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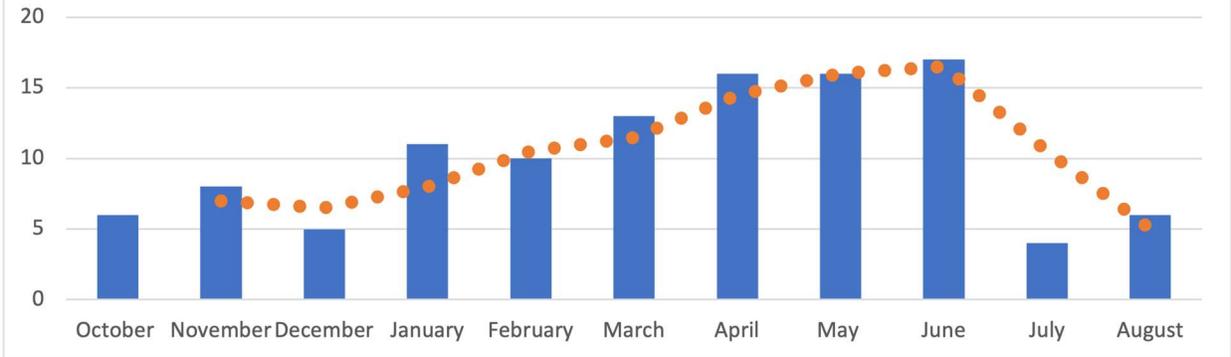
## WORLDWIDE OUTBREAK OF ACUTE HEPATITIS IN CHILDREN: INTERIM RESULTS FROM THE SEVERE HEPATITIS IN PEDIATRIC PATIENTS (SHIPP) INTERNATIONAL REGISTRY

*Saeed Mohammad<sup>1</sup>, Maria Amendola<sup>2</sup>, Anna Banc-Husu<sup>3</sup>, Catherine Chapin<sup>4</sup>, Kate Cheng<sup>5</sup>, Christopher Chu<sup>6</sup>, Madelyn Cohen<sup>7</sup>, Tamir Diamond<sup>8</sup>, Benjamin Gold<sup>9</sup>, Matthew Goldstein<sup>10</sup>, Alexis Gumm<sup>11</sup>, Nitika Arora Gupta<sup>12</sup>, Saul J. Karpen<sup>13</sup>, Taisa Kohut<sup>14</sup>, Alyssa Kriegermeier<sup>15</sup>, Jody Mackling<sup>16</sup>, Vikram Raghu<sup>17</sup>, Sheetal Wadera<sup>16</sup>, Phoebe Wood<sup>18</sup> and Rohit Kohli<sup>19</sup>, (1)Pediatrics, Vanderbilt University Medical Center, (2)UPMC, (3)Department of Pediatrics, Section of Gastroenterology, Hepatology and Nutrition, Texas Children's Hospital/Baylor College of Medicine, (4)Department of Pediatrics, Northwestern University, Feinberg School of Medicine, Ann & Robert H. Lurie Children's Hospital of Chicago, Division of Gastroenterology, Hepatology and Nutrition, (5)Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of California, San Francisco, (6)Central Texas Veterans Health Care System, Temple, TX, USA, (7)Pediatrics, Section of Gastroenterology Hepatology & Nutrition, Texas Childrens Hospital/Baylor College of Medicine, (8)Children's Hospital of Philadelphia, (9)GI Care for Kids, (10)Emory University/Childrens Healthcare of Atlanta, (11)Pediatrics, Boston C, (12)Pediatrics, Emory University School of Medicine, (13)Division of Pediatric GI/Hepatology, Emory University School of Medicine, (14)Division of Pediatric Gastroenterology, Hepatology, and Nutrition, University of Miami, (15)Pediatrics; Division of GI/Hepatology and Nutrition, Ann & Robert H. Lurie Children's Hospital of Chicago, (16)Gastroenterology & Hepatology, Phoenix Childrens Hospital, (17)University of Pittsburgh, (18)Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia and the University of Pennsylvania Perelman School of Medicine, Philadelphia, United States, (19)Pediatrics, Children's Hospital Los Angeles*

**Background:** Clusters of acute hepatitis cases in young children were reported worldwide beginning in Oct 2021. Although most children recovered, some progressed to liver failure leading to death or liver transplantation. Beyond these local reports the extent of this worldwide disease is poorly characterized. We aimed to characterize the clinical characteristics, histology, and outcomes of this group of children through an international collaborative effort. **Methods:** Data prospectively accrued by individual sites per WHO/CDC request was collated into an IRB approved REDCap registry created in July 2022. An email invitation was sent through multiple listservs to pediatric gastroenterologists worldwide with 26 sites responding. Patients <18yrs, ALT >500, no known chronic liver disease or acetaminophen ingestion were eligible. IRB approval was obtained from 11 sites-the participants' data are presented in this interim analysis **Results:** 112 cases have been reported with a median age at presentation of 43 months, (IQR 17,100) 57% were male, and 59% were white. The cases peaked in incidence, within our cohort, in June 2022 (Figure 1). At presentation, 80% reported gastrointestinal symptoms followed by fever (26%) and respiratory symptoms(23%). Eighteen patients were on chronic medication, with 4 on immunosuppressants. 11% had SARSCoV2 infection in the past year. 95% of our cohort were hospitalized for a median of 6 days (IQR 3,13) with 29 (26%) requiring ICU level care. Median lab values were AST 2259 (IQR 747,3763) ALT 1949 (IQR 934,3503) Total bilirubin 5.1 (IQR1.5,11.4) and INR 1.4 (IQR 1.1,1.9) Adenovirus serum/whole blood DNA was detected in 15/90 (17%) and 5 patients were treated with cidofovir. CMV and EBV serologies were positive in 6% and 16% respectively. 44% had a positive respiratory panel test result with Rhino/Enterovirus being the most common (57%) Two patients each were positive for SARSCoV2 and Adenovirus. Liver biopsies were performed in 46/112 of which 93% had portal and lobular inflammation with none identifying a viral etiology. One patient was thought to have medication toxicity due to minocycline and one had features consistent with Autoimmune Hepatitis. 7 patients underwent liver transplantation, 3 of whom were adenovirus positive. Two patients died, one from cerebral herniation from intracranial hemorrhage and the other from their underlying seizure disorder. **Conclusion:** In this large and diverse dataset of pediatric patients with acute hepatitis, the majority did not have a singular definitive etiology but did recover spontaneously. Continued community surveillance and close cooperation within centers through the SHIPP registry are critical towards understanding the etiology of such clusters of acute hepatitis in pediatrics.

# Cases of Acute Hepatitis

Oct 2021-August 2022



**Disclosures:**

Saeed Mohammad - Albireo: Advisory Committee or Review Panel; Mirum: Advisory Committee or Review Panel;

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### EFFICACY AND SAFETY OF MARALIXIBAT IN PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (MARCH-PFIC): A RANDOMIZED PLACEBO-CONTROLLED PHASE 3 STUDY

Alexander Miethke<sup>1</sup>, Adib Moukarzel<sup>2</sup>, Gilda Porta<sup>3</sup>, Joshue Covarrubias Esquer<sup>4</sup>, Piotr Czubkowski<sup>5</sup>, Felipe Ordóñez<sup>6</sup>, Manila Candusso<sup>7</sup>, Amal A. Aquil<sup>8</sup>, Robert H. Squires<sup>9</sup>, Âtienne Sokal<sup>10</sup>, Daniel D'Agostino<sup>11</sup>, Ulrich Baumann<sup>12</sup>, Lorenzo D'Antiga<sup>13</sup>, Nagraj Kasi<sup>14</sup>, Nolwenn Laborde<sup>15</sup>, Cigdem Arikan<sup>16</sup>, Chuan-Hao Lin<sup>17</sup>, Susan Gilmour<sup>18</sup>, Naveen Mittal<sup>19</sup>, Fang Kuan Chiou<sup>20</sup>, Simon P Horslen<sup>9</sup>, Wolf-Dietrich Huber<sup>21</sup>, Arthur Van Leerberghe<sup>22</sup>, Susanne Weber RÃ,nn<sup>22</sup>, Tiago Nunes<sup>22</sup>, Anamaria Lascau<sup>22</sup>, Lara Longpre<sup>22</sup>, Will Garner<sup>22</sup>, Pamela Vig<sup>22</sup>, Vera F. Hupertz<sup>23</sup>, Regino P. Gonzalez-Peralta<sup>24</sup>, Udeme Ekong<sup>25</sup>, Jane Hartley<sup>26</sup>, Noemie Laverdure<sup>27</sup>, Nadia Ovchinsky<sup>28</sup> and Richard J. Thompson<sup>29</sup>, (1)Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, (2)Hotel Dieu De France Saint Joseph University Hospital, Beirut, Lebanon, (3)Hospital Sirio Libanes, Sao Paulo, Brazil, (4)Nois De Mexico SA De CV, Jalisco, Mexico, (5)Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw Poland, (6)Cardioinfantil Foundation - Lacardio, Bogota, Colombia, (7)Ospedale Pediatrico Bambino Gesu Irccs, Lazio, Italy, (8)University of Texas Southwestern Medical Center, Dallas, Texas, (9)Pediatrics, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, (10)Pediatric Hepatology, Uclouvian, Cliniques Universitaires St Luc, Brussels, Belgium, (11)Hospital Italiano De Buenos Aires, Buenos Aires, Argentina, (12)Pediatric Gastroenterology and Hepatology, Hannover Medical School, Hannover, Germany, (13)Paediatric Hepatology, Gastroenterology and Transplantation, Hospital Papa Giovanni XXIII, Bergamo, Italy, (14)Medical University of South Carolina, Charleston, South Carolina, (15)HÃ,pital Des Enfants - CHU Toulouse, Toulouse, France, (16)Koc University School of Medicine, Istanbul, Turkey, (17)Children's Hospital Los Angeles, Los Angeles, California, (18)Pediatrics, University of Alberta, Alberta Canada, (19)University of Texas Health Science Center at San Antonio, San Antonio, Texas, (20)Kk Women's and Children's Hospital, Singapore, (21)Medical University of Vienna, Vienna, Austria, (22)Mirum Pharmaceuticals, Inc, Foster City, California, (23)Cleveland Clinic Children's, Cleveland, Ohio, (24)Pediatric Gastroenterology, Hepatology, and Liver Transplant, Adventhealth for Children and Adventhealth Transplant Institute, Orlando, Florida, (25)Medstar Georgetown Transplant Institute, Medstar Georgetown University Hospital, Washington DC, (26)Birmingham Women and Children's Hospital, Birmingham, United Kingdom, (27)Pediatric Hepato Gastroenterology and Nutrition Unit, Hopital Femme Mere Enfant, Hospices Civils De Lyon, Lyon, France, (28)Children's Hospital at Montefiore, Bronx, New York, (29)Institute of Liver Studies, King's College London, London, United Kingdom

**Background:** Progressive familial intrahepatic cholestasis (PFIC) is a group of autosomal recessive genetic disorders resulting in disrupted bile composition, cholestasis, and pruritus. The most prevalent PFIC types are deficiencies of bile salt export pump (BSEP), familial intrahepatic cholestasis-associated protein 1 (FIC1) and multi-drug resistant 3 protein (MDR3). Other types include tight junction protein 2 (TJP2) or myosin VB (MYO5B) deficiencies. Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter inhibitor (IBATI) which interrupts the enterohepatic circulation and reduces bile acids returning to the liver. Children with BSEP deficiency, treated with MRX 266 Åµg/kg once to twice daily in the Phase 2 INDIGO study, with a serum bile acid (sBA) response showed improved pruritus, growth, and 5-year transplant-free survival. Here, we evaluated MRX efficacy and safety in a Phase 3 placebo-controlled study at higher doses open to participants with all PFIC types with pruritus. **Methods:** A 26-week multicenter, randomized, double-blind, parallel-group, placebo-controlled study was conducted in children with PFIC aged 1-18 years. Eligible participants had moderate to severe pruritus and elevated sBA levels. Patients were randomized 1:1 to receive either placebo or MRX 570 Åµg/kg twice daily. The primary and first secondary efficacy endpoints were the mean change from Baseline to Week 26 in pruritus and sBA, respectively, in participants with non-truncating (nt) BSEP deficiency (primary cohort). These were repeated in the population of all PFIC types. A step-down hierarchical approach was used for all endpoints. Additional analyses included safety, quality of life, and exploratory endpoints. **Results:** The intent-to-treat (ITT) population (all randomized) included 93 participants. Biallelic mutations included: 45 BSEP (36-nt, of which 31 were in the primary cohort, and 9 truncated), 17 FIC1, 9 MDR3, 8 TJP2, 4 MYO5B. Additionally, there were 8 PFIC participants with variants not found, and 2 with heterozygous mutations. Overall, 8 participants had previous surgery (Kasai or biliary diversion). Topline results will be available for the presentation as the trial is still ongoing at the time of abstract submission. **Conclusion:** This trial is the largest interventional study conducted in this rare genetic disease. This study incorporates five PFIC types, some of which have not previously been studied in a clinical trial of an IBATI and will be presented for the first time.

Disclosures:

Alexander Miethke - Mirum Pharma: Grant/Research Support;

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## SERUM Z POLYMER IS A BIOMARKER FOR INCREASED LIVER FIBROSIS IN ADULTS WITH ALPHA 1 ANTITRYPSIN DEFICIENCY

*Anandini Suri<sup>1</sup>, Zidong Zhang<sup>2</sup>, Keith Burling<sup>3</sup>, Nina Heyer-Chauhan<sup>4</sup>, David A. Lomas<sup>5</sup>, Brent A Tetri<sup>2</sup>, Rohit Loomba<sup>6</sup>, David A. Brenner<sup>7</sup>, Andrew Wilson<sup>8</sup> and Jeffrey H. Teckman<sup>9</sup>, (1)Pediatrics, Division of Pediatric Gastroenterology, Saint Louis University, SSM Health Cardinal Glennon Children's Hospital, (2)Saint Louis University, (3)Cambridge University Hospitals NHS Foundation Trust, (4)UCL Respiratory, Division of Medicine,, University College London, (5)UCL Respiratory, Division of Medicine, University College London, London, UK, (6)University of California, San Diego, (7)Department of Medicine, University of California San Diego, La Jolla, CA, 92093, USA, (8)Boston University, (9)Pediatrics, Division of Pediatric Gastroenterology, Saint Louis University*

**Background:** Homozygous ZZ Alpha 1 antitrypsin deficiency (AATD) liver disease causes cirrhosis in a subgroup of individuals. Predictors and biomarkers of severe disease are being identified. Accumulation of mutant Z protein in polymerized conformation in liver incites injury. Small amounts of protein polymer detectable in serum are of unknown significance. Hypothesis: Increased circulating Z polymer levels are associated with advanced disease in adults with AATD. **Objective:** Use data from a cohort of AATD ZZ patients enrolled at 3 US sites to examine circulating Z polymer levels as a biomarker for disease severity. **Methods:** Since 2014, AATD individuals >18 years were enrolled at 3 US sites. Demographic, history, physical exam, laboratory data were collected at enrollment and follow-up visits. Enrollment liver evaluations were performed, including liver biopsy, unless the previous biopsy confirmed cirrhosis. Z protein polymer level determined using 2C1 antibody in Meso Scale Discovery (MSD) ELISA-based assay. **Results:** Of the 93 subjects enrolled, 55 not on protein replacement had sufficient data for analysis. Higher circulating Z polymer levels were associated with increased liver fibrosis on biopsy (10.7  $\hat{A}$ ±6.5  $\hat{A}$ µg/ml, Ishak 0-1 vs 15.1  $\hat{A}$ ±7.4  $\hat{A}$ µg/ml, Ishak >2, p= 0.03), increased portal inflammation (absent to mild 10.6  $\hat{A}$ ± 6.3  $\hat{A}$ µg/ml, vs. moderate to marked 17.0  $\hat{A}$ ±6.7  $\hat{A}$ µg/ml; p= 0.03) and lobular inflammation (no acidophil bodies, 10.6 $\hat{A}$ ± 6.1  $\hat{A}$ µg/ml; vs few acidophil bodies 19.3 $\hat{A}$ ± 7.1  $\hat{A}$ µg/ml; p =. 0.0109). Z polymer levels correlated with AST (AST > 35, increased polymer by 4.2 units; p=0.04) but not ALT levels. Z polymer levels were not associated with increased BMI or steatosis. Regression showed a weak negative association between Z polymer and FEV1 %, ( $\hat{I}^2$ = -0.55; p=0.04). Elastography scores correlated with polymer levels. Z polymer increased by 0.46 units for every unit increase in scores (Pearson's coefficient 0.35, p= 0.04). **Conclusion:** High circulating Z polymer levels are associated with increased fibrosis and inflammation. Association with a reduction in lung function is observed. Levels are independent of changes in BMI in our cohort. This biomarker could have the potential to predict both liver and lung disease activity in AATD. Further study, including scheduled 5-year follow-up biopsy in this cohort, may determine how to incorporate polymer levels into clinical care and study enrollments.

Disclosures:

The following people have nothing to disclose: Anandini Suri

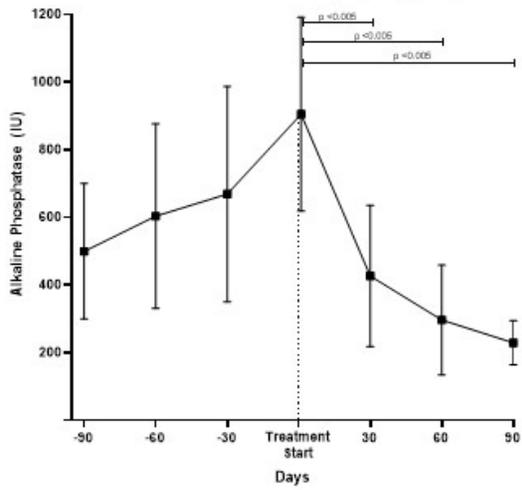
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### FENOFIBRATE IMPROVES CHOLESTASIS IN LIVER ALLOGRAFT ISCHEMIC CHOLANGIOPATHY

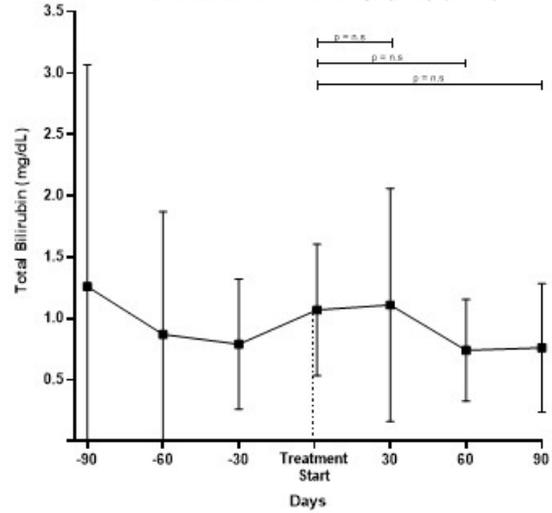
*Michele Barnhill<sup>1</sup>, Rahul Pannala<sup>2</sup>, Motoyo Yano<sup>3</sup>, David M. Chascsa<sup>1</sup>, Amit Mathur<sup>4</sup>, Bashar A. Aqel<sup>1</sup>, Elizabeth J. Carey<sup>1</sup>, Hugo E. Vargas<sup>1</sup> and Channa R. Jayasekera<sup>1</sup>, (1)Liver Transplant Program, Mayo Clinic Arizona, (2)Gastroenterology and Hepatology, Mayo Clinic Arizona, (3)Radiology, Mayo Clinic Arizona, (4)Transplant Surgery, Mayo Clinic Arizona*

**Background:** Ischemic cholangiopathy (IC), a progressive bile duct stricturing syndrome with no definitive treatment besides re-transplantation, occurs in up to 15% of liver allografts, causing allograft failure in 60% of cases. The differential rate of IC drives the 12:1 preference for livers donated after brain death, over more abundant but more IC-prone livers donated after circulatory death (DCD). Any intervention to ameliorate IC could increase DCD organ utilization, and reduce waitlist morbidity and mortality. Cholestasis leading to increased bile acid (BA) concentration and activity is postulated to be a reason why IC progresses even after ischemia resolves at transplantation. Peroxisome proliferator-activated receptor (PPAR) alpha agonists, such as the generic medication fenofibrate (costing <\$25/month), potentially down-regulate BA synthesis and promote BA excretion, and are safe and superior to the standard of care in some cholestatic diseases. We investigated whether fenofibrate could improve cholestasis--a proxy for biliary inflammation--in recipients of DCD allografts who have cholangiographically-confirmed IC. **Methods:** From February-May 2022, we treated 10 sequential LT recipients with IC who were undergoing endoscopic retrograde cholangiography (ERC) treatment, with 90 days of once-daily, maximum dose oral fenofibrate. Medication tolerance and liver and kidney biochemistries were monitored. Liver and kidney biochemistries in the 90 days prior to treatment served as an internal control. All patients receive the standard of care, including ERC, during fenofibrate treatment. **Results:** All patients were DCD recipients with mean warm ischemia time 24.6 minutes (SD 4.9) and mean cold ischemia time 6.2 hours (SD 1.3). IC was diagnosed by ERC at a mean 195 days (SD 177) after LT. Fenofibrate was started at a mean 289 (43-645) days after LT. Mean ALP was 499 IU (SD 261) 90 days prior to treatment start and 905 IU (SD 401) at start of treatment, implying progressive cholestatic injury before fenofibrate initiation. After 90 days of fenofibrate, mean ALP improved to 229 IU (SD 85), representing a 74.6% reduction from baseline. ALP improvement was statistically significant at days 30, 60, and 90 ( $p < 0.005$ ). ALP improvement was more pronounced in those who underwent ERC during treatment. The more aggressive multifocal progressive and confluence-dominant IC subtypes demonstrated better responses. Fenofibrate was stopped in one patient at 60 days due to worsening jaundice. One patient reported myalgia with normal creatinine kinase, but completed treatment. **Conclusion:** This proof-of-concept study is the first demonstration of a potential pharmacologic intervention to improve cholestasis in progressive IC after LT. Further studies are required to validate the role of PPAR agonists in IC, including their use as prophylactic therapy, and their impact on ERC utilization and re-transplantation rates.

