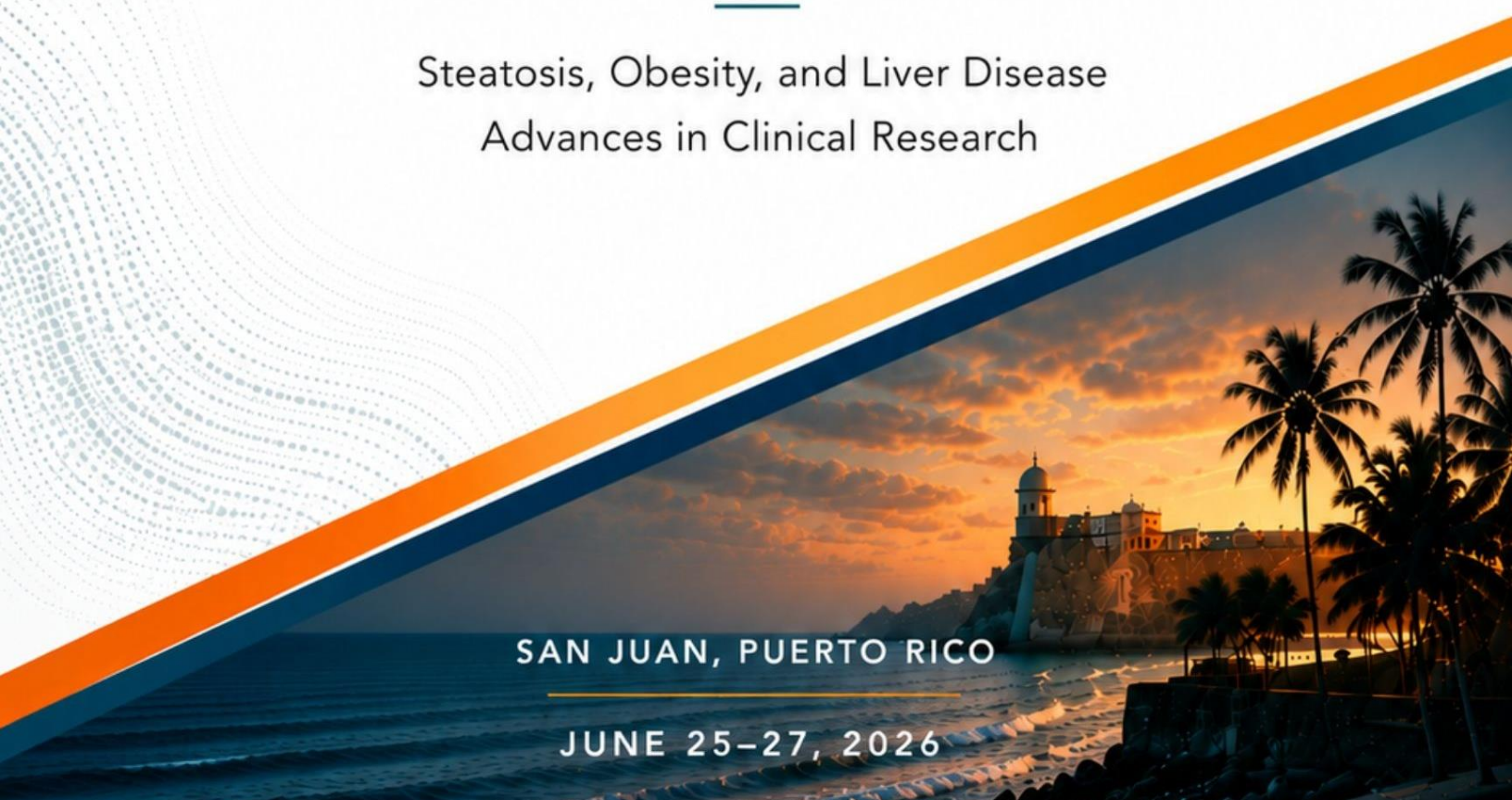
SOLAR

STEATOSIS, OBESITY, AND LIVER DISEASE
ADVANCES IN CLINICAL RESEARCH

2026 ANNUAL SCIENTIFIC CONFERENCE

# SCIENTIFIC ABSTRACT BOOK

Steatosis, Obesity, and Liver Disease
Advances in Clinical Research



SAN JUAN, PUERTO RICO

JUNE 25–27, 2026

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## NON-INVASIVE TESTING AND BIOMARKERS

### [A.1 – POSTER OF DISTINCTION]

### THE UTILITY OF ROUTINELY COLLECTED NON-INVASIVE TESTS TO ASSESS MORTALITY RISK IN A LARGE REAL-WORLD COHORT OF PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS FROM THE UNITED STATES

**Abstract category:** Non-Invasive Testing and Biomarkers

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#### BACKGROUND/AIM

It is crucial to identify people at high risk for metabolic dysfunction–associated steatohepatitis (MASH) to enable healthcare providers to appropriately focus on early interventions. Fibrosis Score 4 (FIB-4) is a well-established liver fibrosis risk assessment tool. High scores are indicative of severe disease and are associated with increased mortality. Nevertheless, it is uncertain whether other biomarkers that are collected in routine clinical practice can serve as prognostic indicators. This study aimed to establish whether aspartate transaminase (AST), alanine transaminase (ALT), the AST/ALT ratio, platelet count, estimated glomerular filtration rate (eGFR), and glycated hemoglobin (HbA1c) are reliable predictors of prognosis in people at high risk for MASH.

#### METHODS

This was a retrospective cohort study using Optum Market Clarity data (2016-2021). MASH was identified by International Classification of Disease, 10th Revision, Clinical Modification (ICD10-CM) code K75.81, with AST, ALT, and platelets tests within 3 months of diagnosis, excluding prior liver diseases. At MASH diagnosis, patients were classified by presence of cirrhosis based on ICD-10 codes, and a FIB-4 score was subsequently calculated. Fine-Gray models were used to assess the association between non-invasive tests (NITs) and all-cause mortality, and were adjusted for age, sex, region, and ethnicity.

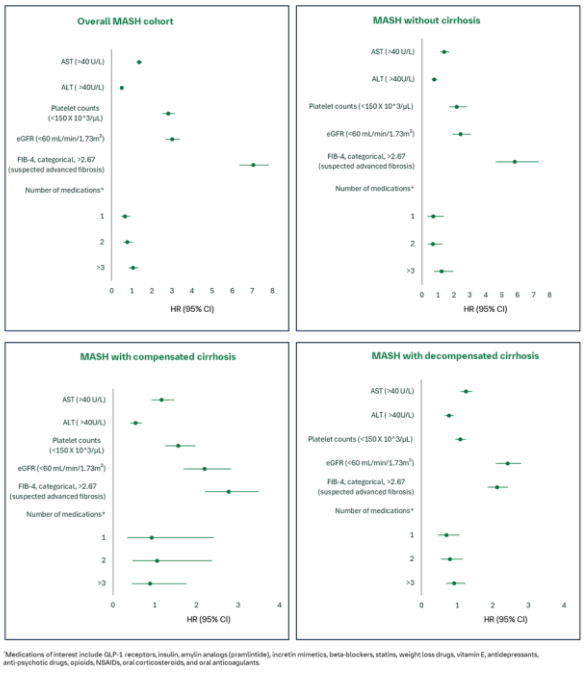
#### RESULTS

A total of 18,710 patients with MASH were included in the study. In the overall MASH population, a FIB-4 score greater than 2.67, compared to a score of 2.67 or lower, was a strong predictor of mortality, associated with a seven-fold increase in risk (adjusted hazard ratio [aHR] = 7.06; 95% confidence interval [CI] = 6.37–7.83). Elevated AST levels (>40 U/L vs ≤40 U/L; aHR = 1.38, 95% CI = 1.24–1.53) and lower platelet counts (<150 × $10^3$/µL vs ≥150 × $10^3$/µL; aHR = 2.83, 95% CI = 2.54–3.14) were linked to increased mortality. Additionally, reduced kidney function (eGFR <60 mL/min/1.73 m² vs ≥60 mL/min/1.73 m²) was associated with a more than two-fold heightened risk of mortality (**Figure**).

#### CONCLUSIONS

It is important to measure FIB-4, its components (AST or platelets), and eGFR in routine practice, as they show potential as prognostic biomarkers for overall mortality. The eGFR association with mortality suggests that assessing kidney disease severity in MASH is also important. However, more research is needed to confirm the prognostic value of these biomarkers in different populations and countries. The findings from this study can inform future MASH clinical guidelines regarding risk stratification and clinical assessment.

**Figure. Fine-gray models investigating factors associated with mortality**




**Previously presented at:** The American Association for the Study of Liver Diseases (AASLD) Annual Meeting (The Liver Meeting®) Washington, DC, USA; November 7–11, 2025; Liver Connect, Chula Vista, CA, USA; 26–28 February 2026; AMCP, 13–16 April 2026, Nashville, Tennessee, USA

**Sponsorship:** Boehringer Ingelheim

**Conflicts of Interest:**

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**ZAT**, **RY** and **CS** are employees of Boehringer Ingelheim.

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# THERAPEUTIC TRIALS – STEATOTIC LIVER DISEASE, CHOLESTATIC LIVER DISEASE, VIRAL HEPATITIS, OBESITY, AND LIVER FIBROSIS (HUMANS)

## [A.7 – POSTER OF DISTINCTION]

### PHASE 3 TRIAL OF SURVODUTIDE IN ADULTS WITH OBESITY AND MASLD

**Abstract category:** Therapeutic Trials – Steatotic Liver Disease, Cholestatic Liver Disease, Viral hepatitis, Obesity, and Liver Fibrosis (Humans)

*Carel W. le Roux, MBChB, PhD[1,2], on behalf of the SYNCHRONIZE™-MASLD Committees and Investigators*

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## BACKGROUND

Obesity is the leading cause of metabolic dysfunction–associated steatotic liver disease (MASLD). The high global prevalence and burden of obesity and MASLD, including its inflammatory phenotype, metabolic dysfunction–associated steatohepatitis (MASH), has created an urgent need for effective treatments for these diseases. Early treatment for MASLD is needed to reduce inflammation and alleviate the risk of cardiometabolic conditions. In previous phase 2 trials, survodutide, an investigational glucagon receptor/glucagon-like peptide-1 receptor dual agonist, induced substantial weight reduction in adults with obesity without type 2 diabetes (NCT04667377), and reduced liver fat content and improved liver histology in adults with biopsy-confirmed MASH and stage 1–3 liver fibrosis (NCT04771273; N=293).

## METHODS

This phase 3 trial (SYNCHRONIZE™-MASLD; NCT06309992) included adults aged ≥18 years with a body mass index of ≥30 kg/m$^2$ or ≥27 kg/m$^2$ with ≥1 metabolic obesity complication and presumed or

confirmed MASH, defined using imaging-based and non-invasive test criteria, or histology from a recent liver biopsy. Participants were randomized 2:1 to receive once-weekly, subcutaneous survodutide at a dose of 6.0 mg or placebo. The two co-primary endpoints were achievement of a ≥30% reduction in liver fat content (assessed by magnetic resonance imaging proton density fat fraction) and relative change (%) in body weight from baseline to Week 48. Safety was evaluated throughout the study.

### RESULTS

Enrollment and follow-up of all participants in the trial have been completed. The final patient visit occurred in December 2025. Results will be available in June 2026.

### CONCLUSIONS

SYNCHRONIZE™-MASLD will provide a robust evaluation of the efficacy, safety and tolerability of survodutide in adults with obesity and MASLD. Given the scope of the growing need for effective therapeutic options for MASLD, this analysis offers timely insights for healthcare providers.

**Previously presented at:** The American Diabetes Association (ADA) 86th Scientific Sessions, New Orleans, LA, USA; June 5–8, 2026.

