The Liver Meeting 2021
Late-breaking Abstracts

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Oral Presentations

LO1: PRIMARY RESULTS OF THE NIMBLE STAGE 1-NASH CRN STUDY OF CIRCULATING BIOMARKERS FOR NONALCOHOLIC STEATOHEPATITIS AND ITS ACTIVITY AND FIBROSIS STAGE

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**Background:** There are scientific gaps in the literature on non-invasive tests (NITs) for NAFLD impeding their regulatory evaluation as diagnostic tests. The NIMBLE consortium of the FNIIH was established to generate the evidence needed to
fill these knowledge gaps. **Aim:** The current study represents a collaboration between NIMBLE and the NIH/NIDDK NASH CRN to establish the comparative performance of 5 blood-based biomarker panels for NAFLD using AUROCs and sensitivity/specificity at Youden’s cutoff for their intended diagnostic use in a multi-center US cohort with NAFLD/NASH.

**Methods:** Selected biomarker panels were tested in aliquots of the same blood sample from each participant obtained within 90 days of a liver biopsy demonstrating NAFLD. Their performance was tested for their prespecified intended use (in parentheses): (1) NIS4™: (NASH diagnosis, high NAFLD activity score (NAS) ≥ 4, Fibrosis stage ≥ 2, ≥ 3 or 4), (2) One-way Lipidomics (OWL): (NASH diagnosis, high NAS), (3-5) Enhanced liver fibrosis (ELF), PROC3 and Fibrometer-VCTE (FM-VCTE): (fibrosis). The cohort was selected a priori to avoid fibrosis severity spectrum bias. The primary compound statistical hypothesis for the intended use of each of the NITs required: (i) an AUROC estimate numerically > 0.70 and (ii) a lower 95% AUROC confidence limit of at least 0.50. The secondary statistical hypotheses required: (i) the AUROCs of NITs for NASH diagnosis and high NAS were significantly higher (p<0.05) than for ALT, and (ii) the AUROCs of NITs for fibrosis were higher than the AUROC for FIB4 (p<0.05) for each intended use. The sample sizes provided a power of 0.8 or higher for AUROC testing. For OWL, categorical results were provided; thus, only sensitivity/specificity was reported. Rigorous protocols ensured data-integrity.

**Results:** 1073 patients with NAFL (n=220) or NASH (n=853) with fibrosis stages 0 (n=222), 1 (n=114), 2 (n=262), 3 (n=277) and 4 (n=198) were studied. The AUROCs, Youden’s cutoff with its sensitivity/specificity are tabulated below. NIS4 met criteria for NASH diagnosis and NAS≥4. NIS4, ELF and FM-VCTE all met both criteria for success for diagnosis of fibrosis stage ≥ 2. The performance of ELF and FM-VCTE further improved for fibrosis stage ≥3 and stage 4.

**Conclusion:** These data establish the sensitivity and specificity of the NITs studied and will inform stage 2 studies in varying intended use populations, alone and in combination, to support regulatory qualification.

<table>
<thead>
<tr>
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<th>AUROC (Youden cutoff)</th>
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<tr>
<td></td>
<td>[sensitivity, specificity]</td>
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<tr>
<td>NASH diagnosis</td>
<td>0.678 (40) [63.2, 64.6]</td>
</tr>
<tr>
<td>NAS ≥ 4</td>
<td>0.726 (42) [71.1, 64.1]</td>
</tr>
<tr>
<td>F stage ≥ 2</td>
<td>0.796 (1.4) [65.4, 80.6]</td>
</tr>
<tr>
<td>F stage ≥ 3</td>
<td>0.793 (1.4) [75.1, 66.8]</td>
</tr>
<tr>
<td>F stage 4</td>
<td>0.81 (1.5) [85, 63.4]</td>
</tr>
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* p<0.05 for comparison with either ALT or FIB4 for their intended use
** p<0.001 for comparison with either ALT or FIB4 for their intended use

All AUROCs are significantly superior to AUROC=0.5 (p<0.001)
LO2: VONAFEXOR, A FXR AGONIST, INDUCED HEPATIC AND RENAL IMPROVEMENT IN THE RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED LIVIFYNASH TRIAL

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Background: The Farnesoid X Receptor (FXR), a key target in NASH pathogenesis, is also involved with renal fibrosis. Vonafexor (VONA, previously EYP001) is a highly selective FXR agonist with anti-fibrotic effects in NASH and Chronic Kidney Disease (CKD) models. Up to 64% of NASH patients have decreased estimated glomerular filtration rate (eGFR <90 mL/min/1.73 m2) which can evolve into CKD. Phase 2a results in NASH patients with normal or mildly decreased eGFR treated are reported here.

Methods: 96 patients were randomized 1:1:1 to daily oral Placebo (PBO, (n=32) or VONA 100 mg (n=31) or 200 mg (n=33) for 12 weeks (W12). Inclusion criteria required phenotypic stage 2 or 3 fibrosis NASH with an absolute liver fat content (LFC by MRI-PDFF) ≥10% and liver stiffness by transient elastography [LSTE] ≥8.5 kPa or previous biopsy-proven NASH. Randomization was stratified by diabetes and LFC.

Results: Baseline characteristics were similar between arms. There was a statistically significant reduction in absolute LFC at W12 in VONA-treated patients (-6.3% with 100 mg, -5.5% with 200 mg, and -2.3% with PBO, p<0.001) (Table 1). Absolute LFC reduction of >5% was achieved in 58% of patients in the 100 mg group vs 22% in the PBO group, and relative LFC reduction of >30 % was achieved in 50% of VONA-treated vs 13% of PBO patients. VONA treatment achieved a significant 26 % mean reduction in ALT vs 13% for PBO. A rapid and sustained 42 % mean reduction in GGT was also observed in VONA-treated subjects (p<0.001). The liver fibro-inflammation marker cT1 (Liver Multiscan®) was reduced by 81 msec in the 100 mg VONA arm compared to 10 msec in the PBO arm (p<0.001). A significant mean improvement in eGFR [+5.6 mL/min/1.73 m2] was observed in VONA 100 mg treated subjects, while a decrease in eGFR [-2.8 mL/min/1.73 m2] was observed in the PBO group. Over the 12-week treatment period, 76% of the patients receiving VONA had an eGFR increase >0.1 mL/min/1.73m2, while 66% of patients receiving placebo had a decrease of their kidney function. A 34% increase in low density lipoprotein-cholesterol (LDL-C) was observed. Statin dose adjustment normalized LDL-C levels to 70 mg/dL. 9% of patients discontinued participation with VONA 100 mg due to pruritus, which was mostly mild, transient and localized. No ALT increases ≥Grade 2 were reported. Five non-drug related severe adverse events were reported (1 in the PBO group and 2 in each of the VONA 100mg and 200mg groups).

Conclusion: VONA induced a strong, consistent LFC reduction, and improvement in biochemical and imaging markers of liver inflammation with an added benefit on eGFR. VONA was safe and well tolerated, with the 100 mg dose showing a more favorable tolerability-efficacy profile. Larger trials are warranted to confirm the hepatic and renal benefits.
LO3: ACCURATE DIAGNOSIS OF NASH USING NOVEL PROTEASE BASED LIQUID BIOPSY

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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

| Table 1. Baseline values and change from baseline to W12 in key study outcomes |
|-----------------------------|-----------------------------|-----------------------------|
| Liver fat content (LFC) | Placebo (n=32) | VONA 100mg (n=31) | VONA 200mg (n=33) |
| Baseline LFC, % | 20.9 (7.2) | 19.8 (6.3) | 20.1 (6.7) |
| Change Absolute LFC, % | -2.3 (0.9) | -6.3 (0.9) #§ | -5.5 (0.9) #§ |
| % Patients with > 5% absolute LFC reduction | 22% | 57% § | 43% § |
| Change Relative LFC, % | -10.5 (4.3) | -30.0 (4.7) #§ | -25.5 (4.6) #§ |
| % Patients with > 30% absolute reduction | 13% | 50% § | 39% § |

Non-invasive NASH Biomarkers

| Non-invasive NASH Biomarkers | Placebo (n=32) | VONA 100mg (n=31) | VONA 200mg (n=33) |
|-----------------------------|-----------------------------|-----------------------------|
| Baseline ALT (IU/L) | 51.7 (28.0) | 53.4 (29.9) | 49.8 (27.7) |
| ALT, absolute change (IU/L) | -11.5 (3.2) | -19.3 (3.2) | -10.8 (3.3) |
| % Patients with > -17 IU/L reduction | 25% | 52% § | 36% |
| GOT, absolute change (IU/L) | -3.9 (3.1) # | -40.6 (3.1) #§ | -34.1 (3.1) #§ |
| Alpha-2-Macroglobulin, absolute change (mg/dL) | +4.3 (3.8) # | -25.9 (4.3) #§ | -18.4 (4.5) #§ |
| Baseline fibro-inflammation marker cT1 (msec) | 903 (95) | 874 (128) | 925 (99) |
| cT1, absolute change (msec) | -10.2 (14.5) | -80.6 (15.4) #§ | -71.9 (14.2) #§ |
| % Patients > 88 msec absolute reduction | 12% | 36% * | 36% * |

Clinical Biomarkers

| Clinical Biomarkers | Placebo (n=32) | VONA 100mg (n=31) | VONA 200mg (n=33) |
|---------------------|-----------------------------|-----------------------------|
| Baseline BMI | 34.3 (4.3) | 34.3 (4.1) | 35.4 (5.1) |
| Body Weight, absolute change (kg) | -0.1 (0.5) | -1.7 (0.5) #§ | -2.5 (0.5) #§ |
| Waist-to-Hip Ratio, absolute change | 0.01 (0.1) | -0.02 (0.0) #§ | -0.01 (0.0) |
| Baseline eGFR (mL/min/1.73m²) | 91.4 (18.1) | 86.4 (16.4) | 93.0 (21.7) |
| eGFR, absolute change (mL/min/1.73m²) | -2.8 (14.2) | +6.0 (9.5) #§ | +2.5 (14.5) #§ |
| % Patients with any eGFR increase | 24% | 76% § | 65% § |

Shown are mean (SD) or % patients at baseline and changes at W12. LFC measured by MRI-PDFF. # p<0.05 vs baseline. § p<0.05 vs Placebo. * p<0.06
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.

**Conclusion:** 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.

**LO4: BURDEN OF ILLNESS AND ECONOMIC IMPACT OF NONALCOHOLIC STEATOHEPATITIS (NASH) IN THE UNITED STATES ACCORDING TO THE PRESENCE OF OBESITY**

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**Background:** NASH is driven by the growing global prevalence of obesity. We aimed to model clinical and economic burden of NASH in the US, stratified by presence or absence of obesity.

**Methods:** We used a discrete-time Markov model to simulate 20-year outcomes for hypothetical cohort of NASH patients in the U.S. We stratified cohorts by age and presence of obesity using the U.S. population projections data for 2019-2040 and published literature. The Markov model included 9 health states and 3 absorbing death states in each year with defined transition probabilities (TPs). The estimated age-obesity impact on all-cause, cardiac- and liver-specific deaths among NAFLD with high fibrosis scores were obtained from the National Health and Nutrition Examination (NHANES) III, National Vital Statistics System (NVSS) and Scientific Registry of Transplant Recipients (SRTR) data. These data were used to adjust TPs from health states to death. The TPs between health states were then rescaled to sum to one at each state. We then split all TPs for NASH with all ages into the age-obesity group using information from the literature. Costs included inpatient, outpatient, professional services, emergency department, and drug costs, which were obtained from the Center for Medicare and Medicaid Services Fee Schedule 2019 and published data. 95% uncertainty interval (UIs) were calculated as the 25th and 975th ranked values across all 1,000 simulations. Costs were reported in 2019 US dollars and a discount rate of 3% was used. Main outcomes were Cardiac- and Liver-specific deaths, Liver transplants (LT), years of decompensated cirrhosis (DCCy), years of hepatocellular carcinoma (HCCy) and costs.
Results: In 2019, 4.48% of the U.S. population (N=11.2 million) was estimated to have NASH. Of those with NASH, 80.1% were obese. Over 2 decades (2019-2040), we estimated that obese NASH will have higher all cause (74.1% vs 59.1%), cardiac (26.4% vs 7.4%) and liver-specific mortality (2.7% vs. 2.3%) compared to non-obese NASH. During this period, we estimated that the obese NASH cohort will experience 48,855 LT (48,692-49,018), 1,138,665 DDCy (1,137,750-1,139,694) and 743,833 HCCy (742,738-745,009). In contrast, non-obese NASH will have 8,332 LT (8,259-8,413), 193,988 DCCy (193,215-194,569) and 103,795 HCCy (103,414-104,250). Finally, the expected costs for obese NASH and the non-obese NASH cohorts were estimated to be $161.91B ($161.77B-$162.05B) and $30.99B ($30.94B-$31.05B), respectively.

Conclusion: The growing prevalence of obesity and related NASH will have a major clinical and economic impact in the U.S. These data should inform policy makers and other stakeholders to address the growing burden of NASH in the U.S.

LO5: EFFICACY AND SAFETY OF PEGBELFERMIN IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS AND STAGE 3 FIBROSIS: RESULTS FROM THE PHASE 2b, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED FALCON 1 STUDY

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Background: Pegbelfermin (PGBF) is a PEGylated fibroblast growth factor 21 analog. In a 16-wk phase 2a trial in patients (pts) with NASH, stage 1-3 fibrosis, and HFF ≥10%, PGBF reduced hepatic steatosis and improved biomarkers of fibrosis, metabolism, and liver injury. This phase 2b study evaluated efficacy and safety of PGBF in pts with NASH and bridging fibrosis.

Methods: FALCON 1 (NCT03486899) was a randomized (1:1:1:1), double-blind, placebo (PBO)-controlled study conducted in the US and Japan. Eligible adults had biopsy-confirmed NASH and NASH CRN stage 3 liver fibrosis. Pts received subcutaneous injections of PGBF (10, 20, or 40 mg) or PBO once weekly for 48 weeks. Liver biopsies were performed within 6 months of screening and at wk 24. The primary endpoint was ≥1 stage fibrosis improvement without NASH worsening or NASH improvement with no fibrosis worsening at wk 24. Secondary and exploratory endpoints were additional histological and noninvasive measures of steatosis, fibrosis, and liver injury.

Results: 197 pts were randomized; mean age was 56.9 y, 59% were women, 74% had T2DM. Baseline characteristics were similar across arms and consistent with NASH and advanced fibrosis (table). The primary endpoint was observed in 14% (PBO), 31% (10 mg PGBF), 24% (20 mg PGBF), and 27% (40 mg PGBF) of pts; however, statistical significance was not reached (P=0.13; Cochran- Armitage trend test of proportions, 1-sided α=0.05) due to lack of dose response across PGBF arms. At wk 24, PGBF arms had numerically larger decreases in mean percentage change from baseline in liver stiffness relative to PBO. At wk 48, ≥30% relative reduction from baseline in HFF occurred in 9% (PBO), 21% (10 mg PGBF), 20% (20 mg PGBF), and 23% (40 mg PGBF) of pts. In PGBF arms, mean PRO-C3, ALT, and AST concentrations decreased, and mean adiponectin concentration improved (increased) compared with PBO. Adverse events (AEs) were reported at similar frequencies in all arms. Seven pts discontinued the study due to AEs (n=3 PBO; n=2 each in 10 and 20 mg PGBF arms). There were no treatment-related serious AEs in any study arm.

Conclusion: PGBF led to numerically higher rates of fibrosis improvement without NASH worsening or NASH improvement without fibrosis worsening at wk 24 compared with PBO. PGBF demonstrated evidence of improvements in steatosis, fibrosis, and inflammation based on noninvasive measures, and was generally safe and well tolerated in pts
with NASH and stage 3 fibrosis.

Summary of FALCON 1 Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=49)</th>
<th>10 mg PGBF (n=49)</th>
<th>20 mg PGBF (n=50)</th>
<th>40 mg PGBF (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.5 (8.6)</td>
<td>56.4 (9.6)</td>
<td>56.3 (10.1)</td>
<td>57.4 (10.5)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>28 (58.2)</td>
<td>28 (59.2)</td>
<td>27 (54.0)</td>
<td>31 (83.3)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>35.2 (8.1)</td>
<td>36.3 (6.7)</td>
<td>35.1 (6.4)</td>
<td>35.7 (6.6)</td>
</tr>
<tr>
<td>T2DM, n (%)</td>
<td>34 (73.9)</td>
<td>34 (72.3)</td>
<td>39 (74.5)</td>
<td>34 (73.9)</td>
</tr>
<tr>
<td>n</td>
<td>44</td>
<td>45</td>
<td>48</td>
<td>46</td>
</tr>
<tr>
<td>CPA, %</td>
<td>7.6 (3.0)</td>
<td>6.7 (3.3)</td>
<td>6.6 (3.4)</td>
<td>6.9 (3.2)</td>
</tr>
<tr>
<td>MRI-PDIFF, %</td>
<td>12.5 (5.9)</td>
<td>13.9 (6.3)</td>
<td>13.4 (6.3)</td>
<td>13.0 (6.2)</td>
</tr>
<tr>
<td>n</td>
<td>40</td>
<td>39</td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td>MRE, kPa</td>
<td>4.3 (1.2)</td>
<td>4.0 (1.8)</td>
<td>4.1 (1.1)</td>
<td>4.0 (1.6)</td>
</tr>
<tr>
<td>PRO-C3, ng/ml</td>
<td>19.0 (9.2)</td>
<td>18.0 (8.5)</td>
<td>20.1 (11.9)</td>
<td>19.5 (8.8)</td>
</tr>
</tbody>
</table>

Primary endpoint (n=141)

| Fibrosis improvement without NASH worsening or NASH improvement without fibrosis worsening at week 24, n (%) |
| 7 (14.3) | 15 (30.6) | 12 (24.0) | 13 (26.5) |

Key secondary endpoints (n=141)

| Fibrosis improvement at week 24, % (n/N) |
| 8.2 (4/49) | 16.3 (8/49) | 14.0 (7/50) | 20.4 (10/49) |

NASH improvement at week 24, % (n/N) |
| 10.2 (5/49) | 24.5 (12/49) | 18.0 (9/50) | 16.3 (8/49) |

NASH resolution without worsening of fibrosis at week 24, % (n/N) |
| 6.1 (3/49) | 8.2 (4/49) | 4.0 (2/50) | 2.0 (1/49) |

Key exploratory endpoints (completer analysis)

| MRI-PDIFF, % of pts with ≥30% relative reduction at week 24, (n/N) |
| 5.6 (2/36) | 27.5 (11/40) | 22.0 (9/41) | 35.9 (14/39) |
| MRI-PDIFF, % of pts with ≥30% relative reduction at week 48, (n/N) |
| 8.8 (3/34) | 21.1 (8/38) | 20.0 (8/40) | 23.1 (9/39) |
| MRI-L, % of pts with ≥15% relative reduction at week 24, (n/N) |
| 15.2 (5/33) | 14.3 (5/35) | 10.8 (4/37) | 30.6 (11/36) |
| MRI-L, % of pts with ≥15% relative reduction at week 48, (n/N) |
| 30.3 (10/33) | 41.2 (14/34) | 28.8 (10/35) | 41.2 (14/34) |

* Percentages shown were calculated based on the total number of patients in the US. ** Fibrosis improvement ≥1 point decrease in NASH ORN fibrosis score. NASH worsening ≥1 point increase in NASH.

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**Background:** Cotadutide (cota), a peptide with activity at the glucagon-like peptide-1 and glucagon receptors, has demonstrated robust effects on non-alcoholic steatohepatitis (NASH) resolution and fibrosis improvement in preclinical NASH models and reductions in body weight, glycemia, and hepatic steatosis in clinical studies in obese type 2 diabetes mellitus (T2DM) patients. We examined the safety and efficacy of cota in patients with non-cirrhotic NASH with fibrosis in
the PROXYMO Phase 2 trial.

**Methods:** In this 19-week, double-blind, placebo-controlled study, participants were randomized to receive once-daily subcutaneous injections of cota titrated to 300 μg, 600 μg, or placebo (pbo), (NCT04019561). Eligible participants were aged ≥ 18 years, with a BMI ≥ 30 kg/m² and biopsy-proven non-cirrhotic NASH with fibrosis (NAS ≥ 4 and F1, F2, or F3), with and without T2DM and hepatic fat fraction (HFF) ≥ 10% (per MRI-PDFF) at screening. Following randomization, subjects were monitored for safety and hepatic steatosis, and biomarkers were evaluated at baseline, end-of-treatment, and serially during the trial. The primary endpoint was measures of overall safety of cota versus pbo.

