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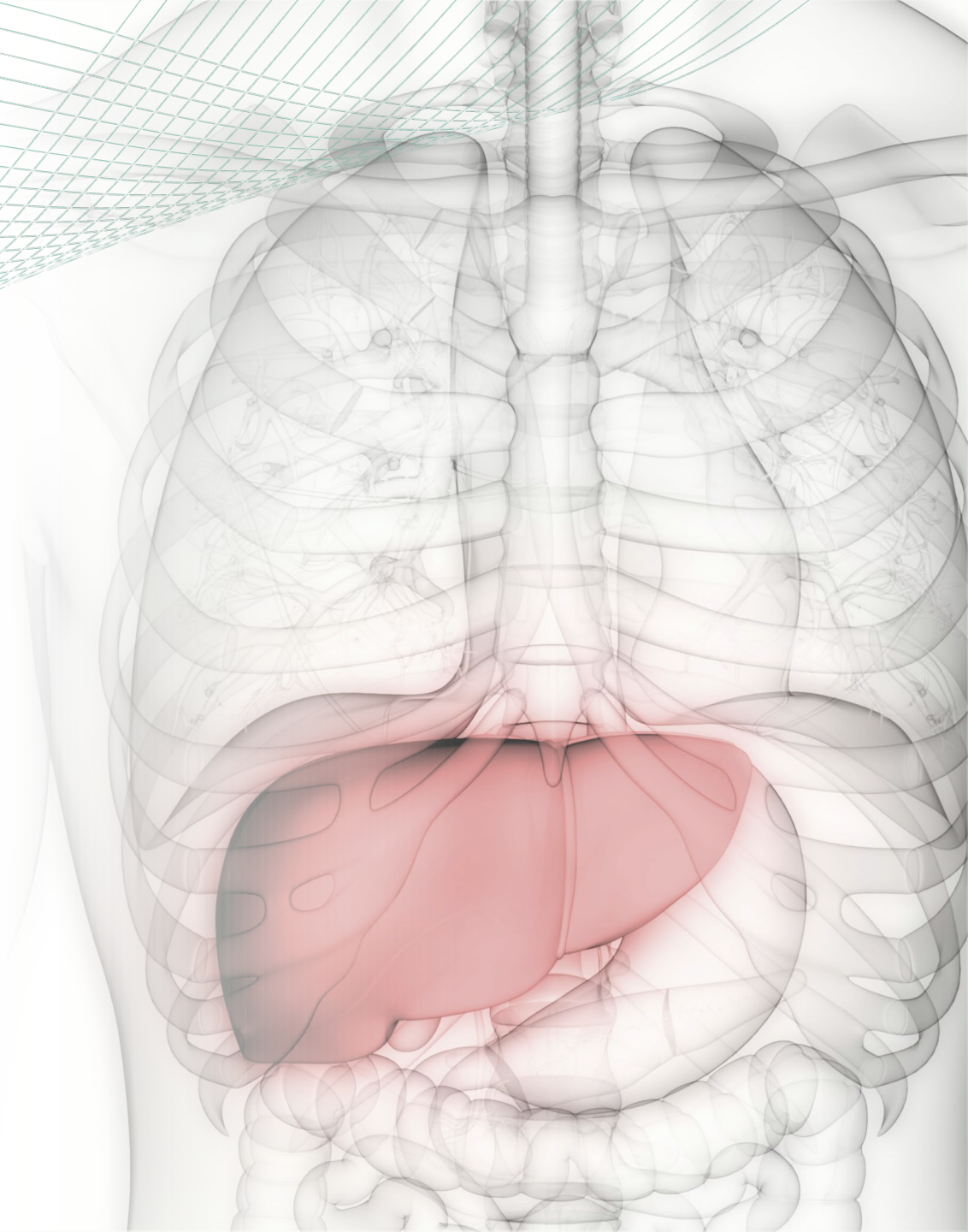
Denifanstat/Resmetirom Combination Development Program

May 29, 2025



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Agenda

1:00pm ET	1:10pm ET	1:35pm ET	1:45pm ET
Introduction	Phase 2b Denifanstat Data & Rationale for Combination Therapy	FDC Clinical Development Program	Q&A and Conclusion
Dave Happel CEO	**Rohit Loomba, MD, MHSc** KOL	**Eduardo Martins, MD, DPhil** CMO	**Dave Happel** CEO

FDC = Fixed Dose Combination of denifanstat and resmetirom

Dr. Rohit Loomba, M.D., M.H.Sc., Biography

- Gastroenterologist and Hepatologist
- Chief, Division of Gastroenterology and Hepatology
- Director, UC San Diego MASLD Research Center
- Professor of Medicine
- Principal Investigator on the Phase 2b FASCINATE-2 clinical trial
- Scientific advisor for Sagimet on its ongoing development of denifanstat

Disclosures: Rohit Loomba serves as a consultant to Aardvark Therapeutics, Altimmune, Arrowhead Pharmaceuticals, AstraZeneca, Cascade Pharmaceuticals, Eli Lilly, Gilead, Glympse bio, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Lipidio, Madrigal, Neurobo, Novo Nordisk, Merck, Pfizer, Sagimet Biosciences, 89 bio, Takeda, Terns Pharmaceuticals and Viking Therapeutics. Rohit Loomba has stock options in Sagimet Biosciences. In addition, his institution received research grants from Arrowhead Pharmaceuticals, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly, Galectin Therapeutics, Gilead, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, Novo Nordisk, Pfizer, Sonic Incytes and Terns Pharmaceuticals. Co-founder of LipoNexus Inc.

Development Pipeline: Multiple Indications and Clinical Milestones

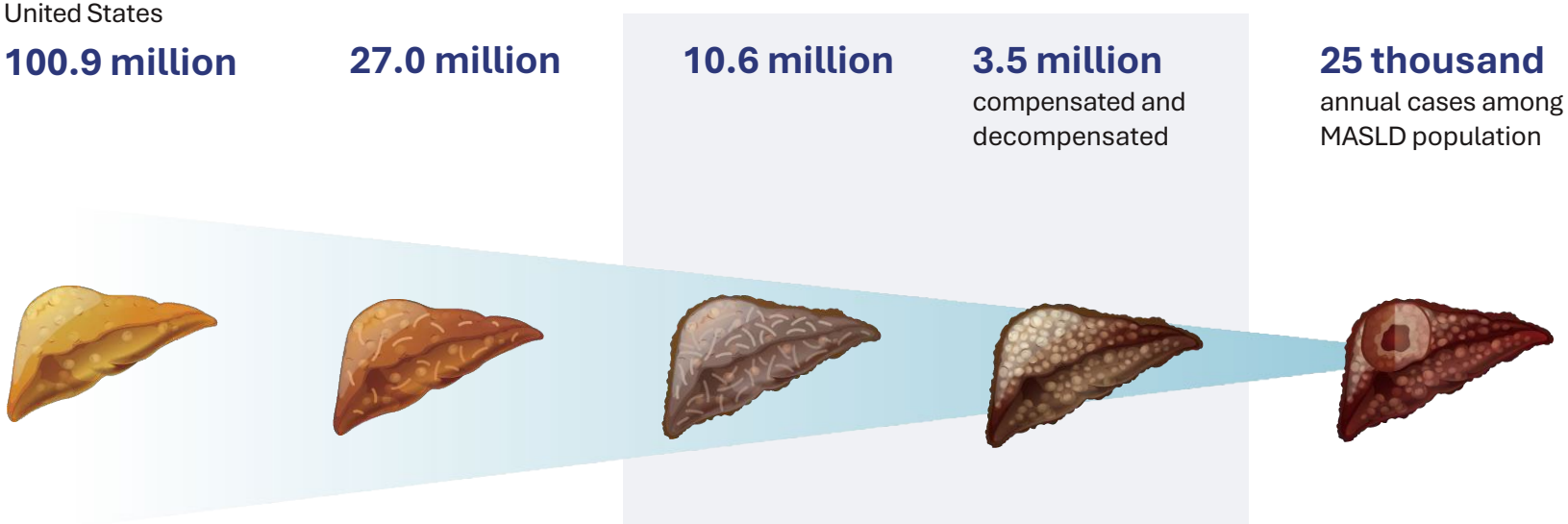
Therapeutic Area	Indication	Stage of Development	Expected Milestone / Status
Metabolic Disease	MASH	Denifanstat (Phase 2)	Phase 2b positive topline data announced 1Q2024; FDA Breakthrough Therapy designation; Phase 3 F2/F3 ready
		Denifanstat (Phase 1)	Phase 1 hepatic impairment results reported 1Q2024
		Denifanstat/resmetirom (Preclinical)	Phase 1 clinical PK trial initiation planned 2H 2025
Dermatology	Acne	TVB-3567 (Preclinical)	Phase 1 FIH in acne expected to initiate 2H 2025; IND cleared in 1Q2025
		歌礼 ascletis Denifanstat (ASC40) (Phase 2)	Phase 3 clinical study enrollment completed in Nov 2024; topline results expected in 2Q2025*
Oncology	Solid tumors	TVB-3567 (Preclinical)	Identifying FASN-dependent tumor types for potential FASN inhibitor development
		Denifanstat (Phase 1)	
	Recurrent glioblastoma (GBM)	歌礼 ascletis Denifanstat (ASC40) (Phase 2)	Phase 3 enrollment of 120 patients achieved in 3Q2023*