**Conflicts of Interest: CWlR** reports personal fees: Boehringer Ingelheim, Eli Lilly, GI Dynamics, Herbalife, Johnson & Johnson, Keyron and Novo Nordisk outside the submitted work.

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## PHARMACOLOGY AND EMERGING THERAPEUTICS

### [A.17 – POSTER OF DISTINCTION]

### FIRST-IN-CLASS ORAL IKKA/B INHIBITOR HPN-01 DEMONSTRATES DISEASE-MODIFYING ACTIVITIES THROUGH SUPPRESSION OF HEPATIC FIBROGENESIS AND INFLAMMATION ASSOCIATED WITH MASH

### First-in-Class Oral IKKα/β Inhibitor HPN-01 Demonstrates Disease-Modifying Activities through Suppression of Hepatic Fibrogenesis and Inflammation Associated with MASH

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### BACKGROUND

Metabolic dysfunction-associated steatohepatitis (MASH) with fibrosis is a leading cause of cirrhosis and hepatocellular carcinoma (HCC). Current therapies primarily target hepatic steatosis but incompletely address inflammation and fibrogenesis, key drivers of disease progression. Hepatic stellate cell (HSC) activation plays a central role in fibrosis development and remains an important unmet therapeutic target. HPN-01 is a first-in-class, orally administered, highly selective long-acting dual IKKα/β inhibitor designed to simultaneously modulate steatosis, inflammation, and fibrosis. We evaluated the mechanistic and comparative efficacy profile of HPN-01, with emphasis on its anti-fibrotic and anti-inflammatory activities.

### METHODS

Mechanistic studies investigated IKKα-regulated pathways involved in hepatic inflammation, lipogenesis and fibrogenesis using transcriptomic analyses by RNA-Seq. Anti-fibrotic activity was

evaluated in diet-induced MASH animal models through histopathology, collagen deposition, fibrosis scoring, and molecular analyses of key inflammatory and fibrogenic mediators. Comparative efficacy studies were performed against resmetirom. Clinical safety and pharmacokinetic (PK) characteristics were assessed in a randomized, placebo-controlled Phase 1 study in healthy volunteers (25–150 mg; n=8/cohort).

### RESULTS

HPN-01 directly suppresses multiple IKKα-regulated pathways involved in hepatic inflammation, fibrogenesis and HSC activation. Treatment significantly reduced expression of fibrosis- and inflammation-associated mediators including MCP-1, LOX, TGF-β, and ITGA2, accompanied by reductions in α-SMA expression, collagen-I deposition, and fibrosis scores. Concurrent improvements in steatosis and inflammatory activities resulted in reduced NAS scores in MASH models. Compared with resmetirom, HPN-01 demonstrated greater suppression of key fibrogenic pathways, stronger attenuation of liver inflammation, and improved protection against liver injury without ALT/AST elevation. While resmetirom primarily improved lipid parameters, HPN-01 exhibited disease-modifying activities centered on inflammation and fibrosis pathway regulation. HPN-01 additionally suppressed HCC progression and tumor burden in preclinical models. In a Phase 1 study, HPN-01 was well tolerated without dose-limiting toxicities and demonstrated an extended half-life, supporting infrequent oral dosing.

### CONCLUSIONS

HPN-01 is a mechanistically novel first-in-class IKKα/β inhibitor that directly suppresses MASH-related liver injury including inflammation, fibrogenesis and steatosis in preclinical models. Its unique anti-fibrotic/inflammatory activities, favorable safety profile, and long-acting PK support further clinical development as a potential disease-modifying therapy for advanced MASH and prevention of progression to HCC.

## PEDIATRIC STEATOTIC LIVER DISEASE AND OBESITY

### [A.26 – POSTER OF DISTINCTION]

### IRON-CORRECTED T1 REFLECTS ONGOING DISEASE ACTIVITY IN PAEDIATRIC METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

**ENCORE abstract**

Alessandro Fichera, Elizabeth Shumbayawonda, Luis Felipe Cardiel, Benito de Celis Alonso, Marine Kleim, Andrea Dennis, Helena Thomaides Brears, Carlos Duncker, Silvia S. Hidalgo-Tobón, Po-Wah So

**Background and Aims:** Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasingly prevalent in children, particularly in those with obesity, but the underlying inflammatory mechanisms remain poorly defined. Current guidelines recommend MRI-PDFF for assessing steatosis in children with suspected MASLD. Iron-corrected T1 (cT1) is a biomarker of liver disease activity in adults, but its role in paediatric MASLD remains unclear. We investigated associations between circulating cytokines and cT1 in a Mexican paediatric cohort.

### METHODS

Eighty-nine Hispanic schoolboys (6-11 yrs) underwent non-contrast MRI for liver fat (PDFF) and liver disease activity (cT1); ALT and a 36-cytokines panel. MASLD was defined as PDFF≥5% and ALT>26 U/L. Liver disease severity was stratified using pre-defined cT1 thresholds, with cT1≥800ms indicating metabolic dysfunction-associated steatohepatitis (MASH), and cT1≥875ms high-risk MASH. Spearman correlation and linear regression were used to assess associations between cytokines and imaging biomarkers. Cytokine levels were compared across disease groups using ANOVA.

### RESULTS

Twelve of 89 participants had MASLD; among these, 33% had MASH and 50% high-risk MASH. cT1 positively correlated with cytokines involved in monocyte recruitment (MIP-1a, MCP-1a, MCP-4) and immune activation (IL-10, IL-15, IL-2, IL-4, and IL-7),

and negatively with growth factors (FGF-2, VEGFR1, and VEGF). PDFF was associated with MDC, MIP-1a, FGF-2 and VEGFR1. Increasing disease severity, from MASL to high-risk MASH, was associated with cytokines implicated in monocyte recruitment (MCP-1a, MCP-4), T-cell activation (IL-2), and interferon signalling (IP-10). IL-10 remained independently associated with cT1 after adjustment for BMI and PDFF, suggesting that cT1 detects inflammatory disease activity beyond that driven by obesity or steatosis.

## CONCLUSIONS

: cT1 was strongly associated with inflammatory cytokines in a cohort of Hispanic boys. These findings suggest that cT1 captures disease activity in paediatric MASLD not explained solely by obesity or steatosis. Combining cT1 with liver function tests may improve non-invasive assessment of disease activity, enabling accurate risk stratification and monitoring in paediatric MASLD.

# ORAL PRESENTATIONS

## NON-INVASIVE TESTING AND BIOMARKERS

### [A.4 – ORAL PRESENTATION]

### NONINVASIVE QUANTIFICATION OF LIVER FUNCTION AND PORTAL-SYSTEMIC SHUNTING DISTINGUISHES DIFFERENCES BETWEEN CHILD-PUGH A5 AND A6

**Noninvasive Quantification of Liver Function and Portal-Systemic Shunting Distinguishes Differences between Child-Pugh A5 and A6**

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[6] HepQuant, LLC, Denver, CO, USA

**Category:** Noninvasive testing and biomarkers

**Background and Aims:** Liver function in patients with Child-Pugh (CP) A compensated advanced chronic liver disease may vary from normal to severe functional impairment and shunting. Staging disease severity is important for clinical decisions regarding further diagnostic testing, treatment, follow-up interval, or enrollment in drug trials. We used the oral cholate challenge test (OCCT) results to characterize patients with CP A5 and A6.

**METHODS**

Subjects were enrolled in two U.S. prospective studies linking the OCCT results to endoscopic findings: SHUNT-V (n=238) and HALT-C (n=216). 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. Disease severity index (DSI), a measure of global liver function from 0 (healthy) to 50 (severe disease), and portal systemic shunt fraction (SHUNT%) were calculated.

**RESULTS**

Subjects were age 56 ± 11 years, BMI 32 ± 7 kg/m$^2$, 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). OCCT parameters showed significantly worse function and shunting 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).

**CONCLUSIONS**

Patients with CP A6 have worse hepatic function and more portal-systemic shunting than patients with CP A5. The OCCT 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 OCCT may be useful in staging disease severity, for both the clinic and in clinical trials.

**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. A version of this abstract was presented at Baveno VIII.

# THERAPEUTIC TRIALS – STEATOTIC LIVER DISEASE, CHOLESTATIC LIVER DISEASE, VIRAL HEPATITIS, OBESITY, AND LIVER FIBROSIS (HUMANS)

## [A.8 – ORAL PRESENTATION]

### TRIAL OF SURVODUTIDE ONCE WEEKLY FOR THE TREATMENT OF ADULTS WITH OBESITY: SYNCHRONIZE™-1

**Abstract category**: Therapeutic Trials – Steatotic Liver Disease, Cholestatic Liver Disease, Viral hepatitis, Obesity, and Liver Fibrosis (Humans)

*Carel W. le Roux, MBChB, PhD[1,2], on behalf of the SYNCHRONIZE™-1 trial Committees and Investigators*

[1]University College Dublin School of Medicine, Dublin, Ireland

[2]Ulster University, Coleraine, UK

#### BACKGROUND

Obesity is a chronic metabolic disease that warrants novel pharmacotherapeutic approaches. Despite the effectiveness of existing glucagon-like peptide-1 (GLP-1) medications in treating obesity, unmet needs remain, partly because of the heterogeneity among patients in response to current obesity treatment. Survodutide is an investigational glucagon receptor/GLP-1 receptor dual agonist that induced substantial weight reduction in a phase 2 trial in adults with obesity without diabetes.

#### METHODS

In this multinational phase 3 trial (NCT06066515), adult participants (aged ≥18 years) with a body-mass index (BMI) of ≥30 kg/m$^2$ or ≥27 kg/m$^2$ with ≥1 obesity complication (excluding diabetes), were randomized 1:1:1 to double-blind treatment with once-weekly subcutaneous survodutide up-titrated to 3.6 or 6.0 mg, or placebo. The two primary endpoints were percent change in body weight and a reduction in body weight of ≥5%, each from baseline to Week 76. Safety was evaluated throughout the study.

#### RESULTS

Enrollment and follow-up in the trial were completed, and the final patient visits occurred in October 2025. Results will be available in June 2026.

#### CONCLUSIONS

The SYNCHRONIZE™-1 trial will provide a robust evaluation of the efficacy and safety of survodutide for the treatment of obesity in a multinational cohort of adults with a BMI of at least 27 kg/m$^2$ without diabetes. With the rapidly evolving therapeutic landscape for obesity medications, this analysis will be of broad interest to healthcare providers.

**Previously presented at:** The American Diabetes Association (ADA) 86th Scientific Sessions, New Orleans, LA, USA; June 5–8, 2026.

**Conflicts of Interest: CWlR** reports personal fees: Boehringer Ingelheim, Eli Lilly, GI Dynamics, Herbalife, Johnson & Johnson, Keyron and Novo Nordisk outside the submitted work.

**Acknowledgements:**

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 abstract. Sarah Krisanda, MSc, of Envision Ignite, an Envision Medical Communications agency, part of Envision Pharma Group, provided editorial support, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). BIPI was given the opportunity to review the abstract for medical and scientific accuracy, as well as intellectual property considerations. The study was supported and funded by Boehringer Ingelheim. Survodutide is licensed to Boehringer Ingelheim from Zealand Pharma, with Boehringer solely responsible for development and commercialization globally.

