PARIS
MASH
MEETING

2026
ABSTRACTS BOOK

12th EDITION

SEPTEMBER 10 & 11, 2026

PARIS

ABSTRACTS SUMMARY

N°1 - PATIENT-DERIVED HEPATOCYTES FOR UNDERSTANDING MOLECULAR MECHANISMS UNDERLYING THE DEVELOPMENT OF MASH AND ASH

Author: Dr. MUKHOPADHYAY

N°2 - XANTHONE GLYCOSIDE FROM SWERTIA SP., DEMONSTRATES THERAPEUTIC POTENTIAL AGAINST MASH-INDUCED FIBROSIS IN HEPATIC CELL LINES

Author: Ms DOGRA

N°3 - HEPATOPROTECTIVE ACTIVITY OF SWERTIA PURPURASCENS WALL AGAINST STEATOSIS THROUGH BOTH IN - VITRO AND IN-VIVO STUDIES.

Author: Ms. BALI

N°4 - FIBROSCAN LIVER ELASTOGRAPHY IN THE DIAGNOSIS AND MONITORING OF MASLD IN CHILDREN - CLINICAL ASPECTS.

Author: Prof.Dr. RAJEWSKI

N°5 - ANALYSIS OF A NATIONAL MULTICENTRE COHORT OF PATIENTS WITH HOMOZYGOUS OR HETEROZYGOUS ALPHA-1 ANTITRYPSIN DEFICIENCY

Author: PR CADRANEL

N°6 - INTRODUCING HEPATOSCOPE-DERIVED FAT FRACTION: A NOVEL REAL-TIME QUANTITATIVE ULTRASOUND ESTIMATION OF LIVER FAT

Author: Dr SERDJEBI

N°7 - DOES LIVER STEATOSIS AFFECT LONG-TERM OUTCOMES FOLLOWING ANTIVIRAL TREATMENT IN HCV-INFECTED PATIENTS WITH ADVANCED FIBROSIS/CIRRHOSIS?

Author: Prof. ZSRĘBSKA-MICHALUK

N°8 - DISMANTLING THE DIAGNOSTIC PYRAMID IN MASH: CLINICAL EVIDENCE SYNTHESIS OF HEPATOSCOPE FOR GLOBAL LIVER SCREENING

Author: Dr SERDJEBI

N°9 - DYNAMIC CHANGES IN HEPATIC RESERVE ACROSS INTERVENTIONS AND ETIOLOGIES MEASURED BY THE HEPQUANT DUO TEST

Author: Dr. IMPERIAL

N°10 - NONINVASIVE QUANTIFICATION OF LIVER FUNCTION AND PORTAL-SYSTEMIC SHUNTING DISTINGUISHES DIFFERENCES BETWEEN CHILD-PUGH A5 AND A6

Author: Dr. IMPERIAL

N°11 - LIQUID-BIOPSY ASSESSMENT OF LIVER DAMAGE AND METABOLIC RISK IN MASH VIA MONOCYTE PLIN2 EXPRESSION

Author: Dr. CAFFERATI BELTRAME

N°12 - IN F0-F3 MASH, ≥5% WEIGHT LOSS LOWERS VCTE+ELF INDEPENDENT OF BIOPSY FIBROSIS IMPROVEMENT

Author: Dr LOOMBA

N°13 - THE PREVALENCE OF CARDIOMETABOLIC COMORBIDITIES IN MASLD IN FRANCE

Author: Ms. WALLACE

N°14 - PROJECTED IMPACT OF RESMETIROM ON LIVER TRANSPLANT WAITLIST, MORTALITY, AND ORGAN REALLOCATION IN FRANCE

Author: Dr. KIM

N°15 - CLINICAL OUTCOMES AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) IN FRANCE: A REAL-WORLD CLAIMS ANALYSIS

Author: Professor BOURSIER

N°16 - TRANSCRIPTOMIC ANALYSIS OF LIVER TISSUE IN A PHASE-2 TRIAL OF SURVODUTIDE IN ADULTS WITH MASH

Author: Dr HESSE

N°17 - PAEDIATRIC MASLD EVOLVES INTO ADULT MASLD THROUGH NORMALISATION OF LIVER ENZYMES

Author: Dr SUNDARAM

N°18 - A NOVEL METABOLIC LIVER FIBROSIS RISK SCORE (MLFRS) FOR MASLD: A PILOT STUDY

Author: Dr SUWAŁA

N°19 - LIVER HEALTH IMPROVES IN CHILDREN WITH OVERWEIGHT OR OBESITY DURING A TWO-YEAR COMBINED LIFESTYLE INTERVENTION

Author: Drs. VAN GIESEN

N°20 - SELF-RATED HEALTH AND HEALTHCARE UTILISATION IN RELATION TO INCREASED LIVER STIFFNESS

Author: Miss HUANG

N°21 - RATIONALE AND DESIGN OF AN EVENT-DRIVEN, MULTINATIONAL, RANDOMISED, PLACEBO-CONTROLLED, PHASE 3 TRIAL OF SURVODUTIDE (LIVERAGETM)

Author: Dr SCHATTENBERG

N°22 - NOVEL MEASUREMENTS OF SPATIAL DIFFERENCES IN LIVER FAT DISTRIBUTION BETWEEN MASLD AND CIRRHOSIS

Author: Miss WANG

N°23 - IDENTIFICATION OF IMMUNOLOGICAL AND EXTRACELLULAR VESICLE BIOMARKERS IN A MULTICELLULAR MASLD LIVER MODEL

Author: MSc. PhD. VINCE KÁŽMÉROVÁ

N°24 - ALCOHOL EXPOSURE INCREASES LIVER IRON, WHILE CT1 PREDICTS OUTCOMES ACROSS MASLD, METALD, AND ALD

Author: Mr DIAMOND

N°25 - THE POTENTIAL OF COMBINING FIRST-LINE NON-INVASIVE TESTS FOR EARLY DETECTION OF ADVANCED LIVER DISEASE

Author: Dr KOKKARAKIS

N°26 - A MULTIMODAL NONINVASIVE APPROACH TO INITIATION AND MONITORING OF RESMETIROM THERAPY IN MASH - UPDATE.

Author: Dr SANDHU

N°27 - FAT10 PROMOTES FORMATION OF MALLORY-DENK BODIES THROUGH AUTOPHAGY INHIBITION DURING MASH PROGRESSION TO FIBROSIS.

Author: PhD student CENS

N°28 - CLINICAL, HISTOLOGICAL AND MOLECULAR DETERMINANTS OF GRAFT STEATOHEPATITIS AFTER LIVER TRANSPLANTATION FOR STEATOTIC LIVER DISEASE

Author: Dr ERARD

N°29 - AI METRICS ALIGN WITH MANUAL HISTOLOGY AND BLOOD-BASED BIOMARKERS IN MASH

Author: Dr WINDELL

N°30 - AIM-MASH AI-ASSISTED SCORING OF MASH CLINICAL TRIAL SAMPLES INCREASES INTER-READER PRECISION

Author: Dr. CONWAY

N°31 - METABOLIC BENEFITS OF PAN-PPAR AGONIST LANIFIBRANOR IN PATIENTS WITH AND WITHOUT TYPE 2 DIABETES

Author: Dr HOLLEBOOM

N°32 - PH-FCS, A CONTINUOUS FIBROSIS SEVERITY SCORE, PREDICTS CLINICAL OUTCOMES IN STEATOSITE

Author: Dr JIMENEZ-RAMOS

N°33 - BEYOND THE LIVER: PNPLA3 AND MBOAT7 VARIANTS SHAPE BODY COMPOSITION IN MASLD

Author: Dr CESPIATI

N°34 - PARTIAL PPARγ AGONISM UNDERLIES LANIFIBRANOR'S PRECLINICAL FLUID/CARDIOVASCULAR SAFETY VERSUS FULL AND DUAL PPAR AGONISTS

Author: Dr FRANCQUE

N°35 - ONE-YEAR CHANGES IN LIPID-BASED CARDIOMETABOLIC RISK MARKERS FOLLOWING RESMETIROM INITIATION: A REAL-WORLD ANALYSIS

Author: Dr ALAZAWI

N°36 - LANIFIBRANOR PHASE 1/2A EXPERIENCE - PPARγ ENGAGEMENT AND METABOLIC ACTIVITY WITHOUT EARLY CLINICAL FLUID RETENTION

Author: Dr FRANCQUE

N°37 - LANIFIBRANOR IMPROVES METABOLIC AND HISTOLOGICAL FEATURES OF MASH ACROSS MULTIPLE PRECLINICAL MODELS: CONVERGENT PAN-PPAR ACTIVITY

Author: Dr HOLLEBOOM

N°38 - BEYOND THE LIVER: CARDIOVASCULAR EFFECTS OF THE PAN-PPAR AGONIST LANIFIBRANOR IN PATIENTS WITH MASH

Author: Dr FRANCQUE

ABSTRACT N°1

TITLE: PATIENT-DERIVED HEPATOCYTES FOR UNDERSTANDING MOLECULAR MECHANISMS UNDERLYING THE DEVELOPMENT OF MASH AND ASH

AUTHORS:

Dr. Bani MUKHOPADHYAY, NIAAA,NIH
MS Cheryl MARIETTA, NIAAA,NIH
MS Samantha HOEY, NIAAA,NIH
MS Karolona GAL, NIAAA,NIH
Dr Natalia SCHIMDT, NIAAA,NIH
Dr. Abdul Oiseni, OISENI,, VCU
Mr Faridoddin Mirshahi MIRSHAHI, VCU
Dr Colin HODGKINSON, NIAAA,NIH
Dr George KUNOS, NIAAA,NIH
Dr Arun SANYAL, VCU
Dr David GOLDMAN, NIAAA,NIH

KEYWORDS:

MASH,ASH.MITOCHONDRIA,TRANSCRIPTOME,INFLAMATION

OBJECTIVES:

Genetic predisposition and socio-economic factors influence risky alcohol consumption, dietary habits, and health behaviors that contribute to the development of alcoholic steatohepatitis (ASH) and metabolic dysfunction-associated steatohepatitis (MASH). Given the growing burden of these chronic liver diseases, this study aims to define the molecular and metabolic mechanisms driving disease progression using patient-derived hepatocyte models that better reflect human biology.

METHODS:

Transcriptomic and functional analyses were performed using hepatocyte-like cells (iHLCs) derived from induced pluripotent stem cells (iPSCs). iPSCs were generated from purified CD4+ T cells obtained from blood samples of healthy individuals and patients with MASH and ASH collected at VCU and NIH. Differentiated iHLCs were characterized using established hepatocyte markers. Bioenergetic function was assessed using Seahorse extracellular flux analysis to measure mitochondrial respiration and ATP production rates. Comparative transcriptomic analyses were conducted between iHLCs and matched patient liver biopsy data to validate disease relevance. Additionally, population-level immune profiling was performed using blood samples to assess immune cell marker distribution and potential systemic contributions to disease pathology.

RESULTS:

iHLCs derived from MASH and ASH patients exhibited phenotypic similarities to healthy controls but demonstrated distinct alterations in lipid metabolism, cell death pathways, and cellular senescence. Diseased hepatocytes showed impaired mitochondrial bioenergetics, including reduced ATP production and altered substrate utilization. Transcriptomic analyses revealed dysregulation in key metabolic, inflammatory, and stress-response pathways. Notably, treatment with targeted therapeutic agents improved lipid accumulation patterns and mitochondrial function, indicating partial reversibility of disease-associated phenotypes and highlighting potential therapeutic targets.

CONCLUSIONS:

This patient-derived hepatocyte model provides a robust and human-relevant platform to study the molecular basis of MASH and ASH. The findings underscore mitochondrial dysfunction and metabolic dysregulation as central features of

disease pathogenesis and demonstrate the potential for therapeutic modulation. This approach supports the advancement of precision medicine strategies and aligns with efforts to develop innovative human-based models that reduce reliance on animal studies while accelerating translational impact in chronic liver disease research.

ABSTRACT N°2

TITLE: XANTHONE GLYCOSIDE FROM SWERTIA SP., DEMONSTRATES THERAPEUTIC POTENTIAL AGAINST MASH-INDUCED FIBROSIS IN HEPATIC CELL LINES

AUTHORS:

Ms Shagun Sanjivv DOGRA, 1. Pharmacology and Toxicology Laboratory, Dietetics & Nutrition Technology Division, CSIR- Institute of Himalayan Bioresource Technology, Palampur, Kangra-176061, India; 2. Academy of Scientific and Innovative Research (AcSIR), Ghaziabad- 201002, India

Dr. Vikram PATIAL, 1. Pharmacology and Toxicology Laboratory, Dietetics & Nutrition Technology Division, CSIR-Institute of Himalayan Bioresource Technology, Palampur, Kangra-176061, India; 2. Academy of Scientific and Innovative Research (AcSIR), Ghaziabad- 201002, India

KEYWORDS:

STEATOHEPATITIS, HEPATOPROTECTIVE, GLYCOSIDE, FIBROSIS, IN-VITRO

OBJECTIVES:

Liver fibrosis often results from a combination of factors including oxidative stress, mitochondrial dysfunction, and Metabolic dysfunction associated steatohepatitis (MASH). Due to the multi-factorial origin and asymptomatic nature, liver fibrosis is often undetected until later stages. This study aimed to investigate the hepatoprotective effect of a xanthone glycoside (XG), found in Swertia Sp., against steatohepatitis, oxidative stress, mitochondrial dysfunction and fibrosis-related markers in hepatic cell lines.

METHODS:

Huh-7 and Hepatic stellate cells (HSC) were used for the study. The cytoprotective effect of XG was studied in Huh-7 cells against Transforming Growth Factor-β (TGF-β) + fructose induced toxicity using MTT assay. Lipid accumulation, mitochondrial dysfunction and intracellular reactive oxygen species (ROS) were analyzed using Nile Red, JC-1 and MitoTracker red and DCFDA staining, respectively, followed by fluorescence microscopy and ImageJ quantification. Immunocytochemistry (ICC) was performed for fibrosis-related markers. Gene and protein expressions were checked using qRT-PCR and western blotting techniques.

RESULTS:

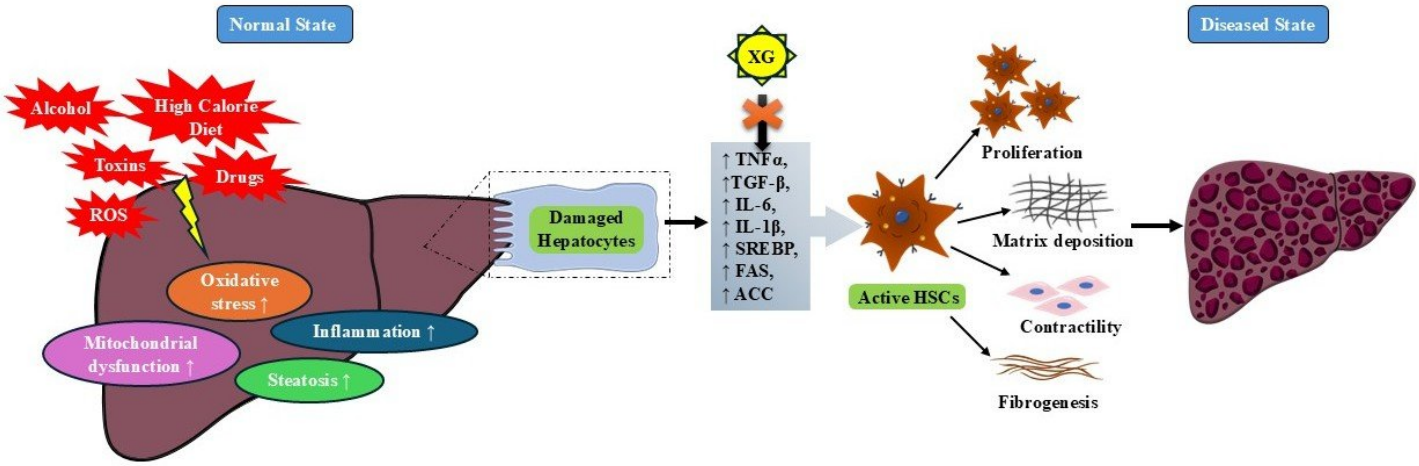
XG significantly reduced lipid accumulation and triglycerides levels in TGF-β + fructose induced Huh-7 cells. DCFDA staining revealed reduction in ROS, indicative of antioxidant potential of XG in Huh-7 and HSC cells. JC-1 and MitoTracker red staining indicated restored mitochondrial membrane potential in XG-treated Huh-7 cells. Inflammatory markers such as Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B (NF-κB), Interleukin-6 (IL-6) and Interleukin-1β (IL-1β) were downregulated upon XG treatment in Huh-7 and HSC cells. Anti-fibrotic effect was indicated in ICC by reduction in the expression of fibrosis-related TGF-β and α-Smooth Muscle Actin (αSMA) in XG-treated Huh-7 cells. Furthermore, XG significantly downregulated the expression of genes involved in steatosis including Sterol Regulatory Element-Binding Protein (SREBP), Acetyl-CoA carboxylase (ACC) and Fatty acid synthase (FAS); and fibrosis including TGF-β, αSMA and Small Mothers Against Decapentaplegic (SMAD) 2, 3 & 4 along with protein expression validation.

CONCLUSIONS:

The study suggested the potential hepatoprotective effect of SXG by reducing lipid accumulation, producing antioxidant effect, improving mitochondrial dysfunction, anti-inflammatory effect and reducing the expression of fibrosis-related

markers in Huh-7 cells.

APPENDICES:



ABSTRACT N°3

TITLE: HEPATOPROTECTIVE ACTIVITY OF SWERTIA PURPURASCENS WALL AGAINST STEATOSIS THROUGH BOTH IN -VITRO AND IN-VIVO STUDIES.

AUTHORS:

Ms. Sheetal BALI, Dietetics and Nutrition Technology Division, CSIR-Institute of Himalayan Bioresource Technology (IHBT), Palampur, Himachal Pradesh, India.

KEYWORDS:

STEATOSIS,HEPATIC FIBROSIS, SWERTIA PURPURASCENS, ROS,MMP

OBJECTIVES:

"To assess the efficacy of S. purpurascens fraction against steatohepatitis using the in-vitro and in-vivo studies.”

METHODS:

After collecting the plant material, it underwent solvent extraction and fractionation before being characterized using UPLC. ROS, MMP, Nile Red, gene expression and western blotting were among the in-vitro tests used to evaluate the obtained fractions. Additionally, a 4-month in-vivo experimental investigation was conducted to determine their therapeutic potential.

RESULTS:

Four main bioactive chemicals were identified by UPLC analysis: mangiferin, sweroside, swertiamarin, and swertianolin. In vitro studies demonstrated that the fraction significantly reduced intracellular ROS levels, prevented intracellular lipid accumulation, and regulated gene expression and western blotting to preserve cell viability without inducing cytotoxicity. The fraction's hepatoprotective and anti-steatotic properties were further demonstrated by the in-vivo study, which showed a notable decrease in liver fibrosis in mice.

CONCLUSIONS:

“Because of the presence of bioactive substances such as mangiferin, sweroside, swertiamarin, and swertianolin, the study shows that the butanol fraction has strong hepatoprotective and anti-steatotic potential. The fraction effectively reduced oxidative stress, maintained mitochondrial integrity, decreased lipid accumulation, and alleviated liver fibrosis in mice, suggesting its potential as a promising therapeutic candidate for the management of hepatic fibrosis and related liver disorders.”

ABSTRACT N°4

TITLE:

FIBROSCAN LIVER ELASTOGRAPHY IN THE DIAGNOSIS AND MONITORING OF MASLD IN CHILDREN - CLINICAL ASPECTS.

AUTHORS:

Prof.Dr. Pawel RAJEWSKI, 1. Provincial Hospital for Infectious Diseases, Bydgoszcz, Poland. 2. University of Health Sciences, Bydgoszcz, Poland
Dr. Jakub CIESCINSKI, 3. Szubinska Medical Center - Radiology, Bydgoszcz, Poland

KEYWORDS:

MASLD, CHILDREN, FIBROSCAN, VCTE

OBJECTIVES:

The aim of the study was to analyze the possibility of using VCTE - FibroScan liver elastography in the rapid diagnosis and monitoring of MASLD in the pediatric population.

METHODS:

A literature search was conducted in PubMed, Scopus, and Web of Science, covering the period from January 2010 to November 2025. The following keyword combinations were used: "FibroScan," "transient elastography," "CAP," "LSM," "children,""pediatric," "NAFLD," "MASLD," "steatosis," and "fibrosis." Original studies, meta-analyses, systematic reviews, and clinical reports were included. The analysis was performed independently by two authors who assessed the quality of the studies using the Newcastle-Ottawa scale and the level of evidence according to the Oxford Centre for Evidence-Based Medicine (OCEBM) guidelines. Results were presented descriptively and tabulated, including correlation coefficients (r), AUC, ICC, PPV, and NPV values, where available. In cases of discrepancies in methodological assessments, consensus was adopted after joint analysis of the data.

RESULTS:

In pediatric studies, CAP showed a strong association with histological severity of steatosis (e.g., r ≈ 0.8), and LSM moderately associated with fibrosis (r ≈ 0.45–0.6). In reviews and meta-analyses, the accuracy of VCTE for ≥ F2 was high (AUROC up to ~0.90), although cutoffs varied between centers (5.5–8.5 kPa) (Tables 1, 2, Figs. 1–3). Reproducibility and influencing factors According to pediatric data, LSM measurement is characterized by high reproducibility (ICC > 0.9), while CAP shows greater variability; the failure rate increases with obesity. In the healthy population, LSM/CAP increases with BMI-SDS; Interpretation of results requires clinical context, laboratory tests, and appropriate probe (S/M) and preparation (fasting test).

CONCLUSIONS:

FibroScan elastography is a key non-invasive diagnostic tool for pediatric MASLD. FibroScan has three main applications in children with MASLD: (1) initial screening and risk stratification, (2) monitoring the effects of interventions, and (3) qualifying for further diagnostics when significant fibrosis is suspected. Trends in LSM/CAP over time are more valuable than individual values. It is rapid, safe, and reproducible. Development of pediatric norms and thresholds related to age and body weight relative to percentile charts in younger children and BMI in older children, as well as validation of models combining VCTE with serological markers, is necessary.

APPENDICES:

Table 1. Selected pediatric examinations using FibroScan (VCTE).

Autor (rok)	n	Wiek (śr.)	BMI (śr.)	Parametry	Najważniejsze wyniki
Alkhouri et al., 2013 [4]	68	13±2	34	LSM, CAP, PNFI	AUC=1,00 dla ≥F2
Mandelia et al., 2021 [2]	96	14±3	30	LSM, CAP	ICC LSM>0,9; CAP bardziej zmienne
Chaidez et al., 2022 [3]	216	12±2	32	LSM, CAP	r(CAP–steatoza)=0,84; r(LSM–włóknienie)=0,47
Brunnert et al., 2022 [5]	482 zdrowe	11±1	—	LSM, CAP	Percentyle pediatryczne; wpływ BMI-SDS
Lee et al., 2022 [7]	46	6–16	—	LSM, CAP	Zależności z ALT/AST; ograniczenia korelacji z USG/CT

Table 2. Working Interpretation Thresholds (Children). Note: Approximate values, dependent on age/BMI and methodology.

Parametr	Zakres/prog	Interpretacja
CAP	<~248 dB/m	S0 (brak/minimalna steatoza)
CAP	248–280 dB/m	S1–S2
CAP	>~280 dB/m	S3 (znaczna)
LSM	<~5,5 kPa	F0
LSM	5,5–8,5 kPa	F1–F2
LSM	≥~10,0 kPa	F3–F4

Fig. 1. Mean LSM (kPa) and degree of fibrosis (scheme).

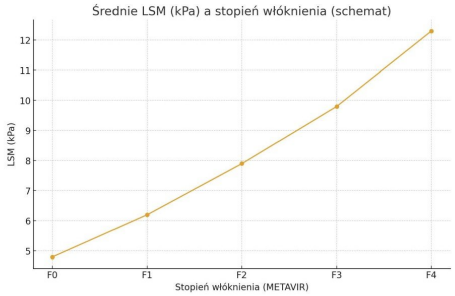


Fig. 2. Example CAP values for steatosis degrees (scheme).

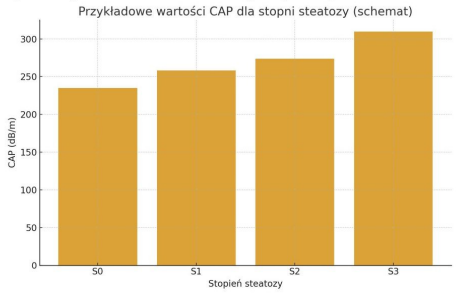


Fig. 3. Schematic diagram of shear wave propagation in healthy and fibrotic liver (VCTE).



ABSTRACT N°5

TITLE: ANALYSIS OF A NATIONAL MULTICENTRE COHORT OF PATIENTS WITH HOMOZYGOUS OR HETEROZYGOUS ALPHA-1 ANTITRYPSIN DEFICIENCY

AUTHORS:

PR Jean-François CADRANEL, GHPSO Creil
Dr Audrey PAYANCE, Beaujon Clichy
Dr Christophe BUREAU, CHU Toulouse
Dr Isabelle ROSA, CH Créteil
Dr Caroline LEMAITRE, CH Le Havre
Dr Paul CARRIE, CH Limoges
Dr Jessy CATTELAN, CH Haguenau
Dr Alban DEROUX, CHU Grenoble
Dr Auguste HERISSAY, CH Quimper
Dr José URSIC-BEDOYA, CHU Montpellier
Dr Frédéric EHRHARD, CH Lorient
Dr Cyril MAURER, CH Montfermeil
Dr Isabelle OLLIVIER HOURMAND, CHU Caen
Pr Thierry THEVENOT, CHU Besançon
Dr Lucia PARLATI, Cochin Paris
Dr Amine ACHEMLAL, Tenon Paris
Dr David ZANDITENAS, CH Bry sur Marne
Pr Eric NGUYEN-KHAC, CHU Amiens
Pr François DURAND, Beaujon Clichy
Dr Camélia MOKHTARI, GHPSO Creil
Dr Vincent HAGHNEJAD, CHU Nancy
Dr Mike HABIB, GHPSO Creil
Dr Honoré ZOUGMORÉ, GHPSO Creil
Dr Philippe PULWERMACHER, GHPSO Creil

KEYWORDS:

EPIDEMIOLOGY, ALPHA1-ANTITRYPSINE DEFICIENCY,LIVER ELASTOMETRY

OBJECTIVES:

A non-academic study showed that among practitioners working in non-academic settings, knowledge of alpha-1 antitrypsin deficiency was low, and that Fibroscan® was the most commonly used method for assessing fibrosis in these patients. A study was initiated in June 2025 to evaluate a cohort of patients with homozygous or heterozygous AAT deficiency and to assess the factors associated with liver fibrosis.

