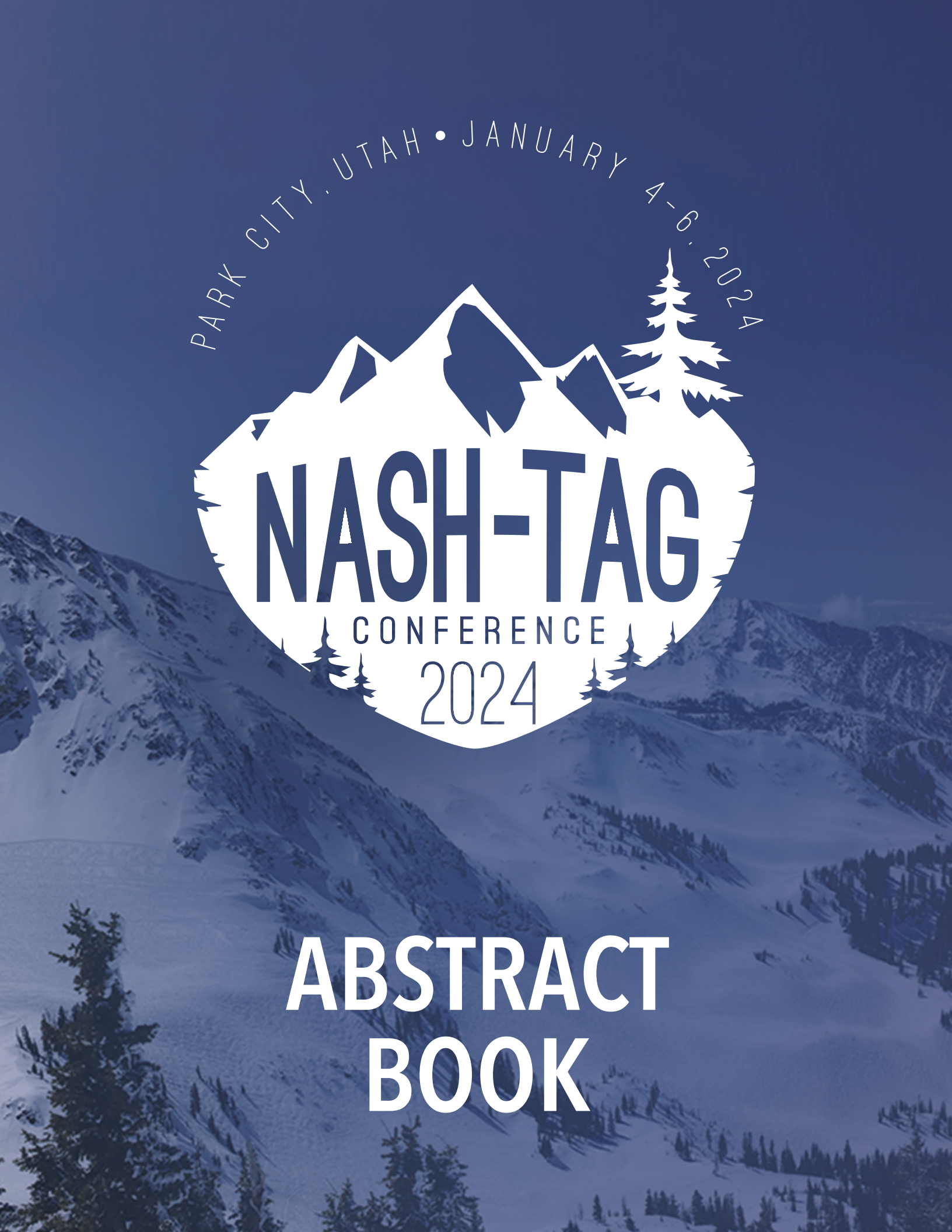


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## [4 – DISTINGUISHED ABSTRACT] GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND RISK OF MAJOR ADVERSE LIVER OUTCOMES IN PATIENTS WITH CHRONIC LIVER DISEASE AND TYPE 2 DIABETES

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**Abstract Category:** Clinical Epidemiology-NASH/Liver Fibrosis

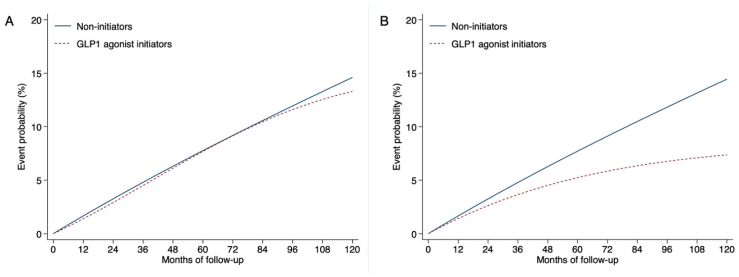
**Background and Aims:** Phase II trials suggest glucagon-like peptide-1 receptor (GLP1) agonists resolve non-alcoholic steatohepatitis, but do not affect regression of fibrosis. We aimed to determine the long-term causal effect of GLP1 agonists on the risk of major adverse liver outcomes (MALO) in patients with any chronic liver disease and type 2 diabetes.

**Methods:** We used observational data from Swedish healthcare registers between 2010 and 2020 to emulate a target trial of GLP1 agonists in eligible patients with chronic liver disease and type 2 diabetes. We used an inverse probability weighted marginal structural model to compare estimates of 10-year MALO risk (decompensated cirrhosis, hepatocellular carcinoma, liver transplantation, or MALO-related death) in initiators of GLP1 agonists with non-initiators.

**Results:** Initiators of GLP1 agonists (n=1,026) had a 10-year risk of MALO at 13.3% compared to 14.6% in non-initiators (n=15,633) in the intention-to-treat analysis (risk ratio [RR]=0.91, 95% confidence interval [CI]=0.50-1.32). Of note, 496 (48%) of initiators of GLP-1 agonists discontinued their treatment during the follow-up period. The corresponding risk estimates in the per-protocol analysis were 7.4% and 14.4%, respectively (RR=0.51, 95%CI=0.14-0.88). There was no clear effect of GLP1 agonists in patients with a diagnosis of non-alcoholic fatty liver disease (438 initiators; 4,618 non-initiators; intention-to-treat RR=1.41, 95%CI=0.53-2.30) or compensated cirrhosis (161 initiators; 1,869 non-initiators; intention-to-treat RR=1.05, 95%CI=0.20-1.91).

**Conclusion:** In patients with chronic liver disease and type 2 diabetes who adhered to therapy over time, treatment with GLP1 agonists resulted in a lower risk of MALO. This suggests that GLP1 agonists are promising agents to reduce risk of chronic liver disease progression in patients with concurrent type 2 diabetes, although this needs to be corroborated in randomized clinical trials.

**Figure:** Inverse probability weighted risk curves of major adverse liver outcomes comparing initiators of glucagon-like peptide-1 receptor (GLP1) agonists with non-initiators. A: intention-to-treat effect, B: per-protocol effect.




## [6 – DISTINGUISHED ABSTRACT] AASLD/AGA MASLD PRACTICE GUIDANCE FOR SCREENING DIABETICS: FACTORS ASSOCIATED WITH ADVANCED FIBROSIS, IMPLICATIONS FOR CARE DELIVERY, AND COST-REDUCTION USING AGE-ADJUSTED FIB-4 CUT-OFFS

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**Abstract Category:** Clinical Epidemiology-NASH/Liver Fibrosis
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**Background/Aim:** Patients with MASLD and advanced fibrosis have the highest risk of liver-related mortality. AASLD/AGA recommends a sequential algorithm of FIB-4 score followed by VCTE to identify diabetic patients with advanced fibrosis requiring hepatology evaluation. This study aimed to characterize a diverse urban DM population, calculate FIB-4 scores, identify factors associated with FIB-4>2.67, and determine cost implications of algorithm adherence.

**Methods:** Using the Mount Sinai Health System's DM registry, we identified patients aged 18+ who received primary care in 2022. Labs to calculate FIB-4 scores and baseline demographic and referral data were extracted from the EMR. FIB-4 scores were stratified as low (<1.30), indeterminate (1.3-2.66), high risk for advanced fibrosis (2.67-3.24), and cirrhosis (≥3.25). Chi square and Anova tests were used to compare demographics and BMI across FIB4 groups. Logistic regression was used to determine factors associated with FIB4≥2.67. Total referral costs for VCTE/hepatology were calculated using insurance-specific rates (cohort: 49% Medicare, 36% commercial, 15% Medicaid), and sub-analyses were conducted to evaluate different age-specific cut-offs.

**Results:** Among 57,151 adult diabetic patients, FIB-4 scores could be calculated for 91.6% (n=52,342). Age, BMI, sex, and racial/ethnic categories were examined across FIB-4 categories. Male (1.53, 95% CI: 1.43, 1.65), Hispanic (1.30; 95% CI: 1.19, 1.43), and non-Hispanic Black (1.29, 95% CI: 1.16, 1.42) patients had increased odds of FIB4≥2.67 compared to women and non-Hispanic white patients, respectively. BMI was inversely associated with FIB-4≥2.67 (0.95, 95% CI: 0.95, 0.96). Only a small percentage of patients with FIB-4 1.3-2.66 (4%) were referred to VCTE or hepatology, while 14% with FIB-4≥2.67 were referred to hepatology. The total cost associated with following the algorithm in our DM population was about $6.7 million. Adjusting the cut-off for patients over 65 to FIB-4≥2 reduced the number of patients in the indeterminate zone from 57% to 17%, leading to potential cost savings of approximately $2.3 million. For patients aged 18-35, using a lower cut-off of FIB-4≥1 increased potential costs by $24K as more patients would require further evaluation.

**Conclusion:** FIB-4 scores can be easily calculated for most diabetic patients based on routinely ordered labs, making it an ideal score to rule out advanced fibrosis in patients with "diabetic hepatopathy". Male sex, Hispanic and Black race/ethnicity were significantly associated with higher FIB-4 scores. The low referral rates to hepatology suggest a lack of awareness regarding FIB-4 for risk stratification and adherence to AASLD/AGA guidance. Age-adjusted cut-offs can help reduce costs and unnecessary referrals. Implementing an EMR-based FIB-4 calculator, provider usage and patient outcome reports, and robust educational programs may improve adherence to the AASLD/AGA guidance pathway. The efficacy of these interventions is currently under evaluation.

Abstract presented at The Liver Meeting, Boston, November 11, 2023.

## [7 – DISTINGUISHED ABSTRACT]
## CORE: A NEW RISK SCORE MEASURING GGT, AST, AND ALT OUTPERFORMS FIB-4 WHEN PREDICTING THE RISK OF CIRRHOSIS IN A PRIMARY CARE SETTING

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**Abstract Category:** Clinical Epidemiology-NASH/Liver Fibrosis

**Background and Aims:** Metabolic associated steatotic liver disease (MASLD) has a high prevalence in the general population, and the incidence of MASLD-associated cirrhosis is increasing. The Fibrosis-4 score (FIB-4) is a diagnostic model used in patients at risk for MASLD to estimate the present degree of fibrosis, but the FIB-4 score is inadequate for predicting the risk of progression to cirrhosis. The aim of this study is to develop a risk score—the Cirrhosis Outcome Risk Estimator (CORE)—allowing physicians to identify individuals at a high risk of developing cirrhosis. Correct identification would allow for early intervention and preventive measures.

**Method:** We used a large Swedish population-based cohort, free of known liver diseases other than possibly MASLD, with available laboratory data—including biomarkers associated with liver disease—and national registry data. Using flexible parametric survival models, a 10-year risk model of cirrhosis or associated complications was created, employing non-liver death as a competing event. The new comprehensive risk score includes age, sex, body mass index (BMI), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), cholesterol, platelet count, albumin, bilirubin, glucose, and triglycerides. From this, a simplified but clinically feasible model was developed which includes age, sex, GGT, AST, and ALT. The performance was assessed in terms of discrimination (time-dependent area-under-curve (AUC)), calibration (calibration curves), and clinical utility (decision curve analysis). The model was compared to the FIB-4 score.

**Results:** We used data of 504,359 individuals that were followed over an average follow-up time of 25 years. During follow-up, 7604 liver-related outcomes were observed. The cumulative risk of liver cirrhosis at ten years was 0.22%. The new risk score CORE achieved a 10-year AUC of 81% (95%CI: 80-84) compared to the FIB-4 AUC of 73% (95%CI: 71-75). The calibration was considerably better in CORE than FIB, and according to the decision curve analysis CORE has a a higher net benefit than FIB-4 for all risk thresholds.

**Conclusion:** The new risk score, the Cirrhosis Outcome Risk Estimator (CORE), based on a flexible modeling approach and using biomarkers easily accessible in primary care, outperforms FIB-4 when predicting liver-related outcomes in the general population. External validation is needined before use in primary care.

## [11 – DISTINGUISHED ABSTRACT]
## MASH RESOLUTION INDEX: DEVELOPMENT AND VALIDATION OF A NON-INVASIVE SCORE TO DETECT HISTOLOGIC RESOLUTION OF MASH

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**Abstract Category:** Diagnostic Procedures NASH/Liver Fibrosis
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**Background:** Emerging data suggest that dynamic changes in non-invasive tests, such as changes in alanine aminotransferase (ALT) and magnetic resonance imaging proton-density-fat-fraction (MRI-PDFF) may help to detect metabolic dysfunction-associated steatohepatitis (MASH) resolution, but a combination of non-invasive tests may be more accurate than either alone. We developed a novel non-invasive score, the MASH Resolution Index, to detect the histologic resolution of MASH.

**Methods:** This study included a derivation cohort of 95 well-characterized adult participants (67% female) with biopsy-confirmed MASH who underwent contemporaneous laboratory testing, MRI-PDFF, and liver biopsy at two time points. The primary objective was to develop a non-invasive score, comprising a change in alanine aminotransferase (ALT), a change in MRI-PDFF, and a third clinical variable, to detect MASH resolution with no worsening of fibrosis. The most predictive model was selected based on the highest area under the receiver operating curve (AUC), and the lowest Akaike information criterion and Bayesian information criterion. The model was then externally validated in a distinct cohort of 163 participants with MASH from a clinical trial who underwent paired lab testing, MRI-PDFF, and liver biopsies.

**Results:** The median (IQR) age and body mass index (BMI) were 55 (22-75) years and 32.0 (21.0-47.0) kg/m$^2$, respectively, in the derivation cohort. The most accurate model (MASH Resolution Index) included a change in MRI-PDFF, a change in ALT, and baseline aspartate aminotransferase. The MASH Resolution index had an AUC of 0.79 (95% CI 0.67-0.92) for detecting MASH resolution in the derivation cohort. The score calibrated well and performed robustly in a distinct external validation cohort (AUC 0.81, 95% CI 0.73-0.89), outperforming MRI-PDFF (decline of ≥ 30%), ALT response (decline of ≥ 17 U/L), and combined PDFF and ALT response (all P<.001) (Figure 1).

**Conclusion:** The MASH Resolution index may be a useful score to non-invasively identify MASH resolution.

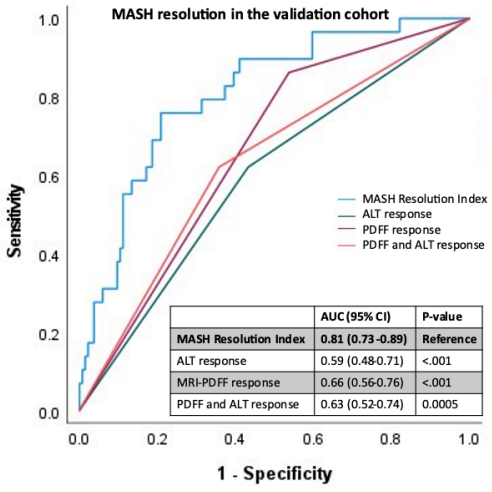


Figure 1. The area under the receiver operating curve for detecting metabolic dysfunction-associated steatohepatitis (MASH) resolution in the validation cohort

## [16 – DISTINGUISHED ABSTRACT] MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING IMPROVES DETECTION OF PATIENTS WITH HIGH RISK NAFLD: REAL WORLD EXPERIENCE IN NAFLD CARE

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**Abstract Category:** Diagnostic Procedures NASH/Liver Fibrosis

**Background:** Early identification of patients with nonalcoholic fatty liver disease (NAFLD) at risk for advanced fibrosis (AF) is important in preventing disease progression to cirrhosis and decompensated liver disease. Non-invasive tests (NITs) including multiparametric magnetic resonance (mpMR) imaging have emerged as clinically useful tools to stratify patients and identify those at risk for NASH and AF. Despite advancements in NITs, current clinical guidelines recommend using the Fibrosis-4 (FIB-4) score as the primary tool for risk stratification. We aimed to evaluate 1) the application of recent AASLD 2023 practice guidance recommendations for patients with suspected or established NAFLD and 2) the potential benefits of utilization of mpMR to improve detection of patients with NAFLD and AF.

**Methods:** A prospective observational study was conducted on patients with NAFLD who received mpMR between 1/2019 and 12/2021 as part of standard clinical care. Patient demographics, medical comorbidities, and laboratory data were collected. We then applied the 2023 AASLD clinical practice guidance algorithm for patients with suspected or established NAFLD based on initial FIB-4 to our cohort. We compared this risk stratification with mpMR results, for which a cT1 value cutoff ≥800ms was considered an indicator of high risk for NASH or fibrosis.

**Results:** Of 103 patients with NAFLD diagnosed by hepatologists at two large, academic medical centers, 64% (66/103) had a FIB-4 <1.3. Of these patients at low risk for NASH or AF by initial stratification, 57 patients had cT1 data available; 58% (33/57) had cT1 ≥800ms on mpMR. Compared with patients with cT1 <800ms on mpMR, there were trends for those with cT1 ≥800ms to be younger (55 v. 50, p=0.22), more likely to be women (p<0.01), have higher BMI (32 v. 30, p=0.75), and more likely to have diabetes (27% v. 17%, p=0.52). Despite higher rates of dyslipidemia among patients with cT1 <800ms (63% v. 52%, p=0.84), fewer patients were on treatment for dyslipidemia in this group compared with those with cT1 ≥800ms (40% v. 76%). cT1 was positively correlated with ALT (r=0.26), AST (r=0.26), liver fat from PDFF (r=0.72), and fasting glucose levels (r=0.23).

**Conclusions:** In this real-world application of mpMR to aid in risk stratification of patients with NAFLD, ***over half*** of patients stratified as low risk by FIB-4 <1.3 had cT1 ≥800ms on mpMR, suggestive of increased risk for developing NASH or AF. Incorporation of mpMR earlier in the algorithm for patients with suspected or established NAFLD may improve our detection of those with advanced disease and allow for earlier intervention to prevent disease progression and complications.

*Abstract was presented as a poster at The Liver Meeting on 11/11/2023.*

## [24 – DISTINGUISHED ABSTRACT] COMBINATION OF LIVERSTAT (LST) AND FIBROSCAN (LSM) OUTPERFORMS FIB-4 AND LSM, FOR MASLD ADVANCED FIBROSIS F3F4.

Naim Alkhouri[1], Anita Kohli[1], Phillip Leff[1], Rida Nadeem[1], Parvez Mantri[2], Yong Wen Leow[3], Lee Lee Lai[3], Nik Raihan Nik Mustapha[4], Sanjiv Mahadeva[3], Wah Kheong Chan[3], Amon Asgharpour[5], Ronald Quiambao[6], Mona Munteanu[6], Adèle Delamarre[7], Julie Dupuy[7], Paul Hermabessière[7] and Victor deLédinghen

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**Abstract Category:** Diagnostic Procedures NASH/Liver Fibrosis
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**Background:** LiverSTAT (LST) is a new blood test for MASLD risk stratification based on common biochemistry biomarkers.

**Aims:** To retrospectively compare the efficacy of two combinations in one step approach with two biomarkers: LST&LSM versus FIB-4&LSM, for the identification of histological advanced fibrosis (F3F4) in a multicenter multiethnic meta-dataset of MASLD patients.

**Methods:** Retrospective data from 5 hepatology centers on MASLD patients that underwent biopsy along with LSM by Fibroscan, FIB-4 and LST blood biomarkers. Efficiency has been assessed using concordance rates against liver biopsy (LB), number needed to screen (NNS) and double false positive/negative rates (DFP/DFN) whenever both LST and LSM disagreed with LB staging.

