NAFLD/NASH Abstracts Post AASLD

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AASLD November 2021
The Liver Meeting®
Digital Experience

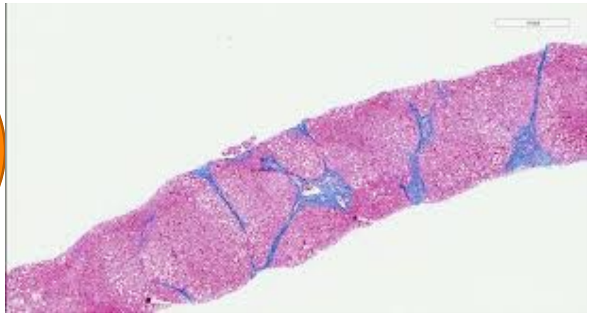
Disclosures

- **Faculty: Mazen Noureddin, MD, MHSc**
- MN has been on the **advisory board** for 89BIO, Gilead, Intercept, Pfizer, Novartis, Novo Nordisk, Allergan, Blade, EchoSens, Fractyl, Terns, OWL, Siemens, Roche diagnostic and Abbott; MN has **received research support** from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Shire, Viking and Zydus; MN is a **minor shareholder** or has stocks in Anaetos and Viking.
- Federal Funding: NCI
- Editorial boards: Gastroenterology, Hepatology , CGH
- Boards of Editors: CGH 2022

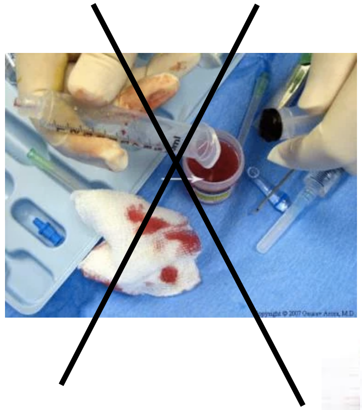
Objectives

- **Natural History**
- **Diagnostics**
- **Therapeutics**

Genetics
$
Role of NITs



Consortia
AI
Combo



Many successful stories

Objectives

- **Natural History**

Genetics
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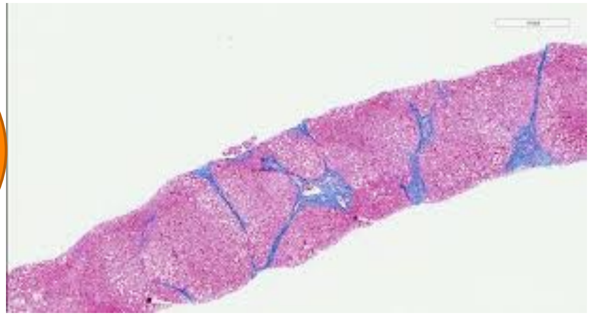
Role of NITs

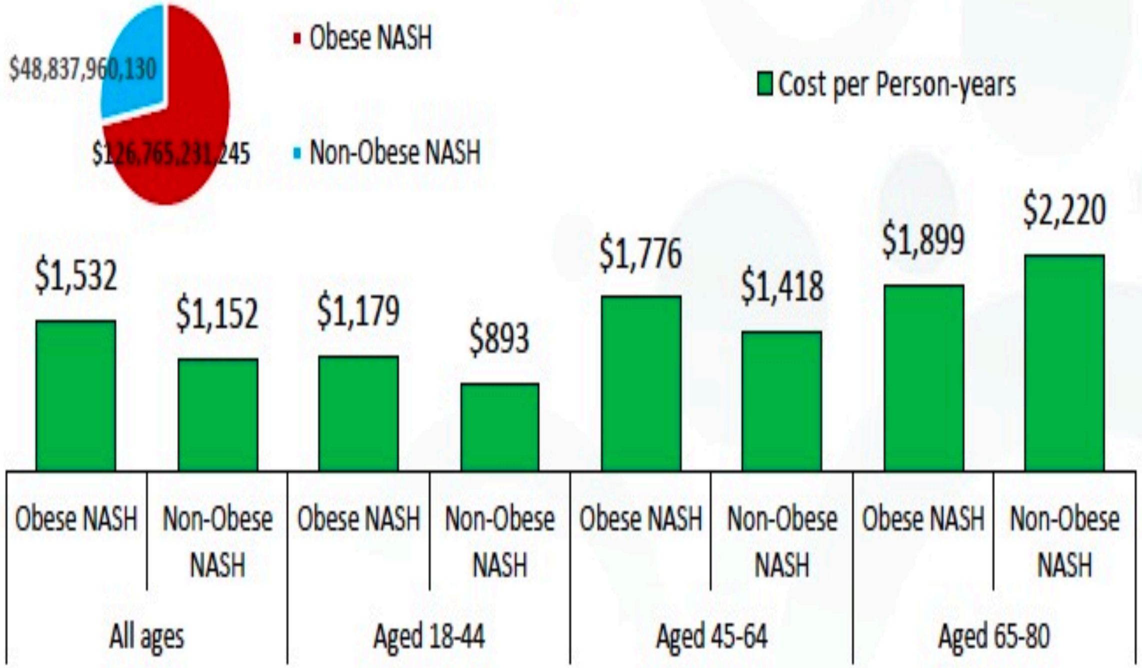


Burden of illness and economic impact of non-alcoholic steatohepatitis (NASH) in the United States according to the presence of obesity

Mortality for 2019 NASH prevalent cases over 20 years

	All ages		Aged 18-44		Aged 45-64		Aged 65-80	
	Obese NASH	Non-Obese NASH	Obese NASH	Non-Obese NASH	Obese NASH	Non-Obese NASH	Obese NASH	Non-Obese NASH
Subject, n	7,865,809	3,350,236	2,332,396	1,369,375	3,175,620	1,276,951	2,357,793	703,910
Mortality, %								
All-causes	74.85	62.52	43.22	35.87	84.63	77.28	92.98	87.57
Liver-specific	2.23	2.30	1.18	0.44	2.35	2.74	3.11	3.91
CVD-specific	28.26	8.51	13.63	1.71	31.23	10.54	38.73	13.25

Economic burden for 2019 NASH prevalent cases over 20 years



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Younossi Z, et al., Abstract LO4

A genome-wide association study of chronic ALT-based NAFLD in the Million Veteran Program with histological and radiological validation

Aim

- To expand insights to NAFLD gene… phenotype based on chronic ALT… population in the VA's Million V…

Methods

- Trans-ancestry and ancestry… (GWAS) of **90,408 cases** with… known causes of liver disease… in MVP
- External replication cohorts: biopsy… 56,785 controls); radiological hepatic fa…
- Detailed post-GWAS analyses

Conclusions

- Our triangulated approach based on chronic ALT elevation with histological and radiological validation expands our insights to genetic susceptibility for NAFLD.

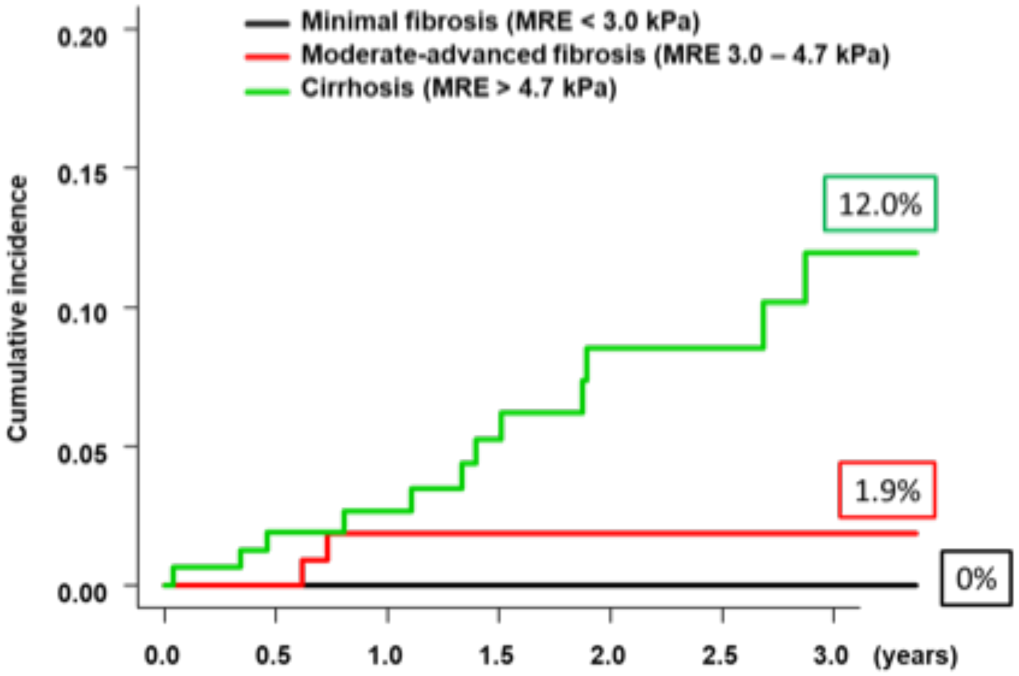
…s

- …estry SNPs were associated with cALT with genome-…e, including 10 known GWS NAFLD SNPs, plus… ancestry-specific SNPs.
- …ere validated in external replication cohorts with …diological NAFLD—including 8 novel SNPs (*FTO*, …*RN*, *MTTP*, *COBLL1*, *IFI30*, *APOH*, *PPARG*).
- …0/77) cALT SNPs were pleiotropic with metabolic and/or …atory trait associations.
- …RS derived from cALT SNPs were predictive of histological NAFLD—especially those with greater pleiotropy.

8 novel SNPs
(FTO, SERPINA1,
IL1RN, MTTP, COBLL1,
IFI30, APOH, PPARG)

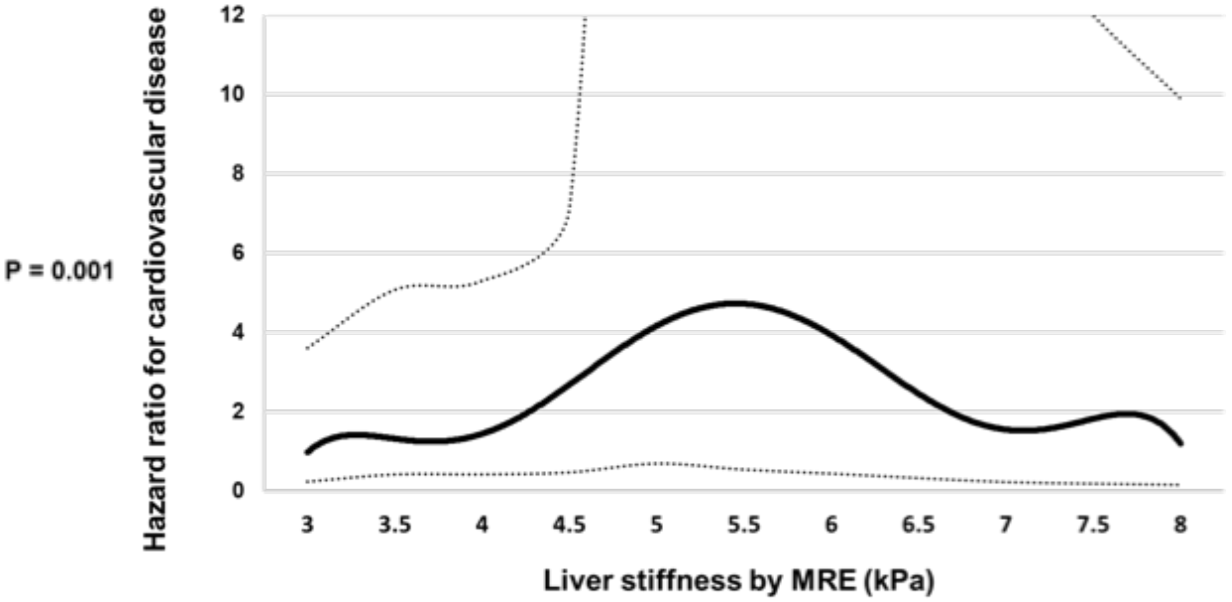
Chang K-M, et al., Abstract 9

Longitudinal association between magnetic resonance elastography and liver-related events and cardiovascular events in nonalcoholic fatty liver disease



Number at risk

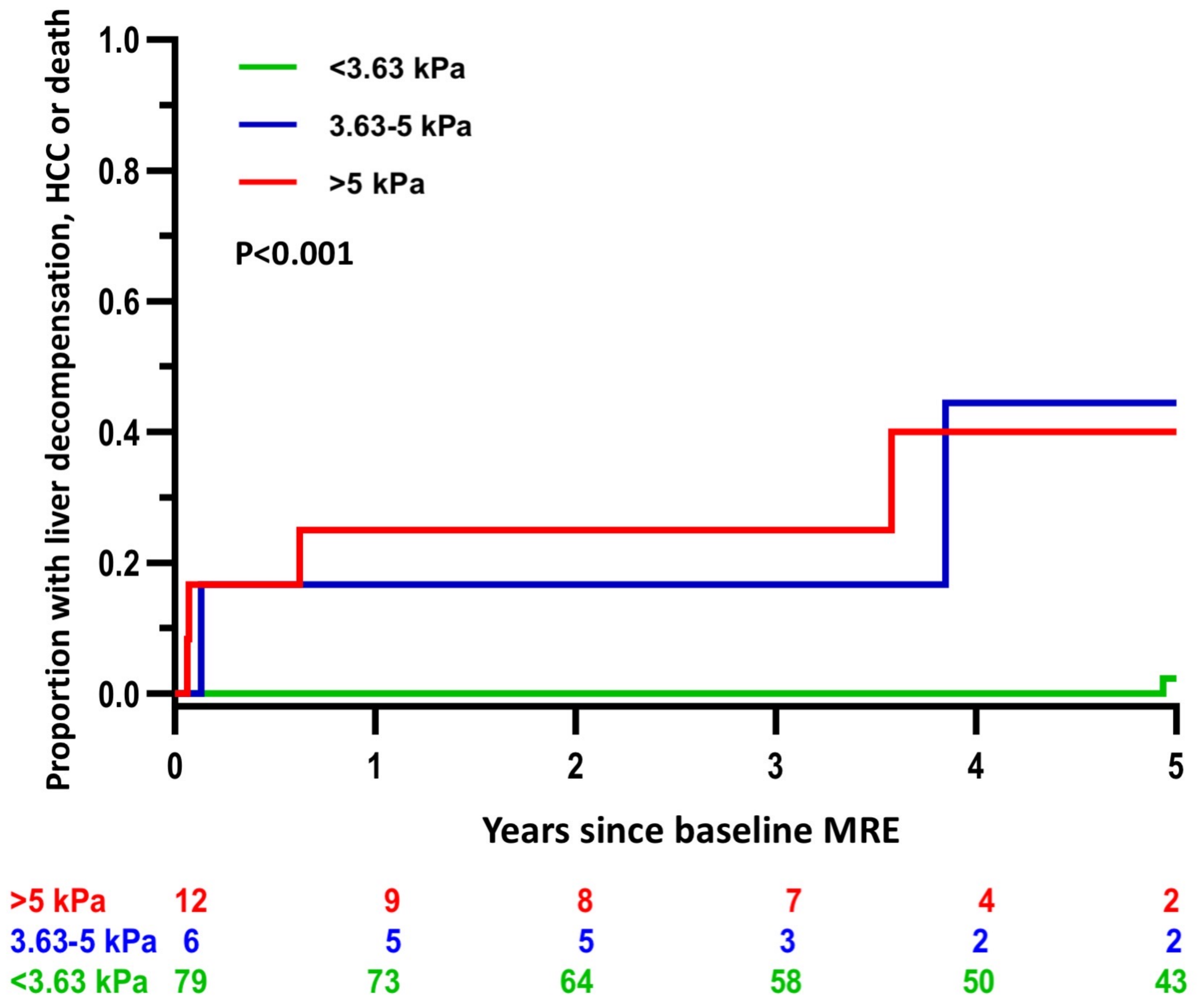
Minimal fibrosis	140	140	95	72	56	39	25
Moderate-Advanced fibrosis	127	127	91	71	57	42	28
Cirrhosis	153	150	125	102	76	60	47



- HCC and decompensation risk increased as MRE increased.
- CVD risk was peaking at 5–5.5 kPa, and after that, CVR risk decreased as MRE increased.

Tamaki N, et al., Abstract 10

Five-year Cumulative Incidence of Hepatic Decompensation, Hepatocellular Carcinoma or Death by Baseline MRE



- 453 person-years of follow up in 97 patients
- Three-year risk of composite outcome was
  - 0 for MRE < 3.63 kPa,
  - 16.7% for 3.63 – 5 kPa and
  - 25% for MRE > 5kPa

Ajmera el al; Abstract #75

NAFLD risk and histologic severity are associated with genetic polymorphisms in children

Aims

- Nested family trio study to investigate candidate SNPs that influence the risk for NAFLD in children
- Study of children with biopsy confirmed NAFLD to determine the association of candidate SNPs with histologic severity

Methods

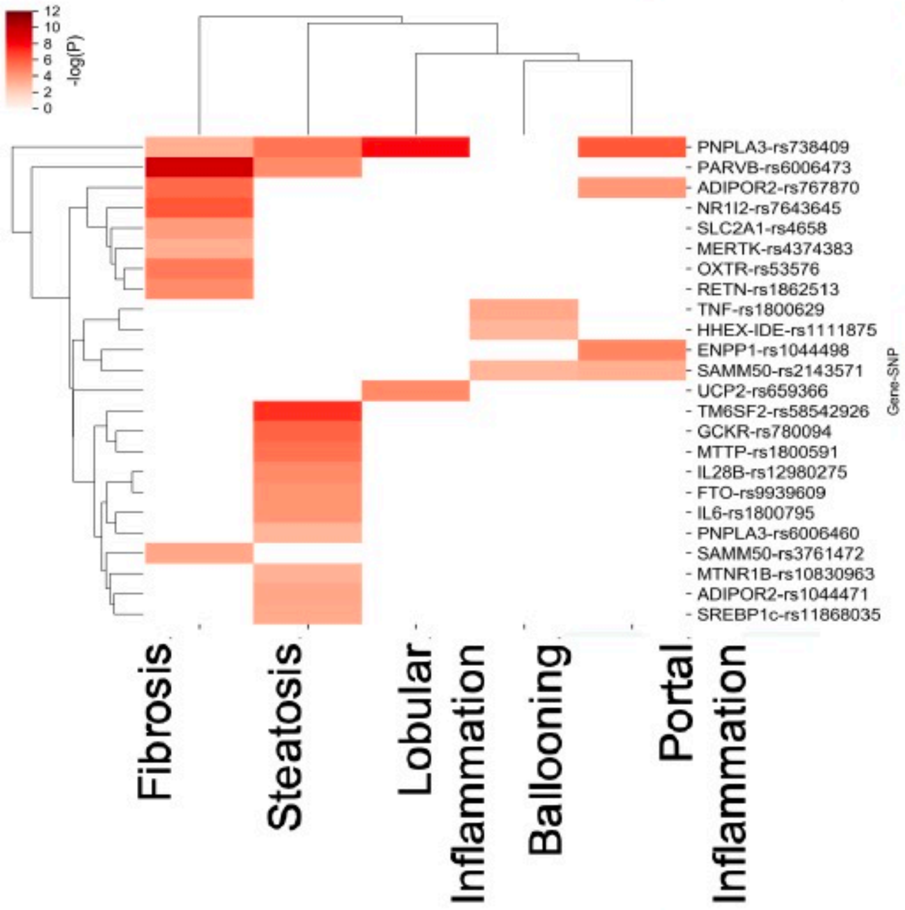
- Multicenter study of 822 children with biopsy-confirmed NAFLD including 252 complete trios
- 60 candidate SNPs tested via FDR corrected TDT analysis (Aim 1) and FDR corrected regression analysis (Aim 2)

Main Findings

- *PNPLA3* rs738409 strongest associated SNP with risk for NAFLD. Associated with steatosis and inflammation, but not fibrosis. Also strongly associated with borderline zone 1 NASH (pediatric subtype of NASH).
- *PARVB* rs6006473 strongest SNP associated with fibrosis severity.

