Denifanstat, a fatty acid synthase (FASN) inhibitor, shows significant fibrosis improvement and MASH resolution in FASCINATE-2, a Ph2b 52 week global, randomized, double blind, placebo-controlled trial in patients with F2 or F3 fibrosis

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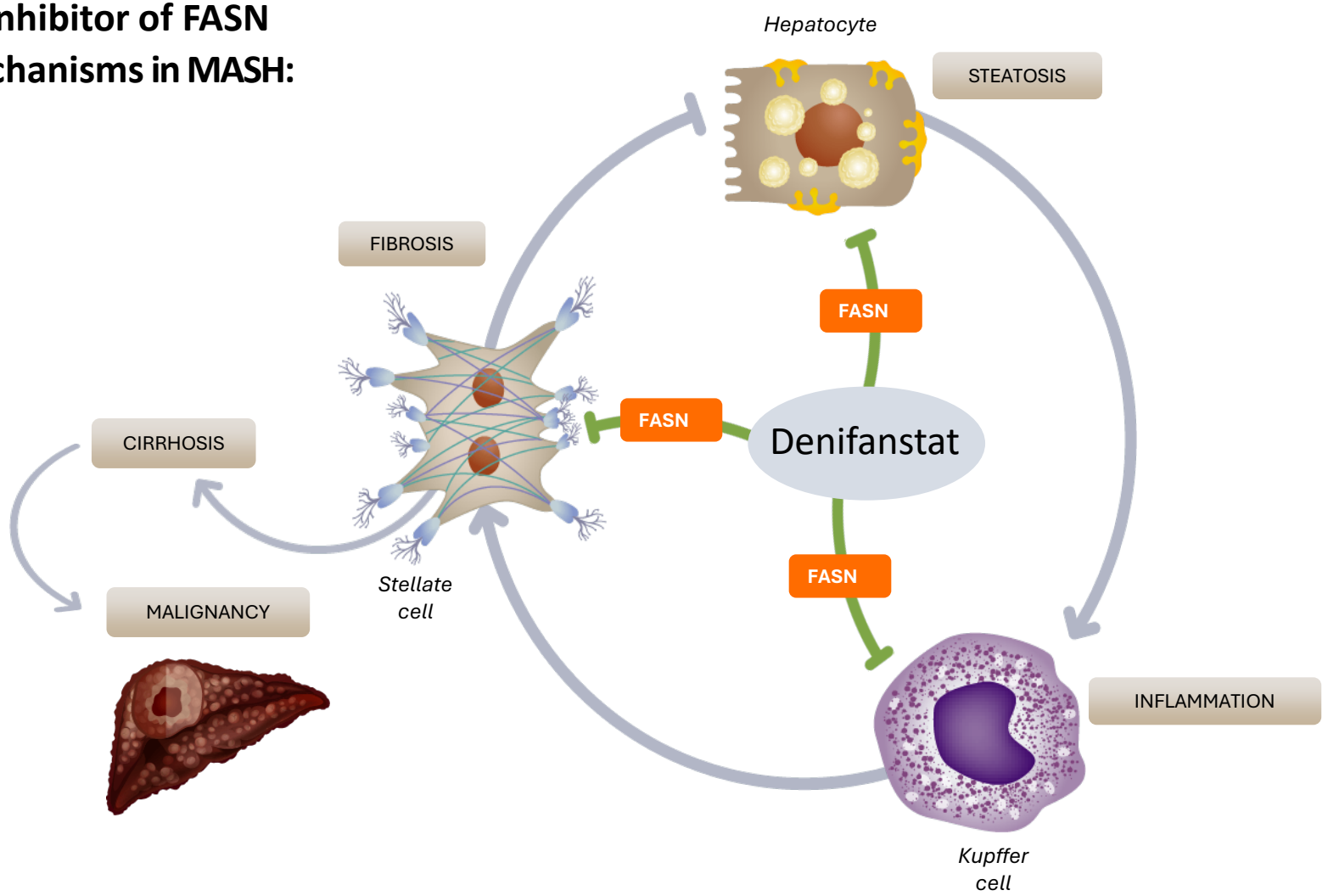
Disclosures

- Consultant or advisory board member for 89bio, Alnylam, Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol-Myer Squibb, Cirius, CohBar, DiCerna, Galmed, Gilead, Glympse bio, Intercept, Ionis, Metacrine, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sagimet, and Viking Therapeutics. In addition, my institution has received grant support from Allergan, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, NGM Biopharmaceuticals, Novartis, Pfizer, pH Pharma, and Siemens. Co-founder of Liponexus, Inc.

FASN Inhibition Addresses Three Independent Mechanisms of MASH Development and Progression

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

1. Blocks **steatosis** via inhibiting de novo lipogenesis in hepatocytes
2. Reduces **inflammation** via preventing immune cell activation
3. Blunts **fibrosis** via inhibiting stellate cell activation

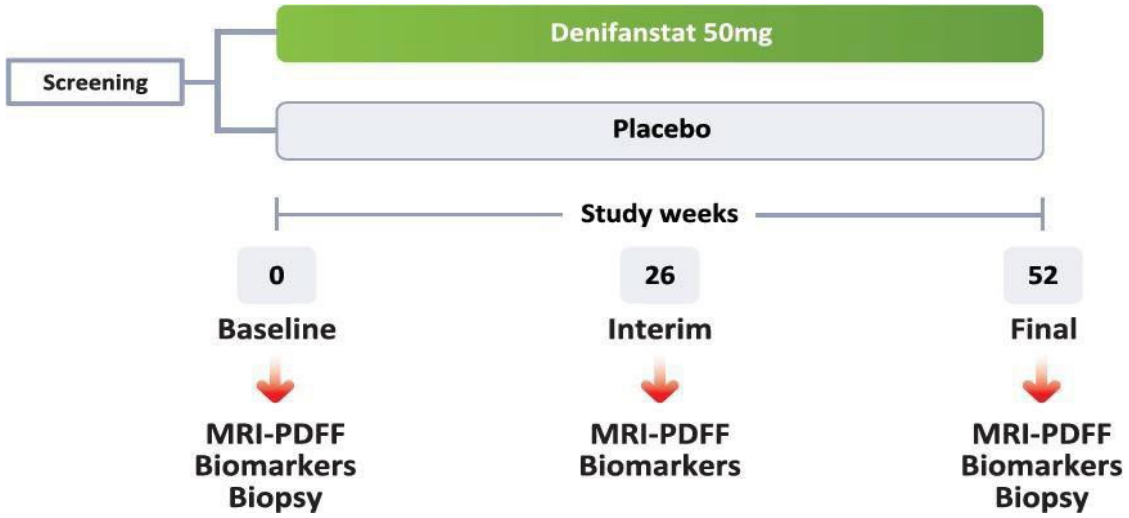


FASCINATE-2 Phase 2b Biopsy Trial Design
Measuring Histological Improvement

FASCINATE-2 Phase 2b

Aim of this trial: Examine safety and efficacy of denifanstat vs placebo in improving fibrosis and NASH resolution after 52 weeks of treatment

