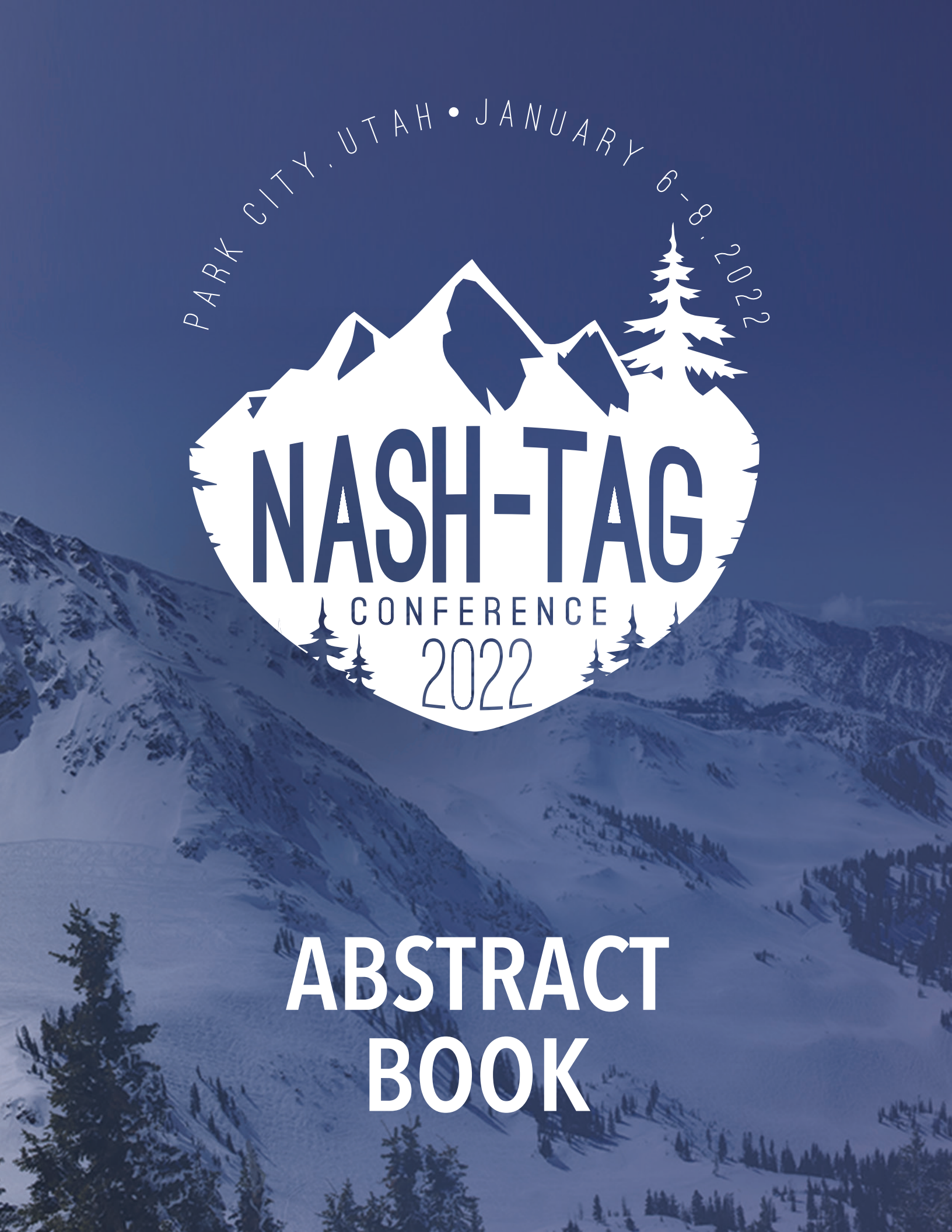

ABSTRACT BOOK

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[1 – DISTINGUISHED ABSTRACT] A PLACEBO-CONTROLLED, DOUBLE-BLIND, FIRST-IN-HUMAN STUDY OF PEMVIDUTIDE (ALT-801), A NOVEL GLP-1/GLUCAGON DUAL RECEPTOR AGONIST FOR THE TREATMENT OF NASH AND OBESITY

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Abstract Category: Therapeutic Trials NASH/Liver Fibrosis
Corresponding Author's Email: sharris@altimmune.com
Author Disclosure: This abstract has not been presented elsewhere.

Background/Aims: Pemvidutide (ALT-801) is a GLP-1/glucagon dual receptor agonist under development for the treatment of NASH and obesity. Pemvidutide combines the reduced caloric intake effects of GLP-1 receptor agonists with the increased energy expenditure and lipometabolic effects of glucagon receptor agonists on the liver. The 1:1 ratio of GLP-1 and glucagon agonism within pemvidutide is hypothesized to provide the optimal balance of efficacy and tolerability, while the EuPort domain, a glycolipid side chain, is hypothesized to prolong serum half-life ($t_{1/2}$) and slow bloodstream entry. The aim of the current study was to assess the safety and pharmacokinetics (PK) of pemvidutide and to evaluate its effects on weight loss and liver fat content (LFC), both important attributes in the treatment of NASH.

Methods: This was a placebo-controlled, double-blind, first-in-human trial comprised of single ascending dose (SAD) cohorts of 0.4, 1.2, 2.4, 3.6 and 4.8 mg and multiple ascending dose (MAD) cohorts of 1.2, 1.8, and 2.4 mg administered weekly by subcutaneous (SC) injection for 12 weeks, without use of dose titration. Overweight and obese but otherwise healthy subjects (BMI 25-40 kg/m^2) were randomized 3:1 and 4:1 in SAD and MAD cohorts to pemvidutide or placebo, respectively, with placebos pooled for analyses. The primary endpoint of the study was safety and tolerability. Secondary endpoints included change in body weight and PK; change in LFC by MRI-PDFF was evaluated in exploratory analyses.

Results: 36 subjects across the SAD cohorts and 34 subjects across the MAD cohorts received 1 or more doses of study drug. Pemvidutide was well-tolerated to single doses of 3.6 mg. Nausea was the most frequently reported adverse event (AE), with most being mild in severity. No subjects experienced diarrhea at 1.2 mg and 1.8 mg, and no study discontinuations due to AEs were reported at any dose. One subject receiving pemvidutide 1.8 mg and 1 subject receiving placebo experienced 3-5x elevations of ALT without other significant findings. Time to peak drug concentration (C_{max}) was slow at 70 hrs, while t1/2 was extended at 110 hours, compatible with weekly dosing. Weight loss occurred rapidly and consistently across study weeks. By Week 12, subjects receiving pemvidutide achieved mean weight losses of 4.9%, 10.3%, and 9.0% at the 1.2 mg, 1.8 mg, and 2.4 mg doses, respectively, with the placebo group experiencing a mean weight loss of 1.6% (statistically significant at 1.8 mg and 2.4 mg vs. placebo) (Figure 1). Trend lines of individual subject plots at 1.8 mg (Figure 2) suggested that sustained effects could be observed over longer dosing durations. MRI-PDFF analyses following 6 weeks of treatment revealed all 5 subjects with fatty liver, defined as >5% at baseline, including some as high as 19.5%, that received 1.8 mg or 2.4 mg pemvidutide had reductions in LFC to undetectable levels (limit of detection 1.5%), a >90% mean reduction.

Conclusion: The rapid and potent reductions in body weight and LFC, including double-digit weight loss in 12 weeks and decreases in LFC to levels below the limit of detection, without the need for dose titration, suggest pemvidutide could be a promising new agent for treatment of NASH and its co-morbidities.

Figure 1

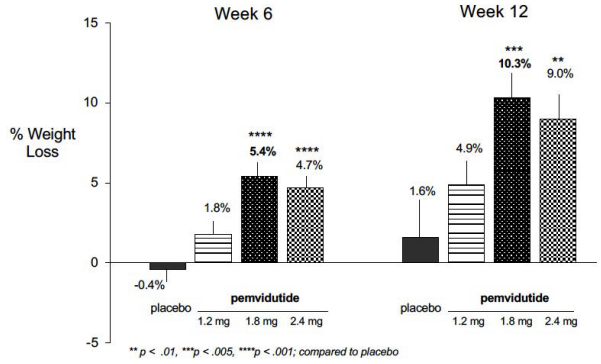
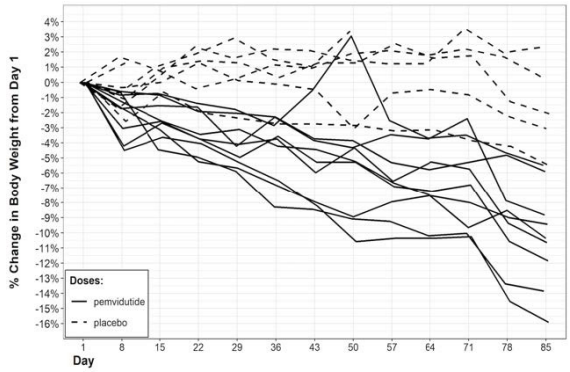


Figure 2



[3 – DISTINGUISHED ABSTRACT] ACCURATE DIAGNOSIS OF NASH USING NOVEL PROTEASE BASED LIQUID BIOPSY

Sophie Cazanave,[1] Faycal Touti,[1] Amon Asgharpour,[2] Sabrina Ibarra,[1] Mehar Cheema,[1] Anatoly Myaskovsky,[1] Andrea Shepard,[1] Julia Amaral,[1] Aleksey Molodtsov,[1] Christopher Gulka,[1] Mackenzie Rowe,[1] Faridoddin Mirshahi,[2] Maciej Pacula,[1] Tram Tran,[1] Arun Sanyal, [2] and Wendy Winckler[1]

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Abstract Category: Diagnostic Procedures NASH/Liver Fibrosis
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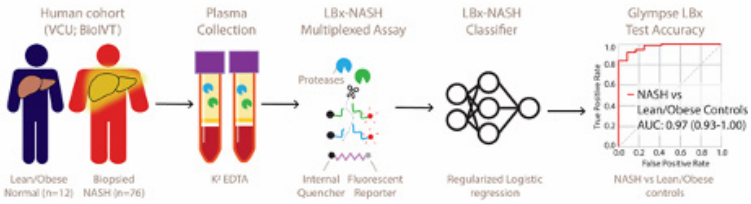
Background: There is an urgent need for non-invasive, accurate NASH diagnostics as an alternative to liver biopsy. Glympse previously developed injectable protease activity biosensors to identify NASH, as liver disease specific proteases cleave these biosensors. Now a simplified liquid biopsy (blood draw) approach to the Glympse technology, LBx-NASH directly measures protease activity using fluorogenic protease sensors, improving accessibility and convenience for patients.

Methods: K2 EDTA plasma were from (1) C57BL/6 NASH mice fed a choline-deficient high fat diet (CD-HFD) or a healthy chow diet (n=10-28); (2) a human pilot study on 35 Fibroscan or liver biopsy confirmed NASH patients and 24 healthy controls (BioIVT, DSL, iSpecimen); (3) a

large human cohort of 76 liver-biopsy confirmed NASH (VCU, Richmond VA, 60.5% female and 77.3% BMI ≥ 30kg/m2, 50.7% diabetic (4) 12 prospective healthy lean and obese controls without clinical evidence of diabetes, liver disease or other comorbidities (BioIVT). Histological score evaluated according to NASH CRN criteria was applied to stage disease. Biosensor cleavage was assayed in plasma by fluorimetry, and the relative signal was used for classification by regularized logistic regression (using 80% train, 20% validation splits). Protease abundance was measured using a commercial ELISA kit.

Results: Proteolytic cleavage of Glympse biosensors in plasma was highly effective at predicting NASH vs. healthy and detecting diet-induced NASH regression in mice (both AUC=1.00). The most significantly cleaved biosensor in NASH mice was N11, a peptide sensing cathepsin L (CTSL) activity. CTSL activity was far superior to CTSL abundance in plasma to classify NASH (AUC=1.00 vs AUC=0.52; 95% CI 0.35-0.67, n=28). N11 was tested in 3 independent human NASH pilot cohorts (n=35) compared to healthy controls (n=24), significantly discriminating NASH vs. healthy (*p=0.003*) and replicating the effect observed preclinically. We screened >600 peptide substrates to identify a panel of 20 biosensors (LBx-NASH) to interrogate diverse disease biology in NASH. We tested LBx-NASH in 88 human NASH and control plasma samples, predicting NASH from healthy and obese controls with an AUC=0.97 (95% CI 0.93-1.00), independent of gender, obesity and type 2 diabetes



Conclusions: The Glympse liquid biopsy platform using protease biosensors can very accurately identify NASH from healthy lean and obese controls as demonstrated in mice and human studies. This diagnostic approach could potentially diagnose patients with NASH who require further clinical management and reduce unnecessary testing and invasive liver biopsies. Prospective studies are planned in NASH.

[8 – DISTINGUISHED ABSTRACT] *EX-VIVO* HUMAN 3D NASH MODEL AS A SCREENING-BASED DISCOVERY APPROACH FOR SELECTING AND PRIORITIZING DRUG CANDIDATES

Simon Ströbel[1], Jana Rupp[1], Katia Fiaschetti[1], Agnieszka Pajak[1], Katarzyna Sanchez[1], Mathieu Petitjean[2], Li Chen[2], Manuela Bieri[1], Armin Wolf[1], Sue Grepper[1], Francisco Verdeguer[1], Eva Thoma[1], Radina Kostadinova[1]

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Abstract Category: Pathogenesis, Translational Science, NAFLD/NASH, Liver Fibrosis, Humans
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Background: Non-alcoholic fatty liver disease (NAFLD) is an emerging chronic liver disease characterized by hepatic steatosis that often progresses into steatohepatitis (NASH). Poor translation of animal studies to humans have resulted in a lack of approved NAFLD/NASH-specific drug therapies. We have modeled NAFLD/NASH *ex vivo* using human microtissues technology as a high-throughput tool for drug discovery.

We present here a novel human 3D *in vitro* NASH model, which incorporates primary hepatocytes, Kupffer cells, liver endothelial cells, and hepatic stellate cells, for high-throughput-compatible drug efficacy testing.

Methods: We generated liver microtissues by culturing human primary hepatocytes, Kupffer cells, liver endothelial cells, and hepatic stellate cells in InSphero plates. Upon exposure to defined lipotoxic and inflammatory stimuli, including free fatty acids and LPS in media containing high levels of sugar and insulin, this 3D NASH model displayed pathophysiologically relevant features within 10 days of treatment. The methods for assessing characteristic markers for NASH included accumulation of intracellular triglycerides (bioluminescent assay), secretion of pro-inflammatory cytokines/chemokines (Luminex), and secretion of pro-collagens type I and III (HTRF/ELISA). Quantification of fibrosis based on Sirius Red-stained tissue slices was performed using the PharmaNest imaging platform.

Results: We observed increases in intracellular triglyceride content and the secretion of proinflammatory (e. g. IL-6, IL-1b, TNF-a) and profibrotic (e.g. IL-10, GRO-a, IP-10, MCP-1) cytokines/chemokines in the NASH-treated tissues as compared to the untreated controls. Further, we detected increased fibril collagen deposition, and increased secretion of procollagen type I/III peptides under NASH conditions. Whole transcriptome analysis of NASH-treated tissues versus control revealed activation of pathways and differential regulation of genes associated with lipid metabolism, inflammation, and fibrosis induction. Treatment with the anti-TGF-β antibody and ALK5i (TGF-βRI inhibitor) concentration dependently decreased secretion of pro-collagen type I/III. Decreased deposition of fibril collagens based on quantification of fibrosis of Sirius Red-stained tissues was observed in the presence of anti-TGF-β antibody and ALK5i. The results from the biochemical readouts of the NASH-treated tissues with drug clinical candidates (Selonsertib and Firsocostat) were in line with clinical observations.

Conclusion: In summary, this high-throughput and compatible 3D human NASH model represents a promising approach for NASH drug candidate efficacy selection early within the drug discovery process.