**Results:** Data from 786 patients (22.1%US, 39.2%Asia, 38.7%EU) was analyzed [age 57.1years, female 54.5%, BMI 31.4kg/m2, ALT 52U/L]. Prevalence of F3F4 was 32.8% based on LB.

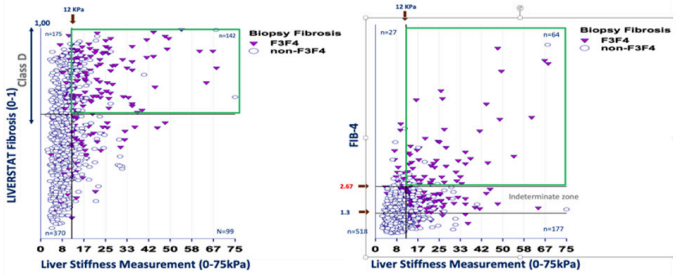
In the overall cohort, LB confirmed F3F4 among concordant LST&LSM and FIB-4&LSM, respectively, in 107/142(75%) vs 54/64(84.4%) with a screening efficiency (NNS) of 1.8 vs 2.2; the combination LST&LSM correctly identified twice more F3F4 patients than FIB-4&LSM.

In the subgroup with LB≥20mm, LB confirmed F3F4 among concordant LST&LSM and FIB-4&LSM in 43/50(86%) vs 30/33(90%), NNS 1.6 and 1.8, respectively; the combination LST&LSM correctly identified 43% more F3F4 patients than FIB-4&LSM.

DFP rate was higher with FIB4-&LSM than with LST&LSM (11.3% vs. 7%).

**Conclusion:** The combination LST&LSM outperforms FIB-4&LSM for the identification of MASH advanced fibrosis F3F4.

**Figure 1. Scatterplots of the combinations LiverSTAT and LSM and FIB-4 and LSM plotted against liver biopsy fibrosis staging (NASH-CRN).**



## [35 – DISTINGUISHED ABSTRACT]
## GM-60106, A NOVEL CLINICAL DRUG CANDIDATE FOR NON-ALCOHOLIC STEATOHEPATITIS (NASH)

Peter C. Goughnour

**Abstract Category:** Pathogenesis, Translational Science, NAFLD/NASH, Liver Fibrosis, Humans

Nonalcoholic fatty liver disease (NAFLD) is currently the leading cause of chronic liver disease worldwide.[1] NASH (Nonalcoholic Steatohepatitis) is an advanced form of NAFLD that can progress to liver fibrosis, cirrhosis, and hepatocellular carcinoma.[2]

Our recent findings demonstrate that liver $5HT_{2A}$ (Htr2A) knockout mice suppressed steatosis and reduced fibrosis-related expression. We developed a peripheral $5HT_{2A}$ antagonist for NASH named GM-60106. It showed good in vitro activity, stability, and PK in rats and dogs. Compound GM-60106 showed good in vivo efficacy in STAM, CDAHFD, MCD and DIO mice models, which effectively reduce fatty liver and fibrosis. A tissue distribution study with [$^{14}$C]-labeled GM-60106 wasn't detected in brain tissue, which determined this compound to be a peripheral $5HT_{2A}$ antagonist. In human phase I clinical trials, GM-60106 showed no adverse side effects in nine cohorts of SAD and three cohorts of MAD. Taken together, compound GM-60106 shows promise as a safe therapeutic agent for the treatment of NAFLD and NASH.

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## [46 – DISTINGUISHED ABSTRACT]
## IMPROVEMENT IN FAST AND FIB-4 COMPOSITE BIOMARKER SCORES IN PHENOTYPIC NASH PATIENTS TREATED FOR 12 WEEKS WITH MONTHLY AND BI-WEEKLY SUBCUTANEOUS DOSING OF BOS-580

Tatjana Odrljin[1], Rohit Loomba[2], Jose Rodriguez[3], Nomita J. Kim[4], Alina Maria Alvarez[5], Linda Morrow[6], Alicia Clawson[1], Mark Woodruff[1], Jose Trigo[1], Eric Svensson[1] and Gerard Bain[1]

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**Abstract Category:** Therapeutic Trials NASH/Liver Fibrosis
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**Background:** BOS-580, a highly engineered fusion of human FGF-21 and IgG1 Fc, has a 21-day half-life that enables once monthly dosing. BOS-580 has shown a statistically significant reduction in liver fat content and markers of liver injury/fibrosis and improved markers of metabolic health in a Ph2a, double-blind, placebo-controlled, randomized study in phenotypic NASH patients. Several noninvasive biomarker composite scores have been developed to assess fibrosis in NASH patients. Such biomarkers have been correlated with levels of liver inflammation, steatosis, and fibrosis. Here we describe changes in Fibroscan-AST (FAST), Fibrosis-4 Index (FIB-4), and NAFLD Fibrosis Score (NFS).

**Methods:** Trial inclusion criteria included a BMI of 30-45 kg/m$^2$, ≥10% hepatic magnetic resonance imaging proton density fat fraction (MRI-PDFF), 7.0 to 9.9 kPa vibration controlled transient elastography liver stiffness measurement (VCTE-LSM), and > 20 IU/L serum aspartate transaminase (AST). Multiple dosing regimens were explored, with cohorts of 75 mg every 2 (Q2W) or 4 weeks (Q4W), 150 mg Q2W or Q4W, and 300 mg Q4W, and a treatment ratio 4:1 of BOS-580 to placebo, per cohort. Calculation of composite biomarker scores was performed according to standard procedures.

**Results:** 102 patients of both sexes were enrolled, with demographic and baseline disease characteristics evenly balanced across cohorts. For the overall trial population, the mean baseline value for MRI-PDFF was 21%, AST was 33.0 IU/L, and 8.2 kPa for VCTE-LSM. The mean baseline FAST score was 0.38, FIB-4 was 1.24, and NFS was -0.83. While NFS did not significantly change, both FAST and FIB-4 scores were significantly reduced after 12 weeks of BOS-580 treatment (excluding 75 mg Q4W, shown earlier to be suboptimal), with significant decreases occurring as early as 2 weeks following the first dose (FIB-4). The mean percent change from baseline in FAST score was -57.4% in the treatment group versus +5.6% in the placebo group (LS means, $p<0.001$). In addition, of 27 of 44 patients in the treated group who had a FAST score >0.35 at baseline (moderate-high risk of significant fibrosis), 26 showed reduced scores (<0.35, low risk of fibrosis) after treatment, while only 5 of 13 such patients showed improvement on placebo. The mean percent change from baseline in FIB-4 after 12 weeks of treatment was -20% compared to +8.2% in placebo patients (LS means, $p<0.001$). Of 14 treated patients with FIB-4 scores ≥1.3 (intermediate-high risk) at baseline, 7 were reduced to <1.3 (low risk) after treatment compared to 1 of 10 patients on placebo.

**Conclusion:** Monthly and bi-weekly BOS-580 dosing results in significant reductions in FAST and FIB-4 scores, suggesting that treatment may lead to clinical benefit in NASH patients.

Primary analysis of the Phase 2a clinical study described here was presented at EASL 2023.

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## [49 – DISTINGUISHED ABSTRACT]
## ASSOCIATION BETWEEN ADVANCED FIBROSIS AND NASH-CRN ACTIVITY SCORE (NAS) COMPONENTS: COMBINED DATA FROM MULTIPLE THERAPEUTIC TRIALS INCLUDING MORE THAN 6,000 PATIENTS

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**Abstract Category:** Therapeutic Trials NASH/Liver Fibrosis
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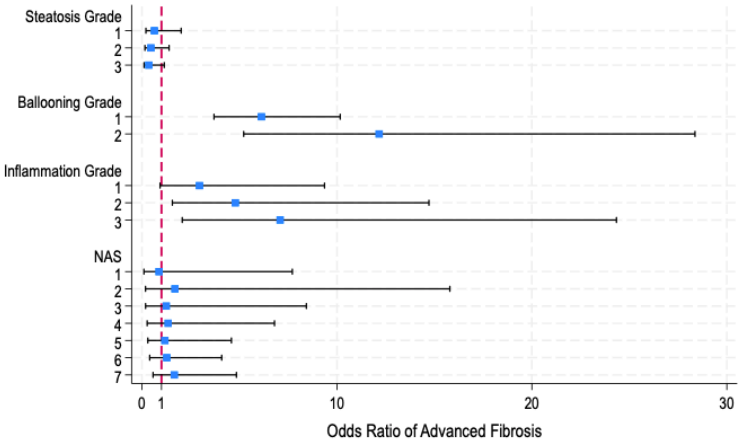
**Background/Aim:** The association of advanced fibrosis and severity of MASH have been previously described. We aimed to assess the association between NAS, NAS components and advanced fibrosis.

**Methods:** We combined screening data from 8 ongoing NASH non-cirrhotic phase 2 trials. We performed univariate and multivariate logistic regression analyses to assess the association between NAS, NAS components and advanced fibrosis, as defined as fibrosis stages 3 or 4.

**Results:** 2,274 patients with centrally assessed liver biopsy were included. The prevalence of advanced fibrosis in this population was 32%. In univariate analysis, higher NAS, hepatocyte ballooning and lobular inflammation were associated with advanced fibrosis. Advanced fibrosis was observed in 5%, 4%, 13%, 18%, 29%, 42%, 53%, 65%, and 58% of patients with NAS 0 to 8, respectively. The odd of advanced fibrosis was statistically significantly increased in patients with a NAS of 4 or more. Advanced fibrosis was observed in 4%, 22%, 48% and 69% in patients with inflammation grade 0 to 3, respectively. Advanced fibrosis was observed in 9%, 38% and 62% in patients with ballooning grade 0 to 2, respectively. In a multivariate model, only ballooning and inflammation grades remained associated with advanced fibrosis (Figure). The severity of ballooning and fibrosis (up to stage 3) was associated with an overestimation of the steatosis grades, when compared with liver fat content assessed by MRI-PDFF. Regarding the association of cirrhosis and NAS component, in a multivariate analysis, the presence of ballooning was a strong predictor of cirrhosis (OR=3.5, 95% CI: 2.0 – 6.0) while the presence of grade 3 steatosis was a strong predictor of absence of cirrhosis (OR=0.12, 95% CI: 0.04 – 0.41).

**Conclusions:** Advanced fibrosis is strongly associated with the presence and severity of hepatocyte ballooning and to a lesser extent with the presence and severity of inflammation, independently of the NAS.




## [50 – DISTINGUISHED ABSTRACT] ICOSABUTATE (ICO) IN NON-ALCOHOLIC STEATOHEPATITIS WITH FIBROSIS: RESULTS FROM A RANDOMISED, MULTICENTER, DOUBLE-BLIND, PLACEBO CONTROLLED, PHASE 2B TRIAL (ICONA)

Dr. Stephen A. Harrison[1], Dr. Naim Alkhouri[2], Jacques Benun[3], Dr. Grisell Ortiz-Lasanta[4], Madhavi Rudraraju[1], Gideon Ho[5], Dean Tai[5], Dr. Hilde H. Steineger[6], Dr. David Fraser[6], Prof. Arun J Sanyal[7] and ICONA Study Investigators

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**Abstract Category:** Therapeutic Trials NASH/Liver Fibrosis

**Background:** Icosabutate (ICO) is a free-fatty acid receptor (FFAR) 1 and 4 (beta-arrestin2) agonist. With tissue specific regulation of endogenous GLP-1 production, glucose stimulated insulin secretion and peripheral insulin sensitivity, FFAR1 and 4 are putative targets for the treatment of type 2 diabetes (T2D). With additional anti-inflammatory effects in liver macrophages, they may also serve as highly attractive targets for the treatment of MASH/NASH. We performed a phase 2b, 52-week, placebo-controlled trial (ICONA) testing the efficacy of ICO in NASH/MASH patients with F1-F3 fibrosis.

**Methods:** 280 patients were randomized, of which 178 PP subjects met the histologic criteria (F1-3, NAS ≥4, ≥1 ballooning, ≥1 inflammation) based on a 3-member panel read. Patients were randomized 1:1:1 to receive once-daily, oral ICO 300mg, ICO 600mg or placebo for 52 weeks. The primary objective was to establish the proportion of patients with NASH/MASH resolution without worsening in fibrosis, with secondary objectives evaluating fibrosis improvement, as well as changes in markers of liver injury, glycemic parameters, lipids and safety and tolerability of ICO. A subgroup analysis was performed in patients with T2D. As an exploratory endpoint, artificial intelligence slide reading (qFibrosis) using second harmonic generation/two photon excited fluorescence (SHG/TPEF) was employed to measure the effect on fibrosis on serial liver biopsy using both continuous and quantitative scoring.

**Results:** Patients (69% female; mean age 53 yrs; mean BMI 36.7 kg/m$^2$, 81% F2/F3, 46% T2D) were randomized to 300mg ICO (n= 57), 600mg ICO (n=62), or placebo (n=59). Although the SAP defined primary endpoint was not met, an increase in the proportion of patients achieving the more stringent endpoint that includes a ≥2 point decrease in NAS was seen in the 600mg ICO treated arm (25.8%, p=0.04) compared with placebo (11.9%) (Table). A greater treatment effect (placebo adjusted) was observed in patients with T2D, with 35.5% (p=0.007) of T2D patients treated with ICO 600 mg achieving NASH resolution and ≥2 point decrease in NAS compared to 4% in placebo. For fibrosis, 28.6% (p=0.005) and 19.4% (p=0.02) of T2D patients achieved a ≥1-stage improvement without worsening of NASH in the 300mg and 600mg arms respectively, versus none in placebo. For qFibrosis, 34.3% (p=0.32) and 51.6% (p=0.03) of T2D patients achieved a ≥1-stage improvement in the 300mg and 600mg arms respectively, versus 20.6% in placebo. ICO markedly improved multiple markers of liver injury, inflammation, fibrosis, glycemic control (placebo corrected ~1% decrease in HbA1c in T2D patients with HbA1c ≥6.5% without increased incidence of hypoglycaemia), atherogenic lipids and hsCRP. Both doses of ICO were well tolerated, with mild-to-moderate GI events the most frequently reported AEs. Consistent with the mechanism of action, neutral effects on both MRI-PDFF and bodyweight were seen.

**Conclusion:** Icosabutate improves histology according to conventional and AI pathology, multiple non-invasive markers of liver injury/ inflammation/ fibrosis, glucose, and lipid metabolism in patients with F1-F3 fibrosis due to NASH/MASH. The enhanced results in subjects with T2D support further development in this patient population, with potential for attenuation of both liver related and CV outcomes.

| **Histologic assessments in all patients** | | | |
|---|---|---|---|
| **Proportion of patients achieving primary endpoint, n (%)** | **Placebo (n=59)** | **ICO 300mg (n=57)** | **ICO 600mg (n=62)** |
| NASH resolution without worsening of fibrosis | 13.6 | 19.3 | 25.8 |
| NASH resolution without worsening of fibrosis and ≥2-point decrease in NAS | 11.9 | 15.8 | 25.8* |
| ≥1-stage fibrosis improvement | 11.9 | 28.1 | 24.2 |
| ≥1-stage fibrosis improvement without worsening of NASH | 11.9 | 26.3 | 22.6 |
| **Histologic assessments in T2D patients** | | | |
| Proportion of patients, n (%) | **Placebo (n=23)** | **ICO 300mg (n=28)** | **ICO 600mg (n=31)** |
| NASH resolution without worsening of fibrosis | 8.7 | 17.9 | 35.5** |
| NASH resolution without worsening of fibrosis and ≥2-point decrease in NAS | 4.3 | 14.3 | 35.6** |
| ≥1-stage fibrosis improvement | 0 | 28.6** | 19.4* |
| ≥1-stage fibrosis improvement without worsening of NASH | 0 | 28.6** | 19.4* |
| **Histologic assessments in F2/F3 T2D patients** | | | |
| Proportion of patients, n (%) | **Placebo (n=17)** | **ICO 300mg (n=26)** | **ICO 600mg (n=23)** |
| NASH resolution without worsening of fibrosis and ≥2-point decrease in NAS | 0 | 15.4 | 30.4* |
| ≥1-stage fibrosis improvement | 0 | 30.8* | 21.7* |
| **AI qFibrosis assessments in all patients** | | | |
| Proportion of patients, n (%) | **Placebo (n=70)** | **ICO 300mg (n=67)** | **ICO 600mg (n=63)** |
| ≥1-stage fibrosis improvement | 25.7 | 34.3 | 49.2* |
| **AI qFibrosis assessments in T2D patients** | | | |
| Proportion of patients, n (%) | **Placebo (n=34)** | **ICO 300mg (n=35)** | **ICO 600mg (n=31)** |
| ≥1-stage fibrosis improvement | 20.6 | 34.3 | 51.6* |

*p<0.05, **p<0.01. CMH test. PP analysis (excludes 6 subjects who initiated therapy with/increased dose of GLP-1 RA, 3 subjects with low-compliance)

## [1]
## USING ARTIFICIAL INTELLIGENCE TO IDENTIFY PATIENT CHARACTERISTICS ASSOCIATED WITH RAPID FIBROSIS PROGRESSION IN NASH: A RETROSPECTIVE COHORT STUDY

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*[1]Novo Nordisk Inc., Plainsboro, NJ, USA; [2]Novo Nordisk A/S, Søborg, Denmark; [3]OM1 Inc., Boston, MA, USA*

**Abstract Category:** Clinical Epidemiology-NASH/Liver Fibrosis
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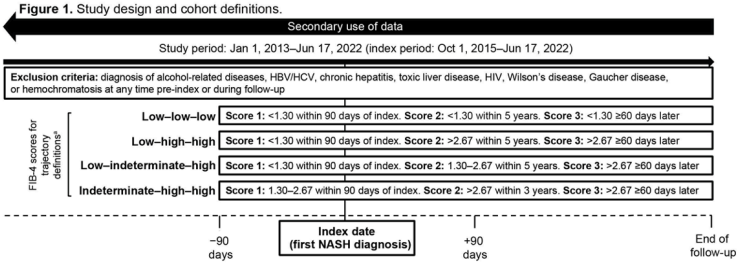
**Background:** Understanding patient characteristics associated with rapid fibrosis progression in NASH (also termed metabolic dysfunction-associated steatohepatitis [MASH]) could enable identification of individuals requiring more regular monitoring and suggest new approaches for management. We used artificial intelligence phenotyping to identify and characterize patients with rapid fibrosis progression.

**Methods:** Patients with NASH diagnosis (index date) were identified in the OM1 Real-World Data Cloud, a multisource dataset derived from US electronic medical records and claims data from >300 million people. Cohorts were defined by Fibrosis-4 score trajectories (Fig. 1). Inputs included diagnoses, procedures, lab values, medications, and demographic data pre-index. Features differentiating rapid progressors from nonprogressors were isolated.

**Results:** Of ~500,000 patients with a NASH diagnosis in the dataset, 175 rapid progressors (low–high–high: n=6; low–indeterminate–high: n=44; indeterminate–high–high: n=125) were identified and compared with 1620 nonprogressors (low–low–low) over up to ~5 years of follow-up. Notable absolute differences in proportions between groups were identified for anemia, thrombocytopenia, myocardial infarction, heart failure, and kidney issues, and relative differences (ratios) for atrial fibrillation, dilated cardiomyopathy, coronary artery disease, myocardial infarction, and congestive heart failure (Fig. 2).

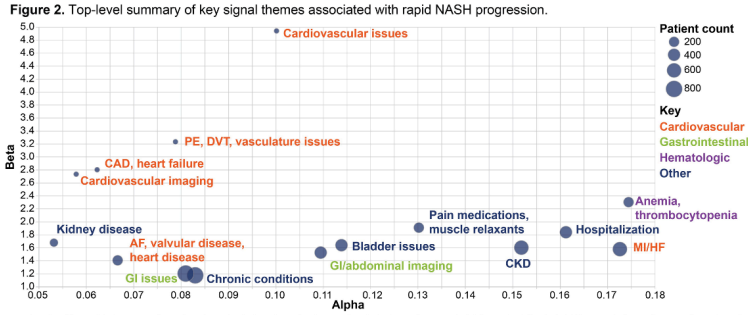
**Conclusions:** This proof-of-concept study demonstrates the application of artificial intelligence phenotyping to multidimensional real-world data, and its ability to isolate characteristics associated with rapid fibrosis progression in NASH. This approach could support new methods to proactively identify patients requiring closer monitoring and improved management.

