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LO1: RESULTS OF MSDC-0602K IN A LARGE PHASE 2b NASH STUDY DEMONSTRATE IMPROVEMENT IN MARKERS OF INSULIN RESISTANCE, GLUCOSE METABOLISM, SERUM AMINOTRANSFERASES, NON INVASIVE MARKERS OF NASH AND HISTOPATHOLOGY

Stephen A Harrison, Pinnacle Clinical Research Center, Guy Neff, Florida Digestive Health Specialist Research Institute; Florida Research Institute, Bradenton, FL, USA, Beth Davison, Biometrics, Momentum Research Inc, Sam Moussa, Medical, Adobe Gastroenterology; University of Arizona for Medical Sciences, Naim Alkhouri, Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, Kenneth Cusi, Division of Endocrinology, Diabetes and Metabolism, University of Florida, Gainesville, Florida, USA, Jerry Colca, Western Michigan University, Arun J Sanyal, Virginia Commonwealth University and Mcguire VA Medical Center, Rohit Loomba, NAFLD Research Center, Division of Gastroenterology, Department of Medicine, University of California, San Diego, San Diego, Gad Cotter, Medical, Momentum Research Inc and Howard Dittrich, Medical, Cirius Therapeutics Inc

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LO2: TOP LINE RESULTS FROM THE FIRST RANDOMIZED, DOUBLE-BLIND, SHAM-CONTROLLED, PROSPECTIVE, MULTICENTER STUDY OF DUODENAL MUCOSAL RESURFACING (DMR) EFFICACY, SAFETY, AND IMPACT ON NASH BIOMARKERS IN PATIENTS WITH TYPE 2 DIABETES (T2D)

J.J.G.H.M Bergman¹, Jacques Deviere², David Hopkins³, Eduardo Guimarães Hourneaux De Moura⁴, Harith Rajagopalan⁵, Juan Carlos Lopez-Talavera⁶, Kelly White⁷, Vijeta Bhambhani⁵, Geltrude Mingrone⁶,⁷,⁸, Guido Costamagna⁶,⁷,⁸, Rehan Haidry⁹, Eduardo Grecco¹⁰, Manoel Galvão Neto¹⁰, Guruprasad Athal¹¹, Alessandro Repici¹², Bu Hayee¹³, Amyn Haji¹⁴, John Morris¹⁵, Raf Bisschops¹⁶, Manil Chouhan¹⁷ and Arun Sanyal¹⁸, (1)Gastroenterology and Hepatology, Amsterdam University Medical Center, (2)Department of Gastroenterology and Hepatopancreatology and Digestive Oncology, Cliniques Universitaires De Bruxelles Hôpital Erasme, Université Libre De Bruxelles, Bruxelles, Belgium, (3)Institute of Diabetes, Endocrinology, and Obesity, King’s Health Partners, (4)University of São Paulo Medical School, (5)Fractyl Laboratories, Inc, (6)Fondazione Policlinico Universitario a. Gemelli Irccs, (7)Università Cattolica Del S, Cuore, (8)King’s College London, (9)University College Hospital, (10)ABC School of Medicine, (11)Nottingham University Hospitals NHS Trust and the University of Nottingham, (12)Humanitas Research Hospital, (13)Department of Gastroenterology, King’s College Hospital, (14)King’s Health Partners, (15)Glasgow Royal Infirmary, (16)University of Leuven, (17)UCL Centre for Medical Imaging, University College London, (18)Medicine, Virginia Commonwealth University, Richmond, VA

Background: The duodenum is a key metabolic signaling center, and duodenal mucosal hyperplasia is a potential therapeutic target for insulin-resistance (IR)-related metabolic diseases. DMR is a novel, minimally invasive, endoscopic mucosal ablative procedure designed to promote healthy regrowth of the duodenal mucosa. Prior studies showed DMR improves glycemic and hepatic parameters in patients with T2D, indicating potential benefit in T2D with concomitant nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH).

Methods: First sham-controlled, double-blind, prospective study of DMR in patients with sub-optimally controlled T2D, conducted across 11 sites (9 in EU, 2 in Brazil). Eligible patients (HbA1c of 7.5-10%, BMI ≥24 to ≤40kg/m², on stable treatment with ≥1 oral anti-diabetic medication) were randomized 1:1 to receive DMR or sham procedure. Primary efficacy endpoints are change in liver magnetic resonance imaging -proton density fat fraction (MRI-PDFF) from baseline to 12 weeks in patients whose baseline liver MRI-PDFF was >5% and change in HbA1c from baseline to 24 weeks. Secondary endpoints assessed include change in relative MRI-PDFF from baseline to week 12 and weight from baseline to week 24. The primary analysis population (modified intent to treat [mITT]) included randomized patients in whom study procedure was attempted.

Results: A total of 108 patients were enrolled (DMR, n=56; sham, n=52). Prespecified interaction testing revealed non-homogeneity between one country and the remaining patient populations; therefore analyses were stratified. In the mITT cohort (DMR, n=39; sham, n=36), most patients were male (77%); mean (SD) age was 57.2 (8.9) years, BMI was 31.1 (3.9) kg/m², HbA1c was 8.3 (0.6), HOMA-IR was 5.1 (2.7), and liver MRI-PDFF (in patients with MRI-PDFF >5% at baseline, n=60) was 17.1 (7.2) at baseline — parameters were well balanced between DMR/sham groups. Median change from baseline at 12 weeks in liver MRI-PDFF was −5.4% (DMR) and −2.4% (sham; P<0.05; Table). Median change from baseline in HbA1c at 24 weeks was −0.6% (DMR) compared with −0.3% (sham; P<0.05). No serious adverse events or unanticipated adverse device effects were reported through 24 weeks. The rate of hypoglycemia was similar between DMR and sham groups.

Conclusion: A single DMR procedure safely elicits favorable, disease modifying, metabolic effects with improvements in hepatic, glycemic, and body weight parameters through 24 weeks in patients with sub-optimally controlled T2D.
### Table. Other Key Hepatic and Glycomic Study Findings

<table>
<thead>
<tr>
<th>Hepatic Parameters</th>
<th>DMR (N = 39)</th>
<th>Sham (N = 36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute change in liver MRI-PDFF from baseline at 12 weeks, %</td>
<td>-5.4</td>
<td>-2.4</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Relative change in liver MRI-PDFF from baseline at 12 weeks, %</td>
<td>n = 30</td>
<td>n = 27</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weight change from baseline at 24 weeks, kg</td>
<td>n = 38</td>
<td>n = 34</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Liver MRI-PDFF at 12 weeks, n (%)&lt;sup&gt;a&lt;/sup&gt; Reduction &gt; 30%</td>
<td>16 (53)</td>
<td>6 (22)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glycomic Parameters</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c change from baseline at 24 weeks, % (mTT)</td>
<td>-0.5</td>
</tr>
<tr>
<td>HbA1c change from baseline at 24 weeks, % (FP)</td>
<td>-0.8</td>
</tr>
<tr>
<td>Reduction in HbA1c, n (%)</td>
<td></td>
</tr>
<tr>
<td>≥ 0.5% at 24 weeks</td>
<td>21 (60)</td>
</tr>
<tr>
<td>≥ 0.75% at 24 weeks</td>
<td>18 (51)</td>
</tr>
<tr>
<td>&lt;7% at 24 weeks</td>
<td>10 (29)</td>
</tr>
<tr>
<td>FPG change from baseline at 12 weeks, mg/dL</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>-40</td>
</tr>
<tr>
<td>Patients with baseline FPG ≥180 mg/dL</td>
<td>n = 19</td>
</tr>
<tr>
<td>HbA1c, mean % change at 12 weeks</td>
<td>-1.4</td>
</tr>
<tr>
<td>FPG, mean mg/dL change at 12 weeks</td>
<td>-75</td>
</tr>
<tr>
<td>HOMA-IR change from baseline at 24 weeks</td>
<td>n = 33</td>
</tr>
</tbody>
</table>

Median data are presented, unless otherwise noted.

<sup>a</sup>Data from patients with baseline liver MRI-PDFF > 0%

DMR = duodenal mucosal resurfacing; FPG = fasting plasma glucose; HbA1c = hemoglobin A1c; HOMA-IR = homeostatic model assessment of insulin resistance; mTT = modified intent to treat; MRI-PDFF = magnetic resonance imaging proton density fat fraction; mTT = per-protocol.

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- Juan Carlos Lopez-Talavera – Fractyl Laboratories, Inc: Employment; Fractyl Laboratories, Inc: Stock Shareholder;
- Kelly White – Fractyl Laboratories, Inc: Employment; Fractyl Laboratories, Inc: Stock Shareholder;
- Vijeta Bhamhani – Fractyl Laboratories, Inc: Employment; Fractyl Laboratories, Inc: Stock Shareholder;
- Rehan Haidry – Cook Endoscopy: Grant/Research Support; Cook Endoscopy: Consulting; Pentax Europe: Consulting; Pentax Europe: Grant/Research Support; Medtronic: Consulting; Medtronic: Grant/Research Support; C2 Therapeutics: Grant/Research Support; C2 Therapeutics: Consulting; C2 Therapeutics: Grant/Research Support; Fractyl Laboratories, Inc: Consulting; Fractyl Laboratories, Inc: Grant/Research Support;
- Eduardo Grecco – Fractyl Laboratories, Inc: Consulting; Apollo Endosurgery: Consulting; Medtronic: Consulting;
- Manoel Galvão Neto – Fractyl Laboratories, Inc: Consulting; GI Windows: Consulting; GI Dynamics: Consulting; Apollo: Consulting; Ethicon: Speaking and Teaching; Medtronic: Speaking and Teaching; Olympus: Speaking and Teaching;
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Geltrude Mingrone: DMR from Fractyl Laboratories Inc

Disclosure information not available at the time of publication: Guruprasad Aithal
LO3: DURABILITY OF TREATMENT EFFECT WITH LONG-TERM MARALIXIBAT IN CHILDREN WITH ALAGILLE SYNDROME: 4-YEAR SAFETY AND EFFICACY RESULTS FROM THE ICONIC STUDY


Background: Maralixibat (MRX), a minimally absorbed apical sodium-dependent bile acid transporter (ASBT) inhibitor, is in development for treatment of chronic cholestatic diseases. ICONIC is a long-term phase 2 study of MRX in children with Alagille syndrome (ALGS). Primary results (week 48) have been presented. Here we present results of patients who entered long-term extension.

Methods: Participants reaching week 48 of ICONIC were eligible to continue MRX 400 µg/kg once daily in this open-label extension. From the end of year 2, participants could receive up to 400 µg/kg twice daily if serum BA (sBA) was >ULN and/or pruritus was persisting. Safety and efficacy were monitored every 12 weeks, including sBA levels, Itch Reported Outcome (Observer) (ItchRO) score for pruritus, Clinician Xanthoma Severity Scale and Clinical Scratch Score (CSS). Changes from baseline to week 48 and to last data point were analyzed with 2-sided t-tests.

Results: Of 31 enrolled participants in ICONIC, 29 were analyzed at week 48 of treatment with MRX 400 µg/kg/day. Statistically significant reductions from baseline to week 48 were observed in sBA levels, ItchRO score, xanthoma score and CSS. Of 23 participants who consented to long-term extension, 15 remain on MRX with a median duration of 44.5 months (range, 42.1–51.7). During the extension phase, 4 withdrew consent, 2 had liver transplant, 1 had renal failure unrelated to MRX and 1 met the ALT stopping rule (≥20 x ULN). In line with the 48-week results, reductions in sBA and pruritus remained significant in the 15 participants receiving MRX; with mean changes from baseline to last data point available in sBA levels of −158.5 µmol/L (95% CI −260.1, −56.9; p=0.0048), ItchRO score of −2.3 (−2.8, −1.8; p<0.0001), xanthoma score of −0.7 (−1.3, −0.02; p=0.0453) and CSS of −2.2 (−2.9, −1.5; p<0.0001). MRX was generally safe and well tolerated long term, with no increases in frequency or severity of adverse events. Asymptomatic and reversible ALT and AST elevations were isolated and not unlike those reported in natural history studies. MRX 400 µg/kg twice-daily dosing had a similar efficacy and safety profile as once-daily dosing. Conclusion: In ICONIC, long-term treatment with MRX was associated with durable control of sBA, pruritus and xanthomas. MRX was generally well tolerated, with over 4 years maximum treatment duration. MRX 400 µg/kg once daily is an effective dose to control cholestasis and pruritus in children with ALGS. This study is ongoing.

LO4: TROPIFEXOR, A HIGHLY POTENT FXR AGONIST, PRODUCES ROBUST AND DOSE-DEPENDENT REDUCTIONS IN HEPATIC FAT AND SERUM ALANINE AMINOTRANSFERASE IN PATIENTS WITH FIBROTIC NASH AFTER 12 WEEKS OF THERAPY: FLIGHT-FXR PART C INTERIM RESULTS

Kathryn Jean Lucas1, Patricia Lopez2, Eric J. Lawitz3, Aasim Sheikh4, Diego Aizenberg6, Stanley Hsia6, George Boon Bee Goh7, John M. Vierling8, Juan Pablo Frias9, Judith White9, Yuichiro Eguchi10, Donald Lazas11, Guy Neff12, Masato Yoneda13, Salvador Augustin14, Won Kim15, Juergen Loeffler 2, Felicity Ann Schaefer 16, Sophie Lamle 2, Miljen Martic 2, Clifford Brass 16 and Arun Sanyal17, (1)Diabetes and Endocrinology Consultants, Morehead City, NC, USA, (2)Novartis Pharma AG, Basel, Switzerland, (3)Texas Liver Institute, University of Texas Health, San Antonio, TX, USA, (4)Gastrointestinal Specialists of Georgia, Marietta, GA, USA, (5)Centro Medico Viamonte, Buenos Aires, Argentina, (6)National Research Institute, Los Angeles, CA, USA, (7)Singapore General Hospital, Singapore, (8)Advanced Liver Therapies, Baylor College of Medicine, Houston, TX, USA, (9)Bioclinica Research, Orlando, FL, USA, (10)Liver Center, Saga University, Saga, Japan, (11)Digestive Health Research / Objective GI, Nashville, TN, US, (12)Florida Digestive Health Specialist Research Institute; Florida Research Institute, Bradenton, FL, USA, (13)Department of Gastroenterology and Hepatology, Yokohama City University Hospital, Yokohama, Japan, (14)Hospital Vall d’Hebron, Barcelona, Catalonia, Spain, (15)Boramae Medical Center, Seoul National University Hospital, Seoul, Korea, (16)Novartis Pharmaceutical Corporation, East Hanover, USA, (17)Virginia Commonwealth University School of Medicine, Richmond, Virginia, USA

Background: FLIGHT-FXR (NCT02855164) is a phase 2 randomized, double blind, placebo-controlled, 3-part, adaptive-design study to assess the safety, tolerability, and efficacy of several doses of tropifexor (LJN452, TXR) in patients with non-alcoholic steatohepatitis (NASH). Results from the first two parts (A and B) demonstrated anti-inflammatory and anti-steatotic efficacy of 60 and 90 µg TXR based on biomarkers, and favorable safety at Week 12 (W12). Here, we present prespecified interim results at W12 from Part C. Methods: In Part C, the effects of higher doses of TXR on biomarkers and histology will be evaluated over 48 weeks in patients with biopsy-proven NASH and fibrosis stages 2-3. In all, 152 patients (64% females) were randomized to receive placebo (N = 51), TXR 140 µg (N = 50) or TXR 200 µg (N = 51) once daily. Prespecified endpoints assessed at W12 included overall safety and changes in alanine aminotransferase (ALT), hepatic fat fraction (HFF), gamma glutamyl transferase (GGT), and body weight. Results: Prespecified endpoints were met for TXR at a dose of 200 µg. Efficacy results are presented in the table below. Relative HFF reduction (without imputation for missing values) by ≥30% was achieved in 20%, 32%, and 64% of patients in the placebo, TXR 140 µg, and TXR 200 µg groups, respectively. The frequency of serious adverse events was low and comparable across groups. Among patients with pruritus, >60% in both TXR groups and all in the placebo group experienced events with mild (Grade 1) severity. Treatment discontinuation rates due to pruritus were low (TXR 140 µg: n = 1 [2%]; TXR 200 µg: n = 3 [6%]; placebo: 0%). A dose-related increase in low density lipoprotein-cholesterol (LDL-C) was seen. None of the lipid changes led to treatment discontinuation or dose reduction. Conclusion: In this prespecified interim analysis of Part C, higher doses of TXR resulted in robust and dose-dependent decreases in ALT, HFF, and body weight with good safety and tolerability after 12 weeks of treatment. Similar to other farnesoid X receptor agonists, these higher doses were associated with mild pruritus and minor dose-related increase in LDL-C. Changes in liver histology resulting from this trial, along with trials of TXR in combination with drugs with other mechanisms of action, will define future therapeutic options in fibrotic NASH.
Table: Least squares means of absolute changes in ALT, GGT, and body weight, and relative change in HFF from baseline to Week 12 estimated in repeated measures analysis of covariance models (full analysis set)

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Placebo (N = 51)</th>
<th>TXR 140 µg (N = 50)</th>
<th>TXR 200 µg (N = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 49</td>
<td>-6.19 (4.19)</td>
<td>-20.1 (4.57)</td>
<td>-23.6 (4.88)</td>
</tr>
<tr>
<td>Relative change in HFF* (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 51</td>
<td>-10.26 (4.21)</td>
<td>-16.89 (4.64)</td>
<td>-31.37 (4.30)</td>
</tr>
<tr>
<td>GGT (U/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 49</td>
<td>-2.53 (3.55)</td>
<td>-39.2 (3.70)</td>
<td>-40.9 (3.62)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
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<td></td>
</tr>
<tr>
<td>n = 50</td>
<td>-1.14 (0.38)</td>
<td>-2.46 (0.38)</td>
<td>-3.20 (0.37)</td>
</tr>
</tbody>
</table>

*Measured as magnetic resonance imaging proton density fat fraction (MRI-PDFF).