## [A.20 – ORAL PRESENTATION]

### CHANGES IN LIVER FIBROSIS FOLLOWING 24 WEEKS OF PEMVIDUTIDE TREATMENT IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: QUANTITATIVE DIGITAL PATHOLOGY ANALYSIS FROM THE IMPACT PHASE 2B MULTICENTER RANDOMIZED PLACEBO-CONTROLLED TRIAL

**Changes in Liver Fibrosis Following 24 Weeks of Pemvidutide Treatment in Patients with Metabolic Dysfunction-Associated Steatohepatitis: Quantitative Digital Pathology Analysis from the IMPACT Phase 2b Multicenter Randomized Placebo-Controlled Trial**

Naim Alkhouri,[1,2] Shaheen Tomah,[3] Julio A. Gutierrez,[3,4] John J. Suschak,[3] Yukti Choudhury,[5] Elaine Chng,[5] Jay Yang,[3] M. Scot Roberts,[3] Rachel Garner,[3] Sarah K. Browne,[3] M. Scott Harris,[3] Christophe Arbet-Engels[3], Mazen Noureddin[1,6,7]

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**Background Information:** Pemvidutide is a balanced 1:1 glucagon/GLP-1 dual receptor agonist in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) where the direct hepatic effects of glucagon may provide greater efficacy over existing therapies. IMPACT was a 48-week, phase 2b, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3 (NCT05989711). At the week 24 (W24) primary endpoint, pemvidutide treatment showed statistically significant histologic MASH resolution and trends toward fibrosis improvement by conventional pathology reading. Artificial intelligence (AI) and noninvasive tests (NITs)-based analyses showed consistent evidence of anti-fibrotic activity as early as 24 weeks. Here, we evaluated fibrosis regression using second harmonic generation (SHG)/two-photon excited fluorescence (TPEF) microscopy imaging with a quantitative AI-based image analysis algorithm, Histoindex qFibrosis®.

## METHODS

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 (PBO). Between January and March 2026, biopsies from 183 patients (1.2 mg [n = 35]; 1.8 mg [n = 77]; PBO [n = 71]) with unstained slides available at baseline (BL) and W24 were imaged by SHG/TPEF and analyzed using qFibrosis®. The qFibrosis® analysis incorporated a correction for the steatotic area of each BL and W24 slide image.

## RESULTS

At W24, qFibrosis®-based continuous analyses showed significant improvements in fibrosis in both the 1.2 mg and 1.8 mg pemvidutide doses. Mean changes in continuous qFibrosis® values of -1.25 and -1.08 were observed in the 1.2 mg and 1.8 mg, respectively, compared with -0.15 in PBO ($p < 0.001$ for both). Regression of fibrosis by at least 1-stage occurred in 68.6% ($p < 0.001$ vs. PBO), 54.5% ($p = 0.002$ vs. PBO), and 29.6% of patients in the 1.2 mg, 1.8 mg, and PBO groups, respectively. Overall, 58.9% of patients receiving pemvidutide had a ≥ 1 qFibrosis® stage regression.

## CONCLUSIONS

Pemvidutide treatment for 24 weeks resulted in significant fibrosis regression in patients with F2 or F3 MASH as measured by qFibrosis® quantitative digital pathology. These data, together with previous AI- and NIT-based analyses, may support an antifibrotic effect with pemvidutide treatment as early as 24 weeks.

# EXPERIMENTAL/BASIC SCIENCE –LIVER DISEASE AND OBESITY (NON-HUMAN)

## [A.11 – ORAL PRESENTATION]

### MIRICORILANT, A SELECTIVE GLUCOCORTICOID RECEPTOR MODULATOR, REPROGRAMS HEPATIC GENE NETWORKS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

**Miricorilant, a Selective Glucocorticoid Receptor Modulator, Reprograms Hepatic Gene Networks in Metabolic Dysfunction-Associated Steatohepatitis**

*Rafael Mayoral Monibas[1], Jan Kroon[1,2], Hazel J. Hunt[1], Aprille Espinueva[1], William Guyer[1], Kavita Juneja[1]*

**Affiliations**: [1]Corcept Therapeutics Incorporated, Redwood City, California, USA; [2]Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, Leiden, Netherlands

**Background & Aims:** The hormone cortisol, which regulates metabolism and stress, has been implicated in the development and progression of metabolic dysfunction-associated steatohepatitis (MASH).

Miricorilant (MIRI) is an orally delivered, nonsteroidal selective glucocorticoid receptor modulator (SGRM). In a phase 1b study, patients with presumed MASH treated with MIRI 100 mg twice weekly had a 28.2% mean reduction in liver fat content, with improvements in hepatic, lipid, and glycemic markers (Alkhouri et al. *Hepatology* 2024). This study aims to explore MIRI's mechanism of action by determining its effects on gene expression in human cells in vitro.

### METHODS

Transcriptomic profiling was conducted in HepaRG cells, a human bipotent progenitor cell line that can differentiate into hepatocyte-like cells. Steatosis was induced by culturing cells in an oleic acid-rich medium for 7 days. Short-term treatment (8 hours) and sub-chronic treatment (5 days) with MIRI 400 nM (171.36 ng/mL) or vehicle was performed, and RNA-sequencing was used to assess gene expression changes induced by MIRI.

### RESULTS

MIRI induced a dual regulatory signature with distinct temporal dynamics. At the early time point (8 hours), MIRI treatment led to the upregulation of genes involved in lipid transport (APOA4, APOA5, CREB3L3), ketogenesis (HMGCS2), bile acid synthesis (CYP7A1), and antioxidant defense (GPX2). Balanced chemokine regulation (increased CXCL8/decreased CXCL13) indicates modulation of hepatocyte pathways for immune cell recruitment, while reducing chronic inflammatory signals. Genes associated with cell cycle and proliferation (AURKB, TOP2A, KIFC1, KIF4A, KIF14) were downregulated. Following sub-chronic treatment with MIRI for 5 days, prolonged upregulation of APOA4, CREB3L3, GPX2, and VNN1 suggested continued enhancement of lipid handling and antioxidant defense. Downregulation of CYP51A1 and gluconeogenic G6PC1 and PCK2 genes suggested longer-term reduction in steatosis and improved glucose metabolism. Downregulation of WNT6 supported reduced fibrogenesis.

### CONCLUSIONS

MIRI selectively modulated key genes in pathways that regulate hepatic steatosis, metabolism, oxidative stress, inflammation, and fibrosis. These findings provide insights into MIRI's molecular mechanism of action, potentially informing future therapeutic strategies. The ongoing phase 2b MONARCH trial (NCT06108219) is further evaluating MIRI in patients with biopsy-confirmed or presumed noncirrhotic MASH.

## DISEASE MANAGEMENT OF STEATOTIC/VIRAL/CHOLESTATIC LIVER DISEASE AND METABOLIC COMORBIDITIES

### [A.13 – ORAL PRESENTATION]

#### EFFECT OF CT-388 ON LIVER FAT IN ADULTS WITH OBESITY, WITH OR WITHOUT TYPE 2 DIABETES

Alexandra Steinberg, MD, PhD[1]; Federico A Argüelles-Tello, MD, MSc[2]; Leyla Leticia Sanchez-Sanchez, MD, MSc[2]; Helena B Thomaides Brears, DPhil[3]; Michael A Elliott, MA[1]; Caitlin R Langford, PhD[3]; Luis Acosta, BA[1]; Anna Karen Salinas Sanchez, M.D[2]; Jiawen Zhu, PhD[1]; Muhamed Barakovic, PhD[4]; Manu V Chakravarthy, MD, PhD[1]

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### BACKGROUND

CT-388, a cAMP signal-biased GLP-1/GIP receptor agonist, was evaluated vs placebo (pbo) in a 12-week phase 1b trial (NCT04838405) in participants (pts) with obesity (BMI ≥30 kg/m2), with or without (w/o) type 2 diabetes (T2D). Expanding on previously reported results from the trial that showed clinically meaningful reductions in body weight of ~9% (with T2D) to ~12% (w/o T2D), we report the effect of CT-388 on liver fat content (LFC) in pts with and w/o T2D.

### METHODS

Pts (N=50) were randomized 4:1 to receive CT-388 22 mg or pbo. MRI-proton density fat fraction was used to evaluate LFC; pts with baseline (BL) and Week 12 MRI data were included in the analysis (n=42: 29 w/o T2D, 13 with T2D). Median percentage change from BL, proportion of pts achieving target LFC reduction of ≥30% or

normalization (<5%) by Week 12, and descriptive statistics are reported.

## RESULTS

Baseline characteristics for the MRI population are summarized in the Table below. Overall, 71% (30/42) of pts had BL LFC ≥5% and 45% (19/42) had BL LFC ≥10%. In pts with BL LFC ≥5%, CT-388 was associated with reductions in LFC of 50% w/o T2D and 59% with T2D at Week 12 vs BL (Figure). Overall, 78% (18/23) of pts on CT-388 achieved LFC reduction ≥30% (67% w/o T2D and 100% with T2D vs 14% for pooled pbo pts), and 53% (12/23) reached normal (<5%) LFC levels (47% w/o T2D and 63% with T2D vs 14% for pooled pbo pts). In pts with significant liver steatosis (BL LFC ≥10%), similar results were observed with CT-388 – LFC reductions of 46% w/o T2D and 54% with T2D, 73% [11/15] pts with LFC reduction >30% and 27% [4/15] reaching normal LFC levels. No liver-related adverse events were reported with CT-388 treatment.

## CONCLUSIONS

In this phase 1 trial, CT-388 treatment was associated with clinically meaningful reductions in LFC in pts with obesity, with or w/o T2D. After 12 weeks of CT-388 treatment, pts with LFC ≥5% at BL, indicative of metabolic dysfunction-associated steatotic liver disease (MASLD), experienced median LFC reductions of 50%–60%, and most of these pts achieved target LFC reductions of ≥30%. Together with previously reported weight loss and glycemic control improvements for CT-388 treatment, these data suggest enhancements in metabolic health. Further trials are warranted to explore the potential benefit of CT-388 on MASLD in obesity.

# ABSTRACTS

## REAL-WORLD EVIDENCE AND OUTCOMES RESEARCH

### [A.2 – ABSTRACT]

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

**Abstract category:** Real-World Evidence and Outcomes Research

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#### BACKGROUND/AIM

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 who live with MASH but without cirrhosis, and to estimate progression to cirrhosis in the real-world setting.

#### METHODS

This was a retrospective observational study using electronic health records and claims data from the Optum® Market Clarity (OMC) database in the US. Eligibility criteria included ≥1 claim or medical encounter with a diagnosis code for MASH (International Classification of Disease, 10th Revision, Clinical Modification [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, 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 was 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/m$^2$. 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.

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**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.

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## [A.9 – ABSTRACT]

### ABSENCE OF BASELINE COMPLICATIONS DOES NOT EQUATE TO LOW RISK: INCIDENT OBESITY RELATED COMPLICATIONS AND MULTIMORBIDITY AMONG HEALTHY PEOPLE WITH OBESITY IN THE US

**Introduction**: Obesity is a chronic, progressive, relapsing, multisystem disease associated with a wide range of obesity-related complications (ORCs). However, treatment is often prioritized for patients with established complications, and limited evidence exists characterizing the risk trajectory among people with obesity (PwO) who are free of ORCs at baseline. Understanding disease progression in this population is critical to inform timely intervention and prevent downstream multimorbidity.

**METHODS**

: This retrospective observational study utilized the NorstellaLinQ Real-World Data to evaluate adult PwO and people with healthy weight (PwHW) without any baseline ORCs in the United States between 2017 and 2025. BMI categories were defined using EMR-derived measures and ICD-10 codes. A total of 48 ORCs across multiple organ systems (cardiovascular, metabolic, renal, hepatic, musculoskeletal, and mental health) were assessed. Cox proportional hazards models, adjusted for demographic and socioeconomic factors, estimated the risk of incident ORCs and multimorbidity across BMI categories.