METHODS:

Age, patient gender, homozygous or heterozygous (H) status, alpha-1 antitrypsin levels, transaminases, liver tests, platelets, fibrosis assessment (Fibroscan®, liver biopsy) were evaluated.

RESULTS:

177 pts records were analysed(63.5% male), mean age 49.7 years (15.8). 108 patients were H(61%). The AAT level was 0.58(0.34), AST 35(24), and ALT 43.5(60). Total bilirubin 13 µmol/l(11.2), albumin 40.5 g(15.24); prothrombin time was 94% (16.9), and platelet count was 233 × 10^{12},/l (73.3). 150 patients were F0 or F2 (84%), and 24 had cirrhosis(13.5%). Liver fibrosis(F) was assessed in 151 patients using Fibroscan® with a result of 7 kPa(6) 1. 11 patients(6.25) had type 2

diabetes, 20% (34) had hypertension. 176 pts(15%) had excessive alcohol consumption. 46 patients(26.1%) were on replacement therapy. 4 patients were awaiting transplantation. 10 had undergone transplantation (13.6%). There was no difference between homozygous and HZ patients apart from a lower AAT level ($p < 0.001$). 42 HZ patients were receiving replacement therapy compared with 4 HZ patients (5.71%) ($p < 0.001$). Homozygous pts were more likely to have undergone transplantation: 9(8.40%) vs 1 (1.43%) ($p = 0.05$). Pts with F3F4 fibrosis (28 patients) had higher AST and ALT levels (42.2 (56.1) vs 31 (16.1), $p=0.005$, ALT 39.6(61) vs 64.2(55.1), $p = 0.043$, lower total protein 74.9 (18.4) vs 98.2 (13.4), $p < 0.001$), a higher elastometry score: 19, and a tendency towards a higher prevalence of diabetes: 0.077 in cases of F3-F4 fibrosis. Alcohol consumption was present in 28.6% of pts with extensive fibrosis (8 vs 18, $p = 0.04$). Pts with extensive fibrosis were most often awaiting transplantation: 4 (2.27%) and/or had undergone transplantation: 10 (5.68%) vs 166 (94.3%) ($p<0.001$).

CONCLUSIONS:

In this multicentre cohort, the majority of patients with AATD have moderate fibrosis. Liver fibrosis is assessed using Fibroscan®.

ABSTRACT N°6

TITLE: INTRODUCING HEPATOSCOPE-DERIVED FAT FRACTION: A NOVEL REAL-TIME QUANTITATIVE ULTRASOUND ESTIMATION OF LIVER FAT

AUTHORS:

Dr Cindy SERDJEBI, E-Scopics, 235 rue Léon Foucault, Aix-en-Provence
Dr Adrien BESSON, E-Scopics, 235 rue Léon Foucault
Dr Nicolas ETAIX, E-Scopics, 235 rue Léon Foucault
Pr Alina ALLEN, Department of Medicine, Division of Gastroenterology & Hepatology, Mayo Clinic, Rochester, Minnesota
Pr Christophe AUBÉ, Department of Radiology, University Hospital of Angers, CHU d'Angers, 49933 Angers, France
Pr Jérôme BOURSIER, Department of Hepatogastroenterology, CHU Angers, 49933 Angers, France
Pr Laurent CASTERA, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris (AP-HP), Service D'hépatologie, 92110 Clichy, France
Pr Cyrielle CAUSSY, Département Endocrinologie, Diabète et Nutrition, Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, Lyon, France.
Dr Marco DIOGUARDI BURGIO, Department of Radiology, Hôpital Beaujon, AP-HP Nord, 100 Boulevard du Général Leclerc, 92110 Clichy, France
Pr Olivier LUCIDARME, Sorbonne Université, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale et Hôpital Pitié Salpetrière Paris, France
Dr Raluca PAIS, Service d'hépato-gastro-entérologie, Hôpital la Pitié-Salpêtrière, Paris, France
Dr Anita PAISANT, Department of Radiology, University Hospital of Angers, CHU d'Angers, 49933 Angers, France
Dr Claude COHEN-BACRIE, E-Scopics, 235 rue Léon Foucault, Aix-en-Provence

KEYWORDS:

ULTRASOUND, STEATOSIS, ATTENUATION, MRI-PDFF, BACKSCATTER

OBJECTIVES:

Magnetic resonance imaging-proton density fat fraction (MRI-PDFF) is the gold standard for the assessment of liver fat content. However, its global use is limited because of low availability, cost and the incompatibility for some patient's body habitus. Attenuation and backscattering coefficient have been used for years as quantitative ultrasound parameters to assess steatosis. This work aimed at introducing and clinically validating the Hepatoscope-derived fat fraction (HDFF), a novel real-time ultrasound parameter to estimate liver fat content.

METHODS:

Ultrasound per channel raw data from 93 adult participants with metabolic-dysfunction associated steatotic liver disease (MASLD) or benign liver lesions from three clinical cohorts were retrospectively used. An algorithm combining attenuation and backscattering coefficient via second-order polynomial regression was evaluated against MRI-PDFF using a stratified 5-fold cross-validation protocol. Diagnostic performance was evaluated at established MRI-PDFF thresholds of >5%, >10%, and >20%.

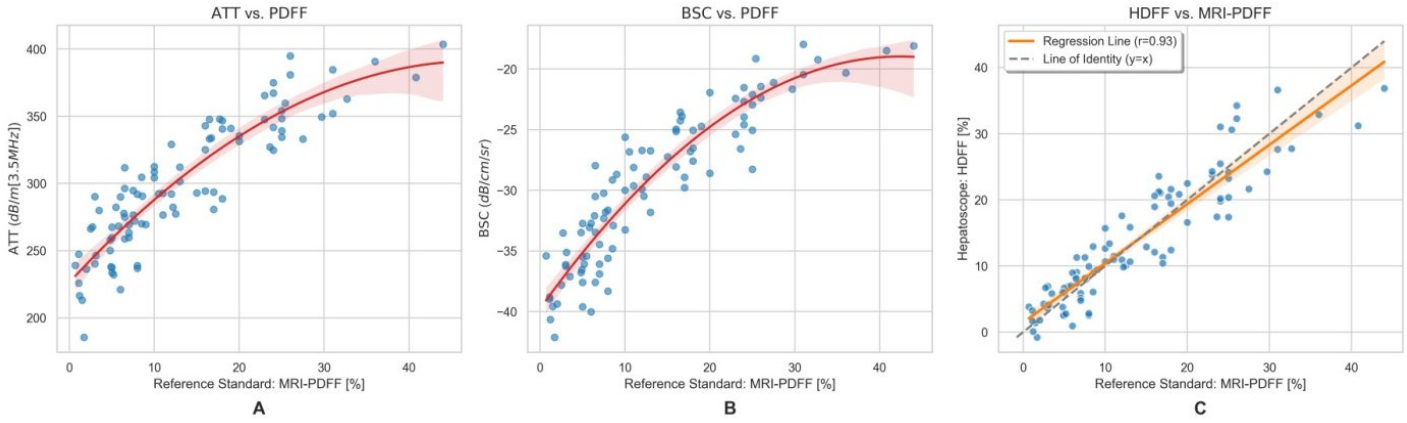
RESULTS:

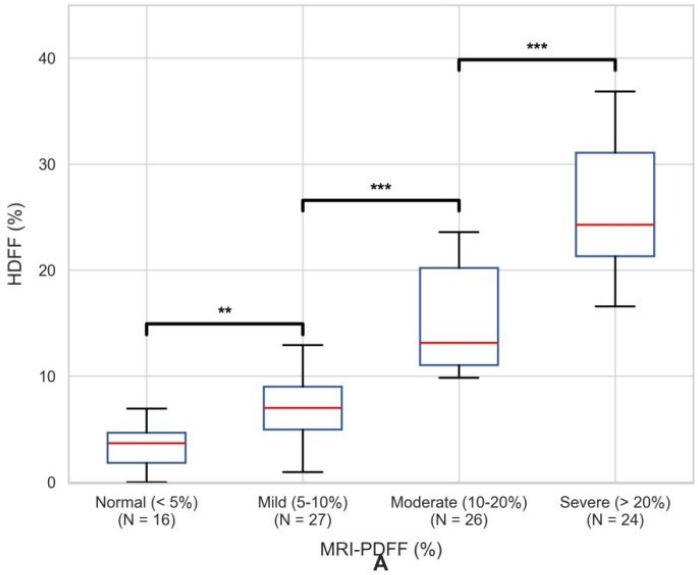
HDFF strongly correlated with MRI-PDFF (r=0.93, 95%CI: 0.89-0.95), with higher correlation than attenuation (r=0.90, 95%CI: 0.85-0.93) and backscattering (r=0.92, 95%CI:0.88-0.94) measurements alone. Bland-Altman analysis revealed a non-significant systematic bias of +0.04% (95% limits of agreement: -7.3% to +7.4%). Areas under the receiver operating characteristic curve for detecting thresholds of >5%, >10%, and >20% were 0.93 , 0.99, and 0.97, respectively. Algorithmic performance remained highly stable across all demographic subgroups, including in patients with obesity.

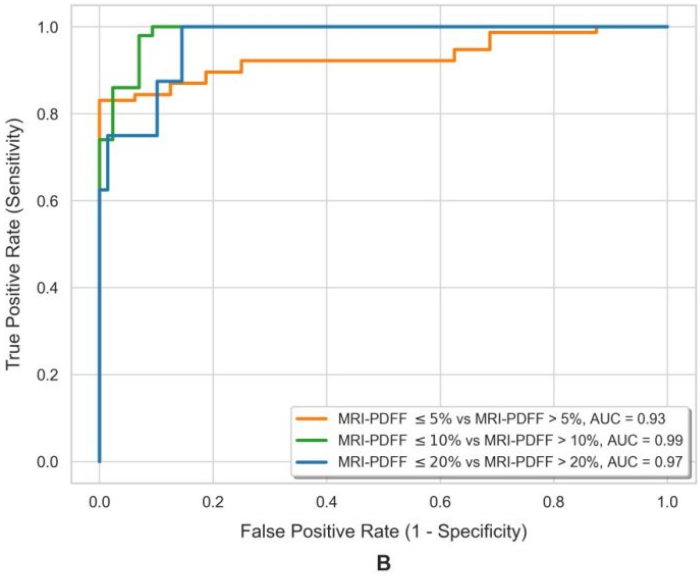
CONCLUSIONS:

HDFF provides an accurate, real-time surrogate for MRI-PDFF. Integrated into an ultraportable software system, Hepatoscope®, it offers distinct point-of-care workflow advantages for large-scale screening and potential longitudinal monitoring of populations with steatotic liver diseases. HDFF was 510(k)-cleared by the FDA.

APPENDICES:







ABSTRACT N°7

TITLE: DOES LIVER STEATOSIS AFFECT LONG-TERM OUTCOMES FOLLOWING ANTIVIRAL TREATMENT IN HCV-INFECTED PATIENTS WITH ADVANCED FIBROSIS/CIRRHOSIS?

AUTHORS:

Prof. Dorota ZSRĘBSKA-MICHALUK, Department of Infectious Diseases and Allergology, Jan Kochanowski University Kielce, Poland
Dr Krystyna DOBROWOLSKA, Collegium Medicum, Jan Kochanowski University Kielce, Poland
Dr Jakub JANCZURA, Collegium Medicum, Jan Kochanowski University Kielce, Poland

Dr Michał BRZDĘK, Collegium Medicum, Jan Kochanowski University Kielce, Poland

Dr Kinga BRZDĘK, Department of Rheumatology and Connective Tissue Diseases, Nicolaus Copernicus Memorial Hospital, Lodz, Poland

Prof. Robert FLISIAK, Department of Infectious Diseases and Hepatology, Medical University of Białystok, Białystok, Poland

KEYWORDS:

HEPATITIS C, STEATOTIC, LIVER CANCER

OBJECTIVES:

Steatotic liver disease (SLD) worsens the prognosis for other chronic liver diseases, including hepatitis C virus (HCV) infection. This real-world study aimed to assess whether the presence of SLD in patients with chronic hepatitis C affects long-term outcomes following direct-acting antiviral (DAA) treatment.

METHODS:

The study included 435 consecutive HCV-infected patients with advanced liver disease who were undergoing long-term monitoring after DAA treatment. Data were obtained retrospectively from medical records.

RESULTS:

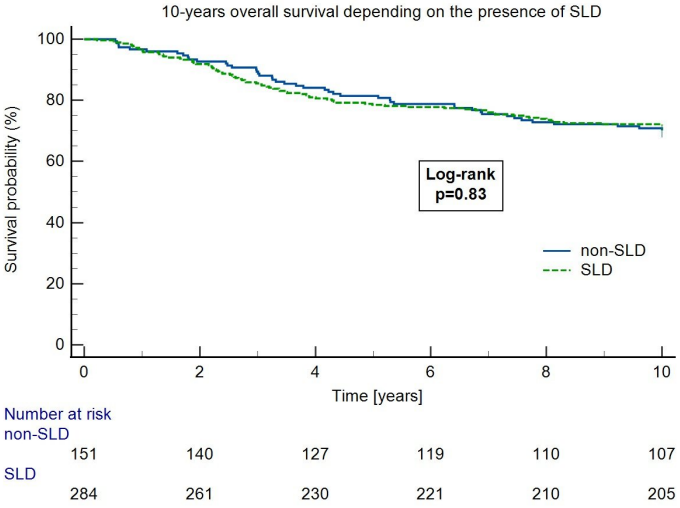
Two-thirds of the study population were diagnosed with SLD on the basis of ultrasound examination. In this group, the percentage of patients with cirrhosis was significantly higher compared to the non-SLD population (71.8% vs. 62.3%, p=0.041) (Table 1). Patients with SLD were significantly younger (p=0.0361), had higher burden with comorbidities (p<0.0001), including obesity (p=0.0001) and hyperlipidemia (p=0.0001) as compared to non-SLD individuals. Significantly higher rates of SLD patients reported alcohol abuse in the past (23.2% vs 9.9%, p=0.0007). The response rate to DAA treatment was high, at 98% in both groups. The median time of long-term observation (LTO) after antiviral therapy was 5.2 years (IQR 4.47-6.14). During LTO, 35 cases of de novo liver cancer were documented, 18 in the SLD group and 9 in the non-SLD group (p=0.24). In the Cox univariate proportional hazards model, the presence of SLD did not show a statistically significant association with the risk of de novo liver cancer in LTO (Figure 1). However, the combination of SLD with at least four of the following factors—male gender, age ≥50 years, diabetes, hypertension, hyperlipidemia, and past alcohol abuse—has a statistically significant impact on the risk of de novo liver cancer following treatment with DAA (HR=4.08 (1.58–10.53), p=0.0036). The overall long-term survival rates were 79.5% at 5 years and 71.3% at 10 years, with no differences between the SLD and non-SLD groups (p=0.46 and p=0.83 for 5 and 10 years, respectively) (Figure 2, 3).

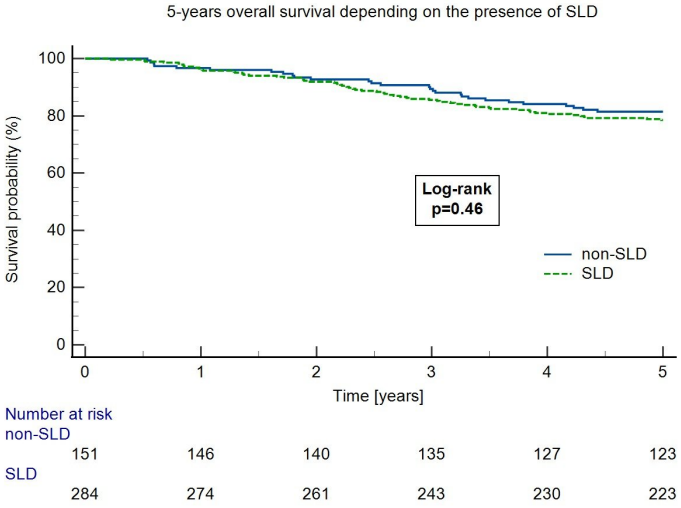
CONCLUSIONS:

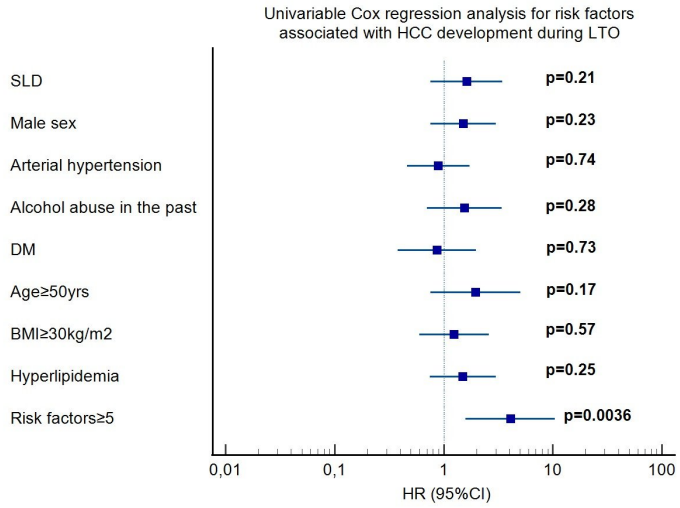
The presence of steatotic liver disease in patients with advanced fibrosis/cirrhosis did not affect the overall survival and

did not increase the risk of de novo liver cancer during long-term follow-up after antiviral treatment.

APPENDICES:







Parameter	F3-F4 non-SLD n=151	F3-F4 SLD n=284	*p-value*
F3/F4, n(%)	57(37.7)/94(62.3)	80(28.2)/204(71.8)	0.041
Gender, females/males, n (%)	78(51.7)/73(48.3)	120(42.3)/164(57.7)	0.06
Age [years], median (IQR), [min-max]	62 (50.5-71) [21-90]	59 (48-67), [26-94]	0.0361
Age ≥50 years old, n (%)	115(76.2)	208(73.2)	0.51
Genotype, n(%)			0.06
1	11(7.3)	24(8.5)	
1A	2(1.3)	2(0.7)	
1B	115(76.2)	208(73.2)	
2	0	0	
3	17(11.3)	47(16.5)	
4	4(2.6)	1(0.4)	
Not determined	0	2(0.7)	
BMI [kg/m^2], median (IQR)	24.84 (22.42-28.06)	27.47 (24.54-31.05)	<0.0001
BMI≥30 [kg/m^2], n(%)	21(13.9)	87(30.6)	0.0001
Any comorbidity, n (%)	139(92.1)	284(100)	<0.0001
Hypertension, n (%)	80(53)	141(49.6)	0.51
Diabetes, n (%)	32(21.2)	65(22.9)	0.69
Renal disease, n (%)	12(7.9)	27(9.5)	0.59
Autoimmune disease, n (%)	10(6.6)	21(7.4)	0.77
Hyperlipidemia, n(%)	19(12.6)	85(29.9)	0.0001
Cholelithiasis, n(%)	30(19.9)	57(20.1)	0.58
Non-liver malignancies in the past, n (%)	9(6)	19(6.7)	0.77
Concomitant medications, n (%)	128(84.8)	231(81.3)	0.37
HCC diagnosis in the past, n (%)	3(2)	11(3.9)	0.29
HIV coinfection, n (%)	0	0	NA
HBV coinfection (HBsAg(+)), n (%)	2(1.3)	2(0.7)	0.52
Anti-HBc total(+), HBsAg(-), n (%)	30(19.9)	51(18)	0.63
Alcohol abuse in the past, n (%)	15(9.9)	66(23.2)	0.0007
OLTx, n(%)	0	1(0.4)	0.47

Table 1. Baseline characteristics of patients with F3-F4 fibrosis by the presence of SLD.

Abbreviations: BMI, body mass index; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; anti-HBc total, hepatitis B core antibodies; HIV, human immunodeficiency virus; HCC, hepatocellular carcinoma; IQR, interquartile range; SLD, steatotic liver disease.

ABSTRACT N°8

TITLE: DISMANTLING THE DIAGNOSTIC PYRAMID IN MASH: CLINICAL EVIDENCE SYNTHESIS OF HEPATOSCOPE FOR GLOBAL LIVER SCREENING

AUTHORS:

Dr Cindy SERDJEBI, E-Scopics, 235 rue Léon Foucault, Aix-en-Provence
Dr Adrien BESSON, E-Scopics, 235 rue Léon Foucault, Aix-en-Provence
MSc Joël GAY, E-Scopics, 235 rue Léon Foucault, Aix-en-Provence
Dr Nicolas ETAIX, E-Scopics, 235 rue Léon Foucault, Aix-en-Provence
Dr Claude COHEN-BACRIE, E-Scopics, 235 rue Léon Foucault, Aix-en-Provence

KEYWORDS:

LSM; ELASTOGRAPHY; ULTRASOUND; DECENTRALIZATION; EQUITY

OBJECTIVES:

The global escalation of MASLD presents an unprecedented public health crisis. Intercepting requires massive, decentralized screening. However, the current diagnostic landscape remains centralized, cost-prohibitive, and restricted to highly specialized operators. Hepatoscope was engineered to integrate transient elastography, fat-fraction estimation, image guidance, and ultraportability into a single platform. This work summarized the cumulative clinical evidence and validation data evaluating how the scientific convergence of these four distinct features impacts diagnostic accuracy, operator democratization, and global patient triage workflows.

METHODS:

We gathered evidence from PubMed, international hepatology, gastroenterology and diabetology conferences and publicly available information from the US Food and Drug Administration, about Hepatoscope, from the inception to July 10th, 2026. Our aim was to identify information about clinical performance and utility of Hepatoscope to screen, risk stratify, diagnose or monitor patients with MASH-related signs, i.e. steatosis and fibrosis. Information comparing Hepatoscope with other clinically established medical devices was also sought.

RESULTS:

The literature search retrieved a total of 5 peer-reviewed papers, 14 posters, and 3 US FDA 510(k) clearances. In terms of performance, Hepatoscope demonstrated good to excellent reproducibility, with an ICC ranging from 0.79 to 0.96. Its QUS measurements remain uniform across varying depths, and using a large region of interest (ROI) significantly reduces variability. For diagnostic accuracy, the Hepatoscope-derived fat fraction (HDFF) achieved an AUROC of 0.95 in detecting patients with steatosis. Additionally, liver stiffness measurements showed a strong and consistent correlation with FibroScan (r = 0.61 - 0.63), were independent of BMI (r = 0.008), and supported the standard 8 kPa threshold for risk stratification in MASLD. Because of this reliability, Hepatoscope can be utilized by a wide range of healthcare personnel—including nurses, clinical research assistants, and physicians like radiologists—across diverse clinical settings such as hepatology, diabetology, community care, or outreach initiatives.

CONCLUSIONS:

The gathered clinical evidence validates Hepatoscope as a timely, structural solution to global MASH screening deficits. By combining validated elastography, fat-fraction estimation, and novice-friendly usability into an ultra-portable system, Hepatoscope offers a scientifically sound, highly scalable strategy to democratize liver care and intercept progressive MASH on a global scale.

ABSTRACT N°9

TITLE: DYNAMIC CHANGES IN HEPATIC RESERVE ACROSS INTERVENTIONS AND ETIOLOGIES MEASURED BY THE HEPQUANT DUO TEST

AUTHORS:

Dr. Joanne IMPERIAL, HepQuant, LLC
Dr. Michael MCRAE, Custom DX Solutions LLC
Dr. Gregory EVERSON, HepQuant, LLC

KEYWORDS:

LIVER FUNCTION TEST, CHOLATE, MASH

OBJECTIVES:

The HepQuant DuO test (DuO) generates parameters of liver health including Hepatic Reserve (HR%), which 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. DuO 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. HR% was 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. For each treatment arm, the mean change from baseline in HR% (delta) was calculated. Treatment response was categorized relative to the MDD as improved (delta ≥ +3.3%), stable/improved (+3.3% > delta ≥ 0%), stable/worsened (0% > delta ≥ −3.3%), or worsened (delta < −3.3%).

