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Correlation between AI-based digital pathology and non-invasive tests (NITs) Baseline data from the FASCINATE-2 phase 2b clinical study of denifanstat in patients with F2/F3 NASH

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DISCLOSURES

DISCLOSURES: I disclose the following financial relationship(s) with a commercial interest:

Stephen A. Harrison, M.D reports:

Principal Investigator of Grant Research: Akero Therapeutics, Inc., Axcella Health, Inc., Cirius Therapeutics, Inc., Cymabay Therapeutics, Inc., Enyo Pharma S.A, Galectin Therapeutics, Inc., Genfit Corp, Gilead Sciences, Inc., Hepion Pharmaceuticals, Inc., Hightide Therapeutics, Inc., Intercept Pharmaceuticals, Inc., Madrigal Pharmaceuticals, Inc., Metacrine Inc., NGM Biopharmaceuticals Inc., Northsea Therapeutics , Novartis Pharmaceuticals Corp, Novo Nordisk, Poxel, Sagimet Biosciences, Viking Therapeutics, Inc.

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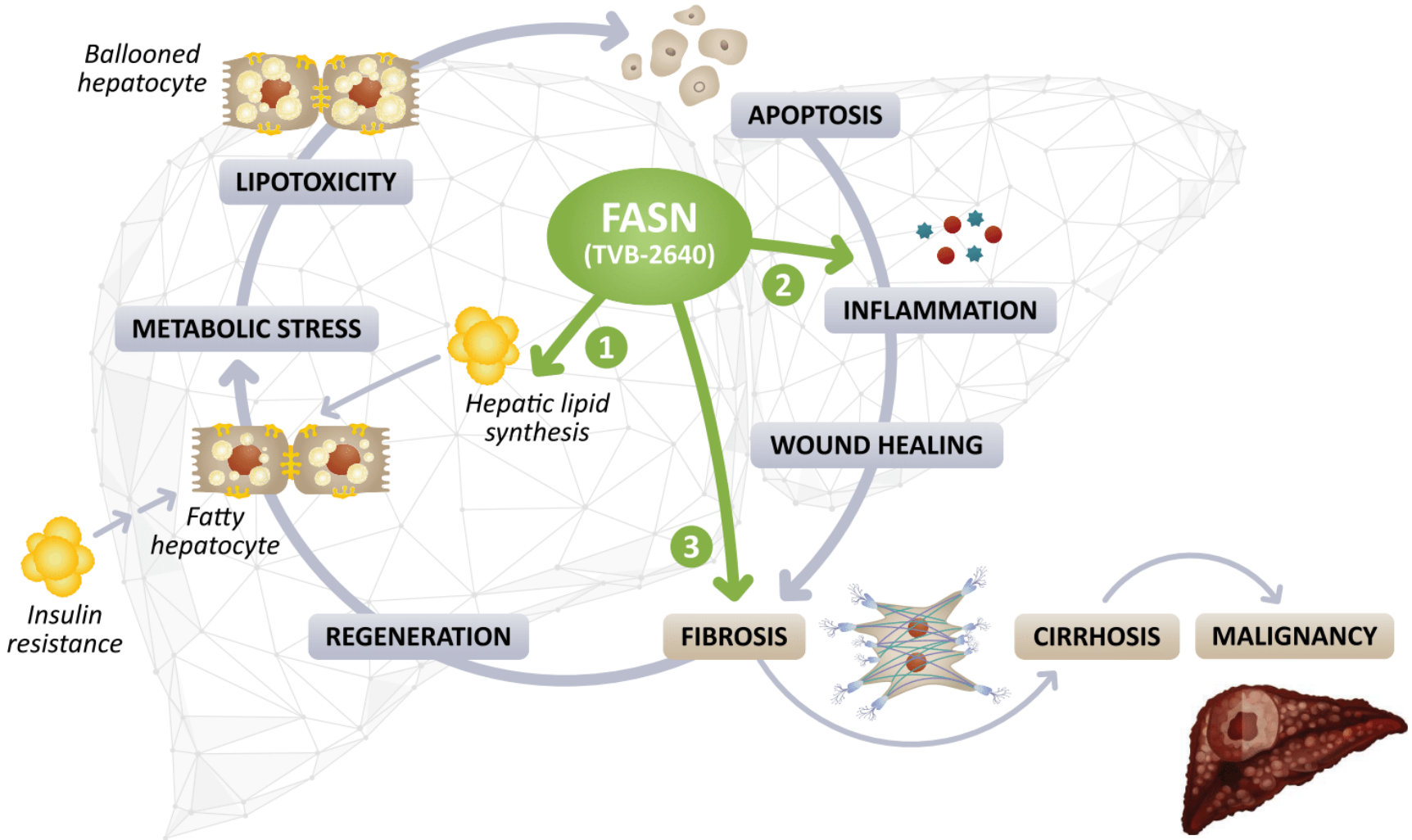
Denifanstat: Mechanism of Action

Independent mechanisms designed to:

1. Block steatosis
2. Reduce inflammation
3. Blunt fibrosis

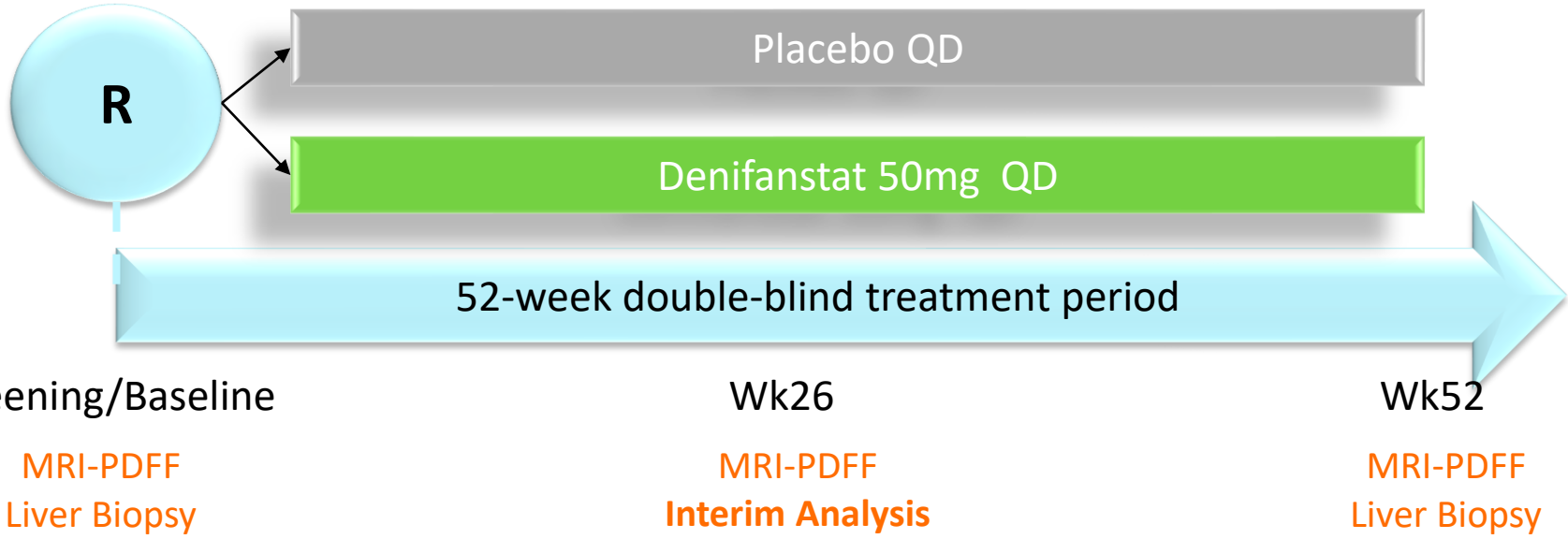


Adapted from Wegermann et al, Clinical Liver Disease, Vol 11, No 4, April 2018 , DOI: 10.1002/cld.709

FASCINATE-2 – Phase 2b - Study Design

KEY ELIGIBILITY CRITERIA

F2-F3 NASH
NAS ≥ 4



- **Post-Hoc Exploratory Analysis**
  - Random selection of a subset of patients from screening (F0 to F4)
  - Correlation of screening/baseline non-invasive data with AI digital pathology using the HistoIndex platform parameters