- Biopsy confirmed F2-F3 MASH patients
- Randomized 2:1 50mg or placebo, double-blind



Primary endpoints

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

OR

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

Other selected endpoints

- Improvement in liver fibrosis ≥1 stage without worsening of MASH (Bx)
- Digital AI pathology
- MRI-PDFF: absolute decrease, % change from baseline, % pts ≥30% reduction from baseline (responders)

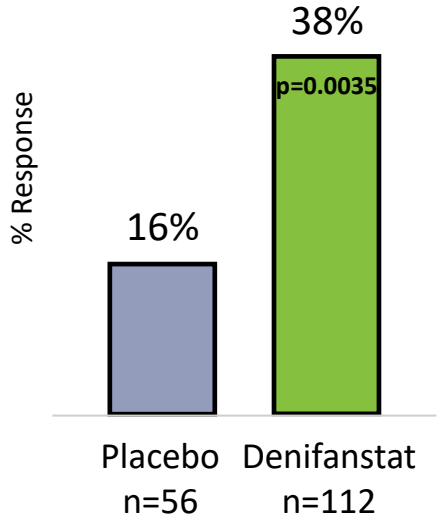
AI: Artificial Intelligence, Bx; biopsy, MRI-PDFF; magnetic resonance imaging derived proton density fat fraction, NAS; NAFLD Activity Score.

FASCINATE-2 Baseline Characteristics
Typical F2/F3 MASH ITT Population

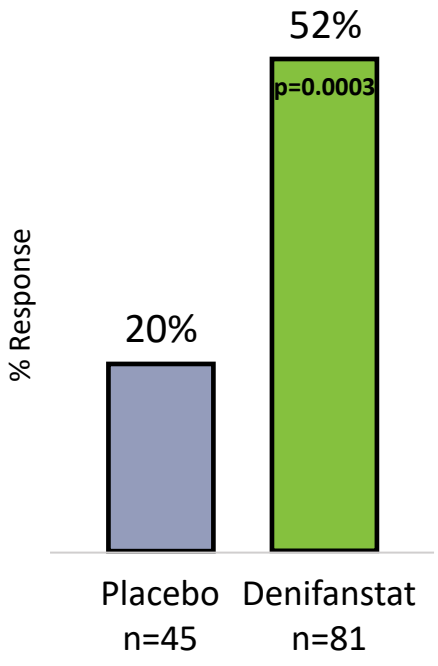
Characteristic	Placebo (n=56)	Denifanstat 50mg (n=112)	Total (n=168)
Age – yr	58·4±11·9	56·3±10·5	57·0±11·0
Male sex – no. (%)	22 (39·3)	46 (41·1)	68 (40·5)
White race – no. (%)	50 (89·3)	100 (89·3)	150 (89·3)
Hispanic or Latino ethnic group – no. (%)	21 (37·5)	34 (30·4)	55 (32·7)
Body mass index	36·2±6·6	34·4±5·8	35·0±6·1
Type 2 diabetes – no. (%)	34 (60·7)	69 (61·6)	103 (61·3)
Alanine aminotransferase – U/liter	64·5±35·4	50·5±25·1	55·2±29·6
Aspartate aminotransferase – U/liter	51·8±30·8	41·9±22·7	45·2±26·0
F2	27 (48·2)	48 (42·9)	75 (44·6)
F3	29 (51·8)	64 (57·1)	93 (55·4)
Liver fat (MRI-PDFF) - %	18·8±6·9	16·8±7·2	17·5±7·2
Liver fat (Fibroscan CAP)	344·9±35·7	336·5±36·4	339·3±36·3
Liver Stiffness - kPa	12·2±4·6	11·2±3·9	11·6±4·2
FAST Score	0·6±0·2	0·6±0·2	0·6±0·2
LDL-cholesterol – mg/dL	103·1±38·9	93·3±37·9	96·5±38·4
Triglycerides – mg/mL	176·6±152·2	170·2±82·9	172·3±110·4

Primary Endpoints: Liver Biopsy
Denifanstat Achieved Statistical Significance at 52 Weeks