Conclusions

- This study advances the knowledge of genetic associations with NAFLD in children.



Goyal N, et al., Abstract 12

HIV is independently associated with elevated FibroScan-AST (FAST) score

Aim

- To determine the association of HIV infection with an elevated FAST score, a non-invasive measurement of NASH with significant activity and fibrosis

Methods

- 1309 participants of the Women's Interagency HIV Study (928 women living with HIV [WLWH] and 318 HIV seronegative [SN]) underwent Vibration Controlled Transient Elastography to estimate liver stiffness (LS) and steatosis using the Controlled Attenuation Parameter (CAP). FAST score was calculated using CAP, LS, and AST.
- Multivariable logistic regression was used to determine the factors associated with FAST score >0.35.

Main Findings

- Prevalence of FAST >0.35: 6.3% WLWH, 1.8% SN (p=0.001)
- See Tables 1 and 2 for factors associated with FAST >0.35.

Conclusions

- These findings suggest that HIV is an independent risk factor for NASH with significant activity and fibrosis. Studies validating FAST in persons living with HIV are warranted.

Table 1. Factors associated with FAST score >0.35 in entire cohort*

	Odds Ratio (95% CI)	p-value
HIV infection	3.70 (1.64, 8.34)	0.002
Race (ref=white)		
Black	0.44 (0.22, 0.88)	0.02
Other	1.09 (0.42, 2.79)	0.86
Waist circumference (per 10 cm)	1.65 (1.37, 1.99)	<0.001

*Also adjusted for age, Hispanic ethnicity, HOMA-IR, and alcohol use

Table 2. Factors associated with FAST score >0.35 in WLWH*

	Odds Ratio (95% CI)	p-value
Race (ref=white)		
Black	0.43 (0.20, 0.93)	0.03
Other	1.29 (0.46, 3.65)	0.63
Waist circumference (per 10 cm)	1.62 (1.32, 1.98)	<0.001
Undetected HIV viral load	0.40 (0.22, 0.72)	0.002
Protease inhibitor use	0.34 (0.14, 0.82)	0.02

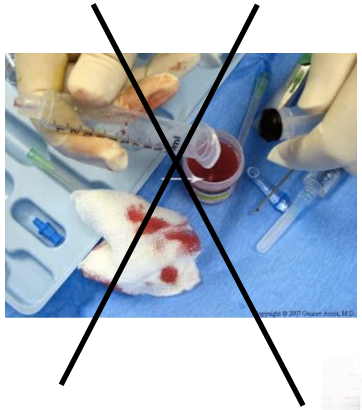
*Also adjusted for age, Hispanic ethnicity, HOMA-IR, and alcohol use

Price J, et al., Abstract 191.

Objectives

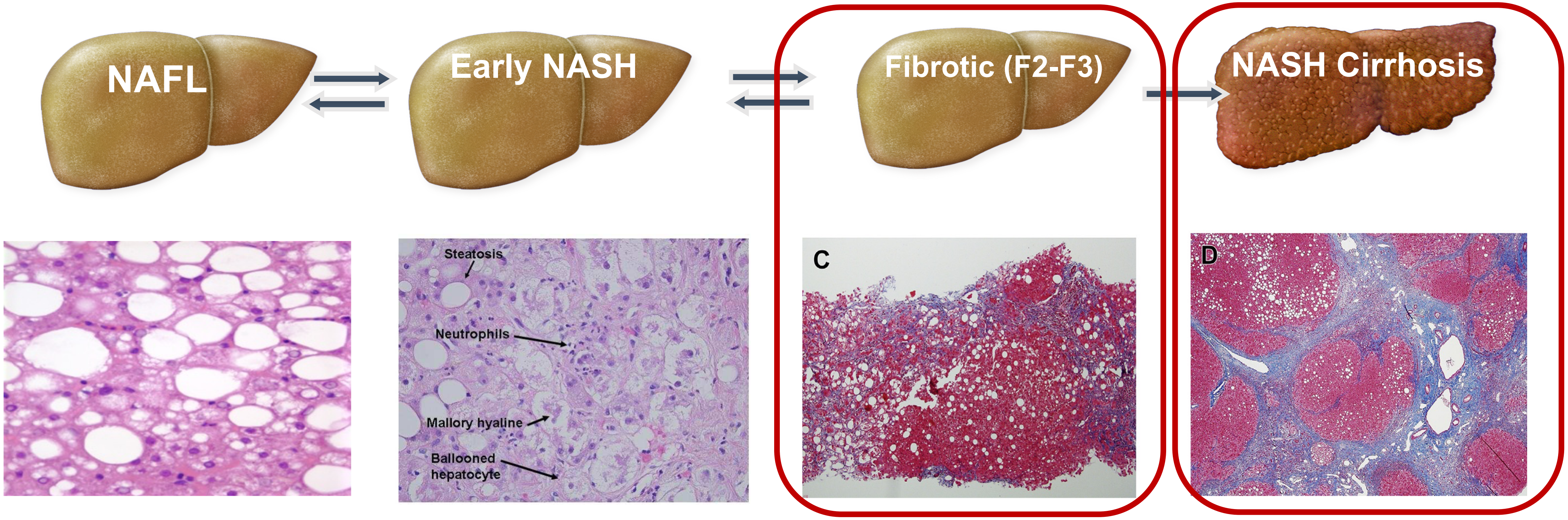
- **Diagnostics**

Consortia
AI
Combo



Reminder

High Risk Population/Inclusion Criteria RCTs



FDA: Liver Histologic Improvement Endpoints Likely to Predict Clinical Benefit

Reminder

NASH Resolution

- **Resolution of steatohepatitis**

and

- **No worsening of liver fibrosis**

Fibrosis Improvement

- Improvement ≥ 1 fibrosis stage

and

- **No worsening of steatohepatitis**

Or Both

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NIMBLE: Biomarker panels Selected for Evaluation for Specific Intended Use

Panels were selected based on prior rigorous analytical validation and promising clinical data

	NASH	NAS ≥ 4	Clinically significant fibrosis (stage ≥ 2)	Advanced fibrosis (stage 3-4)	Cirrhosis	At risk NASH
NIS-4	+	+	+	+	+	+
OWL panel	+	+				
ELF test			+	+	+	
PRO-C3			+	+	+	
Fibrometer-VCTE			+	+	+	

NIS-4 (GENFIT SA): mir34a + alpha2 macroglobulin + HBA1c + YKL40- ***score 0-1***
One-Way Liver (OWL Metabolomics): 16 lipids- ***probability score or yes/no score***
ELF test (Siemens): hyaluronic acid + procollagen 3 n terminal peptide + TIMP1- ***numerical score***
PRO-C3 (Nordic Biosciences): collagen fragments – ***score µg/ml***
Fibrometer-VCTE (Echosens): platelets +AST +ALT + ferritin + glucose + alpha2 macroglobulin- ***score 0-1***

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Sanyal et al LB #1

AT RISK NASH	NIS-4	FIB-4
AUROC	0.81*^	0.72*

AT RISK NASH	SENSITIVITY	SPECIFICITY
OWL	63.3	75.4

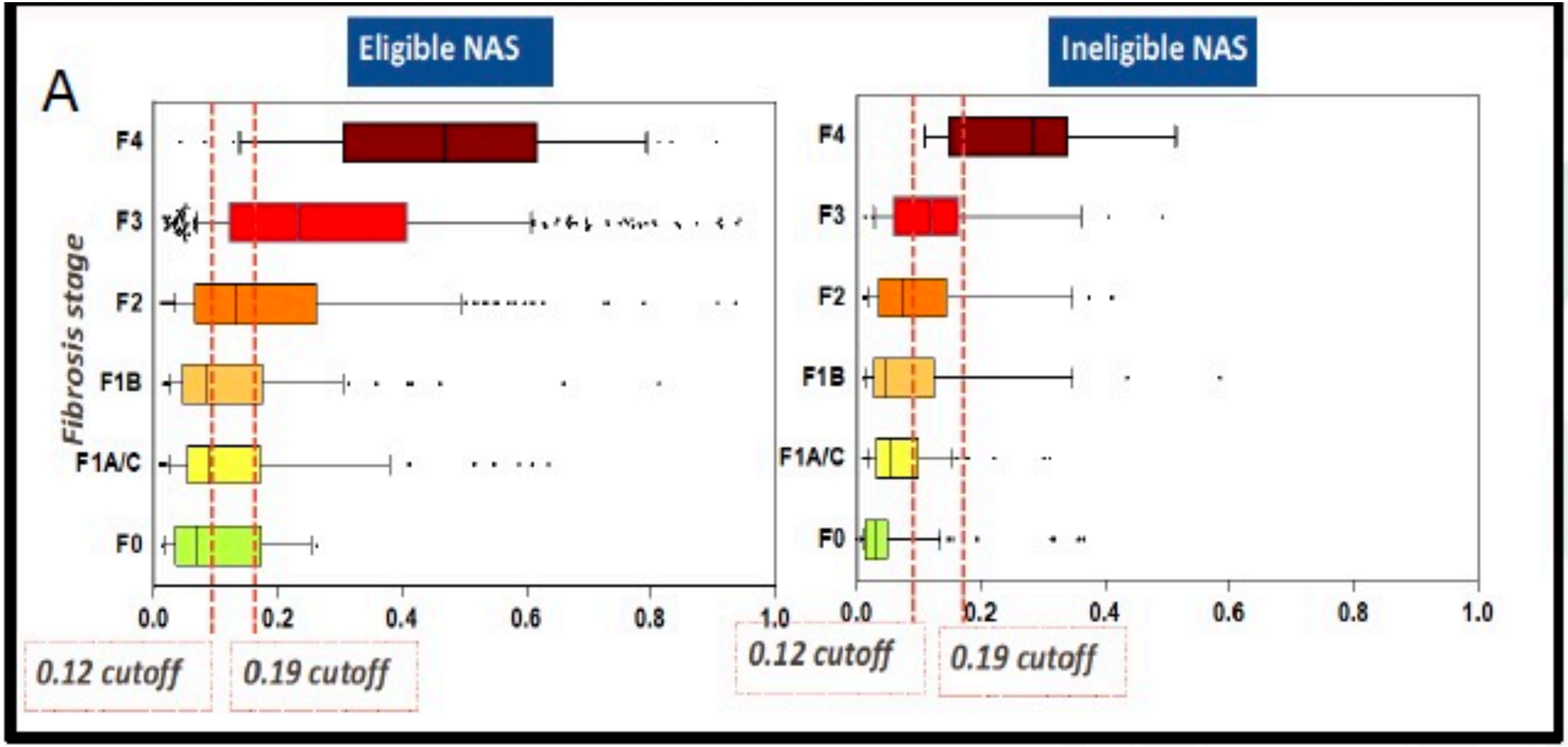
FIBROSIS stage diagnosis	≥ STAGE 2	≥ STAGE 3	CIRRHOSIS
FIB-4	0.80*	0.79*	0.81*
ELF Test	0.82*^	0.83*^	0.85*^
Pro-C3	0.80*	0.76*	0.72*
Fibrometer-VCTE	0.84*^	0.86*^	0.90*^

AUROC rounded off to 2 decimals
**p significantly superior (<0.05) to AUROC of 0.5*
^p for AUROC significantly superior (<0.05) to AUROC for FIB4

TLM dx

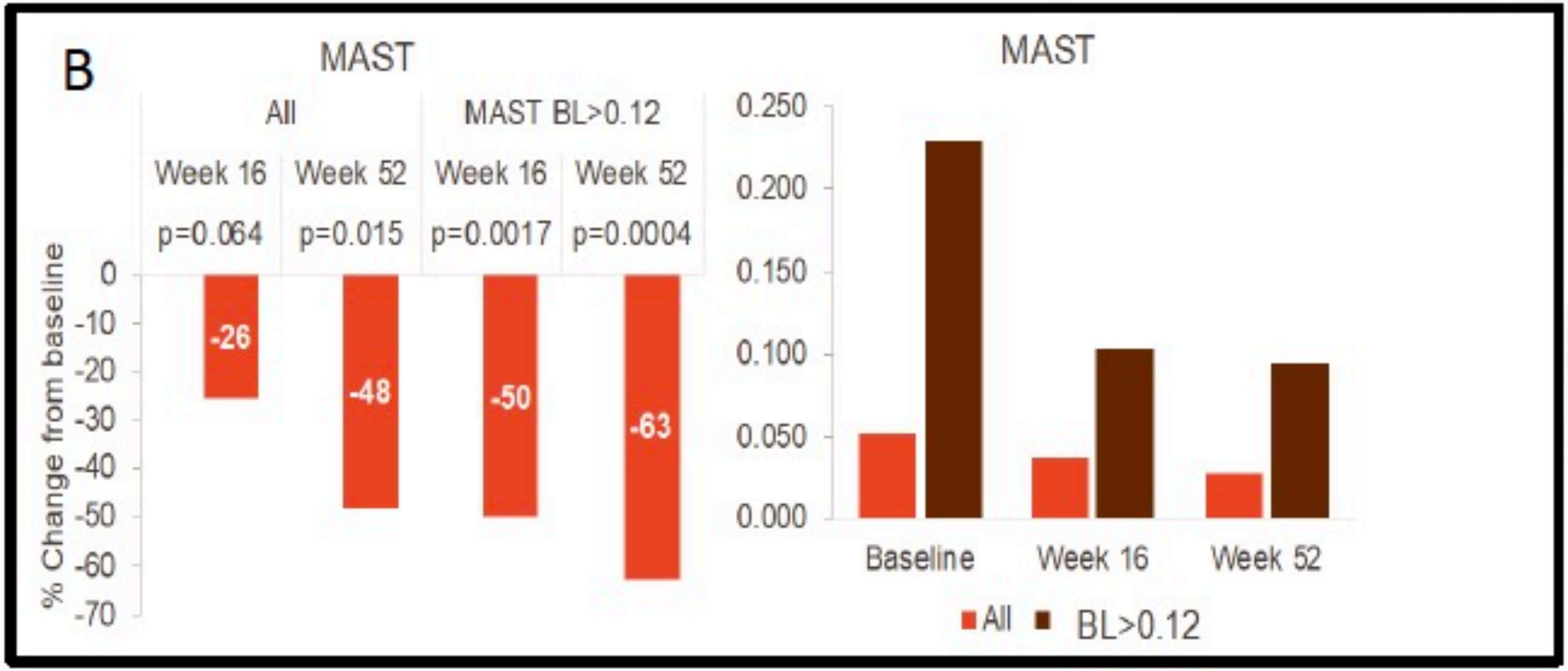
Sanyal et al LB #1

Utilization of the MAST (MRI-PDFF-MRE-AST) score to predict NASH on liver biopsy in MAESTRO-NASH and assess response to Resmetirom in MAESTRO NAFLD-1

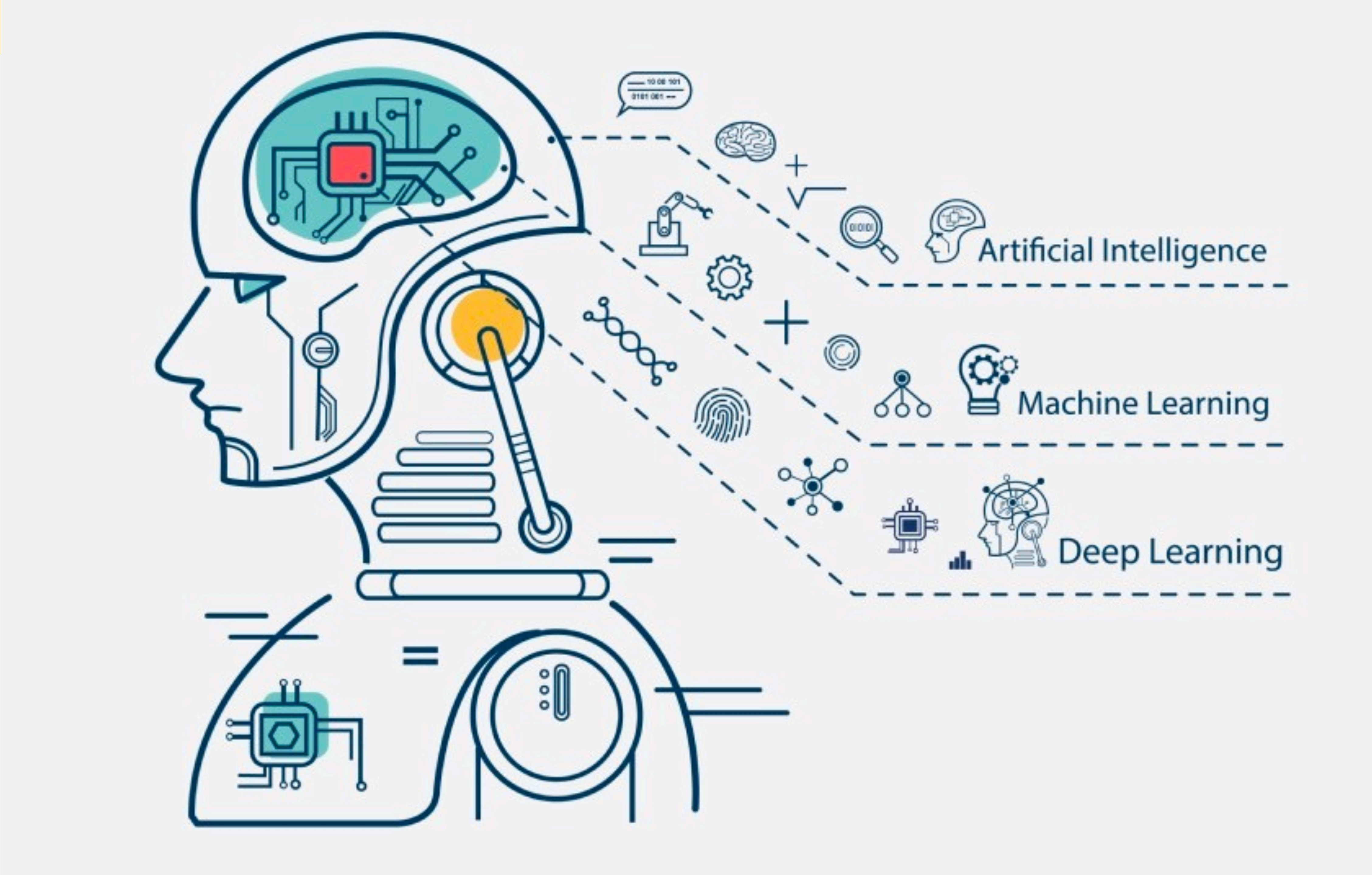


Noureddin et al; Abstract 118

Utilization of the MAST (MRI-PDFF-MRE-AST) score to predict NASH on liver biopsy in MAESTRO-NASH and assess response to Resmetirom in MAESTRO NAFLD-1