Baseline Characteristics

	Screen Fail Patients F0-F1 (n=38)	Randomized patients F2-F3 (n=48)	Screen Fail Patients F4 (n=9)
Age, year	56.0 (13.0) / n=38	60.5 (15.5) / n=48	67.0 (13.5) / n=8
AST, U/L	26.5 (12.0) / n=38	38.0 (26.5) / n=48	41.0 (13.0) / n=9
ALT, U/L	30.5 (24.0) / n=38	50.0 (33) / n-=48	44.0 (33.0) / n=9
FibroScan LSM, kPa	9.6 (3.0) / n=23	9.4 (5.2) / n=47	23.1 (14.2) / n=7
FAST	0.4 (0.4) / n=22	0.6 (0.3) / n=43	0.7 (0.4) / n=6
AGILE3+	0.5 (0.2) / n=14	0.6 (0.5) / n=46	0.97 (0.0) / n=2
ELF	-	9.9 (1.0) / n=45	-
Liver Fat Content, % (MRI-PDFF)	-	17.1 (10.0) / n=48	-
Fibrosis Stage – Central Reading	F0: 50% / F1:50%	F2: 48% / F3:52%	F4: 100%
qFibrosis **% Collagen**	1.7 (0.3) / n=38 3.0 (1.6) / n=38	2.3 (0.9) / n=48 6.9 (4.0) / n=48	3.5 (1.3) / n=9 12.7 (7.0) / n=9
qSteatosis **% Steatosis**	1.1 (2.0) / n=38 16.3 (25.0) / n=38	2.2 (0.8) / n=48 33.7 (18.4) / n=48	1.6 (1.2) / n=9 19.9 (12.7) / n=8

Data are Median (IQR) or (%)

Non-Invasive Markers of Fibrosis

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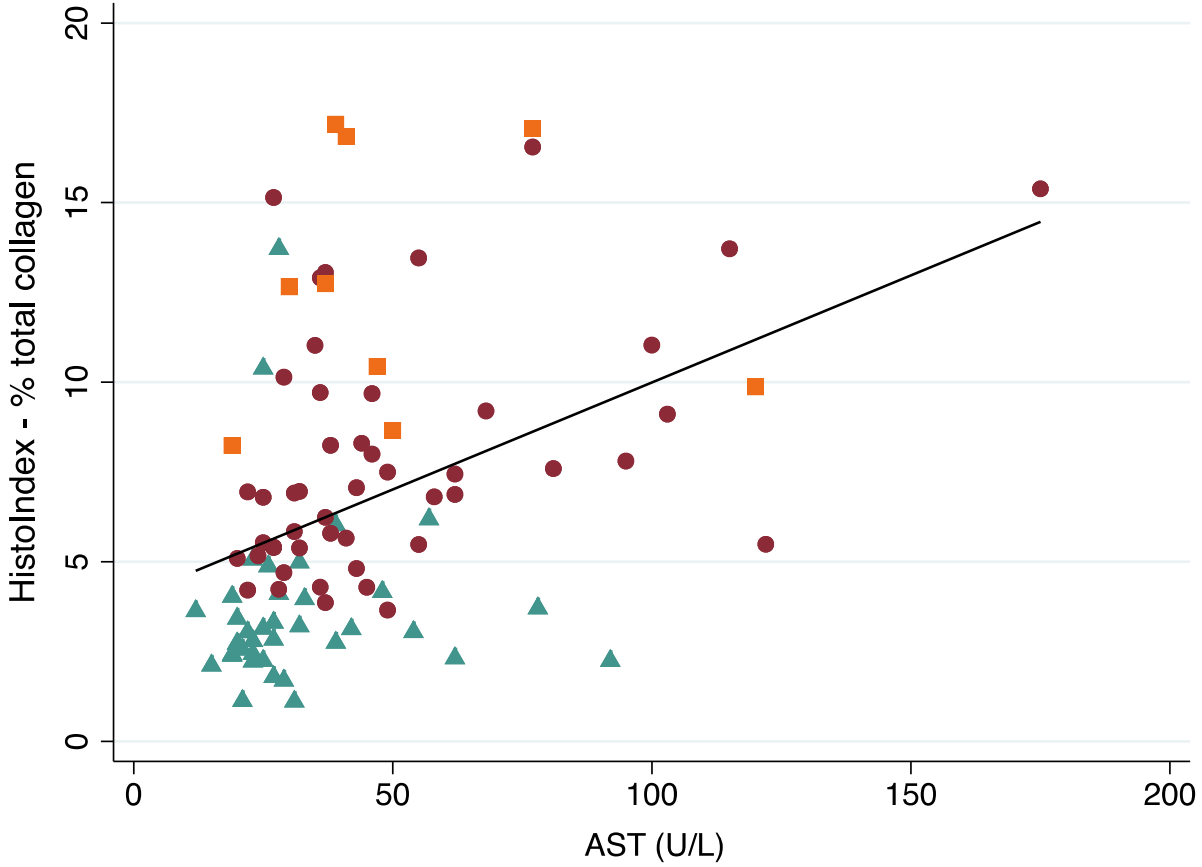
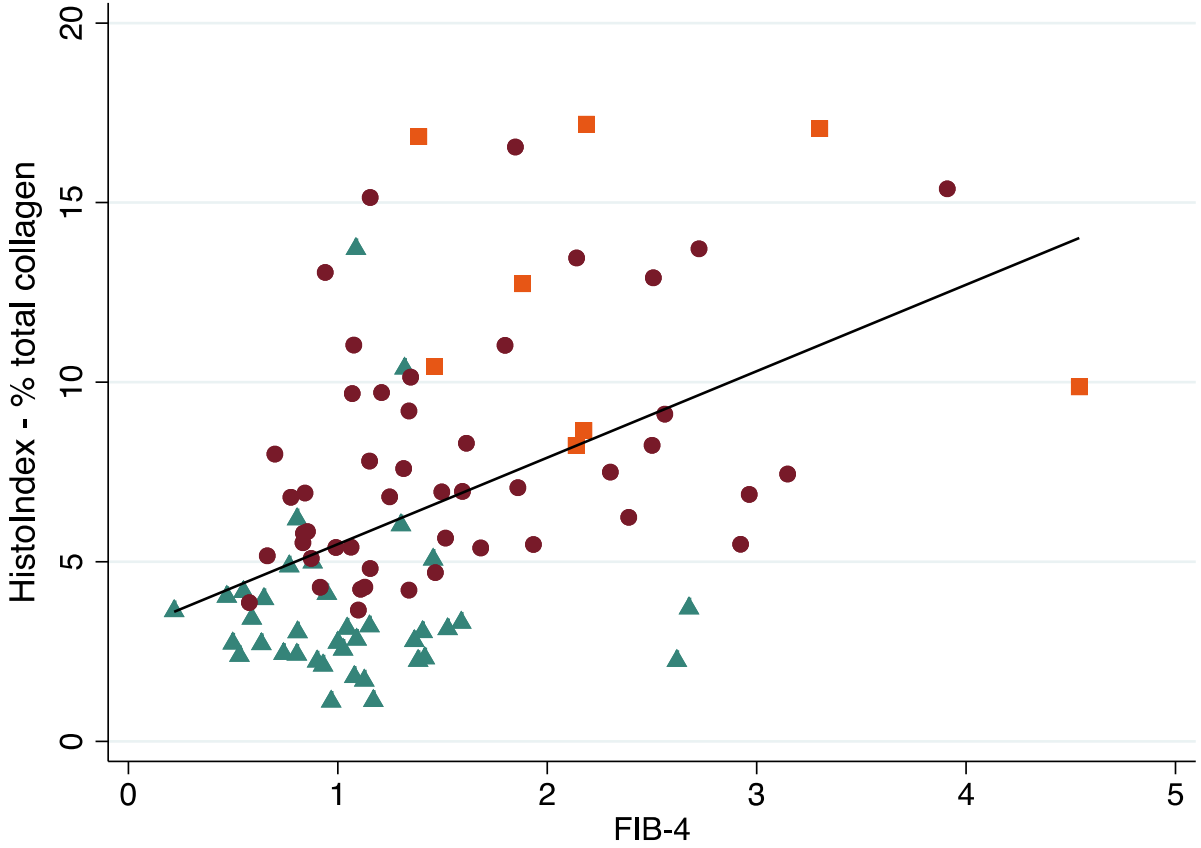
AST – n=95

Correlation: **0.478** (95%CI: 0.306-0.620)



FIB-4 – n=94

Correlation: **0.469** (95%CI: 0.295-0.614)



Fibrosis Stage (NASH-CRN)

