SAGIMET BIOSCIENCES

Demonstrating denifanstat's differentiated approach in MASH with mechanistic and clinical data showing direct anti-fibrotic activity

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September 2024

Outline

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

MASH: A Burgeoning Epidemic

Patients in 2016[1]

United States

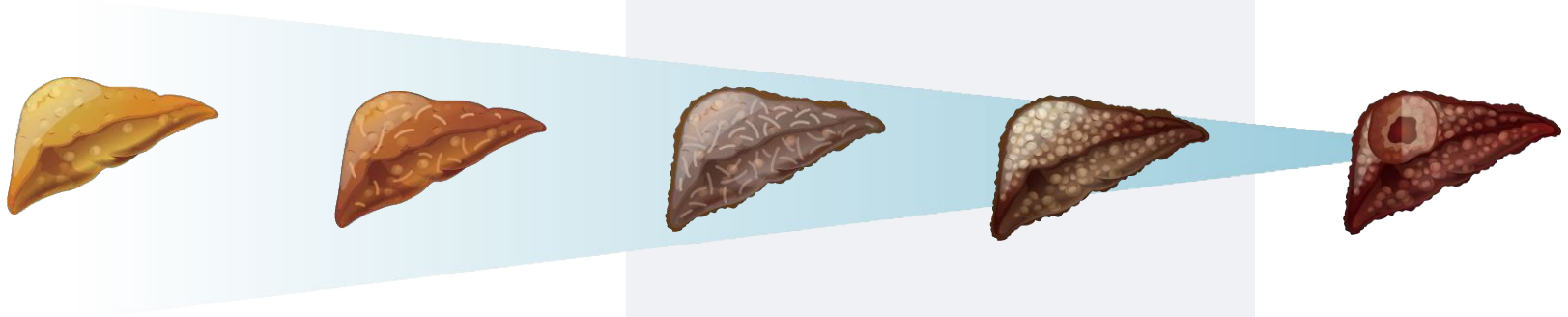
85.3 million

17.3 million

5.7 million

1.4 million
compensated and decompensated

11 thousand
annual cases among MASLD population



MASLD
Metabolic Dysfunction-Associated Liver Disease

MASH
Metabolic Dysfunction-Associated Steatohepatitis **F1**

MASH mod-adv Fibrosis F2-F3

Cirrhosis F4

Hepatocellular carcinoma

MASH

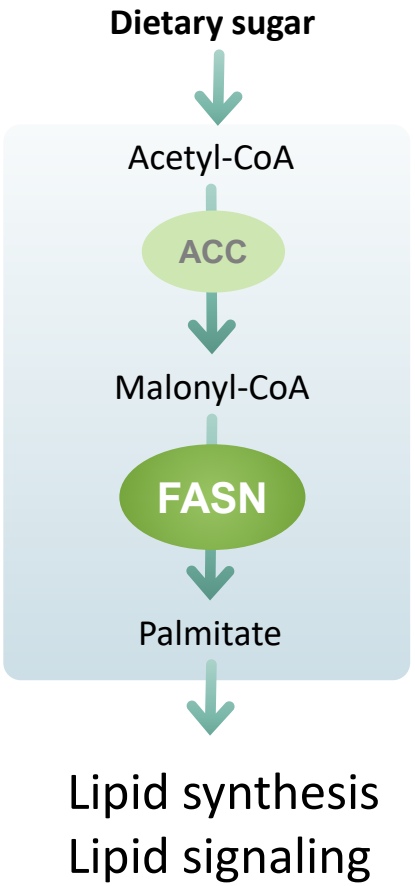
- Expected to almost double in size within next 2 decades[2]
- Complex disease with heterogeneous patient population
- Significant opportunity for differentiated MOA

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

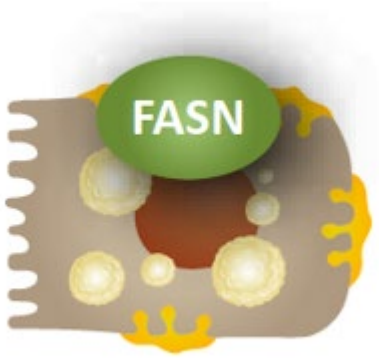
2 Yonoussi et al. 2023; The Growing Economic and Clinical Burden of Nonalcoholic Steatohepatitis (NASH) in the United States

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

De novo lipogenesis



Lipid synthesis
Lipid signaling



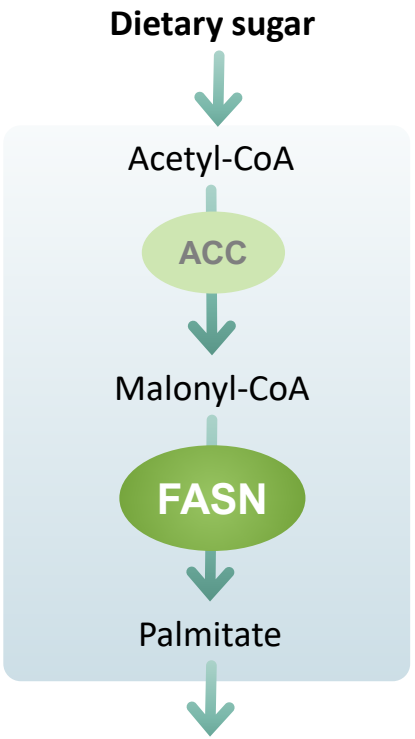
Hepatocyte

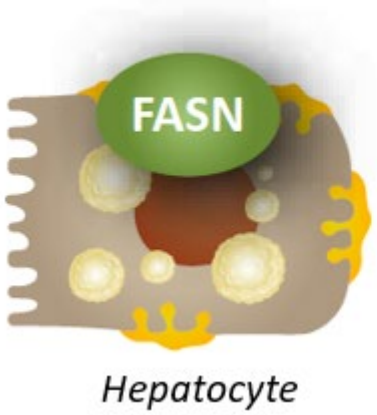
<u>Increases</u>
Fatty acids
Triglycerides
Lipotoxins

- Hepatic DNL is increased in MASLD/MASH which leads to increased liver fat in hepatocytes
- Important initiating event in MASLD/MASH
- FASN 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