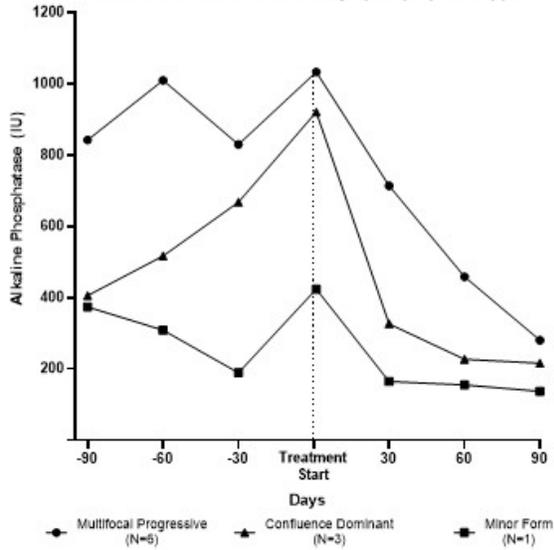
(a) Alkaline Phosphatase Trend During Fenofibrate Therapy in Patients with DCD Cholangiopathy (N=10)



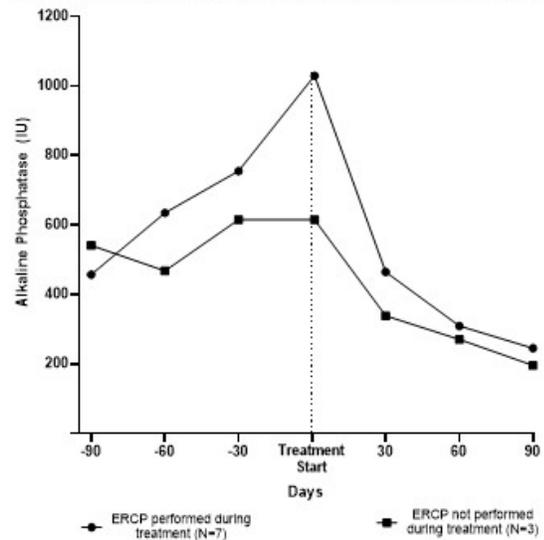
(b) Bilirubin Trend During Fenofibrate Therapy in Patients with DCD Cholangiopathy (N=10)



(c) Alkaline Phosphatase Trend During Fenofibrate Therapy in Patients with DCD Cholangiopathy by Sub-type



(d) Alkaline Phosphatase Trend During Fenofibrate Therapy in Patients with DCD Cholangiopathy by ERCP need During Treatment



Disclosures:

The following people have nothing to disclose: Channa R. Jayasekera

## ODEVIXIBAT TREATMENT IN RESPONSIVE PATIENTS WITH BILE SALT EXPORT PUMP DEFICIENCY RESTORES BILIARY BILE ACID SECRETION, AS INDICATED BY SERUM BILE ACID COMPOSITION

Mark Nomden<sup>1</sup>, Henkjan J. Verkade<sup>2</sup>, Folkert Kuipers<sup>2</sup>, Qifeng Yu<sup>3</sup>, Jan P. Mattsson<sup>3</sup>, Erik Lindström<sup>3</sup> and Velichka Valcheva<sup>3</sup>, (1)Division of Pediatric Surgery, Department of Surgery, University Medical Center Groningen, (2)Department of Pediatrics, University of Groningen, Beatrix Children's Hospital/University Medical Centre Groningen, (3)Albireo Pharma, Inc.

**Background:** Odevixibat blocks the ileal bile acid transporter and thereby reduces bile acid (BA) absorption. In the 24-week PEDFIC 1 study, odevixibat was evaluated in children with progressive familial intrahepatic cholestasis (PFIC). Serum BAs (sBAs) comprise a mixture of primary and secondary species in conjugated or unconjugated form. Here, we evaluated the sBA composition in patients from PEDFIC 1 with bile salt export pump (BSEP) deficiency (ie, PFIC2) categorized by sBA response (R) or nonresponse (NR). **Methods:** PEDFIC 1 (NCT03566238) eligibility criteria included elevated sBAs at screening; concomitant ursodeoxycholic acid was allowed if the patient was on a stable dose. Two categories of patients with PFIC2 randomized to odevixibat were assessed in this analysis: sBA Rs (sBAs reduced  $\geq 70\%$  from baseline or levels reaching  $\leq 70 \mu\text{mol/L}$  at the end of treatment) and sBA NRs (did not meet sBA R criteria). The following sBAs were measured by liquid chromatography-tandem mass spectrometry in Rs and NRs at week 24: unconjugated BAs, cholate (CA), chenodeoxycholate (CDCA), ursodeoxycholate (UDCA), deoxycholate (DCA), lithocholate (LCA), and total glycine- and taurine-conjugated BAs. Composition was expressed as a percentage of total sBAs, excluding UDCA. **Results:** Thirty odevixibat-treated patients with PFIC2 (15 R; 15 NR) were included in the analysis. As expected, unconjugated BAs made up a small percentage of the total BA pool. Nevertheless, the percentage of unconjugated sBAs was  $\sim 70$ -fold higher in Rs vs NRs ( $P < 0.001$ ; **Table**). The secondary sBAs DCA and LCA were virtually absent in both Rs and NRs ( $P = 0.19$ ; **Table**). Hence, the higher percentage of unconjugated BAs in Rs was mainly due to the unconjugated primary BAs CA and CDCA. Additionally, Rs had a 66% lower CA/CDCA ratio and a  $>2$ -fold higher glycine-conjugated/taurine-conjugated BA ratio compared with NRs ( $P = 0.002$  and  $P < 0.001$ , respectively; **Table**). **Conclusion:** sBA responsiveness to odevixibat treatment in patients with BSEP deficiency was not only defined by a decrease in sBA concentration, but also by alterations in sBA composition. Exclusively in Rs, odevixibat treatment was associated with a strongly increased relative contribution of unconjugated BAs. Since unconjugated BAs originate from deconjugation of biliary BAs by the intestinal microbiome, our data indicate that odevixibat restored biliary BA secretion in treatment-responsive patients with BSEP deficiency.

**Table. Serum Bile Acid Composition After 24 Weeks of Odevixibat Treatment in Patients With BSEP Deficiency (n=30) Who Were Classified as Responders or Nonresponders**

Variable	Responder	Nonresponder	P Value
<b>% (range)</b>			
Unconjugated sBA	3.7 (0.06–28.4)	0.05 (0.03–0.3)	<b>&lt;0.001</b>
Secondary sBA	0 (0–26.9)	0.1 (0.04–0.6)	0.19
CA sBA <sup>a</sup>	37.9 (21.1–75.5)	64.4 (47.4–79.5)	<b>&lt;0.001</b>
CDCA sBA <sup>a</sup>	61.2 (24.4–78.9)	35.1 (20.4–52.6)	<b>&lt;0.001</b>
Glycine conjugated <sup>b</sup>	80.3 (64.6–90.7)	74.6 (61.0–80.8)	0.19
Taurine conjugated <sup>b</sup>	13.5 (6.7–33.5)	25.4 (18.9–39.0)	<b>&lt;0.001</b>
<b>Ratio (range)</b>			
CA/CDCA <sup>a</sup>	0.6 (0.3–3.1)	1.8 (0.9–3.9)	<b>0.002</b>
Glycine/taurine conjugation <sup>b</sup>	6.0 (2.0–12.7)	2.9 (1.6–4.3)	<b>&lt;0.001</b>

Median percentages and ratios are shown. Percentages of unconjugated sBAs; secondary sBAs; and CA, CDCA, and glycine- and taurine-conjugated sBAs are calculated from the total concentration of sBAs from which the UDCA concentration is subtracted. <sup>a</sup>Includes both conjugated and unconjugated sBAs;

<sup>b</sup>Includes both primary and secondary sBAs. BSEP, bile salt export pump; CA, cholate; CDCA, chenodeoxycholate; sBA, serum bile acid; UDCA, ursodeoxycholate.

### Disclosures:

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## EFFICACY AND SAFETY OF ODEVIXIBAT IN PATIENTS WITH ALAGILLE SYNDROME: TOP-LINE RESULTS FROM ASSERT, A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY

*Nadia Ovchinsky<sup>1</sup>, Madeleine Aumar<sup>2</sup>, Alastair Baker<sup>3</sup>, Ulrich Baumann<sup>4</sup>, Philip Bufler<sup>5</sup>, Mara Cananzi<sup>6</sup>, Piotr Czubkowski<sup>7</sup>, A-zlem Durmaz<sup>8</sup>, Ryan Fischer<sup>9</sup>, Giuseppe Indolfi<sup>10</sup>, Wikrom Karnsakul<sup>11</sup>, Florence Lacaille<sup>12</sup>, Way S. Lee<sup>13</sup>, Giuseppe Maggiore<sup>14</sup>, Philip Rosenthal<sup>15</sup>, Mathias Ruiz<sup>16</sup>, Étienne Sokal<sup>17</sup>, Ekkehard Sturm<sup>18</sup>, Wendy Van Der Woerd<sup>19</sup>, Henkjan J. Verkade<sup>20</sup>, Andrew Wehrman<sup>21</sup>, Christine Clemson<sup>22</sup>, Qifeng Yu<sup>22</sup>, Quanhong Ni<sup>22</sup>, Jessica Ruvido<sup>22</sup>, Susan Manganaro<sup>22</sup> and Jan P. Mattsson<sup>22</sup>.* (1)Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Montefiore - Albert Einstein College of Medicine, (2)Pediatric Gastroenterology, Hepatology, and Nutrition, Univ Lille, CHU Lille, (3)Pediatric Liver Center, King's College Hospital, (4)Pediatric Gastroenterology and Hepatology, Hannover Medical School, Hannover, Germany, (5)Department of Pediatric Gastroenterology, Nephrology and Metabolic Diseases, Charité Universitätsmedizin Berlin, (6)Department of Children's and Women's Health, University Hospital of Padova, (7)Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics, The Children's Memorial Health Institute, (8)Istanbul University, (9)Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Children's Mercy Hospital, (10)Pediatric and Liver Unit, Meyer Children's University Hospital of Florence, (11)Division of Pediatric Gastroenterology, Nutrition, and Hepatology, Department of Pediatrics, Johns Hopkins University School of Medicine, (12)Pediatric Gastroenterology-Hepatology-Nutrition Unit, Hôpital Universitaire Necker-Enfants Malades, (13)Department of Pediatrics, University of Malaya, (14)Hepatology, Gastroenterology, Nutrition, Digestive Endoscopy, and Liver Transplantation Unit, Bambino Gesù Children's Hospital Ircss, (15)Department of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition, University of California San Francisco, (16)Department of Pediatric Gastroenterology, Hepatology, and Nutrition, Hospices Civils De Lyon, Hôpital Femme Mère Enfant, (17)Université Catholique De Louvain, Cliniques St Luc, (18)Pediatric Gastroenterology and Hepatology, University Children's Hospital Tübingen, (19)Department of Pediatric Gastroenterology, Wilhelmina Children's Hospital, University Medical Center Utrecht, (20)Department of Pediatrics, Beatrix Children's Hospital/University Medical Center Groningen, (21)Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, (22)Albireo Pharma, Inc.

**Background:** Alagille syndrome (ALGS) is a rare, multisystem disorder caused by mutations in *JAG1* or *NOTCH2* that often manifests as cholestasis with elevated serum bile acids in infancy. Clinical features that may be associated with cholestasis include impaired growth, severe intractable pruritus, disfiguring xanthomas, and progressive liver disease limiting survival with native liver. Odevixibat is a potent, selective inhibitor of the ileal bile acid transporter, a regulator of the enterohepatic circulation of bile acids. Here, we present top-line results from the ASSERT study, which evaluated the efficacy and safety of odevixibat in patients with ALGS. **Methods:** This double-blind, randomized, placebo-controlled, multicenter, phase 3 trial (NCT04674761) was conducted from March 2021 to September 2022. Patients of any age with a genetically confirmed diagnosis of ALGS, history of significant pruritus, and elevated serum bile acids were eligible. Patients were randomized 2:1 to once-daily oral odevixibat 120 mg/kg or placebo, respectively, and received treatment for 24 weeks. The primary efficacy endpoint was change from baseline to month 6 in observer-reported (ObsRO) scratching score. A key secondary endpoint was change in serum bile acid levels from baseline to the average of values at weeks 20 and 24. Safety endpoints included incidence of treatment-emergent adverse events (TEAEs). **Results:** Overall, 52 patients were enrolled (mean age, 6.3 years [range, 0.5-15.5 years]; 48% female). The majority were white (83%), non-Hispanic (85%), and enrolled at sites in the European Union (69%). Patients with *JAG1* and *NOTCH2* mutations were included. At baseline, most patients were taking a concomitant antipruritic medication (98%), and the mean ObsRO pruritus score at baseline was 2.9 out of 4 (SD 0.6). Mean height and weight Z scores at baseline were -1.7 (SD 1.5) and -1.7 (SD 1.2), respectively. Mean baseline values for serum bile acids, aminotransferases, gamma-glutamyl transferase, total and direct bilirubin, and cholesterol were elevated in these patients (**Table**). **Conclusion:** ALGS is a disease with high unmet needs, and more noninvasive treatment options that address the potentially serious signs and symptoms of ALGS would be valuable. Top-line, unblinded efficacy and safety data from the ASSERT study, including the effects of odevixibat versus placebo on pruritus, serum bile acids, and TEAEs will be presented.

**Table. Mean Baseline Laboratory Parameters From Patients in ASSERT**

<b>Parameter</b>	<b>Mean (SD)</b>
<b>Serum bile acids, <math>\mu\text{mol/L}</math></b>	240 (116)
<b>Serum ALT, U/L</b>	174 (84)
<b>Serum AST, U/L</b>	167 (83)
<b>Serum GGT, U/L</b>	422 (271)
<b>Total bilirubin, mg/dL</b>	3.2 (2.8)
<b>Direct bilirubin, mg/dL</b>	2.9 (2.4)
<b>Cholesterol, mg/dL</b>	325 (123)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

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**EFRUXIFERMIN (EFX) IN NONALCOHOLIC STEATOHEPATITIS WITH FIBROSIS: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2b TRIAL (HARMONY)**

*Stephen A Harrison<sup>1</sup>, Juan P. Frias<sup>2</sup>, Guy W Neff<sup>3</sup>, Gary A. Abrams<sup>4</sup>, Kathryn Jean Lucas<sup>5</sup>, William Sanchez<sup>6</sup>, Sudhanshu Gogia<sup>7</sup>, Muhammad Y Sheikh<sup>8</sup>, Cynthia Behling<sup>9</sup>, Pierre Bedossa<sup>10</sup>, Lan Shao<sup>11</sup>, Erica Fong<sup>12</sup>, Brittany De Temple<sup>12</sup>, Reshma Shringarpure<sup>12,13</sup>, Erik J Tillman<sup>12</sup>, Timothy P Rolph<sup>12</sup>, Andrew Cheng<sup>12</sup> and Kitty Yale<sup>12</sup>, (1)Pinnacle Clinical Research Center, (2)National Research Institute, (3)Covenant Metabolic Specialists, LLC, (4)Greenville Health System, Greenville Medical Hospital, (5)Lucas Research, (6)Floridian Clinical Resrach, (7)Texas Digestive Disease Institute, (8)Fresno Clinical Research Center, (9)Department of Pathology, Sharp Memorial Hospital, (10)Liverpat, (11)Statitics, Labcorp, (12)Akeru Therapeutics, (13)Clinical Research, Akeru Therapeutics*

**Background:** In a Ph2a study<sup>1</sup>, efruxifermin (EFX), a long-acting FGF21 analog, significantly reduced liver fat content (LFC) in patients with F1-F3 NASH fibrosis as well as improving noninvasive markers of liver inflammation / injury / fibrosis, and glucose and lipid metabolism. Although not powered statistically, important changes in liver histology were observed in these patients and in a second cohort of patients with compensated cirrhosis<sup>2</sup>. To further evaluate these findings, a placebo-controlled, Ph 2b study (HARMONY) was conducted in NASH patients with F2/3 fibrosis. **Methods:** Patients (N=128) with NASH and F2 or F3 fibrosis were randomized 1:1:1 to receive once-weekly EFX 28mg, EFX 50mg, or placebo for 96 weeks, with a primary endpoint analysis at 24 weeks. The primary objective was to evaluate the proportion of patients with fibrosis improvement by  $\geq 1$  stage and no worsening of NASH at week 24. Secondary and exploratory objectives evaluated the effects of EFX on NASH resolution; a composite endpoint of NASH resolution and fibrosis improvement, as well as changes in LFC, markers of liver injury, fibrosis, glycemic control and lipid metabolism; and safety and tolerability of EFX. **Results:** Patients (62% female; mean age 55 yrs; mean BMI 38.0 kg/m<sup>2</sup>) were randomized to 28mg EFX (n= 42), 50mg EFX (n=43), or placebo (n=43). Approximately 70% had type 2 diabetes and 66% had F3 fibrosis. A significantly higher proportion of patients treated with 50mg (41.2%; p=0.036) and 28mg (39.5%; p=0.025) compared to placebo (19.5%) achieved the primary endpoint. A significantly higher proportion of EFX-treated patients compared to placebo achieved resolution of NASH and no worsening of fibrosis, as well as a composite endpoint of fibrosis improvement and NASH resolution (Table). EFX also significantly improved LFC as well as serum markers of liver injury, fibrosis, and glucose and lipid metabolism. The most frequent drug-related adverse events (AEs) were mild /moderate gastrointestinal (GI) events of diarrhea and nausea. Five patients discontinued due to AEs (n=2, EFX 28mg, both drug-related; n=3, EFX 50mg, 2 drug-related). **Conclusion:** EFX significantly improved liver histology, LFC, and noninvasive markers of liver injury, fibrosis, and glucose and lipid metabolism in patients with F2/F3 fibrosis due to NASH. Both doses of EFX were generally well-tolerated, with mild-to-moderate GI events the most frequent AEs, and few AE-related study discontinuations.

**Table 1: Effects of efruxifermin treatment for 24 weeks in NASH with F2-F3 fibrosis**

<b>A. Histologic Assessments</b>			
<b>Proportion of patients, n (%)</b>	<b>Placebo n = 41</b>	<b>EFX 28 mg n = 38</b>	<b>EFX 50 mg n = 34</b>
Fibrosis improvement by $\geq 1$ stage and no worsening of NASH	8 (19.5)	15 (39.5) *	14 (41.2) *
NASH resolution without worsening of fibrosis	6 (14.6)	18 (47.4) **	26 (76.5) ***
Fibrosis improvement by $\geq 1$ stage and resolution of NASH	2 (4.9)	11 (28.9) **	14 (41.2) ***
<b>Change in Liver Fat Content and Markers of Liver Injury and Fibrosis</b>			
<b>LS Mean Change from baseline</b>	<b>Placebo (N = 40–42)</b>	<b>EFX 28 mg (N = 35–38)</b>	<b>EFX 50 mg (N=34–36)</b>
Relative (%) change in LFC	-6	-52 ***	-64 ***
Change in ALT (U/L)	-3.0	-22.4***	-32.9***
Change in AST (U/L)	-2.0	-21.0***	-28.2***
Change in Pro-C3 ( $\mu\text{g/L}$ )	0.1	-5.1 ***	-5.2 ***
Change in Enhanced Liver fibrosis (ELF) Score	0.1	-0.6 ***	-0.7 ***
Change in liver stiffness by transient elastography, kPa	-0.7	-2.6 <sup>†</sup>	-4.3 **
<b>Summary of Key Metabolic Markers</b>			
<b>LS Mean Change from baseline</b>	<b>Placebo (N=42)</b>	<b>EFX 28 mg (N=35–37)</b>	<b>EFX 50 mg (N=35–36)</b>
HbA1c (% absolute)	-0.0	-0.3 <sup>†</sup>	-0.4 *
Triglycerides (%)	+9	-25 ***	-29 ***
HDL Cholesterol (%)	-2	+24 ***	+30 ***
Non-HDL Cholesterol (%)	+8	-13 ***	-13 ***
LDL Cholesterol (%)	+9	-8 **	-8 **
Body Weight (kg)	-0.6	-0.2	-2.9 <sup>††</sup>
<b>Incidence of study-drug related treatment emergent adverse events (<math>\geq 15\%</math> in any group)</b>			
<b>Preferred Term</b>	<b>Placebo N=43</b>	<b>EFX 28 mg N=40</b>	<b>EFX 50 mg N=43</b>
Patients with any study drug-related TEAEs, n (%)	21 (48.8)	30 (75.0)	35 (81.4)
Diarrhea, n (%)	6 (14.0)	14 (35.0)	14 (32.6)
Nausea, n (%)	5 (11.6)	10 (25.0)	14 (32.6)
Increased appetite, n (%)	2 (4.7)	7 (17.5)	10 (23.3)
Frequent bowel movements, n (%)	1 (2.3)	8 (20.0)	0 (0.0)
Injection site erythema, n (%)	5 (11.6)	6 (15.0)	7 (16.3)
Injection site bruising, n (%)	1 (2.3)	6 (15.0)	3 (7.0)

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001 vs placebo; <sup>†</sup>p<0.05, <sup>††</sup>p<0.01 vs baseline; Cochran-Mantel-Haenszel test [histology endpoints]; ANCOVA [Fat fraction and liver stiffness]; MMRM [all other endpoints]

<sup>1</sup>Harrison 2021, Nat Med; <sup>2</sup>Harrison 2022 JHEP Rep

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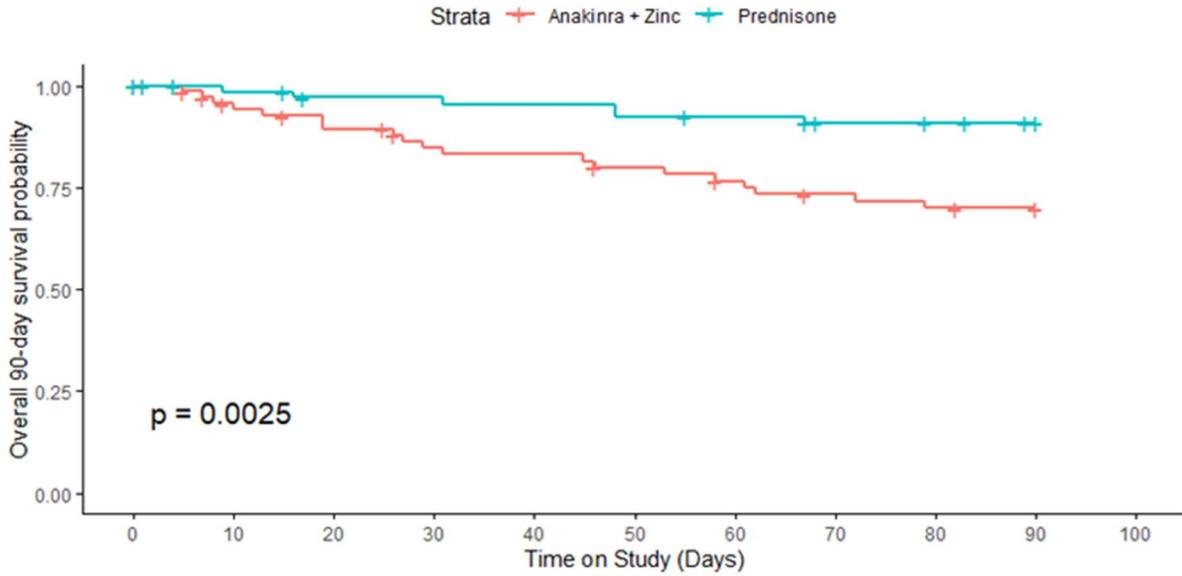
Reshma Shringarpure - Akero: Employment; Akero: Stock Shareholder;

**ANAKINRA PLUS ZINC VERSUS PREDNISONE FOR TREATMENT OF SEVERE ALCOHOL-ASSOCIATED HEPATITIS: A RANDOMIZED CONTROLLED TRIAL**