**Results:** 74 subjects were randomized approximately equally to the 3 treatment groups. Baseline characteristics were similar across groups and consistent with the target population. Treatment with cota at both doses was generally safe and well-tolerated. The adverse event profile was consistent with the incretin class, with majority of events mild to moderate in severity. Treatment with cota led to dose- and time-dependent reductions from baseline in absolute and relative HFF and ALT and AST, with statistically significant ($p < 0.05$) treatment effects on all measures at 19 weeks in the 600 μg group (absolute HFF: least squares [LS] mean difference vs pbo, $–6.2\%\ [95\%\ CI: –10.5, –1.8]$; relative HFF: LS mean difference vs pbo, $–30.6\%\ [95\%\ CI: –56.8, –5.4]$. ALT: LS mean difference vs pbo $–26.2$ IU/L $[95\%\ CI: –50.3, –2.5]$. AST: LS mean difference vs pbo $–16.9$ IU/L $[95\%\ CI: –33.1, –0.8]$). Improvements in adiponectin, NIS-4, Pro-C3, and other markers were observed in the 600 μg group at 19 weeks.

**Conclusion:** PROXYMO demonstrates safety and efficacy of cotadutide in patients with biopsy-proven non-cirrhotic NASH with fibrosis, providing support for further evaluation of cotadutide in this target population.

**LO7: APPLICATION OF REAL-WORLD EVIDENCE ANALYTICS: A 6-YEAR EVENT-FREE SURVIVAL ANALYSIS IN ALAGILLE SYNDROME OF THE GALA CLINICAL RESEARCH DATABASE AND MARALIXIBAT TREATED PATIENTS**

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Methods: RWE to a MRX cohort with the aim to compare event-free survival (EFS) in patients with ALGS. GALA was filtered to align key MRX eligibility criteria. The index time was determined via maximum likelihood estimation. Sensitivity and subgroup analyses, and adjustments for covariates were applied. Missing outcomes data were pruned events to 12 months were consistent with the primary result. Limitations include no standardized measure of pruritus and limited sBA data in GALA, and inherent bias for patients who enter a clinical trial.

Conclusion: This 6-year analysis suggests the potential for improved EFS with MRX in patients with ALGS. This RWE
analysis provides a potential method to evaluate outcomes in long-term intervention studies where placebo comparisons are not feasible. Limitations will always be present given lack of prospective conduct and inherent biases, though sensitivity analyses can help mitigate and aid interpretation.

Kaplan-Meier Plot for Event-Free Survival: Maralixibat Cohort versus GALA Control Group

Primary Analysis: HR=0.305 (95% CI:0.189-0.491), p<0.0001

*Cox regression - effect of MRX vs. GALA log likelihood test adjusted for age, sex, bilirubin, and ALT
Background: Obeticholic acid (OCA) received conditional approval for primary biliary cholangitis (PBC) based on surrogate markers of disease. There are no published data on the effect of OCA on clinical endpoints (death or liver transplant), and randomized placebo-controlled trials to derive such data face significant feasibility and ethical challenges post-approval. This study sought to address this by implementing a novel statistical approach using propensity scores to compare PBC patients treated with OCA in the open-label long-term safety extension (LTSE) of the POISE trial to external controls from two large PBC patient databases.

Methods: The treatment arm included patients in the OCA LTSE study. External controls were patients from the GLOBAL PBC and UK-PBC real-world databases who were diagnosed with PBC from 1990 onwards, that were untreated or treated with ursodeoxycholic acid (UDCA) with at least 1 year of follow-up but were not treated with OCA or other therapies. Eligible follow-up visits were determined based on the POISE eligibility criteria, including alkaline phosphatase (ALP) >1.67xULN or abnormal bilirubin, and bilirubin <2xULN. External control patient visits with an ALT >10xULN or with a history of liver complication (SBP, variceal bleeding, ascites, hepatic encephalopathy, or HCC) within first 6 months were excluded. Index date (baseline) for controls was a random visit of all eligible visits. The primary endpoint was time to liver transplantation or death. Multivariable and
weighted (estimated with propensity scores) Cox regression methods with Firth’s correction were applied separately for each external control group. The following baseline confounders were considered: bilirubin, ALP, AST or ALT, age, PBC duration, UDCA use, diagnosis year, and sex. Sensitivity analyses with different selections for index time were performed.

**Results:** The OCA LTSE study included 209 patients with a maximum follow-up time of 6.3 years. Time was censored similarly in the external control cohorts. In the GLOBAL/UK-PBC external control cohorts, there were 1391/2138 patients included with 6715/8562 eligible visits. Patients were 90.7%/89.3% female and 91.6%/86.6% received UDCA. In the OCA arm, 3 events were observed versus 146/276 events in the GLOBAL/UK-PBC external control cohorts. In univariate, multivariable, and weighted Cox regression analyses, the OCA arm had reduced risk of liver transplantation and death compared to either external control group. In weighted analysis, the hazard ratio for OCA was 0.20 (0.06-0.64, p=0.001) in GLOBAL and 0.28 (0.09-0.90, p=0.033) in UK-PBC (Figure). Consistent findings were observed in multiple sensitivity analyses.

**Conclusion:** When compared with two external real-world data control datasets, treatment with OCA in a trial-setting is associated with better transplant-free survival in patients with PBC.

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**LO9: SERUM AUTOANTIBODIES AGAINST ANNEXIN A11 MIGHT WEAKEN THE BILIARY BICARBONATE UMBRELLA IN IgG4-RELATED CHOLANGITIS**

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**Background:** Annexin A11 was identified by us as the first specific IgG4/IgG1-autoantigen in IgG4-related cholangitis (IRC), the hepatobiliary manifestation of a B-cell driven disease (Gut 2018;67:728). Annexin A11 modulates calcium-dependent exocytosis in insulin secreting β-cells (FEBS Lett 2000;479:46), a crucial mechanism also in
human cholangiocytes to insert proteins like the chloride/bicarbonate exchanger AE2 and the chloride channel ANO1 into the apical plasma membrane, their site of action. These proteins form a 'biliary bicarbonate umbrella' on the apical cholangiocyte surface regarded as defense against harmful hydrophobic bile acid influx (Hepatology 2010;52:1489). Here, we unraveled the function of annexin A11 in human cholangiocytes and a potential role of an IgG1/IgG4-mediated autoreactivity against annexin A11 in the pathogenesis of IRC.

**Methods:** Expression of annexin A11 in human liver was studied by immunohistochemistry and immunofluorescence. In human control and ANXA11 knockdown H69 cholangiocytes, intracellular pH, AE2 and ANO1 surface expression, and bile acid influx were examined using ratio microspectrofluorometry, cell surface biotinylation, and 22,23-3H-glycochenodeoxycholic acid permeation, respectively. Annexin A11-mEmerald and ANO1-mCherry localization in H69 cholangiocytes after incubation with IRC patient serum containing anti-annexin A11 IgG1/IgG4-autoantibodies or disease control serum was investigated by live-cell microscopy.

**Results:** Annexin A11 was strongly expressed in human cholangiocytes, but not hepatocytes. Knockdown of ANXA11 led to reduced plasma membrane expression of ANO1, but not AE2, alkalization of intracellular pH and uncontrolled bile acid influx. High intracellular calcium conditions led to annexin A11 membrane shift and colocalization with ANO1. Incubation with IRC patient serum containing anti-annexin A11 IgG1/IgG4-autoantibodies inhibited annexin A11 membrane shift and reduced ANO1 surface expression.

**Conclusion:** Annexin A11 mediates apical membrane abundance of the chloride channel ANO1 in human cholangiocytes, thereby supporting biliary bicarbonate secretion. This function of annexin A11 is inhibited by IRC patient serum containing anti-annexin A11 IgG1/IgG4-autoantibodies. Anti-annexin A11 autoantibodies might therefore contribute to the pathogenesis of IRC by weakening the 'biliary bicarbonate umbrella'.


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**Background:** JNJ-3989 is an siRNA designed to target all hepatitis B virus (HBV) RNAs, thereby reducing all viral proteins. JNJ-6379 is a CAM that inhibits viral replication by inducing the formation of viral capsids devoid of genomic material. The REEF-1 study assessed the efficacy and safety of monthly (Q4W) s.c. injections of JNJ-3989 (3 dose levels of 40, 100, and 200mg) and/or 250mg QD oral JNJ-6379 in combination with QD oral NA in currently not treated (CNT) or virally suppressed (VS) patients with HBeAg positive or negative CHB.

**Methods:** In this Phase 2b, multicenter, active-controlled study, CHB patients (N=470) were randomized (2:2:2:2:1:1) to 6 arms (see Figure) and dosed for a 48-week double-blind PBO-controlled treatment period and 48 weeks of follow up (FU). The primary endpoint was the proportion of patients meeting NA stopping criteria (ALT <3x ULN, HBV DNA <LLOQ, HBeAg-negative [<LLOQ], and HBsAg <10 IU/mL) at Week 48. Week 48 data are shown here; Week 72 data (FU Week 24) will be presented.

**Results:** Patients in REEF-1 were 66% male, 52% White, 41% Asian, 70% HBeAg negative, and 63% VS at baseline (BL). The proportions of patients achieving primary endpoint are depicted in the Figure, with the highest proportion (19.1%) in the JNJ-3989 200mg + NA arm. The JNJ-3989 200mg + NA arm had the highest proportion
of patients (33%) achieving HBsAg levels <10 IU/mL by Week 44, and 72% reached <100 IU/mL. Significant mean log₁₀ reductions from baseline to end of treatment in HBsAg were observed with JNJ-3989 200, 100, and 40mg + NA (with dose-response pattern), and JNJ-3989 + JNJ-6379 + NA (–2.58, –2.09, –1.50, and –1.76 log₁₀ IU/mL), but not with PBO or JNJ-6379 + NA (–0.22 and –0.07 log₁₀ IU/mL); <3% of patients achieved HBsAg loss. Levels of hepatitis B core-related antigen (HBcrAg), HBV RNA, and HBV DNA (in patients not currently treated at BL), and HBeAg (in HBeAg-positive patients) were reduced on treatment; <1% of patients achieved HBeAg loss. All regimens within this long-term, triple therapy study were generally well tolerated and safe; 2 of 10 reported SAEs (ALT flare and rhabdomyolysis) were considered related to study drug. Treatment discontinuation rates were low (≤6.3% in all arms).

**Conclusion:** JNJ-3989 showed a dose dependent response with up to 19.1% meeting the primary endpoint at Week 48 compared to 0% in the JNJ-6379 + NA and 2.2% in the PBO + NA arm. Reduction of HBsAg levels was greatest with JNJ-3989 200mg s.c. Q4W + NA.

**LO11: DELAYED AND SUBOPTIMAL RESPONSE TO TWO DOSES OF SARS-COV-2 MESSENGER RNA VACCINE IN EUROPEAN PATIENTS WITH COMPENSATED AND DECOMPENSATED CIRRHOSIS OF DIFFERENT AETIOLOGIES: INTERIM ANALYSIS**

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Background: SARS-CoV-2 mRNA vaccines have been approved to prevent SARS-CoV-2 infection, with a reported efficacy of 95% in the general population, but response in patients with cirrhosis is still unknown.

Methods: We conducted a prospective study to assess humoral and cellular response to vaccine in patients with cirrhosis compared to healthy controls according to previous SARS-CoV-2 infection. SARS-CoV-2 IgG antibodies directed against the Spike-protein (anti-S Ab) were tested at baseline, 21 days after the first dose, 21 after the second dose. Healthy volunteers were tested at the same timepoints. In 13 unselected patients with cirrhosis (2 with previous COVID-19), the cellular response to vaccine has been studied and compared to controls by quantification of IFN-γ and IL-2 production. Side effects after vaccination were also reported.

Results: 182 cirrhotics were enrolled: age 61 years, 75% males, 59% viral-related cirrhosis, 74% Child-Pugh A, 31% HCC, 15% enlisted for liver-transplantation, 16% with a previous SARS-CoV-2 infection. 38 healthy subjects were also enrolled, 31% with previous exposure to SARS-CoV-2. After the first dose of vaccine, anti-S Ab titres were significantly lower in patients with cirrhosis than in controls [22.8 (0.4-12,500) U/mL vs 84.75 (0.4-12,500) U/mL, p=0.0001], findings confirmed in the subgroup of patients without previous SARS-CoV-2: 13.9 (0.4-12,500) U/mL vs 43.1 (0.4-345) U/mL, p=0.001]. After the second dose of vaccine, anti-S Ab titre was significantly lower in patients with cirrhosis without previous SARS-CoV-2 infection compared to controls [1,034 (0.4-12,500) U/mL vs 1,520 (259-12,500) U/mL, p=0.05]. Among patients without previous SARS-CoV-2, those with decompensated cirrhosis, HCC and undetectable anti-S Ab after first dose had significantly lower anti-S Ab titres after the second dose of vaccine [637 (0.4-12,500) U/mL vs 1,377 (0.4-12,500) U/mL, p=0.01; 1,116 (0.4-7,500) U/mL vs 1,810 (0.4-12,500) U/mL, p=0.02; 469 (0.4-4,780) U/mL vs 3,908 (91.7-12,500) U/mL, p<0.0001; respectively]. The evaluation of the spike-specific T cell response after the first and second dose indicates that patients with cirrhosis mount a weaker IFN-γ and IL-2 response compared to healthy subjects (Figure 1). No serious adverse events were reported.

Conclusion: In patients with cirrhosis, specifically in those with advanced disease, response to SARS-CoV-2 vaccines was delayed and suboptimal compared to the general population.

LO12: HBsAg LOSS IN CHRONIC HEPATITIS B PATIENTS WITH SUBCUTANEOUS PD-L1 ANTIBODY ASC22 (ENVAFOLIMAB) PLUS
NUCLEOS(T)IDE ANALOGS TREATMENT: INTERIM RESULTS FROM A PHASE IIb CLINICAL TRIAL

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Background: Blockade of PD-1/PD-L1 pathway may lead to a potential cure for HBV. ASC22 (Envafolimab) is a humanized single-domain PD-L1 antibody administered subcutaneously. Here we report the interim efficacy and safety data of ASC22 in patients with chronic hepatitis B (CHB).

Methods: This randomized, single-blind multi-center Phase IIb trial enrolled a total of 149 CHB patients (negative HBeAg and HBV DNA < 20 IU/ml) in two cohorts for 24-week treatment of different dose of ASC22 and 24-week follow-up (NCT04465890). In cohort 1, 75 patients were treated with 1 mg/kg ASC22 Q2W (n=60) or placebo (PBO) Q2W (n=15) + Nucleos(t)ide Analogs (NAs). The efficacy and safety were assessed in patients who completed 24-week treatment of 1 mg/kg ASC22 (n=33) or PBO (n=11) + NAs.

Results: The median (range) baseline HBsAg levels were 2.7 (0.2~3.7) and 2.7 (1.0~3.6) log10 IU/mL in ASC22 and PBO groups. Mean Week 24 HBsAg changes from baseline were -0.38 and 0.00 log10 IU/mL in ASC22 and PBO groups. Patients with baseline HBsAg ≤ 500 IU/mL receiving 1 mg/kg ASC22+NAs (n=16) had more significant HBsAg reduction compared to those receiving PBO+NAs (-0.70 VS 0.00 log10 IU/mL, P < 0.01). In patients with baseline HBsAg ≤ 500 IU/mL, 7/16 (44%) patients in ASC22 group compared to none in PBO group achieved HBsAg reduction ≥ 0.5 log10 IU/mL. 3/16 (19%) patients obtained HBsAg loss (undetectable, < 0.05 IU/mL) at Week 4, 16 and 16, respectively, and remained HBsAg negative until the end of treatment (Fig.1). All three patients maintained HBsAg negative after last dosing of ASC22. ALT flares were observed in 4/7 (57%) and 2/3 (67%) patients with HBsAg reduction ≥ 0.5 log10 IU/mL and HBsAg loss, respectively. Patients treated with ASC22+NAs had a similar AE profile with those treated with PBO+NAs. Any AEs or Grade ≥ 3 AEs were reported in 79% (26/33) and 82% (9/11), or 6% (2/33) and 9% (1/11), of patients treated with ASC22+NAs and PBO+NAs. No SAE occurred during treatment. PK data showed that Cmin value of ASC22 at steady state was predicted to be > 3 μg/mL one month after dosing, indicating > 90% receptor occupancy and ASC22 has the potential to be given once monthly.

Conclusion: Subcutaneous administration of ASC22 Q2W for 24 weeks is shown to be safe and well-tolerated, and can induce HBsAg decline, even HBsAg loss, in CHB patients, especially in those with baseline HBsAg ≤ 500 IU/mL. Further analyses will be performed when all 149 patients complete treatment and follow-up.
Background: Hepatitis E virus (HEV) is responsible for a liver disease that affects millions of people worldwide, especially in low- and middle-income countries with poor socioeconomic conditions. The scope of the study was to determine the seroprevalence of HEV infection among a selected juvenile population living in urban Bogotá, Colombia using an enzyme-linked immunosorbent assay (ELISA).

Methods: We recruited children from 5 to 18 years old in a cross-sectional survey in 2020 and 2021. Inclusion criteria were residency in Bogotá, Colombia, enrollment in one of the local educational institutions, and the authorization of a parent or guardian to participate. We first collected data on demographics, social, clinical, and exposure variables in a structured interview. Then we collected venous blood by venipuncture. We used the ELISA kit (Axiom Diagnostic, Germany) for the detection of human anti-HEV IgG antibodies. We performed a descriptive analysis of the data to present the main characteristics of the participants, and calculated the proportion of the anti-HEV IgG reactive participants. The responsible ethics committees approved the study.

Results: Three-hundred-and-five students participated, of which 276 (90.5%) completed the entire process and had both questionnaires and enough sample volume drawn for the analysis. The median age of the recruited participants was nine years (interquartile range 8-11 years), and 150 (54%) participants were males. Based on the ELISA results, we found three reactive cases for anti-HEV IgG. All the reactive cases were from participants born and raised in Colombia, who lived in the locality of Engativá, who parents had an income between one and two minimum wages.
(280-560 USD), and did not report any contact, symptoms, or diagnosis of viral hepatitis. Based on the structured interviews, all participants reported to have access to drinking water and sanitary systems in their houses. Participants also reported frequent hand washing (77- 89%), no contact with pigs (80%), and occasional pork consumption (91%). Conclusion: The seroprevalence of anti-HEV IgG in the study population was 1%. We can highlight that the participants living in the urban setting of BogotÁl, Colombia, have good access to drinking water and sanitary systems, have good hand washing practices, and rare contact with pigs and moderate consumption of pork. These factors may have contributed to the low HEV seroprevalence found in our study.


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Background: The pandemic of the respiratory disease (COVID-19) associated with the novel coronavirus (SARS-CoV-2) has highlighted the need for biomarkers that can detect the risk of infection (SI) before exposure, which we call “predisposing biomarkers”. Retrospective population-based studies have shown that low A1 is associated with a significant risk of SI 10 years later. NAFLD is also a subset of patients at high risk of severe SI due to type-2 diabetes, hypertension, age and male gender, factors that have been validated as independent predisposing and prognostic factors.¹,² We hypothesize that A1 could have two predictive qualities for SI multivariate biomarkers in patients with NAFLD: both for stratification of risk and SI diagnostic. Our aim is to show that before the pandemic the prevalence of low A1 (pLowA1) in patients with NAFLD was significantly higher than the reference values in the general population (GP).

Methods: For each sera, pLowA1 was defined as a value below the 2.5% lowest percentile for the standardized (age and gender) reference interval of GP (2.5%Ref), assessed by logistic regression in, 28,919 and 7,482 adult healthy volunteers in the USA,³ and France, respectively.⁴ The primary endpoint was a predisposing higher pLowA1 between 2018 and 2019 in a population at risk of NAFLD who were routinely followed for the risk of liver fibrosis in the USA (n=131,626) compared to the 2.5%Ref, which was externally validated by the same comparison in France (n=19,177). We then compared the pLowA1 during the pandemic years 2020-August-2021 (USA n=135,155; France n=9800) to the pLowA1 observed in 2018 and 2019 to confirm the temporal association between pLowA1 and the peaks of the pandemic.

Results: Figure 1 represents the pLowA1 before and during the pandemic in the US NAFLD cohort. Before the pandemic, the pLowA1 in NAFLD was indeed significantly greater (10%) than the expected 2.5%, in USA and France (not shown). The highest pLowA1 was observed, in the subset of both men and women older than 50, with glucose > 7 mmol/L and BMI >30 kg/m², 10.3% and 7.7% respectively (all P<0.001). During the pandemic, the overall pLowA1 was even higher (all P<.001 vs 2.5%Ref and vs 2018-2019) in women and in men. The main limitation is the high prevalence of Caucasian patients in the reference GP. Therefore, the findings may not be applicable to other ethnic groups. Indeed the pLowA1n in the French GP Caucasian (89%) vs non-Caucasian (11%) was 2.0% vs 4.5% respectively (P<.001).

