SAGIMET BIOSCIENCES

Highlighting Mechanism of Action of FASN Inhibitor Denifanstat in MASH

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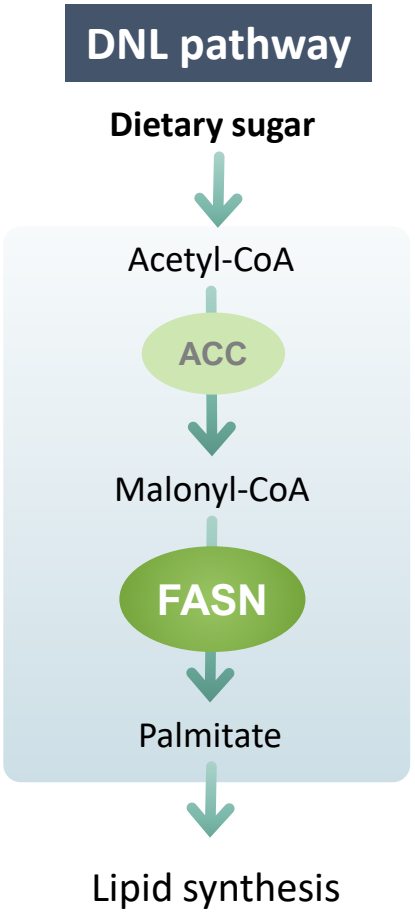
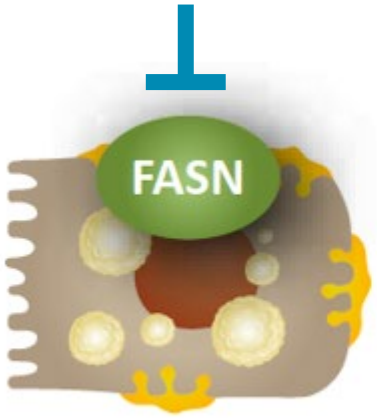
Outline

- Denifanstat mechanism of action
- Clinical results from FASCINATE-2 Ph2b study in MASH
- Combination with semaglutide
- Combination with resmetirom

FASN Plays Key Roles in Three Major Cell Types in MASH



Denifanstat



Hepatocyte

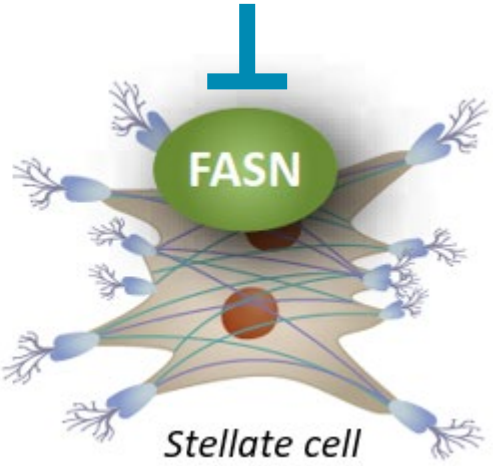
<u>Increases</u>
Fatty acids
Triglycerides
Lipotoxins

Denifanstat

Immune cell

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

Denifanstat



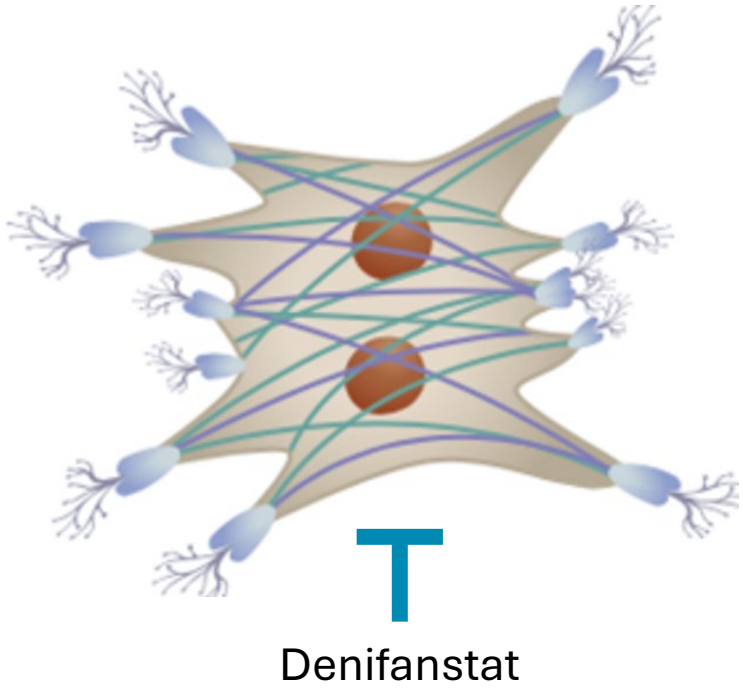
Stellate cell

<u>Increases</u>
Fibrogenesis
Cell activation

FASN Inhibition Directly Blocks Human Liver Stellate Cell Function

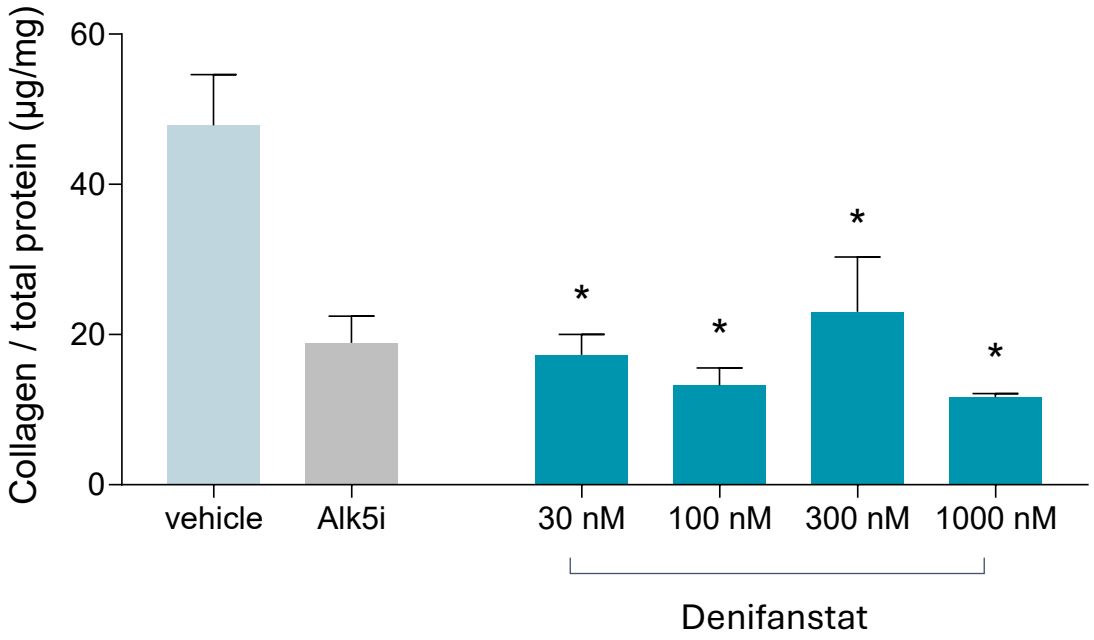
Stellate cells require DNL for fibrogenesis

Denifanstat blocks stellate cell activation



Denifanstat directly inhibits fibrogenic activity[1]

Primary human stellate cell assay



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

*p<0.05. DNL: de novo lipogenesis

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

FASN Inhibitor Reversed Hepatic Fibrosis

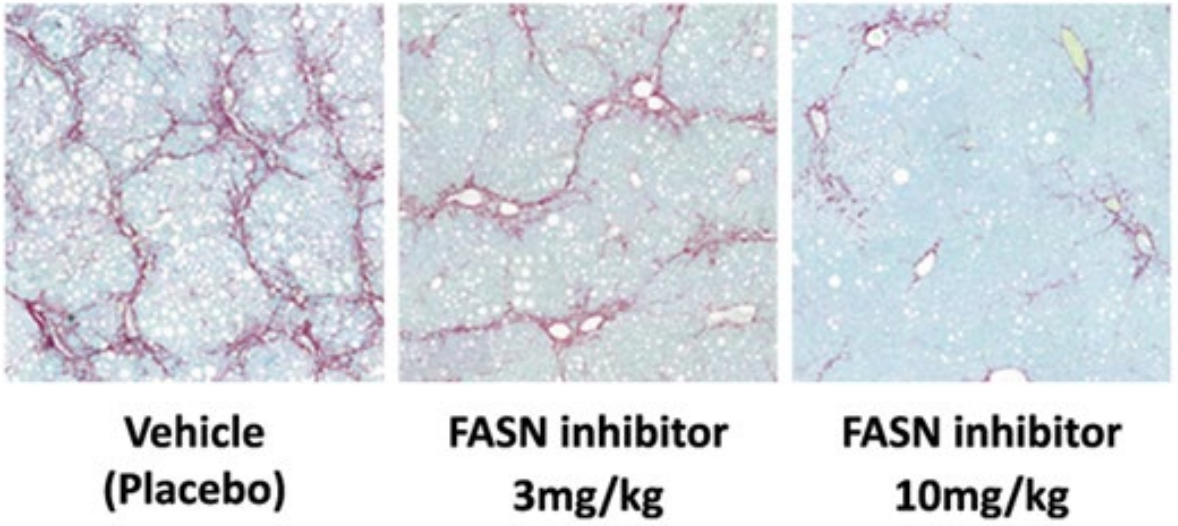
Collaboration with Dr. Scott Friedman

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

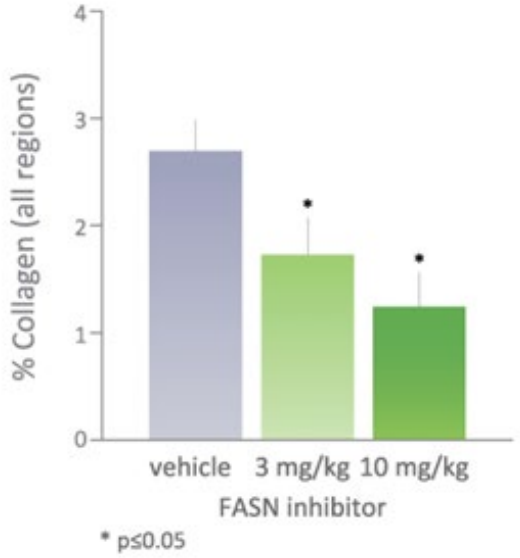
High fat and high sugar diet
CCl4 1x/week
3 months
+/- FASN inhibitor