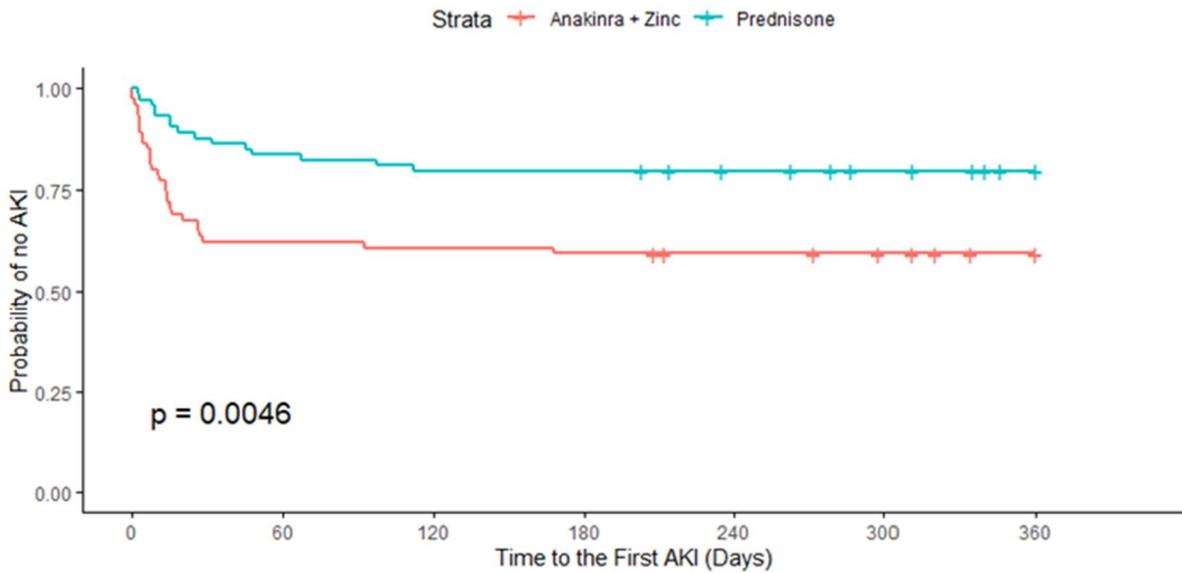
*Samer Gawrieh<sup>1</sup>, Srinivasan Dasarathy<sup>2</sup>, Wanzhu Tu<sup>3</sup>, Patrick S. Kamath<sup>4</sup>, Naga P. Chalasani<sup>1</sup>, Craig J. McClain<sup>5</sup>, Ramon Bataller<sup>6</sup>, Gyongyi Szabo<sup>7</sup>, Qing Tang<sup>3</sup>, Svetlana Radaeva<sup>8</sup>, Bruce Barton<sup>9</sup>, Laura Nagy<sup>10</sup>, Vijay Shah<sup>11</sup>, Arun J Sanyal<sup>12</sup>, Mack C Mitchell<sup>13</sup> and The AlcHepNet Investigators, (1)Gastroenterology and Hepatology, Indiana University, (2)Inflammation and Immunity, Cleveland Clinic Foundation, (3)Department of Biostatistics, Indiana University School of Medicine, (4)Division of Gastroenterology and Hepatology, Mayo Clinic, (5)University of Louisville, (6)University of Pittsburgh Medical Center, (7)Gastroenterology, Beth Israel Deaconess Medical Center, (8)National Institute on Alcohol Abuse and Alcoholism, Rockville, Maryland, (9)University of Massachusetts Medical School, (10)Cleveland Clinic, (11)Division of Gastroenterology and Hepatology, Mayo Clinic Rochester, (12)Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, (13)Medicine, UT Southwestern*

**Background:** Severe alcohol-associated hepatitis (SAH) has a 90-day mortality up to 30%. Treatment with corticosteroids improves 30, but not 90-day survival. The IL-1 receptor antagonist anakinra demonstrated efficacy signals in a phase 2 study, but there are no large trials comparing anakinra with standard of care. **Methods:** The NIAAA-funded Alcoholic Hepatitis Network conducted a double-blind randomized placebo-controlled trial at 8 sites in the US between 7/2020 and 8/2022 (NCT04072822). Adults with SAH and MELD 20-35 were randomized to receive either anakinra 100 mg subcutaneously daily for 14 days plus ZnSO<sub>4</sub> 220 mg orally daily for 90 days (A+Z), or prednisone 40 mg orally daily for 30 days (Pred). Matching placebos for Pred (in A+Z) or anakinra & ZnSO<sub>4</sub> (in Pred) were also administered. The primary endpoint was overall survival at 90 days; the two treatment arms were compared with log-rank test. Pred (or matching placebo in the A+Z arm) was stopped if day 7 Lille score was >0.45. All study drugs were stopped for persistent infection or  $\geq 5$  points increase in MELD. **Results:** 74 participants were randomized to A+Z vs 73 to Pred. Mean baseline MELD (25.0 $\pm$ 3.6), age (44.7 $\pm$ 9.9 years), BMI (29.6 $\pm$ 7.0 kg/m<sup>2</sup>), creatinine (0.8 $\pm$ 0.3 mg/dL); and %Whites (82.3%) were similar between the two arms. The study was stopped early after a planned interim analysis showed a significant difference in 90-day overall survival (69.9% in A+Z vs 91% in Pred,  $p=0.0025$ , Fig 1A). 4 participants in A+Z underwent liver transplant vs. 1 in Pred. Transplant-free survival was lower in A+Z vs Pred ( $p=0.0007$ ). Only 11 participants (15%) in Pred triggered the Lille stopping rule; all 11 survived 90 days. 136 serious adverse events in 49 (66.2%) participants occurred in A+Z vs 111 in 41 (56.2%) participants in Pred ( $p=0.14$ ). 30 (41%) participants in A+Z developed acute kidney injury (AKI) vs 15 (21%) in Pred ( $p=0.0046$ , Fig 1B). Most AKIs occurred in the first 30 days of study. 15 (79%) participants who died in A+Z had AKI. 23 (31%) participants in A+Z experienced infections (3 COVID-19) vs 20 (27%) in Pred (5 COVID-19) ( $p=0.6$ ). Only 1 non-fatal fungal infection (in A+Z) occurred during the study. **Conclusion:** Participants with SAH treated with A+Z had a significantly lower 90-day survival and higher incidence of AKI than those treated with Pred. The 90-day survival rate was higher in both the A+Z and Pred groups than reported in previous treatment trials of SAH.

### A. Overall 90-day Survival



### B. Time to the first AKI



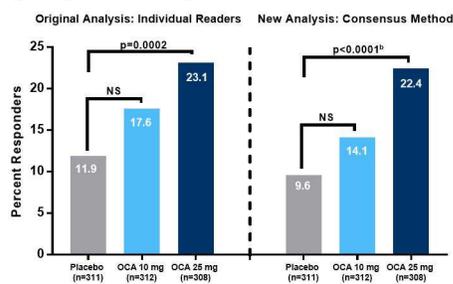
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## TOPLINE RESULTS FROM A NEW ANALYSIS OF THE REGENERATE TRIAL OF OBETICHOLIC ACID FOR THE TREATMENT OF NONALCOHOLIC STEATOHEPATITIS

Arun J Sanyal<sup>1</sup>, Rohit Loomba<sup>2</sup>, Quentin M. Anstee<sup>3</sup>, Vlad Ratziu<sup>4</sup>, Kris V Kowdley<sup>5</sup>, Mary E Rinella<sup>6</sup>, Muhammad Y Sheikh<sup>7</sup>, James F Trotter<sup>8</sup>, Whitfield L Knapple<sup>9</sup>, Eric J. Lawitz<sup>10</sup>, Manal F Abdelmalek<sup>11</sup>, Philip N Newsome<sup>12,13,14,15</sup>, Bettina E Hansen<sup>16</sup>, Philippe Mathurin<sup>17</sup>, Jean-Francois Dufour<sup>18</sup>, M Michelle Berrey<sup>19</sup>, Steven J. Shiff<sup>19</sup>, Sangeeta Sawhney<sup>19</sup>, Thomas Capozza<sup>19</sup>, Rina Leyva<sup>19</sup>, Stephen A Harrison<sup>20</sup> and Zobair M. Younossi<sup>21</sup>, (1)Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, (2)University of California San Diego, (3)Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK, (4)Sorbonne Université, Assistance Publique-Hôpitaux De Paris, Hôpital Pitié-Salpêtrière, Institute of Cardiometabolism and Nutrition (ICAN), (5)Liver Institute Northwest, (6)Feinberg School of Medicine, Northwestern University, Chicago, IL, USA, (7)Fresno Clinical Research Center, (8)Baylor Health, Liver Consultants of Texas, (9)Arkansas Gastroenterology, (10)Texas Liver Institute, University of Texas Health San Antonio, (11)Division of Gastroenterology and Hepatology, Mayo Clinic, (12)Centre for Liver & Gastrointestinal Research, Institute of Immunology and Immunotherapy, University of Birmingham, (13)University Hospitals Birmingham NHS Foundation Trust, (14)National Institute for Health Research, Birmingham Biomedical Research Centre, (15)University of Birmingham, (16)Angers University Hospital, Angers University, (17)Hepatogastroenterology, CHU Lille, (18)Department of Biomedical Research, University of Bern, (19)Intercept Pharmaceuticals, (20)Pinnacle Clinical Research Center, (21)Beatty Liver and Obesity Research Program, Center for Liver Diseases, Inova Medicine

**Background:** Nonalcoholic steatohepatitis (NASH) is a major cause of liver-related morbidity, mortality, and transplantation in the US. Liver fibrosis is a robust predictor of clinical outcomes in NASH. Obeticholic acid (OCA), a first-in-class farnesoid X receptor agonist, demonstrated efficacy as an antifibrotic agent in the phase 3 REGENERATE trial in NASH (Younossi, Ratziu, et al., *Lancet* 2019). The goal of this investigation was to confirm the original 18-month biopsy single-pathologist analysis with a new 3-pathologist consensus panel analysis and to evaluate safety data from >8000 total patient-years of exposure with ~1000 subjects receiving the study drug for ~4 years in the REGENERATE study. **Methods:** In this multicenter, randomized, double-blind, placebo-controlled, phase 3 study, subjects were randomized 1:1:1 to receive once-daily oral placebo, OCA 10 mg, or OCA 25 mg. This new interim analysis used a consensus approach with a panel of 3 pathologists reading digital slide images to assess liver biopsies as per the NASH Clinical Research Network criteria and US Food and Drug Administration recommendations. Cumulative safety data were evaluated from 2477 subjects who received ~1 dose of study drug. **Results:** In the new analysis of the modified intent-to-treat population (n=931) from REGENERATE, 22.4% of subjects receiving OCA 25 mg achieved ~1 stage improvement of fibrosis with no worsening of NASH at month 18 vs 9.6% of subjects receiving placebo (primary endpoint; **Figure 1**). Treatment-emergent adverse events (TEAEs), serious TEAEs, and deaths were balanced across treatment groups. Pruritus was the most common TEAE. There were more hepatobiliary TEAEs for OCA 25 mg vs placebo. The frequency of adjudicated acute kidney injury events and adjudicated core major adverse cardiovascular events were low and balanced across treatment groups. OCA treatment led to an early, modest increase in low-density lipoprotein, which returned to near baseline by month 12. **Conclusion:** In the ongoing REGENERATE trial, the response rate for OCA 25 mg was double that for placebo, with response defined as ~1 stage improvement in liver fibrosis with no worsening of NASH at 18 months. This consensus analysis by a panel of 3 pathologists independently confirms the original, single-pathologist assessment. The confirmed antifibrotic effect, together with extended exposure within the largest safety database in NASH to date, supports the long-term use of OCA to treat NASH fibrosis.

Figure 1. Primary endpoint of REGENERATE: improvement of fibrosis by ≥1 stage without worsening of NASH\*



Abbreviations: NASH, nonalcoholic steatohepatitis; NS, not statistically significant; OCA, obeticholic acid.  
\*Modified intent-to-treat population (N=931).  
†Nominal and supportive of the original results.

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**EX SITU END ISCHEMIC HYPOTHERMIC OXYGENATED PERFUSION (HOPE) VERSUS STATIC COLD STORAGE PRIOR TO LIVER TRANSPLANTATION - EARLY RESULTS OF THE BRIDGE TO HOPE PIVOTAL MULTICENTER RANDOMIZED CONTROLLED CLINICAL TRIAL ON THE SAFETY AND EFFECTIVENESS OF THE VITASmart LIVER MACHINE PERFUSION SYSTEM**

**(CLINICALTRIALS.GOV: Nct05045794)**

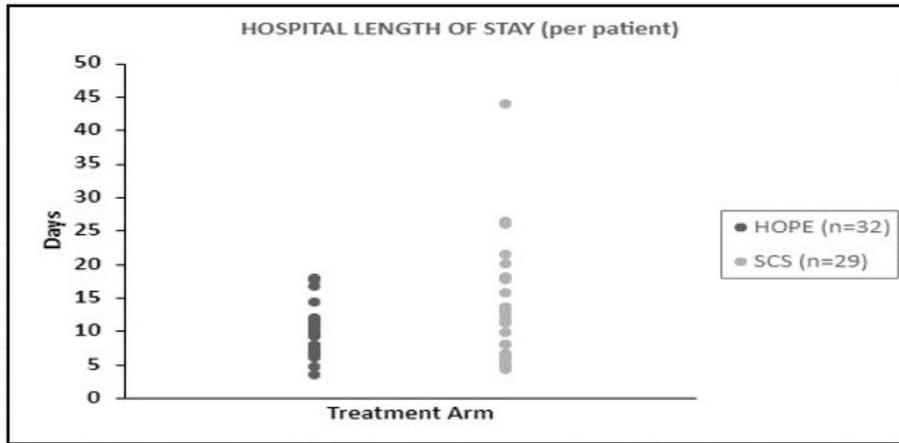
*David J. Reich<sup>1</sup>, Andrea Schlegel<sup>2</sup>, Michael Rizzari<sup>3</sup>, Koji Hashimoto<sup>4</sup>, Sander S. Florman<sup>5</sup>, Michael E. De Vera<sup>6</sup>, David P. Foley<sup>7</sup>, Shennen A Mao<sup>8</sup>, William C Chapman<sup>9</sup>, Garrett Roll<sup>10</sup>, Antonio Pinna<sup>1</sup>, Ashish Saharia<sup>11</sup>, Shaheed Merani<sup>12</sup>, Humberto E Bohorquez<sup>13</sup>, Mohamed Akoa<sup>14</sup>, Chandrashekhar A. Kubal<sup>15</sup> and Sophoclis Alexopoulos<sup>16</sup>, (1)Cleveland Clinic, Weston, FL, (2)Policlinico, Milan, Italy, (3)Henry Ford, Detroit, MI, (4)Cleveland Clinic, Cleveland, OH, (5)Mount Sinai, NY, NY, (6)Loma Linda, Loma Linda, CA, (7)U Wisconsin, Madison, WI, (8)Mayo, Jacksonville, FL, (9)Washington U, St. Louis, MO, (10)UCSF, San Francisco, CA, (11)Methodist, Houston, TX, (12)U Nebraska, Omaha, NE, (13)Ochsner, New Orleans, La, (14)Lahey, Burlington, MA, (15)Indiana U, Indianapolis, in, (16)Vanderbilt, Nashville, TN*

**Background:** Ex-situ end-ischemic hypothermic oxygenated perfusion (HOPE) is a simple technique to improve liver transplant (LT) results and the donor shortage. HOPE after static cold storage (SCS) reduces ischemia reperfusion injury, early allograft dysfunction (EAD), cholangiopathy and other poor outcomes. A pivotal, US multicenter RCT opened in early 2022 to compare HOPE after SCS to HOPE alone for LT using extended criteria DBD and DCD grafts.

**Methods:** Consented adults matched to a higher risk donor liver that the investigator committed to transplant were randomized 1:1 to SCS followed by HOPE at the transplant center or to SCS only. Livers randomized to the HOPE arm were perfused with the VitaSmart machine, through the portal vein only, at <4mm Hg pressure, using actively oxygenated (pO<sub>2</sub>>60 kPa) Belzer machine perfusion solution, for 1.5-5 hr. The primary efficacy endpoint is EAD and the primary safety endpoints are patient and graft survival. Other endpoints include primary non-function (PNF), ischemic cholangiopathy, adverse events, and length of stay (LOS). A centralized, blinded radiologist evaluated cholangiograms for cholangiopathy. Recipients were assessed post-transplantation on days 1-7, 14 and 30, and months 3, 6 and 12 post-LT. Target total enrollment is 244 patients completing transplant. **Results:** The study has reached the 25% enrollment milestone (61 of 244 targeted LTs, at 11 centers), with key outcomes depicted below. There were no device malfunctions or device-related AEs. **Conclusion:** Early results of this first US RCT of end-ischemic portal venous HOPE with VitaSmart for LT of extended criteria donor livers reveal promising outcomes, including device safety, lower risk of EAD and shorter hospital LOS.

### INITIAL TRIAL RESULTS

	HOPE (n=32)	SCS (n=29)
Donor Age (mean years ± SD)	49 ± 15	49 ± 14
DCD (#, %)	6 (19%)	6 (21%)
Recipient Age (mean years ± SD)	56 ± 10	54 ± 12
MELD (mean ± SD)	21 ± 12	18 ± 9
Cold Ischemia Time (mean min ± SD)	282 ± 65	369 ± 143
HOPE Time (mean min ± SD)	123 ± 32	n/a
Total Cold Preservation Time (mean min ± SD)	405 ± 76	369 ± 143
Post-Transplant Follow-Up (mean days ± SD)	88 ± 56	84 ± 56
EAD (#, %)	7 (22%)	10 (35%)
Post-Transplant Hospital LOS (median days)	9.5	11.4
Non-Anastomotic Ischemic Cholangiopathy (#, %)	0	0
PNF (#, %)	0	0
Graft Survival (#, %)	32 (100%)	28 (97%)
Patient Survival (#, %)	32 (100%)	29 (100%)



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David J. Reich; Neha Jakhete

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**PXL065 (DEUTERIUM-STABILIZED R-ENANTIOMER OF PIOGLITAZONE) REDUCES LIVER FAT CONTENT AND IMPROVES LIVER HISTOLOGY WITHOUT PPAR $\gamma$  -MEDIATED SIDE EFFECTS IN PATIENTS WITH NASH: ANALYSIS OF A 36 WEEK PLACEBO-CONTROLLED PHASE 2 TRIAL (DESTINY1)**

*Stephen A Harrison<sup>1</sup>, Carole Thang<sup>2</sup>, Sophie Bozec<sup>2</sup>, SÃ©bastien Bolze<sup>2</sup>, Sheila DeWitt<sup>3</sup>, David E. Moller<sup>2</sup> and Pascale Fouqueray<sup>2</sup>, (1)Pinnacle Clinical Research, (2)Poxel SA, (3)Deuterx*

**Background:** Pioglitazone (Pio) is effective as a NASH therapy and recommended by practice guidelines. However, PPAR $\gamma$ -driven side effects - weight gain and edema - limit its use. Pio is a mixture of 2 enantiomers that rapidly interconvert. PXL065, a new chemical entity (NCE), is the deuterium-stabilized R-enantiomer of Pio which lacks PPAR $\gamma$  activity but retains non-genomic target activities (mitochondrial pyruvate carrier and acyl-CoA synthetase 4) and preclinical efficacy in NASH models. DESTINY1, a Phase 2 study, was designed to validate this concept in noncirrhotic NASH patients. **Methods:** 117 patients ( $\approx 8\%$  liver fat, NAS  $\approx 4$ , F1-F3) were randomized 1:1:1 to receive daily oral doses of PXL065 (7.5mg, 15mg, 22.5mg) or placebo for 36 weeks. The primary endpoint was relative % change in liver fat content (LFC) assessed by MRI-PDFF; secondary/exploratory endpoints included histology from paired liver biopsies, liver enzymes, biomarkers of fibrosis, adiponectin, lipids and glycemic parameters as well as safety-tolerability. The study was not powered for histology analysis. **Results:** All PXL065 groups met the primary endpoint, and up to 40% achieved a relative reduction  $\approx 30\%$  in LFC. Improvements in ALT, biomarkers of fibrogenesis and fibrosis risk scores (Pro-C3, PIIINP, ELF, Fib4, NFS) were observed. On histology, 35%-50% of PXL065 treated subjects achieved  $\approx 1$  stage fibrosis improvement vs. 17% with placebo and 15%-33% achieved NASH resolution and  $\approx 1$  stage fibrosis improvement versus 13% with placebo. Glucose control was improved; placebo-adjusted change in HbA1c reached -0.41% (baseline values 6.07-6.27%) with consistent improvements in insulin, C-peptide and indexes of insulin sensitivity (HOMA-IR, Quicki, Adipo-IR). Adiponectin was modestly increased with PXL065, consistent with some limited PPAR $\gamma$  target engagement. There was no dose dependent effect on body weight (+0.6 kg vs. baseline at 22.5 mg). Incidence of peripheral edema was low and similar across the groups. Overall, PXL065 was safe and well tolerated. **Conclusion:** DESTINY1 results support the concept that PXL065 is a novel PPAR $\gamma$  sparing oral NCE which retains an efficacy profile in NASH similar to that reported with Pio without the side effects. PXL065 demonstrated statistically significant reductions in LFC and histology suggests an effect on fibrosis consistent with improvements in the biomarkers. Histological data need to be confirmed in larger, pivotal clinical trials.