▲ F0-F1 ● F2-F3 ■ F4

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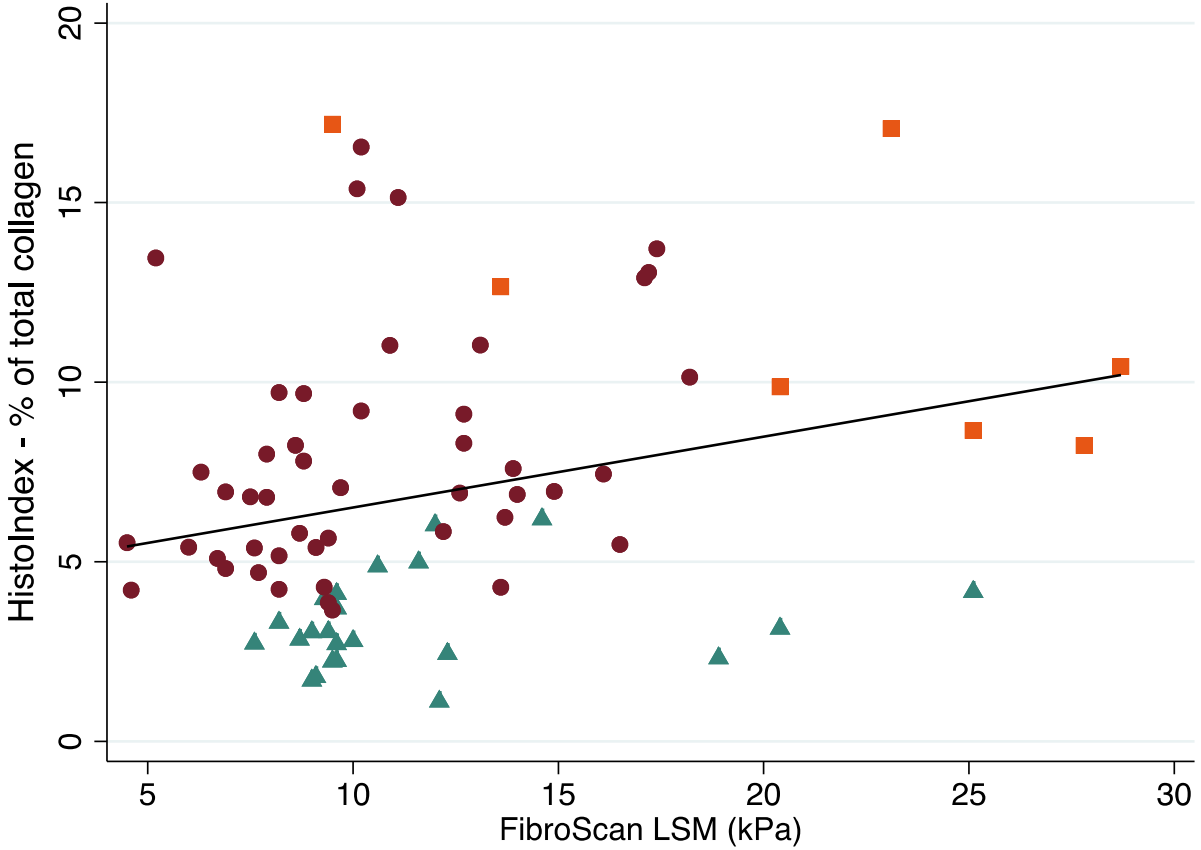
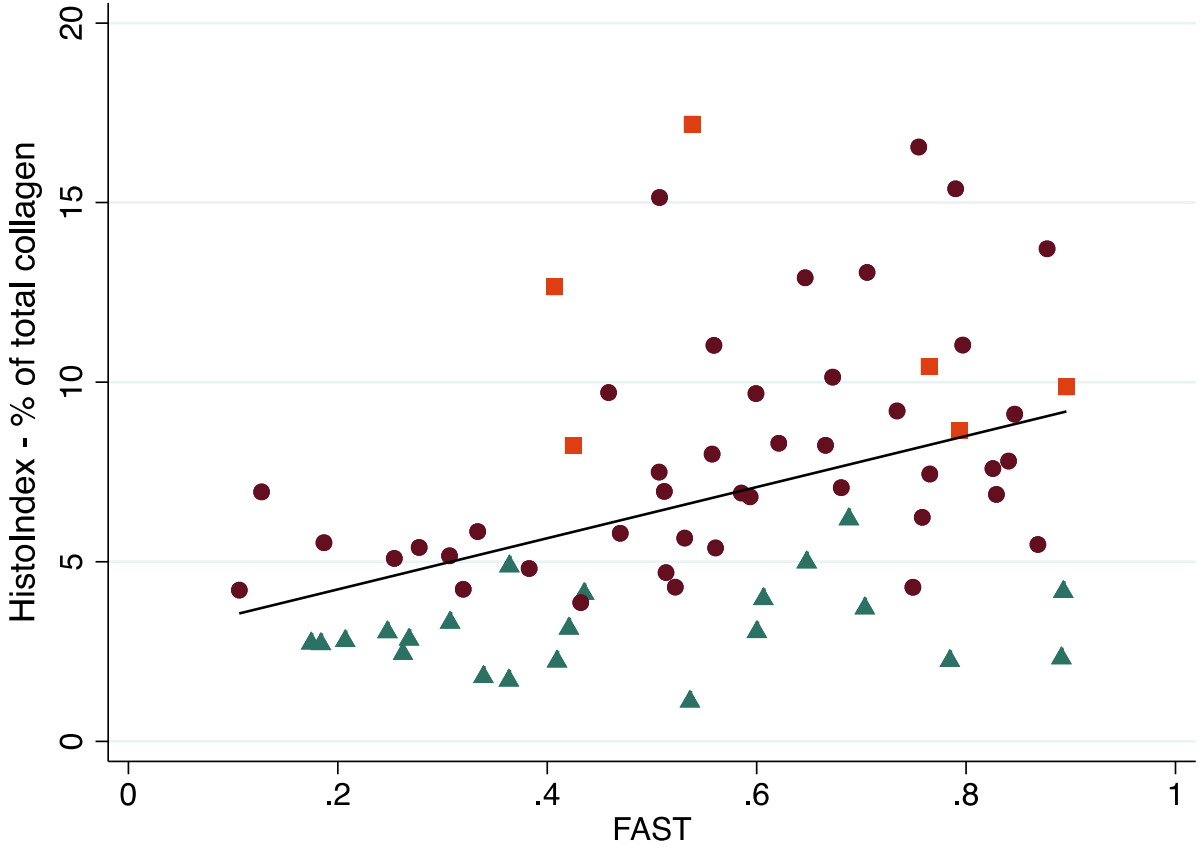
Non-Invasive Markers of Fibrosis

LSM – n=77
Correlation: **0.276** (95%CI: 0.055-0.471)



FAST – n=71
Correlation: **0.449** (95%CI: 0.241-0.617)