* Trials conducted in China by Ascletis, who has licensed development and commercialization rights to all indications in Greater China

MASH: A Burgeoning Epidemic

Estimated Patients in 2030[1]

United States

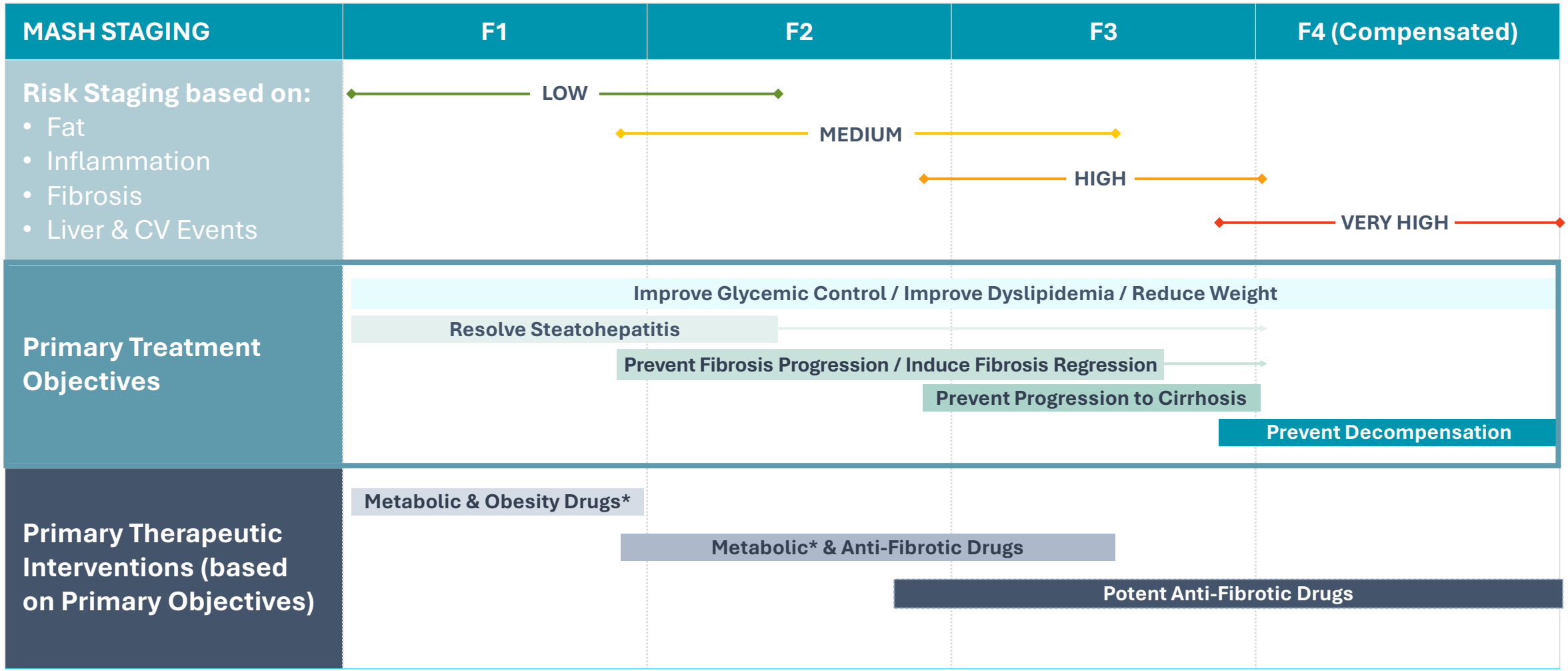


MASH

- 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

Treatment Goals for MASH Across Fibrosis Staging



Kusi et al. Endocrine Practice 28 (2022) 528-562. Rinella et al. Hepatology. 2023 May 01; 77(5): 1797–1835. Tacke et al. Journal of Hepatology, July 2024. vol. - 4 | 1–51
*Metabolic drugs are anticipated to be background therapy for obesity and type 2 diabetes, until clinical data support use in MASH

Strong MASH Data Create Opportunities to Reach Advanced Patient Populations

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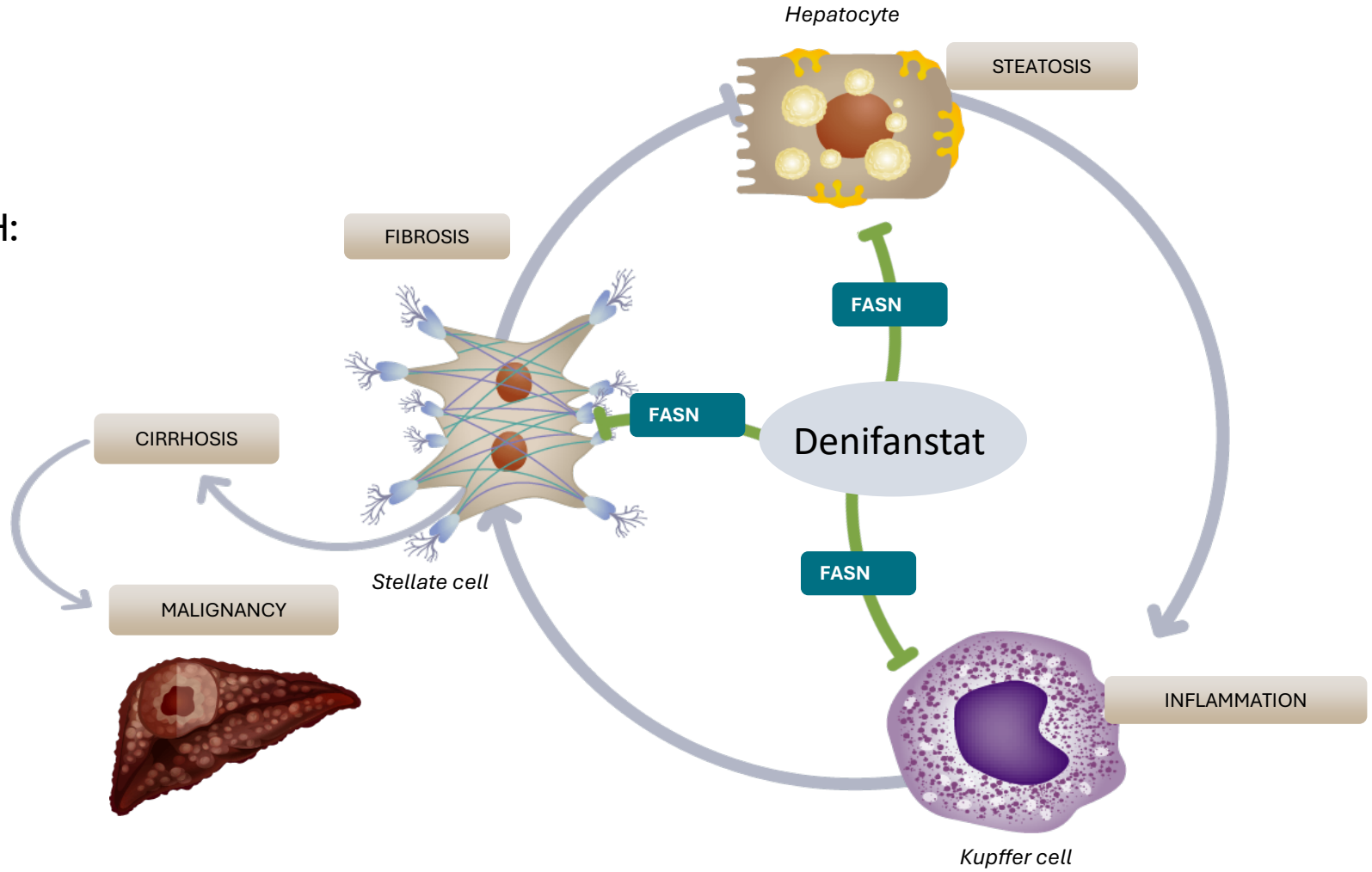
MOA of FASN Inhibition Addresses Three Independent Mechanisms of MASH Development and Progression