Assess liver fibrosis and tumor formation

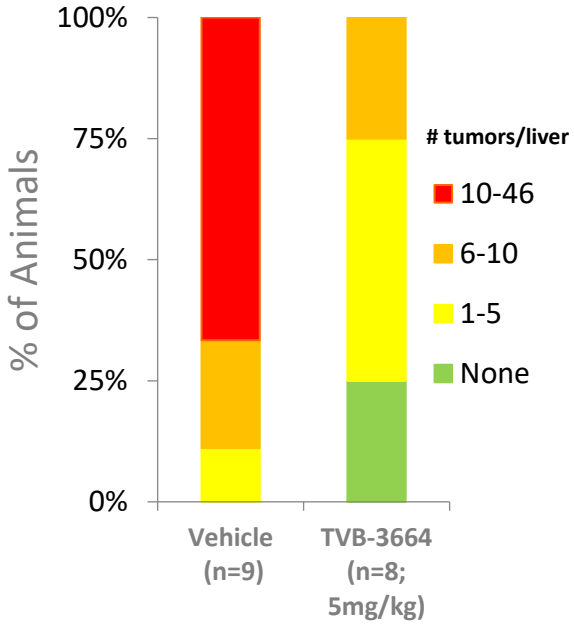
Reversed fibrosis



Quantitated by AI-digital pathology



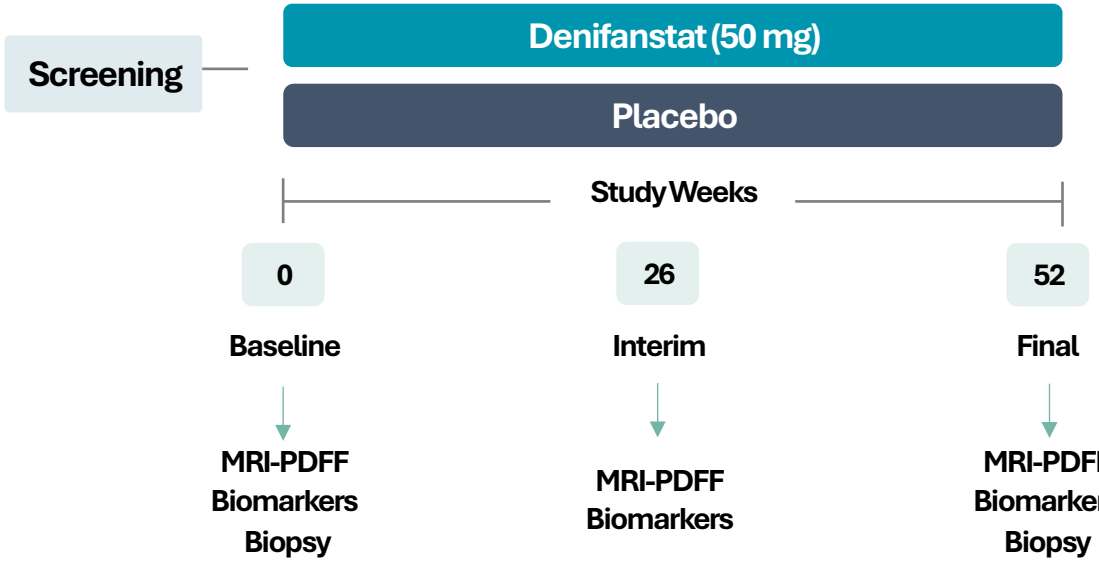
Decreased tumor formation by 85%



O'Farrell M, et al. Sci Rep. 2022;12(1):15661

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 ≥30% reduction from baseline (responders)

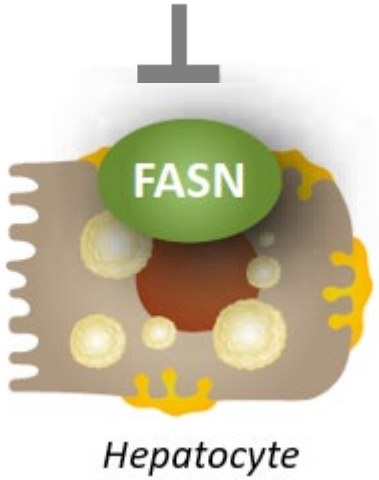
AI: Artificial Intelligence, MRI-PDFF; magnetic resonance imaging derived proton density fat fraction, NAS; NAFLD Activity Score.

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

Denifanstat Rapidly Reduced De Novo Lipogenesis and Decreased Liver Fat

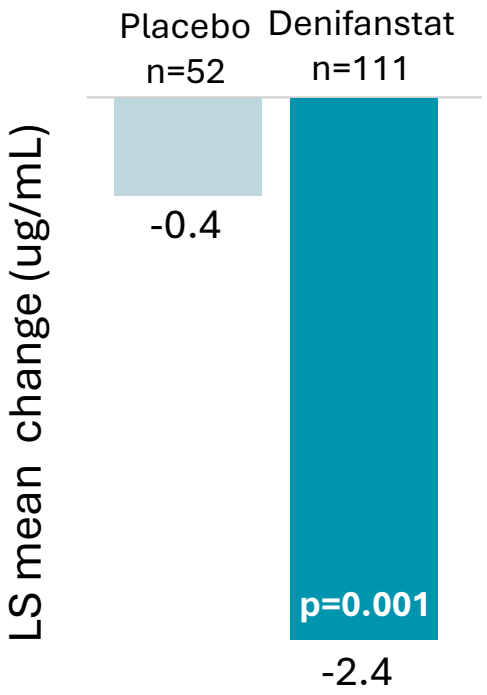
FASCINATE-2 Phase 2b

Denifanstat



Fatty Acids
Triglycerides
Lipotoxins

Tripalmitin
Change from Baseline



Liver Fat
Change from Baseline

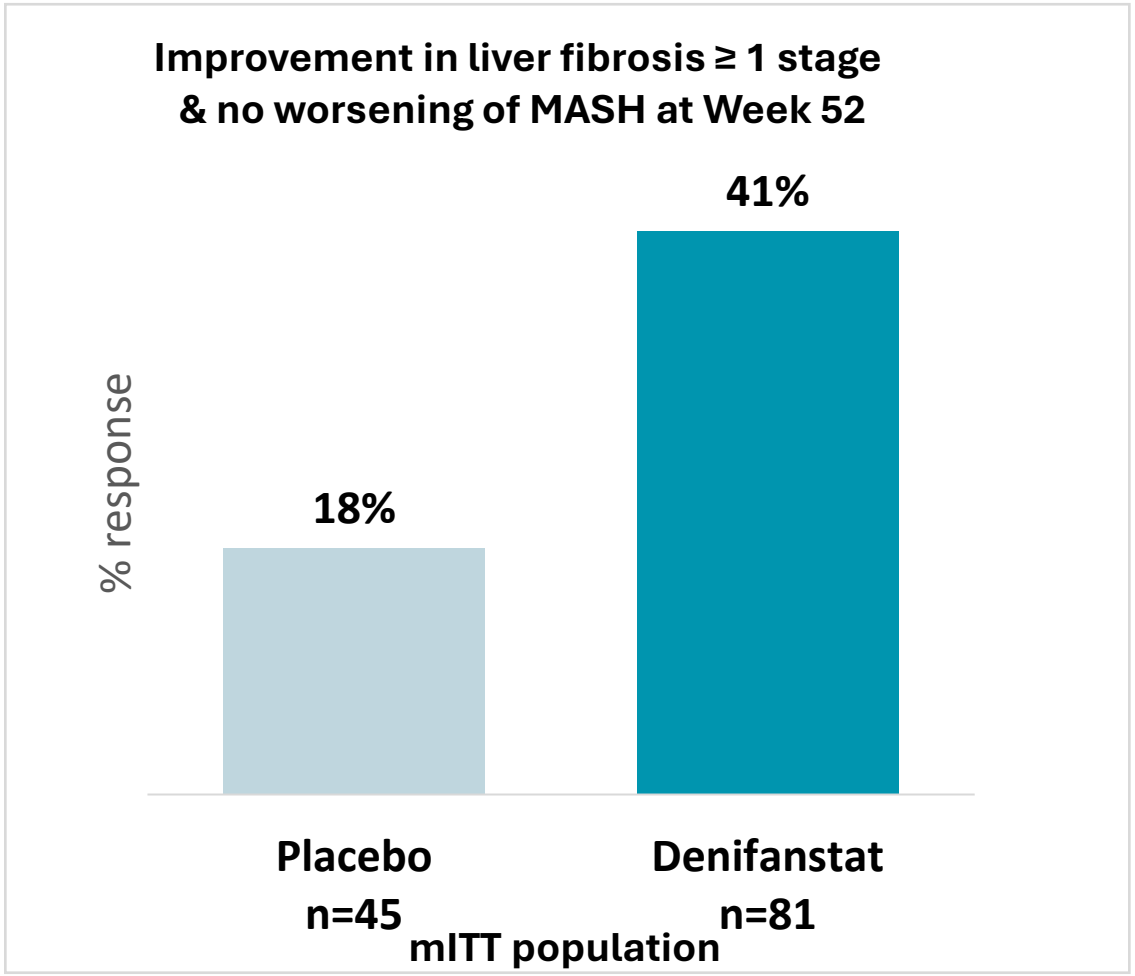
Liver fat by MRI-PDFF	Placebo n=38	Denifanstat n=69	
Relative decrease Week 26	+5%	-23%	p=0.0036
Relative decrease Week 52	-8%	-31%	p=0.0008
≥ 30% relative decrease Week 52	21%	65%	p<0.0001

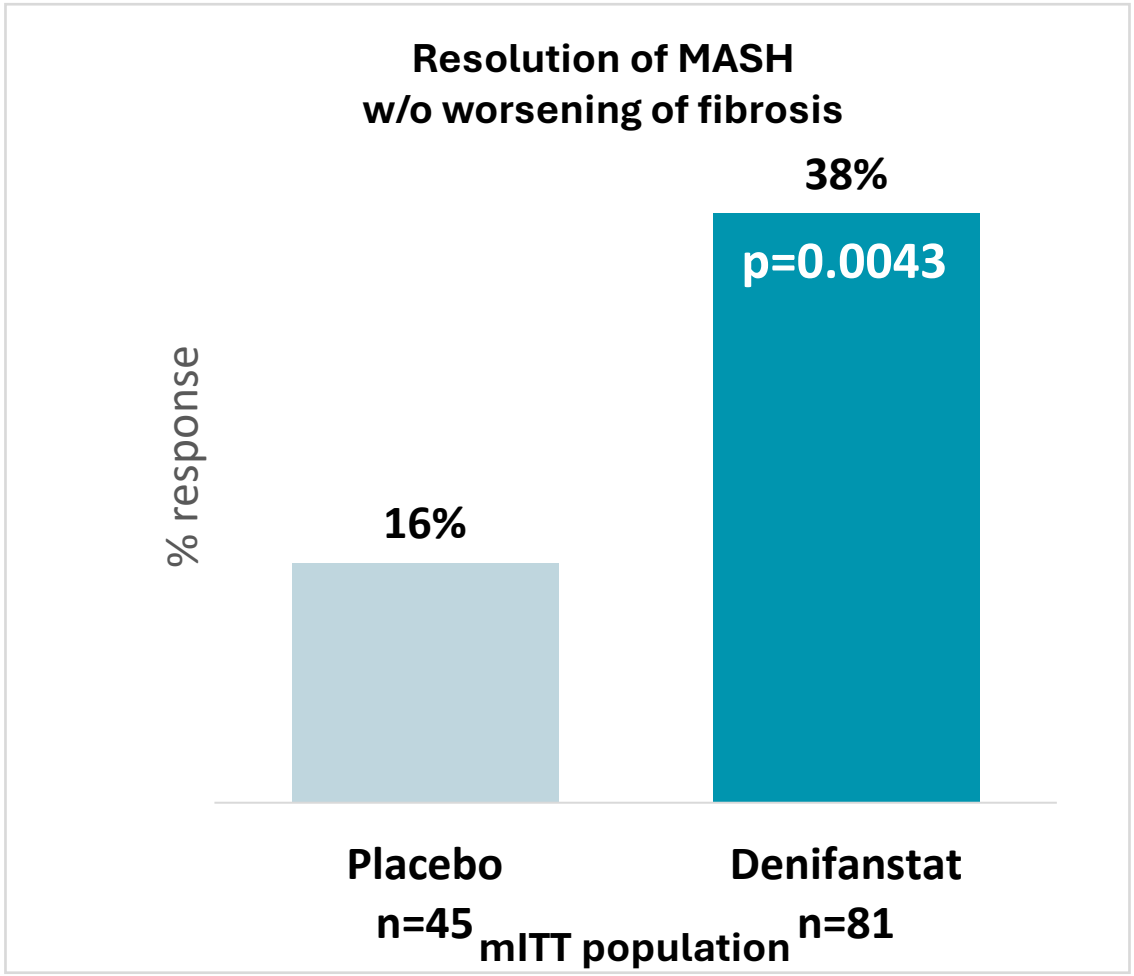
Two sided at the 0.05 significance level, ITT population