Noureddin et al; Abstract 118

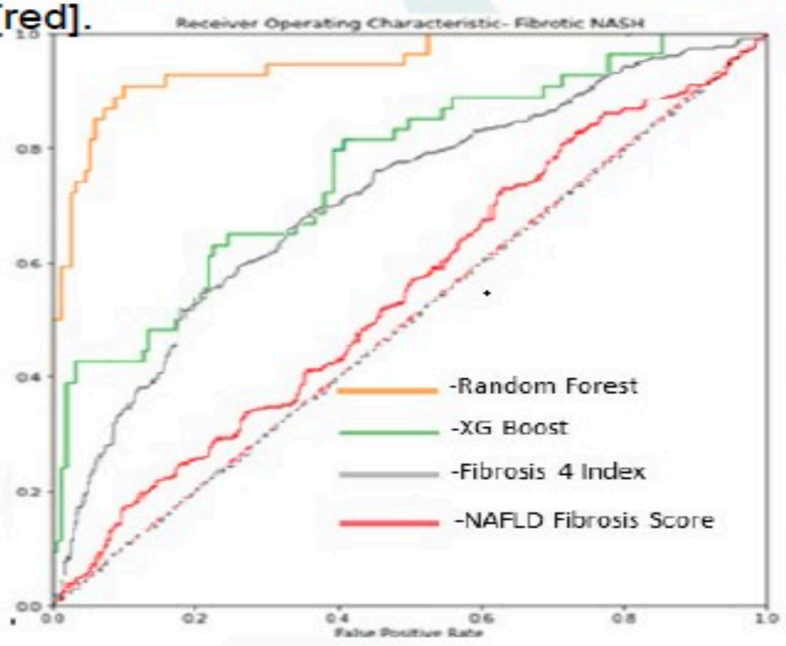

Artificial Intelligence
Machine Learning
Deep Learning

Machine learning model outperforms non-invasive tests to detect fibrotic non-alcoholic steatohepatitis in patients with non-alcoholic fatty liver disease

Table: Summary of performance of machine learning models and traditional non-invasive tests for detection of Fibrotic-NASH.

Performance Characteristics	AUROC	95% Confidence Limit	
Machine Learning Model			
Random Forest	0.95	0.91	0.97
XG Boost	0.76	0.68	0.84
Traditional Non-Invasive Tests			
Fibrosis 4 Index	0.72	0.68	0.75
NAFLD Fibrosis Score	0.55	0.51	0.59

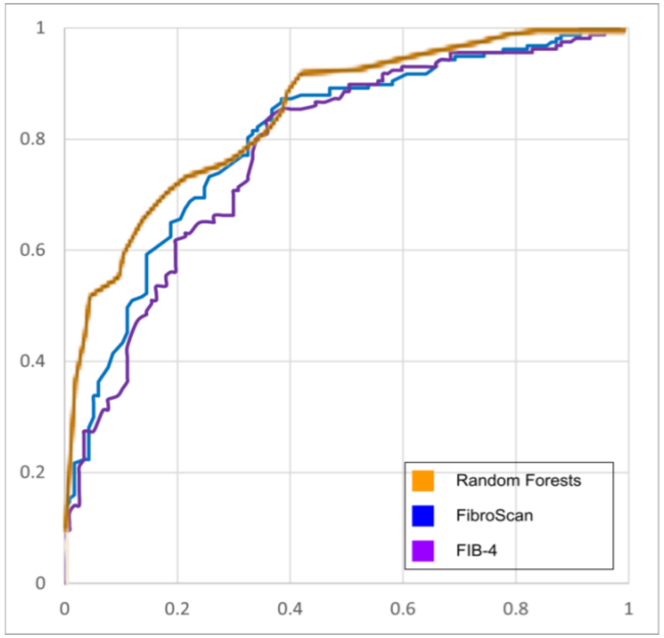
Figure: Area under receiver operating curve (AUROC) for identifying fibrotic-NASH for tested models. Random forest [yellow]; XGBoost [green]; Fibrosis 4 index [grey]; and NAFLD fibrosis score [red].



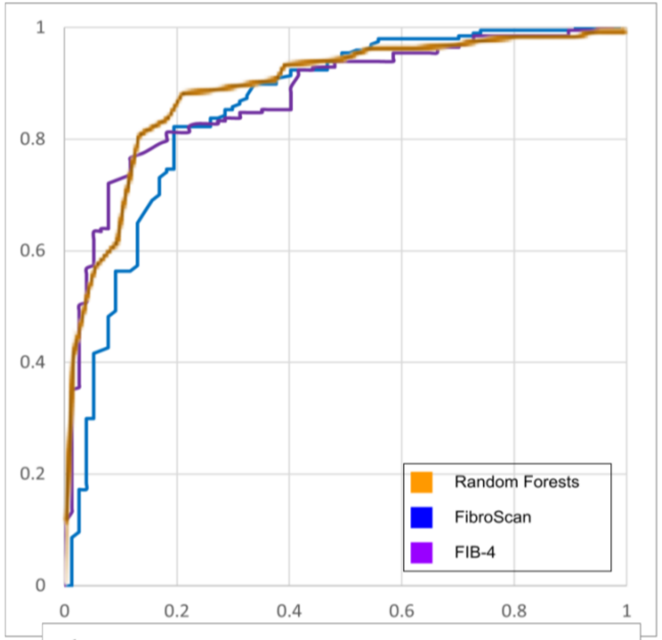
Aggarwal M, et al., Abstract 74.

Machine Learning Models Are Superior to Non-Invasive Tests in Identifying Clinically Significant Stages of NAFLD and NAFLD-Related Cirrhosis

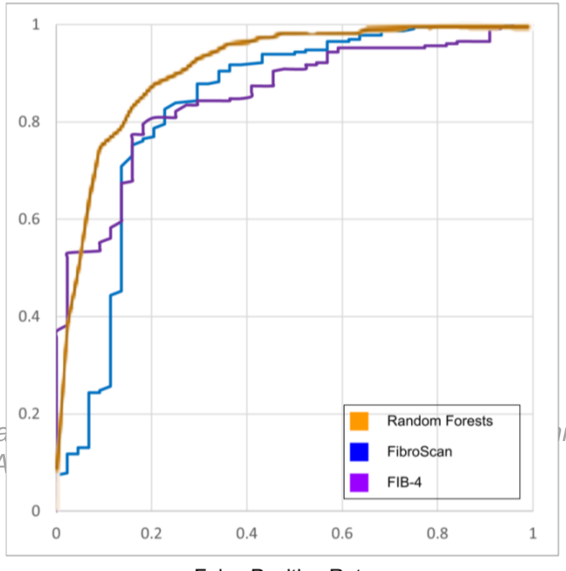
≥ F2 AUC Curve



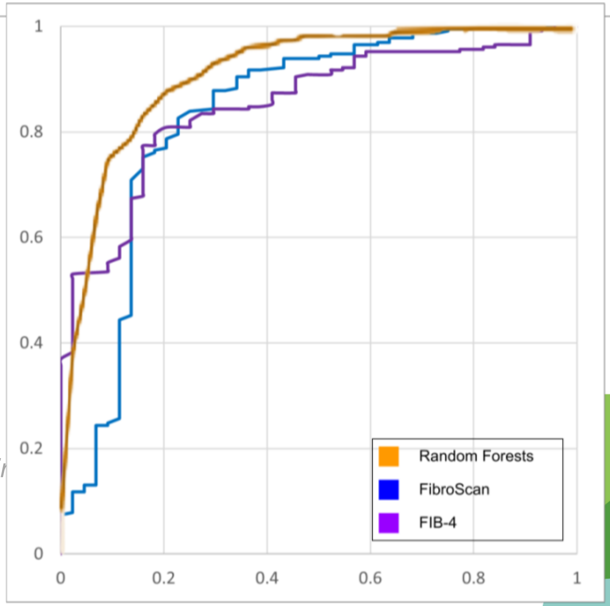
≥ F3 AUC Curve



F4 AUC Curve

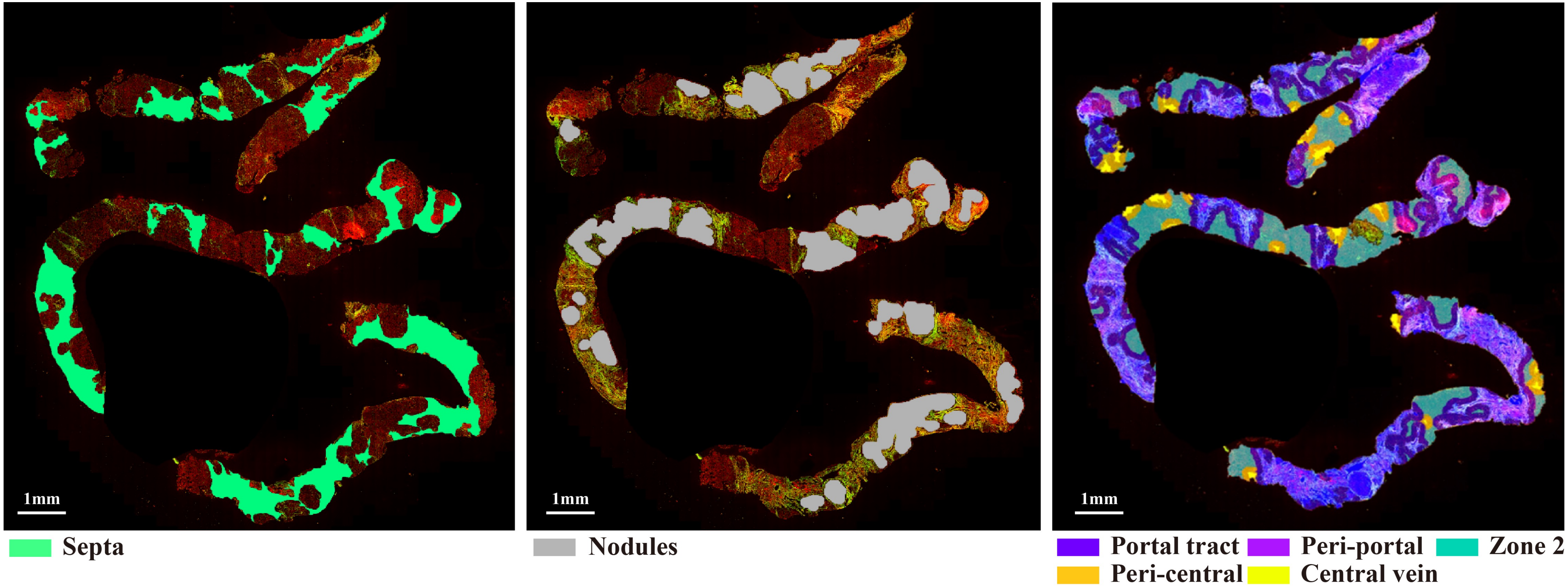


NAS ≥ 4 ≥ F2 AUC Curve



Chang D…Noureddin Poster# 1859

From this Meeting: Second harmonic generation/two-photon excitation fluorescence (SHG/TPE) imaging-based tool provided quantitative assessment of Septa, Nodules, and Fibrosis. (SNOF)



*Noureddin et al Poster with * 1591*

SNOF Score

Parameters	Training with BL samples (R values)			Training with EOT samples (R values)		
	Training	Leave-one-out	EOT	Training	Leave-one-out	BL
Septa only	0.55	0.44	0.18	0.56	0.42	0.28
Nodule only	0.52	0.39	0.40	0.53	0.39	035
Fibrosis only	0.57	0.44	0.19	0.62	0.46	0.31
SNOF	0.67	0.57	0.28	0.70	0.61	0.39

*Noureddin et al Poster with * 1591*

	Baseline					End of treatment				
	AUC	Sensitivity	Specificity	PPV	NPV	AUC	Sensitivity	Specificity	PPV	NPV
SNOF score ≥ 11.78 to predict HVPG ≥ 10 (CSPH)	0.85	73%	86%	91%	62%	0.62	55%	65%	73%	46%
SNOF score ≥ 11.78 to predict HVPG ≥ 12	0.84	83%	74%	75%	81%	0.64	61%	63%	59%	65%
SNOF-V score ≥ 0.57 to predict varices	0.86	77%	86%	85%	78%	0.62	51%	71%	61%	62%
HVPG ≥ 10 to predict varices	0.75	84%	53%	65%	76%	0.72	80%	51%	58%	76%

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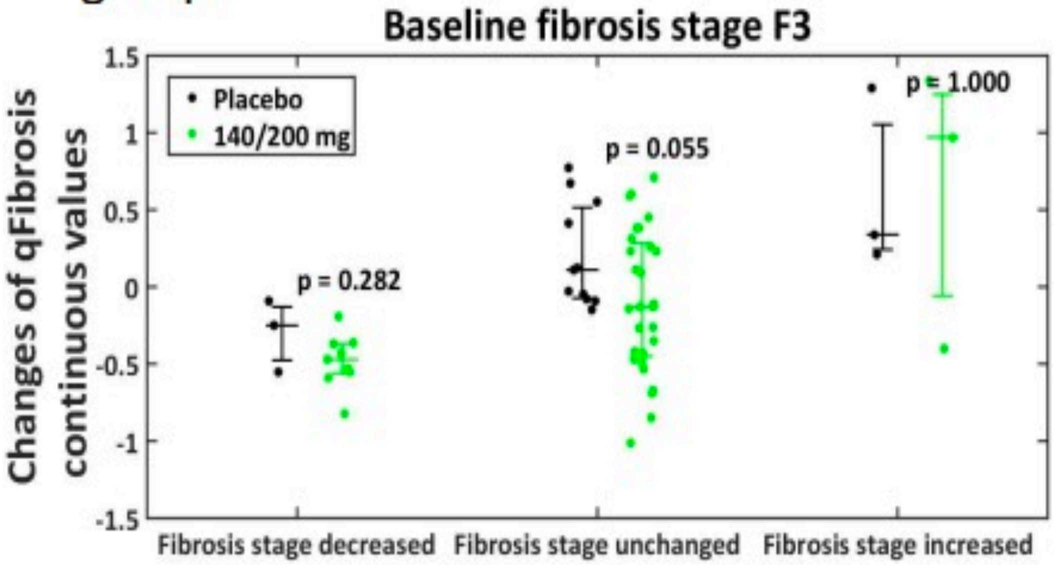
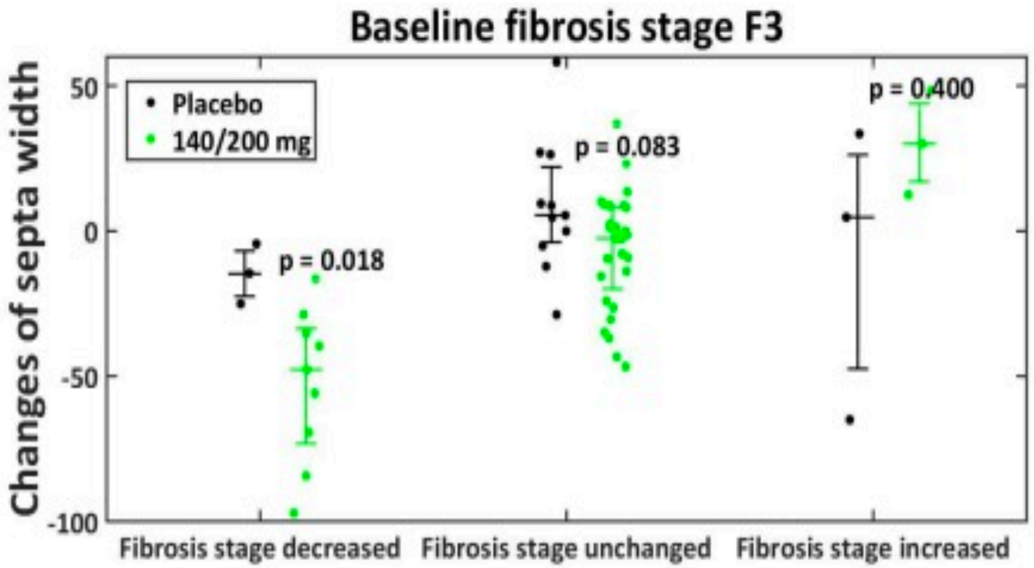
From this Meeting: DIGITAL PATHOLOGY WITH ARTIFICIAL INTELLIGENCE ANALYSES (DP-AI) OVERCOMES THE LIMITATIONS OF CURRENT SCORING SYSTEMS IN ASSESSING FIBROSIS REGRESSION FOR NASH F3 PATIENTS