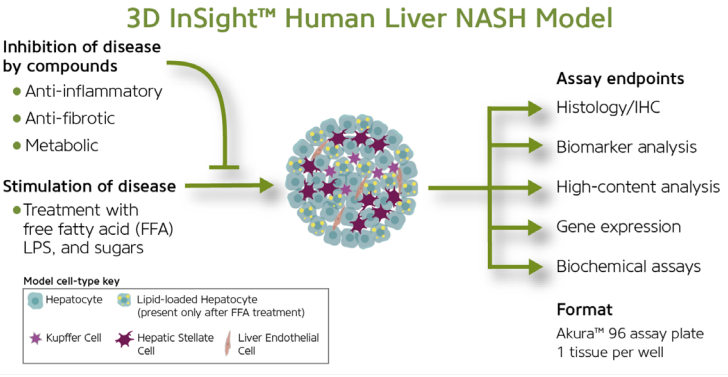

Figure 1. Human primary hepatocytes, Kupffer cells, stellate cells and liver endothelial cells were seeded and aggregated to form liver microtissues in Insphero plates. A specific metabolic and inflammatory stimulation led to the recapitulation of human NASH hallmarks by measuring specific endpoints.

[12 – DISTINGUISHED ABSTRACT]
INTRA- AND INTER-RATER RELIABILITY OF HISTOLOGIC DISEASE ACTIVITY MEASURES IN NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND DEVELOPMENT OF AN EXPANDED NAFLD ACTIVITY SCORE

Rish K. Pai, MD, PhD[1]; Vipul Jairath, MD, PhD[2,3,4]; Malcolm Hogan, MSc[4]; Guangyong Zou, PhD[3,4,5]; Oyedele A. Adeyi, MD[6]; Quentin M. Anstee, MD, PhD[7,8]; Bashar A. Aqel, MD[9]; Cynthia Behling, MD, PhD[10]; Elizabeth J. Carey, MD[9]; Andrew D. Clouston, MBBS, PhD[11]; Kathleen Corey, MD, MPH[12,13]; Brian G. Feagan, MD[2,3,4]; David Kleiner, MD, PhD[14]; Christopher Ma, MD, MPH[4,15,16]; Stefanie C. McFarlane, BMath[4]; Mazen Noureddin, MD[17]; Vlad Ratziu, MD, PhD[18]; Mark A. Valasek, MD, PhD[10]; Zoubair M. Younossi, MD, MPH[19,20]; Stephen A. Harrison, MD[21,22]; Rohit Loomba, MD, MHSc[23,24]

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Abstract Category: Diagnostic Procedures NASH/Liver Fibrosis
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Background/Aim: Histologic assessment of liver biopsies varies greatly in clinical trials of nonalcoholic steatohepatitis (NASH), with the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN) histologic scoring system being the current gold standard. However, this assessment is associated with intra- and inter-observer variability. Moreover, an expert panel previously determined in a Research and Development/University of California Los Angeles (RAND/UCLA) process that existing histologic scoring systems do not fully capture NASH disease activity and fibrosis. We aimed to evaluate the intra- and inter-rater reliability of existing histologic indices, the component items of these indices, and additional RAND/UCLA-identified items. We also correlated these measures with a disease activity visual analog scale (VAS) to propose an exploratory expanded nonalcoholic fatty liver disease (NAFLD) activity score (NAS) index comprising optimized items.

Methods: Forty liver biopsies representing the full spectrum of NAFLD were assessed by 4 liver pathologists who were blinded to clinical information. These central readers completed standardized training and scored indices and items twice, with ≥2 weeks between each assessment. Reliability was assessed using intra-class correlation coefficients (ICCs) and interpreted according to Landis and Koch benchmarks (slight, 0.00-0.20; fair, 0.21-0.40; moderate, 0.41-0.60; substantial, 0.61-0.80; almost perfect, 0.81-1.00). Correlations with the disease activity VAS were interpreted using Cohen's benchmarks (0.1, 0.3, and 0.5 indicate small, medium, and large effects, respectively).

Results: Existing NAFLD activity indices had substantial to almost perfect intra-rater reliability (ICC, 0.80-0.85) and moderate to substantial inter-rater reliability (ICC, 0.60-0.72). Substantial inter-rater reliability was demonstrated for ballooning degeneration items (ICC, 0.68-0.79), including those that extended scores from 0-2 to 0-4, and steatosis items (ICC, 0.72-0.80). However, steatosis measures were poorly correlated with the disease activity VAS (r = –0.02 to 0.12). Ballooning degeneration and Mallory-Denk bodies (MDBs) were used to develop an expanded NAS (intra-rater ICC, 0.90; inter-rater ICC, 0.80) on the basis of their large correlations with the disease activity VAS (r = 0.66-0.96). Fibrosis measures, including a staging system that expands measurements of bridging fibrosis, demonstrated substantial to almost perfect inter-rater agreement (ICC, 0.70-0.87).

Conclusions: Existing histologic indices and the expanded NAS are associated with almost perfect intra-rater reliability and moderate to substantial inter-rater reliability. Ballooning degeneration and MDBs correlated strongest with disease activity and were used for the expanded NAS. Future evaluation of the responsiveness of these measures is needed.

The content of this abstract has not been presented elsewhere.

[13 – DISTINGUISHED ABSTRACT]
INVESTIGATING CRV431 IN NASH PATIENTS: DATA FROM THE PHASE 2A AMBITION STUDY

Harrison S; Hobbs T; Mayo PR; Canizares C; Zhao C; Foster E; Ure D; Trepanier D; Foster R.

Abstract Category: Therapeutic Trials NASH/Liver Fibrosis
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Background: Global prevalence of nonalcoholic steatohepatitis (NASH) is increasing and is associated with significant morbidity and mortality with no approved pharmacotherapy. CRV431 is a clinical phase drug candidate that inhibits cyclophilin isomerases and demonstrated attenuated hepatic fibrosis in multiple NASH rodent models.

Methods: A Phase 2a Single-Blind, Placebo-Controlled trial (NCT04480710) was conducted at 10 U.S research sites in 43 subjects with presumed NASH Fibrosis stage 2 or 3. Primary endpoints assessed safety, tolerability, and pharmacokinetics (PK) of CRV431. Exploratory efficacy endpoints evaluated NASH biomarkers (transaminases, ELF-score, Pro-C3, Fibroscan, collagens, matrix metalloproteinases, whole blood transcriptome, and serum lipidome). CRV431 was dosed orally once daily at 75 mg (n=12), 225 mg (n=17) with matching placebo subjects (n=14) for 28 days with a 14-day safety follow-up. Adverse events were evaluated using Common Terminology Criteria for Adverse Events (CTCAE v5.0). PK was used to evaluate exposure and concentration-effect relationships.

Results: Safety: No deaths or Serious Adverse Events were reported. At 75 mg, 11 mild-moderate adverse events were reported by 5 subjects where 9 of the 11 adverse events were deemed unrelated to study drug. At 225mg, 18 adverse events were reported by 8 subjects with 1 Severe AE (constipation) and 4 mild AEs (constipation, diarrhea, headache & weight gain) which were classified as probably related to drug. No dose response in AEs was observed. Biomarkers: ALT decreased in 53.8%, 66.7%, 85.7% of the subjects in the placebo, 75 mg, and 225 mg cohorts, respectively. The magnitude of the reduction was positively correlated with higher baseline values and higher CRV431 concentrations. Mean Pro-C3 was (N=23),

reduced by 2.1 ng/mL in subjects where baseline Pro-C3 was ≥ 17.5 ng/mL. Discriminant analyses could correctly classify ALT and Pro-C3 responders with a misclassification error of 4% and 2%, respectively. Responders were more likely to be female and have Day14 CRV431 concentrations of at least 785.5 ng/mL and 882.5 ng/mL for ALT and Pro-C3, respectively. Transcriptome analysis revealed a concentration-dependent downregulation of a network of collagen and anti-inflammatory genes including COL6A5, COL7A1 (log2Fold = -4.7, p = 0.0052), COL8A2 (log2Fold = -4.8, p = 0.00076), COL13A1 (log2Fold = -2.4, p = 0.02), COL18A1 (log2Fold = -3.1, p = 0.03). Weighted gene correlational network analysis (WGCNA) identified separate gene modules where CRV431 regulated C6M (r = 0.72, $p < 10^{-200}$), Pro-C3 (r = 0.78, $p< 10^{-200}$) and ALT (r = 0.59, $p=8.9 \times 10^{-136}$) production. The observed predilection towards biomarker responders in females may be related to PK exposure and/or transcriptomic differences where a module denoted by gender was identified (r = 0.97, p = 1.7×10^{-88}). PopPK-PD modeling directly linked CRV431 concentration to serum ALT and Pro-C3 amounts. CRV431 exposures in presumed F2/F3 NASH subjects were within the 95% CI for exposure in healthy subjects.

Conclusion: Twenty-eight days of CRV431 dosing at 75 mg or 225 mg was safe and well-tolerated. Exposures in presumed F2/F3 NASH subjects were similar to those observed in healthy subjects. Changes in ALT, Pro-C3, and C6M were consistent with a positive effect of CRV431 in NASH subjects. Transcriptomics confirmed regulation of genes associated with anti-fibrosis and anti-inflammatory effects. CRV431 exposure can directly predict ALT and Pro-C3 levels at 28 Days. This Phase 2a data supports further clinical development of CRV431 in a NASH Phase 2b study.

[16 – DISTINGUISHED ABSTRACT] LIVER-DISTRIBUTED FXR AGONIST TERN-101 DEMONSTRATES FAVORABLE SAFETY AND EFFICACY PROFILE IN NASH PHASE 2A LIFT STUDY

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Category: Therapeutic Trials NASH/Liver Fibrosis
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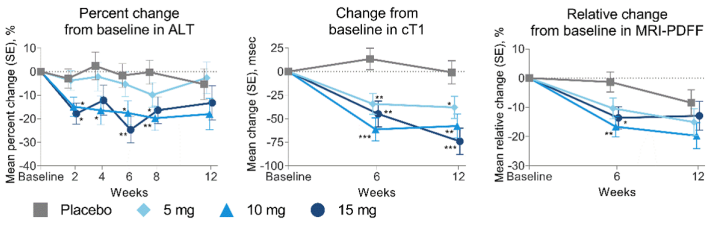
Background: Farnesoid X receptor (FXR) agonists hold promise for non-alcoholic steatohepatitis (NASH) treatments but have had safety/tolerability constraints. TERN-101 is a potent, non-steroidal FXR agonist with enhanced liver distribution, being developed for NASH treatment.

Methods: LIFT was a double-blind, placebo-controlled, phase 2a study. Adults with clinical or histological NASH without cirrhosis, MRI proton density fat fraction (MRI-PDFF) of ≥10%, and alanine aminotransferase (ALT) level of ≥43 IU/L (men) or ≥28 IU/L (women) were randomized to placebo or TERN-101 (5, 10, or 15 mg) for 12 weeks. The primary endpoint was safety; secondary and exploratory endpoints included change in ALT, MRI-PDFF, and corrected T1 (cT1) relaxation time.

Results: A total of 100 patients (65% female, mean age 50.6 yrs) were randomized and received TERN-101 5 mg (N=25), 10 mg (N=26), 15 mg (N=23), or placebo (N=26). At baseline, patients had mean BMI of 36.6 kg/m^2, ALT of 57.2 IU/L, MRI-PDFF of 21.3%, liver stiffness of 10.3 kPa, and cT1 of 935.6 msec. Adverse events (AEs) were overall similar across treatment groups; most were mild or moderate, with no discontinuations due to AEs. Two SAEs, both unrelated to study drug, occurred (1 in placebo, 1 in 15 mg group). The most common AE was pruritus, occurring in 4 (16%), 3 (11.5%), 4 (17.4%), and 0 patients receiving TERN-101 5, 10, 15 mg, and placebo, respectively; events were mild (localized, 73%) or moderate (27%), did not result in discontinuation, and most resolved with continued dosing. No significant % change in LDL cholesterol was observed with 5 or 10 mg TERN-101; 15 mg significantly increased LDL, with a peak mean change of 21% at Week 8. Significant HDL % decreases occurred with TERN-101 at Weeks 4 and 8 and returned to baseline in the 5 and 10 mg groups at Week 12. ALT declined by Week 2, with 20.8%, 44%, 38.1%, and 16% of patients decreasing ≥30% at Week 12 for 5, 10, 15 mg, and placebo, respectively. cT1 declined significantly at 6 and 12 weeks, with mean changes of -38.0 (P=0.0325), -57.7 (P=0.0021), -74.0 (P=0.0002), and -0.8 msec for 5, 10, 15 mg TERN-101 and placebo, respectively at Week 12. MRI-PDFF decreased at Week 6 for the higher doses (P<0.05).

Conclusion: TERN-101 was overall safe and well-tolerated, with no discontinuations due to AEs. Treatment resulted in significant decreases in ALT, cT1, and MRI-PDFF. Future investigation of TERN-101 is warranted.

Figure: TERN-101 improves ALT, cT1, and MRI-PDFF



*p-value<0.05; **p-value<0.01;***p-value<0.001; SE, standard error

[28 – DISTINGUISHED ABSTRACT] UTILIZATION OF THE MAST (MRI-PDFF-MRE-AST) SCORE TO PREDICT NASH ON LIVER BIOPSY IN MAESTRO-NASH AND ASSESS RESPONSE TO RESMETIROM IN MAESTRO-NAFLD-1

Mazen Noureddin[1]; Naim Alkhouri[2]; Brandon Hill[3]; Rebecca A. Taub[3]; and Stephen A Harrison[4]

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Abstract Category: Therapeutic Trials NASH/Liver Fibrosis
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Background: Resmetirom is a liver-directed, orally active, highly selective THRβ agonist in Phase 3 development for the treatment of NASH with stage 2/3 fibrosis. MAESTRO-NASH (NCT03900429) is a 52-week Phase 3 registrational, double blind, placebo-controlled NASH clinical trial to study the safety and efficacy of resmetirom in biopsy-confirmed F1-F3 NASH patients. MAESTRO-NAFLD-1 is a 52-week Phase 3 randomized double-blind placebo-controlled NASH clinical trial to study safety and biomarker effects of resmetirom in presumed NASH patients with F1-F4 fibrosis identified using non-invasive biomarkers and imaging (NCT04197479). Use of MRI and AST (MAST) and Fibroscan and AST (FAST) scores for non-invasive identification of patients with nonalcoholic steatohepatitis (NASH) with significant fibrosis has been described before.[1] The purpose of this analysis was to investigate the utility of these scores in the MAESTRO studies.

Methods: Data was assessed in over 2000 patients with fibroscan, MRE and MRI-PDFF; ~1000 patients with fibroscan, MRE, MRI-PDFF and baseline liver biopsies from the screening programs of MAESTRO-NASH and MAESTRO-NAFLD-1 to predict the relationship between MAST and FAST and baseline liver biopsy. Patients were required to have at least three metabolic risk factors (metabolic syndrome), a fibroscan VCTE with kPa ≥8.5 (MAESTRO-NASH), and kPa 5.5 to <8.5 kPa (MAESTRO-NAFLD-1), controlled attenuation parameter (CAP) ≥280, eligibility labs and magnetic resonance imaging proton density fat fraction (MRI-PDFF) ≥8%. Using Spearman's correlation, associations were assessed between screening MAST and liver biopsy NAS and fibrosis scores.

Results: Ninety-one % of those meeting pre-screening, lab test, fibroscan and MRI-PDFF requirements in MAESTRO-NASH had fibrosis stage >=1 on liver biopsy (F4 4%, F3 42%, F2 27%, F1B 10%, F1A/C 17%). MAST score showed a correlation (rho=0.531; Figure) than FAST score (rho=0.413) to biopsy fibrosis stage. FAST and MAST also showed a correlation with NAS (rho=0.449, p<0.0001; rho=0.487, p<0.0001, respectively). Open label non-cirrhotic NASH patients (MAESTRO-NAFLD-1) with baseline MRE >=2.9 kPa, 100 mg resmetirom lowered MAST score at week 16 by 26% and at week 52 by 48% (p=0.015 (week 52)). In patients with baseline MAST >1.2 (median baseline MRE 3.4 kPa (IQR 3.0,4.0)) MAST score was reduced at week 16 by 50% and at week 52 by 63% with a 0.134 (0.045, 0.139) median reduction in score.