Fibrosis Stage (NASH-CRN)
F0-F1 F2-F3 F4

Non-Invasive Markers of Fibrosis

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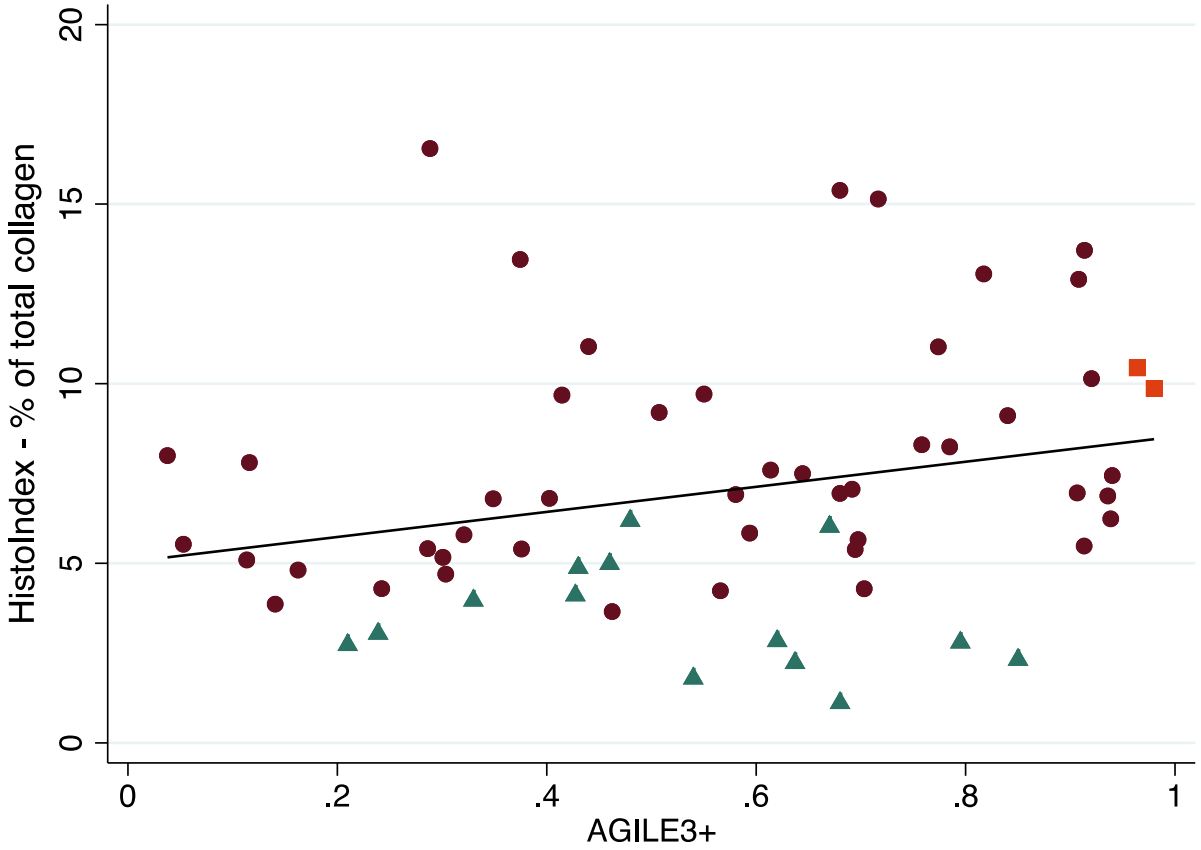
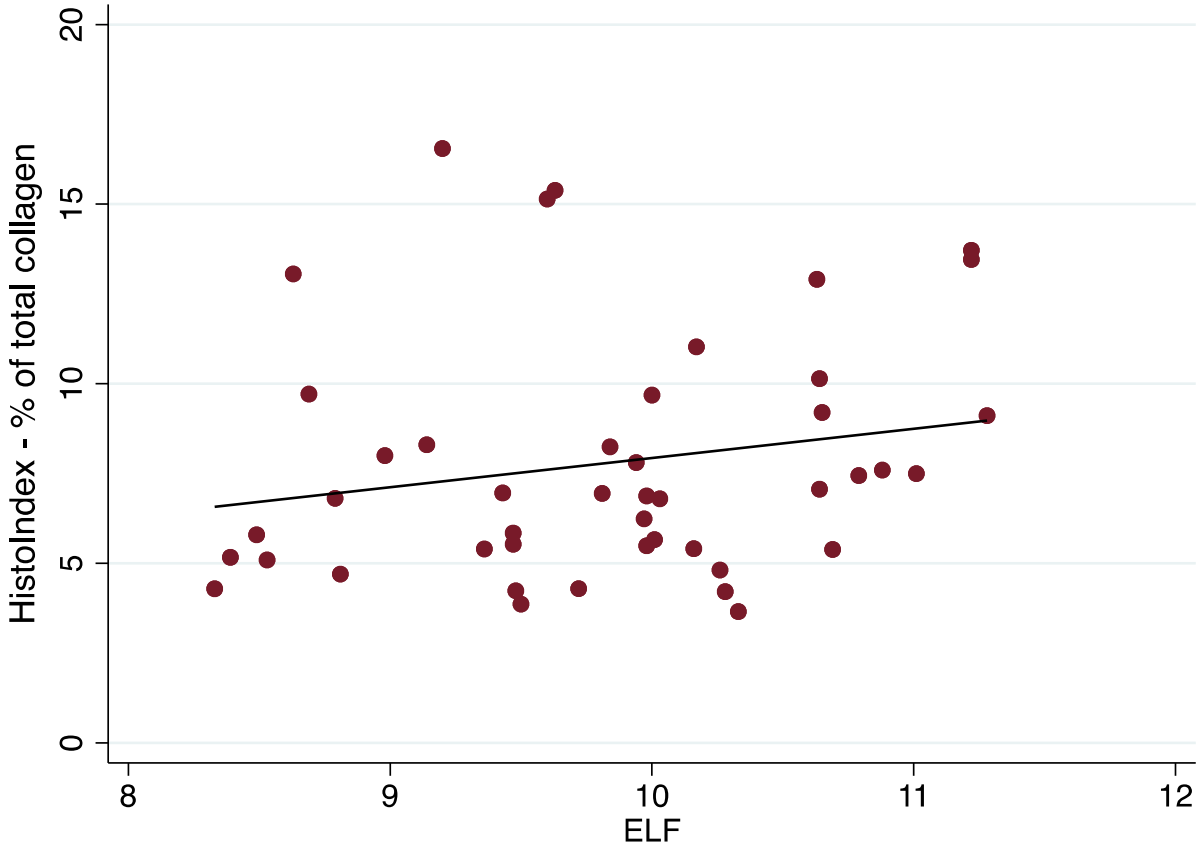
AGILE3+ – n=62
Correlation: **0.325** (95%CI: 0.082-0.532)



ELF – n=45
Correlation: **0.221** (95%CI: -0.078-0.483)