C. Changes of qFibrosis continuous values for P/N/R groups



D. Changes of septa width for P/N/R groups



Sanyal et al Abstract #78

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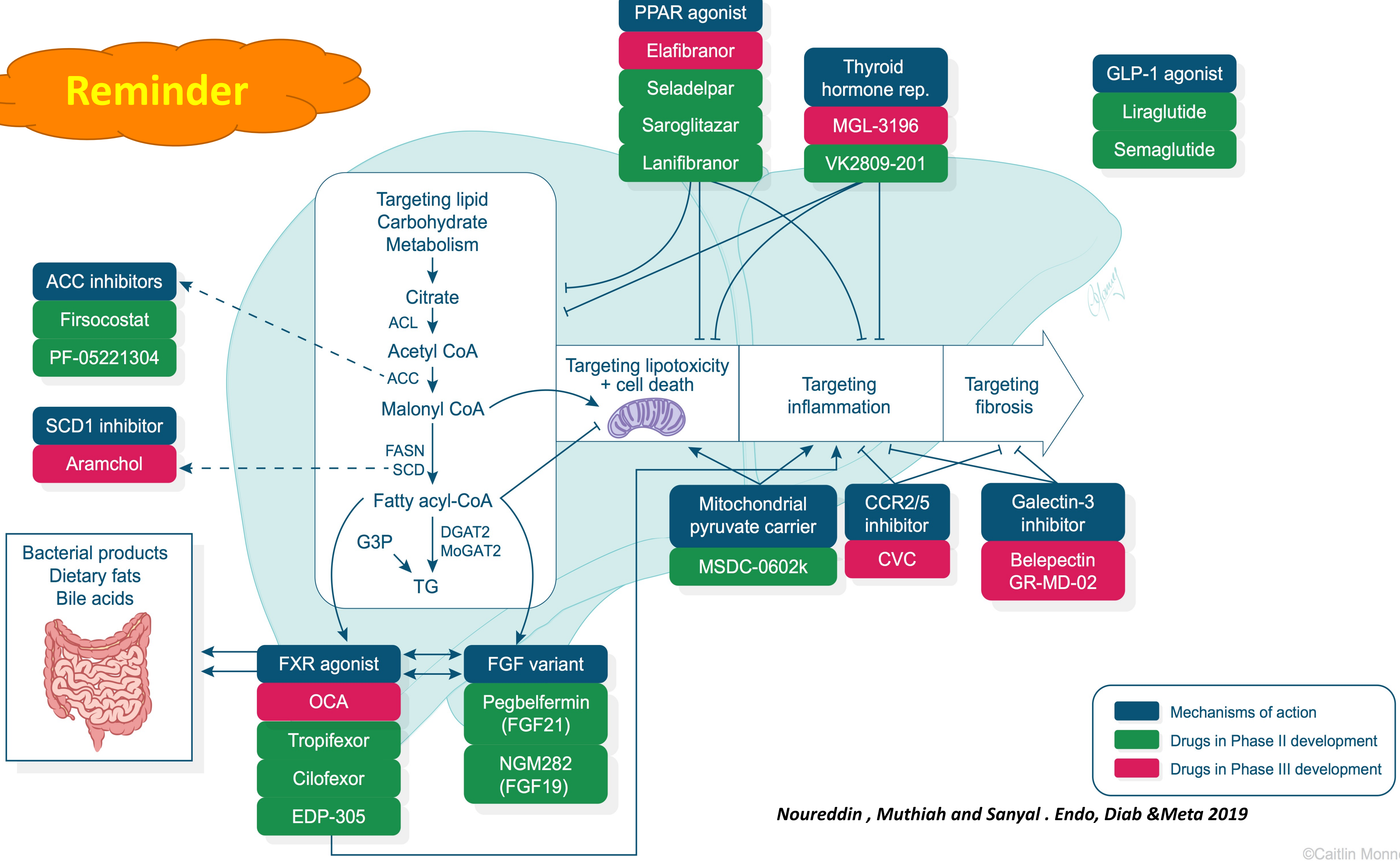
Objectives

- **Therapeutics**

Many successful stories

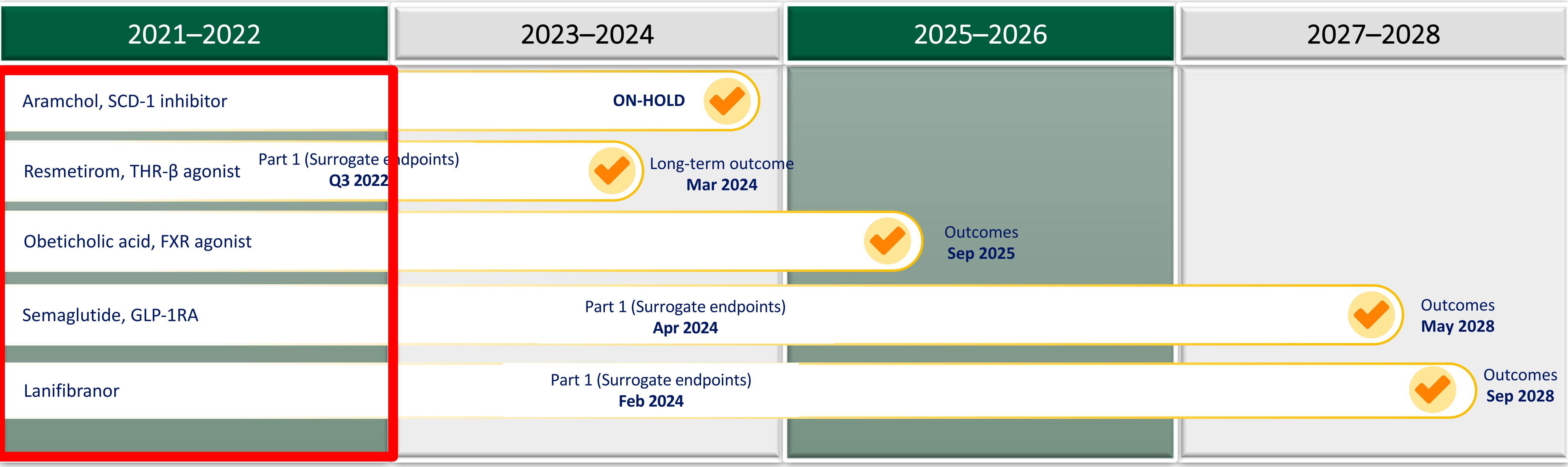
Reminder



Noureddin , Muthiah and Sanyal . Endo, Diab &Meta 2019

The future of NASH therapeutics
Ongoing phase 3 trials

From the PG course



Courtesy of S. Harrison

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From the PG course

NASH Cirrhosis Studies

Drug Candidate	Phase	Study Status	N	Mechanism of Action
Obeticholic Acid	P3	Active, not recruiting	919	FXR-Agonist
Belapectin	Adaptive P2b/3	Recruiting	1010	Galectin-3 Inhibitor
Aldafermin	P2	Active, recruiting	150	FGF19 Analog
Efruxifermin	P2	Active, not yet recruiting	200	FGF21 Analog
Semaglutide + Cilofexor + Firsocostat	P2	Active, not recruiting	440	GLP-1 analog + FXR Agonist + ACCi

Courtesy of S. Harrison

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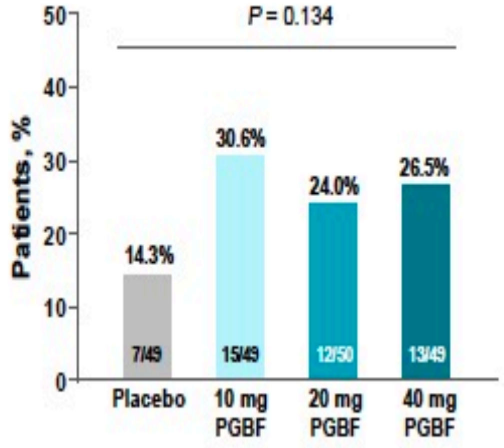
Pegbelfermin (PGBF) in patients with NASH and stage 3 fibrosis: results from the FALCON 1 study

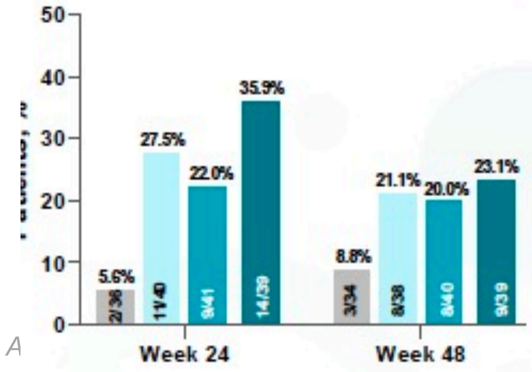
FALCON 1 study design (NCT03486899)

FALCON 2 in Cirrhotics
Same Fate

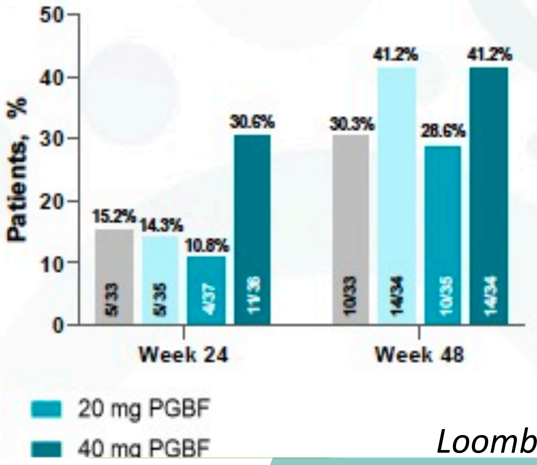
Primary endpoint:
≥1 stage improvement i
without worsening of NAS
NASH improvement wit
worsening of fibrosis at we



≥30% relative reduction in HFF measured by MRI-PDFF



≥15% relative reduction in liver stiffness measured by MRE



Loomba et al; LB05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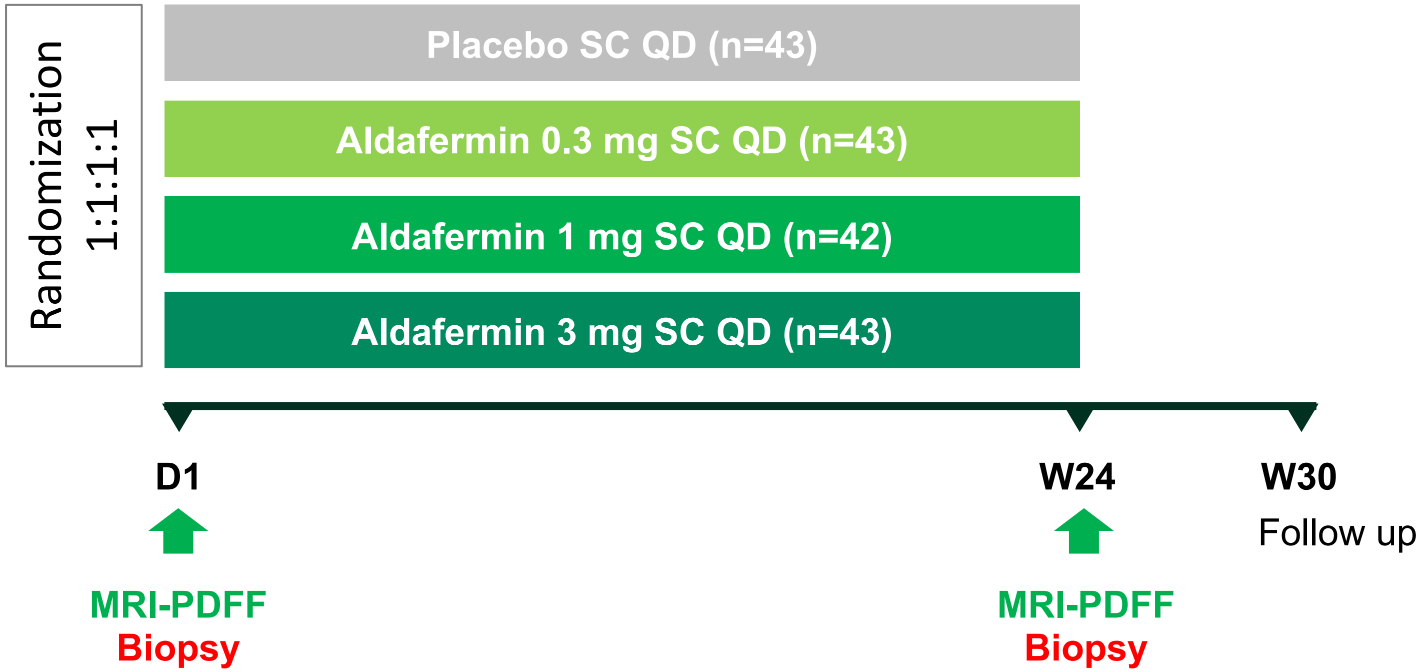
Aldafermin Phase 2b ALPINE 2/3 Study

Key Inclusion Criteria

- Biopsy-confirmed NASH, NAS ≥ 4
- Stage 2 or 3 fibrosis (NASH-CRN)
- LFC by MRI-PDFF ≥ 8%



Study Endpoints

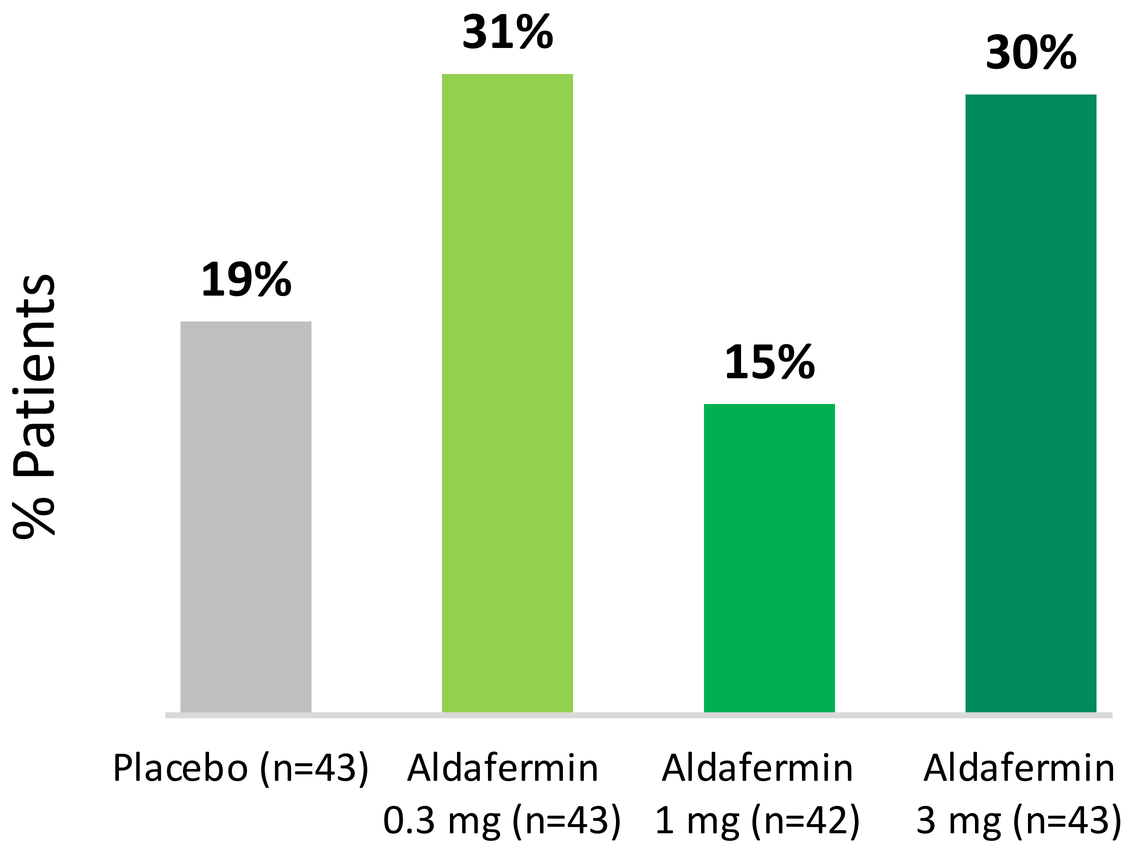
- **Primary endpoint:** improvement in liver fibrosis by ≥ 1 stage with no worsening of NASH at Week 24 (dose-response by MCP-Mod method)
- **Secondary endpoints** include: NASH resolution, fibrosis improvement <u>and</u> NASH resolution, NAS, LFC, ALT, AST, C4, bile acids and biomarkers of fibrosis at Week 24

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C4, 7alpha-hydroxy-4-cholesten-3-one; LFC, liver fat content; MCP-Mod, multiple comparison procedure—modeling; MRI-PDFF, magnetic resonance imaging—proton density fat fraction; NAS, NAFLD activity score; QD, once daily; SC, subcutaneous

