PARK CITY, UTAH - JANUARY 8-10, 2026

MASH-TAG

CONFERENCE

2026

ABSTRACT BOOK

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[2- DISTINGUISHED ABSTRACT]
NIMBLE STAGE 2.0 FOR MASH-TAG

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Abstract Category: Clinical Trial Design

Background Information/Purpose – Liver biopsy-based histopathology is the reference standard for detecting patients at risk of developing serious liver conditions secondary to metabolic dysfunction-associated steatohepatitis (MASH). However, liver biopsy is a highly variable invasive technique with risks for complications and mortality. Alternative biomarkers are needed to replace liver biopsy for diagnosis and staging of MASH with fibrosis. The Non-Invasive Biomarkers for Metabolic Liver Disease (NIMBLE) project was commissioned by the FNIH Biomarkers Consortium to qualify non-invasive tests (NITs) for MASH. It represents a collaborative effort involving the FNIH, Food and Drug Administration, academic, industry partners, and patient advocates. The NIMBLE project plan was designed to occur across two stages, generating data on NITs to support seeking regulatory approval of one or more biomarker(s) for the diagnostic enrichment of MASH. The purpose of this abstract is to introduce Stage 2 of the project to the scientific community.

Methods – Data generated within NIMBLE Stage 1 were able to successfully identify candidate NITs that met prespecified criteria for further evaluation in Stage 2. The current study aims to confirm and extend the findings from Stage 1 in the setting of a prospective, non-interventional, cross-sectional, single-period, multi-center trial in a population at risk for MASH with fibrosis. To that end, Stage 2.0 is primarily designed to evaluate the performance characteristics of prespecified blood-, VCTE- and imaging-based NITs when calibrated against liver biopsy-based histology, as well as currently available tools for diagnosis and staging of at-risk MASH. Stage 2.0 is designed to enroll approximately 450 subjects.

Results –NIMBLE Stage 2.0 is an ongoing study. Primary endpoints of Stage 2.0 are to 1) evaluate the diagnostic performance of biomarkers for identifying at-risk MASH and 2) for detecting clinically significant fibrosis; 3) evaluate imaging-based biomarkers for hepatic steatosis monitoring; 4) identify biomarkers that enhance participant selection for clinical trials, and 5) investigate exploratory NITs, including AI-based histological scoring, for novel diagnostic workflows. Enrollment began in May 2025 and is projected to be completed by Q3 of 2026.

Conclusions – NIMBLE 2.0 will generate the base to support letters of intent (LOI) for qualification of noninvasive biomarkers as diagnostic enrichment for MASH.

[4- DISTINGUISHED ABSTRACT]
THE RESTORE STUDY: PHASE 1/2 CLINICAL TRIAL OF KRIYA-497, A NOVEL AAV GENE THERAPY FOR ADULTS WITH MASH

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Background Information/Purpose –Adeno-Associated Virus (AAV) gene therapies have demonstrated substantial clinical benefit to date for the treatment of rare diseases, and as such have the potential to transform the management of more prevalent chronic diseases. KRIYA-497 is an intramuscularly administered AAV gene therapy designed to express the native human FGF21 protein for the treatment of MASH. In preclinical studies, a one-time administration of KRIYA-497 demonstrated dose dependent reductions in reducing liver fat, body weight, histological fibrosis and improving overall metabolic health in multiple animal models of MASH. Overall safety of KRIYA-497 has also been demonstrated in multiple non-human primate studies. The RESTOREstudy is a first-in-human study designed to evaluate the safety, efficacy, PK and PD of KRIYA 497 in adults with MASH.

Methods – The RESTORE study is a Phase 1/2 adaptive dose-escalation study in adults with MASH. The study will enroll adult MASH patients aged 18-75 with biopsy-confirmed fibrosis stage F3 or F4 (compensated) MASH, BMI of 25 to <40 kg/m², and a history or presence of ≥ 2 metabolic risk factors (obesity, hypertension, dyslipidemia or type 2 diabetes mellitus). Eligible patients will receive ultrasound-guided intramuscular injections of KRIYA-497 into the quadriceps muscles bilaterally in a one-time, outpatient procedure. Patients will be followed for 52 weeks with longitudinal assessments using non-invasive imaging modalities and serum biomarkers of metabolic health.

Results – Part 1 primary endpoints include safety, tolerability, preliminary efficacy, and determination of the Part 2 dose. Part 2 primary endpoints are changes in liver fat content assessed by MRI PDFF and CAP as well as safety. Key secondary endpoints for Part 1 and Part 2 include liver stiffness assessed by MRE and transient elastography (FibroScan®). Changes in serum biomarkers of metabolic health (lipoproteins, triglycerides, glycemic markers, adiponectin, liver enzymes, and non-invasive inflammatory and fibrosis biomarkers) will also be evaluated.

Conclusions – The RESTORE study represents the first ever clinical trial of an AAV gene therapy for the treatment of MASH. This one-time therapy could offer the potential for durable and steady expression of FGF21, addressing limitations of recombinant FGF21 analogs that require frequent administrations due to their relatively short half-life with the aim of enabling lasting metabolic improvements in patients with fibrosis due to MASH.

[20- DISTINGUISHED ABSTRACT]
Pemvidutide Treatment Yields Significant Reductions in Non-Invasive Tests of Liver Fibrosis and AI-Based Digital Pathology: Results from the Pemvidutide Phase 2b IMPACT Trial

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Abstract Category*:* Therapeutic Trials - MASH/liver fibrosis – Humans

***B*ackground Information/Purpose –** Pemvidutide is a glucagon/GLP-1 dual receptor agonist in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). IMPACT is a Phase 2b, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3 (NCT05989711). Non-invasive tests (NITs) can assess liver steatosis, inflammation, and fibrosis progression. LiverExplore™,† is an artificial intelligence (AI) algorithm that provides granular quantification of fibrosis subtypes beyond the categorical grades provided by conventional NASH Clinical Research Network (CRN) staging. Here, we present a comprehensive assessment of IMPACT liver fibrosis by NITs and AI-digital pathology at 24 weeks.

Methods – 212 subjects were randomized 1:2:2 to once-weekly subcutaneous pemvidutide [1.2 mg (N=41) or 1.8 mg (N=85)], without dose titration, or placebo (N=86). Biopsies were assessed by NASH CRN staging. Key secondary endpoints included NITs of inflammation and fibrosis. Biopsy results were also quantified for the proportionate areas of total, early (periportal and perisinusoidal), and advanced fibrosis (bridging and nodular), adjusted for steatosis area, by LiverExplore. Patients with missing biopsy data or who discontinued treatment early were considered non-responders (ITT analysis).

Results – Significant reductions in multiple NITs, including alanine aminotransferase (ALT) and enhanced liver fibrosis (ELF), were observed at both doses ($p<0.001$ vs. placebo). AI-based quantitative fibrosis analyses showed significant improvements at the 1.2 mg and 1.8 mg pemvidutide doses. In a responder analysis, 31% of patients in the 1.8 mg group achieved a 60% relative reduction in the area of total fibrosis vs. 8% of placebo patients ($p=0.0003$). Subcomponent fibrosis analyses revealed a significant proportion of patients had reductions in early fibrosis, with 24% of patients in the 1.2 mg group ($p=0.017$) and 34% of patients in the 1.8 mg group ($p<0.0001$) achieving a 60% relative decrease vs. 9% of placebo patients. Importantly, 27% of patients in the 1.8 mg group had a 60% relative reduction in advanced fibrosis vs. 11% of placebo patients ($p=0.0063$).

Conclusions – Pemvidutide significantly reduced multiple NITs of liver inflammation and fibrosis. These results were supported by reductions in the AI-quantified total fibrosis burden at 24 weeks.

†LiverExplore is For Research Use Only. Not for use in diagnostic procedures.

[12]
UNDERSTANDING THE FUNCTIONAL AND PHYSIOLOGIC HETEROGENEITY OF ADVANCED MASH AS DEFINED BY THE ORAL CHOLATE CHALLENGE TEST MAY ENHANCE CLINICAL TRIAL DESIGN

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Abstract Category: Clinical Trial Design

Background Information/Purpose – Liver function in patients with advanced MASH may vary from normal to severe impairment and portal-systemic shunting which may impact treatment responses in drug trials. The oral cholate challenge test (HepQuant DuO) characterized baseline liver function and shunting in three recent MASH drug trials.

Methods –Subjects were enrolled in 3 clinical trials linking the Test results to treatment response. Trial 1 was a Phase 2 trial conducted in patients with CP A MASH cirrhosis. Trial 2 was a Phase 3 open-label trial in patients with well-compensated CP A MASH cirrhosis. Trial 3 was a Phase 2 open-label trial in patients MASH ≥F3 fibrosis. Test parameters were quantified from 20- and 60-min concentrations of orally administered d4-cholate. Serum was analyzed for cholate concentrations by LC-MS/MS. Baseline Test parameters, including the disease severity index (DSI) and portal systemic shunting (SHUNT%), were calculated.

Results- A total of 134 subjects with MASH underwent the Test. Subjects were on average 61 ± 9 years of age, BMI 37 ± 8 kg/m2, 99% overweight, 86% obese, 43% male, and 58% Hispanic ethnicity. A wide range of functional impairment and shunting was observed in these cohorts of patients with MASH. Mean (± SD) values for the Test were 18.7 ± 5.5 for DSI and 29.4% ± 10.5% for SHUNT%. The diagram below, based on DSI (function) and SHUNT% indicated 6 (4.4%) with normal function, 19 (14.2%) with only portal-systemic shunting, 67 (50%) with mild functional impairment, 18 (13.4%) with significant functional impairment, and 24 (18%) with significant functional impairment and shunting. Using the RISK ACE model (Kittelson 2025), the individual estimated 1-year risk for clinical outcome ranged from 0.4% (DSI 7.7) to 61.4% (DSI 40.0).

Conclusions- The oral cholate challenge test (HepQuant DuO) uncovered significant heterogeneity in functional and physiologic impairment at baseline in patients enrolled in MASH drug trials. Quantitative functional assessment to risk stratify study populations to reach clinical liver events could improve efficiency and lower the cost of clinical trials by enhancing statistical power, thereby reducing sample size and study duration.

Disclosures: MPM is a paid consultant for HepQuant, LLC. JCI and GTE are employees and equity members of HepQuant, LLC. MPM and GTE have issued and pending patents. This abstract was presented at AASLD 2025.

[18]
A Phase 2b, Multicenter, Randomized, Placebo-Controlled Trial of Pemvidutide in Metabolic Dysfunction-Associated Steatohepatitis: The IMPACT Trial

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Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose – Pemvidutide is a balanced 1:1 glucagon/GLP-1 dual receptor agonist in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), alcohol use disorder (AUD), and alcohol-associated liver disease (ALD). IMPACT is a Phase 2b, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3 (NCT05989711). Here, we present the results of the primary analyses of the study at 24 weeks of treatment.

Methods –Between July 2023 to April 2025, 212 patients were randomized 1:2:2 to receive once-weekly subcutaneous pemvidutide (1.2 mg or 1.8 mg) administered without dose titration, or placebo. The mean age was 53 yrs, the mean BMI was 39 kg/m2, 58% were female, and 43% had type 2 diabetes. The dual primary endpoints were MASH resolution without worsening of fibrosis or ≥1 stage liver fibrosis improvement without worsening of MASH at 24 weeks. An ITT analysis (N=212) was employed in which patients with missing biopsy data or who discontinued treatment early were considered non-responders.

