The FASN Inhibitor Denifanstat in MASH

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Disclosures

Dr. O'Farrell is an employee of Sagimet Biosciences Inc. and holds stock options in the company

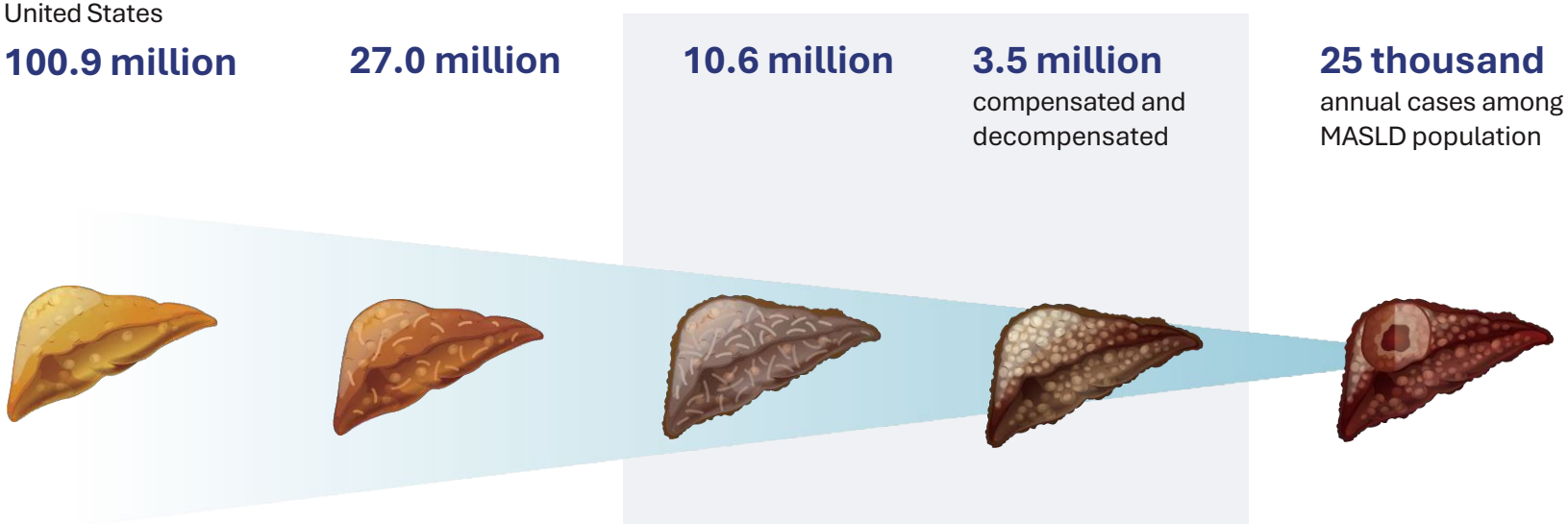
Outline

- Introduction to FASN and denifanstat
- Mechanism of action studies
- Phase 2b FASCINATE-2 study results in F2/F3 MASH

MASH: A Burgeoning Epidemic

Estimated Patients in 2030[1]

United States

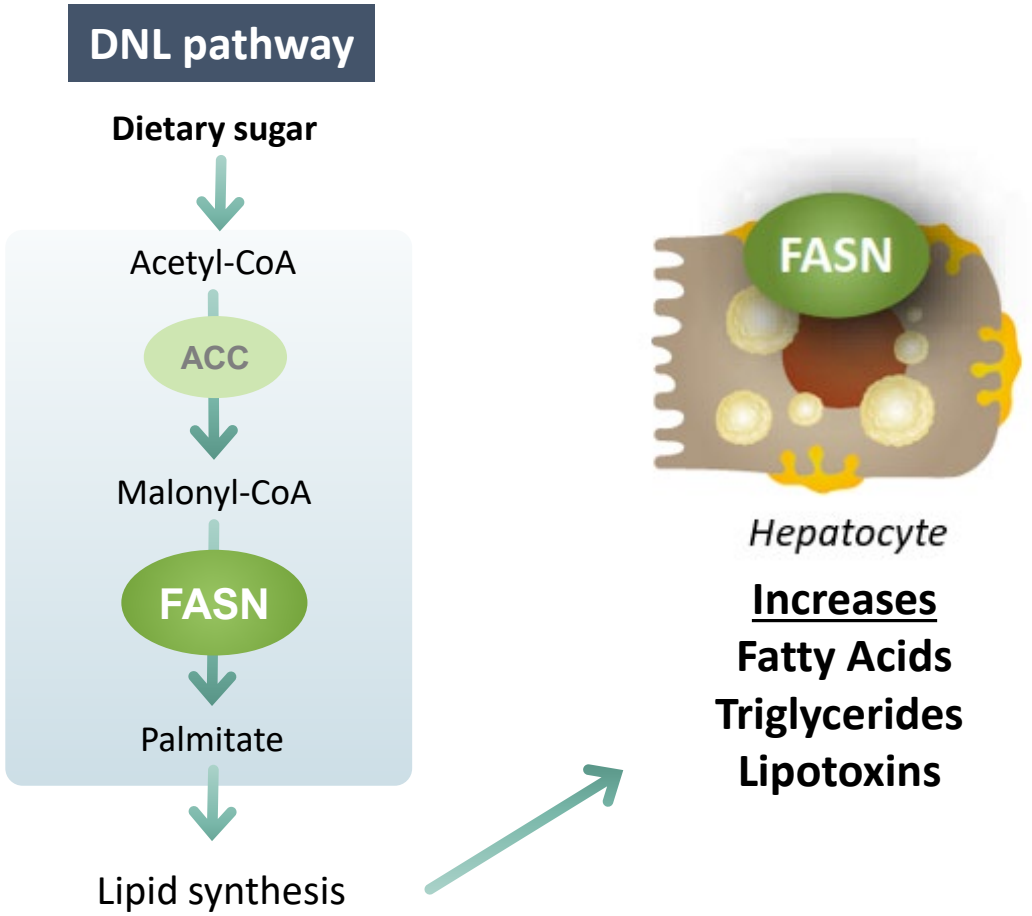


MASH

- Complex disease with heterogeneous patient population
- Significant opportunity for differentiated MOA