Conclusion: Thanks to our reference populations, this study confirms the interest of using A1 as a component of predisposing, diagnostic and prognostic multivariate tests for the risk of SARS-CoV-2 infection in adult Caucasian NAFLD patients. References. ¹Dabbah 2021. ²Poynard 2020. ³Ritchie 2006, ⁴Poynard 2010.
Background: Fatty liver diseases (FLD), including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), are a growing global health concern. Long-term in vitro models of FLD have emerged as valuable tools for various studies including pre-clinical mechanistic, drug discovery and screening, and drug induced steatosis. Previous studies have demonstrated lipid loading and lipid induced toxicity capabilities of the HEPATOPAC® and HEPATOMUNE® models, which are long-term (at least 28 days) micropatterned culture systems containing primary human hepatocytes and supporting mouse stromal cells, with the addition of primary human Kupffer cells in the HEPATOMUNE system.

Methods: In HEPATOPAC and HEPATOMUNE cultures lipid loading was induced either free fatty acids (FFA), high glucose and fructose (HGF), or a combination (FFA+HGF). Cultures were treated with steatosis inducers for 4 days followed by 3 days with and without lipid inducing agents. For gene knockdown studies homozygous wildtype (WT) PNPLA3 and 148M genotyped primary human hepatocytes were treated with siRNA to PNPLA3 to model the effects of the mutation and potential ASO therapy on steatosis endpoints in vitro. Steatosis was induced by either FFA or ethanol (100mM) and immune cells were activated with lipopolysaccharide (LPS) (50ng/mL). In all experiments, steatosis was assessed by high content imaging (HCI) of neutral lipid stained cultures.

Results: In all media conditions, the addition of Kupffer cells increased lipid loading approximately 2-fold. Additionally, the presence of Kupffer cells strongly prevented lipid clearing when cultures were switched to control medium. Interestingly, media containing high glucose and fructose also reduced the ability of the cultures to clear excess lipid when returned to control conditions. A number of genetic variants have been shown to influence NAFLD and NASH risk including the I148M variant in patatin-like phospholipase domain-containing protein 3 (PNPLA3).
Notably, PNPLA3 knockdown reduced FFA induced lipid loading only in hepatocytes having the I148 mutation, with no effect on WT donors. Interestingly, these findings were replicated when steatosis was induced by ethanol, instead of FFA. Furthermore, immune stimulation with LPS in either the presence or absence of ethanol inhibited the siRNA induced reduction in lipid loading in hepatocytes with the PNPLA3 I148 mutation.

**Conclusion:** These data suggest that both immune cells and high sugar conditions play a role in the persistence of established steatosis. Additionally, lipid loading differences in cultures treated with FFA, ethanol, and/or LPS in genotyped donors with PNPLA3 knockdown suggest the existence of variant pathways for steatosis potentiation. Together, these data support the ability of the HEPATOPAC and HEPATOMUNE models to create a complex, multi-functional in vitro FLD model for a wide range of applications.

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**LP4: PRECLINICAL CHARACTERIZATION OF ABI-4334, A NOVEL, HIGHLY POTENT CORE INHIBITOR FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS INFECTION**

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**Background:** Core inhibitors (CIs) are a new class of HBV antivirals with the potential to improve cure rates. Clinical trials combining CIs with nucleos(t)ide reverse transcriptase inhibitors (NrtIs) have demonstrated enhanced viral suppression compared to NrtIs alone. CIs have multiple mechanisms of action (MOA), including (1) inhibition of pgRNA encapsidation which prevents assembly and release of new viral particles, and (2) disruption of incoming capsids which prevents de novo cccDNA formation. To date, CIs in development have significantly greater potency against pgRNA encapsidation compared to cccDNA formation; however, activity against both MOAs is likely to be important for maximal clinical activity. Here we summarize the preclinical profile of ABI-4334 (4334), a novel CI with high potency against both pgRNA encapsidation and cccDNA formation.

**Methods:** EC50s for pgRNA encapsidation (HBV DNA endpoint) and cccDNA formation (HBeAg endpoint) were measured in AD38 and HepG2-NTCP cell lines as well as primary human hepatocytes (PHH) by qPCR and ELISA, respectively. Protein adjusted EC50s (paEC50) were determined in AD38 cells cultured in human serum albumin and alpha acidic glycoprotein. A panel of viral genotypes (A-J) and CI binding pocket variants was assessed for 4334 sensitivity in a HepG2 transient transfection assay. Pharmacokinetic (PK) modeling was performed using mouse, rat, dog, and monkey PK data to predict human Cmin.

**Results:** In PHH, 4334 potently inhibited pgRNA encapsidation (EC50= 0.51 nM) and cccDNA formation (EC50= 2.4 nM). Comparable potency was observed in AD38 (EC50= 1.2 nM, HBV DNA) and HepG2-NTCP (EC50= 2.4 nM, HBeAg) cell lines. A 5.5-fold serum shift was observed for 4334, resulting in paEC50s of 2.8 nM and 13.2 nM for pgRNA encapsidation and cccDNA formation, respectively. No cytotoxicity was observed across 7 cell lines and primary cells (CC50 >20 ÅM). 4334 demonstrated pan-genotypic activity and an improved activity profile against CI binding pocket variants relative to other CIs. PK modeling predicts a 300 mg dose of 4334 would achieve Cmin values 196- and 42-fold over pgRNA encapsidation and cccDNA formation paEC50s, respectively.

**Conclusion:** 4334 is a novel, orally bioavailable core inhibitor with single digit nM potency against pgRNA encapsidation and cccDNA formation and is predicted to achieve Cmin values at high multiples of both MOAs paEC50s. 4334 is advancing in development with a Phase 1 study planned for 2022.
Background: CB4211, an analog of the natural mitochondrially encoded peptide MOTS-c (mitochondrial open-reading-frame of the twelve S rRNA-C), showed potential for improving NASH and obesity in pre-clinical models. The aim of this multicenter, double-blind, randomized, placebo-controlled trial was to examine the safety, tolerability, pharmacokinetics, and pharmacodynamics of CB4211 in obese subjects with NAFLD.

Methods: This proof-of-concept trial randomized 23 NAFLD subjects with ≥10% liver fat content (LFC) by MRI-PDFF, body mass index ≥30 kg/m², and Fibroscan CAP ≥300 dB/m at baseline. Subjects were monitored in an in-patient unit during the entire 4-week treatment period at 4 centers in the US and were randomized 1:1 to receive once daily subcutaneous CB4211 25 mg or placebo for 4 weeks. Endpoints were safety and tolerability (Primary) and pharmacokinetics (Secondary). Exploratory endpoints included changes from baseline to week-4 in ALT, AST, glucose, liver fat content, and body weight.

Results: Baseline characteristics were similar across the treatment and placebo groups. CB4211 was safe and well-tolerated and there were no serious adverse events. CB4211 treatment for 4-weeks produced significantly greater reductions from baseline compared to placebo in mean ALT (-21% vs 4% for placebo, p<0.05) (Figure), AST (-18% vs -11%, p<0.05), and fasting glucose (-6% vs 0%, p<0.05), respectively. The proportion of responders achieving ≥17 U/L reduction in ALT was 27% on CB4211 vs 11% on placebo. There was a trend to decreased body weight for CB4211 vs placebo. Both groups received a standardized diet as in-patients and absolute LFC decreased substantially in both treatment arms (-5.03% for CB4211 vs -4.88% for placebo).

Conclusion: In obese subjects with NAFLD, 4 weeks of CB4211 treatment was safe and well tolerated. CB4211 treatment produced statistically significant reductions in biomarkers of liver injury, ALT and AST, compared to placebo and reduced fasting glucose levels, independent of reducing liver fat, with a trend to reduced body weight. These data support the further development CB4211, a first in class MOTS-c analog, as a potential treatment for NASH.

Figure: Time Course of Reduction in Serum ALT and AST with CB4211 Treatment
LP6: LIVER INJURY IN THE SETTING OF IVERMECTIN PROPHYLAXIS FOR COVID-19 INFECTION

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Background: Ivermectin belongs to the anthelmintics class of medications. It is commonly used as an anti-infective agent to prevent parasitic nematodes and scabies. The drug is typically given in one to two oral doses. Ivermectin has been associated with minor and rare instances of apparent liver injury. With the recent COVID-19 pandemic, home remedies and off-label uses for drugs have become popular as a preventative measure for COVID-19. To our knowledge, this is the first case of medication-induced acute hepatocellular injury and jaundice likely resulting from self-treatment with Ivermectin 1.87% paste.

Methods: A 61-year-old Caucasian female took Ivermectin paste to prevent COVID-19 while traveling. Medical history included hypertension and back problems. Medications included Metoprolol Succinate 25 mg daily and cyclobenzaprine 10 mg PRN. Ivermectin 1.87% Paste was obtained from her local tractor supply store. Dose calculated based on her weight of 150 lbs. Dosage of 1/4 teaspoon consisting of three doses. The second dose was taken three days after the first and the third dose was taken two weeks after the second. Symptoms of clay-colored stool started immediately after the first dose 6/27/21 and dark urine after the third dose on 7/11/21. Jaundice and scleral icterus were noticed on 7/14/21 by the family who were picking up the patient from the airport and who later brought the patient to the hospital. On exam, the patient was alert and orientated x 4. Blood pressure elevated at 175/82. Skin appeared jaundiced. HEENT exam significant for scleral icterus. There was no tenderness to palpation to the abdomen on the exam. Labs revealed direct hyperbilirubinemia (t.bili 8.5, direct bili 6.3) and transaminitis (ALT 1,825, AST 1,81). Ferritin, CRP, ANA, AMA M2 IgG, anti-LKM, & viral hepatitis were also sent.

Results: Ferritin and CRP elevated due to inflammation of her liver. ANA, AMA M2 IgG, anti-LKM, and viral hepatitis negative. Other labs were unremarkable. Repeat labs 24 hours later indicated down-trending transaminitis (ALT 1,462, AST 978) and hyperbilirubinemia (t.bili 6.9, direct bili 4.6). Coagulopathy (INR 1.32) was exhibited, thus Vitamin K 10 mg x 3 days was given. Patient remained asymptomatic and was discharged later that day. Recommendations were given to the patient to follow up with her PCP back home in Missouri was recommended to confirm down-trending liver enzymes.

Conclusion: This case indicates the need to increase awareness of potential, but serious side effects when certain medications are used off-label. Additionally, this case supports the idea that Ivermectin use can result in serious hepatocellular injury. Thus, it should be used with caution if the drug is taken over-the-counter without a prescription.

LP7: SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF THE NOVEL HBV CAPSID ASSEMBLY INHIBITOR ZM-H1505R FOLLOWING MULTIPLE ASCENDING DOSES IN HEALTHY SUBJECTS (PART 2)
Zhijun Zhang, Xiuhong Jiang, Bo Hua, Gang Liu, Tian Xia, Aiyun Deng, Hui Lu, Ruoling Guo, Zhe Wang, Ming Ren, Bo Liang and Huanming Chen, Zhimeng Biopharma

**Background:** ZM-H1505R is a small-molecule HBV capsid assembly modulator with a novel pyrazole structure currently being evaluated for the treatment of chronic hepatitis B (CHB). It is active against most HBV variants that show resistance to other HBV capsid modulators. Previously, we have reported the safety, tolerability, and pharmacokinetics (PK) results of ZM-H1505R after single ascending dose (SAD) oral administration in healthy subjects (Part 1). Here, we report the results of its safety and PK following multiple ascending doses (MAD) study (Part 2) (ClinicalTrials.gov NCT04220801).

**Methods:** This was a randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, tolerability, and PK of ZM-H1505R following oral administration. The study included 2 parts, SAD and MAD. In this Part 2 MAD study, 24 healthy subjects were randomized 3:1 to receive ZM-H1505R (75, or 150 and 300 mg) or placebo once-daily for 14 consecutive days. Safety and tolerability were assessed using vital signs, PE findings, Electrocardiogram (ECG) and laboratory investigations, and adverse events (AEs). The plasma PK parameters measured include AUCs, Cmax, Cmin, Tmax, and t1/2.

**Results:**

**Safety:** During oral administration of 75, 150, or 300 mg, QD, for 14 consecutive days, ZM-H1505R was found safe and well tolerated. Twelve subjects (50.0%) reported a total of 19 treatment-emergent adverse events (TEAEs), including 11 of 18 subjects who received ZM-H1505R and 1 of 6 who received placebo. The most common TEAEs are gastrointestinal disorders (reported in 4 of 18 subjects receiving ZM-H1505R and 1 of 6 receiving placebo) and are all deemed mild. One subject in the 300mg cohort discontinued study participation due to the increases in amylase and lipase. There were no deaths or SAEs. Pharmacokinetics: Following MAD of ZM-H1505R, its mean plasma AUC and Cmax increased in a dose-proportional manner. A steady-state was achieved by days 13 and 14 with a t1/2 of 12.2-21.7h. At day 14, the mean plasma Cmin, at 75, 150, and 300mg doses were 6.3, 18.2, and 37.5 folds of its protein-binding adjusted HBV DNA EC50, respectively.

**Conclusion:** Multiple doses of up to 300 mg of ZM-H1505R were safe and well tolerated in healthy subjects. Its plasma exposure was well above its effective inhibitory concentration and increased in a dose-proportional manner. The safety and PK profile of ZM-H1505R supports its further evaluation in CHB patients.

LP8: EFFICACY AND SAFETY OF PEGBELFERMIN IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS AND COMPENSATED CIRRHOSIS: RESULTS FROM THE PHASE 2b, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED FALCON 2 STUDY

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**Background:** Pegbelfermin (PGBF) is a PEGylated fibroblast growth factor 21 (FGF21) analog, a non-mitogenic hormone that is a key regulator of energy metabolism. In a 16-week phase 2a study in patients (pts) with NASH, stage
1-3 fibrosis, and MRI-PDFF ≥10%, PGBF reduced hepatic steatosis and improved biomarkers of fibrosis, metabolism, and liver injury. This phase 2b study evaluated safety and efficacy of PGBF in pts with NASH and compensated cirrhosis.

**Methods:** FALCON 2 (NCT03486912) was a randomized (1:1:1:1), double-blind, placebo (PBO)-controlled study conducted in the US and Japan. Eligible adults (18-75) had biopsy-confirmed NASH and stage 4 fibrosis (NASH CRN criteria) without history of hepatic decompensation. PGBF (10, 20, or 40 mg) or PBO was administered by subcutaneous injection once weekly for 48 weeks. The primary endpoint was fibrosis improvement (≥1 point decrease in NASH CRN fibrosis score) without NASH worsening (≥1 point increase in NAFLD activity score [NAS]) at week 48. Secondary and exploratory endpoints were additional histological assessments and noninvasive measures of steatosis, fibrosis, and liver injury.

**Results:** 154 pts were randomized and received study drug; mean age was 59.4 y, 64% were women, 79% had T2DM. Baseline characteristics were similar between study arms (table). At week 48, fibrosis improvement without NASH worsening was observed in 31% (PBO), 28% (10 mg), 24% (20 mg PGBF), and 28% (40 mg PGBF) of pts; statistical significance was not reached on the Cochran-Armitage trend test of proportions (P=.361; 1-sided 1α=.05). NAS improvements were more frequent in the PGBF dose arms compared with the PBO arm and were largely driven by reductions in lobular inflammation. MRI-PDFF and MRE indicated that PGBF numerically improved steatosis and liver stiffness measurements compared with PBO. Decreases in PRO-C3, ALT, and AST were observed in the 20 mg and/or 40 mg PGBF arms relative to the PBO arm. Numerical increases in serious adverse events (AEs) were observed in the PGBF arms compared with the PBO arm; none were treatment-related. One pt in the 40 mg PBGF arm discontinued study treatment due to a treatment-emergent AE of ascites.

**Conclusion:** While the primary histopathologic endpoint was not met, PGBF improved noninvasive measures of fibrosis, steatosis, or inflammation. PGBF was generally safe and well tolerated in this advanced NASH population.
LP9: SELECTIVE INHIBITION OF ESTROGEN RECEPTOR ALPHA RESTORES REGULATORY T CELL FUNCTIONAL PHENOTYPE IN AUTOIMMUNE HEPATITIS

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Background: Dysfunction in regulatory T cells (Tregs) is a hallmark of autoimmune hepatitis (AIH) and has been linked to impaired expression and activity of CD39, an ectonucleotidase that scavenges pro-inflammatory nucleotides
generating immunosuppressive adenosine. CD39 can be induced upon engagement of aryl-hydrocarbon-receptor (AhR), a modulator of toxins and adaptive immunity. Previously, we have shown Tregs from AIH patients display aberrant immune responses upon AhR ligation, possibly due to an overexpression of estrogen receptor alpha (ERα), an AhR non-canonical binding partner. In this study, we investigated whether targeted antagonism of ERα could ameliorate Treg response to AhR activation in AIH.

Methods: Tregs were obtained from the peripheral blood of 10 AIH patients and 7 healthy controls (HC) upon CD4-cell polarization in the presence of IL-2 and TGF-β. Following exposure to the ERα specific antagonist methyl piperidinopyrazole (MPP), Tregs were stimulated with unconjugated bilirubin (UCB), a known AhR endogenous ligand, and expression of CD39, IL-10, IL-17 and IFN-γ measured by flow cytometry. Additionally, expression of CYP1A1, the primary gene controlled by AhR, and CD39 were quantified using RT-PCR.

Results: Stimulation with UCB resulted in minimal changes in expression of CD39 and cytokine profiles in AIH Tregs. However, exposure to a combination of UCB and MPP resulted in an upregulation of CD39 at both mRNA and protein level (p<0.05). Moreover, a trend towards an increase in IL-10+ Tregs and IL-10 expressing CD39+ Tregs was also observed. A significant elevation in CYP1A1 expression following MPP exposure in the presence of UCB confirmed these effects were mediated through an AhR dependent mechanism. No significant changes were noted in HC Treg phenotype upon exposure to UCB and MPP.

Conclusion: Selective inhibition of ERα restores Treg functional phenotype in AIH patients following AhR activation and could provide a novel therapeutic strategy in the quest to boost and maintain immune tolerance in AIH.

LP10: ARO-AAT TREATMENT REDUCES INTRA-HEPATIC Z-AAT LEADING TO IMPROVED PARAMETERS OF LIVER HEALTH AND FIBROSIS REGRESSION

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Background: AATD due to homozygous PiZZ mutation produces mutant Z-protein (Z-AAT) globules in hepatocytes leading to liver fibrosis. ARO-AAT, an investigational RNAi therapeutic, silences liver Z-AAT mRNA to reduce Z-AAT synthesis. Patients (pts) with PiZZ AATD received ARO-AAT in an ongoing, open-label, Phase 2 study.

Methods: ARO-AAT 200 mg (Group 1 [N=4] and Group 2 [N=8]) or 100 mg (Group 1b; N=4) was administered subcutaneously at Week (wk) 1, 4 and then every 12 wks. Serum Z-AAT and liver enzymes were measured. Paired biopsies collected at baseline (BL) and post-BL (Wk24 for Groups 1/1b and Wk48 for Group 2) are available for 14/16 pts. Histology was assessed and adjudicated by 3 pathologists blinded to subject and time point. Key endpoints include METAVIR fibrosis, liver Z-AAT levels, and globule burden (PAS+D staining for extent of portal tract and perportal hepatocyte involvement and zonal location).

Results: At BL, mean age was 52 years (range 20-66 years); 14/16 were men; 11/14 had ≥F2 fibrosis. ARO-AAT substantially reduced serum Z-AAT in all pts after the first dose which was sustained throughout observation. Mean % reduction in liver total Z-AAT ranged from 80% to 89% at Wk24/48. All pts had reduced globule burden (mean score
7.3 of a maximum of 9 at BL vs. 2.5 at Wk24/48). Improvement in fibrosis (≥1-stage) was achieved in 6/11 pts with 200 mg and 0/3 pts with 100 mg. Two pts in Group 2 had worsening of fibrosis from BL to Wk48 (both from F2 to F3), although both had profound reductions in globule burden (scores of 9 and 4 at BL and 0 at Wk48), and reduced ALT and GGT levels after treatment. All groups showed normalized ALT and GGT following treatment. Mean % reduction from baseline ranged from 42% to 56% for ALT and from 33% to 54% for GGT at Wk 28 and Wk72. ARO-AAT was well tolerated, with no sustained clinically meaningful changes from BL in ppFEV1 and no AEs leading to study or study drug discontinuation. Four SAEs were reported: EBV-related myocarditis, diverticulitis, dyspnea, and vestibular neuronitis, all of which involve confounding factors or alternative etiology.