Results- MASH resolution without fibrosis worsening was observed in 18 [20%] of 86 patients in the placebo group, 24 [58%] of 41 patients in the 1.2 mg pemvidutide group ($p<0.0001$), and 45 [52%] of 85 patients in the 1.8 mg pemvidutide group ($p<0.0001$). Fibrosis improvement without worsening of MASH was observed in 24 [28%] of 86 patients in the placebo group, 13 [33%] of 41 patients in the 1.2 mg pemvidutide group ($p=0.59$), and 30 [36%] of 85 patients in the 1.8 mg pemvidutide group ($p=0.27$). Pemvidutide treatment also resulted in significant reductions in non-invasive markers of hepatic injury [alanine aminotransferase (ALT)] and inflammation [corrected (c)T1]. AI-based analyses of the liver biopsies and non-invasive tests for fibrosis were statistically significant at both pemvidutide doses, consistent with anti-fibrotic activity. Mean weight losses were 0.5% in the placebo group vs. 4.8% ($p<0.001$) in the 1.2 mg group and 5.8% ($p<0.001$) in 1.8 mg group. Pemvidutide was well-tolerated despite the absence of dose titration, with discontinuations due to adverse events of 2% in the placebo group and 0%, and 1%, in the 1.2 mg, and 1.8 mg groups, respectively.

Conclusions: Pemvidutide was well tolerated without dose titration and led to significant MASH resolution, weight loss, and anti-fibrotic activity at only 24 weeks of treatment.

[24]
PLASMA CFDNA METHYLATION ENABLES VIRTUAL PATHOLOGY OF MASH, VALIDATED BY LIVER METHYLATION, GENE EXPRESSION, AND SINGLE-CELL MULTI-OMICS

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Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose –Liver biopsy is the reference standard defining and studying the histopathology of MASH, but it is invasive, tissue sampling-limited, and impractical for large scale studies. We hypothesized that ultra-deep plasma cell-free DNA (cfDNA) methylation data paired with advanced AI could provide a non-invasive "virtual pathology" that reports on liver pathway activities and liver cell composition. Our objective was to build a multi-omics atlas integrating liver tissue and plasma to test whether the pathway activities and cell cycle changes that are involved in the pathogenesis of MASH can be quantitatively and non-invasively recapitulated in cfDNA.

Methods – Using the Duke MASLD Biobank, we performed whole methylome sequencing of plasma cfDNA from 217 biopsy-proven MASLD (F0: 59, F1: 53, F2: 31, F3: 47, F4: 27) and 59 control subjects without histologic MASLD and matched liver DNA methylation in 50 of those MASLD patients. Bulk liver RNA-seq was generated from 310 MASLD livers, and single-nucleus RNA-seq plus ATAC-seq from 50 MASLD patients to define cell-type–specific expression and regulatory programs. Analyses compared mild versus advanced fibrosis, adjusting for age, sex, BMI, and type 2 diabetes. A novel AI architecture, purpose-built for liquid biopsy modeling up to a billion cfDNA molecular interactions across over 28 million CpGs including 2.85 million CpG islands, was applied to deconvolve liver-derived changes from cfDNA.

Results – In liver tissue, promoter hypermethylation with concordant downregulation of hepatocyte metabolic pathways ($p<0.001$), and hypomethylation with upregulation of repair, wound-healing and inflammatory pathways ($p<0.001$) tracked with increasing fibrosis stage. Single-nucleus confirmed the loss of hepatocyte signatures and expansion of ductular/cholangiocyte programs in advanced fibrosis. The same gene and pathway methylation changes in the liver were reproduced in plasma cfDNA ($p<0.001$), enabling the non-invasive tracking of disease related pathways capturing key features of the underlying histopathology.

Conclusions – Using an integrated multi-omics atlas of MASH, we show that plasma cfDNA methylation provides a non-invasive readout of liver epigenetic state, cell composition, and pathway activity. These data support cfDNA-based methylation profiling paired with advanced AI as a "virtual pathology" that can quantify different aspects of MASH biology without tissue biopsy. AI-powered cfDNA methylome profiling as a true liquid biopsy of the liver enables non-invasive risk stratification, mechanistic phenotyping, and pathway-informed therapy selection, and motivates studies of cfDNA derived pathway scores as predictive and pharmacodynamic biomarkers in MASH.

[26]
BROADLY ACCESSIBLE AND ACCURATE QUANTITATIVE LIVER FAT ASSESSMENT IN MASLD

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Abstract Category- Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose – MRI-PDFF is a dependable standard for measuring liver fat in MASLD/MASH, but traditional MRI can be expensive and difficult to access for routine or decentralized applications. To solve this, a compact, bed-mounted, office-based open Magnetic Resonance (MR) device operating at 0.2 T was developed, which analyses liver signals and does not produce images (LiverScope®, Livivos Inc.). LiverScope® uses diffusion contrast to assess hepatic fat without requiring high-field MRI infrastructure. We present preliminary results from an upgraded point-of-care probe with increased penetration depth and a new patient-positioning protocol aimed at enhancing consistency and alignment with MRI-PDFF.

Methods – Hepatic steatosis was evaluated in 21 subjects with MASLD (BMI, 28-46 kg/m²) using the LiverScope® at the Fresno Clinical Research Center. Each participant fasted for 3 hours prior to the test and was positioned comfortably in the right lateral decubitus position, with the liver area on the MR device portion of the LiverScope®. A well-trained operator followed a guided positioning protocol based on anatomical markers. Automated quality-control mechanisms excluded measurements suspected of visceral fat contamination. The procedure lasted approximately 10-15 minutes. The analysis algorithm excluded three participants due to the detection of non-liver signals. Each participant then received a reference MRI-PDFF within 1 to 2 hours at a nearby Perspectum-certified imaging center using a 1.5T GE scanner. MRI PDFF values were provided by Perspectum (UK).

Results – LiverScope®'s MR-PDFF values showed strong agreement with MRI-PDFF, with $R^2 = 0.93$ and a mean absolute difference of 1.7 percentage points (Figure 1).

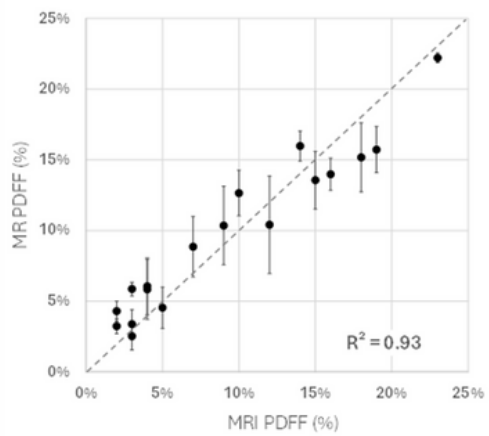

Figure 1. Point-of-care MR-PDFF values vs. same-day MRI-PDFF. A dashed line indicates perfect correlation.

Conclusions – The point-of-care LiverScope® device accurately measures liver fat and correlates well with MRI-PDFF results in patients with MASLD/MASH. These initial findings suggest that point-of-car MR PDFF has strong potential as an office-based tool for MASLD diagnosis, a screening method for clinical trials, and a means to monitor patients over time during MASH therapy, making access easier outside specialized centers. Ongoing research with LiverScope® will further validate its usefulness in larger, multi-site studies.
LiverScope® is an investigational device. Limited by Federal (or United States) law to investigational use.

[30]
PROGRESSION TO CIRRHOSIS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) IN A REAL-WORLD COHORT IN THE US

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Abstract Category: Clinical Epidemiology – MASH/liver fibrosis

Background Information/Purpose – Metabolic Dysfunction-Associated Steatohepatitis (MASH) can progress to cirrhosis; a disease state associated with significant healthcare resource utilization. It is key to understand the comorbidity burden and clinical profile in patients with MASH that live without cirrhosis and estimate progression to cirrhosis in the real-world setting.

Methods – This was a retrospective observational study using electronic health records and claims data from Optum® Market Clarity (OMC) in the US. Eligibility criteria included ≥1 claim or medical encounter with a diagnosis code for MASH (ICD-10-CM: K75.81) during the identification period (January 2016–May 2021), age ≥18 years at the diagnosis date, and laboratory values for aspartate aminotransferase (AST), alanine aminotransferase, and platelets (to calculate Fibrosis-4 score [FIB-4]). Individuals with a diagnosis code or medical claim for other liver diseases were excluded, as were those with prior reporting of cirrhosis (claim or medical encounter with a diagnosis code for cirrhotic conditions in the 3 months before or after diagnosis date). Patients were followed from the MASH diagnosis date to the earliest of liver transplant, death, loss to follow-up, or end of study (May 2022).

Results – Out of 18,710 patients with MASH in OMC, 13,754 (73.5%) did not have cirrhosis (mean age 42.1 years. 7,181 [52.2%] were female, 10,796 [78.5%] non-Hispanic White, and 10,028 [72.9%] had a FIB-4 score <1.3. The mean weight was 100 kg while mean BMI was 35kg/m2. Comorbidity prevalence was high, with hypertension (72.0%), ≥3 metabolic conditions (71.7%), and CVD at 1 year before index (67.7%) being the most reported conditions. At the median follow-up of 1,169 days (3.2 years), the cumulative incidence of progression to cirrhosis was 5.7%. The incidence rates for progression to cirrhosis was 1.8 per 100 patient-years.

Conclusions – Preventing progression to cirrhosis is especially important for patients with MASH. The incidence rate for cirrhosis observed in the present study is three times higher than previously reported in the general population. Further studies should assess which patient characteristics predict progression to cirrhosis to improve risk-stratification in routine practice.
Encore: Originally presented at the American Association for the Study of Liver Diseases (AASLD) Annual Meeting (The Liver Meeting®) 2025

Conflicts of Interest:
JMS reports consultancy fees from 89Bio, Akero, Boehringer Ingelheim, Inventiva Pharma, Ipsen, Madrigal, NorthSea Therapeutics, Novo Nordisk, Roche, Siemens Healthineers; research funding from Boehringer Ingelheim; stock options from AGED diagnostics, Hepta Bio, and speaker honorarium from Madrigal, MedPublico GmbH, and Novo Nordisk.
ZAT, RY, and CS are employees of Boehringer Ingelheim.
MR and MY are employees of Thermo Fisher Scientific and members of the PPD™ Evidera™ Real-World Data & Scientific Solutions team.
Acknowledgements:
This study is supported and funded by Boehringer Ingelheim. The authors met the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) as supported by Good Publication Practice (GPP) guidelines. Ronald Herrera, PhD, participated in technical editing of the abstract. Sarah Krisanda, MSc, of Envision Ignite, an Envision Medical Communications agency, part of Envision Pharma Group, provided medical writing support, which was funded by Boehringer Ingelheim. The authors did not receive payment related to the development of this poster. Boehringer Ingelheim was given the opportunity to review the poster for medical and scientific accuracy, as well as intellectual property considerations.
Data availability statement:
To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the International Committee of Medical Journal Editors criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim policy on transparency and publication of clinical study data, scientific and medical researchers can request access to clinical study data, typically, 1 year after the approval has been granted by major regulatory authorities or after termination of the development program. Researchers should use the https://vivli.org/ link to request access to study data and visit www.mystudywindow.com/msw/datasharing for further information.

[1]
WITHDRAWAL OF SEMAGLUTIDE RESULTS IN WEIGHT REGAIN, INCREASED ALCOHOL INTAKE AND METABOLIC DISORDERS IN A DIET-INDUCED OBESE HAMSTER MODEL OF METALD

François Briand[1], Estelle Grasset[1], Claire Bigot[1], Natalia Breyner[1], Thierry Sulpice[1].

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Abstract Category: Experimental/basic science, NAFLD/MASH, non-humans

Background Information/Purpose – As an alternative to mice and rats, we have developed a free-choice diet-induced obese hamster model, that exhibits human-like dyslipidemia, MASH, heart failure with preserved ejection fraction (HFpEF) and a spontaneous preference for alcohol. In a recent publication (Briand et al. Eur J Pharmacol, 2025), we have demonstrated that semaglutide shows multiple cardiometabolic benefits in our model, including improved HFpEF and reduced alcohol consumption. In the present study, we evaluated the effects of semaglutide withdrawal in diet-induced obese hamsters with free access to alcohol, as a model of MetALD.

Methods – Diet-induced obese hamsters, with free access to chow or high fat diet, tap water or fructose/alcohol water, were treated s.c. three times per week with vehicle for 4 weeks or semaglutide 15nmol/kg for 2 weeks, followed by a 2-week withdrawal period.