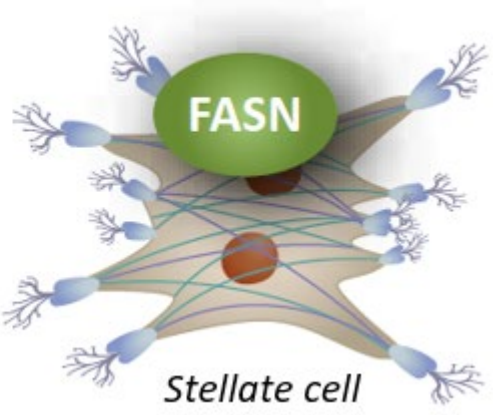
De novo lipogenesis





Increases
- Fatty acids
- Triglycerides
- Lipotoxins

Increases
- Cytokines
- Chemokines
- Cell activation

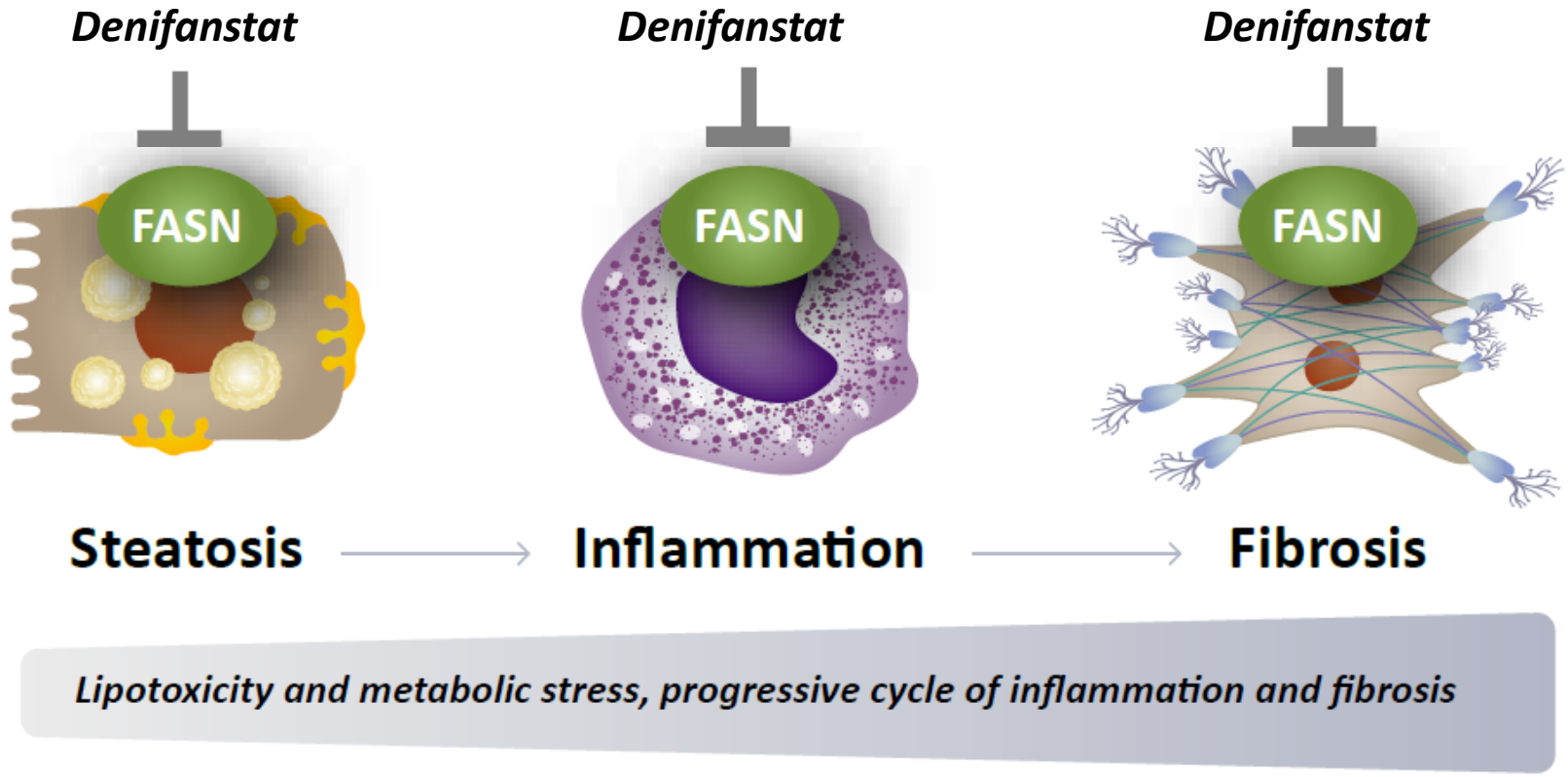


Increases
- Fibrogenesis
- Cell activation

Denifanstat Directly Inhibits Three Hallmarks of MASH

Denifanstat

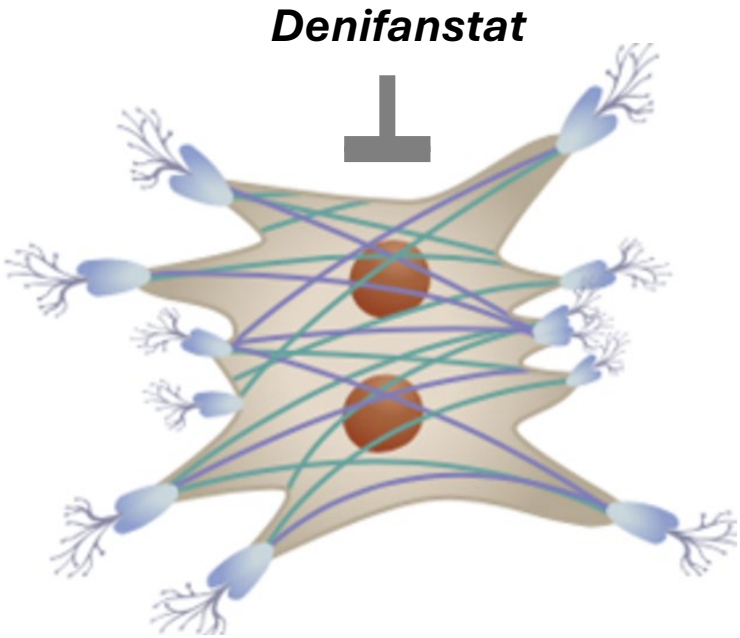
- Potent & selective
- EC50 approx. 50 nM
- 12 hr half life in human
- Oral once a day



FASN Inhibition Directly Blocks Human Liver Stellate Cell Function

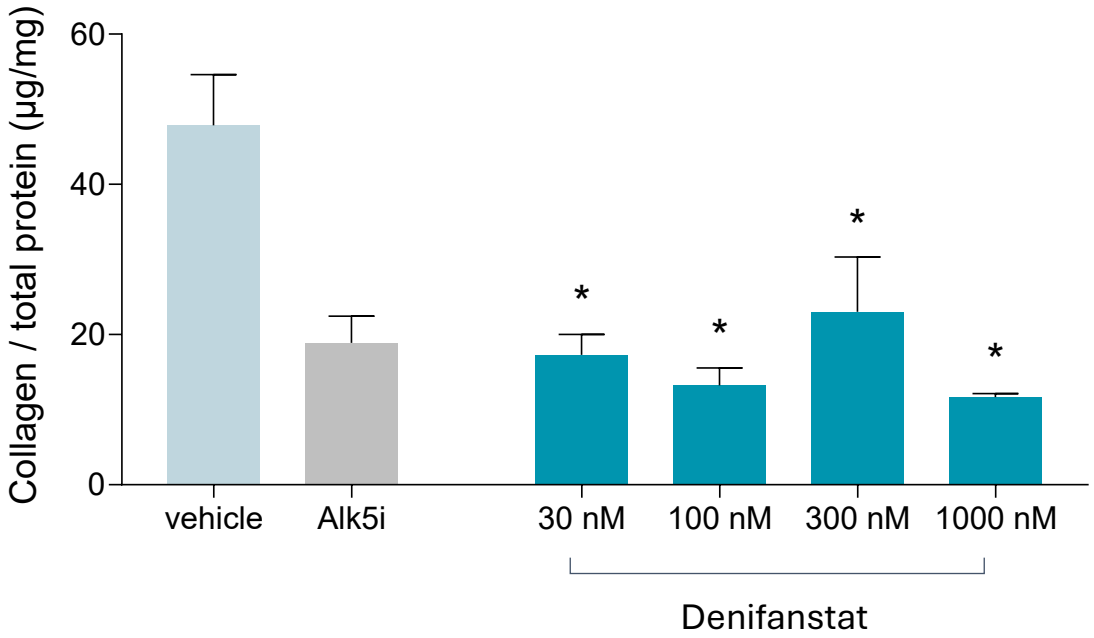
Stellate cells require DNL for fibrogenesis

Denifanstat blocks stellate cell activation



Primary human stellate cell assay

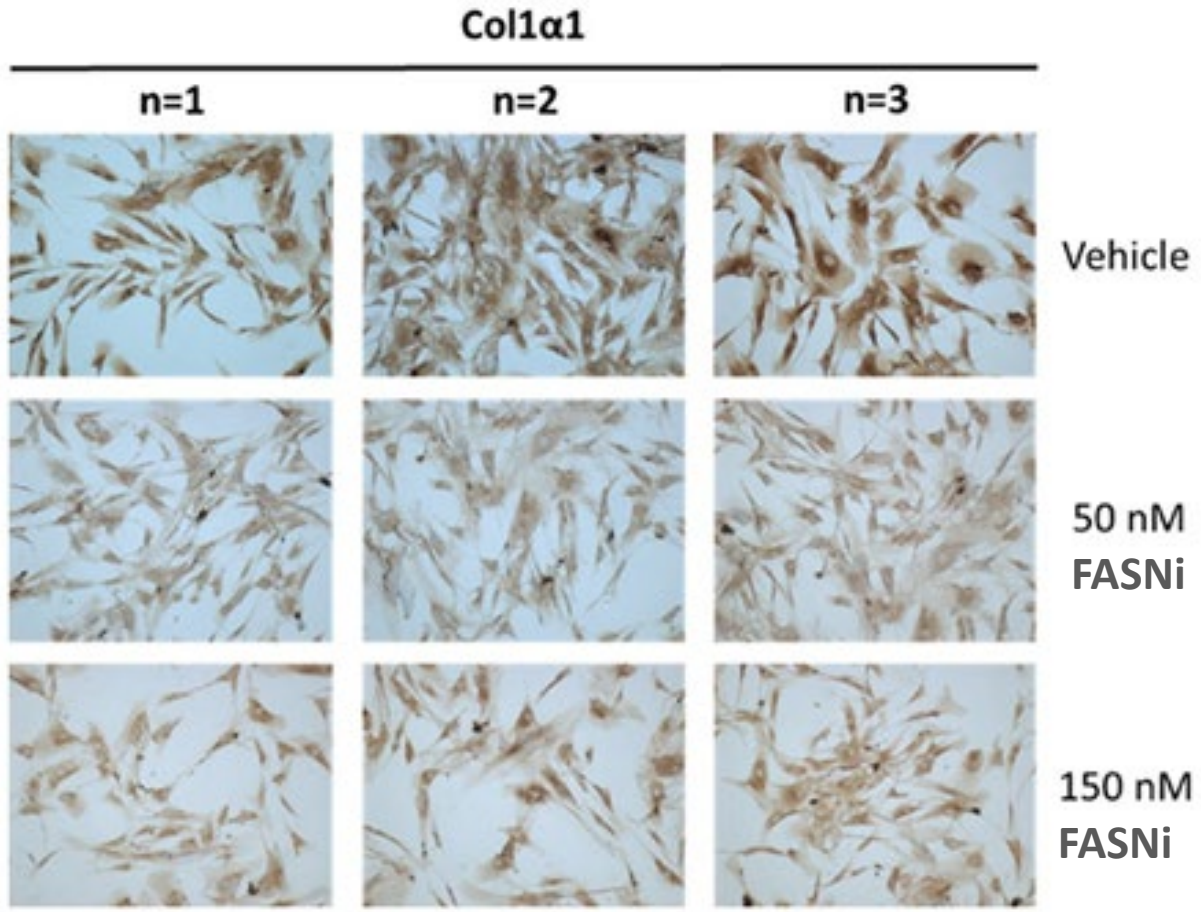
Denifanstat directly inhibits fibrogenic activity