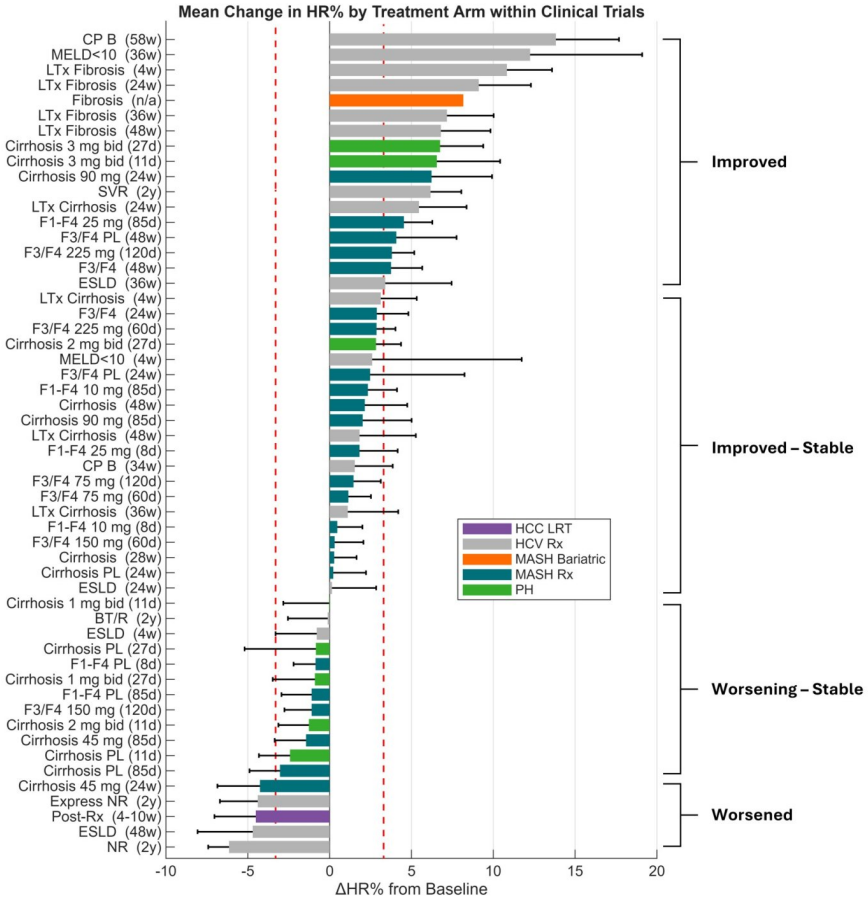
RESULTS:

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). Among 54 treatment groups, 17 (31%) improved, 20 (37%) were stable/improved, 12 (22%) were stable/worsened, and 5 (9%) worsened. The largest improvements (+10–15%) occurred in HCV virologic responders and subjects with fibrotic MASH who underwent bariatric surgery (delta +8.2%). DuO detected rapid functional improvement within 27 days in subjects with Child-Pugh A cirrhosis treated with the highest dose of avenciguat (delta +6.8%). Among MASH treatment cohorts, 18 of 24 (75%) were improved or stable/improved. Hepatotoxicity (delta -4.5%) was observed in patients undergoing locoregional therapy for hepatocellular carcinoma. Worsening HR% was observed in antiviral nonresponders and patients with ESLD.

CONCLUSIONS:

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.

APPENDICES:


Mean Change in HR% by Treatment Arm within Clinical Trials
CP B (58w)
MELD<10 (36w)
LTx Fibrosis (4w)
LTx Fibrosis (24w)
Fibrosis (n/a)
LTx Fibrosis (36w)
LTx Fibrosis (48w)
Cirrhosis 3 mg bid (27d)
Cirrhosis 3 mg bid (11d)
Cirrhosis 90 mg (24w)
SVR (2y)
LTx Cirrhosis (24w)
F1-F4 25 mg (85d)
F3/F4 PL (48w)
F3/F4 225 mg (120d)
F3/F4 (48w)
ESLD (36w)
LTx Cirrhosis (4w)
F3/F4 (24w)
F3/F4 225 mg (60d)
Cirrhosis 2 mg bid (27d)
MELD<10 (4w)
F3/F4 PL (24w)
F1-F4 10 mg (85d)
Cirrhosis (48w)
Cirrhosis 90 mg (85d)
LTx Cirrhosis (48w)
F1-F4 25 mg (8d)
CP B (34w)
F3/F4 75 mg (120d)
F3/F4 75 mg (60d)
LTx Cirrhosis (36w)
F1-F4 10 mg (8d)
F3/F4 150 mg (60d)
Cirrhosis (28w)
Cirrhosis PL (24w)
ESLD (24w)
Cirrhosis 1 mg bid (11d)
BT/R (2y)
ESLD (4w)
Cirrhosis PL (27d)
F1-F4 PL (8d)
Cirrhosis 1 mg bid (27d)
F1-F4 PL (85d)
F3/F4 150 mg (120d)
Cirrhosis 2 mg bid (11d)
Cirrhosis 45 mg (85d)
Cirrhosis PL (11d)
Cirrhosis PL (85d)
Cirrhosis 45 mg (24w)
Express NR (2y)
Post-Rx (4-10w)
ESLD (48w)
NR (2y)
HCC LRT
HCV Rx
MASH Bariatric
MASH Rx
PH
-10
-5
0
5
10
15
20
ΔHR% from Baseline
Improved
Improved – Stable
Worsening – Stable
Worsened

ABSTRACT N°10

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

AUTHORS:

Dr. Joanne IMPERIAL, HepQuant, LLC, Denver, CO, USA
Dr. Naga CHALASANI, Indiana University School of Medicine, Indianapolis, IN, USA
Dr. Mitchell SHIFFMAN, Bon Secours Liver Institute of Virginia, Richmond, VA, USA
Dr. Timothy MORGAN, Veterans Affairs Long Beach Healthcare System, Long Beach, CA, USA
Dr. Michael LEISE, Mayo Clinic, Rochester, MN, USA
Dr. Michael MCRAE, Custom DX Solutions LLC, Houston, TX, USA
Dr. Gregory EVERSON, HepQuant, LLC, Denver, CO, USA

KEYWORDS:

CHILD-PUGH, LIVER FUNCTION TEST, CHOLATE

OBJECTIVES:

Liver function in patients with Child-Pugh (CP) A chronic liver disease may vary from normal to severe impairment and shunting. Compared to CP A5, patients with CP A6 are at greater risk for complications. Staging disease severity is important for clinical decisions regarding testing, treatment, follow-up, or enrollment in trials. We used the HepQuant DuO® test (DuO) results to characterize patients with CP A5 and A6.

METHODS:

Subjects were enrolled in two U.S. prospective studies linking DuO 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.

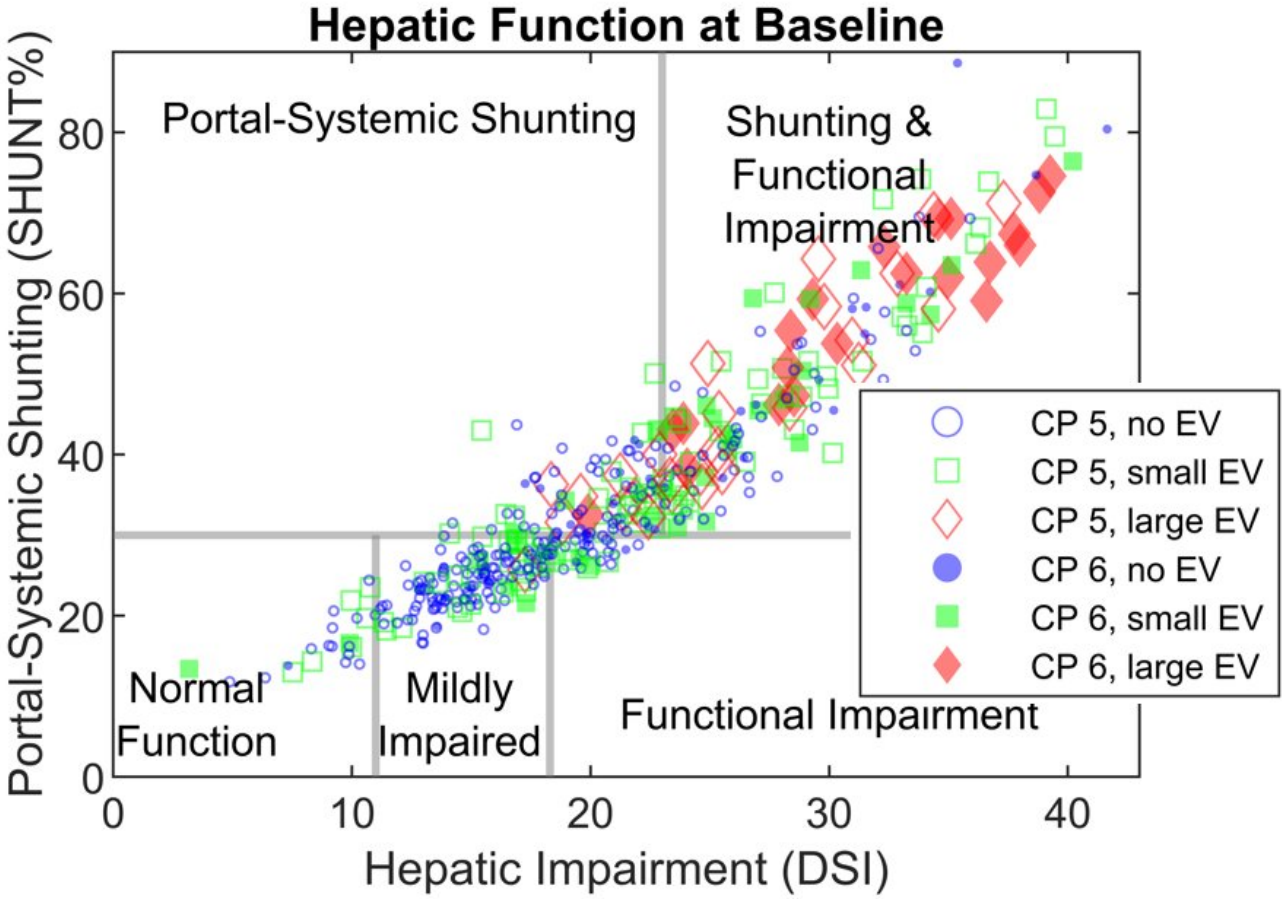
RESULTS:

Subjects were age 56 ± 11 years, BMI 32 ± 7 kg/m2, 86% overweight, and 54% obese. 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. Subjects with CP A6 were more likely to have hepatitis C (p=0.018) and less likely to have MASH (p=0.008); laboratory values and MELD scores were 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). DuO parameters showed worse function and shunting in 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, AUROCs for DSI (0.82) and SHUNT% (0.83) were higher than CP score (0.63) (p<0.0001).

CONCLUSIONS:

Patients with CP A6 have worse function and more shunting than patients with CP A5 – explaining the previously observed greater risk for clinical outcome in CP A6. DuO 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, DuO may be useful in staging disease severity, for both the clinic and in clinical trials.

APPENDICES:


Hepatic Function at Baseline
Portal-Systemic Shunting
Shunting &
Functional
Impairment
Normal
Function
Mildly
Impaired
Functional Impairment
CP 5, no EV
CP 5, small EV
CP 5, large EV
CP 6, no EV
CP 6, small EV
CP 6, large EV
Portal-Systemic Shunting (SHUNT%)
Hepatic Impairment (DSI)
0
20
40
60
80
0
10
20
30
40

ABSTRACT N°11

TITLE: LIQUID-BIOPSY ASSESSMENT OF LIVER DAMAGE AND METABOLIC RISK IN MASH VIA MONOCYTE PLIN2 EXPRESSION

AUTHORS:

Dr. Lucas CAFFERATI BELTRAME, Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
Dr. Patrizia INFELISE, Cardiometabolic Risk Laboratory, Institute of Clinical Physiology (IFC), National Research Council (CNR), Pisa, Italy.
Dr. Sara RUSSO, Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
Dr. Fabrizia CARLI, Cardiometabolic Risk Laboratory, Institute of Clinical Physiology (IFC), National Research Council (CNR), Pisa, Italy.
Dr. Silvia SABATINI, Cardiometabolic Risk Laboratory, Institute of Clinical Physiology (IFC), National Research Council (CNR), Pisa, Italy.
Prof. Geltrude MINGRONE, Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
Prof. Amalia GASTALDELLI, Cardiometabolic Risk Laboratory, Institute of Clinical Physiology (IFC), National Research Council (CNR), Pisa, Italy.

KEYWORDS:

METABOLOMICS, MONOCYTES, MASH, PLIN2, STEATOHEPATITIS

OBJECTIVES:

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease, with obesity and type 2 diabetes (T2D) are risk factors. PLIN2 stabilizes lipid droplets, and promotes their accumulation within cells. Altered monocyte expression of this protein has been proposed as a potential liquid-biopsy marker for severe MASLD/metabolic dysfunction-associated steatohepatitis (MASH). We investigated the association of PLIN2 with disease severity and metabolomic alterations in MASH, obesity and T2D.

METHODS:

We included 190 individuals stratified by the presence of MASH, obesity and/or T2D (114 with and 76 without MASH). Serum metabolomics and lipidomics were assessed by advanced mass-spectrometry and monocyte PLIN2 expression by flow cytometry.

RESULTS:

Omics analysis showed impaired metabolism in obesity and MASH, with elevated branched-chain amino acids (BCAA) and aromatic (AAA) aminoacids, TCA cycle intermediates, TAG, ceramides (CER), lysophosphatidylcholines (LPC) and decreased -hydroxybutyrate (BHB). Independent of age, sex, HbA1c and BMI, 11 metabolites/lipids predicted MASH risk in obesity. Higher levels of succinate, GSG-index, lactate, glutamic acid, LPE(18:1), LPC(16:0), LPC(16:0e) and α-hydroxybutyrate increased risk (OR > 1) while higher α-ketobutyric acid, PC(37:4) and α-ketoisovaleric reduced it. PLIN2 was increased with obesity and further increased in presence of MASH compared to noMASH. At the same time, the presence of T2D didn't impact PLIN2 expression. PLIN2 was associated with features of liver disease; in particular with steatosis, ballooning, inflammation and fibrosis. PLIN2 was positively associated with a wide range of metabolites, including lactate, BCAA, AAA, and GSG-index. In contrast, the negative correlations were fewer than the positive and mainly with lipid species. PLIN2 showed strong positive correlation with NAS score, age, BMI, glycemia, HbA1c, insulin,

free fatty acids (FFA), HOMA-IR and Adipo-IR (rho > 0.35, p < 0.001) and negatively with C-HDL (rho = -0.42, p < 0.001).

CONCLUSIONS:

Elevated monocyte PLIN2 expression characterizes individuals with obesity and MASH, independent of T2D, and reflects hepatic injury. Its association with insulin resistance and specific metabolomic and lipidomic profiles, supporting their use as noninvasive biomarker for assessing hepatic damage and metabolic risk, and as a potential tool for liquid biopsy–based monitoring of MASH progression. PNRR-MCNT2-2023-12377036_Finanziato dall'Unione Europea – NextGenerationEU.

ABSTRACT N°12

TITLE: IN F0-F3 MASH, ≥5% WEIGHT LOSS LOWERS VCTE+ELF INDEPENDENT OF BIOPSY FIBROSIS IMPROVEMENT

AUTHORS:

Dr Rohit LOOMBA, University of California San Diego
Dr Quentin ANSTEE, Anstee Medical Services Ltd
Dr Rebecca TAUB, Madrigal Pharmaceuticals, Inc.
Dr Dominic LABRIOLA, Madrigal Pharmaceuticals, Inc.
Dr Robin MOGG, Madrigal Pharmaceuticals, Inc.
Dr Suneil HOSMANE, Madrigal Pharmaceuticals, Inc.
Dr Jorn SCHATTENBERG, Saarland University Medical Center
Dr Vladimir RATZIU, Sorbonne University and Pitié-Salpêtrière Hospital

KEYWORDS:

FIBROSIS, WEIGHT, ELF, VCTE, BIOPSY

OBJECTIVES:

Weight loss (WL) reduces liver stiffness and collagen markers in F0-F1 pts. The impact of ≥5% WL on VCTE and ELF and association with biopsy fibrosis improvement (FI) was examined in F0-F1+F2-F3 MASH from MAESTRO program.

METHODS:

Baseline and week52 VCTE+ELF components were determined in MAESTRO-NASH and MAESTRO-NAFLD-1. Logistic regression models explored associations between resmetirom or placebo changes, weight change, and biopsy FI.

RESULTS:

In F0-F1, resmetirom did not significantly reduce ELF v. placebo. 14% pts w/F0-F1 had ≥5% WL at W52; ELF showed greater reduction in those with ≥5% WL, with the P3NP component (major fibrogenesis marker in ELF) showing the greatest reduction in pts w/WL, independent of treatment. Baseline F0-F1 VCTE was mean 7.4 kPa, median 6.5 kPa. Resmetirom did not significantly reduce VCTE compared with placebo in F0-F1 pts. VCTE was significantly reduced in ≥ 5 %WL vs. <5% WL independent of treatment. In F2-F3, mean baseline ELF score was 9.8. At W52, 17% and 22% (80 and 100 mg resmetirom) v. 12% (placebo) had ≥5% WL. There were independent associations of WL and FI w/changes in ELF, and associations of change in ELF w/WL were more pronounced than associations of change in ELF w/FI; most noticeable effects were observed in F3. ≥5% WL on ELF attenuated a relationship between ELF and FI in resmetirom and placebo patients with <5% WL. Changes in ELF were strongly associated with FI only in F3 pts with <5% WL. In F2-F3 baseline VCTE was 13.3 kPa. There were independent associations of WL+FI w/changes in VCTE, and associations of change in VCTE+WL were more pronounced than associations of change in VCTE+FI. The association of VCTE+FI was pronounced in <5% WL vs. ≥5% WL in both groups. Change in liver stiffness by VCTE predicted FI on biopsy in F2-F3 without WL.

CONCLUSIONS:

In F2-F3 MASH, WL ≥5% and FI independently associated with reductions in VCTE and ELF. FI was clearly associated with VCTE and ELF reduction in patients without weight loss treated with resmetirom or placebo. Confounding effects of WL on ELF and VCTE, independent of histologic fibrosis improvement, should be considered when evaluating MASH treatments.

ABSTRACT N°13

TITLE: THE PREVALENCE OF CARDIOMETABOLIC COMORBIDITIES IN MASLD IN FRANCE

AUTHORS:

Ms. Carolyn WALLACE, Center for Disease Analysis, Lafayette, CO, USA
Dr. Paul BARDOT, Madrigal Pharmaceuticals, Boulogne, France
Dr. Francois BOER, Madrigal Pharmaceuticals, Boulogne, France
Dr. Melinda J DAUMONT, Madrigal Pharmaceuticals, GmbH, Baar, Switzerland
Dr. Isabelle DURAND-ZELESKI, Department of Public Health, Hôpitaux de Paris, Paris, France

KEYWORDS:

MASH, DIABETES, OBESITY, COMORBIDITY, FRANCE

OBJECTIVES:

Metabolic dysfunction-associated steatotic liver disease (MASLD) is inherently associated with metabolic comorbidities, notably type II diabetes mellitus (T2DM) and obesity, which stand as drivers of disease progression to liver-related events and mortality. Documenting the cardiometabolic disease burden at the national level has elevated importance with continued MASH growth and EMA approval of the first F2/F3 treatments resmetirom and semaglutide. The objective of this analysis was to quantify the prevalence of diabetes, obesity, hypertension, and dyslipidemia among individuals with MASLD, MASH, and significant-to-advanced fibrosis in France to provide a comprehensive glimpse at the current disease burden.

METHODS:

A Markov model was utilized to estimate the prevalence of MASLD by disease stage in the French adult population. Empirical data for prevalence of MASLD/MASH along with the rates of comorbidity with diabetes, obesity, hypertension, and dyslipidemia in France were gathered through a targeted literature review. Literature reporting representative French data was prioritized. Comorbidity results for diabetes and obesity were triangulated from the CONSTANCES studies to validate the size of the comorbid populations and the prevalence of multiple cardiometabolic comorbidities.

RESULTS:

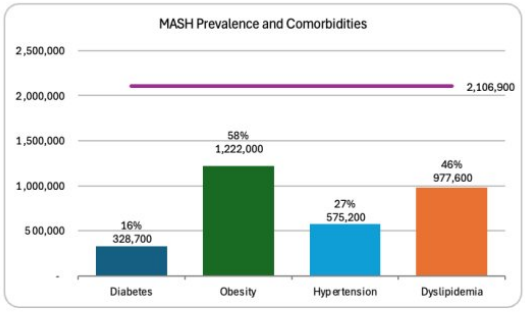
From the model, the estimated sizes of the comorbid populations in France in 2025 are as follows: MASH with diabetes – 328,700, obesity – 1,222,000, hypertension – 575,200, dyslipidemia – 977,600. The F2 comorbid populations (diabetes – 94,900, obesity – 197,100, hypertension – 107,000, dyslipidemia – 149,300) and F3 comorbid populations (diabetes – 71,800, obesity – 91,100, hypertension – 85,800, dyslipidemia – 64,800) were also calculated. Triangulation of data sources confirmed the estimated MASLD-diabetes and MASLD-obesity populations, with differences of 17% and 11%, respectively. The size of the French population with MASH and diabetes and an additional cardiometabolic comorbidity were sized: obesity – 219,200, hypertension – 293,800, hypertriglyceridemia – 242,600; as well as the F3 and diabetes population with an additional cardiometabolic comorbidity: obesity – 49,700, hypertension – 32,800, hypertriglyceridemia – 46,400.

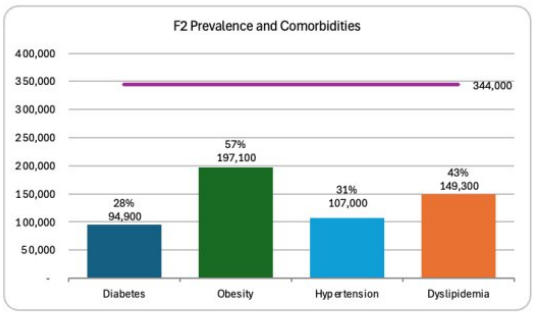
CONCLUSIONS:

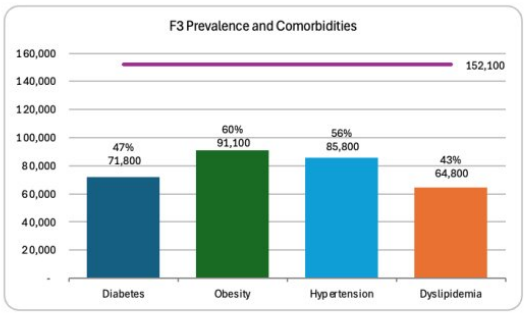
Integrating modeling with real-world epidemiologic data provides insight of the burden of MASLD and its major comorbid conditions in France at present. These findings can guide frameworks for public health planning and support evidence-based strategies for screening, diagnosis, and care for high-risk populations.

APPENDICES:

Size of comorbid populations by disease stage - 2025







ABSTRACT N°14

TITLE: PROJECTED IMPACT OF RESMETIROM ON LIVER TRANSPLANT WAITLIST, MORTALITY, AND ORGAN REALLOCATION IN FRANCE

AUTHORS:

Dr. Daniel KIM, Harvard Medical School/Massachusetts General Hospital, Boston, MA, USA
Dr. Jagpreet CHHATWAL, Harvard Medical School/Massachusetts General Hospital, Boston, MA, USA
Dr. Jérôme DUMORTIER, Université Claude Bernard Lyon 1, Villeurbanne, France
Dr. Melinda DAUMONT, Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA
Dr. John O'DONNELL, Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA
Dr. Yestle KIM, Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA

KEYWORDS:

RESMETIROM, LIVER-TRANSPLANTATION, MICROSIMULATION, ORGAN-ALLOCATION, WAITLIST-MORTALITY

OBJECTIVES:

Resmetirom received conditional marketing authorization from the EU Commission in August 2025 for adults with noncirrhotic MASH with moderate-to-advanced fibrosis. In France, the large population affected by MASH may contribute to increasing liver transplantation (LT) needs as disease progresses, while demand for transplantation continues to exceed available donor organs. We evaluated how the first approved MASH-directed therapy could affect future LT demand, waitlist outcomes, and organ reallocation in France.

METHODS:

We developed a microsimulation model to estimate MASH progression in France across disease stages, including steatosis, fibrosis, cirrhosis, and end-stage liver disease leading to LT waitlisting. The modeled resmetirom-eligible population included patients with moderate-to-advanced fibrosis, consistent with the European Summary of Product Characteristics label. To conservatively account for limited initial uptake in France, outcomes were projected over 40 years, from 2027 to 2067, under two scenarios: a counterfactual scenario without MASH pharmacotherapy and a resmetirom scenario. In the resmetirom scenario, 1% of eligible patients initiated treatment in 2027, followed by 5% annual uptake from 2028 onward. A sensitivity analysis evaluated higher uptake of 15% annually. Treatment effects were informed by MAESTRO-NASH, and transplant-related characteristics were derived from the organ procurement and transplantation reports from Agence de le Biomédecine.

RESULTS:

In the base case, resmetirom was projected to prevent 346 LT waitlist entries, representing a 7.23% reduction, by delaying or reversing MASH progression. These avoided MASH-related waitlist entries enabled 247 donor livers to be reallocated to other candidates with end-stage liver disease from any indication, preventing 259 deaths and shortening mean wait time by 10.56 days per waitlisted patient compared to the counterfactual scenario. With 15% annual uptake from 2028, the model projected 923 avoided waitlist entries, 643 livers available for reallocation, 667 deaths averted, and a 24.95-day reduction in mean wait time compared to the counterfactual scenario.

CONCLUSIONS:

Resmetirom may reduce future LT demand in France by modifying the course of progressive MASH before end-stage liver disease develops. Greater resmetirom uptake could expand donor-liver availability for other candidates, lower waitlist mortality, and improve the efficiency of organ allocation.

