment = F3 (Pathologist Read)

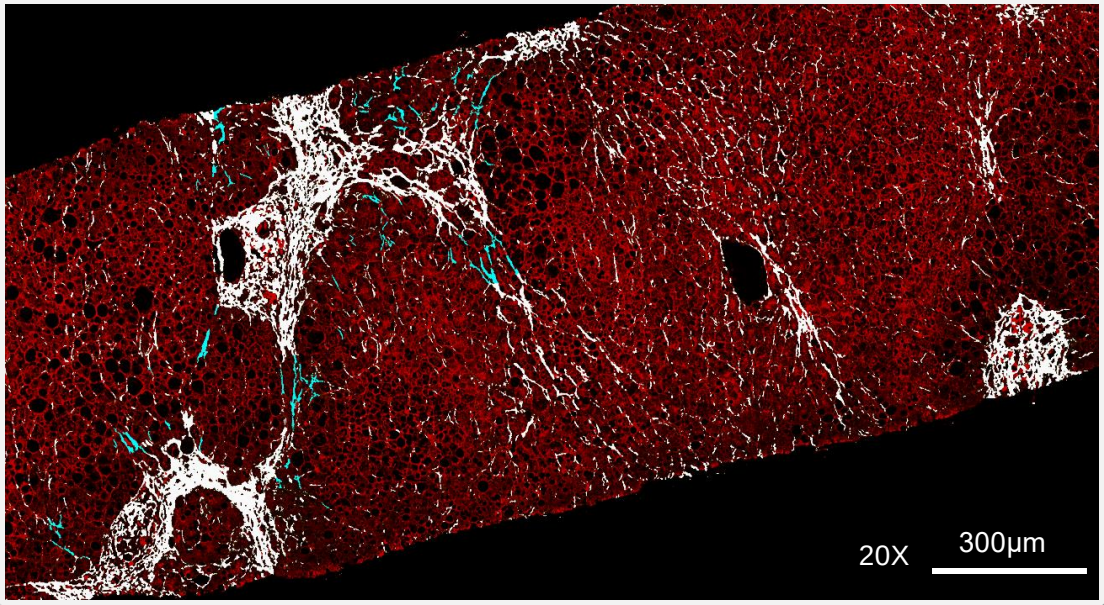


Baseline = 60 PPLS (HistoIndex)