**RESULTS**

: The study included 552,746 PwHW and 190,736 individuals with overweight or obesity, distributed across overweight (n=98,995), Class I obesity (n=52,685), Class II obesity (n=22,588), and Class III obesity (n=16,468). Compared with PwHW, individuals with overweight and obesity had significantly higher risks of incident ORCs, with incrementally higher risks observed with higher BMI. For metabolic and hepatic outcomes, HRs up to 10.26 (95% CI: 8.00–13.17) for MASH and 6.48 (95% CI: 6.09–6.89) for MASLD were observed for Class III obesity vs. PwHW. Cardiovascular risks were also elevated, including HRs up to 4.88 (95% CI: 4.09–5.83) for pulmonary embolism and 4.30 (95% CI: 3.64–5.08) for deep vein thrombosis. Elevated risks extended beyond cardiometabolic disease, including osteoarthritis (HR up to 3.30; 95% CI: 3.15–3.47) and rheumatoid arthritis (HR up to 2.18; 95% CI: 1.68–2.84). Over 4 years, PwO without baseline ORCs demonstrated significantly higher risk of incident multimorbidity, with up to 2.52-fold (95% CI: 2.47–2.56) increased risk of a first ORC, 3.04-fold (95% CI: 2.97–3.11) for two ORCs, and 3.68-fold (95% CI: 3.58–3.79) for three ORCs compared with PwHW.

**DISCUSSION**

These findings demonstrate that absence of baseline ORCs does not equate to low risk among PwO. Obesity confers substantial, short-term risk of a broad range of complications across organ systems, leading to multimorbidity. The observed gradient of risk across the BMI spectrum supports obesity as a key driver of multimorbidity risk. These findings extend understanding of the risk continuum in obesity, highlighting the need for earlier identification and proactive management of PwO, even in the absence of overt complications. Strengths of the study include a large, nationally representative dataset and

comprehensive multisystem ORC assessment. Limitations include potential BMI misclassification and reliance on administrative data.

## CONCLUSIONS

Obesity is a progressive, multisystem disease driving substantial and increasing risk of diverse, high-impact complications across organ systems. These findings suggest that treatment decisions should not be contingent on the presence of established complications, and that PwO without baseline ORCs also warrant timely and proactive management. Collectively, results underscore the need for earlier intervention to mitigate downstream clinical and economic burden.

**Disclosures:** The authors meet criteria for authorship as recommended by Good Publication Practice (GPP) and the International Committee of Medical Journal Editors (ICMJE) and did not receive payment related to the development of this abstract. Boehringer Ingelheim was given the opportunity to review the abstract for medical and scientific accuracy as well as intellectual property considerations. The study was supported and funded by Boehringer Ingelheim.

## [A.10 – ABSTRACT]

### BMI AND RISK OF DEVELOPING OBESITY RELATED COMPLICATIONS (ORCS) AND MULTIMORBIDITY AMONG PEOPLE WITH OBESITY IN THE US

## BACKGROUND

: Obesity affects approximately 40% of US adults and is associated with increased risk of multisystem obesity-related complications (ORCs). However, the real-world prevalence, incidence, and progression of ORCs across BMI categories remain incompletely characterized. This study aimed to assess ORC prevalence, incidence, progression to multimorbidity, and the association between obesity severity and incident ORCs among people with obesity (PwO) in US.

## METHODS

This retrospective observational study used NorstellaLinQ Real-World Data, a de-identified, tokenized database integrating EMR, closed and open claims, and mortality data (January 2017-March 2025). Adult individuals with overweight or obesity were compared with people with healthy weight (PwHW). A total of 48 ORCs across multiple organ systems were assessed. Cox proportional hazards models adjusted for demographic and clinical characteristics (including sex, race, smoking status, geographic region, coverage type, index year, and baseline ORCs) were used to estimate incident ORC risk and multimorbidity (≥1, ≥2, ≥3 ORCs). BMI categories included overweight, Class I (OC1), Class II (OC2), and Class III (OC3) obesity.

## RESULTS

: The study included 1,693,851 PwHW and 1,655,837 people with overweight or obesity (overweight: n=680,419; OC1: n=491,107; OC2: n=259,801; OC3: n=224,510). Baseline ORC burden was higher in people with overweight or obesity compared with PwHW, with ≥1 ORC observed in 67.3% of PwHW versus 85.4% in overweight, 88.5% in OC1, 91.3% in OC2, and 92.7% in OC3. The most prevalent ORCs were hypertension, dyslipidemia, and lumbago, each more prevalent with higher BMI (PwHW<overweight<OC1<OC2<OC3): hypertension (22.9%, 41.9%, 51.9%, 57.1%, 61.5%), dyslipidemia (8.9%, 15.2%, 22.8%, 26.0%, 30.2%), and lumbago (7.2%, 10.1%, 15.6%, 21.9%, 26.0%). During follow-up, time to first ORC was markedly shorter in people with overweight or obesity compared with PwHW (13.9 vs 3.4 months), decreasing further with increasing obesity class (2.6, 2.1, and 1.64 months for OC1–OC3). People with overweight and obesity had significantly and incrementally higher hazards of incident ORCs across all outcomes. For instance, risk of MASH increased from HR 2.24 (95% CI: 2.13–2.37) in overweight to 3.26, 4.16 and 4.66 in OC1-OC3, respectively. Similar patterns were observed for ORCs across different organ systems. The risk of multimorbidity also increased, with hazards of first ORC rising from 1.70 (95% CI: 1.70–1.71) in overweight to 2.15 (95% CI: 2.13–2.16) in OC3, with higher risks observed for ≥2 and ≥3 ORCs (p<0.0001).

## DISCUSSION

These findings demonstrate that obesity is strongly and incrementally associated with higher baseline morbidity burden, earlier onset, and faster progression to

multimorbidity stage across organ systems. ORCs appeared to accumulate rapidly (1-3 months) among people with overweight or obesity, stressing the need for timely and effective management of obesity to preserve wellbeing and minimize multimorbidity. Strengths of the study include the large dataset and comprehensive multisystem ORC assessment; limitations include potential BMI misclassification and reliance on administrative data.

## CONCLUSIONS

: Obesity is associated with higher ORC burden, earlier onset of complications, and accelerated progression to multimorbidity. These findings highlight the need for early and effective management of obesity to mitigate downstream clinical and economic burden.

**Disclosures:** The authors meet criteria for authorship as recommended by Good Publication Practice (GPP) and the International Committee of Medical Journal Editors (ICMJE) and did not receive payment related to the development of this abstract. Boehringer Ingelheim was given the opportunity to review the abstract for medical and scientific accuracy as well as intellectual property considerations. The study was supported and funded by Boehringer Ingelheim.

## [A.21 – ABSTRACT]

### CME LEARNERS CODE FOR MASLD AND MASH AT MORE THAN DOUBLE THE RATE OF NON-LEARNERS

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**Introduction:** The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) are increasing along with rising rates of obesity and metabolic disease. Increased awareness of steatotic liver disease is resulting in more individuals receiving diagnoses. The aim of this study was to compare rates of diagnosis of MASLD and MASH among CME learners and non-learners.

## METHODS

CME learners were identified from Medscape internal registration data for 16 Madrigal-supported activities addressing MASLD and MASH that launched between September 2024 to April 2026. Because Medscape registration captures the National Provider Identifier (NPI) for each clinician, learners were linked by NPI to Medscape's licensed claims universe, which is likewise indexed by NPI. This NPI-level overlap defined the analyzable population of clinicians appearing in both the Medscape universe and the claims universe. Within that population, diagnostic coding activity was compared between CME learners and a non-learner cohort of clinicians who did not participate in the activities. The outcome of interest was the average number of patient claims per clinician for MASLD (ICD-10 K76.0) and MASH (ICD-10 K75.81) over the claims reporting period of November 2024 through October 2025, calculated for each cohort and compared by diagnosis category.

## RESULTS

CME-learners had greater than 2-fold higher average diagnostic claims compared to non-learners. Among CME learners there was an average of 34.0 claims per clinician (N = 6299) for MASLD, compared to 14.5 claims for non-learners (N =75,250) (+19.5; $p$ <.0001). For diagnosis of MASH, CME learners (N =3,039) made an average of 15.0 claims vs 6.2 for non-learners (N =25,366) (+8.8; $p$ <.0001).

## DISCUSSION

This study demonstrates that CME-learners are coding more diagnoses for patients with MASLD or MASH compared to non-learners, potentially leading to a greater number of patients identified for treatment. Future studies will examine real-world data on the effect of CME on risk-stratification, diagnosis, and treatment initiation.

| Diagnosis | Learners (mean, N) | Non-learners (mean, N) | Rate ratio | Difference | z | p value |
|---|---|---|---|---|---|---|
| MASLD (K76.0) | 34.0, N = 6,239 | 14.5, N = 76,250 | 2.34x (95% CI 2.33–2.36) | +19.5 | 259.7 | < 0.0001 |
| MASH (K75.81) | 15.0, N = 3,039 | 6.2, N = 25,366 | 2.42x (95% CI 2.39–2.44) | +8.8 | 122.3 | < 0.0001 |

*Because the number of patient claims per clinician represents count data, differences between CME learners and non-learners were evaluated as rate ratios, with*

*statistical significance assessed using each cohort's observed claim rate and clinician count. For both diagnoses, CME learners coded at more than twice the rate of non-learners: 2.34 times for MASLD (ICD-10 K76.0; 34.0 versus 14.5 average claims per clinician) and 2.42 times for MASH (ICD-10 K75.81; 15.0 versus 6.2 average claims per clinician). Both differences were highly statistically significant ($p < 0.0001$), with narrow confidence intervals around each rate ratio reflecting the large clinician populations analyzed.*

## [A.22 – ABSTRACT]

### CARDIOMETABOLIC RISK PROFILE OF PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IN ENGLAND: A REAL-WORLD COHORT STUDY

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OBJECTIVES: Metabolic dysfunction-associated steatohepatitis (MASH) is associated with increased risk of liver-related and cardiovascular outcomes, contributing to substantial healthcare burden. This study aimed to assess the cardiometabolic characteristics of patients with MASH in England.

METHODS: A retrospective cohort study design was conducted using Clinical Practice Research Datalink Aurum data linked to the Hospital Episode Statistics and death registrations. Adults diagnosed with MASH between 2011 and 2020 were included. Cardiometabolic risk factors and related treatments were assessed 90 days after earliest MASH diagnosis (landmark date) based on all available prior data. A landmark date was used to prevent the inclusion of patients with advanced disease, with those who had a diagnosis of advanced liver disease before or within 90 days after MASH diagnosis excluded.

RESULTS: A total of 2,696 patients with MASH were included (mean [SD] age 56 (15) years; mean follow-up 4 years). Cardiometabolic comorbidities were common among the study population: 61.8% (n=1,667) had overweight/obesity, 47.3% (n=1,274) had hypertension, 47.1% (n=1,269) had diabetes, and 19.2% (n=517) had cardiovascular disease, while 16.6% (n=448) met criteria for metabolic syndrome. Mean (SD) LDL cholesterol was 106.7 (41.8) mg/dL and QRISK3 score was 20.9 (17.2), indicating elevated cardiovascular risk among patients in this study. Approximately half (49.1%, n=1,324) of patients received statins and 62.3% (n=1,680) antihypertensive therapy. Among patients with diabetes, use of GLP-1 receptor agonists (12.5%, n=159) and SGLT-2 inhibitors (8.9%, n=113) was limited.

CONCLUSION: Patients with MASH in England exhibit a high burden of cardiometabolic risk factors and elevated predicted cardiovascular risk. Treatment patterns suggest potential opportunities for improved cardiometabolic management in this population.

## [A.24 – ABSTRACT]

### PROGRESSION TO ADVANCED LIVER DISEASE TRAJECTORIES IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: REAL-WORLD TRANSITION ESTIMATES FOR ECONOMIC MODELLING

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OBJECTIVES: Economic models of metabolic dysfunction-associated steatohepatitis (MASH) require robust estimates of progression to advanced liver disease (ALD) states; however, such progression trajectories from real-world data remain limited. Here, we characterise progression to advanced liver disease among patients with MASH in England using time-to-event analyses to inform future disease modelling.