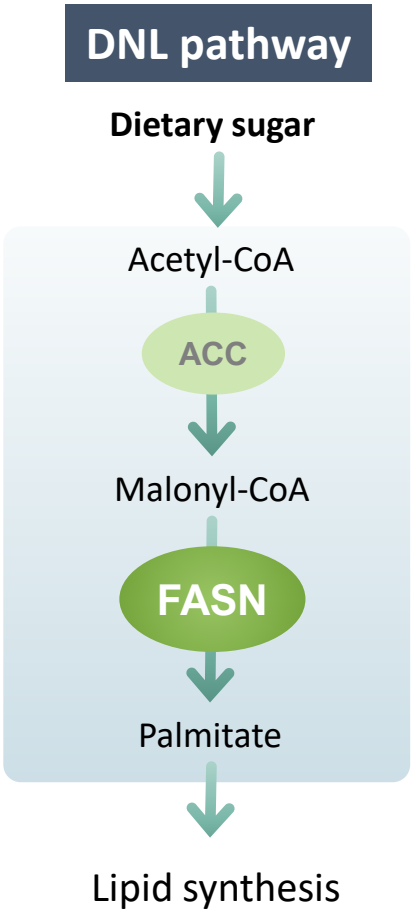
1 Estes, et al. 2018; http://dx.doi.org/10.1016/j.jhep.2018.05.036. Note: MASH, or metabolic dysfunction-associated steatohepatitis, was formerly known as NASH, or nonalcoholic steatohepatitis

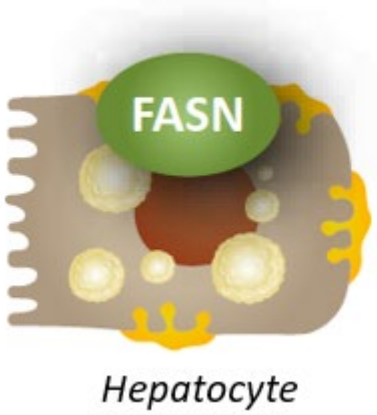
FASN is Well Known for its Role in Hepatic De Novo Lipogenesis (DNL)



- Hepatic DNL is increased in MASLD/MASH which leads to increased liver fat in hepatocytes
- Important initiating event in MASLD/MASH
- FASN (fatty acid synthase) is the last committed step in DNL and an attractive target for drug development

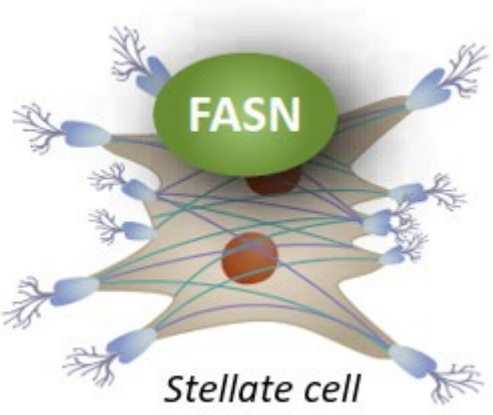
FASN Also Plays Key Roles in Two Other Major Cell Types in MASH





<u>Increases</u>
Fatty acids
Triglycerides
Lipotoxins

<u>Increases</u>
Cytokines
Chemokines
Cell activation

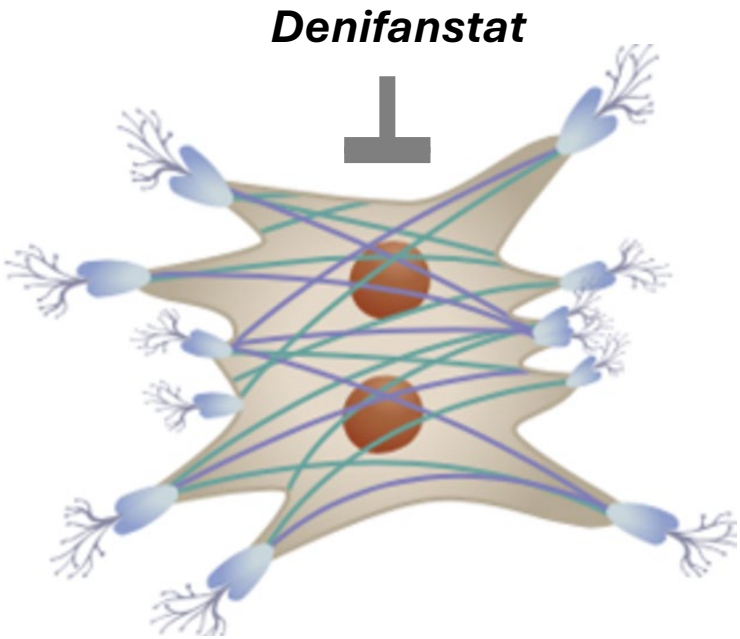


<u>Increases</u>
Fibrogenesis
Cell activation

FASN Inhibition Directly Blocks Human Liver Stellate Cell Function

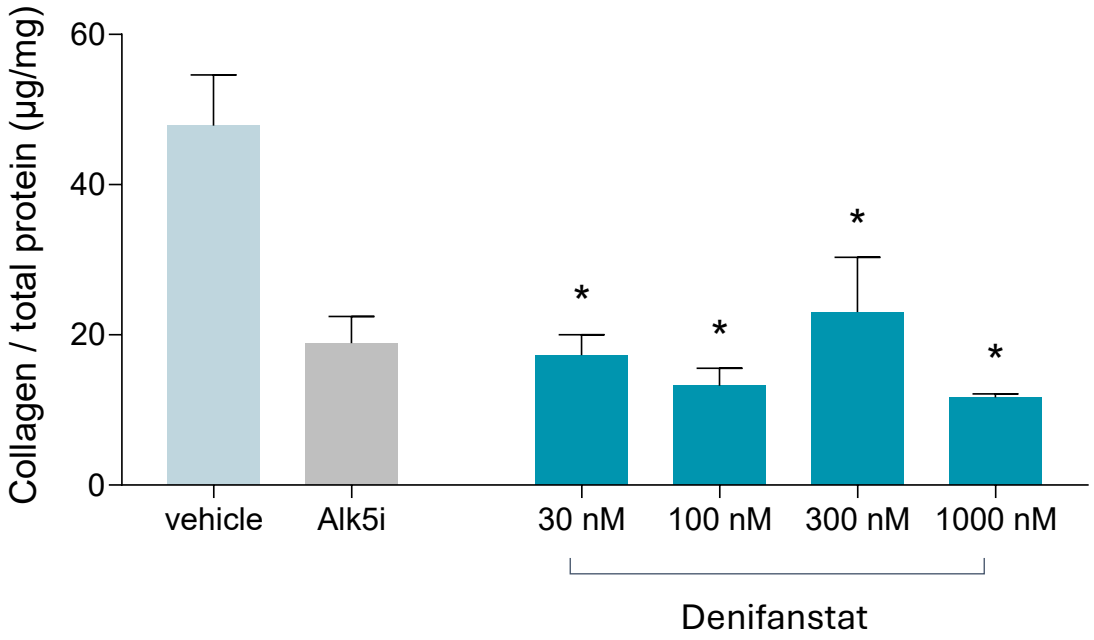
Stellate cells require DNL for fibrogenesis