ABSTRACT N°15

TITLE: CLINICAL OUTCOMES AMONG PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH) IN FRANCE: A REAL-WORLD CLAIMS ANALYSIS

AUTHORS:

Professor Jérôme BOURSIER, Université d'Angers, HIFIH, SFR ICAT, Angers, France; Department of Hepato-Gastroenterology and Digestive Oncology, CHU Angers, Angers, France
Ms Emma FONTVIEILLE, Cencora, Paris, France
Dr Alexandre VIMONT, Cencora, Paris, France
Dr François BOER, Madrigal Pharmaceuticals, Inc, West Conshohocken, PA, USA
Dr Paul BARDOT, Madrigal Pharmaceuticals, Inc, West Conshohocken, PA, USA
Dr Melinda DAUMONT, Madrigal Pharmaceuticals, Inc, West Conshohocken, PA, USA
Dr Yestle KIM, Madrigal Pharmaceuticals, Inc, West Conshohocken, PA, USA
Dr Christina PARRINELLO, Madrigal Pharmaceuticals, Inc, West Conshohocken, PA, USA
Professor Isabelle DURAND-ZALESKI, URCEco, Hôpital Hôtel Dieu, AP-HP, Paris, France

KEYWORDS:

MASH, REAL-WORLD, ESND, OUTCOMES

OBJECTIVES:

The study aimed to describe real-world incidence of liver disease progression, cardiovascular events, and mortality among hospitalized adults diagnosed with MASH in France.

METHODS:

This retrospective cohort study used data from the 2% representative sample of the French national health claims database (Echantillon National des Données de Santé, ESND), from 2017 to 2024. Adults aged ≥18 years with an inpatient diagnosis of MASH or metabolic dysfunction-associated steatotic liver disease (MASLD) between 2019 and 2024 were identified by ICD-10 codes K75.8 and/or K76.0. Patients with other chronic liver disease etiologies during the 2-year historical period were excluded. Baseline disease severity was classified as non-cirrhotic or advanced liver disease (compensated cirrhosis [CC], decompensated cirrhosis [DCC], hepatocellular carcinoma [HCC], and liver transplantation [LT]). Baseline comorbidities were described, and Kaplan-Meier analyses assessed 5-year mortality, progression, and major adverse cardiovascular events (MACE-5).

RESULTS:

A total of 4,206 patients were included with a median follow-up of 2.9 years. At baseline, 84.0% were non-cirrhotic and 15.9% had advanced liver disease (1.8% CC, 11.8% DCC, 1.8% HCC, 0.5% LT). Patients with advanced liver disease were older (63.6 vs 54.9 years). Among all patients, cardiometabolic comorbidities were common (30% obesity, 35% type 2 diabetes, 31% hypercholesterolemia, 47% arterial hypertension). Five-year mortality was higher in patients with advanced liver disease compared to non-cirrhotic patients (28.2% vs 7.8%). Five-year progression through disease stages or death was estimated to be 33.6% and 12.5% in advanced liver disease and non-cirrhotic, respectively. Among non-cirrhotic patients at baseline, 1.1% progressed to CC, 6.0% to DCC, 0.3% to HCC, 0.03% to LT, and 5.12% died. Five-year cardiovascular event rates were higher in advanced liver disease than in non-cirrhotic patients (MACE-5, 8.8% versus 6.1%, respectively).

CONCLUSIONS:

In this real-world French study, hospitalized adults diagnosed with MASH experienced substantial liver, cardiovascular, and mortality burden, with markedly worse outcomes among those with advanced liver disease. Up to one-third of the

patients with advanced liver disease progressed during the follow-up, highlighting the severity of the underlying liver disease and therefore the need for treatments that prevent disease progression.

ABSTRACT N°16

TITLE: TRANSCRIPTOMIC ANALYSIS OF LIVER TISSUE IN A PHASE-2 TRIAL OF SURVODUTIDE IN ADULTS WITH MASH

AUTHORS:

Dr Raphael HESSE, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
Dr Panagiotis PAPAVASILEIOU, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
Mr Ahmad ALHUSSEIN, Boehringer Ingelheim International GmbH, Ingelheim, Germany
Dr Renee MARSHALL, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, Connecticut, United States
Dr Elena STARTSEVA, Boehringer Ingelheim International GmbH, Ingelheim, Germany
Dr Ramy YOUNES, Boehringer Ingelheim International GmbH, Ingelheim, Germany
Dr Amalia GASTADELLI, Cardiometabolic Risk Unit, CNR Institute of Clinical Physiology, Pisa, Italy
Dr Arun J. SANYAL, Virginia Commonwealth University, School of Medicine, Richmond, Virginia, United States
Dr Corinna SCHOELCH, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

KEYWORDS:

FIBROSIS, MASH, GLP-1RA, GCGR.

OBJECTIVES:

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 Gene Set Enrichment Analysis (GSEA), single sample GSEA and Ingenuity Pathway Analysis (IPA) with REACTOME canonical pathways and curated gene sets from the literature.

RESULTS:

Biopsy samples that passed quality check 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. GSEA indicated that cellular pathways involved in tissue remodelling, fibrosis, and inflammation were suppressed, while IPA 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 messenger RNA 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.

ABSTRACT N°17

TITLE: PAEDIATRIC MASLD EVOLVES INTO ADULT MASLD THROUGH NORMALISATION OF LIVER ENZYMES

AUTHORS:

Dr Paul SUNDARAM, University Hospitals of Leicester
Dr Lauren JOHANSEN, Liver Unit, Birmingham Children's Hospital
Dr Yang Yang LEE, Liver Unit, Birmingham Children's Hospital
Dr Jake MANN, Liver Unit, Birmingham Children's Hospital

KEYWORDS:

MASLD, HISTORY, TRANSAMINASES, MONITORING, FIBROSCAN

OBJECTIVES:

Liver enzymes, particularly alanine aminotransferase (ALT), are the mainstay of monitoring paediatric metabolic dysfunction-associated steatotic liver disease (MASLD). Whereas in adults, transaminases correlate poorly with disease activity. We characterised the longitudinal natural history of biochemical, metabolic and structural markers in a paediatric MASLD cohort to determine whether falling enzymes reflect true disease resolution.

METHODS:

We present a planned first-stage (interim) analysis of an ongoing retrospective single-centre cohort of children with MASLD; data collection toward a total cohort of ~600 children is underway. MASLD was diagnosed based on imaging and/or histology demonstrating steatosis plus meeting cardiometabolic criteria. Serial liver biochemistry, metabolic markers, anthropometry and imaging (Fibroscan liver stiffness; ultrasound spleen size expressed as an age- and sex-adjusted z-score) were extracted from electronic patient records. For each patient, the first hepatology assessment (T0) defined baseline; every subsequent measurement was expressed as percent change from baseline (absolute change for z-scores). Baseline and latest follow-up were compared using Wilcoxon signed-rank tests.

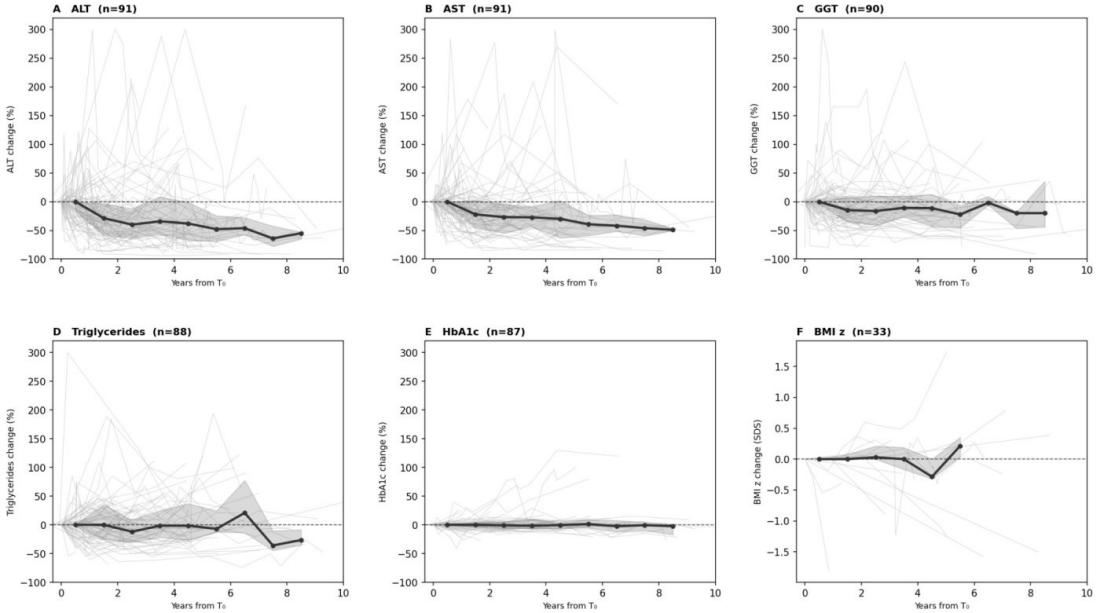
RESULTS:

97 children (65% male; median age 12.5 years, interquartile range [IQR] 10.1–14.3) contributed 3,054 measurements over 414 patient-years (median follow-up 4.4 years [IQR 2.1–6.3], maximum 14.4). Liver enzymes declined significantly: alanine aminotransferase (ALT) −34% (81→48 IU/L; n=80; p<.001), aspartate aminotransferase (AST) −29% (n=79; p<.001) and gamma-glutamyl transferase (GGT) −10% (n=78; p=.015). In contrast, metabolic and structural markers did not improve: triglycerides (−5%; p=.744), glycated haemoglobin (0%; p=.931), body mass index standard deviation score (3.0→2.8; p=.509), Fibroscan liver stiffness (7.7→6.5 kPa; p=.622) and splenic size z-score (1.0→1.8; p=.461) were all unchanged. Children therefore remained severely obese with persistent dyslipidaemia and unchanged fibrosis measures despite substantial transaminase normalisation.

CONCLUSIONS:

Paediatric MASLD evolves over follow-up into an adult-type phenotype: liver enzymes fall progressively, without resolution of metabolic dysfunction and indices of liver stiffness remain unchanged. Falling transaminases provide false reassurance, and enzyme-based monitoring alone will systematically under-detect ongoing disease. Serial liver stiffness measurements and metabolic surveillance are needed to guide follow-up and identify adolescents & young adults at risk of progression.

APPENDICES:



G

Marker	n	Baseline med [IQR]	Latest med [IQR]	Median Δ (% or z)	Wilcoxon p
ALT	80	81 [48–124]	48 [27–90]	-34%	<.001
AST	79	46 [34–74]	35 [22–52]	-29%	<.001
GGT	78	34 [25–57]	30 [20–47]	-10%	.015
Triglycerides	75	1.6 [1.1–2.4]	1.6 [1.1–2.4]	-5%	.744
HbA1c	72	36 [33–40]	36 [32–39]	0%	.931
BMI z	24	3.0 [2.5–4.1]	2.8 [2.4–3.8]	0.0	.509
Fibroscan	13	7.7 [4.5–12.6]	6.5 [5.3–10.3]	0%	.622
Spleen z	11	1.0 [-0.1–2.4]	1.8 [-0.0–2.5]	0.0	.461

Figure 1. Natural history of paediatric MASLD demonstrates evolution into adult MASLD with lower liver enzymes and persistent metabolic dysfunction.

A–F, Individual trajectories (grey) and median with IQR band (black) for each biochemical marker, expressed as change from the T₀ (baseline value). Liver enzymes (ALT, AST, GGT) declined significantly over follow-up, whereas triglycerides, HbA1c, BMI z-score, Fibroscan and splenic z-score showed no significant change, indicating that falling transaminases do not reflect resolution of the underlying metabolic or fibrotic burden. G, summary of results.

ABSTRACT N°18

TITLE: A NOVEL METABOLIC LIVER FIBROSIS RISK SCORE (MLFRS) FOR MASLD: A PILOT STUDY

AUTHORS:

Dr Szymon SUWAŁA, Department of Endocrinology and Diabetology, Collegium Medicum – Faculty of Medicine, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland

Dr Paweł RAJEWSKI, Department of Internal and Infectious Diseases, Provincial Infectious Disease Hospital, Bydgoszcz, Poland; Faculty of Health Sciences, University of Health Sciences in Bydgoszcz, Bydgoszcz, Poland

Prof. Roman JUNIK, Department of Endocrinology and Diabetology, Collegium Medicum – Faculty of Medicine, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland

KEYWORDS:

MASLD; LIVER FIBROSIS; RISK PREDICTION

OBJECTIVES:

To compare commonly used non-invasive fibrosis scores and develop a simple metabolic risk score for identifying liver fibrosis in patients with metabolic dysfunction-associated steatotic liver disease (MASLD).

METHODS:

This pilot study included 100 adults with MASLD diagnosed on the basis of cardiometabolic risk factors and hepatic steatosis confirmed by transient elastography. Liver stiffness was assessed using FibroScan. The diagnostic performance of the Fibrosis-4 Index (FIB-4), NAFLD Fibrosis Score (NFS), and BARD score was evaluated using receiver operating characteristic analysis. A logistic regression model incorporating routinely available clinical and laboratory variables was used to derive the Metabolic Liver Fibrosis Risk Score (MLFRS).

RESULTS:

Results: The study population included 52 men and 48 women, with a mean age of 55.5 ± 11.9 years and a mean body mass index of 31.1 ± 4.6 kg/m²; 58% had type 2 diabetes. Median liver stiffness was 5.4 kPa (interquartile range: 4.2–8.2), and 36 patients met the elastography-based criterion for fibrosis. Among the established scores, NFS showed the highest overall accuracy (72.0%), whereas FIB-4 had the highest sensitivity (81.8%) and negative predictive value (87.2%). BARD was the most specific score (76.1%) but had low sensitivity (48.5%). The newly derived MLFRS, based on age, body mass index, glycated haemoglobin, and aspartate aminotransferase, achieved a sensitivity of 86.2%, specificity of 73.4%, positive predictive value of 59.5%, negative predictive value of 92.2%, and overall accuracy of 77.4%, outperforming the evaluated conventional scores.

CONCLUSIONS:

In this pilot MASLD cohort, MLFRS demonstrated better diagnostic performance than FIB-4, NFS, and BARD while relying exclusively on readily available clinical and laboratory variables. These findings support further validation of MLFRS in larger, independent cohorts before its potential clinical implementation.

ABSTRACT N°19

TITLE: LIVER HEALTH IMPROVES IN CHILDREN WITH OVERWEIGHT OR OBESITY DURING A TWO-YEAR COMBINED LIFESTYLE INTERVENTION

AUTHORS:

Drs. Guusje H. J. VAN GIESEN, Centre for Overweight Adolescent and Children's Healthcare (COACH), Maastricht University Medical Centre+, MosaKids Children's Hospital, Maastricht, the Netherlands and NUTRIM School of Nutrition and Translational Research, Maastricht University, Maastricht, The Netherlands.
Dr. Judith W. LUBRECHT,
Prof. Dr. Anita C. E. VREUGDENHIL, Centre for Overweight Adolescent and Children's Healthcare (COACH), Maastricht University Medical Centre+, MosaKids Children's Hospital, Maastricht, the Netherlands and NUTRIM School of Nutrition and Translational Research, Maastricht University, Maastricht, The Netherlands.

KEYWORDS:

MASLD, PEDIATRIC OBESITY, LIFESTYLE INTERVENTION

OBJECTIVES:

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the predominant chronic liver disease in children, paralleling the worldwide epidemic of childhood obesity. Combined lifestyle intervention (CLI) is the only recommended treatment for MASLD in children. Elevated serum alanine aminotransferase (ALT) concentration serves as a marker for MASLD. Knowledge on the long-term effects of CLI on ALT concentration in children is limited. The aim of this study is to explore the course of ALT concentration during two years of CLI in children with overweight or obesity and its association with changes in BMI z-score (SDS).

METHODS:

A total of 823 children with overweight or obesity participating in a personalized CLI at the Centre for Overweight Adolescent and Children's Healthcare (COACH) at Maastricht University Medical Centre (MUMC+) in the Netherlands between December 2010 and February 2023 were included. Serum ALT concentrations and BMI z-scores were measured at baseline, after one year (T1) and after two years (T2) of CLI.

RESULTS:

At T1, median ALT concentration had already decreased significantly in children with a reduction in BMI z-score compared to baseline (ALT 21 [17–28] vs ALT 24,5 [18–32] U/L; p<0,001). At T2, liver health improved in the vast majority of children compared to baseline (ALT 22 [17,25–30] vs ALT 26 [18-34] U/L; p=0,008). Only children with a BMI z-score increase of ≥0,25 SDS showed no significant improvement in ALT concentration at T2 compared to baseline. At T2, BMI z-score change was significantly associated with change in ALT concentration.

CONCLUSIONS:

Liver health (reflected by ALT concentration) improved in the overall cohort of children during the two-year combined lifestyle intervention. BMI z-score change was associated with sustained reductions in ALT concentration, and the most responsive children already showing these benefits after one year.

ABSTRACT N°20

TITLE: SELF-RATED HEALTH AND HEALTHCARE UTILISATION IN RELATION TO INCREASED LIVER STIFFNESS

AUTHORS:

Miss He HUANG, Department of Gastroenterology and Hepatology, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, Netherlands
MD Charlotte DATTATREYA, Department of Gastroenterology and Hepatology, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, Netherlands
MD Jesse PUSTJENS, Department of Gastroenterology and Hepatology, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, Netherlands
Prof. dr. Harry L.A. JANSSEN, Department of Gastroenterology and Hepatology, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, Netherlands
Dr. Willem Pieter BROUWER, Department of Gastroenterology and Hepatology, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, Netherlands
Dr. Laurens A. VAN KLEEF, Department of Gastroenterology and Hepatology, Erasmus Medical Center, University Medical Center Rotterdam, Rotterdam, Netherlands

KEYWORDS:

SELF-RATED HEALTH; LIVER STIFFNESS; MASLD.

OBJECTIVES:

Given the relatively low incidence of advanced liver disease in the general population, population-wide screening remains controversial. Opportunistic screening within routine healthcare settings, alongside self-reported health, may represent a pragmatic alternative. We therefore assessed the prevalence of increased liver stiffness measurements (LSM) and incidence of major adverse liver outcomes (MALO) across healthcare utilisation patterns to assess its value as an entry point for opportunistic screening.

METHODS:

We analysed adults aged 18-80 years with LSM data without heart failure from NHANES 2017-2023. LSM cut-offs of ≥8, ≥10, and ≥12 kPa were applied, with ≥8 kPa as the primary threshold. Self-rated health, healthcare utilisation and medication use were assessed using standardised questionnaires. In UK Biobank, 10-year risks of MALO (cirrhosis, hepatic decompensation, hepatocellular carcinoma, liver transplantation or liver-related death), were described across self-rated health categories.

RESULTS:

In NHANES (n=12,942; weighted mean age, 47 years; 49% male), the weighted prevalence of LSM ≥8 kPa was 9.8%. The prevalence of LSM ≥8 kPa showed a strong gradient across self-assessed health strata, ranging from 5.3% among individuals reporting excellent health to 6.6% (very good), 12% (good), 16% (fair), and 22% (poor health). Medication use, particularly use of anti-diabetic medication, anti-hypertensives, or lipid-lowering drugs, identified individuals with high risk of LSM ≥8 kPa (13.1%–26.7%), whereas when none of these drugs were used the prevalence was 6.9%. Insurance type, health care access and seeing a mental health professional did not result in meaningful liver health risk stratification. Results were consistent at higher LSM thresholds and were confirmed in 498,188 UK Biobank participants, where 10-year MALO risk increased from 0.2% for excellent self-rated health to 1.7% for poor self-rated health.

CONCLUSIONS:

Poor self-rated health, similar to medication use for T2DM, hypertension or dyslipidaemia, did result in a meaningfully increased risk of increased LSM and 10-year MALO risk. Most other healthcare utilisation measures showed limited differentiation in LSM prevalence. These findings suggest that self-rated health may provide a simple way to prioritise individuals for opportunistic liver fibrosis screening.

ABSTRACT N°21

TITLE: RATIONALE AND DESIGN OF AN EVENT-DRIVEN, MULTINATIONAL, RANDOMISED, PLACEBO-CONTROLLED, PHASE 3 TRIAL OF SURVODUTIDE (LIVERAGETM)

AUTHORS:

Dr Jörn M. SCHATTENBERG, Department of Internal Medicine II, University Medical Center Homburg, Homburg and Saarland University, Saarbrücken, Germany
Dr Mazen NOUREDDIN, Houston Research Institute, Houston Methodist Hospital, Houston, United States
Dr Naim ALKHOURI, Hepatology Division, Arizona Liver Health, Phoenix, United States
Dr Luiza BOROWSKA, Boehringer Ingelheim, Ingelheim, Germany
Dr Daniel F. MAZO, Boehringer Ingelheim, Ingelheim, Germany
Dr Martina BRUECKMANN, Boehringer Ingelheim, Ingelheim, Germany and First Department of Medicine, Faculty of Medicine Mannheim, University of Heidelberg, Mannheim, Germany
Dr Mandy FRAESSDORF, Boehringer Ingelheim, Ingelheim, Germany
Dr Samina Ajaz HUSSAIN, Boehringer Ingelheim, Ingelheim, Germany
Dr Ramy YOUNES, Boehringer Ingelheim, Ingelheim, Germany
Dr Arun J. SANYAL, Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, Virginia Commonwealth University, Richmond, Virginia, United States

KEYWORDS:

FIBROSIS, MASH, GLP-1RA, GCGR

OBJECTIVES:

We describe the design of an ongoing phase 3 trial of survodutide, a glucagon receptor and glucagon-like peptide-1 receptor dual agonist, for non-cirrhotic metabolic dysfunction-associated steatohepatitis (MASH) (LIVERAGETM).

METHODS:

In this 2-part trial in ~1800 participants in ~40 countries (NCT06632444), eligibility criteria included age ≥18 years, biopsy-proven diagnosis of MASH and F2-F3 fibrosis (MASH Clinical Research Network [CRN] stage), screened through the following parameters: aspartate aminotransferase (AST) >20 U/L, liver stiffness (FibroScan vibration-controlled transient elastography; VCTE) ≥7.5 kPa, FibroScan-AST score >0.36, and liver fat fraction (magnetic resonance imaging-proton density fat fraction) ≥8% . Exclusion criteria include AST and/or alanine aminotransferase ≥5x upper limit of normal [ULN], platelets <140,000/mm3, albumin <3.5 g/dL, international normalised ratio of prothrombin time >1.3, bilirubin ≥1.5x ULN, acute or other chronic liver disease, cirrhosis, portal hypertension, decompensated liver disease, hepatocellular carcinoma, Model for End-stage Liver Disease (MELD) score ≥12, or liver transplant. Participants are randomised 2:1 to double-blind, once-weekly, subcutaneous injections of survodutide uptitrated to 6.0 mg or placebo. In part 1, two primary endpoints will be assessed in the first 700 participants at week 52: 1) resolution of MASH without worsening of liver fibrosis by MASH CRN stage and 2) ≥1-point improvement in fibrosis stage with no worsening of MASH. Key secondary endpoints are percent change from baseline in body weight, absolute change from baseline in glycated haemoglobin (in participants with type 2 diabetes), Enhanced Liver Fibrosis score and liver stiffness (VCTE), and achievement of no progression of fibrosis. In part 2, the primary endpoint evaluated in all participants is a composite outcome of time to first event of progression to cirrhosis, all-cause mortality, liver transplant, hepatic decompensation event(s), worsening of MELD score to ≥15, or progression to clinically significant portal hypertension (Figure). Safety evaluation is based on treatment-emergent adverse events and laboratory tests.

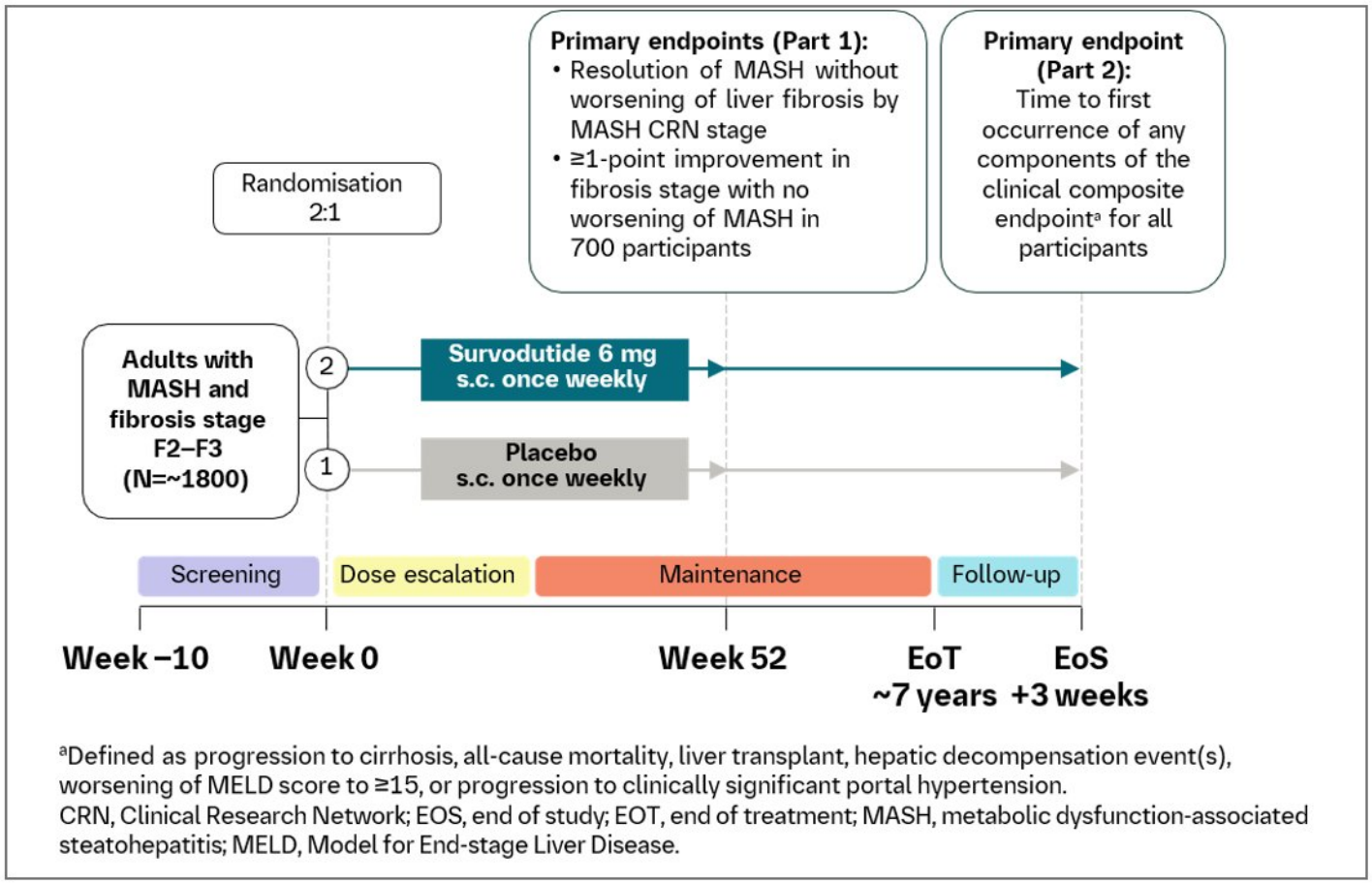
RESULTS:

Recruitment of participants began in October 2024. Follow-up is estimated to end in 2031.