Conclusion: These data suggest that MAST is predictive of fibrosis stage in NASH and of the level of NASH activity (steatosis, inflammation and ballooning) in the NASH liver and may better distinguish early fibrosis stages than FAST. In the absence of a liver biopsy, elevated MAST score in the setting of metabolic syndrome may predict NASH with significant liver fibrosis.

Spearman Correlations with FAST-MAST and Components of FAST/MAST

	NAS		Fibrosis Stage	pvalue
	rho	p-value	rho	p-value
FAST	0.449	<0.0001	0.413	<0.0001
MAST	0.487	<0.0001	**0.531**	<0.0001
Fibroscan				
VCTE	0.145	<0.0001	0.368	<0.0001
CAP	0.040	0.073	-0.045	0.044
MRE	0.317	<0.0001	**0.593**	<0.0001
MRI-PDFF	0.246	<0.0001	-0.153	<0.0001
AST	0.480	<0.0001	0.355	<0.0001

Higher F score was assigned to F1B (moderate fibrosis) than F1A/C. F1B has a higher incidence of active NASH (>=4) than F1A/C

[29 – DISTINGUISHED ABSTRACT] LPCN 1144 THERAPY DEMONSTRATES HISTOLOGIC BENEFITS IN THE PHASE 2 LIFT STUDY IN NONALCOHOLIC STEATOHEPATITIS (NASH) SUBJECTS

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Abstract Category: Therapeutic Trials NASH/Liver Fibrosis – Humans

Background and Aims: NASH is the fastest growing chronic liver diseases and can progress to cirrhosis, HCC, and death. NASH is a serious condition with great unmet medical need. Low testosterone (T) is associated with the presence of NASH. LPCN 1144 is an oral prodrug of endogenous T developed for noncirrhotic NASH treatment. The recently-completed LiFT (NCT04134091) study investigated LPCN 1144 for safety and efficacy in men with biopsy-confirmed NASH.

Methods: LiFT was a randomized, double-blind, placebo-controlled, 36-week treatment study that enrolled 56 men with NASH and F1-3 fibrosis. Subjects were randomized 1:1:1 to three arms administered twice daily (Treatment A: n=18, 142 mg T equivalent, Treatment B: n=19, 142 mg T equivalent with 238 mg of d-alpha tocopherol equivalent, and Placebo: n=19, matching placebo). The primary endpoint was change from baseline (BL) in hepatic fat fraction via MRI-PDFF at 12 weeks. A key secondary endpoint was the rate of NASH Resolution with no worsening of fibrosis at Week 36 (FDA Phase 3 guidance). Additionally, slides were digitized and analyzed using the FibroNest platform, which reports a continuous score for fibrosis severity. Reported p-values are comparisons to placebo.

Results: ILiver fat was significantly reduced in both treatment groups at Week 12, with up to a mean absolute decrease of 9.4% (p<0.05) in subjects with BL MRI-PDFF >5%. Both LPCN 1144 treatment arms met the endpoint of proportion of subjects with NASH resolution and no worsening of fibrosis (Placebo: 0%; A: 46% (p<0.05); B: 69% (p<0.001). While there was no statistical difference in rates of fibrosis improvement by NASH CRN staging (p>0.05), digital pathology assessment revealed a numerical improvement in fibrosis (parenchymal tissue-normalized phenotypic fibrosis composite score) for both treatment arms. Statistically significant reductions of ALT and AST were observed during study visits: up to a mean of 24.5 U/L decrease (p<0.01) in ALT, and 12.3 U/L decrease (p<0.01) in AST.

During the 36 weeks of treatment, the observed rate and severity of Treatment Emergent Adverse Events in both the treatment arms were comparable to the placebo arm. There were no reported cases of HCC or drug-induced liver injury.

Conclusions: LPCN 1144 resolved NASH with no worsening of fibrosis, improved liver injury markers, and reduced liver fat in men with biopsy confirmed NASH and fibrosis in the LiFT study. LPCN 1144 was well tolerated, with rates and severity of AEs similar in all arms. These data support the potential for this novel approach as a treatment of NASH.

[32 – DISTINGUISHED ABSTRACT]
CHANGE IN SERIAL LIVER STIFFNESS MEASUREMENT BY MAGNETIC RESONANCE ELASTOGRAPHY AND OUTCOMES IN NON-ALCOHOLIC FATTY LIVER DISEASE

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Abstract Category: Diagnostic Procedures NASH/Liver Fibrosis
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Background & Aims: The impact of disease progression in non-alcoholic fatty liver disease (NAFLD) on liver outcomes remains poorly understood. We aimed to investigate NAFLD progression using longitudinal liver stiffness measurements (LSM) by serial MREs and the association with liver outcomes.

Methods: All adult NAFLD patients who underwent at least 2 serial MREs for clinical evaluation at Mayo Clinic, Rochester between 2007-2019 were identified from the institutional database. Progression and regression were defined based on LSM change of 19% above or below 19% of initial LSM, respectively, based on QIBA consensus. The association between change in LSM and liver-related outcomes occurring after the last MRE was examined using time-to-event analysis.

Results: A total of 128 participants underwent serial MREs (53% female, median age 59 years). The median time between paired MREs was 3.4 (range 1-10.7) years. NAFLD progression (LSM of +0.61 kPa/year) was identified in 17 patients (13.3%). NAFLD regression (-0.40 kPa/year) occurred in 35 patients (27.3%). Stable LSM was noted in 76 participants (59.4%). In NAFLD without cirrhosis at baseline (n=75), cirrhosis development occurred in 14% of LSM progressors and 2.9% of non-progressors (p=0.059) over a median of 2.7 years follow-up from the last MRE (Figure 1A). Among those with compensated cirrhosis at baseline MRE (n=29), events (decompensation, liver transplant or death) occurred in 100% of LSM progressors and 19% of non-progressors (p<0.001) over a median of 2.5 years follow-up after the last MRE.

Conclusion: Noninvasive monitoring of LSM by conventional MRE is a valuable method of longitudinal NAFLD monitoring and risk estimation of liver-related outcomes in NAFLD.

Figure 1A. Probability of cirrhosis development in NAFLD with LSM progression versus stable/regression on serial MREs. Time 0 is date of *last* MRE.

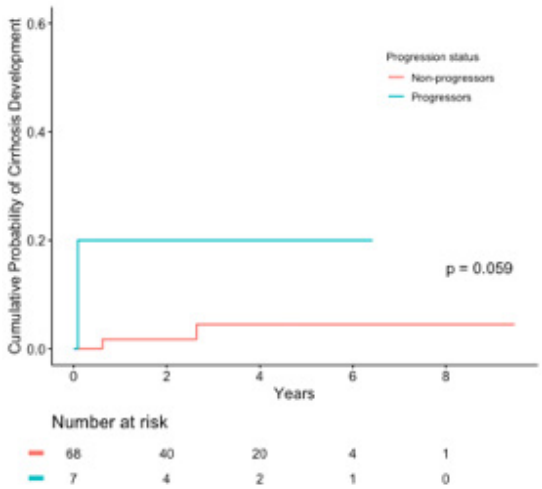
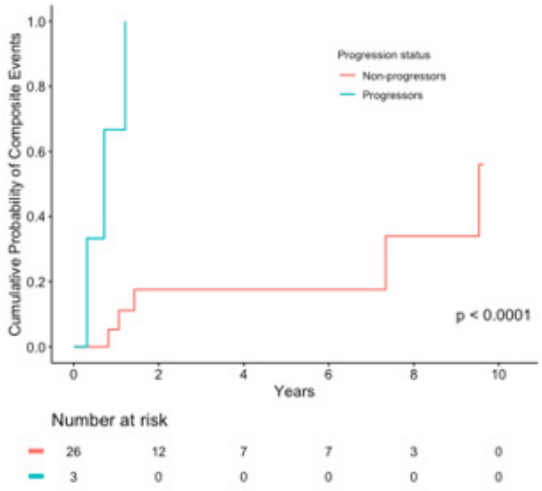


Figure 1B. Probability of decompensation, liver transplantation or death in compensated NASH cirrhosis with LSM progression versus stable/regression on serial MREs. Time 0 is date of *last* MRE.



[9]
HEALTH OUTCOMES AND RISK ASSESSMENT IN CHRONIC LIVER DISEASE (HERALD): A LARGE SWEDISH RESEARCH PLATFORM

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Abstract Category: Clinical Epidemiology – NASH/Liver Fibrosis
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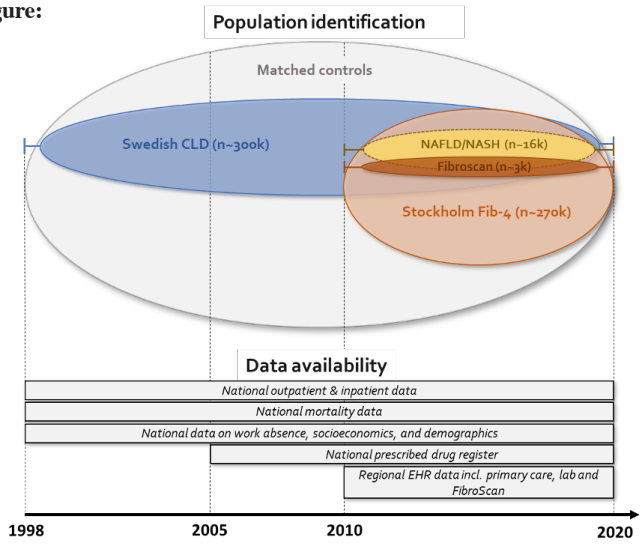
Background and Aims: The 'HEalth outcomes and Risk Assessment in chronic Liver Disease' (HERALD) study is a multi-stakeholder Swedish research-platform linking national and regional registries to investigate the epidemiology and risk factors of liver outcomes, resource-use and costs, in patients with chronic liver diagnoses (CLD) or liver-related laboratory tests. HERALD is also planned to include data from the National Diabetes Register and other countries during 2022, and is open to international collaboration.

Methods: A CLD cohort will consist of all patients ≥ 18 years with ≥ 1 CLD diagnosis (ICD-10) in the Swedish Patient Register, or primary care from the Stockholm region. A Fib-4 cohort will consist of patients with laboratory tests (AST, ALT and platelets), required for estimating the non-invasive Fibrosis-4 (Fib-4) score in all care settings in Stockholm. All patients will be linked with longitudinal data on diagnoses, comorbidities, healthcare utilization, prescribed medicines, mortality, work absence, socioeconomic status and demographics. For a subset, other laboratory data and data on transient elastography (FibroScan) are extracted from electronic health records (EHR) and FibroScan-devices, respectively. High-risk subgroups and costs will be compared with matched controls from the general population.

Results: A feasibility study was completed in 2020 and ethical approval for HERALD was granted in August, 2020. During 2001-2019, the number of patients with NAFLD was 16,285, with at least 46,122 patient years of follow-up. The number of patients with chronic HCV, AIH or PBC were n=53,602, n=5,337 and n=5,247, respectively. 200,000 to 300,000 patients with CLD are expected, partly overlapping with the ~270,000 patients expected in the Fib-4 cohort.

Conclusion: This study is the result of a research collaboration between academia and analytical and pharmaceutical industry. HERALD will be the largest data collection to date to estimate a contemporary prevalence of liver disease, as well as risk for advanced fibrosis in a broad, unselected population of healthcare-seeking individuals in Sweden, with and without recorded liver diagnoses. Furthermore, HERALD will utilize clinical and non-clinical information to characterize patients with different risk profiles and to estimate long-term societal burden associated with severe liver outcomes in clinical practice over a 20-year period.

Figure:



[21]
PNPLA3 RS738409 AND RISK OF FIBROSIS IN NAFLD: EXPLORING MEDIATION PATHWAYS THROUGH INTERMEDIATE HISTOLOGICAL FEATURES

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Abstract Category: Clinical Epidemiology – NASH/Liver Fibrosis

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Background & Aims: It is unclear whether rs738409 (p.I148M) missense variant in patatin-like phospholipase domain-containing 3 (PNPLA3) rs738409 promotes fibrosis development by triggering specific fibrogenic pathways or by creating an unfavorable microenvironment by promoting steatosis, inflammation, and ultimately fibrosis. We tested the hypothesis that intermediate histologic traits, including steatosis, lobular and portal inflammation, and ballooning may determine the effect of rs738409 on liver fibrosis among individuals with NAFLD.

Methods: This is a cross-sectional analysis involving 1153 non-Hispanic White with biopsy-confirmed NAFLD enrolled in the NASH CRN studies. A mediation model including multiple mediators was conducted to examine the effect of rs738409, by decomposing its total effect on fibrosis severity into direct and indirect effects, mediated by steatosis, lobular inflammation, ballooning, and portal inflammation. Since age, gender, BMI, type 2 diabetes mellitus (T2DM), and non-heavy alcohol intake may be significantly associated with both the mediators and the outcome, all mediation analyses were adjusted by these relevant confounding factors.

Results: The total effect of rs738409 on fibrosis was β=0.188 (95% CI: 0.091-0.284). The direct effect of rs738409 on fibrosis removing mediators' effect was β=0.096 (95% CI: 0.016-0.176), which represents 51% of the total effect of rs738409 on fibrosis. The indirect effect of rs738409 on fibrosis through all mediators' effect was β=0.092 (95% CI: 0.034-0.151), signifying the 49% of the total effect of rs738409 on fibrosis. Among all mediators, the greatest estimated effect size was displayed by portal inflammation (β=0.082, 95% CI: 0.047-0.120), meaning the 89% of the total indirect effect of rs738409 on fibrosis (**Table 1**).

Conclusion: Our findings suggest that 51% of the total effect of the rs738409 G allele on fibrosis severity could be explained by a direct pathway, supporting the hypothesis that rs738409 likely promotes fibrosis development by activating specific fibrogenic pathways. The other half of the total effect of rs738409 appears to be mediated primarily through portal inflammation.

Table 1. Role of intermediate histology traits as mediators between *PNPLA3* rs738409 and risk of fibrosis. Results based on covariate-adjusted causal mediation analyses including multiple mediators in parallel.

	Bootstrapped estimates (n=10,000)		
	Estimates *	95% confidence intervals	SEs
Total effect of rs738409 †	0.188	0.091-0.284	0.049
Direct effect of rs738409 ‡	0.096 **	0.016-0.176	0.041
Percentage	51%	-	-
Indirect effect through all mediators §	0.092 **	0.034-0.151	0.029
Percentage mediated	49%	-	-
Indirect effect of through each mediator §			
Steatosis (0-3)	-0.011 **	-0.023 to -0.002	0.005
Percentage mediated	-12%	-	-
Ballooning (0-2)	0.012	-0.022 to 0.048	0.018
Percentage mediated	13%	-	-
Lobular inflammation (0-3)	0.008 **	0.001-0.019	0.005
Percentage mediated	9%		
Portal inflammation (0-2)	0.082 **	0.047-0.120	0.018
Percentage mediated	*89%*	-	-

* Bootstrapped β coefficients.
Analysis adjusted for age, gender, BMI, type 2 diabetes mellitus (T2DM), and non-heavy alcohol intake.
† Effect of rs738409 on the risk of fibrosis including the mediator (intermediate histology features) effects.
‡ Effect of rs738409 on the risk of fibrosis excluding the mediator (intermediate histology features) effects.
§ Effect of rs738409 on the risk of fibrosis through the mediator (intermediate histology features).
If the 95% bias-corrected CIs do not contain zero, the associations are considered significant. The double star symbol (**) represents statistically significant effects.

The abstract has not been presented elsewhere.