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)

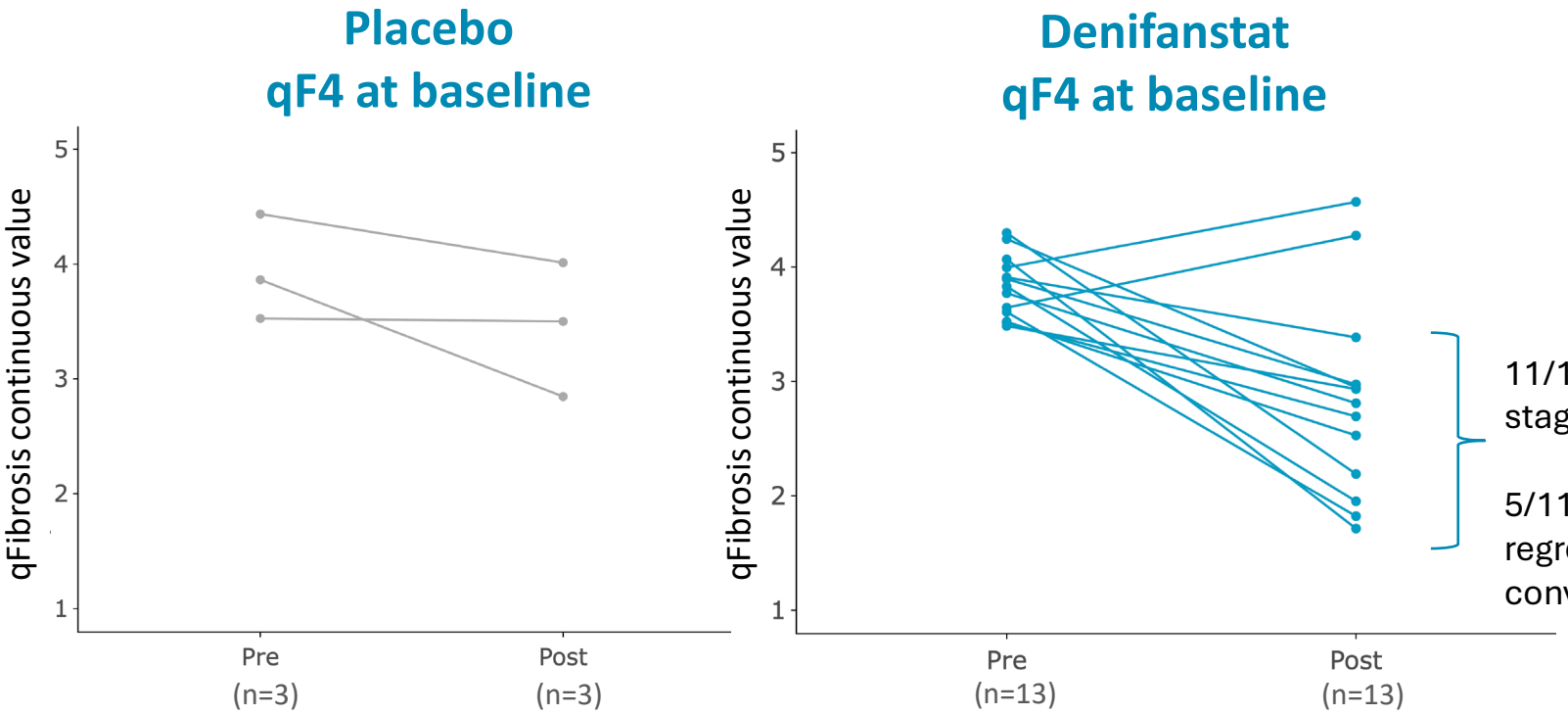




Cochran-Mantel-Haenszel Test – Two sided at the 0.05 significance level

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

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



11/13 (85%) qF4 patients decreased by 1 or 2 qfibrosis stages measured by AI-based pathology

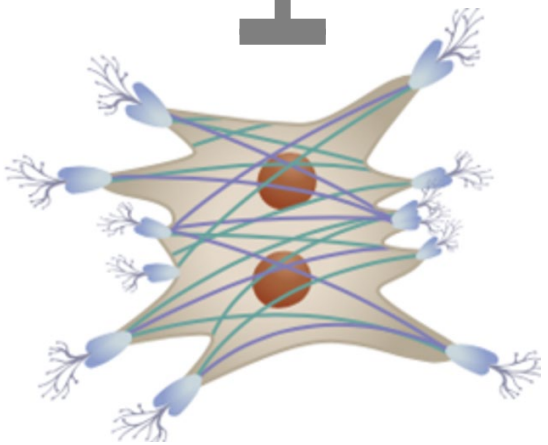
5/11 of qF4 patients showed ≥1 stage fibrosis regression, with 4 of these being 2-stage, measured by conventional pathology

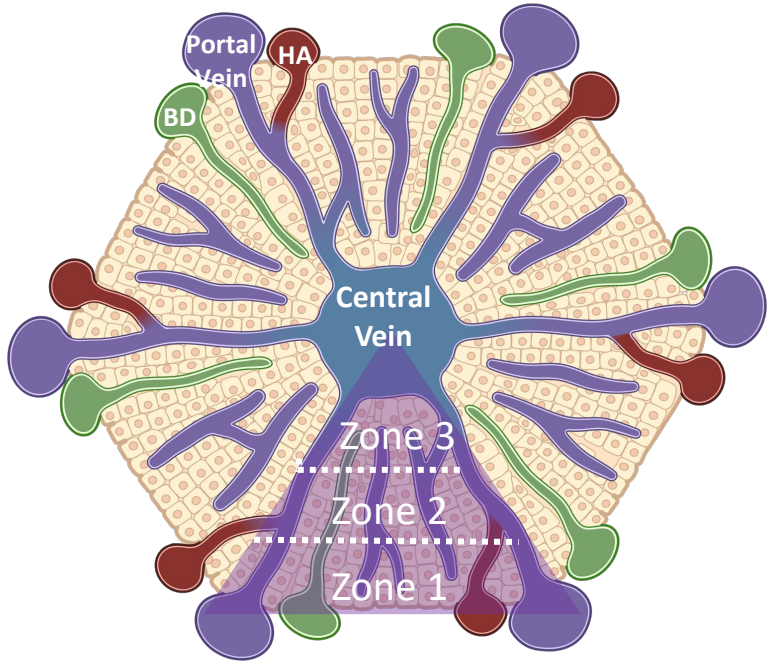
- AI may detect fibrosis regression at an earlier point in time, compared to conventional pathology
- qF4 population (defined on AI platform by HistoIndex) are likely the most advanced subgroup of F3 patients in Phase 2b trial

Sagimet Biosciences data on file. FASCINATE-2 HistoIndex.

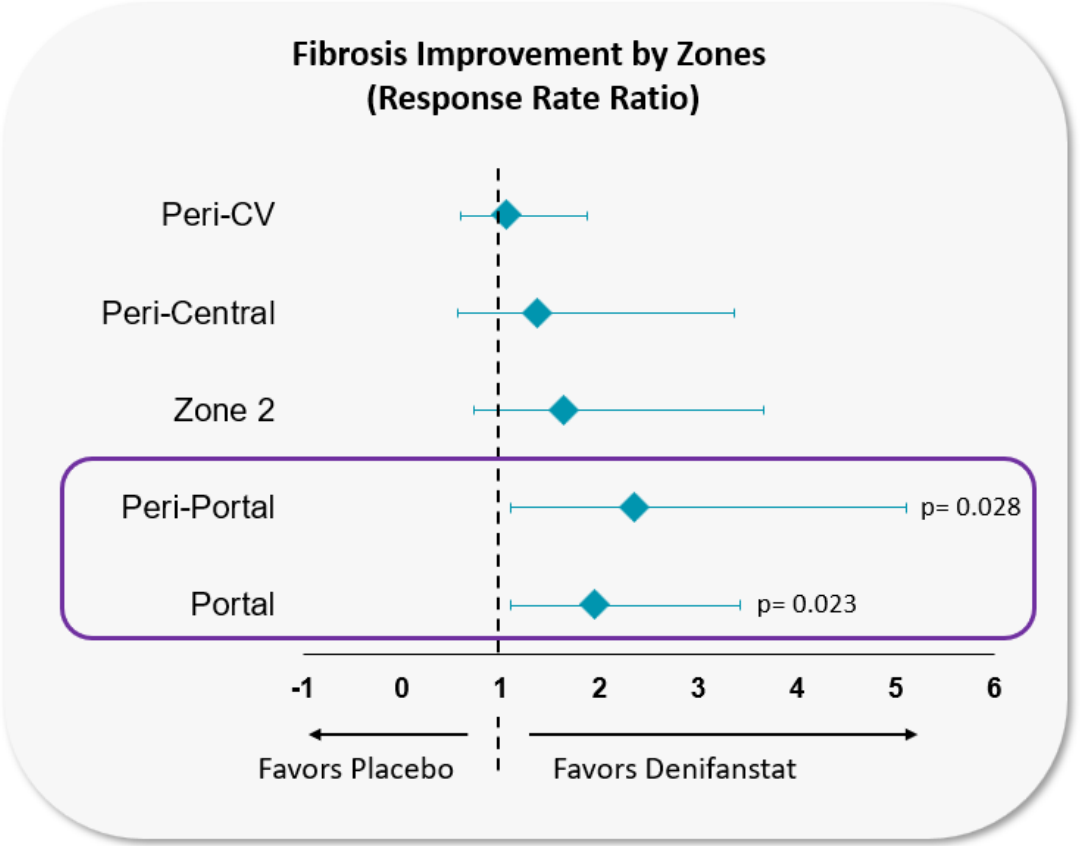
qFibrosis Zonal Analysis Demonstrated that Denifanstat Improved Parameters Linked to Liver Outcomes