CONCLUSIONS:

The phase 3 LIVERAGETM trial will elucidate the long-term effects of survodutide on steatohepatitis, fibrosis, liver outcomes, and all-cause mortality in people with fibrotic MASH without cirrhosis, as well as its tolerability and safety.

APPENDICES:



[a]Defined as progression to cirrhosis, all-cause mortality, liver transplant, hepatic decompensation event(s), worsening of MELD score to ≥15, or progression to clinically significant portal hypertension.
CRN, Clinical Research Network; EOS, end of study; EOT, end of treatment; MASH, metabolic dysfunction-associated steatohepatitis; MELD, Model for End-stage Liver Disease.

ABSTRACT N°22

TITLE: NOVEL MEASUREMENTS OF SPATIAL DIFFERENCES IN LIVER FAT DISTRIBUTION BETWEEN MASLD AND CIRRHOSIS

AUTHORS:

Miss Yi-Chun WANG, 1 Perspectum Ltd, Oxford, United Kingdom
Dr Yu Jun WONG, 2 Department of Gastroenterology & Hepatology, Changi General Hospital, Singapore. 3 Medical Academic Clinical Programme, Duke-NUS Medical School, Singapore
Dr Edward JACKSON, 1 Perspectum Ltd, Oxford, United Kingdom
Dr Andrea DENNIS, 1 Perspectum Ltd, Oxford, United Kingdom
Miss Sophie RIDDELL, 1 Perspectum Ltd, Oxford, United Kingdom
Dr Jeremy Wei Song CHOO, 4 SingHealth Polyclinics, Singapore
Dr Sulaiha Binte ITHNIN, 4 SingHealth Polyclinics, Singapore
Dr Guan Huei LEE, 5 Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore. 6 National University Centre for Digestive Health, National University Hospital, Singapore
Dr Kalki R CHANDRASEKARAN, 7 Department of Gastroenterology and Hepatology, Sengkang General Hospital, Singapore
Dr Kok Kiong ONG, 4 SingHealth Polyclinics, Singapore
Dr Patricia Ching Yen CHIA, 4 SingHealth Polyclinics, Singapore
Dr Kee Tung TAN, 4 SingHealth Polyclinics, Singapore
Dr Ngiap Chuan TAN, 4 SingHealth Polyclinics, Singapore
Dr Han Chong TOH, 8 Division of Medical Oncology, National Cancer Centre Singapore, Singapore
Dr Oi Fong CHONG, 4 SingHealth Polyclinics, Singapore
Dr Jason Pik Eu CHANG, 9 Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore
Dr Wei Lyn YANG, 10 Gastroenterology and Hepatology, Tan Tock Seng Hospital, Singapore
Dr Xin Yi YEAP, 4 SingHealth Polyclinics, Singapore
Prof Pierce K.H. CHOW, 11 Department of Hepato-pancreato-biliary and Transplant Surgery, Division of Surgery and Surgical Oncology, Singapore General Hospital and National Cancer Centre Singapore, Singapore. 12 Surgery Academic Clinical Programme, Duke-NUS Medical School, Singapore

KEYWORDS:

MASLD,CIRRHOSIS,COUINAUD SEGMENTS,QMRI, REGIONAL PDFF DISTRIBUTIONS

OBJECTIVES:

Progression from MASLD to cirrhosis is accompanied by characteristic hepatic remodelling and lower whole-liver fat content. However, regional changes in hepatic fat distribution remain poorly characterised. To investigate the clinical potential of spatial fat measurements, the aim of this cross-sectional study is to use quantitative MRI to determine whether there are segmental differences in fat distribution between participants with MASLD and those with cirrhosis.

METHODS:

Participants with MASLD, with or without clinically-defined cirrhosis, from the ELEGANCE study (NCT04965259) who had undergone quantitative MRI were included for analysis. Three-dimensional liver segmentation was performed using Hepatica software to derive Couinaud segment volumes and segmental PDFF. The right lobe was defined as segments 5-8 and the left included segments 1-3. Liver fat (PDFF) was reported for left, right liver lobes and the left-to-right lobe ratio (L-to-R). Regional volume, PDFF, and PDFF ratios were compared between participants with and without cirrhosis, with adjustment for regional volume.

RESULTS:

278 participants were included: 166 without cirrhosis and 112 with MASLD-related cirrhosis. (90% Chinese, mean age 62 (±8) years, 44% female, mean BMI 26.5 (±4.3), 40% cirrhosis). Compared to non-cirrhotic MASLD, cirrhosis resulted in significantly lower liver fat across the whole liver (9% vs 12% P<.001) and larger left lobe volume (391mL vs 298mL, P<.001). Participants with cirrhosis had lower fat in both right (8% vs 12%) and left lobes (9% and 13%) compared to those without cirrhosis but an increase in the ratio of liver fat in the left lobe (1.12 vs 0.96). This remained significant following adjustment for liver volume, age and BMI.

CONCLUSIONS:

Liver fat content shows a distinct spatial pattern with cirrhotic MASLD having less liver fat overall and a greater concentration of the remaining fat in the left lobe compared with the right. Further work should focus on whether these changes are replicated in longitudinal data. This would have applications both for characterising progression from MASLD to cirrhosis and for monitoring the effect of metabolic therapies on patients with cirrhosis.

APPENDICES:

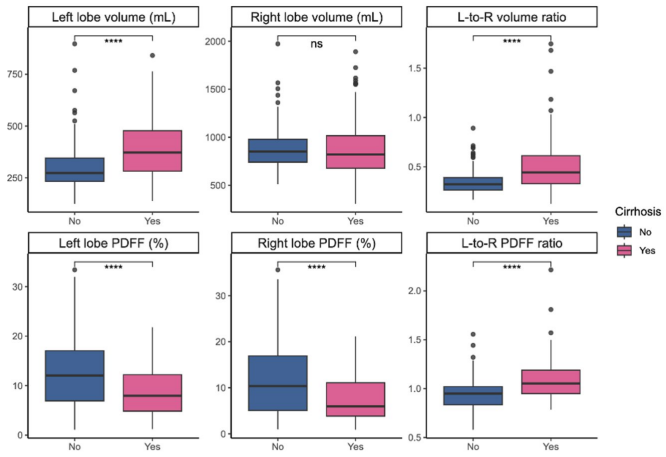


Figure.1 Differences in lobular volume and PDFF between MASLD patients with or without cirrhosis. Left lobe included s1-s3. Right lobe included s5-8, L-to-R ratio was calculated as (s1-s3)/(s5-s8). Lobular PDFF were adjusted with segmental volume.

Table.1 Patient demographics

Characteristic	**MASLD** N = 166[1]	**Cirrhosis (MASLD origin)** N = 112[1]	**p-value**[2]	**P-value**[3]
Age (years)	59 (6)	65 (9)	**<0.001**	**<0.001**
Sex			0.4	0.4
Female	69 (42%)	53 (47%)		
Male	96 (58%)	59 (53%)		
BMI (kg/m^2)	25.9 (3.7)	27.5 (4.8)	**0.003**	**0.003**
Ethnicity			**0.025**	**0.025**
Chinese	154 (93%)	95(85%)		
Indian	2 (1.2%)	8 (7.1%)		
Malay	8 (4.8%)	6 (5.4%)		
Others	1 (0.6%)	3 (2.7%)		
PDFF (%)	11 (8)	8 (5)	**<0.001**	**<0.001**
Liver volume (mL)	1,362 (304)	1,430 (397)	0.12	0.3
Left lobe volume	298 (109)	391 (145)	**<0.001**	**<0.001**
Left lobe PDFF	13 (8)	9 (5)	**<0.001**	**<0.001**
Right lobe volume	881 (207)	872 (311)	0.8	0.4
Right lobe PDFF	12 (8)	8 (5)	**<0.001**	**<0.001**
L-to-R volume ratio	0.34 (0.12)	0.51 (0.28)	**<0.001**	**<0.001**
L-to-R PDFF ratio	0.96 (0.19)	1.12 (0.24)	**<0.001**	**<0.001**
Spleen volume (mL)	121 (57)	241 (201)	**<0.001**	**<0.001**

[1]Mean (SD); n (%)
[2]Welch Two Sample t-test; Pearson's Chi-squared test
[3]ANCOVA test p-values adjusted for Age and BMI for PDFF, Liver volume, Left lobe and Right lobe volume and PDFF, L-to-R volume ratio and L-to-R PDFF ratio
Left lobe included s1-3; Right lobe included s5-8

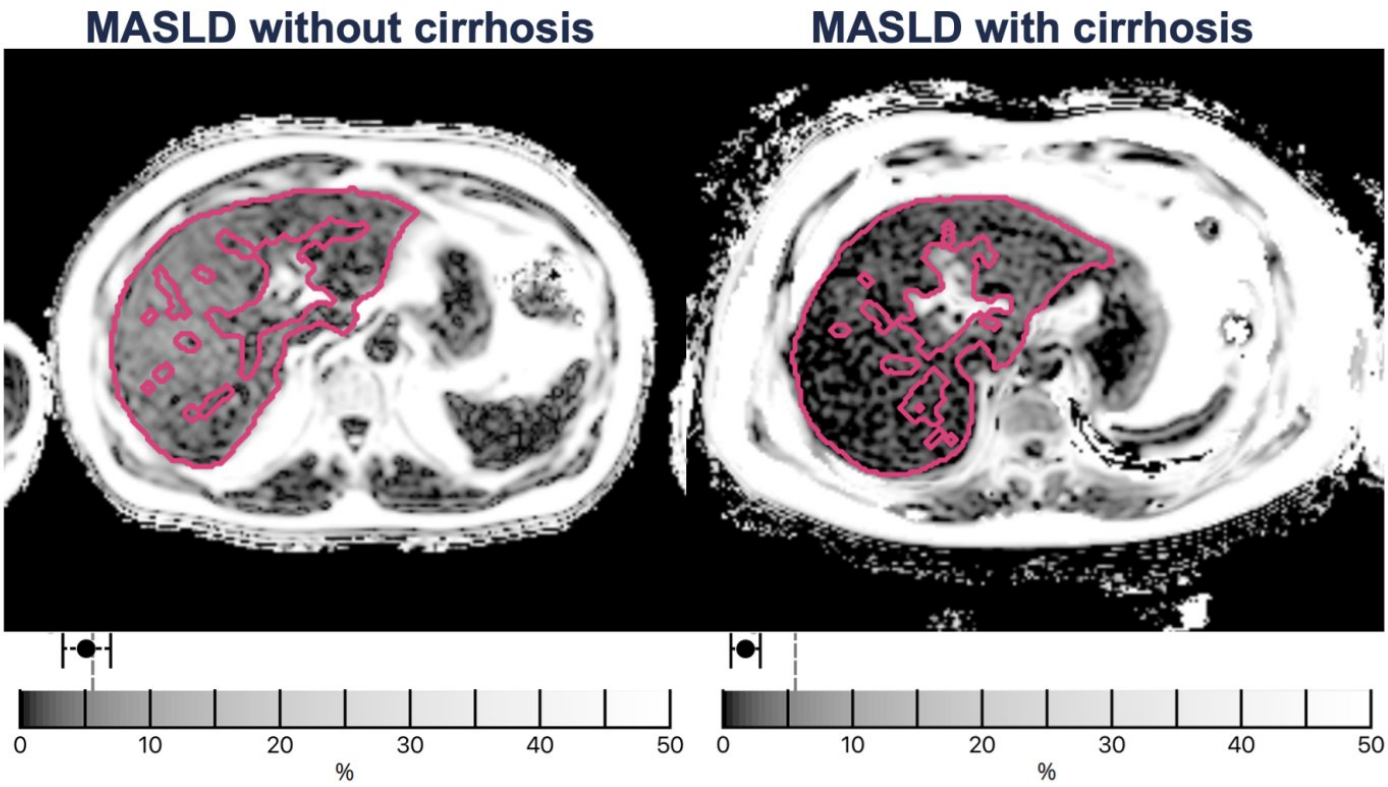


Figure.2 MRI PDFF maps of two example cases. (Left) MASLD without cirrhosis and (Right) MASLD with cirrhosis

ABSTRACT N°23

TITLE: IDENTIFICATION OF IMMUNOLOGICAL AND EXTRACELLULAR VESICLE BIOMARKERS IN A MULTICELLULAR MASLD LIVER MODEL

AUTHORS:

MSc. PhD. Zuzana VINCE KÁŽMÉROVÁ, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
MSc. PhD. Jakub JANKO, Institute of Molecular Biomedicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia
MSc. PhD. Peter BARÁTH, Institute of Chemistry, Slovak Academy of Sciences, Bratislava, Slovakia
MSc. Veronika LUKÁČOVÁ, Institute of Chemistry, Slovak Academy of Sciences, Bratislava, Slovakia; MediXbank, n.o., Nitra, Slovakia
MSc. PhD. Lucia BALÁŽOVÁ, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia
MSc. PhD. Radka OBOŘILOVÁ, CEITEC Masaryk University, Brno, Czech Republic
MSc. PhD. Jan PŘIBYL, CEITEC Masaryk University, Brno, Czech Republic
assoc. prof., MD, Dr. Rer. Nat., PhD. Roman GARDLÍK, Institute of Molecular Biomedicine, Faculty of Medicine, Comenius University, Bratislava, Slovakia

KEYWORDS:

MASLD; EXTRACELLULAR VESICLES; IMMUNOLOGY; BIOMARKERS

OBJECTIVES:

Metabolic dysfunction-associated steatotic liver disease (MASLD) is characterized by hepatocyte steatosis, fibrosis, and chronic inflammation driven by complex interactions between liver and immune cells. This study aimed to establish a multicellular liver–immune co-culture model that recapitulates key features of MASLD and enables the identification of immunological and extracellular vesicle (EV)-associated biomarkers.

METHODS:

A multicellular co-culture model was established using HepG2 hepatocytes, human hepatic stellate cells (HSCs), and THP-1-derived macrophage-like cells cultured in the lower compartment of a 6-well plate. Peripheral blood mononuclear cells (PBMCs) isolated from healthy donors were cultured in transwell inserts above the liver co-culture to allow paracrine communication without direct cell contact. Lipotoxic stress was induced using palmitic acid, high glucose, and insulin, while fibrosis was induced by 24-hour stimulation with transforming growth factor-β (TGF-β). Lipid accumulation was assessed by HCS LipidTOX™ Neutral Lipid Stain and Oil Red O staining. Fibrogenic activation was evaluated by immunofluorescence and Western blot analysis of α-SMA, pSMAD3 and collagen type I (COL1A). Immune phenotypic changes in THP-1 cells and PBMCs were analysed by multiparametric flow cytometry. EVs were isolated from conditioned medium of the HepG2–HSC–THP-1 co-culture using size exclusion chromatography (SEC), and their protein cargo was analysed by liquid chromatography–tandem mass spectrometry (LC–MS/MS).

RESULTS:

The multicellular co-culture model successfully reproduced major pathological features of MASLD. Lipotoxic stimulation induced intracellular lipid accumulation in hepatocytes, whereas TGF-β treatment promoted HSC activation, demonstrated by increased α-SMA, phospho-SMAD3, and COL1A expression. Flow cytometric analysis identified phenotypic changes in THP-1 cells and PBMCs following lipotoxic and fibrogenic stimulation, indicating activation of liver

–immune communication. Proteomic analysis of SEC-isolated EVs is ongoing to identify disease-associated protein signatures and candidate EV biomarkers.

CONCLUSIONS:

This multicellular liver–immune co-culture model represents a physiologically relevant platform for studying MASLD pathogenesis. Combining immune phenotyping with EV isolation and LC–MS/MS proteomics provides a comprehensive approach for identifying novel immunological and extracellular vesicle biomarkers with potential diagnostic and therapeutic relevance. Funding/Acknowledgments: This work was funded by the EU NextGenerationEU through the Recovery and Resilience Plan for Slovakia under the project No. 09I03-03-V04-00463, A4L_Bridge grant agreement No. 101136453, and Support of the projects Seal of Excellence No. 101278822.

ABSTRACT N°24

TITLE: ALCOHOL EXPOSURE INCREASES LIVER IRON, WHILE CT1 PREDICTS OUTCOMES ACROSS MASLD, METALD, AND ALD

AUTHORS:

Mr Charlie DIAMOND, Perspectum Ltd, Oxford, UK
Dr Edward JACKSON, Perspectum Ltd, Oxford, UK
Dr Anneli ANDERSSON, Perspectum Ltd, Oxford, UK
Prof Rohit LOOMBA, Division of Gastroenterology and Epidemiology, University of California at San Diego, La Jolla, California, USA
Dr Carlos DUNCKER, Perspectum Ltd, Oxford, UK
Dr Andrea DENNIS, Perspectum Ltd, Oxford, UK

KEYWORDS:

MASLD, METALD, MRI, CT1, IRON

OBJECTIVES:

MetALD describes individuals whose liver pathology is in a continuum between metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD), depending on alcohol consumption. Diagnosis of MetALD poses challenges due to the limited reliability of self-reported alcohol consumption. Quantitative multiparametric MRI is increasingly used to diagnose and monitor chronic liver disease, with biomarkers of liver fat, iron and disease activity. Using population-based data from the UK Biobank, this study aimed to determine whether liver MRI biomarkers differentiate MASLD, MetALD, and ALD and predict clinical outcomes.

METHODS:

Multiparametric MRI (LiverMultiScan) was used to measure iron-corrected T1 (cT1, ms), liver fat content (LFC, %) and liver iron concentration (LIC, mg Fe/g) in 55,638 UK biobank participants. Self-reported alcohol consumption stratified MetALD and ALD from MASLD in individuals with LFC ≥5% and at least one cardiometabolic risk factor. Associations between SLD subclassification, MRI biomarkers and clinical outcomes (from linked healthcare records) were investigated using Cox proportional hazard models.

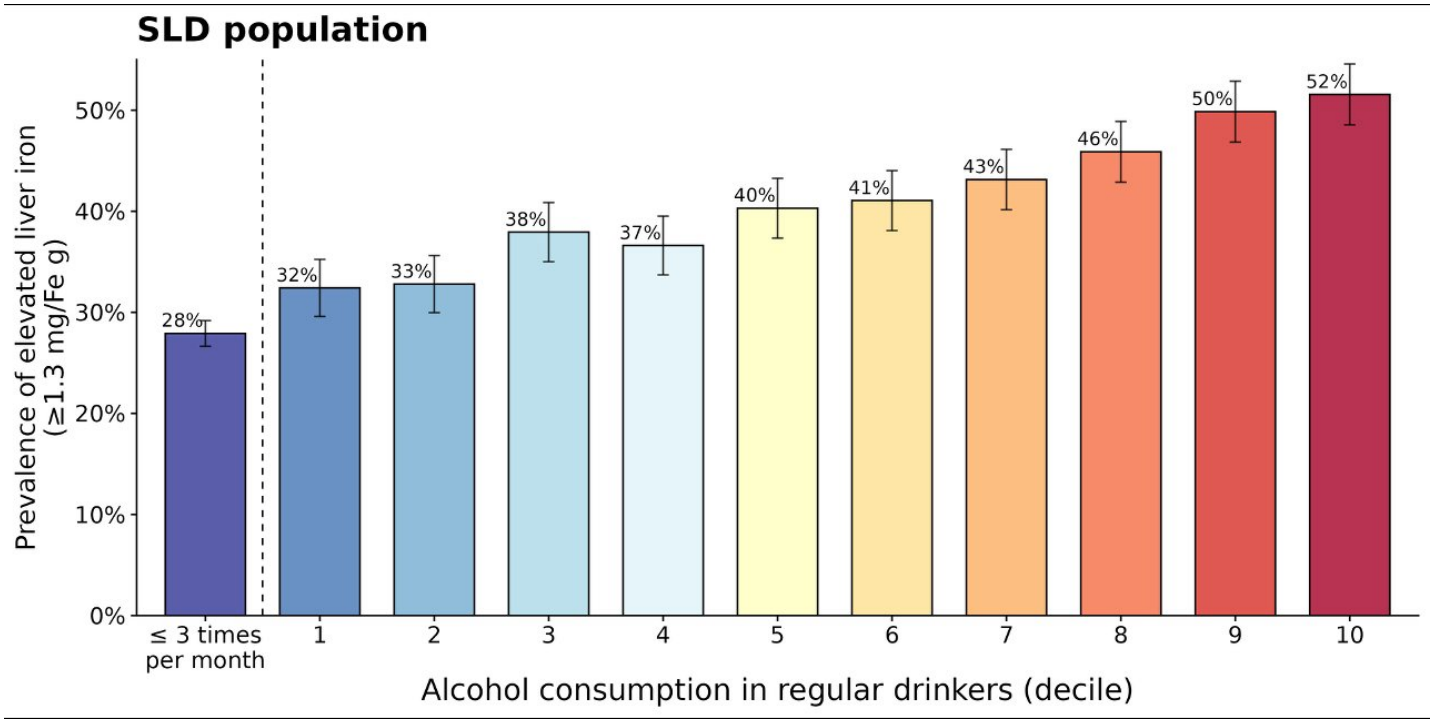
RESULTS:

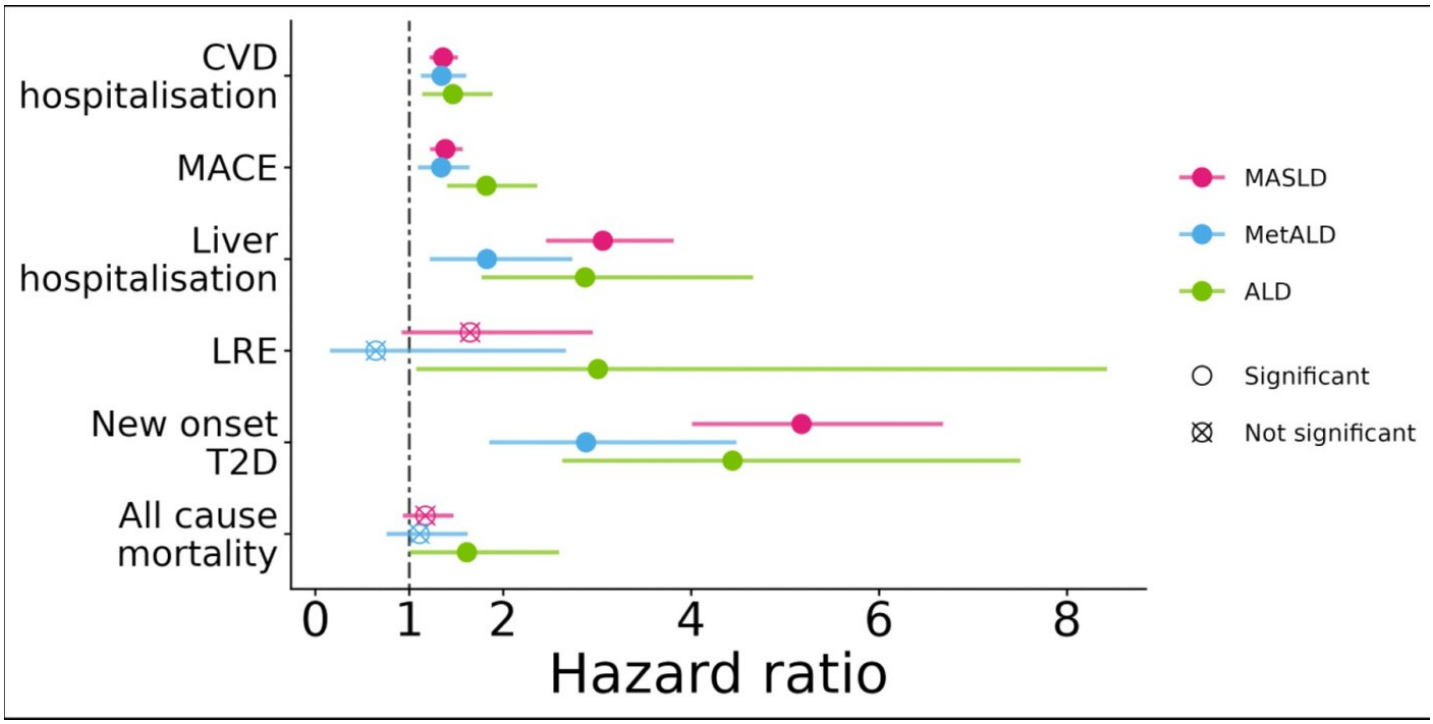
SLD was common and occurred in 29% of the general population. MASLD was diagnosed in 10,664 participants (aged 66 years, 55% male, 96% White), MetALD in 3,387 (aged 65 years, 64% male, 98% White) and ALD in 1,401 (aged 65 years, 75% male, 99% White). Prevalence of elevated LIC (≥1.3 mg Fe/g) progressively increased with alcohol consumption in SLD (Fig 1). LIC and cT1 discriminated SLD subclassifications, with MetALD and ALD exhibiting the highest prevalence of elevated LIC, whilst MASLD had most elevated cT1 (≥800ms), both p-value <0.05. All SLD subgroups exhibited an increased risk of CVD hospitalisation, MACE, liver related hospitalisation and new onset type 2 diabetes (Fig 2). Higher cT1 was associated with increased risk of LREs in non-SLD (HR 2.4 [1.8-3.2]), MASLD (HR 2.1 [1.4-3.1]) and MetALD/ALD (HR 2.3 [1.1-4.2]) populations. Increased LIC however was not associated with any outcome.