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

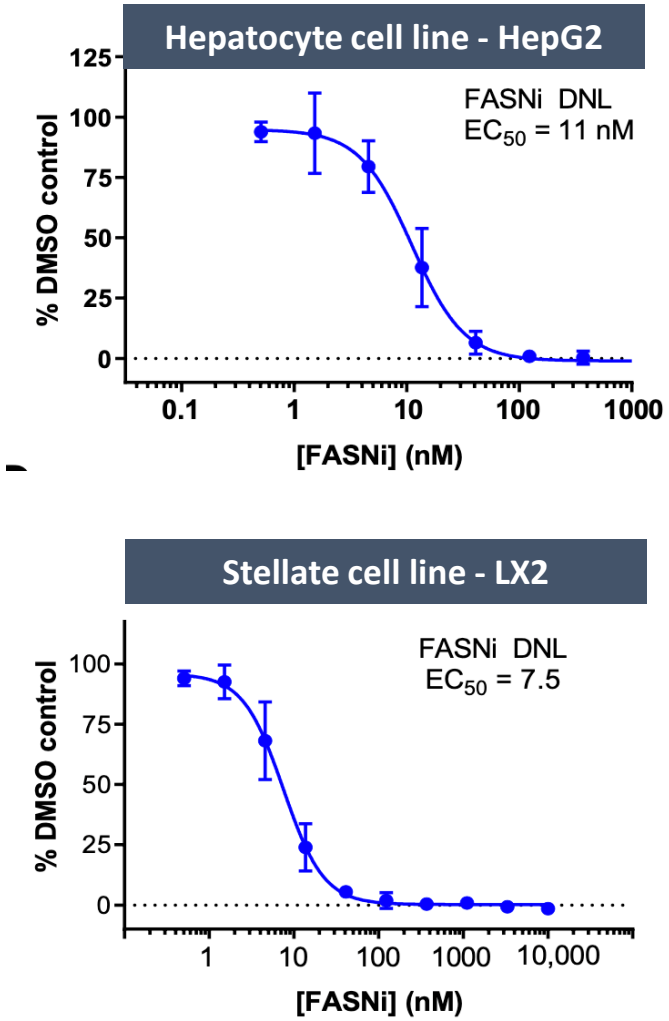
*p<0.05. FASNi directly inhibits fibrosis published in O'Farrell et al.,2022. Scientific Reports. 12:15661

FASN Inhibitor Decreased Collagen Expression in Primary Human Hepatic Stellate Cells

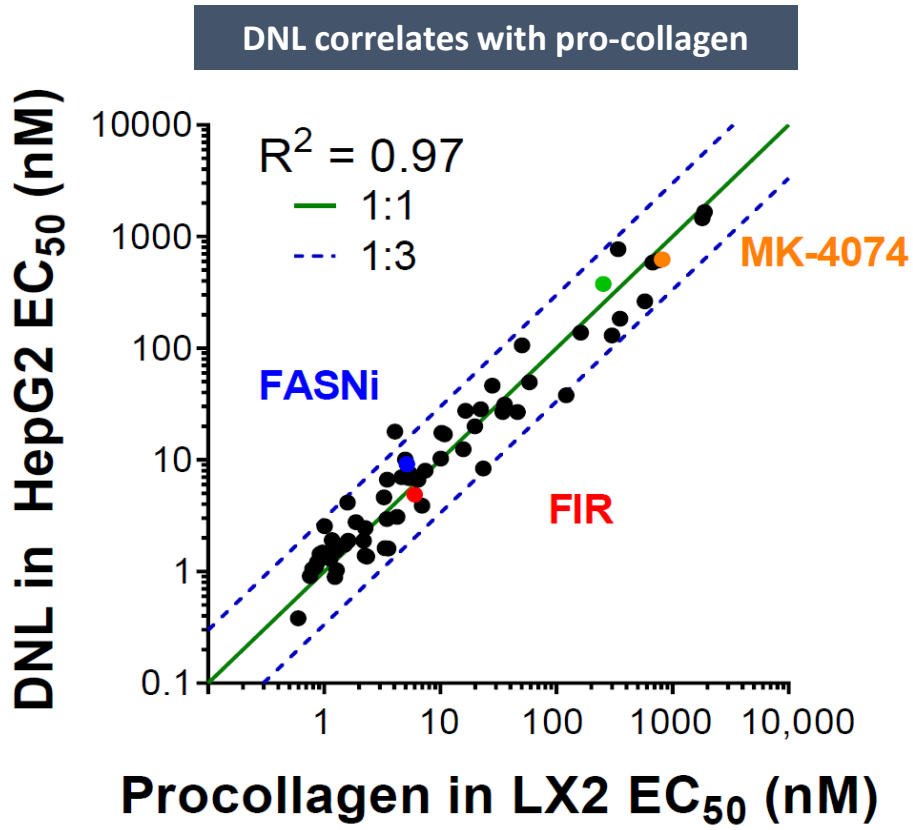


*O'Farrell et al.,2022. Scientific Reports. 12:15661

DNL Inhibition Correlates with Collagen Inhibition Across DNL Inhibitors



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



- Hepatic stellate cells became quiescent

FASN Inhibitor Reversed Hepatic Fibrosis

Collaboration with Dr. Scott Friedman

High fat and high sugar diet
CCl4 1x/week

3 months

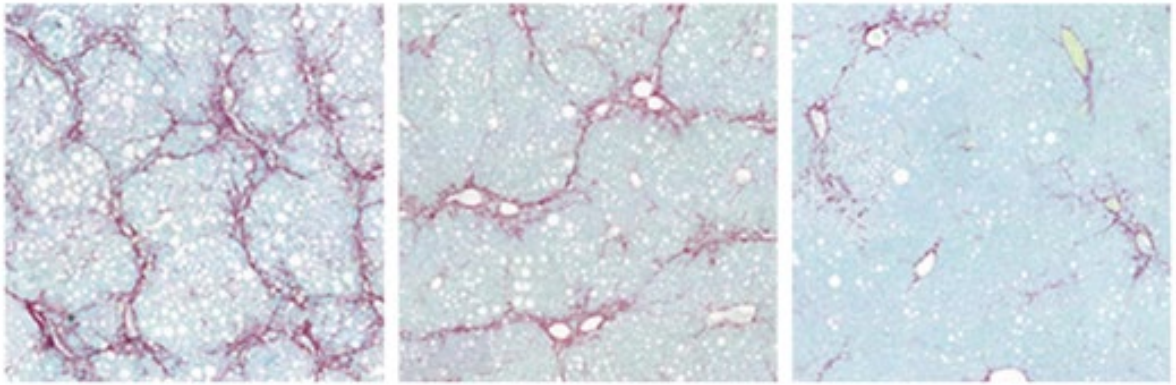
High fat and high sugar diet
CCl4 1x/week

3 months

+/- FASN inhibitor
TVB-3664 QD

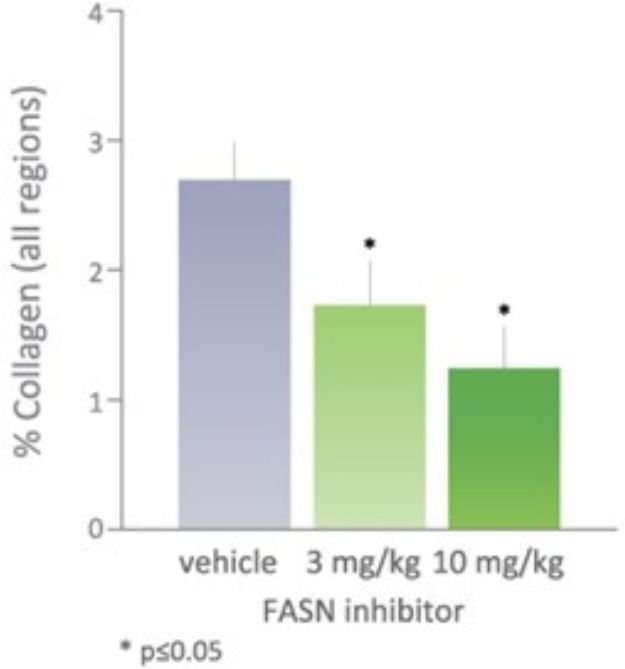
Assess liver fibrosis and tumor formation

Reversed fibrosis



Vehicle (Placebo) | **FASN inhibitor 3mg/kg** | **FASN inhibitor 10mg/kg**

AI-digital pathology (Pharmanest)



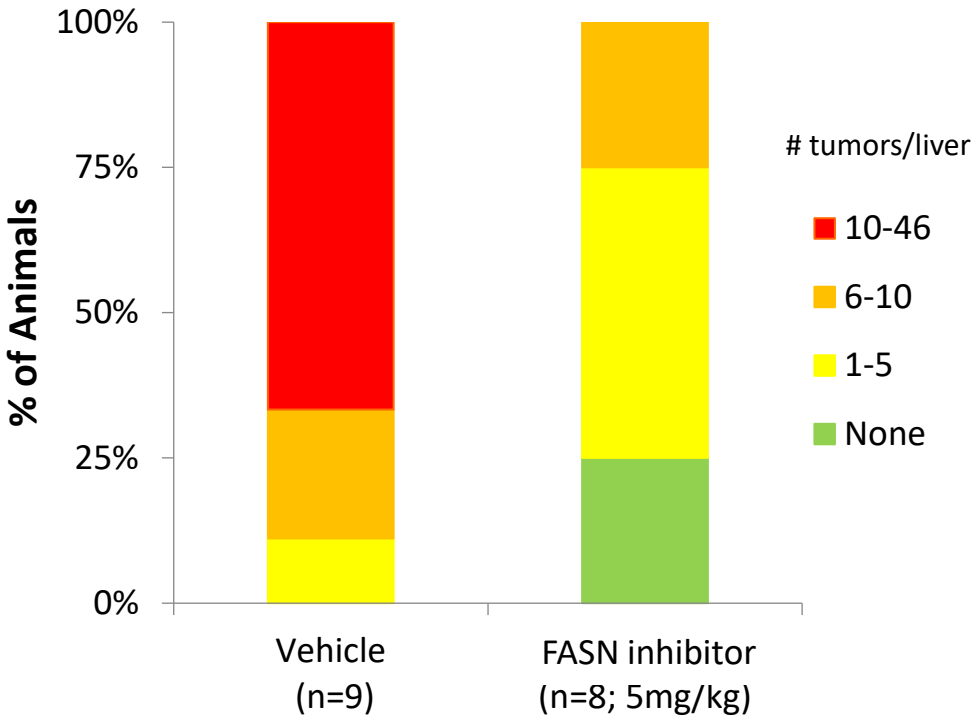
O'Farrell et al.,2022. Scientific Reports. 12:15661

FASN Inhibitor Reduced Formation of Liver Tumors

Collaboration with Dr. Scott Friedman

Blocked tumor formation

- *85% reduction of tumors in treated animals*



O'Farrell et al.,2022. Scientific Reports. 12:15661. FASN inhibitor is TVB-3664.