**Figure 1.** Study design and cohort definitions.




*A FIB-4 score at baseline (score 1) and at least two FIB-4 scores during follow-up were required for inclusion.
FIB-4, Fibrosis-4; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NASH, nonalcoholic steatohepatitis.

**Figure 2.** Top-level summary of key signal themes associated with rapid NASH progression.




Key signal theme labels represent signal clusters of individual elements. Higher values indicate greater absolute (alpha) and relative (beta) differences between the proportions of rapid progressors and nonprogressors with each signal. For example, a signal present in 40% of the rapid progressor group and 10% of the nonprogressor group would have an alpha value of 0.3 and a beta value of 4.0; in this study, the absolute difference between groups for cardiovascular issues was small (0.10) but the relative difference was large (~5.0).
AF, atrial fibrillation; CAD, coronary artery disease; CKD, chronic kidney disease; DVT, deep vein thrombosis; GI, gastrointestinal; HF, heart failure; MI, myocardial infarction; NASH, nonalcoholic steatohepatitis; PE, pulmonary embolism.

## [2]
## BARRIERS TO AND OPPORTUNITIES FOR IMPROVED MASLD/MASH EDUCATION: A QUALITATIVE DISCUSSION WITH MEDICAL TRAINING PROGRAM LEADERS

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**Abstract Category:** Clinical Epidemiology-NASH/Liver Fibrosis
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**Background/Aim:** Metabolic dysfunction-associated steatotic liver disease (MASLD, formerly NAFLD) and metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH) are increasingly prevalent in the United States. However, MASLD and MASH remain substantially underdiagnosed, and many patients with MASH are not receiving care in accordance with the latest guidelines. We aimed to understand how MASLD/MASH-specific training is currently offered in medical training programs

and to identify barriers to and opportunities for the improvement of MASLD/MASH education.

**Methods:** We conducted two qualitative 90-minute virtual focus groups with leaders of medical training programs on August 24 and 28, 2023. One group included leaders of primary care (nurse practitioner/physician assistant, internal medicine, family medicine) programs (PCP, n = 5). The second group included leaders of specialist (endocrinology, gastroenterology, hepatology) programs (n = 6). Participants were recruited by email from a pool of participants who participated previously in a larger quantitative survey on MASH curricula. They were knowledgeable about their curricula (self-reported) and only one participant per institution was allowed. An institutional review board (IRB) exemption was issued.

**Results:** PCP program leaders reported 4 to 23 years in their current roles; specialist program leaders reported 3 to 16 years. Both PCP and specialist program leaders agreed that little time (1-3 hours) is devoted specifically to MASLD/MASH education, though trainees gain practical experience due to the high prevalence of MASH among their patients. Virtually all participants agreed that MASH is substantially underdiagnosed and there is a need for greater awareness among healthcare professionals and the public. Leaders of PCP and specialist programs agreed that MASH management requires both primary and specialist care, though consensus regarding specific responsibilities is lacking and not outlined in curricula. MASLD/MASH nomenclature updates evoked mixed feelings from program leaders; while understanding the rationale, they foresee challenges implementing the new nomenclature. Almost all believed the introduction of MASH-specific pharmacotherapies would encourage institutions to expand MASLD/MASH education in their curricula.

**Conclusions:** Leaders of medical education programs believe MASLD/MASH education is important, but minimal time within curricula is dedicated to it. Novel pharmacotherapies and changes in nomenclature may offer opportunities to expand or improve MASLD/MASH education. These findings suggest that, absent a broad change in medical training, knowledge of MASLD and MASH evaluation and management is unlikely to improve.

**Prior presentation:** None.

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## [3]
## WHEN TO INTERVENE IN TIMING THE DEVELOPMENT OF OBESITY-RELATED METABOLIC DERANGEMENTS AFTER LIVER TRANSPLANT.

Post, Z.[1], Moran, J.[2], Rosario, D.[2], Shah, V.[1], Janardhan, SV.[1]

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**Abstract Category:** Clinical Epidemiology-NASH/Liver Fibrosis
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**Background/Aim:** Orthotopic liver transplantation (OLT) is the standard therapy for end-stage liver disease. Cardiovascular events are a common cause of death in post-OLT patients. The development of metabolic derangement post-transplant increases the risk of cardiovascular events and can be exacerbated by immunosuppressive regimens. In addition, weight gain is common 1-2 years after liver transplant as patients transition into an anabolic state. However, the metabolic consequences of weight gain in the post-OLT population are less well described. Understanding the magnitude and timing of this consequence can help better define the timing of interventions to prevent or attenuate it. To this end, this study was designed to better characterize the temporal correlation of weight gain with metabolic derangement (as measured by changes in glycemic control) in the post-OLT population.

**Methods:** We performed a retrospective analysis of all patients who received a liver transplant at our institution from 2013 to 2021. We compared changes in weight and Hemoglobin A1c (HbA1c) from the time of transplant to 6 months (+/- 3 months), 1 year (+/- 3 months) or 2 years (+/- 3 months).

**Results:** A total of 256 patients were included in the analysis. Appropriately timed weight data was available for 265, 256, 232, and 171 patients at baseline, 6 months, 1 year, and 2 years respectively. HbA1c data was available for 99, 81, 67, and 52 patients at baseline, 6 months, 1 year, and 2 years respectively. The mean BMI at baseline was 25.64. 164/251 (65%), 177/227 (78%), and 137/166 (83%) had weight gain at 6 months, 1 year and 2 years respectively. A statistically significant change in mean BMI was noted at 1 year (28.2 (+2.56 from baseline, p <0.0001)) and 2 years (29.57 (+3.93 from baseline, P<0.0001)) but not at 6 months (26.4 (+0.76 from baseline, p=0.313)). The mean HbA1c at baseline was 5.46%. A statistically significant change in mean HbA1c was noted at 1 year (6.05 (+0.59 from baseline, p <0.001)) and 2 years (6.32 (+0.86 from baseline, p<0.0002)) but not at 6 months (5.79 (+0.33 from baseline, p=0.282)). There was a positive correlation between HbA1c and BMI between baseline through year 2 (Pearson correlation r=0.9812, p=0.0188).

**Conclusion:** There was a prominent and statistically significant increase in weight beginning at 1 year post liver transplant. This correlated with the development of a significant increase in HbA1c over the same time. Our data would suggest that targeted interventions to prevent obesity-related complications in this population should begin at around 1-year post-transplant and may prevent associated morbidity and/or mortality.

Figure 1. Positive correlation between mean BMI and mean HbA1c over a 2-year period.

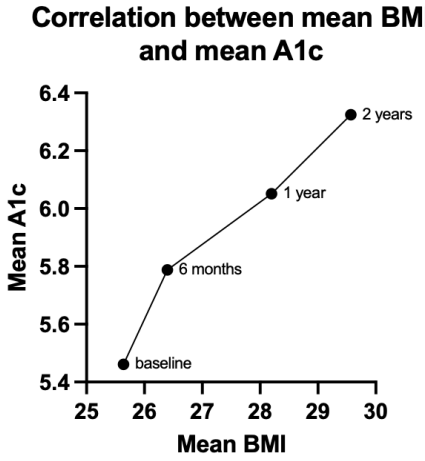


Table 1. Mean BMI and mean HbA1c in post-transplant patients

| **BMI** | | | | |
|---|---|---|---|---|
| **Time post-OLT** | **N** | **Mean** | **Absolute change from baseline** | **p-value** |
| *Baseline* | 265 | 25.64 | - | - |
| *6 months* | 256 | 26.40 | 0.76 | 0.313 |
| *1 year* | 232 | 28.20 | 2.56 | <0.0001 |
| *2 years* | 171 | 29.57 | 3.93 | <0.0001 |
| **HbA1c** | | | | |
| **Time post-OLT** | **N** | **Mean** | **Absolute change from baseline** | **p-value** |
| *Baseline* | 99 | 5.46 | - | - |
| *6 months* | 81 | 5.79 | 0.33 | 0.282 |
| *1 year* | 67 | 6.05 | 0.59 | 0.0104 |
| *2 years* | 52 | 6.33 | 0.86 | 0.0002 |

## [5]
## ASSOCIATION BETWEEN LONGITUDINAL BIOMARKERS AND MAJOR ADVERSE LIVER OUTCOMES IN PATIENTS WITH NON-CIRRHOTIC METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE

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**Abstract Category:** Clinical Epidemiology-NASH/Liver Fibrosis

**Background and Aims:** Non-invasive biomarkers provide prognostic information for the development of major adverse liver outcomes (MALO) in patients with metabolic dysfunction associated steatotic liver disease (MASLD), but the predictive value of longitudinal biomarker measurements has not been evaluated. Here, we assessed whether changes in biomarkers could predict incident MALO in MASLD.

**Method:** We analysed a cohort of 1,260 patients with non-cirrhotic MASLD, among whom 904 (71.7%) had biopsy-proven MASLD, from three university hospitals in Sweden between 1974 and 2019. Data at baseline and follow-up visits were obtained from medical charts. MALO was determined through medical charts and linkage to national registers until the end of 2020. A joint modelling approach was used to quantify the associations between the trajectory of biomarkers (including the latest sampled value and the slope) with the risk of MALO.

**Results:** The median age at MASLD diagnosis was 52 years (IQR: 39-60), and 59% were male. During a median follow-up of 12.2 years, 111 (8.8%) patients developed MALO. The multivariable joint modelling showed that an elevated FIB-4 (HR 2.60, 95% CI 1.89-3.50), AST (HR 2.77, 95% CI 1.98-3.94), and lower platelet count (HR 0.93, 95% CI 0.90-0.97) at any time point were associated with an increased risk of MALO, whereas the rate of change in these biomarkers had no significant association with this risk.

**Conclusion:** In addition to baseline measurements of non-invasive biomarkers such as FIB-4 and AST, and platelets taken at MASLD diagnosis, monitoring their values over time is important, as the latest value of these biomarkers is closely associated with the risk of future MALO. The rate of change may not be as important.

## [8]
## MONARCH: A PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF MIRICORILANT IN ADULT PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS/ METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (NASH/MASH)

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**Abstract Category:** Clinical Trial Design
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**Background:** Cortisol, a hormone that regulates metabolism and stress, has been implicated in the development and progression of nonalcoholic fatty liver disease/metabolic dysfunction-associated steatotic liver disease. Miricorilant is an orally delivered, nonsteroidal, selective glucocorticoid receptor modulator (SGRM) that may reduce hepatic steatosis by modulating cortisol activity and improving liver health. In a phase 1b multi-cohort, dose-finding trial (NCT05117489), adult patients with presumed NASH/MASH were treated with miricorilant doses ranging from 30 to 200 mg daily or intermittently for 12 or 24 weeks. Miricorilant 100 mg twice weekly had the best benefit-risk profile: at week 12, there was a mean relative reduction in liver fat content (LFC) of –28.2% (standard deviation [SD]: 13.5), with a corresponding decline in liver enzymes (mean change from baseline: alanine aminotransferase, –4.0 [SD: 21.4]; aspartate aminotransferase, –6.0 [SD: 7.2]). Additionally, this dose of miricorilant was safe, well-tolerated, and resulted in improved hepatic, lipid, and glycemic markers (Alkhouri et al. AASLD 2023). Based on these data, miricorilant 100 mg twice weekly is currently being evaluated in the phase 2b MONARCH study.

**Methods:** MONARCH (NCT06108219) is a phase 2b, randomized, double-blind, placebo-controlled study of miricorilant. Approximately 150 adult (18–75 years) patients with biopsy-confirmed NASH/MASH (fibrosis stage of 2 or 3), LFC by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) of ≥8%, and risk factors for NASH/MASH (type 2 diabetes mellitus or metabolic syndrome) are being enrolled. Patients are randomized 2:1 to miricorilant 100 mg or placebo twice weekly for 48 weeks, with stratification by type 2 diabetes status and fibrosis stage. The primary endpoint is change from baseline in LFC at week 24, as assessed by MRI-PDFF. A key secondary endpoint is resolution of steatohepatitis and no worsening of liver fibrosis at week 48, as assessed by biopsy. Other secondary and exploratory endpoints include change in liver enzymes, liver fibrosis markers, inflammatory markers, glycemic markers, and lipids, as well as safety and pharmacokinetics.

**Results/Conclusion:** The MONARCH trial is currently enrolling.

## [9]
## CAROTID, AORTIC INTIMA MEDIAL THICKNESS IN NON ALCOHOLIC FATTY PANCREATIC DISEASE

Reda Albadawy

**Abstract Category:** Clinical Trial Design

**Background and aim:** Non-alcoholic fatty pancreatic disease (NAFPD) or fatty pancreas emerged as a health problem parrlel to obesity, and have serious complications more than Non-alcoholic fatty liver disease (NAFLD) as both liver and pancreas develope from the same embryological origin. NAFPD can lead to diabetes mellitus, chronic pancreatitis, pancreatic insuffiency and lastly adenocarcinoma of the pancreas. Also there is extrapancreatic complications to cardio-vascular system is reported too more than expected. The aim of the study is to evaluate the associatin between both aortic, carotid intima-media thickness abnormalties (AIMT, CIMT) as subclinical atherosclerosis and in NAFPD grading patients.

**Methodology:** Eighty eight patients with NAFPD recruited from shib elkom hospital, Menofyia governorate were divided into 4 groups, group (1) diabetics with normal Body Mass Index( BMI), group (2) diabetics with BMI over 25 kg/m2, group (3) non diabetics with normal BMI, group (4) non diabetics with BMI over 25kg/m2. All routine investigations were done. NAFP (grades from 0-3) and AIMT were evaluated using transabdominal ultrasonography (TUS). if the thickness > 0.5mm is abnormal for both AIMT and CIMT. CIMT was evaluated with neck ultrasonography.

**Results:** The mean age of the studied subjects was 44.08±12.41 years. The average body mass index (BMI) was 29.73±8.15 kg/m2. Males made up 73 percent of the patients, while females made up 27 percent. The mean of AIMT is increased in diabetic groups and non diabetics obese group with highly statistically significant difference, while the mean of CIMT is increased in diabetics only with statistically significant difference, also the grade of fatty pancreas increased in obese and diabetics either obese or not with highly statistically significant difference . The more increasing of fatty pancreas grading, the more increasing of AIMT and CIMT. At cut-off , 1.15 mm the sensitivity of AIMT in the prediction of the fatty pancreas was (86.4%), specificity (72.7%) and area under the curve was 0.896 in non-diabetics with normal BMI and diabetics with BMI >25 while, At cut-off , 0.75 mm the sensitivity of CIMT in the prediction of the fatty pancreas was (95.5%), specificity (86.4%) and area under the curve was 0.94 in non-diabetics with normal BMI and diabetics with BMI >25.

**Conclusions:** Fatty pancreas is significantly associated with obesity and diabetes. CIMT and AIMT are significantly higher among patients with higher grade of NAFPD indicating that atherosclerosis is significantly associated with high grade of fatty pancreas.

**Key words:** Atherosclerosis, carotid and aortic Intima-media thickness, Non-alcoholic fatty pancreatic disease

## [10]
## THE EFFECTS OF A COMBINED EXERCISE INTERVENTION ON GUT MICROBIOMES AND SYSTEMIC INFLAMMATORY BIOMARKERS IN MASLD PATIENTS: A STUDY PROTOCOL

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**Abstract Category:** Clinical Trial Design
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**Background/Aim:** Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent liver disease world-wide, with disease progression and severity associated with systemic inflammation, poor diet, inadequate exercise, unfavourable body composition, and gut microbiome dysbiosis. Currently, there are no licensed pharmaceutical agents for the treatment of MASLD, however increasing exercise levels and modifying diet have been shown to reduce disease severity and slow progression - though the underlying mechanisms responsible for these improvements remain unclear. This project aims to examine whether 1) gut microbiome diversity, key inflammatory markers, body composition, cardiorespiratory fitness and muscular strength are related to the severity of MASLD, and 2) changes in the gut microbiome, systemic markers of inflammation, cardiorespiratory fitness, and muscular strength after a 12-week exercise intervention are related to MASLD severity.

**Methods:** Men and women diagnosed with MASLD (n = 46) will be invited to participate in a 12-week exercise intervention. Primary outcome measures include shotgun metagenomics to analyse gut microbiome alpha diversity, elastography using FibroScan™ for liver fibrosis and steatosis scores, and analysis of general blood biochemistry and key inflammatory markers (tumour necrosis factor-α, interleukin [IL]-1β, IL-1, IL-6, IL-10, and high-sensitivity C-reactive protein). Secondary outcome measures will be body composition (fat and fat-free mass), cardiorespiratory fitness ($VO_2$max test), muscular strength (predicted 1 repetition maximum test), and health-related quality of life (SF-36). All outcome measures will be assessed at baseline and again at 6 and 12 weeks. Multivariate linear regression and Pearson's product-moment correlation coefficients will be used to examine relationships between the variables, and linear mixed effects modelling will assess group-time interactions (Alpha 0.05).

**Discussion:** We hypothesise that gut microbiome composition will be related to markers of chronic systemic inflammation and disease severity in MASLD patients, and that exercise training will elicit changes in gut microbiome and systemic inflammation, in line with cardiorespiratory fitness, muscular strength and body composition. Overall, this project aims to advance understanding of the mechanism/s through which exercise improves outcomes for MASLD patients. The findings can potentially inform the development of improved treatment options and evidence-based exercise recommendations for patients with MASLD.

**Ethics:** Human research ethics approval from the Gold Coast Hospital and Health Service Human Research Ethics Committee (HREC) – HREC/2022/QGC/88548.

**Key words:** MASLD; Exercise; Inflammation; Gut Microbiome; Steatosis; Fibrosis; Physical Activity; Health-related quality of life; Cardiovascular fitness, Muscular strength; Body composition.

## [12]
## NEXT GENERATION HEPQUANT TESTS FOR THE CLINIC AND CLINICAL TRIALS: WITHIN-INDIVIDUAL REPRODUCIBILITY AND DIAGNOSTIC PERFORMANCE FOR LARGE ESOPHAGEAL VARICES

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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**Background/Aim:** The HepQuant SHUNT Test (V1.0) uses stable isotopes of cholate administered both intravenously (13C-CA) and orally (d4-CA) to quantify liver function and physiology. The Test has been used in over 26 clinical trials and studies, encompassing a broad range of etiologies and stages of liver disease, where it has compared favorably to other liver diagnostic tests. However, the Test is subject to variability in the timing of collection of the 5-minute blood sample and difficulty in maintaining intravenous access. The aim of this study was to enhance the Test and its performance by simplifying the administration. Herein we evaluate three next generation test versions: V1.1, V2.0, and DuO.

**Methods:** In V1.0, the volume of distribution (Vd) is calculated from log-linear regression of 5- and 20-minute 13C-CA concentrations versus time. V1.1, V2.0, and DuO estimate Vd based on body weight and height (Lemmens et al. 2006), eliminating the requirement for the 5-minute blood sample. V2.0 (IV and oral) and DuO (oral only) are based on our published compartmental analysis (McRae et al. 2022) and further simplify sampling requirements to 2 timepoints at 20 and 60 minutes. To compare reproducibility, coefficients of variation (CV) and intraclass correlation coefficients (ICC) with one-sided test for lower acceptable limit of 0.7 were analyzed in a study of 16 controls, 16 NASH patients, and 16 HCV patients, each with 3 replicate tests conducted on 3 separate days (Burton et al. 2021). We assessed differences in AUROC for predicting large esophageal varices (LEVs) in HCV subjects from the HALT-C study (N = 217) (Everson et al. 2012) by the DeLong method. Test outputs include a Disease Severity Index (DSI) and portal-systemic shunting (SHUNT%).