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

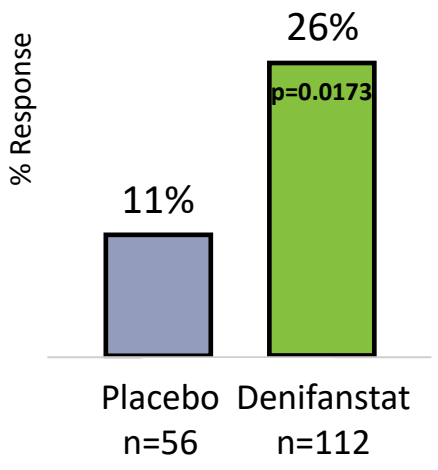


ITT population

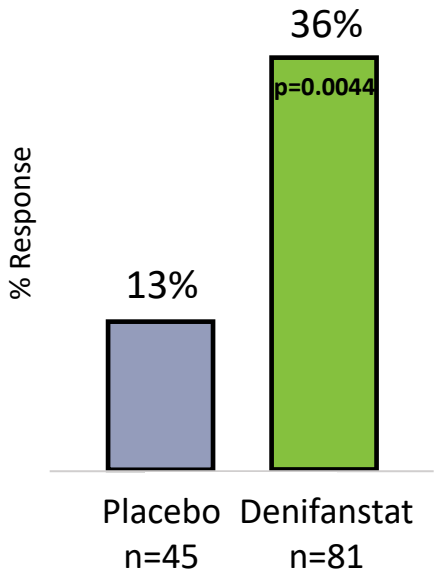


mITT population

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



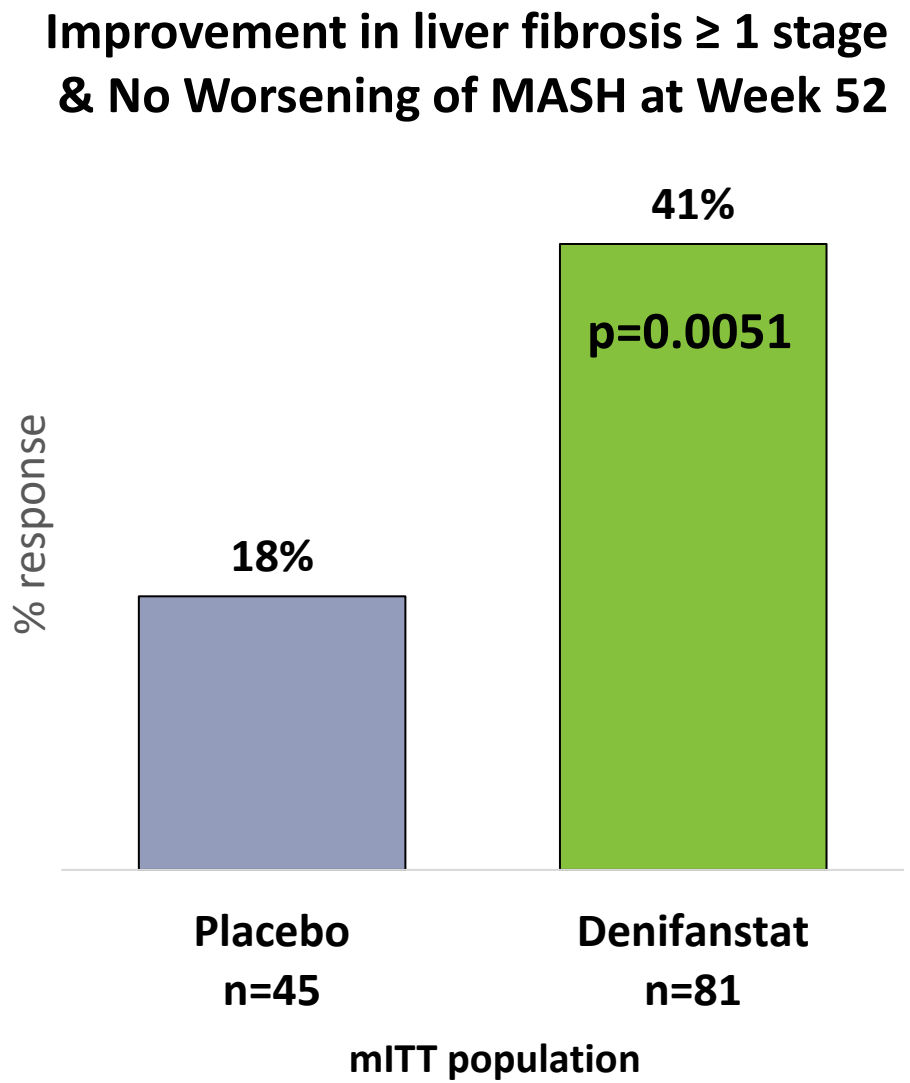
ITT population



mITT population

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

Secondary Endpoint: Liver Fibrosis
Denifanstat Achieved Statistical Significance



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

SAGIMET BIOSCIENCES

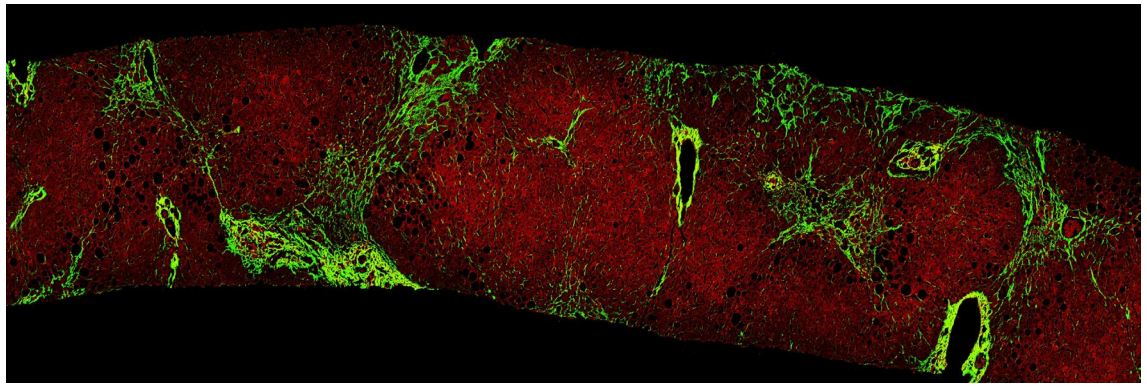
Secondary Endpoints: Liver Fibrosis

Denifanstat Achieved Profound Improvement of Fibrosis

Fibrosis Endpoints	Subgroup	Placebo	Denifanstat	p-value
≥1 stage improvement in fibrosis w/o worsening of MASH	ITT	14%	30%	0.0199
	mITT	18%	41%	0.0051
	F3	13%	49%	0.0032
≥2 stage improvement in fibrosis w/o worsening of MASH	mITT	2%	20%	0.0065
	F3	4%	34%	0.0050
Progression to cirrhosis (F4)	mITT	11%	5%	>0.05

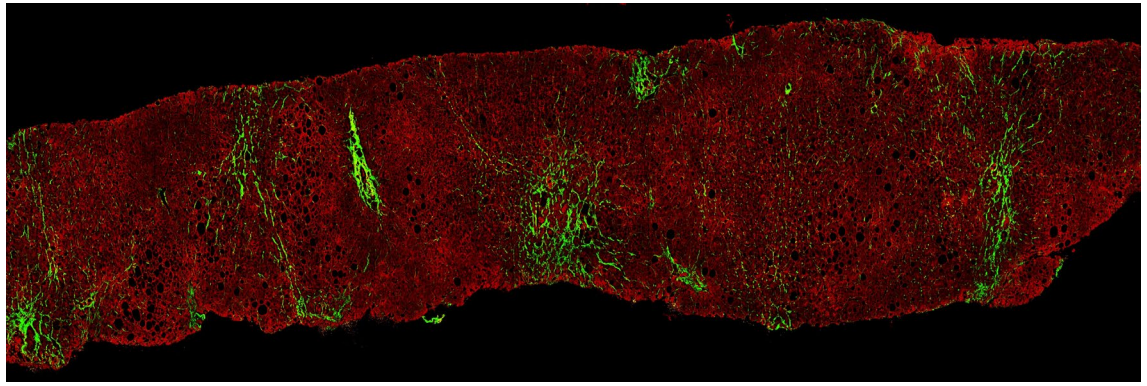
Additional Fibrosis Analysis Using AI-based Digital Pathology
Supporting Evidence that Denifanstat Significantly Reduced Fibrosis