<b>Baseline Demographics and Summary of Results</b>				
	<b>PXL065 (Daily Oral Dosing)</b>			
<b>Demographics</b> Parameter (reported as mean unless specified)	<b>Placebo N=30</b>	<b>7.5 mg N=25</b>	<b>15 mg N=32</b>	<b>22.5 mg N=30</b>
Age (Years)	55	51	54	53
Sex (N, Female/Male)	21 / 9	14 / 11	18 / 14	14 / 16
BMI (kg/m <sup>2</sup> )	36	34	38	36
% Type 2 Diabetes (T2DM)	43	40	41	40
Liver Fat Content (% via MRI-PDFF)	20	22	20	20
ALT (U/L)	54	72	59	61
NAFLD Activity Score (NAS)	5.4	5.1	4.9	5.5
Fibrosis Stage (% F2-F3)	67	64	66	63
<b>Summary of Results (Non-Invasive)</b>				
Relative Reduction in Liver Fat (%)	+2	-23	-19	-21
LFC % Responder ( $\geq 30\%$ reduction)	17	32	34	40
ALT % Responder ( $\geq 17$ U/L decrease)	26	53	38	54
Pro-C3 Change from Baseline (ng/mL)	-1.0	-2.1	-1.8	-2.5
PIIINP Change from Baseline (ng/mL)	-1.1	-2.4	-2.7	-3.4
ELF Score Change from Baseline	-0.1	-0.1	-0.2	-0.4
NAFLD Fibrosis Score Change from Baseline	+0.2	+0.2	0	-0.3
Fib-4 Score Change from Baseline	0	0	-0.1	-0.2
HbA1c (%) Change from Baseline	+0.2	+0.1	-0.1	-0.2
HbA1c (%) Change from Baseline (T2DM)	+0.3	+0.3	0	-0.3
HOMA-IR (C-Peptide) Change from Baseline	+0.1	-0.1	-0.1	-0.2
QUICKI (C-Peptide) Change from Baseline	+7.9	-2.3	-5.8	-0.7
Adipo-IR Change from Baseline	+12.8	-36.2	-17.0	-41.9
Adiponectin ( $\mu\text{g/mL}$ ) Change from Baseline	-0.1	+1.5	+2.7	+4.7
<b>Summary of Results (Histology – % of Patients Achieving Endpoint)</b>				
Fibrosis improvement by $\geq 1$ stage	17	43	50	35
Fibrosis worsening by $\geq 1$ stage	26	10	9	12
$\geq 2$ -point improvement in NAS with no worsening of fibrosis	30	38	50	50
NASH resolution AND Fibrosis improvement by $\geq 1$ stage	13	33	32	15

**Disclosures:**

Stephen A Harrison - Akero Therapeutics, Inc., Axcella Health, Inc., Cirus Therapeutics, Inc., CiVi Biopharma Inc., Corcept, Cymabay Therapeutics, Inc., Enyo Pharma S.A, Galectin Therapeutics, Inc., Galmed Research & Dev. LTD., Genfit Corp, Gilead Sciences, Inc., Hepion Phar: Grant/Research Support; Akero Therapeutics, Inc., Alentis Therapeutics AG, Alimentiv, Inc., Altimmune, Axcella Health, Inc., Boston Pharmaceuticals, B Riley FBR Inc., BVF Partners LP, Chronwell, Corcept Therapeutics, Inc, Cymabay Therapeutics, Inc., Echosens North America Inc., : Consulting; Akero Therapeutics, Inc., Altimmune, Arrowhead, Axcella Health, Inc., Chronwell, CiVi, Cymabay Therapeutics, Inc., Echosens North America Inc., Foresite Labs, LLC, Galectin Therapeutics, Inc., Genfit Corp, Gilead Sciences, Inc, Hepion Pharmaceuticals, In: Advisory Committee or Review Panel; Akero Therapeutics, Inc., Chronwell Inc., Cirus Therapeutics, Inc, Galectin Therapeutics, Inc., Genfit Corp, Hepion Pharmaceuticals Inc., HistoIndex PTE LTD, Metacrine Inc., NGM Biopharmaceuticals., Northsea Therapeutics B.V.: Stock Shareholder;

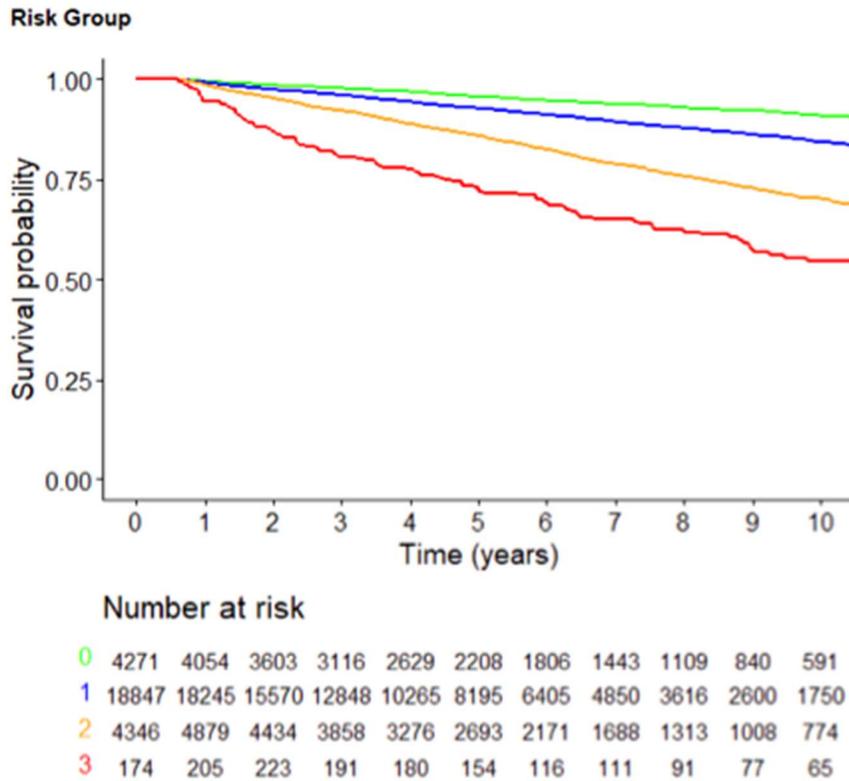
5011

**CLINICAL AND LABORATORY SCORES CAN PREDICT LONG-TERM CIRRHOSIS IN PATIENTS PRESENTING WITH ALCOHOL USE DISORDER, LONGITUDINAL DATA FROM LARGE HEALTHCARE NETWORK.**

*Amir Gougol<sup>1</sup>, Ramon Bataller<sup>2</sup>, Dhiraj Yadav<sup>3</sup>, Gavin E. Arteel<sup>3</sup>, Andrew Althouse<sup>3</sup>, Robert Feldman<sup>3</sup> and Melissa Saul<sup>3</sup>, (1)University of California, San Francisco (UCSF), (2)Barcelona Clinic, (3)University of Pittsburgh*

**Background:** Little is known about the long-term risk of alcohol-related advanced liver disease (AALD) morbidity and mortality in patients presenting with any alcohol use disorder (AUD) to a healthcare center. Clinical and laboratory markers predicting AALD are not known. We aimed to determine the long-term incidence, clinical risk factors, laboratory markers associated with development of AALD, and mortality in patients presenting with alcohol-related problems. To assess the accuracy of fibrosis-4 (FIB-4) score to predict the long-term risk of AALD in AUD patients with no pre-existing liver disease. **Methods:** Data were obtained from a historical cohort of AUD patients who were seen in a large healthcare system between January 2006 to June 2017. Patients with pre-existing AALD at the time of AUD diagnosis were excluded. AALD was defined by a diagnosis of alcoholic hepatitis, cirrhosis (compensated or decompensated), or hepatocellular carcinoma. Patients were followed longitudinally until August 2021 for incidence of AdvLD and mortality rate. Fibrosis-4 (FIB-4) scores were calculated for all patients at the time of AUD diagnosis. **Results:** 32,081 patients presenting AUD and without any pre-existing liver disease were included, with an average follow-up of 5.7 years. The average age was 48.7 yrs, 65% were male, and mean body mass index (BMI) was 27.8. To ensure the absence of any undiagnosed liver disease at the time of entry, we excluded patients who had FIB-4 >2.6 (n=4,454). During follow-up period, 2806 (10.2%) patients developed incident AALD and 5068 (18.3%) died. Among various clinical characteristics, we found presence of diabetes mellitus (DM) [hazard ratio (HR), 1.6; 95% CI, 1.5-1.7,  $P < 0.001$ ] and hepatitis C (HR, 2.9; 95% CI, 2.7-3.2,  $P < 0.001$ ) were associated with a higher risk of AALD, whereas African American (AA) race had protective effect (HR, 0.75; 95% CI, 0.68-0.82,  $P < 0.001$ ). These risk factors had an accumulative effect proposing a simple clinical score to predict the risk of AALD in AUD patients; presence of DM, Hep C, and non-AA race was associated 50% risk of AALD, whereas absence of all three factors had 8% risk over the follow-up period (Figure 1). FIB-4 at the time of AUD presentation had moderate accuracy to predict the 1-year risk of AALD with the area under curve (AUC) of 0.62, specificity of 86%, and sensitivity of 38%. In the Cox regression model, patients who had FIB-4 >2.67 had 3 times higher risk of developing AALD in follow-up (HR, 3.1; 95%CI, 2.9-3.3;  $p < 0.001$ ). When selecting patients with FIB-4 >5 at baseline, the long-term risk of AALD increased greater than 3.7 times (HR, 3.7; 95%CI, 3.4-4.1;  $p < 0.001$ ). **Conclusion:** Patients presenting with AUD are at high risk for developing long-term AALD and mortality. Clinical and laboratory scores can identify patients at higher risk of AALD. Early interventions in patients presenting with AUD are urgent.

Figure 1: Clinical Score Predicating risk of Alcohol-associated Advanced Liver Disease in Patients Presenting with AUD



The score ranges from 0-3. The score should be calculated as the presence of DM=+1, presence of Hep C=+1, and non-African American race=+1.

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5012

**EFFICACY AND SAFETY OF COMBINATION TREATMENT WITH siRNA JNJ-73763989 AND CAPSID ASSEMBLY MODULATOR JNJ-56136379 (BERSACAPAVIR) IN HBEAG NEGATIVE VIROLOGICALLY SUPPRESSED CHRONIC HEPATITIS B PATIENTS: FOLLOW-UP WEEK 48 END OF STUDY RESULTS FROM REEF-2**

*Kosh Agarwal<sup>1</sup>, Maria Buti Sr.<sup>2</sup>, Florian Van Bommel<sup>3</sup>, Pietro Lampertico<sup>4,5</sup>, Ewa Janczewska<sup>6</sup>, Marc Bourliere<sup>7</sup>, Thomas Vanwolleghem<sup>8,9</sup>, Oliver Lenz<sup>10</sup>, Thierry Verbinnen<sup>10</sup>, Thomas N. Kakuda<sup>11</sup>, Cristiana Mayer<sup>11</sup>, John Jezorowski<sup>11</sup>, Daniel Muenz<sup>12</sup>, Maria Beumont<sup>10</sup>, Ronald Kalmeijer<sup>11</sup>, Michael Biermer<sup>10</sup> and Isabelle Lonjon-Domanec<sup>10</sup>, (1)Institute of Liver Studies, King's College Hospital, (2)Hospital Universitario Valle De Hebrón, (3)University Hospital Leipzig, (4)Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda, Ospedale Maggiore Policlinico, (5)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy, (6)Faculty of Health Sciences, Medical University of Silesia, (7)Hôpital Saint Joseph, (8)Antwerp University Hospital (UZA), (9)Viral Hepatitis Research Group, Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, (10)Janssen Pharmaceutica NV, (11)Janssen Research & Development, LLC, (12)Iqvia*

**Background:** REEF-2 (NCT04129554) assessed the efficacy and safety of JNJ-3989, JNJ-6379, and nucleos(t)ide analogs (NA) in virologically suppressed hepatitis B e antigen negative (HBeAg-) chronic hepatitis B (CHB) patients. **Methods:** In this phase 2b, double-blind, multicenter, placebo-controlled study, HBeAg- CHB patients with hepatitis B surface antigen (HBsAg) >100 IU/mL on NA treatment for ≥2 years were randomized (2:1) to receive add-on JNJ-3989 + JNJ-6379 (active) or placebos (control). All treatments, including NA, were discontinued after 48 weeks followed by 48 weeks of follow-up (FU; total study duration: 96 weeks). Here, we report end of study (EOS; FU Week 48 [FU W48]) results. **Results:** Of 130 patients randomized (85 active, 45 control), 121 (81 active, 40 control) completed the study. Mean (SE) changes in HBsAg from baseline were greater in the active versus control arm at Week 48 (W48; end of treatment; -1.89 [0.06] vs -0.06 [0.01] log<sub>10</sub> IU/mL) and FU W48 (EOS; -1.46 [0.07] and -0.49 [0.12] log<sub>10</sub> IU/mL). 71.1% and 46.9% of patients in the active arm achieved HBsAg <100 IU/mL at W48 and FU W48, respectively, compared with 2.4% and 15.0% in the control arm. 19.7% and 14.8% of patients in the active arm achieved HBsAg <10 IU/mL at W48 and FU W48, respectively, versus 0% and 7.5% in the control arm. No patients in the study achieved HBsAg loss (<0.05 IU/mL) without restarting NA at FU Week 24 (primary endpoint) or at FU W48. Of those who stopped NA, fewer patients in the active versus control arm restarted NA (6/77 [7.8%] vs 12/41 [29.3%]). Of patients not on NA at FU W48, more in the active versus control arm had HBV DNA <2000 IU/mL with HBsAg <100 IU/mL (31/71 [43.7%] vs 3/28 [10.7%]) and HBV DNA <lower limit of quantitation with HBsAg <100 IU/mL (12/71 [16.9%] and 0/28 [0%]). More frequent and pronounced off-treatment ALT flares (ALT ≥3× upper limit of normal and ≥3× nadir) and virologic relapses (HBV DNA >2000 IU/mL) were observed in the control versus active arm during FU. The frequency of adverse events was similar between the active and control arms during FU (65.5% vs 68.3%), and there were no deaths. **Conclusion:** Treatment with JNJ-3989 + JNJ-6379 + NA for 48 weeks was generally safe and well tolerated. After stopping all treatments, including NA, at W48, no patient achieved the primary endpoint, but lower HBsAg levels and greater HBV DNA suppression were observed for patients in the active arm after 48 weeks of FU.

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5013

## EXTENSION OF BULEVIRTIDE MONOTHERAPY TO 72 WEEKS IN HDV PATIENTS WITH COMPENSATED CIRRHOSIS: EFFICACY AND SAFETY FROM THE ITALIAN MULTICENTER STUDY (HEP4Di)

Maria Paola Anolli<sup>1</sup>, Elisabetta Degasperì<sup>1</sup>, Gianpiero Doffizi<sup>2</sup>, Maurizia Brunetto<sup>3</sup>, Gabriella Verucchi<sup>4</sup>, Alessandro Federico<sup>5</sup>, Alessia Ciancio<sup>6</sup>, Alessandra Mangia<sup>7</sup>, Teresa Antonia Santantonio<sup>8</sup>, Nicola Coppola<sup>9</sup>, Adriano Pellicelli<sup>10</sup>, Alessandro Loglio<sup>11</sup>, Mauro Viganò<sup>2,12</sup>, Francesca Pileri<sup>13</sup>, Monia Maracci<sup>14</sup>, Massimo Puoti<sup>15</sup>, Fabio Piscaglia<sup>16</sup> and Pietro Lampertico<sup>1,17</sup>, (1)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy, (2)Irccs Istituto Nazionale Malattie Infettive "L. Spallanzani", Rome, Italy, (3)Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, University Hospital of Pisa, (4)Department of Medical and Surgical Sciences, Unit of Infectious Diseases "Alma Mater Studiorum", University of Bologna, S. Orsola-Malpighi Hospital, Bologna, Italy, (5)Division of Hepatogastroenterology, Department of Precision Medicine, Università Della Campania "Luigi Vanvitelli", Naples, Italy, (6)Department of Medical Sciences, University of Turin, Gastroenterology Division of Città Della Salute e Della Scienza of Turin, University Hospital, Turin, Italy, (7)Liver Unit, Fondazione Irccs "Casa Sollievo e Della Sofferenza", San Giovanni Rotondo, Italy, (8)Department of Medical and Surgical Sciences, Infectious Disease Unit, Università Di Foggia, Foggia, Italy, (9)Department of Mental Health and Public Medicine - Infectious Diseases Unit, University of Campania "Luigi Vanvitelli", Naples, Italy, (10)Liver Unit, San Camillo Hospital, Roma, Italy, (11)Gastroenterology, Hepatology and Trasplantation Division, Asst Papa Giovanni XXIII, Bergamo, Italy, (12)Division of Hepatology, San Giuseppe Hospital, Milan, Italy, (13)Division of Internal Medicine 2 and Center for Hemochromatosis, University of Modena and Reggio Emilia, Modena, Italy, (14)Institute of Infectious Diseases and Public Health, Università Politecnica Delle Marche, Ancona, Italy, (15)Asst Grande Ospedale Metropolitano Niguarda, Division of Infectious Diseases, Milan, Italy, (16)Division of Internal Medicine, Hepatobiliary and Immunoallergic Diseases, Irccs Azienda Ospedaliero-Universitaria Di Bologna, Bologna, Italy, (17)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

**Background:** In phase II studies and in the week 48 analysis of the phase III trial, Bulevirtide (BLV) significantly reduced HDV-RNA and aminotransferase (ALT) levels in patients with chronic hepatitis Delta virus (HDV) infection, however, data on efficacy and safety beyond week 48 in real-world settings are limited. **Methods:** HDV patients with compensated cirrhosis treated with BLV 2 mg monotherapy up to 72 weeks were retrospectively evaluated in this multicenter Italian real-life study. Clinical and virological variables were collected at baseline, weeks 4, 8 and every 8 weeks until week 72. **Results:** 87 patients with compensated cirrhosis under nucleos(t)ide analogue (NUC) treatment were included: age 52 (29-77) years, 52% males, BMI 25 (18-37) Kg/m<sup>2</sup>, liver stiffness measurement (LSM) 17.4 (4.7-68.1) kPa, 47 (54%) with varices, 46 (53%) previously treated with IFN, 8 (9%) with active HCC. Median ALT levels were 80 (26-383) U/L, albumin 3.9 (2.9-4.7) g/dL, INR 1.2 (1.0-2.4), HDV RNA 5.2 (2.1-7.6) Log IU/mL, qHBsAg 3.7 (0.8-4.5) Log IU/mL, AFP 7 (1-596) ng/mL, bile acids were above normal range in 95% of patients before BLV start (median 18 [3-306]  $\mu$ mol/L). CPT score was A in all patients. A virological response (HDV RNA  $\geq$  2 Log decline vs. baseline) was achieved by 14%, 49%, 71%, 67%, 69% of patients at week 8, 16, 24, 48 and 72, respectively. HDV RNA became undetectable in 8%, 23% and 33% at weeks 24, 48 and 72, respectively. At the same time points, ALT normalization was observed in 63%, 56% and 72% of the patients while a combined response (virological + biochemical) in 54%, 67% and 62%. In patients with detectable viremia between week 48 and 72, HDV RNA levels remained stable ( $\Delta$  < 1 Log) in 70%, increased in 10% and further decreased in 20%. Besides ALT, significant on-treatment declines were also observed for AST, GGT, IgG, gammaglobulins (p < 0.001 vs. baseline), while albumin values increased (p < 0.001). Platelets, LSM and HBsAg levels remained unchanged. Two patients underwent liver transplantation during BLV treatment (W64 and W72) due to HCC and decompensation following portal vein thrombosis, respectively. BLV was well tolerated, no patient discontinued treatment for adverse events, an asymptomatic increase in bile acid levels occurred in all patients. **Conclusion:** Extension of BLV monotherapy to 72 weeks is safe and effective in patients with HDV-related compensated cirrhosis. Virological and clinical responses increase over time.

Disclosures:

The following people have nothing to disclose: Mauro Viganò<sup>2</sup>

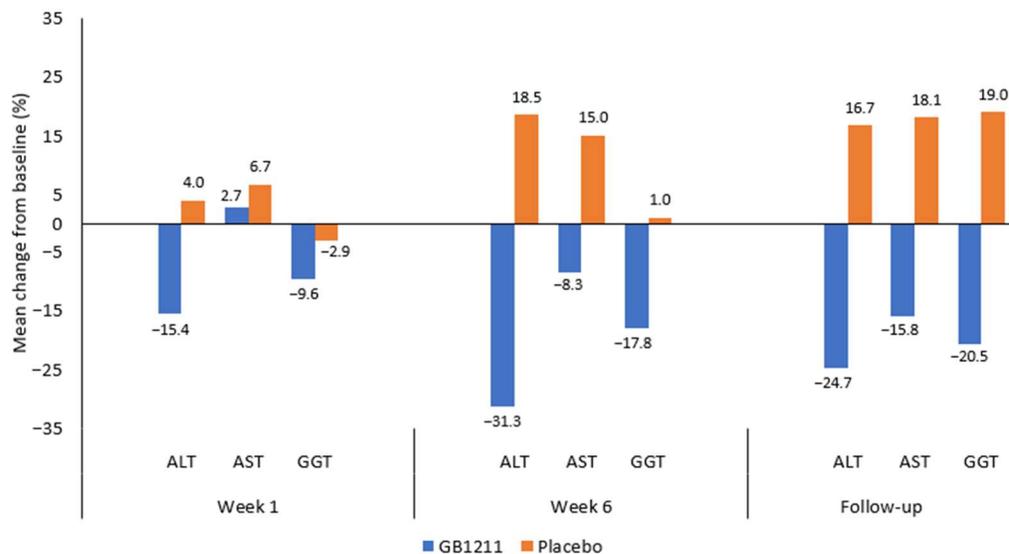
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## GB1211, AN ORAL GALECTIN-3 INHIBITOR, IN DECOMPENSATED CIRRHOTIC PATIENTS: INITIAL FINDINGS FROM THE PHASE 2 RANDOMIZED, PLACEBO-CONTROLLED GULLIVER-2 TRIAL

Bertil Lindmark<sup>1</sup>, Jordan Genov<sup>2</sup>, Rozalina Balabanska<sup>3</sup>, Diana Stefanova-Petrova<sup>4</sup>, Dimitar Tonev<sup>1</sup>, De Phung<sup>1</sup>, Vassilios Aslanis<sup>1</sup>, Becky Smith<sup>1</sup>, Robert Slack<sup>1</sup>, Brian Jacoby<sup>1</sup>, Mike Gray<sup>1</sup> and Zahari Krastev<sup>5</sup>, (1)Galecto Biotech AB, (2)University Multiprofile Hospital for Active Treatment (UMHAT) "Tsaritsa Yoanna - Isul" Ead, (3)Acibadem City Clinic Tokuda University Hospital, (4)DCC "Aleksandrovska" Eood, (5)Medical Center, Comac Medical Ltd.

**Background:** Galectin-3 (Gal-3) is a beta-galactoside binding lectin which regulates fibrosis, inflammation and coagulation in the liver. GB1211 is a novel oral Gal-3 inhibitor which has shown potential in preclinical studies for reducing fibrosis. The GULLIVER-2 trial (NCT05009680) is an innovative, hybrid-design, 3-part study investigating safety, pharmacokinetics (PK), and exploratory efficacy of GB1211 in patients (pts) with hepatic impairment (Child-Pugh B and C). Here, we report the findings from Part 2. **Methods:** Part 2 of this trial is a Phase 2, randomized, double-blind, placebo-controlled, repeat dose study of GB1211 in pts with Child-Pugh B (CP-B) liver cirrhosis. Pts were randomized 1:1 to GB1211 100 mg twice daily for 12 weeks, or matched placebo. Primary endpoints were safety and PK of GB1211. Secondary endpoints included the effect of GB1211 on clinical parameters and hepatic function. Vibration controlled transient elastography (VCTE), and model for end-stage liver disease (MELD) score are also assessed. **Results:** Thirty pts were randomized to GB1211 (n = 15) or placebo (n = 15). Seventeen treatment-emergent adverse events (TEAEs) were reported (9 with GB1211 and 8 with placebo). Three serious TEAEs were observed in 1 patient on GB1211 but were deemed unrelated to the drug. Steady-state PK was reached by Day 7. GB1211 reduced markers of liver damage vs placebo (Figure 1), and this reduction deepened from Week 1 to Week 6. Furthermore, improvements in liver stiffness and the controlled attenuation parameter (CAP) were observed with GB1211 vs placebo: mean change from baseline at Week 12 of  $\hat{\mu}$ 9.66 (standard deviation [SD] 22.52) kilopascal (kPa) and  $\hat{\mu}$ 20.23 (SD 42.81) decibels per meter (dB/m) vs  $\hat{\mu}$ 7.62 (SD 11.34) kPa and 4.13 (SD 63.35) dB/m, respectively. In GB1211 treated pts, the MELD score decreased as compared to an increase in placebo-treated pts. **Conclusion:** In a cohort of pts with decompensated cirrhosis, GB1211 was well tolerated with predictable PK, and showed early signs of clinical effect, demonstrating that the drug can be administered to pts with hepatic impairment. The observed reduction of transaminases and CAP indicate a decrease in liver inflammation and a potential effect on steatosis which, in combination with the reduction in VCTE, prompt further exploration of anti-fibrotic effects and clinical benefit.