[24]
PREVELANCE OF NON ALCOHOLIC FATTY LIVER DISEASE, ITS COMPLICATIONS AMONG EMPLOYEES AT BANHA UNIVERSITY HOSPITAL, EGYPT

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Abstract Category: Clinical Epidemiology – NASH/Liver Fibrosis
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Background: Non Alcoholic Fatty liver Disease(NAFLD) encompasses a spectrum of diseases prognostically sub-categorized into non-progressive non-alcoholic fatty liver (NAFL), progressive non-alcoholic steatohepatitis (NASH), and NAFLD-cirrhosis. Between 20% and 33% of patients with NAFLD develop progressive nonalcoholic steatohepatitis (NASH) with fibrosis, which in turn can lead to cirrhosis, decompensated liver disease, and liver-related mortality. Beyond the association with HCC, NAFLD was also associated with a small but significantly increased risk of developing pancreatic cancer, kidney/bladder cancer, and melanoma

Methodology: This was cross sectional study at Banha University Hospital among employees. Inclusion Criteria: All subjects was appear healthy with and without DM or hypertension, also obese or non. Exclusion Criteria: Any chronic liver disease, Hepatitis C virus patients (HCV) , Hepatitis B virus patients(HBV) and autoimmune liver disease. Age of the subjects from 20-60 years old both males and females. All investigations done accordingly includes liver function, lipid profile. Fatty Acid Binding protein 1 by Elisa. Abdominal ultrasound for grading of fatty liver and dopler for external carotid intima media thickness. All subjects whom have fatty liver by abdominal ultrasound included in group 1 NAFLD, and whom do not have fatty liver by abdominal ultrasound included in group 2.both groups was age and sex matched.

Results: NAFLD was detected in 56.4% of participants. It was more in urban, elder and obese subjects. NAFLD-patients had higher frequency Diabetes, hypertension, hypothyroidism and fatty pancreas than NAFLD-free subjects. L-FABP levels were higher in NAFLD-patients than non-NAFLD (3.68±1.84vs.2.88±2.19;P=0.08). There were significant positive correlations between L-FABP(P=0.02),HOMA-IR(P=0.02) and carotid intimal thickness (P<0.001).

Conclusion: The high prevalence of NAFLD among Benha University employees was linked to old age, obesity and endocrinal disorders. NAFLD is associated with systematic disorders such as fatty pancreas with impaired glucose metabolism, and atherosclerosis with potential cardiac affection. L-FABP is a novel surrogate biomarker for fatty acid disorders especially atherosclerosis and fatty liver.

Key Words: Non-Alcoholic Fatty Liver Disease (NAFLD); fatty pancreas; Liver Fatty Acid Binding protein (L-FABP); Homeostasis model assessment estimate of insulin resistance (HOMA-IR); Carotid Intimal thickness (CIT)

The project was funded from Banha University Research Center.
Submitted for publication at Japanes Journal of Gastroenterology November 2021. Clinicaltrial.gov **NCT04367012**

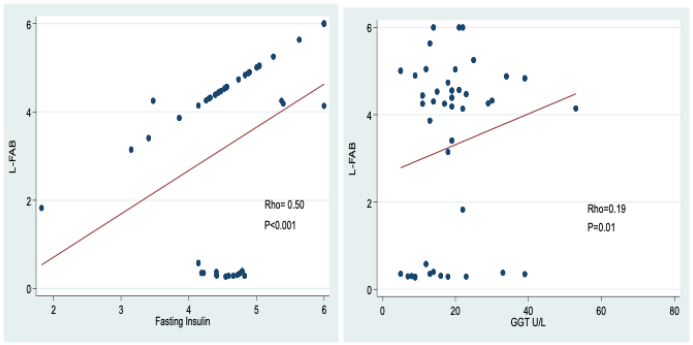

Figure (1): Correlation between serum L-FABP levels and fasting insulin levels (Panel A) and GGT levels (Panel B)

[26]
STATIN PRESCRIPTION BEFORE AND AFTER CARDIOVASCULAR EVENTS IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE COMPARED TO MATCHED CONTROLS

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Abstract Category: Clinical Epidemiology – NASH/Liver Fibrosis
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Background & Aims: Patients with non-alcoholic fatty liver disease (NAFLD) often have comorbid diseases such as hyperlipidemia and are at high risk of cardiovascular disease (CVD). As a first line lipid-lowering drug, statins are widely used for primary and secondary CVD prevention. However, there have been concerns about underprescribing statins for patients with NAFLD owing to fear of hepatoxicity. We aimed to describe and compare patterns of statin prescription before and after CVD events in patients with NAFLD to the general population.

Methods: The study participants were derived from the EpiCir cohort of all patients diagnosed with NAFLD between 1987 to 2016 from the Swedish National Patient Register (NPR) and their controls (1:10 matching on age, sex, and municipality) from the general population. Study participants who survived a CVD event of a stroke or myocardial infarction from NPR were enrolled and linked to the Swedish Prescribed Drug Register available from 2006 to 2016 to track drug prescription before and after a CVD event. Statin prescription before and within six months of CVD events was determined.

Results: Among 10,023 patients with NAFLD and 96,313 matched controls, 2,195 individuals (n=623, 6.2 % of NAFLD; n=1572, 1.6% of matched controls) survived a CVD event during 2006 to 2016. The mean (standard deviation) age of CVD diagnosis was 68.9 (11.0) and 52.1% were male. At enrollment, patients with NAFLD had worse metabolic profiles than the controls. The proportion of statin ever prescribed before CVD was 48.1% for NAFLD and 26.7% for controls (p<0.001). Six months prior to the CVD event, 31.8% of patients with NAFLD and 17.6% of matched controls had a statin prescription (p<0.001). Approximately 10% of study participants discontinued statin therapy after CVD, but this was offset by new users after CVD. There was no difference in statin prescribed within six months after a CVD event between patients with NAFLD (65.7%)

and controls (62.6%) (p=0.20). The prescription of other drugs (i.e., beta-blockers, aspirin) after CVD was significantly higher for patients with NAFLD than controls.

Conclusions: Statins were not underprescribed for patients with NAFLD before or after CVD compared to general population also with a CVD event. Patients with NAFLD were more likely to have prescriptions of other drugs after a CVD event suggesting that they had a worse metabolic profile. With recent evidence of no increased mortality after a CVD for patients with NAFLD in this cohort, this difference in drug therapy might have an impact on mortality.

Table. Drugs use before and after cardiovascular events by non-alcoholic fatty liver disease status

	NAFLD	Matched cohort	*p*-value
Number of participants	623	1572	
Statins use			
User before CVD	198 (31.8)	277 (17.6)	<0.001
User who stopped after CVD	14 (7.1)	32 (11.6)	0.103
Nonusers before CVD	425 (68.2)	1295 (82.4)	<0.001
Nonusers who started after CVD	225 (52.9)	741 (57.2)	0.123
User after CVD	409 (65.7)	986 (62.6)	0.199
Other drugs user after CVD			
Ezetimib	14 (2.3)	14 (0.89)	0.011
Beta-blockers	391 (62.7)	625 (39.8)	<0.001
Aspirin	380 (61.0)	817 (52.0)	<0.001
Other antiplatelets	3 (0.2)	1 (0.1)	0.881
Calcium channel blockers	162 (26.0)	525 (33.4)	0.001
ACE inhibitors	379 (60.8)	817 (52.0)	<0.001
ARBs	121 (19.4)	248 (15.8)	0.039
GLP1-RA	13 (2.1)	1 (0)	<0.001
SGLT-2 inhibitors	4 (0.6)	2 (0.1)	0.037
Metformin	135 (21.7)	152 (9.7)	<0.001

Abbreviations: NAFLD: non-alcoholic fatty liver disease; CVD: cardiovascular disease; ACE: Angiotensin-converting-enzyme; ARBs: Angiotensin II receptor blockers; GLP1-RA: Glucagon-like peptide-1 receptor agonist; SGLT-2: Sodium-glucose co-transporter-2
Values are n (%)v

[5]
COMBINED MR ELASTOGRAPHY AND PDFF PHANTOM FOR QUALITY ASSURANCE OF NAFLD/NASH CLINICAL STUDIES

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Background/Aim: Non-alcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are characterized by elevated liver fat and fibrosis[1-3]. In the past decade, magnetic resonance imaging (MRI) proton-density fat fraction (PDFF) and magnetic resonance elastography (MRE) tissue stiffness measurements have emerged as non-invasive alternatives to biopsy for quantitative assessment of liver fat and fibrosis. PDFF and MRE measurements are frequently used clinically to evaluate patients with known or suspected NAFLD or NASH and are used as endpoints for clinical trials evaluating new NAFLD/NASH therapeutic agents. Quantitative PDFF reference standards (phantoms) are currently available for quality assurance[4,5] and MRE phantoms are available to evaluate the technical success of MRE methods[6]. However, currently available phantoms mimic only a single tissue property and current MRE phantoms do not provide a quantitative reference for quality assurance. A phantom in a single compact unit that simultaneously and quantitatively mimics PDFF and stiffness would more realistically mimic diseased liver and would enable robust and convenient quality assurance for clinical trials and clinical practice.

This study was aimed at designing and validating a multi-PDFF, multi-stiffness quantitative phantom in a single compact unit, through the development of chemical formulations for composite materials that simultaneously span the clinically relevant ranges of liver PDFF and liver tissue stiffness for NAFLD/NASH studies.

Methods: A three-layer multi-PDFF, multi-stiffness quantitative phantom (Figure 1) was developed by stacking layers of emulsified bovine gelatin and oil at various concentrations. The stacked phantom was fabricated by making one emulsion, pouring it, letting it cool and cure, and then repeating the process for each subsequent layer. This stacked-layer design was selected so that the in-plane dimension of each PDFF/stiffness layer was the full diameter of the phantom. Maximizing the in-plane dimension is important to ensure enough mechanical wavelengths across the phantom for accurate MRE values to be calculated[6].The manufacturing process required a total elapsed time of three days (one day per layer) due to the need for each layer to cure completely before pouring the next layer.

The phantom was imaged on a 3.0T clinical MRI system (Signa Premier, GE Healthcare, Waukesha, WI) using a commercial MR elastography system (Resoundant, Rochester, MN USA) and 48-channel head coil. The MRE passive driver and a rubber friction pad were fixed to the flat cylindrical surface of the phantom by wrapping the phantom-driver unit with a neoprene belt. MRE stiffness images were acquired using a spin-echo EPI-based MR elastography acquisition (MR Touch, GE Healthcare) (20cm FOV, 32x32 matrix, 8mm slice thickness, 3 slices, 60Hz frequency, 10% amplitude).

Quantitative PDFF maps were acquired using an investigative version of a confounder-corrected chemical shift encoded MRI acquisition (IDEAL IQ, GE Healthcare) (28cm FOV, 2x2mm resolution, 2mm slice thickness, 66 slices, TR=9.5, FA=4°, first/last echo=1.15/7.76, 8 echoes interleaved in two echo trains).

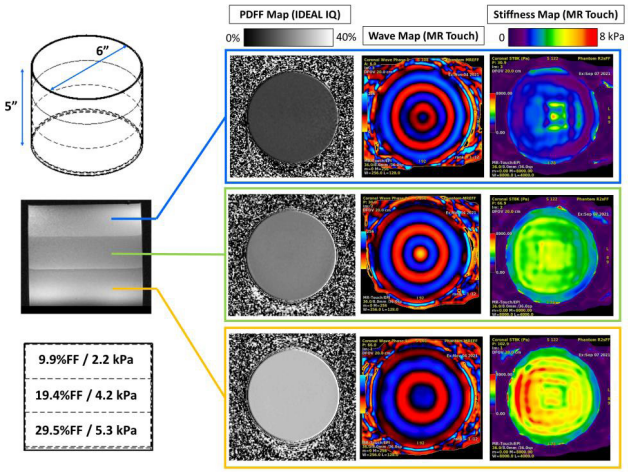

Figure 1. *Layout and quantitative measurements of a three-layer phantom that mimics the simultaneous presence liver fat and fibrosis(stiffness).*

Results: A multi-layer MRI/MRE phantom was created with three compartments of unique PDFF/Stiffness formulations measuring 9.9%/2.2kPa, 19.4%/4.2kPa, and 29.5%/5.3kPA, as shown in Figure 1.

Conclusions: In this work, we successfully created a multi-PDFF, multi-stiffness quantitative phantom in a single compact unit. The PDFF and

stiffness values span the clinically relevant range of liver fat and stiffness values seen in patients with NAFLD/NASH.

Acknowledgements: The authors wish to acknowledge Phil Rossman for helpful discussions regarding MRE phantom development, and GE Healthcare who provides research support to the University of Wisconsin.

References: 1. Ahmed A, et al. Clin Gastroenterol Hepatol. 2015; **2.** Lai M, et al. Gastroenterology clinics of North America. 2019; **3.** Reeder SB, et al. Magn Reson Imaging Clin N Am. 2010; **4.** Hu H, et al. Radiology. 2021.; **5.** Panagiotopoulos N, et al. ISMRM 2020; 6.Arunachalam SP, et al. Magn Reson Med. 2017.

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[2]
ACCURACY OF VELACUR™ AI POWERED LIVER GUIDE IN IDENTIFICATION OF LIVER

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Abstract Category: Diagnostic Procedures NASH/Liver Fibrosis
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Background/Aim: As non-invasive testing for liver disease becomes widespread and a part of clinical care pathways, it is imperative that these tests are accurate and easy to use by any medical practitioner. Velacur™ is a new point of care liver health assessment test that can be performed by any user as it offers unique features: an ultrasound image of the liver which provides users with visual feedback on where to position the ultrasound probe to collect the best data, as well as a new AI powered liver guide. This guide is an interface feature which creates a mostly transparent overlay on top of the ultrasound image to help users identify liver, continue to reinforce the initial Velacur™ training, and learn what a variety of liver ultrasound images look like.

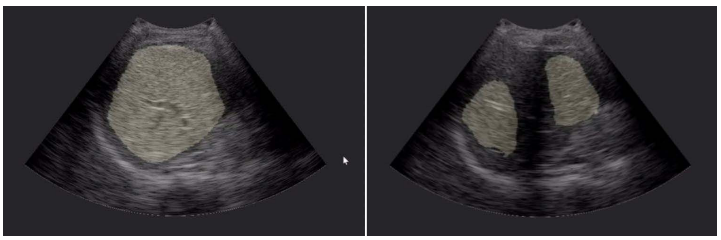

Figure 1. *Example of the liver guide as a transparent overlay in a case with a good view of the liver (left) and with rib artifacts (right).*

Methods: The liver guide is a machine learning based algorithm that automatically segments the liver from surrounding tissue and acts as an assistant for image interpretation, providing guidance to new users about the features and quality of the ultrasound image at a given location.

The original data used to train the liver guide was collected during a clinical trial sponsored by Sonic Incytes Medical Corp. Data included healthy volunteers and participants with increased levels of fibrosis caused by NAFLD/NASH or prior Hepatitis C infection. 65 patients and volunteers with 150 images/per patient, for a total of approximately 9,750 images, were used for training. In each image, the liver was manually segmented by one of three expert users. The segmentations were then reviewed by the lead expert for quality assurance and overall consistency.

For validation testing, the algorithm was tested on two different data sets: one smaller quantitative set, and one larger qualitative set. These images came from 15 patients not included in the training set. These scans were also collected by different users than those who completed the scans for the training set.

The first set of testing data was comprised of 50 images. These images were carefully selected to represent both difficult (ambiguous) images, easy images (liver is very clear), and images with artifacts (such as rib shadowing, kidney or lungs). This data set was segmented by an expert sonographer.

In addition to segmenting the images, the expert graded the images on two scoring systems:

1. Difficulty in segmentation (segmentation score)
As some images are much more difficult to segment even for a human expert, it is important to understand the challenge level of the image. A scale of 1 to 5 was used to define the challenge levels, where **5 is very clear where the liver is** and **1 is impossible to tell where the liver is.**

2. Comparison of liver segmentation (detection score
The expert was then shown the results of the liver guide and asked to score the results based on a scale where **5 is exactly as they would have segmented it**, and **1 is totally incorrect.**

This data set was also measured for overlap between the expert segmentation and the liver guide results. The Dice coefficient is used to measure the pixel overlap of two different segmentation methods; in this case, the manual segmentation and the resulting liver detection mask.

*Dice = (2*overlap)/(manual segmentation + algorithm segmentation)*

Although a very common measure of overlap, the Dice coefficient decreases very quickly as the segmentation diverges.

The second set of 510 images were randomly selected from the testing set of 15 patients, with an even distribution of images from each patient. This set of images were only scored by the expert on the two descriptive scales.

Results: The Dice overlap measures the percentage of overlap between the expert segmentation and the liver guide segmentations. 32/50 (64%) images had a Dice measure greater than 0.7, which is considered to be excellent. Only 8 images had a Dice < 0.6.

