AASLD Nov. 12-15, 2021

The Liver Meeting®

DIGITAL **EXPERIENCE**

# The Best of The Liver Meeting®

## NAFLD/NASH

## About the program:

Best of The Liver Meeting 2021 was created by the Scientific Program Committee for the benefit of AASLD members, attendees of the annual conference, and other clinicians involved in the treatment of liver diseases. The program is intended to highlight some of the key oral and poster presentations from the meeting and to provide insights from the authors themselves regarding implications for patient care and ongoing research.

## Use of these slides:



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# Transient VEGFA expression using VEGFA mRNA-LNPs induces cholangiocyte-driven liver regeneration and reversion of steatosis and fibrosis in a NASH mouse model

## Aim

To harness the regenerative potential of cholangiocytes by promoting their conversion to hepatocytes to treat liver diseases

## Methods

*Krt*19-Cre-ERT2; *R26*-STOP$^{Fl/Fl}$-tdTomato mice were used to fate trace cholangiocytes.

AAV8-*Tbg*-p21 was administered to mimic impaired hepatocyte proliferation observed in many human liver diseases.

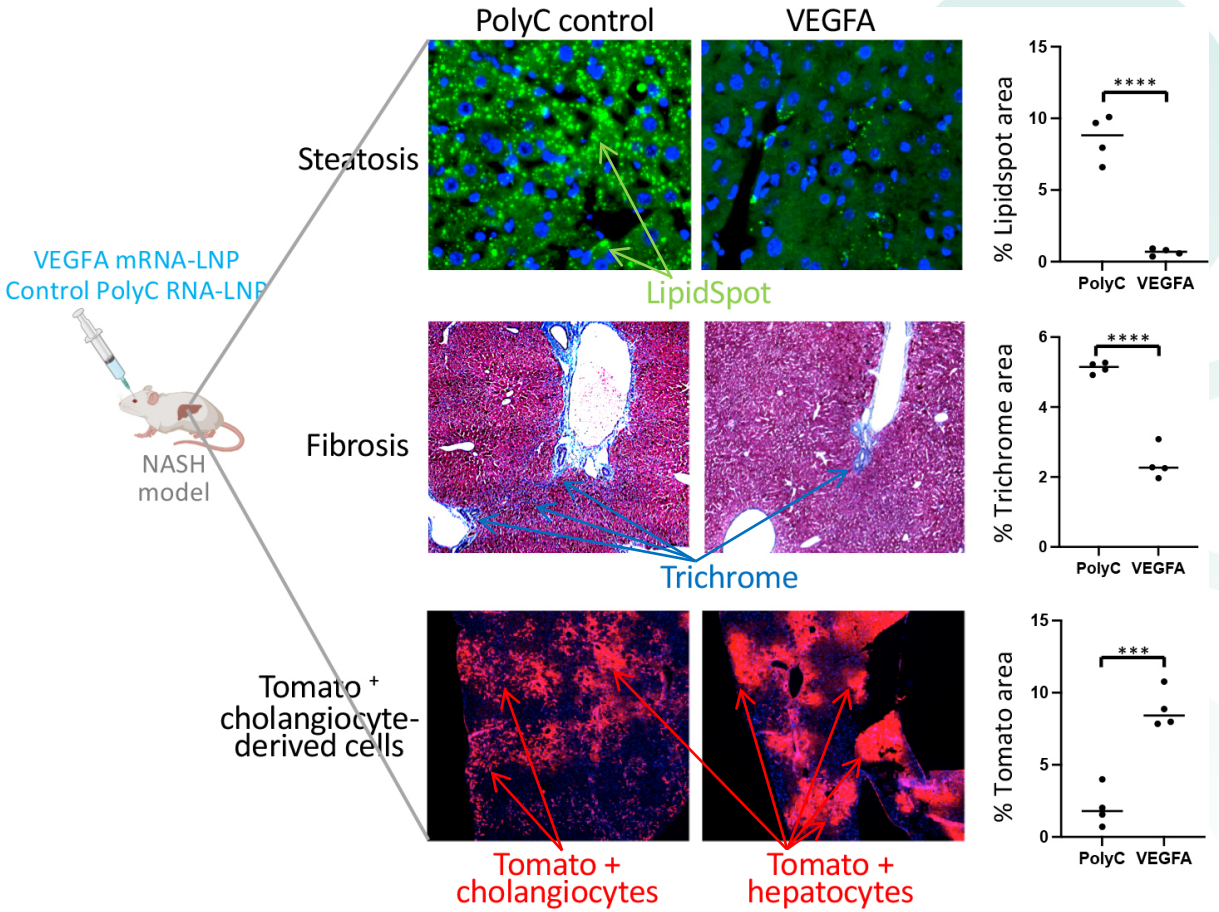
Following CDE (0.1% ethionine) induced injury (2 weeks), injections of nucleoside modified mRNA encoding VEGFA complexed to lipid nanoparticles (mRNA-LNP) or control Poly(C) RNA-LNP were administered through intra-orbital sinus to efficiently transfect hepatocytes.

## Main Findings

Transient VEGFA expression and secretion by hepatocytes via liver-targeted mRNA-LNP delivery robustly and significantly increases the numbers of cholangiocyte-derived tdTomato-positive hepatocytes, as well as significantly reverts steatosis and fibrosis in chronically injured livers.

## Conclusions

The study reveals a novel therapeutic benefit of VEGFA mRNA-LNP to harness cholangiocyte-driven liver regeneration to treat chronic and acute liver diseases in which hepatocyte-driven liver regeneration is compromised.

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Rizvi F, et al., Abstract 2.

# Topline results from the ALPINE 2/3 study: A randomized, double-blind, placebo-controlled, multicenter, phase 2b trial evaluating 3 doses of the FGF19 analogue aldafermin on liver histology in patients with nonalcoholic steatohepatitis and stage 2 or 3 fibrosis

## Objective

- To evaluate the effect of 3 doses of aldafermin, an FGF19 analog, on liver histology in a randomized, double-blind, placebo-controlled 24-week study

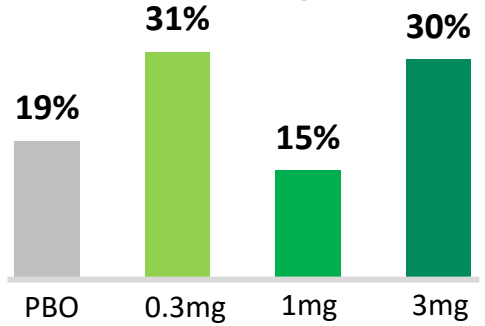
## Methods

- 171 patients were randomized 1:1:1:1 to receive placebo (n=43), aldafermin 0.3mg (n=43), 1mg (n=42), or 3 mg (n=43).
- Key inclusion criteria included biopsy-proven NASH with NAS≥4, stage 2 or 3 fibrosis and absolute liver fat content ≥8%. The primary endpoint was the dose response in fibrosis improvement of ≥1-stage by NASH CRN criteria with no worsening of NASH.