**Results:** For the measurement of DSI, all test versions demonstrated excellent within-individual reproducibility in terms of CV (9.6%–11.1%) and ICC (0.93–0.94, all $p<0.001$). For SHUNT%, next generation test versions demonstrated improved reproducibility (CVs of 9.2%–12.6%; ICCs of 0.84–0.9, all $p<0.01$) relative to V1.0 (CV 14.9%; ICC 0.74, $p=0.212$). Diagnostic performance for predicting LEVs was equivalent between next generation tests and V1.0 for DSI (AUROCs 0.82–0.84, p=NS); however, AUROCs for SHUNT% were higher for V1.1 (AUROC 0.83, $p=0.0171$), V2.0 (AUROC 0.83, $p=0.1105$), and DuO (AUROC 0.87, $p=0.0572$) relative to V1.0 (AUROC 0.80).

**Conclusions:** By simplifying administration, the next generation of HepQuant tests should enhance utilization of HepQuant for assessing liver disease severity and effects of treatments. The oral-only version, DuO, is particularly well-suited for application in both the clinic and clinical trials. Diagnostic performance for LEVs suggests that DuO may well be a surrogate endpoint likely to predict clinical outcome.

**Disclosures:** MPM is a paid consultant for HepQuant LLC. SMH and GTE are employees and equity members of HepQuant LLC. MPM, SMH, and GTE have provisional patents pending. This abstract has been presented as a poster at EASL 2023.

## [13]
## THE DISEASE SEVERITY INDEX FROM HEPQUANT DUO AND LIKELIHOOD FOR LARGE ESOPHAGEAL VARICES IN THE SHUNT-V STUDY

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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**Background/Aim:** Large esophageal varices (LEVs) and other endoscopic findings of portal hypertension are associated with risk for variceal hemorrhage, liver decompensation, and liver-related death. For these reasons we evaluated the relationship of the disease severity index (DSI) score from the HepQuant DuO test with endoscopically confirmed LEVs and other lesions of portal hypertension.

**Methods:** The validation dataset was comprised of 238 US subjects with CP A cirrhosis who had been participants in the SHUNT-V study. Fifty percent of subjects had MASH, 24% had hepatitis C, 18% had alcoholic liver disease, 85% had BMI >25 kg $m^{-2}$, and 64% had BMI >30 kg $m^{-2}$. Exclusions were known LEVs, prior treatment of varices, history of variceal bleeding, refractory ascites, refractory encephalopathy, CP C cirrhosis, or prior liver transplantation. DSI was determined from serum concentrations of d4-cholate, 20 and 60 minutes after its oral administration. DSI from lean and overweight controls were plotted alongside subjects with no, small, or large esophageal varices. Diagnostic performance for ruling out LEVs was evaluated at the prespecified cutoff of DSI ≤18.3 based on the sensitivity (≥95%) of the HepQuant SHUNT test in the HALT-C quantitative liver function test (QLFT) ancillary study.

**Results:** The AUROC for DSI was 0.81 (95% CI: 0.72–0.87). Applying the DSI ≤18.3 cutoff resulted in sensitivity 96% (81–100%), specificity 39% (33–46%), NLR 0.09 (0.01–0.65), and Miss Rate 3.7%. DSI ≤18.3 would have prevented 35.3% of unnecessary EGDs. DSI captured all but one LEV case, 96.2% of treated esophageal varices, all cases with red wale signs, all cases with large gastric varices, and all cases with severe portal hypertensive gastropathy.

**Conclusions:** The DSI score from HepQuant DuO test predicts the likelihood of LEVs and other endoscopic findings of portal hypertension across a wide spectrum of patient characteristics and disease etiologies. The link to endoscopic lesions of portal hypertension suggests that DSI from DuO may be a surrogate likely to predict clinical outcomes.

**Disclosures:** MPM is a paid consultant for HepQuant LLC. SMH and GTE are employees and equity members of HepQuant LLC. MPM, SMH, and GTE have provisional patents pending. This abstract has been presented as a poster at AASLD 2023.

## [14]
## STRATIFYING DISEASE SEVERITY AND PREDICTING RISK FOR CLINICAL DECOMPENSATION IN PRIMARY SCLEROSING CHOLANGITIS: RESULTS WITH NEXT GENERATION HEPQUANT TESTS

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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**Background/Aim:** We quantified liver function and portal-systemic shunting in primary sclerosing cholangitis (PSC) using V1.1 of the HepQuant SHUNT test (Everson et al. 2007) and NEXT GENERATION tests (V2.0 and DuO) based on a compartmental model (McRae et al. 2022). We compared test results to standard laboratory tests and clinical models in the prediction of clinical outcome.

**Methods:** Forty-seven patients, spanning the clinical spectrum of PSC, underwent baseline tests. Forty-six were retested at baseline for reproducibility by intraclass correlation coefficient (ICC). The cohort was followed prospectively for clinical outcomes, and forty were retested after 1 year. For each test, 20 mg of [24-13C]cholate (13C-CA) was injected intravenously and [2,2,4,4-2H]cholate (d4-CA) was administered orally. Blood was sampled at 0, 5, 20, 45, 60, and 90 minutes for serum cholate concentrations. In V1.1, clearances were calculated from the measured 13C-CA and d4-CA concentrations. The clearances for V2.0 were derived from model parameters fit to the 13C- and d4-CA concentrations at 20 and 60 minutes and for DuO, only d4-CA concentrations at 20 and 60 minutes. A disease severity index (DSI) and portal-systemic shunt (SHUNT%) were calculated.

**Results:** The within-subject reproducibility was excellent and comparable across Test versions with ICCs ≥0.89 for DSI and SHUNT%. Three risk subgroups, low (n=28), moderate (n=16), and high (n=3), were suggested from age-related degree of hepatic impairment. High-risk patients were characterized by high SHUNT% at relatively young age. Moderate/high-risk patients had higher DSI, SHUNT%, and lower Portal HFR and hepatic reserve, worse laboratory tests, higher levels of IL-6, IL-8, and GM-CSF, and were more likely to experience clinical outcome compared to low-risk patients. In univariate analysis SHUNT% was the strongest single predictor of new clinical decompensation, liver-related death, or liver transplantation (n=13 with clinical outcomes, AUROC 0.886 for V1.1, 0.853 for V2.0, and 0.834 for DuO) with no significant differences in operating characteristics between Test versions.

**Conclusions:** HepQuant's Test parameters of liver function and physiology correlate with laboratory and clinical evidence of PSC disease severity, identify risk subgroups, and predict risk for clinical outcome. All versions of the HepQuant Test had excellent reproducibility.

**Disclosures:** MPM is a paid consultant for HepQuant LLC. SMH and GTE are employees and equity members of HepQuant LLC. MPM, SMH, and GTE have provisional patents pending. This abstract has been presented as a poster at AASLD 2023.

## [15]
## THE NEXT GENERATION HEPQUANT TESTS MEASURE REDUCTION IN RISK FOR CLINICAL EVENTS IN COMPENSATED NASH CIRRHOSIS SUBJECTS TREATED WITH RESMETIROM

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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**Background/Aim:** HepQuant SHUNT test (V1.1) quantifies liver function and physiology from the portal and systemic clearances of stable isotopes of carbon-13-labeled cholate (13C-CA) intravenously (IV) and deuterium-labeled cholate (d4-CA) orally. Simplified versions of the Test (SHUNT V2.0 and DuO), which require fewer blood samples and shorter testing time, have been proposed for clinical applications. The objective of this study was to determine whether these NEXT GENERATION (NGEN) HepQuant Tests, using Risk ACE as endpoint, could detect treatment effects in MAESTRO-NAFLD-1 (NCT04197479), an open label, single arm study of resmetirom, a thyroid hormone receptor-β agonist being studied for the treatment of NASH (Harrison et al., Lancet 2019, 394:2012-24).

**Methods:** Thirty-four subjects with compensated NASH cirrhosis (eligibility required at least 3 metabolic risk factors, and NASH cirrhosis diagnosed on liver biopsy or according to accepted criteria) underwent baseline testing and subsequent retesting at 28 and 48 weeks. For each test, IV 13C-CA and oral d4-CA were administered. Blood was sampled at 0, 5, 20, 45, 60, and 90 minutes for serum cholate concentrations. Using a compartmental model (McRae et al., 2023), SHUNT V2.0 was calculated from IV and oral data; DuO from only oral data; both at 20 and 60 minutes. Previously, a Poisson model (Risk ACE) was developed to estimate an individual's annual clinical event rate based on 220 subjects with 52 clinical events from the HALT-C trial. Risk ACE was calculated for each subject from the baseline and week 48 disease severity index (DSI). Risk ACE results between methods were compared.

**Results:** For DuO, Risk ACE decreased with resmetirom treatment in 21 of 23 subjects, with significant decrease in the mean (–0.0182 clinical events per person-year, p=0.0407). At 48 weeks, Risk ACE decreased in 19 of 23 subjects (–0.0355, p=0.1222). SHUNT V1.1 and SHUNT V2.0 also showed similar reductions in Risk ACE at 28 weeks (V1.1: –0.0194, p=0.1028; V2.0: –0.0170, p=0.1145) and 48 weeks (V1.1: –0.0257, p=0.1389; V2.0: –0.0325, p=0.1605).

**Conclusions:** This study demonstrated that NGEN Tests measured a reduction in estimated clinical event rate after 28 weeks of resmetirom. These results show potential for these Tests and Risk ACE to provide a sensitive and interpretable metric of risk for All Clinical Events in monitoring patients. Further evaluation and clinical validation of NGEN Tests and Risk ACE is warranted.

**Disclosures:** MPM is a paid consultant for HepQuant LLC. SMH and GTE are employees and equity members of HepQuant LLC. RT is an employee of Madrigal Pharmaceuticals. MPM, SMH, and GTE have provisional patents pending. This abstract has been presented as a poster at AASLD 2023.

## [17]
## COMPARISON OF COSTS AND REFERRAL RATES OF NON-INVASIVE TESTING STRATEGIES FOR METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) IN VETERAN POPULATION

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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**The abstract has not been presented at any other meeting.**

**Background/Aim:** Patients with metabolic dysfunction-associated steatohepatitis liver disease (MASLD) and significant fibrosis (F2-F4) are at risk for adverse outcomes. We compared 10 different non-invasive testing (NIT) strategies to rule in/out significant fibrosis in endocrinology/primary care setting among veterans at risk for metabolic dysfunction-associated steatohepatitis (MASH) utilizing real-world data.

**Methods:** Electronic medical records of adult patients receiving care in the Veteran Affairs (VA) healthcare system were reviewed to identify patients with body mass index (BMI) >30 and/or type 2 diabetes mellitus (T2DM). Eligible participants (N=254) underwent serum biomarker screening by the Fibrosis-4 (FIB-4) index, the Enhanced Liver Fibrosis (ELF) test, and vibration-controlled transient elastography (VCTE). A subset of patients (N=59) selected on the basis of FIB-4 index scores underwent magnetic resonance elastography (MRE). A total of ten NIT strategies categorized into single-test, two-tests, and three-tests were evaluated for referrals rates to secondary care and cost savings.

**Results:** Patients (N=254) were enrolled with a mean age 65.3+/-9.3 years, and a mean BMI of 31.7+/-6. Of the 254 patients, 87.4% were male, 78.3% non-Hispanic/Latino, and 96.5% had T2DM. The mean +/- SD score of NITs were: FIB-4 1.2+/-0.7 (range, 0.26-4.6), ELF 9.9+/-0.8 (range, 7.7-12.2), TE 6.7+/-3.8 kPa (range, 2.6-39.3 kPa), and MRE 2.6+/-0.8 kPa (range, 1.6-7.0 kPa). Six out of ten strategies showed lower referral rate and lower costs compared to the FIB-4 only strategy. FIB-4/TE, FIB-4/ ELF/TE, FIB-4/MRE, FIB-4/ ELF/MRE, TE only, and FIB-4/ELF strategies kept the highest proportion of patients within primary care at 91.9% (170/185), 90.9% (149/164), 87.9% (51/58), 86.2% (50/58), 81.1% (150/185), and 72.7% (165/227) respectively. These six strategies incurred the following costs per-patient: $172.92, $204.07, $408.35, $400.34, $299.58, and $411.70 respectively. FIB-4 alone strategy resulted in 63.1% (93/252) patients kept within primary care and $445.4 per-patient costs.

**Conclusions:** Among ten strategies assessed, six strategies resulted in lower referral rates to hepatology clinics and lower costs compared to the FIB-4 only strategy. These six strategies in comparison to the FIB-4-only strategy realized substantial cost savings ranging from 7.6% to 61.1%.

## [18]
## REAL-WORLD RISK-STRATIFICATION OF PATIENTS WITH CHRONIC LIVER DISEASE USING QUANTITATIVE MAGNETIC RESONANCE IMAGING

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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**Background/Aim:** To assess the comparative diagnostic value of multiparametric MRI (mpMRI) and magnetic resonance elastography (MRE) in real-world clinical practice for managing suspected chronic liver disease. MRE is a well-accepted non-invasive measure of advanced fibrosis and cT1 a marker of liver disease activity which when elevated has been associated with liver and cardiac clinical outcomes.

**Methods:** A retrospective analysis of the prospective MR exams of 77 patients referred to tertiary chronic liver disease practices. Patients underwent both MRE and mpMRI (LiverMultiScan) as a part of their routine clinical care. MRE measures liver fibrosis with liver stiffness (kPa). LiverMultiScan quantifies liver fibro-inflammatory disease activity (iron-corrected T1, cT1), fat (proton density fat fraction, PDFF) and iron content (T2*). MRE ≥3kPa indicates any level of fibrosis; cT1≥800ms and ≥875ms indicate active and high-risk disease, respectively.

**Results:** Of those included, 55% (42) were diagnosed with MASLD/MASH and 45% with mixed chronic liver diseases including alcoholic liver disease, viral hepatitis, hemochromatosis, high ferritin, etc. The majority, 71% (55), had normal liver stiffness (≤3kPa), however, 29% (22) of these had active disease (cT1>800ms) with 14% (11) having elevated cT1 indicative of high-risk disease (cT1>875ms). There was a linear significant correlation between MRE and cT1 (r=0.411, p-0.0004), and those with elevated MRE (MRE>3kPa) had cT1 864±74ms. cT1 correlated with PDFF (r=0.5, p<0.001), but MRE did not (r=-0.055, p=0.65).

In terms of technical performance, cT1 was successful in 99% (76) of patients, whilst MRE was successful in 90% (69), with technical failure in 9% (7); both had an unreliable result in 1 patient. Majority of MRE technical failures were in patients with elevated liver iron (T2*<12.5ms).

**Conclusion:** MRE and cT1 provide clinically useful complementary information on the state of liver health, with cT1 identifying patients with underlying liver disease activity who are at risk of worse outcomes but who have normal liver stiffness. Since inflammatory activity drives fibrosis these patients would benefit from more intense clinical management or surveillance to prevent clinical outcomes. Caution should be taken in utilizing MRE in patients with suspected high liver iron.

## [19]
## THE PERFORMANCE OF VELACUR AGAINST LIVER BIOPSY FOR ASSESSING ADVANCED FIBROSIS AND STEATOSIS

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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**Background/Aim:** As non-invasive biomarkers have become the standard of care for diagnosis and monitoring of patients with metabolic dysfunction-associated steatotic liver (MASL) and metabolic dysfunction-associated steatohepatitis (MASH), it is essential to understand how they compare to liver histology. This is the first study to validate the performance of Velacur with recent liver biopsy findings in a cohort of patients with suspected MASLD/MASH.

**Methods:** This prospective open label study recruited consecutive patients at Fresno Clinical Research Center (Fresno, California). Patients with suspected or confirmed MASLD/MASH who had or were planning to undergo a biopsy within 3-6 months were enrolled. Patients received a Velacur scan during their clinical appointment before or after the liver biopsy.

For this interim analysis, the AUROC for Velacur for detection of significant fibrosis (≥F2) and moderate steatosis (≥ S2) were calculated.

**Results:** Of 40 subjects have been recruited so far, 38 had biopsy data. Three subjects were removed due to poor Velacur quality. 35 subjects were included in this analysis. The mean age of the studied population was 56.9 ± 12.6 years. Mean body mass index was 33 ± 5.8 kg/m$^2$.

The number of subjects with fibrosis, labeled according to the NASH CRN scoring system, in stages F0-F4 was 5, 15, 1, 13 and 1 respectively. For steatosis, 0, 11, 14, and 10 subjects had grades S0-S3 respectively. The mean time (± standard deviation) between the biopsy and Velacur scan was 81 ± 85 days.

The AUROC [95% CI] for the detection of advanced fibrosis was 0.87 [0.71-0.97] and for the detection of moderate steatosis, the AUROC [95% CI] was 0.82 [0.56-0.93].

**Conclusions:** The reported AUROC's for Velacur in this cohort of patients with liver histology results were in line with or better than the reported AUC's for VCTE (0.82 for advanced fibrosis (Hsu et al 2019) and 0.73 for ≥ S2 (Imajo et al 2016).

| CHACTERISTICS | RESULTS |
|---|---|
| Number of enrolled subjects | 40 |
| Number of analyzed subjects | 35 |
| Age: mean (± std) | 56.9 ± 12.6 years |
| BMI: mean (± std) | 33 ± 5.8 kg/m$^2$ |
| Days between scan and biopsy | 81 ± 85 days |
| AUROC for detection of advanced fibrosis | 0.87 [0.71-0.97] |
| AUROC for detection of moderate steatosis | 0.82 [0.56-0.93] |

Similar data may be submitted to DDW.

## [20]
## FIBROSIS DISTRIBUTION IN LEAN VERSUS OBESE NASH-CIRRHOSIS PATIENTS USING SHG/TPE MICROSCOPY

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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**Background:** Inclusion criteria for drug trials focusing on Non-Alcoholic Steatohepatitis (NASH) cirrhosis require patients classified fibrosis stage as F4 by pathologists. However, F4 classification lacks comprehensive recording of zonal fibrosis parameters based on NASH Clinical Research Network (CRN). Second Harmonic Generation/Two Photon Excitation (SHG/TPE) microscopy-based qFibrosis (qF) offers fully quantitative evaluations. This study compares zonal fibrosis distribution between lean [Body Mass Index (BMI)<25] and overweight/obese (BMI≥25) patients using qF.

**Methods:** 133 patients from Phase 2b Belapectin drug trials (NCT04365868) were included. Paired liver biopsies were evaluated using qF based on NASH-CRN parameters. Patients were categorized into two groups: lean (n=9) and overweight/obese (n=124) in Baseline (BL) group, and lean (n=7) and overweight/obese (n=126) in End-of-Treatment (EOT) group. Statistical analysis by Wilcoxon-rank-sum-test, heat maps employed for visualization.

**Results:** BL group had statistically significant difference in periportal fibrosis parameters between lean and overweight/obese patient (Figure 1). Despite smaller number of patients in lean group compared to overweight/obese group, consistent observation of this significant difference of fibrosis parameters such as fiber length, thickness, etc. in periportal region in BL and EOT groups indicates a possible difference in fibrosis morphology patterns based on BMI.

**Conclusions:** Consistent differences in periportal fibrosis parameters between lean and overweight/obese patients using qF indicates SHG/TPE imaging provides additional information compared to conventional pathologist staging. These findings suggest there could be variations in zonal fibrosis distribution among NASH cirrhosis patients, based on BMI status. Further research with larger patient cohorts would be recommended to expand upon these preliminary observations.

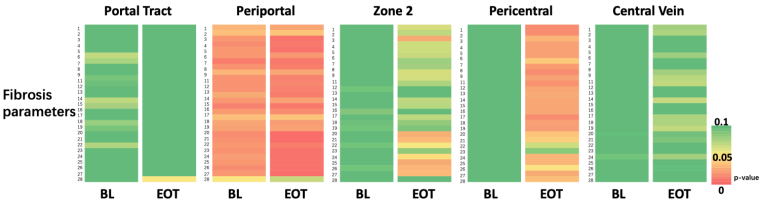


**Figure 1:** Difference of collagen parameters between lean patients versus overweight/obese patients. In SHG/TPE microscopy, 28 fibrosis parameters based on collagen morphology such as fiber length, thickness, etc. are evaluated and quantified in each zone. These were then correlated between BL and EOT cohorts, and the results are shown via heat map with statistical significance (p≤0.05) depicted in red.