Fibrosis Stage (NASH-CRN)
▲ F0-F1 ● F2-F3 ■ F4

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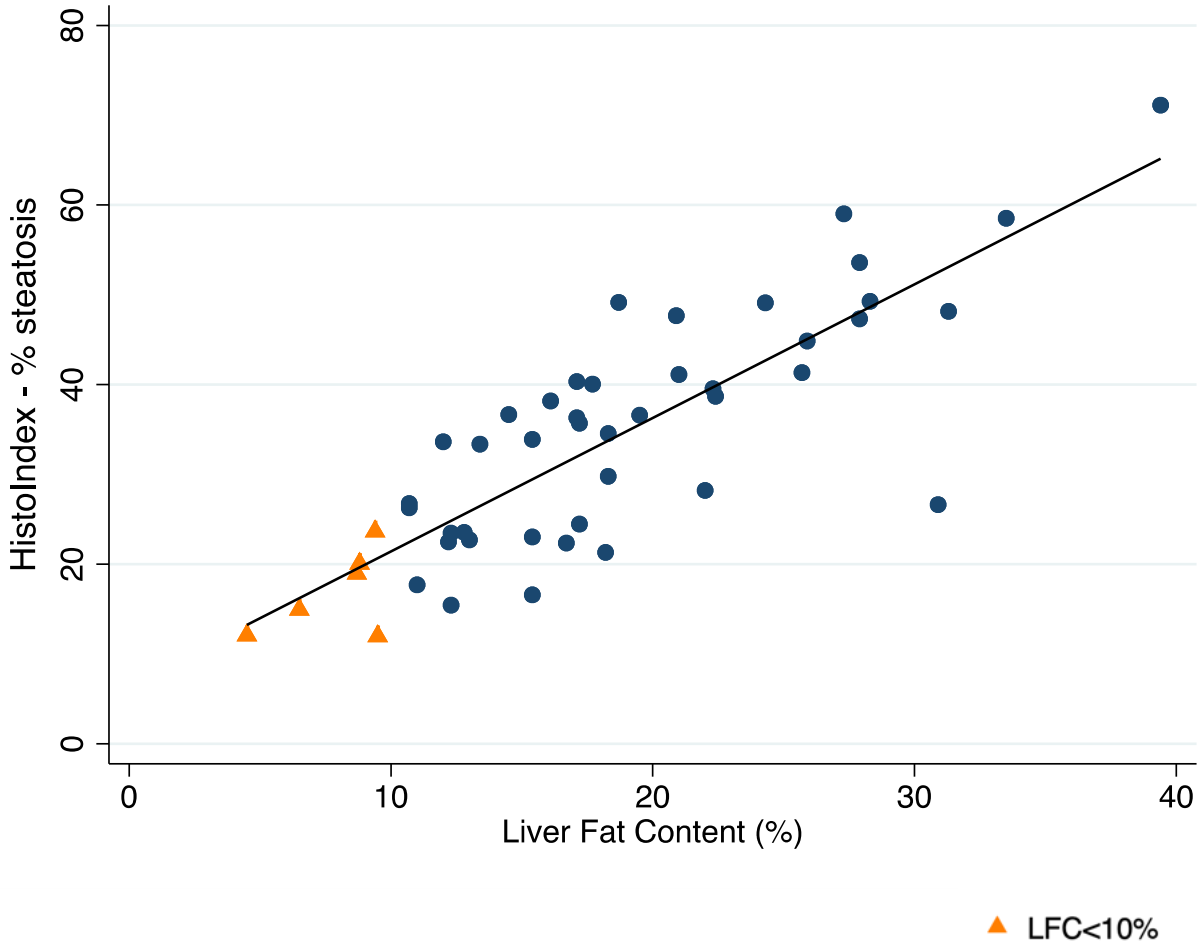
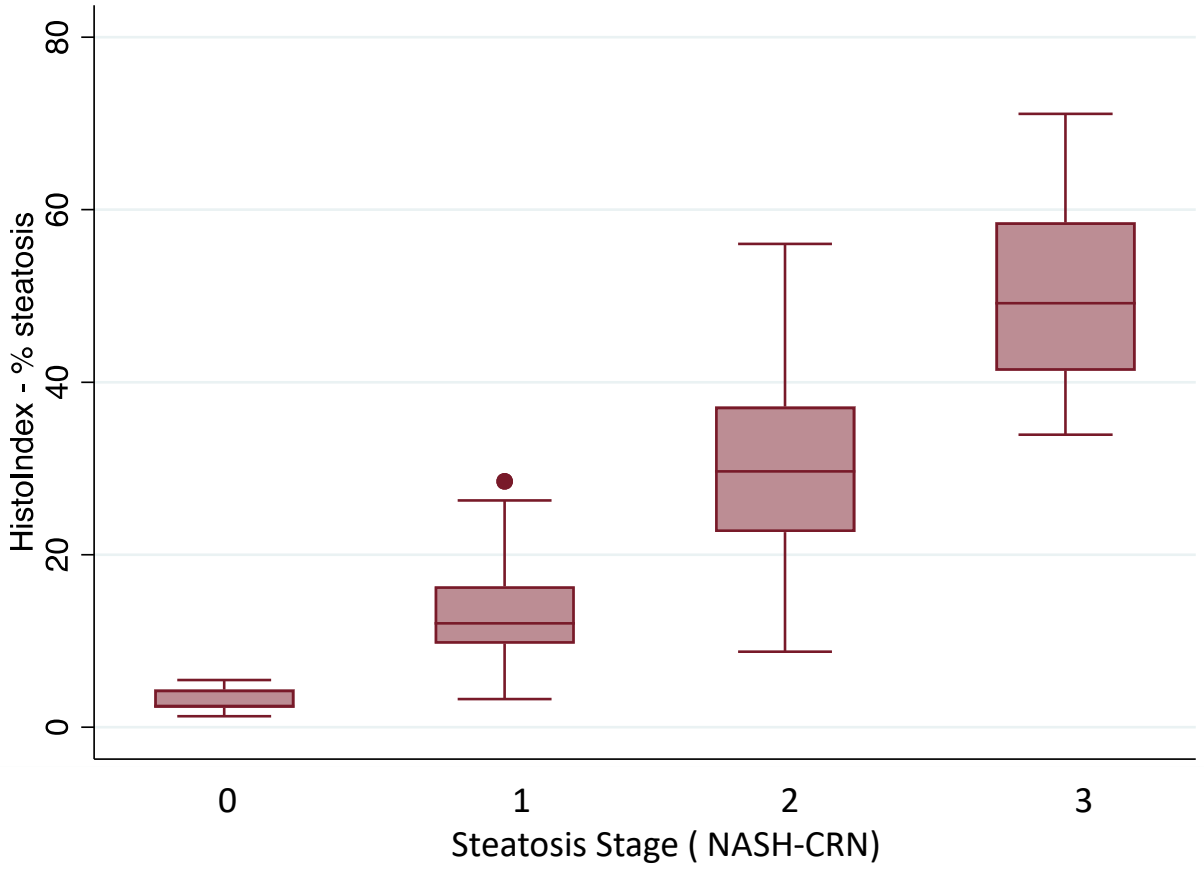
Non-Invasive Markers of Steatosis

Liver Fat Content (MRI-PDFF) – n=48
Correlation: **0.816** (95%CI: 0.692-0.893)