Pre-Treatment Pt A
NASH-CRN Fibrosis stage F3

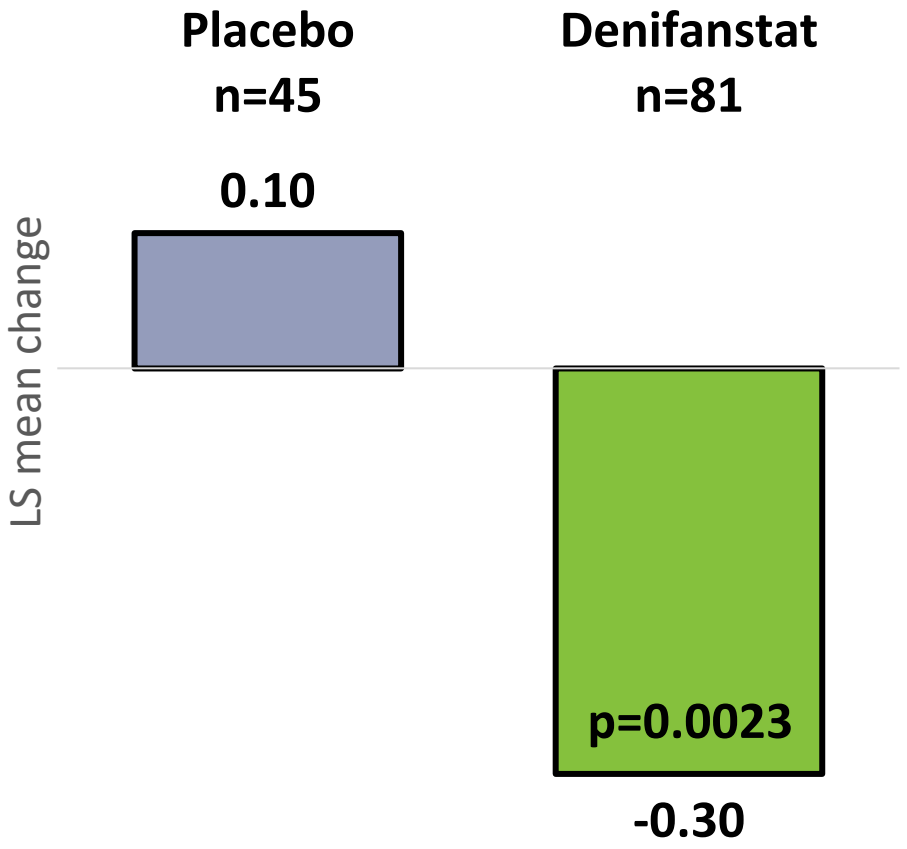


Denifanstat

Post-Treatment Pt A
NASH-CRN Fibrosis stage F1

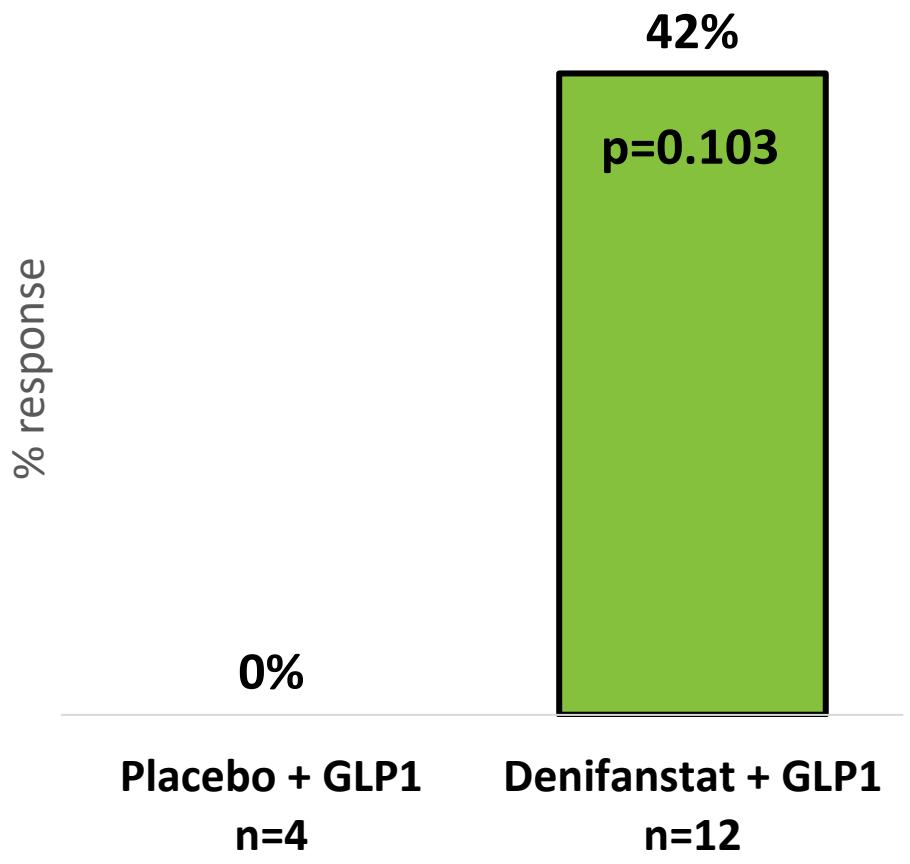


qFibrosis Continuous Value
Change from Baseline

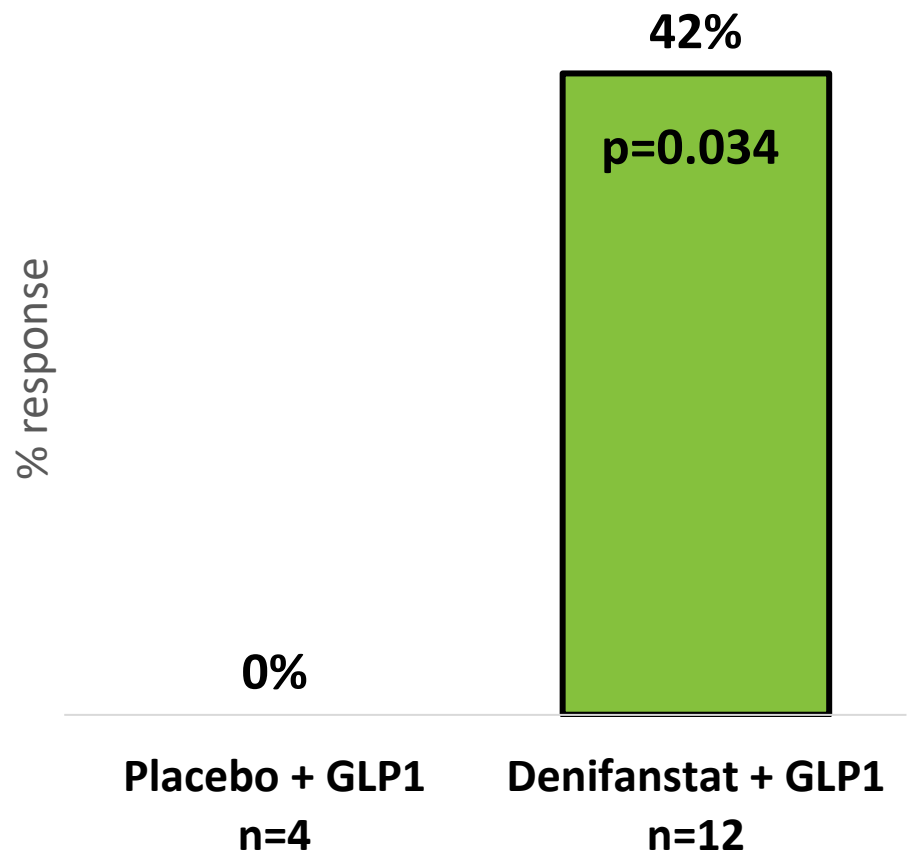


Patient Subset on Stable GLP1-RA at Baseline: Liver Biopsy
Denifanstat Improves MASH Resolution and Fibrosis

Resolution of MASH w/o worsening of fibrosis



Improvement in liver fibrosis ≥ 1 stage w/o worsening of MASH



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 with GLP1 and denifanstat

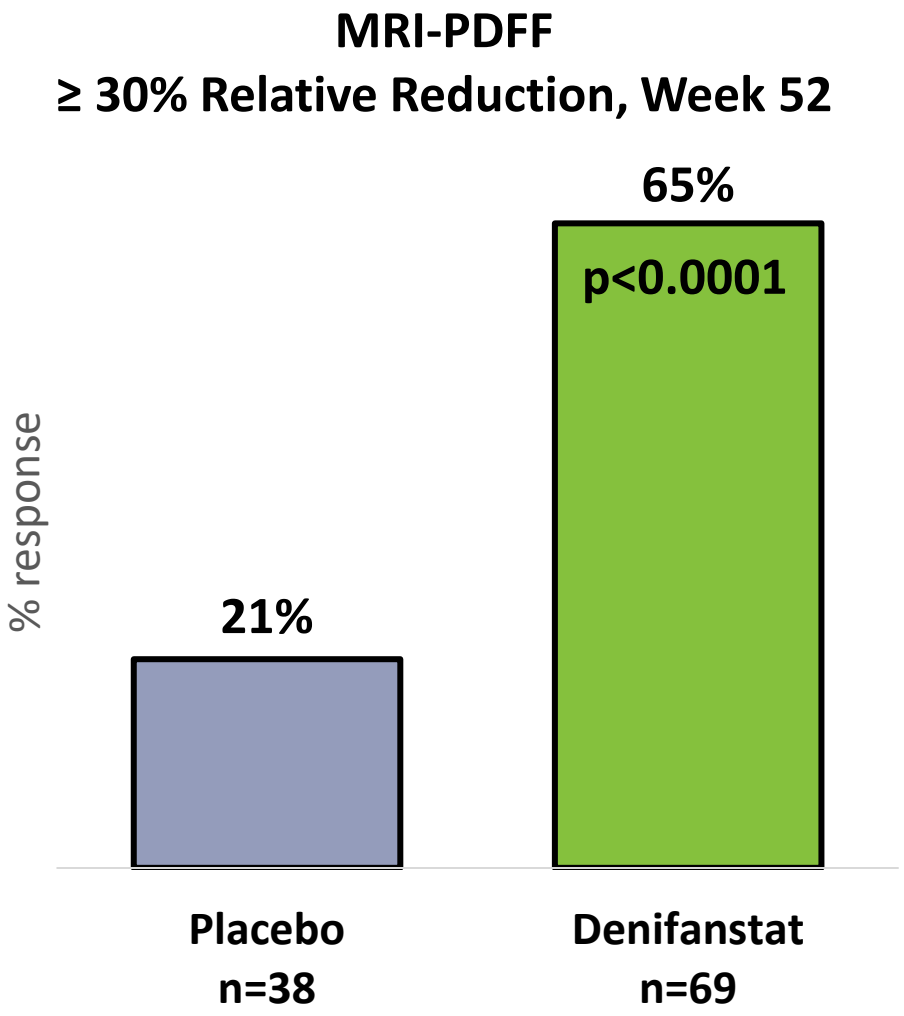
FASCINATE-2: Safety