Data are presented as LS mean change (SE) with 2-sided P values reported for statistical significance.

ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; HFF, hepatic fat fraction; LS, least square; SE, standard error; TXR, Tropifexor
Background: HRS-1 is a serious, potentially reversible form of acute kidney injury (AKI) in patients with cirrhosis and ascites. The aim of the CONFIRM study was to confirm the efficacy and safety of terlipressin plus albumin versus albumin alone for the treatment of HRS-1 in patients with well-defined HRS-1. Methods: HRS-1 was defined based on modified prior criteria outlined by the International Club of Ascites (ICA), as rapidly deteriorating renal function to SCr ≥2.25 mg/dL, with actual or projected doubling of SCr within 2 weeks, without improvement in renal function (<20% decrease in SCr 48 hours after both diuretic withdrawal and albumin-fluid challenge) in adult patients with cirrhosis and ascites. Subjects were randomized 2:1 to terlipressin (1 mg IV every 6 hours) or placebo, plus albumin in both groups. Treatment was continued to Day 14 unless the following occurred: verified HRS reversal (VHRSR), renal replacement therapy (RRT), liver transplantation (LT) or SCr at or above baseline (BL) at Day 4. VHRSR, the primary endpoint, was defined as 2 consecutive SCr values ≤1.5 mg/dL, at least 2 hours apart, with subjects alive without RRT for at least 10 days after the second SCr ≤1.5 mg/dL; HRS reversal (HRSR) was a decrease in SCr to ≤1.5 mg/dL. Results: (Table): 300 subjects were enrolled; 199 randomized to terlipressin, 101 to placebo. Demographic and BL clinical characteristics were similar between treatment groups. 132/300 (44%) of subjects met systemic inflammatory response syndrome (SIRS) criteria. The proportion of patients in each group who underwent LT was 23.1% for terlipressin and 28.7% for placebo. Overall adverse events (AEs) were similar for the 2 groups; serious AEs were reported in 130/200 (65%) subjects in the terlipressin group vs. 60/99 (60.6%) subjects in the placebo group. Ischemia-associated AEs occurred in 4.5% of the terlipressin group vs. 0% in the placebo group; no new or unexpected AEs were reported. Conclusion: Applying strict criteria defining HRS-1, CONFIRM demonstrates a significant reversal of worsening renal function in cirrhotic patients treated with terlipressin plus albumin when compared to those treated with albumin alone, including patients with SIRS criteria. This response was durable and associated with less need for early RRT. Terlipressin is effective in improving renal function and achieving HRS reversal in patients with HRS-1 and progressive advanced liver disease.
Obeticholic acid (OCA) is a selective and potent farnesoid X receptor agonist indicated for treatment of primary biliary cholangitis (PBC). POISE was a placebo-controlled, phase 3 study of the efficacy and safety of OCA in PBC, and included a 12-month double-blind phase with a 5-year open-label extension (OLE). The OLE was to assess the long-term safety of OCA and the durability of OCA effects on serum markers of cholestasis. Methods: Key inclusion criteria included PBC diagnosis, alkaline phosphatase (ALP) ≥1.67× upper limit of normal (ULN) and/or total bilirubin >ULN to <2× ULN, and on a stable dose of—or intolerant of—ursodeoxycholic acid. During the double-blind phase, 216 patients were randomized to daily placebo, OCA 5-10 mg (titrated after 6 months based on response and tolerability), or OCA 10 mg. 193/198 patients completing the double-blind phase enrolled in the OLE and received OCA. The POISE composite primary endpoint was the percentage of patients with ALP <1.67× ULN, with a reduction of ≥15% from baseline, and total bilirubin ≤ULN at 12 months. This analysis pooled double-blind placebo (OCA baseline was OLE day 0) and double-blind OCA patients to evaluate the efficacy and safety of up to 72 months of OCA treatment. Results: 146 patients (76%) completed the protocol as specified following administrative shutdown of the study. 158 patients (82%) completed 4 years of OCA treatment and 116 (60%) patients completed 5 years of OCA treatment; 52 patients who had received OCA in the double-blind phase completed 6 years on treatment. The percentage of patients meeting the primary endpoint was 46% at 12 months and 50% at 48, 60, and 72 months. Significant and durable reductions were observed for ALP, alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase throughout the study. Mean total bilirubin remained stable through 72 months of OCA treatment. Throughout the study there was no significant worsening in hepatic stiffness as measured by transient elastography in a subset of patients. During the OLE, 8 patients (4%) discontinued treatment due to pruritus. Adverse events were consistent with the established safety profile of OCA in PBC, with no new safety observations during long term treatment out to 6 years. Conclusion: OCA treatment resulted in sustained improvement in liver biochemistry during up to 6 years of follow-up.
**Table. Serum markers of cholestasis from baseline through 72 months of OCA treatment**

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Baseline (N=193)</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 months (N=185)</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/L)</td>
<td>317 (120)</td>
<td>-105 (88)*</td>
<td>-118 (128)*</td>
</tr>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>11.5 (7.0)</td>
<td>-0.9 (4.1)†</td>
<td>-0.1 (4.5)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (U/L)</td>
<td>51.2 (33.5)</td>
<td>-12.8 (24.7)*</td>
<td>-14.1 (18.2)*</td>
</tr>
<tr>
<td>Alanine aminotransferase (U/L)</td>
<td>56.7 (37.0)</td>
<td>-21.5 (24.4)*</td>
<td>-28.2 (29.4)*</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase (U/L)</td>
<td>275.2 (306.0)</td>
<td>-157.7 (205.1)*</td>
<td>-156.1 (200.1)*</td>
</tr>
<tr>
<td>Liver stiffness (kPa)</td>
<td>11.4 (9.4)</td>
<td>0.5 (5.6)</td>
<td>1.2 (10.1)</td>
</tr>
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</table>

*p<0.0001; †p=0.004; ‡Baseline N=79, 12 months N=71, 72 months N=32; kPa, kilopascal. P-values for the within-treatment comparisons were obtained using a paired t test.

Disclosures:
Frederik Nevens – Cook Medical: Consulting; Gilead: Consulting; Genkyotex SA: Consulting; Gore: Consulting; TwinPharma: Consulting; Intercept Pharmaceuticals: Consulting; Ipsen: Grant/Research Support; AbbVie: Consulting; Promethera Biosciences: Advisory Committee or Review Panel; Astellas: Grant/Research Support;
Mitchell L Shiffman  – Abbvie: Advisory Committee or Review Panel; Abbvie: Consulting; Abbvie: Speaking and Teaching; Enanta: Grant/Research Support; Galmed: Grant/Research Support; Genfit: Grant/Research Support; Gilead: Advisory Committee or Review Panel; Gilead: Grant/Research Support; Gilead: Speaking and Teaching; HepQuant: Grant/Research Support; HepQuant: Advisory Committee or Review Panel; Intercept: Advisory Committee or Review Panel; Intercept: Grant/Research Support; Intercept: Speaking and Teaching; CymaBay: Grant/Research Support; BMS: Grant/Research Support;
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The following people have nothing to disclose: Victor Vargas, Karel J. Van Erpecum;
LO7: LIK066 (LICOGFLIFLOZIN), AN SGLT1/2 INHIBITOR, ROBUSTLY DECREASES ALT AND IMPROVES MARKERS OF HEPATIC AND METABOLIC HEALTH IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE: INTERIM ANALYSIS OF A 12-WEEK, RANDOMIZED, PLACEBO-CONTROLLED, PHASE 2a STUDY

Stephen A Harrison1, Frederico Perez Manghi2, William B Smith3, Diana Alpenidze4, Diego Aizenberg5, Koos Burggraaf6, Chi-Ye Chen7, Eli Zuckerman8, Eric Ravussin9, Phunchai Charatcharoenwittaya10, Pin-Nan Cheng11, Helena Katchman12, Samuel Klein13, Ziv Ben-Ari14, Anisha Mendonza15, Yiming Zhang16, Miljen Martic17, Shenglin Ma18, Sheena Kao19, Sandra Tanner19, Alok Pachori19, Yan-Ling He20, Chinweike Ukomadu20 and Eric Sicard21, (1)Pinnacle Clinical Research, San Antonio, TX, (2)Cinme,Buenos Aires, Argentina, (3)New Orleans Center for Clinical Research, Knoxville, TN, (4)City Outpatient Clinic #117, St. Petersburg, Russia, (5)Centro Medico Viamonte, Buenos Aires, Argentina, (6)Center for Human Drug Research, Leiden, Netherlands, (7)Chiayi Christian Hospital, Taiwan, (8)Carmel Medical Center, Haifa, Israel, (9)Pennington Biomedical Research Center, Baton Rouge, La, (10)Siriraj Hospital,Bangkok, Thailand, (11)National Cheng Kung University Hospital, Taiwan, (12)Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, (13)Washington University School of Medicine, Center for Human Nutrition, (14)Liver Diseases Center, Sheba Medical Center, Ramat Gan, Israel, (15)Novartis Institutes for Biomedical Research, Cambridge, MA, (16)Novartis Institutes for Biomedical Research, East Hanover, NJ, (17)Novartis Pharma AG, Basel, Switzerland, (18)Novartis Institutes for Biomedical Research, Shanghai, China, (19)Novartis Institutes for Biomedical Research, Basel, Switzerland, (20)Novartis Institutes for Biomedical Research,Cambridge, MA, (21)Altasciences Algorithme Pharma, Quebec, Canada

Background: Non-alcoholic fatty liver disease is a chronic disorder associated with obesity and diabetes that can progress to non-alcoholic steatohepatitis (NASH). Licogliflozin is an inhibitor of sodium-glucose co-transporters 1 and 2, which inhibits glucose absorption from gut and reabsorption from kidney. The aim of this study is to demonstrate safety, tolerability and efficacy of licogliflozin in patients with either histologically confirmed NASH or a phenotype suggestive of NASH. Methods: This randomized, double blinded, placebo-controlled study was conducted in subjects with histologically confirmed or phenotypic NASH (defined as BMI ≥27 kg/m² in non-Asians or ≥23 kg/m² in Asians, ALT≥ 50 (males) or ≥35 (females) and T2DM) who received daily oral licogliflozin at 150 mg, 30 mg or placebo in a 2:2:1 ratio for 12 weeks (NCT03205150). The primary endpoint is the effect on ALT concentration after 12 weeks of treatment. Secondary endpoints include improvement in body weight, liver fat content and AST amongst others. 110 subjects were enrolled of which 77 have completed (placebo (n=18); licogliflozin 30 mg (n=25) and licogliflozin 150 mg (n=34)) and are included in the interim analysis. Results: Treatment with licogliflozin at 150 mg and 30 mg resulted in a 27% (17.2 U/L, p=0.036) and 19% (11.1 U/L, p=NS) placebo adjusted reduction in serum ALT concentrations respectively. There was a similar reduction in AST of 30% (p=0.004) and 23 % (p=0.043), as well as 32% (p=0.001) and 26% (p=0.014) improvement in GGT at 150 mg and 30 mg doses respectively. Placebo adjusted reductions in body weight at both doses (~4 %, p=0.0001) and HBAlc (absolute change: 150 mg: 0.96% (p=0.0001); 30 mg: 0.81% (p=0.001)) were seen. Placebo adjusted relative reduction in liver fat content was 22% (p=0.01) and 10% (p=NS) at 150 mg and 30 mg, respectively, while absolute reduction in liver fat was 4.5% (p=0.01) at 150 mg and 2.7% (p=NS) at 30 mg. The most common AE was diarrhea, reported by similar number of subjects in the placebo and 30 mg groups (38.9% vs. 40%) but at a higher rate in the 150 mg dose group (76.5%). Most diarrhea events (97.4%) were mild. Conclusion: Licogliflozin is safe and tolerable. Twelve weeks of licogliflozin treatment causes dose-dependent improvements in liver biochemistries, HBAlc and liver fat content. Studies of longer duration and in combination with drugs that have different mechanisms of action are needed to define the role of licogliflozin as a therapeutic option for NASH.

Disclosures:
Stephen A Harrison – GENFIT SA: Consulting;
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Yiming Zhang – Novartis: Employment;
Miljen Martic – Novartis AG: Employment; Novartis AG: Stock Shareholder;
Shenglin Ma – Novartis: Employment;
Sheena Kao – Novartis: Employment;
Sandra Tanner – Novartis: Employment;
Alok Pachori – Novartis: Employment;
Yan-Ling He – Novartis: Employment;
Chinweike Ukomadu – Novartis: Stock Shareholder; Novartis: Employment;
The following people have nothing to disclose: Frederico Perez Manghi, William B Smith, Diego Aizenberg, Koos Burggraaf, Phunchai Charatcharoenwittaya, Pin-Nan Cheng, Helena Katchman
Disclosure information not available at the time of publication: Diana Alpenidze, Chi-Ye Chen, Samuel Klein, Eric Sicard
LO8: A PHASE 2 STUDY OF LONAFARNIB, RITONAVIR AND PEGINTERFERON LAMBDA FOR 24 WEEKS: INTERIM END-OF-TREATMENT RESULTS FROM THE LIFT HDV STUDY.