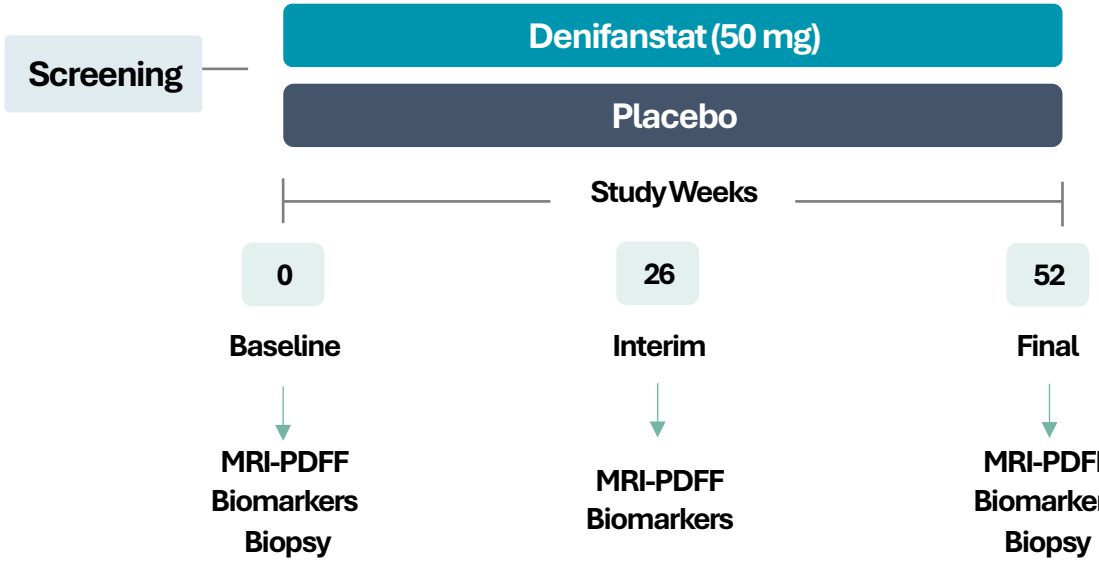
Denifanstat is a specific and potent inhibitor of FASN that functions through three independent mechanisms in MASH:

1. Blocking **steatosis** via inhibiting de novo lipogenesis in hepatocytes
2. Reducing **inflammation** via preventing immune cell activation
3. Blunting **fibrosis** via inhibiting stellate cell activation



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.

FASCINATE-2: Baseline Characteristics Were Typical of the 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

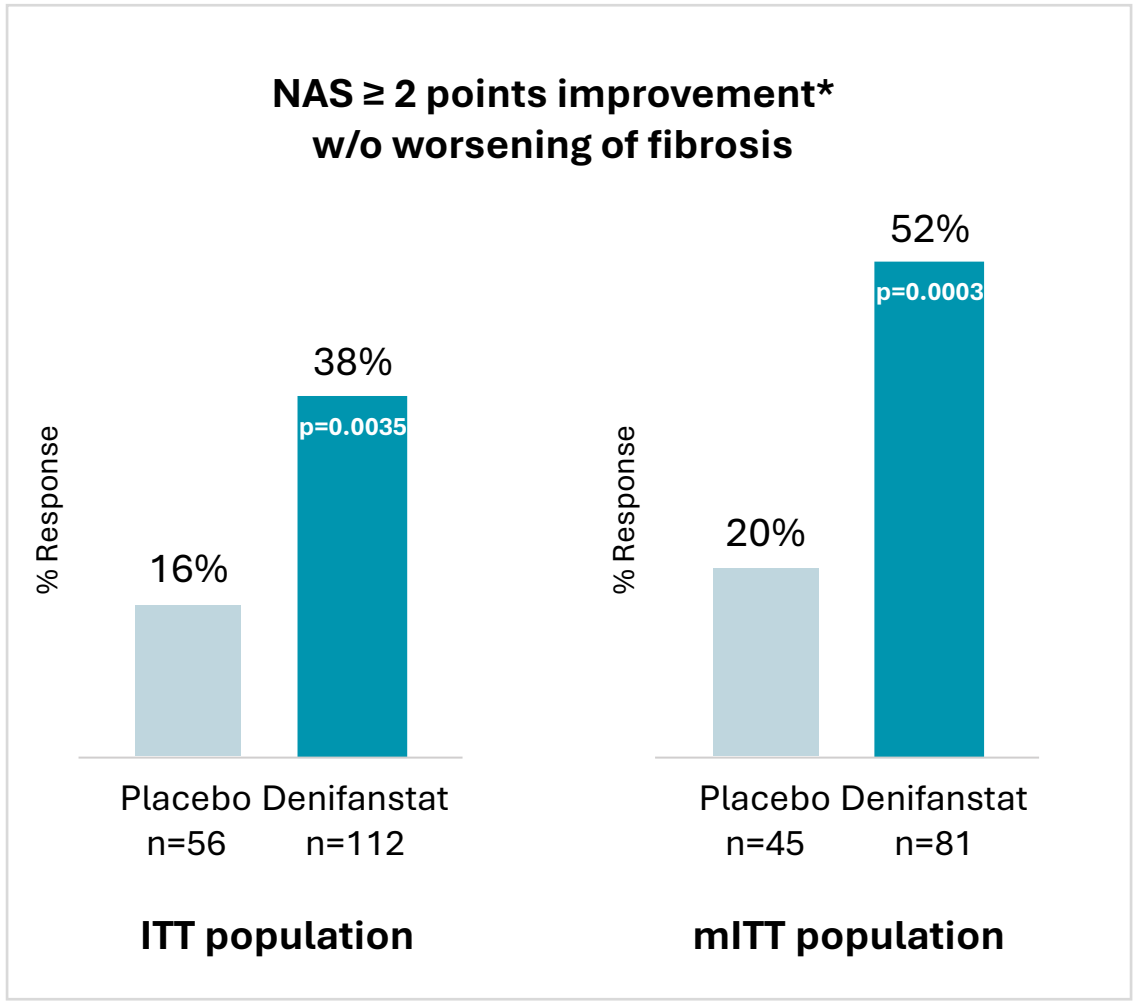
Event n (%)	Placebo (n=56)	Denifanstat 50mg (n=112)	Total (n=168)
Any adverse event (AE)	46 (82.1)	99 (88.4)	145 (86.3)
Adverse event related to denifanstat or placebo	20 (35.7)	51 (45.5)	71 (42.3)
Serious adverse event	3 (5.4)	13 (11.6)	16 (9·5)
TEAE leading to study drug discontinuation	3 (5.4)	22 (19.6)	25 (14.9)
Adverse events affecting ≥ 10% of patients			
COVID-19	6 (10.7)	19 (17.0)	25 (14.9)
Dry eye	8 (14.3)	10 (8.9)	18 (10.7)
Hair thinning	2 (3.6)	21 (18.8)	23 (13.7)

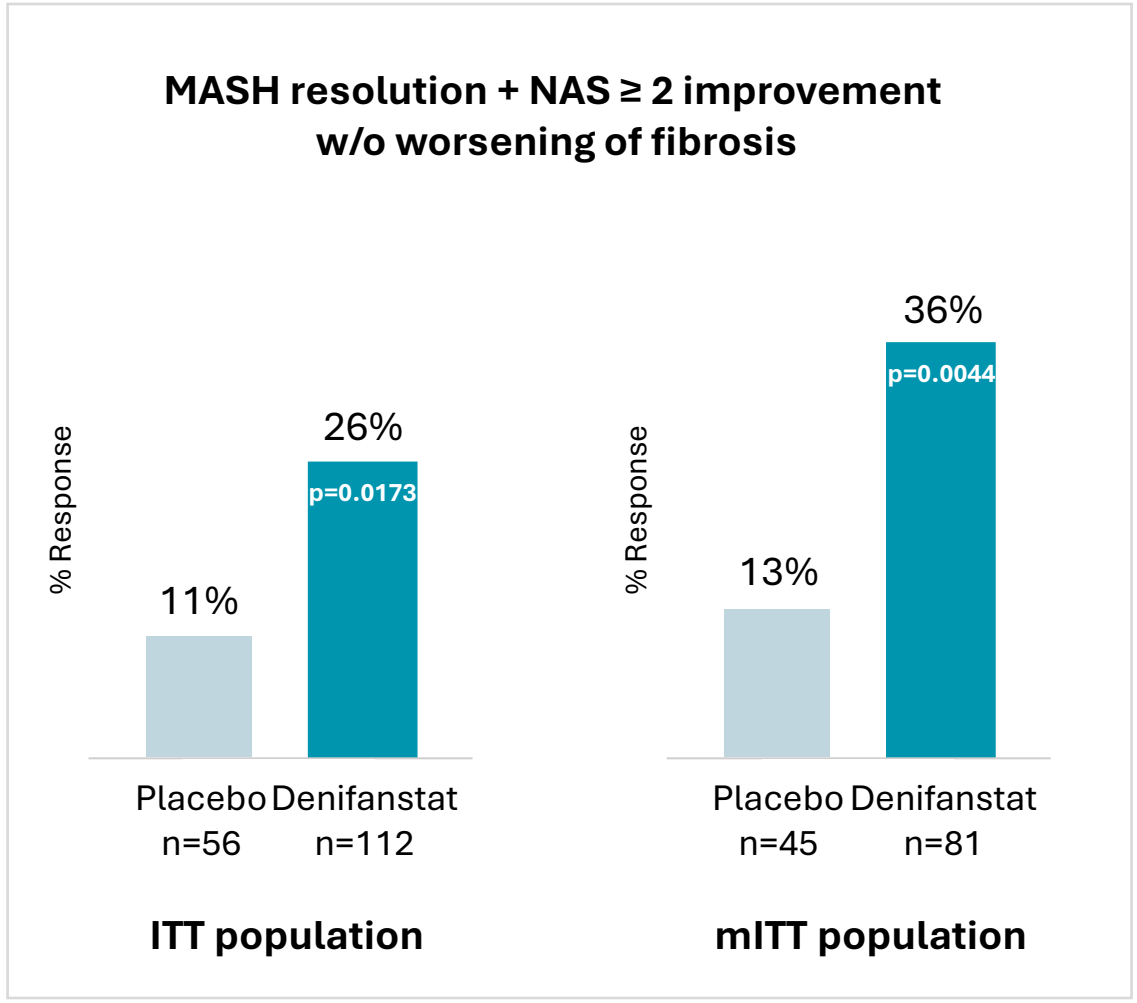
- No DILI (drug-induced liver injury) signal and no muscle wasting were detected, and GI (gastrointestinal) effects were comparable to placebo
- AE of hair thinning stabilized with a 2-to-4 week dose pause and then reversed with down titration or study completion
  - Only 7% of patients discontinued from the study with treatment-related hair thinning. Hair thinning in patients receiving GLP-1 ranges from 7% to 10% [1]
  - In two previous clinical studies of denifanstat, 2% of the patients on denifanstat experienced hair thinning at 50mg [2]