Denifanstat Was Generally Well Tolerated

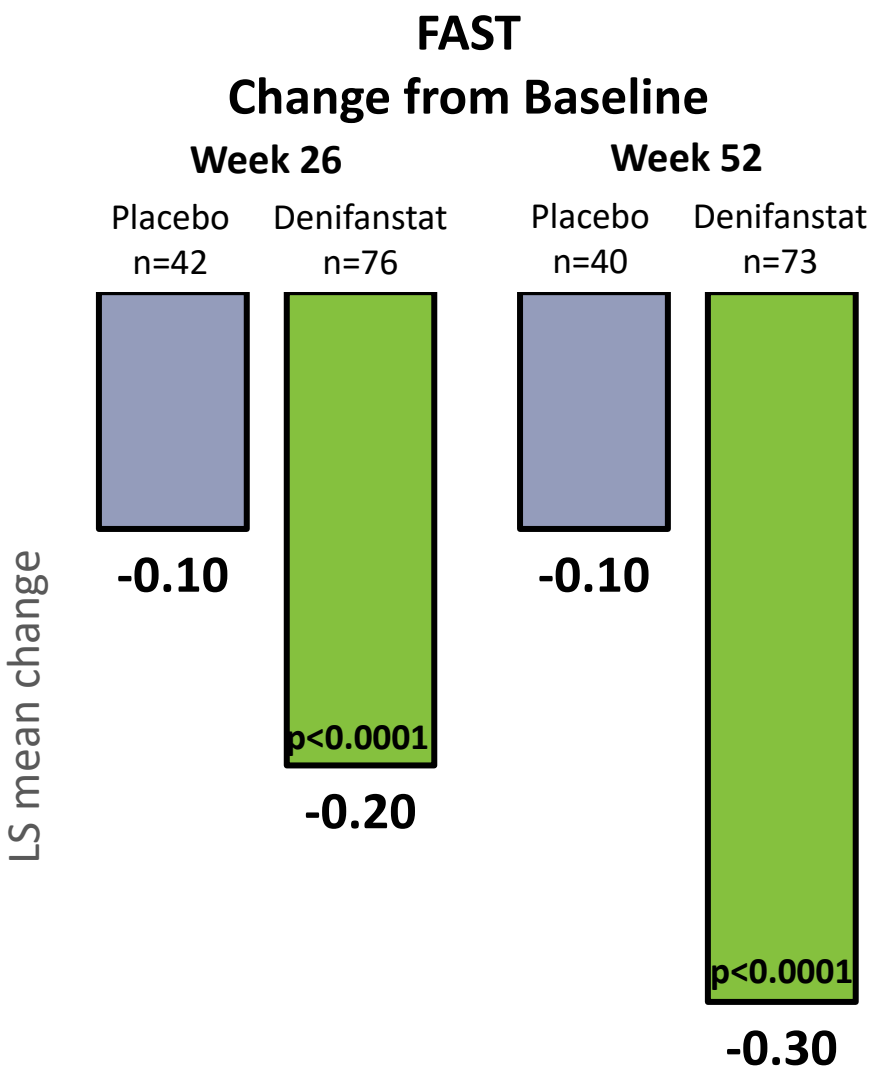
Event n (%)	Placebo (n=56)	Denifanstat 50mg (n=112)	Total (n=168)
Any adverse event	46 (82.1)	99 (88.4)	145 (86.3)
Adverse event related to denifanstat or placebo	20 (35.7)	51 (45.5)	71 (42.3)
Serious adverse event	3 (5·4)	13 (11·6)	16 (9·5)
TEAE leading to study drug discontinuation	3 (5·4)	22 (19·6)	25 (14·9)
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 signal
- AE of hair thinning stabilizes with a 2-4 week dose hold
- 6% of patients discontinued from the study with hair thinning
  - Previously <2% of the patients experienced hair thinning at 50mg
- Hair thinning is reversible