Decreased fibrogenic gene expression, ALT and TGs

Assay	Parameter	Vehicle	FASN inhibitor
mRNA expression (fold-change)	Col1α1	1 ± 0.1	0.3 ± 0.05*
	αSMA	1 ± 0.09	0.5 ± 0.02*
	βPDGFR	1 ± 0.1	0.3 ± 0.03*
	TGFβR1	1 ± 0.2	0.5 ± 0.04
	TIMP1	1 ± 0.2	0.3 ± 0.02*
	TIMP2	1 ± 0.2	0.3 ± 0.02*
	MMP2	1 ± 0.2	0.2 ± 0.03*
Protein expression (fold-change)	Col1α1	100.0 ± 18.3	50.6 ± 11.4*
	αSMA	100.0 ± 20.8	63.6 ± 9.64
Liver enzyme & lipid panel (fold-change)	AST	100.0 ± 12.9	79.5 ± 16.2
	ALT	100.0 ± 12.01	50.8 ± 5.9*
	Chol	100.0 ± 10.6	89.6 ± 8.6
	TriG	100.0 ± 11.9	68.6 ± 5.1*

Clinical Development of Denifanstat

Phase 1

- Subjects with characteristics of MASLD
- 10-day denifanstat treatment
- Denifanstat decreased hepatic DNL in human, study by Dr. Elizabeth Parks[1]

Phase 2a FASCINATE-1

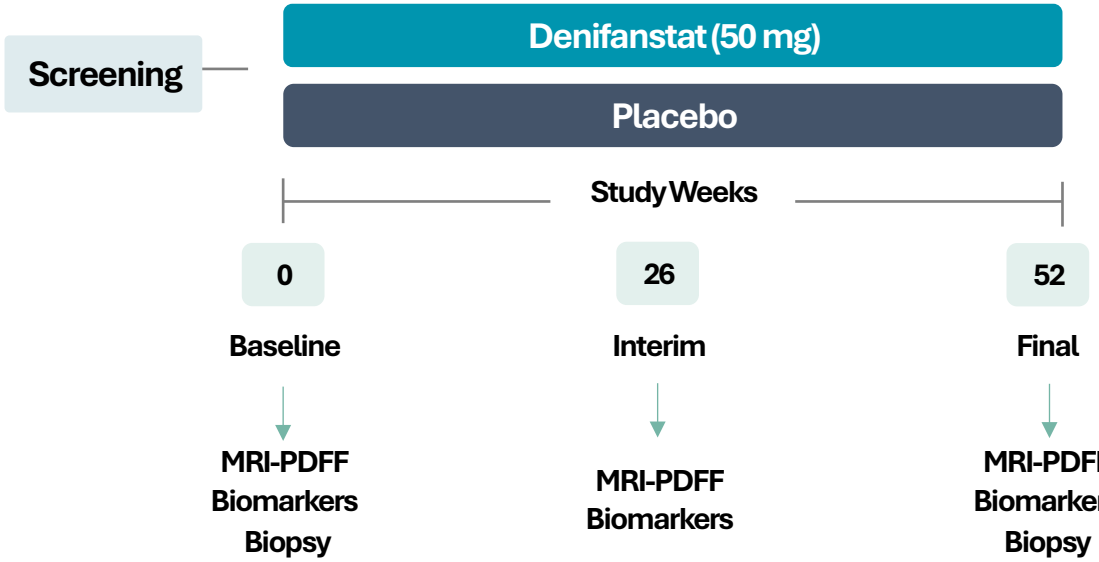
- MASH patients
- 12-week denifanstat treatment
- Denifanstat decreased liver fat by MRI-PDFF, decreased inflammation and fibrosis biomarkers[2]

Phase 2b FASCINATE-2

- MASH patients, F2/F3
- 52-week denifanstat treatment
- Liver biopsy endpoints

[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.

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.

FASCINATE-2: Baseline Characteristics Typical of F2/F3 MASH Population

Parameter	Placebo, n=45	Denifanstat, n=81
Age, years	59.6 (+/- 10.9)	56.1 (+/- 10.8)
Sex, female	27 (60%)	48 (59%)
Race, White	41 (91%)	73 (90%)
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 (alanine aminotransferase) U/L	67 (+/- 33)	57 (+/- 29)
AST (aspartate aminotransferase) U/L	52 (+/- 27)	48 (+/- 29)
Liver Fat Content (MRI-PDFF), %	19.0 (+/- 7.0)	16.6 (+/- 7.1)
Baseline liver biopsy NAS ≥ 5	34 (76%)	63 (78%)
Baseline liver biopsy F2/F3	22 (49%) / 23 (51%)	34 (42%) / 47 (58%)
Statin (at baseline)	21 (47%)	38 (47%)
GLP1-RA (at baseline)	4 (9%)	12 (15%)
LDL, mg/dL	103 (+/- 39)	96 (+/- 34)
Triglycerides, mg/dL	153 (+/- 67)	173 (+/- 79)
ELF (Enhanced Liver Fibrosis) Score	9.8 (+/- 0.8)	9.6 (+/- 0.8)
FAST (Fibroscan AST) Score	0.6 (0.19)	0.6 (0.20)

Modified intent-to-treat population (mITT) includes all patients with paired biopsies. Data are mean (SD) or n (%)

FASCINATE-2: Safety

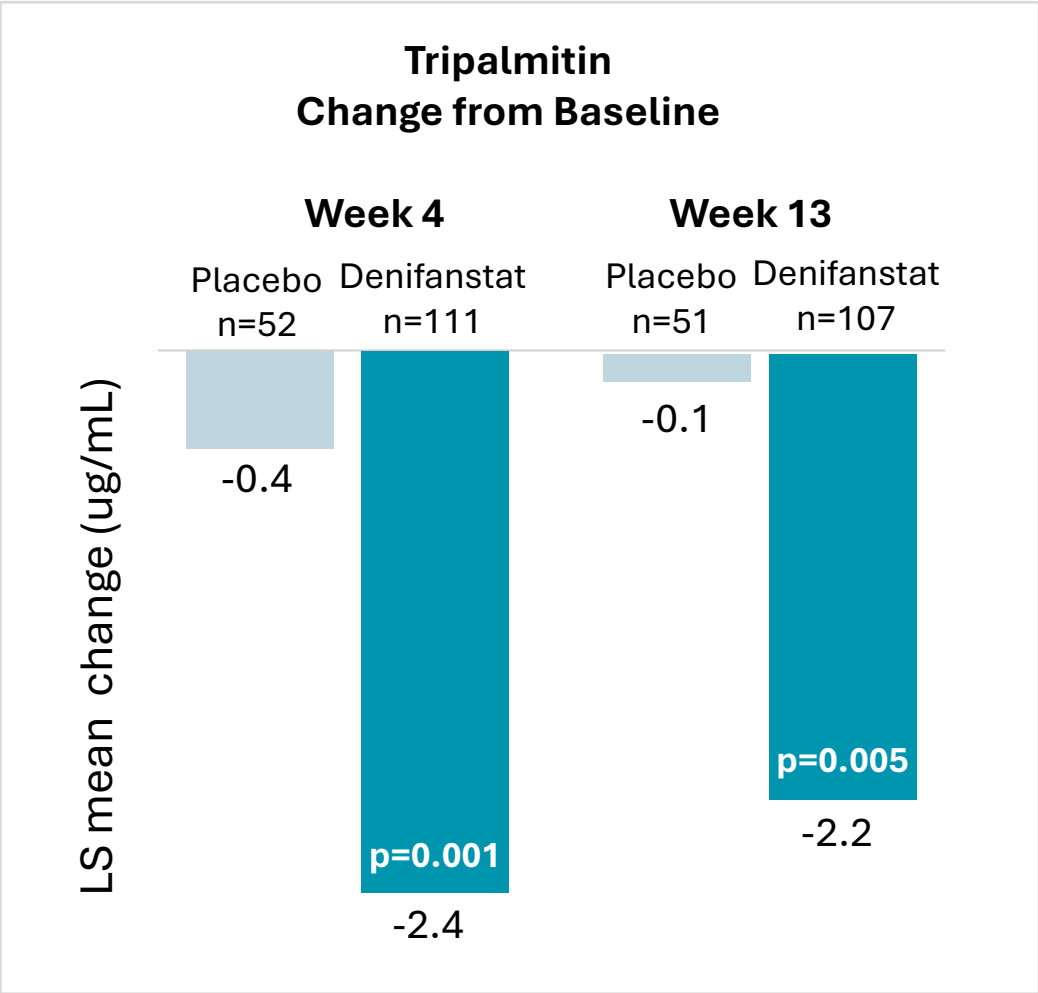
Denifanstat Was Generally Well Tolerated