**Conclusion:** ARO-AAT reduced serum and liver Z-AAT and globule burden in all patients and normalized liver enzymes. These data demonstrate that removal of the causative factor, Z-AAT, in AATD liver disease ameliorates liver injury, and can lead to an improvement in fibrosis.

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<tr>
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<th>ARO-AAT 200 mg</th>
<th>ARO-AAT 100 mg</th>
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<tr>
<td></td>
<td>Group 1 (N=4)</td>
<td>Group 2 (N=8)</td>
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<tr>
<td>Mean % Change (SD) Serum Z-AAT</td>
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<tr>
<td>Wk24/28</td>
<td>-89.5% (3.7)</td>
<td>-85.1% (7.8)</td>
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<td></td>
<td>n=4</td>
<td>n=8</td>
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<tr>
<td>Wk52</td>
<td>-87.0% (7.3)</td>
<td>-82.4% (10.0)</td>
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<td></td>
<td>n=4</td>
<td>n=5</td>
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<tr>
<td>Wk72</td>
<td>-92.0% (3.3)</td>
<td>NA</td>
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<tr>
<td>Mean % Change (SD) Total Liver Z-AAT</td>
<td></td>
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</tr>
<tr>
<td>Wk24</td>
<td>-79.8% (10.5)</td>
<td>NA</td>
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<td></td>
<td>n=4</td>
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<tr>
<td>Wk48</td>
<td>NA</td>
<td>-88.8% (9.0)</td>
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<td>n=6</td>
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<td>PAS+D Total Globule Burden, n/N (%)</td>
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<tr>
<td>≥ 1-point Improvement from BL to Wk24/48</td>
<td>4/4 (100%)</td>
<td>7/7 (100%) a</td>
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<tr>
<td>No Change from BL to Wk24/48</td>
<td>0/4 (0%)</td>
<td>0/7 (0%)</td>
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<tr>
<td>METAVIR Fibrosis Stage, n/N (%)</td>
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<tr>
<td>≥ 1-point Improvement from BL to Wk24/48</td>
<td>2/4 (50%)</td>
<td>4/7 (57.1%)</td>
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<tr>
<td>No Change from BL to Wk24/48</td>
<td>2/4 (50%)</td>
<td>1/7 (14.3%)</td>
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<tr>
<td>≥ 1-point Worsening from BL to Wk24/48</td>
<td>0/4 (0%)</td>
<td>2/7 (28.6%)</td>
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NA = not applicable; Liver biopsies were collected at Wk24 for Groups 1 and 1b and at Wk48 for Group 2

a At data cutoff, one subject in Group 2 had not yet reached Wk48 and was not included in the analysis

b One subject in Group 1b had baseline biopsy that was not evaluable for METAVIR fibrosis

**LP11: ARO-HSD, AN INVESTIGATIONAL RNAi THERAPEUTIC, DEMONSTRATES REDUCTION IN ALT AND HEPATIC HSD17B13**
mRNA AND PROTEIN IN PATIENTS WITH NASH OR SUSPECTED NASH

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Background: Human genetic data indicate that a loss of function (LOF) mutation in HSD17B13 provides protection against alcoholic hepatitis, cirrhosis, and NASH, with approximately 30-50% risk reduction compared to non-carriers. ARO-HSD is an RNAi-based therapy designed to mimic the naturally occurring LOF genetic variation in HSD17B13 by reducing its expression in hepatocytes. We previously reported data from suspected NASH (sNASH) patients administered 100 mg of ARO-HSD. Herein, we report results from additional patients with sNASH administered 25 mg and 200 mg of ARO-HSD.

Methods: ARO-HSD was administered by a single subcutaneous injection to male and female normal healthy volunteers (NHVs) (19-52 yrs old) at doses of 25, 50, 100, and 200 mg (4 active, 4 placebo per dose level) and followed to Day 113. Eighteen sNASH patients (32-61 years old) (based on MRI-PDFF liver fat >8% and ALT>ULN), 4 of whom had confirmed NASH, received 25, 100 or 200 mg of ARO-HSD on Day 1 and Day 29 and have completed the Day 71 liver biopsy, with some completing study at Day 113. Changes in hepatic HSD17B13 mRNA and protein levels from baseline were measured. Safety was assessed in all subjects including laboratory measures of liver function.

Results: Hepatic HSD17B13 mRNA was reduced from baseline by a mean of 56.9%, 85.5% and 93.4% in the 25, 100, and 200 mg dose cohorts, respectively. Hepatic HSD17B13 protein levels were similarly reduced by a mean of >34.2%, >86.0%, and 82.7%, with multiple measurements below the assay’s level of quantitation. In the 200 mg dose cohort, all 6 subjects showed greater than 90% reduction in hepatic HSD17B13 mRNA expression. Dose-dependent decreases in ALT were observed with maximum mean reductions of 7.7%, 44% and 42% at 25, 100 and 200 mg doses, respectively, and were sustained for up to 12 weeks for the ≥ 100 mg doses. ARO-HSD was well-tolerated in both NHVs and patients, with no ARO-HSD-related serious adverse events reported, no AE leading to drug discontinuations, and no ARO-HSD-related clinically significant adverse laboratory trends observed.

Conclusion: ARO-HSD has been well tolerated at doses up to 200 mg given on Day 1 and Day 29. Significant, dose-dependent reductions in liver HSD17B13 mRNA and protein were observed and corresponded with ALT reductions of up to 44%, which may be a clinically meaningful signal of reduced liver inflammation. Based on duration of ALT reduction, quarterly or less frequent dosing appears feasible.
LP12: SUBCUTANEOUS ADMINISTRATION OF REP 2139-MG IN THE COMPASSIONATE TREATMENT OF CIRRHOTIC HBV / HDV CO-INFECTION

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Background: REP 2139-Mg based combination therapy achieves high rates of HBsAg loss, therapeutic transaminase flares and functional cure of HBV and HDV when administered by weekly IV infusion. Like all phosphorothioate oligonucleotides (antisense oligonucleotides), subcutaneous (SC) injection site reactions are common with REP 2139 but, like all NAPs, are significantly stronger because of their increased length. Chelate complex formulation of NAPs (REP 2139-Mg) neutralizes administration reactivity. The safety and efficacy of SC injection of REP 2139-Mg in combination therapy was assessed in a cirrhotic patient with chronic HBV / HDV co-infection.

Methods: The patient (male, Senegalese, 51 years old) had confirmed cirrhosis and chronic HBV / HDV co-infection since 2005 (HDV GT3) and had failed previous therapies with TDF (300mg) + pegIFN (180ug) and later with TDF + pegIFN (180ug) + bulvertide (2mg) and was currently receiving only TDF. Eight months following discontinuation of pegIFN + bulvertide, TDF therapy was supplemented with 90ug pegIFN and 250mg REP 2139-Mg given as two subcutaneous injections of 125mg once each week. Safety assessments included liver, kidney and hematological function. Virologic assessments included HDV RNA (Robogene MK II), HBV DNA (Abbott), HBsAg and anti-HBs (Abbott Architect quantitative).

Results: No evidence of pain or inflammation at the injection sites for REP 2139-Mg was observed for the first 9 weeks. Thereafter, mild to moderate discomfort post injection was transient and not accompanied by inflammation. Mild pruritis after week 6 responded well to supportive therapy. Two mild and superficial indurations were not accompanied by pain or inflammation. Virologic response was rapid, with HDV RNA becoming undetectable at week 4 and HBsAg becoming < 0.05 IU/mL at week 15 and HBsAg seroconversion evident at week 12 of therapy. A strong host-mediated

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<th>Table: ARO-HSD reduces liver HSD17B13 mRNA, Protein, and ALT</th>
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<td><strong>Table:</strong> ARO-HSD reduces liver HSD17B13 mRNA, Protein, and ALT</td>
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| Mean Percent Change from Baseline (Range) | Cohort 1b (25mg) N=6 | Cohort 3b (100mg) N=6 | Cohort 4b (200mg) N=6 |
| --- |
| Liver HSD17B13 mRNA level at D71 | -56.9% (-50.7,-60.5%) | -85.5% (-61.6,-96.1%) | -93% (-91,-99%) |
| Liver HSD17B13 protein level at D71 | <-34.2% (53.5,-92.4%) | <-86.0% (-63.2,-98.0%) | -82.7% (-80.2,-85.2%)** |
| Serum ALT level at Baseline | 45.7 (U/L) | 68 (U/L) | 76 (U/L) |
| Day 71 | -7.7% | -39.3% | -42.2% |
| Day 85 | -3.5% | -43.6% | -41.1% |
| Day 113* | 2.6% | -35.2% | -37.8% |

* 13/18 patients have completed study, remaining 5 patients have completed up to Day 85. ** n=2 (3 samples with baseline HSD17B13 BLOQ, 1 sample failed assay acceptance criteria)
transaminase flare (ALT, AST and GGT) developed after week 6, with its nadir (ALT 373 U/L) at week 9 and rapid normalization (current ALT is 54 U/L at week 16). Liver and kidney functions have remained normal throughout therapy with stable hematological parameters (RBC, WBC, platelets).

**Conclusion:** SC REP 2139-Mg was safe, well tolerated and highly effective against HBV and HDV infection in combination with TDF and low dose pegIFN (90ug) in this cirrhotic patient. The therapeutic transaminase flare was not associated with any adverse effects and was correlated with HBsAg loss.

**LP13: TARGETING TLR7 WITH RO7020531: PHASE 1 STUDY OF THE SAFETY, PK, PD AND ANTIVIRAL ACTIVITY IN PATIENTS WITH CHRONIC HEPATITIS B NOT RECEIVING ANTIVIRAL THERAPY**

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**Background:** Stimulation of toll-like receptors (TLRs) activates innate and adaptive immune responses, potentially allowing functional cure of Chronic Hepatitis B (CHB) in combination therapy. RO7020531 is a double prodrug of a TLR7 agonist, RO7011785, and was previously demonstrated to be safe and acceptably tolerated in healthy volunteers and virally suppressed CHB patients up to 170mg every other day (QOD). Safety, pharmacokinetics (PK), pharmacodynamics (PD) and antiviral activity of RO7020531 were assessed in CHB patients not receiving antiviral treatment.

**Methods:** Twenty CHB patients who were not on antiviral treatment were randomized (3:1) to receive 150mg RO7020531 or matching placebo orally QOD for 6 weeks and followed-up for 6 additional weeks. Adverse events (AEs) were monitored, PK was assessed and circulating biomarkers for TLR7 activation as well as viral biomarkers were assessed.

**Results:** At baseline, median (range) HBV DNA was 4.76 (3.51 - 8.71) and 4.17 (4.02 - 5.73) log10 IU/mL in the active and placebo groups. Median (range) HBsAg was 3.71 (2.76 - 5.15) and 3.40 (2.70 - 4.03) log10 IU/mL in the active and placebo groups. 4/15 active and 0/5 placebo patients were HBe positive. Four patients on active treatment experienced clusters of AEs, including one serious AE, which were considered related to TLR7 activation (flu-like symptoms, pyrexia). Four patients prematurely discontinued study treatment: 2 due to COVID-19 lockdown (1 active, 1 placebo), and 2 due to consent withdrawal (both were on active treatment and experienced TLR7-related AEs). RO7011785 PK profiles on the first and last dosing days were similar and consistent with the PK profiles in virally suppressed CHB. TLR7 activation was demonstrated by increases in IFN alpha and IP-10, consistent with results in virally suppressed CHB. All patients on active treatment experienced a decrease in HBV DNA as early as Day 8 that persisted throughout the dosing period (Figure). At Day 42, the median (range) change from baseline in HBV DNA was -0.68 (-2.68 - -0.18) and -0.12 (-0.29 - 0.18) log10 IU/mL in the active and placebo groups. One patient on active treatment experienced a decrease in HBsAg by >1 log10.

**Conclusion:** RO7020531 was safe and acceptably tolerated in naïve CHB patients and stimulated TLR7 activation, resulting in robust antiviral responses. It is currently under further investigation in the phase 2 PIRANGA platform trial of combination therapy to achieve functional cure in HBV.
LP14: EXTERNAL VALIDATION OF LCR1-LCR2, A MULTIVARIABLE HCC RISK CALCULATOR, IN PATIENTS WITH CHRONIC HEPATITIS B (CHB)


Background: Liver cancer risk test algorithm (LCR1-LCR2) is a multi-analyte blood test combining proteins involved in liver cell repair (apolipoprotein A1, haptoglobin), known HCC risk factors (gender, age, GGT), a marker of fibrosis (alpha2-macroglobulin) and alpha fetoprotein (AFP) a specific marker of HCC, recently externally validated in Pts with chronic hepatitis C,1 but only internally validated in Pts with CHB.2 The aim was to externally validate LCR1-LCR2 in Pts with CHB, treated or not with antivirals.

Methods: Pre-included Pts were from the Hepather multi-ethnic cohort, a prospective study in adult Pts with CHB (n=6,071) enrolled from 32 hepatology centers in France.3 LCR1-LCR2 was assessed retrospectively in the Pts with the LCR1-LCR2 components and AFP, available at baseline. The co-primary study outcome was the negative predictive value (NPV) of LCR1-LCR2 at 5-years (yrs) for the HCC occurrence and for survival without HCC according to the predetermined LCR1-LCR2 cutoffs, adjusted for risk covariables and for the HBV treatment, quantified using time-dependent Cox proportional hazards models.
Results: A total of 3,530 Pts with at least one year of followup were included in the study. A total of 76 HCC occurred during a median (IQR) 6.0 yrs (4.8-7.3) follow-up. Baseline fibrosis stages were cirrhosis (F4) in 193 Pts (6%), 298 F3 (8%), 280 F2 (8%), 818 F1 (23%), and 1,941 F0 (55%). Median age was 42.3 yrs (32.6-53.7). There was 2,231 males (63%), Sub-Saharan (33%), 1,106 European (32 %), 573 Asian (16%), 398 North African (11%); 253 type-2 diabetes (7%), 398 HBeAg positive (12%), 12 current alcohol consumption (0.5%) and 339 past alcohol consumption (10%). 806 Pts were treated by tenofovir or entecavir (23%). The 5- yrs NPV (Figure), the first primary study outcome, was 99.0% (95%CI 98.7-99.4) similar to the NPV observed in the external validation of 4,903 Pts with CHC, 99.4% (99.1-99.6).1 The second primary outcome, the significant Cox hazard ratio (5.5; 2.8-10.6; P<0.0001) was obtained after adjustment for exposure to antivirals, age, gender, geographical origin, HBe-Ag status, previous alcohol consumption, and type 2-diabetes.

Conclusion: The performance of LCR1-LCR2 for identifying patients with chronic hepatitis B at very low risk of HCC at 5 years, was externally validated. NCT01953458 References: ¹Poynard et al 2021, ²Poynard et al 2018, ³Pol et al 2021. Figure legend: Survival without HCC at 10 years. In 3,376 Pts with low-risk LCR1-LCR2, 29 HCC occurred at 5 yrs (survival without HCC= 99.0;98.7-99.4) vs. 18 HCC in 154 Pts with a high-risk LCR1-LCR2 (86.5%;80.7-92.4).

LP15: SAFETY AND IMMUNOGENICITY OF SARS-COV-2 VACCINES IN PATIENTS WITH CHRONIC LIVER DISEASES (CHESS-NMCID 2101): A MULTICENTER STUDY

Jitao Wang¹,², Jingwen Ai³, Dengxiang Liu¹, Huiling Xiang⁴, Ying Guo⁵, Jiaqian Lv⁶, Qiran Zhang⁷, Jinlong Li⁷, XiaoChong Zhang⁸, Qianqian Li⁷, Liang Jing⁹, Xiaoping Guo⁷, Yinong Feng⁷, Xiaoling Lan⁸, XuYing Zhang⁹, Wei Qin⁹, Xiaodong Wang⁹, Wei Rao⁹, Qun Zhang⁹, Qian Tian⁹, Yanliang Zhang¹⁰, Faren Xie¹⁰, Shujun Jiang¹⁰, Yan Yan¹¹, YuanWang Qiu¹¹, HangYuan Wu¹¹, ZhiYun Hou¹¹, Nina Zhang¹¹, Aiguo Zhang¹², Jiansong Ji¹³, Jie Yang¹³, Jiansheng Huang¹³, Zhongwei Zhao¹³, Ye Gu¹³, Li Bian¹⁴, Zhen Zhang¹⁴, Shengqiang Zou¹⁴, Hailei Ji¹⁵, Guohong Ge¹⁵, Xiufang
Background: There are not sufficient evidences about the safety and immunogenicity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines in patients with chronic liver diseases (CLD). We aim to assess the safety and immunogenicity of vaccines in this special population in this study.

Methods: This was a prospective, multi-center, open-label study. Participants aged over 18 years with confirmed CLD and healthy volunteers were enrolled. All participants received whole schedule of SARS-CoV-2 vaccination. Adverse reactions were recorded within 14 days after any dose of SARS-CoV-2 vaccine, laboratory testing results were collected after whole schedule vaccination, and serum samples of enrolled subjects were collected and tested for SARS-CoV-2 neutralizing antibodies at least 14 days after the last dose.

Results: A total of 640 participants (496 patients with CLD and 144 healthy volunteers) were enrolled from 15 sites in China. Most adverse reactions were mild and transient, and injection site pain (39 [7.9%]) was the most frequently reported adverse event. Three participants had Grade 3 aminopherase elevation (defined as alanine aminopherase >5 upper limits of normal) after whole schedule of SARS-CoV-2 vaccination, and one of them was judged as severe adverse event potentially related to SARS-CoV-2 vaccination. The positive rates of SARS-CoV-2 neutralizing antibodies were 76.4% in non-cirrhotic CLD group, 76.4% in compensated cirrhotic group, 70.6% in decompensated cirrhotic group (P=0.745) and 90.3% in healthy controls (P=0.002), respectively (Figure 1A). After adjusted with age and gender, the difference was still not statistically insignificant (P=0.603). The neutralizing antibody concentration were 17.68 (10.17-27.01) AU/ml in non-cirrhotic CLD group, 15.94 (10.37-35.63) AU/ml in compensated cirrhotic group, 17.79 (8.98-32.07) AU/ml in decompensated cirrhotic group and 18.83 (13.42-27.66) AU/ml in control group (P=0.151), respectively (Figure 1B).

Conclusion: SARS-CoV-2 vaccines are safe in patients with CLD. Patients with CLD had lower immunological response to SARS-CoV-2 vaccines than healthy population. The immunogenicity is similar in non-cirrhotic CLD and compensated cirrhosis, but tends to be lower in decompensated cirrhosis.
LP16: PREDICTORS OF 6-YEAR EVENT-FREE SURVIVAL IN PATIENTS WITH ALAGILLE SYNDROME TREATED WITH MARALIXIBAT, AN IBAT INHIBITOR

Ronald J Sokol1, Emmanuel M. Gonzales2, Binita M. Kamath3, Alastair Baker4, Pamela Vig5, Ed Tucker5, Will Garner6, Bettina E. Hansen6, Emmanuel Jacquemin2 and Richard J. Thompson7, (1)Section of Pediatric Gastroenterology, Hepatology and Nutrition and the Digestive Health Institute, Children’s Hospital Colorado and University of Colorado School of Medicine, Aurora, Colorado, USA, (2)Pediatric Hepatology and Liver Transplantation Unit, Bicâtre Hospital, AP-HP, Université Paris-Saclay, Le Kremlin-Bicêtre, and Inserm U1193, Hepatinov, University of Paris-Saclay, Orsay, France, (3)The Hospital for Sick Children and the University of Toronto, Division of Gastroenterology, Hepatology and Nutrition, Toronto, Canada, (4)Paediatric Liver Centre, King’s College Hospital, London, United Kingdom, (5)Mirum Pharmaceuticals, Foster City, California, United States, (6)Toronto General Hospital and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada, (7)Institute of Liver Studies, King’s College London, London, United Kingdom

Background: Refractory pruritus and liver disease progression are indications for liver transplantation (LTx) in patients with Alagille syndrome (ALGS). The aim of this analysis was to examine predictors of long-term event-free survival (EFS) and transplant-free survival (TFS), in ALGS patients enrolled in 3 clinical trials of maralixibat (MRX), an ileal bile acid transporter (IBAT) inhibitor, with up to 6 yrs of follow-up.
**Methods:** MRX-treated ALGS patients from 3 long-term clinical trials were followed for development of clinically significant events (LTx, surgical biliary diversion [SBD], hepatic decompensation [ascites requiring therapy and variceal bleeding], and death) for up to 6 yrs. TFS (LTx and death only) was also assessed. Those who were on MRX 48 weeks from the first dose and had lab results at 48 weeks were included in this analysis. Variables considered in the model included: liver biochemistries, platelets, pruritus (as assessed by ItchRO(Obs) 0-4 scale), total serum bile acids (sBA), and age. Goodness of fit was assessed using Harrell's concordance statistic (C-statistic). Cutoffs were determined via a grid search. P-values are from a log-rank test.