Denifanstat





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]



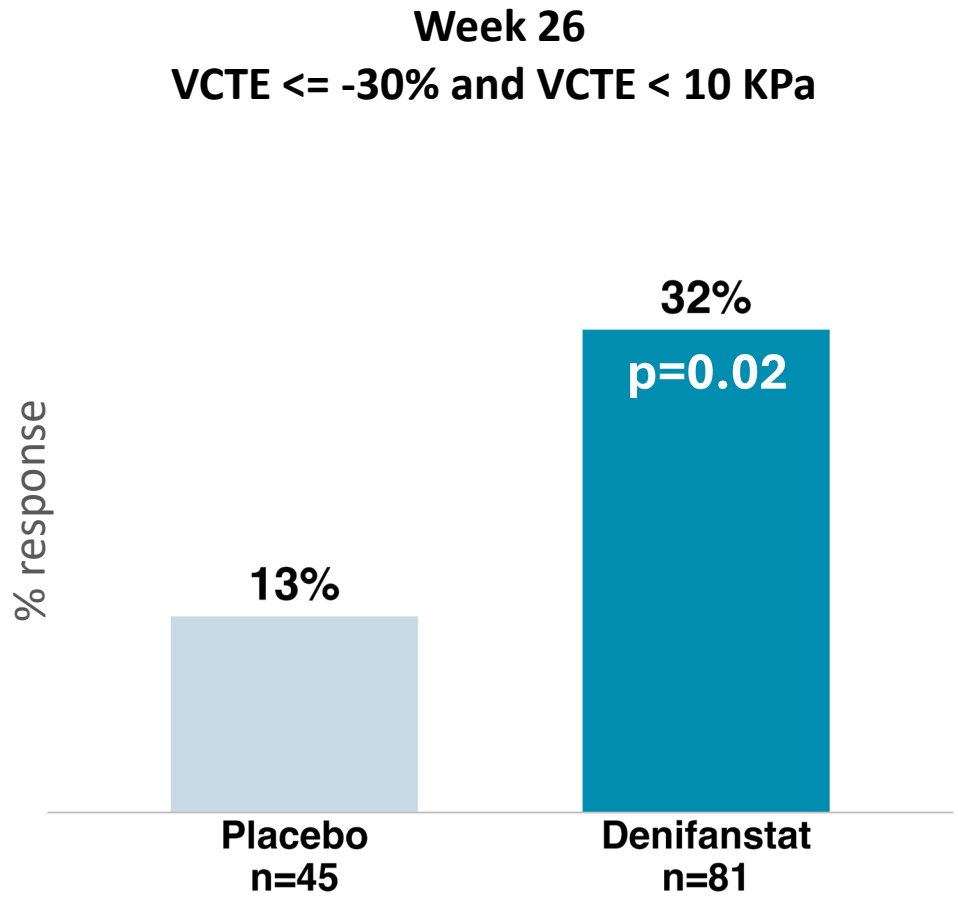
1. Kendall TJ, et al. *Liver Int.* 2024;44(10):2511-2516

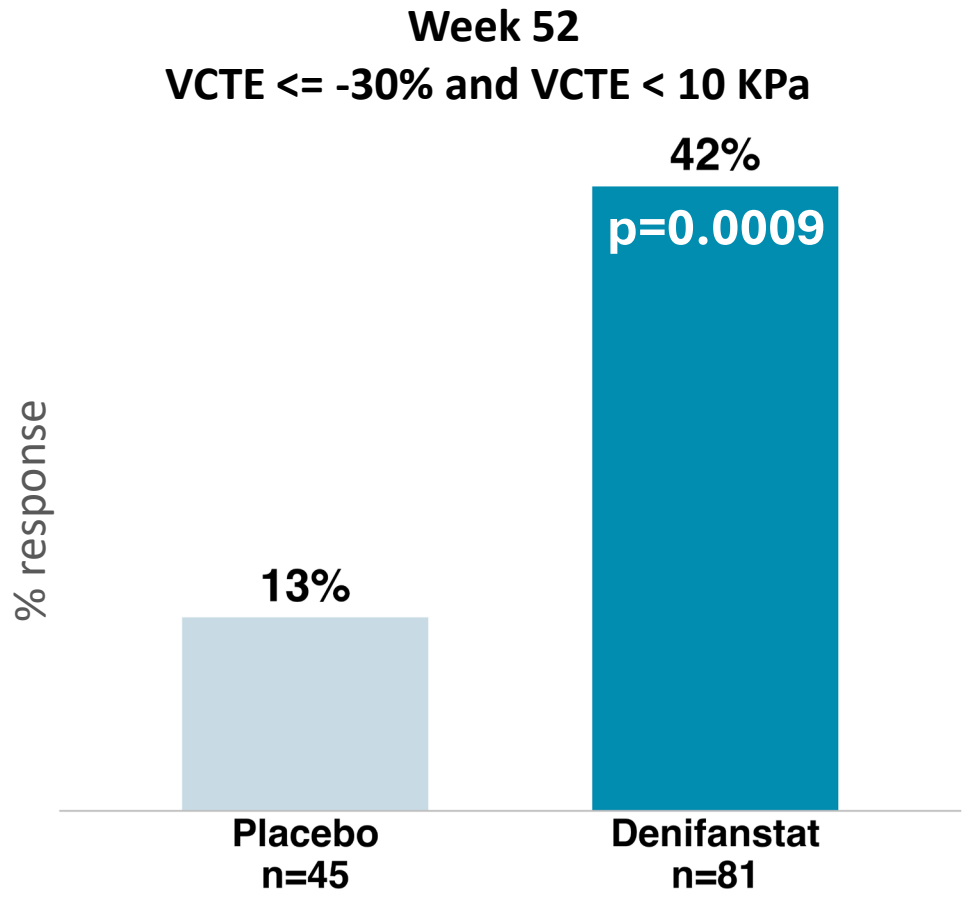
Response at the individual zonal parameter level was defined as ”at least” 30% relative decrease from baseline.

2. Rinella M, et al. Presented at: AASLD 2024; November 15-19, 2024; San Diego, CA. Abstract 0170.

Denifanstat Achieved Statistically Significant VCTE Improvement at Weeks 26 and 52

FASCINATE-2 Phase 2b





Sagimet Biosciences data on file. FASCINATE-2 posthoc analysis. mITT population. Chi-square test. VCTE: Vibration-controlled transient elastography. VCTE <=30% means magnitude of decline from baseline

Combinations

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Combination Potential for Denifanstat in MASH

Preclinical Program Evaluated Complementary Mechanisms

- Objective - increase breadth or depth of MASH resolution, fibrosis improvement and/or metabolic benefit
- Mechanism-based combinations

FASNi + Semaglutide

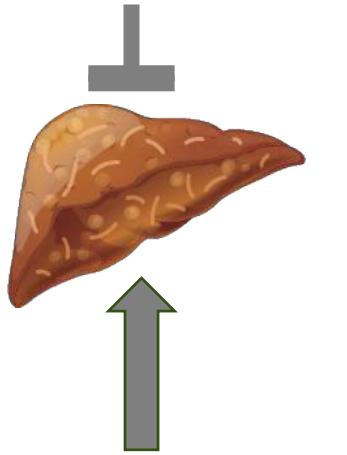
- Mouse MASH diet-induced obesity (DIO) model (Gubra)
- Patients on background GLP1 treatment from Phase 2b FASCINATE-2 clinical trial

FASNi + Resmetirom

- Mouse MASH DIO model (Gubra)
- Mouse Ldlr-/- DIO and dyslipidemia model

FASNi with GLP1 Agonist: Complementary Mechanisms of Action

Denifanstat



Body weight loss

Semaglutide

FASN Inhibitor Direct – hepatic		GLP1 Agonist Indirect – extrahepatic		Combination Hypothesis
Decreases de novo lipogenesis	+	Via periphery (body weight loss)	=>	Enhance liver steatosis and NASH resolution response
Decreases fibrogenesis in stellate cells, liver fat and lipotoxicity	+	Via periphery (body weight loss)	=>	Enhance liver fibrosis response

Combination of FASNi and Semaglutide in Mouse MASH DIO Model (Gubra)

C57B6 WT,

Pre-dose biopsy
Start treatment

Diet lead-in
FFD 38 weeks

Drug treatment
12 weeks

40% fat, 22% fructose, 2% cholesterol

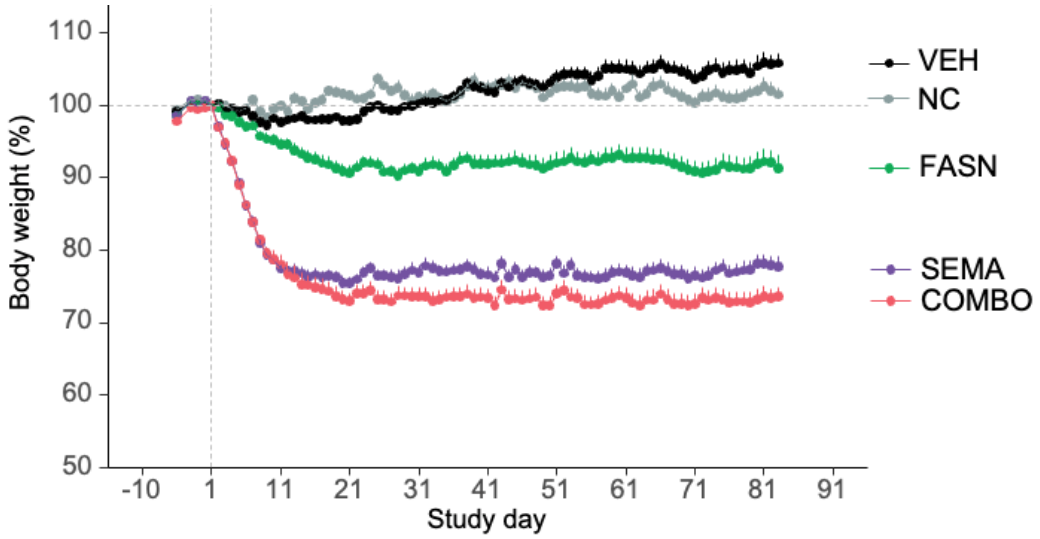
Endpoints

- Liver enzymes, Cholesterols, Triglycerides
- NAS
- Fibrosis
- Exploratory: lipidomics and transcriptomics

Treatment groups

1. NC: Normal chow diet control, n=8
2. VEH: NASH vehicle control, n=16
3. FASN: TVB-3664 (FASN inhibitor), 10mg/kg, PO, QD, n=16
4. SEMA: Semaglutide (weight loss dose), 30 nmol/kg, SC, QD n=16
5. COMBO: TVB-3664/Semaglutide combo, n=16