*This abstract has been presented as a Poster Presentation in Paris NASH 2024

## [21]
## NON-INVASIVE TESTS AS A PREDICTION TOOL TO ASSESS MASH RESOLUTION SCORE

Jesse Fishman[1], Heather L. Morris[2], Breda Munoz[2], Andrea R. Mospan[2], Yestle Kim[1], Rohit Loomba[3], A. Sidney Barritt IV[4], Philip Newsome[5], on behalf of TARGET-NASH Investigators

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis

**Background/Aim:** Liver biopsy remains the reference standard for diagnosing metabolic dysfunction-associated steatohepatitis (MASH, formerly NASH). However, due to drawbacks such as high cost, patient resistance, sampling errors and risk of complications, non-invasive tests (NITs) were developed to help assess liver fibrosis and liver steatosis. There is limited data correlating NIT scoring to nonalcoholic fatty liver disease (NAFLD) activity score (NAS) and fibrosis scores from biopsies. Previous studies have shown that MRI-PDFF and serum ALT can predict MASH resolution. Understanding the correlation between NIT scores and NAS from biopsies may help improve the role and utilization of NITs, such as vibration-controlled transient elastography (VCTE), AST to Platelet Ratio Index (APRI), NAFLD fibrosis score (NFS), or Fibrosis-4 (FIB-4), to diagnose and monitor patients with MASH, and ultimately, help rule out low-risk MASH.

**Methods:** Adults (>18 years old) with MASH enrolled in the ongoing, longitudinal observational TARGET-NASH study, receiving care in the US with at least one available biopsy and NAS score were included. The purpose of the study was to assess use of NITs compared to NAS score to evaluate MASH resolution, defined as no ballooning or inflammation. As opposed to repeated measures, this was an independent measure analysis with the use of a single biopsy and clustered NITs. Fisher exact test and Kruskall-Wallis were used to assess the univariate association between demographic and clinical measures and the presence/absence of MASH resolution. All NITs as described above were calculated for data available around +/-3 months of the biopsy date. All logistic models controlled for age, sex, history of use of vitamin E, fibrosis stage, and body mass index. Sequential algorithms consisting of two or three NITs were investigated following a stepwise approach. The second NIT was applied to patients classified in the indeterminate class of the first algorithm.

**Results:** A total of 812 adults enrolled in TARGET-NASH were included in this analysis. Approximately half with MASH resolution (54.7%) were classified as Fibrosis stage 0 or 1, while those without MASH resolution were Fibrosis Stage 3 or 4 (50.8%) ($p<0.0001$). Overall, patients without MASH resolution have a larger baseline median FIB-4 (1.7 vs. 1.4, $p<0.003$), APRI (0.7 vs. 0.5, $p<.0001$) and VCTE (12.5 vs. 8.4, $p=0.0054$). The use of sequencing reduced the percentage of indeterminates, sometimes by half (i.e.FIB-4 indeterminates = 35.6% vs. FIB-4 to NFS indeterminates=17.4%). Beginning with FIB-4 or NFS followed by VCTE, appeared to produce a larger reduction in the number of indeterminates. The sequence of FIB-4, NFS, and then VCTE achieved larger indeterminate reduction while maintaining moderate to high levels of accuracy (PPV=67%, NPV=83%, specificity=95%, AUC=0.73).

**Conclusions:** In an evaluation of NITs, FAST, VCTE, and APRI demonstrated a strong prediction of MASH resolution, particularly with the use of sequencing, and a better ability to assess MASH resolution providing a reliable alternative in the absence of a liver biopsy. These findings provide a possible alternative for the diagnosis and monitoring of MASH that may be both cost-effective and reliable.

## [22]
## PERFORMANCE OF NOVEL COLLAGEN TURNOVER BIOMARKERS IN COMPARISON TO FIB-4 TO DETECT ADVANCED FIBROSIS IN MASLD

Hannes Hegmar[1,2], Thomas W. Møller[3], Patrik Nasr[4], Johan Vessby[5], Stergios Kechagias[4], Nils Nyhlin[6], Hanns-Ulrich Marschall[7*], Åsa Danielsson Borssén[8], Rickard Strandberg[2], Morten Karsdal[3], Diana Julie Leeming[3], Mattias Ekstedt[4], Hannes Hagström[1,2]

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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**Background/Aim:** Cleaved products from collagen formation and degradation hold potential as biomarkers in individuals with metabolic dysfunction-associated steatotic liver disease (MASLD). Here, we assessed the ability of PRO-C3, PRO-C6, C4M, PRO-C18L, and the ADAPT score in identifying advanced fibrosis, comparing their performance to the FIB-4 score.

**Methods:** Serum from 299 MASLD-patients from six Swedish University Hospitals and 29 healthy controls underwent ELISA-based analysis. Liver stiffness measurement (LSM) by vibration-controlled transient elastography was performed at inclusion, liver biopsy was performed in 134 patients (45%). Advanced fibrosis was defined as fibrosis stage 3-4 on liver biopsy or an LSM >15 kPa. The area under the receiver operating characteristic curve (AUROC) to detect advanced fibrosis was calculated.

**Results:** Advanced fibrosis was found in 48 (14.6%) patients. PRO-C3, PRO-C6, C4M, and PRO-C18L had AUROCs ranging from 0.46 to 0.73. The ADAPT score had an AUROC for diagnosis of advanced fibrosis 0.84 (95%Confidence interval[CI]=0.79-0.90). However, ADAPT was not significantly better than the FIB-4 score (AUROC 0.83, 95%CI=0.78-0.89, $p=0.76$). None of the biomarkers could accurately diagnose presence of metabolic dysfunction-associated steatohepatitis (MASH).

**Conclusions:** In this cohort with a low prevalence of advanced fibrosis, PRO-C3 had the best diagnostic performance among the individual collagen biomarkers, which was improved when implemented in the ADAPT score. FIB-4 and ADAPT had similar high discrimination to separate patients with and without advanced fibrosis. These results suggests that FIB-4 remains a favorable biomarker to, as a first-line test, rule out presence of advanced fibrosis in patients with MASLD.

A preliminary version of this abstract was previously presented at the EASL congress 2023 in Vienna.

## [23]
## LIVERFAST (L-FAST) IDENTIFIES ADVANCED (F3F4, AF) AND CLINICALLY SIGNIFICANT FIBROSIS (F2-F4, CSF) ESPECIALLY WELL WITH FIBROSCAN IN MASLD PATIENTS (PTS) FROM A TERTIARY HEPATOLOGY CENTER.

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**Abstract Category:** Diagnostic Procedures for NASH/Liver Fibrosis
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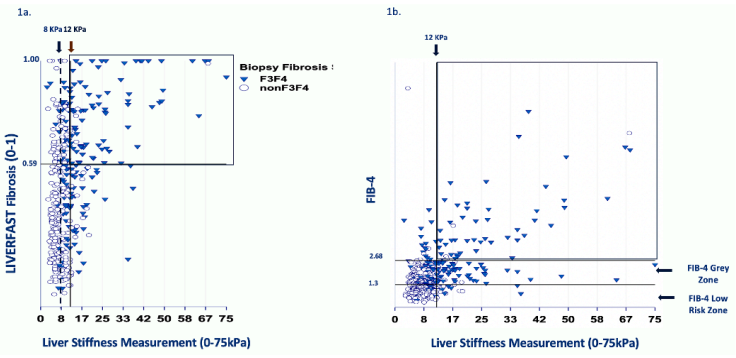
**Background:** The identification of pts with AF and CSF is mandatory in the specialty settings as they require further assessment or specific surveillance or may benefit from targeted interventions. L-FAST is an AI-based blood test that offers an overall assessment of the severity of presumed steatosis, activity, fibrosis (SAF) histological scores for MASLD. L-FAST Fibrosis test (L-FAST-F) demonstrated long-term prognostic value for the liver-related mortality (*Alim Pharmacol Ther.* 2022) and outperformed ELF test for CSF (*J Hepatol Suppl*. 2022). Aims: To compare retrospectively the performance of the combination of two noninvasive tests (NITs): L-FAST-F&LSM versus FIB-4&LSM, for the identification of histological AF and CSF in MASLD pts.

**Methods:** This retrospective study collected data from MASLD pts in a tertiary hepatology center (NCT01241227). LB fibrosis scoring used NASH-CRN. Cutoffs used for AF and CSF were 0.49 and 0.59 for L-FAST-F and 12kPa and 8 kPa for LSM, respectively. For FIB-4 the cutoffs to rule out and to rule in AF were 1.3 and 2.68, respectively.

**Results:** NITs from 583 MASLD pts have been collected (L-FAST-F, LSM, FIB-4) along with LB. A total of 583 pts [males 56.4%, median age 56.4yrs, 51.6%T2DM, median BMI 31.5Kg/m2 and LSM 9.6KPa, 71.3% CSF, 45.2% AF and 17% F4 on LB]. N=399 pts had LB sample size ≥20mm and <6 month between LB and NITs. Among them, L-FAST-F and LSM (12 kPa cutoff) agree for AF in n=74 and LB confirmed AF in 70/74 (94.6%). FIB-4 and LSM, agreed only in n=51 pts and LB confirmed AF in 47/51 (92%). Using a lower LSM cutoff (8kPa), the combination L-FAST-F and LSM agree for AF in n=117 pts and LB confirmed AF in 94/117 (80.3%) correctly identifying 25 pts more (6.3% of the cohort) than with the FIB-4 and LSM combination. (Fig. 1) Among 172 pts with FIB-4 scores in the "grey" zone (1.3-2.27), LB identified 93/172 (54%) pts with AF and 46/93 (49.5%) had L-FAST-F AF. Among 61 pts with FIB-4 scores in the "low risk" zone (<1.3), LB identified 21/61 (34%) pts. with AF and 6/21 (29%) had AF with L-FAST-F. L-FAST-F and LSM (8 kPa cutoff) agree for CSF in n=146 pts and LB confirmed AF in 138/146 (94.5%).

**Conclusion:** The combination L-FAST-F&LSM, when both agreed, identified AF and CSF in more than 94% of pts and, depending on the LSM cutoff, between 50% and 150% more pts identified with AF than the combination FIB-4&LSM.

**Figure 1. Scatterplots of the combinations LIVERFASt-Fibrosis and LSM (1a.) and, FIB-4 and LSM (1b) plotted against LB fibrosis staging. Right upper quadrants display pts in whom NITs and LSM agree for AF; triangles show AF cases confirmed with LB.**




## [25]
## CHARACTERIZING THE MANAGEMENT OF PATIENTS WITH NASH (WITH VERSUS WITHOUT CIRRHOSIS) IN REAL-WORLD CLINICAL PRACTICE – LOW UTILIZATION OF GASTROENTEROLOGY AND HEPATOLOGY SPECIALTY CARE

Michael Charlton, MBBS, FRCP;[1] Christina Qian, MSc;[2] Shelagh M. Szabo, MSc;[2] Rosie Sun, MSc;[2] Hannah Rochon, MSc;[2] Yestle Kim, PharmD;[3] Jesse Fishman, PharmD, MSc[3]

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**Abstract Category:** Disease management of NASH/liver fibrosis patients (including comorbidities)
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**Background:** Guidelines recommend patients with non-alcoholic steatohepatitis (NASH; also known as MASH) undergo regular assessment and follow-up by specialists, particularly gastroenterologists/hepatologists (GIH), to ensure adequate care and monitor for complications. However, recommended follow-up varies; patients with cirrhosis should be assessed annually, versus every 2-3 years for those without cirrhosis. For staging NASH, while there is increased use of noninvasive tests (NITs), liver biopsy remains the reference standard. This analysis aimed to characterize the management of patients with NASH in real-world clinical practice and describe the patient care pathway, considering those with and without cirrhosis.

**Methods:** Optum's de-identified Clinformatics® Data Mart (01Oct2015-31Dec2022) was used to identify adults with NASH. Baseline cirrhosis status was classified by the presence of ≥1 code for cirrhosis, decompensated cirrhosis, liver transplant, or hepatocellular carcinoma (HCC) in the 6 months before or 1 month after the first NASH diagnosis. Patients were followed for ≥12 months (death was exempted), until end of follow-up (defined by the first of death, loss of follow-up, or study end). Demographics, comorbidities, and the annual frequency of specialist visits (including GIH visits) and diagnostic procedures were estimated for patients with vs. without cirrhosis. Average time to and between visits and diagnostic procedures was estimated for specific patient profiles based on patient demographics and metabolic comorbidities.

**Results:** A total of 9,157 patients with and 19,419 patients without cirrhosis were followed up for a median of 2.2 years and 3.0 years, respectively. Despite having regular specialist visits (median[interquartile range (IQR)], 28.4[15.1-50.2] per year per person (PYPP) with cirrhosis vs. 14.4[7.6-25.8] without cirrhosis), GIH visits were estimated to be 1.0(0-2.4) PYPP with cirrhosis

and 0.2(0-0.9) without cirrhosis. These results show that, while ≥50% of those with cirrhosis are seeing a GIH at the recommended frequency of once per year, ≥25% are not being followed up by any GIH annually; and among those without cirrhosis, ≥50% were being assessed less frequently than every 2-3 years, as recommended. The median estimate of 1.4(0.5-2.6) diagnostic procedures, including any abdominal imaging, PYPP with cirrhosis suggest ≥50% of patients were assessed for HCC less than the recommended frequency of twice a year. Liver biopsy was rarely performed over follow-up, even among patients with cirrhosis (occurring among 6%). Those who were older, female, or had cirrhosis and metabolic comorbidities tended to have more frequent visits and diagnostic procedures, albeit at a lower rate than recommended.

**Conclusions:** Results of this analysis suggest a substantial proportion of NASH patients are not being assessed by GIH at the recommended frequency, even when diagnosed with cirrhosis. Screening for HCC for most patients with cirrhosis also occurs less than the recommended frequency. Liver biopsy was not frequently performed and likely reflects increased reliance on NITs. Our findings suggest clinical practice is only partially aligned with clinical guidelines, even for patients with substantial metabolic comorbidities. The low frequency of abdominal imaging may have implications for HCC disease stage at diagnosis.

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## [26]
## CHARACTERIZING THE REAL-WORLD CLINICAL OUTCOMES OF PATIENTS WITH NASH WITHOUT CIRRHOSIS VERSUS WITH CIRRHOSIS

Michael Charlton, MBBS, FRCP;[1] Christina Qian, MSc;[2] Yestle Kim, PharmD;[3] Shelagh M. Szabo, MSc;[2] Rosie Sun, MSc;[2] Hannah Rochon, MSc;[2] Jesse Fishman, PharmD, MSc[3]

*[1]University of Chicago Medicine, Chicago, IL, USA; [2]Broadstreet HEOR, Vancouver, BC, Canada; [3]Madrigal Pharmaceuticals, Conshohocken, PA, USA*

**Abstract Category:** Disease management of NASH/liver fibrosis patients (including comorbidities)
**Corresponding Author's Email:** cqian@broadstreetheor.com

**Background:** Nonalcoholic steatohepatitis (NASH; also known as MASH) is estimated to affect between 3 to 6% of adults, with prevalence increasing in recent years. Approximately 20% of NASH patients progress to cirrhosis within two years of diagnosis and a subsequent 20% progress to more advanced liver diseases (including decompensated cirrhosis [DCC], hepatocellular carcinoma [HCC], and liver transplantation [LT]) over two years. However, real world (defined as non-interventional study) estimates of the risk and clinical outcomes of progression to advanced liver diseases are scarce.

**Methods:** The Optum de-identified Clinformatics® Data Mart (Oct2015-Dec2022) was used to identify adults with NASH. Patients were classified as having cirrhosis at baseline based on the presence of ≥1 code for cirrhosis, DCC, LT, or HCC in the 6 months before or 1 month after (to account for reporting delays) their first observed NASH diagnosis. All patients were required to have a minimum continuous follow-up of 12 months (death was exempted) until end of follow-up as defined as the first of death, loss of follow-up, or study end. Among those without cirrhosis at baseline, time to event analyses were performed using Kaplan Meier (KM) curves, as well as Cox Proportional Hazard (CoxPH) models adjusting for baseline characteristics, to estimate the timing and risk of progressing to a composite outcome comprising all-cause death or a significant hepatic event (cirrhosis, DCC, or LT). The timing and risk of all-cause death was also estimated using similar methods, to quantify the risk associated with having cirrhosis at baseline.

**Results:** A total of 28,576 patients with NASH were identified, of which 19,419 patients did not have cirrhosis at baseline (mean age of 59.8 years) and 9,157 patients had cirrhosis (67.1 years). Those without cirrhosis at baseline had longer mean follow-up of 3.2 years (vs. 2.5 among those with cirrhosis). Among those without baseline cirrhosis, the risk (95% confidence interval, CI) of progressing to the composite outcome increased from 10.5% (10.1-10.9%) in year one to 31.4% (30.5-32.3%) by year five. The CoxPH model showed that the risk of progressing to the composite outcome also increased with age (hazard ratio [HR] [95% CI] 1.4[1.3-1.6] among 45-64 years, 2.1[1.9-2.4] among ≥65 years, compared to those <45 years at index) and baseline cardiovascular disease (CVD) (1.3[1.2-1.4]) or type-II diabetes mellitus (T2DM) (1.3[1.2-1.4]). When compared to those without baseline cirrhosis, those with cirrhosis had significantly higher risk of death throughout the follow-up and the risk increased with increasing age. The risk of death remained significantly higher when adjusted for other baseline covariates (HR [95% CI] of 4.7 [4.3-5.1]), and was significantly higher for those who are male, had CVD or T2DM.

**Conclusions:** For NASH patients without cirrhosis at baseline, the risk of experiencing all-cause death, progression to cirrhosis or DCC, or requiring a LT, increased with time. The risk of death was several fold higher for those with cirrhosis. This study also found that the risk of death and progression increased significantly with age and presence of comorbidities of CVD and T2DM. Therapies that slow NASH progression may help reduce risks for all-cause death and progression to other advanced liver diseases.

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## [27]
## A LONGITUDINAL ASSESSMENT OF CARDIOVASCULAR RISK FOR PATIENTS ENROLLED IN TARGET-NASH

Jesse Fishman[1], Heather L. Morris[2], Andrea R. Mospan[2], Derek Gazis[2], Yestle Kim[1], A. Sidney Barritt IV[3], Arun Sanyal[4], Philip Newsome[5], Rohit Loomba[6], on behalf of TARGET-NASH Investigators

*[1]Madrigal Pharmaceuticals, Conshohocken, PA; [2]Target RWE, Durham, NC; [3]Virginia Commonwealth University Medical Center, Richmond, VA; [4]University of Birmingham, Birmingham, UK; [5]NAFLD Research Center, Division of Gastroenterology, University of California at San Diego, La Jolla, CA*

**Abstract Category:** Disease management of NASH/liver fibrosis patients (including comorbidities)

**Background/Aim:** Cardiovascular (CV) risk can be estimated by risk scores such as the Framingham and the Pooled Cohort Equations (PCE). There is a lack of data assessing CV risk in patients with cirrhotic metabolic dysfunction-associated steatohepatitis (MASH, previously NASH) or non-cirrhotic MASH and a comparison of the CV risk between these cohorts. These risk equations do not factor in the presence of liver disease, let alone severity, which can significantly impact CV outcomes, morbidity, and mortality in patients with MASH.

**Methods:** The population for this analysis includes US adults with MASH enrolled in the ongoing, longitudinal observational TARGET-NASH study. Index date was date of the first eligible NASH diagnosis. Patients with any CV history at or prior to index were excluded. 10-year CV risk was estimated using the Framingham and PCE risk models, and predicted risks were compared between patients with cirrhotic MASH and non-cirrhotic MASH using the Kruskal-Wallis test. Risk was compared overall and among subgroups of patients with and without history of type 2 diabetes (T2DM). Fine-Gray subdistribution hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between disease phenotype and likelihood of experiencing a CV event, adjusted for the risk

factors included in the Framingham and PCE models.