- No treatment related SAEs, no fatal SAEs
- No DILI signal
- GI was comparable to placebo, and no muscle wasting was detected
- Majority of adverse events were Grade 1 or 2; no Grade ≥3 drug-related AEs
- Adverse events affecting ≥ 10% of patients were COVID-19, dry eye and hair thinning^

Event n (%)	Placebo (n=56)	Denifanstat 50mg (n=112)	Total (n=168)
Any adverse event	46 (82.1)	99 (88.4)	145 (86.3)
Adverse event related to denifanstat or placebo	20 (35.7)	51 (45.5)	71 (42.3)
Serious adverse event	3 (5.4)	13 (11.6)	16 (9·5)
TEAE leading to study drug discontinuation	3 (5.4)	22 (19.6)	25 (14.9)

^AE of hair thinning stabilized with a 2 to 4 week dose pause and then reversed with down titration or study completion

Denifanstat Rapidly and Robustly Reduced De Novo Lipogenesis

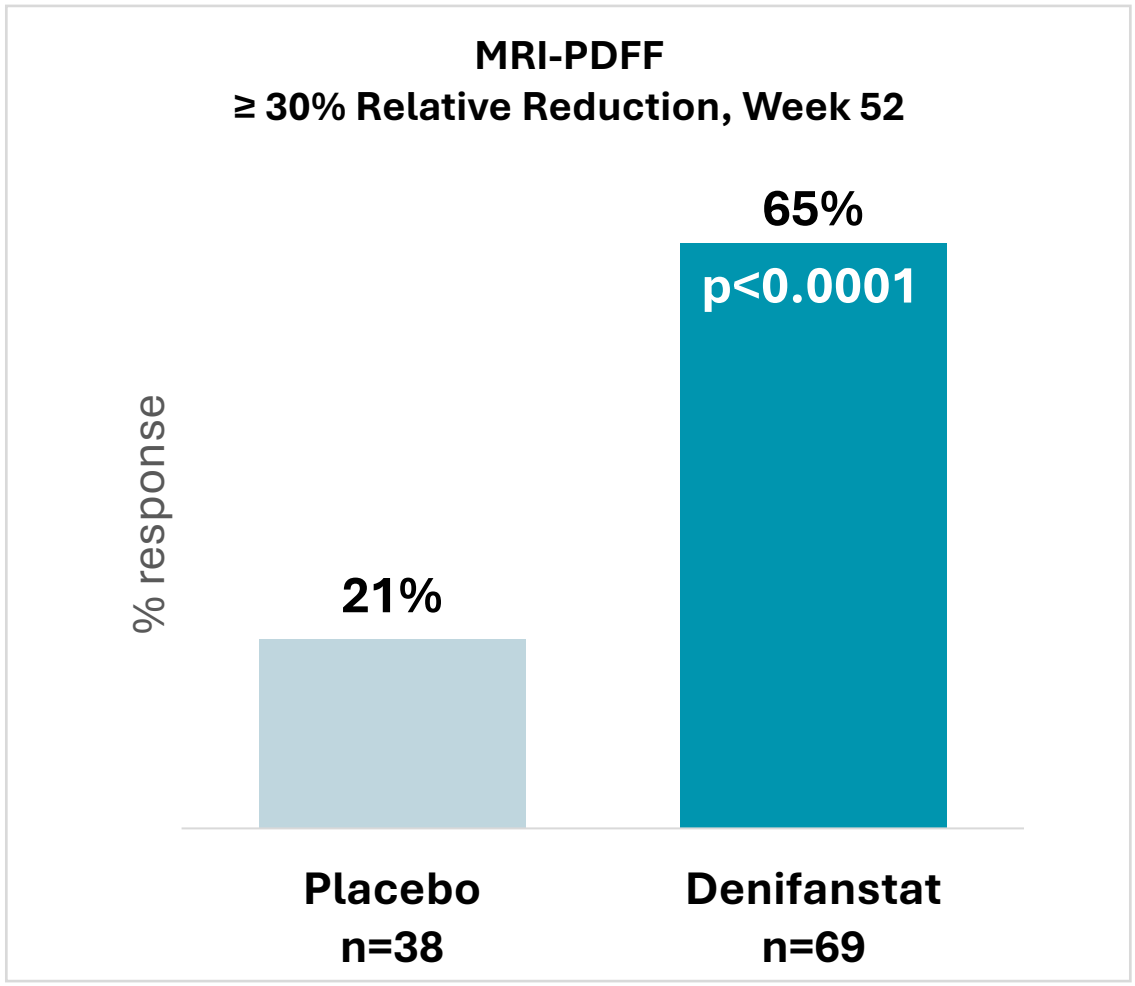


Tripalmitin

- A saturated triglyceride which is a biomarker of DNL inhibition
- Rapidly reduced by denifanstat as early as 4 weeks of treatment
- Consistent with Phase 2a results
- Ongoing: development of tripalmitin and additional markers as potential biomarker(s) of treatment response for denifanstat

Two sided at the 0.05 significance level, ITT population

Denifanstat Significantly Decreased Liver Fat



MRI-PDFF relative decrease

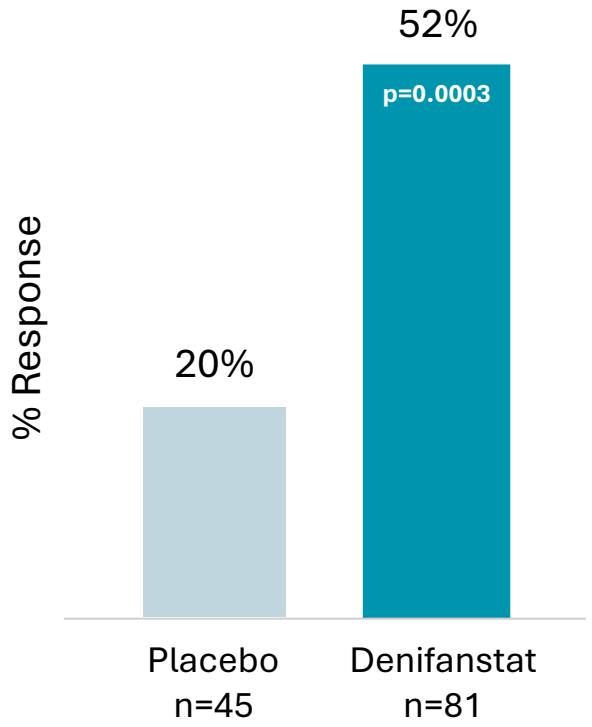
- Week 26: decreased 23% by denifanstat vs 5% increase in placebo (p=0.0036).
- Week 52: decreased 31% by denifanstat vs 8% decrease in placebo (p=0.0008).

≥30% reduction: Cochran-Mantel-Haenszel Test. Relative reduction: Mixed-effects Model for Repeated Measures. mITT population. Two sided at the 0.05 significance level.