Semaglutide reduced body weight by ~25%

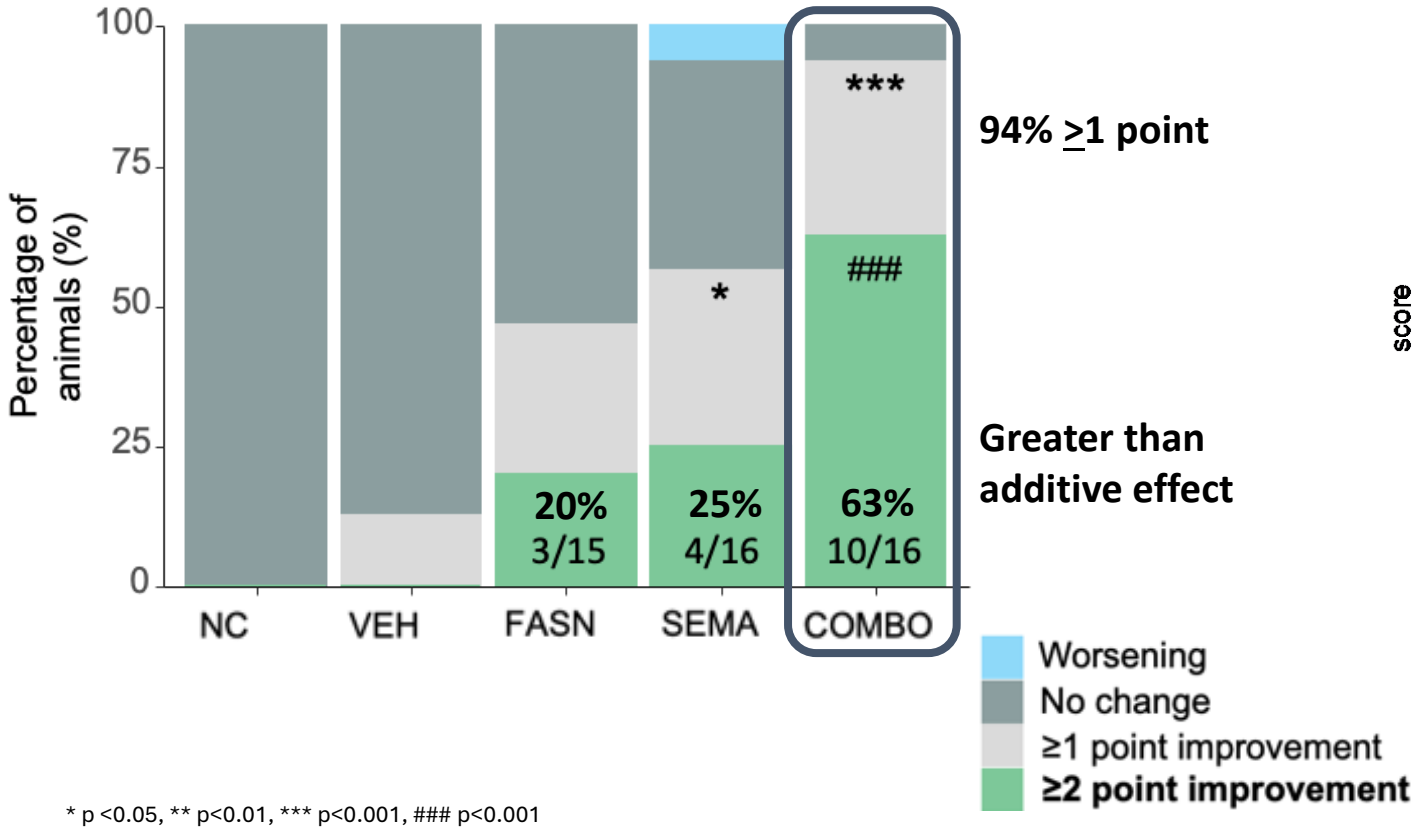


GUBRA DIO MASH mice.
Tsai WW, et al. Presented at: AASLD 2023; November 10-14, 2023; Boston, MA. Abstract 2400-C.

Combination of FASN Inhibitor and Semaglutide Improved Histological Features in MASH Mouse Model

Pre and post treatment liver biopsies

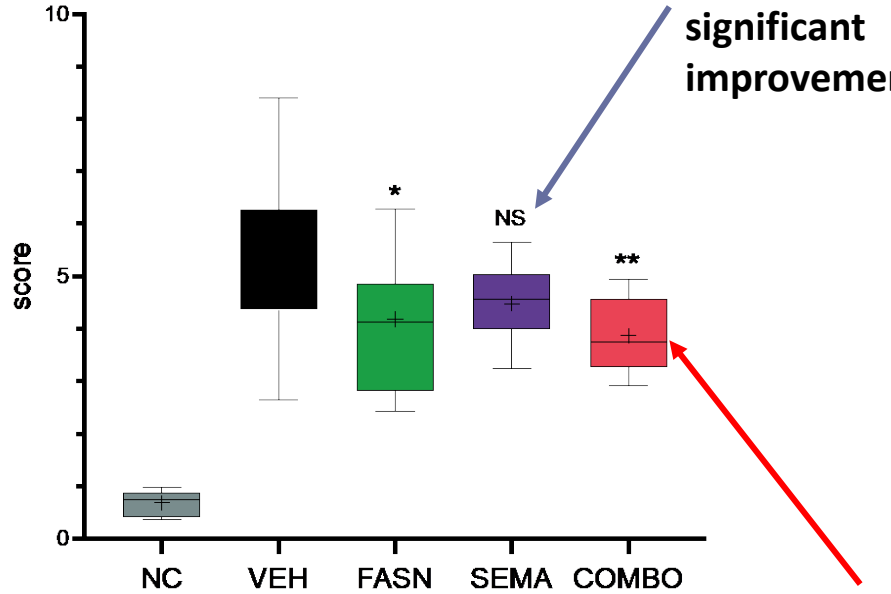
NAS, week 12



94% ≥1 point

Greater than additive effect

Fibrosis, week 12



Semaglutide no significant improvement

Combination significant decrease, like FASNi alone

* p <0.05, ** p<0.01, *** p<0.001, ### p<0.001

GUBRA DIO MASH mice. PSR images were analyzed by FibroNest (PharmaNest), all scores shown with parenchymal correction

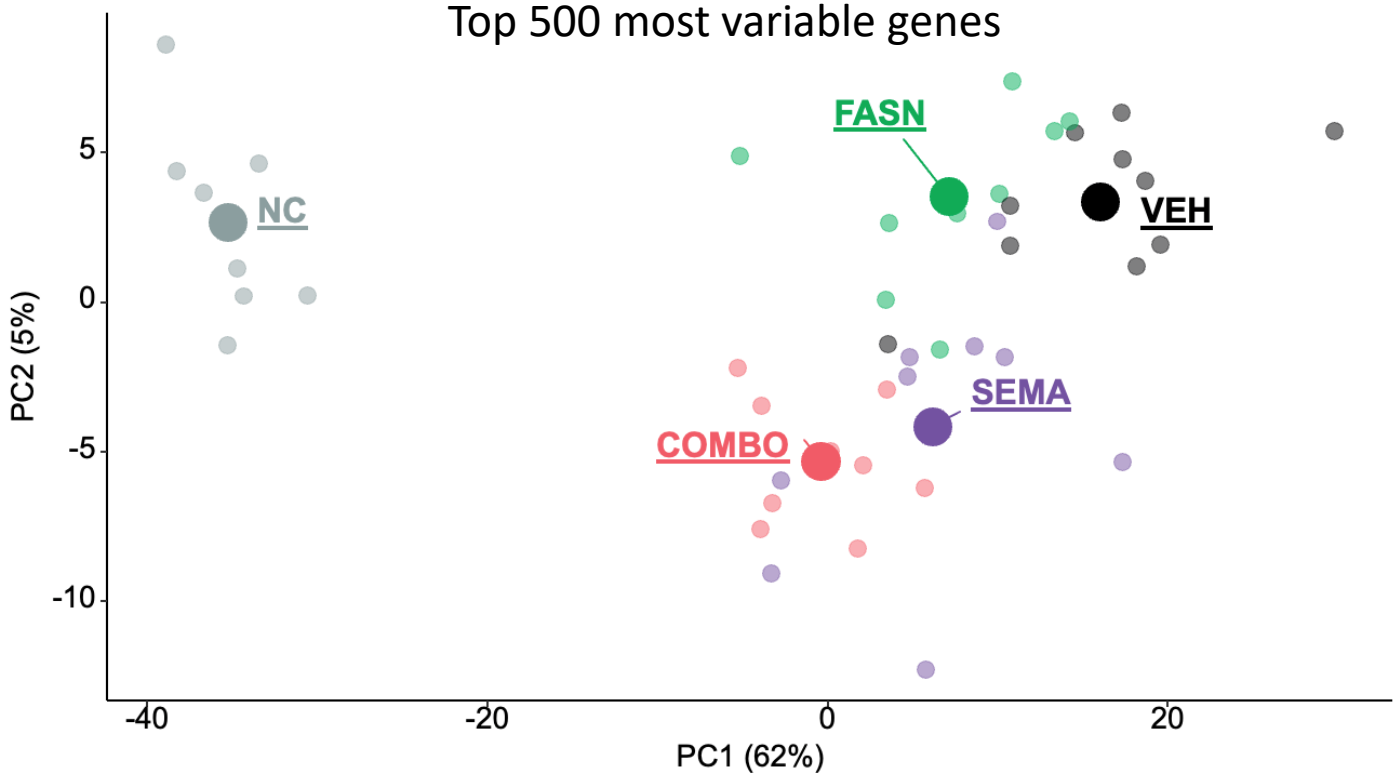
NS: not significant; NC: Normal chow diet control, VEH: MASH vehicle control, FASN: TVB-3664 (FASN inhibitor), SEMA: semaglutide, COMBO: TVB-3664/semaglutide

Tsai WW, et al. Presented at: AASLD 2023; November 10-14, 2023; Boston, MA. Abstract 2400-C.