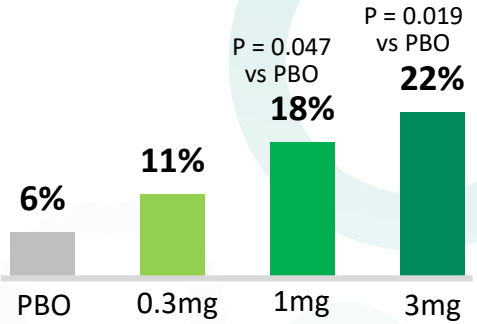
## Conclusions

- Although not reaching a statistical significance on the dose-dependent improvement in fibrosis stage on liver biopsy, aldafermin achieved NASH resolution and robust, dose-dependent reductions in liver fat content and non-invasive markers of liver injury (ALT, AST) and fibrosis (Pro-C3, ELF).

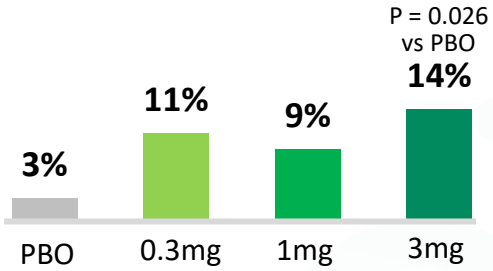
### Fibrosis Improvement ≥ 1 Stage with No Worsening of NASH



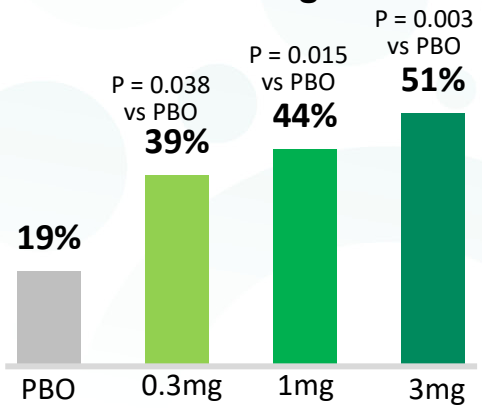

### Resolution of NASH with No Worsening of Fibrosis




### Fibrosis Improvement ≥ 1 stage and Resolution of NASH




### Improvement of NAS by ≥ 2 Points with No Worsening of Fibrosis




ITT population with multiple imputation
(not powered for pairwise comparison between groups)

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Harrison S, et al., Abstract 8.

# 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 genetics by applying a non-invasive phenotype based on chronic ALT elevation in a large, diverse population in the VA's Million Veteran Program (MVP)

## Methods

- Trans-ancestry and ancestry-specific genome-wide association studies (GWAS) of **90,408 cases** with chronic ALT elevation without other known causes of liver disease and **128,187 controls** with normal ALT in MVP
- External replication cohorts: biopsy-proven NAFLD (**7,379 cases**, 56,785 controls); radiological hepatic fat (**n=44,289**)
- 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.

## Main Findings

1. 77 trans-ancestry SNPs were associated with cALT with genome-wide significance, including 10 known GWS NAFLD SNPs, plus additional 3 new ancestry-specific SNPs.

2. 17/77 SNPs were validated in external replication cohorts with histological or radiological NAFLD—including 8 novel SNPs (*FTO, SERPINA1, IL1RN, MTTP, COBLL1, IFI30, APOH, PPARG)*.

3. Most (60/77) cALT SNPs were pleiotropic with metabolic and/or inflammatory trait associations.

4. GRS derived from cALT SNPs were predictive of histological NAFLD—especially those with greater pleiotropy.

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

## Aim

- The association between magnetic resonance elastography (MRE) and complications development (hepatocellular carcinoma [HCC], decompensation, and cardiovascular disease [CVD]) was investigated in nonalcoholic fatty liver disease (NAFLD)

## Methods

- A retrospective cohort study included 428 NAFLD patients who received MRE assessment.
- All patients received standard of care and were assessed complications development every 6 months.

## Main Findings

- 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.

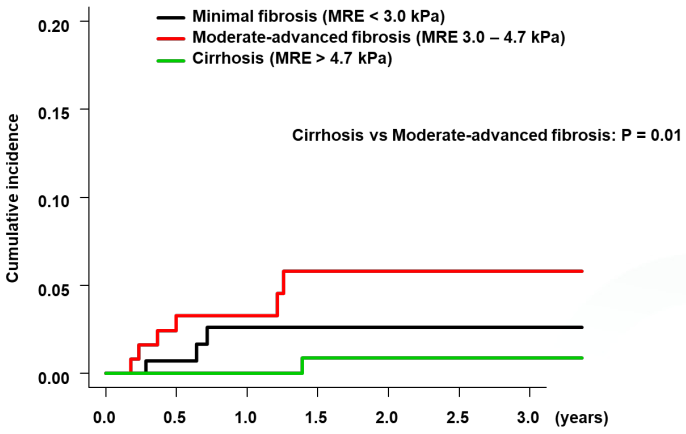
## Conclusions

- The risk of HCC, decompensation, and CVD development differs by fibrosis status in NAFLD.