Results – Compared to vehicle, semaglutide for two weeks resulted in significant weight loss (-11%), including reductions in both fat and lean mass, and reduced high fat diet as well as fructose/alcohol water intake. Semaglutide significantly decreased fasting glycaemia and insulinemia, leading to a strong reduction in the HOMA-IR index of insulin resistance (-73%, $p<0.01$). Semaglutide also reduced levels of fasting plasma free fatty acids, triglycerides and total cholesterol (all $p<0.05$).
During the two-week period of semaglutide withdrawal, the hamsters rapidly regained their initial body weight and fat mass. This was accompanied by an increase in their intake of high-fat diet and fructose/alcohol water. At the end of the 2-week period, withdrawal of semaglutide led to similar HOMA-IR index and plasma total cholesterol levels, as well as significantly higher plasma free fatty acids (+52%) and triglycerides (+80%) levels, as compared to vehicle. This dyslipidemic profile was confirmed by FPLC analysis. While it did not change liver fat content and NAFLD activity scoring, semaglutide withdrawal tended to worsen liver fibrosis with a significantly greater expression of genes involved in fibrosis, as well as higher % Sirius Red labelling.

Conclusions – Withdrawal from semaglutide results in rapid weight regain, increased intake of high-fat diet and fructose/alcohol in the drinking water, dyslipidemia and worsening liver fibrosis. This preclinical hamster model could be used to evaluate novel therapies that would prevent metabolic disorders following semaglutide withdrawal.

[3]
SEMAGLUTIDE 2.4 MG WEIGHT OUTCOMES AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD) IN A REAL-WORLD SETTING

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Abstract Category- Disease Management of MASH/Liver Fibrosis Patients (including comorbidities)

Background Information/Purpose – MASLD and its more progressive subtype, metabolic dysfunction-associated steatohepatitis (MASH), are chronic liver conditions that are underdiagnosed in clinical practice. Overweight and obesity are primary risk factors for MASLD, making many patients eligible for semaglutide 2.4 mg treatment. Although trials report high treatment persistence and efficacy, outcomes may differ in clinical practice. We aim to evaluate real-world semaglutide 2.4 mg use and associated weight loss among patients with MASLD.

Methods – This retrospective cohort study included eligible obese or overweight patients (BMI ≥27 kg/m²) with MASLD initiating semaglutide 2.4 mg treatment (earliest prescription defined as the index date) from 2021-2024 in Optum Market Clarity data. Patients were required to have ≥1 weight measurement ≤60 days pre- and anytime post-index, with no evidence of other liver diseases or severe MASLD complications during the 12-month baseline period. Medication use was evaluated prior to the latest observed weight measurement and defined based on the following categories, Group 1: No titration (no 2.4 mg semaglutide claim) with discontinuation (≥45-day gap in medication coverage); Group 2: No titration with persistence; Group 3: Titration with discontinuation; and Group 4: Titration with persistence. Absolute and percentage weight change from baseline to the latest observed measurement within 12 months were assessed.

RESULTS-
Of 247 patients, 62.8% (n=155) were female, and mean (standard deviation [SD]) age was 47.9 (10.9) years old. Mean (SD) baseline weight and BMI were 114.1 (24.2) kg and 40.0 (8.1) kg/m2; respectively, and mean (SD) time to last weight measurement was 38.0 (13.2) weeks. Mean (SD) weight loss from baseline was 9.0 (11.6) kg, a 7.8% reduction. Less than half of patients (38.1%) achieved a reduction in body weight of at least 10% from baseline, while 18.6% experienced ≥15% weight loss. Groups 1, 2, 3, and 4 comprised 48.2%, 13.0%, 13.4%, and 25.5% of the sample, with mean (kg) (percentage) weight loss of 4.3 (3.8%), 9.6 (8.9%), 14.4 (12.1%), and 15.0 (12.6%), respectively.

CONCLUSIONS-
Findings suggest a lack of alignment between semaglutide 2.4 mg trial results and real-world outcomes in a MASLD population. Most patients did not titrate and/or discontinued medication, both of which were associated with limited weight reduction benefits, despite being generally younger and of high BMI.

[5]
SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH MASH INITIATING RESMETIROM

Jennifer Debenham, Raman Kumar, Joaquim Fernandes, Sheila Thomas, Blake Thomas, Nipun Atreja, Francis Lobo

Abstract Category- Clinical Epidemiology – MASH/Liver Fibrosis

Background Information/Purpose – Metabolic dysfunction-associated steatohepatitis (MASH) is a progressive liver disease with limited treatment options. In March 2024, resmetirom, a thyroid hormone receptor β agonist, became the first liver-directed therapy approved for MASH. Understanding characteristics of patients with MASH initiating resmetirom is vital for optimizing clinical utility and informing management strategies. This study describes the characteristics of patients initiating resmetirom and the associated prescribers using a large prescription fill database.

Methods – This retrospective cohort study used large specialty and retail pharmacy data to identify patients, who initiated resmetirom for MASH from March 2024-August 2025. To be included, patients had to be adults, aged ≥18 years), with at least 2 fills for resmetirom consistent with standard medication measures used to assess treatment adherence. Patient attributes assessed were age, gender, rurality, region, Social Vulnerability Index (SVI), household income and payer type. Prescribing Healthcare Professional (HCP) specialty, practice setting, geography and academic hospital affiliation were summarized. Clinical variables included proportion days covered (PDC) and patient Rx-risk, a burden of disease score based on patient prescription history.

Results – 5,389 patients were evaluated after 6 months of follow up with a mean (SD) age=56.4 (12.7) years, female=56.8%; Commercial payer type=75.8%. Patients were geographically dispersed within the South (39.5%), West (22.7%), Northeast (20.4%), and Midwest (16.8%). Patients lived in rural (43.4%), urban (33.4%), and suburban (23.0%) areas. The median household income was $60,918 ($22,191), and mean SVI was 0.48 (0.23). Resmetirom was mainly prescribed by hepatologists and gastroenterologists (56.4%), with other specialties accounting for 40.4% of new fills. HCP practices were urban (50.6%), suburban (29.1%), and rural (20.2%), and 70.5% were affiliated with an academic hospital. The mean 6-month PDC was 85.3% and the average Rx-risk score was 2.4 (SD 4.0).

Conclusions – Patients initiating resmetirom represent a diverse population, with broad geographic and practice setting representation. High treatment adherence suggests early adoption among engaged patients and provider groups. More understanding of prescribing patterns and patient profiles may support individualized and effective approaches to MASH management.
Sponsorships: Madrigal Pharmaceuticals

[6]
US HEALTHCARE PROFESSIONALS' MANAGEMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS AND KNOWLEDGE OF GLUCAGON, GLP-1, AND GIP RECEPTOR AGONISTS AND DUAL AGONISTS

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Abstract Category- Disease management of MASH/liver fibrosis patients (including comorbidities)

Background Information/Purpose –
Various combinations of agonists of the glucagon receptor (GCGR), glucose-dependent insulinotropic polypeptide receptor (GIPR), and glucagon-like peptide-1 receptor (GLP-1R) are in clinical trials for the treatment of metabolic dysfunction-associated liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). We explored how US healthcare professionals (HCPs) treating people with MASLD/MASH perceive these investigational agents.

Methods – Between November 2024 and January 2025, an online survey was completed by US physicians and advanced practice providers specializing in hepatology/gastroenterology (HEP/GASTRO, n=256), endocrinology (ENDO, n=252), and primary care (PCP, n=252), currently treating people with MASLD/MASH, to assess their self-reported knowledge of GCGR, GIPR, and GLP-1R agonists.

Results – Respondent HCPs reported managing a mean of 13–25 patients with MASLD/MASH per week. Ultrasound was the most common imaging technique to aid diagnosis of MASH across specialty (ENDO, 62.8%; PCP, 79.4%), with the exception of HEP/GASTRO where vibration-controlled transient elastography was most common (71.9%). Liver enzymes (79.7%) and FIB-4 (55.8%) were the most frequently ordered biomarker tests for assessing MASH. Significant barriers to treatment reported were cost, paucity of FDA-approved treatments, and delayed diagnosis due to the asymptomatic nature of the disease. Only 30.2% and 53.9% of HCPs were "very" or "extremely familiar" with GCGR and GIPR, respectively, but most (76.8%) HCPs were "very" or "extremely familiar" with GLP-1R. HCPs were also less familiar with the therapeutic effects associated with activation of GCGR and GIPR compared with GLP-1R. A total of 87.0%, 75.9% and 90.3% of respondents expected GCGR, GIPR, and GLP-1R agonists, respectively, to benefit people with MASH. Most HCPs expected dual GCGR/GLP-1R agonists to be better than GLP-1R mono-agonists for control of many cardiometabolic conditions including MASLD (88.3%), MASH (89.3%), obesity (90.1%), and type 2 diabetes (88.8%).

Conclusions- HCPs report substantial barriers to treating people with MASH, including costs and lack of approved medications. HCPs were generally more familiar with GLP-1R, and the therapeutic effects of its activation, than with GCGR and GIPR. HCPs anticipate that dual GCGR/GLP-1R agonists will have meaningful clinical benefits for MASLD/MASH and many other cardiometabolic conditions.

Encore- Originally presented at the American Association for the Study of Liver Diseases (AASLD) Annual Meeting (The Liver Meeting®) 2025

[CONFLICTS OF INTEREST-
ASB is a consultant for Boehringer Ingelheim, Life-Edit, Madrigal, Merck, and Target-RWE.
DC was an employee of Boehringer Ingelheim Pharmaceuticals, Inc. at the time the work was completed.
JP is an employee of Boehringer Ingelheim Pharmaceuticals, Inc.
HEB's research site institution has received research grants from 89Bio, AbbVie, Aligos, Allergan, Alon Medtech/Epitomee, Altimmune, Amgen, Anji Pharma, AstraZeneca, Bioage, Bionime, Boehringer Ingelheim, Carmot, Chorus/Bioage, Eli Lilly, Esperion, Evidera, Fractyl, GlaxoSmithKline, HighTide, Home Access, Horizon, Ionis, Kallyope, LG-Chem, Madrigal, Merck, Mineralys, New Amsterdam, Novartis, Novo Nordisk, Pfizer, Regeneron, Satsuma, Selecta, Shionogi, Skye/Birdrock, TIMI, Veru, Viking, and Vivus; he has served as a consultant/advisor for 89Bio, Altimmune, Amgen, Boehringer Ingelheim, Kiniksa, HighTide, Lilly, Novo Nordisk, Regeneron, Veru, Zomagen, and ZyVersa.

Acknowledgements-
The study was supported and funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) as supported by Good Publication Practice (GPP) guidelines. The authors did not receive payment related to the development of the poster. Kayleigh Walker, PhD, of Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group, provided writing and editorial support, which was contracted and funded by BIPI. BIPI was given the opportunity to review the poster for medical and scientific accuracy as well as intellectual property considerations.

Data availability statement-
To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the International Committee of Medical Journal Editors criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim policy on transparency and publication of clinical study data, scientific and medical researchers can request access to clinical study data, typically, 1 year after the approval has been granted by major regulatory authorities or after termination of the development program. Researchers should use the https://vivli.org/ link to request access to study data and visit www.mystudywindow.com/msw/datasharing for further information.

[7]
IMPROVEMENTS IN NON-INVASIVE BIOMARKERS AND BIOPSY RESPONSES WITH THE GLUCAGON RECEPTOR/GLUCAGON-LIKE PEPTIDE-1 RECEPTOR DUAL AGONIST SURVODUTIDE: CONCORDANCE ANALYSIS FROM A PHASE 2 TRIAL IN PEOPLE WITH METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS AND FIBROSIS

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Abstract Category- Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose – The combination of elastography and blood biomarker non-invasive tests (NITs) have been proposed to replace histology-based efficacy endpoints. This post-hoc analysis assessed NIT-based efficacy endpoints and examined if the observed changes in histology were corroborated by NITs following treatment with survodutide, a GCGR/GLP-1R dual agonist, in a phase 2 trial in participants with biopsy-confirmed MASH and F1–F3 fibrosis.