**Results:** Of the 6,568 patients included in TARGET-NASH, 2,512 patients aged 30-74 years at index with MASH met inclusion criteria, of which up to 836 patients had data for calculation of CV risk. The median predicted 10-year CV risk from the Framingham model was significantly greater for patients with cirrhotic MASH compared to those with non-cirrhotic MASH (16.6% vs. 12.3%, p<.001). The difference was significant among subgroups of patients with T2DM (18.8% vs. 16.6%, p=0.04) and without T2DM (11.3% vs. 8.4%, p=0.03). These findings were consistent with results from the PCE. Based on observed CV events, patients with cirrhotic MASH had a significantly greater likelihood of experiencing a CV event compared to those with non-cirrhotic MASH (HR 1.70, 95% CI 1.03-2.79).

**Conclusions:** Patients with cirrhotic MASH were found to be at an increased risk of CV events compared to patients with non-cirrhotic MASH, even after adjusting for traditional CV risk factors, which supports the notion that the severity of liver disease impacts the level of cardiovascular risk. Understanding this differential risk is an important consideration that will be instrumental in chronic care management. Treatments that could delay progression to cirrhosis may potentially reduce health events like CV outcomes, morbidity, and mortality in patients with MASH.

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## [28]
## DEPLOYING A CONSENSUS METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) CARE PATHWAY AND EDUCATIONAL PILOT IN THREE U.S. HEALTH SYSTEMS

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**Abstract Category:** Disease management of NASH/liver fibrosis patients (including comorbidities)
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**Background and Aims:** Recent guideline updates regarding metabolic dysfunction-associated steatotic liver disease (MASLD), including those from European Association for the Study of the Liver (EASL 2021) and American Association for the Study of Liver Diseases (AASLD 2023), recommend screening for advanced fibrosis in certain patients with increased risk for MASLD. With therapeutics in the pipeline anticipated to go to market in 2024, it is essential for health systems to establish pathways to risk stratify and triage patients for appropriate care. This pilot was designed to streamline the adoption of guidelines-based care for metabolic dysfunction-associated steatohepatitis (MASH), identify barriers to implementation, and outline a foundation for future real-world evidence generation and quality improvement.

**Methods:** By leveraging the American Gastroenterological Association (AGA) and EASL care guidelines, six expert hepatologists, representing healthcare organizations across the US, were convened in November 2021 to develop a MASH consensus care pathway. The panel-derived care pathway was deployed across three pilot sites: Boston Medical Center (BMC), Methodist Health System, and Weill Cornell Medicine. Site champions conducted educational sessions with respective primary care providers (PCPs) and administered baseline and follow-up assessments.

**Results:** A total of 19 PCPs across the three sites completed the baseline educational assessment, nine PCPs completed the two-month follow-up assessment, and 15 PCPs completed the final four-month follow-up assessment.

While all participants agreed that MASLD is a highly prevalent disease, only 42% (n=8) at baseline felt they had received sufficient training on when to refer a patient suspected of MASLD/MASH to hepatology. Within 12 months of the baseline survey, 79% (n=15) of respondents had referred a patient suspected of MASLD/MASH to hepatology and 53% (n=10) had used FIB-4.

The final four-month follow-up assessment indicated 80% of respondents (n=12) agreed or strongly agreed they received sufficient training on when to refer a patient suspected of MASLD/MASH to hepatology. Additionally, 47% of respondents (n=7) stated they had referred a patient suspected of MASLD/MASH to hepatology for additional workup within 12 months of the final assessment. In that same period, 73% (n=11) had used FIB-4. Respondents indicated barriers to care pathway implementation included burden of calculating FIB-4s for high-risk patients and difficulty ordering non-invasive tests (NITs) within the electronic health record.

**Conclusion:** This pilot study identified gaps in PCP knowledge which were improved with educational interventions and training, and demonstrated improved clinician confidence in identifying, risk stratifying, and referring patients with MASLD/MASH. Electronic integration of MASLD care pathways will be essential to further examine PCP buy-in and adherence to the pathway. Additional evidence generation is also needed to support the performance of the proposed care pathway in a wider range of care delivery settings.

**Disclosure:** This abstract has not previously been presented at any meetings.

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## [29]
## COMPARING CARDIOVASCULAR AND INFECTION COMPLICATIONS IN LIVER TRANSPLANT PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS VERSUS OTHER INDICATIONS

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**Abstract Category:** Disease management of NASH/liver fibrosis patients (including comorbidities)
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**Background:** In recent years, nonalcoholic steatohepatitis (NASH) has emerged as a leading indication for liver transplants prompting extensive research into its underlying causes and potential therapeutic interventions. The aim of this study was to assess the post liver transplant cardiovascular and infection complications in NASH patients to help identify early interventions that could potentially mitigate these serious post-transplant complications.

**Methods:** A single center retrospective study was performed at Methodist Dallas Medical Center from January 2017 to September 2022 on NASH vs non-NASH patients who underwent liver transplant. Propensity matching analysis matched the disease cohorts on: MELD, age, and gender at time of transplant.

Demographic, clinical, and transplant-related outcomes (cardiovascular event, infection, mortality) were collected at one year. Groups were compared using the Student's t-test, Chi Square Test of Independence, Fisher's exact test, Wilcoxon Rank-sum test, and Logistic/Cox regression.

**Results:** 124 liver transplant patients (67 NASH vs. 57 non-NASH) were analyzed. NASH patients had significantly higher mean BMI at time of transplant (31.99 vs 28.40, p=0.0126) and at one-year post-transplant (32.95 vs. 30.10, p = 0.0126). Similar cardiovascular outcomes were observed at one year between the NASH vs. non-NASH groups as can be seen in the MI rate (0% vs. 0%), and CVA rate (1.49% vs 3.64%, p = .588). Surprisingly, there were no differences in post-transplant infection rates (58.21% vs. 61.82%, p=0.686) and the types of infection were similar between the two groups. Of note, mean number of hospitalizations in one year was higher in the control cohort (1.23 vs 3.8, p = .0001) while mortality rate at one, two, and three months and 1, 3, and 5 years was not significantly different between the two cohorts. The Hazard ratio (HR) for mortality was insignificant for NASH vs non-NASH (HR = .3694438, p = .159).

**Conclusions:** Our study revealed no difference in mortality nor cardiovascular/infection complications but an interesting difference in one-year hospitalizations and BMI. The retrospective nature of analysis and limited post-transplant follow-up period limit the study. A thorough cardiovascular assessment and careful patient selection in patients with metabolic syndrome could explain these findings. Larger patient samples with a longer follow-up period will be included in future publication to further investigate the cardiovascular complications and other post-transplant complications of NASH patients.

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## [30]
## SEMAGLUTIDE AND LANIFIBRANOR DIFFERENTIALLY ALTER MASH AND LIVER FIBROSIS IN DIET-INDUCED OBESE HAMSTERS WITH OR WITHOUT FREE ACCESS TO ALCOHOL.

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**Abstract Category:** Experimental/basic science, NAFLD/NASH, Non-Humans
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**Background/Aim:** GLP-1 receptor agonist semaglutide (SEMA) and pan-PPAR agonist lanifibranor (LANI) are currently evaluated in humans for metabolic dysfunction-associated steatohepatitis (MASH) treatment. While chronic alcohol intake may aggravate liver lesions in patients, rodent studies suggested that both GLP-1 and PPAR agonists reduce alcohol intake in mouse and rat, but these species are not truly alcohol dependent. The golden Syrian hamster spontaneously shows a high preference for alcohol and may represent a better animal model. Here we tested the effects of SEMA and LANI in diet-induced obese hamsters, a preclinical model with human-like MASH, with or without free access to alcohol.

**Methods:** Hamsters' preference for alcohol and selection of alcohol % in drinking water were first confirmed in pilot studies. Next, obesity and MASH were induced with a free choice diet, which presents hamsters with a choice between control chow or high fat/cholesterol diet, and normal water or 10% fructose water. After a 20-week diet induction, hamsters were maintained on the same diet with the 10% fructose water supplemented without or with 15% alcohol, and animals were simultaneously treated with vehicle, SEMA 0.06mg/kg s.c. QD or LANI 30mg/kg p.o. QD for 5 weeks.

**Results:** When no alcohol was provided, SEMA induced a 17% body weight loss ($p<0.01$ vs. vehicle) with a transient food intake lowering, but a continuous reduction in 10% fructose water intake and a higher normal water intake. Although SEMA did not reduce NAFLD Activity Scoring (NAS), including hepatocyte ballooning and fibrosis scores, it reduced liver triglycerides levels (-25%, $p<0.01$). When alcohol was provided, SEMA had similar effects on body weight, food intake and normal water intake, while it significantly reduced fructose and alcohol intake during the 5-week treatment. However, SEMA had no effect on NAS and did not lower hepatic triglycerides levels anymore. When no alcohol was provided, LANI induced body weight loss (-5%), a gradual reduction in 10% fructose water intake and a higher normal water intake. LANI reduced liver lipids levels, NAS, and fibrosis score (all $p<0.05$ vs. vehicle). As well, when alcohol was provided, LANI significantly reduced fructose and alcohol intake, liver lipids levels and NAS.

**Conclusion:** SEMA and LANI both reduced fructose and alcohol intake but had different effects on MASH and liver fibrosis in obese MASH hamsters. This preclinical model will help to evaluate drugs targeting MASH on alcohol intake and their potential benefits in humans.

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## [31]
## TARGETING EF-HAND DOMAIN FAMILY MEMBER D1 (EFHD1) IN LIVER DISEASE

David R. Eberhardt

**Abstract Category:** Experimental/basic science, NAFLD/NASH, Non-Humans

**Background:** Examining genes from GWAS offers potential liver disease treatments. EFHD1, a gene associated with liver injury biomarkers in multiple GWAS analyses, shows increased expression with higher serum biomarkers. EFHD1, a poorly studied mitochondrial $Ca^{2+}$-binding protein, has unknown regulatory mechanisms in liver function. We assessed whether inhibiting hepatic EFHD1 could treat metabolic liver disease.

**Methods:** EFHD1 is primarily expressed at low levels in hepatocytes of human and mouse livers, with little expression in other cell types. To study EFHD1 inhibition's effects on liver injury, we subjected wild-type and EFHD1 knockout (*Efhd1*-/-) mice to a high-fat diet (HFD).

**Results:** Following a HFD, hepatic EFHD1 levels increased in wild-type mice, while male *Efhd1*-/- mice gained less weight (10.6±1.6% less after 28 weeks), despite similar food intake, activity, and insulin resistance. RNA sequencing of *Efhd1*-/- livers from mice on an HFD showed significantly reduced inflammation-associated genes compared to wild-type mice, confirmed by histological analysis. We observed fewer large lipid droplets in *Efhd1*-/- hepatocytes (32.9±3.1% in WT; 21.1±3.5% in *Efhd1*-/-). Increased mitochondrial fission is linked to liver injury, and EFHD1 was found at ER-mitochondrial contact sites on the outer membrane. Remarkably, *Efhd1*-/- hepatocytes were approximately twice the size of control mitochondria and showed reduced remodeling after activating cytoplasmic $Ca^{2+}$ signals. This suggests interactions between EFHD1 and the mitochondrial fission/fusion machinery.

**Conclusions:** Deleting EFHD1 to reduce fission may prevent mitochondrial damage and subsequent liver injury. EFHD1 inhibition shows promise as a therapy for liver injury.

## [32]
## PRECLINICAL CHARACTERIZATION OF BI-FUNCTIONAL NK-AHSC ENGAGER FOR LIVER FIBROSIS

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**Abstract Category:** Experimental/basic science, NAFLD/NASH, Non-Humans
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**Background:** Activated Hepatic Stellate Cells (aHSC) are the primary source of hepatic myofibroblasts, which are the main contributors for liver fibrogenesis. Depletion of aHSC using either genetic manipulations or pharmacological approaches (e.g. ADC, CART) has consistently demonstrated anti-fibrosis effect in various animal models. However, these approaches have not been applied to clinical setting. To translate these findings, we have designed the antibody-based bi-functional NK-aHSC engagers. By harnessing the innate immune system in the liver, these molecules promote aHSC killing, which results in fibrosis amelioration in the animal models for liver fibrosis.

**Methods:** Targets that are highly expressed on aHSC cell surface were selected and the antibodies against these targets were identified. Based on anti-aHSC antibodies, bi-functional NK-aHSC engagers were designed by modulating Fc effector function or conjugating with an immune-activation moiety. The aHSC depletion activity of the engagers were characterized in *in vitro* ADCC cytotoxicity assay or phagocytosis assay. The anti-fibrosis activity of the engagers against one of aHSC targets, PDGFRβ, was evaluated in CCL4 or CDAA HFD diet-induced liver fibrosis models.

**Results:** *In vitro*, a panel of antibodies targeting to various aHSC targets have demonstrated potent and dose dependent aHSC killing activity in the presence of human NK cells. Additionally, the antibodies also promoted phagocytosis of aHSC cells by human macrophage. The Fc effector function was critical for the antibodies to exert aHSC killing activity. The immune-activation moiety on the bi-functional engagers could further enhance the killing. Anti-PDGFRβ antibodies were evaluated *in vivo*. In PK/PD study, single dose of anti-PDGFRβ antibody displayed time and dose dependent effect on multiple PD markers in the liver. In both CCL4 and CDAA HFD diet-induced liver fibrosis model, only anti-PDGFRβ antibodies/engagers with enhanced effector function had anti-fibrosis effect, demonstrating aHSC depletion activity was critical to inhibit fibrosis *in vivo*.

**Conclusions:** We have established a proprietary antibody-based platform for aHSC depletion. Preclinical characterization of tool molecules has demonstrated effective aHSC killing and anti-fibrosis activity. These results support the further development of the platform and the lead molecules for liver fibrosis, with the potential to further expand to other fibrotic disease indications.

**Abbreviations:** NK: Natural Killer; aHSC: Activated Hepatic Stellate Cell; HSC: Hepatic Stellate Cell; ADC: Antibody Drug Conjugate; CART: Chimeric Antigen Receptor T cells; ADCC: Antibody Dependent Cytotoxicity; CDAA: Choline Deficient L-Amino Acid-defined; HFD: High Fat Diet; PK: Pharmacokinetics; PD: Pharmacodynamics.

## [33]
## LYSOPHOSPHATIDIC ACID RECEPTOR 1 ANTAGONIST (EPGN2154) IMPROVES MURINE MASH.

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**Abstract Category:** Experimental/basic science, NAFLD/NASH, Non-Humans
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**Background/Aim:** Metabolic dysfunction-associated steatohepatitis (MASH) has become the second leading cause of liver transplantation in the USA. FDA has not approved any therapy for MASH to date, and the overall disease burden has increased. A Lysophosphatidic acid receptor 1 (LPAR1) antagonist (EPGN2154) has shown anti-fibrotic activity in preclinical kidney and liver disease models. A recent clinical trial in MASH using a glucagon-like peptide 1 (GLP-1) analogue (Semaglutide) has shown improvement in hepatic steatosis. In the present study, we have investigated the MASH remission potential of EPGN2154 and the combination of semaglutide (Sema) drug treatment on a preclinical MASH model.

**Methods: Experiment: 1)** 6-8 weeks old male C57BL6/J mice fed a high-fat, high-carbohydrate (HFHC) diet for 16 weeks. After 16 weeks, mice were randomly distributed into four experimental groups: (i) HFHC no drug treatment( HFHC), (ii) HFHC with EPGN2154 (oral gavage (p.o.)10mg/kg body weight/day; HFHC+2154), (iii) HFHC with Semaglutide (subcutaneous(s.c.) 6.17µg/kg body weight every alternate day; HFHC+Sema) and (iv) HFHC with combine EPGN2154 (p.o.10mg/kg body weight/day) and Semaglutide (s.c. 6.17µg/kg body weight every alternate day) (HFHC+2154+Sema). After 8 weeks of drug treatment, the mice were euthanized, and experimental readouts were recorded. **Experiment: 2)** 6-8 weeks old male ob/ob mice fed a trans-fat containing amylin liver NASH (AMLN) diet for 16 weeks. After 16 weeks, mice were randomly distributed into four experimental groups: (i) AMLN no drug treatment, (AMLN), (ii) AMLN with EPGN2154 (p.o.10mg/kg body weight/day; AMLN+2154), (iii) AMLN with Semaglutide (s.c. 6.17µg/kg body weight every alternate day; AMLN+Sema) and (iv) AMLN with combine EPGN2154 (p.o.10mg/kg body weight/day) and Semaglutide (s.c. 6.17µg/kg body weight every alternate day) (AMLN+2154+Sema). After 8 weeks of drug treatment, the mice were euthanized, and experimental readouts were recorded.

**Results: Experiment: 1)** After 8 weeks of treatment, combination therapy causes maximum body weight loss (HFHC+2154+Sema) (13.740±1.096g) and least adiposity (27.042±2.421%) among the HFHC-fed experimental groups. EPGN2154 and Sema treatment lower plasma alanine transaminase (ALT) and liver weight. EPGN2154 and Sema improved hepatic steatosis and fibrosis. **Experiment 2)** After 8 weeks of treatment, drug therapy did not cause body weight loss in ob/ob mice. EPGN2154 lowered hepatic steatosis and fibrosis in the AMLN-fed ob/ob mice. EPGN2154 decreases the expression of hepatic fibrosis markers like galectin-3 (Gal-3), collagen type I alpha 1 (Col1A1), and laminin (Lam). Sema did not lower hepatic steatosis, fibrosis, or expression of hepatic fibrosis markers in AMLN-fed ob/ob mice.

**Conclusions:** (i) EPGN2154 has shown reversal independent of body weight loss; (ii) the hepato-protective activity of Semaglutide is dependent on the body weight loss; and (iii) The additive effect of EPGN2154 and Semaglutide combination therapy is dependent on the body weight loss.

## [34]
## LANIFIBRANOR REVERSES HEPATIC AND PERIPHERAL INSULIN RESISTANCE, IMPROVES LIPID AND GLUCOSE METABOLISM IN PATIENTS WITH TYPE 2 DIABETES (T2D) AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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**Abstract Category:** Pathogenesis, Translational Science, NAFLD/NASH, Liver Fibrosis, Humans

**Background:** Lanifibranor, a pan-PPAR agonist, improves steatohepatitis and fibrosis in patients with nonalcoholic steatohepatitis (NASH) (NATIVE trial), but the mechanism of the effects are not fully elucidated. Insulin resistance (IR) has a central role in the cardiometabolic and liver health of patients with MASLD. We assessed the effect of lanifibranor on IR in liver, muscle and adipose tissue and on intrahepatic triglyceride (IHTG) content.

**Methods:** In this single-center study, 38 patients with T2D and MASLD were randomized 1:1 to lanifibranor 800 mg or placebo o.d. for 24 weeks (NCT03459079). Primary efficacy endpoint was IHTG change quantified by $^1$H-MRS from baseline to end of treatment (EOT). Secondary endpoints included: a) proportion of patients with ≥ 30% IHTG decrease; b) with steatosis resolution (≤5.5% IHTG); c) change in hepatic, muscle and adipose tissue IR using the euglycemic insulin clamp with stable 6-6$D_2$-glucose and indirect calorimetry; d) changes in HbA1c and lipid profile.

**Results:** Patient characteristics of Full Analysis Set [FAS]): mean±SD age: 60±9 years, HbA1c: 6.9±0.7%, weight: 97±17 kg, BMI: 34±6 kg/m2, 37% male; 87% Caucasian; IHTG content: 19.6±7.1%; 28 completers (14 per arm). Lanifibranor compared to placebo significantly lowered IHTG at EOT (FAS -44% vs. -12%, respectively; least squares [LS] means difference -31%, 95% CI -51 to -12%; completers -50% vs. -16%; both p<0.01. At EOT, more patients reached ≥30% IHTG reduction with lanifibranor compared to placebo (FAS 65% vs. 22%; completers 79% vs. 29%; both p<0.01), and steatosis resolution (FAS 25% vs. 0%; p<0.05). Lanifibranor significantly improved hepatic and peripheral IR: fasting hepatic glucose production, hepatic IR index, and insulin-stimulated muscle glucose disposal. Secondary metabolic endpoints also improved: fasting plasma insulin/glucose concentration and HOMA-IR; HbA1c; plasma HDL-C, >2-fold adiponectin increase (p<0.001). Compared to placebo, lanifibranor caused modest weight gain (+2.7%), and in 1 patient mild edema. Adverse events were mild (GI side effects, hemoglobin decrease) and drug-related TEAE leading to discontinuation were balanced between groups.