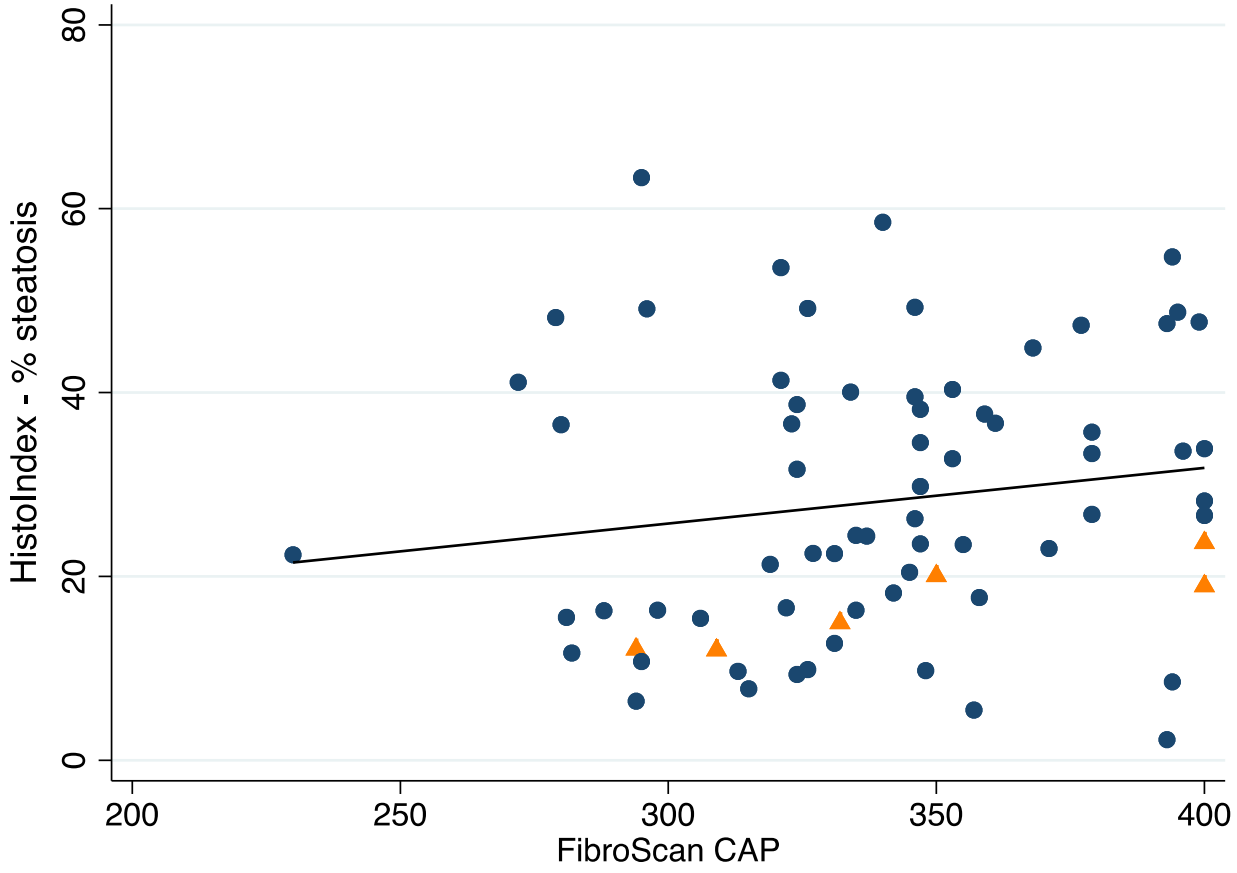
HistoIndex versus NASH-CRN



Non-Invasive Markers of Steatosis

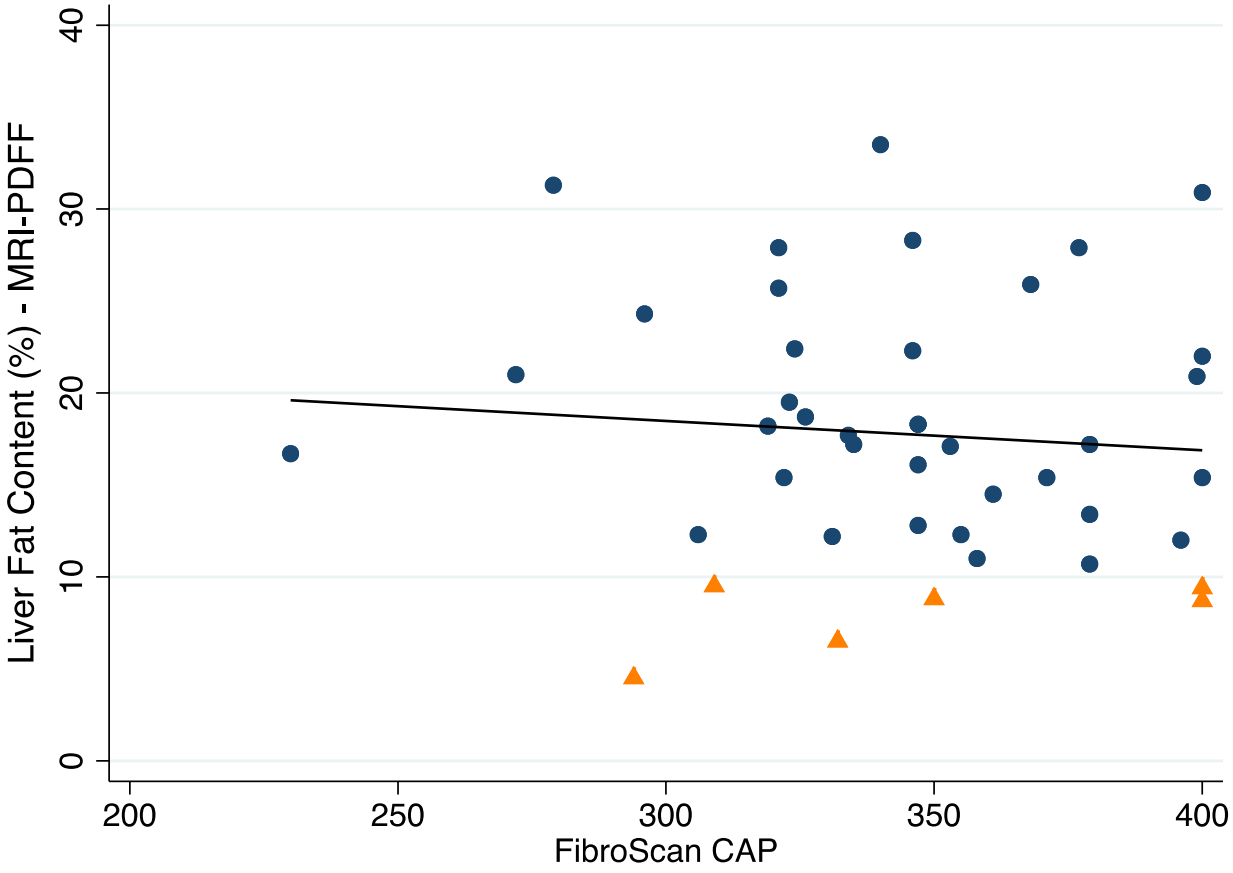
CAP – n=72

Correlation: **0.196** (95%CI: -0.083-0.371)



CAP – n=43

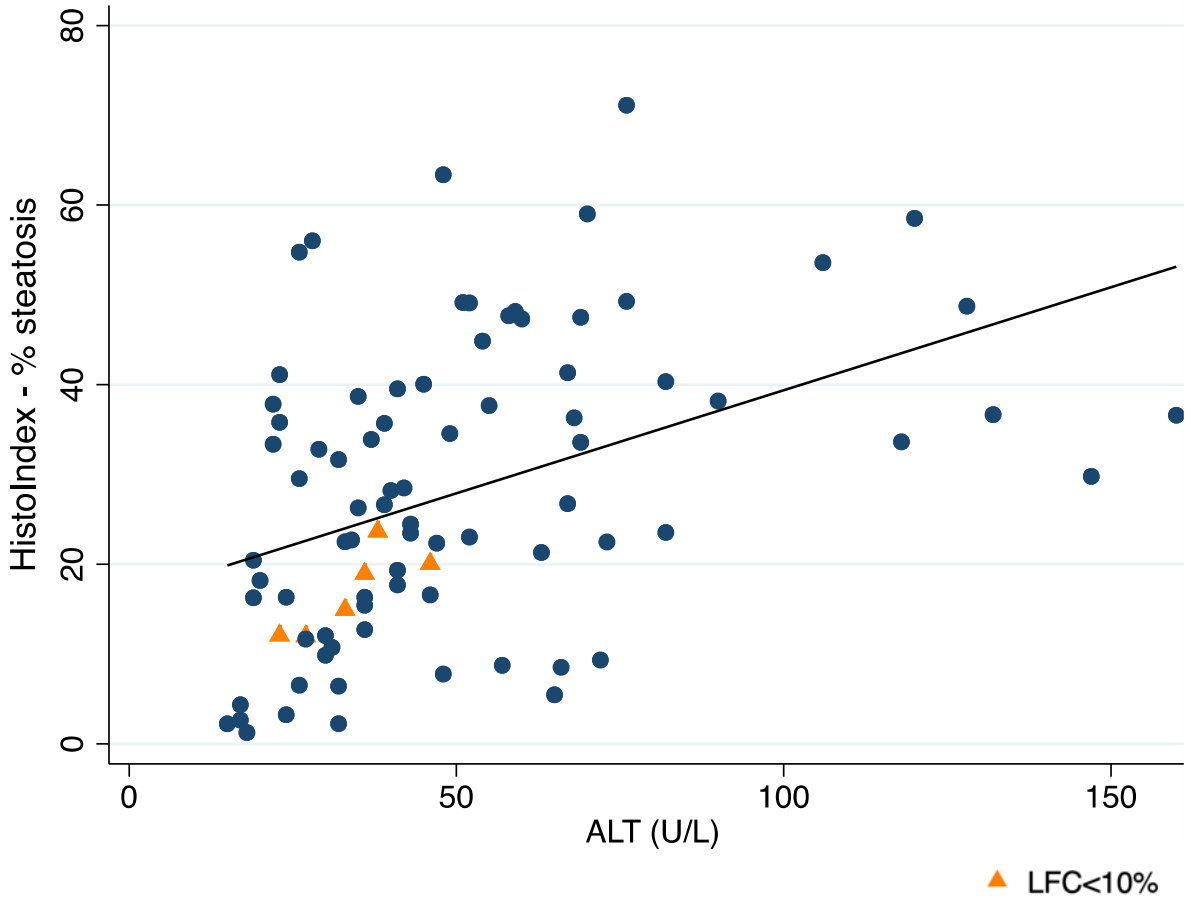
Correlation: **-0.164** (95%CI: -0.442-0.144)