Methods – Among 295 people aged 18–80 years randomized to once-weekly s.c. survodutide 2.4, 4.8, or 6.0 mg, or placebo (PBO) for 48 weeks, 170 participants had F2–F3 fibrosis stage at baseline, and paired biopsy results were included in this analysis (NCT04771273). We evaluated the concordance among participants of ≥0.5 absolute reduction in enhanced liver fibrosis (ELF™) score and ≥30% reduction in liver stiffness measurement (LSM; by vibration-controlled transient elastography [FibroScan®]) with histological improvement in fibrosis with no worsening of MASH, as well as ≥30% reduction in liver fat content (LFC) (magnetic resonance imaging proton density fat fraction assessed) and ≥17 U/L reduction in alanine aminotransferase (ALT) with histological resolution of MASH with no worsening of fibrosis.

Results –A ≥0.5 reduction in ELF™ score and ≥30% reduction in LSM was observed in 38.9 vs 4.1% of participants treated with survodutide vs PBO, respectively; improvement in fibrosis with no worsening of MASH was observed in 52.8 vs 24.5%, respectively. A reduction in ELF™, LSM, and improvement in fibrosis with no worsening of MASH was observed in 18.5 vs 2.0% of participants treated with survodutide vs PBO, respectively ($p<0.05$ for all doses). A ≥30% reduction in LFC and ≥17 U/L reduction in ALT was observed in 58.8 vs 5.6% of participants treated with survodutide vs PBO, respectively; resolution of MASH with no worsening of fibrosis was observed in 62.3 vs 13.0%, respectively. A reduction in LFC, ALT, and resolution of MASH with no worsening of fibrosis was observed in 38.6 vs 1.9% of participants treated with survodutide vs PBO, respectively ($p<0.001$ for all doses).

Conclusions –The concordance of multiple NITs and biopsy results provides clear evidence of a robust effect from survodutide (over and above the PBO response) in the improvement of fibrosis (reduction of ELF™ and LSM) and resolving steatohepatitis (reduction of LFC and ALT) across all doses after 48 weeks.

Encore: Originally presented at the American Society of Nephrology Kidney Week 2025.

Conflicts of Interest:
QMA Research Grant Funding: AstraZeneca, Boehringer Ingelheim, Intercept. Consultancy on behalf of Newcastle University: Alimentiv, Akero, AstraZeneca, Axcella, 89Bio, Boehringer Ingelheim, Bristol Myers Squibb, Corcept, Enyo Pharma, Galmed, Genfit, Genentech, Gilead, GlaxoSmithKline, Hanmi, HistoIndex, Intercept, Inventiva, Ionis, IQVIA, Janssen, Madrigal, Medpace, Merck, Metadeq, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk, PathAI, Pfizer, Pharmanest, Poxel, Prosciento, Resolution Therapeutics, Roche, Ridgeline Therapeutics, RTI, Shionogi, Terns. Speaker: Fishawack, Integritas Communications, Kenes, Novo Nordisk, Madrigal, Medscape, and Springer Healthcare.
NA Grant/research support: 89Bio, Akero, Arbutus, Better Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb, Corcept, DSM, Galectin, Genentech, Genfit, Gilead, Hepagene, Healio, Intercept, Inventiva, Ionis, Madrigal, Merck, NGM, Noom, NorthSea, Novo Nordisk, Perspectum, Pfizer, Poxel, Viking, and Zydus; speaker's fees from AbbVie, Alexion, Echosens, Eisai, Gilead, Intercept, Madrigal, Perspectum, Salix, and Theratechnologies; Consultant for 89Bio, Boehringer Ingelheim, Echosens, Fibronostics, Gilead, Intercept, Madrigal, NorthSea, Novo Nordisk, Perspectum, Pfizer, and Zydus.

AJS Stock options: Genfit, Exhalenz, Tiziana, Indalo, NorthSea, Durect, HemoShear, and Rivus. Consultant: Intercept Pharmaceuticals, Inc., AstraZeneca, Amgen, Salix, Janssen, Gilead, Mallinckrodt, Terns, Merck, Siemens, 89Bio, NGM Bio, Poxel, Boehringer Ingelheim, Eli Lilly, HemoShear, Bristol Myers Squibb, Novartis, Novo Nordisk, Pfizer, Albireo, Regeneron, Genentech, Alnylam, Roche, Madrigal, Inventiva, Covance, ProSciento, HistoIndex, PathAI, and Genfit. Research grant support: Virginia Commonwealth University from Intercept Pharmaceuticals, Inc., Gilead, Bristol Myers Squibb, Eli Lilly, Merck, Boehringer Ingelheim, Novo Nordisk, Fractyl, Mallinckrodt, Madrigal, Inventiva, Novartis, and Pfizer. Royalties: Elsevier and UpToDate.
JMS Consultant: 89Bio, Akero, Alentis, Alexion, Altimmune, Astra Zeneca, Bionorica, Boehringer Ingelheim, Boston Pharmaceuticals, Eli Lilly, Gilead Sciences, GSK, HistoIndex, Ipsen, Inventiva Pharma, Kríya Therapeutics, Madrigal Pharmaceuticals, MSD Sharp & Dohme GmbH, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Siemens Healthineer. Speaker honorarium: AbbVie, Boehringer Ingelheim, Gilead Sciences, Ipsen, Lilly, Novo Nordisk, Madrigal Pharmaceuticals. Stockholder options: Hepta Bio.
VWSW Advisor/consultant: AbbVie, Allergan, Echosens, Gilead Sciences, Janssen, Novo Nordisk, Perspectum Diagnostics, Pfizer, and Terns; and a speaker for Bristol-Myers Squibb, Echosens, Gilead Sciences, and Merck.
MS Employment: Houston Methodist, and Houston Research Institute. Stock options: Rivus Pharma, CIMA, Cytodyn, and ChronWell.
LB, CS, MF, RM, DFM, and RY are employees of Boehringer Ingelheim.

Acknowledgements:
This study is supported and funded by Boehringer Ingelheim. The authors met criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE) as supported by Good Publication Practice (GPP) guidelines. The authors did not receive payment related to the development of the presentation. Sarah Krisanda, Msc, of Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group, provided writing support, which was contracted and funded by Boehringer Ingelheim. Boehringer Ingelheim was given the opportunity to review the presentation for medical and scientific accuracy as well as intellectual property considerations. Survodutide is licensed to Boehringer Ingelheim from Zealand Pharma, with Boehringer solely responsible for development and commercialization globally.

Data availability statement:
To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the International Committee of Medical Journal Editors criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim policy on transparency and publication of clinical study data, scientific and medical researchers can request access to clinical study data, typically, 1 year after the approval has been granted by major regulatory authorities or after termination of the development program. Researchers should use the https://vivli.org/ link to request access to study data and visit www.mystudywindow.com/msw/datasharing for further information.

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REAL-WORLD SEMAGLUTIDE TREATMENT PATTERNS AMONG MASH PATIENTS IN ENGLAND: AN ANALYSIS OF PRIMARY CARE PRESCRIPTION DATA

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Abstract Category: Disease Management of MASH/Liver Fibrosis Patients (including comorbidities)

Background Information/Purpose – Metabolic dysfunction–associated steatotic liver disease (MASLD), and its severe form, metabolic dysfunction–associated steatohepatitis (MASH), are major causes of chronic liver disease and liver-related morbidity and mortality. To date, no pharmacologic therapies have been approved for treating MASH in England. However, ongoing clinical trials are investigating semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, as a potential therapy. This study aimed to describe real-world semaglutide prescription patterns among MASH patients in England.

Methods – This retrospective analysis analyzed primary care prescription data from Prescription Episodes Statistics (PES) linked to hospital data from Hospital Episode Statistics (HES). The study period spanned from June 2020 to May 2025. Adults (≥18 years) prescribed any dose of semaglutide (based on British National Formulary codes) between June 2021 and November 2024 were identified, with a ≥1-year pre-index period and ≥6-month follow-up. The index date was defined as the first semaglutide prescription. Patients with prior GLP-1 receptor agonist use, advanced liver disease, or other exclusionary comorbidities were excluded. Eligible patients had ≥1 inpatient diagnosis of MASH/MASLD. Thereof, a subset of Wegovy® (semaglutide 2.4 mg/week) users was identified. Study outcomes included patient demographics, clinical characteristics, and treatment patterns.

Results – Between June 2021 and November 2024, 76,025 patients initiated semaglutide therapy. Among them, 5% (n=4,055) had an inpatient diagnosis of MASH/MASLD (mean (SD) age: 55 (12) years; male: 38%). In the subset of 2,100 patients prescribed semaglutide 2.4 mg/week, 110 had a diagnosis of MASH/MASLD (mean (SD) age: 52 (13) years; male: 32%). Among semaglutide users with MASH/MASLD, 76% (n=3,095) discontinued therapy, with a median time to discontinuation of 454 days (95% CI: 424–483). Nearly half (45%) discontinued within the first year. Among semaglutide 2.4 mg/week users with MASH/MASLD, 82% (n=90) initiated treatment at the recommended starting dose of 0.25 mg, while <10% titrated to higher doses within 16 weeks.

Conclusions – Real-world treatment patterns of semaglutide 2.4 mg/week use show deviations from recommended/per-label dosing schedule as outlined in the ESSENCE clinical trial (NCT04822181), coupled with high discontinuation rates. These findings underscore key challenges in maintaining long-term semaglutide therapy and optimizing treatment adherence in the MASH population.

[10]

SURVODUTIDE IMPROVED LIVER HISTOLOGY IN PEOPLE WITH MASH AND MODERATE-TO-SEVERE FIBROSIS REGARDLESS OF AGE, SEX, ETHNICITY, OR TYPE 2 DIABETES: SUBGROUP ANALYSIS OF A RANDOMIZED PHASE 2 TRIAL

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Abstract Category- Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose – Survodutide is a glucagon receptor/glucagon-like peptide-1 receptor (GCGR/GLP-1R) dual agonist in phase 3 trials for treatment of metabolic dysfunction-associated steatohepatitis (MASH) and obesity. In a phase 2 trial in people with biopsy-confirmed MASH and F1–F3 liver fibrosis, survodutide improved both steatohepatitis and liver fibrosis. We evaluated its efficacy in clinically important subgroups.

Methods –This 48-week, multinational, double-blind trial (NCT04771273) randomized 295 people aged 18–80 years with biopsy-proven MASH (Non-alcoholic fatty liver disease Activity Score [NAS] ≥4) and liver fibrosis stage F1–F3 to once-weekly subcutaneous placebo or survodutide, escalated over ≤24 weeks to maintenance doses of 2.4, 4.8, or 6.0 mg. Endpoints included: resolution of MASH (absence of ballooning [score of 0], no or mild inflammation [score of 0 or 1], and possible steatosis [score of 0 to 3]) without worsening of fibrosis; improvement in fibrosis (≥1 stage decrease) without worsening of MASH; % change in liver fat content (LFC) by magnetic resonance imaging–proton density fat fraction; absolute change in Enhanced Liver Fibrosis (ELF™) score; and % change in N-terminal propeptide of type III collagen (PRO-C3). We analyzed these endpoints post hoc by age (<65/≥65 years), sex (male/female), ethnicity (Hispanic/Latino or not), and presence or absence of type 2 diabetes (T2D) in participants with F2–F3 fibrosis who received ≥1 dose of trial drug and had baseline and end of treatment biopsies (n=170).

Results – At baseline, 138 (81.2%) participants were aged <65 years, while 85 (50.0%) were female, 48 (28.2%) Hispanic/Latino, and 71 (41.8%) had T2D. Resolution of MASH without worsening of fibrosis, and improvement in fibrosis without worsening of MASH, occurred in more of the survodutide groups than the placebo group across subgroups based on age, sex, ethnicity, and T2D. Similarly, survodutide was associated with larger reductions in LFC, ELF™ score, and PRO-C3 level across these subgroups.