**Conclusions:** Lanifibranor therapy significantly improves hepatic and peripheral insulin sensitivity, resulting in improved lipid and glucose metabolism and IHTG reduction, confirming its cardiometabolic benefits. Treatment with lanifibranor was well tolerated.

(Presented at The Liver Meeting, AASLD, November 2023)

## [36]
## ORAL $\alpha_v\beta_6/\alpha_v\beta_1$ INTEGRIN INHIBITION IN PRIMARY SCLEROSING CHOLANGITIS: 12-WEEK INTERIM SAFETY AND EFFICACY ANALYSIS OF INTEGRIS-PSC, A PHASE 2A TRIAL OF BEXOTEGRAST

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**Abstract Category:** Pathogenesis, Translational Science, NAFLD/NASH, Liver Fibrosis, Humans
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**Background:** There is no approved medical therapy for patients with primary sclerosing cholangitis (PSC). In PSC, integrins expressed on cholangiocytes ($\alpha_v\beta_6$) and myofibroblasts ($\alpha_v\beta_1$) regulate transforming growth factor-β (TGF-β) activity, a key driver of fibrosis. Bexotegrast (BEXO) is an oral, once-daily inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ in development for PSC. INTEGRIS-PSC is an ongoing, double-blind, dose-ranging, randomized, placebo-controlled Phase 2a study of BEXO in patients with PSC and evidence of liver fibrosis evaluating safety, tolerability, pharmacokinetics, and effects on markers of fibrosis (enhanced liver fibrosis [ELF] and N-terminal type III collagen propeptide [PRO-C3]).

**Methods:** The study had a 3:1 (BEXO:placebo) randomization and stratification by ursodeoxycholic acid (UDCA) use; with doses of 40mg, 80mg or 160mg evaluated over a 12-week treatment period. A 320mg dose cohort is ongoing and will be evaluated over 24-48 weeks. Key entry criteria included: large duct PSC with stable inflammatory bowel disease, if present, and liver fibrosis (without cirrhosis) as evidenced by ≥1: ELF ≥ 7.7, liver stiffness by transient elastography (TE) ≥8 kPa or magnetic resonance elastography ≥2.4 kPa or historical biopsy.

**Results:** At Baseline (n=85), the mean age was 45y, 75% male, 65% on concomitant UDCA for the entire cohort. Baseline characteristics (mean (standard deviation)) included: alkaline phosphatase 264 (152) U/L, bilirubin 0.8 (0.4) mg/dL, TE 9.0 (2.9) kPa, ELF 9.4 (0.92) and PRO-C3 47.1 (23.12) ug/mL; BEXO-treated and placebo groups were comparable. Incidence of treatment emergent adverse events (TEAE) and study discontinuations was not significantly different between BEXO-treated or placebo groups. Most common TEAEs were (BEXO/placebo %) pruritus (14/24), fatigue (14/9), headache (9/19) and nausea (9/0). Rates of cholangitis were lower with BEXO (14/3). No serious TEAEs were deemed related to BEXO. At Week 12, mean change in ELF score with the 160 mg group was 84% lower compared to placebo (p<0.05). Similar findings were observed for PRO-C3.

**Conclusions:** In this 12-week interim analysis of Bexotegras, an oral $\alpha_v\beta_6/\alpha_v\beta_1$ inhibitor, safety and tolerability in PSC were similar to placebo. Increases in ELF scores and PRO-C3 observed in the placebo group, in this fibrosis-enriched population, were attenuated by BEXO at all doses with statistical significance observed with 160 mg. This analysis supports proof of mechanism for antifibrotic activity of BEXO in PSC. *Abstract previously presented at AASLD 2023*.

## [37]
## INHIBITION OF INTEGRIN $\alpha_v\beta_1$ ATTENUATES PROFIBROGENIC GENE EXPRESSION BY MYOFIBROBLASTS IN FIBROTIC HUMAN LIVER EXPLANTS

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**Abstract Category:** Pathogenesis, Translational Science, NAFLD/NASH, Liver Fibrosis, Humans

**Background:** Integrin $\alpha_v\beta_1$ is a (myo)fibroblast-specific integrin that activates transforming growth factor (TGF)-β, promoting fibrogenesis. Inhibition of $\alpha_v\beta_1$ is antifibrotic in mouse models of liver fibrosis; however, data in human tissue are limited. Precision-cut liver slices (PCLivS) bridge the gap between cell-based models and *in vivo* models of liver fibrosis, providing a translational assay platform for investigating fibrogenesis in small sections of intact fibrotic human tissue cultured *ex vivo*. Here we use human PCLivS and single nuclei RNA-Seq (snRNA-Seq) to evaluate the effects of an $\alpha_v\beta_1$-selective inhibitor on individual cell populations present in fibrotic human liver tissue.

**Methods:** Human liver tissue with or without evidence of fibrosis (fibrotic and normal, respectively) was obtained from rejected organ donors. PCLivS were generated from fibrotic liver tissue and cultured for 2 days in the presence of a selective $\alpha_v\beta_1$ inhibitor, a TGF-β receptor I kinase inhibitor (ALK5i; R-268712) or vehicle (dimethylsulfoxide - DMSO). Intact nuclei were isolated from slices using a combination of detergent-based lysis, mechanical disruption, and filtration. Transcriptomic analysis of PCLivS single nuclei was performed using 10x Chromium Next GEM 3' technology. Custom annotation of cell types was performed using gene markers established from recently published data sets. Integrin $\alpha_v\beta_1$ protein levels in donor tissues were quantified by custom Meso Scale Discovery electrochemiluminescence assay.

**Results:** Fibrotic livers had elevated $\alpha_v\beta_1$ protein concentrations relative to normal livers. Sequencing of single nuclei isolated from cultured PCLivS identified multiple unique cell populations, with hepatocytes, cholangiocytes, myofibroblasts, and endothelial cells comprising the most abundant annotated clusters. Differential gene expression analysis on the myofibroblast cluster showed $\alpha_v\beta_1$ inhibition significantly reduced *COL1A1* expression (false discovery rate<0.05) as well as several other genes related to collagen-containing extracellular matrix (GO:0062023) such as *BGN*, *GREM1*, and *CTHRC1*. Overlap in the specific genes downregulated by $\alpha_v\beta_1$ inhibition and ALK5i was observed, with a similar degree of effect from $\alpha_v\beta_1$ inhibition and complete TGF-β signaling inhibition with ALK5i.

**Conclusion:** Treatment of fibrotic human PCLivS with an $\alpha_v\beta_1$ inhibitor resulted in clear reductions in profibrogenic gene expression by myofibroblasts. The overlap with the effect of ALK5i demonstrates the importance of the $\alpha_v\beta_1$ integrin-TGF-β activation pathway in fibrotic liver disease. These data support $\alpha_v\beta_1$ integrin inhibition as a promising approach for targeted inhibition of TGF-β signalling in fibrotic liver disease.

Abstract previously presented at AASLD 2023

## [38]
## POSTPRANDIAL PLASMA PROTEOMICS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE.

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**Abstract Category:** Pathogenesis, Translational Science, NAFLD/NASH, Liver Fibrosis, Humans
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**Background/Aim:** The accumulation of liver fat, the hallmark of metabolic dysfunction- associated steatotic liver disease (MASLD), reflects an imbalance of energy availability and utilization across the liver. Most human studies focus on long-term energy imbalance and the fasting state, while the acute alterations of metabolism after a single caloric load are relatively unstudied. We have previously identified unique dysregulation of postprandial plasma lipidome in subjects with MASLD. Beyond changes in energy substrates, the postprandial period is also characterized by dynamic hormonal and signaling processes. We therefore aimed to identify postprandial changes in plasma proteome that are unique to MASLD as a tool to explore disease pathophysiology.

**Methods:** A single-center prospective study (NCT02520609). Subjects with MASLD and healthy controls were fed a standardized liquid mixed meal (Ensure Plus). Plasma and serum samples were obtained at fasting, 30 min, 1, 2 and 4 hours after the meal. The plasma proteome was assessed using the SomaScan assay. Key proteins identified by SomaScan were validated by ELISA. Repeated measures ANOVA for group (MASLD vs. control), time, and interaction was used to assess temporal patterns. KEGG database used for pathway analysis.

**Results:** In 37 subjects with MASLD and 10 controls, 1317 unique proteins could be quantified with SomaScan. Of these, 42 plasma proteins were significant for interaction, i.e. had postprandial temporal patterns that significantly differed between MASLD and controls, independently of fasting levels. Pathway analysis revealed enrichment of pathways in energy metabolism (as anticipated), cytokine signaling, complement cascade and acute phase reaction, most likely derived from the liver. Key proteins IGFBP1, IGFBP7, leptin R, hepcidin, CCL16, CCL21, CCL23, ST2/IL-33R, and TNFRSF1B were validated using ELISA. The pattern of postprandial changes in IGFBP1, CCL16, and CCL23 differed significantly between the groups, where subjects with MASLD demonstrated a blunted postprandial response compared to controls.

**Conclusions:** In this first study in humans exploring the postprandial plasma proteome in MASLD we demonstrated blunting of the physiological postprandial changes in plasma levels of IGFBP1, a binding protein for insulin-like growth factors, and of the chemokines CCL16 and CCL23. Our findings suggest impaired compensatory mechanisms in MASLD after a meal.

## [39]
## THE CROSS-LINKED TYPE III COLLAGEN BIOMARKER, CTX-III, REFLECTS FIBROSIS RESOLUTION AND IS RELATED TO INTERVENTION AND SURVIVAL IN CHRONIC LIVER DISEASE

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**Abstract Category:** Pathogenesis, Translational Science, NAFLD/NASH, Liver Fibrosis, Humans

**Background & Aims:** The liver extracellular matrix (ECM) is a scaffold of proteins and glycans supporting and regulating all liver cells. Progressing liver fibrosis results in a change of liver structure with increased ECM deposition. Thus, regression of fibrosis, upon insult removal or therapy, should tilt the balance towards ECM degradation. As therapies against fibrosis advance, biomarkers to prognosticate and monitor fibrosis regression become a necessity. Here, we aimed to investigate whether a MMP degraded and cross-linked fragment of type III collagen, called CTX-III, could 1) mark decreasing disease activity and fibrosis regression following intervention and 2) predict survival in chronic liver disease.

**Approach & Results:** We confirmed *in vitro* that CTX-III is present in human liver tissue segments (healthy n=1; diagnosed with steatohepatitis n=2; steatohepatitis and bridging fibrosis n=2; steatohepatitis, ballooning and bridging fibrosis n=1), with higher levels in diseased tissue. Then, we assessed the monitoring properties of CTX-III in a cohort of 65 patients with non-alcoholic fatty liver disease (NAS Score 0 points=0 patients; 1=6; 2=19; 3=16; 4=10; 5=13; 6=1; 7=0, 8=0) and liver fibrosis (F0=1; F1=55; F2=8; F3 and F4=0) (undergoing bariatric surgery with blood samples taken at 3-, 6-, and 12-months follow-up. We found a 23% (IQR 4-63%) median CTX-III increase after surgery ($p \leq 0.001$), while PRO-C3 showed a non-significant increase ($p=0.161$). CTX-III increase coincided with decreases in body mass index and liver enzymes (ALT $p=0.006$; GGT $p=<0.001$). We then measured CTX-III and PRO-C3 in a cohort of 86 patients with decompensated cirrhosis receiving transjugular intrahepatic porto-systemic shunt. A CTX-III:PRO-C3 ratio below the median was associated with shorter transplant-free survival (Hazard ratio 1.69, 95% CI 1.02-2.86; $p=0.04$) in these patients.

**Conclusions:** *In vitro*, increased CTX-III presence suggests diseased ECMs are richer in crosslinked collagen. When measured in patients undergoing bariatric surgery, CTX-III levels suggest therapy increased ECM degradation, and thus CTX-III potential as a monitoring biomarker associated with liver structure remodeling. Additionally, assessing both ECM formation (PRO-C3) and degradation (CTX-III) might aid in better prognosis stratification in patients with decompensated cirrhosis.

## [40]
## LIVER FIBROSIS IS ASSOCIATED WITH CLINICAL AND ECONOMIC BURDEN OF CARDIOVASCULAR DISEASE AMONGST PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS: THE UNCOVER-NASH LONGITUDINAL COHORT STUDY

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**Abstract Category:** Pharmacoeconomic / Societal Aspects

**Background/Aim:** The clinical and economic burden of cardiovascular (CV) disease (CVD) in patients with non-alcoholic steatohepatitis (NASH) is incompletely understood. This study addresses this knowledge gap in patients with NASH without cirrhosis stratified by Fibrosis-4 Index (FIB-4) using real-world US healthcare data (TriNetX).

**Methods:** Patients (aged ≥18 years) were identified using the International Classification of Diseases code (ICD-10-CM) for NASH from October 2015 to June 2022 and required: ≥1 FIB-4 measurement(s) calculated from data obtained 180 days prior to, or 30 days after, NASH diagnosis (index date); ≥12 months of data prior to index date (baseline period); and no evidence of cirrhosis during baseline or at index date. FIB-4 score categories were low (<1.30), intermediate (1.30–2.67), and high (>2.67). Baseline characteristics and prevalence (during baseline), and incidence and economic burden of CVD during follow-up (index date to end of enrollment, death, or study end) were analyzed. Incidence was assessed in patients with no history of CV events. CVD-related economic burden was estimated by total healthcare cost (medical and pharmacy cost from claims data) and resource utilization (type of visit and length of stay from electronic health records) amongst patients with ≥6 months of follow-up data available.

**Results:** Of 717 patients included, 102 had high, 201 had intermediate, and 414 had low FIB-4. Mean age was 60, 57, and 44 years, respectively, and most were female (71%, 54%, and 57%, respectively). Cumulative incidence (using Aalen-Johansen curve, not shown) and incidence rate (per 100 person-years; Table) of any CV event increased with FIB-4 score. Risk of CV events was higher for high and intermediate vs low FIB-4 and remained significant for high vs low FIB-4 after adjustment for CV risk factors (Table). Similar results were obtained for individual CV events. CV-related resource utilization increased with FIB-4 score (length of stay: 12.7, 2.5, and 1.5 days; inpatient visits: 1.0, 0.5, and 0.3 per person per year [PPPY] for high, intermediate, and low FIB-4, respectively). Total healthcare and medical costs were higher for high vs low FIB-4 ($7,775 vs $1,828 [p<0.0001] and $7,228 vs $1,661 [p<0.0001] PPPY, respectively; Table).

**Conclusions:** Clinical and economic burden of CVD in patients with NASH without cirrhosis was higher in those with higher baseline FIB-4 score, indicating a direct relationship between CV-related burden and hepatic fibrosis.

**Table: Incidence and CV-related healthcare cost at follow-up**

| Outcome | Low FIB-4 (<1.3) | Intermediate FIB-4 (1.30–2.67) | High FIB-4 (>2.67) |
|---|---|---|---|
| N | 318 | 145 | 66 |
| Incidence rate of any CV event | 10.4 | 17.2 | 24.6 |
| HR (95% CI) vs low FIB-4 | — | 1.53 (1.01, 2.23) | 3.43 (2.21, 5.31) |
| p value | — | 0.0422 | <0.0001 |
| Adjusted HR* (95% CI) vs low FIB-4 | — | 0.87 (0.55, 1.37) | 2.05 (1.23, 3.41) |
| p value | — | 0.54 | 0.006 |
| N | 335 | 166 | 78 |
| Total healthcare costs, $ PPPY | 1,828 | 3,241 | 7,775 |
| Estimate (95% CI) vs low FIB-4** | — | 1.4 (0.93, 2.1); | 3.93 (2.32, 6.63) |
| p value | — | 0.1074 | <0.0001 |
| Medical costs, $ PPPY | 1,661 | 3,081 | 7,228 |
| Estimate (95% CI) vs low FIB-4** | — | 1.48 (0.95, 2.31) | 4.08 (2.32, 7.16) |
| p value | — | 0.08 | <0.0001 |
| Pharmacy costs, $ PPPY | 167 | 161 | 547 |
| Estimate (95% CI) vs low FIB-4** | — | 1.0 (0.64, 1.57) | 3.05 (1.59, 5.86) |
| p value | — | 0.9879 | 0.0008 |

Incidence rate of any CV event (atrial fibrillation and flutter, angina pectoris, cardiac arrest, deep vein thrombosis, heart failure, ischemic heart disease, atherosclerosis, cerebrovascular disease, and peripheral artery disease) by FIB-4 risk category was calculated per 100 person-years. HRs were estimated using a Cox proportional hazard model. Generalized linear models with log link were used to compare healthcare cost (using gamma distribution) and resource utilization and length of stay (using negative binomial distribution). Total healthcare cost included medical and pharmacy costs.

*HRs were adjusted for age, sex, and comorbidities (T2D, hyperlipidemia, hypertension, chronic kidney disease, and obesity).

**Estimates were adjusted for age, sex, comorbidities (T2D, hyperlipidemia, hypertension, chronic kidney disease, and obesity), race, type of insurance, and number of distinct baseline CV-related inpatient events in the last 6 months.

CI, confidence interval; CV, cardiovascular; FIB-4, Fibrosis-4 Index; HR, hazard ratio; PPPY, per person per year; T2D, type 2 diabetes.

## [41]
## ENHANCING ASCVD RISK PREDICTION IN NASH/NAFLD PATIENTS

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**Abstract Category:** Pharmacoeconomic / Societal Aspects

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**Background/Aim:** Non-alcoholic steatohepatitis (NASH), also known as metabolic dysfunction-associated steatohepatitis, and non-alcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated steatotic liver disease, are linked to increased cardiovascular disease (CVD) risks. The American Heart Association's (AHA) Atherosclerotic Cardiovascular Disease (ASCVD) Risk Estimator Plus lacks validated efficacy for mortality prediction in NASH/NAFLD patients suggesting that additional variables may be required to enhance the accuracy. This study aims to augment the predictive accuracy of ASCVD risk among this demographic by proposing an alternative logistic regression model.

**Methods:** A retrospective dataset from a large US integrated delivery network health system encompassing multiple sites within the US was curated. A 9,185 patient cohort of biopsy confirmed NASH patients was curated using structured and unstructured data. Demographic, clinical, and laboratory variables underwent a recursive feature elimination process. The variables were constrained to be within 30 days of the NASH diagnosis, and the outcomes were limited to within 10 years and censored by the last available data. The performance of the AHA's ASCVD Risk Estimator Plus was compared against our model, which incorporated alternative predictors. The Area Under the Receiver Operating Characteristic curve (AUC) was employed to evaluate and compare both models. A survival curve was generated and evaluated for statistical significance at a predetermined alpha of 0.05.

**Results:** The ASCVD Risk Estimator Plus demonstrated suboptimal predictive accuracy for mortality and myocardial infarction (MI) events in NASH/NAFLD patients (AUC of 0.63). In contrast, our logistic regression model exhibited a higher AUC (0.67), indicating enhanced predictive accuracy. The inclusion of liver-specific markers, such as alanine aminotransferase and other novel predictors such as INR help to achieve greater accuracy. A Kaplan-Meier survival analysis for 10-year MI risk was generated to evaluate the prediction over 10 years. Pearson's chi-squared test yielded a statistic of 127.22 (p=1.67e-29). These findings underscore the potential limitations of the ASCVD Risk Estimator Plus in predicting outcomes for NASH/NAFLD patients and highlight the significance of incorporating liver-specific markers and novel predictors for more accurate risk assessment, which could lead to improved clinical decision-making and patient management strategies in this population.

**Conclusions:** Our findings underscore the necessity of revisiting the current CV risk models for NASH/NAFLD patients to incorporate more holistic and disease-specific variables. The proposed logistic regression model that includes liver-specific biomarkers improves the prediction of cardiovascular mortality and MI events, thereby facilitating better clinical decision-making and patient-centered care.