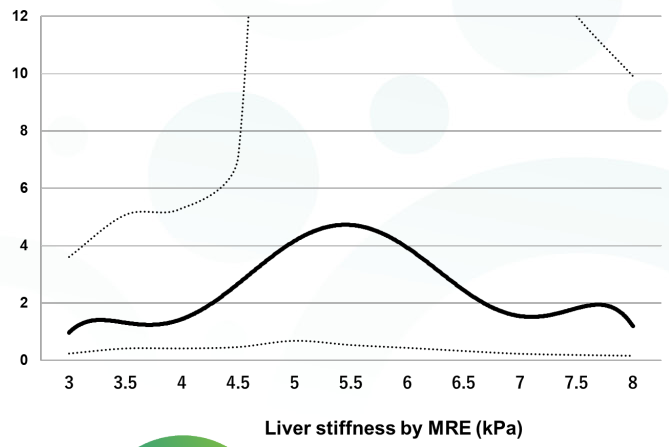
**Multivariable analysis**

| | HCC development | | Decompensation | | CVD | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | p value | HR (95% CI) | p value | HR (95% CI) | p value |
| Liver stiffness by MRE (per 1 kPa) | **1.37 (1.1-1.7)** | **0.01** | **1.34 (1.1-1.6)** | **0.001** | 0.71 (0.5-1.1) | 0.06 |
| Age (per 10 years) | **3.75 (1.7-8.4)** | **0.001** | 1.10 (0.7-1.8) | 0.7 | 1.03 (0.6-1.8) | 0.9 |
| Male | 3.11 (0.8-12) | 0.1 | 0.78 (0.3-2.3) | 0.7 | 2.02 (0.6-7.3) | 0.3 |
| DM | 1.05 (0.3-3.9) | 0.9 | 1.38 (0.4-4.3) | 0.6 | **6.83 (1.2-37)** | **0.02** |
| Dyslipidemia | 1.84 (0.5-7.3) | 0.4 | 0.83 (0.3-2.3) | 0.7 | 3.54 (0.7-17) | 0.1 |
| Hypertension | 1.54 (0.4-5.6) | 0.5 | 1.11 (0.4-3.3) | 0.8 | 1.18 (0.3-4.5) | 0.8 |

**CVD incidence by MRE**




**Hazard ratio for CVD by MRE**




Tamaki N, et al., Abstract 10.

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# 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

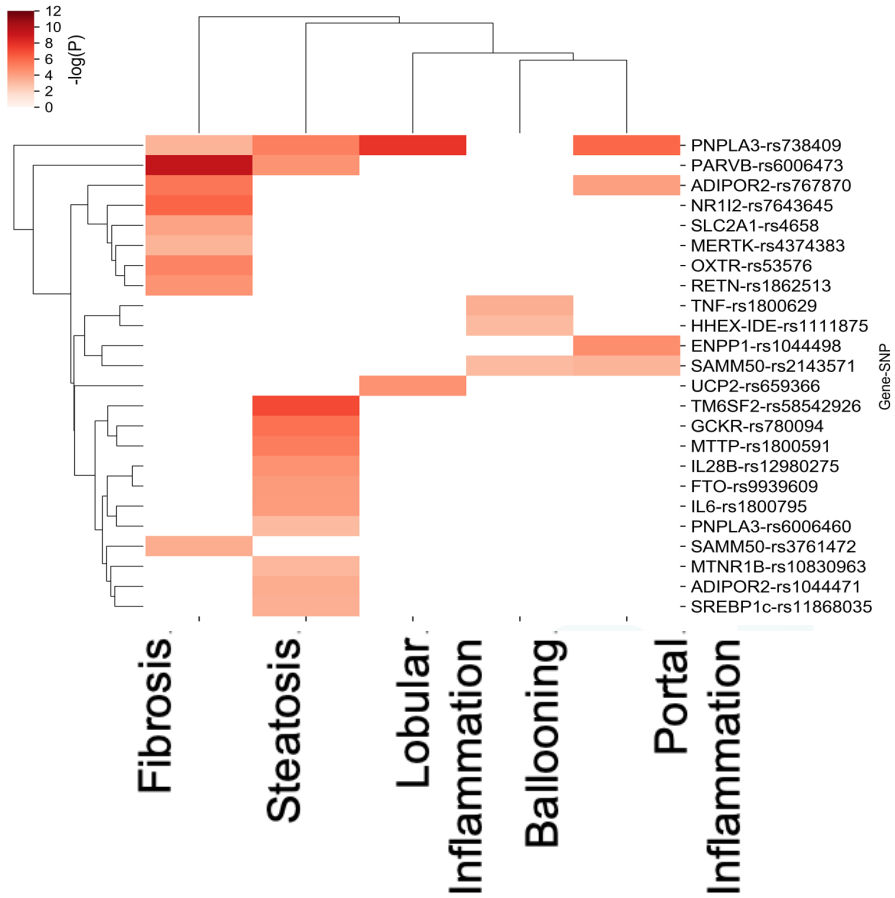
- Multicenter study of 822 children with biopsy-confirmed NAFLD including 252 complete trios
- 60 candidate SNPs tested via FDR corrected TDT analysis (Aim 1) and FDR corrected regression analysis (Aim 2)

## 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.

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

## Aim

- Develop and compare machine learning (ML) models for diagnosis of fibrotic NASH in histologically-diagnosed NAFLD

**Methods** Single-center cross-sectional study

- Developed and compared three different ML models
- Random forest (RF), XGBoost and logistic regression
- Patient population: histologically assessed NAFLD

## Main Findings

- Seven parameters were included after feature selection for model building.
- Random forest (RF) was the best performing model with AUROC =0.95 with accuracy of 89.2%

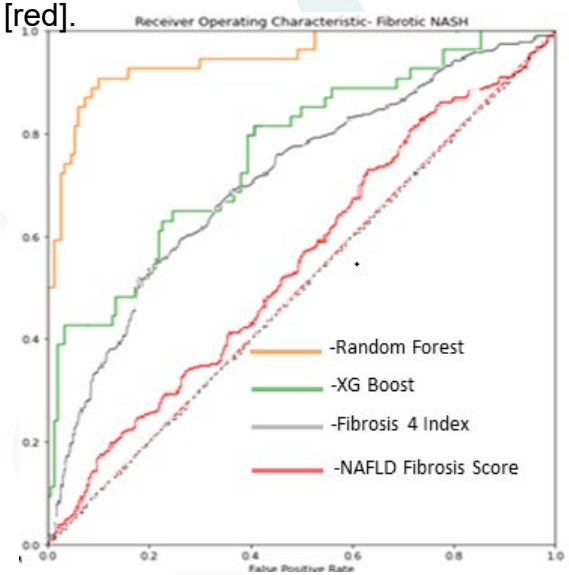
## Conclusions

- ML model outperformed traditional NITs (FIB-4 and NFS) for diagnosis of Fibrotic NASH.

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.