Christopher Koh1, Ben L. Da2, Pallavi Surana3, Amy Huang4, Devika Kapuria5, Yaron Rotman6, Anusha Vittal7, Christy Gilman3, Gil Ben-Yakov3, Chunwei Lai4, David Kleiner8, Fariah Rahman9, Julian Hercun10, Jeffrey Glenn11 and Theo Heller3, (1)Liver Disease Branch, National Institute of Diabetes Digestive and Kidney Diseases, National Institutes of Health, DHHS, (2)Digestive Diseases Branch, Nih/Niddk, (3)Liver Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases, (4)Liver Diseases Branch, Niddk, (5)Liver Disease Branch, National Institutes of Health, (6)Liver Diseases Branch, Niddk, (7)Liver Diseases Branch, Niddk, Nih, (8)Liver Disease Branch, Niddk, (9)Laboratory of Pathology, National Cancer Institute, (10)The Program for Experimental & Theoretical Modeling, Division of Hepatology, Department of Medicine, Loyola University Medical Center, Maywood, IL, USA, (11)Div of Gastroenterology and Hepatology, Stanford University Medical Center

Background: Hepatitis Delta Virus (HDV) infection, the most aggressive form of human chronic viral hepatitis, is still without an approved FDA therapy. Separate clinical trials have demonstrated anti-HDV activity with the prenylation inhibitor lonafarnib (LNF) boosted with ritonavir (RTV) and peginterferon lambda-1a (LMD) monotherapy. In a first-in-humans clinical trial, the Lambda InterFeron combination Therapy (LIFT) study evaluated the safety and antiviral effects of combination therapy with LNF/RTV/LMD in patients with chronic HDV infection. Methods: In a phase 2a open-label study, 26 adult patients with chronic HDV and quantifiable HDV RNA in serum (lower limit of quantitation <40 IU/mL) were treated with oral LNF 50mg and RTV 100mg twice daily and subcutaneous LMD 180mcg weekly for 24 weeks and then monitored post-therapy for 24 weeks. Tenofovir or Entecavir was started prior to therapy. Serial assessments of safety parameters, liver tests, pharmacokinetics, histology, and virologic (HDV RNA and HBV DNA) markers were obtained. Results: In this ongoing study, patients were 60% male, median age of 40 years and included Asian (52%), White (32%) and African (16%) subjects. Median baseline evaluations included: ALT (64 IU/mL), AST (47 IU/mL), Ishak Fibrosis (3), modified HAI inflammation (9), HBV DNA (<21 IU/mL) and log HDV RNA (4.74 IU/mL). After 12 weeks of therapy (21 of 26 subjects), the median HDV RNA decline from baseline was 3.6 log IU/mL (IQR: 2.6-4.2, p<0.0001) with 5 patients (24%) achieving undetectable HDV RNA and 5 patients (24%) with HDV RNA below the lower limit of quantification (BLOQ). At the end of therapy (19 of 26 subjects), the median HDV RNA decline was 3.4 log IU/mL (IQR: 2.9-4.5, p<0.0001) with 7 patients (37%) achieving undetectable HDV RNA and 3 patients (16%) BLOQ. 18 of 19 patients (95%) achieved >2 log decline during 24 weeks of therapy. Adverse events were mostly mild to moderate and included GI related side effects, weight loss, hyperbilirubinemia, and anemia. Therapy was dose reduced in 3 patients and discontinued in 4 patients. Conclusion: Triple combination therapy with LNF/RTV/LMD in chronic HDV patients appears to be safe and tolerable for up to 6 months in most patients. After 24 weeks, almost all achieve >2 log decline in HDV RNA during therapy with >50% achieving undetectable or BLOQ HDV RNA levels. These interim results support continued exploration of this therapeutic combination in HDV.

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Disclosure information not available at the time of publication: Gil Ben-Yakov

1001 NORTH FAIRFAX STREET 4TH FLOOR ALEXANDRIA, VA 22314 PHONE 703 299 9766 FAX 703 299 9022 WEB: AASLD.ORG THE LIVER MEETING 2019 | NOVEMBER 8-12 | BOSTON, MA | Hynes Convention Center
Background: The mortality of Severe Alcoholic Hepatitis (SAH) remains high in the absence of effective treatment. The use of corticosteroids is limited to a select group of patients. The need for new and innovative therapies for AH, especially for SAH is urgent. DUR-928 is an endogenous sulfated oxysterol. It modulates inflammatory responses, promotes cell survival, stimulates hepatic regeneration, and reduces lipotoxicity. It was well tolerated in multiple Phase 1 studies. The aim of our study was to evaluate safety and tolerability of DUR-928 in patients with AH, especially SAH, and to explore the pharmacodynamic signals related to its efficacy.

Methods: A total of 19 patients were enrolled into this open-label Phase 2a multi-center trial, of whom 15 had Maddrey’s Discriminant Function (DF) ≥32 (SAH), 12 had MELD scores at 21-30, and 11 had baseline serum bilirubin levels >8 mg/dL. All patients received IV infused DUR-928 (at 30, 90, or 150 mg) on Day 1 and Day 4 (if still hospitalized), and were followed for 28-days. Results: DUR-928 at all 3 doses was safe with no drug-related serious adverse events. All patients, including SAH patients, survived the 28-day follow-up period. Treatment responders (Lille score <0.45) among all DUR-928 treated AH patients (1 patient did not return for the Day 7 visit) were 89%; among 15 SAH patients (DF ≥32), 87%; and among 12 patients with MELD 21-30, 83%. In particular, 100% of SAH patients treated with 30 or 90 mg DUR-928 (n = 11) responded to the treatment (Table). Although patients received only 1 or 2 doses of DUR-928, their MELD scores on Day 28 in SAH patients were significantly reduced from baseline (-17.5%, p=0.01). The median reduction of MELD on Day 28 from baseline in SAH patients treated with 30 or 90 mg of DUR-928 was -19.0% (p=0.01). DUR-928 also significantly reduced serum bilirubin levels on Day 7 in AH patients, especially in patients with baseline bilirubin >8.0 mg/dL (-25.1%, p=0.02). Comparing our data to a set of data used for developing Lille score by Louvet et al., which evaluated 145 AH patients (with comparative DF scores, prothrombin times, and serum creatinine, albumin and bilirubin levels as those in this study), Lille scores from our study were significantly lower, p<0.0001, than that from the historical data, 0.24 (0.07, 0.60). Conclusion: In this Phase 2a trial, DUR-928 was well tolerated at the 3 doses tested by all AH patients, including SAH patients. One or two doses of the drug significantly reduced serum bilirubin levels at Day 7 after treatment and MELD scores at Day 28. Lille scores of DUR-928 treated patients were significantly better than comparative published historic data. These initial findings are encouraging for further development of DUR-928 in patients with AH, including SAH.

References:

1. Louvet et al., 2007, Hepatology 45:1348-1354
2. Louvet et al., 2015, Gastroenterology, 149:398–406
<table>
<thead>
<tr>
<th>AH Patient Category (n)</th>
<th>Responders</th>
<th>Lille Median (1st, 3rd quartile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (18) with 30 or 90 mg DUR-928 (14)</td>
<td>89%</td>
<td>0.10 (0.04, 0.20)</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>0.05 (0.04, 0.19)</td>
</tr>
<tr>
<td>SAH (15) with 30 or 90 mg DUR-928 (11)</td>
<td>87%</td>
<td>0.19 (0.05, 0.22)</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>0.12 (0.05, 0.19)</td>
</tr>
<tr>
<td>MELD 21-30 (12) with 30 or 90 mg DUR-928 (8)</td>
<td>83%</td>
<td>0.19 (0.11, 0.25)</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>0.19 (0.10, 0.19)</td>
</tr>
<tr>
<td>Baseline bilirubin &gt;8 mg/dL (11) with 30 or 90 mg DUR-928 (8)</td>
<td>82%</td>
<td>0.10 (0.05, 0.20)</td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>0.10 (0.05, 0.19)</td>
</tr>
</tbody>
</table>

Disclosures:
Tarek Hassanein – DURECT Corporation: Grant/Research Support; Assembly Biosciences, Inc.: Grant/Research Support;
Lance L. Stein – Gilead: Speaking and Teaching; Gilead: Advisory Committee or Review Panel; Abbvie: Speaking and Teaching; Intercept: Speaking and Teaching; Durect: Grant/Research Support; Conatus: Grant/Research Support;
Steven L Flamm – Gilead Sciences, Inc.: Advisory Committee or Review Panel; Gilead Sciences, Inc.: Speaking and Teaching; Gilead Sciences, Inc.: Grant/Research Support; Abbvie: Advisory Committee or Review Panel; Abbvie: Speaking and Teaching; Abbvie: Grant/Research Support; Merck: Advisory Committee or Review Panel; Merck: Speaking and Teaching;
Paul Martin – Gilead: Advisory Committee or Review Panel;
Matthew C. Cave – Gilead: Speaking and Teaching; Dova: Speaking and Teaching; Intercept: Speaking and Teaching; Abbvie: Speaking and Teaching; Abbvie: Advisory Committee or Review Panel; Intercept: Grant/Research Support; Hightide: Grant/Research Support; Conatus: Grant/Research Support; Durect: Grant/Research Support;
Christina Blevins – DURECT Corporation: Employment; DURECT Corporation: Stock Shareholder;
Deborah Scott – Durect corporation: Employment;
WeiQi Lin – Durect Corporation: Employment;
The following people have nothing to disclose: William Krebs
LO10: A PHASE 2, PROSPECTIVE, MULTICENTER, DOUBLE-BLIND, RANDOMIZED STUDY OF SAROGLITAZAR MAGNESIUM 1 MG, 2 MG OR 4 MG VERSUS PLACEBO IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE AND/OR NONALCOHOLIC STEATOHEPATITIS (EVIDENCES IV)

Samer Gawrieh, Gastroenterology & Hepatology, Indiana University School of Medicine, Mazen Noureddin, Digestive and Liver Diseases, Cedars Sinai Medical Center, Nicole M. Loo, Hepatobiliary Cancer, Texas Liver Institute, Rizwana Mohseni, Catalina Research Institute, LLC, Vivek R. Awasty, Internal Medicine, Ohiohealth Marion General Hospital, Kenneth Cusi, Endocrinology, Diabetes & Metabolism, University of Florida, Kris V. Kowdley, Liver Care Network and Organ Care Research, Swedish Medical Center, Michelle Lai, Gastroenterology and Hepatology, Beth Israel Deaconess Medical Center, Eugene R. Schiff, Schiff Center for Liver Diseases, University of Miami School of Medicine, Deven V. Parmar, Zydus Discovery Dmcc, Pankaj R. Patel, Zydus Research Centre, Cadila Healthcare Ltd. and Naga P. Chalasani, Gastroenterology and Hepatology, Indiana University School of Medicine

Background: Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are major health problems without approved therapies. Pre-clinical studies suggest that Saroglitazar (a novel dual peroxisome proliferator activated receptor α/γ agonist) is an effective treatment for NAFLD/NASH. This phase-2, prospective, multicentre, double-blind, randomized trial was conducted to determine efficacy and safety of Saroglitazar Magnesium (Saro) 1 mg, 2 mg or 4 mg compared to placebo in patients with NAFLD/NASH. Methods: A total 106 adult subjects with NAFLD/NASH who had alanine aminotransferase (ALT) ≥50 U/L and body mass index ≥25 kg/m² were randomized in a 1:1:1:1 ratio to Saro 1 mg, 2 mg or 4 mg and placebo at 23 centers in the US. Primary efficacy endpoint was percentage change in ALT levels from baseline to week -16 in Saro groups vs placebo group. Key secondary efficacy endpoints included proportion of patients with ≥50% reduction in ALT levels and change in liver fat content (measured by MR-PDFF) from baseline to week-16 in Saro groups vs placebo group. Results: Baseline characteristics were similar across the 4 study groups. The primary efficacy endpoint was met (Table). A significant reduction in mean ALT from baseline to week-16 was observed with Saro 1 mg (-27.3%), 2 mg (-33.1%), and 4 mg (-44.3%) vs placebo (4.1%) (p<0.001 for all). A significantly higher proportion of patients had ≥50% reduction in mean ALT from baseline to week-16 with Saro 4 mg vs placebo (51.8% versus 3.5%; p<0.0001). At week-16, Saro 4 mg compared to placebo significantly reduced HOMA-IR (-5.1 vs -2.5), triglycerides (-70.3 vs -3.4), total cholesterol (-24.2 vs -4.4), APRI (-0.16 vs 0.09), and mean liver fat content (-4.2% versus -0.3%) (p<0.05 for all). A significantly higher % of patients had reduction in liver fat content by > 30% on Saro 4 mg vs placebo (40.7% vs 8%, p=0.006). There was not significant percent change in body weight with Saro 4 mg vs placebo (1.88% vs 0.28%, p=0.9). Overall, Saro was well-tolerated and no death or cardiovascular events occurred during the study. Conclusion: Saroglitazar Magnesium 4 mg significantly improved serum ALT, hepatic steatosis, insulin resistance, and dyslipidemia in patients with NAFLD/NASH.
### Table. Changes in efficacy endpoints in full analysis set population from baseline to week-16

<table>
<thead>
<tr>
<th>Efficacy Endpoints</th>
<th>Saroglitazar 4 mg (n=27)</th>
<th>Saroglitazar 2 mg (n=23)</th>
<th>Saroglitazar 1 mg (n=26)</th>
<th>Placebo (n=28)</th>
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<tr>
<td><strong>Primary Efficacy Endpoint</strong></td>
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<tr>
<td>Percentage change in ALT (U/L)</td>
<td>-44.39</td>
<td>-33.16</td>
<td>-27.31</td>
<td>4.16</td>
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<tr>
<td>*p value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0002</td>
<td></td>
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<tr>
<td><strong>Secondary Efficacy Endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change in liver fat content (%) by MR-PDFF</td>
<td>-4.21</td>
<td>-0.42</td>
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<td>% of patients with reduction in liver fat content by &gt; 10%</td>
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<td>28.57</td>
<td>23.08</td>
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<td>*p value</td>
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<td>% of patients with reduction in liver fat content by &gt; 30%</td>
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<td>*p value</td>
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<td>% change in weight (kg)</td>
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*p value derived from comparison between Saroglitazar 4 mg vs placebo, Saroglitazar 2 mg vs placebo, and Saroglitazar 1 mg vs placebo.
LP1: CONTINUED THERAPY WITH ABI-H0731+NRTI RESULTS IN SEQUENTIAL REDUCTION/LOSS OF HBV DNA, HBV RNA, HBeAg, HBcrAg AND HBsAg IN HBeAg POSITIVE PATIENTS

Mark S. Sulkowski1, Kosh Agarwala2, Scott K. Fung3, Man-Fung Yuen4, Hany Zayed5, Katia Alves5, Qi Huang5, Eric Ruby5, Dongmei Qiang5, Steven Knox5, Richard Colonno5 and on behalf of the ABI-H0731 Study Team, (1)Johns Hopkins University, (2)Institute of Liver Studies, King’s College Hospital, (3)Toronto Centre for Liver Disease, Toronto General Hospital, University Health Network, (4)The University of Hong Kong, (5)Assembly Biosciences

Background: Standard of care nucleos(t)ide analogs (NrtI) are effective in chronic HBV (CHB) infection, but achieve low rates of sustained responses off therapy. The combination of the HBV Core Inhibitor ABI-H0731 (731) with a NrtI has demonstrated potent antiviral activity in prior clinical studies and is being evaluated in a long-term treatment study. Methods: Studies ABI-H0731-201 and ABI-H0731-202 were 24-wk double-blind, placebo (Pbo)-controlled studies in CHB patients (pts). After 24 wks of treatment, pts could enter the open-label extension study ABI-H0731-211 and receive 731+NrtI for up to an additional 52 wks. The study diagram summarizes study design, patient flow and monitored parameters. This interim report summarizes data for HBeAg+ pts only. Results: Final Wk 24 results confirmed greater mean log10 declines in HBV DNA (5.27 vs 3.99; p=0.017) and RNA (2.34 vs 0.61; p<0.001) are achieved with 731+ETV vs ETV in Study 202. By Wk 24 in Study 201, the proportion of pts on 731+NrtI vs NrtI achieving DNA “TND” was 69% vs 0% (p<0.001), and the proportion of pts achieving RNA <35 U/mL whose baseline RNA ≥ 35 U/mL was 52% vs 0% (p=0.0013) respectively. There are 64 HBeAg+ pts currently on treatment in Study 211, having received an overall treatment duration of ≥32 wks. Among the 27 HBeAg+ pts receiving 731+NrtI in Study 201, 41% (11/27) have now achieved DNA TND along with RNA <35 U/mL and HBeAg <1 IU/mL. At their last timepoint, Study 202 (Rx naïve) pts now in Study 211 (n=22) have demonstrated mean DNA and RNA declines of 6.1 and 3.0 logs, respectively, with observed mean log changes of ≥0.6 for HBeAg (11 pts ≥0.5, 4 pts ≥1.0), >0.8 log for HBcrAg (7 pts ≥1.0, 3 pts ≥2.0) and ≥0.4 log for HBsAg (7 pts ≥0.5, 3 pts ≥1.0). When, administered in combination with NrtI for up to 1 year, 731 has been well-tolerated, with only mild/moderate adverse events and lab abnormalities, and only a single discontinuation due to a Grade 1 rash. Conclusion: ABI-H0731 continues to exhibit a favorable safety and tolerability profile in pts treated for up to 1 yr. The combination of 731+NrtI results in faster, deeper declines in HBV DNA and RNA than NrtI alone, as well as subsequent declines in the surrogate markers of cccDNA (pgRNA, HBeAg and HBcrAg) predictive of cccDNA pool depletion, and HBsAg. The emergent data supports the continued development of ABI-H0731. Updated safety and efficacy data will be presented.
<table>
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<td>ETV + 731 300 mg (N=13)</td>
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<td>Primary Assays</td>
<td>DNA (LLOQ = 20 IU/mL), RNA (LLOQ = 135 IU/mL) HBeAg, HBsAg and HBCrAg Safety and PK</td>
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<td>52</td>
</tr>
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*N values represent number of patients who transitioned to 211 and remain on treatment and included in this analysis.

