BACKGROUND: Cenicriviroc (CVC), an oral chemokine receptor CCR2/5 antagonist, has potent anti-inflammatory and anti-fibrotic activity in animal models of acute and chronic liver diseases. Its efficacy and safety as a treatment for non-alcoholic steatohepatitis (NASH) and liver fibrosis are being evaluated in adults at increased risk of progression to cirrhosis (CENTAUR; NCT02217475). Methods: Phase 2b, randomized, double-blind, placebo-controlled, ongoing 2-year multinational study; primary analysis at Year 1. Subjects with histologically advanced disease characteristics. Improvement in fibrosis by 2 stages was observed in 11 subjects (8 CVC; 3 placebo). Seven subjects progressed to cirrhosis (2 CVC; 5 placebo). IL-6, hs-CRP, and fibrinogen levels were significantly decreased with CVC vs. placebo. Drug-related, clinical TEAEs of Grade ≥2 severity occurring in ≥2% of subjects were fatigue (2.8%) and diarrhea (2.1%) for CVC; headache (3.5%) for placebo. There were no differences in laboratory abnormalities or premature discontinuations between CVC and placebo. Conclusions: In the ITT population, CVC was well tolerated and resulted in twice in many subjects achieving ≥1 stage improvement in fibrosis and no worsening of steatohepatitis vs. placebo, after only 1 year of treatment. Importantly, greater treatment benefits were observed in subjects with higher disease activity and stage.

RESULTS: 289 subjects were randomized: 53% female; 52% diabetes; 72% MetS; 74% NAS ≥3; 67% fibrosis stage 2–3. Mean BMI (SD) was 34 kg/m² (6.5). A similar proportion in each group achieved the NAS and resolution of steatohepatitis endpoints (Table). Improvement in fibrosis by ≥1 stage and no worsening of steatohepatitis was obtained in significantly more CVC-treated subjects than placebo overall (p=0.023) and in subgroups with histologically advanced disease characteristics. Improvement in fibrosis by 2 stages was observed in 11 subjects (8 CVC; 3 placebo). Seven subjects progressed to cirrhosis (2 CVC; 5 placebo). IL-6, hs-CRP, and fibrinogen levels were significantly decreased with CVC vs. placebo. Drug-related, clinical TEAEs of Grade ≥2 severity occurring in ≥2% of subjects were fatigue (2.8%) and diarrhea (2.1%) for CVC; headache (3.5%) for placebo. There were no differences in laboratory abnormalities or premature discontinuations between CVC and placebo. Conclusions: In the ITT population, CVC was well tolerated and resulted in twice in many subjects achieving ≥1 stage improvement in fibrosis and no worsening of steatohepatitis vs. placebo, after only 1 year of treatment. Importantly, greater treatment benefits were observed in subjects with higher disease activity and stage.

Centaur primary and key secondary efficacy endpoints (ITT; missing Year 1 biopsy is non response; logistic regression analysis)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CVC</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>p value (logistic regression)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint: 2-point improvement in NAS (≥1-point reduction in lobular inflammation or hepatocellular ballooning) and no worsening of fibrosis, n (%)</td>
<td>23 (16%)</td>
<td>27 (19%)</td>
<td>0.8 (0.44, 1.52)</td>
<td>0.519</td>
</tr>
<tr>
<td>Key secondary endpoint (1): Complete resolution of steatohepatitis and no worsening of fibrosis, n (%)</td>
<td>11 (8%)</td>
<td>8 (6%)</td>
<td>1.4 (0.54, 3.63)</td>
<td>0.494</td>
</tr>
<tr>
<td>Key secondary endpoint (2): Improvement in fibrosis by ≥1 stage (NASH CRN system) and no worsening of steatohepatitis, n (%)</td>
<td>29 (20%)</td>
<td>15 (10%)</td>
<td>2.2 (1.11, 4.35)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Subgroup analyses for fibrosis improvement

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Results</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH ≥2</td>
<td>21.09% (24%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Hepatocellular ballooning grade ≥2</td>
<td>18.64% (28%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Fibrosis stage 1</td>
<td>6.44% (14%)</td>
<td>0.375</td>
</tr>
<tr>
<td>Fibrosis stages 2 and 3</td>
<td>23.82% (28%)</td>
<td>0.049</td>
</tr>
</tbody>
</table>

Disclosures:
Vlad Ratziu - Advisory Committees or Review Panels: Galmed, Abbott, Genfit, Enterome, Gilead, Consulting: Tobira, Intermet, Exalenz, Boehringer-Ingehelm
Manal F. Abdelmalek - Advisory Committees or Review Panels: Tobira, NGM Pharmaceuticals; Consulting: BHV Pharma, Taiwan Pharma; Grant/Research Support: Tobira, Gilead Sciences, NIH/NIDDK; Genfit Pharmaceuticals, Immuran, Galmed, Taiwan Pharma, Intermet, NGM Pharmaceuticals, BMS Pharma, Conatus, Galactin, Speaking and Teaching: Alexion
Kris V. Kowdley - Advisory Committees or Review Panels: Abbvie, Gilead, Intermet, Merck, Novartis, Trio Health, Verlyx; Consulting: Enanta; Grant/Research Support: Tobira, Trio Health, Abbvie, Evidera, Galenic, Gilead, Immuran, Intermet, Merck, NGM biopharma, Novartis; Independent Contractor: Gilead, Intermet; Speaking and Teaching: Gilead, Intermet
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Star Seyedkazemi - Employment: Tobira Therapeutics, Inc.; Stock Shareholder: Tobira Therapeutics, Inc.
in the two cohorts, its performance was lower in GOLDEN (AUROC=0.60, 95%CI=0.53-0.67, p=0.004) than in OBESE (AUROC=0.77, 95%CI=0.70-0.84). Conversely, mir200a was more powerful in GOLDEN (AUROC=0.69, 95%CI=0.62-0.75) than in OBESE (AUROC=0.56, 95%CI=0.46-0.65). Finally, mir34a, mir122 and ALT had comparable diagnostic performances in OBESE (AUROC for ALT=0.80, 95%CI=0.73-0.86) while mir34a, mir122 and mir200a outperformed ALT in GOLDEN (AUROC for ALT=0.61, 95%CI=0.54-0.68).

Conclusion: This is the largest study addressing the potential of circulating miRNA’s as biomarkers of NASH. It validates circulating levels of mir34a and mir122 as predictors of histological lesions in two distinct cohorts. Serum miRNA levels hold promise to identify TBT patients as defined for inclusion in phase 3 trials in NASH.

Disclosures:
Vlad Ratziu - Advisory Committees or Review Panels: Galmed, Abbott, Genfit, Enterome, Gilead; Consulting: Tobira, Intercept, Exalenz, Boehringer-Ingelheim
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The following people have nothing to disclose: Sven M. Francque, Guruprasad P. Aithal, Juan Caballeria, Sven M. Francque, Cecfrey C. Farrell, Antonia Craxi, Laurent Fischer, Jeffrey Yest

LB-3
GS-4997, an Inhibitor of Apoptosis Signal-Regulating Kinase (ASK1), Alone or in Combination with Simtu-zumab for the Treatment of Nonalcoholic Steatohepatitis (NASH): A Randomized, Phase 2 Trial
Rohit Loomba1, Eric Lawitz2, Parvez S. Mantry3, Saumya Jayakumar4, Stephen H. Caldwell5, Hays Arnold6, Anna Mae Diehl7, Constantine S. Djedjos8, Catherine Jia9, Robert P. Myers10, Mani Subramanian11, John G. McHutchison12, Zachary D. Goodman13, Nezam H. Afdhal14, Michael R. Charlton15, 1University of California at San Diego, San Diego, CA; 2Texas Liver Institute, San Antonio, TX; 3The Liver Institute at Methodist Dallas, Dallas, TX; 4University of Calgary, Calgary, AB, Canada; 5University of Virginia, Charlottesville, VA; 6Gastroenterology Consultants of San Antonio, San Antonio, TX; 7Duke Clinical Research Institute, Durham, NC; 8Gilead Sciences, Inc., Foster City, CA; 9Inova Fairfax Hospital, Falls Church, VA; 10Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; 11Intermountain Medical Center, Salt Lake City, UT

Background: ASK1 is a serine threonine kinase that promotes hepatic inflammation and fibrosis in the setting of oxidative stress. Our aim was to describe the preliminary efficacy of GS-4997, a selective inhibitor of ASK1, alone or in combination with simtuzumab (SIM), in patients with NASH and moderate to severe liver fibrosis. Methods: In this multicenter, randomized, open-label trial, 72 subjects with biopsy-confirmed NASH (NAFLD Activity Score [NAS] ≥5) and F2-3 fibrosis received either GS-4997 at 6 mg or at 18 mg orally QD
alone or in combination with SIM (125 mg SQ weekly) or SIM alone for 24 weeks (W24). Liver biopsies were performed at baseline and W24. Hepatic proton density fat fraction (PDFF) and stiffness were measured by Magnetic Resonance Imaging (MRI) and Magnetic Resonance Elastography (MRE), respectively, at baseline, W12, and W24. W12 data are complete and 47/72 subjects have undergone W24 biopsies (complete histological data will be presented). Because no differences were observed between combination and monotherapy, data are presented by GS-4997 treatment group only. Results: At W24, subjects treated with GS-4997 were more likely to have a reduction in fibrosis stage and a ≥15% decline in hepatic stiffness by MRE, and were less likely to progress to cirrhosis than patients on SIM monotherapy (Table). At W24, changes in fibrosis correlated with changes in hepatic collagen content by morphometry (r=0.49, P=0.007, N=29) and steatosis grade (r=0.27, P=0.07, N=47). Changes in hepatic stiffness by MRE correlated with changes in ELF test (r=0.39, P=0.007, N=47) and hepato-cellular ballooning (r=0.32, P=0.047, N=38). Furthermore, subjects treated with GS-4997 18 mg QD were most likely to have a ≥30% decline in hepatic PDF by MRI (Table). Decreases in PDF correlated with changes in steatosis on biopsy, ELF test, and serum ALT, AST, GGT, alkaline phosphatase, glucose, CK18 (M30 and M65), and body weight (r=0.30-0.55, all P<0.05). Conclusion: In this multicenter study including paired liver histology and MR-based endpoints, preliminary data suggest that a 24-week course of GS-4997 has dose-dependent anti-fibrotic and anti-steatotic effects in patients with NASH and moderate to severe fibrosis.

Table: Histologic, MRI-PDF, and MRE Responses at W24

<table>
<thead>
<tr>
<th>GS-4997 18 mg</th>
<th>GS-4997 6 mg</th>
<th>SIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS-4997 18 mg</td>
<td>55% (11/20) (31.5%, 61.9%)</td>
<td>66% (9/13) (28.6%, 89.9%)</td>
</tr>
<tr>
<td>6% + SIM</td>
<td>32% (6/19) (12.6%, 56.6%)</td>
<td>40% (4/10) (10.7%, 80.0%)</td>
</tr>
<tr>
<td>20% + SIM</td>
<td>14% (2/15) (1.6%, 79.9%)</td>
<td>20% (2/10) (0.9%, 80.4%)</td>
</tr>
<tr>
<td>40% + SIM</td>
<td>7% (1/15) (1.6%, 24.1%)</td>
<td>20% (2/10) (0.9%, 80.4%)</td>
</tr>
<tr>
<td>20% + SIM</td>
<td>5% (1/20) (1.6%, 19.5%)</td>
<td>5% (1/20) (1.6%, 19.5%)</td>
</tr>
<tr>
<td>40% + SIM</td>
<td>20% (4/20) (5.7%, 43.7%)</td>
<td>20% (4/20) (5.7%, 43.7%)</td>
</tr>
</tbody>
</table>

All data are presented as % (n/N) (95% CI).