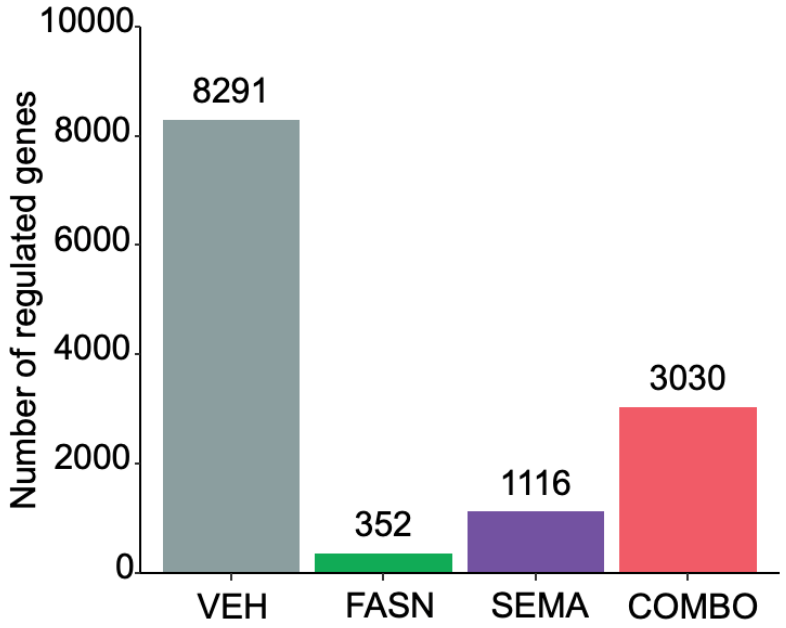
FASNi, Semaglutide and Combination Showed Different Patterns of Gene Expression – Consistent with Distinct Mechanisms

Principal component analysis

Top 500 most variable genes



Differential expression analysis

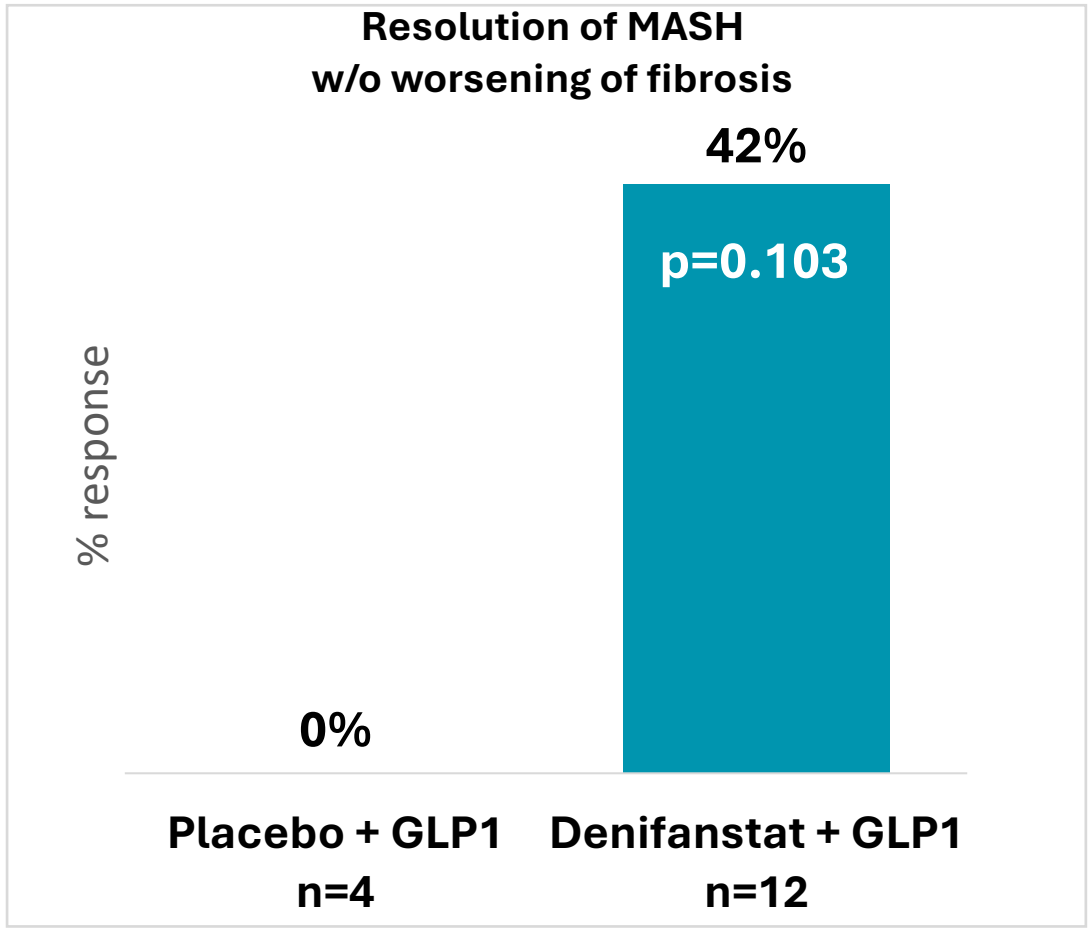


VEH compared to chow group,
FASN, SEMA, COMBO compared to VEH)

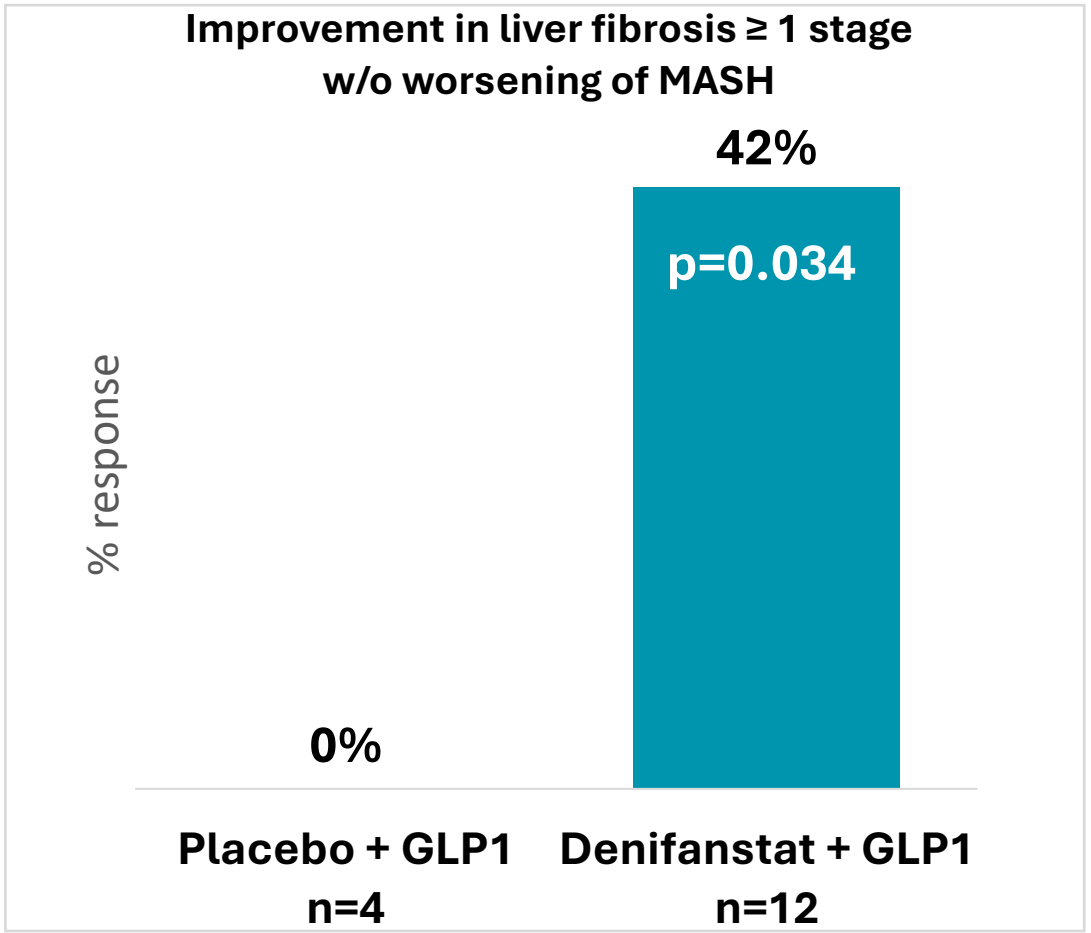
GUBRA DIO MASH mice. VEH: MASH vehicle control, FASN: TVB-3664 (FASN inhibitor), SEMA: semaglutide, COMBO: TVB-3664/semaglutide

Patient Subset on Stable GLP1-RA at Baseline: Liver Biopsy

FASCINATE-2 Phase 2b - 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

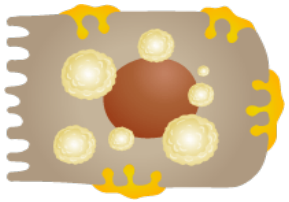
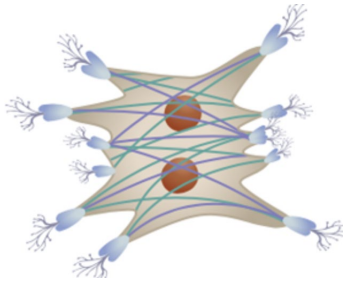


AI digital pathology results also supports fibrosis improvement in patients receiving GLP1 and denifanstat

Loomba R, et al. Lancet Gastroenterol Hepatol. 2024;9(12):1090-1100.
Loomba R, et al. Presented at: EASL 2024; June 5-8, 2024; Milan, Italy. https://sagimet.com/wp-content/uploads/2024/06/Denifanstat_a_fatty_acid_synthase_FASN_inhibitor_shows_significant_fibrosis_improvement_and_MASH_resolution_in_FASCINATE-2_a_Ph2b_52_week.pdf