Conclusions – Survodutide reduced MASH, fibrosis, and LFC across participant subgroups in this phase 2 trial, suggesting consistent benefits of this GCGR/GLP-1R dual agonist in different patient populations. There was no difference in MASH resolution based on age, sex, ethnicity, or T2D—and no difference in fibrosis improvement based on age, sex, or ethnicity, although response rate was possibly lower in those with T2D.
Encore: Originally presented at the American Society of Nephrology Kidney Week 2025

Encore: Originally presented at the American Society of Nephrology Kidney Week 2025

Abstract topic Therapeutic trials - MASH/liver fibrosis – Humans

Conflicts of Interest:
NA Grant/research support: 89Bio, Akero, Arbutus, Better Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Corcept, DSM, Galectin, Genentech, Genfit, Gilead, Healio, Hepagene, Intercept, Inventiva, Ionis, Madrigal, Merck, NGM, Noom, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, Poxel, Viking, and Zydus; speaker's fees from AbbVie, Alexion, Echosens, Eisai, Gilead, Intercept, Madrigal, Perspectum, Salix, and Theratechnologies; consultant for 89Bio, Boehringer Ingelheim, Echosens, Fibronostics, Gilead, Intercept, Madrigal, NorthSea Therapeutics, Novo Nordisk, Perspectum, Pfizer, and Zydus.
JMS reports consultancy fees from 89Bio, Akero, Boehringer Ingelheim, Inventiva Pharma, Ipsen, Madrigal, NorthSea Therapeutics, Novo Nordisk, Roche, and Siemens Healthineers; research funding from Boehringer Ingelheim, and stock options from AGED diagnostics and Hepta Bio; and speaker honorarium: Madrigal, MedPublico GmbH, and Novo Nordisk.
EB reports disclosures for Gilead Sciences Inc., Intercept Pharmaceuticals, Inc., and Novo Nordisk.
VWSW has served as an advisor/consultant for AbbVie, Allergan, Echosens, Gilead Sciences, Janssen, Novo Nordisk, Perspectum Diagnostics, Pfizer, and Terns; and a speaker for Bristol Myers Squibb, Echosens, Gilead Sciences, and Merck.
AJS reports stock options for Durect, Exhalenz, Genfit, HemoShear, Indalo, NorthSea Therapeutics, Rivus, and Tiziana; consultant: 89Bio, Albireo, Alnylam, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Covance, Eli Lilly, Genentech, Genfit, Gilead, HemoShear, HistoIndex, Intercept Pharmaceuticals, Inc., Inventiva, Janssen, Madrigal, Mallinckrodt, Merck, NGM Bio, Novartis, Novo Nordisk, PathAI, Pfizer, Poxel, ProSciento, Regeneron, Roche, Salix, Siemens, and Terns; research grant support: Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Fractyl, Gilead, Inventiva, Madrigal, Mallinckrodt, Merck, Novartis, Novo Nordisk, Pfizer, and Virginia Commonwealth University from Intercept Pharmaceuticals, Inc.; royalties: Elsevier and UpToDate.
MF, **SAH**, **RM**, and **RY** are employees of Boehringer Ingelheim.

Acknowledgements:
This study is supported and funded by Boehringer Ingelheim. The authors met the criteria for authorship as recommended by the ICMJE as supported by GPP guidelines. Sarah Krisanda, MSc, of Envision Ignite, an Envision Medical Communications agency, part of Envision Pharma Group, provided medical writing support, which was funded by Boehringer Ingelheim. The authors did not receive payment related to the development of this poster. Boehringer Ingelheim was given the opportunity to review the poster for medical and scientific accuracy, as well as intellectual property considerations.

Data Availability Statement:
To ensure independent interpretation of clinical study results and enable authors to fulfil their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data pertinent to the development of the publication. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data when it becomes available on Vivli - Center for Global Clinical Research Data, and earliest after publication of the primary manuscript in a peer-reviewed journal, regulatory activities are complete and other criteria are met. Please visit Medical & Clinical Trials | Clinical Research | MyStudyWindow for further information.

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IMPACT OF RESMETIROM ON LIVER TRANSPLANT DEMAND AND OUTCOMES IN MASH PATIENTS IN GERMANY: A MICROSIMULATION APPROACH

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Abstract Category: Pharmacoeconomic/Societal Aspects

Background Information/Purpose – Resmetirom received conditional marketing authorization from the EU Commission in August 2025 for the treatment of noncirrhotic metabolic dysfunction–associated steatohepatitis (MASH) in patients with moderate-to-advanced fibrosis. Germany faces a substantial MASH burden (≈5 million adults projected in 2030) and low liver transplantation (LT) rates due to limited organ donation (≈705 LTs/year). This project aimed to look at the potential impact of the first approved treatment for MASH on LT demand and waitlist constraints.

Methods –A microsimulation model was built to project disease progression among MASH patients, from steatosis to fibrosis, cirrhosis, and end-stage liver disease, at which patients become eligible for LT and enter the waiting list in Germany. Two scenarios were simulated over a 20-year horizon (2025–2045): (1) No-Resmetirom scenario and (2) Resmetirom scenario, in which it was assumed that 1% of MASH patients with moderate-to-advanced fibrosis initiate resmetirom in 2025 and 5% annually from 2026. Sensitivity analyses increased the annual uptake to 15%. Treatment effects were parameterized from MAESTRO-NASH, and transplant-related patient attributes were modeled using published Eurotransplant statistics.

RESULTS- In the base case, the model estimated 353 (7.11%) avoided LT waiting-list entries due to delayed progression or resolution of MASH with resmetirom. These avoided entries made 245 livers available for reallocation to other candidates with any end-stage liver diseases, averting 271 deaths and reducing average time on the waiting list by 10.27 days per waitlisted patient. Adjusting resmetirom uptake to 15%/year from 2026, the model estimated 883 (17.79%) avoided entries, 621 livers available for reallocation, 660 deaths averted, and a 24.73-day reduction in average wait time.

CONCLUSIONS- Resmetirom has the potential to alleviate LT demand in Germany's constrained transplant system by slowing or reversing MASH progression to end-stage liver disease. Broader treatment uptake may improve organ availability, reduce waitlist mortality, and enhance overall transplant equity, highlighting the population-level benefits of early MASH intervention.

[13]
ORAL CHOLATE CHALLENGE TEST CHARACTERIZES FUNCTIONAL DIFFERENCES BETWEEN CHILD-PUGH A5 AND A6

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Abstract Category- Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose –Liver function in patients with Child-Pugh (CP) A cirrhosis may vary from normal to severe functional impairment and shunting. Staging disease severity in patients with CP A cirrhosis is important for clinical decisions regarding further diagnostic testing, treatment, or follow-up interval. We used the oral cholate challenge test results to characterize and compare patients with CP A5 and A6.

Methods –Subjects were enrolled in two US prospective studies linking the oral cholate challenge test results to endoscopic findings. Test parameters were quantified from 20- and 60-min concentrations of orally administered d4-cholate. Serum was analyzed for cholate concentrations by LC-MS/MS. A disease severity index (DSI) and portal systemic shunting (SHUNT%) were calculated. We combined data from subjects with CP A cirrhosis from two studies: SHUNT-V (n=238) and HALT-C (n=216). Standard laboratory values included albumin, alkaline phosphatase, ALT, AST, bilirubin, INR, and platelet count.

Results – Subjects were age 56 ± 11 years, BMI 32 ± 7 kg/m2, 86% overweight, 54% obese, 61% male, 84% White race%, and 13% Hispanic ethnicity. Etiologies included hepatitis C (61%), MASLD/MASH (25%), and alcohol-associated liver disease (8%). Out of 454 subjects, 128 (28%) had small esophageal varices (EV), and 48 (11%) had large EV. Demographics were similar between CP A5 and A6; subjects with CP A6 were more likely to have hepatitis C (p=0.018) and less likely to have MASLD/MASH (p=0.008); laboratory values and MELD scores were significantly worse for CP A6 (p<0.001), except ALT (p=0.449); subjects with CP A6 were more likely to have large EV (23%) compared to CP A5 (8%) (p=0.0001). Oral cholate challenge test parameters showed significantly worse function and shunting (Figure 1) in subjects with CP A6 (DSI, 25.2 ± 7.9; SHUNT%, 43.8% ± 16.7%) versus CP A5 (DSI, 19.8 ± 6.4; SHUNT%, 33.0% ± 12.4%) (p<0.0001). For the detection of large EV on endoscopy, AUROCs for DSI (0.82) and SHUNT% (0.83) were significantly higher than CP score (0.63) (p<0.0001).

Conclusion- Patients with CP A6 cirrhosis have worse hepatic function and more portal-systemic shunting than patients with CP A5 cirrhosis. The oral cholate challenge test allowed characterization of functional differences in CP A5 versus A6 and was more predictive for EV than CP score. Given the heterogeneity within the CP classification, the cholate challenge test may be useful clinically in staging disease severity.

Disclosures- MPM is a paid consultant for HepQuant, LLC. JCI and GTE are employees and equity members of HepQuant, LLC. MPM and GTE have issued and pending patents. This abstract was presented at AASLD 2025.

[15]
INTRODUCING MASHTRACK, AN FNIH BIOMARKERS CONSORTIUM COLLABORATION TO VALIDATE PROGNOSTIC BIOMARKERS IN MASLD AND MASH

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Category: Diagnostic procedures - MASH/liver fibrosis

Abstract Category: Diagnostic procedures for MASH/Liver fibrosis

Background Information/Purpose –Drug development for treatment of metabolic dysfunction–associated steatohepatitis (MASH) and liver fibrosis remains constrained by reliance on histology to predict clinical outcomes. The Foundation for the NIH (FNIH) Biomarkers Consortium launched MASHtrack (Tracking Liver Fibrosis and Outcomes Through Non-Invasive Prognostic Biomarkers) to evaluate the prognostic performance of analytically robust, fit-for-purpose noninvasive tests (NITs) in patients with metabolic dysfunction–associated steatotic liver disease (MASLD). The study aims to determine whether serum-based and liver stiffness-based biomarkers can predict liver-associated clinical events (LACE) – including but not limited to overt ascites, hepatic encephalopathy, variceal hemorrhage, or new varices – and all-cause mortality. We hypothesize that biomarkers including NIS2+, ADAPT, MASEF, ELF, liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE), and composite scores (FAST, Agile 3+, Agile 4) will (1) predict future LACE and mortality, and (2) provide significant incremental prognostic value beyond the Fibrosis-4 (FIB-4) score.

Methods –MASHtrack applies a prospective specimen collection, retrospective-blinded evaluation (PRoBE) design using data and samples from the NIDDK NASH Clinical Research Network's (NASH CRN) Nonalcoholic Fatty Liver Disease Adult Database 2 cohort and baseline samples from placebo arms of MASH clinical trials with liver outcomes. Biomarkers will be analyzed across the disease spectrum. Statistical analyses will assess associations between biomarker values and subsequent LACE and all-cause mortality and evaluate whether these markers provide incremental prognostic value beyond FIB-4.

Results – MASHtrack is an ongoing project. Preliminary data review indicates that both the number of clinical outcome events and the breadth of biomarker data available are sufficient to conduct statistically meaningful assessments of prognostic performance across the included biomarkers.

Conclusion- MASHtrack will generate a harmonized evidence base to support letters of intent (LOI) for qualification of noninvasive biomarkers as prognostic tools for MASLD. By establishing standardized performance benchmarks, the project seeks to accelerate the adoption of NITs in both clinical research and practice, improving patient stratification, reducing biopsy dependence, and informing disease management and therapeutic development strategies.