Disclosures:
Eric Lavitz - Advisory Committees or Review Panels: AbbVie, Achillion Pharmaceuticals, Regulus, Theravance, Enanta, Idenix Pharmaceuticals, Janssen, Merck & Co, Novartis, Gilead; Grant/Research Support: AbbVie, Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Idenix Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Merck & Co, Novartis, Nito Denko, Theravance, Salix, Enanta: Speaking and Teaching: Gilead, Janssen, AbbVie, Bristol-Myers Squibb, Merck, interpret
Saumya Jayakumar - Grant/Research Support: Merck, Gilead
Stephen H. Caldwell - Advisory Committees or Review Panels: Vital Therapy: Grant/Research Support: Genthi, Gilead Sciences, Immunom, Taiwan, Immunur, NQM
Hays Arnold - Grant/Research Support: NGM, Tabira
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Michael R. Charlton - Consulting: Gilead Sciences; Grant/Research Support: Gilead Sciences, Merck, Janssen, AbbVie, Novartis, Intercept

The following people have nothing to disclose: Anna Mae Diehl, Catherine Jia

LB-4
Granulocyte-Colony Stimulating Factor (G-CSF) plus N-Acetyl Cysteine (NAC) in Severe Alcoholic Hepatitis
Virendra Singh1, Amjit Keisham2, Akash Singh2, Ashish Bhalla2, Navneet Sharma3, Ratiram Sharma1,1; Transfusion Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India; 2Government Medical College and Hospital, Chandigarh, India; 3Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India; 4Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Background: Alcoholic hepatitis has very high short-term mortality. Recently, we had shown that granulocyte-colony stimulating factor (G-CSF) induced bone marrow-derived stem cells improve survival in alcoholic hepatitis. N-Acetyl Cysteine (NAC) could have a potential therapeutic role in the treatment of acute alcoholic hepatitis. The aim of the study was to assess efficacy of combined G-CSF and NAC therapy in improving outcomes in patients with severe alcoholic hepatitis.

Methods: Fifty-two patients with severe alcoholic hepatitis were randomized to either standard medical therapy plus G-CSF at the dosage of 5 µg/kg subcutaneously every 12 hours for 5 consecutive days (Group A; n=15) or standard medical therapy plus G-CSF and intravenous NAC (day 1: NAC at 150, 50, and 100 mg/kg in 250, 500, and 1000 ml of 5% glucose solution over 30 minutes, 4 hours, and 16 hours, respectively; days 2 through 5: 100 mg/kg/day in 1000 ml of 5% glucose solution) (Group B; n=17) or standard medical therapy alone (Group C; n=20). The primary outcome was 90-day survival. The secondary outcomes were mobilization of CD34+ cells at day 6; Child Turcotte Pugh (CTP), model for end stage liver disease (MELD), and modified discriminant function (mDF) scores until day 90.

Results: There was a significantly better survival in groups A and B as compared to group C (86.7% vs. 30.0%, P=0.002; and, 64.7% vs. 30.0%, P=0.035, respectively) at day 90; however, the survival was similar in group A and B. There was a statistically significant increase in the CD34+ cells improve survival in alcoholic hepatitis. N-Acetylating factor (G-CSF) induced bone marrow-derived stem cells and improves liver function. However, the use of NAC was not found to have any additional benefit compared to G-CSF.
Fungal Dysbiosis in the Gut Microbiota is Associated with Culture-negative Infections in Cirrhotic Patients

Jasmohan S. Bajaj1, Eric J. Liu2, Raffi Kheradman2, Andrew Fagan3, Douglas M. Heuman1, Melanie White1, Dinesh Ganapathy1, Phillip Hylemon1, Masoumeh Sikaroodi1, Patrick M. Gillevet4, 5

1Virginia Commonwealth University and McGuire Veterans Affairs Medical Center, Richmond, VA; 2Microbiome Analysis Center, George Mason University, Manassas, VA

Cirrhotics have high rate of developing infections, which due to rampant antibiotic (Abx) use are increasingly fungal or culture-negative in nature. Infected cirrhotics have gut bacterial dysbiosis, but the role of fungal dysbiosis is unclear. Aim: To define the presence of bacterial and fungal dysbiosis in culture-negative infected cirrhotics on Abx compared to uninfected cirrhotics and healthy controls using a cross-sectional & longitudinal design. Method: Cross-sectional: Age-matched controls, infected & uninfected cirrhatics were enrolled within 48 hrs of admission. All infected pts were culture negative & on Abx, while uninfected patients were not & were admitted for other reasons. Stool was analyzed for bacterial & fungal diversity using Shannon Index and compared for individual taxa using LEFSe. Results: Cross-sectional analysis showed reduction in bacterial diversity at day 5 compared to baseline and NAbx group (p=0.001). Abx group showed a significantly reduced bacterial & fungal diversity compared to the other groups (Fig). Infected pts had lower beneficial, autochthonous bacteria (Ruminococcaceae, Lachnospiraceae, Clostridiales XIV, p<0.001) & a higher relative abundance of Candida (median 80% vs 31% & 21%, p=0.01) compared to the rest. Correlations between bacteria & fungi were complex in uninfected control groups but were markedly skewed in infected pts. Longitudinal: 14 age-matched cirrhotics (7 with Abx & 7 nol) were included. The Abx group showed a significantly reduced bacterial & fungal diversity at day 5 compared to baseline and NAbx group (Fig). Specifically, there was a decrease in autochthonous bacteria compared to baseline in Abx (p=0.002) without change in NAbx groups (p=0.5). At day 5, Abx group showed a higher Candida relative abundance compared to NAbx (p=0.001).

Conclusions: There is a significantly higher fungal dysbiosis due to Candida overabundance in culture-negative infected cirrhotics and those who were started on antibiotics, which parallels bacterial dysbiosis. Reduction in bacterial diversity due to widespread antibiotic use leads to reduced fungal diversity and Candida overabundance, which could influence the development of culture-negative and fungal infections in cirrhosis.
defined as development of ascites, bleeding or overt encephalopathy. Secondary end-points included all the above separately, development of HCC, changes in liver function and adverse events. Among 631 patients evaluated, 210 were eligible and 201 were finally randomized and followed until decompensation, death or transplantation, for a median of 36 months [IQR: 24-47 months]. 101 patients were randomized to placebo and 100 to active treatment (67 responders received propranolol and 33 non-responders carvedilol). The primary end-point occurred less frequently in patients treated with propranolol/carvedilol than in those receiving placebo: 16% vs 27% (HR: 0.60, 95%CI: 0.33-1.12, P=0.11), the difference being statistically significant when non-liver related death was analyzed as a competing event (HR: 0.51, 95%CI: 0.27-0.97, P=0.041) (Figure). This difference was largely due to a significant reduction in the incidence of ascites, the more frequent decompensating event, occurring in 9% vs 20% of cases (HR: 0.44, 95%CI:0.20-0.97, P=0.037). There were no differences in other end-points or according to etiology or to administration of propranolol/carvedilol.

Conclusions: In patients with compensated cirrhosis and CSPH, long-term treatment with β-blockers did not significantly improved decompensation-free survival. However, β-blockers significantly decreased the risk of decompensation or liver-related death, mainly by decreasing the incidence of ascites. This suggests that these patients might benefit from β-blockers by reducing progression to decompensation.

**LB-7**

**Preliminary safety and efficacy of REP 2139-Mg or REP 2165-Mg used in combination with tenofovir disoproxil fumarate and pegylated interferon alpha 2a in treatment naive Caucasian patients with chronic HBeAg negative HBV infection**

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Nucleic acid polymers (NAPs) block HBsAg release from HBV infected hepatocytes. The NAP REP 2139 clears serum HBsAg in chronic HBV infection, improving the efficacy of immunotherapy and facilitating establishment of functional control off treatment. The REP 401 protocol (NCT02565719) is a randomized, controlled trial assessing the safety and efficacy of REP 2139 and a REP 2139 derivative with improved clearance (REP 2165) in combination with tenofovir disoproxil fumarate (TDF) and pegylated interferon alpha 2a (peg-IFN) in treatment naive patients with chronic HBeAg negative HBV infection. Forty patients will receive 26 weeks of lead-in TDF (300mg PO qD) followed by randomization (1:1) into experimental and control groups. The experimental group will receive 48 weeks of TDF, peg-IFN (180ug SC qW) and REP 2139-Mg or REP 2165-Mg (1:1, 250 mg IV infusion qW). Patients in the control group will receive 48 weeks of TDF + peg-IFN but will crossover to 48 weeks of experimental therapy in the absence of a log drop in HBsAg after 24 weeks of peg-IFN. Serum viremia is being monitored offsite at the Institute for Virology, University Hospital at the University Duisburg-Essen, Essen, Germany. Enrolment is complete and 22 patients have received ≥ 12 weeks of treatment in control and experimental groups. After TDF lead-in, most patients have serum HBV DNA ≤ 10 IU / ml prior to peg-IFN exposure. Triple combination therapy is well tolerated in all patients and no infusion reactions have been observed with either NAP. Serum HBsAg reductions, increases in serum anti-HBs or serum ALT / AST / GGT flares were negligible or absent in all patients during TDF lead-in and in the control group to date. In patients having completed 12 weeks of NAP exposure, 4 / 5 receiving REP 2139-Mg and 4 / 6 patients receiving REP 2165-Mg have experienced multilog reductions in serum HBsAg and increases in serum anti-HBs. Two patients in the REP 2139-Mg group experienced multilog drops after only 4 weeks. An additional REP 2165-Mg patient (a 5th responder in this group) has also experienced a multilog HBsAg drop after 4 weeks of exposure. NAP-mediated HBsAg reductions are accompanied by otherwise asymptomatic ALT / AST / GGT flares substantially greater than those in the control group. These preliminary data demonstrate the tolerability and efficacy of REP 2139 and REP 2165 when used in combination with peg-IFN and TDF in patients with HBeAg negative chronic HBV infection. Early clearance in serum HBsAg mediated by NAPs is correlated with the onset of an intense transaminase flare and suggests NAP-mediated HBsAg clearance improves the efficacy of peg-IFN in this patient population.

**Disclosures:**

LB-8
Intravenous Immunoglobulin (IVIG) Following Portointerostomy in Infants with Biliary Atresia: a Phase 1/2A Trial

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Objective: Increasing evidence suggests that inflammation or autoimmunity is involved in the pathogenesis of biliary atresia (BA). Intravenous Immunoglobulin (IVIG) has broad effects on inflammatory pathways. In the murine Rhesus Rotavirus model of BA, intraperitoneal IG reduces bile duct injury. We conducted a phase 1/2A clinical trial (PRIME) to determine the feasibility, acceptability and safety, as well as preliminary clinical efficacy, of IVIG in infants with BA following hepatic portointerostomy (HPE). Methods: BA subjects <120 days old (without BA splenic malformation) were enrolled between Oct 2013 and Jul 2015 at 8 US and Canadian sites in the NIDDK-sponsored ChILDReN Network. Three infusions of IVIG (Gammagard Cx1, 1 g/kg over 4-8 hours) were given on days 3-5, 30 and 60 after HPE, ursodiol for 360 days and TIPS-Sulfate for 180 d. Corticosteroid treatment was not allowed. Feasibility was defined as % of subjects who received ≥80% of all 3 IVIG doses, acceptability as % of subjects whose families allowed critical study procedures, and safety as % of subjects with SAEs, expected AEs, and level 3, 4, or 5 NCI CT Epstein toxicities. Efficacy was defined as good bile drainage (% subjects alive with native liver and serum total bilirubin (TB) < 1.5 mg/dl) at 90, 180 and 360 days (d) post-HPE, and survival with native liver (SNL) at 360 d post-HPE. For efficacy analysis, subjects were compared to the placebo group from the BA steroid trial (JAMA 2014; 311: 1750-9) (historical control group). Modified ITT analyses were performed, using exact CIs and tests for estimation of the primary and good bile drainage outcomes, respectively. Kaplan-Meier and Cox models were used to compare SNL in IVIG vs. historical controls (N=64). Results: 30 BA subjects were enrolled; 29 were eligible; 97% completed the study. IVIG infusions were feasible and acceptable in 79% subjects. No infusion-related SAEs were reported, while 28% of subjects had expected IVIG infusion-related AEs. Demographics and baseline characteristics were comparable between IVIG and the historical controls: mean age at HPE was 60 vs. 67 d, mean TB prior to HPE was 8.3 vs. 7.8 mg/dl. Good bile drainage at 90, 180 and 360 d was present in 38%, 48% and 24% of IVIG group vs. 47%, 52%, and 44% of control group (p>0.05 for each). SNL at 360 d was 59% in IVIG and 71% in control group (p>0.05). Conclusion: In this phase 1/2A study, 3 infusions of IVIG were administered without difficulty or safety concerns and were acceptable to caregivers. Compared to the historical control group, IVIG therapy following HPE for BA did not result in significantly improved bile drainage at 90, 180 or 360 d post-HPE or greater SNL at 360 d.

Disclosures:
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LB-9
A phase 2 proof of concept study of MBX-8025 in patients with Primary Biliary Cholangitis (PBC) who are inadequate responders to ursodeoxycholic acid (UDCA)

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Aim: Many patients with PBC show an inadequate response to first line therapy with UDCA. MBX-8025 is a potent, selective PPAR-r agonist that decreases alkaline phosphatase (AP) in healthy volunteers and patients with dyslipidemia and appears well tolerated in these populations. This study (NCT02609048) evaluated the anti-cholestatic effects and safety of MBX-8025 in PBC patients who are inadequate responders to UDCA.