Disclosures:
Mark S. Sulkowski – AbbVie: Grant/Research Support; Allergan: Grant/Research Support; Biogen: Advisory Committee or Review Panel; Arbutus: Advisory Committee or Review Panel; Assembly Biosciences; Grant/Research Support; Proteus Digital Health; Grant/Research Support; Gilead: Grant/Research Support; Gilead: Advisory Committee or Review Panel; AbbVie: Grant/Research Support; Immunocore: Advisory Committee or Review Panel; Kosh Agarwal – arbutus: Advisory Committee or Review Panel; MSD: Grant/Research Support; Gilead: Speaking and Teaching; Springbank: Advisory Committee or Review Panel; shinoig: Advisory Committee or Review Panel; Scott K. Fung – Gilead Sciences Inc.: Advisory Committee or Review Panel; Merck: Speaking and Teaching; Abbvie: Advisory Committee or Review Panel; Gilead Sciences: Speaking and Teaching; Abbvie: Speaking and Teaching; Merck: Grant/Research Support; Man-Fung Yuen – Gilead: Consulting; arrowhead pharmaceuticals: Grant/Research Support; clear B therapeutics: Advisory Committee or Review Panel; dicerna pharmaceuticals: Consulting; clear B therapeutics: Consulting; springbank pharmaceuticals: Advisory Committee or Review Panel; dicerna pharmaceuticals: Advisory Committee or Review Panel; springbank pharmaceuticals: Grant/Research Support;assembly biosciences: Grant/Research Support; janssen: Advisory Committee or Review Panel; springbank pharmaceuticals: Consulting; symex corporation: Grant/Research Support; gilead sciences: Grant/Research Support; bristol myer squibb: Grant/Research Support; janssen: Advisory Committee or Review Panel; fujirebio incorporation: Grant/Research Support; abbvie: Consulting; abbvie: Advisory Committee or Review Panel; merck sharp and dohme: Consulting; bristol myer squibb: Advisory Committee or Review Panel; arbutus: Consulting; bristol myer squibb: Consulting; arbutus: Advisory Committee or Review Panel; GlaxoSmithKline: Advisory Committee or Review Panel; GlaxoSmithKline: Consulting; janssen: Consulting; gilead: Advisory Committee or Review Panel; merck sharp and dohme: Consulting; Hany Zayed – Assembly Biosciences: Employment; Assembly Biosciences: Stock Shareholder; Katia Alves – Assembly Biosciences: Stock Shareholder; Assembly Biosciences: Employment; Qi Huang – Assembly Biosciences: Stock Shareholder; Assembly Biosciences: Employment; Eric Ruby – Assembly Biosciences: Stock Shareholder; Assembly Biosciences: Employment; Dongmei Qiang – Assembly Biosciences: Stock Shareholder; Assembly Biosciences: Employment; Steven Knox – Assembly Biosciences: Employment; Assembly Biosciences: Stock Shareholder; Richard Colombo – Assembly Biosciences: Stock Shareholder; Assembly Biosciences: Employment;
Short course duration sofosbuvir/velpatasvir is inferior to standard duration therapy in the treatment of recently acquired HCV infection: results from REACT study

Gail Matthews1,2, Sanjay Bhagani3, Marc Van Der Valk4, Juergen K Rockstroh5, Arthur Y Kim6, Christine Thurnheer7, Jordan J. Feld8, Julie Bruneau9, Edward J. Gane10, Margaret Hellard11, Jason Grebely1, Tanya Applegate1, Pip Marks1, Marianne Martinello1, Kathy Petoumenos1 and Gregory Dore1,2, (1)Kirby Institute, Unsw Sydney, Australia, (2)St Vincent’s Hospital, Sydney, Australia, (3)Infectious Diseases, Royal Free NHS Foundation Trust, London UK, (4)Academic Medical Centre, (5)Department of Internal Medicine I, University Hospital Bonn, (6)Infectious Disease Unit, MGH, (7)Bern University Hospital, (8)Toronto Centre for Liver Disease, University of Toronto University Health Network, (9)Centre De Recherche Du Centre Hospitalier De L’université De Montréal (CRCHUM), (10)Auckland City Hospital, (11)The Alfred Hospital, Melbourne, Australia

Background: Shortened duration therapy for acute and recently acquired HCV infection has been shown to be highly effective in several small non-randomised studies with direct-acting antiviral agents (DAAs), however guidelines remain conservative in their recommendations with no currently approved regimens for this indication. Methods: The REACT study was an NIH-funded multicentre international, open-label, randomised, phase 4 non-inferiority trial examining the efficacy of short course (6 weeks, Arm A) versus standard course (12 weeks, Arm B) therapy with sofosbuvir/velpatasvir for recently acquired HCV infection (estimated duration of infection <= 12 months). Randomisation was at week 6 and stratified by site and HIV status. The primary endpoint was sustained virologic response at 12 weeks post-treatment (SVR12) reported in the intention-to-treat (ITT) population. A total of 250 participants were planned for enrolment and DSMB analysis was scheduled after the first 50 participants in each arm reached SVR12. Following the initial DSMB review, a second review was scheduled following 60 participants through SVR12 in each arm. Results: At second DSMB review, 185 participants were enrolled, 165 had been randomised and 127 were through SVR12; n=65 in Arm A and n=60 in Arm B. Of those randomised, 98% were male, and 72% HIV positive. The predominant genotype was 1 (65%) and median baseline viral load 5.6 log10IU/ml. 38% were reinfections. At second review (May 2019), the DSMB recommended study cessation for evidence of inferiority in the short arm (A). By ITT SVR12 was 78% (53/65) in Arm A (95%CI 70-90) versus 95% (57/60) in Arm B (95%CI 86-99) (p=0.021). Relapse occurred in 6/65 participants in Arm A (9%, 95%CI 3-19) versus 0 in Arm B (95% CI 0-6). Median baseline viral load in people with viral relapse was 6.4 log10IU/ml (range 5.9-7.1 log10IU/ml). Two further participants in Arm A had virological failure at end of treatment, one had reinfection, two died, and four lost to follow-up. Conclusion: In this randomised study of treatment for recently acquired HCV infection, 6 weeks sofosbuvir/velpatasvir was inferior to 12 weeks. Final analysis of the full randomised dataset will be completed October 2019.

Disclosures:
Gail Matthews – Gilead and Abbvie: Grant/Research Support; Sanjay Bhagani – abbvie: Speaking and Teaching; Merck: Speaking and Teaching; Juergen K Rockstroh – Abivax, Gilead, Janssen, Merck, ViIV: Advisory Committee or Review Panel; Abbvie, Gilead, Janssen, Merck and ViIV: Speaking and Teaching; Arthur Y Kim – Biomarin, Inc.: Advisory Committee or Review Panel; Jordan J. Feld – Abbvie, Abbott, Enanta, Gilead, Janssen, Merck, Roche: Grant/Research Support; Abbvie, Abbott, Enanta, Gilead, Janssen, Merck, Roche: Consulting; Julie Bruneau – Gilead: Advisory Committee or Review Panel; Gilead: Grant/Research Support; Abbvie: Advisory Committee or Review Panel; Edward J. Gane – AbbVie, Gilead, Janssen, Novartis, Roche and Merck: Advisory Committee or Review Panel; Abbvie, Gilead; Speaking and Teaching; Jason Grebely – AbbVie, Cepheid, Gilead, and Merck/MSD: Grant/Research Support; AbbVie, Cepheid, Gilead, and Merck/MSD: Advisory Committee or Review Panel; AbbVie, Cepheid, Gilead, and Merck/MSD: Speaking and Teaching; Gregory Dore – Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, N.J. USA: Board Membership; Gilead: Speaking and Teaching; Gilead: Grant/Research Support; Gilead: Board Membership; AbbVie: Speaking and Teaching; AbbVie: Grant/Research Support; AbbVie: Board Membership; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, N.J. USA: Grant/Research Support; The following people have nothing to disclose: Christine Thurnheer, Tanya Applegate, Pip Marks, Marianne Martinello.

Disclosure information not available at the time of publication: Marc Van Der Valk, Margaret Hellard, Kathy Petoumenos.
LP3: TENOFOVIR FOR PREVENTING PROGRESSION OF CHRONIC HEPATITIS B IN PATIENTS WITH MINIMALLY RAISED AMINOTRANSFERASE: FINAL RESULTS OF A MULTI-CENTER DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

Yao-Chun Hsu,1,2 Chi-Yi Chen,1,3 I-Wei Chang,1 Chi-Yang Chang,4 Chun-Ying Wu,1 Teng-Yu Lee,1 Ming-Shiang Wu,1 Ming-Jong Bai,1 Jyh-Jou Chen,10 Chi-Ming Tai,11 Wen-Hui Ku,12 Lein-Ray Mo,13 and Jaw-Town Lin14

(1)Gastroenterology and Hepatology, E-DA Hospital, (2)Center of Liver Diseases, E-Da Hospital, (3)Chia-Yi Christian Hospital, (4)Taipei Medical University Hospital, (5)Fu-Jen Catholic University Hospital, (6)Taipei Veterans General Hospital, (7)Taichung Veterans General Hospital, (8)National Taiwan University Hospital, (9)Division of Gastroenterology and Hepatology, Department of Internal Medicine, Taitung Mackay Memorial Hospital, (10)Chi-Mei Medical Center, (11)E-Da Hospital, (12)Taipei Pathology Institutes, (13)Tainan Municipal Hospital, (14)Digestive Medicine Center, China Medical University Hospital

Background: Chronic hepatitis B (CHB) is the leading cause of liver-related morbidity and mortality worldwide. Antiviral therapy is currently recommended for patients with CHB at advanced disease status. Whether treatment can prevent disease progression in patients with minimally raised alanine aminotransferase (ALT) is unclear.

Methods: In this multi-center, double-blind, placebo-controlled trial, we randomly assigned 160 CHB patients without liver cirrhosis, who presented with viremia above 2,000 IU/mL and ALT elevation between 1~2 folds the upper limit of normal range, to receive either tenofovir disoproxil fumarate (TDF) or matching placebo for 3 years. The primary outcomes were histological deterioration (≥2-point increase in Knodell necroinflammatory score or any worsening of fibrosis) and fibrosis progression (any increase in Ishak scale). We also explored virological, biochemical, serological outcomes and adverse events. This study is registered with the ClinicalTrials.gov, number NCT01522625.

Results: From January 2012 to November 2015, 79 and 81 patients were randomly allocated to TDF and placebo, respectively. After 3-year treatment, 146 patients (n=73 in each group) completed the trial with paired liver biopsy. Histological deterioration occurred in 31.5% (n=23) and 57.5% (n=42) in the TDF and placebo group, respectively (P=0.03). The relative risk of TDF for histological deterioration was 0.55 (95% CI, 0.37~0.81). Liver fibrosis progressed in 26.0% (n=19) and 46.6% (n=34) in the TDF and placebo group, respectively (P=0.02). The relative risk for fibrosis progression was 0.56 (95% CI, 0.35~0.88). TDF achieved higher rates of viral and biochemical remission but the two groups were similar in serological outcomes. More patients in the placebo group (16.1% vs. 2.5%, P=0.005) experienced hepatitis events that required rescue therapy.

Conclusion: Antiviral therapy prevents histopathological progression in non-cirrhotic CHB patients who present with minimally raised ALT and significant viremia.
Disclosures:
Yao-Chun Hsu – Bristol-Myers Squibb: Speaking and Teaching; Gilead Sciences: Speaking and Teaching; Gilead Sciences: Grant/Research Support; Gilead Sciences: Advisory Committee or Review Panel; AbbVie: Speaking and Teaching;
The following people have nothing to disclose: Chi-Yi Chen, I-Wei Chang, Chi-Yang Chang, Teng-Yu Lee, Ming-Shiang Wu, Ming-Jong Bair, Jyh-Jou Chen, Chieh-Chang Chen, Cheng-Hao Tseng, Chi-Ming Tai, Wen-Hui Ku, Jaw-Town Lin

Disclosure information not available at the time of publication: Chun-Ying Wu, Lein-Ray Mo
**LP4: FIRST CLINICAL EXPERIENCE WITH RNA INTERFERENCE [RNAi]-BASED TRIPLE COMBINATION THERAPY IN CHRONIC HEPATITIS B (CHB): JNJ-73763989 (JNJ-3989), JNJ-56136379 (JNJ-6379) AND A NUCLEOS(T)IDE ANALOGUE (NA)**

Man-Fung Yuen1, Stephen Locarnini2, Bruce Given3, Thomas Schluep3, James Hamilton3, Michael Biermer4, Ronald Kalmeijer5, Maria Beumont-Mauviel6, Oliver Lenz7, Gavin Cloherty8, Kathy Jackson2, Carlo Ferrari7, Ching Lung Lai1, Kevin Sze-Hang Liu1, Lung Yi Mak1, Danny Ka Ho Wong1, Wai Pan To1, Kwan-Lung Ko1 and Robert G. Gish8, (1)The University of Hong Kong, (2)Victorian Infectious Disease Reference Laboratory, (3)Arrowhead Pharmaceuticals, (4)Janssen Pharmaceuticals BV, (5)Janssen R&D, (6)Abbott Diagnostics, (7)University of Parma, (8)Hepatitis B Foundation

**Background:** JNJ-3989 (RNAi) silences HBV RNA transcripts from integrated HBV DNA and episomal cccDNA. JNJ-6379 (novel class N capsid assembly modulator [CAM-N]; normal empty capsids) blocks HBV viral replication and de novo cccDNA formation in preclinical models, and reduced HBV DNA and RNA in CHB patients (pts) (AASLD 2018). AROHBV1001 showed that 3 monthly JNJ-3989 doses (100–400mg) with a NA: achieved >1 log₁₀ HBsAg reductions; reduced all measurable viral products; was well tolerated (EASL 2019). Combining agents with different modes of action may lead to additive/synergistic antiviral effects, possibly increasing functional cure rates after finite treatment. To help design longer term studies, a cohort was added to explore triple combination therapy of JNJ-3989, JNJ-6379 and a NA.

**Methods:** HBeAg +ve or -ve, NA -experienced (regardless of HBV DNA level) or -naïve CHB pts were enrolled. 12 pts received 3 JNJ-3989 doses (200mg subcutaneously, days [D] 1, 29 and 57) + oral JNJ-6379 250mg once daily for 12 wks. Pts started/continued NA on D1 and continued beyond JNJ-6379 dosing. Assessments included safety, qHBsAg, qHBeAg, qHBV DNA, qHBV RNA and qHBcrAg levels. Planned follow-up is 1 yr with continued NA treatment.