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# The metabolic vulnerability index (MVX) predicts the risk of mortality and liver outcomes in nonalcoholic fatty liver disease

## Hypothesis/Aim/Objective

- The MVX was originally developed as a prognostic biomarker panel (score 0-100) to predict future death and cardiac outcomes in individuals with high cardiovascular (CVS) risk
- The aim of this study was to evaluate its prognostic performance in those with histologically characterized nonalcoholic fatty liver disease a condition with high CVS risk

## Methods

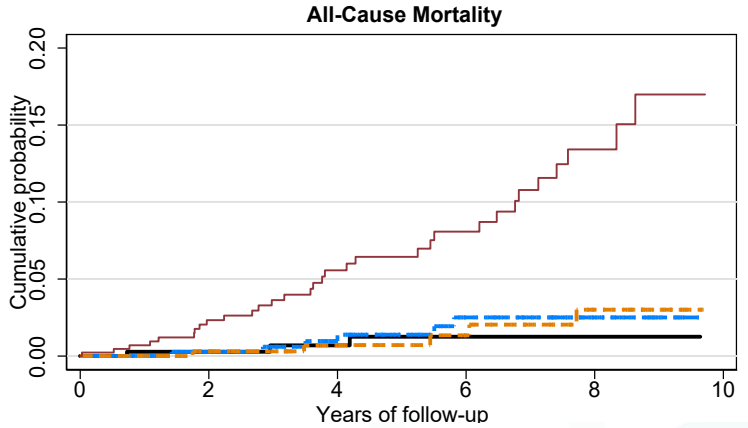
The utility of the MVX was tested for the following context of use:

- Intended use population: Biopsy-proven NAFLD covering full spectrum of disease
- To predict prognosis with respect to death, MACE, liver events, and other NASH related endpoints to inform risk-based future management approaches
- Study Population: NIDDK NASH CRN DB2 cohort study where a liver biopsy was performed within 90 days of entry (n=1663, 75% with NASH, mean fibrosis stage 1.6). Serum samples obtained at entry, i.e. within 90 days of a liver biopsy was used for analysis to compute the MVX.
- Outcomes data captured prospectively over median duration of 4.8 years.
- MVX related to outcome probability using Cox regression.

**Main Findings** MVX was related exponentially (mainly in 4$^{th}$ quartile) to future death and liver events but not MACE, T2DM, cancers (hepatic and non-hepatic)

## Conclusions

The MVX predicts all-cause mortality, liver-related outcomes, and death in those with NAFLD. Those with the highest quartile are particularly at risk.




| Outcome | HR/10 pt increase | P value |
|---|---|---|
| Mortality | 2.59 | <0.0001 |
| Liver event* | 1.64 | 0.003 |
| Liver-related death | 5.1 | <0.0001 |
| Cardiac event | 1.04 | 0.78 |
| Cancers | 1 | 0.9 |

* ascites, encephalopathy, variceal bleed

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Sanyal A, et al., Abstract 115.

# 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

## Hypothesis

- MAST score can distinguish patients with NASH with significant fibrosis and assess response to Resmetirom

## Methods

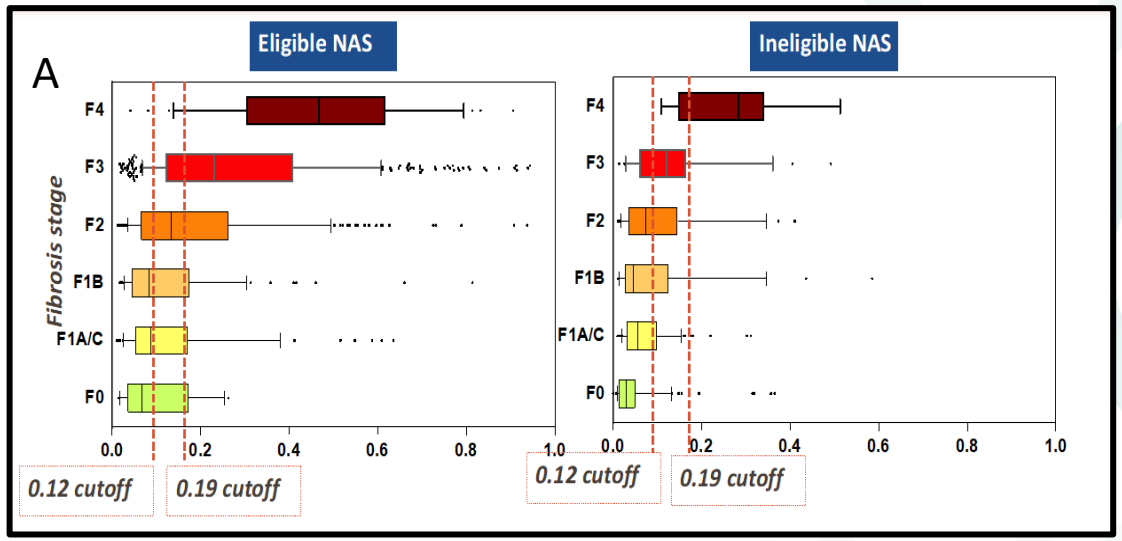
- In the MAESTRO-NASH study, baseline MAST (MRI-PDFF-MRE-AST) score was assessed in >1000 patients with liver biopsy.
- In the MASTERO NAFLD-1study, MAST score assessed the response to Resmetirom in >100 patients.

## Main Findings

- MAST score using either the rule-in or rule-out cutoffs performed well in identifying patients with NASH and significant fibrosis (Fig A).
- In open-label non-cirrhotic NASH patients (MAESTRO-NAFLD-1) 100 mg Resmetirom per day lowered MAST significantly (by 50% and 63%, respectively, in those with baseline MAST of >0.12) at week 16 and 52 of treatment (Fig B).

## Conclusions

- MAST score offers a robust non-invasive tool to identify NASH patients with significant fibrosis and monitor response to Resmetirom and other effective therapies in NASH trials.




Noureddin M, et al., Abstract 118.

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# Environmental pollutant exposures are associated with nonalcoholic fatty liver disease severity and enrichment in the metabolic pathways associated with liver fibrosis (#120)

## Objective

- To determine the metabolic pathways and environmental exposures associated with liver disease severity in adult NAFLD subjects

## Methods

- Cross-sectional analysis of subjects with NAFLD (n=140). Disease severity was assessed by the VCTE biomarkers, LSM (fibrosis), and CAP (steatosis).
- Untargeted plasma metabolomics ($LC/MS^2$) and exposomics ($GC/MS^2$) were performed. Associations were determined between VTCE biomarkers and the metabolome/exposome. Pathway enrichment analyses were performed. Statistical significance was set at $p<0.05$.