Methods: 12 week, double-blind, parallel, placebo-controlled, phase 2 in patients with AP >1.67 ULN despite UDCA for at least 12 months. The study planned to randomize 75 patients to placebo, 50 or 200 mg/day of MBX-8025 +UDCA. The primary outcome (blinded) was the AP % change. Secondary outcomes were response rate, changes in γ-glutamyl transferase (GGT) and other markers of cholestasis. Other outcomes, e.g. 7α-hydroxy-4-cholest-3-one (C4), a marker of bile acid synthesis, explored the mechanism of action of MBX-8025. Safety monitoring consisted of adverse event (AE), hematology and biochemistry. Results: During study, significant decreases in un-blinded cholestatic markers (GGT and 5’nucleotidase) were observed. Three patients developed grade 3 alanine aminotransferase (ALT) increases (one on 50, two on 200 mg). Increases were rapid, asymptomatic, not associated with increased bilirubin, considered drug-related, and fully reversible. As the proof-of-concept was established, the study was discontinued half-way through recruitment. Since MBX-8025 is predominantly excreted in bile, and PBC impairs bile flow, these subjects may have experienced higher hepatic drug exposure than in previous studies in patients with normal biliary function where no such elevations were observed. One patient discontinued MBX-8025 200 mg for a muscle AE considered drug-re-
larded. Mean baseline AP were 233, 312, and 248 U/L in the placebo, 50, and 200 mg groups, respectively. AP decreases were significant compared to placebo (both p<0.0001), but there were no differences between 50 and 200 mg. There was no indication that MBX-8025 was associated with drug-induced pruritus. Conclusion: In PBC patients who do not respond adequately to UDCA, treatment with MBX-8025 provided a striking anti-cholestatic effect without being associated with pruritus. The effect appears mediated, at least partially, by a profound decrease in bile acid synthesis. However, MBX-8025 was associated with transaminases increase. As this was not seen in other populations and appears dose-related, the benefit of MBX-8025 in patients affected with cholestasis should be further explored at lower doses.

<table>
<thead>
<tr>
<th>% change</th>
<th>N</th>
<th>AP b</th>
<th>GGT c</th>
<th>C4 c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>12</td>
<td>-2</td>
<td>-3</td>
<td>+29</td>
</tr>
<tr>
<td>MBX-8025 50 mg</td>
<td>13</td>
<td>-53</td>
<td>-43</td>
<td>-55</td>
</tr>
<tr>
<td>MBX-8025 200 mg</td>
<td>10</td>
<td>-63</td>
<td>-48</td>
<td>-72</td>
</tr>
</tbody>
</table>

a Last Observation Carried Forward, b Mean, c Median

Disclosures:
David Jones - Consulting: Intercept, GSK, Novartis; Speaking and Teaching: Falk
Mark G. Swain - Advisory Committees or Review Panels: Merck, Gilead, Intercept, Lupin; Grant/Research Support: Gilead, Merck, Bristol-Myers-Squibb, Intercept, Cymabay, Abbvie, Takeda
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**LB-10**

**Nivolumab (Nivo) in Patients (Pts) With Advanced Hepatocellular Carcinoma (HCC): the CheckMate 040 Study**

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Background: For pts with advanced HCC, standard-of-care therapy with sorafenib has limited benefit and those who progress have few effective treatment options. Nivo is a fully human IgG4 monoclonal antibody inhibitor of the programmed death-1 (PD-1) receptor that provides survival benefit in multiple malignancies. Here we report safety, tolerability, and preliminary efficacy of nivo in pts with advanced HCC in the CheckMate 040 trial (NCT01658878; data cut-off March 15, 2016).

Methods: During phase 1 dose escalation and phase 2 dose expansion, pts with advanced HCC were treated with nivo [0.1–10 mg/kg] Q2W and nivo 3 mg/kg Q2W, respectively. Enrollment included pts with or without chronic hepatitis C or B virus (HCV or HBV) infection, and pts with or without prior sorafenib treatment. Primary endpoints were safety/tolerability (escalation arm) and objective response rate (ORR) by RECIST v1.1 (expansion arm). HCV RNA and quantitative HBV surface antigen (qHBsAg) levels were assessed in infected pts. Results: Nivo 3 mg/kg was selected for dose expansion (n=214). One of 48 pts enrolled in the dose-escalation uninfected arm who was treated with nivo 10 mg/kg had a dose-limiting toxicity of grade 2 liver disorder in the setting of progressive disease. Few pts experienced treatment-related serious adverse events (TRSAEs; 7%) and TRAEs leading to discontinuation (4%); there were no treatment-related deaths. Overall, 42/262 pts (16%; 95% CI, 12–21) achieved an OR; median duration of response was 17 mos (95% CI, 6–24). Overall disease control rate was 68% (177/262). In the dose escalation cohort, median overall survival (OS) was 14.1 mos (95% CI, 3.15–28.58) and 15.0 mos (95% CI, 4.99–18.92) in sorafenib-naive and –treated pts, respectively. Transient declines in HCV RNA >1 log were reported in 12/61 HCV-infected pts (20%). Declines in qHBsAg >1 log were reported in 3/66 HBV-infected pts (5%). Additional viral kinetic data will be presented. Conclusions: Nivo had a manageable safety profile and provided durable responses in pts with advanced HCC irrespective of infection status. OS was encouraging and notable disease stabilization was observed. Limited antiviral activity was reported in HCV or HBV infected pts. Results support continued investigation of nivo in advanced HCC.

<table>
<thead>
<tr>
<th>Uninfected (N=135)</th>
<th>HCV Infected (N=66)</th>
<th>HBV Infected (N=66)</th>
<th>All Pts (N=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%) [95% CI]</td>
<td>25 (19) [12, 26]</td>
<td>10 (16) [8, 28]</td>
<td>7 (11) [4, 21]</td>
</tr>
<tr>
<td>Best OR, n (%)</td>
<td>25 (19) [12, 26]</td>
<td>10 (16) [8, 28]</td>
<td>7 (11) [4, 21]</td>
</tr>
<tr>
<td>Complete response</td>
<td>4 (3) [1 (2)]</td>
<td>0 (0) [0 (0)]</td>
<td>0 (0) [0 (0)]</td>
</tr>
<tr>
<td>Partial response</td>
<td>21 (16) [9, 35]</td>
<td>7 (11) [4, 21]</td>
<td>37 (14) [19, 54]</td>
</tr>
<tr>
<td>Stable disease</td>
<td>72 (53) [34, 69]</td>
<td>29 (44) [16, 53]</td>
<td>135 (52) [73, 197]</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>35 (26) [14, 38]</td>
<td>29 (44) [16, 53]</td>
<td>78 (30) [42, 114]</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>3 (2) [1 (2)]</td>
<td>1 (2) [1 (2)]</td>
<td>7 (3) [4, 11]</td>
</tr>
</tbody>
</table>

* Investigator assessed.

Disclosures:
Igancio Melero - Advisory Committees or Review Panels: Pfizer, Bristol Myers Squibb, Merk Serono; Consulting: Digna Biotech
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LB-11
EXPEDITION-IV: Safety and Efficacy of GLE/PIB in Adults with renal impairment and Chronic Hepatitis C Virus Genotype 1 – 6 Infection

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BACKGROUND: Combinations of first-generation direct acting antiviral agents (DAAs) have demonstrated high rates of sustained virologic response (SVR) in patients with chronic hepatitis C virus (HCV). However, HCV patients with severe renal impairment have limited treatment options. Glecaprevir (GLE, formerly ABT-493) and pibrentasvir (PIB, formerly ABT-530) are two pangenotypic DAAs that have potent activity against HCV NS3/4A and NS5A, respectively. Neither compound undergoes significant renal excretion which makes them potentially suitable for patients with renal disease. Phase 1 studies demonstrated no clinically relevant increases in the exposure of GLE/PIB in patients with renal disease compared to those with normal renal function. Here we report on the safety and efficacy of GLE/PIB administered for 12 weeks in GT1-GT6 HCV-infected patients with severe renal impairment [GLE was identified by AbbVie and Enanta]. METHODS: Participants had GT1-6 chronic HCV infection and were either treatment-naive (TN) or treatment-experienced (TE) with interferon- or sofosbuvir-based regimens and either had no cirrhosis or compensated cirrhosis. An eGFR < 30 mL/min/1.73 m² was required at screening. Patients were treated with GLE/PIB 300mg/120mg once daily for 12 weeks. The primary efficacy endpoint was SVR12. Safety was assessed in all patients who received at least 1 dose of the study drugs. RESULTS: A total of 104 participants (76% male and 62% white) were enrolled in this study, of whom 42% were TE and 19% had compensated cirrhosis. Patients had either GT1 (52%), GT2 (16%), GT3 (11%), GT4 (19%), GT5 (1%) or GT6 (1%) chronic HCV infection and had either CKD stage 4 (13%) or stage 5 (87%). 82% were on dialysis. SVR4 was achieved by 103/104 (99%) patients. The patient not achieving SVR4 prematurely discontinued treatment. Most treatment emergent adverse events (AEs) were mild or moderate in severity. Of the 24% of patients who experienced serious AEs, none were related to study-drug. Four AEs (4%) led to study-drug discontinuation and one patient died after achieving SVR4 due to a serious AE not-related to study drug [intracerebral hemorrhage]. CONCLUSIONS: The fixed dose combination of GLE/PIB administered once daily for 12 weeks was well tolerated in patients with severe renal impairment with 99% of patients achieving SVR4. Serious AEs were considered unrelated to study drugs and associated with the patients’ underlying comorbidities. These results suggest that GLE/PIB is a suitable option for patients with advanced renal disease and support the pangenotypic efficacy of this regimen. Complete SVR12 data will be presented at the conference.

Disclosures:
Edward J. Gane - Advisory Committees or Review Panels: AbbVie, Janssen, Gilead Sciences, Achillion, Merck; Speaking and Teaching: AbbVie, Gilead Sciences, Merck, Aleylam
Eric Lawitz - Advisory Committees or Review Panels: AbbVie, Achillion Pharmaceuticals, Regulus, Theravance, Enanta, Idenix Pharmaceuticals, Janssen, Merck & Co, Novartis, Gilead; Grant/Research Support: AbbVie, Achillion Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Idenix Pharmaceuticals, Intercept Pharmaceuticals, Janssen, Merck & Co, Novartis, Nitto Denko, Theravance, Enanta; Speaking and Teaching: Gilead, Janssen, AbbVie, Bristol Meyers Squibb, Merck, intercept
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**LB-12**

A Randomized 3 Phase Trial of Sofosbuvir/Velpatasvir/Voxilaprevir for 8 Weeks Compared to Sofosbuvir/Velpatasvir for 12 Weeks in DAA-Naive Genotype 1-6 HCV-Infected Patients: The POLARIS-2 Study

Ira M. Jacobson1, Tarik Asselah2, Ronald Nahass3, Bal R. Bhandari4, Albert Tran5, Robert H. Hyland6, Luisa M. Stamm6, Hadas Dvory-Sobol6, Yanni Zhu6, Diana M. Brainard6, Mani Subramanian7, Edward Doo8, Averell H. Sherker8, William M. Lee9; 1Virginia Commonwealth University, Richmond, VA; 2Université Paris Diderot, Clichy, France; 3ID Care, Hillsborough, NJ; 4Gastroenterology & Nutritional Medical Services, Bastropp, LA; 5Digestive Center, Centre Hospitalier Universitaire de Nice, Nice, France; 6Gilead Sciences, Inc., Foster City, CA; 7Department of Medicine, University of Alberta, Edmonton, AB, Canada; 8Digestive Care-South Florida Center of Gastroenterology, Wellington, FL; 9Gastroenterology Department, Christchurch Hospital, Christchurch, New Zealand; 10Texas Liver Institute, University of Texas Health Science Center, San Antonio, TX; 11Auckland Clinical Studies, Auckland, New Zealand

**Introduction:** Voxilaprevir (VOX, GS-9857) is a pan-genotypic HCV protease inhibitor. This Phase 3 study (NCT02607800) compared treatment with SOF/VEL/VOX fixed dose combination (FDC) for 8 weeks to SOF/VEL FDC for 12 weeks in patients with genotype 1-6 HCV infection with and without compensated cirrhosis who have not previously received treatment with an HCV direct-acting antiviral agent (DAA). **Methods:** Genotype 1-4 HCV-infected patients were randomized equally to receive open-label SOF/VEL/VOX (400 mg/100 mg/100 mg daily) FDC for 8 weeks or SOF/VEL (400 mg/100 mg daily) FDC for 12 weeks and stratified according to HCV genotype, prior treatment with an interferon-based regimen, and cirrhosis status. Patients with other genotypes assessed at screening were enrolled in the SOF/VEL/VOX treatment arm. Patients with genotype 3 HCV infection and cirrhosis were excluded from this study but eligible for another Phase 3 trial (POLARIS-3). The primary endpoint is SVR12 with a pre-specified non-inferiority margin of 5%. **Results:** Of 941 HCV-infected patients enrolled and treated, 52% were male, 80% were white, 18% had cirrhosis, 23% had failed prior interferon-based therapy, 32% had the IL28B CC genotype; the median HCV RNA was 6.3 log10 IU/mL. HCV RNA declined rapidly in both treatment groups with >90% of patients becoming HCV RNA < LLOQ at treatment week 4. No patient experienced on-treatment virologic breakthrough. SVR4 rates overall and by genotype are presented in the table. At the post-treatment week 4 visit, the relapse rate for the SOF/VEL/VOX group was 3.2% (16/498) and for the SOF/VEL group was 0.5% (2/439). Complete SVR12 results and viral sequencing data will be presented. Two patients (<1%) both in the SOF/VEL group, discontinued treatment prematurely due to adverse events (AEs) assessed by the investigator as unrelated to study drug. The most common AEs (>10% in either group) were headache, fatigue, diarrhea and nausea; diarrhea and nausea were more common in the SOF/VEL/VOX group. No serious AEs were assessed by the investigator as related to study drug; there were no deaths. **Conclusions:** Treatment with the single tablet regimens of either SOF/VEL/VOX for 8 weeks or SOF/VEL for 12 weeks resulted in high SVR4 rates and was safe and well tolerated in genotype 1-6 DAA-naive patients with and without compensated cirrhosis.