1. Wadden et al. 2023, Nature Medicine; Daniel et al. 2025, Journal of Drugs and Dermatology
2. Phase 2a FASCINATE-1 study; Phase 2a study of denifanstat in acne conducted by Ascletis in China

Phase 2b Primary Endpoints: Liver Biopsy

Denifanstat Achieved Statistical Significance at Week 52

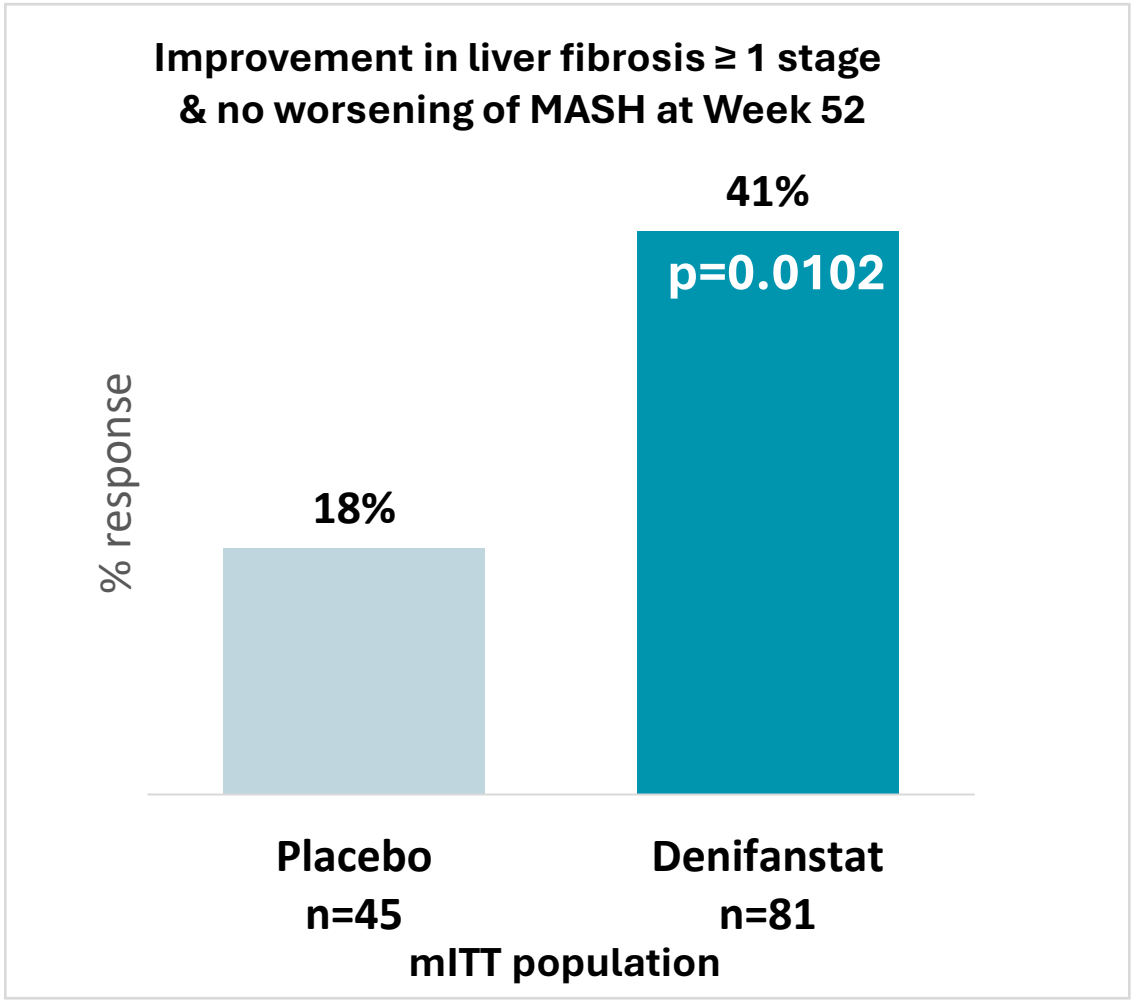


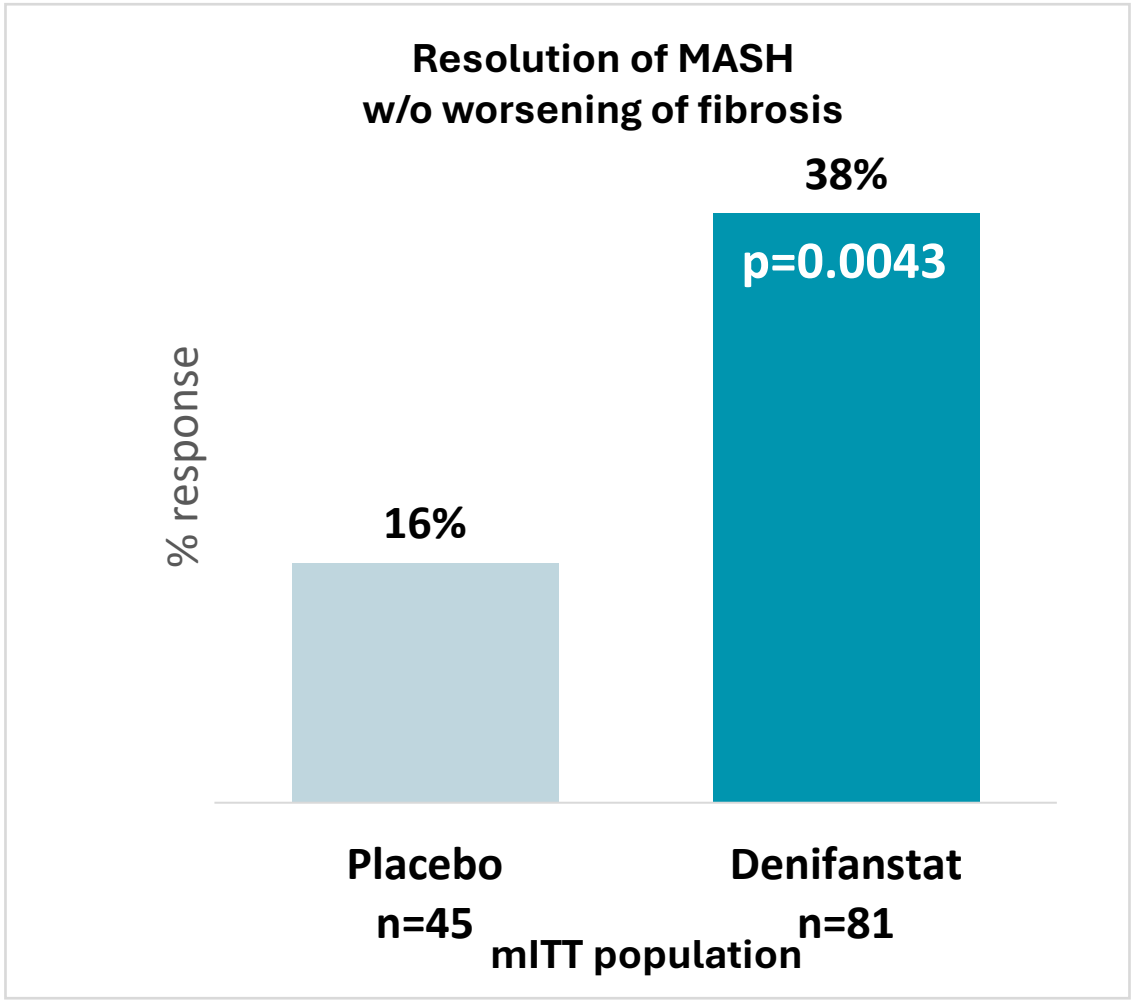


Cochran-Mantel-Haenszel Test – two sided at the 0.05 significance level. * ≥1-point improvement in ballooning or inflammation.