[16]
DURABILITY OF RESMETIROM RESPONSE IN MASLD PATIENTS AFTER TWO YEARS OF TREATMENT IN MAESTRO-NAFLD-OLE

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[1]Summit Clinical Research, [2]Madrigal Pharmaceuticals, [3]Madrigal Pharmaceuticals, [4]Lucas Research, [5]University of Arizona for Medical Sciences

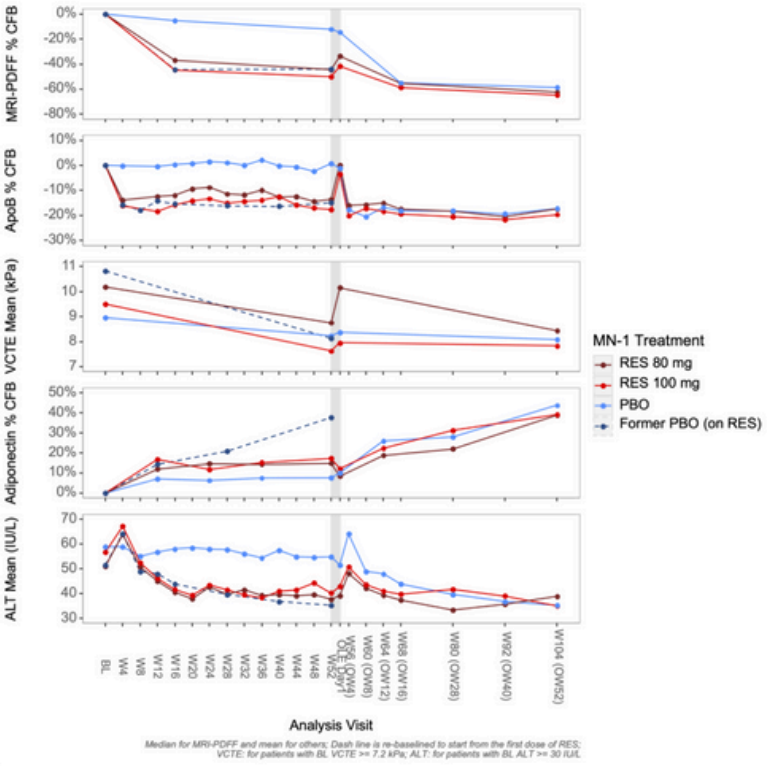
Abstract Category- Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose – Resmetirom (RES) is approved for treatment of adults with MASH and liver fibrosis. MAESTRO-NAFLD-1 (MN-1; NCT04197479) was a randomized, double-blind Phase 3 trial comparing placebo (PBO) with RES, a once-daily oral selective thyroid hormone receptor-β agonist. A total of 972 MASLD patients identified non-invasively were randomized 1:1:1 to RES 80 mg, 100 mg, or PBO for 52 weeks. MAESTRO-NAFLD-OLE (MN-OLE; NCT04951219) was a 1-year extension enrolling 515 MN-1 patients for an additional 52 weeks of RES treatment. Efficacy was evaluated after 2 years of RES and 1 year of RES in prior PBO patients.

Methods –MN-1 details are published (Nat. Med. 2023; doi:10.1038/s41591-023-02603-1). Inclusion criteria included ≥3 metabolic risk factors, FibroScan VCTE ≥5.5 kPa/CAP ≥280 dBm, and MRI-PDFF ≥8%. After a mean (SD) gap of 120 (84) days, 515 double-blind patients enrolled in MN-OLE (prior treatment: 168 RES 80 mg, 175 RES 100 mg, 172 PBO). MN-OLE participants received RES 80 or 100 mg for 12 weeks, then 100 mg through Week 52.

Results – MN-OLE baseline (n=515): mean age 57 (11) years, 52% female, 29% Hispanic, BMI 35 (6), type 2 diabetes 56%, hypertension 79%, dyslipidemia 77%, and VCTE 7.4 (4.7) kPa. RES for 2 years produced sustained biomarker improvements: lipids (mean [SE] % change) LDL -15% [2%], ApoB -19% [1], triglycerides -23% [2%]; liver enzymes ALT -25% [3%], AST -9% [4%], GGT -27% [3%]; MRI-PDFF median reduction -63%; VCTE -18% (baseline ≥7.2 kPa). PBO patients from MN-1 treated with RES in MN-OLE showed similar benefits. Adiponectin, a fibrosis-related biomarker, increased by 16% [2%] at 1 year and 39% [4%] at 2 years. The treatment gap between MN-1 and MN-OLE caused temporary biomarker loss, reversed after RES reinitiation. RES was well tolerated; restarting or titrating to 100 mg rarely caused new or recurrent GI AEs.

Conclusion: In a 52-week Phase 3 extension (MN-OLE), RES treatment for a second year resulted in durable effects on biomarkers including reductions atherogenic lipids, VCTE, MRI-PDFF and improvements in markers of liver injury and fibrosis in patients with MASLD and metabolic risk. PBO patients from MN-1 who received treatment with RES in MNOLE showed an improvement in biomarkers with RES in MN-OLE compared to treatment with PBO in MN-1.



[17]

ANALYSIS OF BIOMARKERS PRO-C3 AND ELF COMPONENTS IN BASELINE MASH/MASLD AND MASH CIRRHOSIS PATIENTS; CORRELATIONS BETWEEN CHANGE IN PRO-C3 AND ELF IN RESMETIROM-TREATED PATIENTS FROM THE MAESTRO-NASH TRIAL

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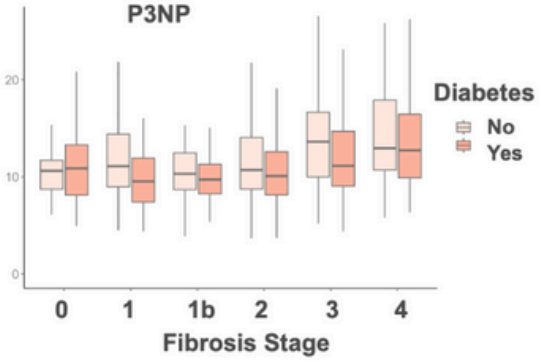
Abstract Category- Therapeutic Trials - MASH/Liver Fibrosis – Humans

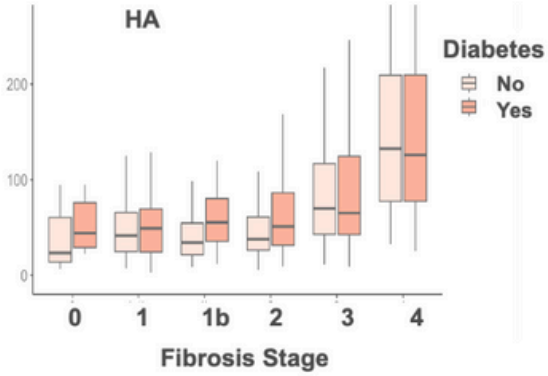
Background Information/Purpose – Resmetirom (RES) is approved for treating adults with MASH and liver fibrosis via the accelerated approval pathway based on histologic improvements in MASH and fibrosis. Noninvasive tests, including ELF and PRO-C3, characterize fibrosis and predict outcomes. RES reduces ELF and its components P3NP and TIMP-1, but not hyaluronic acid (HA) (N Engl J Med 2024;390:497–509). This study evaluated baseline ELF and components (TIMP-1, P3NP, HA) by biopsy fibrosis stage in MAESTRO-NASH (NCT03900429) and assessed correlations between baseline and Week 52 (wk52) ELF/P3NP and PRO-C3, as well as RES vs. placebo (PBO) effects on PRO-C3 and P3NP/ELF.

Methods –ELF and components were measured centrally in biopsy-proven cohorts from MAESTRO-NASH and MAESTRO-NAFLD-1 (NCT04197479): F0 (N=51), F1a/1c (N=126), F1b (N=126), F2 (N=356), F3 (N=540), F4 (N=107). PRO-C3 was analyzed in MAESTRO-NASH F1b/F2/F3 using the ELISA GEN2 assay. ANCOVA compared wk52 change (wk52CHG) in PRO-C3 and ELF between RES (80mg, 100mg) and PBO. Mean differences (95% CI, nominal p-values) were derived. Scatterplots and Spearman correlations (95% CI) assessed relationships between P3NP/ELF and PRO-C3 at baseline and wk52CHG.

Results – In biopsy-confirmed MASH, ELF increased from mean 9.4–9.6 (F0–F2) to 10.0 (F3) and 10.6 (F4). TIMP-1 and P3NP rose ~20% from F2 to F3/F4; HA was variable and higher in diabetics, increasing 1.9-fold from F3 to F4, explaining ELF rise in F4 patients. Baseline P3NP and ELF correlated with PRO-C3 (r=0.563 and 0.458). At week 52, PRO-C3 wk52CHG for RES 100mg -23.05 (4.76), 80mg, -17.93 (4.61), PBO, -0.19, (4.07) with mean difference (95% CI) in PRO-C3 wk52CHG, 80mg and PBO, -16.9 (-27.0, -6.76), p= 0.0011; 100mg and PBO, -22.1(-32.3, -11.84, p < 0.0001). In F3 patients, larger PRO-C3 reductions were seen 80 mg,-22.42 (6.38); 100mg, -27.42 (6.72); PBO, -0.50(5.46). Wk52CHG correlations between P3NP and PRO-C3 were 0.557, 0.548, and 0.524 for 100mg, 80mg, and PBO, respectively; ELF and PRO-C3 correlations were 0.483, 0.484, and 0.487, respectively.

Conclusion- Increased ELF in F3/F4 reflects rising HA, an extracellular matrix protein cleared by sinusoidal endothelial cells impaired in F4. PRO-C3 and P3NP, both fibrosis markers, were correlated and significantly reduced by RES vs. PBO, with greater reductions in F3. Evaluating ELF changes with treatment should consider its individual components.





[19]

Effect of Pemvidutide on Hepatic Injury, Inflammation, and Fibrosis in MASH: A Responder Analysis of the Phase 2b IMPACT Trial

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Abstract Category- Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose – Pemvidutide is a balanced 1:1 glucagon/GLP-1 dual receptor agonist in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). IMPACT is a Phase 2b, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3 (NCT05989711). Here, we present the results of responder analyses at 24 weeks to identify the proportion of patients achieving clinically meaningful improvements in non-invasive tests (NITs) of hepatic inflammation and fibrosis.

Methods –212 patients were randomized 1:2:2 to receive once-weekly subcutaneous pemvidutide [1.2 mg (N=41) or 1.8 mg (N=85)], administered without dose titration, or placebo (N=86). The mean age was 53 yrs, the mean BMI was 39 kg/m2, 58% were female, and 43% had type 2 diabetes. The proportion of patients achieving MASH resolution without worsening of fibrosis was determined by a histological analysis of serial biopsy specimens. NITs of hepatic steatosis [MRI-PDFF], hepatic injury [alanine aminotransferase (ALT)], hepatic inflammation [corrected T1 (cT1)], and hepatic fibrosis [enhanced liver fibrosis (ELF); liver stiffness measurement (LSM)] were analyzed, and responder analyses using cut-points reflecting meaningful clinical outcomes were performed.

Results –MASH resolution without fibrosis worsening was observed in 20% of patients in the placebo group, 58% of patients in the 1.2 mg pemvidutide group, and 52% of patients in the 1.8 mg pemvidutide group (each dose group $p<0.0001$ as compared to placebo, respectively). Compared to placebo, pemvidutide resulted in significantly greater proportions of patients achieving normalization of liver fat (4%, 31%, 44%; placebo, 1.2 mg, 1.8 mg, $p<0.0001$ for each dose), normalization of ALT (27%, 69%, 69%; $p<0.0001$ for each dose), and a ≥80ms reduction in cT1 (28%, 78%, 74%; $p<0.0001$ for each dose). Pemvidutide also resulted in a higher proportion of patients achieving a concurrent ≥0.5 reduction in ELF and 25% reduction in LSM [placebo (7%), 1.2 mg (43%; $p<0.0001$) and 1.8 mg (23%; $p=0.008$)].