Harrison et al Abstract #8

ALPINE 2/3 Primary Endpoint Not Met

Fibrosis Improvement ≥ 1 Stage with No Worsening of NASH[1] at W24



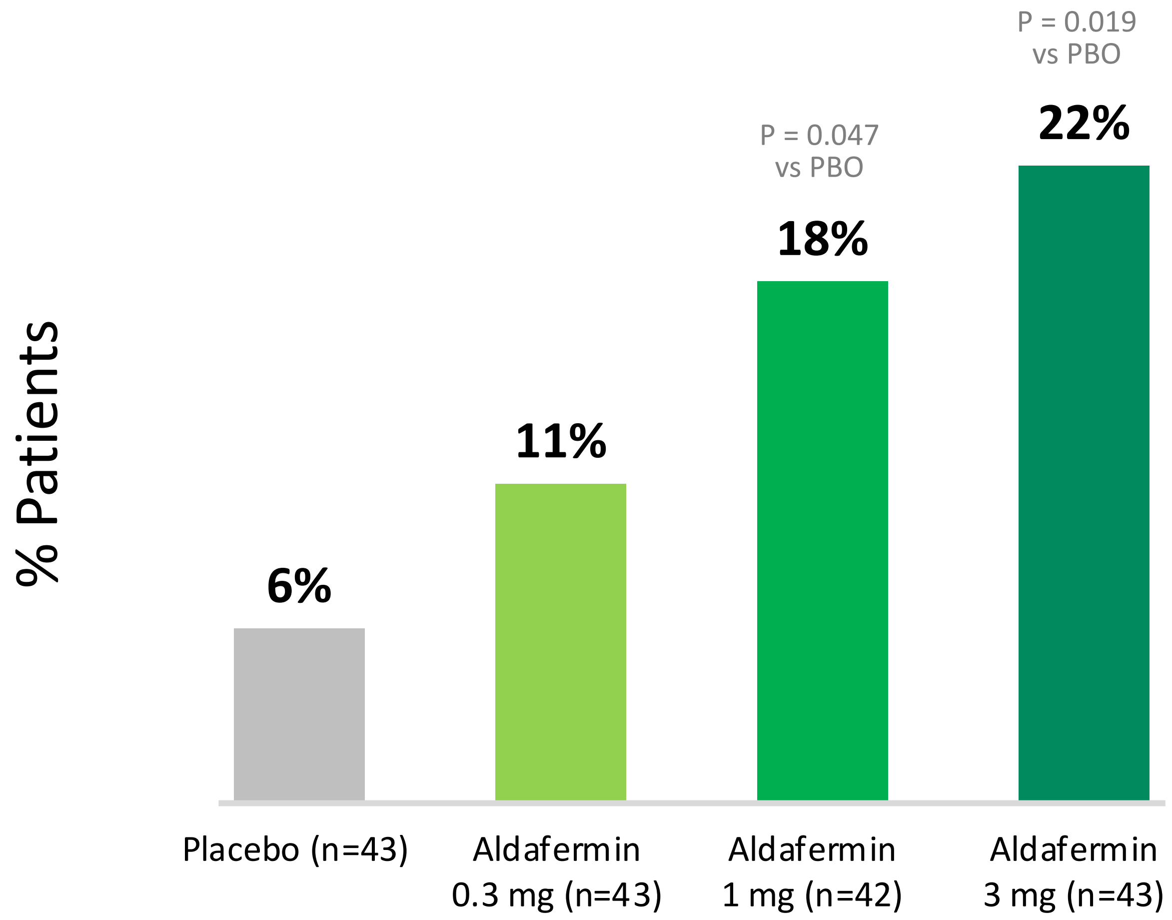
- Protocol prespecified the analysis of the primary endpoint (fibrosis improvement) using the **MCP-Mod[2]** method for detecting a **dose-response**
- The primary endpoint was not met (P=0.55 by MCP-Mod in ITT population with multiple imputation)
- ALPINE 2/3 was not powered for pairwise comparison between groups
- In ALPINE 2/3, the 1 mg did NOT produce a similar fibrosis response as in Cohort 4 (placebo: 18%; aldafermin 1 mg: 38%) [3]

[1] Defined as patients who have an improvement in liver fibrosis by ≥1 stage with no worsening of NASH (no worsening of steatosis, lobular inflammation or hepatocyte ballooning grade) from baseline to W24; [2] MCP-Mod, Multiple Comparison Procedure-Modeling, as pre-specified in the protocol and Statistical Analysis Plan, in ITT population with multiple imputation; [3] Harrison et al., Gastroenterology. 2021;160:219-231

Harrison et al Abstract #8

Aldafermin Dose-Dependently Improved NASH Resolution

Resolution of NASH with No Worsening of Fibrosis[1] at W24

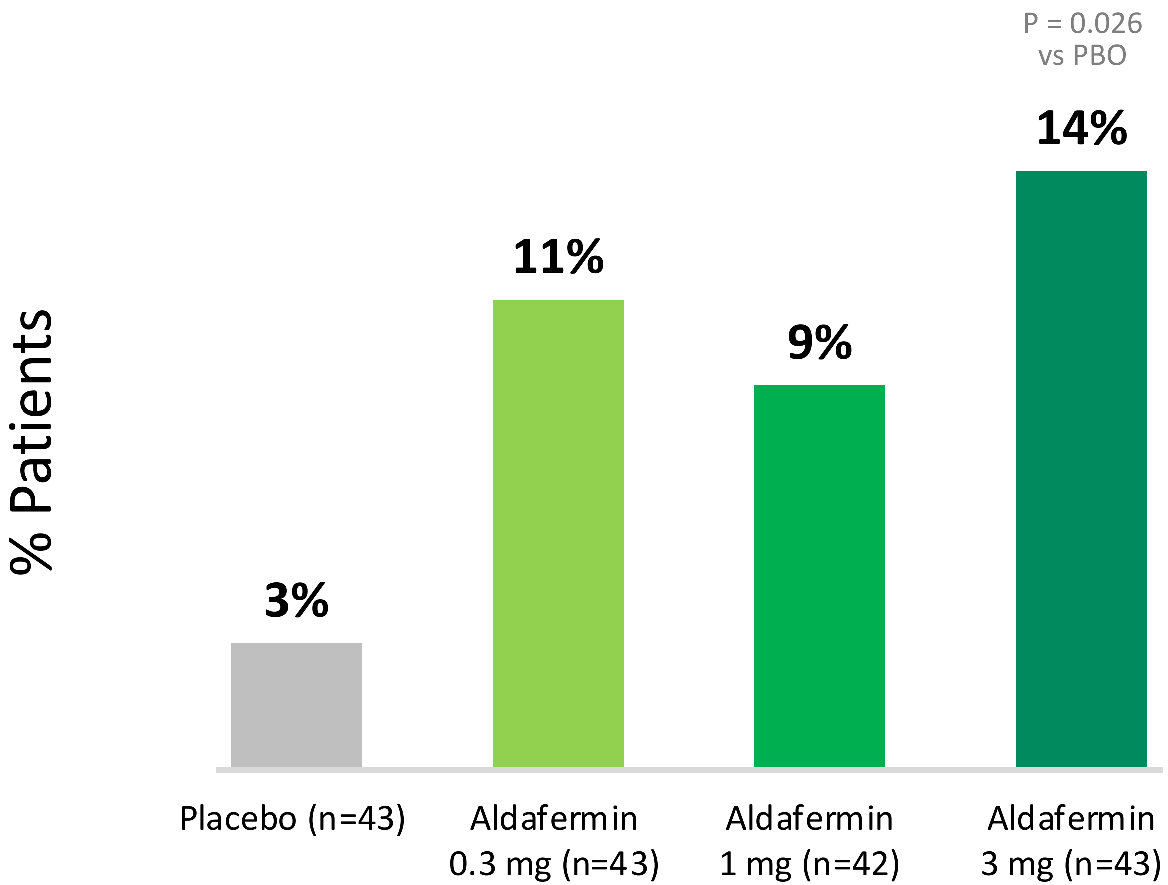


ITT population with multiple imputation (not powered for pairwise comparison between groups); [1]Defined as subjects having a NAS score of 0 or 1 for inflammation and 0 for ballooning, with no worsening of fibrosis (no progression of NASH CRN fibrosis stage) from baseline to W24; PBO, placebo

Harrison et al Abstract #8

Aldafermin 3 mg Achieved the Composite Endpoint of Fibrosis Improvement and Resolution of NASH

Fibrosis Improvement ≥ 1 stage and Resolution of NASH[1] at W24

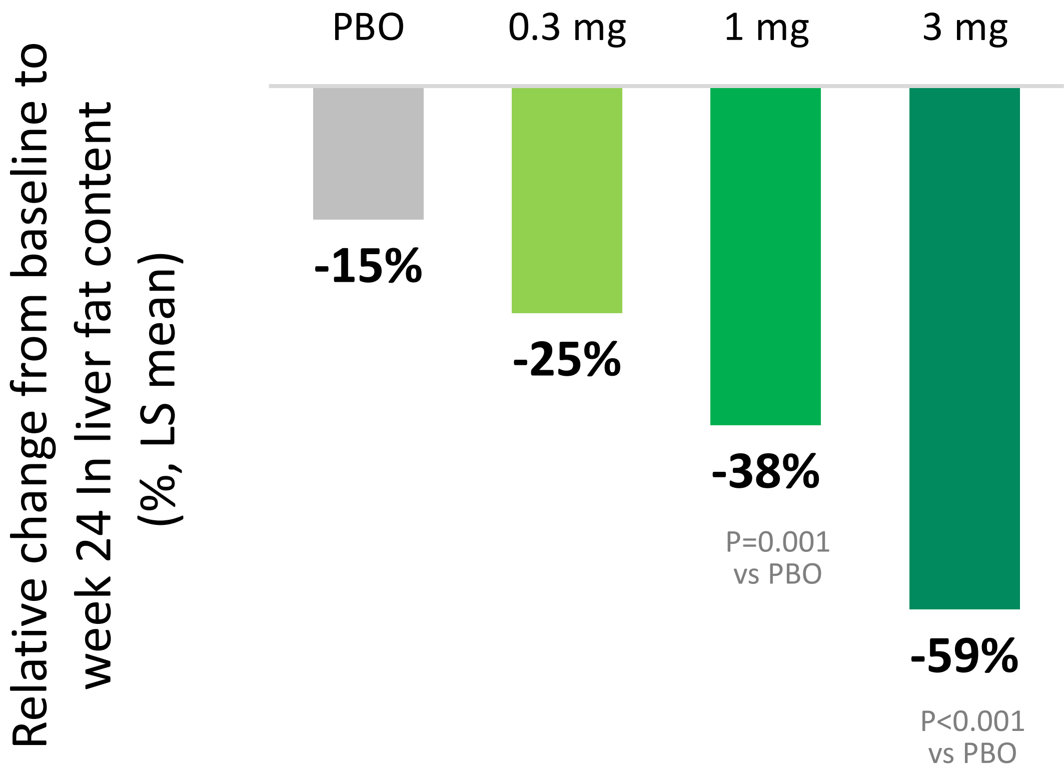


ITT population with multiple imputation (not powered for pairwise comparison between groups); [1]Defined as patients who have an improvement in liver fibrosis by ≥1 stage with no worsening in steatohepatitis AND have a NAS score of 0 or 1 for inflammation and 0 for ballooning at W24

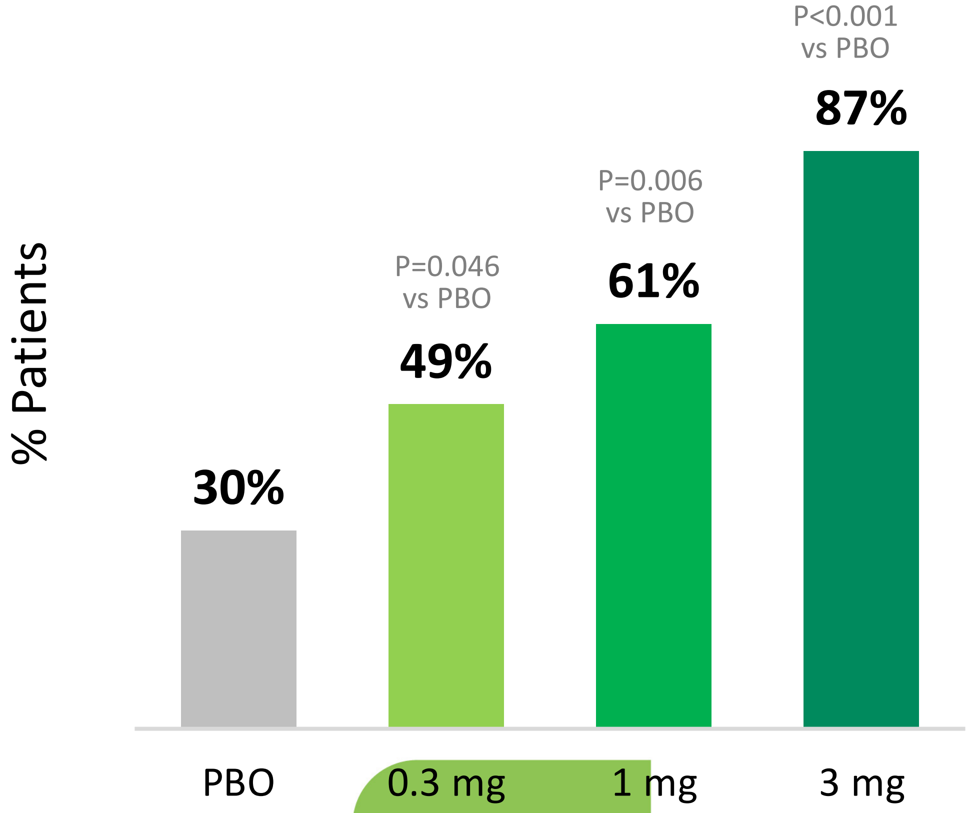
Harrison et al Abstract #8

Aldafermin Achieved Dose-Dependent Reduction in Liver Fat Content as Measured by MRI-PDFF

Relative Change in Liver Fat Content (LFC)[1]



Patients Achieving ≥30% Reduction in LFC



[1] Liver fat content (LFC) as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)

Harrison et al Abstract #8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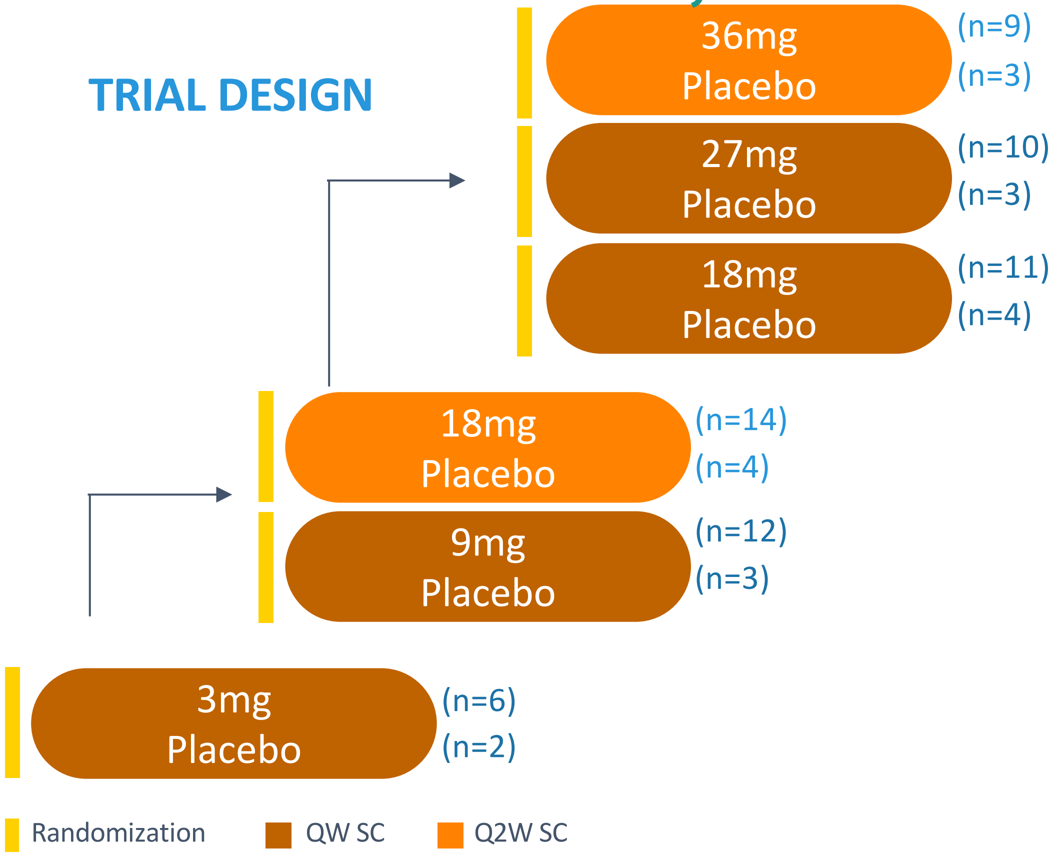
BIO89-100-002 (NCT4048135): A Double Blind, Placebo Controlled, Multi-center, Phase 1b/2a study

TRIAL DESIGN



- 12-week treatment duration + 4-week safety follow up
- Placebo (n=19) combined across cohorts for analysis

KEY INCLUSION CRITERIA

- NASH* or phenotypic NASH (PNASH)#
- PDFF≥10%

*Subjects with biopsy-proven F1-3

#Central obesity plus T2DM or evidence of liver injury

KEY TRIAL ENDPOINTS

- Safety, PK
- Relative changes in liver fat
- Serum lipids, liver and metabolic markers

- Randomized, pharmacodynamic (PD) and safety analysis set n=81; Study completers n=71
- MRI analysis set n=75 (subjects with post-baseline MRI)

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BIO89-100-002 (NCT4048135): Spleen Volume Post Hoc Analysis

36mg Q2W
N=8

27mg QW
N=8

Pooled for analysis

Pooled placebo
N=18

- SV was assessed by MRI at Baseline, Day 50 and Day 92.
- Correlation of baseline SV and change in SV to various clinical and lab parameters was investigated

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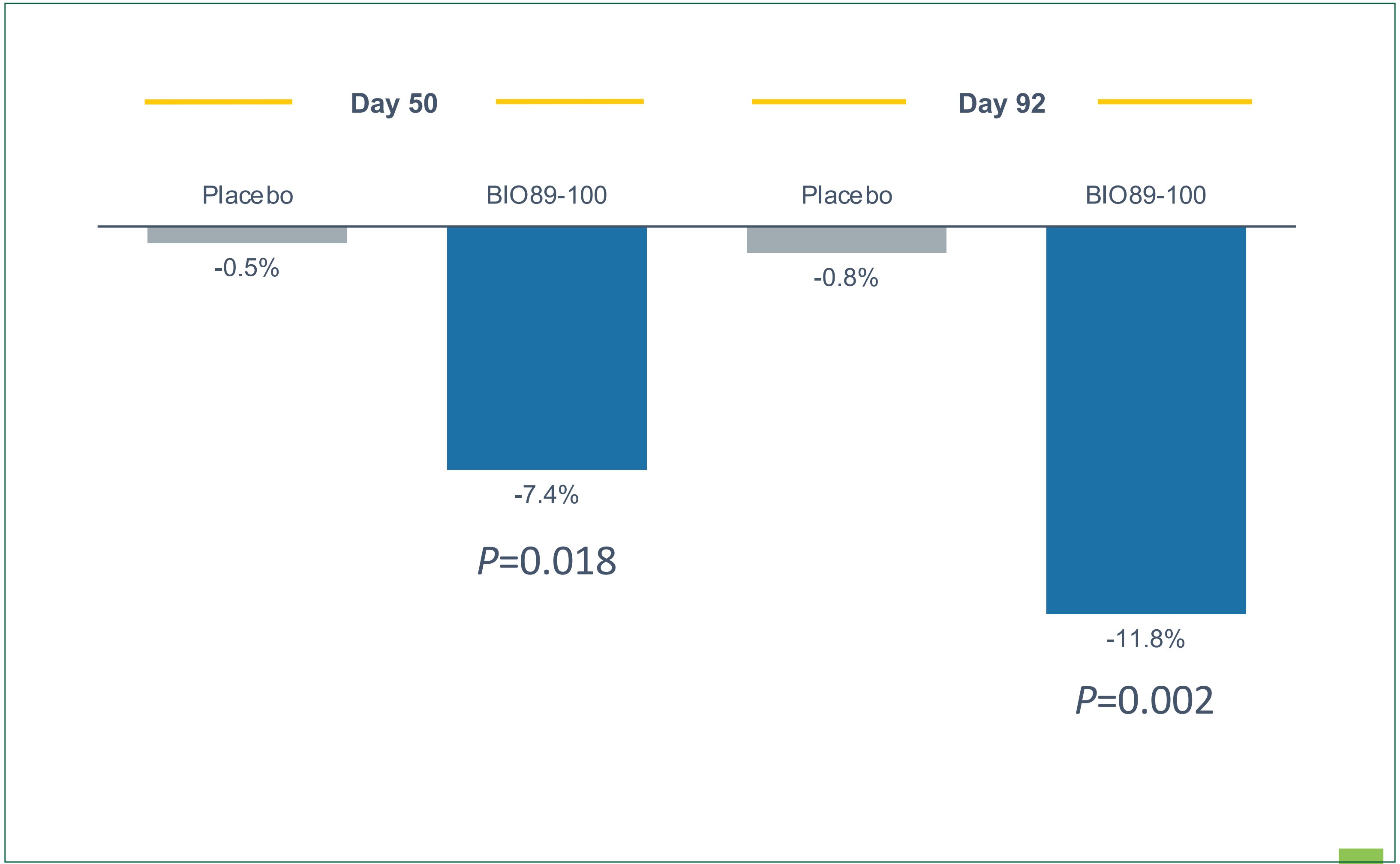
Significant Reduction in Spleen Volume With BIO89-100



Percent changes from baseline to D50 and D92 were estimated using ANCOVA model adjusted for baseline SV.