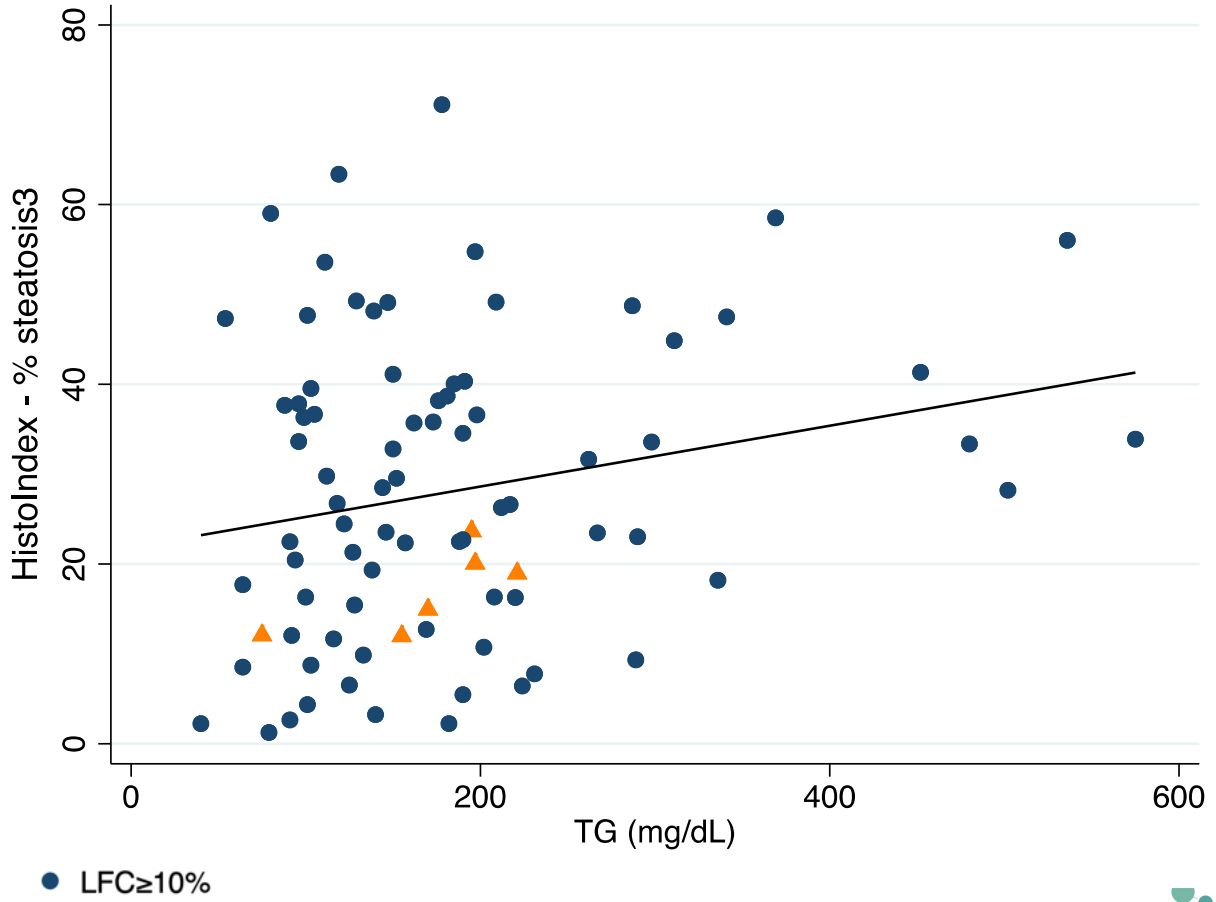
LFC<10% LFC≥10%

HistoIndex / NITs correlation

ALT – n=86
Correlation: **0.483** (95%CI: 0.303-0.631)



TG – n=85
Correlation: **0.177** (95%CI:-0.037-0.376)



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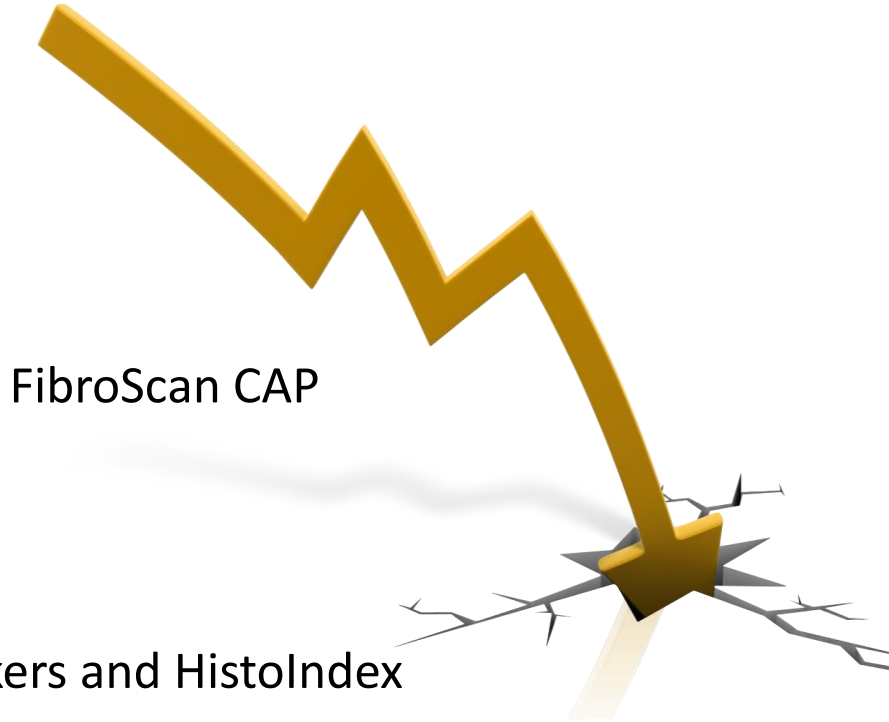
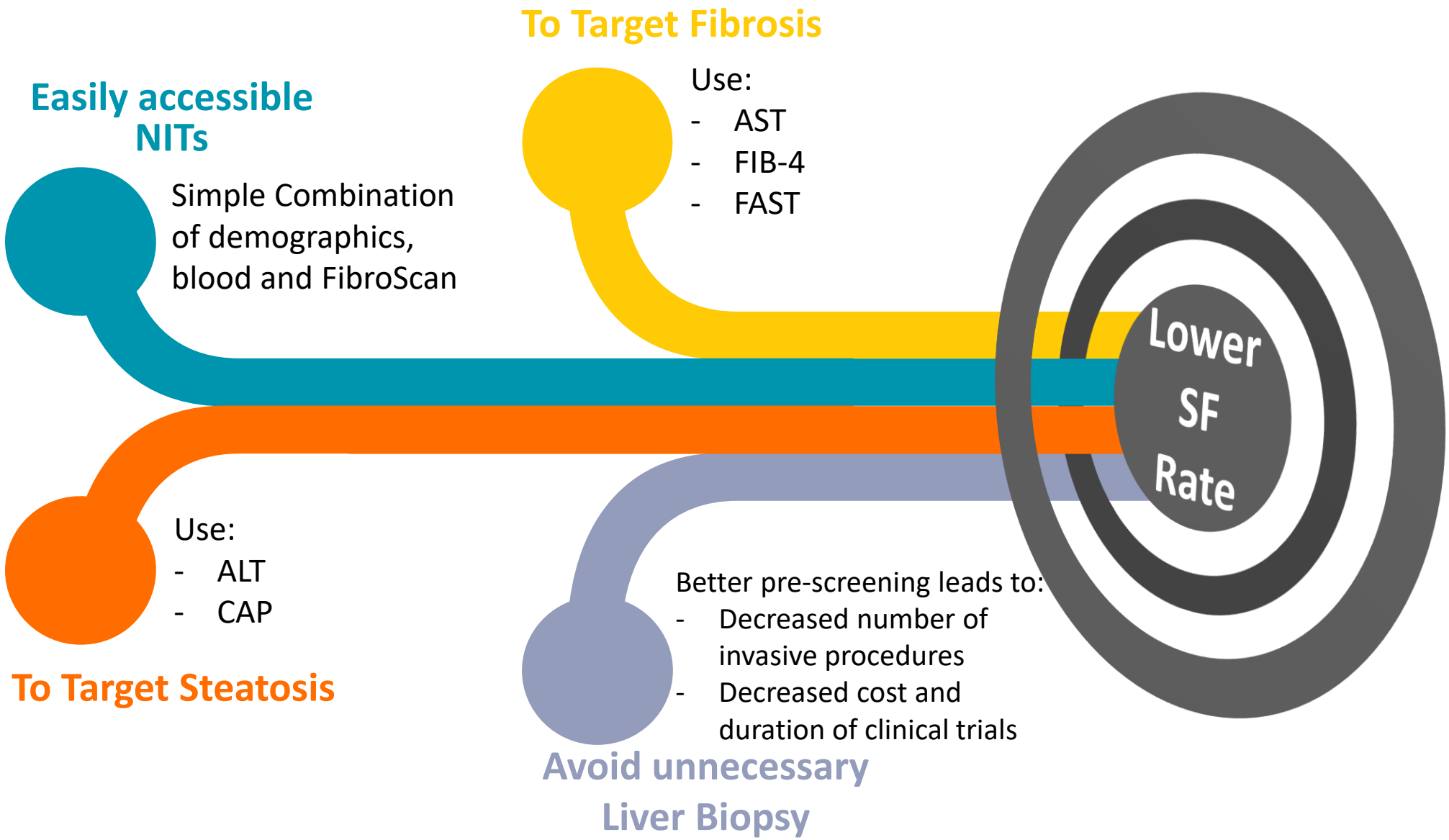
Non-Invasive Tests - Take Home Messages



- High SF rate in biopsy-proven NASH trials (>80%)
- Impact of inclusion/exclusion criteria to mitigate SF rate

  In the current study: a protocol amendment with inclusion of AST and FibroScan CAP thresholds led to decrease in SF rate from 96% to 80%
- We found moderate to good correlations between non-invasive biomarkers and HistoIndex
  - AST, FIB-4 and FAST+++
- Strong correlation between HistoIndex Steatosis and MRI-PDFF