Phase 2b Secondary Endpoints: Liver Fibrosis and MASH Resolution

Denifanstat Achieved Statistical Significance at Week 52





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

Secondary Endpoints: Liver Fibrosis

Denifanstat Achieved Statistically Significant Improvement of Fibrosis

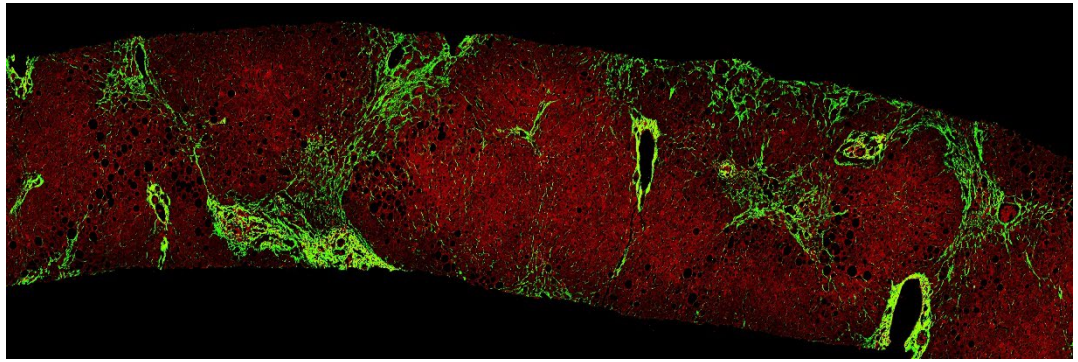
Fibrosis Endpoints	Subgroup	Placebo	Denifanstat	p-value
≥1 stage improvement in fibrosis w/o worsening of MASH	ITT	14%	30%	0.040**
	mITT	18%	41%	0.0102**
	F3	13%	49%	0.0032**
≥2 stage improvement in fibrosis w/o worsening of MASH	mITT	2%	20%	0.0065**
	F3	4%	34%	0.0065**
Progression to cirrhosis (F4)	mITT	11%	5%	0.0386*

*One sided at the 0.05 significance level, **Two sided at the 0.05 significance level

Additional Fibrosis Analysis Using AI-based Digital Pathology

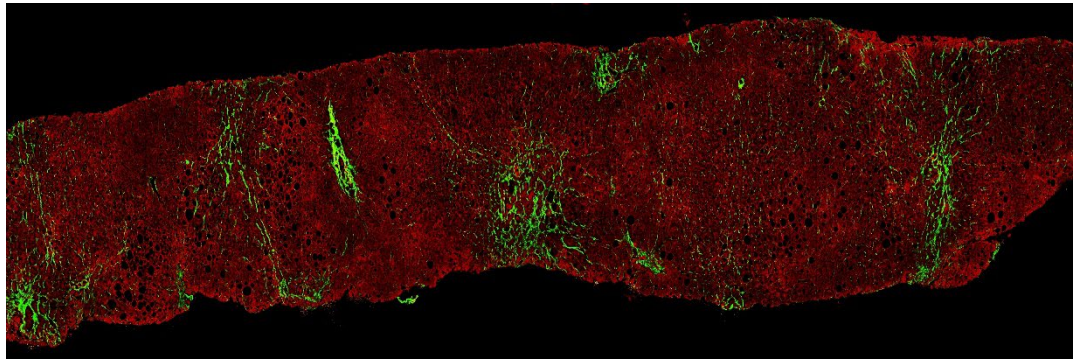
Digital Imaging Showed that Denifanstat Significantly Reduced Fibrosis in Advanced Patients

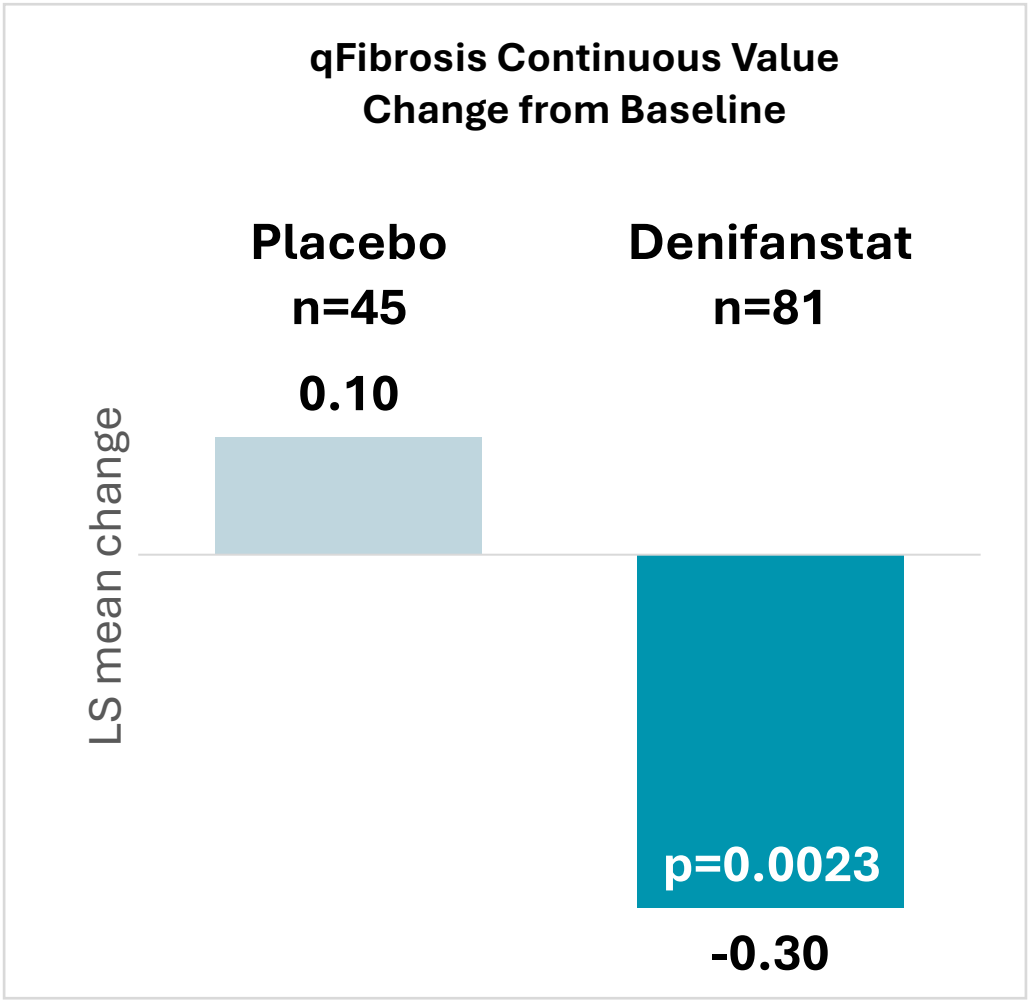
Pre-Treatment Pt A
NASH-CRN Fibrosis stage F3



Denifanstat

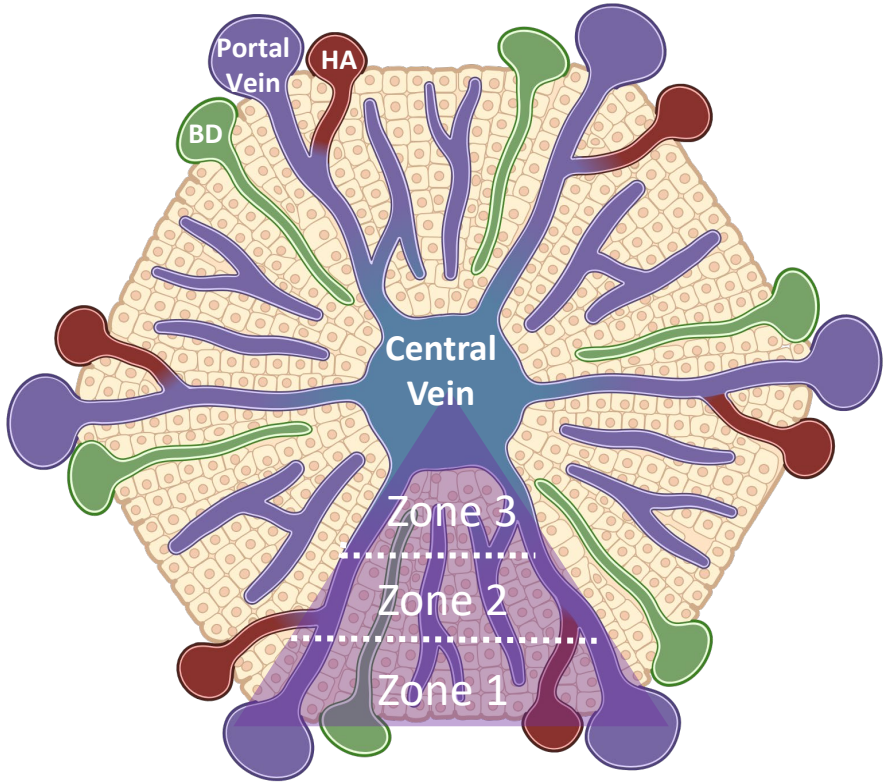
Post-Treatment Pt A
NASH-CRN Fibrosis stage F1