Combination of FASNi with THR-β Agonist

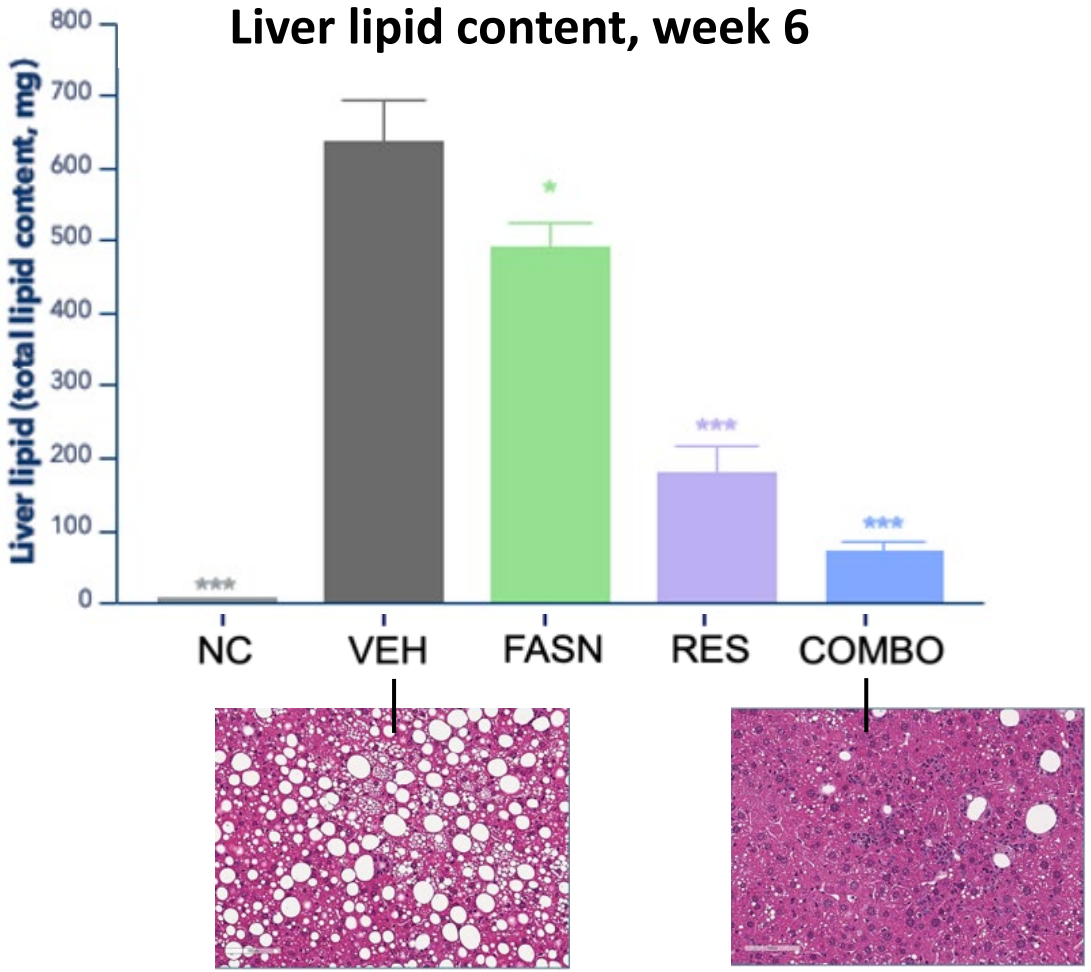
Complementary Mechanisms of Action

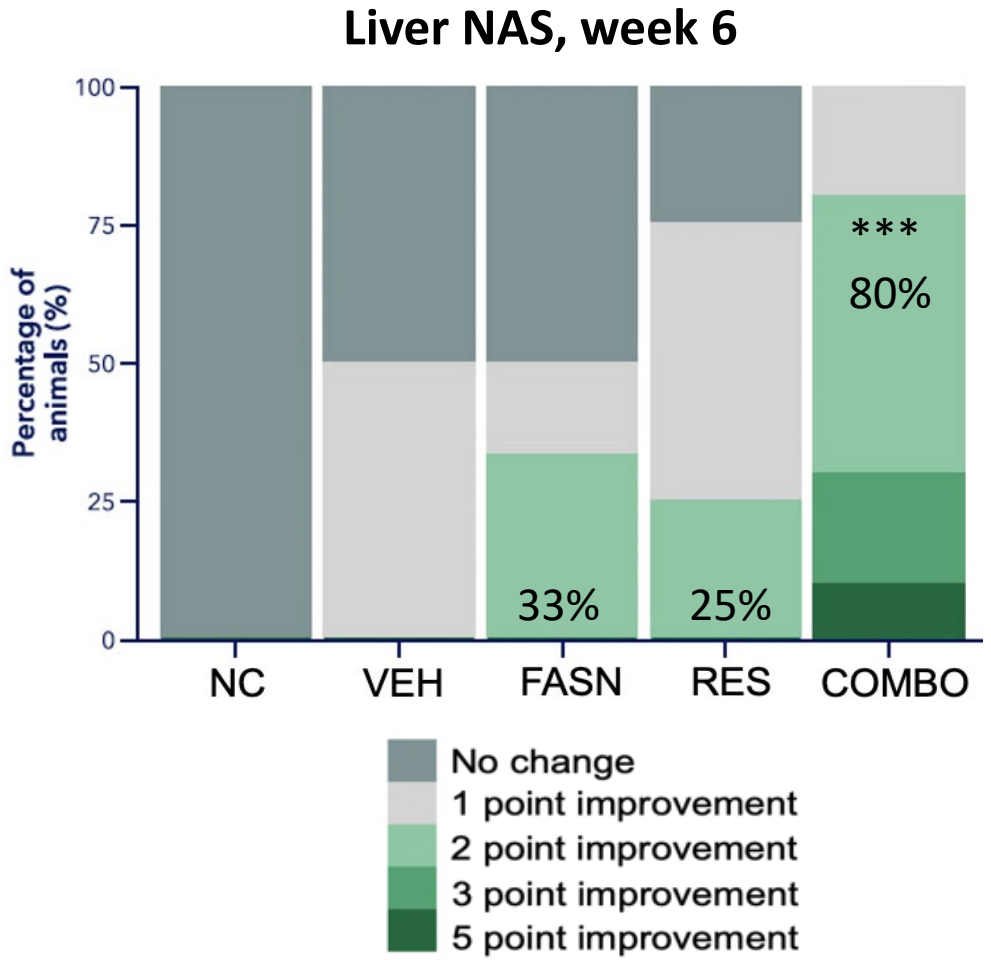
	FASN Inhibitor		THR-β Agonist		Combination Hypothesis
	Decreases de novo lipogenesis	+	Increases fatty acid oxidation	=>	Enhance liver steatosis and NASH resolution response
	Decreases fibrogenesis in stellate cells, liver fat and lipotoxicity	+	Decreases fibrosis due to decreased liver fat and lipotoxicity	=>	Enhance liver fibrosis response

Primary mechanisms are indicated.

Combination Was Superior to Monotherapy in Mouse MASH DIO Model (Gubra)

Liver Histology Shows Rapid Response





*p<0.05, ***p<0.001. GUBRA DIO MASH mice. C57B6 WT, 38 wk lead in on diet 40% fat, 22% fructose, 2% cholesterol. Week 6 too early for fibrosis assessment. FASN inhibitor 5 mg/kg, resmetirom 3 mg/kg (MGL-3196).

Tsai WW, et al. Presented at: EASL 2024; June 5-8, 2024; Milan, Italy. https://sagimet.com/wp-content/uploads/2024/06/2024-EASL-poster-TNO-model-final.pdf

Combination of FASNi and Resmetirom Tested in Ldlr-/- Model

Diet lead-in
FFD 18 weeks

Start Treatment

10 weeks

Ldlr-/-.Leiden, 41% fat, 44% fructose diet (FFD)

Endpoints

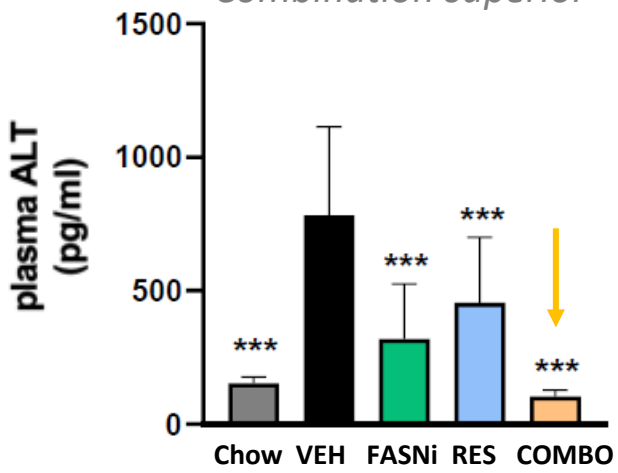
- Liver enzymes
- Cholesterols
- NAS
- Fibrosis
- Atherosclerosis

Treatment groups

1. Chow
2. Vehicle
3. TVB-3664 (5 mg/kg) FASNi
4. MGL-3196 (3 mg/kg)
5. TVB-3664+ MGL-3196

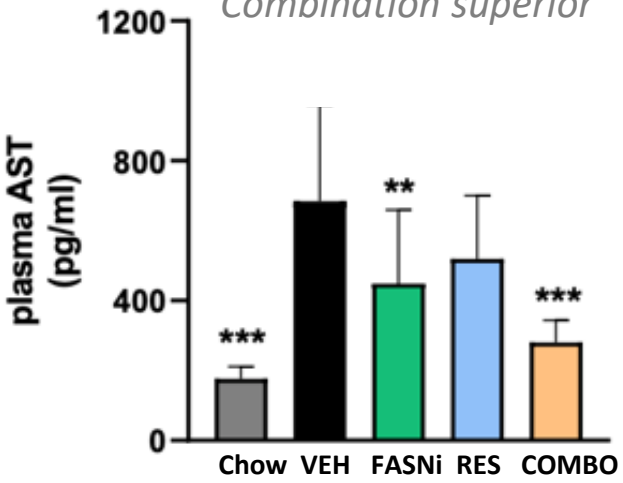
ALT

Combination superior



AST

Combination superior



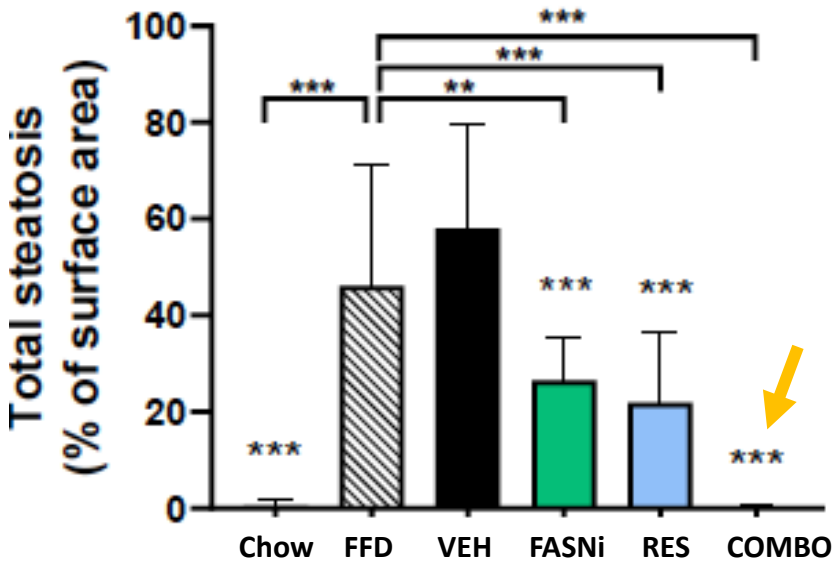
*p<0.05, ***p<0.001. Ldlr-/- Leiden DIO mice. FFD: full fat diet start of drug treatment, VEH: full fat diet end of treatment

Tsai WW, et al. Presented at: EASL 2024; June 5-8, 2024; Milan, Italy. https://sagimet.com/wp-content/uploads/2024/06/2024-EASL-poster-TNO-model-final.pdf

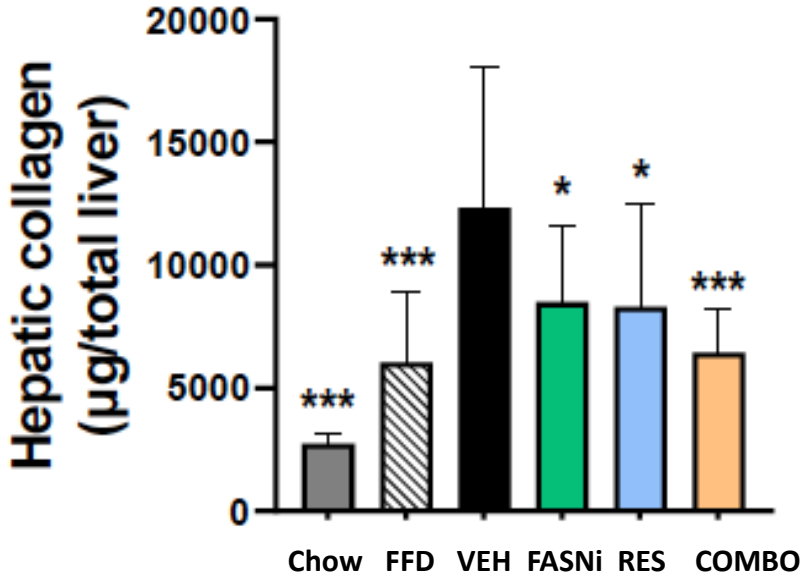
Liver Histology Efficacy in Ldlr-/- Model