**Results:** 76 MRX-treated patients met the criteria for this analysis; over the 6 yrs of MRX treatment, 16 had events (10 LTx, 3 decompensation, 2 death, and 1 SBD); 60 remained event-free. Variables that were predictive of EFS included: total bilirubin (TB), sBA, change from baseline to week 48 in pruritus (measured by ItchRO(Obs)), and age at study initiation (see Table). TB at week 48 showed 6-yr EFS of 90% for those <6.5 vs 43% for those ≥6.5 mg/dL (p<0.0001). sBA at week 48 showed 6-yr EFS of 85% for those <200 vs 49% for those ≥200 Åmol/L (p=0.0010). A >1-pt reduction in ItchRO(Obs) from baseline to week 48 was a significant predictor of EFS; those with >1-pt reduction had 6-yr EFS of 88% vs 57% in those with ≤1-pt reduction (p=0.0046). Age was identified as a predictor where those below 36 months old at initiation had a higher risk for an event (p=0.0059). The same 4 parameters at 48 weeks (TB, sBA, change from baseline in pruritus, and age) were also predictive of long-term TFS.

**Conclusion:** Week 48 TB and sBA levels, as well as improvement in pruritus and age of initiation of MRX, were associated with lower long-term rates of clinically important events and transplantation. These data identify potential prognostic markers which may help guide clinical decisions in patients with ALGS treated with MRX.

**Table: Identified Predictors of EFS and Associated Cutoffs**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Increased EFS</th>
<th>Decreased EFS</th>
<th>P-value</th>
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<tr>
<td>Week 48 Total Bilirubin</td>
<td>&lt;6.5 mg/dL N=52 6-year EFS: 90%</td>
<td>≥6.5 mg/dL N=24 6-year EFS: 43%</td>
<td>&lt; 0.0001</td>
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<tr>
<td>C-Statistic: 0.8176</td>
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<tr>
<td>Week 48 sBA</td>
<td>&lt;200 µmol/L N=56 6-year EFS: 85%</td>
<td>≥200 µmol/L N=18 6-year EFS: 49%</td>
<td>0.0010</td>
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<td>C-Statistic: 0.7367</td>
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<tr>
<td>Change from Baseline to Week 48 ItchRO(Obs)</td>
<td>&gt;1-pt Reduction N=46 6-year EFS: 88%</td>
<td>≤1-pt Reduction N=30 6-year EFS: 57%</td>
<td>0.0046</td>
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<tr>
<td>C-Statistic: 0.6984</td>
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<tr>
<td>Age at Initiation (months)</td>
<td>≥36 N=55 6-year EFS: 83%</td>
<td>&lt;36 N=21 6-year EFS: 57%</td>
<td>0.0059</td>
</tr>
<tr>
<td>C-Statistic: 0.7231</td>
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</tbody>
</table>

**LP17: MACHINE LEARNING TO PREDICT PRESENCE OF NON-ALCOHOLIC STEATOHEPATITIS (NASH) FIBROSIS FROM PATIENT LABORATORY TESTING HISTORY**

Walter Jessen1,2, Cassidy Konzelman1, Margery Connelly3, Katherine Landschulz2, Claudia Filozof5, Ryan Patrick6, Adam Sullivan1 and Stanley Letovsky1, (1)Center of Excellence for Bioinformatics, Data Science and AI, Laboratory Corporation of America Holdings, (2)Laboratory Corporation of America Holdings, (3)Labcorp, (4)Labcorp Drug Development Biomarker Solution Center, Laboratory Corporation of America Holdings, (5)Covance Clinical Development Services, (6)Specialty Medicine: Diagnostics, Laboratory Corporation of America Holdings
Background: The prevalence of non-alcoholic steatohepatitis (NASH), the advanced form of non-alcoholic fatty liver disease (NAFLD), in the United States is currently 12% and is expected to increase, becoming the leading cause of liver transplantation between 2020-2025. Although NASH severity is associated with higher healthcare resource utilization (HCRU) and cost, it remains a largely underdiagnosed disease. The objective of this study was to develop an artificial intelligence (AI) model for early identification of NASH patients using real-world data.

Methods: We describe a machine learning model that predicts the result of a NASH fibrosis score test based on patient laboratory testing history to accurately identify patients trending towards a disease state and to support clinicians and healthcare organizations by informing diagnosis early. The NASH fibrosis model was trained on laboratory testing histories from 62,001 Labcorp patients. Patients with fibrosis scores >0.31 (METAVIR scoring system fibrosis stage F1-F2 and higher) were used as cases.

Results: An Adaptive Boosting (AdaBoost) model consisting of 97 laboratory tests exhibited high performance to predict NASH liver fibrosis as measured by area under the curve (AUC) (0.85) on a holdout testing cohort of 20,642 Labcorp patients.

Conclusion: Early detection of NASH with liver fibrosis allows for interventions to prevent progression and subsequently reduce HCRU and costs. The NASH liver fibrosis AI model is a convenient, predictive tool for clinicians and healthcare organizations to support patients with undiagnosed NASH fibrosis, allowing for early detection and enhanced patient care.

LP18: LOW HBsAg LEVELS MAINTAINED FOLLOWING CESSATION OF THE GALNAC-siRNA, AB-729, IN CHRONIC HEPATITIS B SUBJECTS ON NUCLEOS(T)IDE ANALOGUE THERAPY

Man Fung Yuen1, Elina Berliba2, Wattana Sukeeapaisamjaroen3, Pisit Tangkijvanich4, Apinya Leerapun5, Jacinta A Holmes6, Edward J Gane7, Alina Jucov2, Emily P Thi8, Michael J Sofia9, Heather Sevinsky9, Timothy Eley9, Elina Medvedeva9, Kevin Gray9, Deana Antoniello9, Gaston R. Piccio9, Karen Sims9 and Simone I. Strasser10, (1)The University of Hong Kong, (2)Nicolae Testemitanu State University of Medicine and Pharmacy of the Republic of Moldova, (3)Srinagarind Hospital, Khon Kaen University, Thailand, (4)Center of Excellence in Hepatitis and Liver Cancer, Faculty of Medicine, Chulalongkorn University, (5)Maharaj Nakorn Chiang Mai Hospital, (6)Gastroenterology, St. Vincent's Hospital, Melbourne, (7)University of Auckland, (8)Research/Discovery, Arbutus Biopharma, Warminster, PA, (9)Clinical Development, Arbutus Biopharma, Warminster, PA, (10)Liver Transplant, RPA

Background: AB-729 is an N-Acetylgalactosamine (GalNAc)-conjugated single trigger RNA interference therapeutic that blocks all HBV RNA transcripts, including HBx, resulting in suppression of viral replication and all viral antigens. AB-729 is in Phase 2 clinical development for the treatment of chronic hepatitis B (CHB).

Methods: In AB-729-001 Part 3, 34 non-cirrhotic, HBeAg positive or negative, CHB subjects received AB-729 60mg every 4 weeks (Q4W, Cohort E, N=7), 60mg every 8 weeks (Q8W, Cohort F, N=7), 90mg Q8W (Cohorts I (N=6) and G (N=7)), or 90mg every 12 weeks (Q12W, Cohort J, N=7) through Week 24. On Day 1, Cohort G was HBV DNA+ and initiated TDF; all other Cohorts were virologically suppressed on stable nucleos(t)ide analogue therapy. Eligible subjects (>0.5 log10 HBsAg reduction at Week 20) had the option to continue AB-729 through Week 48: Cohort E switched to AB-729 60mg Q12W while remaining Cohorts maintained their initial regimen. Subjects are followed up to 48 weeks after AB-729 discontinuation.

Results: 34/34 subjects were eligible to participate in the treatment extension, 33 consented. Mean HBsAg declines were similar (p>0.05 via ANCOVA) across Cohorts (Table) to date, with a plateau in mean HBsAg decline observed
beyond Week 20. To date, 25/34 (74%) subjects attained HBsAg levels <100 IU/mL, which were maintained up to 20 weeks and 16 weeks after the last dose of AB-729 in 3/7 and 3/5 subjects with available data in Cohort E and F, respectively. In Cohort G, HBV DNA was unquantifiable at Week 24 in 6/6 subjects with reported data. There were no deaths or discontinuations due to AEs. There was one unrelated SAE of Grade 3 ruptured thigh cyst; all other AEs were Grade 1 or 2. The most common AEs were injection-site related (redness, pain or bruising, N=4, N=4, and N=3 events respectively); all were Grade 1 and none appeared to be dose- or interval-dependent.

**Conclusion:** AB-729 repeat dosing is generally safe and well tolerated. Robust mean declines in HBsAg were sustained with repeat dosing of AB-729, with no meaningful differences observed to date between dose and/or dosing intervals. HBsAg suppression at levels <100 IU/mL is maintained in some subjects up to 20 weeks following the last dose of AB-729. These data support the continued evaluation of AB-729 as the cornerstone of combination treatment to achieve functional cure of chronic HBV.

### Baseline HBsAg and Preliminary Mean (SE) Δlog_{10} HBsAg

<table>
<thead>
<tr>
<th>Nominal Visit</th>
<th>Cohort E N = 7</th>
<th>Cohort F N = 7</th>
<th>Cohort I N = 6</th>
<th>Cohort J N = 7</th>
<th>Cohort G N = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline IU/mL</td>
<td>3.52 (0.20)</td>
<td>3.53 (0.17)</td>
<td>3.36 (0.23)</td>
<td>3.37 (0.28)</td>
<td>3.14 (0.14)</td>
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<tr>
<td>Week 12</td>
<td>-1.10 (0.15)</td>
<td>-1.02 (0.11)</td>
<td>-1.30 (0.19)</td>
<td>-1.06 (0.31)</td>
<td>-1.56 (0.32)</td>
</tr>
<tr>
<td>Week 24</td>
<td>-1.84 (0.16)</td>
<td>-1.57 (0.09)</td>
<td>-1.79 (0.22)</td>
<td>-1.56 (0.25)</td>
<td>-1.82 (0.29)</td>
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<tr>
<td>Week 40</td>
<td>-1.84 (0.19)</td>
<td>-1.78 (0.10)</td>
<td>-1.93 (0.25)</td>
<td>-1.89 (0.35)</td>
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</tr>
<tr>
<td>Week 48</td>
<td>-1.89 (0.18)</td>
<td>-1.90 (0.14)</td>
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<td>---</td>
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<tr>
<td>subjects &lt;100 IU/mL</td>
<td>5</td>
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</tr>
</tbody>
</table>

| HBsAg Post Last AB-729 Dose\(^2\) | Week 20: -1.58 (0.23) | Week 16: -1.73 (0.29) | --- | --- | --- |
| subjects <100 IU/mL | 3/6 | 3/4 | --- | --- | --- |

\(^1\)N=6 entered treatment extension; \(^2\)data will be updated for presentation; \(^3\)subjects with available data

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**LP19: BIOMARKERS, IMAGING AND SAFETY IN RESMETIROM 52 WEEK NON-CIRRHOTIC NASH PHASE 3 CLINICAL TRIAL, COMPLETED OPEN-LABEL ARM OF MAESTRO-NAFLD-1**

*Stephen A Harrison*, Sarah Cubberley, Rebecca A. Taub, Guy W Neff, Naim Alkhouri and Mustafa Bashir.

**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 169 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 55.7 (11.5 (SD)), female 69%, BMI 35.8 (6.0), diabetes 43%, hypertension 62%, dyslipidemia >70%, ASCVD score 11.5%; fibroscan (kPa 7.7 (3.6)), and MRI-PDFF 17% (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 cm³ (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. LV reduction was 2-3 fold 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 was -63% (2.4%). Weight loss ≥5% occurred in ~25% 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 (-22% (1.9%), apolipoprotein-B (-24% (1.6%)), triglycerides (-24%(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 ~2mmHg, (p=0.02); bone mineral density (DEXA) was unchanged at 52 weeks.

Conclusion: 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.
LP20: HIGH DOSES OF ACTIVATED MESENCHYMAL STEM CELLS INCREASE SURVIVAL, IMPROVE HISTOLOGY AND HEPATIC CHEMISTRIES IN HUMANIZED MICE AFTER INDUCTION OF ACUTE LIVER INJURY THROUGH ALCOHOL BINGING

Juan C Hernandez¹, Da-Wei Yeh², Hye Yeon Choi³, Karina Zaragoza⁴, Joel Marh⁴, Julia Kim⁴, Li Ding⁵, Matthew Thornton⁶, Brendan Grubbs⁷, Leonard Makowka⁴, Linda Sher⁸ and Keigo Machida⁹, (¹)University of California Channel Island, (²)Molecular Microbiology and Immunology, University of Southern California, (³)University of Southern California, (⁴)Primegen INC, (⁵)Keck School of Medicine, University of Southern California, (⁶)CHLA, (⁷)University of Southern Califor, (⁸)Surgery, University of Southern California, (⁹)Molecular Microbiology and Immunology, University of Southern California Keck School of Medicine

Background: A prior study demonstrated a significant survival advantage using activated umbilical cord stem cell injections in humanized mice with liver injury induced by high fat diet and alcohol binge drinking. A third set of experiments is conducted to evaluate various doses, impact on hepatic chemistries, pathology findings and survival.

Objectives: The primary objective is to compare various doses of activated human umbilical cord cell cells for the potential to improve survival in mice with alcohol induced liver injury. Secondary objectives included comparison of impact on hepatic chemistries and pathology.

Methods: 62 humanized mice that were fed high fat diet and alcohol binge drinking for 24 days were randomized to receive either 1 million, 500,000, 250,000, 100,000, 28,000 activated umbilical cord cells or vehicle only injections via tail vein three times in the first week and weekly for two additional weeks. AST and ALT were obtained at baseline, at weeks 1,2 and 3 and/or at death. Mice were followed for survival at 4 weeks with surviving mice euthanized. Liver pathology was evaluated for all animals at death. Time-to-event data were analyzed using Kaplan Meier curve and log-rank or Wilcoxon rank test, with Sidak method for multiple comparison adjustment, when appropriate.

Results: All mice had elevated AST and ALT after binge drinking. Baseline ALT was significantly different between the cohorts but had no impact on survival: AST, age and sex were not significantly different across treatment group. Male mice had significantly better survival than female mice (p=0.03) overall. At the highest administered dose, 1 million stem cells, there was a statistically significant survival compared to the placebo group (p=0.03) confirming results from earlier studies (Figure 1). Histologic findings correlated with survival with 27 surviving animals demonstrating 1 to 2+ steatosis with no necrosis and 23 of the 35 animals that died demonstrated necrosis with the remaining mice demonstrating various degrees of steatosis (Table 1).

Conclusion: Repeated injections of high dose activated umbilical cord cells results in marked improvement in survival and histology in humanized mice with alcohol induced liver injury.
Table 1

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mouse</th>
<th>Survived Yes/No</th>
<th># Days Survived</th>
<th>Pathology</th>
<th>Necrosis</th>
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<tr>
<td>1 million cells</td>
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<td>28</td>
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<td>500,000 cells</td>
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<td>&lt;5% Steatosis</td>
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<td>250,000 cells</td>
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<td>100,000 cells</td>
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LP21: COMPARISON OF A NOVEL MULTI-TARGET BLOOD TEST WITH ULTRASOUND AND ALPHA-FETOPROTEIN FOR HEPATOCELLULAR CARCINOMA SURVEILLANCE: SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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Background: Clinical guidelines recommend biannual ultrasound (U/S) surveillance with or without α-fetoprotein (AFP) for hepatocellular carcinoma (HCC) detection in at-risk patients. However, the performance of current surveillance modalities remains suboptimal, especially for early-stage HCC detection. A novel, recently validated, multi-target HCC blood test (mt-HBT) provides an alternative to U/S-based surveillance. Our objective was to conduct a network meta-analysis comparing the performance of mt-HBT against U/S with or without AFP for early detection of HCC in patients with cirrhosis.

Methods: In compliance with PRISMA guidelines, two reviewers searched Pubmed, Cochrane, Embase, and clinical trials.gov databases from January 1990 through December 2020 to identify studies reporting sensitivity and/or specificity of U/S and AFP for overall and early detection of HCC. All studies (case-control or cohort) were required to be conducted in patients with cirrhosis for inclusion. The performance data of mt-HBT were extracted from a clinical validation study including 540 cirrhosis patients (136 HCC cases and 404 controls). Pooled estimates of sensitivity at a fixed specificity were estimated based on Bayesian binormal receiver operating characteristic models for each modality.

Results: The literature search resulted in 7,783 articles, of which 41 studies (comprising 62,517 cirrhosis patients) met inclusion criteria. 34 studies (13,544 patients) reported performance characteristics for U/S, and 14 studies (7,140 patients) evaluated the performance of U/S with AFP. Sensitivities of AFP alone, U/S alone, U/S with AFP, and mt-HBT at 90% fixed specificity are reported in Table 1. Compared with AFP alone, mt-HBT detected any stage HCC with 30% higher sensitivity (95% credible interval (CI) 13.4% - 44.9%) and early-stage HCC with 21.1% higher sensitivity (95% CI 3.3% - 39.4%). Compared with U/S alone, mt-HBT detected early-stage HCC with 18.2% higher sensitivity (95% CI -2% - 37.7%). The differential sensitivities between mt-HBT vs. U/S with AFP in early-stage and with or without AFP in any stage HCC detection did not provide substantial evidence of differences.

Conclusion: Our analysis shows that a novel blood-based mt-HBT is superior to U/S alone and AFP alone in early-stage detection of HCC. mt-HBT could be a meaningful addition to surveillance protocols for HCC in patients with cirrhosis.
Table 1. Sensitivity values by modality with specificity fixed at 90%

<table>
<thead>
<tr>
<th>Primary Analysis of Pooled Sensitivity</th>
<th>Any Stage Sensitivity Mean (95% CI)</th>
<th>Early-Stage Sensitivity Mean (95% CI)</th>
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<tbody>
<tr>
<td>AFP alone</td>
<td>53.5% (48.3% — 59.0%)</td>
<td>48.0% (40.0% — 55.5%)</td>
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<tr>
<td>U/S alone</td>
<td>77.0% (69.7% — 83.6%)</td>
<td>50.9% (42.6% — 59.1%)</td>
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<tr>
<td>U/S+AFP</td>
<td>79.0% (70.9% — 86.9%)</td>
<td>72.4% (60.8% — 80.5%)</td>
</tr>
<tr>
<td>mt-HBT</td>
<td>83.6% (66.8% — 97.5%)</td>
<td>69.1% (51.1% — 87.2%)</td>
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| Sensitivity Comparison                  |                                   |                                      |
|----------------------------------------|                                   |                                      |
| mt-HBT vs AFP alone                    | 30.0% (13.4% — 44.9%)             | 21.1% (3.3% — 39.4%)                 |
| mt-HBT vs U/S alone                    | 6.6% (-11.2% — 23.2%)             | 18.2% (-0.2% — 37.7%)               |
| mt-HBT vs U/S+AFP                      | 5.5% (-13.7% — 21.1%)             | -3.3% (-22.3% — 17.4%)              |

LP22: LIMITED UTILITY OF NONINVASIVE TESTS FOR PREDICTION OF BIOPSY-PROVEN CIRRHOSIS IN CHRONIC HEPATITIS D INFECTED PATIENTS- INSIGHTS FROM THE D-LIVR TRIAL

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Background: We have recently reported the suboptimal performance of non-invasive tests for prediction of biopsy proven cirrhosis in Chronic Hepatitis Delta Virus (CHDV) infected patients. The aim of the current analysis was to explore CHDV-adjusted cutoffs for commonly used noninvasive laboratory and imaging tests for prediction of cirrhosis.

Methods: We prospectively evaluated 330 patients who enrolled in the on-going Phase 3 HDV D-LIVR trial (NCT03719313). At baseline, liver stiffness measurement (LSM) and/or FibroTest were performed, and alanine aminotransferase (ALT), aspartate aminotransferase (AST) and platelet counts were obtained and used for calculation of AST to ALT ratio (AAR), AST to platelet ratio index (APRI) and Fibrosis-4 index (FIB-4). All patients underwent liver biopsy within 45 days from non-invasive testing. Sensitivity (Se), specificity (Sp), positive and negative predictive values (PPV and NPV) for prediction of cirrhosis were calculated based on cut-offs predefined in the literature. Area under the receiver operator curve (ROC) analysis was employed for evaluation of the discriminant capacity of the different tests for diagnosis of cirrhosis. Youden index (YI) was used to explore new optimal cutoff values for prediction of biopsy-proven cirrhosis in this population.