Conclusion- Pemvidutide treatment resulted in statistically significant improvements in non-invasive markers of hepatic injury, inflammation, and fibrosis at 24 weeks compared to placebo. These data suggest that the 1:1 ratio of glucagon/GLP-1 in pemvidutide can rapidly reduce steatosis, yielding early and potent effects on the pathologic characteristics of MASH.

[21]

NON-INVASIVE TESTING TO RULE-IN MODERATE TO SEVERE FIBROSIS WHILE RULING OUT CIRRHOSIS FOR THERAPEUTIC INTERVENTION IN METABOLIC DYSFUNCTION ASSOCIATED STEATOHEPATITIS

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Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose –With the emergence of novel therapeutic interventions approved for the treatment of metabolic dysfunction associated steatohepatitis (MASH) and indicated to treat moderate to severe fibrosis (F2/F3), there is a need to recalibrate noninvasive testing (NIT) and identify MASH patients with high likelihood of F2–F3, while ruling out F4.

Methods- The NIT test is a multianalyte algorithm and an index resulting from a logistic regression equation using three analytes (Tissue Inhibitors of Metalloproteinases-1, hyaluronic acid, and alpha 2-macroglobulin) processed from serum. The model parameters are derived to rule in F2-F3 versus F0-F1 while ruling out F4 versus F0-F3 from a training cohort (n=396) and applied to validation cohort (n=640). The area under the curve (AUC) with sensitivity/specificity and interval likelihood ratio (LR) is calculated. The index is compared with FIB-4 and NAFLD Fibrosis Score.

Results- In the validation cohort, the NIT demonstrates discrimination for ruling in F2/F3 (AUC 0.794 vs 0.747 for FIB-4 [$p=0.034$] and 0.641 for NAFLD fibrosis score [$p<0.01$]) and ruling out F4 (AUC 0.904 vs 0.844 for FIB-4 [$p<0.01$], and 0.744 for NAFLD fibrosis score [$p<0.01$]). An index >13 yields 66% sensitivity and 77% specificity in detecting F2-F3 while an index > 76 yields 61% sensitivity and 94% specificity in detecting F4. LR for F2–F3 and F4 exhibits distinct trajectories. For F2–F3, LRs increases rapidly with rising scores, signaling strong discriminatory power for clinically significant fibrosis. At an index below 13, the LR is 0.4, strongly ruling out F2–F3. Between 13 and 24, the LR rise to 1.5 indicating a slight increase in probability, and by 24–45, the LR reaches 2.7 representing moderate evidence for F2–F3. This upward trend accelerates in the 45–76 interval, where the LR climbs to 6.8 and peaks at 26.2 for an index above 76. In contrast, LRs for F4 remains negative through the lower and mid-index ranges, effectively ruling out cirrhosis up to the 24-45 interval (LR=0.9). Only beyond 45 does the LR for F4 begin to rise meaningfully, reaching 2.7 in the 45–76 range and 10.6 above 76, where cirrhosis becomes highly probable. Thus, a treatment eligible interval between 13 and 76, is delineated where the test favors ruling in F2–F3 while maintaining low probability for F4.

Conclusion- Interval-based interpretation of the index enables staging of fibrosis, supporting clinical decisions for treatment initiation and monitoring.

[22]

REDESIGNING MASLD MONITORING: A GAME-THEORETIC MODEL FOR PERSONALIZED FOLLOW-UP

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Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose –Metabolic dysfunction-associated steatotic liver disease (MASLD) affects over one-third of the global population and is linked to obesity, type 2 diabetes, and metabolic syndrome. Management relies on lifestyle interventions for F1 fibrosis, with pharmacological therapy increasingly used in F2-F3 patients. Adherence to follow-up and treatment is often poor, influenced by social determinants of health (SDoH) such as income, education, and access to care. Optimal follow-up for F1-F2 MASLD remains undefined.

Methods- We developed a Bayesian game theory model to optimize physician–patient interactions in MASLD management. The model incorporates patient types (adherent vs. non-adherent), follow-up strategies - aggressive (AF, frequent visits) or conservative (CF, infrequent visits) - as well as clinical risk factors, SDoH, and adherence signals from non-invasive tests (NITs) and laboratory markers.

Results- The model shows that a patient's initial choice between AF and CF functions as an adherence signal, which physicians interpret using prior probabilities, clinical risk, and SDoH. As currently designed, AF and CF do not resolve adverse selection or moral hazard. To enable self-selection, CF must be redesigned with accountability features—for example, mandatory Enhanced Liver Fibrosis (ELF) testing between visits. In consecutive visits, updated NIT results guide adjustment: improvement or stability supports CF, worsening favors AF, and missed visits are treated as contextual signals requiring SDoH assessment rather than assumed non-adherence.

Conclusion- This model demonstrates that redesigning AF and CF to align incentives with adherence type is essential for minimizing adverse selection and moral hazard. A hybrid Bayesian game approach - combining patient signaling with physician oversight - emerges as the most effective strategy. The framework balances outcomes, resources, and satisfaction, and is adaptable to emerging pharmacological therapies.

[23]

DENIFANSTAT ELICITED A SIGNIFICANT ≥2-STAGE IMPROVEMENT IN FIBROSIS IN F3 MASH PATIENTS, AND IMPROVED LIVER FIBROSIS AND BIOMARKERS IN QFIBROSIS STAGE 4 MASH PATIENTS: SECONDARY ANALYSIS OF PHASE 2B FASCINATE-2 STUDY

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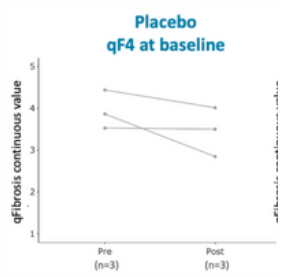
Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

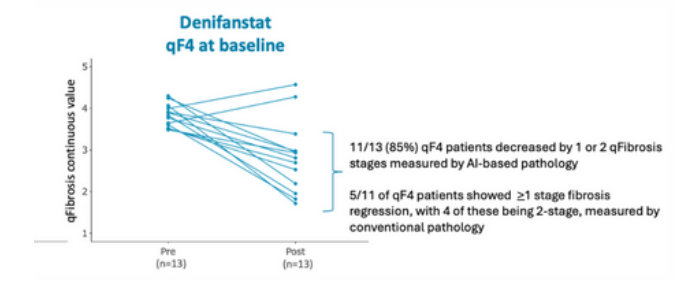
Background Information/Purpose –Therapies are needed for MASH cirrhosis, particularly those that treat liver fibrosis, the primary predictor of poor outcomes. Denifanstat (DENI), an oral fatty acid synthase (FASN) inhibitor, demonstrated significant regression of fibrosis and MASH resolution and prevented progression to cirrhosis in FASCINATE-2, a Ph2b study. AI-based digital pathology was used to identify a subset of patients with advanced fibrosis, defined as qFibrosis stage 4 (qF4), and to explore liver histology improvement with DENI in this subset.

Methods- 168 patients with biopsy-confirmed MASH fibrosis F2/F3 were randomized 2:1 to once daily oral DENI 50mg or PBO for 52 wks. Pre and post-treatment biopsy slides were read by a central pathologist using MASH-CRN scoring. A separate unstained slide was evaluated by second harmonic generation (SHG) AI digital pathology (HistoIndex) to identify patients with baseline qF4 (DENI n=13, PBO n=3). All analyses of qF4 were post-hoc.

Results- In F3 patients the response rate by CRN scoring for fibrosis improvement by ³2 stages w/o worsening of MASH was 34% (16/47) for DENI vs 4% (1/23) for PBO (p=0.0065). In qF4 patients, the response rate for fibrosis improvement by ³1stage w/o worsening of MASH was 39% (5/13) for DENI, of which 4/5 had ³2 stages improvement, vs 0% (0/3) for PBO. By digital pathology, the response rate for ³1 qFibrosis stage regression was 85% (11/13) in DENI vs 33% (1/3) in PBO. Several biomarkers were decreased by DENI at wk 52 in qF4 patients.

Conclusion- DENI demonstrated a robust anti-fibrotic effect as measured by both conventional and AI-based digital pathology. Digital pathology identified a subpopulation of MASH patients with advanced fibrosis (qF4). DENI reduced fibrosis and multiple biomarkers that indicate improvements in steatosis, inflammation and fibrosis in this subgroup. These findings support further clinical evaluation of DENI in patients with advanced fibrosis, including compensated liver cirrhosis.





BIOMARKERS	DENI	PLACEBO
FibroScan (kPa)	-29%	+26%
FAST score	-45%	+9%
MRI-PDFF (% liver fat)	-34%	+14%
ALT	-43%	+5%
AST	-37%	-1%
ELF	-0.3	+0.0
CK18 (M30)	-26%	+84%
CK18 (M65)	-35%	+40%

[25]
VELACUR AS A TOOL TO IDENTIFY PATIENTS WITH POTENTIALLY TREATABLE DISEASE AT POINT OF CARE

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Sonic Incytes Medical Corp.

Abstract Category: Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose –With the increasing prevalence of MASLD and MASH, and available new therapies, tools are needed to locate and identify candidates for treatment. As a cloud connected liver assessment tool, Velacur could provide insights into identifying eligible patients and connecting them to care.
This study examines Velacur exams from Sept 2023 to Sept 2025 to assess the overall prevalence of MASLD and MASH, and treatment eligible patients. Additionally, as many patients have a high BMI, the overall quality and exam success rates (i.e., a valid scan) of different BMI categories were examined.

Methods- The results of anonymous exams were collected from Velacur systems connected to the cloud. The median S-WAVE, ACE, VDFF (where available), scan quality and patient BMI (where available) were used in the analysis. The first week of exams after installation were excluded to avoid learning curve effects. The prevalence of MASLD (>234 dB/m), probable MASH (>5.4 kPa and >234 dB/m), and probable MASH with F2/F3 fibrosis (6-7.4 kPa and >234 dB/m), who would be currently eligible for treatment, were calculated. In patients where BMI was available, patients were grouped by category (Table 2). The mean scan quality and the overall success rate (% of scans >60% quality) were calculated. The quality of scans is assessed by an objective shear wave metric within the Velacur software.

Results- A total of 91 US-based clinics and 26,141 exams were included in the analysis. The prevalence of disease is shown in Table 1, with about 10% of exams representing potentially treatable patients.
When examining the quality and success of exams by BMI, 18,826 exams were included. The distribution of BMI by category is shown in Table 2. Even patients with a BMI >45 kg/m2 were successful >75% of the time, and more than 90% of patients <40 kg/m2 were successful.

One limitation is that these exams could include practice, or additional training exams performed for new operators. Typical training includes 2 half days hands-on training and up to 2 weeks of remote monitoring.

Conclusion- Velacur is a useful tool, for patients of all BMIs, to assess MASLD, MASH and treatment eligibility. As a cloud connected tool, there is great promise to collect and use this data to identify patients and allow them better access to care. Even in the highest BMI categories, Velacur was successful in the vast majority of patients, as assessed by an objective shear wave quality metric.