CONCLUSIONS:

SLD is prevalent in the UK general population, with MASLD the most common subclassification. Individuals with MetALD and ALD have significantly higher levels of LIC compared to MASLD. cT1 is associated with clinical outcomes regardless of SLD subclassification or status.

APPENDICES:


SLD population
Prevalence of elevated liver iron (≥1.3 mg/Fe g)
0%
10%
20%
30%
40%
50%
28%
32%
33%
38%
37%
40%
41%
43%
46%
50%
52%
≤ 3 times per month
1
2
3
4
5
6
7
8
9
10
Alcohol consumption in regular drinkers (decile)


CVD hospitalisation
MACE
Liver hospitalisation
LRE
New onset T2D
All cause mortality
0
1
2
4
6
8
Hazard ratio
MASLD
MetALD
ALD
Significant
Not significant

ABSTRACT N°25

TITLE: THE POTENTIAL OF COMBINING FIRST-LINE NON-INVASIVE TESTS FOR EARLY DETECTION OF ADVANCED LIVER DISEASE

AUTHORS:

Dr Michail KOKKARAKIS, Erasmus MC, Rotterdam, The Netherlands
Dr Jesse PUSTJENS, Erasmus MC, Rotterdam, The Netherlands
Dr Maurice MICHEL, Saarland University Medical Center, Homburg, Germany
Prof Jorn M. SCHATTENBERG, Saarland University Medical Center, Homburg, Germany
Prof Harry L.A. JANSSEN, Erasmus MC, Rotterdam, The Netherlands
Dr James PAIK, The Global NASH/MASH and Liver Councils, Washington, DC, USA
Prof Zobair YOUNOSSI, The Global NASH/MASH and Liver Councils, Washington, DC, USA
Dr Willem Pieter BROUWER, Erasmus MC, Rotterdam, The Netherlands
Dr Laurens A. VAN KLEEF, Erasmus MC, Rotterdam, The Netherlands

KEYWORDS:

MASLD; LIVER FIBROSIS; SCREENING; FIB-4.

OBJECTIVES:

Combinations of non-invasive tests (NITs) may improve diagnostic accuracy and clinical utility. We evaluated combining first-line NITs for advanced liver disease screening in a population-based setting with metabolic dysfunction.

METHODS:

We studied adults with at least one metabolic risk factor and valid liver stiffness measurement (LSM) in the National Health and Nutrition Examination Survey (2017 to March 2020 and August 2021 to 2023). The primary outcome was LSM ≥10 kPa. Eleven first-line NITs were assessed in pairs for diagnostic accuracy and test characteristics at their published cut-offs compared to single test strategies and cut-off optimisation. Sensitivity analysis included different LSM thresholds, Agile 3+ scores and subgroup analysis (sex, BMI categories, and diabetes).

RESULTS:

Among 9,317 adults with metabolic dysfunction (5.9% LSM ≥10 kPa), MAF-5 and sMAF-5 were best in detecting an LSM ≥10 kPa (AUROC 0.82 and 0.81) while FIB-4 and APRI showed a poor performance (0.62 and 0.63). Combining NITs did not improve discrimination with the incremental AUROC change compared to the better single test ranging between -0.05 to 0.04. Requiring both combined NITs to be positive increased specificity but caused a loss in sensitivity that exceeded this gain, whereas requiring either to be positive did the reverse. No combination outperformed MAF-5 alone as a screening test, and adjusting the MAF-5 cut-off matched or exceeded every combination. The marginally higher diagnostic odds ratio of some APRI-based pairs reflected a near-complete loss of sensitivity. The findings were consistent across stiffness thresholds, the Agile3+ target, and subgroups.

CONCLUSIONS:

In the current cross-sectional study, combining first-line NITs did not improve the detection of a liver stiffness measurement above 10 kPa, beyond a single optimized test. Therefore, the objective of screening should govern the choice of test and cut-off rather than the addition of a second test. Findings should be further validated in a longitudinal setting with repeated LSM.

APPENDICES:

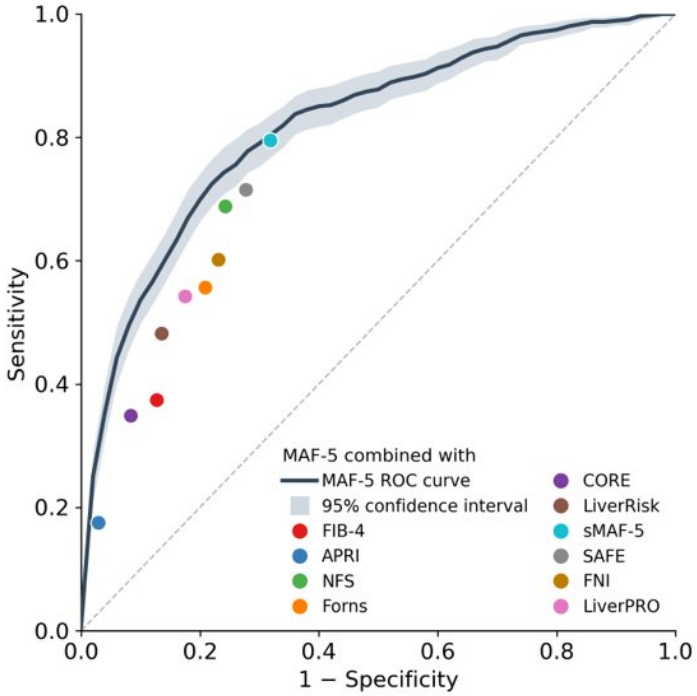


Figure 1. Receiver operating characteristic (ROC) curve of MAF-5 for a liver stiffness of at least 10 kPa. The dark line is the MAF-5 ROC curve and the shaded band its 95% confidence interval; each colored point is the operating point of a both-positive combination of MAF-5 with one of the other ten tests, each applied at its published rule-out (low) cut-off and identified in the legend. Every point lies on or below the band, showing that the same specificity can be reached with equal or greater sensitivity by moving the MAF-5 cut-off rather than adding a second test. Abbreviation: MAF-5, metabolic dysfunction-associated fibrosis-5.

ABSTRACT N°26

TITLE: A MULTIMODAL NONINVASIVE APPROACH TO INITIATION AND MONITORING OF RESMETIROM THERAPY IN MASH - UPDATE.

AUTHORS:

Dr Jeevin SANDHU, Methodist Dallas Medical Center, Division of Hepatology, Internal Medicine, Dallas, United States
Dr Shaheen SHAHEEN MEHRARA, Methodist Dallas Medical Center, Liver Institute, Dallas, United States
Dr Mona MUNTEANU, Fibronostics U.S., Inc, New Orleans, United States,
Mr Akash PAGADALA, University of Southern California, Los Angeles, US;
Dr Ashwini MEHTA, Methodist Dallas Medical Center, Division of Hepatology, Internal Medicine, Dallas, United States
Mr John LEE, Fibronostics U.S., Inc, New Orleans, United States,
Dr Obinna OKOLO, Methodist Dallas Medical Center, Liver Institute, Dallas, United States
Dr Parker WOODS, Methodist Dallas Medical Center, Liver Institute, Dallas, dallas, United States
Dr Parvez MANTRY, Methodist Dallas Medical Center, Liver Institute, Dallas, United States,

KEYWORDS:

RESMETIROM, MASH, LIVERFAST, FIBROSIS, STEATOSIS

OBJECTIVES:

LIVERFAST (Fibronostics US, Inc.) is a new blood-based NIT that assesses quantitatively fibrosis, activity, and steatosis. Aims: To assess the dynamics of LIVERFAST, FIB-4 and VCTE and CAP in monitoring patients on Resmetirom therapy (on-RT) [fibrosis/steatosis ≥10% regression rate (10%RR) from baseline to repeated NIT].

METHODS:

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

RESULTS:

N=147 Eligible patients without RT discontinuation, 62% 80mg-dose, 39%-male, 48.7%-T2D, 37.5% GLP-1RA, mean(se) age 61.8(1.2), BMI 33.1(1.0), ALT 45(3), FIB4 1.80(0.12). T0-prevalence of F2F3 were 61%(LFAST) and 44%(VCTE). Median(max) delays(mths) t0-to-t1 were 6.0 (LFAST), 7.6(VCTE) and 7.3(FIB4). Patients with repeated FIB4 had no change at t1, (1.83vs2.01), or AST (38vs38), platelets count (229vs219*109), and ALT (45vs44), all p=ns. Repeated median t0vs t1 for VCTE were 10.1 vs 8.3kPa(p<0.05) and for CAP 229 vs 219dB/m, p=ns, respectively. Repeated median LFAST scores (t0vs.t1) were for fibrosis 0.46vs0.35,p<0.001), steatosis (0.47vs0.42,p<0.05), activity (0.40vs0.40,p=ns), with similar features in either groups of RT-alone or in combination to GLP-1RA for fibrosis (p<0.05). LFASTfibrosis 10%RR from t0 has been achieved in both 80 and 100 mg-RT groups with asimilar rate at 6mths and 9 mths, respectively: 33.4%vs41.1% and 67.3 %vs45.6%, overall logrank p=ns). LFAST-steatosis 10%RR from t0 has been achieved more within 80mg-RT group (overall logrank p<0.05). The significant decrease t0-to-t1 in the total cholesterol has neither impacted the ApolipoproteinA1 [135vs141mg/dl] nor LFAST-fibrosis score.

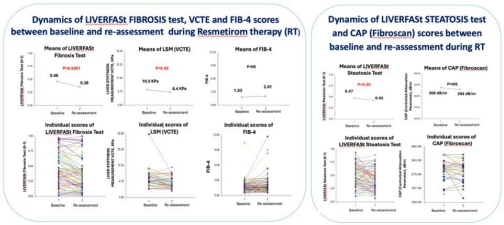
CONCLUSIONS:

Initiation of resmetirom therapy based on the assessment of MASH using LIVERFASt or VCTE is efficient and allows further non-invasive monitoring in fibrosis dynamics. Results suggest that LIVERFASt reflects histology remodeling by providing earlier insights into both fibrosis and steatosis regression during resmetirom therapy. Significant improvement, higher than 10% in LIVERFASt scores being observed since 3rd month of resmetirom therapy without difference between the 80mg and 100 mg groups. FIB-4 showed lower change at reassessment, suggesting limited ability to detect

early fibrosis improvement.

APPENDICES:

Figure 1. Dynamics of fibrosis and Steatosis according to Liverfast Fibrosis/Steatosis , VCTE/CAP and FIB-4 repeated measurements.



ABSTRACT N°27

TITLE: FAT10 PROMOTES FORMATION OF MALLORY-DENK BODIES THROUGH AUTOPHAGY INHIBITION DURING MASH PROGRESSION TO FIBROSIS.

AUTHORS:

PhD student Arthur CENS, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
Dr Cyril BOUROUH, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
Dr Lucie BERNARD, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
IE Claire DEVOS, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
Dr Nathalie HENNUYER, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
Dr Lama HABBOUCHE, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
IE Fabienne GLACIAL, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
Dr Chloé BLONDEL, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
Dr Cindy NGUYEN, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
Dr Sadia RAAB, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
Dr Ludivine CLAVREUL, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
IE Emmanuelle VALLEZ, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
IE Céline GHEERART, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France
IE Anne-Sophie LACOSTE, Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, US 41 - UAR 2014 – PLBS - Plateformes Lilloises de Biologie & Santé, F-59000 Lille, France
Dr Jean-Michel SALIOU, Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, US 41 - UAR 2014 – PLBS - Plateformes Lilloises de Biologie & Santé, F-59000 Lille, France
Pr Dimitri XIRODIMAS, CRBM, Université de Montpellier, CNRS, Montpellier Cedex 05, 34293, France.
Pr François PATTOU, Service des Maladies de l'Appareil Digestif et de la Nutrition, Centre Hospitalier Universitaire de Lille, Lille, France; European Genomic Institute for Diabetes, UMR 1190, Translational Research
Pr Sven FRANCQUE, Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium.
Dr Viviane GNEMMI, Service des Maladies de l'Appareil Digestif et de la Nutrition, Centre Hospitalier Universitaire de Lille, Lille, France; European Genomic Institute for Diabetes, UMR 1190, Translational Research
Pr Guillaume LASSAILLY, Service des Maladies de l'Appareil Digestif et de la Nutrition, Centre Hospitalier Universitaire de Lille, Lille, France; European Genomic Institute for Diabetes, UMR 1190, Translational Research
Pr Bart STAELS, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France

Pr Réjane PAUMELLE, University of Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1011, EGID, Boulevard du Professeur Jules Leclercq 59045 Lille France

KEYWORDS:

MDBS, MASH, FAT10, FIBROSIS, AUTOPHAGY

OBJECTIVES:

The Metabolic dysfunction-Associated Steatohepatitis (MASH) is the first step of hepatocyte suffering development in a liver metabolism disorder, leading to fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Suffering hepatocytes are characterized by ballooning and Mallory-Denk Bodies (MDBs), protein aggregates composed mainly with p62 and Keratin 8/18 (KRT8/18). Patients with MDBs are known to have a higher risk of liver relative death and are likely associated to fibrosis. MDBs are induced after an alteration of proteostasis in ballooned hepatocytes. Previously, the ubiquitin like modifier FAT10 has been shown to correlate with MASH development, and to be involved in MDBs in an acute liver injury context other than MASH. Nowadays, the specific role of FAT10 in MDBs formation in hepatocytes during MASH development still needs to be shown.

METHODS:

To study the role of FAT10 in MDBs formation during MASH development, FAT10 and MDBs markers (p62, KRT8/18) were measured by transcriptomic and histologic analyses in MASH patients. To study the impact of FAT10 on MDBs formation in vitro, FAT10 was downregulated with siRNA transfection, MDBs formation was induced with a MASH like cocktail and assessed with immunofluorescence (IF), Western blot (WB) and proteomic analyses. In vivo, to study the impact of Fat10 on MDBs formation in hepatocyte, MDBs markers were assessed by WB and IF analyses in the liver of mice fed with different MASH diets with a specific deficiency or overexpression of Fat10 in hepatocytes.

RESULTS:

Liver transcriptomic analysis of MASH patients with ballooning and MDBs shows an increase of FAT10 expression associated to fibrosis biomarker. Liver histology revealed that patients with MDBs have an increase of FAT10 positives aggregates. Moreover, FAT10 overexpression in hepatocytes is associated to MDBs formation in vivo and in vitro. Interestingly, FAT10 deficiency in hepatocytes of MASH mice decreases MDBs formation and fibrosis while FAT10 overexpression enhances it. Moreover, proteomic analyses of MDBs and FAT10 partners suggest that FAT10 downregulation in hepatocytes prevents MDBs formation through an autophagy inhibition.

CONCLUSIONS:

Altogether, these results demonstrate that an increase of FAT10 expression during MASH development promotes MDBs formation and hepatocyte suffering, a mechanism that can promote fibrosis in MASH.

ABSTRACT N°28

TITLE: CLINICAL, HISTOLOGICAL AND MOLECULAR DETERMINANTS OF GRAFT STEATOHEPATITIS AFTER LIVER TRANSPLANTATION FOR STEATOTIC LIVER DISEASE

AUTHORS:

Dr Domitille ERARD, Hospices Civils de Lyon, Lyon, France & UMR University Claude Bernard Lyon 1 - INSERM U1350 PaThLiv, Lyon, France & Institut Hospitalo-Universitaire (IHU) EVEREST, Lyon Hepatology Institute, France
Dr Massimiliano COCCA, UMR University Claude Bernard Lyon 1 - INSERM U1350 PaThLiv, Lyon, France & Institut Hospitalo-Universitaire (IHU) EVEREST, Lyon Hepatology Institute, France
Dr Marie Laure PLISSONNIER, UMR University Claude Bernard Lyon 1 - INSERM U1350 PaThLiv, Lyon, France & Institut Hospitalo-Universitaire (IHU) EVEREST, Lyon Hepatology Institute, France
Dr Yasmina CHOUIK, Hospices Civils de Lyon, Lyon, France & UMR University Claude Bernard Lyon 1 - INSERM U1350 PaThLiv, Lyon, France & Institut Hospitalo-Universitaire (IHU) EVEREST, Lyon Hepatology Institute, France
Dr Teresa ANTONINI, Hospices Civils de Lyon, Lyon, France & UMR University Claude Bernard Lyon 1 - INSERM U1350 PaThLiv, Lyon, France & Institut Hospitalo-Universitaire (IHU) EVEREST, Lyon Hepatology Institute, France
Pr Jean-Yves MABRUT, Hospices Civils de Lyon, Lyon, France & UMR University Claude Bernard Lyon 1 - INSERM U1350 PaThLiv, Lyon, France & Institut Hospitalo-Universitaire (IHU) EVEREST, Lyon Hepatology Institute, France
Dr Mirjam ZEISEL, UMR University Claude Bernard Lyon 1 - INSERM U1350 PaThLiv, Lyon, France & Institut Hospitalo-Universitaire (IHU) EVEREST, Lyon Hepatology Institute, France
Pr Fabien ZOULIM, Hospices Civils de Lyon, Lyon, France & UMR University Claude Bernard Lyon 1 - INSERM U1350 PaThLiv, Lyon, France & Institut Hospitalo-Universitaire (IHU) EVEREST, Lyon Hepatology Institute, France
Dr Valerie HERVIEU, Pathology Institute, Hospices Civils de Lyon, Bron, France
Pr Olivier BOILLOT, Fédération des spécialités digestives, Hospices Civils de Lyon, Lyon, France
Pr Jerome DUMORTIER, Fédération des spécialités digestives, Hospices Civils de Lyon, Lyon, France
Pr Massimo LEVRERO, Hospices Civils de Lyon, Lyon, France & UMR University Claude Bernard Lyon 1 - INSERM U1350 PaThLiv, Lyon, France & Institut Hospitalo-Universitaire (IHU) EVEREST, Lyon Hepatology Institute, France

KEYWORDS:

LIVER-TRANSPANTATION, MASH-RECCURRENCE, MASH-DE-NOVO, ALD-RECURRENCE, TRANSCRIPTOMICS

OBJECTIVES:

Steatotic liver disease (SLD) is the most common and increasing indication for liver transplantation (LT) worldwide. SLD risk factors (e.g., metabolic syndrome (MS) and excessive alcohol consumption) can persist after LT, relapse, or appear de novo and impact on liver graft. The aim of this study was to analyze the liver transcriptome in patients transplanted for SLD and to correlate it with the clinical SLD post-LT phenotypes.

METHODS:

Patients receiving a first LT for SLD with a recurrent active steatohepatitis (NAS score ≥3) on systematic liver graft biopsies (LB) were included [n=12 Re-MASH (LT for MASLD with post-LT MS and no alcohol consumption); n=9 MASH de novo (LT for ALD with post-LT features of MS, no alcohol relapse); n=15 Re-ALD (LT for ALD with post-LT severe alcohol relapse, no diabetes, no obesity); n=8 ALD-Met (LT for ALD or ALD-Met with post-LT features of MS and severe alcohol relapse)]. Patients with post-LT normal LB, no MS and no alcohol relapse were used as controls (n=4). Bulk RNA-Seq was performed on FFPE sections using the SMART-Seq® Total RNA Single Cell technology using on an Illumina NovaSeq platform (200-cycles).

RESULTS:

Unsupervised clustering based on RNA-Seq data identified 3 clusters (A to C). Cluster B is driven by Re-ALD as SLD

recurrence category and displays features of hepatocytes/hepatic progenitor cell proliferation; cluster C is driven by the presence of MS components (Re-MASH or other post-LT recurrences associated to metabolic dysfunction) with a strong activation of innate and adaptive immune responses; cluster A is heterogeneous, with less severe fibrosis and decreased expression of the 25 genes core signature previously associated with NAFLD disease progression. Re-MASH and MASH de novo display very similar transcriptomic profiles with notable differences as compared to non-LT MASH cases. Re-ALD transcriptomic profiles are very similar to non-LT acute alcoholic hepatitis (AH). ALD-Met share many transcriptomic features with Re-ALD but display additional changes.

CONCLUSIONS:

Metabolic dysfunction drives transcriptomic changes in post-LT MASH (MASH de novo and Re-MASH) that are similar but not completely overlapping to non-LT MASH. Alcohol is the major transcriptomic driver in both Re-ALD and ALD-Met patients.

ABSTRACT N°29

TITLE: AI METRICS ALIGN WITH MANUAL HISTOLOGY AND BLOOD-BASED BIOMARKERS IN MASH

AUTHORS:

Dr Dylan WINDELL, Perspectum Ltd, Oxford, UK
Dr Jack BREEN, Perspectum Ltd, Oxford, UK
Mr Cayden BEYER, Perspectum Ltd, Oxford, UK
Dr Edward JACKSON, Perspectum Ltd, Oxford, UK
Dr Alastair MAGNESS, Perspectum Ltd, Oxford, UK
Mr Phil WAKEFIELD, Perspectum Ltd, Oxford, UK
Ms Reema KAINTH, Perspectum Ltd, Oxford, UK
Dr Caitlin LANGFORD, Perspectum Ltd, Oxford, UK
Dr Ken FLEMING, Green Templeton College, University of Oxford, UK
Dr Eve FRYER, Department of Cellular Pathology, John Radcliffe Hospital, OUH NHS FT, Oxford, UK
Prof Timothy KENDALL, Institute for Regeneration and Repair, University of Edinburgh, Edinburgh, UK
Prof Robert GOLDIN, Section for Pathology, Imperial College, London, UK

KEYWORDS:

MASH, AI, DIGITAL HISTOLOGY, BLOOD-BIOMARKERS

OBJECTIVES:

Clinical trials in metabolic dysfunction-associated steatohepatitis (MASH) require histologic scoring for eligibility and efficacy endpoints. However, interpretation of key histologic features varies, potentially affecting trial outcomes. To complement AI-assisted ordinal scoring, we evaluated whether anatomically informed, continuous PAIR™ MASH measurements provide concordant and biologically relevant assessments across steatosis, inflammation, ballooning and fibrosis, benchmarked against expert manual histology and blood-based biomarkers.

METHODS:

In this cross-sectional study, digitised liver-biopsy whole-slide images (WSIs) from 156 participants (NCT04054310) with suspected MASLD/MASH were analysed. Steatosis, lobular inflammation, hepatocyte ballooning and fibrosis were scored by two expert pathologists. PAIR™ MASH (v2026.07) generated the following key continuous metrics: steatosis density, calculated as the number of steatotic vesicles/mm²; lobular inflammatory-cell and foci densities, calculated as inflammatory cells or foci/mm² of lobular area; total inflammatory density, calculated as inflammatory cells/mm² across the entire tissue; and large-balloon density, measured using an AI ballooning-hepatocyte detector across anatomically defined regions. For fibrosis, WSIs were partitioned into portal, periportal, pericentral and lobular regions; pathological and non-pathological collagen were distinguished, enabling calculation of corrected collagen proportionate area (CCPA). Spearman rank correlations assessed associations with manual histology; Pearson correlations assessed associations with blood-based measures including Fibrosis-4 Index (FIB-4), gamma-glutamyl transferase (GGT), Enhanced Liver Fibrosis (ELF) score, tissue inhibitor of metalloproteinases (TIMP) and eosinophils.

RESULTS:

Among patients with demographic data, mean age was 57±14 years, mean BMI was 36±6 kg/m², and 62% were female; 71% had hypertension, 45% diabetes and 58% dyslipidaemia. PAIR™ MASH measurements correlated with manual histology scores: steatosis density with steatosis (rho=0.68), lobular foci density with lobular inflammation (rho=0.42), large-balloon density with ballooning (rho=0.62), and CCPA with fibrosis (rho=0.78). Among blood-based measures, CCPA correlated with eosinophils (r=0.49), FIB-4 (r=0.51), ELF (r=0.37), GGT (r=0.36) and TIMP (r=0.34); lobular foci

density correlated most strongly with TIMP (r=0.43), while large-balloon density correlated most strongly with GGT (r=0.42).

CONCLUSIONS:

Selected PAIR™ MASH measurements demonstrated moderate-to-strong concordance with manual histology and associations with blood-based biomarkers. The relationships of CCPA with eosinophils, FIB-4, GGT and ELF, and of lobular foci density with TIMP, support further evaluation of PAIR™ MASH alongside blood-based tests for trial stratification and treatment-response assessment.

APPENDICES:

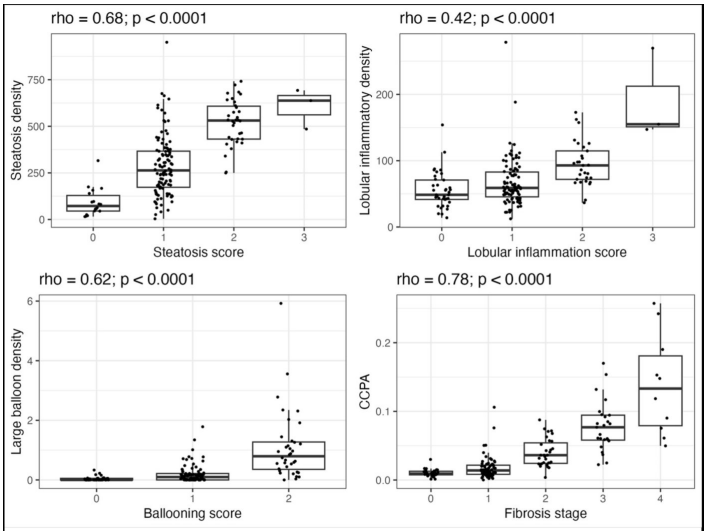


Figure 1. Associations between PAIR™ MASH measurements and manual histology. Points represent individual participants and boxes show the median and interquartile range. Spearman correlations (rho) and corresponding p values are displayed.