**Disclosures:**
Ira M. Jacobson - Consulting: AbbVie, Achillion, Bristol Myers Squibb, Intercept, Gilead, Janssen, Merck, Trek; Grant/Research Support: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck, Speaking and Teaching: AbbVie, Bristol Myers Squibb, Gilead, Janssen
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**LB-13**

Safety, Tolerability and Pharmacokinetics of L-Ornithine Phenylacetate in Patients with Acute Liver Injury/Failure

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**Background:** Cerebral edema (CE) remains a significant cause of morbidity and mortality in patients with acute liver failure (ALF). Ornithine phenylacetate (OPA) generates glutamate, binds ammonia, and promotes its renal excretion as phenylacetylglutamine [PAGN], and may lower ammonia and decrease the risk of CE. **Aims:** To evaluate the safety, tolerability, and pharmacokinetics of OPA in patients with ALF and acute liver injury (ALI; no encephalopathy), including those with renal failure. **Methods:** 47 patients with ALI (N=17) or ALF were enrolled at 8 sites. Inclusion requirements included age 18-70, serum ammonia ≥60μM within 8h of OPA infu-
A Novel Single Daily Fixed Dose Combination of Sofosbuvir400 mg + Ribavirin1000 mg + EGCG400 mg is Superior to the Standard of Care as an Anti-Viral and Safer Causing less Hemolysis in Patients with Chronic Hepatitis C

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Abstract Background & Aims: Chronic Hepatitis C (CHC), the leading cause of liver disease, infects more than 185 million people worldwide. The emergence of new molecules that act directly on the virus itself, such as anti-HCV polymerase Sofosbuvir, improved treatment regimens and outcomes. However, in addition to the extremely high cost of this therapy, there is also a risk of selecting viral escape mutants so a new combination is needed. Ideally, inhibitors should target different steps of the HCV infectious cycle, entry, replication, and assembly/secretion and be efficient against all HCV genotypes. Therefore, the development of novel, better-tolerated, and more-effective anti-HCV agents is urgently needed. The novel patented EHCV (Catvira) formulation composed of Sofosbuvir 400 mg / Ribavirin 1000 mg / Epigallocatechin Gallate 400 mg (EGCG) was developed. Catvira formulation incorporated EGCG for its anti-hemolytic and effective inhibitory activity against viral entry into human host cells. We evaluated the efficacy and safety of a single daily fixed dose EHCV (Catvira) in comparison to the standard of care (Sofosbuvir 400 mg + Ribavirin 1000 mg) multiple tablets per day in CHC genotype 4 patients.

Methods: Randomized open-label study to evaluate the efficacy and safety of Catvira for treating patients with CHC genotype 4 was carried out. Treatment-naive and treatment-experienced patients with genotype 4 HCV infection (N = 80) were randomly assigned to receive a single daily fixed dose EHCV (40 patients) or the standard of care (Sofosbuvir + Ribavirin 40 patients) daily for 12 or 24 weeks. The trial has been registered at clinicaltrials.gov on June 19, 2015 at https://clinicaltrials.gov/ct2/show/NCT02483156?term=ehcv&rank=1

Results: SVR 12 and SVR 24 for EHCV (Catvira) showed no statistical significant difference when compared to the standard of care (P < 0.1 & P < 0.2 respectively). Also EHCV (Catvira) demonstrated a much faster rate of viral load decline (P < 0.01) which could be due to effective viral entry inhibition into human host cells by EGCG. Moreover, EHCV (Catvira) did not affect RBCs count or Hemoglobin levels as compared to the standard of care that resulted in a significant decline (P < 0.05) in both parameters after 24 weeks of treatment. This could be attributed to the anti-hemolytic effect of EGCG. Conclusion: Catvira, administered daily for 12 or 24 weeks, is safe and effective in both naive and treatment-experienced patients with genotype 4 HCV. Catvira’s anti-viral-entry mechanism may also play a role in enhancing efficacy over the standard of care. In addition to potentially enhanced efficacy, Catvira’s anti-hemolytic activity may improve the safety and tolerability of the therapy. Being a single daily dose of Catvira is another advantage leading to better compliance.

Disclosures:
SHAKER A. MOUSA - Patent Held/Filed: Virothera Pharma
The following people have nothing to disclose: Gamal Shiha, Reham Soliman, Waleed Samir
LB-15
Glecaprevir/Pibrentasvir Demonstrates High SVR Rates in Patients with HCV Genotype 2, 4, 5, or 6 Infection without Cirrhosis Following an 8-Week Treatment Duration (SURVEYOR-II, Part 4)

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Background: Hepatitis C virus genotypes (HCV GTs) 2, 4, 5 and 6 have diverse global distributions, and together account for approximately 23% of global HCV infections. Co-formulated glecaprevir (formerly ABT-493; NS3/4A inhibitor identified by AbbVie and Enanta) and pibrentasvir (formerly ABT-530; NS5A inhibitor) [GLE/PIB] are pangenotypic direct-acting antivirals (DAAs) with a high barrier to resistance. In previous phase 2 studies, SVR12 rates of 98% and 100% were achieved following treatment with GLE/PIB for 8 weeks in GT2-infected patients or 12-weeks in GT 4-6 infected patients, respectively. SURVEYOR-II, Part 4 evaluated the safety and efficacy of 8-week GLE/PIB treatment in patients with GT4-6 infection, and a larger cohort of GT2-infected patients. Methods: SURVEYOR-II (NCT02243293) is a phase 2, open-label, randomized, multicenter study. In Part 4, treatment-naive or interferon- or sofosbuvir-experienced patients with GT2, 4, 5 or 6 infection without cirrhosis were enrolled into a single arm to receive 8-weeks of once-daily GLE/PIB (300 mg/120 mg). The primary endpoint was the number of patients with SVR12. For DAA-naive GT2-infected patients, non-inferiority of SVR12 rates was evaluated by comparison to a historical standard-of-care (12 weeks SOF + ribavirin) SVR12 rate of 95%. Safety was also assessed. Results: Of the 203 patients enrolled, 145 (71%) had GT2 infection, and 45 (22%), 2 (1%), and 10 (5%) had GT 4, 5, and 6 infection, respectively. Baseline demographics and safety are summarized in Table 1. The SVR4 rate was 97% [141/145], 98% (45/46), 100% (2/2) and 100% (10/10) for GT2, 4, 5 and 6-infected patients, respectively. Overall, two virologic failures occurred, both as relapses in GT2-infected patients with prior treatment experience. The most common adverse events (AEs) were fatigue (18%), headache (14%) and nausea (11%). No discontinuations were due to AEs, no serious AEs were related to treatment, and grade 3 laboratory abnormalities occurred in <1% of patients. Conclusions: Eight-week treatment with GLE/PIB yielded an overall SVR4 rate of 98% in non-cirrhotic patients with GT 2, 4, 5 or 6 infection, regardless of baseline polymorphisms or prior treatment experience. SVR12 data will be available for presentation at the meeting. These results suggest that GLE/PIB for 8 weeks can successfully treat patients with HCV GT 2, 4, 5 or 6 infection without cirrhosis.

Table 1. Baseline Demographics, Disease Characteristics, Safety and Lab Abnormalities

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>8 Week GLE/PIB N=203</th>
</tr>
</thead>
<tbody>
<tr>
<td>naïve, n (%)</td>
<td>98 (48)</td>
</tr>
<tr>
<td>WHRs, n (%)</td>
<td>155 (176)</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>55 (19-83)</td>
</tr>
<tr>
<td>BMI, median (range), kg/m²</td>
<td>26.8 (17.3-45.7)</td>
</tr>
<tr>
<td>HCV Treatment-naive, n (%)</td>
<td>176 (87)</td>
</tr>
<tr>
<td>SOF treatment-experienced, n (%)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>HCV-RNA, median (range), log (IU/mL)</td>
<td>6.45 (0.75-7.62)</td>
</tr>
<tr>
<td>Baseline Fibrositis F0/F1/F2/F3, n</td>
<td>170/12/21</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Bilirubin Grade 3 (0-10 = ULN), n (%)</td>
<td>0 (0.5)</td>
</tr>
</tbody>
</table>

1) patient had hepatitis A and a second patient had hepatitis C; both assessed as unrelated to study drug.

Disclosures:

David L. Wyles - Advisory Committees or Review Panels: Bristol-Myers Squibb, Gilead, Merck, Abbvie; Grant/Research Support: Gilead, Merck, Bristol-Myers Squibb, Abbvie, Tacere.

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Jeong Heo - Advisory Committees or Review Panels: Abbvie, Gilead; Grant/Research Support: BMS, Roche, GSK, Sillajen.

Ran Liu - Employment: Abbvie

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The following people have nothing to disclose: Susan Greenbloom, Humberto I. Aguilar.
Eight weeks treatment duration with Ledipasvir/Sofosbuvir (LDV/SOF) is effective for appropriately selected patients with genotype 1 Hepatitis C virus (HCV) infection: an analysis of multiple real world cohorts totaling >6,500 patients

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AIMS: A post-hoc analysis of the ION-3 trial indicated that 8 weeks of treatment with LDV/SOF is effective in selected patients with genotype 1 chronic HCV. Several real-world cohort studies also suggest that SVR rates with an 8 week regimen is comparable to a 12 week course. However, these studies are limited by lack of uniform data regarding fibrosis stage or risk factors for relapse. Therefore, current guidelines do not routinely recommend an 8-week regimen. Using individual patient data from multiple real world cohorts, we determined the effectiveness of 8 weeks of treatment, examined variables associated with relapse and compared the efficacy of 8 weeks with 12 weeks of therapy. METHODS: Our primary analysis used pooled data from non-cirrhotic patients from the HCV-TRIO, IFI, Temple University/Burman’s pharmacy, and Kaiser Permanente Southern California cohorts. All patients had fibrosis staging through biopsy, transient elastography, or fibrosure test. Exact logistic regression was used to determine predictors of relapse. Our secondary analysis was a systematic review and meta-analysis of additional real world cohorts to compare the effectiveness of an 8 and 12 week course. RESULTS: Our primary analysis included 868 patients treated for 8 weeks with LDV/SOF. Twelve patients relapsed, yielding a per-protocol (PP) SVR12 rate of 98.6%. SVR12 rates among all subgroups was greater than 95%, including in black patients, those with HIV co-infection and those with stage 3 fibrosis. (Table 1) Sex, age, race, genotype subtype, and fibrosis stage did not predict relapse among patients receiving 8 weeks of treatment. Random effects meta-analysis of 6 additional real world cohorts (n=6,541) demonstrated similar efficacy with 8 weeks (2168/2278, 95.2%) as 12 weeks (3266/3363, 97.1%) duration of treatment (RR=0.99, 95% CI 0.97-1.02). CONCLUSIONS: Real-world data from a large individual patient data cohort and a meta-analysis of additional cohort studies demonstrates that 8 weeks of LDV/SOF achieves high SVR rates >95% in appropriately selected patients, regardless of fibrosis stage, race or HIV co-infection and has comparable outcomes to 12 weeks duration. We propose consideration of the 8 week LDV/SOF regimen be incorporated into treatment algorithms, which may realized cost saving and increase access to therapy.