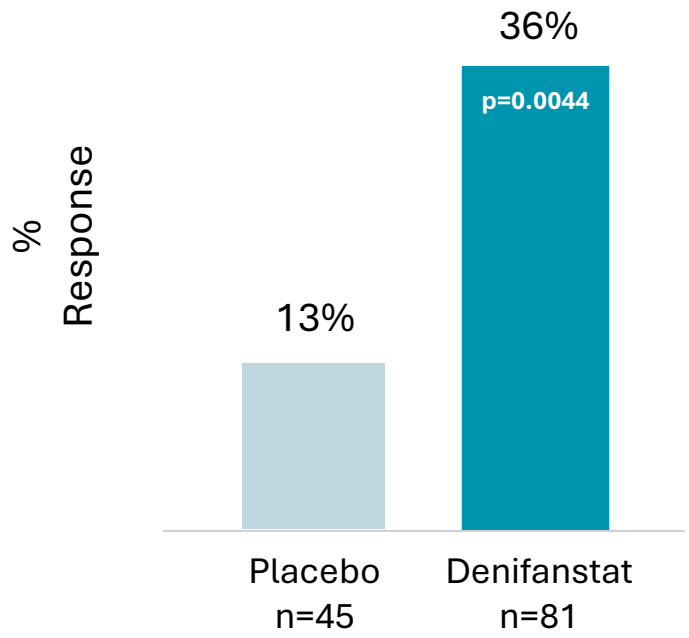
Primary Endpoints: Liver Biopsy

Denifanstat Achieved Statistical Significance at 52 Weeks

NAS ≥ 2 points improvement* w/o worsening of fibrosis



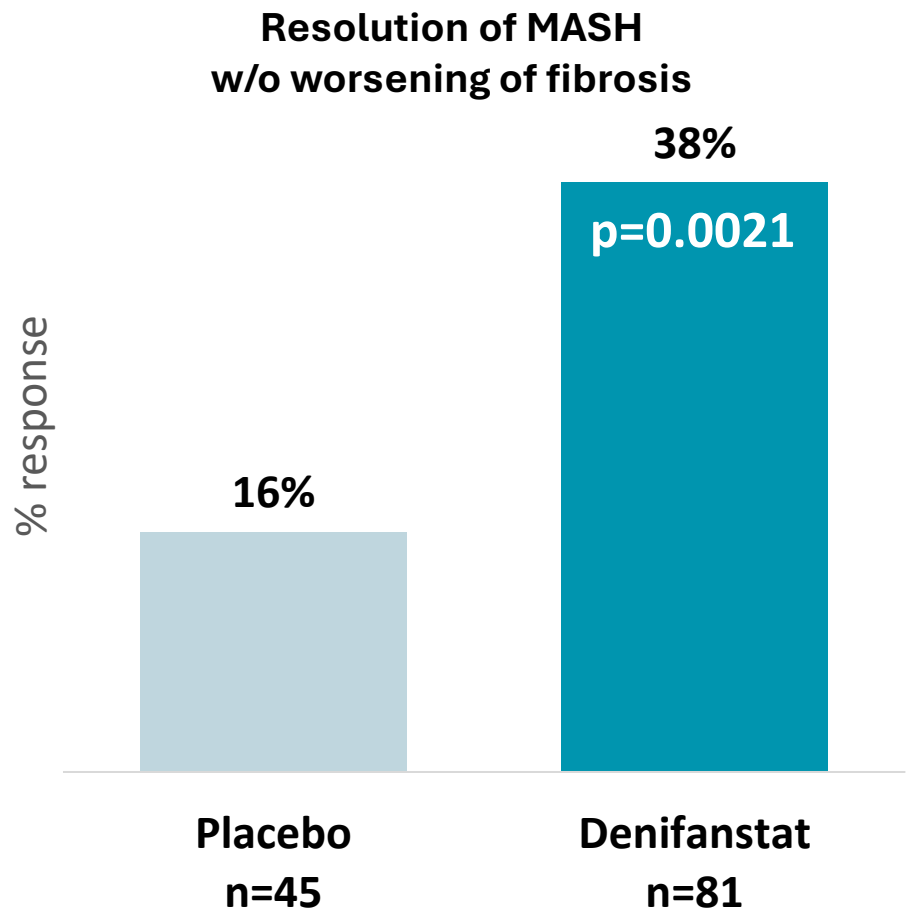
MASH resolution + NAS ≥ 2 improvement w/o worsening of fibrosis



Cochran-Mantel-Haenszel Test – two sided at the 0.05 significance level. * ≥1-point improvement in ballooning or inflammation. mITT population. Statistical significance also reached for ITT population for both endpoints.

Secondary Endpoint: MASH Resolution

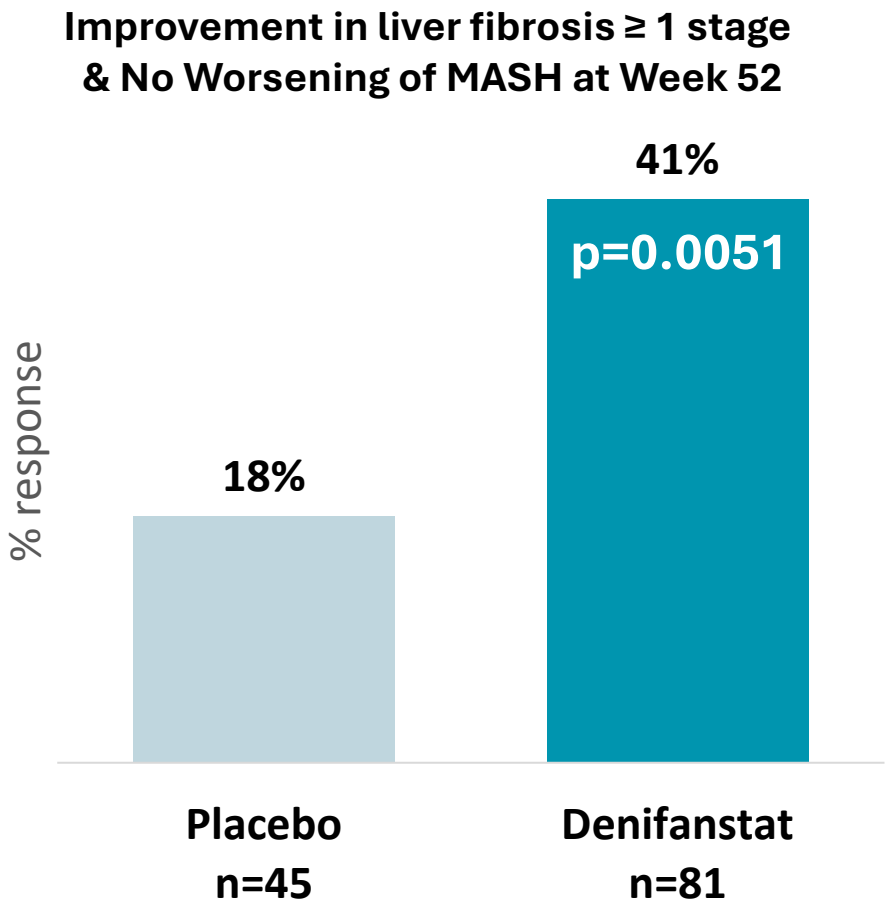
Denifanstat Achieved Statistical Significance (Endpoint per FDA Draft Guidance 2020)



Cochran-Mantel-Haenszel Test – One sided at the 0.05 significance level. mITT population. . Statistical significance also reached for ITT population.

Secondary Endpoint: Liver Fibrosis

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

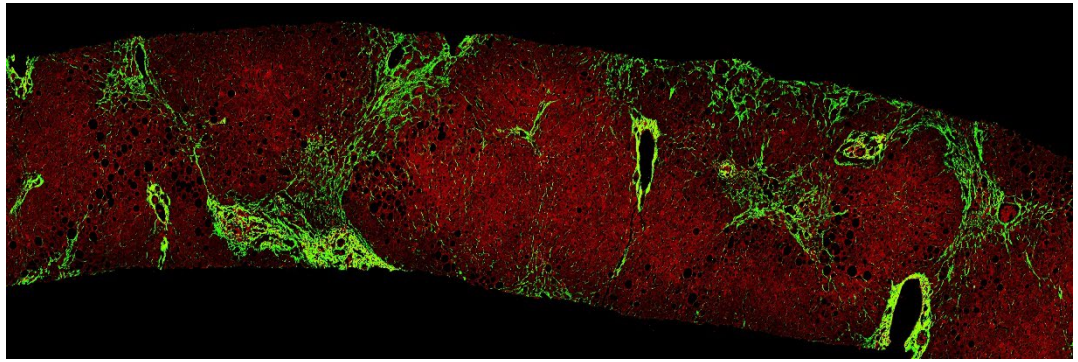


Cochran-Mantel-Haenszel Test – One sided at the 0.05 significance level. mITT population. . Statistical significance also reached for ITT population.

Additional Fibrosis Analysis Using AI-based Digital Pathology

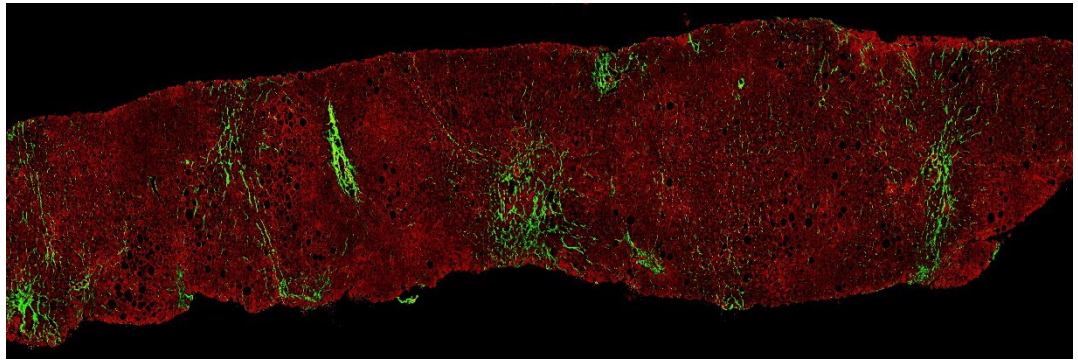
Supporting Evidence that Denifanstat Significantly Reduced Fibrosis