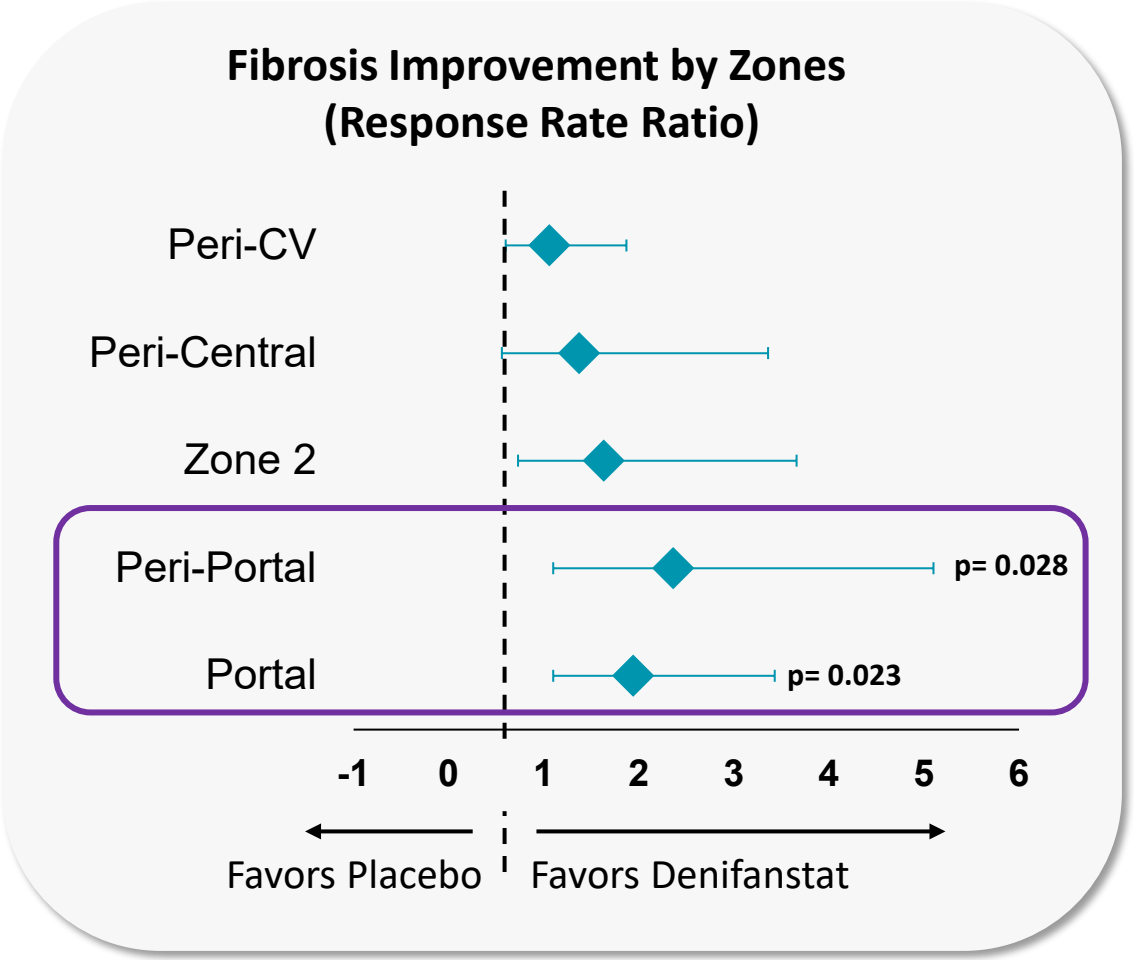
*One sided at the 0.05 significance level

qFibrosis Zonal Analysis Demonstrated that Denifanstat Improves Parameters 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]

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



Response at the individual zonal parameter level was defined as "at least" 30% relative decrease from baseline. FASCINATE-2, AASLD 2024

Denifanstat Potential in Cirrhotic (F4) Patients

Differentiated Mechanism of Action

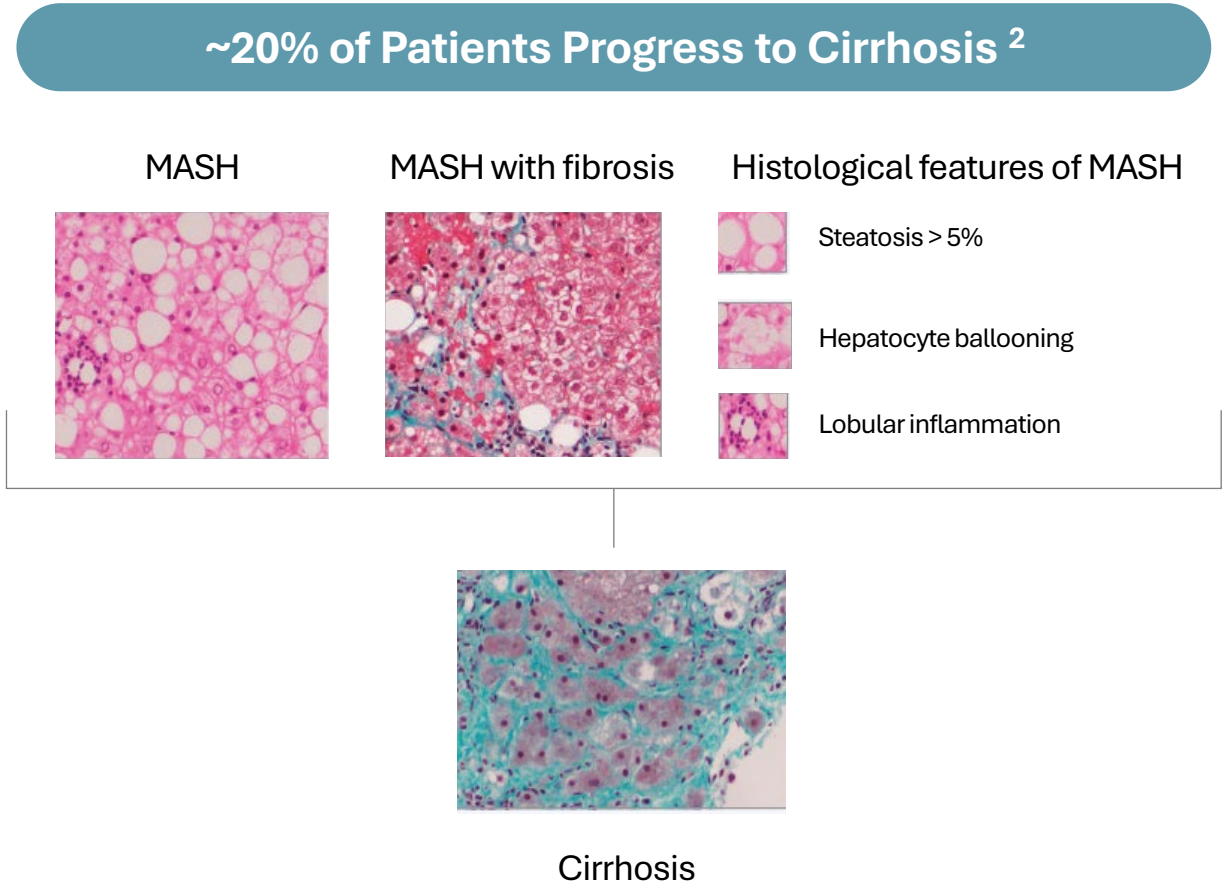
- *In vitro* data demonstrates that denifanstat reduces pro-fibrotic signaling in stellate cells, suggesting that denifanstat has the potential to remove fibrotic scar tissue and reestablish the basal extracellular matrix (ECM) scaffold even in cirrhotic (F4) patients[1]
- Hepatocytes continue to be functional, and patients frequently have increased liver fat

Clinical Data

- PK profiles in cirrhotic (F4) patients in the Phase 1 impaired hepatic function study[3]
- Positive impact on advanced fibrosis in patients in FASCINATE-2[4], including qF4 (quantification of fibrosis stage 4) patients based on AI-based digital pathology [5]