Results: Of the 330 patients enrolled to the study, 67.6% were male, median age of 43 (18-69) and 28% cirrhotic proven by biopsy. The Se and NPV for detection of cirrhosis using predefined cutoffs were 31% and 77% for FibroTest,
47% and 77% for LSM, 29% and 77% for FIB-4, 27% and 76% for APRI and 13% and 73% for AAR. Area under the ROC was highest for FIB-4 (0.74, Standard error [S.E.], 0.036), followed by LSM (0.72, S.E 0.036), APRI (0.70, S.E 0.037), FibroTest (0.69, S.E 0.039) and AAR (0.59, S.E 0.03). No statistical significance was found between ROCs for the different tests. Combination of noninvasive tests did not improve overall accuracy for prediction of cirrhosis. Maximising Se and Sp, YI identified the following optimal cutoffs for prediction of cirrhosis for each test: FIB-4 ≥ 2 (Se 61%, Sp 80%), FibroTest ≥ 0.58 (Se 59%, Sp 76%), LSM ≥ 11 KpA (Se 73%, Sp 62%), APRI ≥ 1.04 (Se 69%, Sp 64%) and AAR ≥ 0.66 (Se 75%, Sp 45%). Correct classification of cirrhotic vs non-cirrhotic patients using these cutoffs was best achieved by FIB-4 (73%), followed by FibroTest (71%), LSM and APRI (65%) and AAR (53%).

**Conclusion:** The utility of commonly used non-invasive laboratory and imaging tests for prediction of cirrhosis is limited in CHDV due to suboptimal performance. Liver biopsy currently remains the most reliable method for assessment of cirrhosis in this population.
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 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 QD Aramchol to 300mg twice daily (BID). Since this higher exposure is 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 16, F1 -3 patients that received Aramchol in whom the scheduled post-baseline biopsy was performed. At baseline, mean age ±SD was 58.3±8.9 years; 69% were females; 81% White; mean BMI 34.0±2.8 kg/m²; 94% had type 2 diabetes; 10 patients had stage 3 fibrosis; 4 stage 2, and 2 stage 1; Mean NAS was 4.9±1.3. Post-baseline biopsies were performed for 8 patients at 24 weeks, 6 at 48 weeks and 2 at 72 weeks. Altogether 8 of 16 patients (50%) showed fibrosis improvement by ≥1 stage (4 of 8 after 24 weeks, 3 of 6 after 48 weeks and 1 of 2 after 72 weeks). In 3 patients, fibrosis was reduced by 2 points. In 7 of 16 (44%) patients there was fibrosis improvement without worsening of NASH. Aramchol continues to show good safety and tolerability.

Conclusion: 50% of the 16 patients treated with Aramchol 300mg BID showed fibrosis improvement. 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.

LP24: GENE THERAPY FOR CRIGLER NAJJAR SYNDROME: RESULTS OF THE DOSE ESCALATION PHASE OF THE CARECN CLINICAL TRIAL

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**Background:** In Crigler Najjar syndrome (CN) the lack of hepatic uridine diphosphoglucuronate glucuronosyltransferase 1A1 (UGT1A1) causes severe unconjugated hyperbilirubinemia that, if left untreated, causes irreversible neurological injury. Prolonged, daily phototherapy (PT) partially controls jaundice, but becomes progressively less effective during childhood, making liver transplantation the only available treatment. We describe the results of the dose escalation part of an international, multicentre, open-label study aimed at evaluating safety and efficacy of a single intravenous infusion of GNT0003, an adeno-associated virus vector serotype 8 (AAV8) encoding the UGT1A1 transgene under the control of a hepatocyte-specific promoter, in severe CN patients aged ≥18 years who require PT.

**Methods:** The protocol involved a single infusion of GNT0003, clinical and biochemical monitoring, and phototherapy withdrawal at week 16. We enrolled five patients whose baseline mean serum bilirubin concentration on phototherapy was 314±80 μmol/l. Two patients received 2x10¹² vector genomes (vg)/kg (Cohort 1) and three patients received 5x10¹² vg/kg (Cohort 2). Primary endpoints included safety, tolerability, and efficacy of GNT0003. Efficacy endpoint was measured at week 17, and was defined by serum bilirubin levels stable at <300 μmol/l at one week after suspension of PT, allowing withdrawal of daily PT.

**Results:** No GNT0003-related serious adverse events were reported. Four patients experienced vector-related adverse events (grade 1 transaminase elevation and grade 2 Gamma-GT elevation), all treated with a steroid course. Participants in Cohort 1 (patients 1 and 2), after a significant reduction of bilirubin at week 4, lost the efficacy by week 16. Participants in Cohort 2 (patients 3, 4 and 5) had the following bilirubin levels: Week 4: 59±9 μmol/l; Week 8: 45±29 μmol/l. Patient 3 and 4 reached week 17 with a bilirubin level of 65 and 31 μmol/l respectively, that allowed successful PT withdrawal. Patient 5, currently at week 12 post-treatment, has a bilirubin level of 45 μmol/l and is due to stop PT shortly (Figure).

**Conclusion:** These results suggest that in patients with Crigler Najjar syndrome, GNT0003 at the dose of 5x10¹² vg/kg is safe and restores UGT1A1 expression to levels allowing safe phototherapy withdrawal. (Sponsored by Genethon and EU Horizon 2020 plan: Grant Agreement No. 755225. ClinicalTrials.gov, NCT03466463.)
LP25: RESTORATION OF A HEALTHY INTESTINAL MICROBIOTA (IM) IMPROVES LIVER FIBROSIS WITHOUT CHANGES IN STEATOHEPATITIS IN A RAT MODEL OF STEATOHEPATITIS WITH FIBROSIS.

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Background: IM has emerged as a key factor conditioning the development and progression of nonalcoholic fatty liver and although fecal microbiota transplant (FMT) has been proposed as a promising therapeutic strategy, effective
colonization of the colon is difficult to achieve. Our group has developed an endoscopic substance-releasing platform (Covergel), biocompatible and bioadhesive, that could improve FMT. Aim: To assess the role of the IM in the mechanisms leading to steatosis and fibrosis and to compare the effectiveness of covergel for the delivery of FMT with single colonoscopy vs the standard-method, in an animal model of steatohepatitis with fibrosis.

Methods: Thirty rats were kept in pathogen free conditions throughout the study (15 weeks). Experiment was divided in two stages. In stage 1, 24 animals were fed with a diet rich in fat/cholesterol/fructose throughout the study (NASH group) and intraperitoneal carbon tetrachloride was administered for 12 weeks. The remaining 6 rats (healthy controls) were fed with standard chow. At week 12, feces were collected to: 1) assess phylogenetic profile, and 2) pooled as “NASH feces” and “Healthy feces” for FMT. In stage 2, 24 animals with steatohepatitis with fibrosis undergo colonoscopy for FMT (week 13th) receiving: Group 1: 0.5 mL of healthy feces (healthy donors) carried in 3.5 mL saline, Group 2: 0.5 mL of healthy feces with 3.5 mL Covergel, Group 3: 0.5 mL of NASH feces (NASH donors) with 3.5 mL Covergel. Animals were euthanized 14 days later (week 15th) and fibrosis (Mason's Trichromic staining) and steatosis (Oil Red staining) degrees were assessed in liver samples.

Results: Although standard-FMT is not effective in reversing liver fibrosis, non-significant improvement is identifiable (group 1 vs group 3, p=0.084). On the other hand, healthy donor covergel-FMT shows a significant improvement on fibrosis compared to standard-FMT (group 2 vs group 1, p=0.034). FMT had no significant effect on steatosis, being similar in all groups.

Conclusion: Covergel-FMT treatment significantly reduces fibrosis in this model without significant attenuation of the ongoing steatosis. The use of covergel would be a therapeutic advantage, since the prolonged residence time of the hydrogel adhered to the mucosa would facilitate microorganisms colonization with a single colonoscopy.

LP26: SAROGLITAZAR REDUCES HEPATIC STEATOSIS IN LIVER TRANSPLANT RECIPIENTS WITH NAFLD: INTERIM RESULTS FROM A PHASE 2A TRIAL

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Background: Development of nonalcoholic fatty liver disease (NAFLD) following liver transplantation (LT) is associated with increased cardiometabolic risk and potential for accelerated graft fibrosis and cirrhosis. There is currently no approved therapy for post-LT NAFLD. Saroglitazar, a novel dual PPAR α/γ agonist, has shown promise in treatment of NAFLD in non-LT patients. Thus, the aim of the current study was to evaluate the impact of Saroglitazar in LT recipients with NAFLD.

Methods: In this proof of concept, open-label trial, 15 adult patients with NAFLD, as determined by controlled attenuation parameter, were treated with Saroglitazar Magnesium 4mg daily for 24 weeks. Key exclusion criteria included graft cirrhosis, more than mild alcohol use, GFR<60, and concomitant use of GLP-1 receptor agonists. The primary endpoint was safety with secondary endpoint of change in liver fat (MRI-PDFF), serum aminotransferases, and body composition assessment.

Results: Ten patients completed the study procedures and were included in this analysis. The mean age and BMI of the study cohort was 59±10 years and 40±6.3kg/m², respectively. The baseline MRI-PDFF value of 8.4±8.2%
decreased to 5.7±6.2% after 24 weeks (p=0.06), corresponding to a 30% reduction in liver fat compared to baseline. Alkaline phosphatase decreased from 102±36 to 58±19 IU/L (p<0.001); however, the decrease in serum ALT from 36±26 to 29±16 IU/L did not reach statistical significance (p=0.1). Treatment with Saroglitazar resulted in insulin dose reduction in the two patients who required exogenous insulin prior to enrollment; however, no significant differences in hemoglobin A1c or fasting plasma glucose in the entire cohort were noted. No significant changes in weight, total fat volume, or muscle volume were noted after Saroglitazar treatment. Saroglitazar was well tolerated with no drug discontinuation or dose reduction. Adverse events that occurred during the study were unrelated to study medications. No adjustment in immunosuppression occurred and no significant changes in serum creatinine were noted over the study duration.

Conclusion: Saroglitazar was well-tolerated and reduced hepatic steatosis in LT recipients with NAFLD. Saroglitazar may offer a potential therapeutic option for treatment of post-LT NAFLD; however, additional well-designed studies are required to further establish its safety and efficacy.

LP27: SAROGLITAZAR ON IMPROVES ATHEROGENIC LIPOPROTEIN PROFILE IN LIVER TRANSPLANT RECIPIENTS

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Background: Cardiovascular disease is an important cause of long-term mortality among liver transplant (LT) recipients, particularly those with post-LT nonalcoholic fatty liver disease (NAFLD). After LT, lipoprotein metabolism is altered, favoring production of atherogenic lipoproteins, particularly large very low-density lipoprotein (VLDL) and small-dense low-density lipoprotein (sd-LDL) particles. These lipoproteins have been linked to cardiovascular events in prospective LT cohorts, irrespective of LDL cholesterol. Saroglitazar, a novel dual PPAR α, γ agonist, improves atherogenic dyslipidemia in non-LT patients; however, its impact in LT recipients is unknown. The aim of the present study was to evaluate the impact of Saroglitazar on lipoproteins in LT recipients.

Methods: In this proof of concept, open-label trial, 15 adult patients with NAFLD, as determined by controlled attenuation parameter, were treated with Saroglitazar magnesium 4mg daily for 24 weeks. Key exclusion criteria included graft cirrhosis, more than mild alcohol use, GFR<60, and concomitant use of GLP-1 receptor agonists. Use of lipid lowering therapy was not exclusionary, as long as there were no dose adjustments within 6 months. All patients had detailed lipoprotein profiling performed at baseline and end of treatment (EOT).

Results: 10 patients completed the study and were included in this analysis. The mean age and BMI of the study cohort was 59±10 years and 40±6.3kg/m², respectively. 3 patients were on statin therapy at the time of enrollment. Saroglitazar reduced serum triglycerides from 134±56 at baseline to 86±40 gm/dL at EOT (p=0.01). Large VLDL particles, which are a precursor to sdLDL, decreased from 5.27±3.10 to 3.07±2.17 nmol/L at EOT (p=0.01). Similarly, the triglyceride concentration within VLDL particles decreased from 86±47mg/dL to 45±27mg/dL (P=0.01), indicative of transitioning to less atherogenic VLDL particles. The sdLDL cholesterol decreased from 21.9±7.6 to 16.9±6.6 mg/dL by EOT (p=0.01). As the serum concentrations of total cholesterol, LDL-C and HDL-C were unaffected by Saroglitazar therapy, these data are indicative of specificity of Saroglitazar to lower atherogenic lipoprotein sub-particles. Saroglitazar was well tolerated and had no impact on immunosuppression.
Conclusion: Saroglitazar favors production of less atherogenic lipoproteins in liver transplant recipients and may have therapeutic implications. However, additional well-designed clinical trials are necessary to fully establish its efficacy.

LP28: CROSS-SECTIONAL STUDY OF SERUM HBV RNA AND HBCRAG IN A REAL-LIFE PROSPECTIVE COHORT OF 1500 CHRONIC HEPATITIS B PATIENTS FOLLOWED IN FRANCE AND ITALY

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Background: Serum HBV RNA and HBcrAg have been shown to reflect intrahepatic cccDNA transcriptional activity and are, therefore, promising candidate biomarkers to better classify disease status and monitor functional cure in chronic hepatitis B (CHB) patients. However, data combining both markers in large real-life cohorts are still limited.

Methods: 1503 CHB patients were prospectively enrolled and followed-up at Hospices Civils de Lyon and at Ospedale Maggiore Policlinico in Milan in the CirB-RNA cohort study. ALT, HBV DNA, HBeAg/HBeAb, and HBsAg were assessed using standard assays. Circulating HBV RNA (CirB-RNA) was quantified by the Roche HBV RNA investigational assay for use on the cobas® 6800 System (LLOQ 10 cp/ml; linearity range 10 to 10^7 cp/ml; LLOD ~3cp/mL). HBcrAg was measured using the Lumipulse platform (Fujirebio; LLOD 2.6 logU/mL). Liver fibrosis was assessed by Fibroscan, Fibrotest or liver histology.

Results: The CirB-RNA cohort comprised patients from sub-saharian Africa (28%); southern Europe (27%); France (15%) and Asia (11%). Consistently, the most prevalent HBV genotypes included A/D (34%), followed by E (14%) and B/C (10%). At inclusion, 91% of patients were HBeAg negative, 49% were under NUC therapy, 3% received a liver transplant (LT), 7.3% had already lost HBsAg, and 0.5% had an acute hepatitis presentation. Of note, 11% were cirrhotic and 4% were co-infected with HDV. Genotype C infected patients showed the highest values for both HBcrAg and cirB-RNA (w/o difference in serum HBV DNA). No differences in median values of HBcrAg and cirB-RNA were observed according to fibrosis categories (mild, moderate, severe), also when looking at treated and non-treated groups separately. The proportion of untreated patients positive for cirB-RNA or HBcrAg was similar in HBeAg- chronic hepatitis (CH) and chronic infection (CI) EASL categories. Interestingly, in HBeAg- CI with intermediate serum HBV DNA (>2,000 and <20,000 IU/ml, n=192) a higher proportion of patients was positive for cirB-RNA than HBcrAg (48% vs 25%). CirB-RNA and HBcrAg were positive in 38% and 51% of NUC treated patients. CirB-RNA was undetectable in all patients who lost HBsAg and LT patients, whereas 20% were still positive for HBcrAg in each group, despite undetectable serum HBV DNA.
Conclusion: To our knowledge, this is the first description of both serum HBV RNA and HBcrAg in a large prospective real-life cohort of chronic HBV infection. Follow-up visits will ascertain the predictive value of these novel biomarkers in refining subcategories of patients.

LP29: LIVER-DIRECTED TARGETING OF PD-L1 WITH RO7191863, A LOCKED NUCLEIC ACID, IN CHRONIC HEPATITIS B: FIRST REPORT OF PHASE 1 TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS

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Background: Targeting the PD-L1/PD1 pathway is an emerging approach in curative strategies for chronic hepatitis B (CHB), to date explored using monoclonal antibodies. RO7191863 is a liver-directed N-acetylgalactosamine (GalNac)-conjugated single stranded oligonucleotide that induces RNAseH-mediated degradation of PD-L1 mRNA. Pre-clinical proof of concept studies showed target engagement, intra-hepatic expansion of primarily CD4, CD8, NK and antigen presenting cells, and induction of dose-dependent antiviral responses. This first study with RO7191863 in patients with CHB was designed to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of different doses and regimens (ACTRN12619000271101).

Methods: Virologically suppressed CHB patients on stable antiviral therapy and with no evidence of significant liver fibrosis entered the multiple ascending dose (MAD) study at sites in Europe and the Western Pacific Region. Participants received RO7191863 or placebo subcutaneously, with escalating dose level, number of doses and frequency of administration up to a maximum of five 3.0 mg/kg doses administered every two weeks (Q2W). PK parameters were calculated by non-compartmental analysis of plasma and urine concentration data. The biomarker plan comprised quantification of viral and immune parameters including soluble PD-L1.

Results: To date, the study population comprised 25 participants (4 females, 21 males) aged 18-65 years, of whom 23 received RO7191863 and 2 received placebo. Following each dose, RO7191863 appeared in plasma with a median T_{max} of 2.0 h, and subsequently decreased with a biphasic profile. Seven patients on active treatment experienced adverse events (AEs) considered related to study treatment; the most prevalent were headache (5/23, 22%) and injection site reactions (2/23, 8%). No serious or immune-related AEs were observed and no protocol-defined stopping criteria were met. At the top dose of 3.0 mg/kg Q2W, 6 patients on active treatment and with a mean (standard deviation) baseline HBsAg level of 3.2 (0.7) log_{10} IU/mL showed a mean maximum HBsAg decline of 0.3 (standard deviation 0.2) log_{10} IU/mL. The largest decline (nadir 0.6 log_{10} IU/mL) was observed in the one patient who started RO7191863 with baseline HBsAg <2.5 log_{10}IU/mL; this was accompanied by a parallel increase in ALT and a decline in soluble PD-L1 confirming target engagement and suggesting immune restoration (Figure 1).

Conclusion: These initial safety and efficacy data indicate the feasibility of targeting the PD-L1/PD1 pathway by liver-directed suppression of PD-L1 mRNA expression, and support continued development of RO7191863 in combination with othernew molecular entities towards a functional cure of chronic HBV infection.
LP30: BIOMARKERS OF BACTERIAL TRANSLOCATION ARE ASSOCIATED WITH PARAMETERS OF GROWTH FAILURE IN PEDIATRIC CHRONIC LIVER DISEASE

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Background: Translocation of intestinal bacteria has been implicated in the inflammatory response of decompensated cirrhosis, however the impact of this pathway on growth in children with chronic liver disease (CLD) is not well established. Lipopolysaccharide (LPS) triggers synthesis of pro-inflammatory cytokines such as TNFa and IL-6 that can reduce transcription of insulin-like growth factor 1 (IGF-1), a key mediator of growth in childhood. In this pilot study, we explore the relationship between LPS triggered inflammation, serum IGF-1 levels, and clinical markers of growth failure in children with CLD.

Methods: Outpatients ages 3 months to 18 years with CLD were enrolled from 05/2015-12/2020. Patients with comorbidities affecting intestinal barrier function or the growth hormone axis were excluded. Clinical data including nutritional assessment with mid upper arm circumference (MUAC), length, and the presence of clinically evident portal hypertension (CEPH) was collected. Serum levels of IGF-1, LPS binding protein (LBP), and 34 cytokines were measured. The relationship between LBP and IGF-1 z-score was tested using Spearman correlation. Hierarchical clustering of 9 cytokines associated with IGF-1 regulation and the LPS pathway was performed: IL10, IL1RA, IL1a,
IL1b, IL4, IL6, TNFa, TNFb, HMGB1. Demographics and clinical variables were compared using Chi-square and Mann-Whitney tests.

**Results:** 38 patients with median age 12.7 (IQR 8.7,15.3) years were included. Biliary atresia (45%) and AIH/PSC (39 %) were the most common diagnoses. Median LBP concentration was 2366 (IQR 1857,3188) ng/mL. The median IGF-1 z-score was -1.6 (IQR-2.8,-0.95). Median length and MUAC z-scores were -0.06 (IQR -0.28,0.24) and -0.13 (IQR -1.21,0.5), respectively. LBP was inversely associated with IGF-1 z-score with r=-0.4 (p = 0.021). Hierarchical clustering identified 2 distinct groups which differed by MUAC (p = 0.019). The clusters did not differ by age, sex, primary diagnosis or CEPH.