These bubble charts show that for both data sets, the Velacur™ liver guide algorithm performs well compared to the expert on the majority of easy and difficult images.

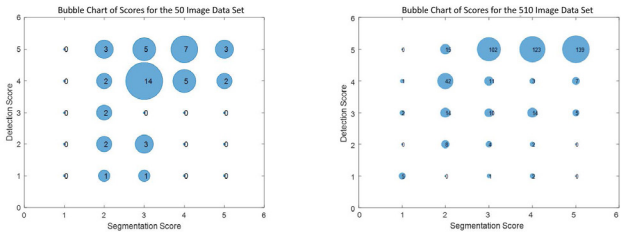

Figure 2. *Bubble chart results of the two data sets, showing that the Velacur™ liver guide performs well compared to expert expectations.*

Conclusions: Velacur™ 's new AI powered liver guide provides accurate guidance to non-expert users on where the liver is located within the image. Initial usability testing also shows increases in user confidence and a decreased learning curve, with fewer user errors during scanning.

[11]
HMG-COA REDUCTASE INHIBITORS (STATINS) AND METFORMIN ARE ASSOCIATED WITH PRESERVATION OF HEPATIC FUNCTION AND LESS PORTAL-SYSTEMIC SHUNTING IN ADVANCED CHRONIC LIVER DISEASE

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Abstract Category: Diagnostic Procedures NASH/Liver Fibrosis
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Background: Disease progression of CLD and nonalcoholic steatohepatitis (NASH) is variable and may be influenced by comorbid conditions and concomitant drug therapy. We used the HepQuant SHUNT test, to evaluate the impact of NASH, diabetes (DM), and drug therapy on hepatic function and portal-systemic shunting in subjects with CLD enrolled in the SHUNT-V study.

Methods: The 270 subjects for this preliminary analysis had either compensated cirrhosis, fibrosis stage F3 with platelet count <175,000, or Child-Pugh B without refractory ascites, refractory encephalopathy, or history of variceal hemorrhage. HepQuant tests involved dosing [24-^{13}C] cholic acid, IV, and [2,2,4,4-^{2}H] cholic acid, PO, and blood sampling at t=0, 5, 20, 45, 60, and 90 minutes. Serum was analyzed for cholate concentrations by LC-MS/MS and a disease severity index (DSI), assessing hepatic function, and portal systemic shunt fraction (SHUNT) were calculated. Lower DSI indicates better hepatic function; lower SHUNT denotes less portal-systemic shunting.

Results: Subject characteristics (means or percentages) were: age 61.6 years, body weight 95.3 kg, BMI 33.4, male 49%, white race 92%, Hispanic ethnicity 14%; 64% were obese, 50% had NASH, and 48% were taking diabetic drug therapy. Compared to other etiologies for CLD, NASH subjects were older, heavier, had higher BMI and more were obese. In contrast, NASH and non-NASH subjects had similar blood tests, clinical scores, elastography and endoscopic findings. In uni-variable regression, NASH, DM, diabetic drug therapy, and statins were associated with lower DSI and SHUNT. In multi-variable regression of prescribed medications, statins and metformin exhibited the strongest associations with lower DSI (p=0.002,p=0.06) and SHUNT (p<0.015, p<0.05). A multi-variable regression model including statins, DM, NASH, and diabetic drug therapy demonstrated that use of statins was the predominant factor associated with both lower DSI and lower SHUNT (see Tables). The estimated effect of combined treatment with statins and diabetic drugs was a 21% lowering of both DSI and SHUNT.

	Impact on SHUNT%		Impact on DSI	
	Decline in SHUNT%	p	Decline in DSI	p
Statin	-6.3%	0.0132	-3.3269	0.0025
Metformin	-5.9%	0.0475	-2.4337	0.0574
Diabetes Diagnosis	-1.4%	0.64	-0.7239	0.5736
NASH Diagnosis	-1.3%	0.61	-0.2246	0.8343

Conclusion: In the SHUNT-V study of clinically stable but advanced CLD, concomitant use of statins was independently associated with preserved hepatic function and reduced portal-systemic shunting. The HepQuant SHUNT test may be useful for quantifying treatment effects in CLD.

[14]
LIVER TRANSPLANT OUTCOMES IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS-ASSOCIATED CIRRHOSIS

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Abstract Category: Disease Management of NASH/Liver Fibrosis Patients (Including Comorbidities)
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Background: The prevalence of nonalcoholic fatty liver disease (NAFLD) has increased dramatically worldwide due to the obesity epidemic. NAFLD is now the most common cause of chronic liver disease. Chronic inflammation in NAFLD leads to liver injury resulting in nonalcoholic steatohepatitis (NASH), which can progress to liver failure and cirrhosis. NASH is currently the third most common indication of liver transplantation worldwide, and is projected to become the leading indication for liver transplantation in the next 10 to 20 years. As obesity rates continue to rise, with NASH prevalence paralleling this trend, it is important to evaluate outcomes of patients who receive liver transplants because of NASH cirrhosis. The limited studies evaluating long-term outcomes and overall survival of liver transplantation for NASH patients have had varying outcomes. Some showed comparable patient survival between NASH patients and patients who had liver transplants due to other indications. In contrast, other studies showed increased mortality for NASH patients. Prior studies varied in their practice pattern, diagnostic criteria for NASH-related cirrhosis, and use of control groups, making it difficult to reach a universal consensus about liver transplantation due to NASH. We assessed the outcomes of liver transplant in patients with end-stage liver disease (ELD) from NASH.

Methods: This is a single center retrospective analysis of all adult patients (18 years or older) who underwent a liver transplant at a metropolitan hospital in Dallas, Texas from January 1, 2010 to December 31, 2020. Demographic, clinical, and transplant-related outcomes data were collected from electronic medical records, a large internal transplant database, and from the United Network for Organ Sharing database. Demographic data included age at transplant, gender, and race. Clinical data included body mass index (BMI), Model for ELD (MELD) score prior to transplant, and comorbidities. Transplant-related data included liver only or combined liver-kidney type transplant, one- and three-year patient survival, and one- and three-year graft survival. Only patients who underwent a primary transplant were included. Patients were stratified into two groups based on the etiology of their underlying liver disease: NASH or non-NASH. NASH was defined by histological features and clinical diagnosis. The NASH group included patients with cryptogenic cirrhosis with the NASH phenotype. Groups were compared using the Mann-Whitney U test, the Chi square test, or the Fisher's exact test.

Results: A total of 677 patients underwent a primary liver transplant between 2010 and 2020. Of these, 112 (16.5%) were transplanted for NASH and 565 (83.5%) were transplanted for other etiologies (non-NASH). The mean age of the NASH patients was higher than the non-NASH patients (59.3 (9.3) vs 56.0 (10.0) years; P< 0.002). Females, in comparison to males, had higher odds of being in the NASH group than the non-NASH group (OR = 1.96; 95% CI = 1.27 – 3.01; p = 0.001). Caucasians (OR = 4.94; 95% CI = 1.51 – 16.13; p = 0.008) and Hispanics (OR = 8.33; 95% CI = 2.49 – 27.90; p = 0.001) had higher odds of having a NASH-related transplant compared to African Americans. A greater proportion of the NASH patients were obese (BMI >30 kg/m2) than the non-NASH patients (47.0% vs 37.8%; p=0.0185). Diabetes at the time of listing was more prevalent in the NASH cohort compared to the non-NASH cohort (53.6% vs 28.9%; OR = 2.85; 95% CI = 1.84 – 4.40; p <0.0001). Those with NASH had higher odds of having a combined liver-kidney transplant than a liver transplant alone compared to the non-NASH group (OR = 2.10; 95% CI 1.16 – 3.67; p = 0.006). The percentage of liver transplants done for NASH increased throughout the study period from 12.9% in 2010 to 33.9% in 2020. Mean hospital length of stay (p = 0.1815), mean MELD scores (p = 0.06), one-year survival (p = 0.272), three-year survival (p = 0.232), one-year graft survival (p = 0.600), and three-year graft survival (p = 0.453) were comparable between the NASH and non-NASH patients.

Conclusion: Our 10-year observational cohort study revealed a substantial increase in the number and proportion of liver transplants performed for NASH cirrhosis between 2010 and 2020. This large increase coincides with the ongoing uncontrolled obesity epidemic. Patients with NASH are likely to have metabolic-related comorbidities, including obesity, diabetes, higher age of onset, hypertension, hyperlipidemia, and coronary artery disease. These comorbidities can make post-transplant care difficult as these patients can be prone to infections, poor wound healing, NAFLD recurrence, and even death. Although statistical significance was not achieved, both one year (89.2% vs 92.39%) and three-year (83.04% vs 87.26%) patient survival was lower in NASH patients, which can be expected given their comorbidities and medical complexities. In patients transplanted for NASH careful patient selection and optimization prior to transplantation remains critical in maintaining acceptable graft outcomes and overall patient survival.

Table 1. Comparison of NASH and non-NASH patient demographics and outcomes

	NASH	Non-NASH
	n=112	n=565
Age at Transplant (Median)	59 (55-67)	56 (51-63)
Sex Female (%)	50.0	33.8
BMI at Transplant	30.1	28.8
MELD at Transplant (Median)	25 (18-32)	23 (15-31)
Diabetes at Transplant (%)	53.5	28.8
Race (%)		
White	60.7	60.8
Black	2.6	13.2
Hispanic	35.7	21.2
Asian	0.8	4.6
Organ (%)		
Liver	80.3	89.5
Liver & Kidney	19.6	10.4
1 Year Patient Survival (%)	89.2	92.3
3 Year Patient Survival (%)	83.0	87.2
1 Year Graft Survival (%)	97.3	95.9
3 Year Graft Survival (%)	97.3	95.2
LOS in Days (Median)	10 (7-14)	9 (7-14)

[27]
UNCOVERING FRONTLINE HEALTHCARE PROFESSIONALS' GAPS IN NASH KNOWLEDGE

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Abstract Category: Disease Management of NASH/Liver Fibrosis Patients (Including Comorbidities)
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Background: The obesity epidemic in the United States has set the stage for an increasing prevalence of nonalcoholic steatohepatitis (NASH), a serious, progressive form of nonalcoholic fatty liver disease (NAFLD). NASH pathogenesis is multifactorial, and it is important that healthcare professionals (HCPs) understand its metabolic origins and that a management approach with a multispecialty team is best suited to address the many facets of the disease and its related comorbidities. With promising new treatments on the horizon, HCPs on the front lines of patient care must possess the knowledge and competence to identify patients at risk for NASH and treat with evidence-based therapy. To that end, Clinical Care Options (CCO) has been providing a series of NASH educational programs to community physicians, nurse practitioners (NPs), physician assistants (PAs), and pharmacists. The 2 most recent NASH programs, which were supported by unrestricted medical education grants, provided us with rich outcomes data that characterized HCPs' current knowledge gaps regarding NAFLD and NASH.

Aim: The goal of this analysis was to determine knowledge gaps among multidisciplinary HCPs pertaining to clinical aspects of NASH. This information could inform future medical education that closes knowledge gaps and arms frontline HCPs with the tools to effectively manage patients with NASH.

Methods: CCO produced 2 online educational programs on NASH between 2019 and 2021.

Program 1: *Hot Topics in NASH Webinar Series*
November 7, 2019 - July 15, 2020

Program 2: *NASH Core Curriculum: A Comprehensive Online Resource Center*

January 29, 2021 - November 9, 2021

We utilized pre/post questions to mine data on HCPs' gaps.

- Questions measuring HCPs' knowledge and competence were asked at baseline ("pre") and then repeated after the education was delivered ("post").
- To uncover key educational gaps, we identified questions with the lowest correct responses at baseline and persistence of incorrect responses post education.

The NASH topics evaluated as pre/post questions were *NAFLD/NASH pathogenesis, determining risk factors for NASH, diagnostic testing, current NASH treatments, and emerging NASH treatments*.

- Questions with the lowest baseline scores suggested the greatest knowledge gaps.
- Analyses comparing posteducation test responses with baseline responses determined the impact of the education on gaps regarding key clinical aspects of NASH.

Results:

HCP Demographics
Program 1: N = 1673; MD: 48%; RPh: 15%; NP/PA: 7%; RN: 7%; other: 22%
Program 2: N = 17,101; MD: 58%; RPh: 10%; NP/PA: 8%; RN: 5%; other: 19%

Baseline Gaps
The questions with the fewest correct responses at baseline (lowest scores) were used to identify the greatest NASH knowledge gaps. Among the subset of learners who answered both pre and post questions, the lowest baseline scores—all well below 50%—were observed for the following topics.

- **Determining Risk Factors for NASH**
  - ◊ Evaluating for risk factors: 37% (n = 274)
  - ◊ Liver enzymes as risk factors: 46% (n = 116)
- **Current NASH Management**
  - ◊ Weight management: 34% (n = 155)
  - ◊ Approaches with currently available treatments: 42% (n = 53)
  - ◊ Drug therapy for patients with NASH and type 2 diabetes: 48% (n = 116)
- **Emerging NASH Therapies**
  - ◊ Mechanism of action of emerging therapies: 47% (n = 206)
  - ◊ FDA approval requirements: 37% (n = 131)

In addition, baseline scores for both programs were low overall.

- *Program 1:* 4 of 5 baseline questions had scores between 34% and 47%.
- *Program 2:* 5 of 6 baseline questions had scores between 37% and 52%.

Education Impact on Gaps
In both programs, the education had a significant impact on addressing HCPs' gaps, as demonstrated by sizable posteducation score lifts ranging from 59% to 96% (P <.0001 for 12 of 14 questions). Further details on posteducation increases will be presented.

Conclusions: This analysis demonstrates that the multispecialty teams of HCPs (MD, NP, PA, RPh) who care for patients with NAFLD and NASH in the community have significant NASH knowledge gaps, especially in areas of **NASH risk factors, current NASH management,** and **emerging NASH therapies**. Frontline HCPs are well-suited to initiate interventions with patients who have NASH risk factors such as obesity, so it is imperative that they recognize these conditions as NASH risk factors and employ strategies to mitigate them. Similarly, HCPs should have the knowledge and competence to initiate available NASH treatments as part of primary care. It also is important that HCPs understand the metabolic rationale for emerging NASH treatments that target NASH pathogenesis so they can appropriately incorporate these therapies when they become available.

This abstract has not been presented elsewhere.

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[6]
DIRECT ANTI-INFLAMMATORY AND ANTI-FIBROTIC EFFECTS OF A NOVEL LONG-ACTING GLUCAGON/GIP/GLP-1 TRIPLE AGONIST, HM15211, IN THIOACETAMIDE-INDUCED MOUSE MODEL OF LIVER INJURY AND FIBROSIS

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Abstract Category: Experimental/Basic Science, Liver Fibrosis, Non-Humans
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Background/Aims: HM15211 is a novel long-acting triple agonist consisting of rationally designed Glucagon/GIP/GLP-1 triple agonist conjugated to human IgG FC fragment via short PEG linker. Previously, therapeutic benefits of HM15211 were demonstrated in diet-induced animal models of NASH and/or fibrosis. Here, we evaluate direct anti-inflammatory and -fibrotic effects of HM15211 in TAA (thioacetamide)-induced liver injury and severe fibrosis mouse, and investigate underlying MoA.

Methods: To induce liver injury and liver fibrosis, gradually increased dose of TAA (thioacetamide) was injected to mouse for 12 weeks. HM15211 was administered during last 10 weeks. Hepatic hydroxyproline (HP) contents were measured and Sirius red staining was conducted. qPCR was performed to evaluate relevant marker gene expression. Multiplex assay was performed to measure blood level of pro-inflammatory cytokines. For mechanistic study, THP-1 cell and LX2 cell were used.