METHODS: Using Clinical Practice Research Datalink linked to Hospital Episode Statistics and death registration datasets, a cohort of adults diagnosed with MASH between 2011 and 2020 was followed longitudinally for progression to compensated cirrhosis (CC), decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant, and death. Kaplan–Meier (KM) analyses were conducted to estimate restricted mean time free from progression and survival probabilities across disease states. Progression was additionally summarised according to timing following diagnosis (<1 year, 1–2 years, and >2 years). Landmark

analysis was used to exclude progression events occurring within 90 days of diagnosis to reduce the inclusion of delayed disease recognition.

RESULTS: 2,696 patients with MASH were included. During follow-up (mean follow-up of 4 years), 356 patients experienced progression to ≥ 1 ALD state; 234 to CC (65.7%), 174 to DCC (48.9% overall; 31.0% for patients with known prior CC [n=54]) and 18 developed HCC (5.1% overall; 61.1% for prior CC patients [n=11]). Most progression events occurred <2 years after MASH diagnosis (to CC: 37.2% <1 year and 29.1% in 1-2 years vs 33.8% in >2 years; to DCC: 28.7% in <1 year and 26.3% in 1-2 years vs 47.7% in >2 years). Among patients progressing to CC, DCC, and HCC, median time to progression was 1.43, 1.74, and 1.11 years, respectively.

CONCLUSION: This study provides real-world progression trajectories from MASH to ALD states based on routinely collected healthcare data, highlighting an important need to prevent progression to CC and may be useful to support future MASH economic models.

## [A.25 – ABSTRACT]

### MULTI-ORGAN MAGNETIC RESONANCE-BASED IMAGING IMPROVES RISK STRATIFICATION AND SUPPORTS TREATMENT ALLOCATION IN INDIVIDUALS WITH CLINICAL OBESITY

**Encore abstract – previously presented at AACE 2026**

*Jackson E, Thomaides Brears H, Duncker C, Harhay M, Cardiel L, Dinani A, Desai N, Samala N, Muthiah M, Cusi K, Davies M, Cuthbertson D, Almandoz J, Kaplan L, Banerjee A*

**Objective:** Current BMI-based criteria may not be sensitive to identify at-risk individuals. Recently obesity was redefined based on body composition and dysfunction of multiple organs. Multi-organ, magnetic resonance-based imaging (MRI) allows early and precise risk stratification.

**METHODS**

We evaluated how multi-organ MRI improves prediction of outcomes and inform treatment allocation. We tested associations between 14 imaging phenotypes and new-onset type 2 diabetes (T2D), cardiovascular (CV), liver events (LRE), and mortality. Associations between clinical measures in standard of care (BMI 30 kg/m$^2$, adiposity-based preclinical and clinical obesity, T2D, hypertension, dyslipidaemia) examined. We modelled the impact of risk-guided treatment, using tirzepatide as an example.

**RESULTS**

23,087 UK Biobank participants were stratified as having preclinical vs. clinical obesity according to the Lancet Commission report (median age 64 years, 50% female, 18% BMI 30 kg/m$^2$, 30% had preclinical and 31% had clinical obesity). Median follow-up time was 4.3 years.

Adding multi-organ MRI improved stratification of individuals at highest risk of any new-onset hospitalisation (adjusted Cox proportional hazard ratio (HR) 6.3) compared to clinical measures alone (HR 2.5).

Clinical obesity, elevated pancreatic and liver fat and liver dysfunction, defined by increased iron-corrected T1 (cT1, a measure of liver disease activity) was associated with an increased risk of new-onset T2D. (HR 27.2)

Elevated liver cT1, reduced LVEF, and low skeletal muscle were together associated with increased all-cause mortality (HR 4.4). In those with clinical obesity and elevated cT1, associations with LREs were also more pronounced. Adding MRI measurements of LVEF and cT1, to obesity status for guiding allocation of tirzepatide treatment, reduced the number needed to treat to prevent one death from 159 to 20.

**CONCLUSIONS**

Quantitative multi-organ multiparametric MRI, especially measurement of LVEF, liver cT1 and skeletal muscle, could refine stratification of individuals with obesity better than BMI alone. Incorporating this approach provides a precision framework for identifying individuals most likely to benefit from obesity treatment.

## [A.29 – ABSTRACT]

### THE IMPORTANCE OF COMMUNITY MASLD SCREENING FOR EARLY DETECTION OF FIBROSIS IN HIGH-RISK PARTICIPANTS

**The Importance of Community MASLD Screening for Early Detection of Fibrosis in High-Risk Participants**

Austin Mahajan, MS-3; Cecily Waynar; Anish Kankipati, Jenna Bseiso; Joey Haddad; Sary Alothman, Colin Walsh, Mark Abbott, Jonah Betel, Sherri Brown; Naim Alkhouri, MD; Michael Betel, MSc, BA

#### BACKGROUND

Community screening may improve early identification of metabolic dysfunction-associated steatotic liver disease (MASLD) and fibrosis among at-risk adults. Social media and community outreach may help recruit high-risk individuals and improve access to noninvasive liver screening. This analysis evaluated the yield of community MASLD screening events using intake questionnaires, FibroScan assessment, and provider counseling.

#### METHODS

Subjects were recruited using targeted social media outreach (primarily Facebook and Instagram) through paid and organic campaigns. Advertisements were geographically restricted to a 16-mile radius from six locations in South Texas and Northeast Ohio, and targeted adults aged 35 years and older with interests or self-reported risk factors associated with metabolic disease, including obesity, type 2 diabetes, hypertension, dyslipidemia, and fatty liver disease. Messaging emphasized liver health awareness, free education, and optional non-invasive liver assessment. Interested individuals registered online in advance of the event. Adults attending six community liver health events completed a questionnaire assessing demographics, anthropometrics, race/ethnicity, liver health, cardiometabolic comorbidities, recent labs, alcohol use, and fasting status. Vibration-controlled transient elastography (VCTE) was performed using controlled attenuation parameter (CAP) and liver stiffness measurement (LSM). Participants reviewed results with a provider, who discussed liver health, cardiometabolic risk, follow-up, and referral. Descriptive statistics were used. CAP ≥240 dB/m was used to identify MASLD/SLD, LSM >8 kPa to identify significant fibrosis, and LSM >20 kPa to identify possible cirrhosis.

#### RESULTS

Across six community screening events, 308 participants underwent VCTE. The mean age was 54.7 yrs, 32.5% were male, with an average weight of 186.5 lbs. 21.1% had a known history of fatty liver/MASLD, yet only 11.0% had a liver scan done prior to the event. Of the participants, 15.6% had type 2 diabetes, 32.8% had hypertension, and 46.1% had high cholesterol. The mean CAP score was 264.8 ± 49.8 dB/m, with 213 subjects having CAP above 240 dB/m, indicating a prevalence of MASLD/SLD of 69.2%. Mean LSM was 7.1 ± 6.4 kPa, with 60 patients having LSM >8 kPa indicating the presence of F2 fibrosis or higher in 19.5% and 8 patients (2.5%) with LSM >20 kPa indicating the presence of possible cirrhosis.

#### CONCLUSIONS

Community screening events for subjects at high risk for MASLD, recruited through social media and community outreach, led to the identification of MASLD/SLD in 69.2% and significant fibrosis in 19.5% of participants who received VCTE. Implementing large scale events could potentially identify subjects who would benefit from early counseling, hepatology referral, follow-up, and potential pharmacologic intervention.

## [A.30 – ABSTRACT]

### SELF-REPORTED CARDIOMETABOLIC RISK STRATIFIES FIBROSCAN SCREENING YIELD IN NORTHEAST OHIO COMMUNITY LIVER HEALTH EVENTS

**Self-Reported Cardiometabolic Risk Stratifies FibroScan Screening Yield in Northeast Ohio Community Liver Health Events**

Austin Mahajan, MS-3; Cecily Waynar; Jenna Bseiso; Colin Walsh, Sary Alothman, Mark Abbott, Jonah Betel, Sherri Brown, Naim Alkhouri, MD; Michael Betel, MSc, BA

#### BACKGROUND

Community liver screening and clinical-trial prescreening events to identify patients with MASLD and significant fibrosis often occur before chart-confirmed diagnoses or laboratory data are available. In high-volume events, limited FibroScan devices, operators,

volunteers, and providers may limit screening capacity. We evaluated if a brief self-reported cardiometabolic risk score could stratify elevated FibroScan controlled attenuation parameter (CAP) and liver stiffness measurement (LSM).

### METHODS

We performed an observational analysis of adults attending three Northeast Ohio community liver health events in spring 2026. Participants completed a questionnaire assessing self-reported height and weight for BMI calculation, type 2 diabetes, blood pressure, and cholesterol, then underwent FibroScan. The analytic cohort included participants with valid CAP and LSM, fasting >3 hours, and complete score data. Elevated steatosis risk was defined as CAP ≥275 dB/m and elevated fibrosis-risk category as LSM ≥8 kPa. The score assigned one point each for BMI ≥30, type 2 diabetes, high blood pressure, and high cholesterol.

### RESULTS

Of 216 screened participants, 178 met analytic criteria. CAP ≥275 dB/m was present in 42.6%participants with ≥1 risk factor, 48.3% with ≥2, and 53.1% with ≥3. Using two-sided Fisher exact testing with α=0.05, all CAP threshold comparisons were significantly associated with CAP ≥275 dB/m. The ≥1 threshold showed strong sensitivity for CAP ≥275 dB/m (89.2%), while the ≥3 threshold showed strong specificity (86.7%). For LSM ≥8 kPa, only the ≥1 threshold achieved statistical significance, with strong sensitivity (90.6%) and NPV (92.9%).

### CONCLUSIONS

A brief questionnaire-derived cardiometabolic risk score may enrich community FibroScan screening yield for elevated CAP and help sequence participants through high-volume events when FibroScan devices, operators, or providers are limited. The score may support intake triage before FibroScan and post-scan triage using CAP and LSM to guide provider evaluation, follow-up, or trial prescreening. For LSM, limited rule-in utility suggests fibrosis-risk assessment still requires objective laboratory data, clinical context, and hepatology evaluation. Future work should assess sampling bias and health literacy, healthcare access, digital access, education, and home monitoring.

## CLINICAL TRIAL DESIGN

### [A.3 – ABSTRACT]

### FROM BIOPSY TO BIOMARKER: DISEASE SEVERITY INDEX (DSI) FROM THE HEPQUANT DUO TEST AS A REASONABLY LIKELY SURROGATE ENDPOINT

**From Biopsy to Biomarker: Disease Severity Index (DSI) from the HepQuant DuO Test as a Reasonably Likely Surrogate Endpoint**

Joanne C. Imperial[1], Michael P. McRae[2], Gregory T. Everson[1]

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### BACKGROUND

Metabolic dysfunction-associated steatohepatitis (MASH) cirrhosis trials face major challenges in predicting clinical outcomes and assessing treatment effects due to patient heterogeneity and reliance on invasive liver biopsies. Current FDA draft guidance recommends composite endpoints such as progression to cirrhosis, hepatic decompensation events, worsening MELD score (≥15), liver transplantation, and all-cause mortality. However, no validated surrogate endpoints (VSE) exist for these outcomes, creating a critical gap in trial design and drug development.

### METHODS

We propose the Disease Severity Index (DSI), derived from the oral cholate challenge test (HepQuant DuO®), as a Reasonably Likely Surrogate Endpoint (RLSE) for compensated advanced chronic liver disease (cACLD). The Test uses stable isotope–labeled cholate and LC-MS methods to quantify hepatic blood flow and portal-systemic shunting. Data from over 3,000 tests in 1,500 patients have been analyzed to evaluate DSI's predictive ability, reproducibility, and responsiveness to treatment.