Denifanstat Decreased Liver Fat by MRI-PDFF and Reduced FAST Score

Denifanstat Achieved Statistical Significance

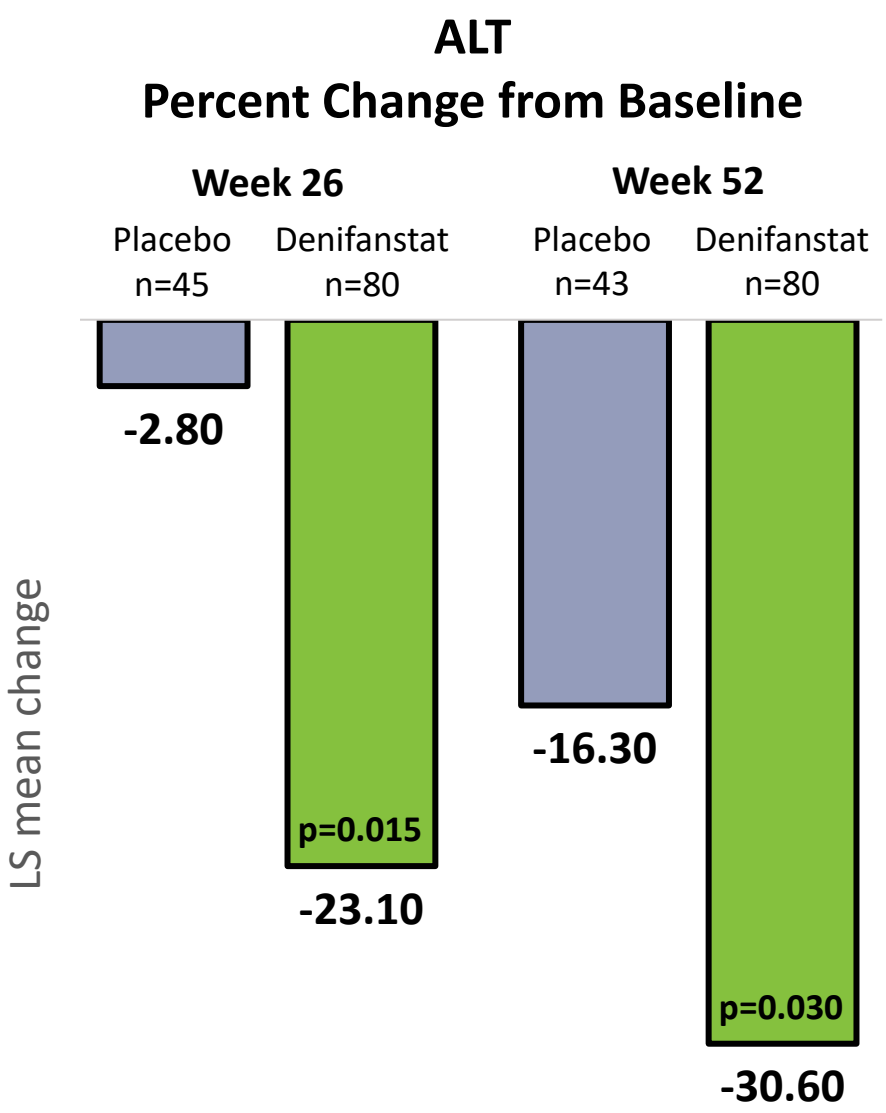


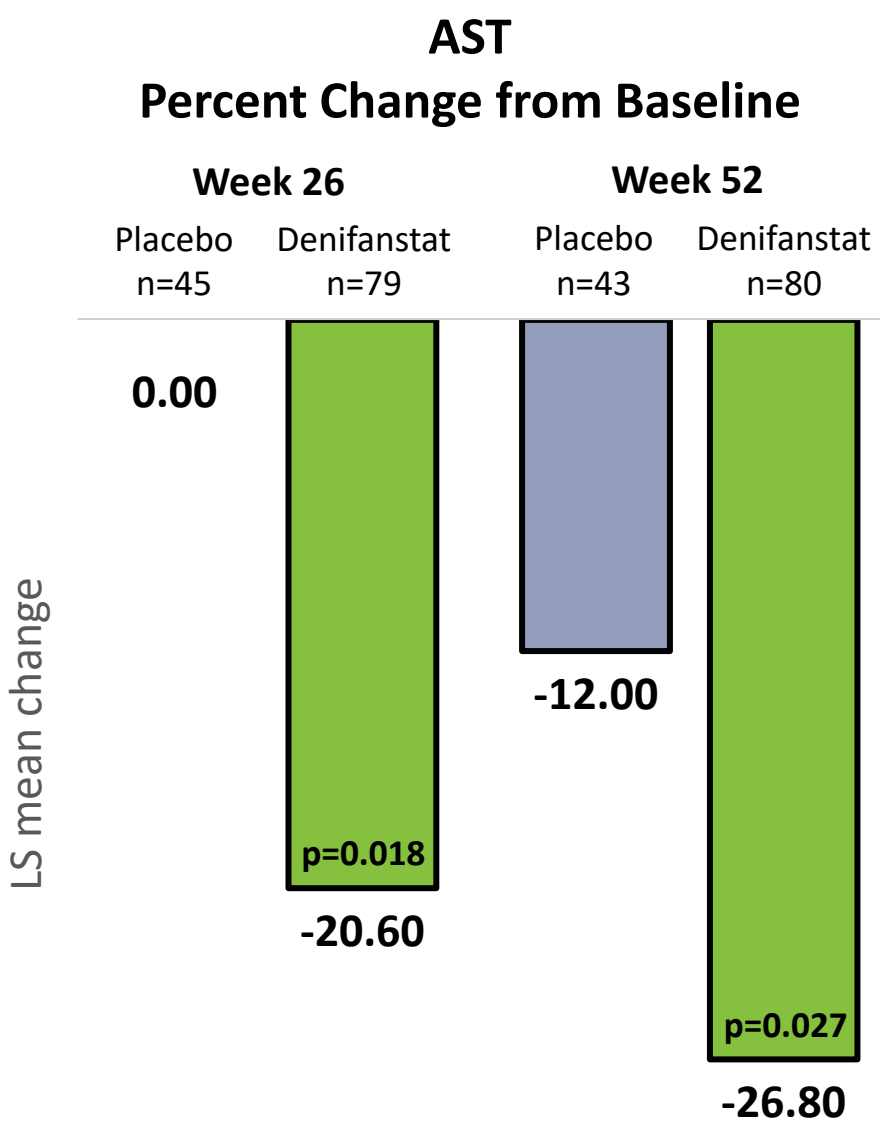


≥30% reduction: Cochran-Mantel-Haenszel Test. Relative reduction: Mixed-effects Model for Repeated Measures . mITT population.