Results: HM15211 treatment significantly reduced HP content (-51% *vs*. vehicle, $p<0.01$), Sirius red positive area (-65% *vs*. vehicle, $p<0.001$), and fibrosis score (0.7 for HM15211 *vs*. 3.0 for vehicle, $p<0.001$) in TAA mice. Considering baseline fibrosis score at week 2 (1.0), HM15211 could confer both potential reversal effect on pre-existing fibrosis and prevention effect on fibrogenesis. Consistently, expression of hepatic marker genes

for fibrosis (i.e. collagen-1α1 and collagen-1α1) and inflammation (i.e. F4/80 and TNF-α) were significantly reduced in HM15211-treated group. Furthermore, multiplex analysis revealed that HM15211 treatment was associated with robust reduction across pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and etc. Significant reduction in blood level of liver enzymes was also confirmed. Mechanistically, PMA/LPS-induced THP-1 cell adhesion and subsequent pro-inflammatory cytokine secretion were significantly attenuated by HM15211. TGF-β-induced collagen production was also reduced in LX2 cell. Based on *in vitro* results, observed benefits in TAA mice might primarily results from direct anti-inflammatory and -fibrotic effects of HM15211.

Conclusion: HM15211 markedly improved liver inflammation and fibrosis in TAA mice, and related MoAs were elaborated by *in vitro* studies. Together with previous results, generalized anti-inflammatory and -fibrotic effects of HM15211 were corroborated. Thus, HM15211 could be a novel therapeutic option for fibrosis due to NASH. Human study is ongoing to assess the clinical relevance of these findings.

[18]
METABOLIC, BIOCHEMICAL, HISTOLOGICAL, AND TRANSCRIPTOMIC EFFECTS OF A LONG-ACTING FGF-21 ANALOGUE IN THE GAN DIET-INDUCED OBESE AND BIOPSY-CONFIRMED MOUSE MODEL OF NASH

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Abstract Category: Experimental/Basic Science, Liver Fibrosis, Non-Humans
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Background: Fibroblast growth factor 21 (FGF-21) plays a key role in hepatic lipid metabolism and holds great promise as therapeutic target for non-alcoholic steatohepatitis (NASH). The long-acting FGF-21 analogue efruxifermin has in a recent phase 2 clinical trial (BALANCED) demonstrated promising efficacy for both NASH resolution and improvement in fibrosis stage as compared to placebo controls (Harrison et al. Nature Medicine, 2021). The present study aimed to evaluate the therapeutic efficacy of the long-acting FGF21 analogue PF-05231023 in the GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model of NASH with hepatic fibrosis.

Methods: Male C57BL/6J mice were fed the GAN diet high in fat, fructose, and cholesterol for 34 weeks prior to study start. Only animals with liver biopsy-confirmed NAFLD Activity Score (NAS) ≥5 and fibrosis (stage ≥F1) were included and stratified into treatment groups. DIO-NASH mice received (SC, BIW) vehicle (n=14) or PF-05231023 (10 mg/kg, n=14) for 12 weeks. Vehicle-dosed chow-fed C57BL/6J mice (n=6) served as lean healthy controls. Pre-to-post liver biopsy histopathological scoring was performed for within-subject evaluation of NAS and Fibrosis Stage. Terminal quantitative liver histology and RNA sequencing as well as blood and liver biochemistry was assessed.

Results: Compared to vehicle treatment, PF-05231023 induced a body weight loss of approx. 8% from baseline and reduced hepatomegaly, plasma transaminases as well as plasma/liver lipids (total cholesterol, triglycerides) in DIO-NASH mice. Notably, PF-05231023 treatment demonstrated ≥2 point significant improvement in NAS and 1-point significant improvement in Fibrosis Stage. Therapeutic effects of PF-05231023 were supported by reduced quantitative histological markers of steatosis (lipids, hepatocytes with lipid droplets) and inflammation (number of inflammatory foci, galectin-3). PF-05231023 did not improve histomorphometry markers of fibrosis (PSR, collagen 1a1), albeit a marker for activated stellate cells (α-SMA) was significantly reduced, suggesting attenuation of fibrogenesis activity. In addition, PF-05231023 improved NASH-associated hepatic transcriptome signatures, including lowered expression of genes associated with inflammation and fibrogenesis.

Conclusions: The long-acting FGF-21 analogue PF-05231023 improved metabolic, biochemical, and liver histological markers of steatosis, inflammation and fibrogenesis in biopsy-confirmed DIO-NASH mice. Furthermore, PF-05231023 treatment improved clinical-derived endpoints for NAS and Fibrosis Stage. These findings highlight FGF21 as a promising therapeutic agent for fibrosing NASH and further validate clinical translatability of the GAN DIO-NASH mouse model.

[25]
SEMAGLUTIDE IMPROVES CARDIOMETABOLIC PARAMETERS IN DIET-INDUCED OBESE NASH HAMSTERS

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Abstract Category: Experimental/Basic Science, Liver Fibrosis, Non-Humans
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Background/Aim: Cardiovascular disease is the leading cause of deaths in nonalcoholic steatohepatitis (NASH) patients. Mouse models, while widely used for drug development, do not fully replicate human NASH nor integrate the associated cardiac dysfunction, i.e. heart failure with preserved ejection fraction (HFpEF). To overcome these limitations, we established a nutritional hamster model developing obesity, NASH and HFpEF. Here we evaluated the effects of the GLP-1 receptor agonist semaglutide (SEMA).

Methods: Hamsters were fed with a free choice diet, which presents hamsters with a choice between control chow (CC) or high fat/cholesterol (HFC) diet, and normal water (NW) or 10% fructose water (FW). After 20 weeks of diet, obese hamsters were treated s.c. QD for 5 weeks with vehicle or SEMA.

Results: Compared with vehicle, SEMA induced a lower HFC/FW and higher CC/NW intake, leading to a 17% body weight loss ($p<0.01$) and a 48% lower visceral fat mass ($p<0.001$). SEMA significantly reduced fasting glycemia, hyperinsulinemia and HOMA-IR index (-77%, $p<0.0001$). SEMA decreased plasma total cholesterol levels (-24%, $p<0.001$) and hypertriglyceridemia (-50%, $p<0.001$). Although SEMA did not improve NAFLD activity scoring and fibrosis score significantly, significant improvement in liver steatosis was observed with lower liver weight (-28%, $p<0.0001$ vs. vehicle) and liver triglycerides levels (-25%, $p<0.01$). SEMA showed substantial benefits on HFpEF with significantly improved E/A, E'/A' and E/E' ratios measured by echocardiography.

Conclusion: SEMA improves cardiometabolic parameters in the obese hamster. This preclinical model will be useful for validating novel drugs or combination therapies for the treatment of NASH and associated HFpEF.

[7]
EDP-297: A NOVEL, HIGHLY POTENT, FARNESOID X RECEPTOR AGONIST: RESULTS OF A PHASE 1 STUDY IN HEALTHY SUBJECTS

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Abstract Category: Pathogenesis, Translational Science, NAFLD/NASH, Liver Fibrosis, Humans
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Background and Aims: EDP-297 is a potent FXR agonist under development for the treatment of nonalcoholic steatohepatitis (NASH). EDP-297 attenuates NASH-relevant pathways of steatosis, liver injury, inflammation, and apoptosis both in vitro and in vivo. Here, we present pharmacokinetic (PK), and pharmacodynamic (PD), food effect (FE), and safety results of a single ascending dose (SAD) and multiple ascending dose (MAD) phase 1 study in healthy subjects (HS).

Method: A randomized, double-blind, placebo-controlled (PBO) study was conducted to evaluate the safety, tolerability, PK/FE, and PD of single and multiple doses of EDP-297 in HS. Subjects received EDP-297 as a single dose (SAD, 5 cohorts, 20-600μg) or once daily (QD) for 14 days (MAD, 5 cohorts, 5-90μg), (6 active: 2 PBO/cohort), except in the SAD food effect cohort (8 active: 2 PBO). PD measurements included fibroblast growth factor 19 (FGF-19) and 7-α-hydroxy-4-cholesten-3-one (C4).

Results: A total of 82 subjects (n=42 in SAD; n=40 in MAD) received at least one dose of EDP-297 or PBO. EDP-297 was generally well tolerated. No severe adverse events or discontinuations due to adverse events (AEs) in SAD and MAD (up to 60μg) were observed. Most AEs were mild and not related/unlikely related to study drug. In the SAD part, pruritus was observed in 300μg (n=2), 600μg (n=2), PBO (n=1); during the MAD part, pruritus was reported in 30μg (n=1), 60μg (n=2), and 90μg (n=4), PBO (n=2): the majority were mild or moderate, except for n=4 severe cases at 90μg MAD, with n=1 that led to drug discontinuation. There were no clinically significant abnormal laboratory or abnormal ECG findings, except for n=1 Grade 2 ALT elevation (MAD 90ug) that was not associated with other liver enzyme abnormalities. There were no clinically meaningful changes in the lipid profile, except for a trend towards decrease in HDL and increase in LDL at MAD 90ug; and mean lipids values were within normal range during the entire study. Plasma exposures increased with increasing single and multiple doses, with mean t1/2 following multiple doses of ~9-12.5 hours. No food effect was observed. Strong FXR target engagement was demonstrated, with increase in FGF-19 and decrease in C4 up to 95% and 92%, respectively.

Conclusion: Overall, EDP-297, a potent and selective FXR agonist, was safe and well tolerated with PK suitable for once daily oral dosing, a strong target engagement and no food effect.

[19]
MODELLING BIOLOGICAL MECHANISMS OF A PNPLA3 POLYMORPHISM IN EX-VIVO 3D HUMAN LIVER MICROTISSUE FOR NASH PROGRESSION AND DRUG EFFICACY.

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Abstract Category: Pathogenesis, Translational Science, NAFLD/NASH, Liver Fibrosis, Humans
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Background and Aims: Non-alcoholic steatohepatitis (NASH) is a progressive severe disease characterized by lipid accumulation, inflammation and fibrosis in the liver. Single nucleotide polymorphisms (SNPs) at specific loci have revealed differential propensity to develop NASH. Among them, "GG" rs738409 located in patatin-like phospholipase domain-containing protein 3 (PNPLA3), is highly frequent (30-50%) and results in the I148M amino acid change. PNPLA3 is a triacylglycerol lipase localized in lipid droplets but its function in the context of NASH is not fully understood and yet represents an interesting therapeutic target. The aim of this study was to investigate the effect of PNPLA3 I148M mutant on the development of NASH hallmarks in a 3D human liver *ex-vivo* culture model.

Methods: Human 3D NASH model of spheroidal, scaffold free co-culture was developed of single donors of primary hepatocytes, Kupffer cells, liver endothelial cells and hepatic stellate cells. The hepatocytes derived from either wild-type or PNPLA3 I148M mutant donors. Human liver microtissues were exposed to defined lipotoxic and inflammatory stimuli including free fatty acids, high sugar levels, insulin and LPS. To determine NASH progression triglyceride content, inflammatory markers and fibrotic markers were quantified by biochemical, histological and immune-based assays (Luminex).

Results: We show that NASH hallmarks are recapitulated in NASH-treated versus control-treated liver microtissues by showing an increase of triglyceride content and the secretion of the inflammatory markers IL-6, MIP-1α, TNF-α, IL-10, MCP-1 and IL-8. Furthermore, The increased fibril collagens deposition and secretion of procollagen type I and III peptides was detected under NASH conditions in wild type co-cultures. Whole transcriptome analysis of NASH-treated versus control wild-type tissues revealed activation of pathways and differential regulation of genes associated with key lipid metabolism, inflammation and fibrosis induction. Importantly, treatment with anti-NASH drug candidates (Selonsertib and Firsocostat) affected biochemical endpoints indicative of disease progression and the results were to a large extent in line with clinical observations. Importantly, 3D NASH liver microtissues carrying the PNPLA3 I148M mutation in hepatocytes exacerbated NASH phenotype compared to a wildtype counterpart including increased higher triglyceride content and pro-collangen type I secretion.

Conclusion: Stimulated human *ex-vivo* liver microtissues recapitulate human hallmarks of NASH and represent a valuable model for the identification of novel pharmacological strategies and selection of candidates. We furthermore demonstrate the worsening effect of PNPLA3 (I148M) in NASH by generating a new model of study with a defined genetic background for a better efficiency of drug candidates selection and personalized medicine application.

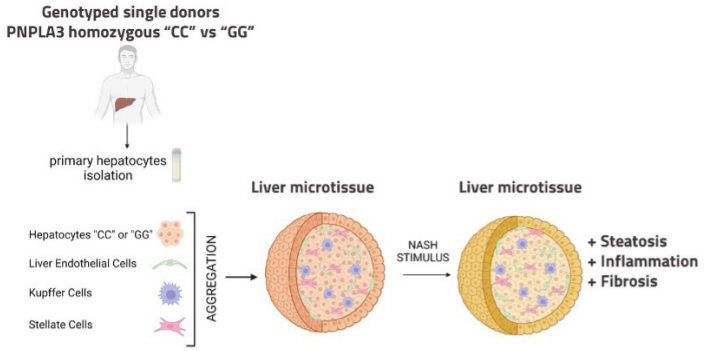

Figure 1. Liver microtissues were generated from wildtype or PNPLA3(GG) single donors to generate liver microtissues *ex-vivo* including liver endothelial cells, Kupffer cells and stellate cells following aggregation in Insphero plates. A NASH stimulus was applied to the liver microtissues to mimic human NASH hallmarks.

[22]
POTENT AND SELECTIVE SMALL MOLECULE HSD17B13 INHIBITOR INI-678 DECREASES FIBROTIC MARKERS IN NASH LIVER-ON-CHIP

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Abstract Category: Pharmacology
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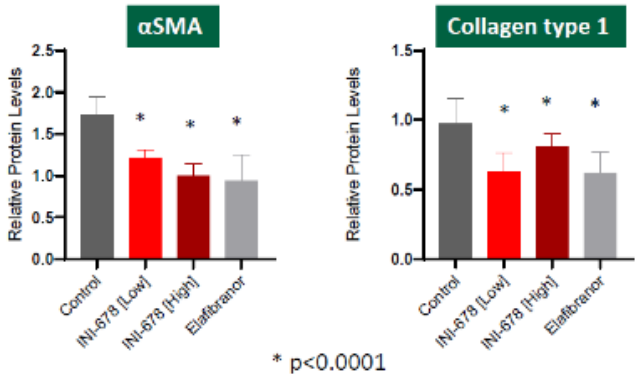
Background: HSD17B13 is a lipid body-associated protein of poorly defined function. Polymorphisms rendering HSD17B13 enzymatically inactive protect against NASH, cirrhosis, and liver cancer and are associated with reduced hepatic inflammation and fibrosis suggesting that inhibitors of HSD17B13 could be useful treatments for NASH.

Methods: The ability of purified human HSD17B13 to oxidize retinol, estradiol and LTB3 was assessed by quantitation of product formation. Liver-on-chip (LOC) co-cultures containing primary human hepatocytes, homozygous for the active HSD17B13 allele; Kupffer cells, and stellate cells were prepared in LC12 microphysiological system plates and were cultured in a high fat containing media to induce a NASH phenotype. On Day 4, cells were exposed to novel, selective inhibitors of HSD17B13 or a DMSO vehicle control for the remainder of the 20 days. NASH phenotype LOC co-cultures were analyzed for fibrotic markers αSMA and collagen type 1 by immunohistochemistry, and media were analyzed for cell health markers albumin and LDH, by ELISA and activity respectively.

Results: We identified potent and selective small molecule HSD17B13 inhibitors using a multipronged screening approach and optimization by structure-aided drug design resulting in compounds including INI-678. INI-678 inhibits HSD17B13-catalyzed oxidation of retinol, estradiol and LTB3 with low nM potency against purified enzyme. INI-678 does not inhibit the other members of the HSD17B family tested nor enzymes and receptors in an off-target panel. Hepatocytes in LOC co-cultures retained robust expression of albumin over all 20 days of the experiment in the presence and absence of INI-678. No evidence of cytotoxicity, as measured by LDH activity in media, was detected in INI-678 or vehicle NASH phenotype LOC co-cultures. INI-678 treatment decreased αSMA (35%, p<0.0001) and collagen type 1 (42%, p<0.0001) compared to high fat-treated, vehicle control in LOC co-cultures. Additional HSD17B13 small molecule inhibitors have reproduced this decrease in fibrotic protein levels in the NASH LOC co-cultures.

Conclusion: Small molecule inhibition of HSD17B13 with INI-678 caused a decrease in fibrotic markers in response to high fat media in LOC co-cultures consistent with decreased fibrosis in NASH subjects carrying inactive HSD17B13 alleles suggesting a precision approach to the treatment of NASH subjects with active HSD17B13.