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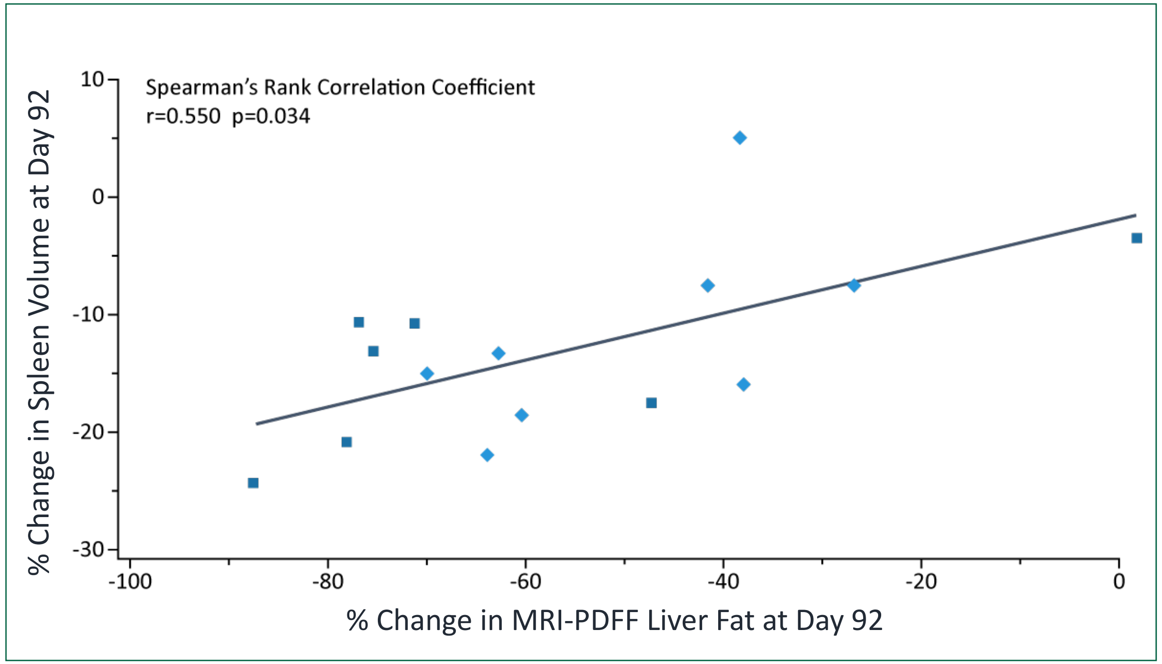
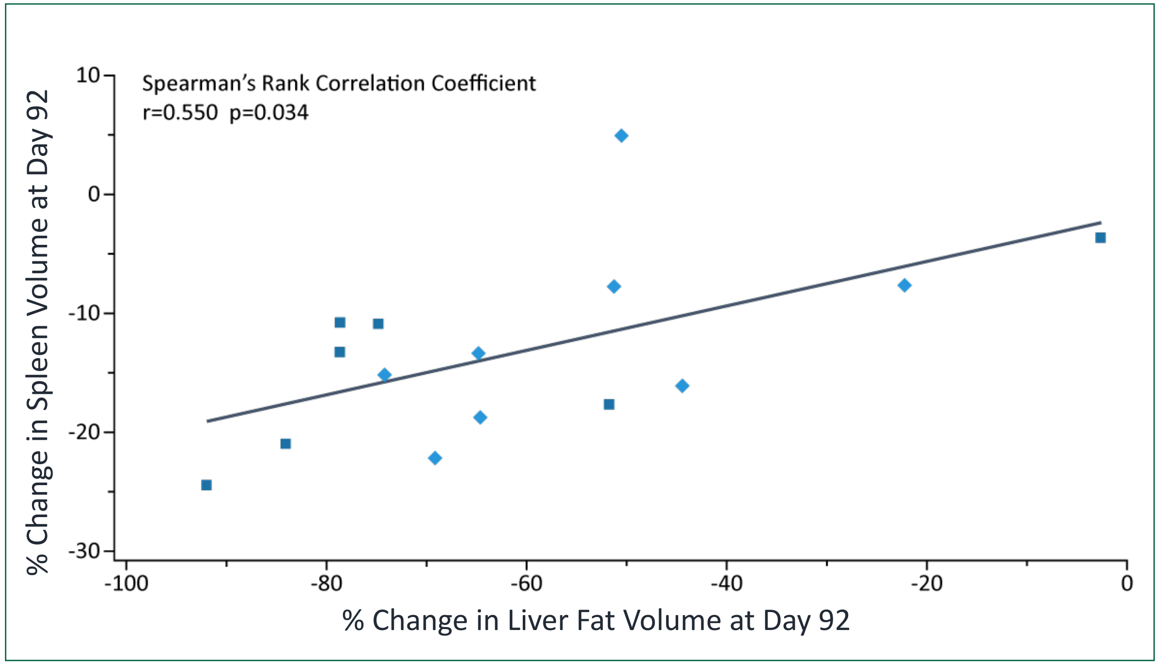
Spleen Volume Change Correlated to Change in Liver Fat at Day 92

% Change in MRI-PDFF



r = 0.55

% Change in Liver Fat Volume



r = 0.55

■ BIO89-100 27mg QW ◆ BIO89-100 36mg Q2W

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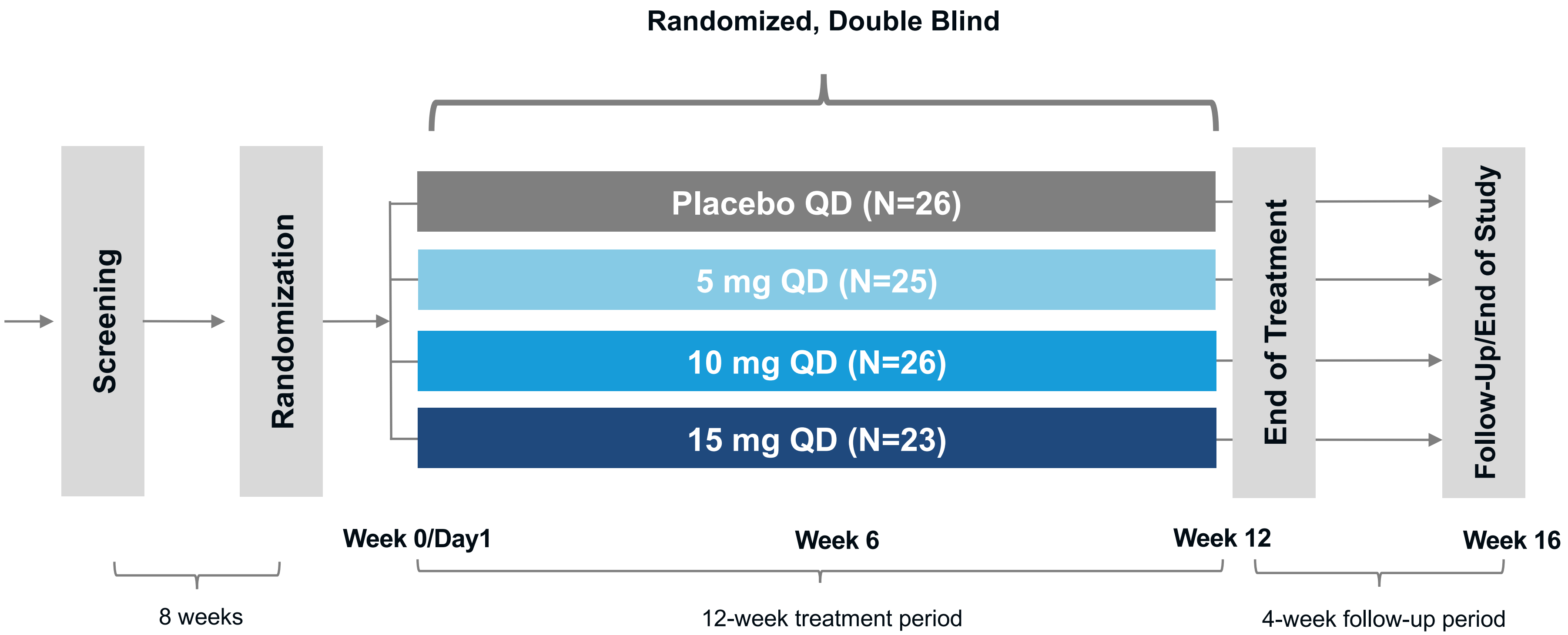
TERN-101 LIFT Study: Phase 2a Study in NASH Patients

Key inclusion criteria:
Adults 18-75 years
BMI ≥ 25 kg/m^2
MRI-PDFF ≥ 10%
ALT ≥ 28 IU/L (women) or
≥ 43 IU/L (men)

NASH based on clinical characteristics:
TE 7.6-21 kPa
CAP > 300 dB/m
Or prior biopsy (n= 23):
F1-3 in last 2 years



MRI-PDFF at Baseline, Week 6, and Week 12; cT1 at available sites

Alanine aminotransferase (ALT), body mass index (BMI), corrected T1 (cT1), magnetic resonance imaging (MRI), once daily (QD), proton density fat fraction (PDFF), transient elastography (TE); NCT04328077

Adverse Event (AE) Summary

- All AEs were mild or moderate except for 2 unrelated Grade 3 events (also considered SAEs)
  - 1 SAE of COVID-19 (placebo) and 1 SAE of UTI requiring hospitalization (TERN-101 15 mg)
- No deaths occurred
- No patient discontinued due to an AE

Patient incidence AEs by category, n (%)	**Placebo (N=26)**	**5 mg (N=25)**	**10 mg (N=26)**	**15 mg (N=23)**
Any AE, all CTCAE grades	10 (38.5%)	13 (52.0%)	14 (53.8%)	15 (65.2%)
CTCAE Grade 3 or higher AEs	1 (3.8%)	0	0	1 (4.3%)
Serious AE	1 (3.8%)	0	0	1 (4.3%)
AE leading to death	0	0	0	0
AE leading to study or drug discontinuation	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events, AE = adverse event, UTI = urinary tract infection; AEs reported refer to treatment-emergent AEs, defined as any AE with a start date on or after the date of first administration of study drug through 30 days after the last administration of study drug or through the Follow-Up Period (Week 16)

Pruritus AE Summary

- All pruritus-related AEs* were mild or moderate
- Patient incidence of pruritus was generally balanced across TERN-101 treatment groups
- No patient discontinued study drug due to pruritus
- Most pruritus AEs were mild, self-limited and resolved without treatment interruption

Patient incidence of any pruritus AE, n (%)	Placebo (N=26)	5 mg (N=25)	10 mg (N=26)	15 mg (N=23)
Pruritus, all CTCAE grades*	0	4 (16.0%)	3 (11.5%)	4 (17.4%)
Grade 1	0	4 (16.0%)	1 (3.8%)	3 (13.0%)
Grade 2	0	0	2 (7.7%)	1 (4.3%)
Grade 3	0	0	0	0
Study drug-related pruritus AEs, per Investigator	0	3 (12.0%)	3 (11.5%)	1 (4.3%)
Study drug discontinuation due to pruritus	0	0	0	0

*All preferred terms reflecting pruritis including an event of pruritic rash (5 mg group) were included which was a pre-specified analysis (MedDRA version 23.0)
Grade 1: Mild or localized; topical intervention indicated; Grade 2: Widespread and intermittent; skin changes from scratching; oral intervention indicated; limiting activities of daily living
CTCAE = common terminology criteria for adverse events

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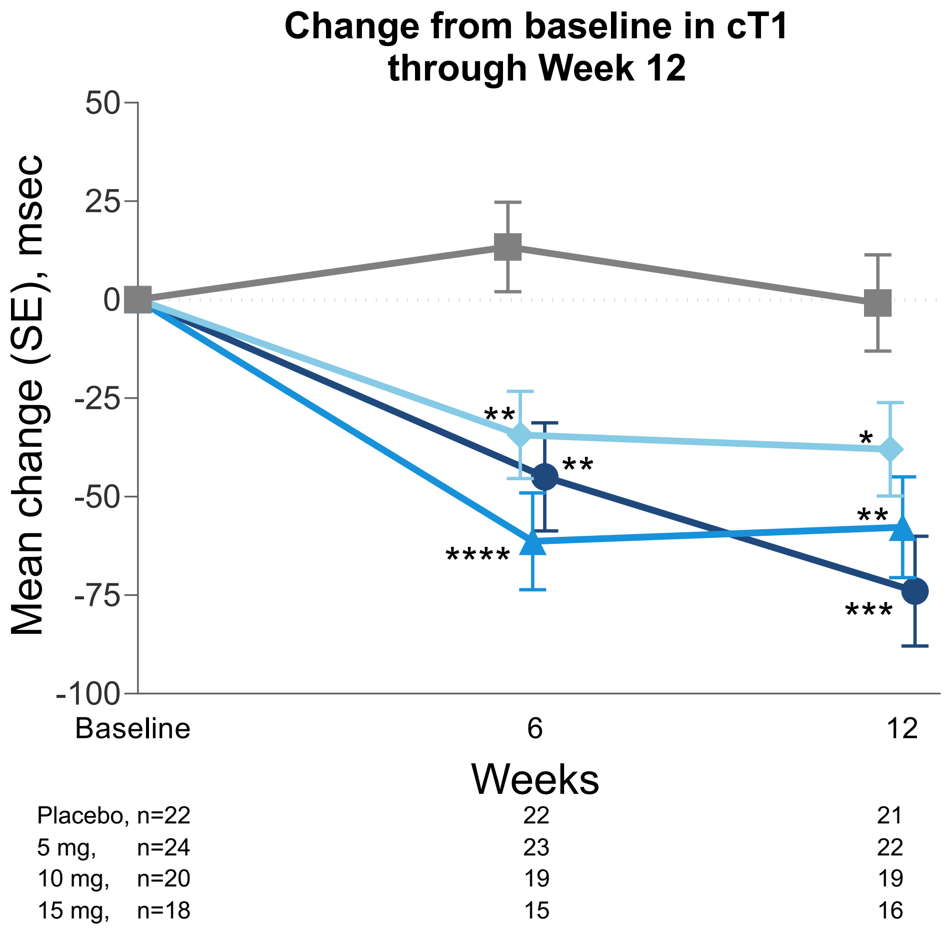
cT1 Change from Baseline

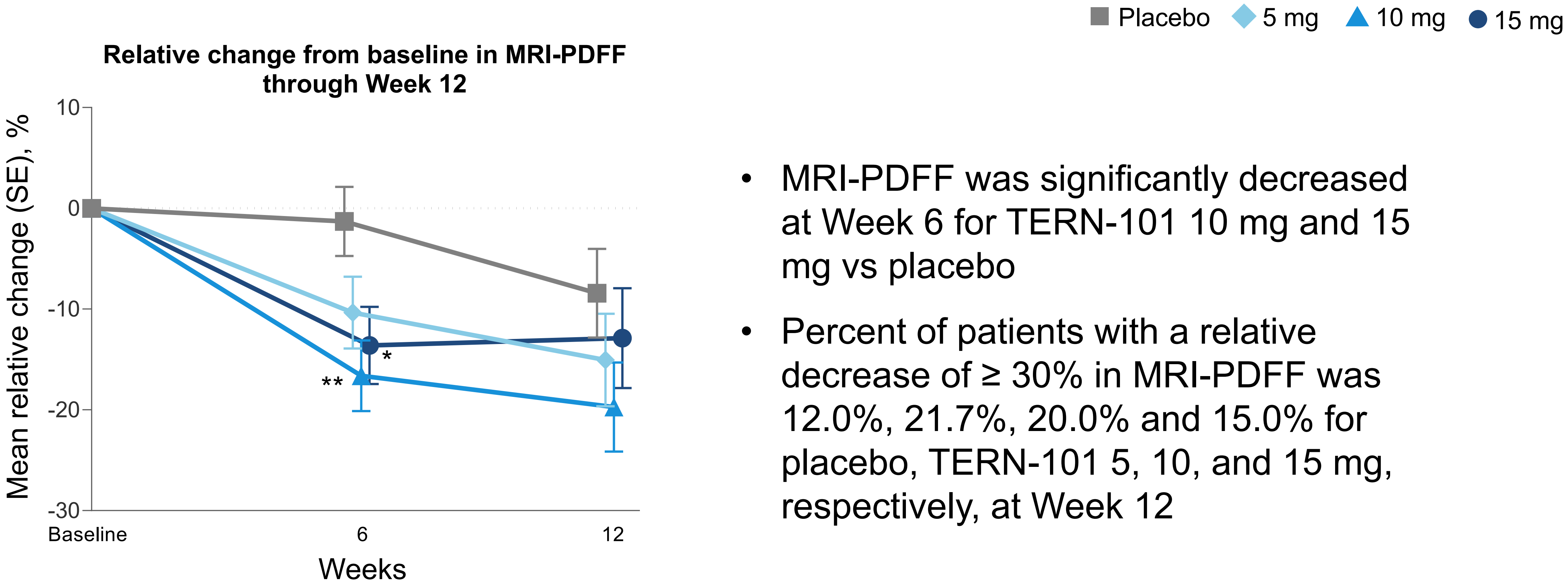


- cT1 declined significantly as early as Week 6 in all TERN-101 groups
- Significant mean cT1 declines persisted at Week 12 in all TERN-101 groups compared to placebo

*p-value < 0.05; **p-value<0.01; ***p-value<0.001; ****p-value<0.0001
Corrected T1 (cT1) was conducted only at available sites.