Combination Normalized Liver Fat and Significantly Reduced Collagen Content

Liver steatosis, week 10



Liver collagen, week 10

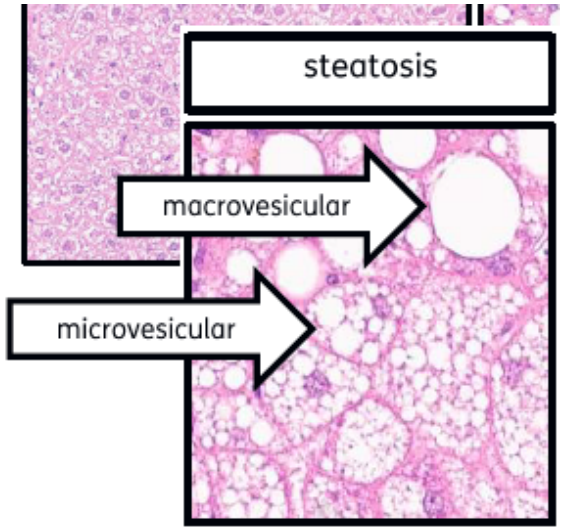


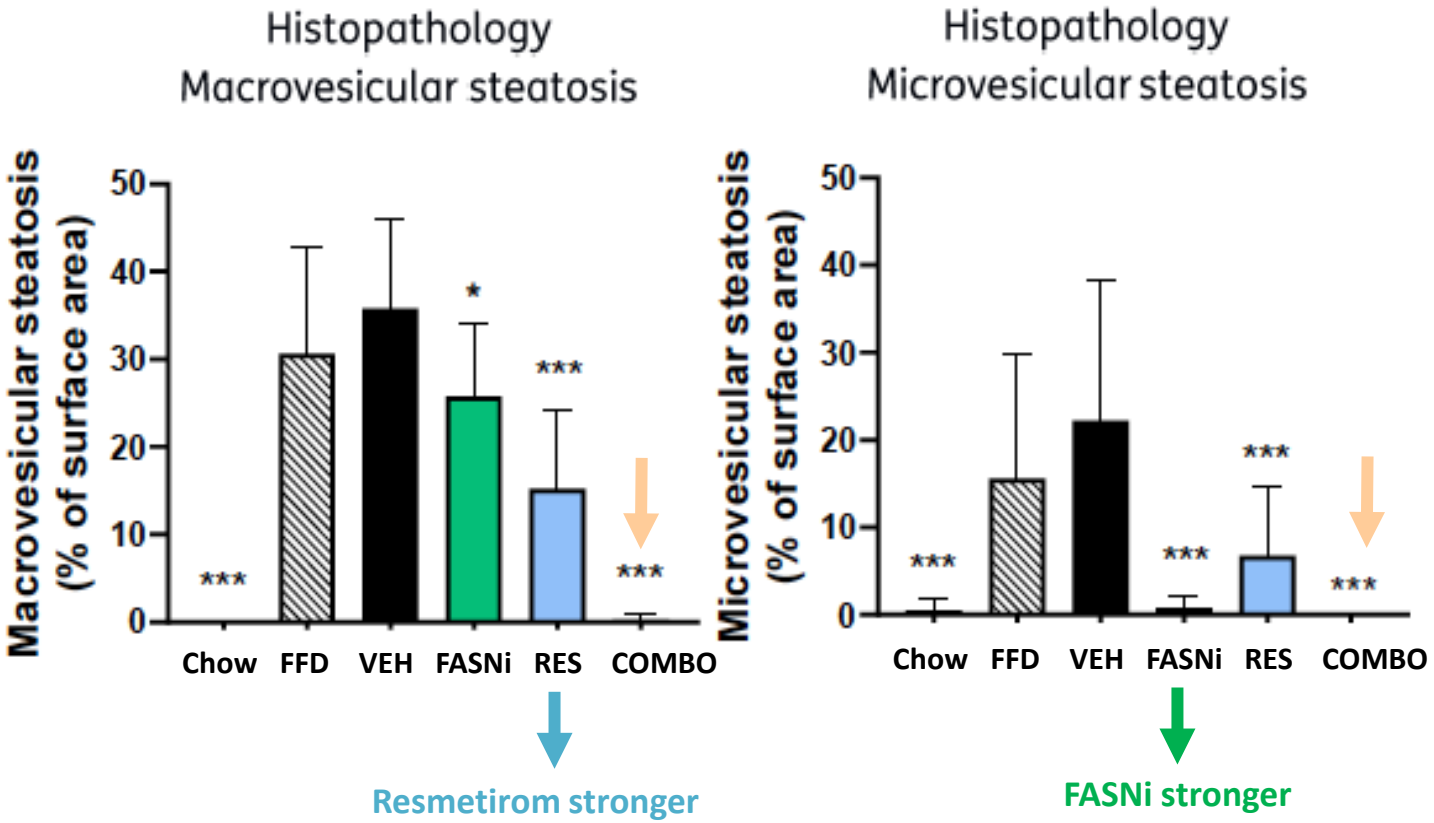
*p<0.05, ***p<0.001. Ldlr-/- Leiden DIO mice. FFD: full fat diet start of drug treatment, VEH: full fat diet end of treatment

Tsai WW, et al. Presented at: EASL 2024; June 5-8, 2024; Milan, Italy. https://sagimet.com/wp-content/uploads/2024/06/2024-EASL-poster-TNO-model-final.pdf

FASNi and Resmetirom Had Distinct Effects on Steatosis in Ldlr-/- Model

Combination Normalized Both Macrovesicular and Microvesicular to Chow Levels





*p<0.05, ***p<0.001, FFD: full fat diet start of drug treatment, VEH: full fat diet end of treatment

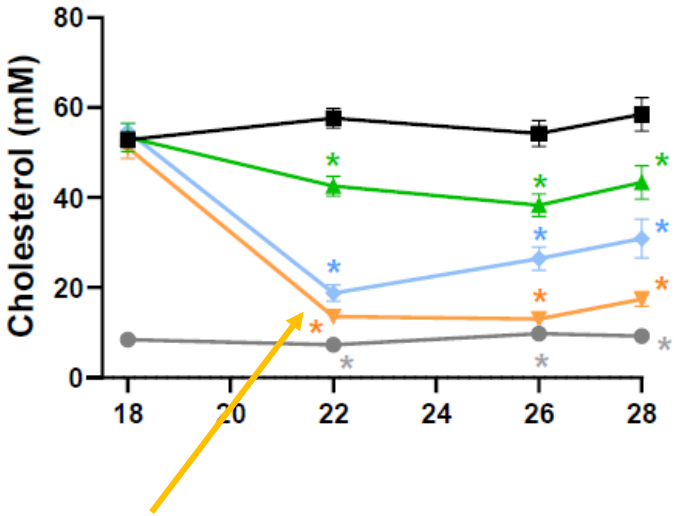
Tsai WW, et al. Presented at: EASL 2024; June 5-8, 2024; Milan, Italy. https://sagimet.com/wp-content/uploads/2024/06/2024-EASL-poster-TNO-model-final.pdf

Combination of FASNi and Resmetirom in Ldlr-/- Model

Combination Decreased Markers of Dyslipidemia

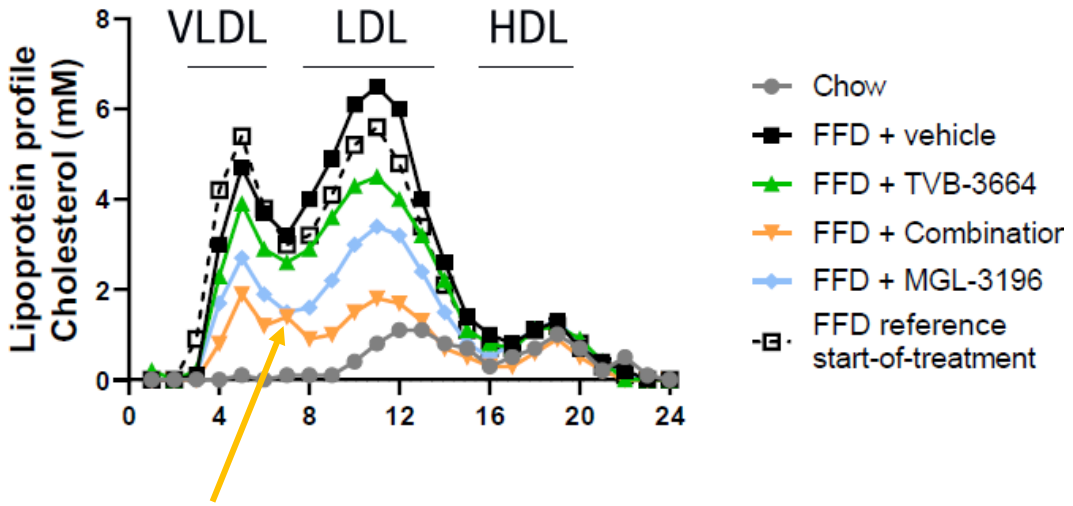
Cholesterol

Combination superior



Lipoproteins

Combination superior



*p<0.05, ***p<0.001. Ldlr-/- Leiden DIO mice. FFD: full fat diet start of drug treatment, VEH: full fat diet end of treatment

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*p<0.05, ***p<0.001

Potential Benefits of Combination Therapy in Advanced MASH Patients

A combination product could potentially offer an opportunity to serve patient groups with the strongest need of treatment, including those with stage 4 fibrosis

Characteristic	Denifanstat [1]	Resmetirom [2]	Potential Combination
Mechanism	**Direct** – decreases de novo lipogenesis **Direct** – decreases fibrogenesis in stellate cells, liver fat and lipotoxicity	**Direct** – increases fatty acid oxidation **Indirect** – decreases fibrosis due to decreased liver fat and lipotoxicity	Potential synergies in the MOA Note: THR-beta upregulates FASN
Formulation	Oral	Oral	Oral
Dosing	Once daily	Once daily	Once daily Fixed-Dose Combination (FDC)
Clinical Data	Met both primary endpoints in Phase 2b trial with significant reduction in fibrosis	Phase 3 data supported FDA approval for treatment of non-cirrhotic MASH	Potential synergistic effect

Note: These data are placebo-adjusted, derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

1. Loomba R, et al. Lancet Gastroenterol Hepatol. 2024;9(12):1090-1100. 2. Harrison SA, et al. *N Engl J Med*. 2024;390(6):497-509.

Conclusions

- Denifanstat met statistical significance for primary and secondary histology endpoints in Ph2b FASCINATE-2, including fibrosis improvement in more severe patients (stage F3)
- Mechanism targeting FASN is unique among MASH drugs in development
- Combination of FASN inhibitor with GLP1 agonists
  - Increased histology response in mouse model and in MASH patients, both MASH resolution and fibrosis
- Combination of FASN inhibitor with THR-β agonist
  - Distinct mechanisms of liver fat reduction normalized liver fat in mouse MASH models
  - Improved NAS response in mouse within 6 weeks, and further decreased collagen and fibrosis
  - Phase 1 combination PK clinical trial with resmetirom is planned.

Acknowledgements

Sagimet Team

Sagimet Advisors

Investigators, sites and patients involved in FASCINATE studies