[23]
PRECLINICAL AND EARLY CLINICAL CHARACTERIZATION OF PXL065 - DEUTERIUM-STABILIZED (R)-PIOGLITAZONE – A POTENTIAL NOVEL ORAL THERAPY FOR NASH

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Abstract Category: Pharmacology
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Background: Pioglitazone (Pio) is an effective therapy for NASH1-3. However, adverse effects driven by PPARγ activity - weight gain and edema - limit its use. Pio is a racemic mixture of 2 stereoisomers that rapidly interconvert both *in vitro* and *in vivo*. PXL065, a novel chemical entity, is the deuterium-stabilized form of R-Pio. The aims of our ongoing studies are to characterize the profile of PXL065 as a potential therapy for NASH.

Methods:

- PXL065 (and deuterium-stabilized S-Pio, d-S-Pio) was profiled in preclinical assays designed to assess its mechanism of action, PK, potential efficacy in NASH, and differentiation from Pio.
- Phase 1 studies were performed in healthy subjects compared to branded Pio (Actos®).
- A 36-week randomized Phase 2 trial in patients with biopsy-proven non-cirrhotic NASH is ongoing. DESTINY 1 includes 3 doses of PXL065 (7.5, 15, and 22.5 mg QD) vs. placebo with 1:1:1:1 randomization. Available screening data (n=205) including biopsy results were analyzed to ascertain screen failure determinants.

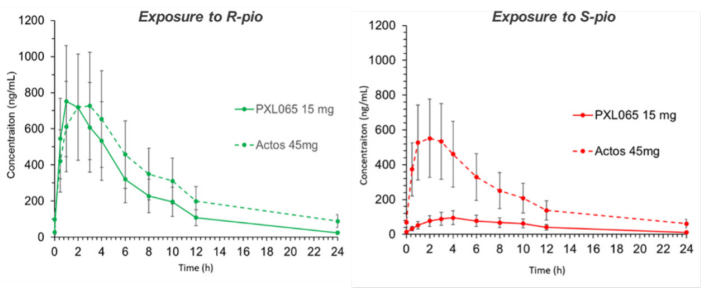
Results:

- *In vitro* assays demonstrated that PXL065 lacks PPARγ agonism but retains the known non-genomic effects of Pio including inhibition of mitochondrial pyruvate carrier (MPC)[4] and acyl-CoA synthetase long chain 4 (ACSL4).
- In murine NASH and diabetes models, PXL065 – retained the efficacy profile of Pio. Less weight gain (*ob/ob* and C57BL/6J) and fluid retention (C57BL/6J) were observed with PXL065 compared to Pio or d-S-Pio.
- In Phase 1 studies, PXL065 was safe and well tolerated. At steady state, exposure to total R-Pio (deuterated + protonated) was similar between PXL065 and Actos at a 3-fold lower dose of PXL065 (15mg vs 45mg) whereas total S-Pio exposure was 5-fold lower (Fig. B). The metabolite profile after administering PXL065 was comparable to Actos.
- DESTINY 1 is now fully enrolled; liver fat (MRI-PDFF), histology, and other endpoints will be assessed in 30 patients per arm. PK/PD modeling predicts that a dose of ≈ 15 mg will result in exposure to R-Pio comparable to that obtained with 45 mg Actos; at that dose, exposure to S-Pio should be similar to, or lower than, 7.5 mg Pio (shown to not cause significant weight gain in humans). Regression analysis of screening characteristics and fibrosis scores shows that both Type 2 diabetes (T2D) and elevated Fib-4 were associated with higher fibrosis scores; a significant T2D status by Fib-4 interaction was also found (p=0.031).

Table A. Preclinical Profile of PXL065

Property	Pio	d-S-pio	PXL065
PPARγ agonism	✓	✓	-
ACSL4 inhibition	✓	✓	✓
MPC inhibition	✓	✓	✓
In Vivo – Murine Models			
Weight gain	✓	✓	-
Fluid retention	✓	✓	-
Glucose lowering	✓	✓	✓
Liver – steatosis	✓	-	✓
Liver – inflammation	✓	+/-	✓
Liver - fibrosis	✓	✓	✓

Figure B. Pio Exposure with 15 mg PXL065 Similar to 45 mg Actos; S-Pio Exposure Decreased ~5-fold



Conclusion: PXL065 is a novel NASH therapeutic candidate. Despite reduced PPARγ activity, it retains non-genomic target activity and preclinical efficacy that are similar to Pio. In preclinical models and humans, dosing of PXL065 results in significantly greater R- vs. S-Pio (PPARγ active) exposure compared to Pio. Deuterium modification of Pio at the stereocenter does not alter its metabolism; however, oral bioavailability is enhanced. PXL065 is predicted to yield efficacy in NASH that is similar to that observed with Pio with minimal weight gain and edema. Lessons learned from DESTINY 1 screening data may inform other NASH programs; results from DESTINY 1 should be available in Q3 2022.

1) Hepatology 2017, 65:1058-61; 2) Diab Obes Metab 2021, 23:980-90; 3) Aliment Pharmacol Ther 2012, 35:66-75; 4) Hepatol Comm 2021, 5:1412-25.

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[4]
BIOMARKERS, IMAGING AND SAFETY IN RESMETIROM 52 WEEK NON-CIRRHOTIC NASH PHASE 3 CLINICAL TRIAL, COMPLETED OPEN-LABEL ARM OF MAESTRO-NAFLD-1

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Abstract Category: Therapeutic Trials NASH/Liver Fibrosis
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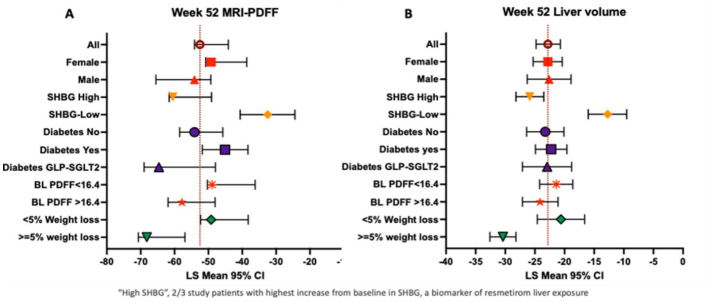
Background: MAESTRO-NASH NCT03900429 and MAESTRO-NAFLD-1 NCT04197479 are 52-week Phase 3 registrational double-blind placebo controlled clinical trials to study the effect of resmetirom, a selective thyroid receptor beta agonist in more than 2000 NASH patients. A goal of MAESTRO-NAFLD-1, a 1200 patient "real life" NASH study is to identify non-invasive markers that correlate with patient response to resmetirom treatment. The 171 patient 100 mg open label (OL) arm completed the 52-week study in July 2021.

Methods: Eligibility required at least 3 metabolic risk factors (Metabolic syndrome), fibroscan kilopascals (kPa) consistent with ≥F1 fibrosis stage, and MRI-PDFF≥8%. The primary and key secondary endpoints of MAESTRO-NAFLD-1 including safety, relative percent reduction of MRI-PDFF (week 16), LDL cholesterol (LDL-C) (week 24), Apolipoprotein B and triglycerides, fibroscan and 52-week endpoints were analyzed in the OL arm.

Results: Mean age was 55.6 (11.5 (SD)), female 69%, BMI 36.1 (6.3), diabetes 48%, hypertension 68%, dyslipidemia >70%, ASCVD score 11.6%; fibroscan (kPa 7.7 (3.3)), and MRI-PDFF 17.8% (7%). Statistically significant ($p<0.0001$) reduction of MRI-PDFF -53% (3.3% (SE)) overall, and in several subgroups were observed at week 52 (figure). Liver volume (LV) was elevated at baseline (2202 cm (535)) by ~50% relative to normal controls and ~15% after correction for BMI (Euro J of Radiol 106, 2018, 32–37). Resmetirom reduced LV-21% (1.0%), -23% (1.0%) respectively, at weeks 16 and 52 ($p<0.0001$), in all demographic groups (figure). LV reduction was greater than predicted by % reduction in MRI-PDFF, a measure of liver fat content (Clin Gastroenterol Hepatol. 2015 13: 561–568); LV-corrected mean MRI-PDFF reduction at Week 52 was -61% (2.4%). Weight loss ≥5% occurred in ~21% and was linked to resmetirom exposure (SHBG). At week 52, MRE (-0.34, p=0.03); fibroscan CAP (-39(4.6)) and VCTE (-1.87; -20%) ($p<0.0001$) were reduced relative to baseline. LDL-C (-21% (1.9%)), apolipoprotein-B (-22% (1.6%)) and triglycerides (-22% (2.6)) were statistically significantly reduced ($p<0.0001$). Decreases from baseline in liver enzymes were ALT -20 IU, AST -11 IU, GGT -25 IU ($p<0.0001$). Significant reductions in inflammatory and fibrosis biomarkers, reverse T3, ELF, and M30 and an increase in adiponectin were observed. No safety flags were identified; BP (systolic, diastolic) was reduced by ~2-4 mmHg,

(p=0.02); bone mineral density (DEXA) was unchanged at 52 weeks.

Conclusions: In this 52-week Phase 3 OL study, noninvasively identified NASH patients treated with 100 mg per day of resmetirom for up to 52 weeks demonstrated rapid and sustained reduction in 1) hepatic fat and liver volume 2) fibrosis as assessed by biomarkers, MRE and fibroscan; 3) LDL and atherogenic lipids, 4) liver enzymes and inflammatory biomarkers, providing support for the use of non-invasive tests to monitor individual NASH patient response to resmetirom treatment.



"High SHBG", 2/3 study patients with highest increase from baseline in SHBG, a biomarker of resmetirom liver exposure

[10]
HIGHER DAILY ARAMCHOL DOSE RESULTS IN HIGHER EFFECT SIZE IN FIBROSIS IMPROVEMENT IN THE ARMOR STUDY OPEN LABEL PART

Vlad Ratziu[1]; Yusuf Yilmaz[2]; Don Lazas[3]; Scott Friedman[4]; Liat Hayardeny[5]; Shaul Kadosh[6]; Tali Gorfine[5]; and Arun Sanyal[7]

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Abstract Category: Therapeutic Trials NASH/Liver Fibrosis
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Background: Aramchol is a partial inhibitor of hepatic stearoyl-CoA desaturase (SCD1) with direct anti-fibrotic activity demonstrated in pre-clinical models. In a 52-week phase 2b study, improvement in fibrosis by ≥1 stage without worsening of Non-alcoholic steatohepatitis (NASH) was observed in 17.5%, 21.3% and 29.5%, in the placebo, aramchol 400 and 600mg, respectively. A 53% higher exposure is achieved when dividing 600mg once daily (QD) Aramchol to 300mg twice daily (BID). Since this higher exposure was expected to improve efficacy, Aramchol 300mg BID was selected for a phase 3 study in patients with NASH and fibrosis. An Open-Label Part is ongoing that is designed to explore the kinetics of histological outcome measures and non-invasive tests as a function of treatment duration.

Methods: 150 patients with histologically confirmed NASH and fibrosis are being enrolled to receive Aramchol 300mg BID in the Open-Label Part of the study. Patients are randomized 1:1:1 to perform a post-baseline liver biopsy at weeks 24, 48 or 72. The primary efficacy endpoints are the kinetics of fibrosis Improvement without worsening of NASH and NASH Resolution without worsening of fibrosis for the different treatment durations. Biopsies are read by 3 independent pathologists individually, followed by a consensus reading.

Results: Herein we report the results from the first 20, F1-3 patients that received Aramchol in whom the scheduled post-baseline biopsy was performed (. At baseline, mean age ±SD was 58.5±8.7 years; 70% were females; 75% White; mean BMI 33.5. ±3.6 kg/m^2; 90% had type 2 diabetes; 13 patients had stage 3 fibrosis; 4 stage 2, and 3 stage 1; Mean NAS was 4.8±1.3. Post-baseline biopsies were performed for 9 patients at 24 weeks, 9 at 48 weeks and 2 at 72 weeks. Altogether 12 of 20 patients (60%) showed fibrosis improvement by ≥1 stage (5 of 9 after 24 weeks, 6 of 9 after 48 weeks and 1 of 2 after 72 weeks). 19/20 patients were either stable or reduced fibrosis measured by liver biopsy. In 5 patients, fibrosis was reduced by 2 points. In 9 of 20 (45%) patients there was fibrosis improvement without worsening of NASH. Statistically significant reductions in ALT, AST and biomarkers associated with liver fibrosis Fib-4 and ProC-3 were also observed which corroborate the histological effects. Reductions of a similar magnitude are seen in a cohort of the first 20 patients for which paired biopsy have been analyzed and a cohort of 50 patients for which biomarker data was analyzed (ARCON Cohort N=50) and cohort of 139 of which ALT, AST and FIB-4 were analyzed (N=139). Aramchol continues to show excellent safety and tolerability. Updated data from the open label study will be presented.

Conclusion: 60% of the 20 patients treated with Aramchol 300mg BID showed fibrosis improvement. Data is corroborated by congruent changes in fibrosis biomarkers and by a biochemical response in aminotransferases. The data presented here, albeit preliminary, is aligned with the hypothesis that higher Aramchol exposure results in an improved efficacy profile and that a direct anti-fibrotic effect may be manifested as early as 24 weeks.

[15]
LIVER VOLUME REDUCTION IN RESMETIROM TREATED NON-CIRRHOTIC AND CIRRHOTIC NASH PATIENTS

Dr. Mustafa Bashir, Duke University; Ms. Sarah Cubberly, Duke University; Ms. Aalanah Valentine, Duke University; Ms. Kassi Sollace, Duke University; Dr. Brandon Konkel, Duke University; Dr. Rebecca A. Taub, Madrigal Pharmaceuticals; Dr. Stephen A. Harrison, Radcliffe Department of Medicine, University of Oxford

Abstract Category: Therapeutic Trials NASH/Liver Fibrosis
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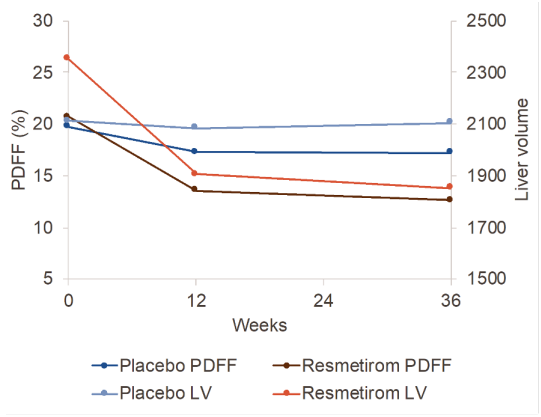
Background: Hepatomegaly may cause symptoms (e.g. pain) in NASH patients, and is thought to be driven primarily by high liver fat content. Resmetirom (MGL-3196) is a liver-directed, orally active, highly selective THR-β agonist in Phase 3 development for the treatment of NASH with significant (stage 2-3) fibrosis. In a 36-week Phase 2 serial MRI-PDFF and liver biopsy study in adults with biopsy-confirmed NASH (NAS≥4, F1-F3) and hepatic fat fraction ≥10%, resmetirom treated patients, compared with placebo, showed statistically significant liver fat reduction that was associated with NASH resolution on liver biopsy. The purpose of this study was to assess the relationship between liver triglycerides as measured by MRI-PDFF and liver volume (LV) in placebo and resmetirom-treated patients.

Methods: Relationship between MRI-PDFF and LV was assessed in MGL-3196-05 (NCT02912260), (n=116), and a NASH-cirrhotic active resmetirom treatment arm of MAESTRO-NAFLD-1 (NCT04197479) (n=105), in patients who had at least baseline and one additional serial PDFF. LV was assessed using a validated artificial intelligence model for segmenting the liver on standard MR images.