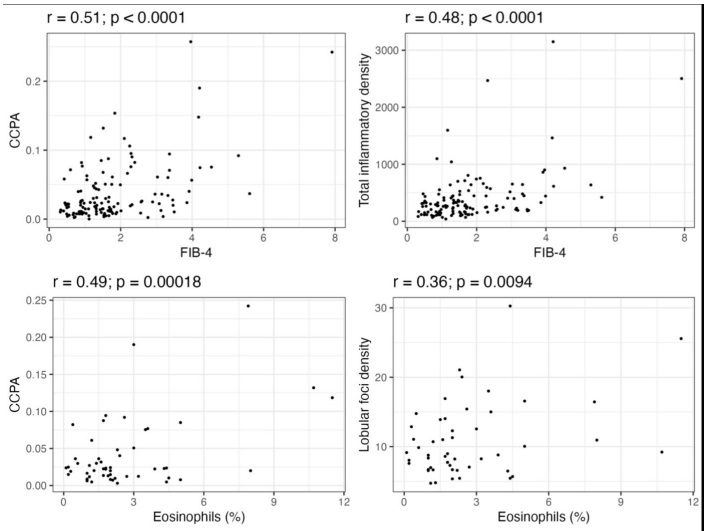


Figure 2. Associations between PAIR™ MASH measurements and FIB-4 and Eosinophils. Points represent individual participants. Pearson correlations (r) and corresponding p values are

ABSTRACT N°30

TITLE: AIM-MASH AI-ASSISTED SCORING OF MASH CLINICAL TRIAL SAMPLES INCREASES INTER-READER PRECISION

AUTHORS:

Dr. Jake CONWAY, PathAI, Boston, MA, USA
Dr. Claire DETWEILER, PathAI, Boston, MA, USA
Dr. Kate ELFER, PathAI, Boston, MA, USA
Dr. Waleed TAHIR, PathAI, Boston, MA, USA
Mr. Kyle DE LA CENA, PathAI, Boston, MA, USA
Mr. Edwin ANDERSON, PathAI, Boston, MA, USA
Mr. Matthew FOLEY, PathAI, Boston, MA, USA
Ms. Morgan SWEENEY, PathAI, Boston, MA, USA
Mr. Darren FAHY, PathAI, Boston, MA, USA
Mr. Nam DO, PathAI, Boston, MA, USA
Mr. André MELO, PathAI, Boston, MA, USA
Mr. Robert SURRATT, PathAI, Boston, MA, USA
Ms. Lily WINDHOLZ, PathAI, Boston, MA, USA
Ms. Nawon LEE, PathAI, Boston, MA, USA
Dr. Jacqueline BROSNAN-CASHMAN, PathAI, Boston, MA, USA
Dr. Katy WACK, PathAI, Boston, MA, USA

KEYWORDS:

CLINICAL TRIALS, HISTOLOGY, CONSENSUS, AI

OBJECTIVES:

The United States Food and Drug Administration (FDA) recently qualified AIM-MASH AI Assist,* which provides MASH clinical research network-aligned scores from digitized liver biopsies, to aid pathologist evaluation of MASH in clinical trials. The FDA qualification stipulated that AIM-MASH AI Assist be used in a gold-standard consensus process, with consensus calls necessary for cases with pathologist-algorithm disagreement. Here, we evaluated this workflow to inform the design of MASH clinical trials incorporating AIM-MASH AI Assist.

METHODS:

Cases (N=50) from a completed Phase 2B MASH trial (NCT02784444) were used. MASH-experienced pathologists (N=6) received training on the workflow prior to scoring cases using AIM-MASH AI Assist on the AISight Clinical Trials (CT)‡ platform; pathologists were organized into three 2-pathologist panels. Following reading of preliminary cases (N=15), harmonization was conducted to review discrepancy patterns and establish alignment on acceptance scenarios. Post-harmonization cases (N=35) were evaluated using AIM-MASH AI Assist, followed by manual review after a two-week washout. 3-pathologist panels were generated through the addition of AI-assisted scores from a held-out pathologist, as well as through simulation of all 3-pathologist combinations. Case-level and component-level agreement were measured.

RESULTS:

Harmonization decreased pathologist-algorithm disagreement from 55.8% to 34.5%. Case-level agreement across all components improved from 18.0% with manual review to 53.0% with AI assistance. Use of an AI-assisted 3-pathologist panel improved the average case-level agreement to 88.0% (i.e., 12.0% consensus call rate) versus 61.9% for AI-assisted 2-pathologist panels (i.e., 38.1% consensus call rate). Agreement was highest for all AI-assisted 3-pathologist

panels assessed, demonstrating 100.0% modal agreement for all components except fibrosis (97.1%; Figure 1).

CONCLUSIONS:

AIM-MASH AI Assist, with pathologist harmonization, increases case-level agreement in 2-pathologist and 3-pathologist panels compared to manual slide evaluation. These results suggest that use of this FDA-qualified tool by 3-pathologist panels maximizes precision and minimizes the number of cases needing consensus calls. * AIM-MASH AI Assist is qualified as a tool in the EU and as a DDT in the US for use in MASH clinical trials. AIM-MASH AI Assist is not for use in diagnostic procedures. ‡ AISight CT is For Research Use Only. Not for use in diagnostic procedures.

APPENDICES:

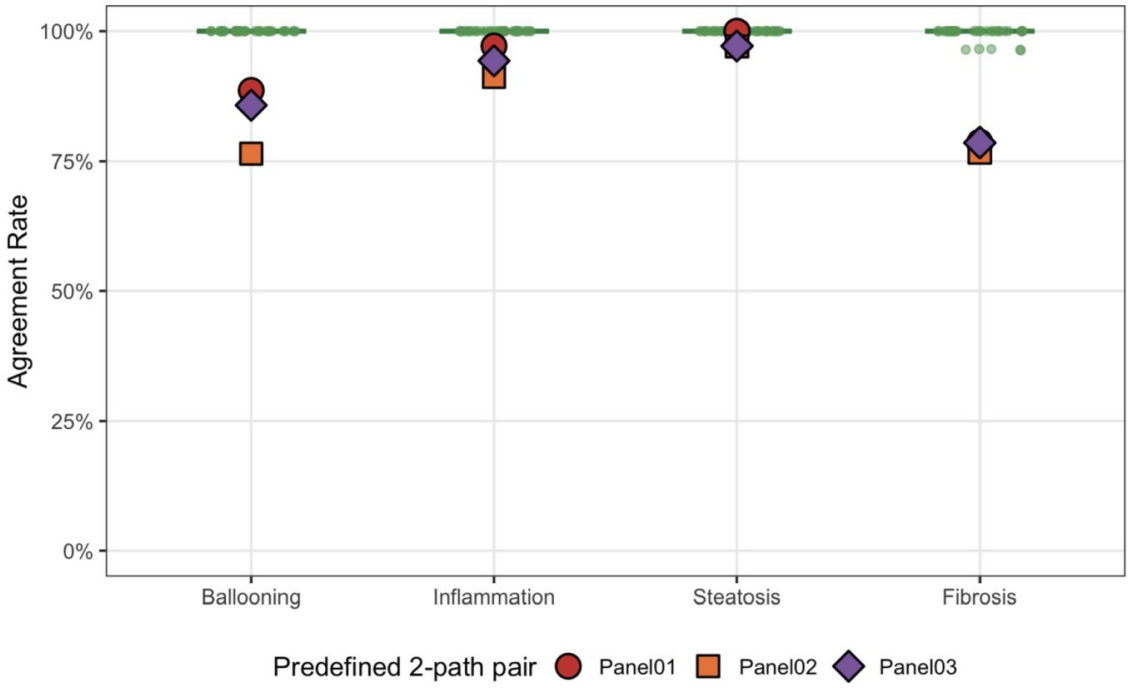


Figure 1. Comparison of 2-pathologist and 3-pathologist panel modal agreement rates for each MASH component. Large symbols represent modal agreement for pre-defined 2-pathologist pairs, while green boxplots represent all possible combinations (N=35) of 3-pathologist panels.

ABSTRACT N°31

TITLE: METABOLIC BENEFITS OF PAN-PPAR AGONIST LANIFIBRANOR IN PATIENTS WITH AND WITHOUT TYPE 2 DIABETES

AUTHORS:

Dr A.G. (Onno) HOLLEBOOM, Amsterdam UMC, Department of Vascular Medicine, Amsterdam, The Netherlands.
Dr Manal ABDELMALEK, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA.
Dr Simon HOGAN, Inventiva, Daix, France
Dr Jason CAMPAGNA, Inventiva, Daix, France
Dr Guillaume WETTSTEIN, Inventiva, Daix, France
Dr Sven FRANCQUE, Antwerp University Hospital, Department of Gastroenterology and Hepatology, Antwerp, Belgium

KEYWORDS:

LANIFIBRANOR, T2DM, INSULIN RESISTANCE, ADIPONECTIN

OBJECTIVES:

Lanifibranor, an oral pan-peroxisome proliferator-activated receptor (PPAR) α/γ/δ agonist in development for metabolic dysfunction-associated steatohepatitis (MASH), has been shown to improve glucose and lipid metabolism. We assessed whether its observed metabolic benefits depend on a type 2 diabetes mellitus (T2DM) diagnosis by comparing outcomes in lanifibranor-treated patients with and without T2DM across four phase II studies.

METHODS:

Data were drawn from S337.2.001 (4-week, T2DM on metformin, non-MASH, N=61); NATIVE (24-week phase IIb MASH, N=247, with pre-specified diabetic-status subgroups [42% T2DM]); a single-center euglycemic-clamp study (NCT03459079; 24-week, T2DM with metabolic dysfunction-associated steatotic liver disease, N=38) providing gold-standard clamp measures of hepatic, muscle and adipose insulin sensitivity; and FASST (48-week systemic sclerosis, non-diabetic, N=145). Comparisons were descriptive, without statistical pooling.

RESULTS:

In NATIVE, placebo-adjusted reductions in glycated hemoglobin (HbA1c), fasting plasma glucose and homeostatic model assessment of insulin resistance (HOMA-IR) were larger in T2DM but directionally consistent in non-T2DM patients (HbA1c -0.60/-0.72% [800/1200 mg] vs -0.21/-0.25%). Adiponectin fold-increase was comparable across strata (T2DM 4.1-4.4; non-T2DM 3.6-4.5; both $p<0.001$). The clamp study confirmed directly measured, tissue-specific insulin sensitisation: hepatic glucose production -13% ($p<0.001$), hepatic insulin-resistance index -18% ($p=0.04$), muscle glucose disposal +29% ($p=0.02$), with HbA1c -0.6% ($p<0.001$), high-density lipoprotein cholesterol (HDL-C) +6.6 mg/dL ($p=0.006$), 2.4-fold adiponectin rise ($p<0.001$) and -31% intrahepatic triglyceride ($p=0.002$); hepatic and muscle sensitivity approached normal, and liver-fat reduction correlated with HOMA-IR, adiponectin and HbA1c improvement.

High-sensitivity C-reactive protein fell significantly (NATIVE, $p\leq0.026$). HDL-C rose and triglycerides fell across T2DM datasets; total and low-density lipoprotein cholesterol and apolipoprotein particle number were unchanged. In the FASST study (without MASH or T2DM) patients, adiponectin still increased 4.6-fold demonstrating adiponectin induction regardless of hepatic status.

CONCLUSIONS:

Metabolic benefits of lanifibranor were seen in these studies regardless of T2DM diagnosis, reflecting direct PPAR action on adipose, muscle and hepatic components that can be drivers of MASH. Tissue-specific insulin sensitization, adiponectin increases, and HDL-C elevation occurred irrespective of diabetes status or underlying disease. Glycemic improvement scales with baseline burden and is greatest in established T2DM. Lanifibranor may address the systemic

metabolic dysfunction underlying MASH, not the hepatic manifestation alone, and can also potentially support the management of T2DM.

ABSTRACT N°32

TITLE: PH-FCS, A CONTINUOUS FIBROSIS SEVERITY SCORE, PREDICTS CLINICAL OUTCOMES IN STEATOSITE

AUTHORS:

Dr Maria JIMENEZ-RAMOS, GSK Stevenage, Gunnels Wood Road, Stevenage, Hertfordshire, United Kingdom
Prof Jonathan A. FALLOWFIELD, Institute for Regeneration and Repair, University of Edinburgh, Edinburgh, United Kingdom
Prof Timothy J. KENDALL, Institute for Regeneration and Repair, University of Edinburgh, Edinburgh, United Kingdom
Dr Mathieu PETITJEAN, PharmaNest Inc. Princeton, NJ, USA
Dr Peter CLEMENTS, GSK Stevenage, Gunnels Wood Road, Stevenage, Hertfordshire, United Kingdom
Dr Emma LAING, GSK Stevenage, Gunnels Wood Road, Stevenage, Hertfordshire, United Kingdom
Dr Marc GOLDFINGER, GSK Stevenage, Gunnels Wood Road, Stevenage, Hertfordshire, United Kingdom

KEYWORDS:

MASLD, FIBROSIS, DIGITAL PATHOLOGY

OBJECTIVES:

Histological fibrosis staging in MASLD is categorical and insensitive to subtle intra-stage changes. FibroNest's AI-assisted single-fiber digital pathology addresses these limitations by generating a phenotypic, multiparametric continuous fibrosis severity score (Ph-FCS), which has shown to be associated with liver related outcomes in a previous investigation (n=403). We aimed to validate the prognostic value of Ph-FCS, and investigate fibrosis-associated sub-components, for adverse clinical outcomes in SteatoSITE, a large (N=599) Scottish MASLD cohort followed long-term.

METHODS:

In SteatoSITE, liver biopsies were digitally analysed using the fibroNest method to generate a continuous Ph-FCS (phenotypic) and its sub-components CCS (Collagen Deposition), MCS (Fiber morphometric) and FACS (Fibrosis architecture), from Picrosirius Red-stained, FFPE sections images acquired at 40X on conventional WSI scans. Liver outcomes were defined per FDA Guidance (first event of liver decompensation, liver transplantation, or all-cause mortality). Composite scores were compared between groups using Wilcoxon rank-sum test; cross-sectional associations with blood biochemistry (AST, ALT, FIB-4 and triglycerides) were assessed by linear regression adjusted for age and sex (FDR<0.05); and associations with time to event were modelled.

RESULTS:

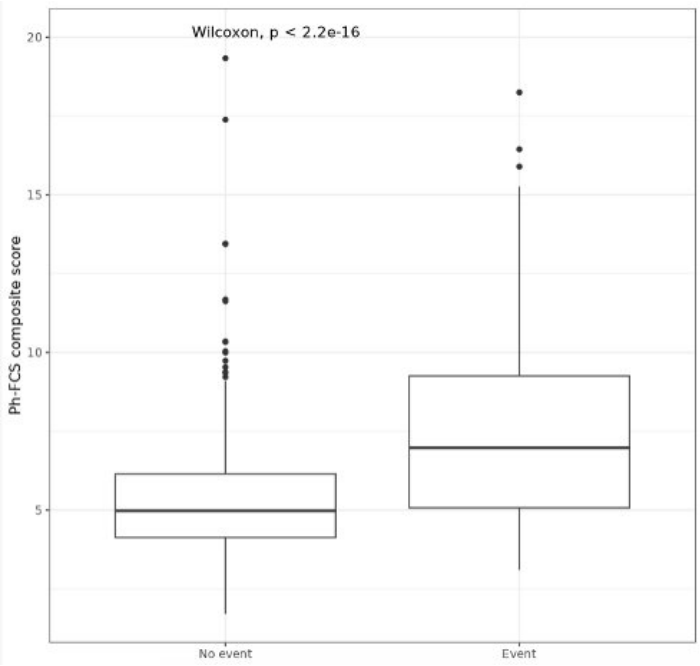
The cohort comprised 599 patients with MASLD (53.4% male; mean age 51.86 years [SD 13.45]), with mean follow-up of 9.66 years (SD 5.48). Baseline fibrosis stage was F0 30.7%, F1 22.7%, F2 14.4%, F3 17.5%, F4 14.7%. Ph-FCS was significantly associated with AST, FIB-4 (positively) and with ALT and HDL (negatively); CCS and MCS showed the same pattern; FACS showed no significant biochemical associations. Over follow-up, 28.7% developed an event, and Ph-FCS was higher in patients with an event than without (mean 7.65 vs 5.39; p<0001), with a bootstrap-corrected AUC of 0.817 (95% CI: 0.804 – 0.825) at year 3 and 0.819 (95% CI: 0.806-0.827) at year 5. CCS and MCS performed comparably (AUC 0.809–0.817); FACS was more modest with AUC 0.766 (95% 0.757-0.772) for year 3 and AUC 0.772 (95% CI 0.765 – 0.778) for year 5.

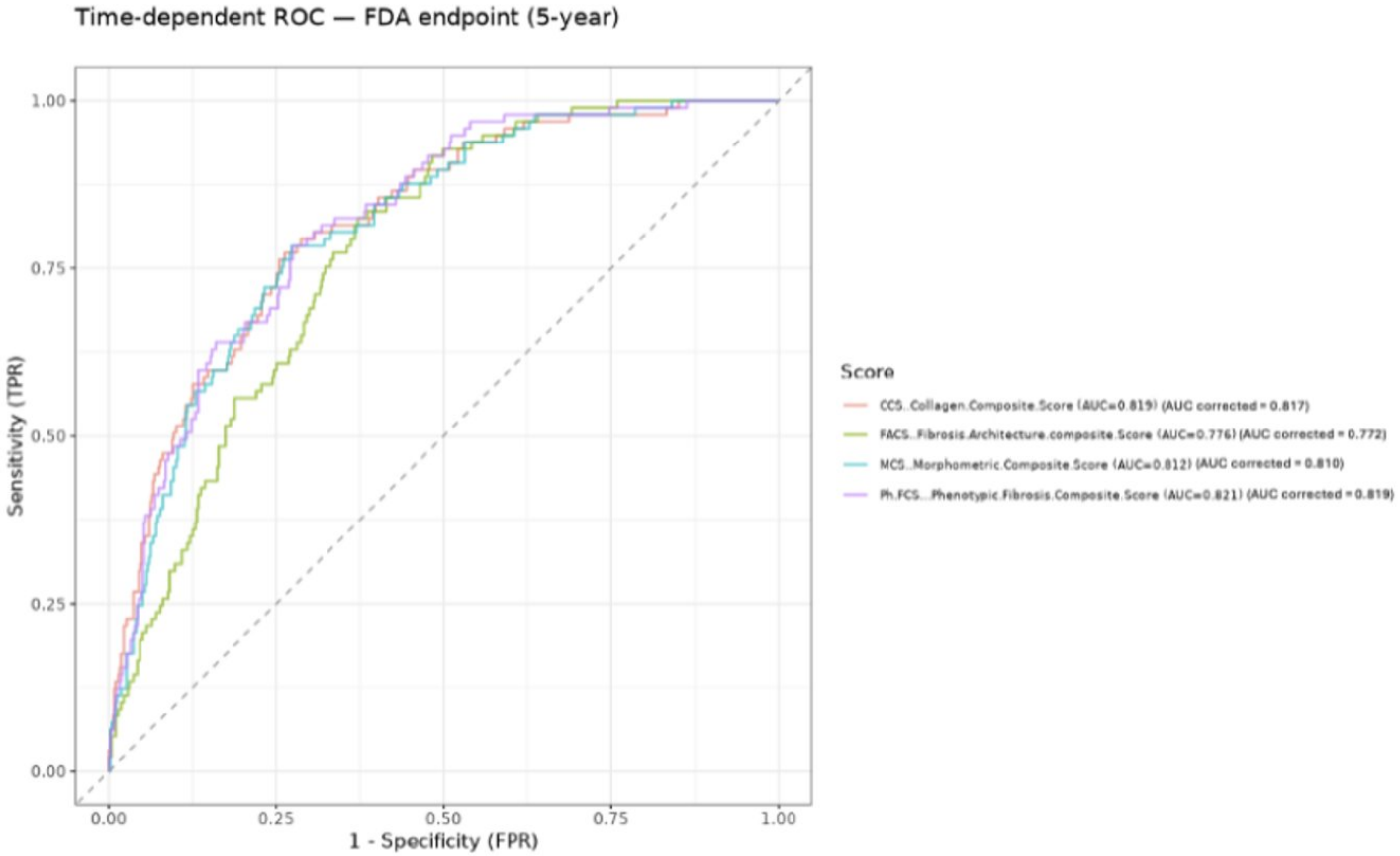
CONCLUSIONS:

Ph-FCS was able to predict liver outcomes with an AUC = 0.81 and significant associations with liver biochemistry and clinical events. These findings support continuous digital pathology scoring, particularly Ph-FCS, over categorical fibrosis

staging for MASLD risk stratification.

APPENDICES:





ABSTRACT N°33

TITLE: BEYOND THE LIVER: PNPLA3 AND MBOAT7 VARIANTS SHAPE BODY COMPOSITION IN MASLD

AUTHORS:

Dr Annalisa CESPIATI, SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
Dr Paola DONGIOVANNI, SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
Dr Marica MERONI, SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
Dr Daniel SMITH, SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Department of Pathophysiology and Transplantation, University of Milan, Italy
Dr Erika FATTA, SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
Dr Edoardo Alessandro PULIXI, SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy
Dr Felice CINQUE, SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Department of Pathophysiology and Transplantation, University of Milan, Italy
Prof Rosa LOMBARDI, SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Department of Pathophysiology and Transplantation, University of Milan, Italy
Prof Anna Ludovica FRACANZANI, SC Medicina ad Indirizzo Metabolico, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy; Department of Pathophysiology and Transplantation, University of Milan, Italy

KEYWORDS:

MASLD, GENETICS, BODY COMPOSITION

OBJECTIVES:

The pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD) is multifactorial. Among genetic determinants, PNPLA3 and MBOAT7 are expressed not only in the liver but also in skeletal muscle and adipose tissue. Aim: to evaluate the association between PNPLA3 and MBOAT7 genotypes and body composition parameters in MASLD patients.

METHODS:

We enrolled 566 MASLD patients (mean age 50±12 ys, 63% male). Body composition parameters was assessed by bioimpedance analysis (BIA). Skeletal muscle index (SMI), adipose tissue index (ATI), and trunk adipose tissue index (TATI) were calculated as mass/height2 (kg/m2).

RESULTS:

PNPLA3 genotype distribution was 16% GG, 43% CG, and 41% CC; MBOAT7 distribution 22% TT, 48% CT, and 30% CC. Mean LSM was 5 kPa. Mean SMI was 10.7±1.2 kg/m2 in men and 8.1±1.1 kg/m2 in women; ATI was 8.44±3.3 kg/m2 in men and 12.1±4.2 kg/m2 in women. Given the similar SMI values observed in CC and CG individuals (9.9 vs 9.8 kg/m2, respectively), a recessive genetic model was applied. Under this model, GG carriers had significantly lower SMI compared with CC/CG in univariate analysis (p = 0.02). However, this association was no longer significant after adjustment for sex. Regarding adiposity, PNPLA3 GG carriers showed no differences in ATI (p=0.15). In sex-stratified analyses, women carrying the GG variant had higher TATI compared with CC (4.9 vs 4.2 kg/m2, p=0.04). At adjusted models, GG genotype remained significantly associated with higher TATI in women (β=0.32 kg/m2, 95% CI 0.02 to 0.63,

p=0.038). Regarding MBOAT7, TT carriers showed lower SMI compared with CC (9.4 vs 9.9 kg/m2, p=0.01), without differences in adipose tissue distribution. This association remained significant after full adjustment (=-0.18 kg/m2, 95%CI -0.3 to -0.04, p=0.03).

CONCLUSIONS:

Our findings reveal that PNPLA3 was linked to increased trunk adiposity in women, suggesting a sex-specific effect on fat distribution.MBOAT7 was independently associated with lower skeletal muscle mass, supporting a potential role in muscle regulation. These findings highlight a differential extrahepatic impact of genetic variants in MASLD, with PNPLA3 primarily influencing adipose tissue distribution and MBOAT7 showing a more consistent association with muscle mass. Such genetic stratification may help refine phenotypic characterization of MASLD beyond liver involvement.

ABSTRACT N°34

TITLE: PARTIAL PPARγ AGONISM UNDERLIES LANIFIBRANOR'S PRECLINICAL FLUID/CARDIOVASCULAR SAFETY VERSUS FULL AND DUAL PPAR AGONISTS

AUTHORS:

Dr Sven M. FRANCQUE, Antwerp University Hospital, Department of Gastroenterology and Hepatology, Antwerp, Belgium. .
Dr A.G. (Onno) HOLLEBOOM, Amsterdam UMC, Department of Vascular Medicine, Amsterdam, The Netherlands.
Dr Jason CAMPAGNA, Inventiva, Daix, France
Dr Simon HOGAN, Inventiva, Daix, France
Dr Guillaume WETTSTEIN, Inventiva, Daix, France
Dr Manal ABDELMALEK, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

KEYWORDS:

LANIFIBRANOR, PAN-PPAR AGONIST, CARDIOVASCULAR SAFETY

OBJECTIVES:

Some peroxisome proliferator-activated receptor (PPAR)γ and dual PPARα/γ agonists have been variably associated with plasma volume expansion, secondary cardiac hypertrophy, and heart failure in animal models and clinical trials. Lanifibranor was intentionally designed as a well-balanced pan-PPAR agonist with partial PPARγ activity and a distinct cofactor recruitment profile, aiming to preserve the beneficial metabolic effects of the class while attenuating adverse ones. Here we evaluated whether this calibrated pharmacology translates to a differentiated fluid and cardiac safety profile, characterizing lanifibranor's PPAR isoform activity and its effects on plasma volume and cardiac weight in preclinical studies, in direct comparison with reference PPARγ and dual PPARα/γ agonists.