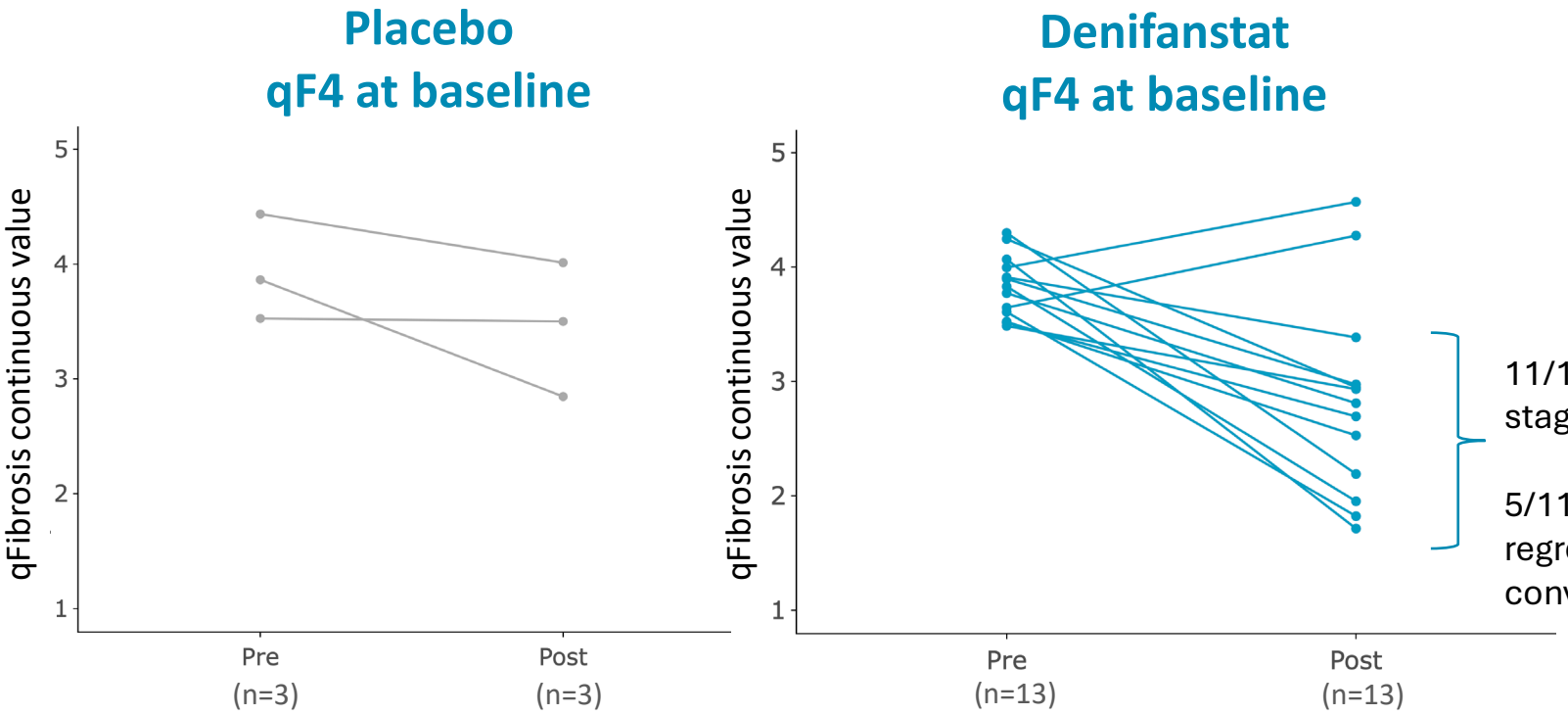
Next Step

- Potential Phase 2 proof of concept in F4 patients



1 Kamm DR and McCommis KS. doi: 10.1113/JP281061. 2 Sheka AC, et al. doi:10.1001/jama.2020.2298. 3. CLIN-009 data on file. 4. Loomba, et al. doi: 10.1016/S2468-1253(24)00246-2 5.HistoIndex FASCINATE-2 data on file

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 study

Source: FASCINATE-2 HistoIndex data on file

Rationale for Combination Therapy

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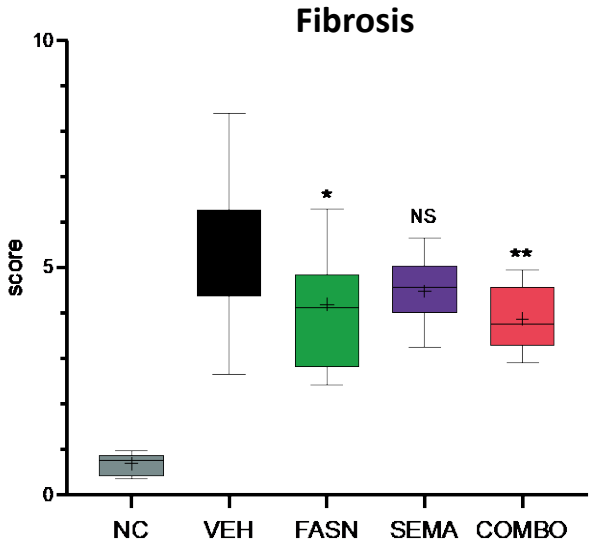
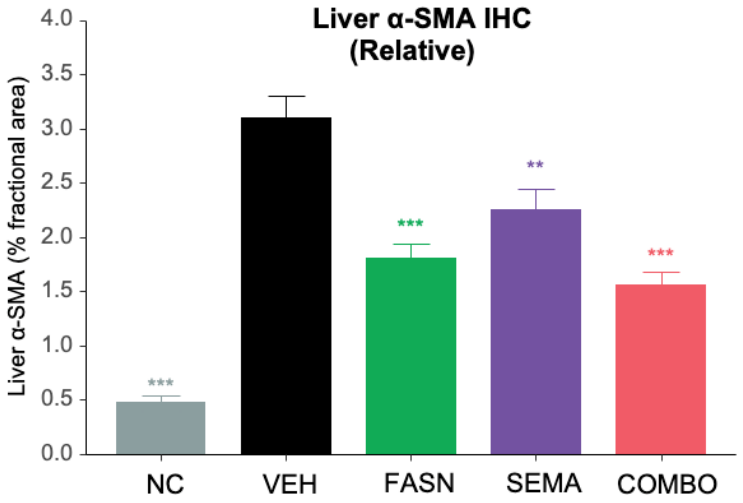
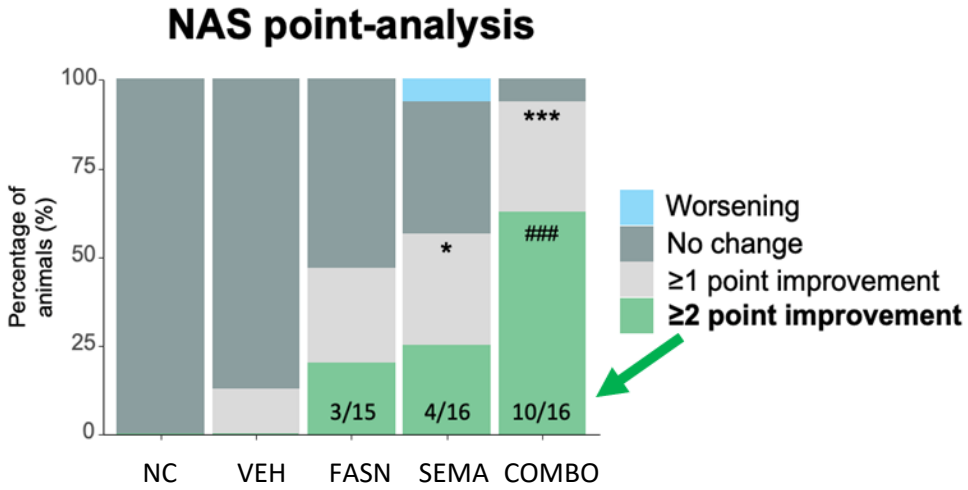
Combination of FASN Inhibitor and Semaglutide Improved Histological Features in MASH Mice

In a mouse model, combination treatment showed: 1) an additive effect on fibrosis reduction, 2) a direct impact on stellate cells and 3) a synergistic effect on NAS reduction