### RESULTS

Baseline DSI strongly predicted risk for liver-related events (LREs), including variceal hemorrhage, ascites, and mortality. A threshold of DSI ≤18.3 was validated to rule out large esophageal varices and clinically significant portal hypertension in F4, majority MASH subjects, while DSI >24 identified the highest-risk subjects. Serial changes in DSI correlated with disease progression and treatment response; a ≥2-unit change

represented a clinically meaningful improvement beyond random variability (MDD = 1.72). Reproducibility studies confirmed excellent reliability (ICC = 0.93). Clinical trial simulations indicated that incorporating DSI as an endpoint could reduce sample size and trial duration. Drug studies (e.g., resmetirom, avenciguat, rencofilstat) showed dose-dependent reductions in DSI, linking functional improvement to reduced estimated risk for clinical outcomes.

## CONCLUSIONS

DSI fulfills FDA criteria for RLSE and offers a noninvasive, validated, pharmacodynamic biomarker for MASH cirrhosis and other cACLD etiologies. Its adoption could accelerate drug development, enable adaptive trial designs, and reduce reliance on invasive biopsies, representing a transformative advance in clinical trial methodology.

**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.

## [A.12 – ABSTRACT]

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

### MONARCH: a Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Miricorilant in Adult Patients with Metabolic Dysfunction-Associated Steatohepatitis (MASH)

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## BACKGROUND

Cortisol, a hormone that regulates metabolism and stress, has been implicated in the development and progression of MASH. Miricorilant, an orally delivered, nonsteroidal, selective glucocorticoid receptor modulator, may reduce hepatic steatosis by modulating cortisol activity and improving liver health. In a phase 1b multi-cohort, dose-finding trial (NCT05117489), adult patients (pts) with presumed MASH were treated with MIRI 30 to 200 mg dosed daily or intermittently for 12 or 24 weeks (wks). MIRI 100 mg twice weekly had the best benefit-risk profile. At wk 12, the mean relative reduction in liver fat content (LFC) was −28.2% (standard deviation [SD]: 13.5), with a corresponding decline in liver enzymes (mean change from baseline: alanine aminotransferase, −4.0 [SD: 21.4]; aspartate aminotransferase, −6.0 [SD: 7.2]). This dose of MIRI was safe, well-tolerated, and resulted in improved hepatic, lipid, and glycemic markers (Alkhouri et al. AASLD 2023). Consequently, twice-weekly MIRI is being evaluated in the phase 2b MONARCH study (NCT06108219).

## METHODS

Adult pts (18–75 years) with LFC ≥8% by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and risk factors for MASH (type 2 diabetes mellitus or metabolic syndrome) were enrolled. Cohort A included 82 pts with liver biopsy-confirmed MASH (NASH-CRN fibrosis stage 2 or 3) and a nonalcoholic fatty liver disease activity score (NAS) ≥4. Cohort B included 93 pts who have a liver biopsy result that does not meet the criteria for inclusion in Cohort A and a NAS ≥3 and NASH-CRN fibrosis score of 1, or a NAS ≥2 and NASH-CRN fibrosis score of 2 or 3. Pts in Cohort A will be randomized 2:1 to MIRI 100 mg or placebo twice weekly for 48 wks. Pts in Cohort B will be randomized 2:1 to MIRI 100 mg or placebo twice weekly for 6 wks, followed by dose escalation to MIRI 200 mg or placebo for 18 wks. Randomization

will be stratified by type 2 diabetes status and fibrosis stage. The primary endpoint is change from baseline in LFC at wk 24, as assessed by MRI-PDFF. Other endpoints include resolution of steatohepatitis and no worsening of liver fibrosis at wk 48, and other histologic endpoints as assessed by biopsy (Cohort A), as well as safety, pharmacokinetics, and changes in liver enzymes, inflammatory markers, glycemic markers, and lipids (Cohorts A and B).

**Results/Conclusion**: Results from the MONARCH trial are expected by the end of 2026.

**Disclosures**

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**Nirupama Esther Jerome** reports nothing to disclose.

**Eric Lawitz** reports: researcher for 89Bio Inc., Akero Therapeutics, Alnylam Pharmaceuticals Inc., Amgen, Astrazeneca, Boehringer Ingelheim, Bristol Myers Squibb, Corcept Therapeutics, COUR Pharmaceuticals, CymaBay Therapeutics, Eli Lilly and Company, Enanta Pharmaceuticals, Enyo Pharma, Exalenz Bioscience, Galectin Therapeutics, Galmed Pharmaceuticals, Genfit, Gilead Sciences, GlaxoSmithKline, Hanmi Pharmaceuticals, Hightide Biopharma, Intercept Pharmaceuticals, Inventiva, Ipsen, Janssen Pharmaceuticals, Madrigal Pharmaceuticals, Merck & Co., NGM Biopharmaceuticals Inc., NorthSea Therapeutics, Novartis, Novo Nordisk Inc., Organovo, Poxel Co., Regeneron, Sagimet Biosciences, Takeda, Terns Pharmaceuticals, Viking Therapeutics, and Zydus Pharmaceuticals; speaker for AbbVie, Gilead Sciences, Intercept, and Madrigal; consultant for 89Bio Inc., AstraZeneca, Boehringer Ingelheim, Corcept Therapeutics, Eli Lilly and Company, Merck & Co., Novo Nordisk Inc., Organovo, Regeneron, and Sagimet Biosciences.

**Mazen Noureddin**: TBD

**Nadege Gunn** reports: nothing to disclose.

**Daniel Santillano** reports: nothing to disclose.

**Iulia Cristina Tudor** reports: employed by and own stock in Corcept Therapeutics.

**Joseph M. Custodio** reports: employed by Corcept Therapeutics.

**Rafael Mayoral Monibas** reports: employed by Corcept Therapeutics.

**Aprille Espinueva** reports: employed by Corcept Therapeutics.

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safety monitoring board or advisory board for CTI, Medpace, Labcorp, and Worldwide Clinical Trials; stock options in Inipharm; and received equipment, materials, drugs, medical writing, gifts or other services from Velacur.

## [A.18 – ABSTRACT]

### PEMVIDUTIDE IN PATIENTS WITH ALCOHOL-ASSOCIATED LIVER DISEASE: RATIONALE AND DESIGN OF THE PHASE 2 MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED RESTORE TRIAL

**Pemvidutide in Patients with Alcohol-Associated Liver Disease: Rationale and Design of the Phase 2 Multicenter, Randomized, Placebo-Controlled RESTORE Trial**

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### BACKGROUND

Alcohol-associated Liver Disease (ALD) is the leading cause of liver-related morbidity and mortality worldwide. Pemvidutide is a balanced 1:1 glucagon (GCG)/GLP-1 dual receptor agonist (RA) in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), alcohol use disorder (AUD), and ALD. In ALD, the GLP-1-RA activity of pemvidutide may decrease the craving for alcohol and decrease body weight while the liver-directed GCG-RA activity may decrease liver steatosis, inflammation and fibrosis. These two complimentary mechanisms of action may represent an attractive option for the treatment of ALD. In a phase 2 trial in patients with MASH, treatment with pemvidutide led to histologic resolution of steatohepatitis and improvements in an array of noninvasive tests (NITs) of inflammation and fibrosis as early as 24 weeks of treatment. Here we describe the rationale and trial design of the Phase 2 RESTORE trial in patients with ALD.

**Study Design and Objectives:** RESTORE is an ongoing phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of pemvidutide in subjects with ALD. Approximately 100 subjects with ALD are planned to be randomized 1:1 to pemvidutide 2.4 mg or placebo once weekly for 48 weeks. Key inclusion criteria include: alcohol intake ≥ 50 grams per day for males and ≥ 40 grams per day for females on average in the past year, phosphatidyl-ethanol (PEth) ≥ 35 ng/mL, liver stiffness measurement (LSM) by vibration-controlled trainset elastography (VCTE) of 10.0 to 24.9 kPa, and liver fat content (LFC) by MRI-PDFF ≥ 8%. The primary endpoint is to assess the efficacy of pemvidutide on hepatic fibro-inflammatory activity measured as the relative (%) reduction in LSM compared to baseline at Week 24. Secondary endpoints include other non-invasive tests (NITs) of hepatic steatosis, inflammation and fibrosis in addition to self-reported measures and serum biomarkers of alcohol consumption at 24 and 48 weeks of treatment.

**Summary:** The RESTORE Phase 2 trial will assess the safety and efficacy of pemvidutide in patients with ALD and is expected to complete enrollment in 3Q26.

## [A.28 – ABSTRACT]

### EFRUXIFERMIN IN MASH: FROM PHASE 2B RESULTS TO PHASE 3 SYNCHRONY PROGRAM

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### BACKGROUND

Efruxifermin (EFX) is a bivalent Fc-FGF21 analog in development for treatment of MASH. In two phase 2b 96-week trials that enrolled participants with MASH and moderate to advanced fibrosis (F2/F3) or compensated cirrhosis, EFX resulted in rapid and sustained fibrosis improvements compared with placebo. EFX also improved MASH histology, noninvasive fibrosis measures, liver injury, lipid profile, and insulin sensitivity. EFX was generally well tolerated. Mild to moderate gastrointestinal adverse events were more common with EFX than placebo.

### METHODS

The SYNCHRONY phase 3 randomized, double-blind, placebo-controlled trials are designed to evaluate the safety and efficacy of EFX in metabolic dysfunction-associated steatohepatitis MASH at over 300 global sites. SYNCHRONY Histology (NCT06215716) will evaluate EFX 28 mg or 50 mg vs placebo in participants with biopsy-defined F2/F3 fibrosis and MASH. Primary outcomes are proportion of participants with MASH resolution and ≥1-stage fibrosis improvement at week 52, and event-free survival through week 240. SYNCHRONY Outcomes (NCT06528314) will evaluate EFX 50 mg vs placebo in participants with MASH cirrhosis. Primary outcomes are proportion of participants with ≥1-stage fibrosis improvement without MASH worsening at week 96, and time to first clinical event including death from any cause or liver-related outcomes. SYNCHRONY Real-World (NCT06161571) will evaluate safety of EFX 50 mg vs placebo for 52 weeks in participants clinically diagnosed with MASH/MASLD. Secondary outcomes in all trials include changes in noninvasive markers of fibrosis, liver injury, lipid profile, and insulin sensitivity.

### RESULTS

SYNCHRONY Real-World completed enrollment in 2025. Of the 788 screened individuals, 608 were randomized. Baseline characteristics reflect the spectrum of MASH disease severity and are representative of the population at risk of developing liver-related outcomes. SYNCHRONY Histology (N≈1650) and Outcomes (N≈2150) are currently enrolling.

### CONCLUSIONS

The phase 3 SYNCHRONY program will evaluate the safety, tolerability, and efficacy of EFX across the spectrum of MASH, including those with cirrhosis who have a high unmet need. Concurrent conduct of the SYNCHRONY trials improved the likelihood for any individual patient to be eligible to participate in an EFX trial. Results of SYNCHRONY Histology will form the basis for application for drug approval in adults with MASH consistent with F2 or F3 fibrosis.


Funded by Akero Therapeutics, a Novo Nordisk company.

## THERAPEUTIC TRIALS – STEATOTIC LIVER DISEASE, CHOLESTATIC LIVER DISEASE, VIRAL HEPATITIS, OBESITY, AND LIVER FIBROSIS (HUMANS)

### [A.5 – ABSTRACT]

### TREATMENT EFFECTS OF SURVODUTIDE, A GLUCAGON/GLUCAGON-LIKE PEPTIDE-1 RECEPTOR DUAL AGONIST, ON HEPATIC BIOMARKERS IN PATIENTS WITH COMPENSATED AND DECOMPENSATED CIRRHOSIS

**Treatment effects of survodutide, a glucagon/glucagon-like peptide-1 receptor dual agonist, on hepatic biomarkers in patients with compensated and decompensated cirrhosis**

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**Background and aims:**

Survodutide is a glucagon/glucagon-like peptide-1 receptor dual agonist under investigation in phase 3 trials for metabolic dysfunction-associated steatohepatitis (MASH) and obesity. In a phase 1 trial investigating safety, survodutide was associated with improvements in liver-related non-invasive tests in patients with advanced liver disease (NCT05296733). We report a longitudinal analysis of survodutide effects on fibrosis and inflammation biomarkers in patients with cirrhosis.