## Main Findings

- The linoleate metabolic pathway was highly enriched with LSM and CAP.
- Over twenty environmental chemical exposures were significantly associated with at least one VCTE biomarker of NAFLD severity.
- Fluorene, PCB-132, and diphenyl-nitrosamine (**Figure 1**) were positively associated with both LSM and CAP ($p<0.05$).
- Some of the same metabolic pathways enriched with LSM and/or CAP (e.g., linoleate/fatty acids, hexose, amino acids) were also enriched with the identified pollutants. This suggests potential modes of action.

## Conclusions

- Environmental pollution exposures may disrupt specific metabolic pathways to worsen fibrosis and/or steatosis in NAFLD.

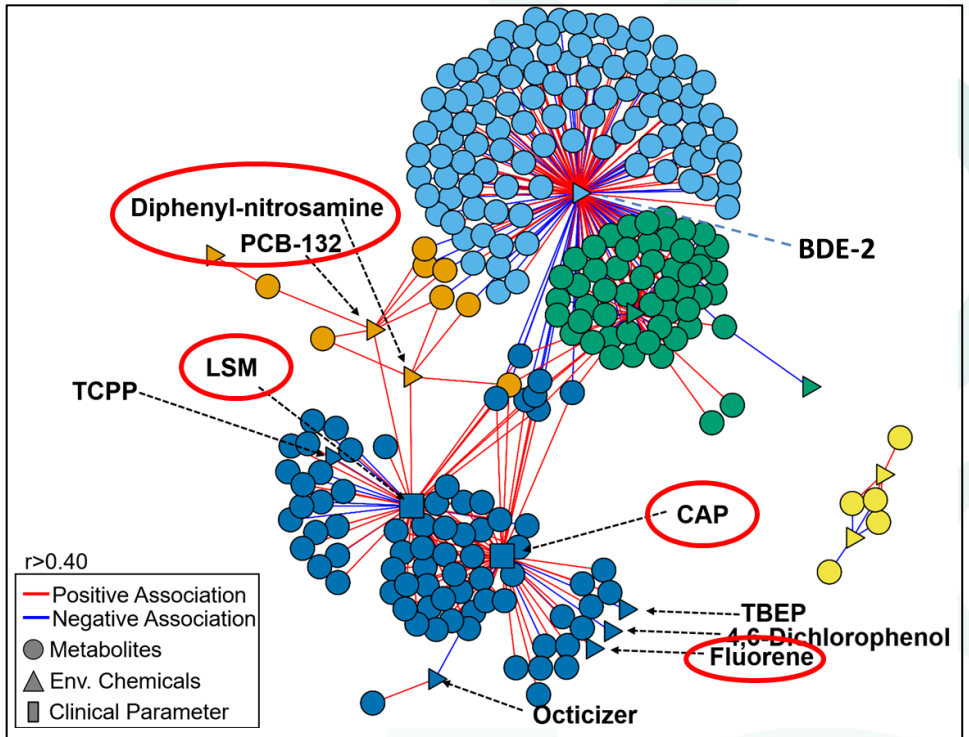



**Figure 1**. Integrated multi-'omics analysis depicting the significant interactions of LSM and CAP (boxes) with environmental chemicals (triangles), and metabolites (circles) in NAFLD subjects (r>0.40) . Communities of interacting molecules are given by color.

Cave M, et al., Abstract 120.

# Treatment with BIO89-100 led to decreased spleen volume in a proof-of-concept study in non-cirrhotic NASH

## Objective

- To assess the effect of 12 weeks of treatment with BIO89-100 vs. placebo on spleen volume

## Methods

- A post-hoc analysis of Study BIO89-100-002 (NCT4048135), a Phase 1b/2a placebo-controlled, double-blind POC study in NASH
- MRI spleen volume data was collected at baseline, Day 50 and Day 92, and compared between subjects treated with BIO89-100 [N=16: 27 mg QW (N=8) or 36 mg Q2W (N=8), pooled] vs. placebo (N=18).

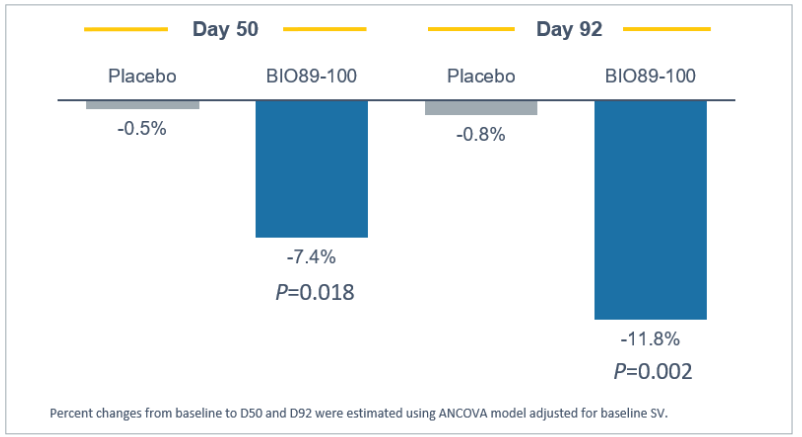
## Conclusions

- SV at baseline was correlated with liver volume.
- Treatment with BIO89-100 led to a progressive, statistically significant decrease in SV compared to placebo.
- SV reduction correlated with reductions in liver fat by MRI-PDFF, liver fat volume, CK-18, and ALT.
- SV reduction was negatively correlated with platelet count.

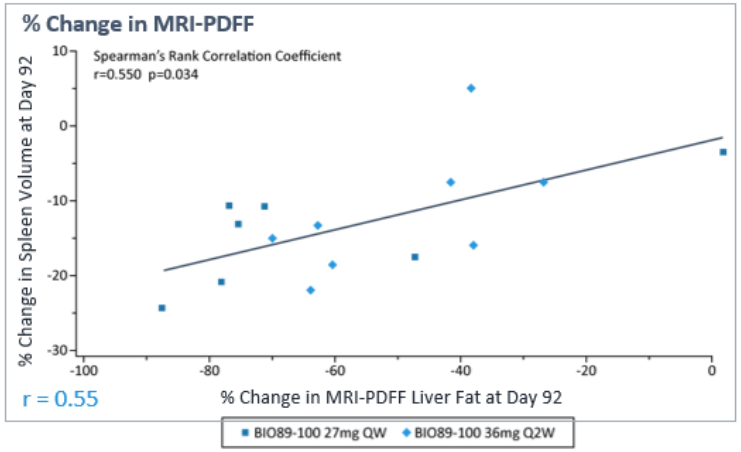
Loomba R, et al., Abstract 139.