Non-Invasive Tests - Take Home Messages



FASCINATE-2 interim results – denifanstat vs. placebo

67% MRI-PDFF responder rate observed at week 26

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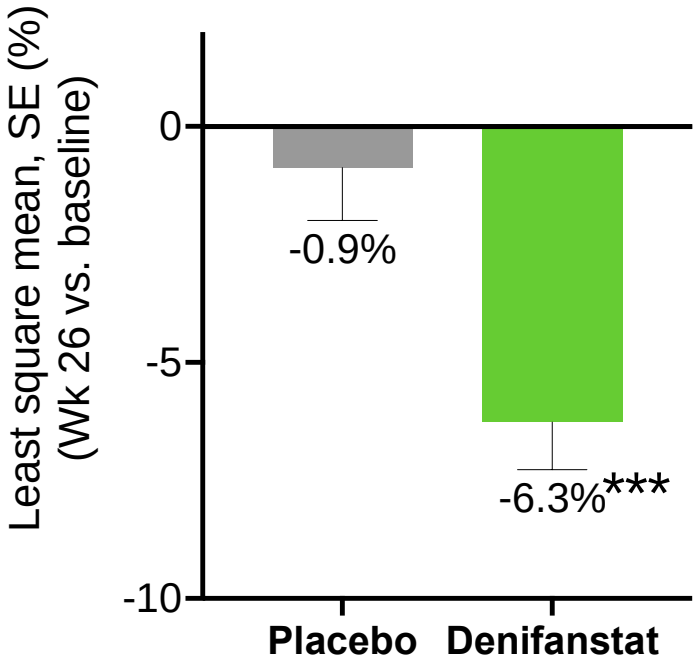
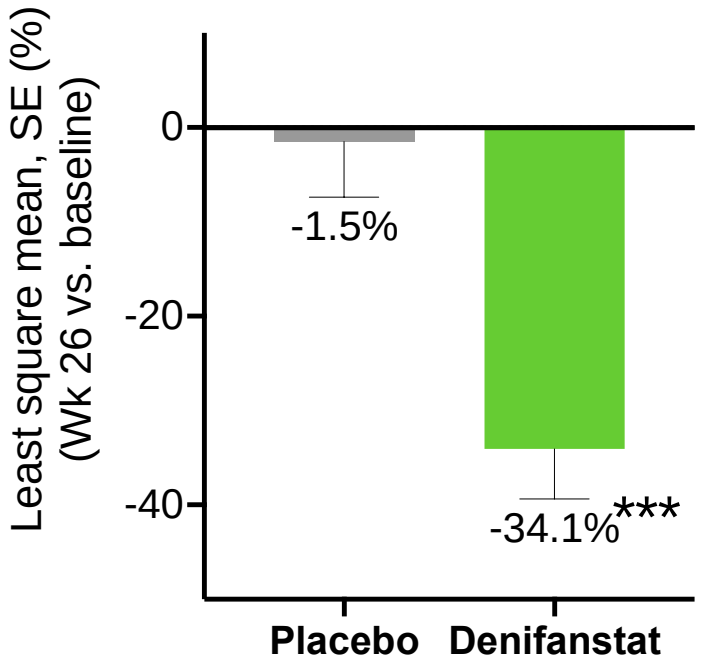
Liver fat absolute change

(MRI-PDFF)



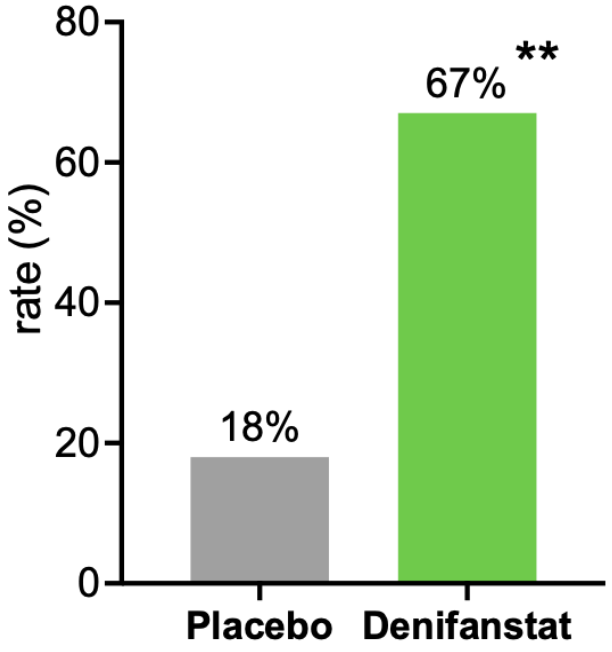
Liver fat % change

(MRI-PDFF)



Responder analysis

(≥30% fat reduction)



9 of 20 denifanstat responders had ≥50% liver fat reduction

*** p < 0.01, *** p < 0.001. placebo (n=22), denifanstat (n=30)*

Two-sided CMH test for response analysis, and two sided ANCOVA for liver fat change

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FASCINATE-2 interim results – denifanstat vs. placebo
Significant reduction in ALT and ELF at week 26

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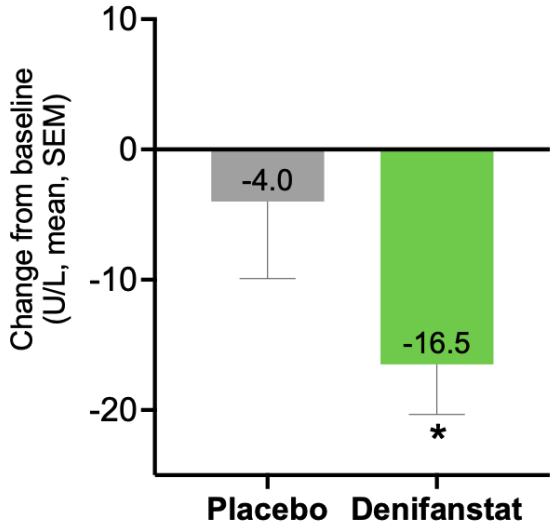
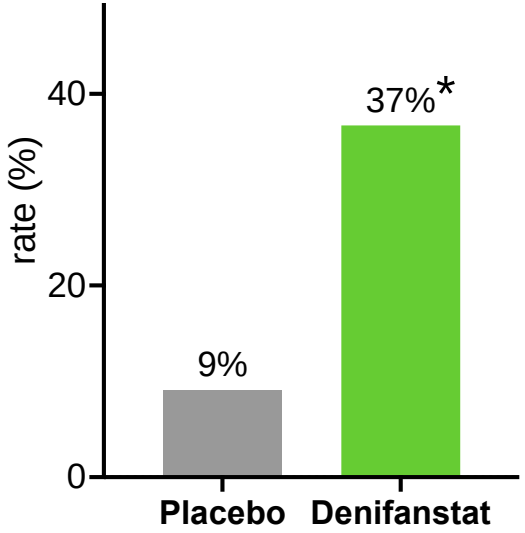
ALT

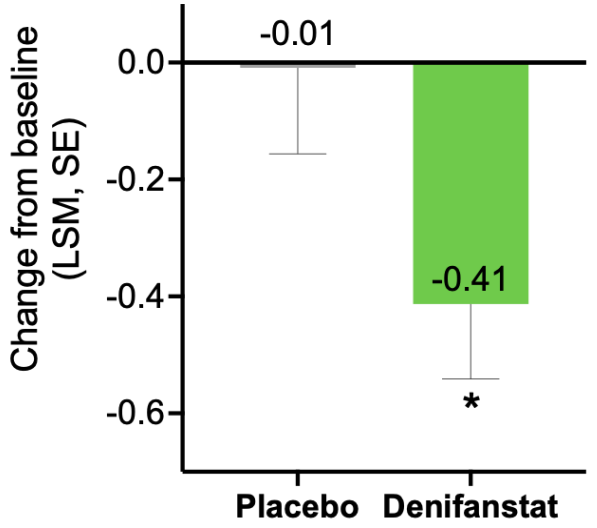


Combined responders

Reduction in ALT ≥17U/L + MRI-PDFF ≥30%



ELF



- No treatment related SAEs, majority of AEs mild to moderate (Grade 1/2)
- Results confirm denifanstat activity in a biopsy-proven advanced NASH population (46% F2/54% F3)
- Inhibition of FASN impacts steatosis, inflammation and fibrosis - 3 key disease characteristics of NASH

** p < 0.05, placebo (n=20), denifanstat (n=29) for ALT; placebo (n=15), denifanstat (n=20) for ELF*
Two sided ANCOVA. ELF results are shown for all patients with data available.

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THANK YOU

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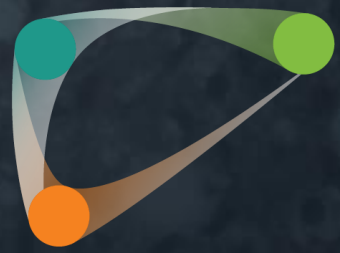

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