Pre-Treatment Pt A
NASH-CRN Fibrosis stage F3

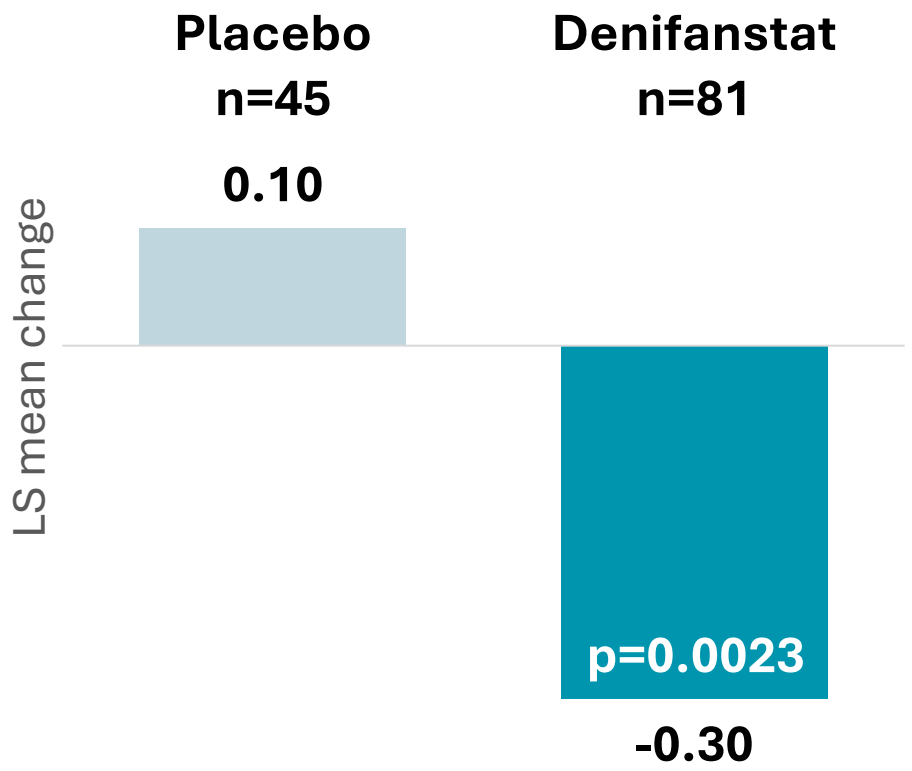


Denifanstat

Post-Treatment Pt A
NASH-CRN Fibrosis stage F1



qFibrosis Continuous Value
Change from Baseline



*One sided at the 0.05 significance level

Secondary Endpoints: Liver Fibrosis

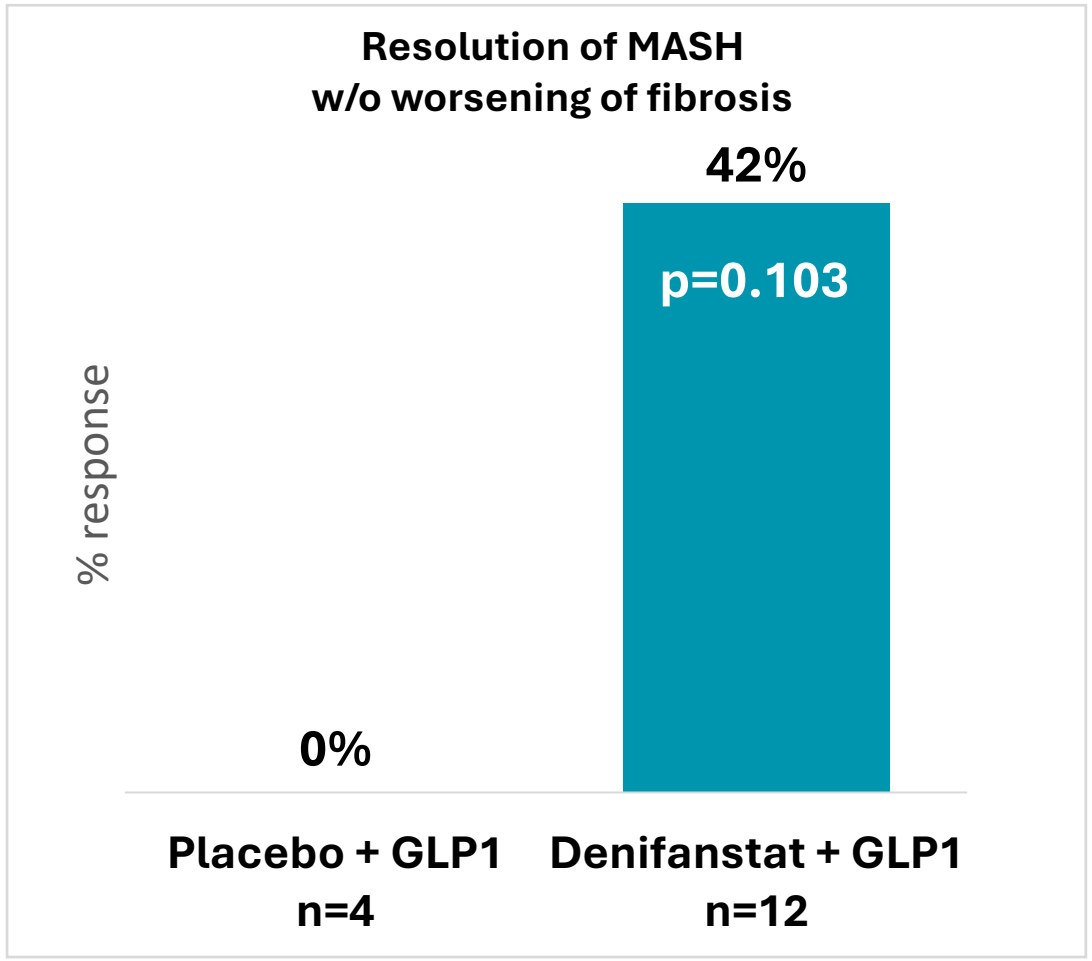
Denifanstat Achieved Profound Improvement of Fibrosis

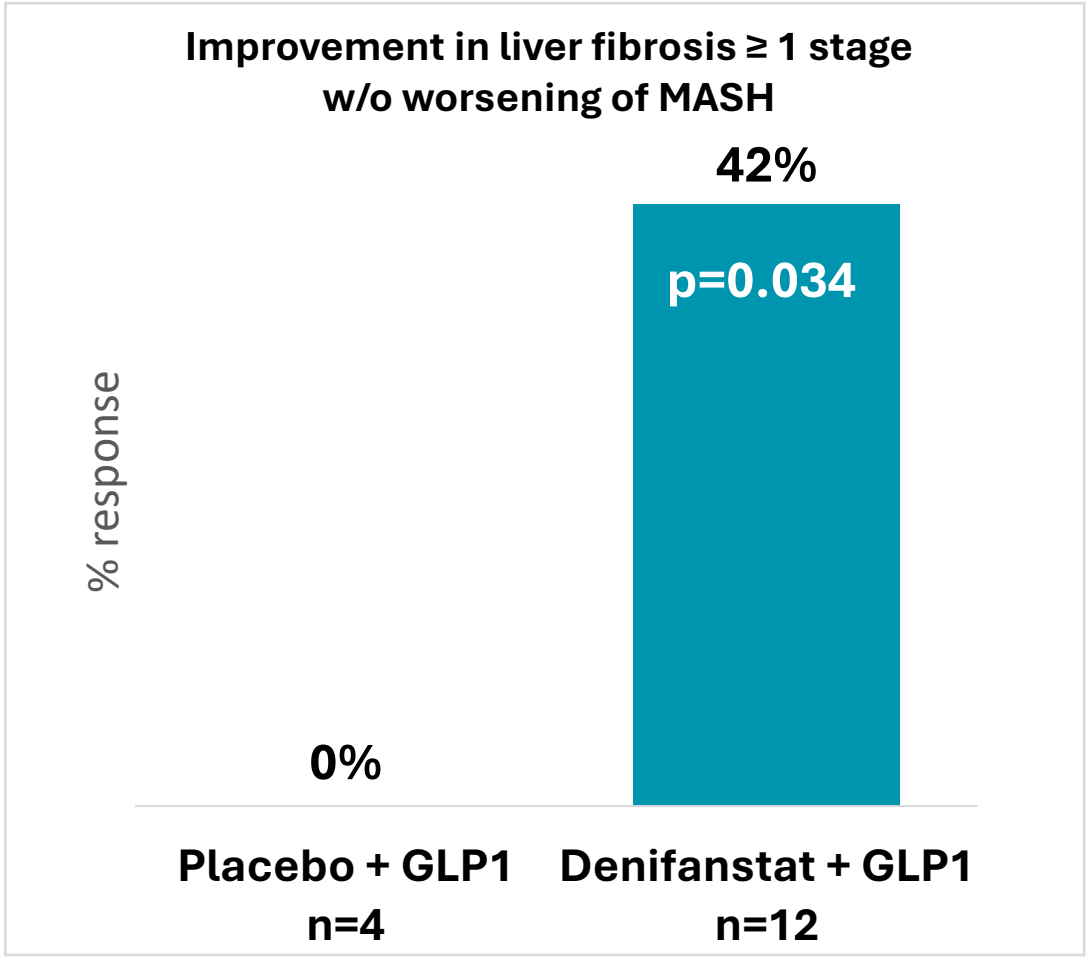
Fibrosis Endpoints	Subgroup	Placebo	Denifanstat	p-value
≥1 stage improvement in fibrosis w/o worsening of MASH	All pts	18%	41%	0.0051*
	F3 only	13%	49%	0.0032**
≥2 stage improvement in fibrosis w/o worsening of MASH	All pts	2%	20%	0.0065**
	F3 only	4%	34%	0.0065**
Progression to cirrhosis (F4)	All pts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

One sided at the 0.05 significance level, **Two sided at the 0.05 significance level. *mITT population shown. ITT response rate for F2/F3 of 14% placebo and 30% denifanstat (p=0.0199)