Denifanstat blocks stellate cell activation



Primary human stellate cell assay

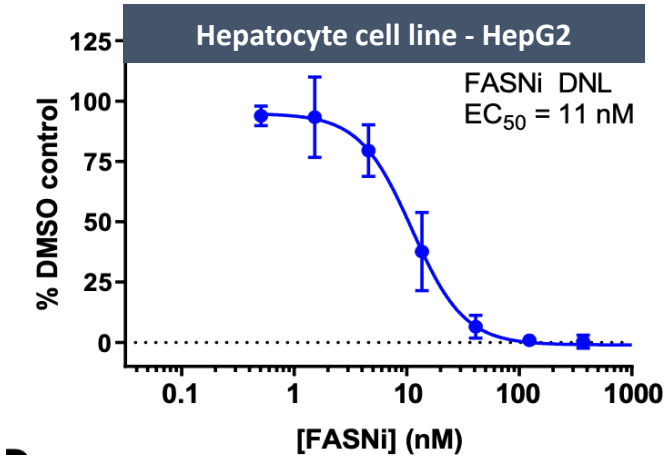
Denifanstat directly inhibits fibrogenic activity

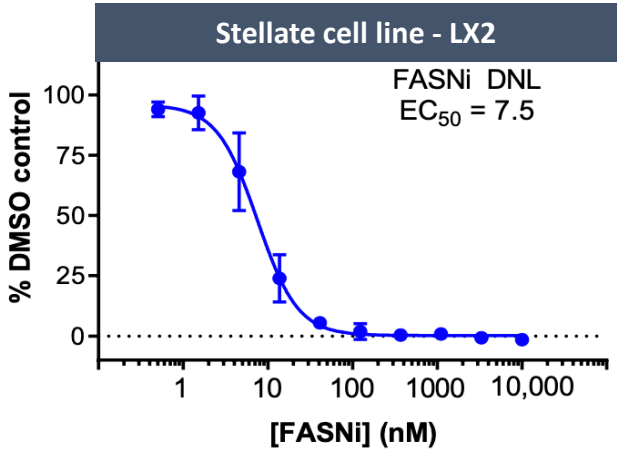


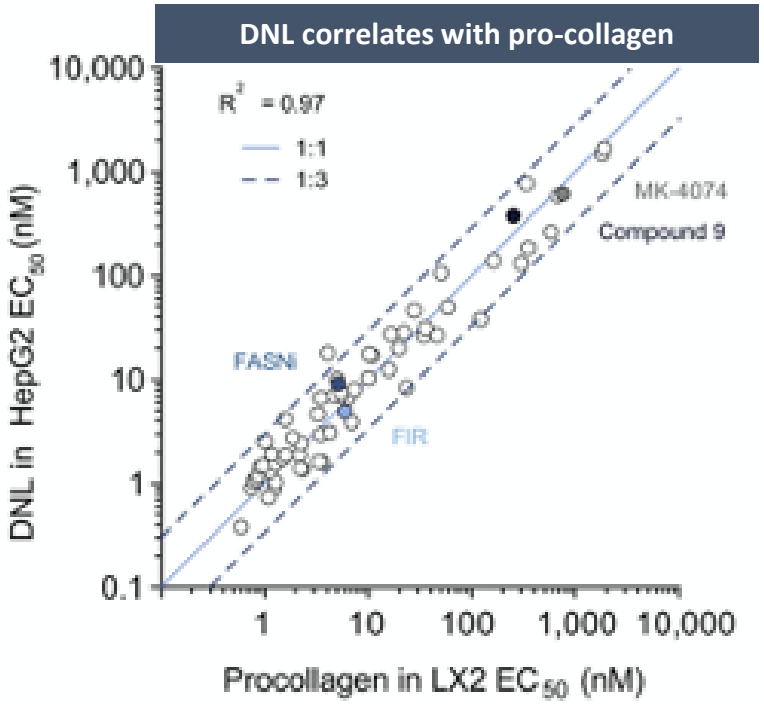
- Stimulated by TGF-beta to activate fibrogenesis
- Denifanstat showed similar inhibition to positive control ALK5 inhibitor

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

DNL Inhibition Correlates with Collagen Inhibition Across DNL Inhibitors







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

FASN Inhibitor Reversed Hepatic Fibrosis

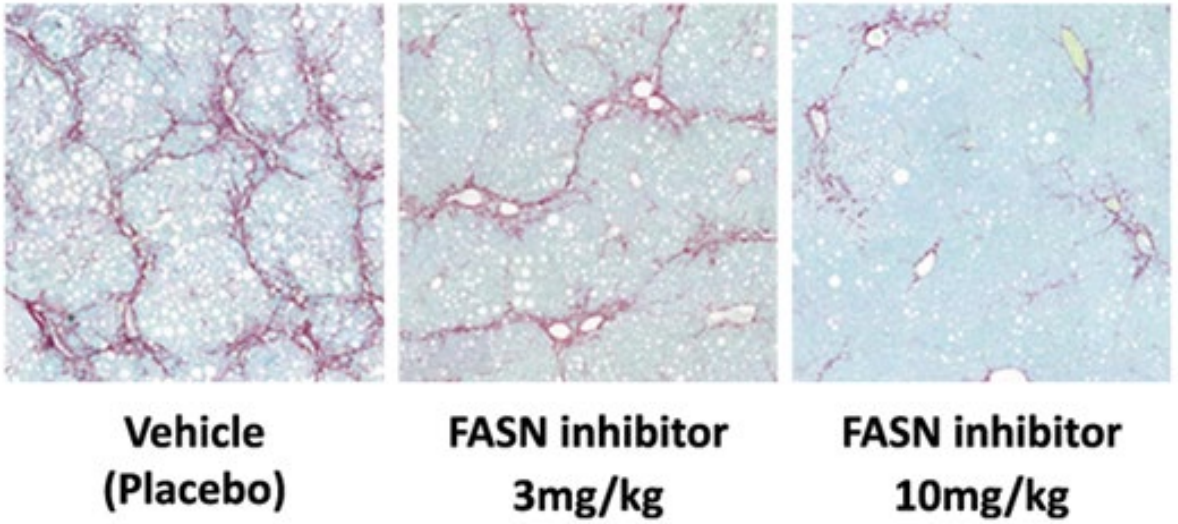
Collaboration with Dr. Scott Friedman

High fat and high sugar diet
CCl4 1x/week
3 months

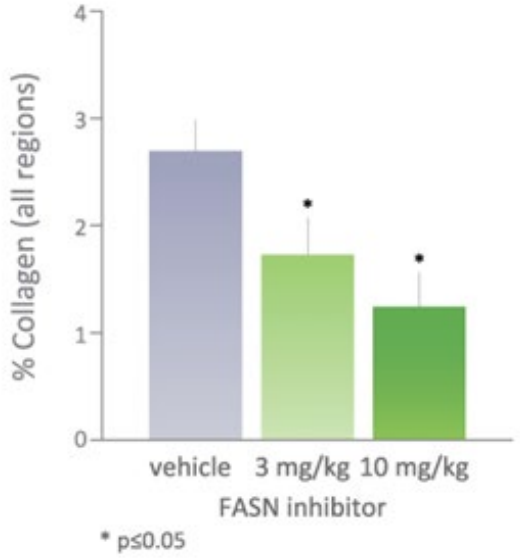
High fat and high sugar diet
CCl4 1x/week
3 months
+/- FASN inhibitor