**Results:** All pts were Asian; median age 46 (34–67) yrs; 8 males; HBeAg 4 +ve 8 –ve; 7 NA-experienced. All pts had 3 JNJ-3989 doses and 84 days of JNJ-6379; follow-up was 17–64 days. No deaths, discontinuations, serious or severe adverse events (AEs) or clinically significant findings on vital signs/ECG/hematology/chemistry were reported. Two AEs (mild respiratory infection, not related) were reported. The only notable laboratory findings were grade 1 transient isolated ALT elevations (n=5, 57–118 U/L), possibly therapeutic response flares. HBsAg levels declined during treatment (Fig). Mean HBsAg (SE) log₁₀ reductions were 1.4 (0.12) on D85 (n=12) and 1.8 (0.11) in 7 pts with D113 data. In pts with >1000 IU/mL HBV DNA on D1 (n=6, 3.7–7.7 log₁₀ IU/mL), all had a rapid decline in DNA. 9 pts had quantifiable HBV RNA (D1, 1.75–7.5 log₁₀ IU/mL); 6 were <limit of quantification by D29. Pts positive (D1) for HBeAg (n=4) and HBcrAg (n=8) all had reductions in these parameters.

**Conclusion:** This is the first study to investigate the safety and efficacy of a triple combination of a RNAi (JNJ-3989), a CAM-N (JNJ-6739) and a NA in CHB pts. This combination was well tolerated and pts achieved robust reductions in HBsAg as well as other measurable viral parameters.
Disclosures:

Man-Fung Yuen – Gilead: Consulting; arrowhead pharmaceuticals: Grant/Research Support; clear B therapeutics: Advisory Committee or Review Panel; dicerna pharmaceuticals: Consulting; clear B therapeutics: Consulting; springbank pharmaceuticals: Advisory Committee or Review Panel; dicerna pharmaceuticals: Advisory Committee or Review Panel; springbank pharmaceuticals: Grant/Research Support; arrowhead pharmaceuticals: Consulting; clear B therapeutics: Advisory Committee or Review Panel; springbank pharmaceuticals: Advisory Committee or Review Panel; arrowhead pharmaceuticals: Grant/Research Support; gilead sciences: Advisory Committee or Review Panel; bristol myers squibb: Grant/Research Support; janssen: Advisory Committee or Review Panel; fujirebio incorporation: Grant/Research Support; bristol myers squibb: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; bristol myers squibb: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristol myers squibb: Advisory Committee or Review Panel; gilead sciences: Advisory Committee or Review Panel; abbot: Consulting; bristle...  


Disclosure information not available at the time of publication: Stephen Locarnini, Bruce Given, Kathy Jackson, Carlo Ferrari
LP5: FENOFIBRATE MITIGATES INCREASES IN SERUM TRIGLYCERIDES DUE TO THE ACC INHIBITOR FIRSOCOSTAT IN PATIENTS WITH ADVANCED FIBROSIS DUE TO NASH: A PHASE 2 RANDOMIZED TRIAL

Eric J. Lawitz1, Guy Neff2, Peter J Ruane3, Ziad Younes4, Jie Zhang5, Catherine Jia5, Jay Chuang5, Ryan Huss5, Chuhan Chung5, Mani Subramanian5, Robert P Myers5, Michael Middleton6 and Rohit Loomba7, (1)Texas Liver Institute, University of Texas Health, San Antonio, TX, USA, (2)Florida Digestive Health Specialist Research Institute, Florida Research Institute, Bradenton, FL, USA, (3)Ruane Clinical Research, Los Angeles, CA, USA, (4)Gastro One, Germantown, TN, USA, (5)Gilead Sciences, Inc., Foster City, CA, USA, (6)Department of Radiology, University of California San Diego, San Diego, CA, USA, (7)Internal Medicine, University of California, San Diego, Division of Gastroenterology, Department of Medicine, San Diego, CA, USA

Background: Inhibition of acetyl-CoA carboxylase (ACC) leads to improvements in liver fat and other hepatic parameters, but may be associated with hypertriglyceridemia. Our objective was to evaluate the safety and efficacy of fenofibrate (FENO) to mitigate increases in serum triglycerides (TGs) in patients with advanced fibrosis due to NASH treated with the ACC inhibitor firsocostat (FIR).

Methods: Patients with advanced (F3-F4) fibrosis due to NASH (by biopsy or liver stiffness by MRE ≥3.64 kPa or FibroScan ≥9.9 kPa) and TGs >150 and <500 mg/dL were randomized to treatment with FENO 48 mg (n=15) or 145 mg (n=16) orally once daily for 2 weeks, followed by the combination of FENO+FIR 20 mg daily for 24 weeks (NCT02781584). Serum lipids, liver biochemistry, markers of fibrosis, liver stiffness by FibroScan, and centrally-read MRI-PDFF and 2D MRE were monitored.

Results: Overall, 71% of patients had diabetes, 87% were obese, and 35% had cirrhosis. At baseline (BL), median (IQR) fasting TGs in the FENO 48 mg and 145 mg groups were 218 mg/dL (166, 245) and 202 mg/dL (164, 354), respectively. After 2 weeks of FENO monotherapy, the median change in TGs was +2 mg/dL in the 48 mg group (p=0.93 vs BL) and -42 mg/dL in the 145 mg group (p=0.015; Figure). After 24 weeks of FENO+FIR combination therapy, TGs were not significantly different from BL (median [IQR] change from BL: +19 mg/dL [-27, 106] in 48 mg group [p=0.095] and +6 mg/dL [-88, 90] in 145 mg group [p=0.99]; Figure). One treatment-emergent Grade 3 TG elevation (>500 mg/dL) was observed in the FENO 48 mg group (405 mg/dL at BL and 974 mg/dL at week 24 of FENO+FIR). FENO and FENO+FIR were well tolerated; no grade 3 or 4 adverse events (AEs), treatment discontinuations due to AEs, or hepatotoxicity were observed. In the combined cohort, significant reductions from BL to week 24 were observed in serum ALT (median: 39 vs 27 U/L, p<0.001), AST (36 vs 29 U/L; p=0.008), GGT (50 vs 32 U/L; p<0.001), bilirubin (0.5 vs 0.4 mg/dL; p<0.001), liver stiffness by FibroScan (11.9 vs 8.3 kPa; p<0.001), FibroTest (0.35 vs 0.25; p=0.001), and hepatic PDFF (12.3% vs 9.5%; p<0.001). At week 24, a ≥30% relative reduction in PDFF was observed in 43% of patients (FENO 48 mg vs 145 mg: 40% vs 47%). Conclusion: In patients with advanced fibrosis due to NASH, fenofibrate is safe and mitigates firsocostat-induced increases in serum TGs. The combination of firsocostat and fenofibrate led to improvements in hepatic fat, liver biochemistry, and markers of fibrosis.
Disclosures:
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LP6: ADDITIVE BENEFICIAL EFFECTS OF FIBRATES COMBINED WITH OBETICHOLIC ACID IN THE TREATMENT OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND INADEQUATE RESPONSE TO SECOND-LINE THERAPY

Pierre-Antoine Soret1, Laurent Lam2, Fabrice Carrat2, Lena Smets3, Vincent Leroy4, Thomas Berg5, Marco Carbone6, Pietro Invernizzi6, Palak Trivedi7, Christina Weiler-Normann8, Laurent Alric9, Isabelle Rosa10, Jean-Paul Cervoni11, Jerome Dumortier12, Pascal Potier13, Olivier Roux14, Christine Silvain15, Cynthia Levy16, Albert Pares17, Christoph Schramm18, Frederick Nevens19, Olivier Chazouilleres1 and Christophe Corpechot1, (1)Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis, Saint-Antoine Hospital, AP-HP Sorbonne University, ERN Rare-Liver, Paris, France, (2)Public Healthcare Department, Saint-Antoine Hospital, AP-HP Sorbonne University, Inserm, Pierre-Louis Institut of Epidemiology and Public Healthcare, Paris, France, (3)Division Liver and Biliopancreatic Disorders, University Hospitals KU, ERN Rare Liver, Leuven, Belgium, (4)Hepatology Department, University Hospital, Grenoble, France, (5)Clinic and Polyclinic of Gastroenterology, Hepatology, Infectiology, and Pneumology, University Hospital, Leipzig, Germany, (6)Center for Autoimmune Liver Diseases, San Gerardo University Hospital, ERN Rare-Liver, Monza, Italy, (7)Centre for Liver Research, University Hospitals, ERN Rare-Liver, Birmingham, UK, (8)Department of Medicine I, University Medical Center Hamburg-Eppendorf, Martin Zeitz Center for Rare Diseases, ERN Rare-Liver, Hamburg, Germany, (9)Department of Internal Medicine and Digestive Diseases, Toulouse University Hospital, (10)Gastroenterology and Hepatology Department, Intercommunal Hospital, Créteil, France, (11)Hepatology and Gastroenterology Department, University Regional Hospital, Besançon, France, (12)Hepatology and Gastroenterology Department, Edouard Herriot Hospital, Hospices Civils De Lyon, Claude Bernard University, Lyon, France, (13)Hepatology and Gastroenterology Department, Regional Medical Center, Orléans, France, (14)Hepatology Department, Beaujon University Hospital, AP-HP, ERN Rare-Liver, Clichy, France, (15)Hepatology Department, University Hospital, Poitiers, France, (16)Division of Hepatology, University of Miami Miller School of Medicine, Miami, USA, (17)Liver Unit, Hospital Clinic, University of Barcelona, ERN Rare-Liver, Barcelona, Spain

Background: Obeticholic acid (OCA) and bezafibrate are the only two drugs that have shown clear benefits on the biochemistries of patients with primary biliary cholangitis (PBC) and an inadequate response to ursodeoxycholic acid (UDCA). However, whether OCA and fibrates given together in combination with UDCA have additive beneficial effects in these patients is poorly known. Methods: Patients with PBC treated for at least 12 weeks with, and with no intolerance to, a combination of OCA (5-10 mg/d), fibrates (bezafibrate 400 mg/d or fenofibrate 200 mg/d) and UDCA (13-15 mg/kg/d) because of a Paris-2 inadequate response to one second-line option were included in a multicenter retrospective cohort study. The index date was time of second-line therapy introduction. Standard biochemical liver tests measured under dual then triple therapy (TT) were collected. The primary outcome was the rate of change in alkaline phosphatase (ALP) level. The secondary outcomes were the rate of ALP normalization and changes in total bilirubin, GGT, AST, ALT, and itch intensity score. These outcomes were analyzed using linear mixed-effect models adjusted for age, sex, and drug dose. Results: Fifty patients from 16 centers and 7 countries (France, Belgium, Germany, Italy, UK, Spain, USA) were included: mean(sd) age at index date, 49.7(11.1) yrs; 88% females; UDCA dose, 15.2(2.9) mg/kg/d; ALP level, 370(240) IU/L; total bilirubin level, 14.8(8.7) µmol/L; liver stiffness measurement, 13(9.8) kPa. Among them, 24 (Group 1) received OCA as second-line and fibrates as third-line therapy while 26 (Group 2) received fibrates as second-line and OCA as third-line therapy, in addition to UDCA. The mean(sd) durations of dual and triple therapies were 39.7(29.3) mo. and 9.4(6.6) mo., respectively. TT was associated with a significant fall in ALP level compared to dual therapy: -27%/yr. (95%CI: -15% – -36%; p<.0001), an effect that was significant in both groups (Figure). TT was associated with an odds ratio for ALP normalization of 5.5 (95%CI: 1.8–17.1; p=0.003), and with a significant decrease in GGT (p<.0001), ALT (p<.001), AST (p<.01), and total bilirubin (p=.02) compared to dual therapy. TT was associated with a reduction in itch intensity score in Group 1 (p=0.02) but not in Group 2. At last visit, no patients had discontinued TT. Conclusion: Triple therapy with fibrates, OCA, and UDCA improves biochemical liver tests and increases the rate of ALP normalization in patients with PBC and incomplete response to second-line therapy.
Figure. Changes in ALP level according to treatment group and sequence.

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AB-506 is an oral, class II, selective HBV CI for the treatment of CHB with activity against genotypes A-H and nucleos(t)ide resistant variants in vitro. The objectives of this ongoing first-in-human study are to evaluate the safety, tolerability, PK, and antiviral activity of AB-506 in HS and HBV-DNA+ CHB subjects.

Methods: In Part 1, 2 cohorts of HS were randomized 6:2 to receive single ascending doses of AB-506 from 30mg to 1000mg or placebo (PBO). In Part 2, 1 cohort of 12 HS was randomized 10:2 to receive AB-506 400mg or PBO once daily (QD) for 10 days. In Part 3, two cohorts of 12 non-cirrhotic, HBV DNA+ subjects were randomized 10:2 to receive AB-506 or PBO for 28 days at either 160mg or 400mg QD. Safety, tolerability, PK, immune markers, viral sequence and antiviral activity were assessed.

Results: No serious adverse events (AEs) were observed in HS; most AEs were mild and considered unrelated to AB-506. No clinically significant abnormalities in laboratory tests, ECGs, or vital signs were noted. CHB subjects were aged 22-59 years and were mostly female, Asian and genotype C or D. HBV DNA and HBV RNA responses by dose and e-antigen status are shown in Table 1. There was no viral breakthrough on treatment. Baseline substitutions at positions Y38, I105, and T109 were noted in 5, 4 and 2 of the 24 subjects respectively; one subject with I105T had no response to treatment. No serious AEs; most AEs were mild. 6 subjects across both cohorts had transient, reversible ALT elevations (2 Grade 2, 4 Grade 4), with 2 subjects discontinuing study drug per protocol on Days 23 and 24. Bilirubin, albumin, and INR values remained normal in all subjects; none met drug-induced liver injury (DILI) criteria. All had declining HBV DNA levels of >2 log10 on treatment, and none had unusual AB-506 exposures. One subject has had persisting HBeAg (>2.6 log10) and HBsAg (>1.4 log10) declines from baseline 8 months-post flare and was the only subject with increases from baseline in interferon gamma (IFN-γ) and other T cell activation markers that preceded the ALT flare. The other Grade 4 flare subjects had accompanying increases in IP-10, but no changes in IFN-γ. A novel, longer duration (28 day) study of AB-506 in HS is ongoing. Conclusion: AB-506 was generally safe and well-tolerated and robust antiviral effects were observed in CHB subjects. The ALT flares observed in CHB subjects may be immune-mediated and may lead to beneficial declines in HBV markers.