Table 1. Intention-to-treat and per-protocol SVR12 outcomes for patients receiving 8 weeks of LDV/SOF therapy

<table>
<thead>
<tr>
<th>SVR12 Regimen</th>
<th>ITT: Intention-to-treat; PP: Per-protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 weeks</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>8 weeks</td>
<td>96.2 - 98.4</td>
</tr>
<tr>
<td>12 weeks</td>
<td>97.8 - 99.3</td>
</tr>
</tbody>
</table>

**LB-17**

**Hepatitis B Reactivation Associated with Direct Acting Antiviral Therapy for Hepatitis C: A Review of Spontaneous Post-Marketing Cases**

Susan J. Bersoff-Matcha, Kelly Y. Cao, Mihaela Jason, Adebola Ajaor, S. C. Jones, Tamra Meyer, Allen D. Brinker; Office of Pharmacovigilance and Epidemiology, US Food and Drug Administration, Silver Spring, MD

**Background:** Direct acting antiviral agents (DAAs) are safe, effective treatments for patients with hepatitis C virus (HCV). There have been several recent published case reports of hepatitis B virus reactivation (HBV-R) in patients with HCV/HBV coinfection. HBV-R, defined as an abrupt increase in HBV replication in patients with inactive or resolved HBV, may result in clinically significant hepatitis. HBV-R is often associated with immunosuppression, yet DAAs are not known to cause immunosuppression, and instead work by inhibiting viral proteins for HCV replication. **Objective:** The purpose of this evaluation was to assess spontaneous reports of HBV-R in the setting of DAA treatment. **Methods:** We queried the FDA Adverse Event Reporting System (FAERS) for cases of HBV-R associated with currently marketed, FDA approved DAAs between...
LB-18
Retreatment with sofosbuvir + grazoprevir + elbasvir + ribavirin of patients with Hepatitis C virus Genotype 1 or 4 with RASs at failure of a sofosbuvir + ledipasvir or + daclatasvir or + simeprevir regimen (ANRS HC34 REVENGE study)

Victor de Ledinghen, Claire Laforest, Christophe Hezode, Stanislas Pol, Alain Renault, Laurent Alric, Dominique G. Larrey, Sophie Metivier, Albert Tran, Caroline Jezequel, Didier Samuel, Fabien Zoulim, Aurélie Paillé, Séverine Gibowski, Marc Bourlière, Eric Bellissant, Jean-Michel Pawlotsky, Aurélie Pailhé, Séverine Gibowski, Eric Bellissant

Disclosures:
The following people have nothing to disclose: Susan J. Bersoff-Matcha, Kelly Y. Cao, Mihaela Jason, Adebola Ajao, S. C. Jones, Tamra Meyer, Allen D. Brinker

Failure to achieve sustained virological response (SVR) with hepatitis C virus (HCV) direct-acting antiviral-based regimens is commonly associated with emergence of variants carrying resistance-associated substitutions (RASs). The optimal retreatment regimen for such patients is unknown. The aim of this randomized open-label study was to evaluate sofosbuvir (SOF) + grazoprevir (GZR) + elbasvir (EBV) + ribavirin (RBV) 16 vs 24 wks in patients with NS5A or NS3 RASs at initial treatment failure. Antiviral efficacy was evaluated using the secondary endpoint of SVR4 (SVR 4 weeks post-treatment). On-treatment responses and safety were also assessed. Twenty-six patients (20 males; mean age: 60 years) chronically infected with HCV genotype 1 (1a: n=8; 1b: n=11; 1d: n=1) or 4 (n=6) were randomized and treated. They had advanced fibrosis or compensated cirrhosis (FibroScan > 9.5 kPa in 21 cases and > 20 kPa in 13 cases). NS5A RAs were present in 24 patients (Y93H, n=17; L31M, n=7; Q30R, n=4); NS3 RAS were present in 2 patients. Baseline HCV-RNA level was 6.1 log IU/mL. All of the 26 patients achieved HCV RNA below lower limit of quantification (either TD[u] or TND) during treatment and 18 patients had a rapid response (week 4). SVR4 was achieved by 16/17 patients with sufficient follow-up (almost all the data set will be available in October). The only patient without SVR4 was a patient randomized to 24 wks treatment who had a liver transplantation, stopped prematurely treatment at W12, had negative HCV RNA 3 weeks later and died. No relapse was observed. Seven serious adverse events (SAE) occurred in 5 patients. No SAE was ascribed to study treatment and no study treatment was discontinued due to SAEs. Among the 4 patients with a history of HCC, 2 patients experienced HCC recurrence during the treatment period (first HCC in 2010 and 2014, respectively), one of whom had a compensated cirrhosis decompensation before HCC recurrence. Our findings suggest that retreated patients who failed a DAA-based regimen with NS5A/NS3 RAs with the combination of SOF + GZR + EBV + RBV for 16 weeks is efficacious and represent an interesting option. Safety will need to be monitored cautiously for this combination.

Disclosures:
Victor de Ledinghen - Board Membership: Janssen, Gilead, BMS, Abbvie, Intercept Pharma, Supersonic Imagine; Grant/Research Support: Supersonic Imagine; Speaking and Teaching: Abbvie, Merck, BMS, Gilead
Stanislas Pol - Board Membership: BMS, Gilead, Abbvie, Janssen, MSD
Dominique G. Larrey - Advisory Committees or Review Panels: BAYER, SANOFI, PFIZER, SERVIER-BIG, AEGERION, MMV, BIALQUINTILES, TEVA, ORION, ASTELLAS, ASTRAZENECA, DNDI, J AND J; Board Membership: BMS, GILEAD, ABBVIE, BMS, GILEAD, ITREAS, MMS, NOVARTIS, INTERCEPT; Grant/Research Support: GILEAD, MSD, BMS, ABBVIE, JANSSEN, BMS, NOVARTIS, INTERCEPT
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The following people have nothing to disclose: Claire Laforest, Christophe Hezode, Alain Renault, Laurent Alric, Albert Tran, Didier Samuel, Fabien Zoulim, Aurélie Paillé, Séverine Gibowski, Eric Bellissant
**LB-19**

**Human FGF19 but not NGM282, an Engineered Variant of FGF19, Causes Hepatocellular Carcinoma (HCC) In A Diet-Induced Mouse Model of Non-Alcoholic Steatohepatitis (NASH)**

Lei Ling¹, Mei Zhou¹, Marc Learned¹, Stephen J. Rossi², Hui Tian¹, Alex M. DePaoli²; ¹Research, NGM Biopharmaceuticals, Inc, South San Francisco, CA; ²Clinical Research, NGM Biopharmaceuticals, Inc, South San Francisco, CA

**Background and Aims:** NASH is a common chronic liver disease associated with obesity, diabetes, and metabolic syndrome and has limited treatment options. There is also an increased risk of HCC in NASH patients, independent of the presence of cirrhosis. The FGF19 biologic pathway has demonstrated positive effects on NASH histopathology in preclinical and human studies. However, FGF19 has also been associated with HCC in both mouse models and post-resection HCC patients. NGM282 is an engineered variant of FGF19 that retains the metabolic activity of FGF19 without the associated tumorigenicity and is currently being studied in a Phase 2 trial in NASH patients. Mice fed a high-fat, high-fructose, high-cholesterol (HFFC) diet are an established preclinical model for NASH which develop liver histology similar to human NASH. We have previously shown that FGF15, the rodent orthologue of FGF19, has similar biologic activity to FGF19 but without an increase in liver tumors, complicating the assessment of FGF19-mediated carcinogenicity in mouse models. Therefore, we evaluated human FGF19 and NGM282 in the HFFC model to assess the comparative biologic activity and tumorigenic risk in NASH.

**Methods:** 9-week old C57BL6/J mice were fed a HFFC diet (40% fat, 22% fructose, 2% cholesterol) for 16 weeks. Mice were then administered a single dose of adeno-associated virus (AAV) carrying NGM282 (n=9), FGF19 (n=9), or a control (n=5) gene and continued on the HFFC diet. Livers were collected 34 weeks post-AAV (50 weeks on HFFC) for liver histology and HCC assessments.

**Results:** Both FGF19 and NGM282 markedly improved NASH-related histology relative to the control group. Hepatic gene expression of Cyp7a1, fibrosis markers (Col1a1, Col3a1, TGF beta-1, Lgals3) and inflammatory cytokines (CCL2, CCR2, TNF-alfa, IL1b) were also significantly reduced by FGF19 and NGM282. However, prolonged exposure to FGF19 induced liver tumors in these mice (Figure 1), consistent with prior data in other mouse models. Liver tumors were not observed in any of the NGM282-treated mice. Neither of the treatment groups has significant fibrosis or cirrhosis that could have contributed to the tumorigenic effect.

**Conclusions:** Both human FGF19 and NGM282 prevent NASH-related histologic changes in a diet-induced mouse model of NASH. However, only FGF19 was associated with an increase in liver tumors, independent of the presence of fibrosis. These data have implications for both the biologic activity and therapeutic potential of NGM282 in human NASH as well as the carcinogenic risk of agents such as FXR agonists that increase the secretion of endogenous human FGF19.

**Figure 1.**

<table>
<thead>
<tr>
<th>Control</th>
<th>FGF19</th>
<th>NGM282</th>
</tr>
</thead>
</table>

**Disclosures:**
Lei Ling - Employment: NGM Biopharmaceuticals, Inc.; Stock Shareholder: NGM Biopharmaceuticals, Inc.
Marc Learned - Employment: NGM Biopharmaceuticals, Inc.; Stock Shareholder: NGM Biopharmaceuticals, Inc.
Stephen J. Rossi - Employment: NGM Biopharmaceuticals, Inc; Stock Shareholder: NGM Biopharmaceuticals, Inc.
Hui Tian - Management Position: NGM Biopharma
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The following people have nothing to disclose: Mei Zhou

**LB-20**

**An RNA-based signature enables high specificity detection of circulating tumor cells in hepatocellular carcinoma**

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**Introduction:** Circulating tumor cells (CTCs) are shed into the bloodstream by invasive cancers, but the difficulty inherent in identifying these rare cells by microscopy has precluded their routine use in monitoring or screening for cancer. We recently described a high-throughput microfluidic CTC-iChip, which efficiently depletes hematopoietic cells from blood specimens and enriches for CTCs with well-preserved RNA. Application of RNA-based digital PCR to detect CTC-derived signatures may thus enable highly accurate tissue lineage-based cancer detection in blood specimens. We examined hepatocellular carcinoma (HCC), which bears a unique gene expression profile consistent with its hepatic origin. Methods: Peripheral blood samples from HCC patients and patients with non-malignant liver disease at risk for developing HCC were processed using the CTC-iChip. After identifying a digital signature of 10 liver-specific RNA transcripts, we used a cross-validated logistic regression model to identify the presence of HCC-derived CTCs in these samples. Results: We identified HCC-derived CTCs in 9/16 (56%) untreated HCC patients versus 1/31 (3%) at-risk patients (P<0.0001). Positive CTC-scores declined in treated...
patients: positive scores were found in 9 of 32 (28%) patients receiving therapy and only 1/15 (7%) patients who had undergone curative-intent ablation, surgery or liver transplantation and had no evidence of neoplastic disease (NED). RNA-based digital CTC scoring was not correlated with the standard HCC serum protein marker alpha fetoprotein (AFP, P=0.57). Modeling the sequential use of these two orthogonal markers for HCC screening in high-risk cirrhosis patients generates positive and negative predictive values of 80% and 86%, respectively. Conclusion: Digital RNA quantitation constitutes a sensitive and specific CTC readout, enabling high-throughput clinical applications, such as noninvasive screening for HCC in populations where viral hepatitis and cirrhosis are prevalent.