Assess liver fibrosis and tumor formation

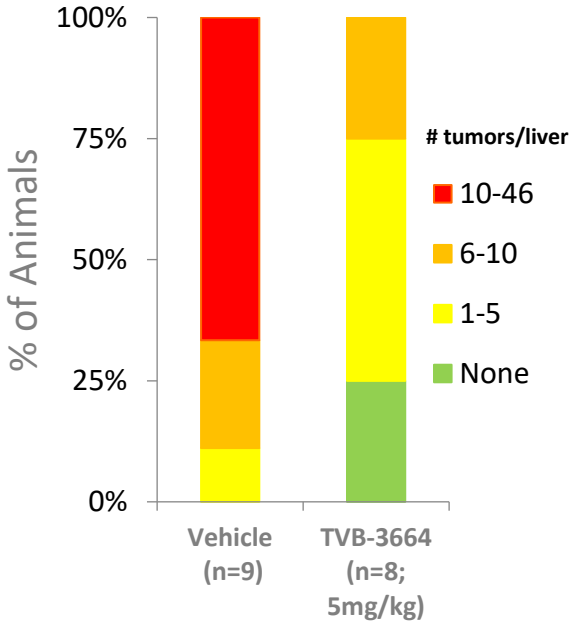
Reversed fibrosis



Quantitated by AI-digital pathology



Decreased tumor formation by 85%



O'Farrell et al.,2022. Scientific Reports. 12:15661

Clinical Development of Denifanstat

Phase 1

- Subjects with characteristics of MASLD
- 10-day denifanstat treatment
- **Denifanstat decreased hepatic DNL in human[1]**

Phase 2a FASCINATE-1

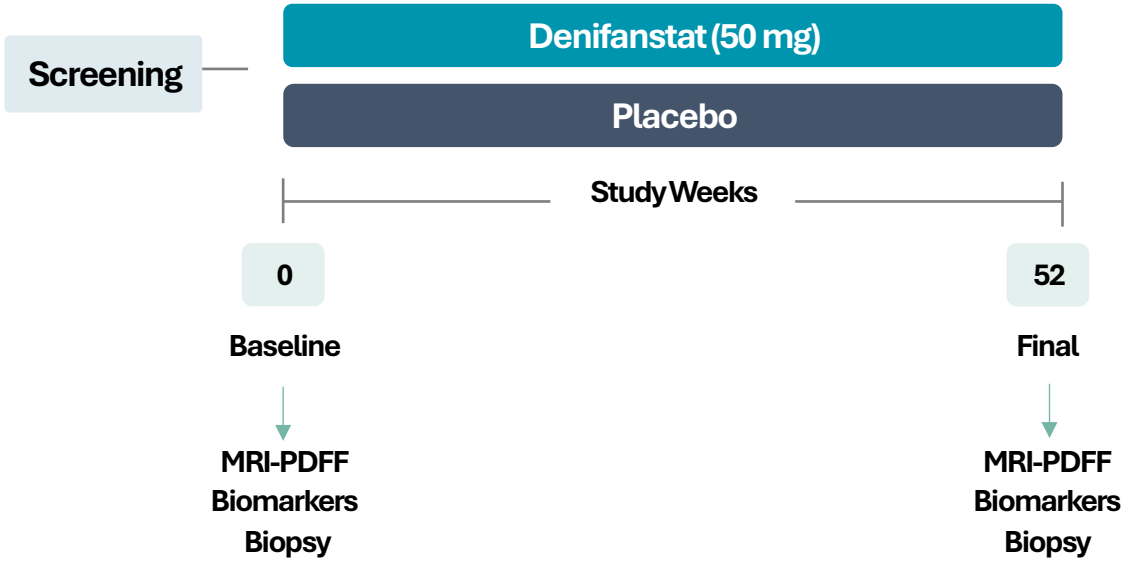
- MASH patients
- 12-week denifanstat treatment
- **Denifanstat decreased liver fat by MRI-PDFF, decreased inflammation and fibrosis biomarkers[2]**

Phase 2b FASCINATE-2

- MASH patients, F2/F3
- 52-week denifanstat treatment
- **Denifanstat demonstrated both MASH resolution and fibrosis improvement[3]**

[1]Phase 1 IST by Dr. Elizabeth Parks. [1]Syed Abdul et al., Hepatology, 2020, 2020 Jul;72(1):103-118. doi: 10.1002/hep.31000, [2]Loomba et al., Gastroenterology, 2021, doi: 10.1053/j.gastro.2021.07.025. [3]Loomba et al., The Lancet Gastroenterology & Hepatology, 9, 1090 – 1100. doi: 10.1016/S2468-1253(24)00246-2.

FASCINATE-2: Biopsy Trial Design Focused on Histological Endpoints



- Biopsy confirmed F2-F3 MASH patients
- 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

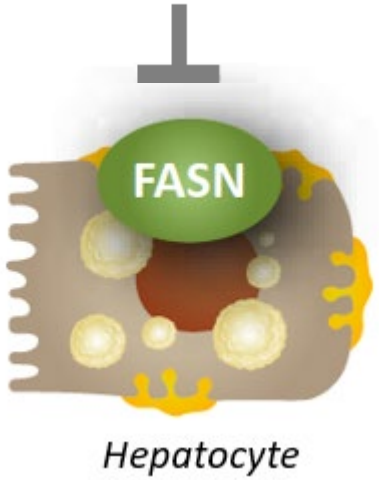
Selected secondary endpoints

- **MASH resolution w/o worsening of fibrosis**
- **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 ≥30% reduction from baseline (responders)