PPLS

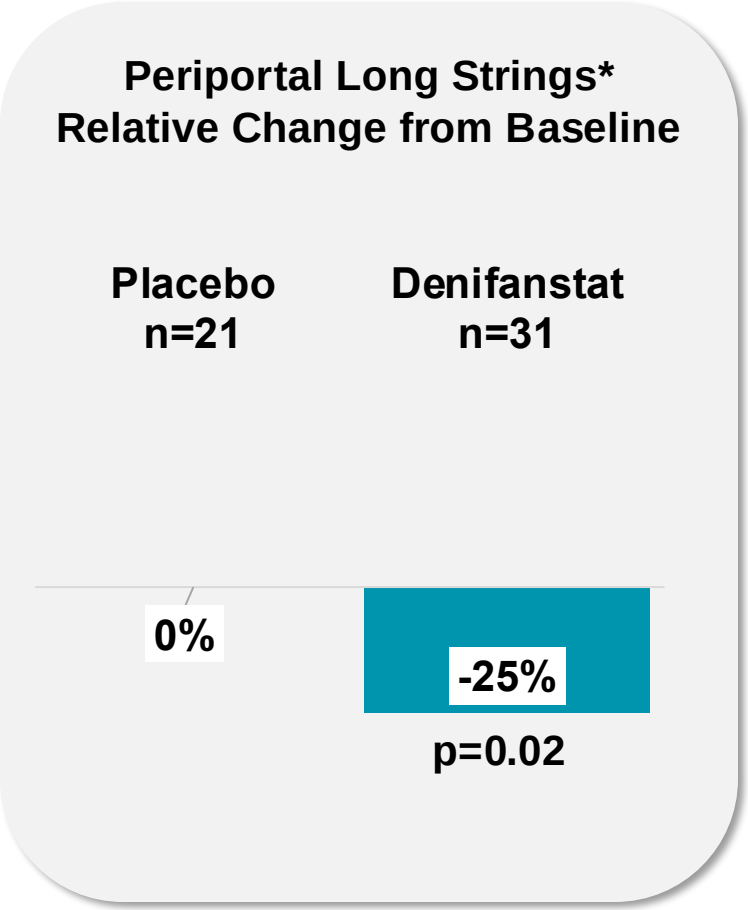


End of Treatment = 38 PPLS (HistoIndex)



Denifanstat Reduced Number of Peri-Portal Long Strings* (PPLS) in Patients with ”No Change” in Fibrosis Stage

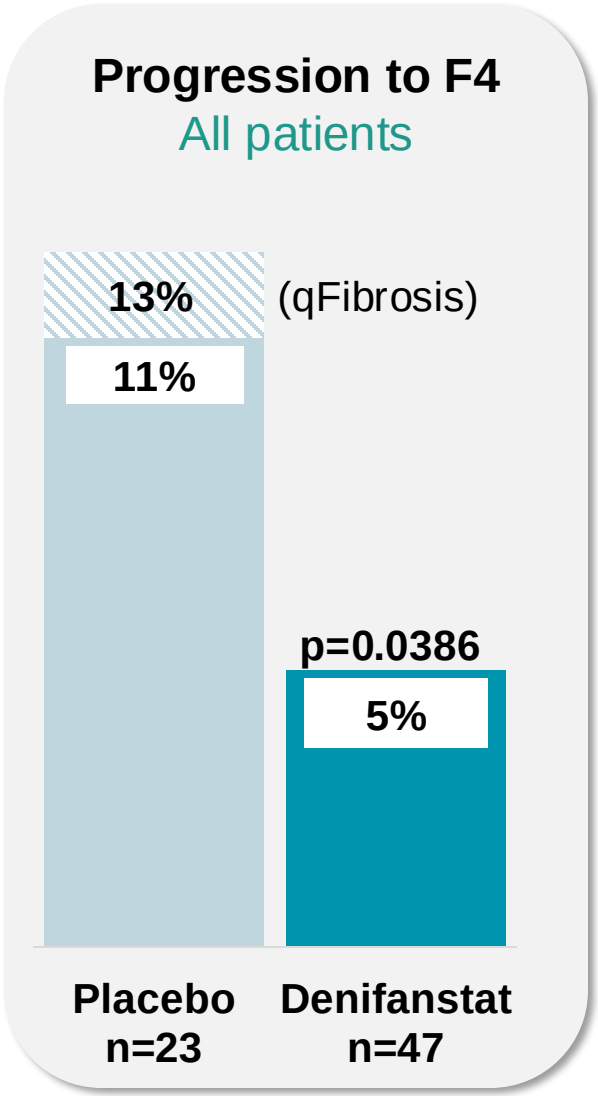
No Change in Fibrosis
(pathologist read)