Figure 1. Mean percentage change in selected biochemistry results from baseline to Week 1, Week 6, and Follow-up



ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase

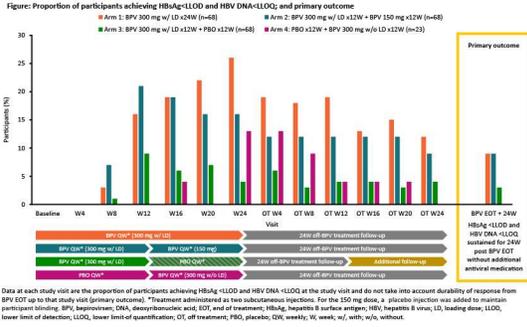
### Disclosures:

Bertil Lindmark - Galecto Biotech AB: Employment; Galecto Biotech AB: Stock Shareholder;

## BEPIROVIRSEN (BPV) IN PATIENTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION CONTROLLED BY NUCLEOS(T)IDE ANALOGUE THERAPY: HBV DNA AND HBsAg LOSS 6 MONTHS AFTER END OF BPV TREATMENT (B-CLEAR STUDY)

*Man-Fung Yuen*<sup>1</sup>, *Seng Gee Lim*<sup>2</sup>, *Robert Plesniak*<sup>3</sup>, *Keiji Tsuji*<sup>4</sup>, *Gheorghe Diaconescu*<sup>5</sup>, *Adrian C. Gadano*<sup>6</sup>, *Tarik Asselah*<sup>7</sup>, *Hyung-Joon Yim*<sup>8</sup>, *Jeong Heo*<sup>9</sup>, *Giuliano Rizzardini*<sup>10</sup>, *Harry L.A. Janssen*<sup>11,12</sup>, *Corneliu Petru Popescu*<sup>13</sup>, *Diana Stefanova-Petrova*<sup>14</sup>, *Alexander Wong*<sup>15</sup>, *Nevin Idriz*<sup>16</sup>, *Cristina Pojoga*<sup>17,18</sup>, *Yasuhiro Tanaka*<sup>19</sup>, *Ewa Janczewska*<sup>20</sup>, *Jennifer Cremer*<sup>21</sup>, *Robert Elston*<sup>22</sup>, *Tamara Lukić*<sup>23</sup>, *Lauren Maynard*<sup>22</sup>, *Stuart Kendrick*<sup>22</sup>, *Punam Bharania*<sup>24</sup>, *Fiona Campbell*<sup>22</sup>, *Melanie Paff*<sup>25</sup> and *Dickens Theodore*<sup>21</sup>, (1)Queen Mary Hospital, the University of Hong Kong, Hong Kong, China, (2)National University Health System, Singapore, (3)University of Rzeszow Centrum Medyczne w Lancucie Sp. z o.o., Lancut, Poland, (4)Department of Gastroenterology, Hiroshima Red Cross Hospital & Atomic-Bomb Survivors Hospital, Hiroshima, Japan, (5)Spitalul Clinic De Boli Infectioase Si Pneumoftiziologie, Craiova, Romania, (6)Hospital Italiano De Buenos Aires, Buenos Aires, Argentina, (7)Universit  De Paris-Cit  & Inserm UMR1149, Department of Hepatology, AP-HP H pital Beaujon, Clichy, France, (8)Korea University Ansan Hospital, Ansan, South Korea, (9)College of Medicine, Pusan National University and Biomedical Research Institute, Pusan National University Hospital, Busan, South Korea, (10)Luigi Sacco Hospital, Milan, Italy, (11)Toronto General Hospital, Toronto, Canada, (12)Erasmus Medical Center, Rotterdam, the Netherlands, (13)Dr Victor Babes Clinical Hospital of Infectious and Tropical Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, (14)Diagnostic Consultative Center Alexandrovska, Sofia, Bulgaria, (15)Department of Medicine, University of Saskatchewan, Regina, Canada, (16)University of Medicine and Hospital for Active Treatment Sofamed, Sofia, Bulgaria, (17)Babe -Bolyai University, Department of Clinical Psychology and Psychotherapy, International Institute for Advanced Study of Psychotherapy and Applied Mental Health, Cluj-Napoca, Romania, (18)Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania, (19)Department of Gastroenterology and Hepatology, Kumamoto University, Kumamoto, Japan, (20)Faculty of Health Sciences in Bytom, Medical University of Silesia, Poland, (21)GSK, Durham, NC, USA, (22)GSK, Stevenage, UK, (23)GSK, Dubai, UAE, (24)GSK, Brentford, UK, (25)GSK, Collegeville, PA, USA

**Background:** Bepirovirsen (BPV; GSK3228836), an antisense oligonucleotide, targets all hepatitis B virus (HBV) mRNAs and decreases viral proteins. The B-Clear trial investigated BPV efficacy and safety in patients (pts) with chronic hepatitis B (CHB) on and not on nucleos(t)ide analogues (NA). We present end-of-study (24 weeks [wks] off-BPV treatment) results for pts on NA. **Methods:** Multicenter, randomized, partial-blind (investigator unblinded), parallel-cohort study in pts with CHB. Pts with alanine aminotransferase (ALT)  $\leq$  upper limit of normal, HBV DNA  $< 90$  IU/mL and hepatitis B surface antigen (HBsAg)  $> 100$  IU/mL were randomized (3:3:3:1) to 1 of 4 treatment arms to receive up to 300 mg BPV administered as two subcutaneous injections weekly for 12 or 24 wks with or without loading doses (see arms in **Figure**). Pts were stratified by baseline hepatitis B e antigen (HBeAg; positive/negative) and HBsAg level ( $\leq 3 \log_{10}$  IU/mL). Primary outcome: proportion of pts achieving HBsAg  $<$  lower limit of detection (LLOD) and HBV DNA  $<$  lower limit of quantification (LLOQ) maintained for 24 wks without additional antiviral medication after planned BPV end of treatment (EOT). Safety was assessed via adverse event (AE) monitoring. **Results:** Intent-to-treat population included 227 pts (73% male, 52% Asian, 69% HBeAg negative, 72% HBsAg  $> 3 \log_{10}$  IU/mL). Primary outcome was achieved in 6 (9%), 6 (9%), 2 (3%) and 0 pts in Arms 1-4, respectively; data at specific study visits are shown in **Figure**. A greater proportion of pts with low ( $\leq 3 \log_{10}$  IU/mL) vs high ( $> 3 \log_{10}$  IU/mL) baseline HBsAg levels achieved the primary outcome (Arm 1: 16% vs 6%). Primary outcome was achieved in a similar proportion of HBeAg negative and positive pts (Arm 1: 10% vs 6%). Serious AEs (SAEs) were reported in 6 (3%) pts and treatment-related SAEs in 1 ( $< 1\%$ ) pt. Treatment was discontinued in 13 pts (6%); 8 (4%) pts had an AE that led to discontinuation. Most common AEs were injection site reactions (64%), pyrexia (14%) and ALT increase (11%). There were no clinically meaningful differences in AEs across treatment arms. **Conclusion:** BPV 300 mg x24 wks (Arm 1) and BPV 300 mg x12 wks + 150 mg x12 wks (Arm 2) were the most efficacious treatment regimens. Pts with low vs high (Arm 1: 16% vs 6%) baseline HBsAg were more likely to achieve HBsAg and HBV DNA loss for 24 weeks after BPV EOT. There were no safety signals to preclude further development. **Funding:** GSK [209668/NCT04449029] [on behalf of the B-Clear Study Group]



**Disclosures:**

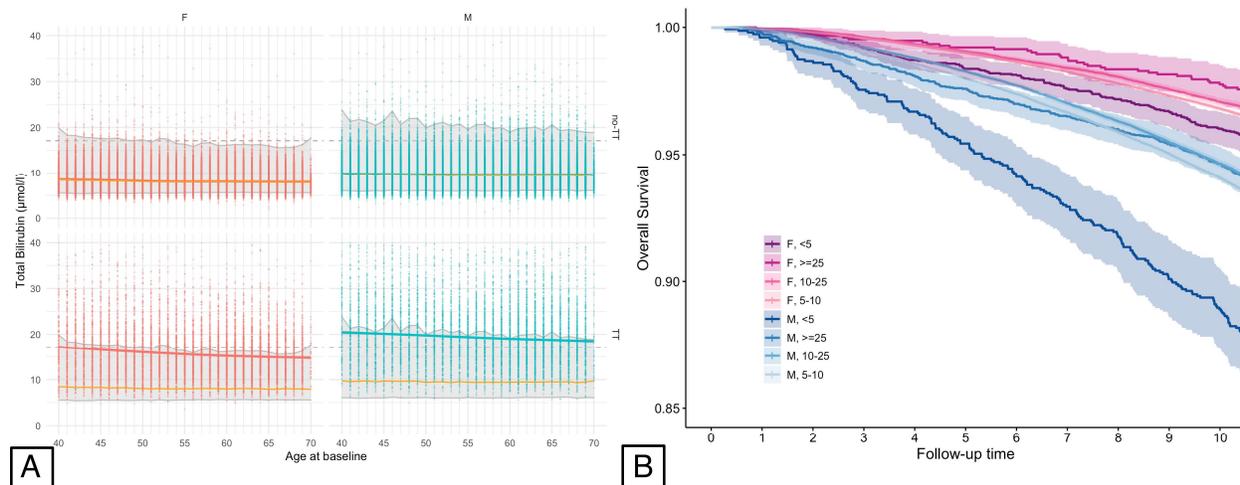
Jennifer Cremer - GSK: Employment; GSK: Stock Shareholder;

## A NEW DEFINITION OF GILBERT SYNDROME (GS) ADJUSTED ON GENDER AND AGE IN LARGE POPULATIONS

Thierry Poynard<sup>1</sup>, Olivier Deckmyn<sup>2</sup>, Valentina Peta<sup>2</sup>, Medhi Sakka<sup>3</sup>, Pascal Lebray<sup>4</sup>, Joseph Moussalli<sup>4</sup>, Raluca Pais<sup>5</sup>, Chantal Housset<sup>6,7</sup>, Vlad Ratziu<sup>8</sup> and Dominique Thabut<sup>9</sup>, (1)Inserm Umr S938, Sorbonne University, (2)Research, Biopredictive, (3)Aphp, (4)Hepatology, Aphp, (5)Inserm, (6)Sorbonne University, (7)Sorbonne Université, UPMC Université Paris 06, Umr\_S 938, Centre De Recherche Saint-Antoine, Paris, France, (8)Hepato-Gastroenterology, Hôpital La Pitié-Salpêtrière, AP-HP, Paris, France, (9)Service D'hépatogastroentérologie, Hôpital Pitié-Salpêtrière, Paris, France

**Background:** GS is genotypically defined by rs887829 homozygosity (TTgen), phenotypically by hyperbilirubinemia, using total bilirubin (TB) cutoff  $\approx 17.1 \mu\text{mol/L}$  (1mg/dl), in the absence of haemolysis or liver damage. However, TB and liver tests vary with gender and age. GS has been associated with reduced mortality, and low level of TB with the opposite trend, but adjustment on gender and age are lacking. The aims were 1) to address accuracy of the current phenotypic definition; 2) to propose bilirubin-based algorithms for accurate GS diagnosis and prognostic value.

**Methods:** We assigned a centile corresponding to an individual's TB measurement according to gender and age. We used TTgen to assess a rational cutoff for defining GS independently of prevalence, according to the Youden Index (sensitivity + specificity-1). We compared the prevalence of TTgen and GS according to the adjusted 4 selection criteria in 467,459 subjects of the UKbioBank (UKB) and the risk of false negative/positive of GS in 2 populations at risk of liver damage, in USA (n=71,478) and in France (n=45,769). Two algorithms, for predicting TTgen (logistic regression) and for assessing the 7-year prognostic value of TB (Cox model), were constructed and validated. **Results:** TB levels in TTgen cases displayed differences ( $P < .0001$ ) according to gender and age (Figure 1A). In healthy UKB subjects, the highest Youden were obtained at  $10.5 \mu\text{mol/L}$  for females (0.71) and  $13.0 \mu\text{mol/L}$  for males (0.71), higher than with the non-adjusted  $17.1 \mu\text{mol/L}$  cutoff, (0.33) and  $0.57 \mu\text{mol/L}$  TB respectively ( $P < .0001$ ). A diagnostic algorithm for predicting TTgen combining 5 components had AUROC=.93 (95%CI .93-.93) higher than TB alone  $0.91(.91-.91; P < .0001)$ , permitting to identify the subjects at high probability of GS and those at high risk of false positive in the US and French populations at risk of liver damage. In subjects with  $\text{TB} < 5 \mu\text{mol/L}$ , a lower 7-years survival was confirmed both in females  $P < .0004$  and in males  $P < .0001$  (Figure 1B). In contrast, higher survival in subjects with  $\text{TB} > 10 \mu\text{mol/L}$  was only observed in those with TTgen. A prognostic algorithm combining 7 components had AUROC=.74(.74-.75;  $P < .0001$ ) for predicting 7-year survival stratified by phenotype. **Conclusion:** For a simple diagnosis or for assessing the patient's prognostic according to total bilirubin, the conventional  $17.1 \mu\text{mol/L}$  cutoff should be modified according to gender and age. We confirm that the  $< 5 \mu\text{mol/L}$  cutoff is associated with lower survival.



**Panel A :** Total Bilirubin median level (umol/l) in patients from the UKB healthy subset (n=196,558), according to age, stratified by gender and rs887829 homozygosity. The orange lines show the normal serum values according to age and gender, the gray ribbon is the 90% confidence interval of the normal value (lower 5% percentile and higher 95% percentile). The red (female) and blue (male) horizontal line show the measured median level of Total Bilirubin.

**Panel B :** Overall survival rate (all death) in patients from the UKB (n=383,446) according to gender and Total Bilirubin level (umol/l) at baseline, in 4 groups.

### Disclosures:

Thierry Poynard - BioPredictive: Employment;

5017

**FIBROSCAN-BASED COMPOSITE SCORES MEET AND EXCEED PRESPECIFIED PERFORMANCE CRITERIA FOR DIAGNOSIS OF CLINICALLY SIGNIFICANT FIBROSIS IN PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE: NIMBLE STAGE 1 RESULTS**

*Arun J Sanyal<sup>1</sup>, Sudha S Shankar<sup>2</sup>, Katherine P Yates<sup>3</sup>, Clayton A. Dehn<sup>4</sup>, James A. Bolognese<sup>5</sup>, Brent A Tetri<sup>6</sup>, Kris V Kowdley<sup>7</sup>, Raj Vuppalanchi<sup>8</sup>, Cynthia D Guy<sup>9</sup>, James Tonascia<sup>10</sup>, Anthony Samir<sup>11</sup>, Claude B. Sirlin<sup>12</sup>, Sarah Sherlock<sup>13</sup>, Kathryn Fowler<sup>12</sup>, Hoda Soltani<sup>14</sup>, Helen Heymann<sup>15</sup>, Tania Kamphaus<sup>16</sup>, Rohit Loomba<sup>17</sup> and Roberto Calle<sup>13</sup>, (1)Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, (2)Astra Zeneca, (3)Department of Epidemiology and Biostatistics, John Hopkins Bloomberg School of Public Health, (4)T Evolution Research Group, (5)Cytel Inc, (6)Saint Louis University, (7)Washington State University, (8)Gastroenterology and Hepatology, Indiana University School of Medicine, (9)Department of Medicine, Duke University, (10)John Hopkins School of Public Health, (11)Radiology, Massachusetts General Hospital, (12)Department of Radiology, University of California, San Diego, (13)Pfizer, (14)11400 Rockville Pike, 11400 Rockville Pike, (15)Nih, (16)Fnih, (17)University of California San Diego*

**Background:** Knowledge gaps impede regulatory qualification of non-invasive tests (NITs) for NAFLD. The NIMBLE Consortium of the FNIH was established to generate evidence to address these gaps including leveraging combinations of blood-based and imaging biomarkers. The aim of this secondary analysis of the NIMBLE Circulating Biomarkers Work Stream stage 1 dataset was to evaluate utility of the Fibroscan-based FAST, Agile 3+ and Agile 4 scores for stratified diagnosis of clinically significant fibrosis (≥ stage 2), advanced fibrosis (≥ stage 3), or cirrhosis (stage 4) in patients with NAFLD. **Methods:** Analysis of a sample set from the NIDDK NASH CRN non-interventional registry (Database2 study-DB2) adult cohort was performed, curated to avoid spectrum bias by balanced representation of fibrosis stages. Histology was centrally read by the NASH CRN Pathology Committee. All blood samples were obtained within 90 days of a liver biopsy indicating NAFLD. FIB-4 scores were computed using laboratory values measured from the same sample as the soluble biomarkers used to compute the composite Fibroscan-based scores. The primary hypothesis tested was that each Fibroscan-based score would diagnose the fibrosis strata noted above with an AUROC > 0.7 with confidence limits that do not intersect 0.5. The secondary hypothesis tested was that the AUROC would be superior to FIB-4 for the same fibrosis strata. **Results:** 396 patients with NAFL or NASH with fibrosis stages 0 (n=85), 1 (n=47), 2 (n=93), 3 (n=100) and 4 (n=71) were studied. AUROCs, Youden cutoffs, and corresponding sensitivity/specificity are provided below. All three panels met criteria for intended use for diagnosis of fibrosis stage ≥ 2, advanced fibrosis, and cirrhosis. All three panels were significantly superior to FIB-4 for the intended use of diagnosis of fibrosis stage ≥ 2, advanced fibrosis, and cirrhosis, except FAST for advanced fibrosis and cirrhosis. **Conclusion:** All three Fibroscan-based composite scores exceeded pre-specified performance criteria for diagnosis of clinically significant fibrosis in patients with NAFLD. These data support their potential use for diagnosis and diagnostic enrichment in clinical trials covering a large spectrum of patients with NAFLD.

Score Type	FIB-4 (comparator)	FAST	Agile 3+	Agile 4
Score Parameters	Age, ALT, AST, PLT	LSM, CAP, AST	LSM, Age, Gender, T2DM, PLT, AST, ALT	LSM, Gender, T2DM, PLT, AST, ALT
Performance Characteristics	AUROC, (Youden cut-off value), [Sensitivity, Specificity at Youden cut-off]			
Fibrosis stage ≥ 2	0.772 [64.3, 78.3]	0.845* (≥ 0.5) [66.7, 86.8]	0.83* (≥ 0.3) [82.6, 71.2]	0.814* (≥ 0.0) [71.6, 78.0]
Fibrosis stage ≥ 3	0.785 [80.9, 66.2]	0.794 (≥ 0.6) [67.9, 81.3]	0.85* (≥ 0.5) [78.4, 76.4]	0.842* (≥ 0.1) [82.5, 72.4]
Fibrosis stage 4	0.837 [89.9, 65.1]	0.74 (≥ 0.6) [65.2, 74.7]	0.909* (≥ 0.7) [88.7, 77.5]	0.913* (≥ 0.1) [94.4, 73.2]

ALT: alanine aminotransferase, AST: aspartate aminotransferase, PLT: platelet count, LSM: liver stiffness by VCTE, CAP: attenuation parameter by Fibroscan, T2DM: Type 2 diabetes mellitus.  
 \*p< 0.001 for comparison with FIB-4 for intended use  
 †p< 0.01 for comparison with FIB-4 for intended use  
 ‡p< 0.05 for comparison with FIB-4 for intended use  
 All AUROCs are statistically significant and superior to AUROC=0.5 (p<0.001)

Disclosures:

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5018

**ADJUVANT IMMUNE CHECKPOINT INHIBITORS FOR HEPATOCELLULAR CARCINOMA PATIENTS WITH HIGH-RISK OF POSTOPERATIVE RECURRENCE: A PROSPECTIVE COHORT STUDY (PREVENT)**

*Le Li<sup>1</sup>, Shan Huang<sup>1</sup>, Lu-Nan Qi<sup>1</sup>, Bang-De Xiang<sup>1</sup>, Liang Ma<sup>1</sup> and Jian-Hong Zhong<sup>1,2</sup>, (1)Guangxi Medical University Cancer Hospital, (2)Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor (Guangxi Medical University), Ministry of Education; Guangxi Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor*

**Background:** No standard adjuvant therapy is recommended for patients with hepatocellular carcinoma (HCC) by official guidelines. This prospective cohort study was designed to assess the safety and efficacy of adjuvant immune checkpoint inhibitors (ICIs) with or without tyrosine kinase inhibitors (TKIs) for HCC patients with high-risk of postoperative recurrence. **Methods:** Patients with high risk of HCC recurrence after curative hepatic resection would be enrolled. Curative hepatic resection was defined as free of recurrence two months after resection by imaging review. The primary endpoint was recurrence-free survival (RFS), defined as the time from the date of resection to tumor recurrence or death from any cause, whichever occurred first. Propensity score matching (PSM) was used to reduce baseline bias. This study is registered with ClinicalTrials.gov, number NCT05221398. **Results:** Between March 2019 and March 2022, 82 (15.8%) patients received adjuvant ICIs with (n= 32) or without TKIs (n= 50) while other 436 (84.2%) patients received no adjuvant therapy. The median age was 50 (range 29 to 74) and 54 (range 23 to 82) years, respectively. ICIs included camrelizumab (n= 20), tislelizumab (n= 24), toripalimab (n= 17) and sintilimab (n= 21). TKIs included lenvatinib (n= 13), sorafenib (n= 7), and apatinib (n= 12). During a median follow-up of 24.2 (range 2.78 to 43.46) months, 281 (54.2%) recurrent events had occurred (21 [42.0%] in the ICIs monotherapy group, 15 [46.9%] in the ICIs plus TKI group, and 245 [56.2%] in the control group). Patients with adjuvant therapy had longer median RFS than those without (21.2 [range 1.17 to 40.43] vs. 14.5 [range 0.48 to 42.87] months). Patients with adjuvant ICIs had a higher trend of RFS than those in the control group before ( $P=0.135$ ) and after PSM ( $P=0.054$ ). Subgroup analyses revealed that patients with adjuvant ICIs with or without TKIs had similar RFS. No treatment-related deaths were observed. **Conclusion:** This prospective cohort study indicate that ICIs with or without TKIs may be not an effective intervention in the adjuvant setting in patients with high risk of HCC recurrence after curative hepatic resection.