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

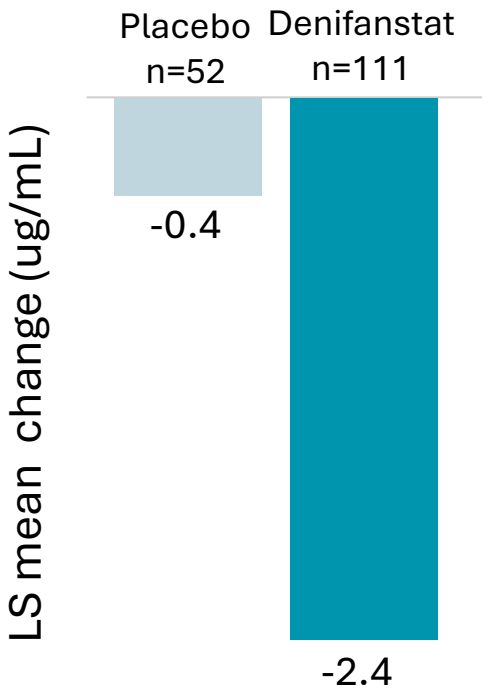
Denifanstat Rapidly Reduced De Novo Lipogenesis and Decreased Liver Fat

Denifanstat



Fatty Acids
Triglycerides
Lipotoxins

Tripalmitin
Change from Baseline



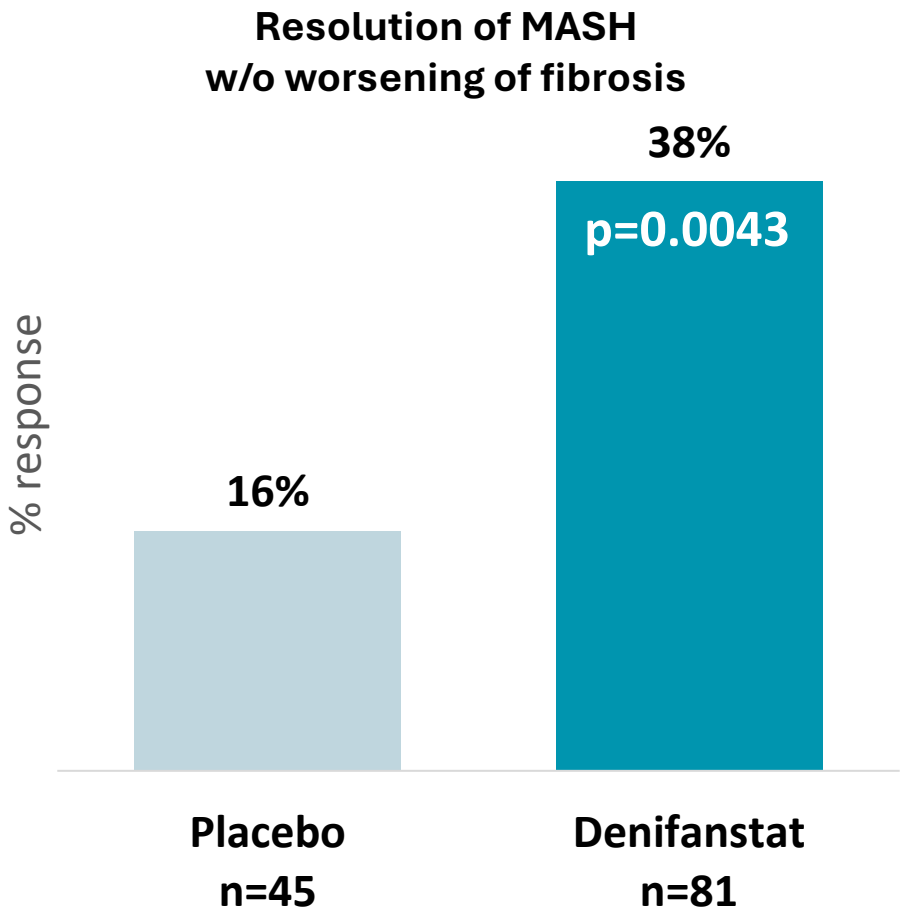
Liver Fat
Change from Baseline

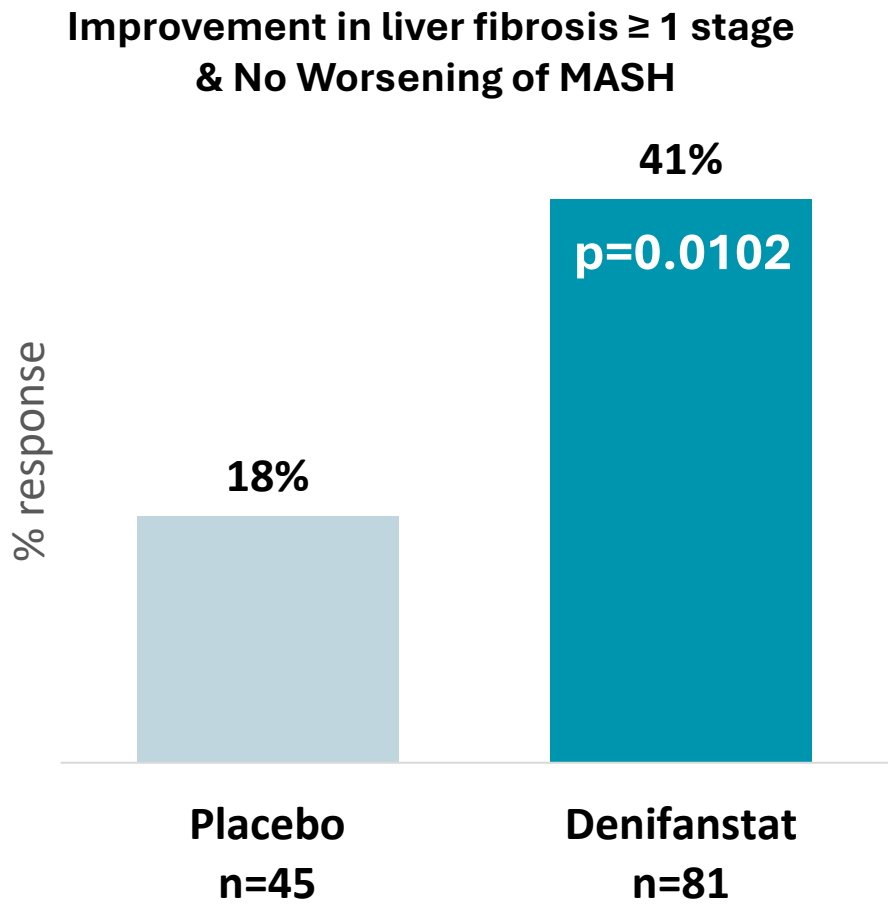
Liver fat by MRI-PDFF	Placebo n=38	Denifanstat n=69	
Relative decrease Week 26	+5%	-23%	p=0.0036
Relative decrease Week 52	-8%	-31%	p=0.0008
≥ 30% relative decrease Week 52	21%	65%	p<0.0001

Two sided at the 0.05 significance level, ITT population

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. mITT population. Statistical significance also reached for ITT population.