α-SMA: a marker of activated hepatic stellate cells



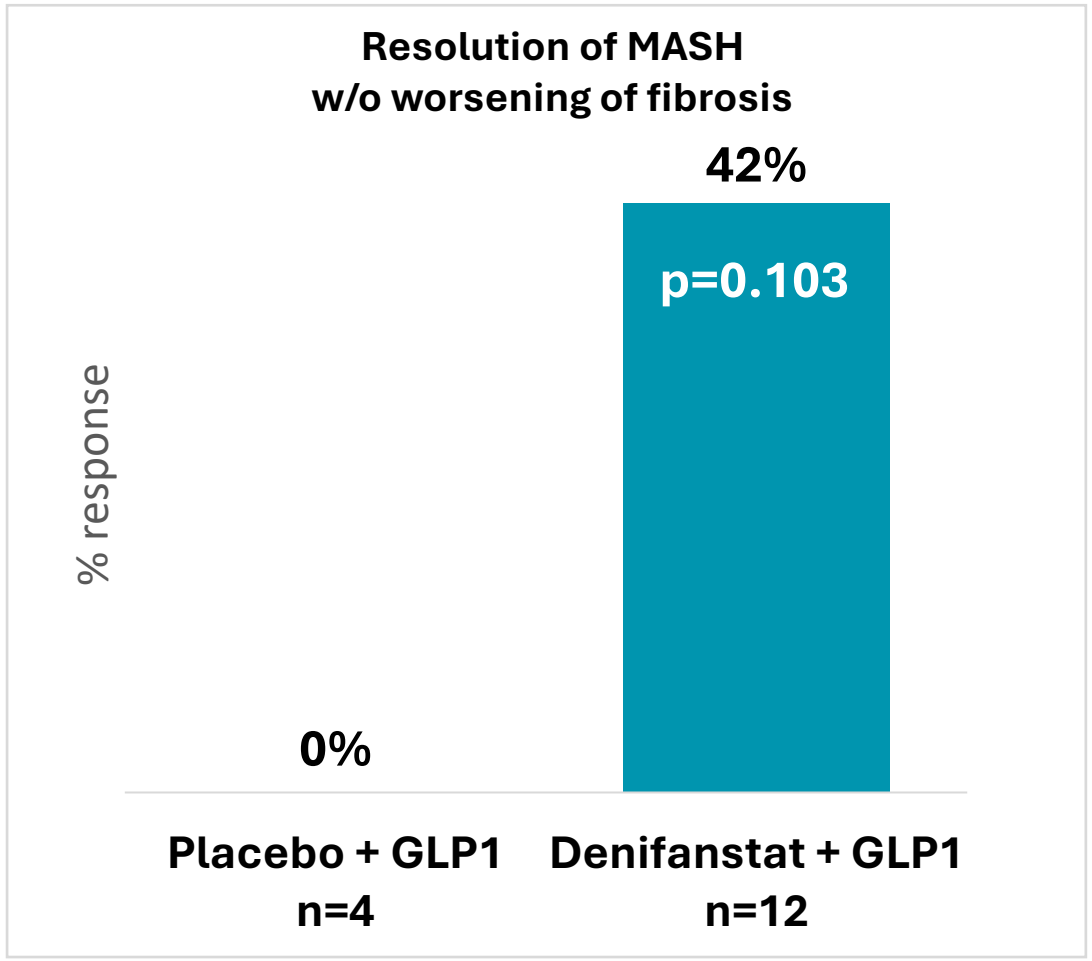
* p <0.05, ** p<0.01, *** p<0.001, ### p<0.001

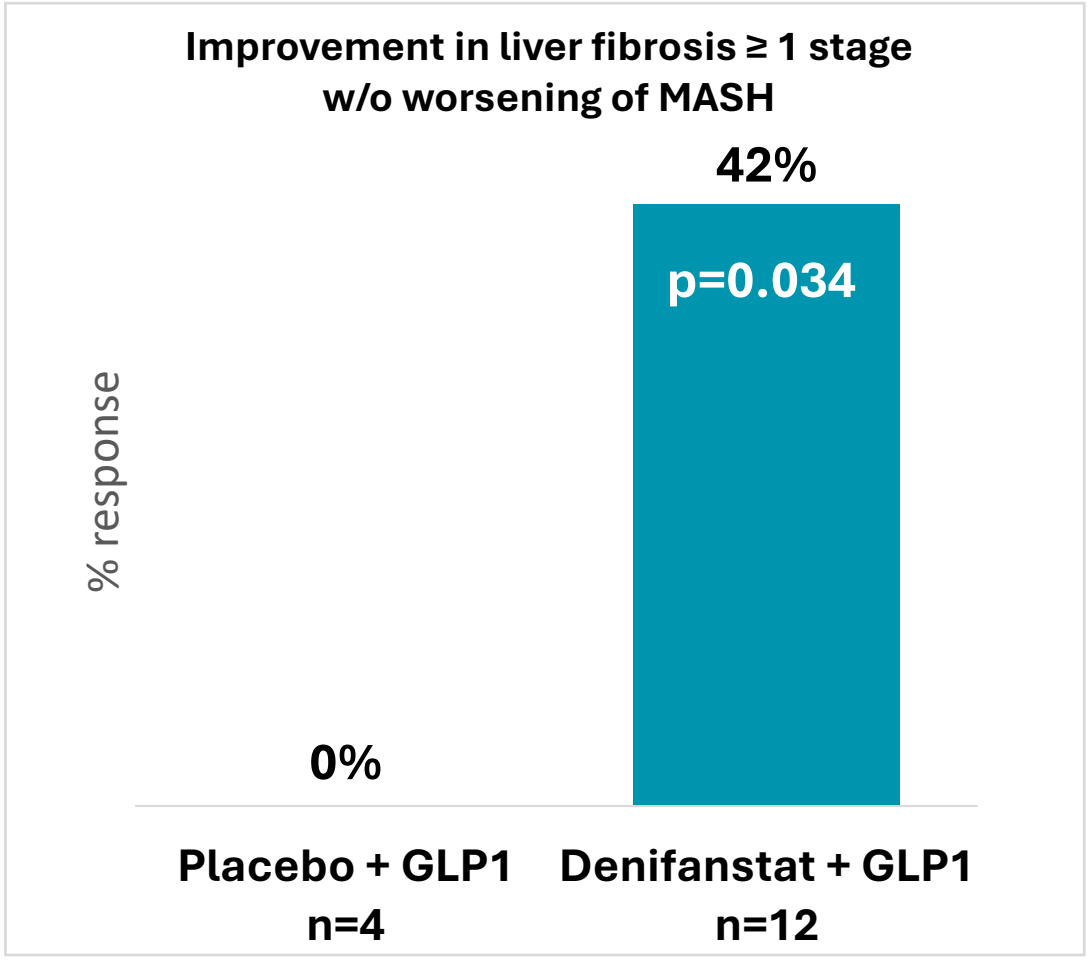
Tsai et al., AASLD 2023, GUBRA DIO MASH mice. PSR images were analyzed by FibroNest (PharmaNest), all scores shown with parenchymal correction

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

Patient Subset on Stable GLP1-RA at Baseline in Phase 2b: Liver Biopsy

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

Mechanism of Action Supports Combination Therapy Opportunity

Potential improved clinical outcome for patients with combination therapy of denifanstat, a fat synthesis inhibitor + a fat oxidizer (THR-beta agonist)

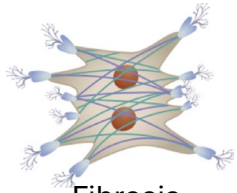
Combination therapy potential:

- Denifanstat MOA complementary to other MOAs – THR-beta, GLPs
- Opportunity for fixed dose combinations with other oral medications

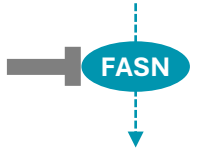
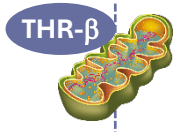
Hypothesis: distinct and complementary mechanisms of the combination lead to synergistic effect

Preclinical combination studies in mouse models showed beneficial impact of FASN inhibitor + resmetirom combination on histology and MASH biomarkers*

Liver fat
(hepatocyte)



Fibrosis
(stellate cell)

Denifanstat Reduces de novo Lipogenesis	Sugar  Fatty acids	**Direct** - decreases de novo lipogenesis	**Direct** – decreases fibrogenesis in stellate cells, liver fat and toxicity
Resmetirom Increases mitochondrial beta-oxidation	Fatty acids  Metabolized	**Direct** - increases fatty acid oxidation and improves mitochondrial function	**Indirect** – due to decreased liver fat and lipotoxicity

MOA- Mechanism of Action
* Preclinical study results presented at EASL 2024 Conference

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 toxicity	**Direct** – increases fatty acid oxidation **Indirect** – 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

Sources: 1. Phase 2b FASCINATE-2 data; 2. Harrison, et al. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. NEJM 2024 (PBO 318 /NR)
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.

FDC Clinical Development Program

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Potential Clinical Development Program for Denifanstat and Resmetirom Combination

Phase 1 plan to start in 2H 2025, subject to consultation with regulatory authorities

Phase 2 study design will be informed by the results of the Phase 1 trial

Step 1 - Phase 1 PK study for denifanstat and resmetirom

- PK to evaluate any drug/drug interaction
- Assess safety/tolerability
- Confirm optimal combination dose levels for later clinical efficacy study in MASH

Step 2 - Phase 2 clinical combination study with denifanstat and resmetirom in F4 MASH patients

- At least 52 weeks combination treatment
- Non-invasive biomarkers for early readout to show potential beneficial impact of the combination
- Primary endpoint: liver biopsies

Attractiveness of the Denifanstat/Resmetirom Combination

Denifanstat in MASH

- Denifanstat directly targets the 3 key drivers of MASH (metabolic dysfunction-associated steatohepatitis) – liver fat, inflammation, and fibrosis
- Successful outcome of Phase 2b trial; met both primary endpoints with significant reduction in fibrosis

Potential of a Fixed Dose Combination

- Pre-clinical data demonstrated synergistic effect of combination of FASN inhibitor and resmetirom
- Combination of a Phase 3-ready drug candidate, with the first drug approved for MASH
- IP for the combination of denifanstat and resmetirom:
  - Application filed 2024; if granted—2044; potential PTE to 2048
- Potential oral, once-daily product
- Potential to address an unmet need in MASH advanced patients (F4)

Next Steps

- Phase 1 clinical trial to evaluate the pharmacokinetics (PK) and tolerability of a combination of denifanstat and resmetirom planned to initiate in 2H 2025; data readout expected 1H 2026
- If the outcome of this Phase 1 trial is positive, will explore moving into the development of a combination product for patients living with MASH
- Prudent deployment of resources with quick path to go/no go decision

Q&A

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