**Conclusion:** Higher levels of LBP were associated with decreased IGF-1 z-scores in this pilot study of ambulatory children with CLD. Hierarchical clustering using cytokines from the LPS inflammatory pathway identified differences in MUAC but not CEPH. Overall, our data suggest that low level endotoxemia in pediatric liver disease may negatively impact IGF-1 and growth independent of portal hypertension.

**LP31: LIVER-SELECTIVE NANOGEL SYSTEM FOR THE DELIVERY OF THYROMIMETICS: APPLICATION IN NON-ALCOHOLIC STEATOHEPATITIS (NASH) DISEASE MODEL**

**Ruiling Wu**, **Steve Faraci**, **Roman Herrera**, **Hang Xiao** and **Sankaran Thayumanavan**, (1)Umass Amherst, (2)Cyta Therapeutics

**Background:** Nonalcoholic steatohepatitis (NASH) is associated with lipid accumulation, inflammation and liver fibrosis, becoming a worldwide prevalent disease. A potential medical intervention involves administration of synthetic thyroid hormone mimetic. However, the positive effects of thyromimetetics on lipid metabolism and reversing liver
inflammation and fibrosis are counterbalanced by their harmful effects on extrahepatic organs such as heart, muscle and bone. Hence there is urgency in developing liver-selective thyromimetic formulations to mitigate this complication.

**Methods:** Herein, we describe the synthesis, characterization and properties of a novel polymeric nanogel for selective delivery to the liver of a thyroid hormone receptor β agonist. The platform allows for the generation of a nanogel library with tunable particle size, ligand targeting density and thyromimetic encapsulation capability. This novel formulation was evaluated in mice for (1) tissue distribution and pharmacokinetic-pharmacodynamic parameters and (2) therapeutic efficacy in an in vivo NASH model.

**Results:** Our results show that a five-week treatment (male C57BL/6J mice fed with a diet high in fat, fructose, and cholesterol for 29 weeks) with our formulation reversed and/or stopped weight gain, development of steatosis and decreased liver injury and fibrosis.

**Conclusion:** These results demonstrate the potential use of our nanogel platform in the treatment of NASH and other liver diseases.

**LP32: USE OF 3D BIOPRINTED PRIMARY HUMAN HEPATOCYTES AND MESENCHYMAL STEM CELLS FOR THE TREATMENT OF ACUTE LIVER FAILURE**

*Christopher Dickman, Stephanie Campbell, Haley Tong, Reza Jalili, Simon Beyer, Tamer Mohamed, Sam Wadsworth and Spiro Getsios, Aspect Biosystems*

**Background:** Liver transplantation is currently the only definitive treatment for acute and acute-on-chronic liver failure (ALF and ACLF). This treatment is severely limited due to the scarcity of acceptable donor organs and the complexity of the surgery. In addition, patients who receive liver transplant must receive lifelong immunosuppression to prevent rejection of the organ which brings an associated increased risk of opportunistic infections and cancer. Recent studies have demonstrated the potential of encapsulated hepatocytes to increase survival in children with acute liver failure. However, it remains a challenge to ensure long term survival of transplanted hepatocytes. Here we demonstrate in vitro and in vivo data to suggest a unique bioprinting technology can be used to generate viable hepatocyte implants that maintain disease-relevant function for extended periods after ectopic implantation.

**Methods:** 3D printing of artificial liver implants is accomplished by embedding cells within an alginate-based cell friendly core, surrounded by an immune isolating shell using our microfluidics based bioprinter. To improve implant longevity and function, human hepatocytes and CD166 positive mesenchymal stem cells (MSCs) were formed into 3D spheroids prior to printing. To test the viability and function of bioprinted implants, 5 healthy NSG mice received intraperitoneal implants containing 1 million hepatocytes. Plasma was collected at regular intervals over 28 days, and implants were retrieved upon the end of the study.

**Results:** Bioprinted implants containing 1 million hepatocytes implanted into NSG mice showed human Alpha 1 Anti-Trypsin (A1AT) reached 739 ng/mL within 3 days. Albumin levels increased to 593 ng/mL over 7 days with levels remaining steady over the 4 week period. Implants retrieved from NSG mice on day 28 had >75% viability and maintained their ability to produce albumin and detoxify ammonia.

**Conclusion:** 3D printed encapsulated hepatocyte and MSC implants show promise for the treatment of multiple liver diseases. As most liver diseases are caused by an insult to, or deficiency of hepatocytes, replacement therapy, where a mass of hepatocytes could be ectopically implanted has the potential to be used with a wide variety of therapeutic
liver indications. This is especially true with ALF and ACLF where implanted hepatocytes could provide functional support until the native liver mass regenerates or liver transplant becomes available.

LP33: ELECTROPORATION-MEDIATED DELIVERY OF CRISPR-CAS9 INTO HEPATOCYTES FOR THE TREATMENT OF INHERITED METABOLIC LIVER DISEASE

Illyda Ates, Tanner Rathbone, Callie Stuart and Renee N. Cottle, Bioengineering, Clemson University

Background: Hereditary tyrosinemia type 1 (HT1) is caused by loss-of-function mutations in the fumarylacetoacetate hydrolase (FAH) gene resulting in the accumulation of toxic metabolites in the liver. Treatment for HT1 uses 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) to inhibit 4-hydroxyphenylpyruvate dioxygenase (HPD). A novel curative therapy consists of ex vivo gene editing using CRISPR-Cas9 to disrupt HPD in hepatocytes isolated from the patient's resected liver. The gene edited hepatocytes would be subsequently transplanted to replace diseased hepatocytes with healthy cells in the liver. Adeno-associated viral vectors (AAV) are the standard delivery method for introducing CRISPR-Cas reagents, but AAVs are associated with severe safety and efficacy concerns. Here, we investigate the delivery of Hpd-CRISPR-Cas9 into hepatocytes using electroporation.

Methods: We optimized electroporation-mediated delivery of CRISPR-Cas9 into primary mouse hepatocytes. We evaluated the effects of modifications in the sgRNA on stabilizing the Cas9 activity, compared the delivery of CRISPR-Cas9 as a mRNA and ribonucleoprotein (RNP) complex, and evaluated on- and off-target indels using next generation sequencing. To evaluate the extent of engraftment after ex vivo gene editing, different numbers of wild type hepatocytes were injected into Fah-/- recipient mice following electroporation. Recipient mice were cycled off- and on-NTBC for 45 days. Hepatocyte repopulation was evaluated by weight data, immunohistochemistry staining of Fah, and biochemical analysis of serum liver enzymes.

Results: We observed similar on-target Cas9 activity for unmodified and modified sgRNA in primary mouse hepatocytes. Further, we observed high levels of on-target indels of 70.3% with Cas9 RNP, and 5-fold reduced off-target indels for HiFi Cas9 RNP compared to wild type Cas9 RNP. We observed correction of biochemical markers of acute liver injury and 46% liver repopulation following transplantation of hepatocytes electroporated with Cas9 RNP.

Conclusion: Our data indicates that Cas9 RNPs provide higher on-target activity and specificity compared to mRNA. HiCas9 RNPs further enhances the specificity of gene editing in hepatocytes. Further, we show that hepatocytes retain their capacity to engraft and repopulate the liver following electroporation of Cas9 RNPs. Therefore, electroporation is a promising approach to further investigate for a liver-directed gene editing therapy.
LP34: MIRICORILANT, A SELECTIVE GR MODULATOR, INDUCED A RAPID AND SIGNIFICANT REDUCTION IN LIVER FAT CONTENT IN A RANDOMIZED, PLACEBO-CONTROLLED PHASE 2a STUDY IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS

Kris V Kowdley¹, Peter Butler², Sarah Cubberley³, Austin L Hand⁴, Robert A Jenders⁵, Jan Kroon⁶, Mark Leibowitz⁷, Ann C. Moore⁷ and Bill Guyer⁴, (1)Liver Institute Northwest, Seattle, WA, USA, (2)Bashir Lab for Liver Imaging Research, Duke University, (3)Duke University, (4)Corcept Therapeutics, (5)National Research Institute, (6)Leiden University Medical Center, (7)Arizona Liver Health

Background: Non-alcoholic fatty liver disease (NAFLD) has a global prevalence of about 20% but no approved pharmacologic treatments. Both the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) have been implicated in the development and progression of NAFLD; antagonists of each receptor have shown beneficial effects in preclinical models. Two studies in mice using an amylin non-alcoholic steatohepatitis (NASH) model have shown reductions in fibrosis stage and NAFLD score with miricorilant, a mixed agonist/antagonist of the GR and an antagonist of the MR. This phase 2a study assessed the safety and efficacy of miricorilant in reducing liver fat content in patients with presumed NASH.

Methods: In this double-blind, placebo-controlled phase 2a study (NCT03823703), adult patients (18-75 years) with presumed NASH were randomized to receive either miricorilant (600 mg or 900 mg) or placebo orally once daily. The primary endpoint was relative reduction in liver fat at week 12, assessed by magnetic resonance imaging-proton density fat fraction (MRI-PDFF). Changes in NASH biomarkers and the safety and tolerability of miricorilant were also assessed.
Results: Twelve patients (n=5, 3, and 4 for miricorilant 600 mg, 900 mg, and placebo) with mean BMI of 38.6±5.3, mean AST of 29.9±9.7 U/L, and mean ALT of 44.9±16.9 U/L at baseline were enrolled. Rapid, large reductions in liver fat content were observed in 4 patients (1 in the 600 mg and all patients in the 900 mg miricorilant arm). After 30-44 days of treatment with miricorilant, mean relative change from baseline in liver fat was -56.15% (range -38.5% to -73.8%), including complete resolution of fatty liver in 1 patient. Hepatic fat reduction was independent of changes in weight and other metabolic parameters. Elevated serum aminotransferase levels (>5x ULN) were observed at around 4 weeks in patients with reduction in liver fat content, leading to suspension of the trial. Liver enzyme increases did not meet the definition of Hy’s Law and resolved in all patients upon discontinuation of miricorilant.

Conclusion: Treatment with miricorilant results in large, rapid reductions in liver fat content. At the doses used in this study, these reductions were accompanied by significant increases in liver enzymes that resolved upon discontinuation of miricorilant. A phase 1b study is planned to evaluate if lower doses of miricorilant are safe and effective in reducing hepatic fat content in patients with NASH.

<table>
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<th>Dose (mg)</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Days on treatment</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>Liver fat (%)</th>
<th>Relative change from baseline in % liver fat</th>
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<tr>
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<td>Max</td>
<td>Baseline</td>
<td>Max</td>
<td>Baseline</td>
<td>Follow-up</td>
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<td>M</td>
<td>31</td>
<td>32</td>
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*complete resolution of fatty liver (MRI-PDFF <5%)

LP35: EFFECTS OF A NOVEL CELL THERAPY IN MICE WITH CHEMICALLY INDUCED ACUTE LIVER INJURY USING HEPATOCYTE-LIKE CELLS DERIVED FROM ADIPOSE STROMAL CELLS REDUCES LIVER DAMAGE AND INFLAMMATION

**Eric Schuur**, Yanina Bogliotti and Mark Vander Roest, Hepatx Corporation

**Background:** There are currently no effective therapies for liver failure other than orthotopic liver transplant. The pathology of liver failure is complex and is not well addressed by drug therapy. As an example, alcoholic hepatitis (AH) is secondary to alcohol mediated injury to hepatocytes and gut leakiness that leads to liver tissue destruction and loss of liver function. If severe enough, circulatory dysfunction and ultimately multiorgan system failure ensue. Interventions that may be effective in halting this spiral of pathology include anti-inflammatory treatments and/or therapies that replace specific hepatocyte functions. Cell therapies have the potential to address the multifaceted nature of AH and other acute liver failure pathologies through multiple mechanisms of action targeting critical underlying pathologies. Building on studies of Xu and Peltz (Cell Transpl 2014) we have developed a cell therapy, SF-Heps, that demonstrates the ability in vitro and in vivo to mitigate pathology of AH or other acute liver pathologies.

**Methods:** Adipose stromal cells (ASCs) were differentiated into the hepatocyte lineage using methods based on those published by Xu et al. (Cell Transpl 2014). Gene expression was assess by qPCR, cytokine secretion by Luminex
multiplex analysis, glycogen synthesis by periodic acid Schiff stain, and LDL uptake using human LDL conjugated to DyLight650. Urea synthesis was assessed using QuantiChrom Urea Assay Kit from BioAssay Systems. Single cell RNA sequencing using the Takara SmartSeq system revealed that the protocol resulted in a stable induced hepatocyte cell type (SF-Heps) with potentially therapeutic properties.

**Results:** *In vitro*, SF-Heps secrete several pro-regenerative cytokines: 48 hour culture supernatants analyzed using multiplex arrays revealed high levels of hepatocyte growth factor, vascular endothelial growth factor, and other cytokines. Co-culture of SF-Heps with M1 human macrophages revealed that the presence of SF-Heps reduced transcription of tumor necrosis factor alpha (TNFa) by as much as 91%, IL1 beta by 85%, and IL6 by 77%. In concert, important hepatocyte functions were upregulated by differentiation including glycogen synthesis and low density lipoprotein receptor expression. Cells were demonstrated to synthesize urea in vitro at a rate of 0.2 mg/dL per 10^5 cells per 48 hours. When administered into a carbon tetrachloride acute liver injury model in C57bl/6 male mice at 6 hours post-CCl4 reductions in ALT and AST were observed at 24 hours as compared to vehicle treated mice. Transcription of proinflammatory cytokines IL1 beta, IL6, and TNFa were also reduced at 24 hours, while glutathione content of liver tissue was increased, suggesting the cell therapy blunted both the acute phase inflammatory response to injury and the damage to hepatocytes.

**Conclusion:** These results support investigation of SF-Heps as a multimodal therapeutic candidate in acute liver injury.

**LP36: EARLY CLINICAL AND VIROLOGICAL CHANGES IN HDV PATIENTS WITH ADVANCED CIRRHOSIS TREATED WITH BULEVIRTIDE MONOTHERAPY IN A REAL-LIFE SETTING**

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**Background:** Bulevirtide (BLV) has been recently approved for the treatment of HDV-related chronic hepatitis or compensated cirrhosis in Europe, but its effectiveness and safety in patients with advanced cirrhosis and severe portal hypertension are still unknown. This study aimed to describe the kinetics of biochemical and virological response to BLV in a real-life, single-centre setting.

**Methods:** All consecutive HDV patients with advanced cirrhosis who started BLV 2 mg/day were enrolled in this prospective single-centre study. All clinical/virological characteristics were collected at treatment baseline, weeks 4, 8 and every 8 weeks thereafter. HDV RNA was quantified by Robogene 2.0 (LOQ 6 IU/mL), HBcrAg by LUMIPULSE® G (LOQ 3 Log U/mL), HBV RNA by cobas® 6800 (LOQ 10 cp/mL) and anti-HBc levels by LG HBcAb-N.

**Results:** 18 patients were enrolled: 48 (29-77) years, 67% males, all Caucasian with HDV genotype-1 and cirrhosis (Child-Pugh A5 in 72%, 17% with mild ascites), 72% esophageal varices (54% under primary endoscopic prophylaxis); spleen length 17 (10-25) cm, platelets 70 (37-227) x10^3/mmC, Fibroscan 16.4 (7.8-57.8) kPa, CAP 194 (100-271) dB/m, 44% BMI >25 kg/m², 2 patients had active HCC, all TDF or ETV treated, 67% received interferon in the past. At BLV baseline: ALT 106 (32-222) U/L, HBsAg 3.7 (2.5-4.3) Log IU/mL, HDV RNA 3.6 (1.9-5.5) Log IU/mL, albumin 3.9 (2.9-4.4) g/dL, bile acids 23 (8-306) μmol/L, AFP 9 (3-596) μg/L; HBcrAg 3.8 (2.3-5) Log U/mL, anti-HBc IgG 10.8 (1.1-55)
COI, HBV RNA undetectable in all while HBV DNA was detectable in 72%. During 6 months of BLV monotherapy, ALT levels declined to 39 (16-91) U/L, normalizing in 88% of patients; HDV RNA showed a 1.8 (1.1-3.4) Log IU/mL reduction, becoming undetectable in 4 patients (22%). While platelets, albumin, AFP and HBsAg remained unchanged, IgG declined from 2,267 (1,047-4,059) to 1,726 (988-2,500) mg/dL. BLV was well tolerated, including in patients with advanced cirrhosis, with active HCC, with platelets <60*10^3/mmc and in those under rivaroxaban and warfarin-based therapies. No significant injection site reactions were observed, the only side effect being a fully asymptomatic increase of bile acids that rose to 48 (11-710) μmol/L.

**Conclusion:** Early changes of virological and clinical parameters confirm the safety and effectiveness of BLV monotherapy even in difficult-to treat HDV patients with advanced cirrhosis and clinically significant portal hypertension.

**LP37: NEUTROPHIL ELASTASE MEDIATES ACUTE LIVER FAILURE THROUGH PROMOTING THE FORMATION OF NEUTROPHIL EXTRACELLULAR TRAPS IN MICE**

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**Background:** Markedly enhanced hepatic infiltration of neutrophils represents a hallmark of acute liver failure (ALF), a severe life-threatening disease with varying etiologies. Neutrophils release web-like structures (known as neutrophil extracellular traps, NETs) in response to the various stimuli. However, whether ALF-induced intrahepatic neutrophils undergo NET formation together with the roles and mechanisms remain poorly characterized.

**Methods:** Focusing on the regulatory role of neutrophil elastase (NE) in the formation of NETs, this study employs loss-of-function strategy to induce experimental ALF in 10-week-old male NE knockout (KO) mice and wild type (WT) controls by intraperitoneal injection of galactosamine hydrochloride and lipopolysaccharide (D-GalN/LPS). Age-matched mice were injected with PBS and served as vehicle controls.

**Results:** We detected evident formation of NETs in the liver with D-GalN/LPS-induced ALF in WT mice. The blockade of NETs by pharmacological inhibitor GSK484 protected against D-GalN/LPS-induced massive liver necrosis in WT mice. Immunofluorescence-based morphological examination revealed the colocalization of NE signals with NET marker citrullinated histone 3 in mouse liver with D-GalN/LPS-induced ALF and ex vivo model of NETs induced in primary mouse neutrophils. In response to ex vivo stimulation, primary neutrophils isolated from NE KO mice exhibited impaired capacity in NET formation, suggesting NE as a key driving factor that is required for NETosis. Likewise, genetic ablation of NE significantly alleviated D-GalN/LPS-induced ALF in mice. Therapeutically, the treatment with sivelestat, pharmacological inhibitor of NE, resulted in a substantial alleviation in D-GalN/LPS-induced ALF in mice.
Conclusion: The present study revealed that NE functions as a key modulator of NETs, thereby potentiating hepatocellular damage and liver necrosis in ALF. Our data suggest NE and NETs may represent promising therapeutic targets against ALF.

Figure 1

Figure 1. Neutrophil elastase is required for the formation of neutrophil extracellular traps to mediate acute liver failure in mice

Acute liver failure (ALF) was induced in 10-week-old male neutrophil elastase (NE) knockout (KO) mice and wild type (WT) controls by intraperitoneal injection of galactosamine hydrochloride and lipopolysaccharide (D-GalN/LPS). (A). The formation of neutrophil extracellular traps (NETs) detected by immunofluorescence of citrullinated histone 3 (H3Cit, red), MPO, and DAPI (blue) in liver sections from WT mice treated with D-GalN/LPS or PBS as vehicle. (B, C). Representative images of H&E staining in liver tissue from WT mice with pre-treatment with PAD4 inhibitor GSK484 or PBS as vehicle control (B, original magnification 400x with scale bar 10 μm. Necrosis areas marked with dash line) and the quantification of necrotic area in H&E staining (C). (D). The formation of NETs detected by immunofluorescence of H3Cit (red), NE, and DAPI (blue) in primary mouse neutrophils stimulated by LPS (200 μg/mL) for 3 hours ex vivo. (E). Representative images of H&E staining in liver sections from NE KO mice and WT controls with original magnification 400x (scale bar, 10 μm. Necrosis areas marked with dash line). (F). Quantification of necrotic area in liver sections according to H&E staining as shown in panel E. Data are expressed as mean ± SEM, n = 5 - 6. *P < 0.05; **P < 0.01.
Background: The risk of hepatocellular carcinoma (HCC) occurrence in chronic hepatitis B (CHB) patients on tenofovir (TDF) or entecavir (ETV) treatment was inconsistent in previous studies, including meta-analyses. We performed a multi-center study to compare the incidence of HCC between the two nucleos(t)ide analogues (NUCs) treated patients with liver cirrhosis from ten medical centers in Taiwan.