Additional Fibrosis Analysis by Conventional Pathology

Denifanstat Achieved Strong Improvement in F3 Population

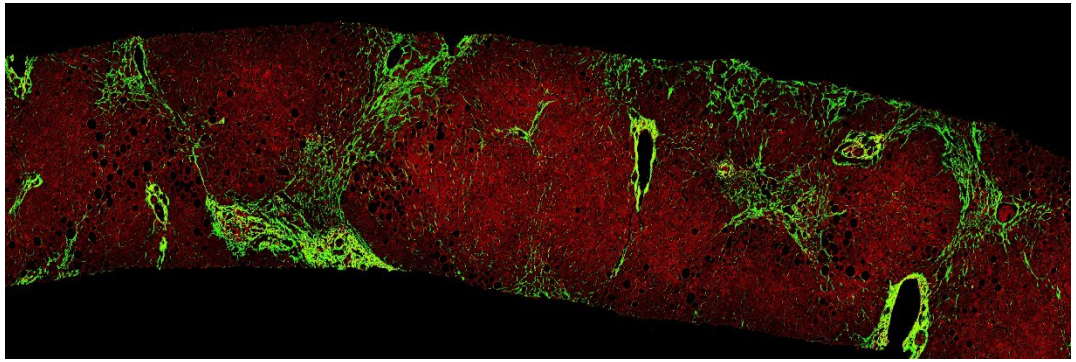
Fibrosis Endpoints	Subgroup	Placebo	Denifanstat	p-value
≥1 stage improvement in fibrosis w/o worsening of MASH	All pts	18%	41%	0.0051*
	F3 only	13%	49%	0.0032**
≥2 stage improvement in fibrosis w/o worsening of MASH	All pts	2%	20%	0.0065**
	F3 only	4%	34%	0.0065**
Progression to cirrhosis (F4)	All pts	11%	5%	0.0386*

mITT population. ITT response rate of 14% placebo and 30% denifanstat (p=0.0199) . *One sided at the 0.05 significance level, **Two sided at the 0.05 significance level.

Fibrosis Analysis by AI-based Digital Pathology

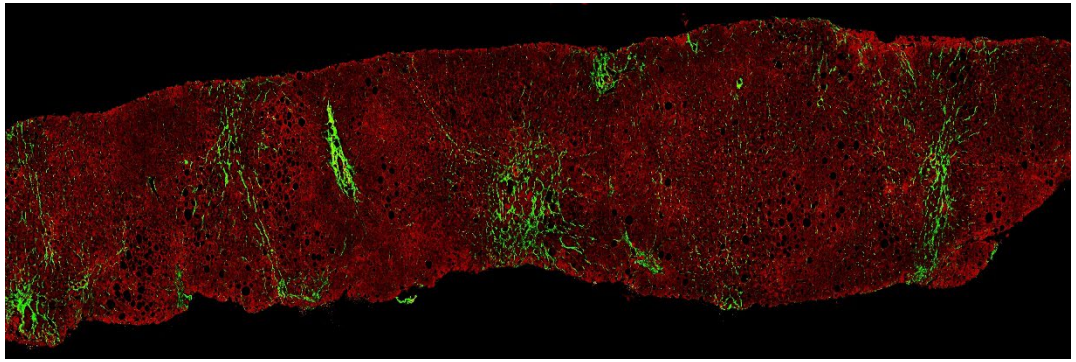
Independent Approach Performed Prospectively – Second Harmonic Generation Microscopy

Pre-Treatment Pt A
NASH-CRN Fibrosis stage F3



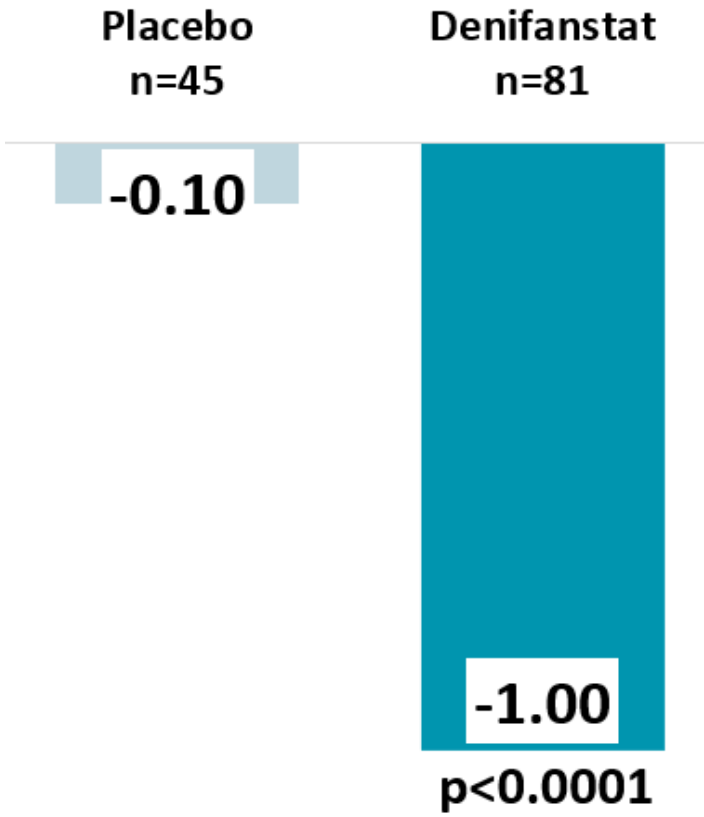
Denifanstat

Post-Treatment Pt A
NASH-CRN Fibrosis stage F1



qFibrosis Continuous Value
with Steatosis Correction

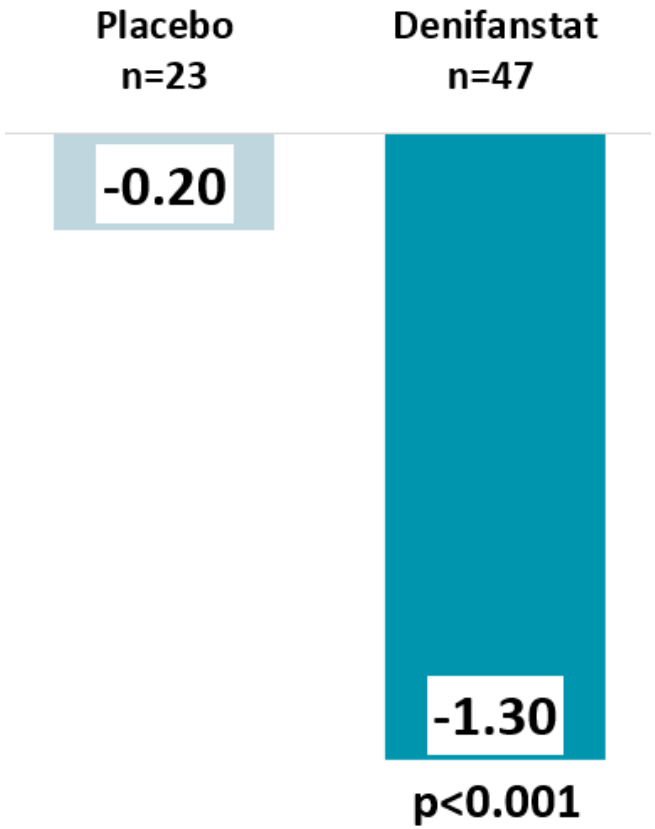
All patients



qFibrosis by AI-based Digital Pathology Provides Supporting Evidence that Denifanstat Significantly Reduced Fibrosis, Notably in F3 Population