Table 1: Summary of patients disease status as measured by collected Velacur exams

Characteristic	Results
MASLD (% of patients)	62.3%
MASH (% of patient)	21.4%
Eligible for MASH treatment (% of patients)	10.2%
BMI (kg/m^2), where available	31.1 ± 6.3

Table 2: Summary of BMI categories and quality metrics

BMI (kg/m^2)	Category	Number of patients (%)	Percentage of Successful exams	Median (IQR) of Exam Quality
<25	1	2934 (15.5%)	98.9	94.6 (12.8)
25-30	2	5947 (31.6%)	97.1	92.1 (16.2)
30-35	3	5432 (28.8%)	95.0	88.0 (20.3)
35-40	4	2958 (15.7%)	91.3	82.8 (25.6)
40-45	5	1104 (5.8%)	85.9	76.8 (30.5)
>45	6	451 (2.4%)	76.2	67.5 (39.6)

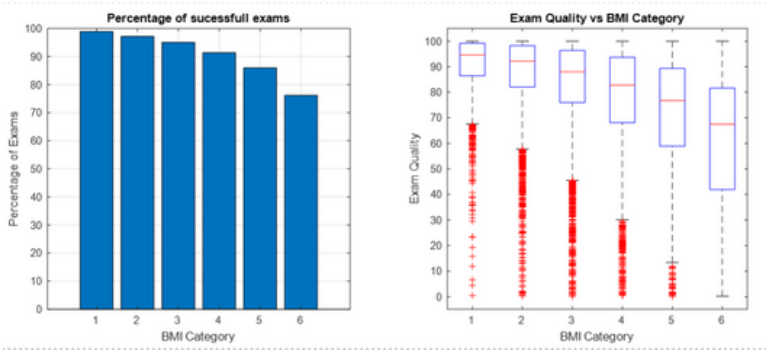

Figure 1: The overall success rates by BMI and the median exam quality

[27]

DYNAMICS OF NONINVASIVE TESTS (NITS, LIVERFAST (LFAST), FIB-4 AND VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY (VCTE, FIBROSCAN), DURING MONITORING THERAPY WITH TNR-BETA AGONIST RESMETIROM (RT) IN PATIENTS WITH MASH- UPDATE.

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Abstract Category- Diagnostic Procedures - MASH/Liver Fibrosis

Background Information/Purpose – LFAST is a new blood-based NIT that assess quantitatively fibrosis, activity, and steatosis. Aims: To assess the dynamics of LFAST, FIB-4 and VCTE and CAP in monitoring patients on-RT [fibrosis/steatosis ≥10% regression rate (10%RR) from baseline to repeated NIT].

Methods- On-RT patients with baseline (t0) and repeated (t1) NITs have been included retrospectively. Statistics included Kaplan Meier non-parametric censored at 10% RR from t0, Tukey-Kramer Multiple-Comparison Test and subgroup analysis for dose/GLP-1 receptor agonists (GLP-1RA) analysis.

Results- Eligible patients without RT discontinuation: n=86, 62% 80mg-dose, 39%-male, 55%-T2D, 46% GLP-1RA, mean(se) age 62.4(1.3), BMI 33.7(0.7), ALT 44(4), FIB4 1.79(0.14). T0-prevalence of F2F3 were 61%(LFAST) and 44% (VCTE). Median(max) delays(mths) t0-to-t1 were 3.4(LFAST), 7.6(VCTE) and 6.7(FIB4). 67pts. with t0-FIB4 had no change at t1, (1.85vs2.02), or AST (44vs36), platelets count (230vs224*109), all p=ns, and ALT (53vs40,p<0.05). 30 pts had repeated VCTE (median t0-10.7 vs t1-10.1Kpa) and CAP (t0-301 vs t1-299dB/m), all p=ns regardless the dose or the association with GLP-1RA. 44pts achieved t1-LFAST with median scores (t0vst1): fibrosis (0.48vs0.38,p<0.001), steatosis (0.50vs0.42,p<0.05), activity (0.45vs0.42,p=ns), mainly in the 80mg group (n=27) and in either groups of RT-alone or in combination to GLP-1RA for fibrosis (p<0.05). LFAST-fibrosis 10%RR from t0 has been achieved more within 80mg-RT group than within 100mg-RT at 3 and 6mths, respectively: 23.8%vs20.7% and 79.2%vs37.5%, overall logrank p<0.05). LFAST-steatosis 10%RR from t0 has been achieved more within 80mg-RT group (overall logrank p<0.05). The significant decrease t0-to-t1 in the total cholesterol has neither impacted the ApolipoproteinA1 [131 vs 146mg/dl] or LFAST-fibrosis score.

Conclusion: RT-Initiation based on NITs is efficient and allows further non-invasive monitoring. LIVERFASt is an efficient monitoring test that reflects histology remodeling and provides earlier insights into disease progression and RT response. A significant improvement (≥10%) in LIVERFASt fibrosis and steatosis scores have been observed after the 3rd month of RT mainly in the 80mg group. FIB-4 and VCTE/CAP scores showed limited change at reassessment.

[28]

TWO-YEAR TIME COURSE OF BIOMARKER AND IMAGING RESPONSES IN WELL-COMPENSATED MASH CIRRHOSIS PATIENTS TREATED WITH RESMETIROM

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Abstract Category- Therapeutic Trials - MASH/Liver Fibrosis – Humans

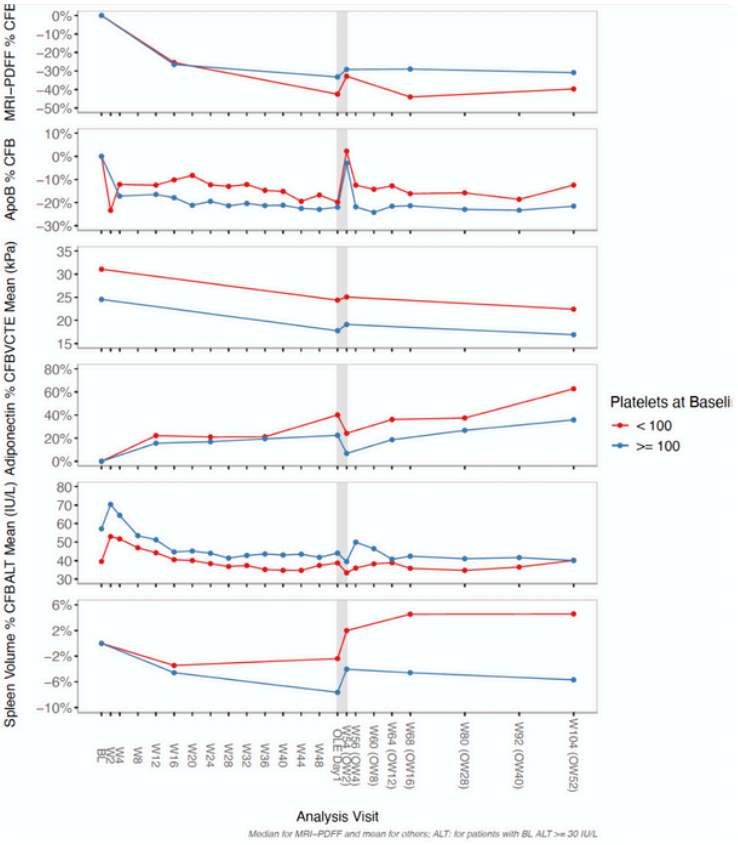
Background Information/Purpose – Resmetirom (RES), a selective thyroid hormone receptor beta agonist, is approved for metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced fibrosis. We evaluated two years of data in 122 compensated MASH cirrhosis patients treated with RES to assess durability of responses and the impact of a treatment interruption between year 1 (Y1) and year 2 (Y2).

Methods- Patients with Child Pugh A MASH cirrhosis (historic biopsy F4 >66% or clinical diagnosis) received 80 mg resmetirom for up to 2 years (MAESTRO-NAFLD-1 [NCT04197479] Y1; open-label extension [NCT04951219] Y2). A mean gap of 77 (58) days occurred between Y1 and Y2. Non-invasive biomarkers and imaging were analyzed at baseline and out to 2 years.

Results-Baseline: mean age 61.3 (9.1), female 56%, Hispanic 27%, BMI 35.3 (7.6) kg/m², T2D 70%. Median (Q1,Q3): VCTE 20.1 (17.1,31.3) kPa; ELF 10.7 (10.0,11.5); MRI-PDFF 8.6% (6.0,11.5). Agile3+ 0.96 (.89,.99); Agile4 0.69 (.35,.84). CSPH predicted in 49%; 93% with PLT <100k; 35% with PLT ≥100k. Spleen volume: PLT <100k (n=30) 867 (319); PLT ≥100k (n=92) 487 (220). Treatment interruption after Y1 led to loss of RES biomarker effects (lipids, MRI-PDFF, VCTE, adiponectin, spleen volume). RES re-initiation restored Y1 effects except in some with baseline PLT <100k. Five of six decompensation events occurred in patients with PLT <100k and elevated spleen volume.

At Y2, mean mean (95% CI) change from baseline in <100K, ≥100k, respectively: VCTE -7.9 (-14.1,-1.8), -6.4 (-8.7,-4.0) kPa; mean (95% CI) % change from baseline, ALT 6%(-11%, 23%), -25%(-32%,-19%); AST 31% (8%, 54%), -18% (-25%, -11%); GGT -19% (-39%, 0), -40% (-47%, -33%) (baseline ALT ≥ 30 IU/L); LDL -9% (-19%, 1%), -17% (-23%, -12%); ApoB -12% (-19%, -6%), -22% (-25%,-18%); TGs -13% (-35%, 9%), -20% (-27%, -14%); Adiponectin 63% (31%, 94%), 36% (26%, 46%); Spleen volume 5% (1%, 9%) and -6% (-9%, -2%).High Agile shifted lower in 35%; CSPH risk score decreased in 65%. Discontinuation rate was 8%. Mild gastrointestinal disorders were the most common adverse events.

Conclusion- Two years of RES treatment produced significant improvements in imaging and biomarker parameters. Temporary interruption between Y1 and Y2 attenuated benefits, which generally reversed with treatment restoration. These findings support resmetirom's potential to demonstrate clinical benefit in MAESTRO-NASH OUTCOMES, an ongoing outcome study.



[29]

COMPARATIVE MODULATION OF ADIPONECTIN ACROSS SELECT THERAPEUTICS IN CLINICAL DEVELOPMENT FOR MASH WITH FIBROSIS IDENTIFIES LANIFIBRANOR AS A DIFFERENTIATED METABOLIC MODULATOR.

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Abstract Category: Therapeutic Trials - MASH/Liver Fibrosis – Humans

Background Information/Purpose -Adiponectin (ADP) regulates lipid oxidation, insulin sensitivity, inflammation and fibrogenesis. Low circulating levels of adiponectin are linked to increased insulin resistance, cardiovascular risk and correlate with MASH histologic severity. Activation of PPAR pathways is known to restore adipose-tissue function and increase circulating ADP. In the phase 2b NATIVE study, lanifibranor produced a dose-dependent increase in circulating ADP together with improvements in histologic MASH resolution and fibrosis regression.

Methods- NATIVE evaluated lanifibranor 800 and 1200 mg/day versus placebo in 247 patients with non-cirrhotic MASH for 24 weeks of treatment. ADP serum levels, markers of lipid and glucose metabolism, Insulin Resistance (IR), inflammation, liver chemistries and hepatic steatosis by Continuous Attenuation Parameter (CAP) were also measured at baseline (BL) and end-of-treatment (EOT). Data from late-stage therapeutics in MASH were collected from publications.

Results-
Comparative modulation of adiponectin among late-stage MASH therapeutics:

	Lanifibranor (NATIVE) 24 weeks[1]		Resmetirom (MAESTRO-NASH) 52 weeks[2]		Efruxifermin (HARMONY) 24 weeks[3]		Pegozafermin (ENLIVEN) 24 weeks[4]		
Dose	800mg	1200mg	80mg	100mg	28mg	50mg	15mg	30mg	44mg
Mean (SD) absolute change of ADP from BL at EOT µg/ml	+ 11.95 (8.97 to14.94)$	+ 17.12f (14.29 to 19.96)$	+ 0.86 (0.19)*	+ 1.1 (0.19)*	+ 1.4 (0.34) £	+ 3.0 (0.34)£	+ 1.1 (0.7)£	+ 1.1 (0.3)£	+ 1.2 (0.4)£
Placebo	-0.35 (-3.20 to 2.50)		- 0.1 (0.18)		+ 0.28 (0.32)		- 0.6 (0.4)		

In NATIVE the magnitude of change of circulating ADP positively correlated with improvement of liver histological endpoints for disease activity, i.e. CRN-NAFLD activity score (NAS) score and individual activity components (ballooning and inflammation), and with improvement in fibrosis stage as well as an improvement in hepatic steatosis (CAP), ALT/AST and cardiometabolic markers 5.

THANK YOU FOR ATTENDING!

PARK CITY, UTAH - JANUARY 8-10, 2026