METHODS:

In vitro PPAR isoform activity and coregulator recruitment were characterized in transactivation and cofactor-recruitment assays. In vivo, the effects of lanifibranor on plasma volume and cardiac weight were evaluated in Sprague Dawley rats versus single PPARγ (rosiglitazone) and dual PPARα/γ (muraglitazar, tesaglitazar) agonists following dietary exposure. Plasma volume was assessed at Week 8, and cardiac weight at Week 10. Rats received 0 (control), 100, or 1000 mg/kg lanifibranor, reflecting the clinical dose and 10-fold respectively). Comparator doses reflected those currently used in diabetic rodents plus a 10-fold higher dose (rosiglitazone: 3 mg/kg, 30 mg/kg; muraglitazar: 10 mg/kg, 100 mg/kg; tesaglitazar: 1 mg/kg, 10 mg/kg).

RESULTS:

Lanifibranor demonstrated partial PPARγ agonism (~79% maximal efficacy) with full activity at PPARα and PPARδ and a distinct cofactor recruitment profile, compared to rosiglitazone. In vivo, lanifibranor had no significant effect on plasma volume, whereas rosiglitazone, muraglitazar, and tesaglitazar produced dose-related increases in plasma volume. Lanifibranor had no significant effect on heart or left ventricular weight. In contrast, rosiglitazone, muraglitazar, and tesaglitazar significantly increased heart weight, paralleled by increased left ventricle weight in a dose-dependent manner.

CONCLUSIONS:

At exposures exceeding 10-fold the clinical dose, lanifibranor did not produce the dose-related plasma volume expansion or cardiac hypertrophy observed with other PPAR agonists in the same model. Partial PPARγ agonism with a distinct

cofactor recruitment profile provides a mechanistic basis for this separation. These findings support a differentiated preclinical fluid and cardiac profile within the PPAR class.

APPENDICES:

Table 1. In vitro pharmacology and preclinical cardiovascular/fluid safety of lanifibranor versus full PPARγ and dual PPARα/γ agonists in Sprague-Dawley rats[a]

Parameter	Lanifibranor	Rosiglitazone (full PPARγ)	Muraglitazar (dual α/γ)	Tesaglitazar (dual α/γ)
PPARγ maximal efficacy (in vitro)	Partial (~79%)	Full (~100%)	Full	Full
Plasma volume	No significant increase (either dose)	↑ significant (dose-related)	↑ significant (high dose)	↑ significant (both doses)
Hematocrit	Mild ↓ (one timepoint)	↓ significant (both doses)	↓ significant (high dose)	↓ significant (both doses)
Heart weight	No significant increase	↑ significant (dose-related)	↑ significant (high dose)	↑ significant (both doses)
Left ventricle weight	No significant increase	↑ significant (dose-related)	↑ significant (high dose)	↑ significant (both doses)

[a]Sprague-Dawley rats, dietary exposure up to 9–10 weeks; comparators at standard diabetic-rodent doses and 10-fold higher. Significance vs. control by Dunnett's test (P<0.05). In vitro PPARγ maximal efficacy from transactivation assays.

ABSTRACT N°35

TITLE: ONE-YEAR CHANGES IN LIPID-BASED CARDIOMETABOLIC RISK MARKERS FOLLOWING RESMETIROM INITIATION: A REAL-WORLD ANALYSIS

AUTHORS:

Dr William ALAZAWI, Queen Mary University of London, UK
Dr Christina M PARRINELLO, Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA
Dr Susan THAPA, Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA
Dr Yestle KIM, Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA
Dr Douglas WELCH, Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA
Dr Francis LOBO, Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA
Ms Isobel MCEWEN, Trio Health, Louisville, CO, USA
Dr John O'DONNELL, Madrigal Pharmaceuticals, Inc., West Conshohocken, PA, USA
Dr Naim ALKHOURI, Summit Clinical Research, San Antonio, TX, USA

KEYWORDS:

MASH, REAL-WORLD, LIPIDS, RESMETIROM

OBJECTIVES:

Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by progressive liver fibrosis and increased cardiovascular risk. This real-world study evaluated one-year lipid changes among patients initiating resmetirom using two US data sources.

METHODS:

Adults (≥18 years) initiating resmetirom on or after March 14, 2024 (index) were identified from two US de-identified EHR databases: Truveta (through April 2026) and Trio Health (aggregated from 3 sources through January 2026). Patients had healthcare activity and no evidence of advanced liver disease (cirrhosis, HCC or liver transplantation) or other chronic liver diseases during the 1 year before index. Among patients with baseline (≤12 months before index) and ~1-year (range: 9-15 months) lipid measurements (low-density lipoprotein cholesterol [LDL-c], high-density lipoprotein cholesterol [HDL-c], total cholesterol [TC], triglycerides [TG] and TG/HDL-c ratio), means, percent changes and p-values from paired t-tests were calculated. LDL-c goal attainment (<1.81 or <2.59 mmol/L among patients above each threshold at baseline) was also evaluated. Analyses were stratified by concomitant statin use.

RESULTS:

Among patients with at least 1 year of observed follow-up (Truveta, N=1,405; Trio, N=1,612), 26-27% and 15-21%, respectively, had paired lipid measurements at baseline and approximately 1 year. Across both data sources, lipids improved consistently after resmetirom initiation. Mean LDL-c decreased by 0.38 mmol/L (10.0%) in Truveta and 0.42 mmol/L (9.5%) in Trio; TC by 0.55 mmol/L (10.4%) and 0.50 mmol/L (6.9%); TG by 0.48 mmol/L (16.6%) and 0.37 mmol/L (15.2%), and TG/HDL-c ratio (mg/dL) by 1.4 (15.8%) and 0.8 (14.4%), respectively. Baseline mean LDL-c was lower than in MAESTRO-NASH (2.40 mmol/L Truveta, 2.42 mmol/L Trio vs ~2.72 mmol/L), potentially contributing to the smaller LDL-c reductions (vs ~17% in MAESTRO-NASH). HDL-c increased modestly (0.03 and 0.02 mmol/L) but was not statistically significant in Trio; all other changes were statistically significant (P<0.05). Among patients above guideline LDL-c thresholds at baseline, 30-34% and 54-62% achieved LDL-c <1.81 mmol/L and <2.59 mmol/L, respectively, after one year. Findings were similar by concomitant statin use.

CONCLUSIONS:

Across two independent real-world data sources, meaningful one-year improvements in lipid profiles and LDL-c goal attainment were observed after resmetirom initiation. Findings were similar regardless of concomitant statin use.

APPENDICES:

Table 1. Mean changes in cardiometabolic risk markers overall and stratified by concomitant statin use

			Means			Mean % Change
	N with 1 year FU	N (%) with both	Baseline Mean (SD)	Follow-up Mean (SD)	Mean Change (SD)	
TRUVETA	1,405					
LDL-c, mmol/L		367 (26%)	2.40 (1.00)	2.02 (0.86)	**-0.38 (0.88)**	-10
HDL-c, mmol/L		370 (26%)	1.12 (0.38)	1.15 (0.38)	**0.03 (0.25)**	5.6
TC, mmol/L		379 (27%)	4.38 (1.19)	3.83 (1.09)	**-0.55 (1.04)**	-10.4
TG, mmol/L		378 (27%)	1.92 (1.28)	1.44 (0.85)	**-0.48 (1.05)**	-16.6
TG/HDL-c ratio*		369 (26%)	4.6 (4.8)	3.2 (2.5)	**-1.4 (3.7)**	-15.8
NO Concomitant Statin Use	630					
LDL-c, mmol/L		146 (23%)	2.68 (0.87)	2.32 (0.77)	**-0.36 (0.78)**	-9.8
HDL-c, mmol/L		148 (23%)	1.19 (0.34)	1.21 (0.33)	**0.03 (0.23)**	4.1
TC, mmol/L		150 (24%)	4.66 (1.01)	4.19 (0.96)	**-0.47 (0.94)**	-8.5
TG, mmol/L		148 (23%)	1.78 (0.96)	1.43 (0.91)	**-0.35 (0.75)**	-12.6
TG/HDL-c ratio*		147 (23%)	3.9 (2.7)	3.0 (2.5)	**-0.9 (1.9)**	-11.9
YES Concomitant Statin Use	775					
LDL-c, mmol/L		221 (29%)	2.22 (1.04)	1.82 (0.86)	**-0.40 (0.94)**	-10.1
HDL-c, mmol/L		222 (29%)	1.07 (0.35)	1.11 (0.35)	**0.04 (0.24)**	6.6
TC, mmol/L		229 (30%)	4.19 (1.28)	3.59 (1.10)	**-0.60 (1.11)**	-11.6
TG, mmol/L		230 (30%)	2.01 (1.45)	1.44 (0.81)	**-0.57 (1.20)**	-19.2
TG/HDL-c ratio*		222 (29%)	5.1 (5.7)	3.4 (2.5)	**-1.7 (4.5)**	-18.4
TRIO HEALTH	1,612					
LDL-c, mmol/L		234 (15%)	2.42 (0.95)	1.98 (0.83)	**-0.42 (0.88)**	-9.5
HDL-c, mmol/L		272 (17%)	1.18 (0.39)	1.20 (0.35)	0.02 (0.23)	3.5
TC, mmol/L		333 (21%)	4.39 (1.15)	3.89 (1.11)	**-0.50 (1.03)**	-6.9
TG, mmol/L		332 (21%)	2.00 (1.20)	1.63 (1.42)	**-0.37 (1.02)**	-15.2
TG/HDL-c ratio*		267 (17%)	4.5 (3.8)	3.8 (4.7)	**-0.8 (3.5)**	-14.4
NO Concomitant Statin Use	1021					
LDL-c, mmol/L		107 (10%)	2.61 (0.81)	2.20 (0.79)	**-0.36 (0.73)**	-5.1
HDL-c, mmol/L		133 (13%)	1.21 (0.43)	1.21 (0.37)	**0.00 (0.24)**	2.0
TC, mmol/L		165 (16%)	4.60 (1.12)	4.09 (1.18)	**-0.50 (0.95)**	-4.6
TG, mmol/L		165 (16%)	1.95 (1.22)	1.68 (1.75)	**-0.27 (1.18)**	-11.3
TG/HDL-c ratio*		130 (13%)	4.3 (3.3)	4.0 (5.9)	**-0.3 (4.1)**	-9.3
YES Concomitant Statin Use	591					
LDL-c, mmol/L		127 (21%)	2.26 (1.03)	1.79 (0.82)	**-0.48 (0.99)**	-13.2
HDL-c, mmol/L		139 (24%)	1.15 (0.34)	1.19 (0.32)	**0.03 (0.22)**	5.0
TC, mmol/L		168 (28%)	4.18 (1.15)	3.69 (1.01)	**-0.50 (1.10)**	-9.1
TG, mmol/L		167 (28%)	2.04 (1.19)	1.58 (1.01)	**-0.46 (0.83)**	-19.0
TG/HDL-c ratio*		137 (23%)	4.7 (4.3)	3.5 (3.2)	**-1.2 (2.6)**	-19.3

Bolded mean change indicates p<0.05 from paired t-test. *TG/HDL-c ratio calculated using TG and HDL-c values expressed in mg/dL.

Group	N paired	LDL-c ≥1.81 mmol/L			LDL-c ≥2.59 mmol/L		
		Baseline n (%)	1 Year Follow-up n (%)	Change ≥1.81 → <1.81 mmol/L n (%)*	Baseline n (%)	1 Year Follow-up n (%)	Change ≥2.59 → <2.59 mmol/L n (%)*
Truveta							
Overall	367	253 (68.9%)	202 (55.0%)	76 (30.0%)	141 (38.4%)	81 (22.1%)	76 (53.9%)
Concomitant Statin use: No	146	124 (84.9%)	105 (72.6%)	24 (19.4%)	78 (53.4%)	50 (34.2%)	35 (44.9%)
Concomitant statin use: Yes	221	129 (58.4%)	96 (43.4%)	52 (40.3%)	63 (28.5%)	31 (14.0%)	41 (65.1%)
Trio Health							
Overall	234	172 (73.5%)	125 (53.4%)	59 (34.3%)	99 (42.3%)	54 (23.1%)	61 (61.6%)
Concomitant Statin use: No	107	89 (83.2%)	72 (67.3%)	21 (23.6%)	57 (53.3%)	34 (31.8%)	30 (52.6%)
Concomitant statin use: Yes	127	83 (65.4%)	53 (41.7%)	38 (45.8%)	42 (33.1%)	20 (15.7%)	31 (73.8%)

*Denominator is patients with baseline LDL-c at or above the respective threshold. Change is from baseline to 1 year. Follow-up window: 9-15 months post-index date.

ABSTRACT N°36

TITLE: LANIFIBRANOR PHASE 1/2A EXPERIENCE - PPARγ ENGAGEMENT AND METABOLIC ACTIVITY WITHOUT EARLY CLINICAL FLUID RETENTION

AUTHORS:

Dr Sven M. FRANCQUE, Antwerp University Hospital, Department of Gastroenterology and Hepatology, Antwerp, Belgium. .
Dr A.G. (Onno) HOLLEBOOM, Amsterdam UMC, Department of Vascular Medicine, Amsterdam, The Netherlands.
Dr Jason CAMPAGNA, Inventiva, Daix, France
Dr Simon HOGAN, Inventiva, Daix, France
Dr Guillaume WETTSTEIN, Inventiva, Daix, France
Dr Manal F. ABDELMALEK, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

KEYWORDS:

LANIFIBRANOR, T2DM, ADIPONECTIN, FLUID RETENTION

OBJECTIVES:

Translation of preclinical peroxisome proliferator-activated receptor (PPAR) pharmacology to human dose selection requires evidence of target engagement, cardiometabolic effects, and an acceptable safety profile at predicted therapeutic exposures. Lanifibranor is a pan-PPAR agonist with balanced PPAR activation in development for the treatment of MASH. We report integrated pharmacokinetic and pharmacodynamic findings from the Phase 1 program and the Phase 2a proof-of-concept study in patients with T2DM.

METHODS:

Data are reported from two randomized, double-blind, placebo-controlled studies of lanifibranor: a Phase 1 investigation of single oral doses (25-1000 mg) and rising multiple oral doses (150-1500 mg) for 14 consecutive days in young healthy males, plus single-dose pharmacokinetics in elderly participants; and a Phase 2a multicenter, parallel-group, 28-day study of lanifibranor (400, 800, or 1400 mg) in patients with T2DM on metformin monotherapy. Focusing on PPARγ, adiponectin was examined as a target-engagement marker, and glycemic and lipid parameters as metabolic efficacy signals.

RESULTS:

In the Phase 1 multiple-dose component, lanifibranor significantly increased adiponectin versus placebo at 400, 1000, and 1500 mg (P=0.0057, 0.0001, and <0.0001, respectively), with high-molecular-weight (HMW) adiponectin increases at 1000 (P=0.0005) and 1500 mg (P=0.0004). In the Phase 2a study, lanifibranor (400, 800, and 1400 mg) consistently induced dose- and time-related increases in total and HMW adiponectin, confirming PPARγ engagement. In patients with T2DM, lanifibranor showed significant (P<0.05) changes from baseline in pro-insulin versus placebo at 1400 mg and triglycerides and HDL cholesterol at 800 and 1400 mg. Dose-related improvements in insulin, pro-insulin, and insulin resistance were observed, with reductions in average and postprandial blood glucose at 1400 mg, consistent with the PPARγ insulin-sensitizing mechanism. At Day 28, lanifibranor showed no clinical signs of fluid retention (pedal edema, ankle foot volume, ankle circumference) versus placebo, with no changes in hematology, albumin, or brain natriuretic peptide.

CONCLUSIONS:

These data support lanifibranor's balanced pan-PPAR activity, inclusive of partial PPARγ activation within the first 28 days of use, with any attenuated PPARγ fluid retention not clinically detectible. Initial efficacy signals in glycemic control

and lipids support further investigation of lanifibranor for metabolic dysfunction and complications of MASH, permitting more accurate characterization of fluid distribution

ABSTRACT N°37

TITLE: LANIFIBRANOR IMPROVES METABOLIC AND HISTOLOGICAL FEATURES OF MASH ACROSS MULTIPLE PRECLINICAL MODELS: CONVERGENT PAN-PPAR ACTIVITY

AUTHORS:

Dr A.G. (Onno) HOLLEBOOM, Amsterdam UMC, Department of Vascular Medicine, Amsterdam, The Netherlands.
Dr Sven M. FRANCQUE, Antwerp University Hospital, Department of Gastroenterology and Hepatology, Antwerp, Belgium. .
Dr Jason CAMPAGNA, Inventiva, Daix, France
Dr Simon HOGAN, Inventiva, Daix, France
Dr Guillaume WETTSTEIN, Inventiva, Daix, France
Dr Manal F. ABDELMALEK, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

KEYWORDS:

LANIFIBRANOR, MASH, INSULIN RESISTANCE, DYSLIPIDEMIA

OBJECTIVES:

MASH is a systemic multi-organ disease characterized by steatosis, inflammation, hepatocyte injury, and progressive hepatic fibrosis, arising in the setting of metabolic disturbances (insulin resistance, dyslipidemia, glucose dysregulation). No single peroxisome proliferator-activated receptor (PPAR) subtype addresses all these disease drivers. Lanifibranor, an investigational, oral pan-PPAR agonist in development for the treatment of MASH, through balanced activation of PPARα, δ, and γ, engages multiple pathological pathways, potentially enabling both direct anti-fibrotic and metabolic improvement.

METHODS:

The metabolic effects of lanifibranor were evaluated across multiple rodent models: diabetic/insulin-resistant models (db/db mice, 3–30 mg/kg; Zucker Diabetic Fatty [ZDF] rats) and dyslipidemic models (human apolipoprotein A1 [apoA1]-transgenic mice; Wistar Ottawa Karlsburg W [WOKW] rats). Treatment comparators included rosiglitazone (3 mg/kg) and fenofibrate (30 and 100 mg/kg). Endpoints included fasting/non-fasting glucose, glucose and insulin tolerance, glycated hemoglobin (HbA1c), adiponectin, triglycerides, cholesterol/apoA1, and body weight. Histological and anti-fibrotic effects were drawn from dietary MASH models (CDAA-HFD and Western-diet mice; free-choice-diet obese hamster).

RESULTS:

In db/db mice, a model of insulin-resistant type 2 diabetes, lanifibranor dose-dependently reduced glucose (−40% at 10 mg/kg; −58% at 30 mg/kg) and triglycerides (−33%; −45%), and improved oral glucose tolerance, comparable to rosiglitazone 3 mg/kg. In ZDF rats, the higher lanifibranor dose (100 mg/kg) significantly reduced HbA1c (−19%), improved glucose tolerance (area under curve −38%), and increased adiponectin, without increasing food intake. Improved glucose tolerance was similarly observed in a diet-induced obesity mouse model. In the dyslipidemic apoA1-transgenic mouse model, lanifibranor increased serum human apoA1 (60%) and reduced triglycerides (52%), uniquely without the liver-weight increase observed with fenofibrate. In WOKW rats, dyslipidemia improved consistently (reduced triglycerides and very-low-density lipoprotein, increased HDL and adiponectin). Across dietary MASH models, lanifibranor reduced steatosis, necroinflammatory activity, and fibrosis (CDAA-HFD: NAFLD activity score −65%, steatosis −74%, ballooning −87%, collagen area −43%; all $P<0.01$); in an obese hamster MASH model it additionally lowered HOMA-IR and plasma ALT, reflecting hepatic benefit.

CONCLUSIONS:

Across multiple animal MASH models, lanifibranor improved hepatic histology and systemic metabolic parameters. Pan-PPAR activation may address many of the drivers of a systemic multi-organ disease collectively rather than individually, effects observed with lanifibranor in the NATiVE clinical study.

ABSTRACT N°38

TITLE: BEYOND THE LIVER: CARDIOVASCULAR EFFECTS OF THE PAN-PPAR AGONIST LANIFIBRANOR IN PATIENTS WITH MASH

AUTHORS:

Dr Sven M. FRANCQUE, Antwerp University Hospital, Department of Gastroenterology and Hepatology, Antwerp, Belgium. .
Dr A.G. (Onno) HOLLEBOOM, Amsterdam UMC, Department of Vascular Medicine, Amsterdam, The Netherlands.
Dr Simon HOGAN, Inventiva, Daix, France
Dr Jason CAMPAGNA, Inventiva, Daix, France
Dr Guillaume WETTSTEIN, Inventiva, Daix, France
Dr Manal F. ABDELMALEK, Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

KEYWORDS:

LANIFIBRANOR, PPAR, CARDIOVASCULAR SAFETY, HFPEF

OBJECTIVES:

Cardiovascular (CV) events are the leading cause of death in metabolic dysfunction-associated steatohepatitis (MASH). CV disease such as heart failure with preserved ejection fraction (HFpEF) and MASH are manifestations of a shared systemic metabolic disorder. We assessed whether the investigational pan-PPAR agonist, lanifibranor, improves CV risk factors, and whether nonclinical data support CV safety and vascular benefit.

METHODS:

CV endpoints were evaluated in the phase 2b NATiVE trial (247 patients, non-cirrhotic MASH; lanifibranor 1200 mg, 800 mg or placebo once daily, 24 weeks): lipids, glucose metabolism, insulin resistance (IR), systemic inflammation, blood pressure (BP), adiponectin and a validated CV-risk classification. Nonclinical data comprised a rat study comparing plasma volume, glomerular filtration rate (GFR) and organ weights with reference PPAR agonists, and a thioacetamide cirrhosis model assessing portal hemodynamics and endothelial phenotype.

RESULTS:

Versus placebo (adjusted mean differences at end of treatment), lanifibranor significantly improved triglycerides (-0.5 mmol/L), HDL cholesterol (+0.10 to +0.16 mmol/L), apolipoprotein-B (-10 mg/dL), HOMA-IR(≈-4.0), HbA1c(-0.5% to -0.7%), fasting glucose(-0.8 to -1.0 mmol/L), hs-CRP(-1.5 to -2.2 mg/L), ferritin (-72 to -84 µg/L) and diastolic BP (-3.9 mmHg at 800 mg), independent of diabetes status. Adiponectin rose ≈4-fold, and 38-44% (1200-800 mg) of high-CV-risk patients improved to lower-risk categories (vs 26% on placebo). Nonclinically, unlike rosiglitazone, muraglitazar and tesaglitazar, lanifibranor did not increase plasma volume or heart weight and did not produce serous effusions (GFR unchanged), indicating attenuated PPARγ-mediated fluid retention; a modest NT-proBNP rise in NATiVE was not linked to any clinical observation. In cirrhotic rats, lanifibranor lowered portal pressure (-15%) and hepatic vascular resistance (-29%) without altering systemic arterial pressure, alongside an improved endothelial phenotype (reduced VCAM-1, ICAM-1 and E-selectin, adhesion molecules central to atherogenesis).

CONCLUSIONS:

Lanifibranor produced coordinated improvement across established cardiovascular risk factors (atherogenic dyslipidemia, IR, systemic inflammation, BP and adiponectin), while nonclinical evidence of favorable fluid handling and an improved endothelial phenotype support cardiovascular benefit and suggests mitigation of the PPARγ-class heart-failure concern. Through improvement of lipids and glucose metabolism, and cardioprotection against oxidative stress

and inflammation, lanifibranor may directly target diseases such as HFpEF. These findings support prospective evaluation of lanifibranor on cardiovascular outcomes in MASH.

APPENDICES:

Parameter	Effect	Dose / significance / notes
A. Clinical cardiometabolic effects - NATIVE Phase 2b; adjusted mean difference vs placebo at week 24 (Cooreman et al., Nat Commun 2024)		
Triglycerides	-0.5 mmol/L	Both doses; significant
HDL-cholesterol	+0.10 to +0.16 mmol/L	1200 / 800 mg; significant
Apolipoprotein-B	-10 mg/dL	Both doses; significant
HOMA-IR	Overall ≈-4.0; T2D -4.5 to -6.3	1200 / 800 mg; larger in T2D subgroup
HbA1c	Overall -0.5%; T2D -0.7%	T2D 95% CI -1.0 to -0.4, both doses, p<0.001; larger in higher-MACE-risk T2D
Fasting glucose	Overall -0.8 to -1.0; T2D -1.2 to -1.7 mmol/L	1200 / 800 mg; larger in T2D
hs-CRP	-1.5 to -2.2 mg/L	1200 / 800 mg; significant
Ferritin	-72 to -84 µg/L	1200 / 800 mg; significant
Diastolic BP	-3.9 mmHg	800 mg (p=0.012); 1200 mg -2.5 mmHg not significant (p=0.110)
Adiponectin	↑ ≈4-fold (4.5× / 3.8×)	1200 / 800 mg; increased in 95% / 86% of patients vs 10% placebo
High-CV-risk ↔ lower risk	38% / 44% of patients	1200 / 800 mg vs 26% placebo
NT-proBNP	↑ ≈ +34 to +71 pg/mL	Correlated with weight gain; no clinical congestion
B. Nonclinical safety / fluid handling - rat, vs reference PPAR agonists (Lanifibranor Nonclinical Overview, 2021)		
Plasma volume	No increase	vs increases with rosiglitazone / muraglitazar / tesaglitazar
Heart weight	No increase	vs increases with reference agonists
Serous effusions	None	Produced by rosiglitazone and tesaglitazar
GFR	Unchanged	All compounds
C. Nonclinical vascular & endothelial effects - thioacetamide-cirrhotic rat (Boyer-Diaz et al., J Hepatol 2021)		
Portal pressure	-15%	p=0.003
Hepatic vascular resistance	-29%	p=0.022
Mean arterial pressure / HR	No change	Systemic haemodynamics preserved
ICAM-1 (endothelial)	-52%	p=0.038
E-selectin (endothelial)	-85%	p=0.020
VCAM-1 (endothelial)	-44%	p=0.097 (not significant)