Loomba et al Abstract #143

MRI-PDFF Relative Change from Baseline

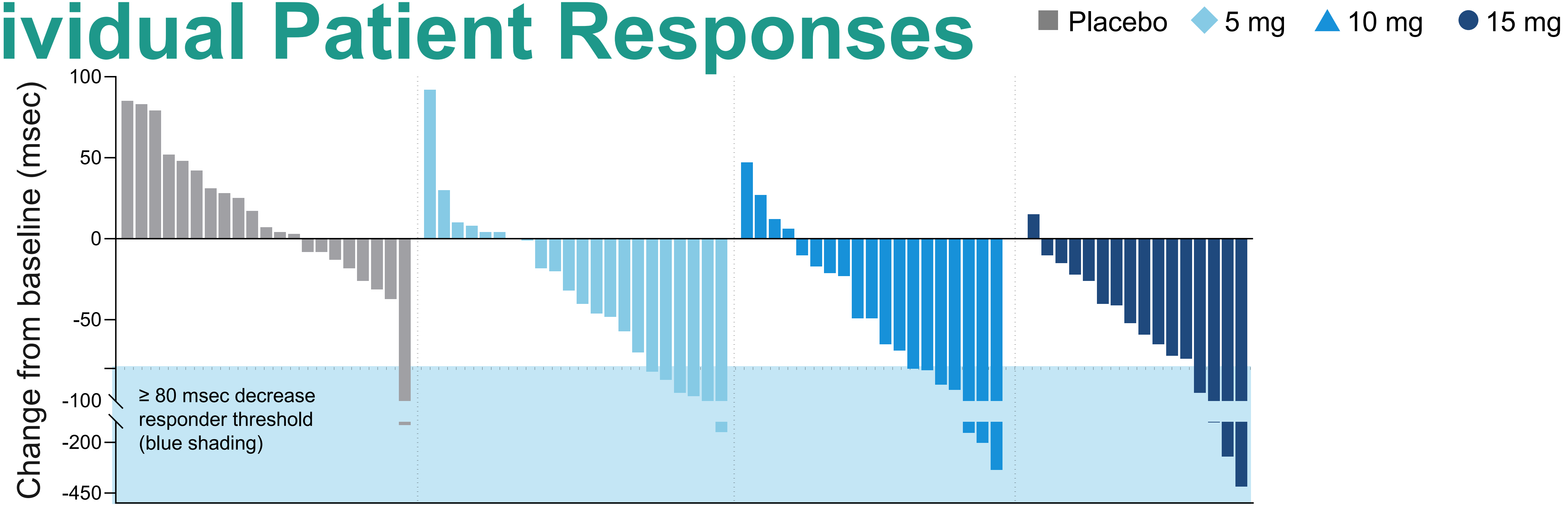


- MRI-PDFF was significantly decreased at Week 6 for TERN-101 10 mg and 15 mg vs placebo
- Percent of patients with a relative decrease of ≥ 30% in MRI-PDFF was 12.0%, 21.7%, 20.0% and 15.0% for placebo, TERN-101 5, 10, and 15 mg, respectively, at Week 12

*p-value < 0.05; **p-value<0.01 Magnetic resonance imaging proton density fat fraction (MRI-PDFF)

Loomba et al Abstract #143

cT1 Change from Baseline to Week 12: Individual Patient Responses



Patients with decline ≥ 80 msec, % (n/N)	5% (1/21)	27%* (6/22)	37%* (7/19)	25% (4/16)

- cT1 values decreased for majority of TERN-101 patients
- Significantly greater proportion of patients with decrease of ≥ 80 msec in the TERN 101 5 mg and 10 mg groups compared to placebo

*p-value < 0.05; corrected T1 (cT1)

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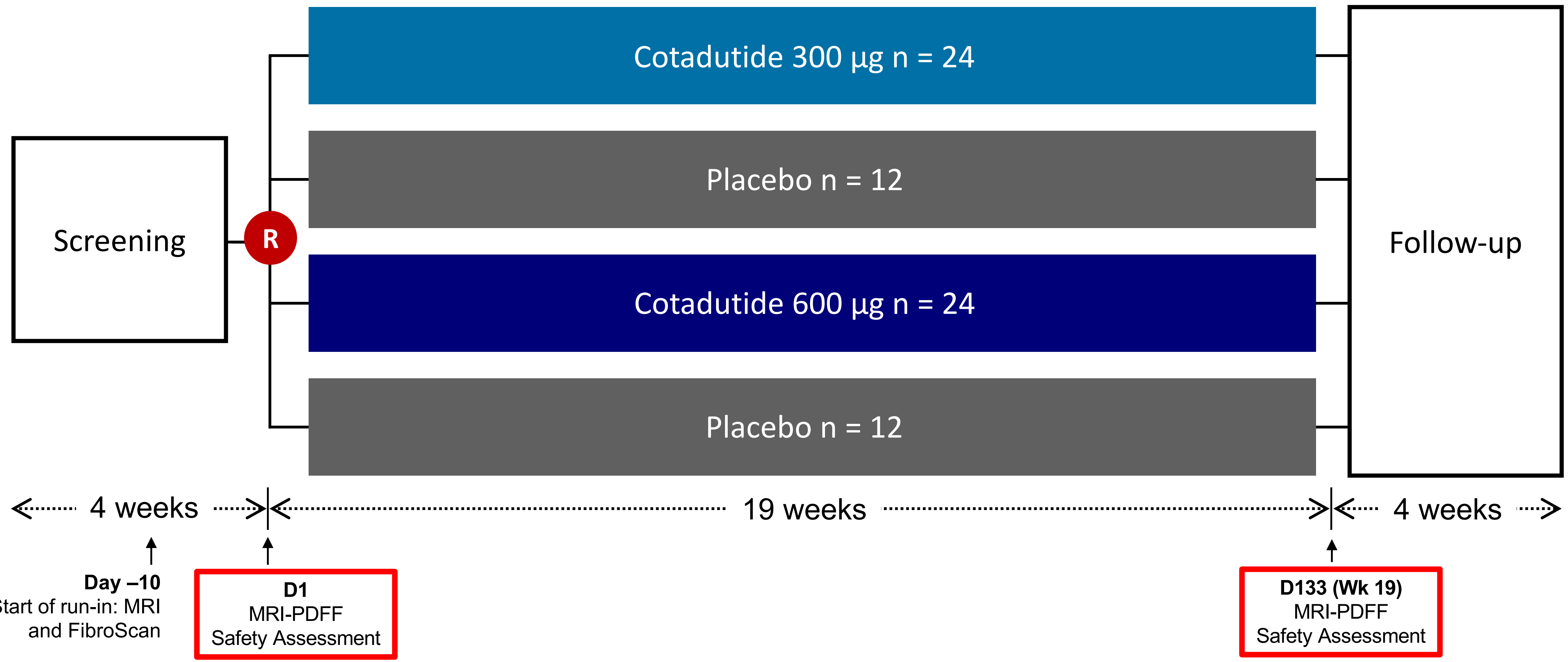
PROXYMO Study Design



Population:

- Adults with biopsy-proven non-cirrhotic NASH with fibrosis (NAS ≥ 4, fibrosis stages F1–3 per NASH CRN criteria)
- Hepatic steatosis ≥ 10% by MRI-PDFF at screening
- BMI ≥ 30 kg/m^2
- T2DM: HbA1c < 9.5% on stable oral anti-diabetic therapy

Sanyal et al LB#6

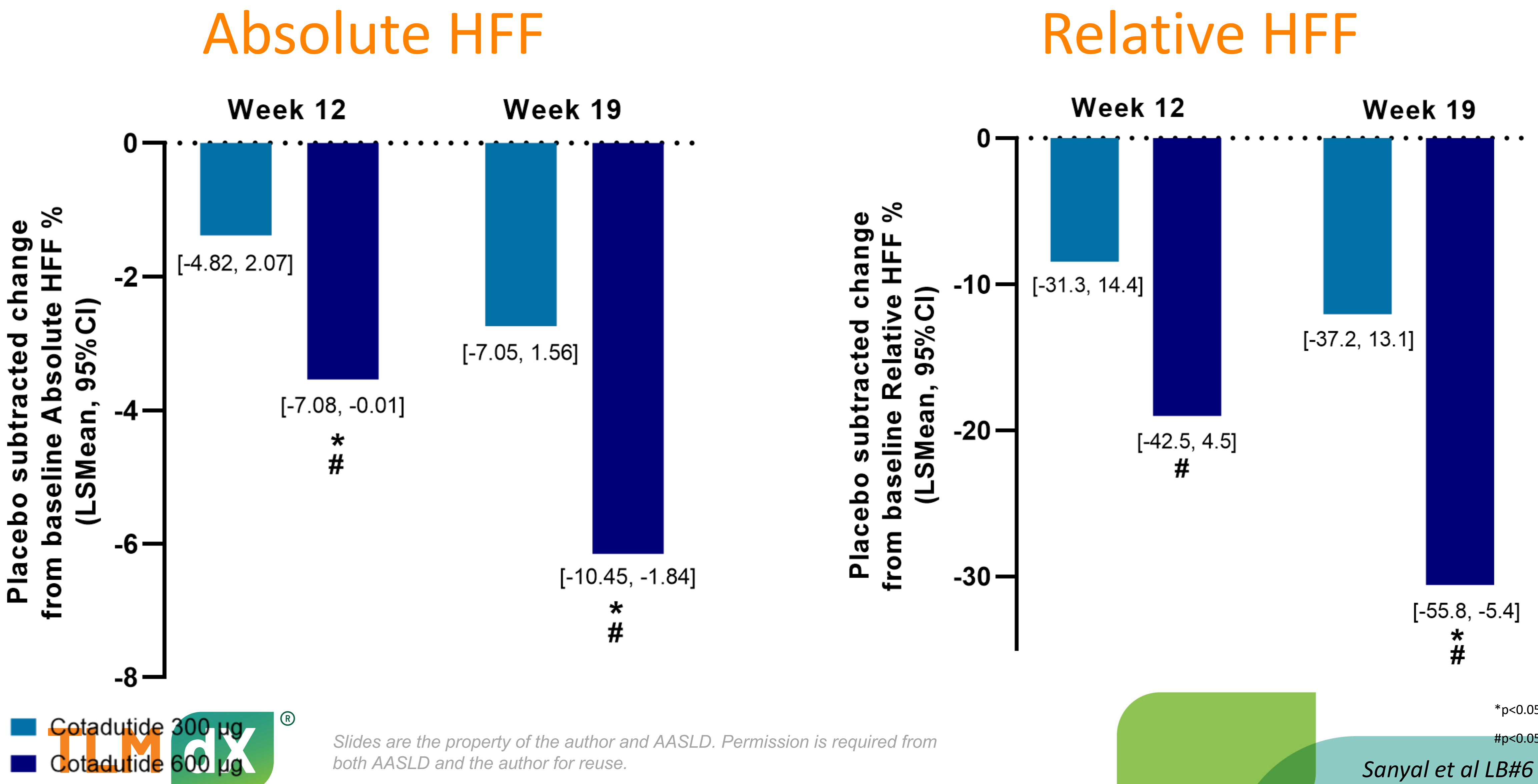
Overall Adverse Events

AE Category	Placebo (n = 24)	Cotadutide 300 µg (n = 26)	Cotadutide 600 µg (n = 24)	Cotadutide Overall (n = 50)
Any AE n(%)	9 (37.5)	20 (76.9)	22 (91.7)	42 (84.0)
Death	0	0	0	0
Any SAE (including death)	1 (4.2)	1 (3.8)	1 (4.2)	2 (4.0)
Any AE leading to discontinuation of IP	1 (4.2)	2 (7.7)	4 (16.7)	6 (12.0)
Any AE leading to withdrawal from study	0	0	0	0

- More AEs noted for cotadutide treated groups versus placebo as expected with this class of molecule
- No deaths and few SAEs which were balanced across treatment arms: Total of 3 SAEs were reported
- Discontinuations were higher on cotadutide and higher in the 600 µg versus the 300 µg group