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

Secondary Endpoints: Liver Enzymes
Denifanstat Decreased ALT and AST Levels

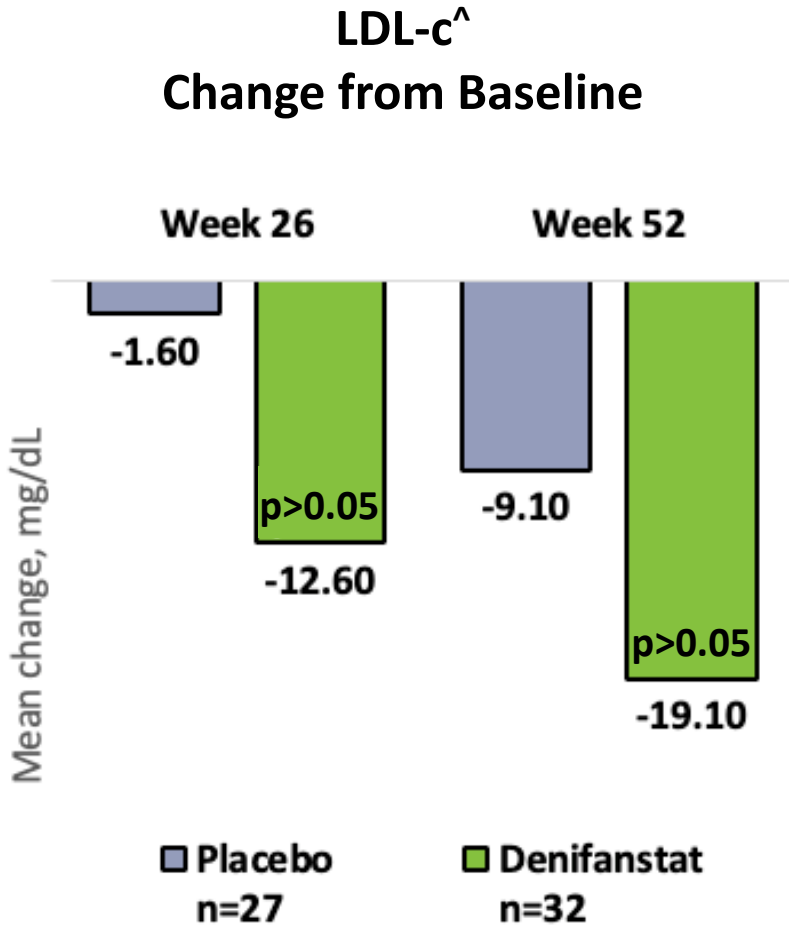


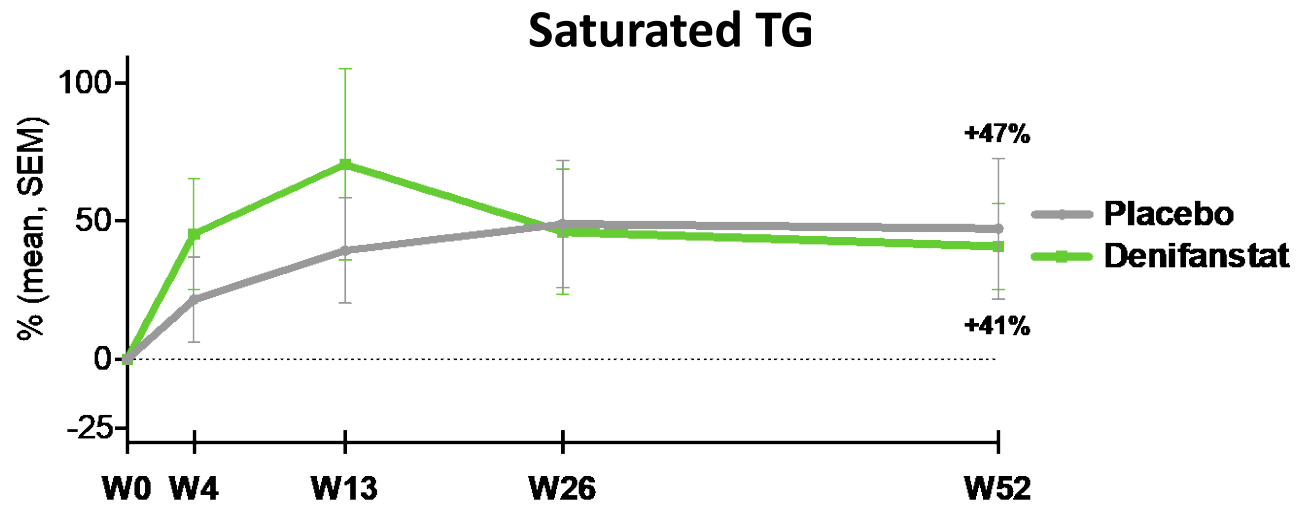


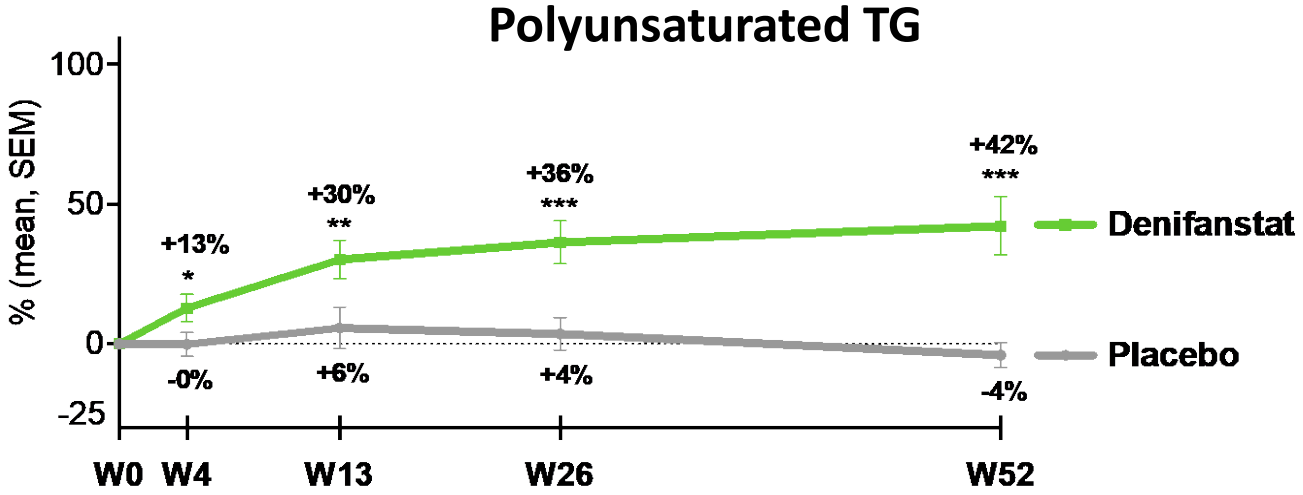
Mixed-effects Model for Repeated Measures – Two sided at the 0.05 significance level. mITT population

Cardiometabolic Health

Denifanstat Decreased LDL-c Levels and Increased Polyunsaturated Triglycerides

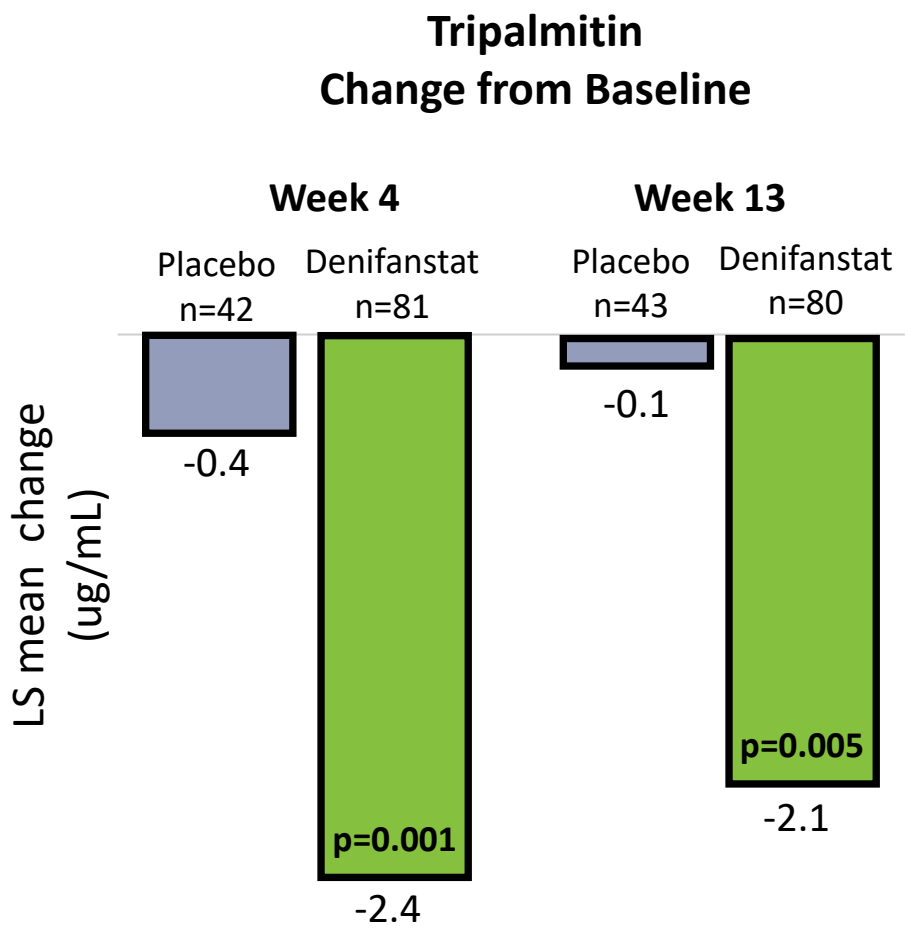






mITT population. ^For LDL-c, baseline > 100 mg/dL. Mixed-effects Model for Repeated Measures – Two sided at the 0.05 significance level. *p<0.05, **p<0.01, ***p<0.001

Denifanstat Rapidly and Robustly Reduces De Novo Lipogenesis



- Tripalmitin is a biomarker of DNL inhibition
- Denifanstat rapidly reduced tripalmitin as soon as 4-weeks of treatment
- We plan to continue the development of tripalmitin and additional markers as potential biomarker(s) of treatment response for denifanstat

Conclusions

- **Denifanstat, a fatty acid synthase inhibitor, was better than placebo for both the subpart H approval pathway endpoint(s) including**
  - **MASH resolution without worsening of fibrosis**
  - **Fibrosis improvement without worsening of MASH**
- **Denifanstat delivered clinically meaningful and statistically significant improvements in liver histology**
  - **Fibrosis regression: 2-stage fibrosis improvement as well as significant improvement in F3 patients**
- **Improvements in MRI-PDFF, FAST, ALT, AST and LDL**
- **Tripalmitin is being developed as an early biomarker of target engagement and treatment response**
- **Denifanstat was generally well tolerated**
  - **Adverse event profile is balanced between active and placebo groups, excluding hair thinning, all of which were Grade 1 or 2, well managed and reversible upon dose reduction/holiday**
- **Response to treatment with denifanstat was similar in those with or without concomitant GLP-1 analogues**
- **Furthermore, we are also developing pre-clinical data regarding combination with GLP-1 and THR-B (posters THU231/#1326 and THU336/#LB235) and others in development**
- **These results support continued clinical development of denifanstat to Phase 3 clinical trials in MASH**

Thank you to the patients and families who participated in our study.

We honor and remember Stephen Harrison for his tireless dedication to the advance of MASH therapies for this unmet need.
He is greatly missed.