**LB-21**

**Genome-wide association study identifies a TLL1 variant associated with development of hepatocellular carcinoma after eradication of hepatitis C virus**

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**BACKGROUND & AIMS:** The risk of developing hepatocellular carcinoma (HCC) is not completely abrogated after eradication of hepatitis C virus (HCV) by antiviral agents. We aimed to identify host genetic variation associated with the development of HCC after achieving sustained virological response (SVR) in chronic hepatitis C (CHC) patients. METHODS: We selected 456 Japanese patients who achieved SVR by interferon-based therapy and either developed HCC at ≥1 year after the end of treatment (EOT) (n=123) or did not develop HCC for ≥5 years after the EOT (n=333), and conducted GWAS in these two groups. We then carried out a replication analysis of 79 candidate single nucleotide polymorphisms (SNPs) in an independent set consisting of 130 HCC and 356 non-HCC patients. RESULTS: SNP rs17047200, located within the intron of TLL1 on chromosome 4, showed a strong association with development of HCC at a genome-wide level of significance when the results of the GWAS and the replication cohort were combined (odds ratio = 2.37, P = 2.66 × 10^-8). The cumulative incidence of HCC up to 10 years after the EOT was significantly higher in patients with rs17047200 AT/TT than those with AA in the GWAS, the replication and their combined cohorts (P = 0.009, P < 0.001 and P < 0.001 by log-rank testing, respectively). Multivariate analysis using the stepwise Cox proportional hazard model showed that rs17047200 AT/TT was an independent risk factor for developing HCC (hazard ratio = 1.86, P = 0.002) in addition to male gender, older age, lower platelet count and albumin level, and higher post-treatment alpha-fetoprotein level. Combining the rs17047200 genotype with other factors, we propose different prediction models for HCC development in patients with mild or advanced hepatitis fibrosis. TLL1 expression analyses showed that mRNA levels in human stellate cell lines increased with activation. Moreover, TLL1/TLL1 mRNA increased in liver tissues in rodent models and CHC patients according to the progression of hepatic fibrosis. Bioinformatic analysis on protein-protein interaction networks indicated that the TLL1 exerted several biological roles in regulating extracellular matrix assembly and in transforming growth factor beta signaling. CONCLUSION: We hypothesize that TLL1 may contribute to HCC development mainly via hepatic fibrogenesis, and suggest that genetic testing for the TLL1 SNP...
would be useful for implementing personalized surveillance of HCC after SVR has been achieved.

Disclosures:
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Norifumi Kawada - Grant/Research Support: Chugai; Speaking and Teaching: MSD, BMS, Gilead, Abbvie

The following people have nothing to disclose: Kentaro Matsuura, Hiromi Sawai, Kazuho Ikeo, Atsumasa Komori, Hitoshi Yoshiji, Naoya Sakamoto, Yasuhiro Asahina, Masayuki Kurosaki, Masao Honda, Katsushi Takunaga

LB-22
WITHDRAWN

LB-23
Reduction in Liver Transplant Wait-Listing in the Era of Direct Acting Anti-Viral Therapy
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Recent approval of direct-acting antiviral (DAA) therapy for patients with decompensated cirrhosis (DC) secondary to hepatitis C (HCV) is associated with improved hepatic function. We analyzed trends in liver transplant (LT) wait-listing (WL) to explore the potential impact of effective medical therapy on WL registration. This is a cohort study using the Scientific Registry of Transplant Recipients database from 2003-2015. 47,591 adults wait-listed for LT due to HCV, hepatitis B (HBV) and non-alcoholic steatohepatitis (NASH) were identified. LT indication was defined as DC if the model for end-stage liver disease (MELD) at WL was ≥ 15 or hepatocellular carcinoma (HCC). Era of listing was divided into “interferon” ([IFN] 2003-2010), “protease inhibitor” ([PI] 2011-2013), and “direct-acting antiviral” ([DAA] 2014-2015). Annual standardized incidence rates (ASIR) of WL were analyzed using Poisson regression. Adjusted incidences of LT WL for DC in HCV patients decreased by 5% in the PI era (P = 0.004) and 32% in the DAA era (P < 0.001) compared to the IFN era. Listing for DC in HBV also decreased in the PI (17%, P = 0.002) and DAA eras (24%, P < 0.001). Conversely, WL for DC in NASH increased by 41% in the PI era (P < 0.001) and 81% in the DAA era (P < 0.001). In 2015, the ASIR of LT WL for DC in NASH was equal to that of HCV (2.80/100,000 vs. 2.73/100,000 respectively). WL for HCC in both the HCV and NASH populations increased in both PI and DAA eras (P < 0.001 for all) while HCC WL in HBV remained stable (P > 0.05 for all). Conclusions: The rate of LT WL for HCV complicated by DC has decreased by over 30% in the era of DAA therapy and is now equal to that of NASH.

Figure: Annual standardized incidence rates (ASIR) of LT wait-listing per 100,000 US population by etiology of liver disease and indication for wait-listing. X-axis is the year of LT wait-listing registration. PI: protease inhibitor; DAA: direct acting antiviral

Disclosures:
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The following people have nothing to disclose: Jennifer A. Flemming

LB-24
RNA interference (RNAi) with ARC-AAT provides deep and prolonged knockdown of alpha-1 antitrypsin levels in healthy volunteers
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PURPOSE: Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder causing pulmonary and liver disease. The PiZ mutation results in mis-folded protein (Z-AAT) which can accumulate in hepatocytes and leads to globule formation, fibrosis, cirrhosis and HCC while reducing secretion into blood. ARC-AAT is an RNAi therapeutic which silences production of hepatic Z-AAT while preserving extra-hepatic production. Studies in transgenic PiZ mice, have shown reductions in AAT mRNA, serum Z-AAT levels and hepatocyte accumulation (Wooddell et al., TIDES 2015). Reduction in PiZ production and Z-AAT globules should benefit AATD-associated liver disease. A first in human study in healthy volunteers and patients with ARC-AAT is ongoing. The healthy volunteer portion of the study is completed and has been unblinded. METHODS: In the healthy volunteer (HV) component (Part A) of this double-blind study, 54 HVS (age 18-50) were randomized in 9 single dose cohorts (2 placebo: 4 active) escalating from 0.38 mg/kg through 8 mg/kg. Assessments include safety, PK and change in serum AAT levels. All subjects were followed until serum AAT returned to normal (> 90 mg/dL) or within 15% of baseline. The patient portion of the trial is ongoing. RESULTS: Reductions in serum AAT of up to 90% were observed. There was a clear dose-response and PK was linear. Duration of effect indicates that monthly or less frequent dosing is likely. There have been no
deaths, drop outs due to AEs, clinically significant changes in ECGs, DLCO or FEV₁, and one SAE in a placebo subject. The most frequently reported AEs were headache and upper respiratory tract infection. **CONCLUSION:** Initial results from Part A of the Phase I study indicate that ARC-AAT is well-tolerated and provides deep and durable knockdown of hepatic AAT production. **AATD patient dosing is underway.**

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**Kwashiorkor Malnutrition is Marked by Reduced Serum Concentrations of Essential Amino Acids**

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**Background:** Malnutrition is a leading cause of childhood mortality and contributes to 45% of all deaths of children younger than 60 months. Variants of severe acute malnutrition, (marasmus and kwashiorkor), are particularly fatal, causing the deaths of over half a million children each year. While there is consensus that the wasting of marasmus is caused by inadequate caloric intake, the cause of kwashiorkor malnutrition is unknown. Although the risk of developing kwashiorkor is increased by a low protein diet, total protein consumption is unknown. Although the risk of developing kwashiorkor and marasmus. **Results and Discussion:** There were notable differences in the serum concentrations of essential amino acids among kwashiorkor and marasmus groups of patients. Although both amino acids necessary for the biosynthesis of carcaine, lysine & methionine, were reduced in kwashiorkor carnitine itself was not significantly different between marasmus and kwashiorkor subjects, (p = 0.99). Moreover, of 42 acyl-carnitine species analyzed only one was significantly reduced in kwashiorkor. Overall, these findings demonstrate that kwashiorkor is clearly distinguished from marasmus by significantly reduced concentrations of numerous essential amino acids. However, serum acyl-carnitine analysis does not support the concept that the characteristic steatosis of kwashiorkor is caused by carnitine deficiency.

**Serum Concentration of Essential Amino Acids in Kwashiorkor and Marasmus**

<table>
<thead>
<tr>
<th>Essential Amino Acid (g/mol/L)</th>
<th>Marasmus (n = 41)</th>
<th>Kwashiorkor (n = 44)</th>
<th>T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tryptophan</td>
<td>29.5 (± 19.31)</td>
<td>12.06 (± 11.0)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lysine</td>
<td>144.63 (± 55.74)</td>
<td>102.93 (± 46.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Methionine</td>
<td>18.68 (± 6.13)</td>
<td>15.78 (± 5.68)</td>
<td>0.03</td>
</tr>
<tr>
<td>Leucine</td>
<td>105.09 (± 39.18)</td>
<td>87.03 (± 40.66)</td>
<td>0.04</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>53.10 (± 21.28)</td>
<td>43.83 (± 23.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Valine</td>
<td>139.6 (± 105.38)</td>
<td>105.87 (± 45.38)</td>
<td>0.01</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>75.09 (± 19.9)</td>
<td>72.85 (± 20.24)</td>
<td>0.59</td>
</tr>
<tr>
<td>Threonine</td>
<td>79.9 (± 28.36)</td>
<td>69.83 (± 19.25)</td>
<td>0.13</td>
</tr>
<tr>
<td>Histidine</td>
<td>76.16 (± 16.96)</td>
<td>79.12 (± 25.27)</td>
<td>0.536</td>
</tr>
</tbody>
</table>

All concentrations expressed in mmol/L

**Disclosures:**
The following people have nothing to disclose: Gabrielle Nord, Bethany L. de la Haye, Sara Adams, Thaddaeus D. May, Mark Manary

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**Addition of simvastatin to carvedilol does not improve hemodynamic response in cirrhotics with varices without prior bleed: Preliminary results of an open label RCT**

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**Background and aims:** Carvedilol, a non selective beta blocker (NSBB), effectively reduces hepatic vein pressure gradient (HVPG) in nearly 50% cirrhotic patients. Simvastatin has been shown to reduce HVPG and improve survival when combined with NSBB. We studied whether adding simvastatin to carvedilol improves hemodynamic response in primary prophylaxis of varices. **Patients and Methods:** Cirrhotics with varices who had never bled, and had not been abusing alcohol or had hepatocellular carcinoma or portal vein thrombosis, were randomized to receive carvedilol (group A) or carvedilol plus simvastatin (Group B) for 3 months. Biochemical tests, UGI endoscopy, liver stiffness (Filбросcan) and HVPG were done at baseline and at 3 months. The primary end-point was hemodynamic response at 3 months (HVPG <12 mmHg or ≥20% reduction). **Results:** 220 consecutive cirrhotics with varices were
enrolled and 97 have so far completed 3 months follow-up and are being presented. Demographic profile including aetiology (NASH 25:25, alcohol 11:12) and HVPG (p=0.396) were comparable between groups. Mean HVPG reduced at month 3 in both Gr. A (17.16±3.26 mmHg to 14.4± 4.7 mmHg, p< 0.001) and B (17.9± 3.4 mmHg to 15.4 ± 3.7 mmHg, p=0.001) though the difference was not significant (16.09% vs 13.87%, p=ns). The reduction in HVPG by ≥20% was seen in 54.4% (n=25) patients in group A and 50% (n=22) in group B (p=0.428). Patients with large varices showed hemodynamic response in more patients in group B than A, though the difference was insignificant(66.7% vs 53.3%, p=0.492). Reduction in LSM was not different but controlled attenuation parameter was decreased more in group B (272/+ 66 to 252 +/- 58, p=0.031) than group A (251+/- 51 to 242÷+ 45, p=0.287). Two patients in group A and one in group B bled during 3rd month and one patient in each group died. Three (5.88 %) patients in group A were intolerant and 8 (15.69 %) and 9 (19.56 %) in Group A and B required carvedilol dose modification. The maximum tolerable median dose of carvedilol in both groups was 25mg/day and of simvastatin was 40mg/day. Extreme lethargy and weakness requiring dose reduction of simvastatin was seen in 4 [%] patients.

Conclusion: Addition of simvastatin to carvedilol neither improved hemodynamic efficacy or reduced the incidence of first bleed in unbled cirrhotics with varices. These interim results need to be confirmed by larger trials.

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LB-27
Quality of Life and Outcomes after Multiple Courses of Granulocyte-Colony Stimulating Factor and Growth Hormone in Patients with Decompensated Cirrhosis

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Background: Decompensated cirrhosis carries a high mortality. Liver transplantation is the treatment of choice; however, the limited availability of donor organs, high costs, and limited expertise has resulted in widened donor-recipient mismatch and high waitlist mortality. The present study investigated whether multiple courses of granulocyte-colony stimulating factor (G-CSF) with or without growth hormone (GH) would promote liver regeneration and improve outcomes in patients with decompensated cirrhosis.