## [42]
## LOW IMMUNOGENICITY RATES IN PHENOTYPIC NASH PATIENTS TREATED FOR 12 WEEKS WITH ONCE-MONTHLY AND BI-WEEKLY SUBCUTANEOUS DOSING OF BOS-580

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**Abstract Category:** Pharmacology
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**Background:** Anti-drug antibodies (ADA) are a clinical measure of therapeutic protein immunogenicity. Immune response to protein therapeutics can alter or reduce their efficacy and may be associated with adverse effects. BOS-580 is a dimer of human FGF21-IgG fusion protein, highly engineered with a unique disulfide bond, and expressed in a mammalian cell line to assure proper glycosylation to enable extended protein stability, circulating half-life, and reduced immunogenicity. In a Phase 1 study, BOS-580 showed a dose-proportional increase in exposure with a half-life of about 21 days, suggesting the feasibility of once-monthly or bi-weekly dosing. Here, we report the immunogenicity of BOS-580 in a randomized, double-blind, placebo-controlled Phase 2a study.

**Methods:** The study was designed to examine the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of a range of doses and dosing frequencies in a 12-week treatment period. This study enrolled 102 patients, 37 and 65 patients in the placebo and active drug groups, respectively. The immunogenicity of BOS-580 was evaluated using a validated immunoassay method for the detection, confirmation, and titration of ADA. The assay can detect both anti-BOS-580 and antibodies against endogenous FGF21 in human serum. Samples were collected on days 1, 29, 57, 85 and 113 for each patient and those that tested positive in the initial screening step were subsequently evaluated in a competition assay using either BOS-580 or human FGF21.

**Results:** In total 13.5% of patients in the placebo group and 13.9% in the active group were confirmed positive for the presence of ADA. Of these, 8.1% (placebo group) and 4.6% (active group) confirmed positive for anti-BOS-580 antibody and 13.5% (placebo group) and 12.3% (active group) confirmed positive for anti-FGF21 (Table 1). Overall, the ADA responses were generally transient with low titers <1:40. The similar abundance of ADA in the placebo and active groups may be due to the high sensitivity of the ADA assay (detection limit 1:10). Only one patient (1/65; <2%) in an intermediate dose group (75mg Q2W) appeared to have treatment-emergent ADA with titer increasing >50% in 2 consecutive measures (maximal titer 1:128). The PK (serum BOS-580 levels) and PD (adiponectin, hepatic fat fraction, ALT and AST, PRO-C3) responses of this patient were similar to the mean values from all patients in the same cohort, indicating no impact of immunogenicity on the PK or PD. This patient did not experience any adverse events that may suggest any immune-mediated effect.

**Conclusions:** BOS-580 shows low immunogenicity and there was no impact of ADA on PK or PD in the one patient who showed the presence of treatment-emergent ADA.

Table 1: ADA data summary for BOS-580 from BOS-580-201 Part A study

| Number of Subjects | | Total Confirmed ADA Positives | | Anti-BOS-580 ADAs | | Anti-FGF21 ADAs | |
|---|---|---|---|---|---|---|---|
| | | No. of Patients | % of Patients | No. of Patients | % of Patients | No. of Patients | % of Patients |
| Placebo | 37 | 5 | **13.5** | 3 | **8.1** | 5 | **13.5** |
| Active | 65 | 9 | **13.9** | 3 | **4.6** | 8 | **12.3** |

This abstract has not been presented elsewhere.

## [43]
## THE SMALL MOLECULE COMPETITIVE INHIBITOR OF ATP CITRATE LYASE, EVT0185, REVERSES LIVER FIBROSIS IN PRECLINICAL MOUSE MODELS BY TARGETING HEPATIC STELLATE CELLS.

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**Abstract Category:** Pharmacology

A key driver of liver fibrosis is activated hepatic stellate cells (HSCs). Like cancer cells, activation of HSCs is linked to changes in aerobic glycolysis, denovo lipogenesis, and free cholesterol; metabolic pathways that are thought to support the HSC proliferation and secretion of extracellular matrix and cytokines. Phenotypic screening in primary mouse hepatocytes identified EVT0185 as a novel small molecule inhibitor of denovo lipogenesis in hepatocytes that competitively inhibits ACLY activity in cell-free assays. Using three distinct preclinical mouse models of Non-Alcoholic Steatohepatitis (NASH), oral delivery of EVT0185 dose-dependently reversed steatosis and ballooning but also effectively reversed fibrosis. This effect on reducing NASH and fibrosis was associated with lower serum triglycerides, cholesterol, and insulin and was independent of changes in adiposity/body weight. Importantly, this reduction in fibrosis was not dependent on delipidating hepatocytes, as effects were also observed in a model not characterized by steatosis, suggesting potentially direct effects on hepatic stellate cells. Consistent with this mechanism of action, RNA sequencing of liver from EVT0185 treated mice revealed marked downregulation of collagen synthesis, ECM (Extracellular Matrix) synthesis, chemokine and cytokine signaling, and angiogenesis while upregulating pathways related to fatty acid metabolism. Treatment of HSCs activated by TGF-β with EVT0185 lowered denovo lipogenesis, proliferation, αSMA, and collagen production; effects that were mirrored by the genetic knockdown of ACLY. These data indicate that EVT0185 directly inhibits HSC activation and effectively reduces steatosis and ballooning while reversing fibrosis without ensuing hypertriglyceridemia supporting potential evaluation in clinical populations.

## [44]
## IMPROVEMENTS IN LIVER FIBROINFLAMMATION (AS ASSESSED BY CORRECTED T1 [CT1]) WITH HTD1801 (BERBERINE URSODEOXYCHOLATE) TREATMENT IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS AND TYPE 2 DIABETES MELLITUS

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**Abstract Category:** Therapeutic Trials NASH/Liver Fibrosis
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**Background:** HTD1801 is a new molecular entity consisting of an ionic salt of berberine and ursodeoxycholic acid with a unique microstructure which has been shown to significantly reduce liver fat content (LFC) as determined by MRI-PDFF in an 18-Week, placebo-controlled Phase 2 study in patients with nonalcoholic steatohepatitis (NASH) and type 2 diabetes (T2DM) (NCT03656744). cT1 is an MRI-based quantitative metric for assessing liver inflammation and fibrosis. Previous studies have reported that cT1 improvements are moderately correlated with histologic improvements in NAS and fibrosis and cT1 levels are associated with clinical outcomes (liver and CVD) in patients with NASH. The purpose of this post-hoc analysis was to evaluate the effects of HTD1801 on cT1 in patients with NASH and T2DM.

**Methods:** One hundred patients were randomized and treated with HTD1801 1000 mg BID (n=34), HTD1801 500 mg BID (n=33), or placebo (n=33) for 18 weeks. MRI data was collected prospectively for evaluation of the primary endpoint (proton density fat fraction), and cT1 was evaluated after the completion of the study for subjects who had been randomized to HTD1801 1000 mg BID or placebo. P-values (nominal) were obtained from an ANCOVA model with treatment group as a fixed effect, and baseline ALT and baseline cT1 as covariates. Values are Mean (SD) unless otherwise specified.

**Results:** On average at baseline, patients were 56 (11) years, 72% female, 91% White, 38% Hispanic or Latino, with an HbA1c of 7.1% (1.0). At baseline, subjects had significantly elevated LFC by MRI-PDFF [19.3% (6.5)] and fibroinflammation by cT1 (942.1 [91.5] ms and 937.5 [97.7] ms for HTD1801 1000 mg BID and placebo, respectively). After 18 weeks of treatment there was a significant reduction in cT1 with HTD1801 compared to placebo (-60.9 [75.9] ms vs -14.7 [68.9] ms, $p<0.05$). Similarly, a significant reduction was observed in ALT, a marker of liver function, in the HTD1801 1000 mg BID group compared to placebo (-19 [27.2] U/L vs -3 [19.2] U/L, $p<0.01$). At Week 18, a larger proportion of subjects receiving HTD1801 compared to placebo (39% vs 16%, respectively) experienced at least an 80 ms reduction in cT1, which has been correlated with a 2-point reduction in the NAS.

**Conclusions:** These data provide further evidence that HTD1801 may improve measures of disease activity in patients with NASH and T2DM and warrant further investigation. A Phase 2b study is currently ongoing to evaluate the histologic effects of HTD1801 in patients with NASH and confirm the findings of this evaluation (NCT05623189).

*Previously presented at the European Association for the Study of the Liver (EASL) 2023 in Vienna, Austria.*

## [45]
## PLN-1474, AN ORAL, SELECTIVE $\alpha_v\beta_1$ INTEGRIN INHIBITOR IS WELL TOLERATED IN HEALTHY VOLUNTEERS

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**Abstract Category:** Therapeutic Trials NASH/Liver Fibrosis
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**Background:** Integrin $\alpha_v\beta_1$ is expressed on hepatic stellate cells and activates transforming growth factor beta, a key driver of liver fibrosis. Integrin $\alpha_v\beta_1$ and down-stream pSMAD pathways are upregulated in human metabolic dysfunction-associated steatohepatitis (MASH) samples and mouse models. PLN-1474 is an oral and selective inhibitor of integrin $\alpha_v\beta_1$ that has demonstrated antifibrotic activity in a mouse model of MASH, as well as in cirrhotic precision-cut liver slices generated from livers of patients with MASH. The aim of this study was to assess the safety, tolerability, pharmacokinetics (PK) and food effect of PLN-1474 in healthy participants.

**Methods:** PLN-1474-101 was a first-in-human, randomized, placebo-controlled Phase 1 study. 40 participants received single ascending doses from 30 to 750 mg (n=6 per cohort), or placebo (n=2 per cohort), and 32 participants received multiple ascending doses (60 to 375 mg BID or 750 mg QD) (n=6 per cohort), or placebo (n=2 per cohort), for 7 days. Further, twelve participants received 100 mg both in the fed and fasted state to evaluate the effect of food on PK.

**Results:** The majority of treatment-emergent adverse events (TEAEs) were mild (Grade 1) and none were severe (≥ Grade 3). There were no discontinuations due to TEAE and no serious TEAEs. The most common TEAEs were headache (n=5), rash papular (n=3), pruritus (n=2), constipation (n=2) and arthralgia (n=2). There was no dose relationship for TEAEs, no notable changes in clinical laboratory values, vital signs, electrocardiograms, or physical examinations. PLN-1474 was rapidly absorbed and achieved maximum concentrations within approximately 1 hour of dosing; its mean half-life ranged from approximately 5 to 17 hours. Increases in exposure (area under curve and $C_{max}$) were slightly less than dose proportional. Concentration-heart rate corrected QT interval (QTc) analysis demonstrated no effect of PLN-1474 on corrected QT interval by Fredericia (QTcF) interval. No meaningful effect of food on drug exposure was observed. Following single doses of PLN-1474, mean cumulative excretion in urine over a 36-hour sampling period ranged from approximately 32% and 40%.

**Conclusions:** PLN-1474 is a novel selective $\alpha_v\beta_1$ integrin inhibitor that was readily absorbed and well tolerated in healthy participants following single and multiple oral doses up 750 mg per day. Findings from this first-in-human study warrant the evaluation of PLN-1474 in patients with MASH and advanced liver fibrosis.

*Abstract has not been presented previously.*

## [47]
## HEPATIC FUNCTIONAL IMPROVEMENT DETECTED BY HEPQUANT DUO WITHIN 120 DAYS OF TREATMENT WITH RENCOFILSTAT IN MASH SUBJECTS WITH ≥F3 FIBROSIS

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**Abstract Category:** Therapeutic Trials NASH/Liver Fibrosis

**Background:** Rencofilstat (RCF), a non-immunosuppressive cyclophilin inhibitor, has been found to reduce levels of collagen biomarkers associated with fibrosis (ProC3) and serum transaminases (ALT and AST), markers of liver damage. The effects of RCF on hepatic function and portal-systemic shunting were examined in ≥F3 NASH subjects using the HepQuant DuO test. Other objectives of the study were to assess safety, tolerability, and pharmacokinetics of RCF.

**Results:** Baseline data demonstrated: Agile 3+ 0.73 (0.39), FibroScan 15.1 (2.68), ELF 9.67 (0.93), ALT 43.3 (6.0), and ProC3 38.4 (4.1). After 120 days of treatment with RCF 225 mg QD, HepQuant Disease Severity Index (DSI) decreased from 16.44 (3.3) to 14.79 (3.4) ($p < 0.05$) with 60% experiencing a 2-point or greater decrease, and portal-systemic shunting (SHUNT%) decreased from 24.98 (4.9) to 23.15 (4.6)%. Hepatic Reserve increased from 87.64% (7.5) to 91.60% (7.5) ($p<0.05$) with increases in both portal and systemic hepatic filtration rates. These changes were associated with a decrease in estimated risk for clinical events per person year from 2.41 to 1.92 ($p< 0.001$). The most functionally impaired subjects (baseline DSI >18.3) had higher response rates.

The 225 mg RCF group after 120 days treatment demonstrated absolute change from baseline in FibroScan of -6.02 (5.42) ($p < 0.0001$), ALT -12.10 (24.1), ELF -0.25 (0.67), and ProC3 -1.65 (9.28). When data were stratified by baseline ProC3 ≥ 37.5 ng/mL, indicative of more advanced fibrosis, the absolute change from baseline improved to: ALT -27.67 (37.7), ELF -0.50 (0.84), and ProC3 -8.65 (12.87) (all $p <0.05$ by Friedman ANOVA). While stratification by ProC3 significantly increased biomarker response, it did not alter HepQuant Duo and FibroScan results. Agile 3+ increased in the ProC3 stratified group to 0.81 (0.13). Treatment with RCF at all doses was well-tolerated and safe, with 38 treatment-related AEs in the trial. No subjects discontinued the trial due to treatment-related AE, and only 1 treatment-related AE was > Grade 2. There was no relationship between AEs and RCF dose level.

**Conclusions:** RCF 225 mg QD for 120 days improved hepatic function and reduced portal-systemic shunting as assessed by HepQuant DuO test. Traditional MASH biomarkers improved, with the greatest effect observed on FibroScan. RCF was safe and well tolerated at daily doses up to 225 mg.

A version of this abstract was presented as a poster at the American Association for the Study of Liver Diseases (AASLD) Annual Conference, November 2023.

## [48]
## MIRICORILANT REDUCED LIVER FAT AND CARDIOMETABOLIC DISEASE MARKERS IN A PHASE 1B, OPEN-LABEL DOSE-FINDING STUDY IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS (NASH)

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**Abstract Category:** Therapeutic Trials NASH/Liver Fibrosis
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**Background:** Miricorilant has a novel mechanism of action as a nonsteroidal selective glucocorticoid receptor modulator (SGRM) with high activity in the liver. In a phase 2a trial, 4 patients (pts) with presumed NASH taking miricorilant (600 or 900 mg daily) had rapid reductions in liver fat content (LFC) of 39–74% after ~4 weeks of treatment; however, improvement was accompanied by increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST). No pts met Hy's Law criteria, and transaminase elevations resolved after miricorilant was discontinued. Our objective was to evaluate if significantly lower doses and intermittent dosing of miricorilant can gradually reduce LFC without a corresponding rise in liver enzymes.

**Methods:** This phase 1b, open-label trial (NCT05117489) of adult pts with presumed NASH included 10 cohorts of pts who received miricorilant doses ranging from 30 to 200 mg with intermittent or daily regimens for 12 or 24 weeks. The primary endpoint was change in LFC from baseline by MRI-PDFF.

**Results:** 63 pts were enrolled, with a mean age of 51.3 years, 60.3% female, mean body mass index of 38.1 kg/m2, mean LFC of 19.1%, and mean ALT of 54.3 U/L at baseline. Across all cohorts, responders (pts with ≥30% reduction in LFC from baseline) receiving intermittent miricorilant lost LFC more gradually and were less likely to have a rise in ALT >3x the upper limit of normal compared to daily dosing. Cohort 6 (100 mg miricorilant twice weekly for 12 weeks, n=6) had the best benefit-risk profile: at week 12, 5 pts had a mean relative reduction in LFC of –28.15% (standard deviation [SD]: 13.5), with a corresponding decline in liver enzymes (mean change from baseline: ALT, –4.0 [SD: 21.4]; AST, –6.0 [SD: 7.2]). Additionally, pts in cohort 6 had improved overall lipid profiles, glycemic markers, and fibrosis biomarkers, with mean change from baseline at week 12 of –9.8 mg/dL for low density lipoproteins, –20.8 mg/dL for triglycerides, –6.8 mg/dL for fasting glucose, –5.40 mIU/L for insulin, –1.92 for homeostatic model assessment of insulin resistance, and –0.19 for enhanced liver fibrosis score. Overall, treatment-emergent adverse events (TEAEs) occurred in 82.5% (n=52) of pts; 4.8% (n=3) of pts had grade ≥3 TEAEs. Two serious TEAEs occurred; neither was related to miricorilant.

**Conclusions:** Twice weekly 100 mg miricorilant was safe and well-tolerated and resulted in reduced LFC and improved hepatic, lipid, and glycemic markers. Based on these findings, a phase 2b study (MONARCH, NCT06108219) of intermittent miricorilant in NASH is underway. Abstract previously presented at the American Association for the Study of Liver Diseases, The Liver Meeting (November 10–14; Boston, MA).

**[51]**

## PEMVIDUTIDE-INDUCED LIVER FAT REDUCTION IN SUBJECTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE CORRELATES WITH IMPROVEMENTS IN NON-INVASIVE MARKERS OF INFLAMMATION AND FIBROSIS: RESULTS OF A 24-WEEK MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

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**Background and Aims:** Pemvidutide is a long-acting, balanced GLP-1/glucagon dual receptor agonist under development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) and obesity. We previously reported that pemvidutide led to a greater than 75% reduction in liver fat content (LFC) by MRI-PDFF after 24 weeks of treatment. This analysis examined the correlations between these changes in LFC and non-invasive markers of inflammation and fibrosis.

**Method:** 64 subjects with metabolic dysfunction-associated steatotic liver disease (MASLD) defined as LFC ≥10% by MRI-PDFF, were randomized in a 1:1:1:1 ratio to receive 1.2 mg, 1.8 mg, 2.4 mg pemvidutide, or placebo QW for 24 weeks. Subjects with baseline serum alanine aminotransferase (ALT) >75 IU/L or evidence of advanced liver fibrosis, defined by liver stiffness measurement (LSM) by Fibroscan® ≥10 kPa, were excluded. Assessments included changes in MRI-based corrected T1 (cT1) imaging, ALT, Enhanced Liver Fibrosis test (ELF), the procollagen type III N-terminal peptide (PIIINP) component of ELF, and LSM. The anti-fibrotic potential of pemvidutide was evaluated in a subpopulation with suspected MASH fibrosis, defined as subjects in the upper tertiles of ELF score and LSM, respectively.

**Results:** Median baseline body mass index (BMI), LFC, cT1, ALT, LSM, PIIINP, and ELF were 36.8 kg/m$^2$, 20.6%, 906.5 ms, 31.0 IU/L, 6.5 kPa, 8.0 $\mu$g/L, and 8.7, respectively. Reductions in LFC correlated with reductions in cT1 ($R^2$: 0.7; $p<0.0001$) across the entire study population and serum ALT in subjects with baseline ALT ≥30 IU/L ($R^2$: 0.4; $p<0.001$). In subgroup analyses of subjects with baseline ELF in the upper tertile (median ELF 9.3, PIIINP 10.3 $\mu$g/L), ELF was decreased by up to 0.5 (5.1%) vs. 0.1 (1.1%) and PIIINP was decreased by up to 3.9 $\mu$g/L (26.2%) vs. 0.8 $\mu$g/L (1.5%), pemvidutide vs. placebo, respectively. Similarly, in a subgroup analysis of subjects with baseline LSM in the upper tertile (median 8.0 kPa), LSM decreased by up to 2.4 kPa (28%) vs. 1.3 kPa (14.7%), pemvidutide vs. placebo, respectively.

**Conclusions:** Pemvidutide administered QW for 24 weeks led to rapid and potent reductions in LFC that strongly correlated with improvements in non-invasive biomarkers of inflammation and fibrosis. These findings are expected to predict meaningful histopathological improvement in MASH.

Some data from this work were presented as a late-breaking abstract during The Liver Meeting in November 2023, Boston, MA.

# THANK YOU FOR ATTENDING!