## Main Findings

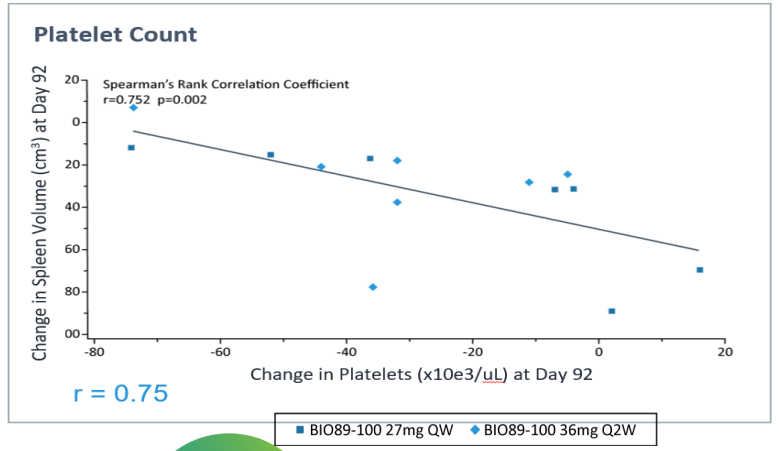
### Significant Reduction in Spleen Volume With BIO89-100




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




### Spleen Volume Change Negatively Correlated with Platelet Count at Day 92

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# Reduction in liver fat content with HTD1801 (berberine ursodeoxycholate) is closely associated with improved glycemic control, weight loss, and reduced ALT

## Objective

- To assess relationship between other study endpoints and change in liver fat content in a retrospective analysis of data from RCT[1] in NASH and type 2 diabetes

## Methods

- 18-week placebo-controlled study assessing effects of HTD1801 on liver fat content (100 subjects)
- Univariate and multivariate analyses were conducted on a pooled patient population across all treatment groups to identify parameters associated with reduction in liver fat content.

## Main Findings

- Change in HbA1C, weight, and ALT were significantly and independently associated with change in LFC in multivariate analysis.

## Conclusions

- Significant reductions in LFC are closely and independently associated with weight loss, improved glycemic control, and reduction in liver injury.

Harrison S, et al., Abstract 140.

## Multivariate Analysis

| Predictor | Slope | p-value | $R^2$ |
|---|---|---|---|
| **Weight** | 0.317 | 0.0111 | |
| **HbA1c** | 1.461 | 0.0049 | 33.3% |
| **ALT** | 0.055 | 0.0081 | |

$R^2$ represents the percentage of LFC variation explained by the model. Thus, only 33% of the LFC effect is accounted for by these factors.

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

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# 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.

Price J, et al., Abstract 191.

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)<br>Black<br>Other | <br>0.44 (0.22, 0.88)<br>1.09 (0.42, 2.79) | <br>0.02<br>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)<br>Black<br>Other | <br>0.43 (0.20, 0.93)<br>1.29 (0.46, 3.65) | <br>0.03<br>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

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# Primary results of the FNIH NIMBLE Stage 1-NASH CRN study of circulating biomarkers for non-alcoholic steatohepatitis (NASH) and its activity and fibrosis stages

**Aim** Comparative assessment of the performance of 5 blood-based biomarker panels selected by the NIMBLE team for their respective intended use to rigorously establish the sensitivity/specificity at Youden's cutoff in a large, cross-sectional, multi-center US cohort of patients with NAFLD/NASH from the NIDDK NASH CRN.

**Hypotheses** (1) Biomarker AUROC at least 0.7 and superior to unit line, and (2) superior to ALT for diagnosis of NASH or disease activity, and FIB4 for fibrosis

## Methods

- Tests were run on **different aliquots of the same blood sample** obtained within 90 days of a liver biopsy in a NAFLD population selected to avoid fibrosis stage spectrum bias.
- Rigorous chain-of-custody of samples and data for data-integrity

**Main Findings** Multiple biomarkers met criteria for success in diagnosis of NASH, high NAS, fibrosis stages ≥ 2, ≥ 3, 4, and diagnosis of "at risk" NASH (NASH + NAS ≥4 + fibrosis stage ≥ 2.

## Conclusions

- Data from Stage 1 of NIMBLE provide robust sensitivity and specificity metrics for various intended use for selected biomarkers.
- The sensitivity and specificity data provide a basis for the design of Stage 2 of NIMBLE where the performance of selected biomarkers will be assessed in a prospective longitudinal study.

| 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*

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Sanyal A, et al., Abstract L01.

# Vonafexor induces hepatic and renal improvements in NASH: LIVIFY trial results

## Objective

- To evaluate the effect of vonafexor, a synthetic, oral, nonbile salt, nonsteroidal, carboxylic acid FXR agonist

## Methods

- Phase 2a, multicenter, randomized placebo-controlled trial
- 96 patients were randomized to 12 weeks of daily placebo (n=32), or vonafexor 100 mg (n=31) or 200 mg (n=33).
- Inclusion criteria were phenotypic F2 or F3 NASH with an absolute liver fat content (LFC by MRI-PDFF) ≥10%, a liver stiffness by transient elastography ≥8.5 kPa, and a Modification of Diet in Renal Disease formula estimated glomerular filtration rate (eGFR) ≥50mL/min/1.73m2.
- LFC was assessed at end of treatment, safety every 2 weeks.

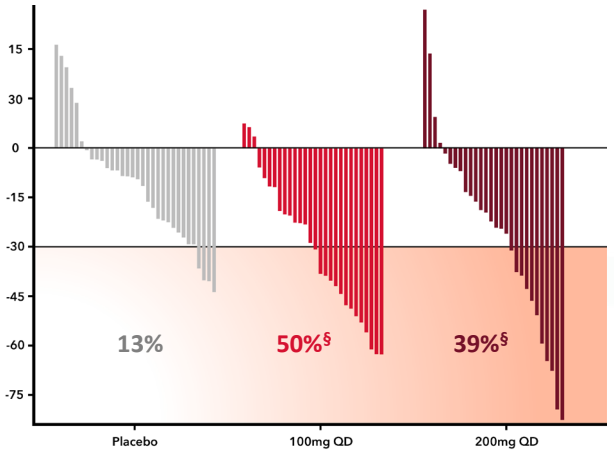
## Conclusions

- Vonafexor induced a consistent LFC reduction, and improvement in biochemical and imaging liver markers.
- An added benefit was obtained on eGFR with a safe and good tolerability-efficacy profile for the 100 mg dose.