Methods: Sixty-five patients with decompensated cirrhosis were openly randomized to either standard medical therapy (SMT) plus G-CSF (5µg/kg subcutaneously every 12h for 5 days then every 3 monthly for 3 days each; 4 cycles) plus GH (1 IU subcutaneously daily) (group A; n=23) or SMT plus G-CSF (group B; n=21) or SMT alone (group C; n=21). Patients were followed up monthly for 12 months. The primary outcome was survival at 12 months. The secondary outcomes were mobilization of CD34+ cells at day 6; improvement in clinical scores (Child Turcotte Pugh [CTP], model for end-stage liver disease [MELD]), liver stiffness, nutritional parameters (Mid-arm-circumference [MAC]; Mid-arm muscle circumference [MAMC]), control of ascites, episodes of infection, quality of life [QOL], and adverse events of treatment at 12 months.

Results: The baseline characteristics were comparable between these groups. There was significantly better 12-month survival in groups A and B than in group C (82.6%, 85.7%, 47.6%, respectively; p=0.019). At day 6 of therapy, CD34+ cells increased in groups A and B compared to baseline with no change in group C (p=0.000, 0.000, and 0.119, respectively). There was a significant decrease in CTP and MELD scores in groups A and B while there was an increase in group C at 12 months as compared to baseline (p<0.05). There was an improvement in MAC and MAMC in groups A and B (p<0.05) while they worsened in group C (p<0.05) as compared to baseline. Ascites was better controlled in groups A and B than in group C (p=0.000). A higher proportion of patients had infection episodes in group C as compared to groups A and B (p=0.008). There was a significant reduction in liver stiffness in groups A and B (p=0.000) while no change in group C at 12 months. Overall QOL scores improved in groups A and B than in group C at 12 months (p=0.000). The therapies were well tolerated with no major side effects.

Conclusions: Multiple courses of G-CSF improve 12-month survival in decompensated cirrhosis. The use of G-CSF led to the mobilization of hematopoietic stem cells, improved liver function, ascites control, nutrition, fibrosis, reduced infections, thus resulting in better QOL in patients with decompensated cirrhosis. The use of GH was however not found to have any additional benefit compared to G-CSF. (NCT02451033)

Disclosures: The following people have nothing to disclose: Virendra Singh, Nipun Verma, Amritjyot kaur, Ratiram Sharma, Ashish Bhalla, Navneet Sharma, Ritesh Agarwal, Akash Singh, Sunita Kumari, Sunil Taneja, Arka De.
effects of CF diet and OCA. **Results:** Compared with CC, CF diet induced significantly higher body weight, HOMA-IR index of insulin resistance, plasma total cholesterol, LDL-C, and ALT levels, by 10%, 46%, 85%, 117% and 27%, respectively. NAS scoring indicated advanced liver complications in CF fed hamsters, with liver steatosis (mean score 2.7±0.2 for grade 0-3), inflammation (1.3±0.2; grade 0-3), hepatocyte ballooning (2±0.3; grade 0-3) and fibrosis (2.7±0.2; grade 0-4). Compared to control CF, CF+OCA fed hamsters showed significant body weight loss, but higher plasma cholesterol ester transfer protein activity by 18% (p<0.01), higher LDL-C levels by 27% (p<0.05), and lower HDLC levels by 20% (p<0.01). Dyslipidemic profile was confirmed by Fast Protein Liquid Chromatography analysis. Compared to CF, CF+OCA significantly reduced intestinal cholesterol absorption, with a trend towards lower hepatic LDL-receptor protein expression. In the liver, CF+OCA blunted gene expression of FXR targets Cyp7a1 and Cyp8b1, and reduced NAS score for inflammation (all p<0.01 vs. control CF). However, only 50% of CF+OCA fed hamsters showed substantial improvement in total NAS score, leading to a non-significant reduction as compared with control CF hamsters. **Conclusion:** Compared to mouse models, the DNL hamster replicates benefits and side effects of OCA observed in humans. This model should be useful to evaluate efficacy and sides effects of novel drugs for better translation to the clinical setting.

Disclosures:
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Marjolaine Quinsat - Employment: PHYSIOGENEX SAS
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**LB-29 Clinical-grade human liver mesenchymal stem cells for the treatment of NASH-Fibrosis through immunomodulation**

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**Background:** Nonalcoholic steatohepatitis (NASH), a severe form of nonalcoholic liver diseases (NAFLD), is one of the prominent liver diseases worldwide. There is currently no approved drug for the treatment of NASH and liver transplantation is the only therapeutic approach for advanced NASH. Mesenchymal stem cells (MSCs) are promising candidates to modulate the pro-inflammatory and pro-fibrogenic environment of chronic liver because of their immunomodulatory properties. HepaStem, Human adult liver-derived MSCs isolated from organs unsuitable for transplantation can be GMP-manufactured, cryopreserved and reconstituted at the bedside as an off-the-shelf product. Safety and tolerability have been shown in a phase I/II clinical trial in patients with metabolic disorders. The proposed mechanism of action in NASH is a systemic hit-and-run suppression of inflammation and stellate cell activation through the secretion of several cytokines in response to the liver inflammation. **Method:** The secretion of pro-inflammatory and anti-inflammatory cytokines including HGF, IDO, PGE2 was measured using multiplexed immunoassays in cell culture with or without inflammation cocktail. The anti-inflammatory effect of HepaStem was investigated in co-culture systems with T-lymphocytes in a mixed leukocyte reaction as well as with immature and mature dendritic cells. In a preclinical high-fat model, the potency of HepaStem was compared to a vehicle, either with or without the use of immunosuppression (cyclosporine), to factor in the use of human cells in an animal model. **Results:** Secretion of anti-inflammatory and anti-fibrotic cytokines was increased with the addition of an inflammatory cytokine cocktail in the culture medium. HepaStem inhibited both T-lymphocyte response and the dendritic cell generation and function in co-culture experiments. In the NASH model, while the immunosuppression by itself did not affect the disease progression, cell-based treatment (3 IV injections 12.5x106 cells/kg) significantly and dose-dependently decreased collagen deposition in the pericentral region as shown by Sirius red staining. A single HepaStem injection significantly decreased the NAS score, which was mainly attributed to reduction in inflammation and thus supporting the proposed mechanism of action. **Conclusion:** Our results suggest that HepaStem has anti-inflammatory, anti-fibrosis and anti-NASH effects, both in vitro and in a pre-clinical NASH model. This observation provides significant evidences to open new phase I/II studies in NASH patients as well as to apply MSCs for the treatment of chronic liver disorders.

Disclosures:
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Sabrina Braibant - Employment: Promethera Biosciences
Joelle J. Thonnard - Employment: Promethera Biosciences
The following people have nothing to disclose: Catherine Lombard, Giuseppe Mazza, Etienne M. Sokal

**LB-30 YH25724, a novel long-acting GLP-1/FGF21 dual agonist improves hepatic steatosis, inflammation and fibrosis in nonalcoholic steatohepatitis (NASH) animal models**

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**Background:** It has been proposed that development of NASH occurs via multiple parallel hits including impaired lipid metabolism, insulin resistance and inflammation. An ideal drug candidate for NASH should reduce hepatic inflammation and liver cell injury, should correct the underlying insulin resistance and should have anti-fibrotic effects. Glucagon-like peptide-1 (GLP-1) is known to suppress lipogenesis and reduce fat accumulation and proinflammatory responses in liver. Fibroblast growth factor 21 (FGF21) is a novel metabolic regulator, which can improve insulin sensitivity and lipid metabolism in addition to having anti-fibrotic effect. Thus, addressing both GLP-1 and FGF21 complementary mechanisms of action. YH25724 is a novel long-acting dual agonist, which is an immunoglobulin Fc-fused protein comprising an GLP-1 variant and an FGF21 variant. In our previous studies, YH25724 substantially improved insulin resistance and significantly lowered glucose, lipid-, and body weight in obese, type 2 diabetic animal models. In this study,
we investigated the therapeutic effects of YH25724 in three different NASH models. **Methods:** Three established NASH mouse models were used. YH25724 was administered by subcutaneous (SC) injection every four days for 2 weeks (3-10 nmol/kg) in a DIO model (60% high fat diet for 37 weeks, n=6/group), every other day for 4 weeks (3-30 nmol/kg) in a methionine choline deficient (MCD) diet model (MCD diet for 8 weeks, n=10/group), and every other day for 8 weeks (3-10 nmol/kg) in an amylin liver NASH (AMLN) diet model (40% AMLN diet for 33 weeks, n=12/group). Body weight, food intake, serum chemistry, hepatic lipids, and liver histology were evaluated. **Results:** In all animal models tested, YH25724 significantly decreased serum ALT, AST levels in a dose dependent manner. In the DIO model, YH25724 treatment resulted in greater improvements in serum levels of triglyceride and total cholesterol, hepatic triglyceride and fat accumulation in the liver along with decreased expression of several lipogenic genes (SREBP-1, ACC1, FAS). In the MCD diet model, YH25724 significantly decreased the expression levels of β-SMA, TGF-β, and collagen deposition related to inflammation and fibrosis in liver tissues. In the AMLN diet model, YH25724 treatment not only improved serum and hepatic lipid profiles, but also decreased the non-alcoholic fatty liver disease (NAFLD) activity score. **Conclusions:** The novel long-acting GLP-1/FGF21 dual agonist YH25724 may therefore be a new promising therapeutic candidate for the treatment of NASH due to its synergistic dual mechanisms which leads to a concomitant reduction of hepatic inflammation, fibrosis and liver cell injury while at the same time addressing the underlying insulin resistance.

**Disclosures:**
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- Tae Wang Kim - Employment: Yuhan Corporation
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- Stock Shareholder: Gubra
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- Su Youn Nam - Employment: Yuhan Corporation
- The following people have nothing to disclose: Michael Feigh

**LB-31**
**Spexin, a novel regulator of lipid & carbohydrate metabolism, is a potential therapeutic for obesity, type 2 diabetes mellitus, & non-alcoholic fatty liver disease**

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As spexin causes weight loss in mice with high fat diet (HFD)-induced obesity by both CNS-mediated processes & peripheral inhibition of adipocyte long chain fatty acid (LCFA) uptake, we studied spexin’s effects on Type 2 Diabetes Mellitus (T2DM) & Non-Alcoholic Fatty Liver Disease (NAFLD), which share these mechanisms. **Protocol:** 32 wk C57BL6/J mice were fed a control (10% fat) or 60% fat HFD. After 30 days, HFD mice were randomized to spexin (25 μg/kg in 0.1 ml PBS) or 0.1 ml PBS (HFD controls) i.p. daily. C57BL/6J mice on the 10% fat diet were low fat diet (LFD) controls. Weight, vital signs, glucose tolerance & other tests were measured on injection days 8, 18 & 28-29. Some mice from all groups were sacrificed on day 28. Livers were removed for biochemical/histologic studies & to examine spexin’s effects on hepatocyte LCFA uptake. **Results:** Pre-Rx, HFD mice had significantly higher food intake, body weight, blood glucose, HbA1C, insulin resistance, & hepatic lipid content than LFD controls. Spexin Rx for 4 wks led to reduced weight compared to PBS (46.9±0.3 SE vs 48.8±0.6 g, p=0.0182), improved or normalized oral glucose tolerance, HbA1C (6.10±0.21 NGS% vs 6.71±0.16, p<0.024), HOMA-IR (4.83±1.45 vs 10.96±1.49, p<0.05), serum ALT (109±17 IU/L vs 170±23, p=0.045) & AST (115±3 IU/L vs 158±14, p=0.035), and markedly [ca.60%] reduced hepatic lipids, assayed by digital scanning (Figure). Incubation with spexin reduced hepatocyte LCFA uptake rate in vitro, with peak (70%) inhibition at 15 ng/mL. **Conclusions:** Spexin reduces body weight, improves glucose metabolism, & decreases hepatic steatosis in DIO mice. It is a promising therapeutic for T2DM & NAFLD as well as obesity.