Disclosures:

The following people have nothing to disclose: Lu-Nan Qi

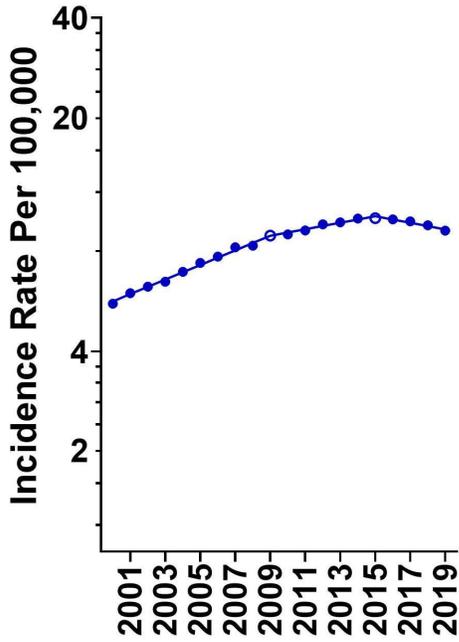
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## DECREASING INCIDENCE OF HEPATOCELLULAR CARCINOMA AMONG ALL US RACIAL/ETHNIC POPULATIONS

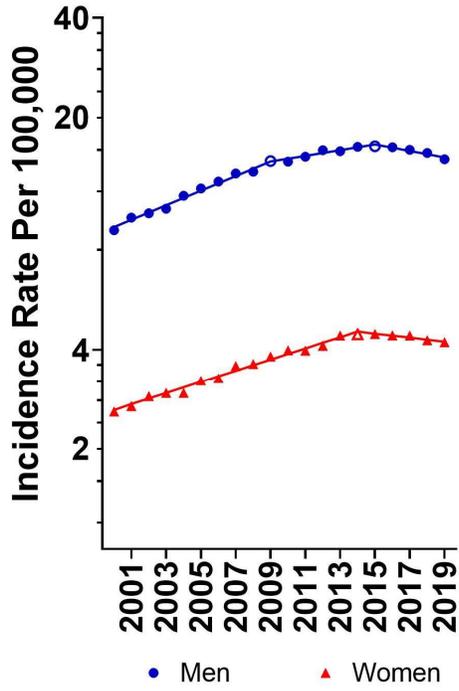
*Thomas R. O'Brien<sup>1</sup>, Susan Devesa<sup>1</sup>, Jill Koshiol<sup>1</sup>, Jorge A Marrero<sup>2</sup> and Meredith Shiels<sup>1</sup>, (1)Division of Cancer Epidemiology and Genetics, National Cancer Institute, (2)University of Pennsylvania*

**Background:** Hepatocellular carcinoma (HCC) is a highly lethal cancer that was rising in incidence in the United States. Previously, using data collected by the Surveillance, Epidemiology, and End Results (SEER) Program through 2017, we found that overall HCC incidence was in decline, although not in the Black and American Indian/Alaska Native populations. Recently, SEER data expanded to encompass ~50% of the US population through 2019. With this larger dataset, we examined secular trends and demographic differences in HCC incidence during 2000-2019. **Methods:** We included cases diagnosed in adults aged  $\geq 20$  years residing in SEER-22 registry areas, defining HCC based on International Classification of Diseases for Oncology, 3rd Edition site C220 and histology codes 8170-8175. We calculated case counts and incidence rates using SEER\*Stat, adjusting rates to the 2000 US standard population. To examine trends in HCC incidence, we used Joinpoint regression to calculate annual percent changes (APCs) and identify calendar years when APCs changed significantly. **Results:** During 2000-2019, overall HCC rates rose and then fell (**Fig 1A**). Incidence (per 100,000 person-years) increased from 5.56 in 2000 to 8.89 in 2009 (APC, 5.17% per year). During 2009-2015, rates rose more slowly (APC, 2.28%), reaching 10.03 in 2015 before falling to 9.20 in 2019 (APC, -2.26%). HCC incidence, higher in men than women, fell in both sexes (**1B**). Rates began to fall in those 20-54 years in 2011 and in 2014 for those 55-64 but did not fall in the older age groups (**1C**). Onset of HCC decline differed among racial/ethnic groups (**1D**). In Asian/Pacific Islanders, a decline began in 2007 and accelerated in 2015 (APCs: 2007-2015, -1.84%; 2015-2019, -5.80%). In 2014, HCC incidence began to fall in the White (APC: 2014-2019, -1.11%) and Hispanic populations (APC: 2014-2019, -1.72%). In 2016, HCC rates began to fall in Black (APC: 2016-2019, -6.05%) and American Indian/Alaska Native populations (APC: 2016-2019, -8.34%), although the decline in the latter group was not statistically significant. In 2019, HCC rates were: White individuals, 6.94; Black individuals, 10.74; Asian/Pacific Islanders, 12.11; American Indian/Alaska Natives, 14.56; Hispanic individuals, 15.48. **Conclusion:** HCC incidence is now decreasing in all US racial/ethnic populations; the onset of decline varied markedly by race/ethnicity. Compared to the White non-Hispanic population, HCC rates remained much higher in all other groups.

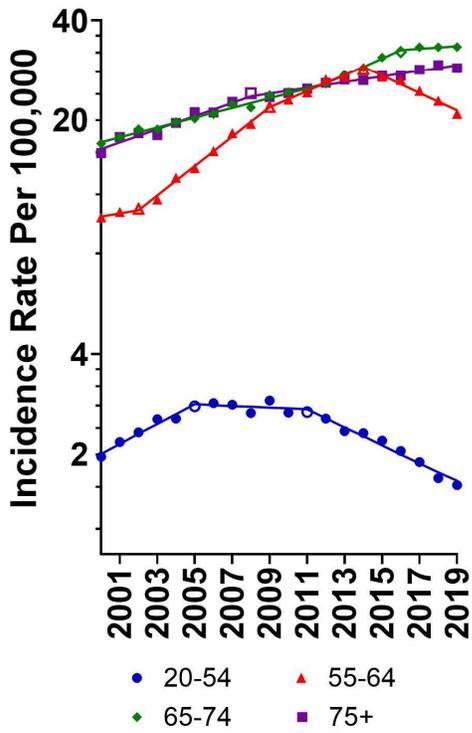
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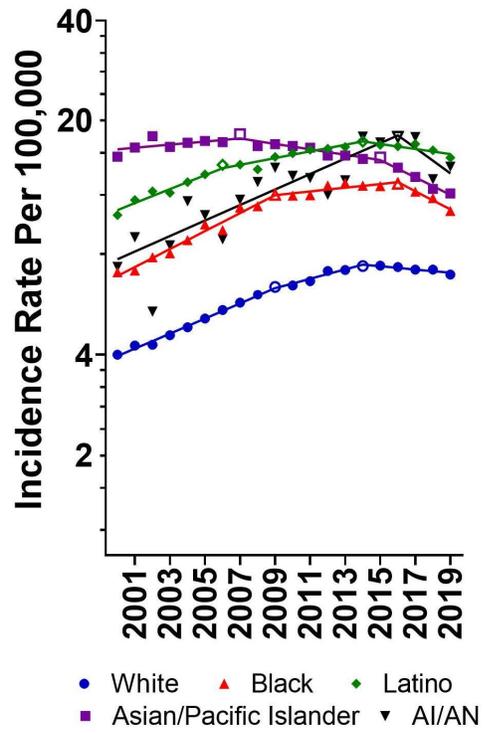
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Disclosures:  
The following people have nothing to disclose: Thomas R. O'Brien

## NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) IS ASSOCIATED WITH SIGNIFICANT IMPAIRMENT OF WORK PRODUCTIVITY: DATA FROM THE GLOBAL NASH REGISTRY<sup>â„¢</sup>

*Zobair M. Younossi<sup>1,2</sup>, Yusuf Yilmaz<sup>3</sup>, Ming-Lung Yu<sup>4</sup>, Vincent Wai-Sun Wong<sup>5</sup>, Marlen Ivon Castellanos Fernandez Sr.<sup>6</sup>, Vasily A Isakov<sup>7</sup>, Ajay K. Duseja<sup>8</sup>, Nahum Mendez-Sanchez<sup>9</sup>, Yuichiro Eguchi<sup>10</sup>, Elisabetta Bugianesi<sup>11</sup>, Patrizia Burra<sup>12</sup>, Jacob George<sup>13</sup>, Jian-Gao Fan<sup>14</sup>, George V Papatheodoridis<sup>15</sup>, Maria Buti Sr.<sup>16</sup>, Wah Kheong Chan<sup>17</sup>, Khalid Aida Alswat<sup>18</sup>, Saeed S. Hamid<sup>19</sup>, Ashwani K. Singal<sup>20</sup>, Manuel Romero-GÃ³mez<sup>21</sup>, Stuart C. Gordon<sup>22</sup>, Stuart Roberts<sup>23</sup>, Mohamed El Kassas<sup>24</sup>, Gamal Esmat<sup>25</sup>, Marcelo Kugelman<sup>26</sup>, Janus Ong<sup>27,28</sup>, Brian P. Lam<sup>2,29,30</sup>, Issah Younossi<sup>31</sup>, Andrei Racila<sup>1,30,32</sup>, Linda Henry<sup>1,31,33</sup>, Maria Stepanova<sup>1,30,31</sup> and Saleh Alqahtani<sup>28,34</sup>*, (1)Inova Medicine, Inova Health System, Falls Church, VA, United States, (2)Center for Liver Diseases, Department of Medicine, Inova Fairfax Medical Campus, Falls Church, VA, United States, (3)Department of Gastroenterology, Marmara University, (4)School of Medicine, College of Medicine, National Sun Yat-Sen University, (5)Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, (6)Institute of Gastroenterology, University of Medical Science., (7)Gastroenterology and Hepatology, Chief of Gastroenterology and Hepatology at Institute of Nutrition in Moscow, Russia, (8)Department of Hepatology, Chandigarh, India, Postgraduate Institute of Medical Education and Research, (9)Liver Research Unit, medica Sur Clinic & Foundation, Mexico City, Mexico, National Autonomous University of Mexico, (10)Locomedical Medical Cooperation, Ogi, Saga, Japan, Locomedical General Institute, (11)Department of Medical Sciences, University of Torino, (12)12. Multivisceral Transplant Unit, Gastroenterology, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy Division of Gastroenterology, Department of Medical Sciences, University of Torino, Torino, Italy, (13)Storr Liver Centre, Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, (14)Department of Gastroenterology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine, (15)General Hospital of Athens "Laiko", Medical School of National & Kapodistrian University of Athens, (16)Hospital General Universitari Vall d'Hebron and Ciberehd, Barcelona, Spain, (17)Gastroenterology and Hepatology Unit, Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia, (18)Liver Disease Research Center, Department of Medicine, College of Medicine, King Saud University, Saudi Arabia, (19)Medicine, Aga Khan University Hospital, Karachi, Pakistan, (20)University of Utah, (21)Department of Digestive Disease, Institute of Biomedicine of Seville, University of Seville, Seville, Andalusia, Spain, (22)Henry Ford Hospital System, Department of Hepatology and Gastroenterology, Detroit MI, United States, (23)Department of Hepatology and Gastroenterology, Melbourne Victoria, Australia, The Alfred, (24)Endemic Medicine Department, Faculty of Medicine, Helwan University, Cairo, Egypt, (25)Endemic Medicine and Hepato-Gastroenterology Department, Cairo University, (26)South Denver Gastroenterology, PC, Denver, CO, United States, (27)College of Medicine, University of the Philippines, Manila, Philippines, (28)Center for Outcomes Research in Liver Disease, Washington DC, United States, (29)Medicine, Inova Fairfax Hospital, (30)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, United States, (31)Center for Outcomes Research in Liver Diseases, Washington, DC, United States, (32)Center for Liver Diseases and Department of Medicine, Inova Fairfax Hospital, Falls Church, VA, United States, (33)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, (34)Liver Transplant Centre, King Faisal Specialist Hospital and Research Center

**Background:** Chronic liver diseases (CLDs) such as NAFLD can cause impairment of health-related quality of life and other patient-reported outcomes. Additionally, CLDs can be responsible for a reduction in work productivity due to both missed time at work (absenteeism) and decreased productivity while working (presenteeism). The aim was to evaluate work productivity impairment (WPI) in patients with NAFLD. **Methods:** The Global NASH Registry<sup>â„¢</sup> includes NAFLD enrolled from real-life practices. The WPI scores including absenteeism and presenteeism (all range 0-1 with higher scores indicating greater work productivity impairment) were calculated from the Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP) instrument. **Results:** A total of 3421 NAFLD patients were included [18 countries; age 52 $\pm$ 13 years, 47% male, 18% cirrhosis, 47% type 2 diabetes, 38% history of anxiety, 21% depression, 47% clinically overt fatigue, 48% employed]. For the subjects, WPI score [mean (SD)] was 0.205 (0.300) including 0.051 (0.182) absenteeism, 0.159 (0.250) presenteeism. In multivariate analysis, independent predictors of higher WPI (worse work productivity) among NAFLD subjects, adjusted for the country of enrollment, were history of anxiety (beta $\pm$ SE = 0.069 $\pm$ 0.020), depression (0.054 $\pm$ 0.026), and clinically overt fatigue (0.095 $\pm$ 0.019) (all  $p < 0.05$ ). On the other hand, there was no associations of WPI in NAFLD with obesity, type 2 diabetes, the presence of cirrhosis or FIB-4 score (all  $p > 0.10$ ). In comparison to historic data from clinical trial enrollees with biopsy-proven NASH (pooled N=2634, 67% diabetes, 33% cirrhosis, 51% employed), subjects with NAFLD enrolled from real-life practices had higher WPI: 0.205 (0.300) vs. 0.135 (0.230), absenteeism 0.051 (0.182) vs. 0.034 (0.140), presenteeism 0.159 (0.250) vs. 0.102 (0.175) (all  $p < 0.01$ ). However, after adjustment for clinico-demographic factors (age, sex, country of enrollment, comorbidities), the association of WPI of NAFLD patients with enrollment setting (real-life setting vs. clinical trial setting) was not significant ( $p = 0.98$ ). **Conclusion:** Patients with NAFLD and NASH have significant impairment of their work productivity which could add substantially to the societal and personal burden of the disease.

Disclosures:

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## **SAFETY AND TOLERABILITY CHARACTERIZATION OF MARALIXIBAT IN INFANTS WITH ALGS FROM 2 MONTHS OF AGE: INTERIM RESULTS FROM THE RISE STUDY**

*Emmanuel Gonzales<sup>1,2</sup>, Irena Jankowska<sup>3</sup>, Simon P Horslen<sup>4</sup>, Udem Ekong<sup>5</sup>, Philip Rosenthal<sup>6</sup>, Aotienne Sokal<sup>7</sup>, Chuan-Hao Lin<sup>8</sup>, Will Garner<sup>9</sup>, Jillian Elliott<sup>9</sup>, Tiago Nunes<sup>9</sup> and Richard J. Thompson<sup>10</sup>, (1)Inserm Umr-1193, Hepatov, Université Paris-Saclay, Orsay, France, (2)Hépatologie Et Transplantation Hépatique Pédiatriques, Centre De Recherche National De l'Association Des Voies Biliaires Et Des Cholestases Génétiques, Fsmr Filfoie, Hôpital Bicêtre, AP-HP, Université Paris-Saclay, Kremlin-Bicêtre, France, (3)Gastroenterology, Hepatology, Nutritional Disorders and Paediatrics, Children's Memorial Health Institute, Warsaw, Poland, (4)Pediatrics, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania, (5)Medstar Georgetown Transplant Institute, Medstar Georgetown University Hospital, Washington DC, (6)Pediatrics, Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of California, San Francisco, San Francisco, California, (7)Pediatric Hepatology, Uclouvian, Cliniques Universitaires St Luc, Brussels, Belgium, (8)Children's Hospital Los Angeles, Los Angeles, California, (9)Mirum Pharmaceuticals, Inc, Foster City, California, (10)Institute of Liver Studies, King's College London, London, United Kingdom*

**Background:** Alagille syndrome (ALGS) is a rare cholestatic liver disease associated with high disease burden due to chronic cholestasis and pruritus. Maralixibat (MRX) is an ileal bile acid transporter inhibitor (IBATI) approved by the FDA for the treatment of cholestatic pruritus in patients with ALGS  $\geq 1$  year of age. MRX has a well-characterized safety profile with  $>5$  years of data in  $>150$  children with cholestasis  $\geq 1$  year of age. The aim of the RISE study is to evaluate the safety of MRX in infants with ALGS and progressive familial intrahepatic cholestasis (PFIC)  $<1$  year of age in an ongoing, open-label, Phase 2 trial. An interim analysis for the ALGS cohort is reported here. **Methods:** The study includes a 13-week core treatment period. At the end of this period, participants continue into a long-term extension. Participants received MRX (380  $\mu\text{g}/\text{kg}$  QD) in addition to standard-of-care. Infants with ALGS and cholestasis who were  $<1$  year of age were enrolled. Eligibility criteria included: body weight of  $\geq 2.5$  kg, gestational age  $\geq 36$  weeks, clinical and laboratory evidence of cholestasis, and exclusion of decompensated cirrhosis. Safety was assessed by the incidence of treatment-emergent adverse events (TEAEs) and change from baseline to week 13 in laboratory parameters. Pharmacokinetics (PK) of MRX was evaluated. **Results:** 8 participants, median age of 7 months (2-10 months) at study entry, with complete 13-week core study follow-up were included (median exposure: 136.5 days). 7 out of 8 participants (87.5%) experienced  $\geq 1$  TEAE; 2 (25%) had a TEAE related to study drug (both Grade 1 diarrhea, resolved). The most frequent TEAEs were infections (6 participants; 75%) and gastrointestinal disorders (5 participants; 62.5%). All events were self-limiting and resolved with no drug interruption or change in dose. Most TEAEs were Grade 1 in severity and not related to study drug. Four participants (50%) had 7 SAEs, not related to study drug, all resolved, and dose not changed. No drug discontinuations or deaths were reported. Fluctuations in AST and ALT were observed without dose adjustment. Variable reductions in bilirubin were seen in some patients, but the clinical significance needs to be evaluated. MRX was below the limit of quantification, or minimally detected, confirming similar PK profile to children  $>1$  year of age. **Conclusion:** MRX was well-tolerated, with minimal to no absorption in infants with ALGS  $<1$  year of age, indicating that MRX may be used in children as young as 2 months of age.

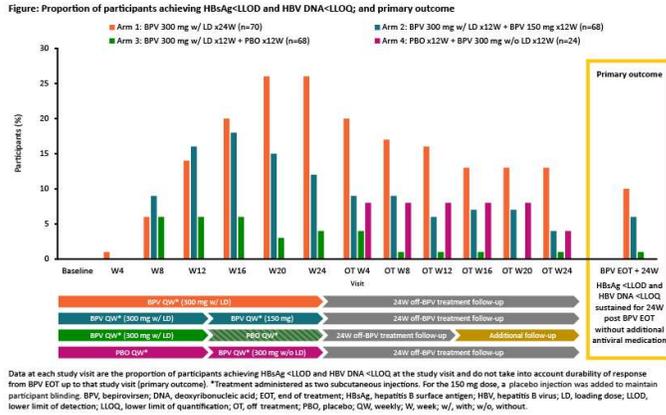
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## HBV DNA AND HBsAg LOSS WITH BEPIROVIRSEN MONOTHERAPY IN PATIENTS WITH CHRONIC HEPATITIS B INFECTION NOT ON NUCLEOS(T)IDE ANALOGUE THERAPY: B-CLEAR STUDY END-OF-STUDY RESULTS

*Seng Gee Lim<sup>1</sup>, Man-Fung Yuen<sup>2</sup>, Cristina Pojoga<sup>3,4</sup>, Harry L.A. Janssen<sup>5,6</sup>, Robert Plesniak<sup>7</sup>, Keiji Tsuji<sup>8</sup>, Ewa Janczewska<sup>9</sup>, Corneliu Petru Popescu<sup>10</sup>, Pietro Andreone<sup>11</sup>, Jinlin Hou<sup>12</sup>, Manuela Arbune<sup>13</sup>, Diana Stefanova-Petrova<sup>14</sup>, Jun Inoue<sup>15</sup>, Teerha Piratvisuth<sup>16</sup>, Young-Suk Lim<sup>17</sup>, Apinya Leerapun<sup>18</sup>, Masanori Atsukawa<sup>19</sup>, Jidong Jia<sup>20</sup>, Madaline Eternity Labio<sup>21</sup>, Jennifer Cremer<sup>22</sup>, Robert Elston<sup>23</sup>, Tamara Lukić<sup>24</sup>, Geoffrey Quinn<sup>23</sup>, Stuart Kendrick<sup>23</sup>, Helene Plein<sup>25</sup>, Fiona Campbell<sup>23</sup>, Melanie Paff<sup>26</sup> and Dickens Theodore<sup>22</sup>*, (1)National University Health System, Singapore, Singapore, (2)Queen Mary Hospital, the University of Hong Kong, Hong Kong, China, (3)Regional Institute of Gastroenterology and Hepatology, Cluj-Napoca, Romania, (4)Babeș-Bolyai University, Department of Clinical Psychology and Psychotherapy, International Institute for Advanced Study of Psychotherapy and Applied Mental Health, Cluj-Napoca, Romania, (5)Toronto General Hospital, Toronto, Canada, (6)Erasmus Medical Center, Rotterdam, Netherlands, (7)University of Rzeszow Centrum Medyczne w Lancucie Sp. z o.o., Lancut, Poland, (8)Department of Gastroenterology, Hiroshima Red Cross Hospital & Atomic-Bomb Survivors Hospital, Hiroshima, Japan, (9)Faculty of Health Sciences in Bytom, Medical University of Silesia, Poland, (10)Dr Victor Babes Clinical Hospital of Infectious and Tropical Diseases, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania, (11)Azienda Ospedaliero-Universitaria Di Modena, Modena, Italy, (12)Nanfeng Hospital, Southern Medical University, Guangzhou, China, (13)Sf.Cuv. Parascheva Infectious Diseases Clinical Hospital, Galati, Romania, (14)Diagnostic Consultative Center Alexandrovska, Sofia, Bulgaria, (15)Tohoku University Hospital, Sendai, Japan, (16)Nkc Institute of Gastroenterology and Hepatology, Songkhla, Thailand, (17)Asan Medical Center, University of Ulsan College of Medicine, South Korea, (18)Chiang Mai University, Chiang Mai, Thailand, (19)Department of Internal Medicine, Division of Gastroenterology and Hepatology, Nippon Medical School, Tokyo, Japan, (20)Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China, (21)Makati Medical Center, Makati, Philippines, (22)GSK, Durham, NC, USA, (23)GSK, Stevenage, UK, (24)GSK, Dubai, UAE, (25)GSK, Brentford, UK, (26)GSK, Collegeville, PA, USA

**Background:** Bepirovirsen, (BPV; GSK3228836) an antisense oligonucleotide, targets all hepatitis B virus (HBV) mRNAs and decreases viral proteins. The B-Clear trial investigated BPV efficacy and safety in patients (pts) with chronic hepatitis B (CHB) on and not on nucleos(t)ide analogue (NA) therapy. We present end-of-study (24-weeks [wks] off-BPV treatment) results for pts not on NA. **Methods:** Multicenter, randomized, partial-blind (investigator unblinded), parallel-cohort study in pts with CHB. Pts with alanine aminotransferase (ALT) <3 $\times$ —upper limit of normal, HBV DNA >2000 IU/mL and hepatitis B surface antigen (HBsAg) >100 IU/mL were randomized (3:3:3:1) to 1 of 4 treatment arms to receive up to 300 mg BPV administered as two subcutaneous injections weekly for 12 or 24 wks with or without loading doses (see arms in **Figure**). Pts were stratified by baseline hepatitis B e antigen (HBeAg; positive/negative) and HBsAg level ( $\geq 3 \log_{10}$  IU/mL). Primary outcome: proportion of pts achieving HBsAg <lower limit of detection (LLOD) and HBV DNA <lower limit of quantification (LLOQ) maintained for 24 wks without antiviral medication after planned BPV end of treatment (EOT). Safety was assessed via adverse event (AE) monitoring. **Results:** Intent-to-treat population included 230 pts (54% male, 57% Asian, 74% HBeAg negative, 81% HBsAg >3 $\log_{10}$  IU/mL). Primary outcome was achieved in 7 (10%), 4 (6%), 1 (1%) and 0 pts in arms 1-4, respectively; data at specific study visits are shown in **Figure**. A greater proportion of pts with low ( $\geq 3 \log_{10}$  IU/mL) vs high (>3 $\log_{10}$  IU/mL) baseline HBsAg levels achieved the primary outcome (Arm 1: 25% vs 7%). Primary outcome was achieved in HBeAg negative but not HBeAg positive pts (Arm 1: 14% vs 0%). Serious AEs (SAEs) were reported in 11 (5%) pts and treatment-related SAEs in 3 (1%) pts. Treatment was discontinued in 23 pts (10%); 9 (4%) pts had an AE that led to treatment discontinuation. Most common AEs were injection site reactions (67%), pyrexia (23%) and ALT increase (21%). There were no clinically meaningful differences in AEs across treatment arms. **Conclusion:** BPV 300 mg x24 wks (Arm 1) was the most efficacious treatment regimen. Pts with low vs high baseline HBsAg (Arm 1: 25% vs 7%) or HBeAg negative vs positive (Arm 1: 14% vs 0%) were more likely to achieve HBsAg and HBV DNA loss 24 weeks after EOT. There were no safety signals to preclude further development. **Funding:** GSK [209668/NCT04449029] [on behalf of the B-Clear Study Group]