## METHODS

This was a multinational, non-randomized, open-label phase 1 clinical trial in patients with overweight/obesity, with or without cirrhosis by Child-Pugh criteria. Once-weekly subcutaneous doses of survodutide were escalated from 0.3 mg to 6.0 mg over 24 weeks then maintained for 4 weeks. Exploratory serological biomarkers measured longitudinally from baseline (BL) to Week 28 (W28) included Enhanced Liver Fibrosis (ELF)™ score and its components (hyaluronic acid [HA], tissue inhibitor of matrix metalloproteinase 1 [TIMP-1], and pro-collagen III amino-terminal peptide [PIIINP]); N-terminal type III collagen propeptide (PRO-C3); cytokeratin 18 (CK18-M30/CK18-M65); and glucagon. Descriptive statistics are reported.

## RESULTS

This analysis included 41 patients: 17 without cirrhosis, 16 with compensated cirrhosis, and 8 with decompensated cirrhosis, mostly due to MASH. Biomarker levels were elevated at BL in patients with cirrhosis vs those without. After 28 weeks of survodutide treatment, those without cirrhosis and those with compensated or decompensated cirrhosis exhibited reductions in mean ELF™ scores (value at BL: 8.65, 11.21, 11.53; W28: 8.46, 10.75, 10.80) and geometric means (gMean) for HA (value at BL: 22.66, 230.38, 289.88; W28: 21.89, 177.90, 152.83 ug/L), PIIINP (BL: 8.24, 15.37, 17.45; W28: 6.89, 11.35, 13.56 ug/L), PRO-C3 (BL: 30.72, 50.51, 48.61; W28: 19.63, 35.49, 36.23 ug/L), CK18-M30 (BL: 98.8, 265.5, 238.6; W28: 65.6, 156.7, 203.0 U/L), CK18-M65 (BL: 161.6, 433.9, 442.3; W28: 111.4, 313.7, 371.4 U/L), and glucagon (BL: 64.83, 68.23, 105.71; W28: 44.47, 49.11, 71.27 pmol/L), respectively. No consistent change in gMean was observed for TIMP-1 (BL: 223.11, 301.44, 326.89; W28: 209.26, 295.66, 328.10 ug/L).

## CONCLUSIONS

Survodutide improved hepatic biomarkers of fibrosis and inflammation in both compensated and decompensated cirrhosis. These findings suggest potential disease-modifying effects in MASH-related cirrhosis; a large phase 3 trial in compensated MASH cirrhosis is ongoing (NCT06632457).

**Character count: 2500** *[SOLAR limit of **2500** <u>including spaces but not the headings</u>]*.

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**Data sharing 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 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, one year after the approval has been granted by major Regulatory Authorities or after termination of the development program. Researchers should use the link to request access to study data and visit for further information.

## [A.6 – ABSTRACT]

### HEPATIC TRANSCRIPTOMIC SIGNATURES REVEAL MECHANISTIC INSIGHTS UNDERLYING IMPROVED METABOLIC DYSFUNCTION–ASSOCIATED STEATOHEPATITIS HISTOLOGY WITH SURVODUTIDE, A GLUCAGON/GLUCAGON-LIKE PEPTIDE-1 RECEPTOR DUAL AGONIST, IN A PHASE 2 TRIAL

**Hepatic transcriptomic signatures reveal mechanistic insights underlying improved metabolic dysfunction–associated steatohepatitis histology with survodutide, a glucagon/glucagon-like peptide-1 receptor dual agonist, in a phase 2 trial**

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**Background and aims:**

Survodutide is a glucagon receptor (GCGR)/glucagon-like peptide-1 receptor (GLP-1R) dual agonist in phase 3 clinical development for the treatment of obesity, and metabolic dysfunction-associated steatohepatitis (MASH). We present data from a prespecified transcriptome analysis from baseline (BL) and W48 liver tissue samples from a phase 2 trial in people with MASH (NCT04771273). The aim was to investigate liver specific on-treatment changes on therapeutic responses to survodutide.

## METHODS

293 participants received ≥1 dose of survodutide or placebo. Liver biopsy samples were obtained from trial participants at visit 1 and W48. Following ribonucleic acid (RNA) extraction libraries were prepared and sequenced on a NovaSeq sequencer. The sequencing reads were processed with a Boehringer Ingelheim internal pipeline, building upon the implementation of the ENCODE "Long RNA-seq" pipeline followed by differential expression analysis with limma/voom. Pathway analyses were performed using GSEA, ssGSEA and IPA with REACTOME canonical pathways and curated gene sets from the literature.

## RESULTS

Biopsy samples that passed QC were available from 48 patients (10 Placebo/38 survodutide). Transcriptomic profiling revealed activation of GCGR signalling in liver tissue following survodutide treatment. Compared with baseline, several genes associated with fibrosis and inflammation, including those involved in TGFB1-, IL4-, and IL13-mediated pathways, were significantly downregulated. Notably, expression of LOXL1, LAMB1, MMP9, PLEC, TGFB1, and multiple collagen genes decreased upon treatment. Gene Set Enrichment Analysis indicated that cellular pathways involved in tissue remodelling, fibrosis, and inflammation were suppressed, while Ingenuity Pathway Analysis suggested that survodutide may mitigate fibrosis progression by limiting hepatic stellate cells migration, preserving hepatocytes, and supporting regeneration. TGFB1 and FOXA2 were identified as potential upstream regulators of these effects.

## CONCLUSIONS

We present a comprehensive transcriptome analysis by next-generation sequencing from liver biopsies collected in a phase 2 clinical trial with the GCGR/GLP-1R dual agonist survodutide. The observed modulation of liver mRNA expression known to be regulated in fibrotic-and inflammatory processes provide a mechanistic basis for the improvement in fibrosis and supports the biological plausibility that survodutide reduces hepatic inflammation and fibrogenesis.

**Character count: 2419** *[SOLAR limit of **2500** including spaces but not the headings]*.

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**Data sharing 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 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, one year after the approval has been granted by major Regulatory Authorities or after termination of the development program. Researchers should use the link

to request access to study data and visit for further information.

## [A.19 – ABSTRACT]

### EFFICACY AND SAFETY OF PEMVIDUTIDE IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS: 48-WEEK RESULTS FROM THE PHASE 2B, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED IMPACT TRIAL

**Efficacy and Safety of Pemvidutide in Patients with Metabolic Dysfunction-Associated Steatohepatitis: 48-Week Results from the Phase 2b, Multicenter, Randomized, Placebo-Controlled IMPACT Trial**

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**Background Information:** Pemvidutide is a balanced 1:1 glucagon/GLP-1 dual receptor agonist in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). IMPACT was a phase 2b, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3 (NCT05989711). At 24 weeks, pemvidutide treatment showed statistically significant histologic MASH resolution and high rates of fibrosis improvement. Here we present the 48-week endpoints, including non-invasive tests (NITs), weight loss, and safety.

### METHODS

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. Week 48 read outs included NITs of liver fat content (LFC), hepatic inflammation [corrected T1 (cT1), alanine aminotransferase (ALT)] and fibrosis [ELF, liver stiffness measurement (LSM) by FibroScan®], and weight loss. There was no histological assessment at week 48.

### RESULTS

The mean age was 53 yrs, the mean BMI was 39 kg/m$^2$, 58% were female, and 43% had type 2 diabetes. At week 48, pemvidutide treatment resulted in LFC changes of -45.2% ($p < 0.0001$), -54.7% ($p < 0.0001$), and -8.2% in the 1.2 mg, 1.8 mg, and placebo groups. Mean changes in cT1 relaxation time in the 1.2 mg, 1.8 mg, and placebo groups were -124 ms ($p < 0.0001$), -140 ms ($p < 0.0001$), and -21 ms. A greater proportion of patients treated with pemvidutide achieved a ≥ 30% reduction in LSM than placebo [1.2 mg (61.1%; $p < 0.0001$), 1.8 mg (63.9%; $p < 0.0001$), placebo (21.2%)]. ELF score changes of -0.49 ($p < 0.0001$), -0.58 ($p < 0.0001$), and +0.16 occurred in the 1.2 mg, 1.8 mg, and placebo groups. A greater proportion of patients receiving pemvidutide achieved concurrent responses in ELF score (≥ 0.5 reduction) and LSM (≥ 30% reduction) compared to placebo [1.2 mg (27.8%; $p = 0.0003$); 1.8 mg (32.4%; $p < 0.0001$); placebo (3.2%)]. The changes in ALT were -37.8 IU/L ($p < 0.0001$), -37.4 IU/L ($p < 0.0001$), and -10.3 IU/L in the 1.2 mg, 1.8 mg, and placebo groups. Mean weight loss in the 1.2 mg, 1.8 mg, and placebo groups was 4.5% ($p < 0.0001$), 7.5% ($p < 0.0001$), and 0.2%. Pemvidutide was well-tolerated with discontinuations due to adverse events of 0%, 1.2%, and 3.5% in the 1.2 mg, 1.8 mg, and placebo groups.

### CONCLUSIONS

Treatment led to significant, dose-dependent reductions in NITs of MASH inflammation and fibrosis, as well as clinically meaningful weight loss at week 48.

## NON-INVASIVE TESTING AND BIOMARKERS

### [A.15 – ABSTRACT]

### QUANTITATIVE LIVER FUNCTION AS AN ALTERNATIVE TO LIVER STIFFNESS IN ASSESSING STAGE OF LIVER FIBROSIS FOR CLINICAL MANAGEMENT AND CLINICAL TRIALS

**Quantitative liver function as an alternative to liver stiffness in assessing stage of liver fibrosis for clinical management and clinical trials**

Joanne C. Imperial[1], Michael P. McRae[2], Gregory T. Everson[1]

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**Background and Aims:** Liver disease progression is characterized by accumulation of fibrosis, impairment of liver function, and alteration in the portal circulation. Liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) is an accepted surrogate for liver fibrosis. However, accuracy of LSM may be compromised by obesity, MASH, and diabetes. Since alternatives to LSM may be useful in the latter populations, we compared the probability of biopsy-defined fibrosis stage as estimated by VCTE with estimation by the oral cholate challenge test (OCCT).

#### METHODS

LSM results from 9 published studies of primarily non-U.S. cohorts, were simulated according to a lognormal distribution parameterized from summary results that included both liver biopsy and VCTE. Separately, data from 9 U.S.-based studies of subjects with compensated advanced chronic liver disease who underwent both liver biopsy and OCCT-based Disease Severity Index (DSI) testing were pooled and analyzed retrospectively. Associations among fibrosis stage, VCTE kPa, and DSI were evaluated using Spearman rank correlations, and ordered differences across fibrosis stages were tested with the Jonckheere trend test. The relationships between VCTE or DSI and the probability of fibrosis category were modeled using ordinal logistic regression, with fibrosis categorized as F0-F1, F2-F3, or F4.