**Disclosures:**
- Jose L. Walawesi - Employment: Columbia University Medical Center; Patent Held/Filed: Columbia University Medical Center
- The following people have nothing to disclose: Paul D. Berk, Fengxia Ge, Dieunine Anglade, Melissa Osborne, Philipp P. Henrich

**LB-32**
**Efficacy of DRX-065, the stabilized R-enantiomer of pioglitazone (pio), in choline-deficient (CD) and methionine/choline deficient (MCD) diet mouse models of nonalcoholic steatohepatitis (NASH)**

**Sharon C. Cheetham**1, Sheila H. DeWitt1, Keith Dickinson2, Vincent Jacques1, Lex H. Van der Ploeg1, Steven Vickers2; 1DeuteRx, Andover, MA; 2Renasci Limited, Nottingham, United Kingdom

**Background:** The efficacy of pio, a drug approved for the treatment of type 2 diabetes, has had favorable outcomes in several clinical trials of NASH patients. However, PPARγ related side effects of weight gain and edema limit pio’s attractiveness for NASH. Pio is a racemate, a mixture of R- and S-enantiomers, which chemically interconvert. As we reported at AASLD last year, stabilizing each enantiomer with deuterium demonstrated that the PPARγ agonist activity and associated weight gain and edema are due to the S-enantiomer. By contrast, the mitochondrial pyruvate carrier (MPC) inhibition and resulting anti-inflammatory activity are due to the R-enantiomer. Here we show that DRX-065 possesses the pharmacological properties of pio required for the treatment of NASH. **Methods:** The efficacy of DRX-065 and the deuterium-stabilized S-enantiomer (d-S-pio) were compared to pio in the CD (DRX-065, d-S-pio) and MCD (DRX-065, pio) models.
and MCD (DRX-065) diet mouse models of NASH with male C57Bl/6J mice on normal chow as controls. All agents were administered orally twice daily for 6 ws at 30, 15, and 15 mg/kg/day for pio, DRX-065, and d-S-pio, respectively. At the end of the study, all animals were sacrificed (n = 11-12/grp). Plasma ALT, AST, ALP, triglycerides (TG), non-esterified fatty acids (NEFA), serum amyloid A, adiponectin were determined using standard methods. Livers were harvested and evaluated for measures of TG, NEFA, and cholesterol as well as for histopathology. Results: The MCD diet produced marked weight loss compared to mice on normal chow. The CD diet also significantly reduced body weight but by a much lesser extent. In the CD model, plasma adiponectin was elevated by all 3 agents, but less by DRX-065. Effects on ALT, AST, and ALP were modest and inconsistent. Plasma TG and NEFA were lower in the CD diet animals than in controls. Treatment with all 3 agents reduced these parameters further. Hepatic TG and NEFA accumulation was significantly reduced by pio and DRX-065 only, DRX-065 being the most potent for TG. Results were confirmed by histopathology, which showed significantly decreased steatosis with DRX-065 and lobular inflammation with DRX-065 and pio. Fibrosis was reduced to the same extent by all 3 agents. The resulting NAFLD activity score (NAS) was significantly decreased by all 3 agents, with DRX-065 being the most potent and d-S-pio showing marginal activity. The beneficial effects of pio and DRX-065 were reproduced in the MCD model where the agents were undistinguishable. Conclusions: DRX-065 is superior to pio in reducing steatosis, NAS, and TG in mouse models of NASH. It is equivalent to pio in reducing hepatic NEFA, cholesterol, inflammation, and fibrosis.

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LB-33

WITHDRAWN

LB-34

Endoscopic duodenal mucosal resurfacing (DMR) improves insulin sensitivity, hepatic transaminase levels and anti-inflammatory markers in type 2 diabetes subjects

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BACKGROUND: Obesity, insulin resistance and type 2 diabetes mellitus (T2DM) are closely linked to the development of nonalcoholic fatty liver disease (NAFLD) and its more aggressive phenotype, nonalcoholic steatohepatitis (NASH). There is currently no approved therapy for NASH and, while many drugs are in development, their pharmacodynamics profiles are not entirely optimal, creating a need for novel NASH treatment approaches. Recent studies indicate that crosstalk occurring between the proximal small intestine and liver modulates metabolic homeostasis in response to nutrient availability. We have developed an endoscopic technique, hydrothermal duodenal mucosal resurfacing (DMR), to denude the proximal duodenal mucosa, which is followed by mucosal restitution via resurfacing with neo-epithelium. Early clinical data shows glycemic improvement and lowering of hepatic transaminases following a single DMR procedure in T2DM. AIMS: To define the impact of endoscopic hydrothermal DMR on insulin resistance and glycemic and hepatic indices in subjects with T2DM. METHODS: A pilot study of DMR was conducted in subjects with T2DM (an ≥1 oral anti-diabetic agent with HbA1c ≥ 7.5%) to evaluate metabolic indices during a standard mixed meal tolerance test (MMTT) pre- and 3-months post-procedure. Metabolomic analysis was also performed from plasma samples in a subcohort of patients. The effects of DMR were assessed by comparing pre- to post-procedure results using paired T-tests. RESULTS: A total of 14 subjects who underwent a single DMR procedure were included (pre-procedure mean fasting plasma glucose: 198 mg/dl; HbA1C: 10.2%). DMR was performed successfully in all subjects and the procedure was well tolerated. A modest reduction in body weight was observed (2.4 kg, p<0.05) at 3 months. DMR lowered fasting and MMTT plasma glucose (-57 mg/dl and -63 mg/dl respectively, both p<0.001) with an accompanying lowering of HbA1c (-2.7%, p<0.001) at 3 months. There was also a lowering of mean HOMA-IR (1.6 units, p=0.05) and a reduction in circulating diacylglycerols, α-OH butyrate, lipoxygenases and oxidized eicosanoids (all p<0.05). CONCLUSIONS: A single endoscopic DMR procedure performed in subjects with T2DM produced a significant improvement in glycemic indices along with improved markers of insulin resistance, systemic inflammation and oxidative stress. These results provide evidence that DMR could become a potential method for correction of hyperglycemia and key pathophysiological drivers of fatty liver disease in subjects with T2DM.

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A single endoscopic duodenal mucosal resurfacing procedure exerts a sustained improvement in hepatic transaminase levels in a cohort of type 2 diabetes patients

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Duodenal mucosal resurfacing (DMR) is an endoscopic intervention that elicits metabolic improvement in type 2 diabetes (T2D), likely through an insulin sensitizing mechanism. A lowering of hepatic transaminase levels has also been observed, suggesting a favorable impact on probable co-existent fatty liver disease. Here we report hepatic transaminase levels from a composite of two clinical studies in T2D patients with a minimum follow-up of 6 months: (i) a single-site, first-in-human study (FIH, n=30) and (ii) a subsequent, multi-center study (Revita-1 trial) (R1, n=22). In both studies, patients underwent a single DMR procedure with circumferential hydrothermal ablation of a median length of ~9 cm of duodenal mucosa. Patient demographics in the studies were similar (mean±SD for FIH vs R1, respectively: age: 52±8 vs 56±8 yrs, BMI: 32±4 vs 32±4 kg/m², duration of diabetes: 5.6±2 vs 6.4±2 yrs), with the exception of pre-procedure HbA1c (9.7±1.4 vs 8.4±0.7%). At 6 months, significant improvements from baseline in glycemia (Δ HbA1c: FIH: -1.2±1.8%, R1: -0.8 ± 0.9%; p<0.001) and trends towards lower HOMA-IR (Δ HOMA-IR: FIH: -0.9±4, R1: -2.4±6.8) were observed after DMR with minimal effect on body weight (Δ weight: FIH: -1.8±3.6, R1: -2.4±3.8 kg) in both cohorts. Decrease of hepatic transaminases was noted for the composite cohort at 6 months: Δ ALT -9.9±22.3 IU/mL (25% decrease) and Δ AST -6.1±14.8 IU/mL (21% decrease), with a sustained effect in the composite cohort observed up to 12 months (FIH: n=28, R1: n=9). A subcohort of FIH subjects who showed ultrasound findings compatible with steatosis pre-procedure (n=23) also experienced a decrease of hepatic transaminase levels [-14.4±23 IU/mL at 6 months, -7.6±9.8 IU/mL at 12 months]. In conclusion, DMR is a minimally invasive procedure that improves both glycemic markers and markers of fatty liver disease in subjects with T2D. A single duodenal mucosal resurfacing procedure resulted in a decrease of liver transaminases sustained for 12 months. This unique endoscopic intervention deserves further study to ascertain its potential efficacy as a treatment for fatty liver disease.

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Discovery of new non-invasive tests algorithms (NITs-Algo) for liver disease in subjects with metabolic factors, using SAF scoring system. A proof of concept demonstrating the impact of disease definitions.

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Background: An unmet need in subjects (Sj) presumed NAFLD, is the availability of NITs for a simple prediction of significant liver disease (activity (A) or fibrosis (F)) and NASH. The interobserver variability of references, was improved recently by the SAF scoring system (A2orF2 defining significant disease) and the FLIP-algo defining NASH (Bedossa 2014). We aimed to propose NITs-algo taking into account remaining limitations (Brunt 2016), which impacted artificially the NITs performance: the choice of 5% or 1% for defining steatosis (S), the requirement of S for defining A or NASH, as well as a lack of sufficient controls A0S0. Methods: The model used concordance tables (3x3) crossing the categories of FLIP-algo (NASH, S-only and No-S), with those presumed by NITs-algo using predetermined cutoffs (C), ActiTest (AT) and SteatoTest (ST) presuming A and S. The 96 combinations were 2 levels for S-C, x2 levels for S requirement, x2 levels for A0S0, adjusted according the choices of x4 ST-C, x3 AT-C. The impact of definitions was assessed using wKappa in 1,081 Sj presumed NAFLD, and 191 supplementary A0S0. The histological algo permitting the highest wKappa independently of NITs-C, was used as reference for a new histological definition of NASH; 2 new NITs were constructed combining 9 blood tests (Pentat-pending), age and gender, NIT-NASH to predict NASH, and NIT-A2F2 for A2 orF2, compared with FibroTest (FT), AT and NAFLD-score. NITs were validated independently in 96 new NAFLD SAF-scored Sj and applied in 7,416 healthy volunteers (HV) and in 79,955 US Sj presumed NAFLD with NAFL-FibroSure. Results: In the construction population, 549 (51%) Sj had a NASH as per FLIP and 638 (59%) were A2orF2. The wKappa varied (P.<0.0001) from .140 (95%CI 106.175) to .430 (.378.482). NASH not requiring S, as well as inclusion of more SOAO, significantly increased wKappa in logistic regression (P.<.001). AUROC were for predicting A2F2 by NIT-A2F2 = .814 (.786.839), and for predicting NASH by NIT-NASH=.796 (.767.821), higher (P.<.001) than those of FT (.761.731.788 and .728.697.757), AT (.761.731.789 and .755.725.782), and NAFLDscore (.570.510.630 and .553.498.605) respectively. In the validation group, both NIT-A2F2 and NIT-NASH reached high positive predictive value, 82/86 (95.3%;88.5.978) and 83/89 (93.3%;85.9.975) for the diagnostic of A2F2 and NASH. According to the definitions the prevalence of NASH varied (P.<0.0001) from 0.8%(n=59) to 17.8%(n=1,317) in the HV, and in US database from 16.3%(n=1,3029) to 61.6%(n=49251). Conclusion: Taking into account the impact of definitions should permit to understand artificial discordances observed between “NAFL-NAFLD-NASH” epidemiological studies, and to construct better biomarkers. “Metabolic liver disease” could be used instead of “NAFL/NAFLD/NASH”.

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Improvement in NASH histological activity highly correlates with fibrosis regression.

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Introduction: A NASH treatment should protect from long-term progression to cirrhosis and its complications by suppressing the underlying cause of fibrogenesis. Whether changes in individual histological features of NASH alter fibrosis progression remains to be determined. Methods: All completers of the 1-year GOLDEN-505, elafibranor vs. placebo trial (N=237) were analyzed. Biopsies were scored by the NASH-CRN classification at baseline and end-of-treatment (EOT). At inclusion, all pts had scores ≥1 for steatosis, lobular inflammation and hepatocyte ballooning. Pts were grouped by changes between EOT and inclusion for steatosis (from -3 to +2), lobular inflammation (from -2 to +2) or ballooning (from -2 to +1) scores. For each group, the percentage of patients experiencing an improvement or a worsening (>1 stage) in fibrosis stage was calculated. Associations between changes in scores and fibrosis evolution were assessed by the Fisher exact test. Results. Changes in both lobular inflammation and ballooning were highly and positively correlated with changes in fibrosis (p<0.001 and p=0.04, respectively). Among pts with a 2 point score reduction in inflammation, 67% improved fibrosis (0% worsened); in contrast, if inflammation progressed by >1 point, 56% of pts worsened fibrosis and only 6% improved. For ballooning changes, a 2 point reduction in score resulted in 71% fibrosis improvement (0% worsening); conversely, a 1 point increase resulted in 35% fibrosis worsening and only 26% improvement. In contrast, there was no association between changes in steatosis scores and changes in fibrosis: 25% improved and 0% worsened for a change ≤2; 45% improved and 18% worsened for a change ≥1. An activity index defined as the sum of lobular inflammation and ballooning scores shows a positive linear relationship with mean changes in fibrosis score (R²=0.95). Similar results were obtained when considering placebo and elafibranor-treated patients separately or when considering only patients with NAS ≥4 and F ≥2 at inclusion. Conclusion: Improvement in NASH activity and regression of fibrosis are highly correlated supporting the concept that resolution of NASH can reverse fibrosis progression and is reasonably likely to predict long term clinical benefit.

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