Conclusion: AB-506 was generally safe and well-tolerated and robust antiviral effects were observed in CHB subjects. The ALT flares observed in CHB subjects may be immune-mediated and may lead to beneficial declines in HBV markers.
### Table 1: Day 28/EOT Mean Change from Baseline

<table>
<thead>
<tr>
<th>HBV viral marker</th>
<th>160mg QD</th>
<th>400mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>log10 (SD)</td>
<td>HBeAg+ [n=3]</td>
<td>HBeAg- [n=7]</td>
</tr>
<tr>
<td>DNA IU/mL</td>
<td>-2.4 (0.39)</td>
<td>-2.0 (1.1)</td>
</tr>
<tr>
<td>RNA copies/mL</td>
<td>-2.5 (0.54)⁴</td>
<td>-2.22⁵</td>
</tr>
</tbody>
</table>

¹PBO excluded; ²2 subjects DC for ALT excluded; ³1 subject < LLOQ; ⁴N=2 (1 < LLOQ by Day 28); ⁵N=1 (5 < LLOQ at baseline, 1 < LLOQ by Day 28); ⁶1 < LLOQ at baseline

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LP8: MULTIPLE DOES OF AN ANTI-FGFR1/KLB BISPECIFIC ANTIBODY (BFKB8488A) ARE ASSOCIATED WITH A DECREASE IN HEPATIC FAT IN PATIENTS WITH NAFLD

Rebecca Kunder1, Felix Yeh1, Leslie W. Chinn1, Ajit Dash1, Nicholas Lewin-Koh1, Nicole Kim1,2, Jill Fredrickson1, Kenta Yoshida1, Shan Chen1, Maria Wilson1 and Chin Wong1, (1)Genentech, Inc., (2)University of the Pacific

Background: BFKB8488A is an agonistic bispecific antibody which binds to fibroblast growth factor receptor 1c (FGFR1) and Klotho β (KLB) that are expressed on adipocytes. Patients with non-alcoholic fatty liver disease (NAFLD) were enrolled to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of BFKB8488A. Methods: Sixty-two patients with NAFLD (>10% hepatic fat fraction by MRI-PDFF) were randomized 3:1 into 6 cohorts to receive BFKB8488A or placebo subcutaneously for 12 weeks in this blinded Phase 1b, multiple ascending dose study. Various BFKB8488A doses and/or dosing frequencies were evaluated in 5 cohorts, while gradual dose up-titration was implemented in a 6th cohort (ongoing; results not reported here). Results: Patients received placebo (n=13) or BFKB8488A once every 2 weeks (Q2W) (50, 75, 100, or 130 mg; n= 8 each) or once every 4 weeks (Q4W) (250 mg; n=9). Overall, BFKB8488A was safe and adequately tolerated with no deaths or life-threatening adverse events. Gastrointestinal effects at the higher dose levels limited tolerability, with 100 mg Q2W and lower dose levels being well-tolerated. There were no drug-related serious adverse events (SAEs) and 2 non-related SAEs (urinary tract infection and lymphadenopathy). BFKB8488A exhibited non-linear PK with extensive between-subject variability. Pharmacodynamic effects were observed as early as 2 weeks, and are reported here only for well-tolerated doses (50, 75, and 100 mg Q4W) as percent change (mean ± SD) from baseline after 12 weeks of treatment. Evidence of adipose-specific PD effect was apparent with increases in adiponectin (up to 17% ± 27%). BFKB8488A had beneficial cardiometabolic effects (e.g., HDL increases up to 14% ± 14%; triglyceride decreases up to 24% ± 36%). In BFKB8488A-treated patients with elevated baseline ALT (>30 U/L for males; >19 U/L for females), ALT decreased by 10% to 30%. Pro-C3, a marker of fibrogenesis, was porently reduced with BFKB8488A treatment (up to 37% ± 17%). These PD effects were associated with a dose-dependent relative reduction in hepatic fat fraction, measured by MRI-PDFF, of up to 38% ± 25% (versus placebo change of 0% ± 28%). Conclusion: In patients with NAFLD, well-tolerated doses of BFKB8488A were highly effective at decreasing hepatic fat fraction and improving liver health. The translation of these effects into clinical efficacy is being further evaluated in a Phase 2 non-alcoholic steatohepatitis (NASH) study.

Background: Glecaprevir/pibrentasvir (G/P) is approved to treat patients with chronic hepatitis C virus (HCV) genotype (GT) 1–6 infection. In a prior analysis of the EXPEDITION-8 study (AASLD 2018), 8-week G/P achieved high rates of sustained virologic response at post-treatment Week 12 (SVR12) and was well tolerated in treatment- naïve (TN) patients with chronic HCV GT1,2,4–6 infection and compensated cirrhosis (CC). Here we report complete data from EXPEDITION-8 for 8-week G/P in GT1–6 TN CC patients including GT3 CC patients.

Methods: EXPEDITION-8 was a Phase 3b, multicenter, single-arm trial evaluating G/P 300/120 mg once daily for 8 weeks in TN CC adults with chronic HCV GT1–6 infection. The primary and key secondary efficacy endpoints were the SVR12 rates in patients with GT1,2,4–6 and GT1–6, respectively, compared with historical SVR12 rates for 12 weeks of G/P in both the per-protocol (PP) and intention-to-treat (ITT) populations. Safety was also assessed.

Results: 343 patients with HCV GT1–6 participated in the trial, of whom 63% were male, 83% were white, 67% had GT1, and 18% had GT3. All primary and key secondary efficacy endpoint analyses were achieved. SVR12 rates in GT1,2,4–6 patients were 100% (274/274; 95% CI 98.6–100) in the PP population and 98.2% (275/280; 95% CI 96.7–99.8) in the ITT population. SVR12 rates in GT1–6 patients were 99.7% (334/335; 95% CI 98.3–99.9) in the PP population and 97.7% (335/343; 95% CI 96.1–99.3) in the ITT population. In GT3 patients, SVR12 rates were 98.4% in the PP population and 95.2% in the ITT population (Figure). Overall, there were no on-treatment virologic failures; 1 GT3 patient relapsed at post-treatment Week 4. 1 GT1 patient discontinued G/P (not due to adverse events [AEs]). 6 patients (4 GT1; 2 GT3) had missing SVR12 data. AEs were mostly Grade 1 in severity (63%). AEs reported in ≥5% were fatigue (9%), pruritus (8%), headache (8%), and nausea (6%). 2% of patients reported serious AEs, none G/P-related. No AEs led to G/P discontinuation. No G/P-related liver-related toxicities or drug-induced liver injury were observed. Conclusion: G/P for 8 weeks was highly efficacious with a favorable safety profile in TN CC patients with chronic HCV GT1-6 infection, including GT3 CC patients. The availability of an 8-week, pangenotypic regimen for all treatment-naïve HCV-infected patients regardless of cirrhosis status may simplify the HCV care pathway, furthering progress towards HCV elimination.
Figure: SVR12 rates by HCV genotype for 8-week G/P in the PP and ITT populations

Error bars represent 95% confidence intervals. *8 patients were excluded from the PP population: 1 patient (GT1) discontinued G/P prior to Week 8; 1 patient (GT1) received G/P for <52 days but achieved SVR12; 6 patients (2 GT1, 2 GT3) had missing SVR12 data (all had undetectable HCV RNA at their last visit). G/P, glecaprevir/pibrentsvir; GT, genotype; HCV, hepatitis C virus; ITT, intention-to-treat; PP, per-protocol; RNA, ribonucleic acid; SVR12, sustained virologic response at post-treatment Week 12.

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Gretja Schnell – AbbVie: Employment; AbbVie: Stock Shareholder;
Chih-Wei Lin – Former employee of AbbVie: Employment; AbbVie: Stock Shareholder;
Jiuhong Zha – AbbVie: Employment; AbbVie: Stock Shareholder;
Stanley Wang – AbbVie: Employment; AbbVie: Stock Shareholder;
Roger Trinh – AbbVie: Employment; AbbVie: Stock Shareholder;
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Background: Pediatric drug trials are challenged to determine safe and effective dosing schedules for toddlers, children, and adolescents. In adults, plasma elbasvir (EBR)/grazoprevir (GZR) concentrations correlate with HCV clearance and sustained virologic response. The fixed-dose combination (FDC) of EBR/GZR (50 mg/100 mg) is approved for adults with HCV GT1 or 4 infection. This study utilized pharmacokinetic (PK) modeling to identify pediatric doses of EBR/GZR that achieve plasma concentrations similar to those of adults receiving the FDC. Methods: Iterative PK modeling was used to bridge efficacy and safety data from adults to children (NCT03379506). Adult models were updated iteratively using pediatric data (accounting for age, body weight, and formulation) to progressively select doses for younger cohorts. Data were assessed by age group in small (n=6-9) followed by expanded cohorts. Cohort 1 (12 to <18 y) received the FDC tablet and Cohorts 2 (7 to <12 y) and 3 (3 to <7 y) received granules. All participants were treated for 12 weeks and then followed for 24 weeks. The primary outcome was treatment week 4 PK; secondary outcomes were safety and efficacy. Results: At the date of abstract submission, 50 of 56 planned participants had received ≥1 dose of EBR/GZR. Overall, 48% were male, 84% were treatment-naive, median age was 10 y (range 3.1-17.9 y), and weight for age percentile was 67. HCV GT1a, 1b, or 4 infection was present in 56%, 40%, and 4% of participants, respectively. The adult PK model predicted EBR/GZR doses of 50 mg/100 mg for children aged 12 to <18 y; thus, Cohort 1 received the FDC. After updating with Cohort 1 data, the PK model supported EBR/GZR doses of 30 mg/60 mg for participants aged 7-12 y. After updating with Cohort 2 data, the PK model supported EBR/GZR doses of 25 mg/50 mg for those aged 3 to <7 y. For each age group, EBR/GZR PK was comparable to that of adults. Final pediatric dose recommendations will be based on the complete study data. Sustained virologic response at 12 weeks after end of therapy is 100% (37/37) in those who have completed dosing and follow-up. There was 1 serious adverse event (fractured finger). No participant discontinued treatment, and no on-treatment alanine aminotransferase elevations occurred. Conclusion: In pediatric programs where therapeutic response is anticipated to be similar to that of adults, iterative PK modeling can be used to efficiently bridge safety and efficacy data to support dose selection and streamline study design.

Disclosures:

Regino P Gonzalez-Peralta – AbbVie: Grant/Research Support; Gilead: Grant/Research Support; Merck: Grant/Research Support; Roche: Advisory Committee or Review Panel; Alexion: Advisory Committee or Review Panel; Kadmon: Advisory Committee or Review Panel; Gilead: Advisory Committee or Review Panel; Robert H. Squires – Up-to-Date: Independent Contractor; Mirum Pharmaceuticals: Advisory Committee or Review Panel; Thomas Lang – GNP: Advisory Committee or Review Panel; Abbvie: Speaking and Teaching; MSD: Grant/Research Support; William Balistreri – MERCK: Grant/Research Support; ALEXION: Advisory Committee or Review Panel; OTSUKA: Advisory Committee or Review Panel; ABBVIE: Grant/Research Support; GILEAD: Grant/Research Support; Maureen M. Jonas – AbbVie: Grant/Research Support; BMS: Grant/Research Support; Echosens: Grant/Research Support; Merck: Grant/Research Support; Roche: Grant/Research Support; Gilead: Grant/Research Support; Gilead: Consulting; Philip Rosenthal – Gilead: Grant/Research Support; Gilead: Advisory Committee or Review Panel; Abbvie: Grant/Research Support; Merck: Grant/Research Support; Roche: Grant/Research Support; Retrophin: Consulting; Retrophin: Grant/Research Support; Alibero: Consulting; Audentes: Consulting; Mirum: Grant/Research Support; Naim Alkhouri – AbbVie, Alexion, Allergan, Eisai, Exelixis, Gilead, Intercept Pharmaceuticals, and Salix: Speaking and Teaching; Allergan, Gilead, and Intercept Pharmaceuticals: Consulting; Alibero, Akero, Allergan, Boehringer Ingelheim, Bristol-Myers Squibb, Galmed, Genfit, Gilead, Intercept Pharmaceuticals, Madrigal Pharmaceuticals, MedImmune, Novartis, Novo Nordisk, Pfizer, Poxel, and Zydus: Grant/Research Support; Rene Romero – Gilead, Merck: Grant/Research Support; Jaime Benner – Merck and Co., Inc: Employment; Merck and Co., Inc: Stock Shareholder; Patricia Castronuovo – Merck and Co., Inc: Employment; Merck and Co., Inc.: Stock Shareholder; Chao Xu – Merck Sharp & Dohme Employment; Barbara A. Haber – Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA: Employment; Merck & Co., Inc., Kenilworth, NJ, USA: Stock Shareholder; The following people have nothing to disclose: Stefan Wirth, Malgorzata Pawłowska, Bjorn Fischer, Nivin Blondet, Anjana Grandhi Disclosure information not available at the time of publication: Ulrich Baumann, Wojciech Sluzewski, Ewa Majda-Stanislaw ska, Luzele na Caro
**LP11: DISCOVERY OF POLYURETHANE CHEMICALS AS NEW ETIOPATHOGENIC AGENTS IN BILIARY ATRESIA**

Nazanin Navabi, Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA and Pranavkumar Shivakumar, Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA.; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

**Background:** Etiology of biliary atresia (BA) remains unknown other than suspected roles for viral infection and toxin exposures. Newborns may be exposed to a range of medical devices, clothing, etc. containing residual amounts of 4,4'-methylenedianiline (MDA) or methylene diphenyl diisocyanate (MDI), two of the most important intermediates and high production volume chemicals of the polyurethane industry. Here, we conceptualized that MDA and MDI can induce symptoms of clinical BA in newborn mice upon oral or dermal exposures. **Methods:** Newborn BALB/c and C57BL/6 mice were exposed to MDA or MDI either orally (50 µg) by hemi-gavage via Hamilton syringe with a blunt end needle or applied to the ventral dermal surface dissolved in DMSO (0.3 mg), within 3-6 hours of birth. Experiments were repeated with chemical exposures at 48 or 72 hours of birth with Rhesus rotavirus (RRV)-induced standard BA model as a positive control. Mice were phenotyped every 6 hrs for surface jaundice, bilirubinuria and acholic stools. Livers and extrahepatic bile ducts (EHBDs) were harvested at 2, 5, and 12 days and outcomes of toxin exposure were measured by plasma bilirubin and ALT levels, H&E and Sirius Red (SR) stains, Cytokeratin (CK+) bile duct profiles, qRT-PCR gene expressions and flow cytometry analysis of hepatic immune cells. **Results:** Exposure of newborn mice to MDA or MDI resulted in prompt development of severe jaundice, bilirubinuria and acholic stools by 72 hours in 100% mice vs 0% corn oil (CO) only treated mice. However, delayed exposures at 48 or 72 hours resulted in varying degrees of transient and reversible cholestasis reflecting differential susceptibility of the developing ductal system. Chemical-exposed mice showed progressive cholestasis, failure to thrive (4.1±1.3 vs CO: 7.6±0.8 gm) and 100% mortality by day 12-14 similar to RRV-BA mice. In contrast to RRV, histology analysis of EHBDs showed rapid epithelial injury and inflammation between 36-72 hours and complete disappearance of the common bile duct (CBD) with atrophic gall-bladder and cystic duct by day 6 associated with increased plasma bilirubin levels (13.9±0.9 vs CO: 1.1±0.3 mg/dL). SR+ and CK+ areas showed moderate fibrosis and reactive duct proliferations by day 12 (13073±4593 vs CO: 3435±818 µm²). Liver gene expressions showed elevated Col1a1, Col1a2, Timp1, Acta2, Vim, Ctgf, Hmox1, Gsta2, Gpx2, Sna1, Bambi, Smurf1, Grem1, Crim1 and Egr1 (1.7 to 193-fold; \( P<0.02\)–0.0001) and decreased levels of Sod1, Cat and Ddit4 (–0.24 to –0.45-fold; \( P<0.01\)–0.0001). Flow cytometry analysis revealed dominant signatures of plasmacytoid and myeloid DCs, macrophages and neutrophils, NK cells and CD8+ T cells (1.2–2.7 fold; \( P<0.001\)). **Conclusion:** Polyurethane chemicals triggered strain-independent atresia of the EHBD and liver fibrosis by altering glutathione pathways and augmenting innate immunity. Our studies warrant an urgent attention to these alarmingly new etiopathogenic chemicals in BA.
Disclosures:
Nazanin Navabi – Alexion Pharmaceuticals, Inc.: Grant/Research Support;
Pranavkumar Shivakumar – Alexion Pharmaceuticals, Inc.: Grant/Research Support;
LP12: CHARACTERIZATION OF HDV, HBsAg AND ALT KINETICS UNDER PEGINTERFERON-LAMBDA MONOTHERAPY: THE PHASE 2 LIMT STUDY

Ohad Etzion1,2, Sarah Duehren3, Saeed S. Hamid4, Yoav Lurie5, Edward J. Gane6, David Yardeni7, Anat Nevo-Shor2,8, Sm Channa9, Om Parkash10, Susan L. Uprichard11,12, Robert G. Gish13, Scott J Cotler11, Jeffrey Glenn14, David Apelian15, Harel Dahari16 and Minaz Mawani17