Patient Subset on Stable GLP1-RA at Baseline

Denifanstat Improved MASH Resolution and Fibrosis



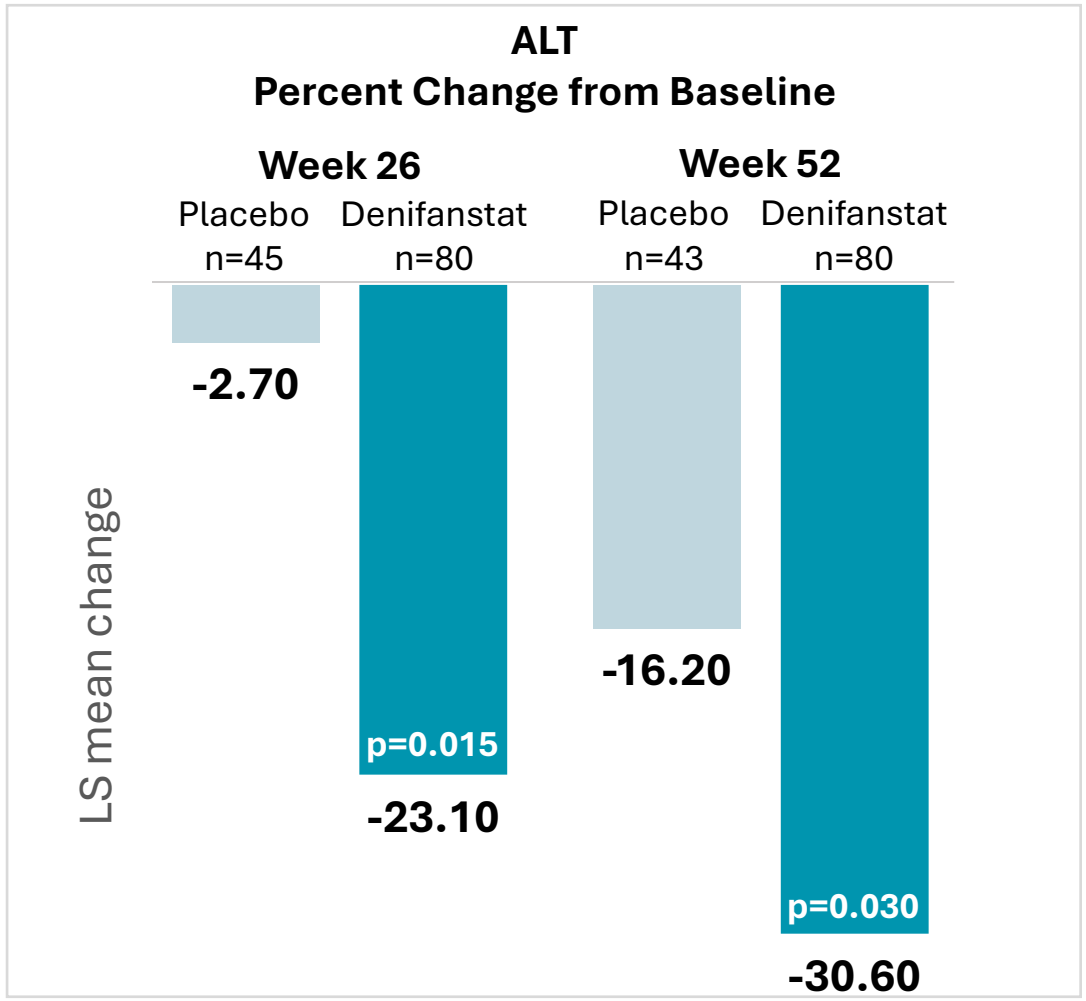


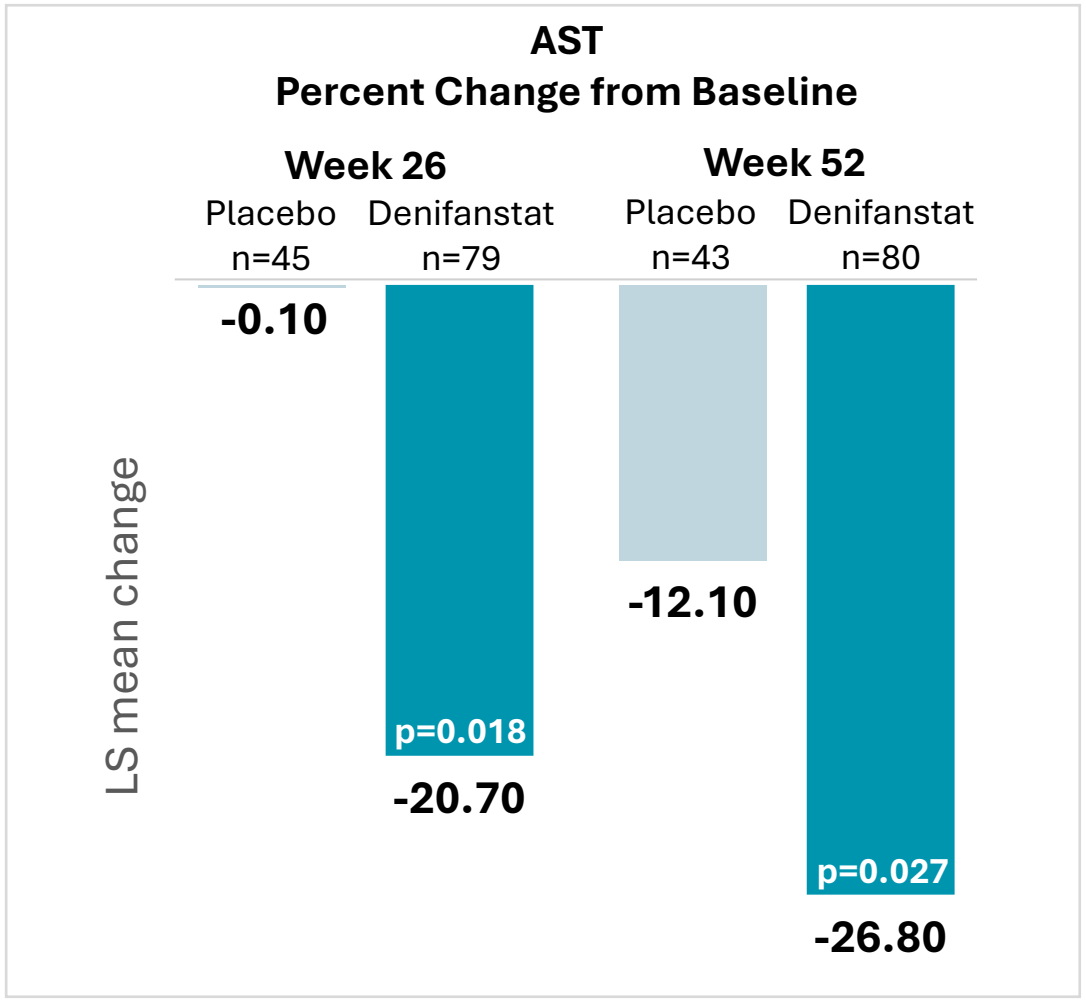
Cochran-Mantel-Haenszel Test – One sided at the 0.05 significance level. mITT population GLP patients were on stable dose for 6 months prior to first biopsy

AI digital pathology results also supports fibrosis improvement in patients receiving GLP1 and denifanstat

Secondary Endpoints: Liver Enzymes

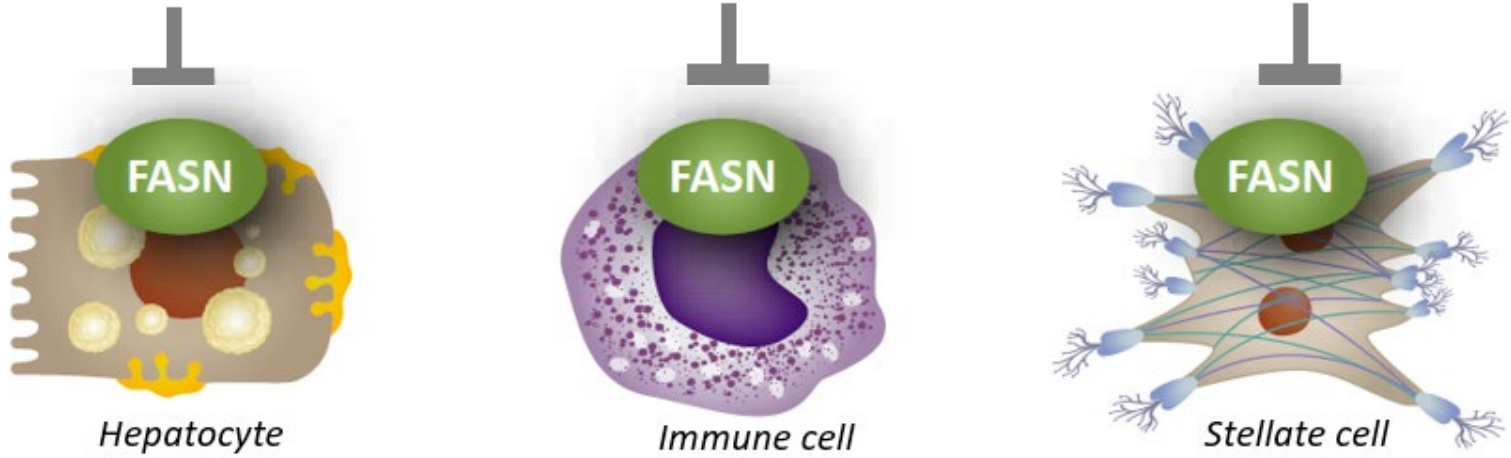
Denifanstat Decreased ALT and AST Levels





Mixed-effects Model for Repeated Measures – Two sided at the 0.05 significance level. mITT population

Phase 2 Results Consistent with Proven Mechanism of Action



Non-invasive biomarkers

- Hepatic DNL
- Tripalmitin
- Liver fat MRI-PDFF

- ALT, AST
- CK-18 M30, M65

- ELF
- FAST

Other benefits

- LDL ↓
- PUFA ↑

Histology

- Steatosis
- Ballooning

- Inflammation

- Fibrosis

MASH resolution

Fibrosis Improvement

Lipotoxicity and metabolic stress, progressive cycle of inflammation and fibrosis

Summary

- FASN mechanism is unique among MASH drugs in development
- Directly targets fibrosis as well as liver fat synthesis and inflammation
- Mechanism demonstrated in primary human cells models, and animal models
- Mechanism translated to the clinic
- Denifanstat met statistical significance for primary and secondary histology endpoints in Ph2b FASCINATE-2
  - Fibrosis improvement without worsening of MASH
  - MASH resolution without worsening of fibrosis
  - Fibrosis improvement in more severe patients (stage F3)
  - Enhanced treatment effect in patients on stable GLP therapy
  - Generally well tolerated

Acknowledgements

Sagimet Team

- Eduardo Martins, Katharine Grimmer, Wen-Wei Tsai, George Kemble, Julie Dubourg, Shipra Gupta

Sagimet Advisors

Investigators, study teams and patients involved in FASCINATE studies