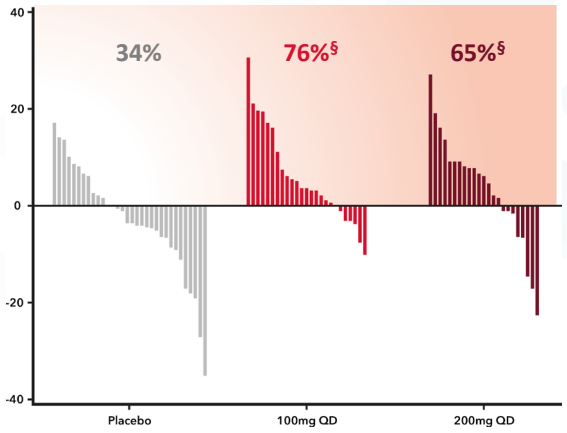
| Week 12 Change | Placebo | Vona 100mg | Vona 200mg |
|---|---|---|---|
| LFC absolute (%) | -2.3 (0.9)#  | -6.3 (0.9)#,§ | -5.5 (0.9)#,§ |
| ALT (IU/L) | -11.5 (3.2)# | -19.3 (3.2)#,§ | -10.8 (3.3)# |
| Alpha-2-Macroglobuline (mg/dL) | 4.3 (3.8)# | -25.9 (4.3)#,§ | -18.4 (4.5)#,§ |
| cT1 (msec) | -10.2 (14.5) | -80.6 (15.4)#,§ | -71.9 (14.2)#,§ |
| eGFR (mL/min/1.73m2) | -2.9 (1.9) | 6.0 (2.2)#,§ | 2.5 (2.2)§ |

*Mean (SE). # p<0.05 vs baseline, § p<0.05 vs placebo.*

**Individual relative LFC changes (%) and rates of ≥30% LFC reduction per study arm**




**Individual eGFR changes (mL/min/1.73m2) and rates of improvement per study arm**




Harrison SA, et al., Abstract LO2.

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

## Aim

- To model clinical and economic burden of NASH in the US, stratified by presence or absence of obesity

## Methods

- The discrete-time Markov model with 1-year cycles and 20-year horizon was created to estimate the economic and clinical burden of NASH, stratified by presence or absence of obesity in the U.S. for adults aged 18 years or older.
- Given that reliable, prospective natural history data for NASH is not available, it is obvious that the observations are internally inconsistent. Thus, we applied the estimated age-obesity pattern from population-based data to determine transition probabilities for age-obesity groups.

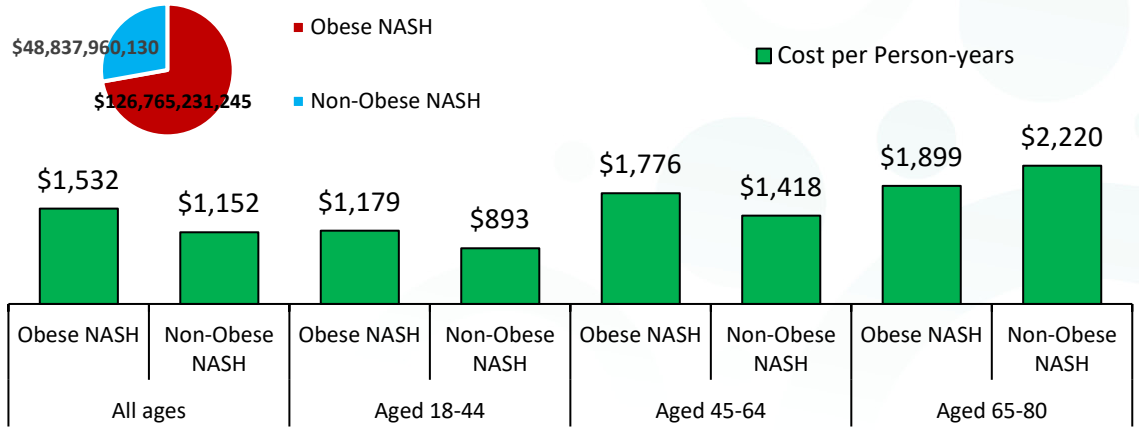
## Conclusions

- The growing prevalence of obesity and related NASH will have a major clinical and economic impact in the US.

### 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.

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

## Objective

- Evaluate the efficacy and safety of PGBF, a PEGylated FGF21 analog, in patients with NASH and bridging fibrosis

## Methods

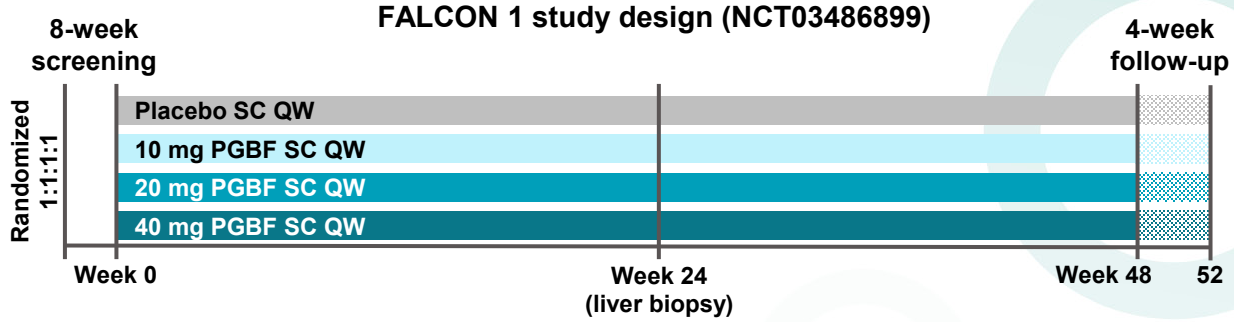
- Phase 2b, randomized, multicenter, placebo-controlled study conducted at sites in the United States and Japan; study patients (n=197) were adults with histologically-confirmed NASH and stage 3 fibrosis according to NASH CRN criteria.