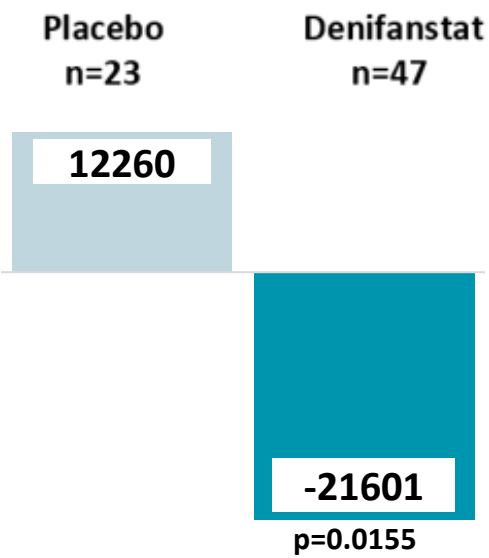
qFibrosis Continuous Value with Steatosis Correction

F3 only



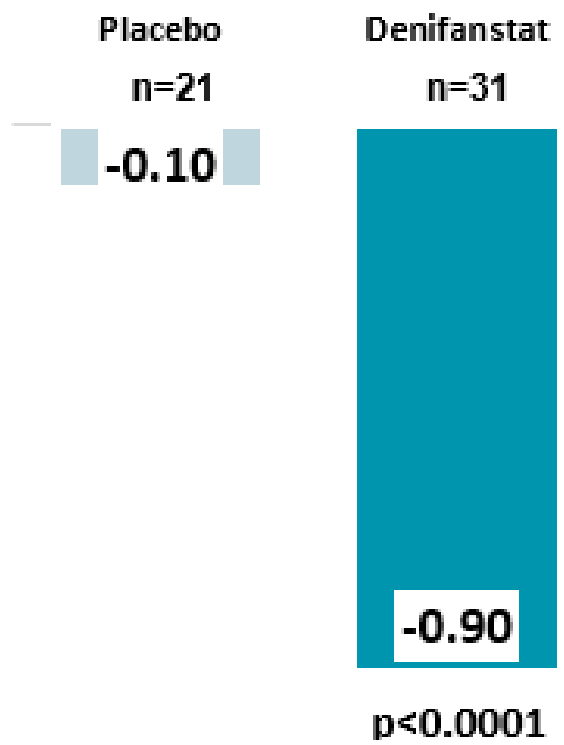
Morphometric Analysis Septa Area (uM^2)