**Disclosures:**

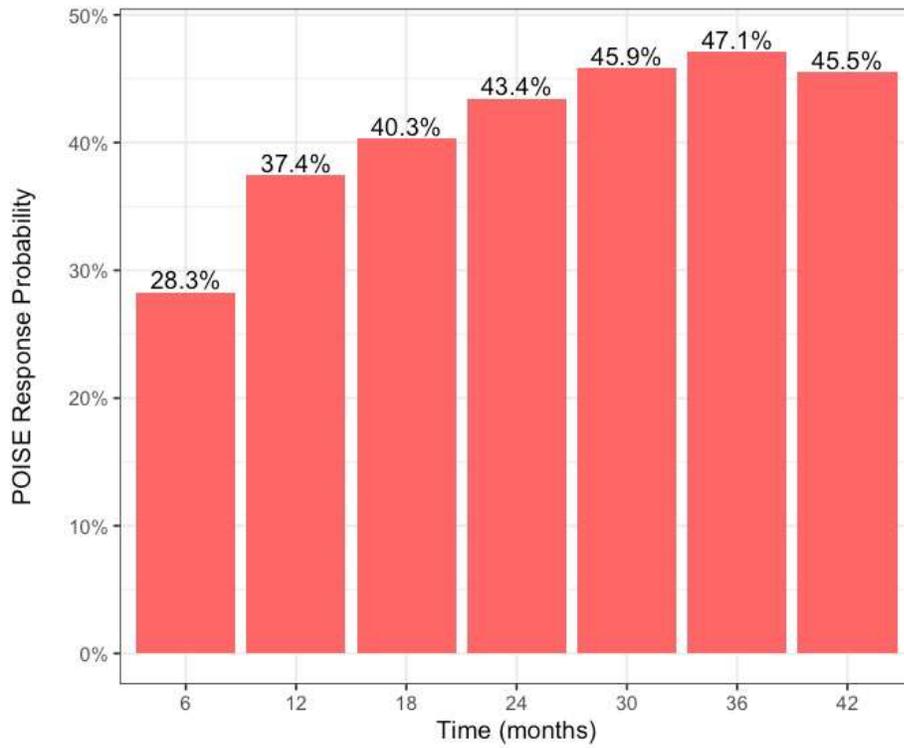
Jennifer Cremer - GSK: Employment; GSK: Stock Shareholder;

**REAL-WORLD DATA ON LONG TERM EFFICACY AND SAFETY OF OBETICHOLIC ACID FOR PRIMARY BILIARY CHOLANGITIS: FIRST RELEASE FROM THE ITALIAN RECAPITULATE STUDY**

Antonio De Vincentis<sup>1</sup>, Francesca Terracciani<sup>1</sup>, Daphne D'Amato<sup>2</sup>, Pietro Invernizzi<sup>3</sup>, Anna Morgando<sup>4</sup>, Ester Vanni<sup>4</sup>, Mauro Vigan<sup>5</sup>, Domenico Alvaro<sup>6</sup>, Rosanna Venere<sup>7</sup>, Ana Lleo<sup>8</sup>, Francesca Colapietro<sup>9</sup>, Elisabetta Degasper<sup>10</sup>, Raffaella Vigan<sup>11</sup>, Edoardo G. Giannini<sup>12</sup>, Sara Labanca<sup>13</sup>, Valentina Feletti<sup>14</sup>, Alessandro Mussetto<sup>14</sup>, Raffaele Cozzolongo<sup>15</sup>, Francesco Losito<sup>16</sup>, Maurizio Pompili<sup>17</sup>, Francesca Romana Ponziani<sup>17</sup>, Grazia Anna Niro<sup>18</sup>, Rosa Cotugno<sup>19</sup>, Pietro Pozzoni<sup>20</sup>, Luchino Chessa<sup>21</sup>, Giuseppe Cuccorese<sup>22</sup>, Valeria Pace Palitti<sup>23</sup>, Maurizio Russello<sup>24</sup>, Mariarita Cannav<sup>25</sup>, Evelise Frazzetto<sup>26</sup>, Gaetano Bertino<sup>26</sup>, Marco Marzoni<sup>27</sup>, Natalia Terreni<sup>28</sup>, Teresa Zolfino<sup>29</sup>, Carlo Saitta<sup>30</sup>, Adriano Pellicelli<sup>31</sup>, Barbara Coco<sup>32</sup>, Maurizia Brunetto<sup>32</sup>, Nora Cazzagon<sup>33</sup>, Annarosa Floreani<sup>34</sup>, Luigi Muratori<sup>35</sup>, Floriano Rosina<sup>36</sup>, Marco Di Stefano<sup>37</sup>, Gaetano Scifo<sup>38</sup>, Leonardo Baiocchi<sup>39</sup>, Giuseppe Grassi<sup>40</sup>, Rodolfo Sacco<sup>41</sup>, Antonio Izz<sup>42</sup>, Saveria Lory Croc<sup>43,44</sup>, Cecilia Fiorini<sup>41</sup>, Fabio Marra<sup>45</sup>, Loredana Simone<sup>46</sup>, Olivia Morelli<sup>47</sup>, Ludovico Abenavoli<sup>48</sup>, Fabrizio Pizzolante<sup>49</sup>, Nicoletta De Matthaeis<sup>49</sup>, Miki Scaravaglio<sup>50</sup>, Giancarlo Gimignani<sup>51</sup>, Valentina Boano<sup>52</sup>, Giulia Francesca Manfredi<sup>53</sup>, Massimo Marignani<sup>54</sup>, Silvia Fanella<sup>54</sup>, Marco Giacchetto<sup>55</sup>, Antonino Castellaneta<sup>56</sup>, Guido Poggi<sup>57</sup>, Valerio Buzzanca<sup>27</sup>, Paolo Scivetti<sup>58</sup>, Annalisa Tortora<sup>17</sup>, Silvia Casella<sup>59</sup>, Valentina Bellia<sup>60</sup>, Barbara Federica Omazzi<sup>61</sup>, Giuliano Alagna<sup>62</sup>, Chiara Ricci<sup>63</sup>, Paolo Poisa<sup>64</sup>, Cristina Rigamonti<sup>65</sup>, Vincenza Calvaruso<sup>65</sup>, Marco Carbone<sup>3</sup> and Umberto Vespasiani-Gentilucci<sup>1</sup>, (1)Internal Medicine and Hepatology, University Campus Bio-Medico of Rome, (2)Gastroenterology Unit, Città Della Salute e Della Scienza, Turin, (3)Division of Gastroenterology and Center for Autoimmune Liver Diseases, San Gerardo Hospital, Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy, (4)Department of Medical Sciences, Division of Gastroenterology and Hepatology, a.O. Città Della Salute e Della Scienza Di Torino, University of Turin, Turin, Italy, (5)Division of Hepatology, Ospedale San Giuseppe, Università Di Milano, (6)Translational and Precision Medicine, Sapienza University of Rome, Italy,, (7)Department of Translation and Precision Medicine, Sapienza University of Rome, Rome, Italy, (8)Humanitas Research Hospital, (9)Humanitas University, Rozzano (Milan), Italy, Division of Internal Medicine and Hepatology, Humanitas Clinical Research Center Irccs, (10)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy, (11)Hepatology and Gastroenterology, Asst GOM Niguarda, (12)Gastroenterology Unit, Department of Internal Medicine, University of Genoa, (13)Ospedale Policlinico San Martino, Genova, (14)Gastroenterology Unit, Santa Maria Delle Croci Hospital, Ravenna, Italy, (15)Division of Gastroenterology, National Institute of Gastroenterology S De Bellis, Castellana Grotte, Bari, Italy, (16)Gastroenterology Unit, National Institute of Gastroenterology "S De Bellis" Reseach Hospital, Castellana Grotte (Bari), Italy, (17)Fondazione a Gemelli Hospital Irccs, Internal Medicine, Gastroenterology, Hepatology, (18)Gastroenterology Unit, Fondazione Casa Sollievo Della Sofferenza Irccs, San Giovanni Rotondo (Foggia), Italy, (19)Medical Sciences, Irccs Casa Sollievo Della Sofferenza, (20)Internal Medicine, Asst Lecco Hospital, (21)University of Cagliari, (22)Internal Medicine, Ospedale Barletta, (23)Hepatology Unit, Pescara General Hospital, (24)Arnas Garibaldi-Nesima, (25)Liver Unit, Arnas Garibaldi, Catania, Italy, (26)Gastroenterology and Hepatology Unit, Policlinico-Vittorio Emanuele, (27)Università Politecnica Delle Marche, (28)Division of Gastroenterology, Valduce Hospital, Como, (29)SC Gastroenterologia AO G. Brotzu, Cagliari, Italy, (30)Department of Clinical and Experimental Medicine, Division of Medicine and Hepatology, University of Messina, (31)Hepatology Unit, San Camillo Forlanini Hospital, Rome, Italy, (32)Hepatology Unit, University Hospital of Pisa, Italy, (33)Department of Surgery, Oncology and Gastroenterology, University of Padova, (34)Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy, (35)Medical Sciences and Surgery, University of Bologna, (36)Medical Team Torino, (37)Department of Infectious Diseases, Umberto I Hospital, Siracusa, Italy, (38)Siracusa, Infectious Diseases Unit, (39)Liver and Transplant Unit, Tor Vergata University Hospital, (40)Malattie Dell' Apparato Digerente, Policlinico Torvergata, (41)Gastroenterology Unit, Ospedali Riuniti, Foggia, Italy, (42)Department of Infectious Diseases, D. Cotugno Hospital, Napoli, Italy, (43)Fondazione Italiana Fegato, (44)Clinica Patologie Fegato, Azienda Sanitaria Universitaria Integrata Di Trieste, (45)Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy, (46)Azienda Ospedaliero-Universitaria Di Ferrara, Ferrara, Italy, (47)S.C. Gastroenterologia Ed Epatologia, Dipartimento Di Medicina, Università Degli Studi Di Perugia, Italy, (48)Department of Health Sciences, University "Magna Graecia" of Catanzaro, Italy, (49)Uoc of Gastroenterology, Gastroenterological, Endocrine-Metabolic and Nephro-Urological Sciences Department, Fondazione Policlinico Universitario a Gemelli Irccs, Università Cattolica Del Sacro Cuore, Rome, Italy, (50)Division of Gastroenterology, Centre for Autoimmune Liver Diseases, Department of Medicine and Surgery, University of Milano-Bicocca, European Reference Network on Hepatological Diseases (ERN RARE-LIVER), San Gerardo Hospital, Monza, Italy, (51)Unit of Internal Medicine, San Paolo Hospital, Civitavecchia, (52)Department of Gastroenterology and Endoscopy, Cardinal Massaia Hospital, Asti, Italy, (53)Dipartimento Di Medicina Traslazionale, Università Del Piemonte Orientale, Novara, Italy and Division of Internal Medicine, Aou Maggiore Della Carità, Novara, Italy, (54)Digestive and Liver Disease Department, School of Medicine and Psychology University "Sapienza", Azienda Ospedaliera S. Andrea, Rome, Italy, (55)Department of Gastroenterology and Hepatology, University of Palermo, Palermo, Italy, (56)Gastroenterology Unit, Policlinico Di Bari Hospital, Bari, Italy, (57)Oncology Unit, Istituto Di Cura Città Di Pavia, Pavia, Italy, (58)Internal Medicine Unit, Azienda Sanitaria Locale Di Biella, Biella, Italy, (59)Hepatology Unit, Spedali Civili Gardone Val Trompia, Brescia, Italy, (60)Hepatology Unit,

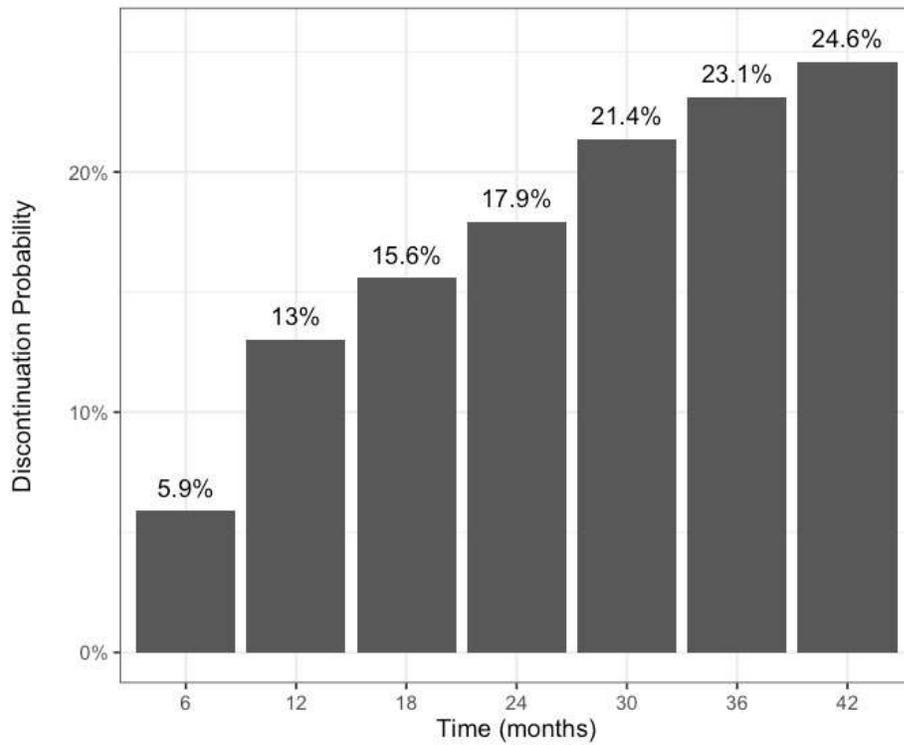
Valtellina e Alto Lario Hospital, Sondrio, Italy, (61)Guido Salvini Hospital, Rho, Italy, (62)Uoc Medocina Interna, Ospedale SS. Annunziata Sassari, (63)Internal Medicine, Spedali Civili, Brescia, Italy, (64)Spedali Civili, Brescia, Italy, (65)Department of Internal Medicine, Università Del Piemonte Orientale, Novara, Italy

**Background:** Results from real-world experiences on obeticholic acid (OCA) in primary biliary cholangitis (PBC) are somehow conflicting and limited by sample size and short follow-up. Aim of the RECAPITULATE study is to provide longer term assessments of clinical effectiveness and safety of OCA in a sizeable cohort. **Methods:** Data from secondary and tertiary centres, enrolled in the "Italian PBC registry", "Club Epatologi Ospedalieri" (CLEO) and "Associazione Italiana Gastroenterologi Ospedalieri" (AIGO) on patients in OCA were captured prospectively. Efficacy was evaluated according to Poise criteria. Cumulative incidences of OCA response and discontinuation were evaluated through Aalen-Johansen (taking into account the competing risk of discontinuation) and Kaplan-Meier estimators, respectively. The analysis of risk factors was carried out through Cox proportional hazard models. **Results:** A total of 442 patients (median age 57.8 years, women 88%, median disease duration 7 years) on OCA therapy for at least 6 months were enrolled until July 31<sup>st</sup> 2022 from 50 Italian centres. Fifty-nine (13%) were PBC/autoimmune hepatitis(AIH) overlap, and 152 (34%) were cirrhotics (Child-Pugh class A/B/C 94/5/1%). Nine patients (2%) received OCA due to UDCA intolerance, while the others for inadequate response (ALP/ULN  $\geq 1.5$  and/or  $1 >$  bilirubin  $< 2$  mg/dL after  $\geq 1$  year of UDCA treatment). Median time on OCA therapy was 24 months (interquartile range 12-36, max 48). Response probabilities were 37.4/43.4/47.1% at 12/24/36 months (**Figure 1, upper panel**). OCA was permanently discontinued by 86 patients (19%). Discontinuation probabilities were 13.0/17.9/23.1% at 12/24/36 months (**Figure 1, lower panel**). The main causes of discontinuation were pruritus (41 patients, 48%) and hepatic events (18 patients, 21%). Cirrhotic patients showed lower response rates (25.9/27.7/34.8% at 12/24/36 months;  $p < 0.01$  Vs non-cirrhotics), mainly due to higher discontinuation rates (19.9/27.6/34.6% at 12/24/36 months;  $p < 0.01$  Vs non-cirrhotics). PBC/AIH overlap did not show significantly different risks of response or discontinuation. Only pre-treatment ALP (aHR 0.67, 95%CI 0.54-0.82) and total bilirubin (aHR 0.42, 95%CI 0.25-0.71) were independent predictors of response, while univariate associations of cirrhosis (HR 0.57, 95%CI 0.41-0.79) and concomitant fibrate therapy (HR 0.11, 95%CI 0.02-0.8) were lost in the multivariate model. **Conclusion:** First results from the RECAPITULATE STUDY confirm long-term efficacy and safety of OCA in patients with PBC in a real-world setting.



Sbjs on OCA

Time (months)	Sbjs on OCA
6	416
12	354
18	294
24	248
30	182
36	132
42	52



Disclosures:  
 The following people have nothing to disclose: Antonio De Vincentis



5024

## ASYMPTOMATIC HEPATITIS A VIRUS INFECTION IN PLASMA DONORS WITH HIGH VIRAL RNA TITERS

*Galileu Barbosa Costa, Henry Stanton and Gerardo Kaplan, Center for Biologics Evaluation and Research, U.S. Food and Drug Administration*

**Background:** Hepatitis A is a vaccine-preventable communicable liver disease caused by the hepatitis A virus (HAV). HAV is a member of the genus *Hepatovirus* (family *Picornaviridae*) and is primarily transmitted via the fecal-oral route. However, parenteral transmission of HAV can also occur by blood and blood products, which poses a significant risk to the safety of the blood supply. The current HAV epidemic in the US that started in 2016 and spread to most States resulted in a significant increase in the number of reported cases with an unprecedented number of hospitalization and deaths. According to the Centers for Disease Control and Prevention as of August 5, 2022, there were a total of 44,436 cases of acute HAV infections that resulted in 27, 163 hospitalizations (61%) and 424 deaths (~1%), (<https://www.cdc.gov/hepatitis/outbreaks/2017March-HepatitisA.htm>). Because changes in the epidemiology of HAV in the US are poorly understood, we evaluated the dynamic of HAV infection among plasma donors to better understand the course of infection and immune response in asymptomatic versus symptomatic infections. **Methods:** We evaluated in serial plasma donations levels of 1) HAV RNA by RT-qPCR (Costafreda et al., 2006); 2) alanine aminotransferase (ALT) using a colorimetric assay (Amplite<sup>®</sup>, AAT Bioquest); 3) anti-HAV IgA, IgG, and IgM antibodies by an in-house developed Luminex assays; and 4) viral particles and exosomes containing HAV RNA using iodixanol density gradients. **Results:** Surprisingly, we identified asymptomatic plasma donors who continued to donate weekly despite having high levels of HAV RNA, ALT, and antibodies commensurate with symptomatic infections. Furthermore, we also detected naked HAV particles circulating in blood in disagreement with published data indicating that only membrane-associated HAV is present in blood (Feng et al., 2013). **Conclusion:** Our results suggest that HAV-infected asymptomatic individuals with high viral loads have a greater potential of spreading the virus than those who develop the disease and are hospitalized or remain isolated. Our data on asymptomatic infections may explain why the current HAV epidemic in the US continues abated compared to other post-vaccination era outbreaks that were successfully contained within months.

Disclosures:

The following people have nothing to disclose: Galileu Barbosa Costa

5025

## **ADENOVIRUS IS NOT DETECTED IN LIVER TISSUE FROM A LARGE MULTICENTER COHORT OF CHILDREN WITH ACUTE LIVER FAILURE**

*Catherine A Chapin<sup>1</sup>, Tamir Diamond<sup>2</sup>, Rebecca M Harris<sup>3</sup>, Olivia Vaccaro<sup>4</sup>, Kathleen M. Loomes<sup>2</sup>, Edward M Behrens<sup>5</sup> and Estella M. Alonso<sup>1</sup>, (1)Division of Gastroenterology, Hepatology, and Nutrition, Ann & Robert H. Lurie Children's Hospital of Chicago, (2)Division of Gastroenterology, Hepatology, and Nutrition, Children's Hospital of Philadelphia, (3)Division of Infectious Diseases, Children's Hospital of Philadelphia, (4)Pathology and Laboratory Medicine, Children's Hospital of Philadelphia, (5)Division of Rheumatology, Children's Hospital of Philadelphia*

**Background:** Since late 2021 there has been an increase in cases of severe acute hepatitis of unknown cause in children, with some progressing to pediatric acute liver failure (PALF) and requiring liver transplantation. Human adenovirus (AdV) viremia, specifically type 41, has been identified in many of these cases. However, AdV has been infrequently associated with acute hepatitis in the past and the causative nature of these findings remains unclear. Our group studies the immune mechanisms driving cases of unknown acute hepatitis and PALF. We previously described dense CD8 T-cell inflammation as a characteristic feature of liver tissue from indeterminate PALF subjects within the multicenter PALF study group (PALFSG) cohort. In the present study we tested these PALFSG liver tissue samples for AdV to determine whether AdV could be a cause of the liver injury. **Methods:** 44 children aged 1-17 years with archived liver tissue specimens from the PALFSG registry between 2007-2014 were included. 35 (80%) had indeterminate diagnosis and 9 had other diagnoses including acetaminophen toxicity (n=2), hemophagocytic lymphohistiocytosis (n=2), Epstein Barr Virus (EBV) (n=1), influenza A (n=1), parvovirus (n=1), Wilson disease (n=1), and other autoimmune (n=1). Results of any previously reported serum viral testing was collected as available. Quantitative polymerase chain reaction (qPCR) testing for AdV 40/41 was performed on DNA isolated from frozen liver tissue. **Results:** Subjects were median age 4 years, 52% male, and all underwent liver transplant. Serum AdV PCR testing was negative for 19 (43%) subjects, with 25 (57%) having no results. Within the indeterminate group, most other viral testing was negative, with 6 cases with a positive test reported: cytomegalovirus (n=3), EBV (n=2), herpes simplex virus (n=2) and human herpes virus-6 (n=1). All archived liver tissue specimens tested were negative for AdV 40/41. **Conclusion:** In a multicenter, longitudinal cohort of children with PALF primarily of indeterminate etiology we did not identify any cases of liver tissue AdV 40/41 qPCR positivity. This is the largest sample of PALF specimens with AdV testing reported to date. These findings suggest that AdV was not a common cause of indeterminate PALF between 2007-2014. The significance of the recent surge of PALF cases with AdV positivity remains unknown and requires further study.