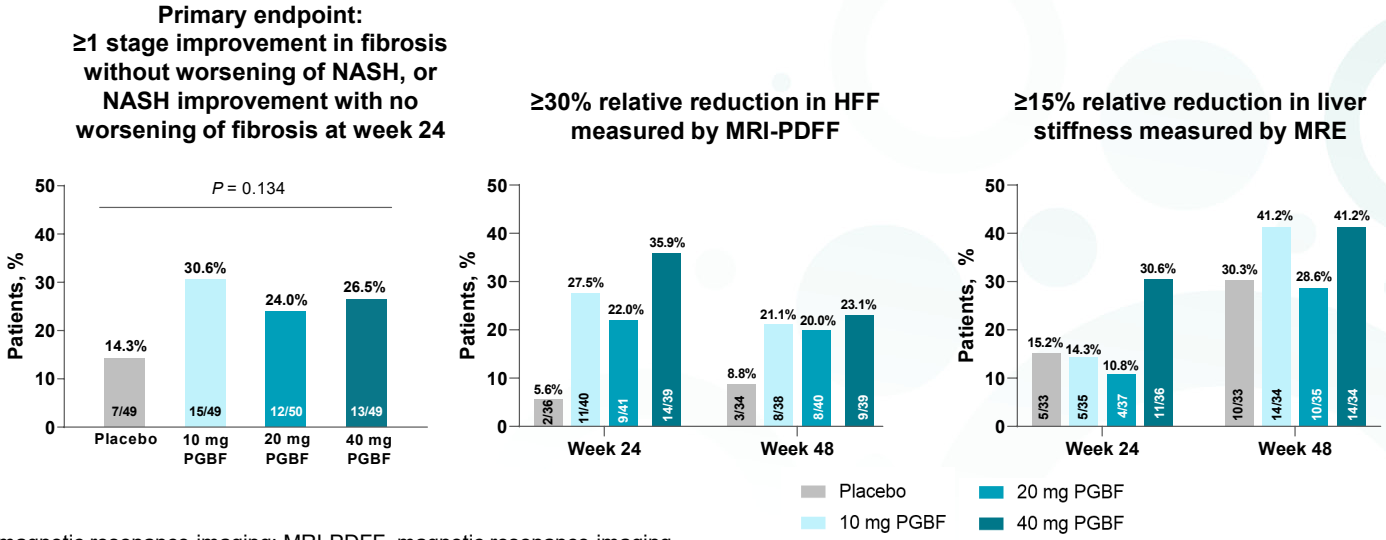
## Main Findings

- The primary efficacy endpoint was not met due to a lack of dose response across PGBF arms; however, improvements in several histological and noninvasive measures of steatosis, inflammation, and fibrosis demonstrated evidence of PGBF activity.

## Conclusions

- PGBF treatment was generally safe and well tolerated and led to numerically higher rates of fibrosis improvement without NASH worsening or NASH improvement without fibrosis worsening at week 24 compared with placebo.
- In addition, PGBF improved NASH disease activity and fibrosis, as measured histologically and by noninvasive assessments.




FGF21, fibroblast growth factor 21; HFF, hepatic fat fraction; MRE, magnetic resonance imaging; MRI-PDFF, magnetic resonance imaging – proton fat fraction; NASH, nonalcoholic steatohepatitis; PEG, polyethylene glycol; QW, once weekly; SC, subcutaneous.

Loomba R, et al., Abstract L05.

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# PROXYMO: Novel incretin co-agonist cotadutide demonstrates robust improvements in markers of disease in biopsy-proven non-cirrhotic NASH with fibrosis

## Objective

- To evaluate the safety and efficacy of cotadutide, a GLP-1 and glucagon receptor co-agonist peptide in biopsy-proven non-cirrhotic NASH with fibrosis

## Methods

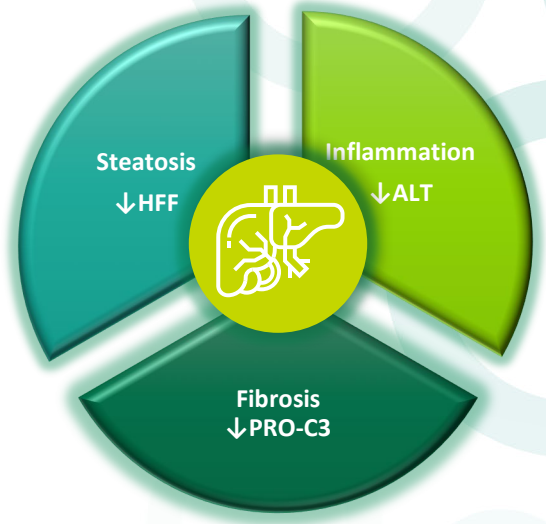
- Randomized double-blind placebo-controlled multicenter 19-week Phase 2 trial with cotadutide (2 active doses) in adult obese subjects (N=74) with biopsy-proven non-cirrhotic NASH with fibrosis

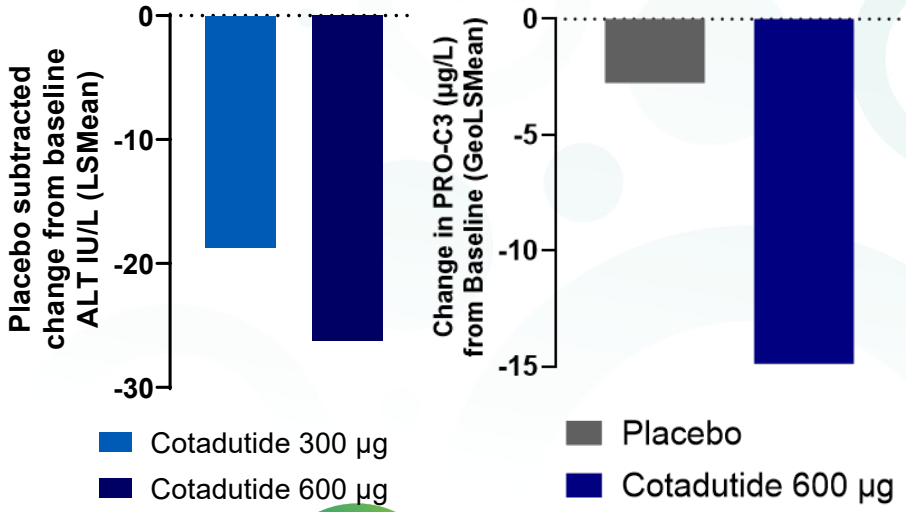
## Main Findings

- Cotadutide was generally safe and well-tolerated with an adverse event profile consistent with the incretin class.
- Cotadutide led to robust and significant dose- and time-dependent improvements in hepatic fat fraction, aminotransferases, Pro-C3, NIS-4, and adiponectin, accompanied by reductions in other markers of NASH disease activity and fibrosis as well as improvements in metabolic parameters consistent with prior reports.

## Conclusions

- In biopsy-proven non-cirrhotic NASH with fibrosis, cotadutide treatment demonstrates robust improvements across the disease components of liver steatosis, inflammation/injury, and fibrosis.

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Shankar S, et al., Abstract LO6.

# NAFLD/NASH

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