Background: We recently reported that peginterferon-lambda (IFN-λ) therapy had better antiviral activity and tolerability compared to historical data for IFN-α (J Hepatology 2019;70(1),e32). The goal of the current study was to characterize HDV RNA, HBV DNA, HBsAg and ALT kinetics during and post IFN-λ monotherapy. Methods: Thirty-three chronic HDV infected patients participated in a randomized, open-label, Phase 2 clinical study (LIMT) of IFN-λ 120 µg (n=19) or 180 µg (n=14), weekly SC injections for 48 weeks with 24 weeks of follow-up. All subjects were on tenofovir or entecavir. Kinetic data was obtained at Week 1 and every four weeks during and post IFN-λ therapy. HDV kinetic phase changes were defined as a 2-fold change in slope. HDV RNA was measured by Robogene®2.0 (limit of quantification of 14 IU/mL). Results: Mean pretreatment HDV RNA, ALT and HBsAg were 3.82 log cp/mL [IQR 1.54], 106 U/L [IQR 56], and 3.95 log cp/mL [IQR 0.69], respectively. Twelve (36%) patients had cirrhosis. Six patients were excluded from HDV kinetic analysis. The remaining 27 patients were categorized into 5 HDV kinetic patterns: monophasic (n=5), biphasic (n=6), flat Partial response (n=5), triphasic (n=9) and staircase (n=2). A transient ALT increase during therapy was seen in 25 (76%) patients, with an average of 3.0 [IQR 2.1] fold from baseline. The average ALT level at the end of treatment (EOT), 119 IU/mL, was similar to pretreatment levels. HBsAg remained at pre-treatment level in 25 (76%) or showed an extremely slow decline (0.03 log/wk [IQR 0.01]) (n=8). A 2 log decline from pre-treatment level, or DNQ at EOT was seen in 15 (45%) patients: 5/5 monophasic, 2/5 flat partial, 2/6 biphasic, 4/9 triphasic, and 2/2 staircase. Twenty-one (64%) patients had pretreatment DNQ HBV DNA and remained DNQ throughout therapy; the remaining 12 had average baseline levels of 2.94 log IU/mL [1.8, 4.8]and exhibited spontaneous fluctuations throughout treatment (n=6) or steady decline to DNQ or not detected (n=6). No differences across all baseline levels, magnitude of decline, phase decline slopes, or phase lengths were found among liver disease stage (cirrhosis vs no cirrhosis), HDV kinetic patterns and/or IFN-λ dosing groups. At end of follow up (EFU), 7/33 patients had HDV DNQ, and the remaining had a mean value of 2.8 log cp/mL [IQR 2.0]. Ten (30%) patients achieved ALT normalization at EFU. HBsAg remained at pre-treatment levels (3.6log cp/mL [IQR 1.0]) at EFU. Conclusion: This study provides, for the first time, a kinetic description of HDV response under IFN-λ therapy. Compared to IFN-α, IFN-λ therapy (i) led to new kinetic patterns, (ii) had lack of association between HBsAg and HDV decline, and (iii) induced a transient increase in ALT on-treatment in the majority of patients followed by post treatment ALT normalization in approximately 1/3 of patients. These findings suggest that IFN-λ and IFN-α may induce HDV viral suppression through different mechanisms of action.

Disclosures:

Disclosure information not available at the time of publication: Yoav Lurie, Sm Channa, Om Parkash, David Apelian, Minaz Mawani
LP13: RAPID INCREASE IN ANTI-HBsAg TITERS AND HIGHER SEROPROTECTION RATES IN ADULTS IMMUNIZED WITH SCI-B-VAC COMPARED TO A MONOVALENT HEPATITIS B VACCINE: RESULTS FROM PROTECT — A DOUBLE-BLIND, RANDOMIZED, CONTROLLED, PHASE-3 STUDY


Background: Sci-B-Vac™, a mammalian cell-derived trivalent vaccine against HBV infection that contains S/pre-S1/pre-S2 antigens containing T and B cell epitopes, may enhance immunogenicity in adults, compared with recombinant monovalent HepB vaccines, such as Engerix-B®. Methods: In a multicentre, multinational, comparator-controlled, and double-blind study, 1607 subjects (≥18 years), including those with stable chronic conditions, received either Sci-B-Vac™ 10 µg or Engerix-B® 20 µg, on days 0, 28, and 168. Randomization was stratified by study center and age. Seroprotection rates (SPR), defined as the percentage of subjects achieving a serum anti-HBs antibody level ≥10 mIU/mL, and geometric mean concentrations (GMC; mIU/ml) of all subjects and ages, were compared 4 weeks after each vaccination, prior to the 3rd vaccination and 48 weeks after the 1st vaccination. The co-primary outcomes were: 1) non-inferiority in subjects ≥ 18 years old and 2) superiority of SPR in subjects ≥ 45 years old achieved with Sci-B-Vac™ compared to Engerix-B®, 4 weeks after the 3rd vaccination, using a 5% margin of non-inferiority and superiority. Subjects were followed for safety to day 336. Results: Of 1607 subjects, males (38.5%) and females (61.5%) comprised the age groups of 18-44 (18.6%), 45-64 (44.6%) and ≥ 65 (36.8%) years; 42.3% from the US, 41.6% EU and 16.1% Canada. The trial met its outcomes of non-inferiority in adults ≥ 18 years old [91.4% vs. 87.6%] and superiority in subjects ≥ 45 years old [85.8% vs. 78.0%]. Sci-B-Vac™ induced higher SPRs compared to Engerix-B® after the first and second vaccinations at day 28 [16.0% vs. 7.7%], day 56 [51.5% vs. 23.9%], and day 168 [66.0% vs. 27.4%], just prior to the 3rd vaccination. Four weeks after the 3rd vaccination, anti-HBs GMC were 5-8-fold higher in subjects who received Sci-B-Vac™ than those who received Engerix-B®, regardless of age, gender, BMI, or diabetes status (Figure). There were no major safety signals and adverse events were consistent with the known vaccine safety profiles. Conclusion: Sci-B-Vac™ induced 5-8-fold higher antibody GMC in subjects compared to Engerix-B®. The SPR of Sci-B-Vac™ was higher than Engerix-B®, at all time points in the first 6 months after the first vaccination, suggesting that Sci-B-Vac™ may provide a more rapid onset of seroprotection compared to monovalent HepB vaccines. No safety signals were observed and safety and tolerability were consistent with the known profile of Sci-B-Vac™.
Disclosures:
Joanne Langley – GSK: Advisory Committee or Review Panel; Merck: Advisory Committee or Review Panel; Sanofi: Advisory Committee or Review Panel; Pfizer: Advisory Committee or Review Panel; GSK: Grant/Research Support; Merck: Grant/Research Support; Sanofi: Grant/Research Support; Pfizer: Grant/Research Support; Janssen: Grant/Research Support; VBI Vaccines: Grant/Research Support; Mediaco: Grant/Research Support; Johanna Spaans – VBI Vaccines Inc: Employment; Bebi Yassin-Rajkumar – VBI Vaccines Inc: Employment; David E Anderson – VBI Vaccines: Management Position; Vladimir Popovic – VBI Vaccines: Employment; Francisco Diaz-Mitoma – VBI Vaccines: Consulting; VBI Vaccines: Stock Shareholder; The following people have nothing to disclose: Timo Vesikari, Brian J Ward, Curtis Cooper, Guillaume Poliquin, Bruce Smith, Pierre Van Damme, Isabel Leroux-Roels, Geert Leroux-Roels; Disclosure information not available at the time of publication: Nathan Segall, Nathalie Machluf

Figure: At 4 weeks after the 3rd vaccination, higher (5-8-fold) antibody GMC were observed in subjects who received Sci-B-Vac™ vs. Engerix-B® regardless of age, BMI, gender, or diabetes status.
LP14: THE SECOND-GENERATION HEPATITIS B VIRUS (HBV) CORE INHIBITOR (CI) ABI-H2158 IS ASSOCIATED WITH POTENT ANTVIRAL ACTIVITY IN A 14-DAY MONOTHERAPY STUDY IN HBeAg-POSITIVE PATIENTS WITH CHRONIC HEPATITIS B (CHB)

Man-Fung Yuen¹, Kosh Agarwal², Edward J. Gane³, Tuan T. Nguyen⁴, Tarek Hassanein⁵, Dong Joon Kim⁶, Katia Alves⁷, Hany Zayed⁷, Dongmei Qiang⁷, Eric Ruby⁷, Marc Evanchik⁷, Qi Huang⁷, Steven Knox⁷, Richard Colombo⁷ and on behalf of ABI-H2158 Study Team,

(1)The University of Hong Kong, (2)Institute of Liver Studies, King’s College Hospital, (3)Auckland Clinical Studies, New Zealand, (4)T Nguyen Research and Education, Inc., (5)Southern California GI and Liver Centers, (6)Hallym University Chuncheon Sacred Heart Hospital, (7)Assembly Biosciences

Background: The HBV core protein plays an integral role in multiple steps of the HBV life cycle. ABI-H2158 is a 2nd generation, potent and selective HBV CI, being developed for the treatment of patients (pts) with CHB. In vitro, ABI-H2158 exhibits enhanced inhibitory potency over 1st generation CIs against both viral replication (EC₉₀ = 69 ng/mL) and surrogate markers (pgRNA, HBeAg and HBsAg) of cccDNA biosynthesis (EC₉₀ = 242-288 ng/mL) in Primary Human Hepatocytes (PHH) infection assays. Here we report the safety and antiviral activity from the initial cohort of pts treated with ABI-H2158 100 mg or placebo. Methods: Sequential cohorts of 9 pts are planned to be enrolled in the ABI-H2158-101 study. Each cohort will be randomized to receive ABI-H2158 or placebo (7:2) QD for 14 days in a blinded manner. Eligible pts include males and females aged ≥18 and ≤65 years, HBV treatment-naive, HBeAg+, with HBV DNA >2x10⁵ IU/mL and F0-F2 fibrosis. Safety will be assessed by adverse events (AEs) and laboratory parameters. Pharmacokinetics are performed on Day 1 and 14. HBV DNA, RNA, HBeAg, HBsAg and HBcrAg are measured on Day 1, 8 and 15. Results: Dosing in the 1st cohort (100 mg) has been completed. Overall, the mean age of pts was 36 years [range 19–49], with the majority being male (n=7), Asian (n=6) and HBV genotype C (n=7). In pts receiving ABI-H2158, mean declines from Baseline to Day 15 in HBV DNA and RNA levels were 2.3 log₁₀ IU/mL [range 1.7 – 3.0] and 2.1 log₁₀ IU/mL [range 1.5 – 2.7] respectively. No serious AEs, dose limiting toxicities or premature discontinuations were reported. Three pts reported a total of 5 mild, drug-related AEs that recovered without intervention; dizziness, fatigue, rash, headache and upper abdominal pain. Treatment emergent laboratory abnormalities were infrequent, mild and transient, with no ALT elevations Grade >1 severity. Day 14 plasma ABI-H2158 Cmax and AUC₀-24hr were 3,390 ng/mL and 46,100 hr*ng/mL, respectively. A second cohort receiving 300 mg QD is ongoing. Conclusion: Results from the initial 100 mg low dose of ABI-H2158 cohort demonstrated potent antiviral activity, a favourable safety profile when administered for 14 days, and support once daily dosing in CHB patients. Data from additional cohorts may be presented if available at the time of the conference.

Disclosures:

Hepatitis B (CHB)

POTENT ANTIVIRAL ACTIVITY IN A 14-DAY MONOTHERAPY STUDY IN HBeAg-POSITIVE PATIENTS WITH CHRONIC HEPATITIS B (CHB)

Background: The HBV core protein plays an integral role in multiple steps of the HBV life cycle. ABI-H2158 is a 2nd generation, potent and selective HBV CI, being developed for the treatment of patients (pts) with CHB. In vitro, ABI-H2158 exhibits enhanced inhibitory potency over 1st generation CIs against both viral replication (EC₉₀ = 69 ng/mL) and surrogate markers (pgRNA, HBeAg and HBsAg) of cccDNA biosynthesis (EC₉₀ = 242-288 ng/mL) in Primary Human Hepatocytes (PHH) infection assays. Here we report the safety and antiviral activity from the initial cohort of pts treated with ABI-H2158 100 mg or placebo. Methods: Sequential cohorts of 9 pts are planned to be enrolled in the ABI-H2158-101 study. Each cohort will be randomized to receive ABI-H2158 or placebo (7:2) QD for 14 days in a blinded manner. Eligible pts include males and females aged ≥18 and ≤65 years, HBV treatment-naive, HBeAg+, with HBV DNA >2x10⁵ IU/mL and F0-F2 fibrosis. Safety will be assessed by adverse events (AEs) and laboratory parameters. Pharmacokinetics are performed on Day 1 and 14. HBV DNA, RNA, HBeAg, HBsAg and HBcrAg are measured on Day 1, 8 and 15. Results: Dosing in the 1st cohort (100 mg) has been completed. Overall, the mean age of pts was 36 years [range 19–49], with the majority being male (n=7), Asian (n=6) and HBV genotype C (n=7). In pts receiving ABI-H2158, mean declines from Baseline to Day 15 in HBV DNA and RNA levels were 2.3 log₁₀ IU/mL [range 1.7 – 3.0] and 2.1 log₁₀ IU/mL [range 1.5 – 2.7] respectively. No serious AEs, dose limiting toxicities or premature discontinuations were reported. Three pts reported a total of 5 mild, drug-related AEs that recovered without intervention; dizziness, fatigue, rash, headache and upper abdominal pain. Treatment emergent laboratory abnormalities were infrequent, mild and transient, with no ALT elevations Grade >1 severity. Day 14 plasma ABI-H2158 Cmax and AUC₀-24hr were 3,390 ng/mL and 46,100 hr*ng/mL, respectively. A second cohort receiving 300 mg QD is ongoing. Conclusion: Results from the initial 100 mg low dose of ABI-H2158 cohort demonstrated potent antiviral activity, a favourable safety profile when administered for 14 days, and support once daily dosing in CHB patients. Data from additional cohorts may be presented if available at the time of the conference.

Disclosures:
Background: The co-occurrence of type 2 diabetes (T2D) and NAFLD is associated with increased risk of developing diabetes-related micro- and macrovascular complications and progression to more advanced NASH with fibrosis. Several studies reported significant associations between insulin therapy for T2D and the presence of NASH and advanced fibrosis. Insulin use is also independently associated with increased risk of hepatocellular carcinoma (HCC). In our study of patients with T2D, participants receiving a continuous care intervention (CCI) including nutritional ketosis improved liver enzymes and NAFLD surrogate scores, and 62% of insulin users discontinued insulin therapy at 2 years. No significant changes were observed in patients receiving usual care (UC). The present analysis aims to assess the impact of insulin discontinuation on 2-year liver- and NAFLD-related markers.

Methods: Among participants prescribed insulin at enrollment in the CCI and UC, participants were categorized as those who completely discontinued insulin at 2 years and those who remained on insulin, irrespective of dose adjustment at 2 years. We assessed differences in alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) enzymes, NAFLD liver fat (NLF) and liver fibrosis (NFS) scores, and inflammation marker C-reactive protein (CRP) over time (Table 1) using a linear mixed-effects model (intent-to-treat analysis) in each of the insulin status groups within CCI and UC arms.

Results: There were no significant baseline differences in liver enzymes and NAFLD-related markers between CCI participants who discontinued insulin and those remaining in insulin therapy at 2 years. However, significant reductions in liver enzymes (ALT and ALP), NLF, NFS, and CRP were observed among CCI participants who discontinued insulin at 2 years, while no significant changes were observed in CCI and UC participants continuing insulin therapy at 2 years. Improvements in liver enzymes and markers among CCI participants discontinuing insulin remained significant even after adjusting for weight loss percentage at 2 years.