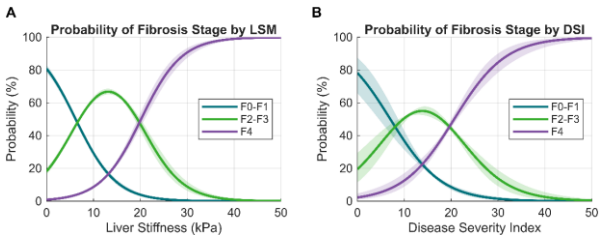
#### RESULTS

Simulated LSM data from 3106 subjects were compared with DSI data from 461 subjects. Subjects with DSI measurements had a mean age 52 ± 9 years and BMI 31 ± 6 kg/m$^2$; 61% were male, 90% were White, 26% were Hispanic, 68% had hepatitis C, and had 32% MASH. Biopsy-defined fibrosis categories were F0-F1 in 15%, F2-F3 in 44%, and F4 in 42%. DSI demonstrated a significant monotonic relationship with fibrosis stage ($\rho$ = 0.48, $p<0.001$). In ordinal logistic regression, each 1 SD increase in kPa was associated with higher odds of more advanced fibrosis category than each 1 SD increase in DSI (DSI OR 2.9, 95% CI 2.3–3.6; kPa OR 13.6, 11.4–16.3). Despite the stronger association for kPa, modeled probability curves for fibrosis categories showed similar patterns for both kPa and DSI (Figure). Transition points (i.e., probability curve intersections) between F0-F1 and F2-F3 were similar for DSI and LSM, occurring at DSI 8 and LSM 7 kPa, respectively. Transitions between F2-F3 and F4 were also similar, occurring at DSI 20 and LSM 20 kPa.

#### CONCLUSIONS

The modeled probability distributions for clinically relevant fibrosis categories were similar between kPa and DSI, particularly near category transition points. These findings warrant confirmation in cohorts undergoing concurrent biopsy, VCTE, and OCCT. Because OCCT measures liver function and physiology rather than fibrosis directly, DSI could serve as another noninvasive method for estimation of fibrosis—particularly in patients where LSM is inaccurate, unreliable, or unable to be performed.

**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.




## [A.16 – ABSTRACT]

### DYNAMIC CHANGES IN HEPATIC RESERVE ACROSS THERAPEUTIC INTERVENTIONS AND LIVER DISEASE ETIOLOGIES AS MEASURED BY THE ORAL CHOLATE CHALLENGE TEST (HEPQUANT DUO®)

**Dynamic Changes in Hepatic Reserve Across Therapeutic Interventions and Liver Disease Etiologies as Measured by the Oral Cholate Challenge Test (HepQuant DuO®)**

Joanne C. Imperial[1], Michael P. McRae[2], Gregory T. Everson[1]

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[2] Custom DX Solutions LLC, Houston, TX, USA

**Background and Aims:** The noninvasive oral cholate challenge test (OCCT) generates parameters of liver health – Disease Severity Index (DSI) and Hepatic Reserve (HR%). DSI represents a patient's cholate clearance relative to maximum clearance while HR% represents a patient's cholate clearance relative to the mean (−1SD) of clearance in healthy persons of lean body mass. Herein we report the changes in HR% relative to baseline in response to therapeutic interventions.

**METHODS**

Data from 14 clinical trials were analyzed, comprising 1258 tests from 473 subjects. The OCCT involved oral administration of deuterium-labelled (d4-) cholate, blood sampling at 20 and 60 minutes, and quantification of the d4-cholate by LC-MS/MS. Test parameters, including HR%, were calculated for each subject. The minimum detectable difference (MDD), which is the smallest difference between treatment and control group that can be detected with statistical significance, was ±3.3% for HR% based on prior within-individual reproducibility studies (McRae et al. 2024). For each treatment arm, the mean change from baseline in HR% (Δ) was calculated. Treatment response was categorized relative to the MDD as improved (Δ ≥ +3.3%), stable/improved (+3.3% > Δ ≥ 0%), stable/worsened (0% > Δ ≥ −3.3%), or worsened (Δ < −3.3%).

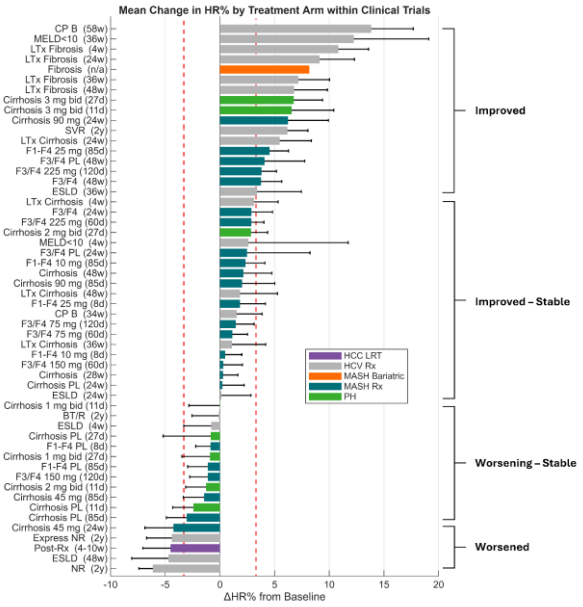
**RESULTS**

The trials represented primarily subjects with HCV and MASH and represented a broad spectrum of disease severity, ranging from fibrosis to cirrhosis to end-stage liver disease (ESLD) (Figure). Among 54 treatment groups, 17 (31%) improved, 20 (37%) were stable/improved, 12 (22%) were stable/worsened, and 5 (9%) worsened. The largest improvements in hepatic reserve (Δ +10 to 15%) occurred in HCV treatment arms achieving sustained virologic response. Substantial improvement was also observed in subjects with fibrotic MASH who underwent bariatric surgery (Δ +8.2%). The OCCT detected rapid functional improvement within 27 days in subjects with Child-Pugh A cirrhosis treated with the highest dose of avenciguat, a guanyl cyclase activator for treatment of portal hypertension (3 mg twice daily; Δ +6.8%). Among MASH treatment cohorts, 18 of 24 (75%) were improved or stable/improved. Hepatotoxicity (Δ of −4.5%) was observed in patients undergoing locoregional therapy for hepatocellular carcinoma (HCC). Worsening HR% was observed in antiviral nonresponders (NR) and patients with ESLD prior to liver transplantation. Similar relationships were observed for DSI.

**CONCLUSIONS**

In addition to DSI, HR% is a dynamic, sensitive indicator of liver function that detects both improvement and worsening across liver disease etiologies, severities, and therapeutic modalities. Incorporation of HR% into clinical trials may support earlier detection of functional response, improve trial design, inform adaptive strategies, and reduce required sample sizes by providing a quantitative functional endpoint.

**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.




## [A.27 – ABSTRACT]

### THE ROLE OF NON-INVASIVE TESTS IN MASH DRUG DEVELOPMENT DECISION MAKING


### BACKGROUND

Liver biopsy remains the gold standard for evaluating histological endpoints and staging in metabolic dysfunction-associated steatohepatitis (MASH) drug development. However, Non-Invasive Tests (NITs) are increasingly integrated into MASH drug development to support proof-of-mechanism (PoM), inform dose selection, enable early efficacy assessment, with the potential to accelerate regulatory decision making. This shift is driven by the limitations of liver biopsy, including its invasive nature, sampling and inter-observer variability, and its negative impact on participant recruitment, retention, and limited feasibility for longitudinal monitoring. A broad range of NIT modalities have demonstrated utility in assessing steatosis, inflammation, and fibrosis. Despite the progress, the relative performance of imaging-based techniques, serum biomarkers, and composite scoring systems across therapeutic classes and mechanisms of action remains incompletely characterized. This analysis evaluates the application and comparative utility of NITs in interventional pharmacology studies of MASLD/MASH therapies.

### METHODS

A targeted literature and trial landscape review was performed using peer-reviewed publications, conference abstracts, ClinicalTrials.gov entries, and publicly available company data through May 2026. Eligible Studies were interventional clinical trials in MASLD/MASH with a defined mechanism of action and quantifiable NIT endpoints. Observational studies, lifestyle-only interventions, and studies without measurable biomarker or imaging outcomes were excluded. Fourteen representative trials were selected across key therapeutic classes, including THR-β agonists, FGF analogs, GLP-1–based therapies, FXR agonists, ACC inhibitors, and other metabolic or fibrosis-directed agents. This allowed for a structured cross-trial comparative analysis to characterize the relative performance of NITs across therapeutic classes.

### RESULTS

MRI-proton density fat fraction (MRI-PDFF) consistently demonstrated the strongest evidence or detecting early pharmacodynamic activity, enabling dose-response differentiation and supporting early efficacy assessment across all therapeutic classes. Relative reductions of approximately ≥30% in MRI-PDFF were reproducibly associated with subsequent histologic response. Imaging-based endpoints outperformed serum biomarkers for short-term dose and exposure-response characterization. Across therapeutic programs, steatosis-oriented endpoints exhibited earlier, and more consistent changes compared with fibrosis-oriented NITs. In contrast, stiffness-based measures, including magnetic resonance elastography (MRE) and vibration-controlled transient elastography (VCTE) demonstrated slower or less pronounced short-term responsiveness. Fibrogenesis markers, including enhanced liver fibrosis (ELF) and PRO-C3 showed supportive utility, particularly when interpreted in conjunction with imaging biomarkers. Emerging evidence suggests that multimodal approaches integrating imaging, serum biomarkers, and composite measures provides a more clinically informative assessment than reliance on single endpoints alone. Composite scores such as FibroScan-AST (FAST) score showed emerging value for corroborating histologic improvement in post hoc analyses.

### CONCLUSIONS

MRI-PDFF emerged as the most consistently responsive NIT for detecting early pharmacodynamic activity, characterizing dose-response relationships, and identifying early efficacy signals, whereas fibrosis-oriented biomarkers and stiffness-based measures exhibited slower and less consistent short-term responsiveness. Collectively, the evidence supports a multimodal NIT strategy integrating imaging, serum biomarkers, and composite indices to enhance interpretation of pharmacodynamic effects and early efficacy signals in MASH clinical trials. Specific studies demonstrated associations between NIT changes and histologic outcomes; however, variability in study design and endpoint reporting highlights the continued need for prospective validation of NIT-biopsy relationships to support future drug-development and regulatory decision-making, and liver biopsy remains the reference standard.

## PHARMACOECONOMIC AND SOCIETAL ASPECTS

### [A.23 – ABSTRACT]

### REAL-WORLD HEALTHCARE COSTS OF ADVANCED METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS IN ENGLAND: A COHORT STUDY WITH COMPARISON TO MODELLED ESTIMATES

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OBJECTIVES: Metabolic dysfunction-associated steatohepatitis (MASH) is associated with substantial clinical and economic burden, with modelling studies projecting increasing healthcare costs as disease severity progresses. Real-world evidence describing healthcare costs in advanced liver disease remains limited. This study aimed to estimate healthcare costs among patients with MASH in England and compare these estimates to published modelled values.

METHODS: A cohort study design was conducted among adults diagnosed with MASH between 2011 and 2020 recorded in the Clinical Practice Research Datalink Aurum dataset linked to the Hospital Episode Statistics and death registrations. Mean all-cause costs were calculated per-patient per-year (PPPY). Costs were estimated using contemporaneous unit costs corresponding to the year in which healthcare utilisation occurred and inflated to 2023/24 £ using the latest available NHS inflation indices. Costs were assessed overall and stratified by progression to cirrhosis, specifically decompensated cirrhosis (DCC) and hepatocellular carcinoma (HCC) among patients with ≥12 months follow-up.

RESULTS: 2,696 patients with MASH were included (mean follow-up 4 years). Among patients who progressed to cirrhosis (n=349), inpatient costs were higher (£4,145 vs £1,477 PPPY) than those without progression (n=2,347). Costs increased further as disease advanced. Among patients with DCC (n=163), healthcare costs were £6,859 PPPY within the first year of follow-up and £7,763 PPPY in the second year. For HCC (n=14), corresponding costs were £5,003 and £6,267 PPPY. This descriptive study contrasted slightly with recent modelling studies (Younossi *et al.* and Morgan *et al.*) that reported higher costs for HCC than DCC; our observed real-world HCC costs were lower than DCC.

CONCLUSION: Healthcare costs associated with MASH increase with disease progression and are concentrated in advanced liver disease. These findings complement existing modelling studies by providing observed NHS-based cost estimates from routine clinical practice. Differences from prior modelling studies may reflect variation in methodology, including limited inclusion of oncology costs and follow-up duration.

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