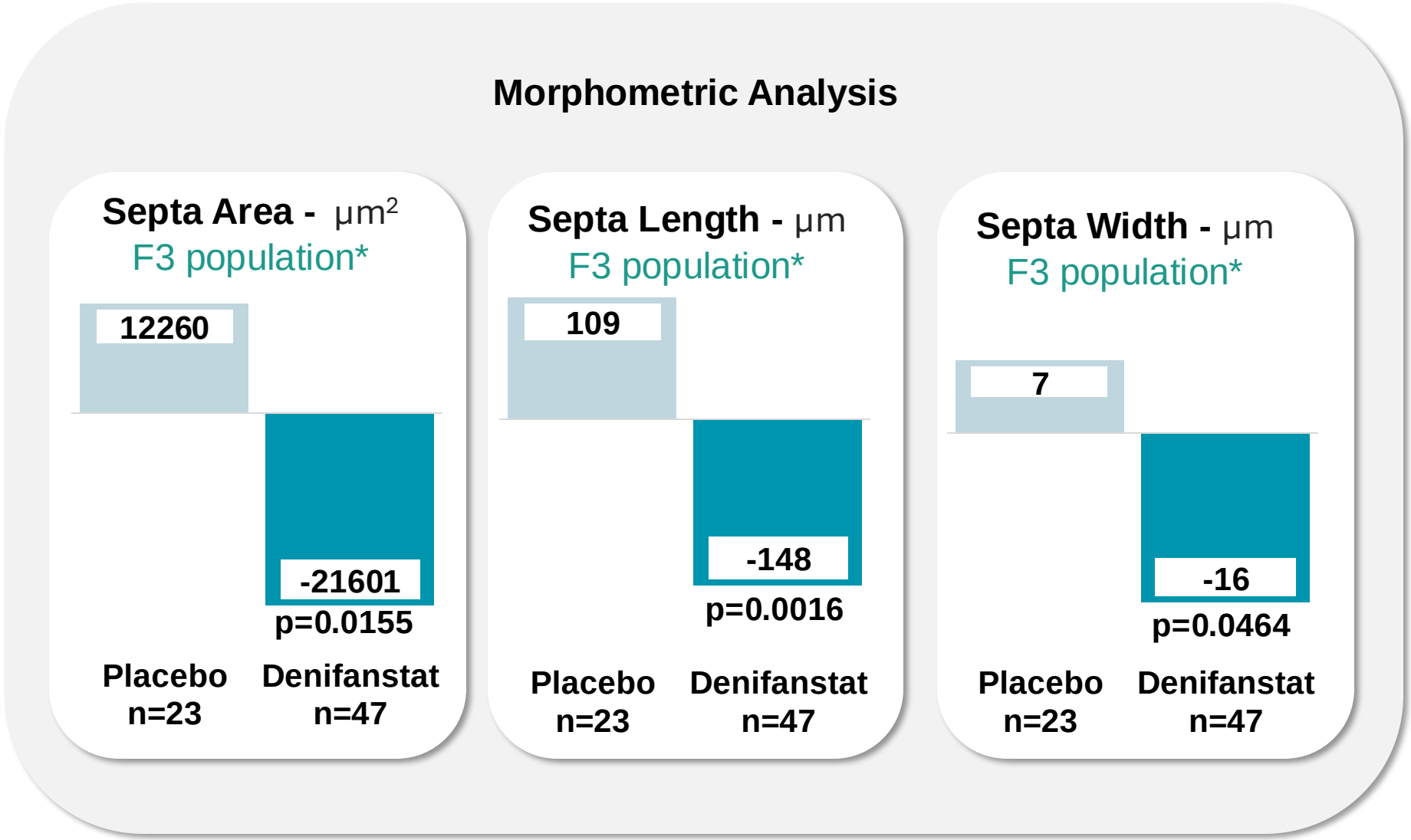


Zonal analysis provides further granularity and evidence of anti-fibrotic effect of denifanstat

* Peri-Portal Long Strings are not impacted by steatosis correction, mITT population

Denifanstat Showed a Strong Antifibrotic Activity in F3 with a Lower rate of Progression to Cirrhosis





* F3 population defined as per pathologist reading

KEY TAKEAWAYS

- Digital analysis corroborated **robust anti-fibrotic effect of denifanstat** shown by conventional pathology and further highlighted additional antifibrotic changes in portal and periportal regions suggesting additional benefit

- These results support the **initiation of Phase 3 studies**

AASLD The Liver Meeting®

AASLD, Boston, 2023

Stephen Anderson Harrison
January 7, 1969 – April 23, 2024

EASL, Vienna, 2023

THANK YOU

Acknowledgements

We would like to thank the patients and their families, the investigators and site teams who participated in this trial, and to recognize the tireless leadership of Dr. Stephen Harrison, a visionary in the field.

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