F3 only



qFibrosis Continuous Value with Steatosis Correction

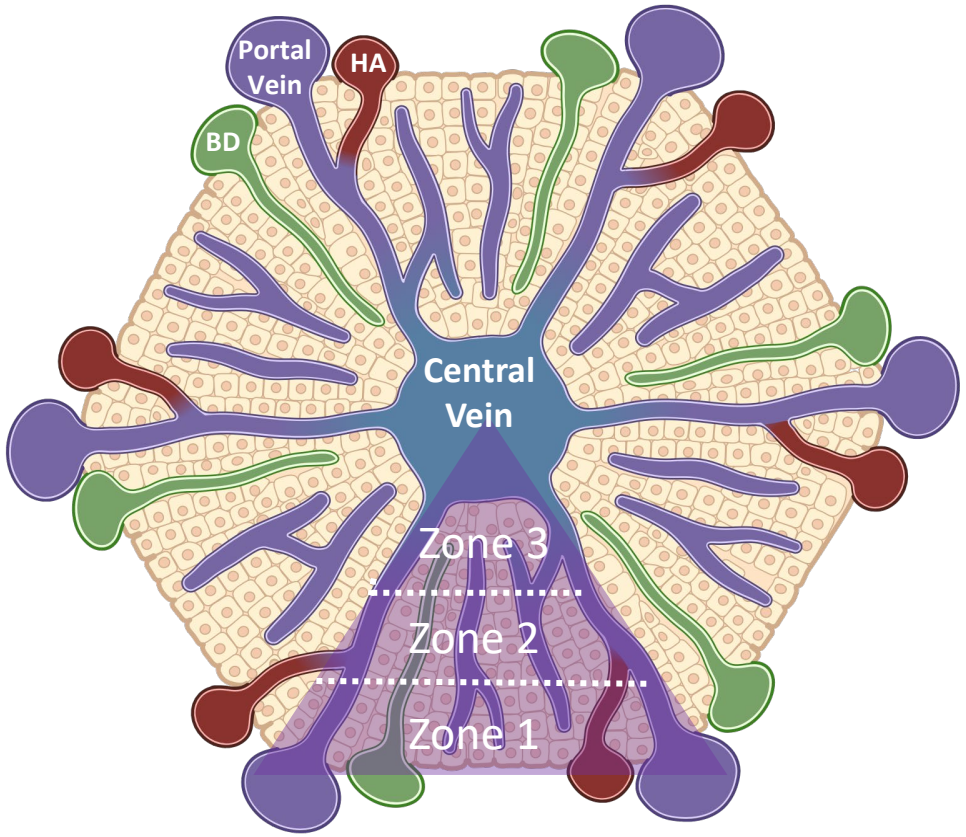
No change by conventional pathology



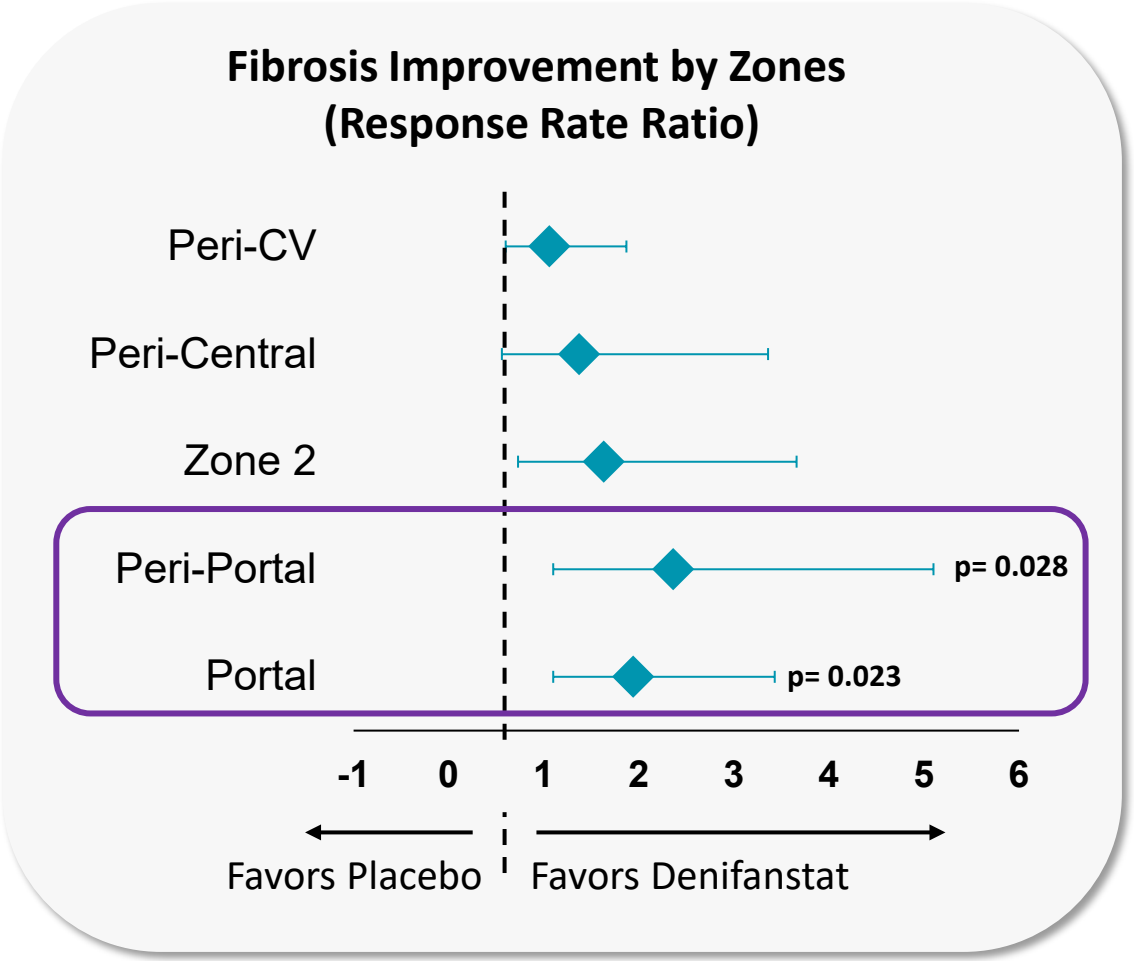
May indicate "early" improvements not detected conventionally

mITT population. * F3 population defined by pathologist reading

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



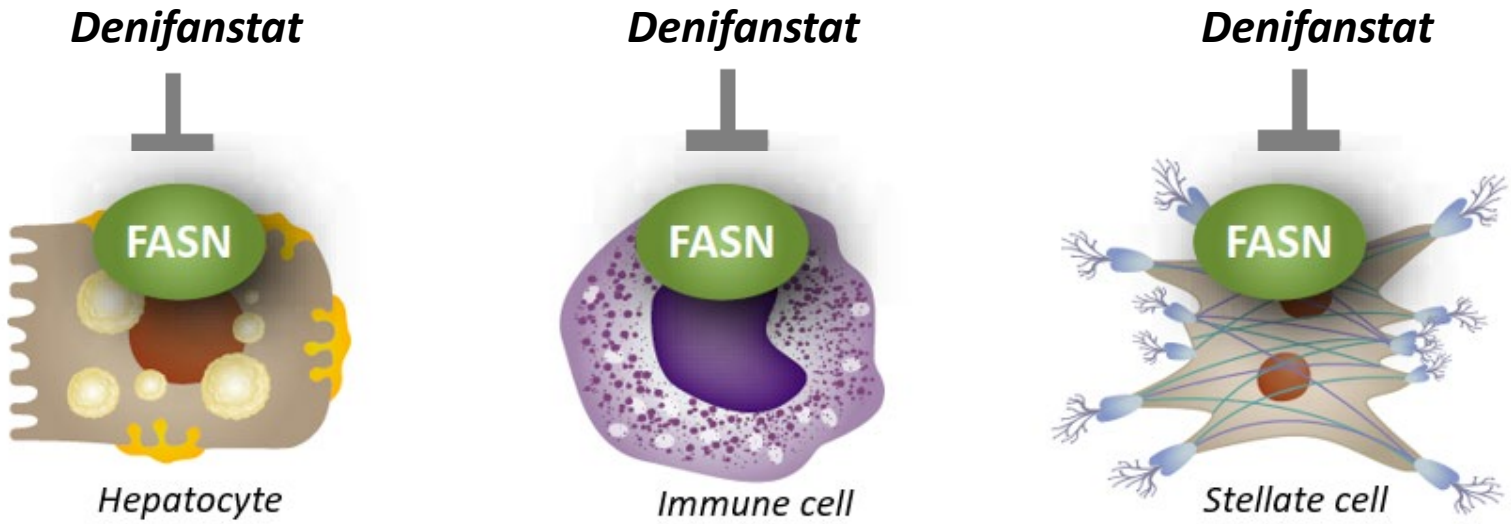
Changes in periportal and portal zones have been correlated with liver outcomes and mortality by analysis of liver biopsies (n=452) from SteatoSITE study[1]



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

[1]Kendall TJ et al. Liver Int. 2024;44:2511-2516)

Phase 2 Results Are Consistent with Mechanism of Action



Non-invasive biomarkers

- Hepatic DNL
- Tripalmitin
- Liver fat MRI-PDFF

- ALT, AST
- CK-18 M30, M65

- ELF
- FAST

Histology

- Steatosis
- Ballooning

- Inflammation

- Fibrosis

F3 high response rate
Septa favorable changes
Portal and periportal decreases

MASH resolution

Fibrosis Improvement

Lipotoxicity and metabolic stress, progressive cycle of inflammation and fibrosis

Rinella et al,
Poster A35
Saturday

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 MASH resolution and fibrosis in Phase 2b FASCINATE-2 study
- Digital analysis corroborated anti-fibrotic effect of denifanstat shown by conventional pathology and highlighted antifibrotic changes in septa, and portal and periportal regions
- Phase 3 program has been initiated with FPI anticipated in 1Q2025

Acknowledgements

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