Methods: From 2008 to 2018, 3374 CHB patients with liver cirrhosis who had been received ETV or TDF treatment were recruited in this multicenter data cohort. By excluding duration of HCC development less than 6 months of NUCs treatment, HCV coinfection, and other unclear clinical parameters, finally 3237 patients were enrolled in this analysis. There were 2428 patients received ETV treatment, and 809 patients on TDF treatment. Factors associated with HCC occurrence were evaluated, and propensity score matching (PSM) analysis was performed.

Results: As of the end of 2018, 419 patients developed HCC, with the incidence of 2.31 per 100 patient-years for ETV, and 1.67 per 100 patient-years for TDF. Importantly, duration of NUCs treatment more than 5 years had a trend with a higher risk of HCC occurrence (HR=1.26, p=0.092). By ETV versus TDF 1:1 (n=631:631), 2:1 (n=1222:611), and 3:1 (n=1437:479) PSM, TDF had consistently lower risk of HCC occurrence than ETV (HR=0.69, p=0.030; HR=0.67, p=0.009; and HR=0.67, p=0.009, respectively). As TDF was reimbursed by Taiwan National Health Insurance since 2011, and longer ETV treatment duration might be a confounder of higher HCC incidence. We further dissected the study cohort by recruiting patients after 2011. A total of 2557 patients, including 1748 on ETV and 809 on TDF, were entered into the subsequent analysis. Age (HR=1.05, p<0.001), male gender (HR=1.92, p<0.001), and platelet count (HR=1.00, p=0.027) were still significant factors associated with HCC occurrence in multi-variate analysis. But the significant of TDF treatment disappeared in this subgroup cohort (HR=0.78, p=0.075), and in 1:1 PSM cohort (n=623:623, HR=0.75, p=0.101). By incorporating gender, age and platelet count, a GAP score was created to differentiate the risk of HCC into average-risk (10% in 9 years, n=1114), high-risk (20% in 9 years, n=826), and extremely high-risk (>40% in 9 years, n=51) for cirrhotic patients on NUCs treatment. The performance of GAP score was superior to PAGE-B model. The risk of HCC occurrence was similar between ETV and TDF groups in high-risk and extremely high-risk patients. Interestingly, for average-risk patients, TDF had a lower risk of HCC occurrence than ETV (Lok rank test, p=0.0448).
Conclusion: ETV treatment duration is a confounder of HCC occurrence. Age, male gender, and platelet count are highly associated with the risk of HCC in cirrhotic patients on NUCs treatment. GAP score might be an appropriate model to differentiate risk of HCC, but further validation is required.

LP39: COMPARISON OF MANUAL VS MACHINE LEARNING APPROACHES TO LIVER BIOPSY SCORING FOR NASH AND FIBROSIS: A POST HOC ANALYSIS OF THE FALCON 1 STUDY

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Background: Manual liver histology evaluation is the gold standard method for NASH staging but has limitations. Machine learning (ML) scoring approaches may help improve reproducibility. This study compared manual and ML pathology scoring of samples from FALCON 1.

Methods: This was an exploratory post hoc analysis of FALCON 1, a phase 2b study of 48-wk pegbelfermin (PGBF) treatment in patients (pts) with NASH and stage 3 fibrosis. The primary endpoint was ≥1 stage NASH CRN fibrosis improvement without NASH worsening or NASH improvement without fibrosis worsening. Liver biopsies were performed within 6 months of screening and at wk 24; pts who completed wk 24 and had paired, evaluable biopsy specimens at both timepoints were included in the analysis. Biopsy tissue was manually scored by a blinded central pathologist (Z.G.) according to NASH CRN fibrosis criteria and NAS components. In addition, PathAI ML algorithms trained using expert liver pathologist annotations and NASH CRN scores were used to blindly evaluate the primary endpoint (ordinal scoring) and NASH CRN fibrosis criteria and NAS components (ordinal and continuous scoring). The Cochran-Armitage trend test was used to assess differences in the proportion of responders or pts with improvements in PGBF vs PBO arms.

Results: Precise agreement between manual and PathAI ordinal scores was relatively low (kappa<0.5) for all NAS components, yet both indicated that the percentage of primary endpoint responders nearly doubled with PGBF vs PBO.
(table). There was a significantly greater number of primary endpoint responders in the PGBF vs PBO arms detected by the PathAI ordinal score \((P=.013)\) but not manual ordinal score \((P=.148)\). For ballooning and inflammation, there was a significant difference \((P<.05)\) in the number of pts in PGBF vs PBO arms with improvements per PathAI ordinal but not manual scoring; the opposite was true for steatosis. PathAI continuous scoring demonstrated a significant difference between PGBF and PBO for all 3 NAS components. There was no significant improvement in fibrosis stage with PGBF vs PBO with any scoring method.

**Conclusion:** Agreement between ML and manual scoring methods was relatively low, but both ML and manual scoring showed improvements in histologic responses with PGBF vs PBO. Determination of the clinical significance of these findings will require larger trials, more detailed evaluation of specific histologic changes, and correlation with clinical outcomes.

**Comparison of manual vs PathAI ordinal scoring for determination of primary endpoint responders and NAS improvements**

<table>
<thead>
<tr>
<th></th>
<th>PBO (n=43)</th>
<th>10 mg PGBF (n=42)</th>
<th>20 mg PGBF (n=45)</th>
<th>40 mg PGBF (n=45)</th>
<th>(P) value* (PGBF vs PBO)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint responders</strong>, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Manual</td>
<td>7 (16)</td>
<td>14 (33)</td>
<td>12 (27)</td>
<td>13 (29)</td>
<td>.148</td>
</tr>
<tr>
<td>PathAI</td>
<td>8 (19)</td>
<td>13 (31)</td>
<td>20 (44)</td>
<td>17 (38)</td>
<td>.013</td>
</tr>
<tr>
<td><strong>≥1 point improvement in NAS component, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>2 (5)</td>
<td>9 (21)</td>
<td>12 (27)</td>
<td>13 (29)</td>
<td>.002</td>
</tr>
<tr>
<td>PathAI</td>
<td>13 (30)</td>
<td>13 (31)</td>
<td>19 (42)</td>
<td>18 (40)</td>
<td>.106</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>14 (33)</td>
<td>16 (38)</td>
<td>14 (31)</td>
<td>13 (29)</td>
<td>.716</td>
</tr>
<tr>
<td>PathAI</td>
<td>6 (14)</td>
<td>12 (29)</td>
<td>15 (33)</td>
<td>15 (33)</td>
<td>.019</td>
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<tr>
<td>Ballooning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>7 (16)</td>
<td>14 (33)</td>
<td>12 (27)</td>
<td>11 (24)</td>
<td>.274</td>
</tr>
<tr>
<td>PathAI</td>
<td>7 (16)</td>
<td>17 (40)</td>
<td>12 (27)</td>
<td>18 (40)</td>
<td>.033</td>
</tr>
<tr>
<td><strong>≥1 stage improvement in NASH CRN fibrosis stage, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manual</td>
<td>4 (9)</td>
<td>8 (19)</td>
<td>7 (16)</td>
<td>10 (22)</td>
<td>.080</td>
</tr>
<tr>
<td>PathAI</td>
<td>7 (16)</td>
<td>8 (19)</td>
<td>6 (13)</td>
<td>9 (20)</td>
<td>.413</td>
</tr>
</tbody>
</table>

* Uncorrected; \(\geq1\) stage NASH CRN fibrosis improvement without NASH worsening or NASH improvement without fibrosis worsening. NASH worsening = increase in NAS by \(\geq1\) point; NASH improvement = decrease in NAS by \(\geq2\) points; NAS, NAFLD activity score; PBO, placebo; PGBF, pegbelfermin.
LP40: EFFECT OF PEGBELFERMIN ON NONINVASIVE BIOMARKERS OF NASH AND FIBROSIS: A POST HOC ANALYSIS OF THE FALCON 1 TRIAL

Arun J Sanyal1, Diane E Shevell2, Elizabeth Brown2, Shuyan Du2, Jennifer Jones2, John Schwarz2, Robert Gagnon2, George Green2, Peter Shafer2, Richard L. Ehman1, Morten Asser Karsdal4, Diana J. Leeming4, Giovanni Cizza2 and Edgar D. Charles2, (1)Div of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, Richmond, VA, USA, (2)Bristol Myers Squibb, (3)Department of Radiology, Mayo Clinic, (4)Biomarkers & Research, Nordic Bioscience

Background: Pegbelfermin (PGBF), a PEGylated fibroblast growth factor 21 analog, was evaluated in patients (pts) with NASH and bridging fibrosis in the phase 2b FALCON 1 trial. The study did not meet the primary histological endpoint; however, improved noninvasive markers of fibrosis, steatosis, and inflammation were observed with PGBF vs placebo (PBO). This exploratory post hoc analysis further assessed the effect of PGBF on biomarkers of NASH and fibrosis.

Methods: Noninvasive serum and plasma tests included composite scores (FIB-4, APRI, ELF), fibrogenesis markers (N-terminal propeptides of type III collagen: PRO-C3 [monomeric and multimeric] and PC3X [multimeric only]), cell necrosis and apoptosis markers (total CK-18 [M65] and caspase-cleaved CK-18 [M30]), and imaging assessments (MRE and MRI-PDFF). Biomarkers predictive of MRE response were also identified. SomaSignal tests for disease state-specific proteomic signatures were performed for NASH fibrosis, steatosis, inflammation, and ballooning. Linear mixed-effect models were fit for each biomarker; measurements were regressed on time and treatment arm, including an interaction between time and treatment and a random effect for each pt.

Results: PGBF reduced FIB-4 and APRI relative to PBO at wk 24, but the effects appeared to attenuate at wk 48 (table). A similar PGBF-associated effect on ELF was observed, but there was no attenuation at wk 48. PGBF reduced the active fibrogenesis markers, PRO-C3 and PC3X, but the effect on PRO-C3 was lessened at wk 48 and the change in PC3X was sustained. Higher screening PRO-C3 or PC3X concentrations were associated with a 17% or 33% higher MRE response rate at wk 48 in PGBF vs PBO arms, respectively. SomaSignal test data suggested that PGBF treatment reduced fibrosis, steatosis, inflammation, and ballooning; effects on fibrosis and ballooning were most durable. In PGBF arms, CK-18 M65 and M30 concentrations were reduced relative to the PBO arms; both markers appeared to show some attenuation by wk 48.
Conclusion: PGBF treatment improved numerous biomarkers of NASH and fibrosis, but response durability differed. Generally, biomarkers measuring short-term drivers of disease, such as fat, tended to attenuate whereas biomarkers measuring long-term drivers of disease, such as fibrosis, attenuated less. Analyses to understand how these biomarkers may be used to assess disease severity and how they correlate with histologically-determined responses are ongoing.

Summary of FALCON 1 Exploratory Biomarker Results

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Mean (SEM) percent change from baseline to week 48</th>
<th>Mean (SEM) percent change from baseline to week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=49)</td>
<td>10 mg PGBF (n=49)</td>
</tr>
<tr>
<td>n-Fib-4</td>
<td>44 (8.2)</td>
<td>-1.7 (4.7)</td>
</tr>
<tr>
<td>n-APRI</td>
<td>4.4 (1.3)</td>
<td>-0.7 (5.9)</td>
</tr>
<tr>
<td>n-ELF</td>
<td>2.3 (1.0)</td>
<td>0.3 (0.9)</td>
</tr>
<tr>
<td>n-HA</td>
<td>36 (31.1)</td>
<td>23.8 (8.0)</td>
</tr>
<tr>
<td>n-TIMP-1</td>
<td>4.4 (2.6)</td>
<td>-3.3 (2.1)</td>
</tr>
<tr>
<td>n-PiNP</td>
<td>17.3 (6.8)</td>
<td>-3.6 (4.6)</td>
</tr>
<tr>
<td>Fibrogenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-PRO-C3</td>
<td>46 (18.3)</td>
<td>-7.2 (3.7)</td>
</tr>
<tr>
<td>n-PC3X</td>
<td>46 (12.9)</td>
<td>-9.4 (4.0)</td>
</tr>
<tr>
<td>Necrosis and apoptosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-CIK-6M65</td>
<td>43 (79.6)</td>
<td>-13.9 (12.9)</td>
</tr>
<tr>
<td>n-CIK-6M30</td>
<td>44 (36.3)</td>
<td>-15.0 (11.1)</td>
</tr>
<tr>
<td>Imaging assessments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-Liver stiffness (via MRE)</td>
<td>5.4 (4.5)</td>
<td>-3.0 (2.5)</td>
</tr>
<tr>
<td>n-Hepatic fat fraction (via MRS/DPRF)</td>
<td>5.9 (8.6)</td>
<td>-12.0 (10.2)</td>
</tr>
<tr>
<td>n-SomaSignal NASH fibrosis</td>
<td>46 (8.5)</td>
<td>-5.2 (2.9)</td>
</tr>
<tr>
<td>n-SomaSignal NASH steatoaadenosis</td>
<td>46 (8.3)</td>
<td>4.5 (8.5)</td>
</tr>
<tr>
<td>n-SomaSignal NASH inflammation</td>
<td>46 (36.3)</td>
<td>3.2 (10.7)</td>
</tr>
<tr>
<td>n-SomaSignal NASH ballooning</td>
<td>46 (13.1)</td>
<td>8.1 (9.6)</td>
</tr>
</tbody>
</table>

* SomaSignal tests express the probability that a histological parameter is above a given threshold; values range from 0-1; APRI, AST to platelet ratio index; AST, aspartate aminotransferase; CIK-6, cytokinin-6; ELF, enhanced liver fibrin; FIB-4, fibrosis-4; HA, hyaluronic acid; NASH, nonalcoholic steatohepatitis; PGBF, pegbifet; PiNP, N-terminal propeptide of type III procollagen; PC3X, crosslinked N-terminal propeptide of type III collagen; PRO-C3, monomeric and multimeric N-terminal propeptide of type III collagen; SEM, standard error of the mean; TIMP-1, tissue inhibitor of metalloproteinases-1.

LP41: LPCN 1144 THERAPY DEMONSTRATES HISTOLOGIC BENEFITS IN THE PHASE 2 LIFT STUDY IN NONALCOHOLIC STEATOHEPATITIS (NASH) SUBJECTS
Background: NASH is the fastest growing chronic liver disease and can progress to cirrhosis, HCC, and death. 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: Liver 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.

Conclusion: 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.

LP42: SAFETY AND TOLERABILITY OF LPCN 1144 TREATMENT IN BIOPSY CONFIRMED NASH SUBJECTS IN THE PHASE 2 LIFT STUDY

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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.

**LP43: HEPATITIS C TREATMENT UPTAKE IN TELEMEDICINE MODEL IS AT LEAST EQUAL TO FACE-TO-FACE OUTPATIENT CLINIC MODEL**

*Nazanin Hooman1, Alyssa A Miller1, Maribeth Wright2, Marressa Starks-Baker1, Stromberg Arnold3 and Jens Rosenau1, (1)GI, University of Kentucky, (2)Pharmacy, University of Kentucky, (3)Statistics, University of Kentucky*

**Background:** Telemedicine (TM) offers patient-centered benefits compared to standard of care (SOC) office-based models with face-to-face visits particularly for patients with long travel distances. We aimed to investigate if patients with chronic hepatitis C (HCV) could be managed solely through TM from first visit to cure.

**Methods:** This ongoing prospective observational cohort study is conducted by the University of KY (UK) Hepatology outpatient program. After an initial HCV-TM-consult, patients were followed through TM unless requested otherwise. We report an interim analysis on the primary endpoint Tx uptake within 6 months after the initial visit. Tx uptake rates in the TM group were compared to a historic cohort managed with face-to-face office visits (SOC). Analyses were performed using Chi-square, Kaplan-Meier time to event analysis, and Cox Proportional Hazards regression. Enrollment periods were 1/2021 to 8/2021 for TM, and 8/2018 to 12/2019 for SOC.

**Results:** Baseline characteristics of 98 TM (vs. 213 SOC) patients were: Male 57.1% (58.7%); Caucasian 91% (93%); rural 36% (26%); Appalachian 40% (40%); cirrhosis 19% (18%); treatment naïve 97% (97%); HCV chronicity documented at baseline 58% (47%). The following baseline characteristics differed in TM (vs. SOC) group: Age 37.4±10 (41±12) years, p=0.03; last IV or IN illicit drug use <6 months/>6 months/never or unreported 47/39/12% (18/65/17%), p<0.01; Medicaid/Medicare/Commercial insurance 90/6/3% (76/9/13%), p=0.01; referring provider Community/UK-ED/UK-Other 36/51/13% (78/8/14%), p<0.001. Median follow up was 4.7 (mean 5.4) months for TM, 6 months for all SOC patients. Adjusting for age, drug use history, chronicity documentation, care model, insurance, and referring provider (Cox regression model) documentation of HCV chronicity at baseline (p<0.001) and last IV or IN drug use >6 months prior to visit (p=0.02) were predictive of earlier Tx uptake. TM showed a trend towards earlier Tx uptake.
(p=0.05). Kaplan Meier analysis confirmed similar treatment uptake for TM patients compared to SOC patients (overall figure 1a, stratified by drug use history figure 1b).

**Conclusion:** Patients referred for TM-based HCV Tx during the COVID 19 pandemic were younger, reported more recent illicit drug use, were referred predominantly internally from our ED, and were more often Medicaid insured compared to the historic SOC cohort. Our TM model showed a trend towards faster Tx uptake without a single office visit.

LP44: A MULTI-ANALYTE BLOOD TEST FOR ACCURATE AND EARLY DETECTION OF HEPATOCELLULAR CARCINOMA

Nan Lin1, Yongping Lin2, Jianfeng Xu3, Mingzhen Li4, Dan Liu4, Max A. Gallant5, Naoto Kubota6, Dhruvajyoti Roy7, Jason Li8, Emmanuel Cruz Gorospe9, Morris Sherman9, Robert G. Gish9, Ghassan K. Abou-Alfa10, Mindie H Nguyen11, David J. Taggart12, Richard A. Van Etten12, Yujin Hoshida5 and Wei Li6, (1)The Third Affiliated Hospital of Sun Yat-Sen University, (2)The First Affiliated Hospital of Guangzhou Medical University, (3)Helio Health Inc., (4)Laboratory for Advanced Medicine, Inc., Beijing, China, (5)Department of Internal Medicine, University of Texas Southwestern Medical Center, (6)Department of Biological Chemistry, University of California, Irvine, (7)Texas Gastro Research, (8)Toronto Centre for Liver Disease, Toronto General Hospital, University Health Network, Toronto, Canada, (9)Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, (10)Memorial Sloan Kettering Cancer Center, (11)Division of Gastroenterology and Hepatology and Department of Epidemiology and Population Health, Stanford University Medical Center, (12)Department of Medicine, University of California, Irvine

**Background:** Hepatocellular carcinoma (HCC) is the fifth most common malignancy worldwide with a poor prognosis and high mortality, largely due to a low early diagnosis rate. Abdominal ultrasound (US) and measurement of serum alpha-fetoprotein (AFP) are widely accepted HCC surveillance methods but suffer from poor sensitivity for early HCC lesions. Therefore, there is a critical need for a more effective surveillance tool for the early detection of HCC. Here, we evaluated the performance of the HelioLiver Test, a multi-analyte blood test that utilizes both cell-free DNA (cfDNA) methylation patterns and protein tumor markers for the detection of HCC.
**Methods:** A blinded, multicenter validation study was performed using blood specimens drawn from 303 subjects. The study included 125 control subjects that were diagnosed with a benign liver disease, 122 subjects diagnosed with HCC, and 56 subjects diagnosed with other cancer types to determine analytical specificity. Serum specimens were collected from each subject and assessed by the HelioLiver Test in a blinded study. The performance of the HelioLiver Test was compared AFP alone and the GALAD model as established HCC surveillance blood tests.

**Results:** The HelioLiver Test showed a sensitivity of 85% for HCC of any stage and 76% for early stage (I and II) HCC. In contrast, the traditional serum protein marker AFP (cutoff 20 ng/mL) alone and the GALAD Score (cutoff -0.63) showed lower sensitivities of 69% (P < 0.0001) and 75% (P < 0.0001) for HCC overall, and 62% (P = 0.008) and 65% (P = 0.06) for early stage (I and II) HCC, respectively. However, the specificities of AFP alone (97%; P = 0.008) and GALAD (94%; P = 0.13) were higher than HelioLiver Test (91%) in the control subjects. For subjects diagnosed with cancers other than HCC, the HelioLiver Test possessed an analytical specificity of 88% compared to 96% for AFP test alone and 96% for the GALAD model.

**Conclusion:** The performance of the multi-analyte HelioLiver Test was superior to both the GALAD model and AFP test alone, particularly for the early detection of HCC. By allowing the detection of HCC at an earlier stage where curative treatment is more likely, the morbidity and mortality induced by HCC is predicted to be reduced through application of such a test.