Results: LV at baseline was elevated in non-cirrhotic and cirrhotic NASH patients relative to literature values for healthy controls and was greater than predicted even after accounting for sex and body weight. PDFF correlated with LV at baseline in non-cirrhotic (r^2=0.19, p<0.001) and more weakly in cirrhotic NASH (r^2=0.079, p=0.01). Reduction in LV (CFB) correlated with reduction in PDFF in placebo (r^2=0.25, p=0.001) and resmetirom (r^2=0.38, p<0.0001) treated patients at 12 (and 36 (not shown)) weeks (Figure). LV reduction was greater in resmetirom (-18.6 % (1.1)), -20.5 % (1.2) compared to placebo (-0.4 % (1.5)), 0.1% (1.9) treated at 12 and 36 weeks, respectively (p<0.0001). A higher percentage of resmetirom (69.2%) than placebo (5.3%) patients had a ≥15% reduction in liver volume (p<0.0001) at Week 12, and similarly at Week 36. The relationship between LV reduction and PDFF reduction was proportionately weaker in placebo compared to resmetirom treated non-cirrhotic NASH patients. In cirrhotic NASH patients treated with resmetirom, LV reduction was much greater than expected based on the small reduction in PDFF, especially in patients with PDFF≤5% at baseline (LV mean %CFB, -15% versus PDFF, mean %CFB, -4% at week 16). Resmetirom treated patients who had NASH resolution and/or fibrosis reduction on biopsy at week 36 all had a PDFF reduction ≥30% and/or LV reduction of ≥15% at week 12.

Conclusion: Reduction in liver volume in resmetirom treated patients may be explained in part by reduction in liver triglycerides (measured by PDFF), but is also likely driven by other changes related to its mechanism of action. LV reduction may be associated with histopathologic improvement of NASH that may be further assessed by data from resmetirom's Phase 3 MAESTRO-NASH study.

Liver volume (LV) and MRI-PDFF (PDFF) Time course in MGL-3196-05 Phase 2 NASH Study



[17]
LIVER-DISTRIBUTED FXR AGONIST TERN-101 LEADS TO CORRECTED T1 (CT1) RESPONSE AND A POPULATION SHIFT TO LOWER CT1 RISK CATEGORIES IN NASH PHASE 2A LIFT STUDY

Eric Lawitz[1], Rohit Loomba[2], Kris Kowdley[3], Matt Kelly[4], Andrea Dennis[4], Vidhya Kumar[4], Rajarshi Banerjee[4], Diana Chung[5], Tonya Marmon[5], Christopher Jones[5], Erin Quirk[5], Daria B. Crittenden[5]

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Abstract Category: Therapeutic Trials NASH/Liver Fibrosis

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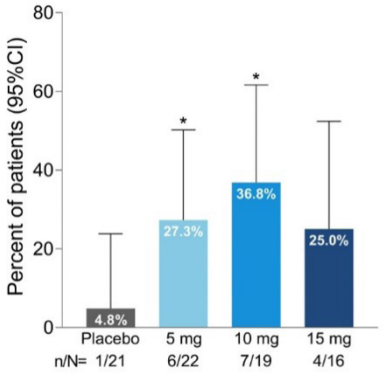
Background: TERN-101 is a non-steroidal FXR agonist with enhanced liver distribution being developed for the treatment of non-alcoholic steatohepatitis (NASH). In the LIFT phase 2a study of TERN-101, corrected T1 (cT1) relaxation time was assessed. cT1 is a magnetic resonance (MRI)-based test that measures free-water content in liver to assess fibroinflammation. cT1 decreases correlate with histologic improvement and clinical outcomes in patients with NASH.

Methods: LIFT was a double-blind, placebo-controlled study in adults with clinically or histologically diagnosed noncirrhotic NASH. Patients (N=100) were randomized and treated with placebo or TERN-101 (5, 10, and 15 mg) for 12 weeks. The primary endpoint was safety; exploratory endpoints included changes in cT1, which was collected at qualified sites (84 patients at baseline). We assessed cT1 response defined as a ≥80 msec decline and percent of patients with low (<800 msec), elevated (800-875 msec), or high (>875 msec) cT1 values, reflecting increasing risk of liver fibrosis/inflammation and disease progression.

Results: At baseline, cT1 mean (SD) values were 909 (91, N=22), 925 (75, N=24), 942 (144, N=20), and 975 (175, N=18) msec, for placebo and TERN-101 5, 10, 15 mg groups, respectively. cT1 values significantly declined from baseline at Weeks 6 and 12 for all TERN-101 doses. The percent of patients with a cT1 decline ≥80 msec at Week 12 was 4.8%, 27.3%, 36.8%, and 25%, for placebo and TERN-101 5, 10, 15 mg, respectively (P<0.05 for 5 and 10 mg vs placebo). Overall, TERN-101 led to an increased proportion of cT1 low risk patients and a decreased proportion of high-risk patients over 12 weeks of dosing. At baseline, 9.1%, 4.2%, 10%, and 5.6% of patients had cT1 low risk values and 59.1%, 75%, 70%, and 77.8% were in the high-risk category for placebo and TERN-101 5, 10, 15 mg groups, respectively. The percent of patients with cT1 low risk values at Week 12 was 13.6%, 9.1%, and 31.3% for TERN-101 5, 10, and 15 mg, respectively vs 0% for placebo. The percent of patients with cT1 high risk values at Week 12 was 63.6%, 59.1%, 43.8% for TERN-101 5, 10, and 15 mg, respectively vs 66.7% for placebo.

Conclusions: TERN-101 treatment resulted in a higher proportion of patients with cT1 decline ≥80 msec and a study population shift to cT1 lower risk categories vs placebo. Improvements in cT1 may serve as a TERN-101 treatment response biomarker and may reflect the impact of this FXR agonist on fibroinflammation.

Figure: cT1 responders by treatment group



Percent of patients with ≥80 msec cT1 decline from baseline at Week 12. *P<0.05

[20]
NOVEL, FIRST-IN-CLASS, FATTY ACID SYNTHASE (FASN) INHIBITOR TVB-2640 DEMONSTRATES ROBUST CLINICAL EFFICACY AND SAFETY IN A GLOBAL PHASE 2 RANDOMIZED PLACEBO-CONTROLLED NASH TRIAL (FASCINATE-1)

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Abstract Category: Therapeutic Trials NASH/Liver Fibrosis

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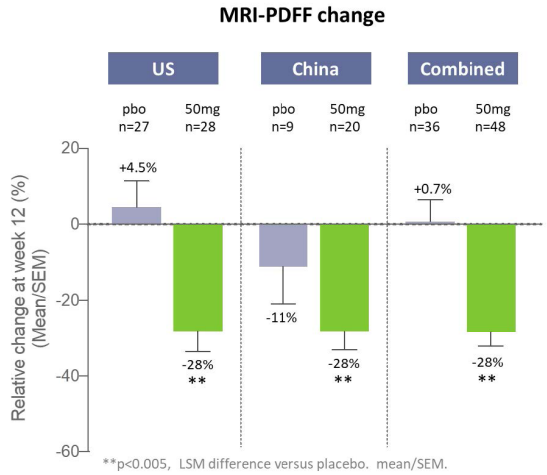
Background: Increased hepatic de novo lipogenesis (DNL) increases liver fat and has been linked to lipotoxicity, a hallmark of nonalcoholic steatohepatitis (NASH). TVB-2640 is an oral, once-daily, first-in-class small molecule FASN inhibitor that reduces excess liver fat, inhibits inflammatory and fibrogenic pathways. This Phase 2a, multicenter, placebo-controlled study assessed efficacy and safety of TVB-2640 in the US and China (NCT03938246).

Methods: Subjects with MRI-PDFF ≥8% and fibrosis (MRE ≥2.5 kPa or biopsy F1-F3) were randomized 2:1 to TVB-2640 or pbo once daily (US N=99; China N=30) for 12 weeks. Response was defined as a ≥30% relative reduction in PDFF at W12. Here, we report safety, efficacy and biomarker results.

Results: US cohorts received 25mg, 50mg (N=35) or pbo (N=15), and were 72% Hispanic. The China cohort received 50mg (N=21) or pbo (N=9). Chinese subjects were younger (mean age 37 v. 52 yr US), had lower weight (84 v. 91 kg), higher ALT (93 v. 40 U/L), and >90% enrolled based on biopsy showing NASH F1-F3. The mean (SD) baseline PDFF was similar (19.5% (9.3) v. 16.9% (6.6) US) between the two groups. TVB-2640 was well-tolerated, with no AEs ≥ Gr. 3 and no on-treatment SAEs. PK profiles of TVB-2640 (50mg) were similar in the US and China. Despite differences in baseline characteristics, TVB-2640 reduced liver fat and decreased ALT in both populations, that combined had a relative PDFF reduction of 28.2% (50mg, N=48) at W12 v. 6.4% pbo (N=19, p=0.019) and absolute PDFF reduction of 5% v. 1.6% pbo (p<0.0001). The PDFF response rates were 56% (50mg) v. 15% pbo. The PDFF decline was observed across BL fibrosis and/or MRE/PRO-C3 levels. ALT decreased in a time-dependent manner, more pronounced at W12 (-19 U/L v. -1.4 U/L pbo (p=0.003), and correlated with PDFF reduction with TVB-2640 (p=0.003, US). A broad panel of biomarkers was assessed in the US patients. A novel marker of DNL, serum tripalmitin, was reduced in TVB-2640 treated subjects compared to placebo, in a dose-dependent manner, confirming inhibition of FASN. Consistent with palmitate as a major substrate for ceramide and di-acylglycerol synthesis, TVB-2640 reduced levels of these lipotoxic mediators, especially species containing saturated acyl chains with 16–18 carbons. Fibrosis markers including PRO-C3 and TIMP1 were also decreased by TVB-2640. Metabolism markers FGF-21 and adiponectin were increased, indicative of improved metabolic function. Metabolomic analysis was performed to evaluate predictive markers of liver fat response. A biomarker signature was identified where combined BL values of 6 serum metabolites predicted PDFF response at 50 mg TVB-2640. These markers included bile acid, amino acid and lipid derivatives, and will be refined in further analyses.

Conclusion: In this global study of TVB-2640 in NASH, decreases in liver fat and ALT were observed in both US and Chinese patients, despite different baseline and racial characteristics. Biomarker analyses showed reduction in liver injury, improvement in metabolic function, reduction of pro-inflammatory lipotoxins, evidence of reduced fibrogenesis, and a favorable effect on serum lipids.

FASN inhibition is a promising therapeutic approach in patients with NASH. A global Phase 2b, randomized, double blind, placebo-controlled biopsy study FASCINATE-2 has been initiated.



[30]
LPCN 1144 IMPROVES BODY COMPOSITION IN BIOPSY-CONFIRMED NASH PATIENTS

Shadi Mehraban

Abstract Category: Therapeutic Trials NASH/Liver Fibrosis – Humans

Background: Non-alcoholic Steatohepatitis (NASH) is a common cause of liver disease and rapidly rising to be the leading indication for liver transplantation. Sarcopenia, loss of muscle mass, occurs in 20-60% of patients with liver disease and reduces survival of cirrhotic patients. There is an unmet need for addressing adverse body composition (BC) in advanced NASH. A decrease in free testosterone (T) and increase in Sex Hormone Binding Globulin (SHBG) are reported with progression of NASH. LPCN

1144, an oral prodrug of endogenous T, is currently being investigated in an ongoing randomized, double-blind, paired biopsy, placebo-controlled, phase 2 study in men with NASH (LiFT, NCT04134091). Here, we present topline BC results post 20 weeks (w) of treatment.

Methods: Biopsy-confirmed NASH (F1-F3) males were randomized 1:1:1 to three arms; 1) Treatment A: oral T twice daily (BID), 2) Treatment B: oral T with d-alpha tocopherol BID, and 3) oral matching placebo (PL) BID. BC parameters, including appendicular lean muscle mass (APLM), whole body fat mass (WBFM) and whole body lean mass (WBLM), were evaluated using Dual Energy X-ray Absorptiometry (DEXA) scan at baseline and w20. Other key outcomes measured were changes in SHBG, hepatic fat fraction, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) at w12.

Results: APLM was significantly elevated with LPCN 1144 treatment compared to PL ($p<0.05$). Additionally, treatment with LPCN 1144 resulted in a significant reduction of WBFM compared to PL ($p<0.01$). Favorable BC changes, defined as a decrease in WBFM and an increase in WBLM, were observed in 64% of the subjects receiving LPCN 1144 compared to 15.4% in the PL arm($p<0.01$). Furthermore, LPCN 1144 reduced progression of adverse muscle composition (AMC); 4% in the treatment arm vs 46.2% in the PL arm had an increase in WBFM and a decrease in WBLM ($p<0.01$). Treatment with LPCN 1144 significantly decreased SHBG from baseline compared to PL ($p<0.001$). Liver fat, ALT, and AST were also significantly reduced in both treatment arms compared to PL ($p<0.001$, <0.05, and <0.05, respectively).

Conclusion: LPCN 1144 significantly improved BC in biopsy-confirmed NASH male subjects. The forthcoming w36 data in the ongoing LiFT trial is expected to further elucidate the effects of LPCN 1144 on changes in BC. This significant impact of LPCN 1144 on BC can be beneficial in cirrhotic subjects. Larger longitudinal investigations may be required to study this potential effect in advanced liver disease.

Table:

Group	Relative Change from Baseline (%)			Percentage of Subjects with Favorable Body Composition Post Therapy	Percentage of Subjects with Adverse Muscle Composition Post Therapy
	Appendicular lean muscle mass	Whole body fat mass	Whole body lean mass		
Placebo (N=13)	-1.65	3.24	-0.47	15.4	46.2
LPCN 1144 Treatment (N=25)	2.43	-5.07	2.40	64.0	4.0
P Value vs placebo	0.0111	0.0018	0.0473	0.0064	0.0035

[31]
SAFETY AND TOLERABILITY OF LPCN 1144 TREATMENT IN BIOPSY CONFIRMED NASH SUBJECTS IN THE PHASE 2 LIFT STUDY

Shadi Mehraban

Abstract Category: Therapeutic Trials NASH/Liver Fibrosis – Humans

Background: Non-alcoholic Steatohepatitis (NASH) is a common cause of liver disease and rapidly rising to be the leading indication for liver transplantation. Acceptable benefit to risk profile of therapeutics for chronic disease states including NASH is critical. LPCN 1144, an oral prodrug of endogenous testosterone (T), was investigated for safety and efficacy potential in a randomized, double-blind, paired biopsy, placebo-controlled, phase 2 study in men with NASH (LiFT, NCT04134091). Here, we present the safety results during 36 weeks of treatment.

Methods: Biopsy-confirmed NASH (F1-F3) males were randomized 1:1:1 to three arms; 1) Treatment A (n=18): oral T twice daily (BID), 2) Treatment B (n=19): oral T with d-alpha tocopherol BID, and 3) oral matching placebo (n=19) BID. An open label extension of this study is ongoing to investigate the effects of treatment A for a total duration of 18 months. Safety outcomes were recorded throughout the study.

Results: LPCN 1144 treatment resolved NASH with no worsening of fibrosis. TEAEs were reported in 16 subjects (84%) in the placebo arm, 12 subjects (67%) in treatment A, and 11 subjects (58%) in treatment B. The most common adverse events were infections (7, 4, and 5 subjects in placebo, treatments A and B, respectively). Additionally, drug-related TEAEs were reported in 3, 2, and 3 subjects in placebo, treatments A and B, respectively. No more than one subject in each treatment arm experienced a drug-related TEAE in the same system organ class, and all were mild to moderate in severity. Four subjects in the placebo arm vs one subject total across both treatment arms discontinued the study drug due to TEAEs.

No cases of hepatocellular carcinoma, Drug Induced Liver Injury (DILI), thromboembolic events, or sleep apnea were reported. Changes in lipid levels including total cholesterol, triglyceride, LDL, and HDL in both treatment arms were similar to placebo. Cardiovascular events including myocardial infarction and cardiac arrest were well-balanced between arms. Additionally, rates of pedal edema, changes in PSA and blood pressure were comparable among groups. Changes in weight and rates of GI events including nausea, vomiting, and diarrhea were similar between groups. Furthermore, one subject in treatment B had elevated hematocrit levels and one subject in each placebo and treatment A experienced pruritis.

Conclusion: LPCN 1144 was well-tolerated in biopsy confirmed NASH male subjects, with no observed signs of adverse androgenic effects, increased cardiovascular or hepatic risks. The observed benefit to risk profile warrants further investigation of LPCN 1144 in a larger trial with a longer duration.

THANK YOU FOR ATTENDING!