Conclusion: In this post-hoc analysis, we observed that CCI participants who discontinued insulin therapy at 2 years significantly improved liver enzymes, steatosis and fibrosis status. These improvements were not observed in those who continued insulin therapy at 2 years. Physiological improvements in CCI participants enabled discontinuation of insulin therapy and reduced progression of liver injury and fibrosis.

Table 1. Adjusted mean changes over time by insulin therapy continuation status at 2 years

<table>
<thead>
<tr>
<th>Variables</th>
<th>Discontinued Insulin Therapy (CCI = 22 and UC = 32)</th>
<th>Continued Insulin Therapy (CCI = 22 and UC = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 2 Years</td>
<td>Change</td>
</tr>
<tr>
<td></td>
<td>Mean(SE)</td>
<td>Mean(SE)</td>
</tr>
<tr>
<td>Alanine Transaminase*</td>
<td>E2I</td>
<td>22.305 (16)</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td>16.350 (16)</td>
</tr>
<tr>
<td>Aspartate Transaminase*</td>
<td>E2I</td>
<td>16.350 (16)</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td>12.305 (16)</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>E2I</td>
<td>76.305 (16)</td>
</tr>
<tr>
<td></td>
<td>UC</td>
<td>68.305 (16)</td>
</tr>
</tbody>
</table>

Estimates reported were obtained from linear mixed-effects models which provide adjusted means and mean changes, controlling for baseline age, sex, race, body mass index, and diabetes duration. This maximum likelihood-based approach uses all available repeated data, resulting in an intent-to-treat analysis. A significance level of P<0.008

The n for those who discontinued insulin in UC is very small; no statistical analysis was performed for this cohort since the interpretation is limited.

Variable is positively skewed and after removing the top 1% of values, skew and kurtosis values fell within acceptable ranges. Analyses were conducted on data excluding the top 1% of values for each variable, although due to the maximum likelihood approach all cases were still included in the analyses.
LP16: BILIARY AND PLASMA BILE ACID PROFILING DURING OBETICHOLIC ACID TREATMENT IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND NON-ALCOHOLIC STEATOHEPATITIS AND IN HEALTHY VOLUNTEERS

Elsemieke De Vries1, Jeffrey Edwards2, Carl LaCerte3, Mary Erickson2, David A. Shapiro2 and Ulrich Beuers3, (1)Department of Gastroenterology & Hepatology, Amsterdam University Medical Center, Location AMC, (2)Intercept Pharmaceuticals, Inc., (3)Department of Gastroenterology & Hepatology, Tytgat Institute for Liver and Intestinal Research, Amsterdam University Medical Center, Location AMC

Background: The nuclear farnesoid X receptor (FXR) agonist obeticholic acid (OCA) has shown promising anticholestatic and antifibrotic effects in primary biliary cholangitis (PBC) and non-alcoholic steatohepatitis (NASH), respectively, and is approved as 2nd line treatment in PBC. We performed the first extensive pharmacokinetic profiling of both plasma and biliary bile acids in patients with PBC and NASH as well as in healthy volunteers (HV) before and after OCA therapy to further elucidate OCA effects on human bile acid metabolism in health and chronic non-viral liver disease. Methods: In 11 PBC patients, 7 NASH patients and 11 HV, duodenal bile retrieved during gastroduodenoscopy and plasma were collected before and after 30 days of OCA treatment (10mg once daily). On day 29, 24-hr pharmacokinetic bile acid profiling was performed. Results: Median (IQR) total endogenous fasted primary and secondary bile acids in plasma decreased from Day 1 to Day 30 in PBC (from 1.94 µM (2.28) to 0.89 (0.50), p<0.01) and HV (from 0.48 µM (1.05) to 0.17 (0.25), p=0.04) and tended to decrease in NASH (from 1.88 µM (1.35) to 0.75 (0.52), p=0.06). OCA treatment reduced the plasma biomarker of bile acid synthesis, 7-alpha-hydroxy-4-cholesten-3-one (C4) in patients with PBC (-79.0%, p<0.01) and NASH (-57.9%, p=0.03) and in HV (-80.2%, p<0.01) confirming adequate activation of FXR. In bile, the median (IQR) percentage of total taurine-conjugated bile acids increased in NASH patients by 16.8% (19.6%, p=0.02) and in healthy volunteers by 19.5% (15.4%, p=0.01) after OCA treatment. Biliary UDCA enrichment in PBC patients continuously treated with UDCA was markedly increased after 30 days of OCA treatment, from 55.5% (18.2%) to 68.2% (11.1%) of total biliary bile acids (p=0.03). A strong correlation of conjugated and unconjugated bile acid levels in bile versus plasma was observed in patients with PBC and NASH and HV for cholic acid (CA, r=0.83, p<0.0001), chenodeoxycholic acid (CDCA, r=0.90, p<0.0001), deoxycholic acid (DCA, r=0.96, p<0.0001) and ursodeoxycholic acid (r =0.96, p<0.0001), but remarkably not for lithocholic acid (r=0.12, p=0.55). Conclusion: Our novel and therapeutically relevant findings indicate that OCA induces remarkable UDCA enrichment in bile of UDCA-treated PBC patients and a shift from glycine to less toxic taurine conjugates in NASH patients and HV. Plasma endogenous bile acids decreased during OCA treatment in PBC and HV and tended to decrease in NASH.

Disclosures:
Jeffrey Edwards – Intercept Pharmaceuticals: Employment; Intercept Pharmaceuticals: Stock Shareholder;
Carl LaCerte – Intercept Pharmaceuticals: Employment; Intercept Pharmaceuticals: Stock Shareholder;
Mary Erickson – Intercept Pharmaceuticals: Employment; Intercept Pharmaceuticals: Stock Shareholder;
David A. Shapiro – Intercept Pharmaceuticals: Consulting; Intercept Pharmaceuticals: Stock Shareholder;
Ulrich Beuers – Falk Foundation: Speaking and Teaching; Intercept: Grant/Research Support; Dr.Falk GmbH: Grant/Research Support; Intercept: Speaking and Teaching;
The following people have nothing to disclose: Elsemieke De Vries
LP17: THE FIRST RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EFFICACY TRIAL OF VACCINES TO PREVENT CHRONIC HEPATITIS C VIRUS INFECTION IN AN AT-RISK POPULATION

Kimberly Page1,2, Michael Melia3, Rebecca Terilli Veenhuis4, Guido Massaccesi5, Katherine Wagner6, William Osburn7, Linda Giudice7, Ellen Stein8, Alice K Asher9, Ventzislav Vassilev10, Lan Lin11, Alfredo Nicosia12, Stefania Capone13, Antonella Folgori13, Michael Wierzbicki14, Soju Chang15, T Jake Liang16, Marc G. Ghany17,18, Richard Gorman15, Peter A. Wolff15, Paula J. Lum8 and Andrea Cox19,
(1)Epidemiology, Biostatistics & Preventive Medicine, University of New Mexico, (2)Internal Medicine, University of New Mexico Health Sciences, (3)Medicine, Johns Hopkins, (4)Molecular and Comparative Pathobiology, Johns Hopkins, (5)Internal Medicine, University of New Mexico, (6)Medicine, Johns Hopkins University, (7)Obstetrics and Gynecology, University of California San Francisco, (8)Medicine, University of California San Francisco, (9)Viral Hepatology, U.S. Centers for Disease Control, (10)Vaccines Discovery & Development, GlaxoSmithKline Biologicals S.A., (11)GSK, (12)Reithera, (13)Emmes Corp., (15)NIAID, National Institutes of Health, (16)Liver Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases, (17)Niddk, National Institutes of Health, (18)National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, (19)Johns Hopkins Hospital

Background: A safe and effective vaccine to prevent chronic hepatitis C virus (HCV) infection is essential to reduce transmission, providing rationale for the first HCV vaccine efficacy trial. Methods: We evaluated safety and efficacy of a recombinant chimpanzee adenovirus-3 vectored vaccine prime followed by a recombinant modified vaccinia Ankara virus boost, both encoding HCV nonstructural proteins in a randomized, multicenter, double-blind, placebo-controlled efficacy trial. HCV uninfected adults 18-45 years old and at-risk for HCV infection due to active injection drug use were randomized to receive the prime-boost regimen or placebo at Days 0 and 56. Participants were monitored for vaccine reactogenicity, adverse events (AEs), and HCV viremia. The primary outcome assessed was progression to chronic HCV infection at 6 months. Secondary outcomes included HCV RNA change from incident infection and peak HCV RNA.

Results: A total of 455 participants received the prime-boost regimen or two doses of placebo (232 and 222, respectively) and 202 and 199 were eligible in these groups for according to protocol analyses. Overall incidence of infection was 13.0 infections/100 person-years. There were no differences in 6-month chronic infection rate between vaccine and placebo arms, with 14 chronically infected participants in each group. Vaccine efficacy in preventing chronic infection was -0.53 (95% confidence interval [CI], -2.5 to 0.34). Significant differences were seen in HCV RNA geometric mean peak (GMP) and geometric mean fold rise (GMFR) from incident infection between vaccine and placebo groups: GMP HCV RNA was 193,795 IU/L and 1,078,092 IU/L (Figure 1) and GMFR was 0.2 and 13.5, respectively at 1 month. Of vaccinated subjects, 78% generated T cell responses to one or more vaccine antigen pools. The vaccine was generally safe and well tolerated with no serious vaccine-related AEs. There were more solicited reports of AEs after either injection in the vaccine group (81%) than in the placebo group (59%), with the difference mainly due to injection-site reactions. Serious unrelated AEs and deaths occurred with similar frequencies in the two groups. Conclusion: This Phase I/II trial demonstrated that a prime-boost HCV vaccine regimen did not provide protection against chronic infection, but elicited immune responses without evident safety concerns and differences in viral trajectory after infection, including significantly decreased GMP HCV RNA vs. placebo recipients.
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LP18: UPDATES FROM THE 2018 OPTN/SRTR ANNUAL DATA REPORT
Allison J. Kwong1, W. Ray Kim1, John R Lake2, Jodi Smith3, Melissa Skeans4, Jon Snyder4,5 and Ajay Israni4,6, (1)Division of Gastroenterology and Hepatology, Stanford University, (2)Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, University of Minnesota, (3)Pediatrics, Seattle Children's Hospital, (4)Scientific Registry of Transplant Recipients, (5)Department of Epidemiology and Community Health, University of Minnesota, (6)Department of Medicine, Hennepin Healthcare, University of Minnesota

Background: OPTN/SRTR collects data on all waitlist, donation, and transplant events in the United States. We report findings and emerging trends from the 2018 annual data report for liver transplant (LT). Methods: OPTN/SRTR data regarding adult and pediatric LT for 2018 were aggregated and interpreted in the context of previous years' data, policy changes, and medical advances. Results: The number of adult LTs performed continued to rise in 2018, reaching an all-time high of 8250; deceased donor LT (DDLT) accounted for 95.1%. Rates of 1-, 3-, and 5-year graft survival continued to improve, to 91.2%, 84.1%, and 76.7%, respectively. Waitlist outcomes also improved, with an overall pretransplant mortality rate of 13.2 per 100 waitlist-years in 2018, despite significant geographic variation by donor service area (range 6.5-37.4). The DDLT rate among active adult waitlist candidates was 54.5 per 100 waitlist-years, a steady increase since 2012, with a persistent but narrowing gap between hepatocellular carcinoma (HCC) and non-HCC candidates. Older (≥65 years) recipients comprised 23.3% of the adult LT population in 2018. Alcoholic liver disease and other/unknown (often NASH) were the most common diagnoses leading to LT, followed by HCC (Figure); 34.5% of adult LT recipients were obese (BMI ≥30 kg/m²), and 29.2% had diabetes. Discard rates for older (age ≥65) and hepatitis C virus (HCV) antibody (Ab) positive livers declined significantly (Figure). HCV Ab+ donor livers accounted for 8.3% of DDLT in 2018. Despite fewer waitlist registrants with HCV, the proportion of adults willing to accept HCV Ab+ donors doubled from 19.8% in 2016 to 34.6% in 2018. Additionally, anoxia overtook stroke and head trauma as the leading cause of death among deceased liver donors. Waitlist and LT volumes for pediatric LT were unchanged overall; 563 pediatric LTs were performed in 2018. However, the proportion of exception cases has doubled in the past 10 years, accounting for 74.2% of pediatric LTs. Conclusion: Changing waitlist demographics are reflected in the adult LT population, with increasing prevalence of NASH, alcoholic liver disease, aging, obesity, and diabetes. Adult LTs increased in 2018, attributable to (1) wider acceptance and use of older and HCV Ab+ organs and (2) more eligible donors due to anoxia. Pediatric LT priority was dominated by exception cases in 2018.

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LP19: USE OF TRANSIENT ELASTOGRAPHY TO ASSESS ALLOGRAFT QUALITY IN DECEASED LIVER DONORS

Andres Duarte-Rojo1, Julie Heimbach2, Gary W. Barone3, Mohammed Shaheen2, Laura W Lamps4, Graham P Rondell2, Ek Khoon Tan2, Waldo Concepcion2, Daniel Borja-Cacho3 and W. Ray Kim5, (1)University of Pittsburgh, (2)Mayo Clinic Rochester, (3)University of Arkansas for Medical Sciences, (4)University of Michigan, (5)Stanford University

Background: Steatosis assessment in current liver allocation system continues to rely on macroscopic characteristics or frozen biopsies, without adopting the use of non-invasive assessment of liver disease. We aimed to investigate the usefulness of controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) from transient elastography (Fibroscan, Echosens, France) to assess steatosis and fibrosis in deceased liver donors, and with posttransplant changes in the recipient. Methods: Three centers (UAMS, Mayo, Stanford) performed CAP/LSM in donors before procurement. A paraffin-embedded biopsy (permanent section) was obtained during procurement, irrespective of standard-of-care frozen section indicated by surgeon as part of allocation process. Primary non-function (PNF) and early allograft dysfunction (EAD) were documented. Results: 160 donors (39±16 years, 59% males, 79% white, BMI 27±6) were included. Frozen section was available from 74 (52%) donors, and we included results from first 58 (36%) analyzed permanent sections. Steatosis by frozen section did not correlate with permanent section (rho=0.17, p=0.32). As seen in the Figure, CAP values were significantly higher with increasing grades of steatosis when using permanent sections as reference but not against frozen. CAP was affected by BMI (p<0.001) and LSM by peak ALT or AST (p<0.001), however, death cause, infection, or use of vasopressors/vasodilators did not affect CAP/LSM performance. A total of 138 recipients were transplanted (54±12 years, 63% males, 90% white). CAP/LSM were assessed in 95 (69%) of them after 112±54 days posttransplant, when BMI was 26±5 (p=0.08 against donors). CAP at procurement and posttransplant was 236 (187-274) and 218 (173-261) dB/m (p=0.06), respectively. Corresponding values for LSM were 7.2 (5.7-10.1) and 6 (4.7-8.8) kPa (p=0.04). When analysis was restricted to donor-recipient pairs evaluated with the same probe (69% of cohort) the trend in CAP difference disappeared (231 [181-278] vs 225 [182-259]; p=0.43) whereas it widened for LSM (7.6 [6.1-10.8] vs. 6 [4.6-8.75]; p=0.01). There were only 4 cases with either PNF or EAD precluding further analysis. However, LSM was elevated in 3 of them (8.3 to 10.6) and CAP in the remaining one (299). ROC curve analysis showed an AUC of 0.77 (0.63-0.91) for the identification of liver steatosis with CAP, with sensitivity of 58% and specificity of 87% (CAP cutoff: 280). Conclusion: These data represent proof of concept on the utility of CAP/LSM for liver allograft assessment and donor-recipient risk estimation, outperforming frozen sections. Posttransplant LSM change suggests higher cutoff values are needed in donors, particularly when ALT/AST are elevated. Larger studies looking into CAP/LSM ability to identify organs with advanced steatosis or fibrosis which are at an increased risk of poor transplant outcomes (PNF/EAD/mortality) are needed.

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