Sanyal et al LB#6

Effect of Cotadutide on Hepatic Steatosis



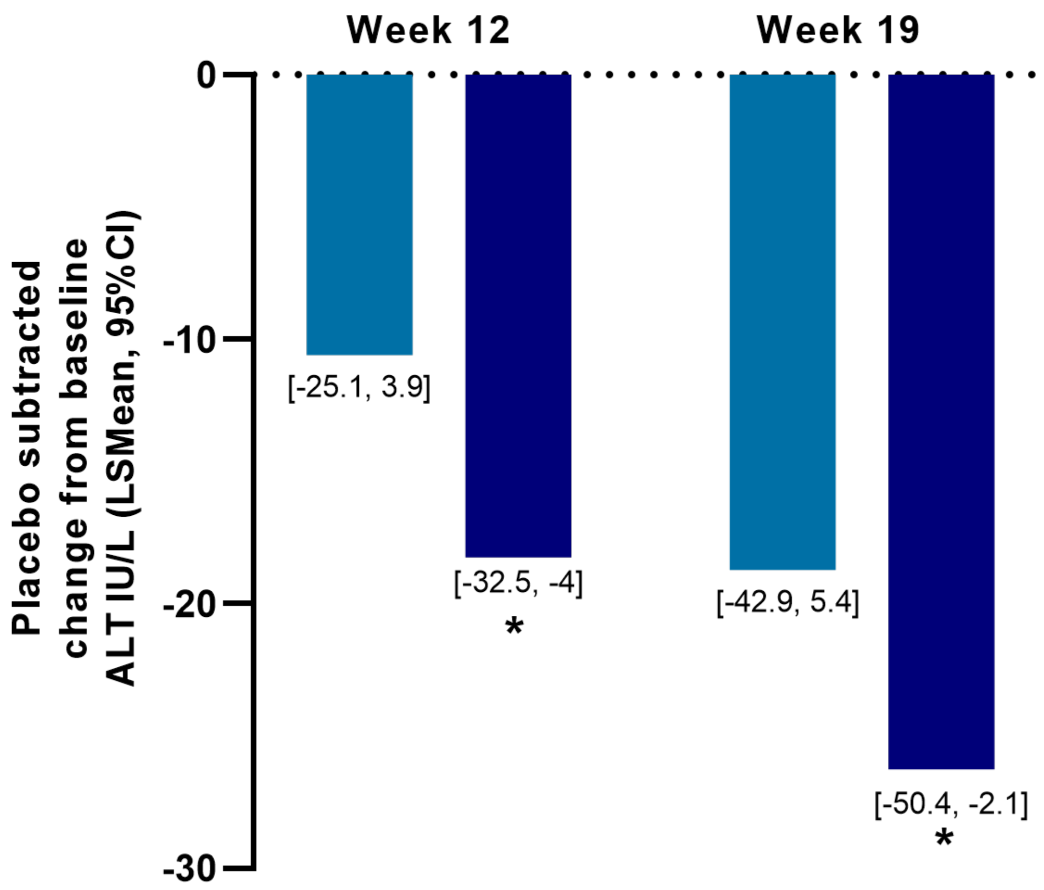
*p<0.05 vs placebo

#p<0.05 vs baseline

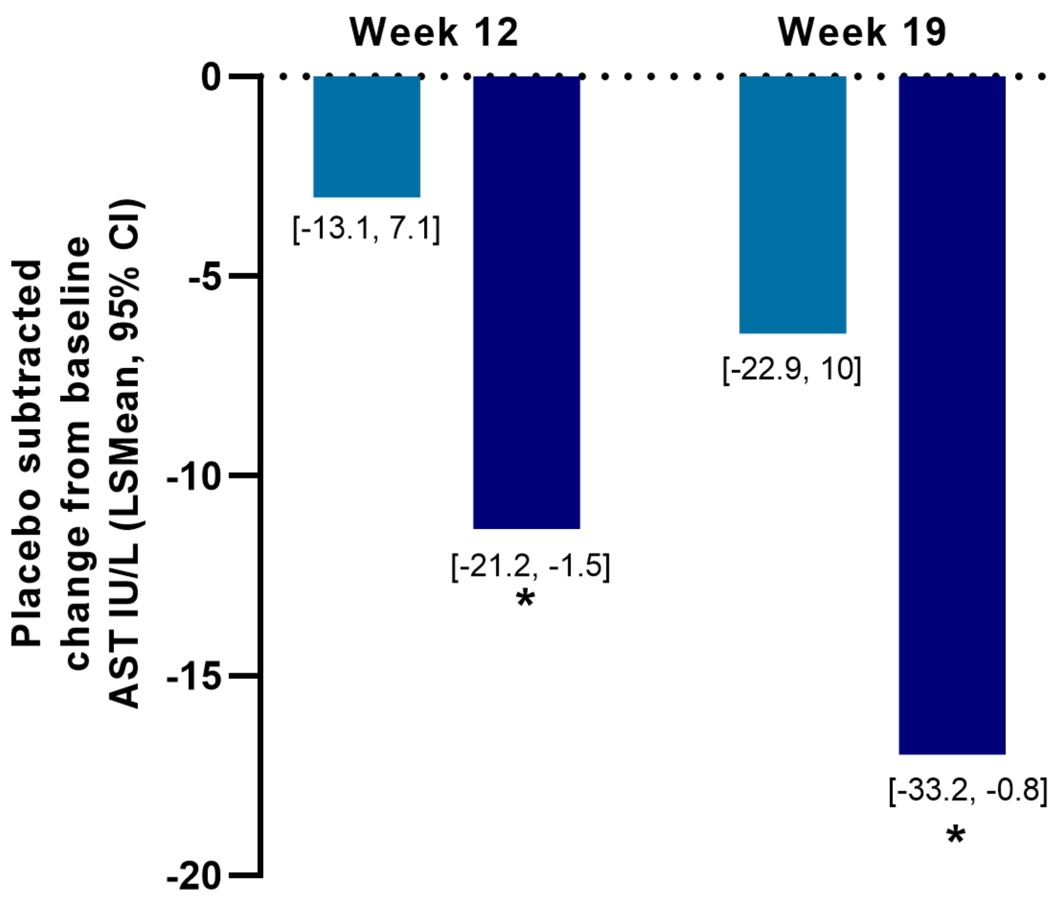
Sanyal et al LB#6

Effect of Cotadutide on Liver Enzymes

Alanine Aminotransferase



Aspartate Aminotransferase

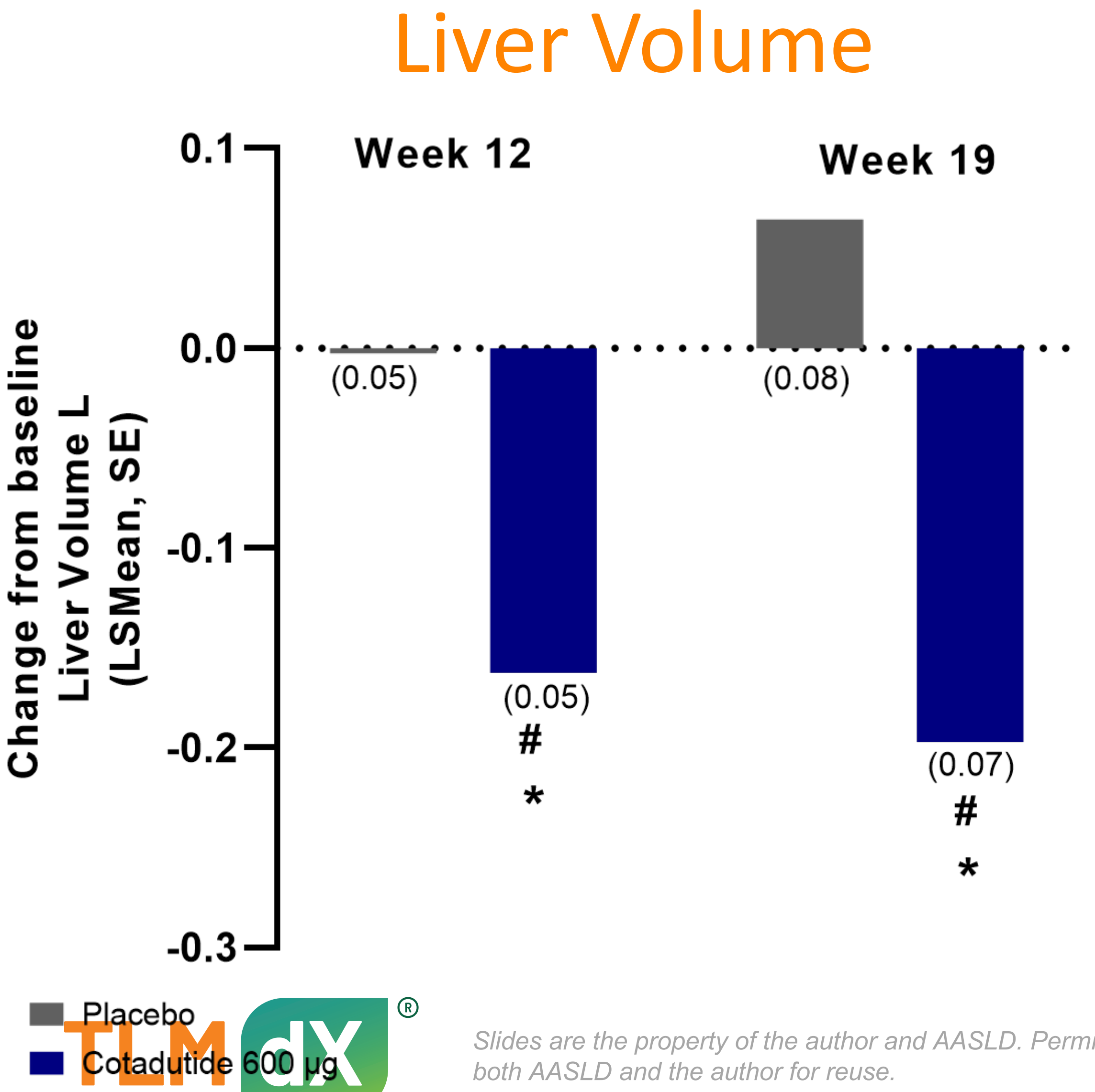


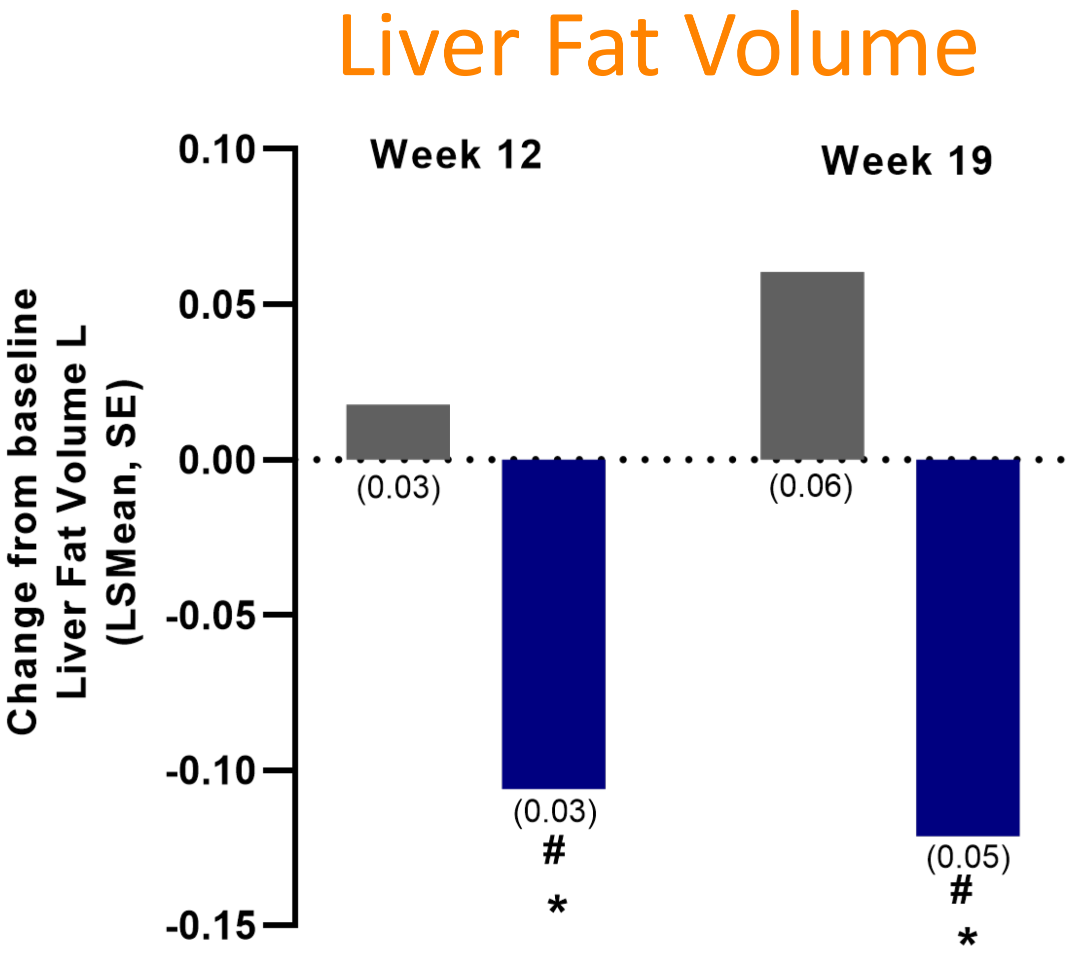
Cotadutide 300 µg
Cotadutide 600 µg

*p<0.05 vs placebo

Sanyal et al LB#6

Effect of Cotadutide on Liver Volume and Liver Fat Volume



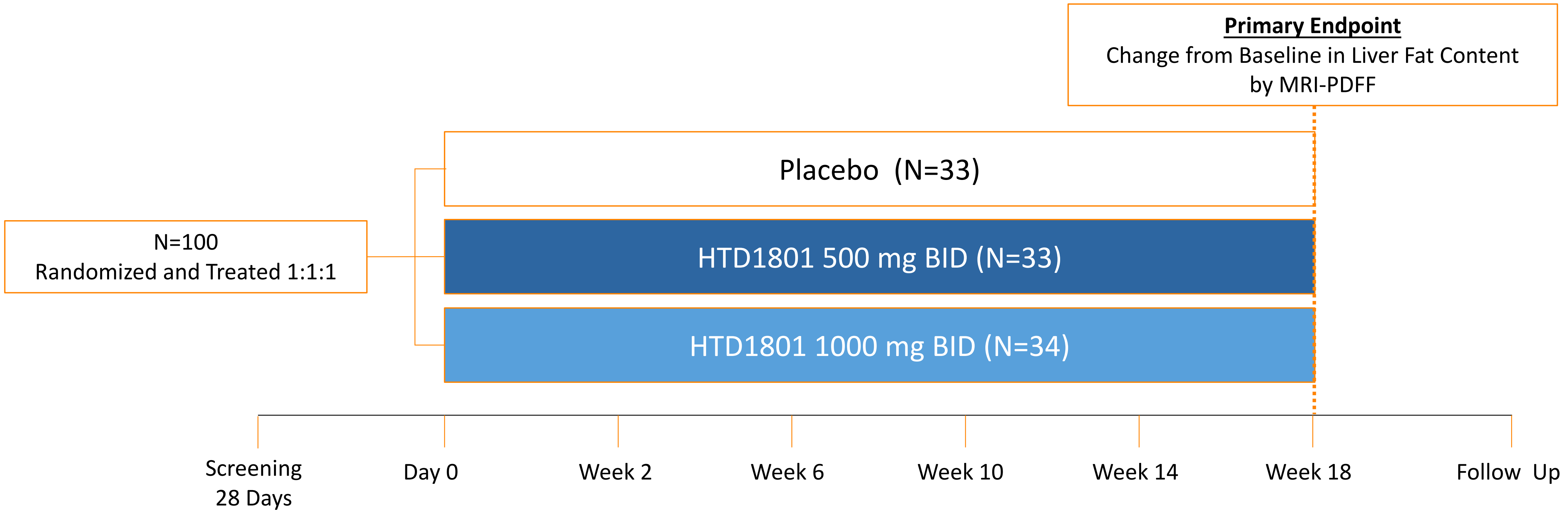


*p<0.05 vs placebo

#p<0.05 vs baseline

Sanyal et al LB#6

HTD1801-Study Design: Phase 2 Double-Blind, Placebo Controlled Study

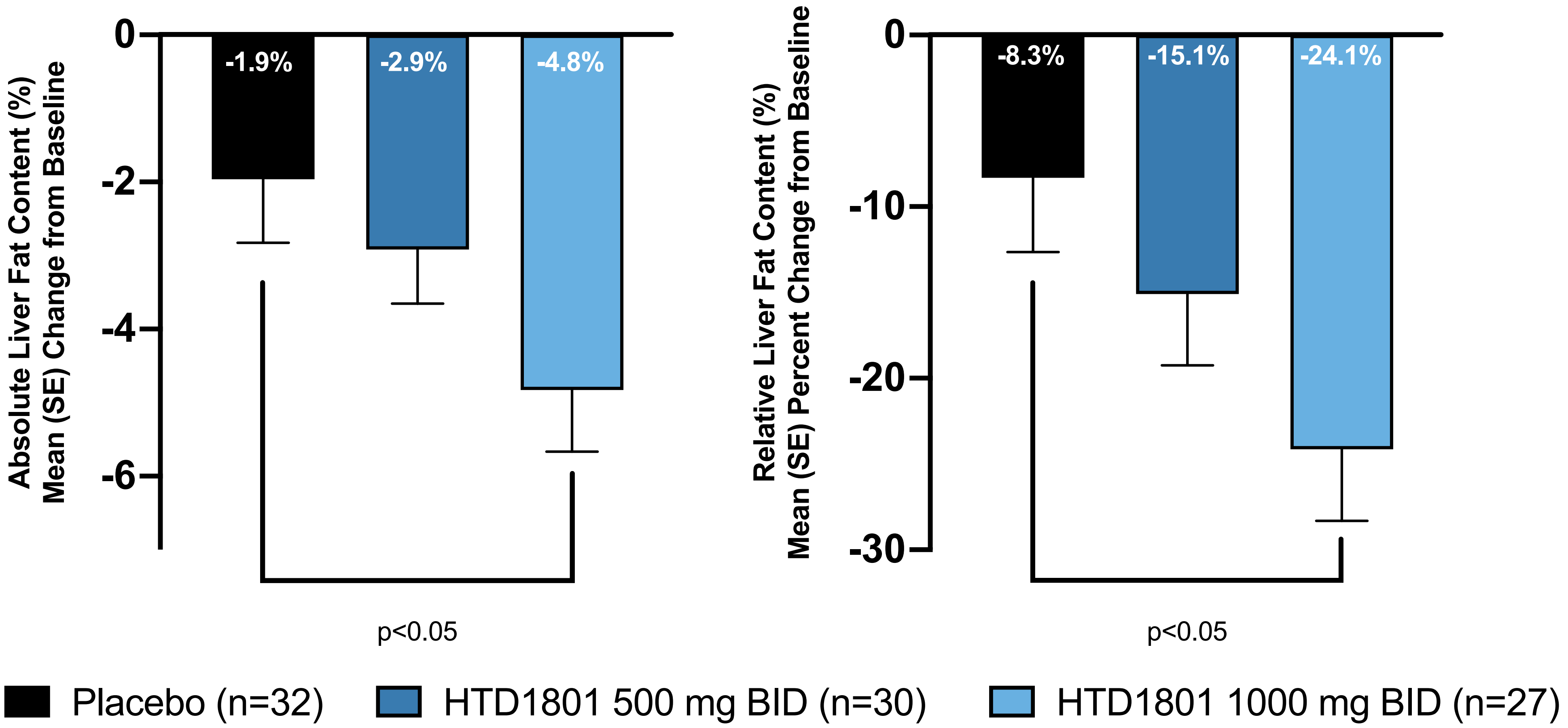


- Secondary endpoints included assessment of liver biochemistry, body weight, LDL-c, triglycerides, and HbA1c

[1]*Harrison et al. Nature Communications 2021 (https://doi.org/10.1038/s41467-021-25701-5)*

Harrison et al Abstract #140

Significant Reduction in LFC with HTD1801 After 18 Weeks of Treatment

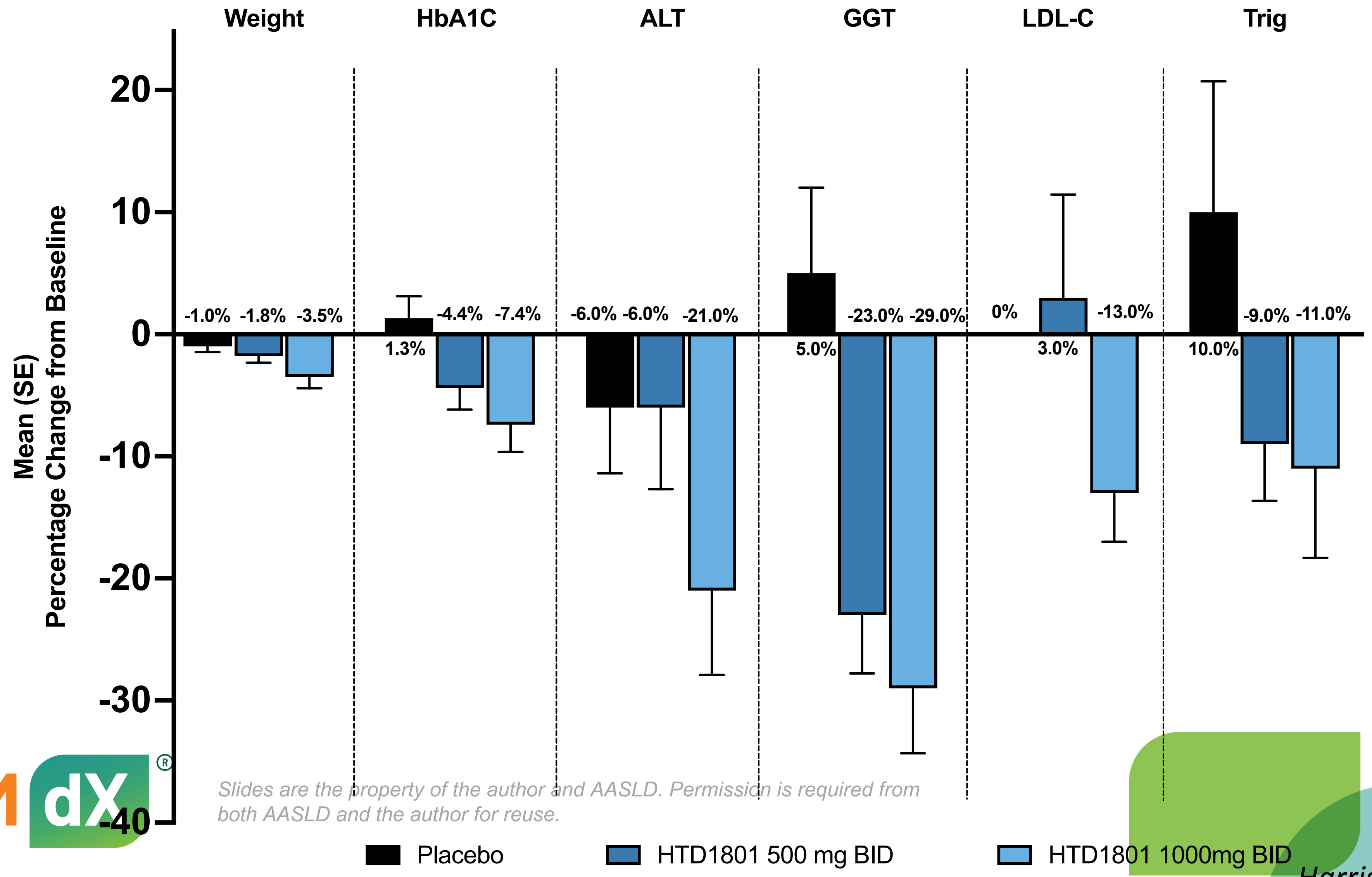


[1]*Harrison et al. Nature Communications 2021 (https://doi.org/10.1038/s41467-021-25701-5)*

LS Means and associated differences, standard errors, confidence intervals and p-values are obtained from an ANCOVA model with treatment group as a fixed effect, and Baseline LFC and Baseline ALT as covariates.

Harrison et al Abstract #140

Percentage Change from Baseline to Week 18 in Parameters Evaluated by Univariate Analysis



Harrison et al Abstract #140

"There is no elevator to success,
you have to take the stairs"

Thank you