Disclosures:

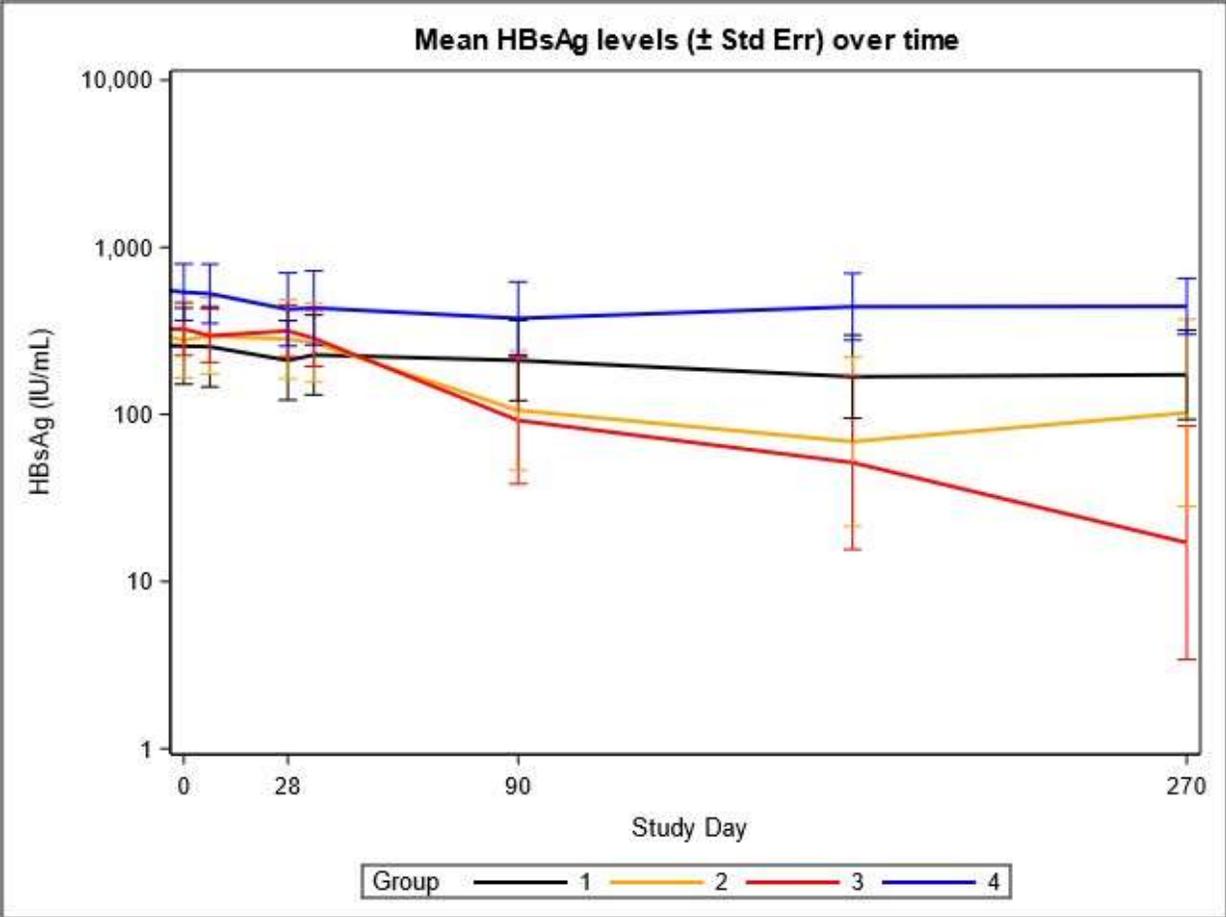
The following people have nothing to disclose: Catherine A Chapin

5026

**PHASE 1b/2a STUDY OF HETEROLOGOUS ChAdOx1-HBV/MVA-HBV THERAPEUTIC VACCINATION (VTP-300) COMBINED WITH LOW-DOSE NIVOLUMAB (LDN) IN VIRALLY-SUPPRESSED PATIENTS WITH CHB ON NUCLEOS(T)IDE ANALOGUES**

*Young-Suk Lim<sup>1</sup>, Tom Evans<sup>2</sup>, Eleanor Barnes<sup>3,4</sup>, Reena Mehta<sup>5</sup>, Louise Bussey<sup>2</sup>, Katie Anderson<sup>6</sup>, Antonella Vardeu<sup>7</sup>, Anthony Brown<sup>8</sup>, Chi-Yi Chen<sup>9</sup>, Wan-Long Chuang<sup>10</sup>, Gin-Ho Lo<sup>11</sup>, Won Young Tak<sup>12</sup> and Kuo-Chih Tseng<sup>13,14</sup>, (1)Department of Gastroenterology and Liver Center, Asan Medical Center, University of Ulsan College of Medicine, (2)Clinical Operations, Vaccitech, (3)National Institute for Health Research, Biomedical Research Centre, University of Oxford, (4)Nuffield Department of Medicine, University of Oxford, (5)Clinical Operations, Vaccitech Plc, (6)Immunology Research, Vaccitech Plc, (7)Research, Vaccitech, (8)Peter Medawar Building for Pathogen Research, University of Oxford, (9)Chia-Yi Christian Hospital, (10)Hepatobiliary Section, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, (11)E-Da Hospital, (12)School of Medicine, Kyungpook National University, Daegu, Republic of Korea, (13)Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, (14)Department of Internal Medicine, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation*

**Background:** Induction of a CD8+ T cell response to HBV is likely a required mechanism to achieve a functional cure of chronic hepatitis B (CHB). The highest magnitude CD8+ T cell responses achieved to date by vaccination in man have been induced using replication incompetent adenoviral vectors followed by attenuated poxvirus boosts. **Methods:** Vaccitech is developing a therapeutic HBV vaccine (VTP-300) using a chimpanzee adenoviral vector (ChAdOx1-HBV) and a heterologous Modified Vaccine Ankara boost (MVA-HBV) encoding polymerase, core, and S antigen from a consensus genotype C virus. A fully enrolled Phase 1b/2a trial is currently ongoing (n=55) in patients with CHB on prolonged antivirals (VL undetectable and HBsAg < 4,000 IU/ml). Group 1 (n=10), MVA-HBV d0 and d28; Group 2 (n=18), ChAdOx1-HBV d0 and MVA-HBV d28; Group 3 (n=18), Group 2 with low dose Nivolumab (LDN) (0.3 mg/kg IV) at d28; Group 4 (n=9) Group 2 with LDN at d0 and d28. HBV-specific T cell responses are assessed using genotype C and D HBV peptides in an IFN $\gamma$  ELISpot assay. **Results:** All 55 patients are enrolled with no concerning safety signal or vaccine-related SAEs reported. Mild transaminase flares associated with HBsAg decline occurred in two patients. Groups 1 and 4 had no appreciable change in HBsAg. In Group 2, three patients with starting HBsAg less than 50 IU/ml had lowering of -0.70, -0.73 and -1.39 log<sub>10</sub>. In Group 3, the mean log<sub>10</sub> reduction was -0.64 (N=12), -0.72 (N=10), and -0.99 (N=7) at 3, 6, and 9 months, respectively. All responses of >0.5 log<sub>10</sub> persisted for 8 months until study end. HBV T cell responses were assessed in 20 patients for HBV core (8/20), SAg (17/20) and pol (8/20). After prime peak mean magnitude total HBV specific T cell responses were 437, 244, 688, 332 SFU/10<sup>6</sup> in Groups 1-4, respectively. After boost vaccination peak (day 35) total HBV-specific T cell responses were 344, 689, 689, 277 SFU/10<sup>6</sup> in Groups 1-4, respectively. Responses were enhanced from baseline in 13 patients after prime and in 16 patients after boost. Responses were sustained out to 3-6 months in the majority. HBV inter-genotype cross reactive T cell responses were highly cross-reactive with genotype D peptides. **Conclusion:** VTP-300 immunotherapy, as monotherapy and when combined with low dose nivolumab at the boosting time point, has been immunogenic and shown reduction in HBsAg in well-controlled CHB patients, while exhibiting an excellent safety profile.



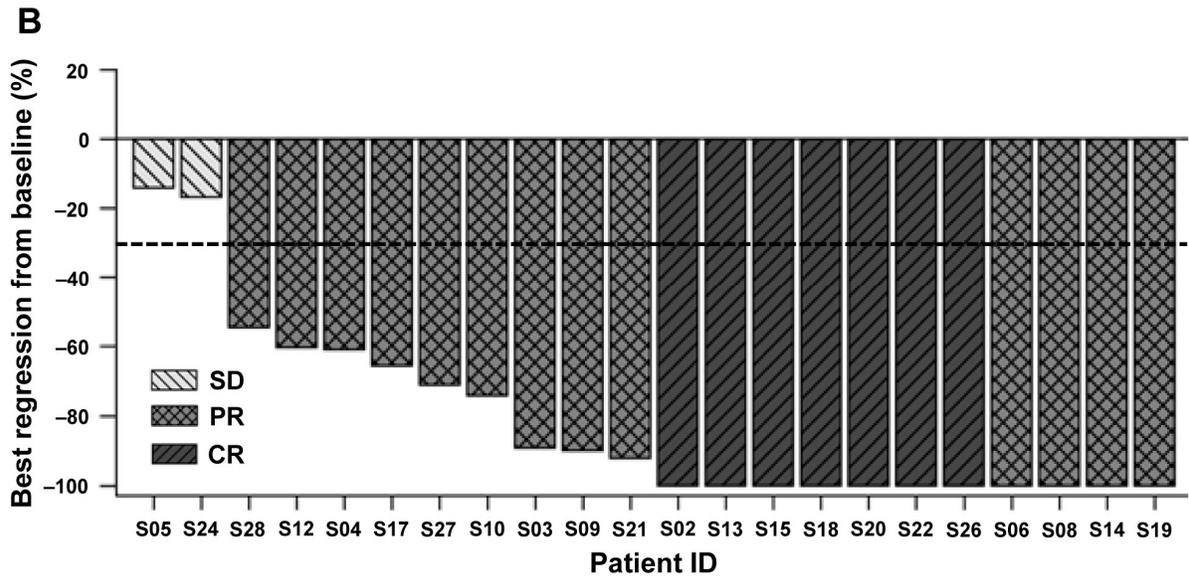
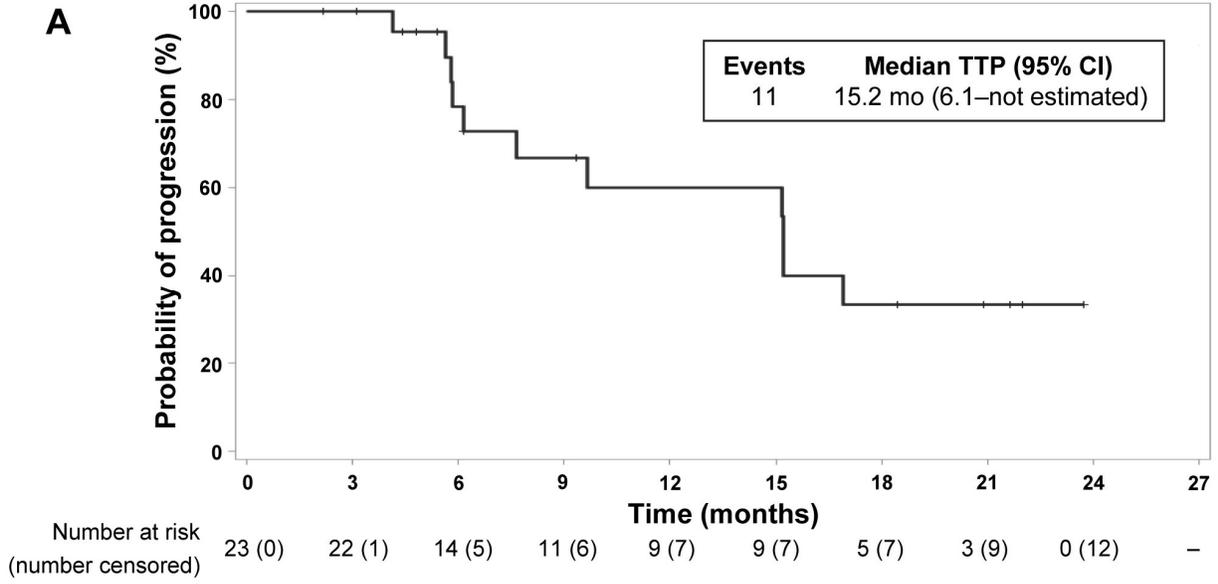
Disclosures:  
Young-Suk Lim - Vaccitech plc: Clinical investigator; Gilead Sciences: Advisory Committee or Review Panel; Gilead sciences: Grant/Research Support;

5027

**RADIOEMBOLIZATION WITH YTTRIUM-90 GLASS MICROSPHERES IN COMBINATION WITH DURVALUMAB IN LOCALLY ADVANCED UNRESECTABLE HEPATOCELLULAR CARCINOMA**

*Yun Bin Lee<sup>1</sup>, Joon Yeul Nam<sup>1</sup>, Eun Ju Cho<sup>1</sup>, Jeong-Hoon Lee<sup>1</sup>, Su Jong Yu<sup>1</sup>, Hyo-Cheol Kim<sup>2</sup>, Jin Chul Paeng<sup>3</sup>, Jung-Hwan Yoon<sup>1</sup> and Yoon Jun Kim<sup>1</sup>, (1)Department of Internal Medicine and Liver Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea, (2)Department of Radiology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea, (3)Department of Nuclear Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea*

**Background:** Synergistic effect of radiotherapy and immunotherapy for the treatment of hepatocellular carcinoma (HCC) has been reported in preclinical and clinical studies. The phase 3 HIMALAYA trial evaluating combination therapy with a single dose of tremelimumab (anti-CTLA-4) plus durvalumab (anti-PD-L1) and durvalumab monotherapy versus sorafenib in patients with unresectable HCC demonstrated the non-inferiority of durvalumab to sorafenib for overall survival (OS). The current phase 1/2a pilot trial evaluated safety and preliminary efficacy of combination treatment with radioembolization with yttrium-90 glass microspheres (Y90-radioembolization) plus durvalumab in patients with locally advanced unresectable HCC (ClinicalTrials.gov number, NCT04124991). **Methods:** Patients with Child-Pugh score  $\leq 7$  and locally advanced HCC, defined as Barcelona Clinic Liver Clinic (BCLC) stage B HCC or BCLC C disease without extrahepatic metastasis, received Y90-radioembolization followed by intravenous durvalumab 1500 mg 7-14 days after Y90-radioembolization and every 4 weeks thereafter. Primary endpoint was time to progression (TTP) assessed by modified RECIST (mRECIST) in the per-protocol population. Secondary endpoints included OS and objective response rate (ORR) determined by mRECIST in the per-protocol population, and safety in the intention-to-treat population. **Results:** Among 24 patients enrolled, all received Y90-radioembolization and 23 received at least one dose of durvalumab. The median duration of follow-up was 19.0 (IQR, 5.8-22.5) months. The median TTP was 15.2 (95% CI, 6.1-not estimated) months (Figure 1A). The median OS was not reached and the 12-month OS rate was 60.9% (95% CI, 38.3-77.4). Seven (30.4%) patients had a complete response and 13 (56.5%) had a partial response; the ORR was 87.0% (95% CI, 66.4-97.2). Eleven (47.8%) patients showed disappearance of arterial enhancement in all target lesions (Figure 1B). Eight (33%) of 24 patients experienced treatment-related adverse events of any grade. The most common any-grade treatment-related adverse event was hyperkalemia (grade 2, 2 [8%] patients). One (4%) patient had a grade 3 treatment-related adverse event (neutropenia). None experienced any treatment-related serious adverse events. **Conclusion:** Combination treatment with Y90-radioembolization plus durvalumab demonstrated encouraging efficacy with favorable tolerability in patients with locally advanced unresectable HCC. Our phase 1/2a pilot study supports further evaluation of this treatment strategy in a randomized controlled trial.



Disclosures:  
Yun Bin Lee - Samjin Pharmaceuticals and Yuhan Pharmaceuticals.: Grant/Research Support;

## MULTI-TARGET HEPATOCELLULAR CARCINOMA BLOOD TEST PERFORMANCE ACROSS A RANGE OF SPECIFICITY CUT-OFF VALUES

*Naga P. Chalasani<sup>1</sup>, Mark Camardo<sup>2</sup>, Kyle Porter<sup>2</sup>, Elle Keilar Grevstad<sup>2</sup>, Lewis R Roberts<sup>3</sup>, John Kisiel<sup>3</sup>, Amit G. Singal<sup>4</sup>, Marilyn C Olson<sup>2</sup> and Janelle J Bruinsma<sup>2</sup>, (1)Gastroenterology and Hepatology, Indiana University, (2)Exact Sciences Corporation, (3)Division of Gastroenterology and Hepatology, Mayo Clinic, (4)Division of Digestive and Liver Disease, UT Southwestern Medical Center*

**Background:** Current hepatocellular carcinoma (HCC) surveillance modalities exhibit suboptimal sensitivity for early-stage HCC detection, generating marked interest in emerging biomarkers. The multitarget HCC blood test (mt-HBT) integrates methylation markers (*HOXA1*, *TSPYL5*, and *B3GALT6*) in combination with AFP and patient sex and has been shown to exhibit promising accuracy (82% early-stage sensitivity and 87% specificity) in a case control clinical validation study. A subsequent modeling study using the same patient cohort suggested mt-HBT could improve effectiveness of early HCC detection vs. ultrasound/AFP surveillance. The objective of this post-hoc analysis was to compare mt-HBT, GALAD (Gender, Age, AFP-L3, AFP, and DCP model), and AFP early-stage HCC performance over a range of specificities, as providers differ in their tolerance of false positive results. **Methods:** The analysis included 156 treatment-naïve HCC cases (78 early-stage) and 245 confirmed at-risk patients with chronic liver disease (226 with cirrhosis) but no HCC. HCC was defined by AASLD criteria, and early stage by Barcelona Clinic Liver Cancer (stages 0 + A). We assessed mt-HBT, GALAD, and AFP early-stage sensitivity across cutoffs corresponding to matched specificities ranging from 80-95%. **Results:** The mt-HBT early-stage HCC sensitivity ranged from 85% (95% CI: 75-91%) at 80% specificity to 72% (95% CI: 61-81%) at 95% specificity (Table 1). Early-stage HCC sensitivity of 82% was preserved when the predefined mt-HBT cutoff corresponding to 87% specificity was raised to the cutoff corresponding to 90% specificity. At specificities of 80-95%, early-stage HCC sensitivities ranged from 83-69% and 69-54% for GALAD and AFP, respectively. As specificity was raised from 85 to 90% the mt-HBT early-stage HCC sensitivity decreased 1%, whereas GALAD and AFP sensitivities decreased by 5% and 9%, respectively. **Conclusion:** High early-stage HCC sensitivity was observed with mt-HBT cut-off values corresponding to a wide range of specificity. The mt-HBT provides consistent performance over a range of specificity values.

Table 1. Mt-HBT, GALAD, and AFP Early-Stage HCC Performance Across a Range of Cutoff Values.

mt-HBT		GALAD <sup>b</sup> Early-Stage Sensitivity % (95% CI) (N=78)	AFP <sup>c</sup> Early-Stage Sensitivity % (95% CI) (N=78)	Specificity % (N=245)
Mt-HBT Cutoff	Early-Stage Sensitivity % (95% CI) (N=78)			
0.4232	72 (61-81)	69 (58-78)	54 (43-65)	95
0.2719	82 (72-89)	73 (62-82)	59 (48-69)	90
0.2255 <sup>a</sup>	82 (72-89)	78 (68-86)	67 (56-76)	87
0.2145	83 (74-90)	78 (68-86)	68 (57-77)	85
0.1794	85 (75-91)	83 (74-90)	69 (58-78)	80

AFP,  $\alpha$ -fetoprotein; CI, Confidence Interval; GALAD, Gender, Age, AFP-L3, AFP, and DCP model; HCC, Hepatocellular Carcinoma; mt-HBT, multi-target Hepatocellular Carcinoma Blood Test; ng/mL, nanograms/milliliter.

In order of decreasing specificity:

<sup>a</sup>0.2255 was the predefined cutoff used in the original validation study (87% specificity).

<sup>b</sup>GALAD cutoffs: -0.5574, -0.9047, -1.1622, -1.2727, -1.5449.

<sup>c</sup>AFP cutoffs: 10.58, 8.41, 6.89, 6.63, and 5.88 ng/mL.

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### A SYSTEMATIC APPROACH TO LIVER BIOPSY INTERPRETATION IN POST-COVID-19 PATIENTS

*Dongling Wu<sup>1</sup>, Rebecca Thomas<sup>1</sup>, Arvind Rishi<sup>1</sup>, Nitzan C. Roth<sup>2</sup>, Sanjaya Kumar Satapathy<sup>2</sup>, Ben L Da<sup>2</sup>, Corey Chang<sup>1</sup>, Deepika Savant<sup>1</sup>, Suganthi Soundararajan<sup>1</sup>, Taisia Vitkovski<sup>1</sup>, Yani Zhao<sup>1</sup>, Vanesa Bijol<sup>1</sup>, Beth Roberts<sup>1</sup>, Alex K Williamson<sup>1</sup>, M. Isabel Fiel<sup>3</sup>, Siraj El Jamal<sup>3</sup>, Judith Martinez<sup>3</sup> and James M. Crawford<sup>1</sup>, (1)Department of Pathology and Laboratory Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, (2)Division of Gastroenterology and Hepatology, Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, (3)Department of Pathology, Icahn School of Medicine at Mount Sinai*

**Background:** For patients with elevated serum liver enzymes following COVID-19 illness, concern is raised for Secondary Sclerosing Cholangitis of Critically Ill Patients (SSC-CIP) and other cholestatic conditions. Our goal was to develop a rigorous approach to liver biopsy interpretation in such patients. **Methods:** Inclusion criteria were patients without prior known liver disease undergoing liver biopsy for evaluation of elevated serum liver enzymes, for whom COVID-19 related liver injury was of concern. The study period was July 2020 to June 2022. Liver histopathology was scored systematically for features of: bile duct and ductule cholangiopathy; microangiopathy of hepatic arteries, portal veins, and terminal hepatic veins (THV); and cholestatic hepatitis, separate from assessment of fibrosis. **Results:** Liver biopsies from 17 patients were evaluated; biopsies were obtained 124±91d (mean±SD, range 4-344d) after first SARS-CoV-2 PCR test positivity. Ten biopsies exhibited: moderate-to-severe interface ductular reaction; moderate-to-severe cholangiocyte hyperplasia, vacuolization, and/or dysmorphism in ducts and ductules; and microangiopathic features in 2 or more vascular compartments (occlusion by endothelial swelling; endothelitis; fibrin thrombi; and in THV, fibrotic occlusion). Six of these 10 biopsies exhibited moderate-to-severe bile duct paucity, and 4 exhibited bridging fibrosis. For these 10 patients, serum liver chemistries at the time of peak Alk Phos levels prior to liver biopsy were: Alk Phos 1928±709 U/L (range 829-2890); Total Bilirubin 8.2±7.1 mg/dL (range 1.0-21.5); AST 297±313 U/L (range 83-991); and ALT 236±260 U/L (range 86-942). Of the remaining 7 biopsies: 2 exhibited severe interface ductular reaction but lacked substantive cholangiopathy or microangiopathy; 2 exhibited bile duct paucity only; and 3 exhibited an inflammatory cholestatic hepatitis with only limited cholangiopathy and no microangiopathy. **Conclusion:** We identify six cardinal histopathologic features, with severity of cholangiocyte injury beyond that described for SSC-CIP, appearing to be unique to a post-COVID-19 cholestatic cholangiopathy. These are: moderate-to-severe cholangiocyte hyperplasia, vacuolization, and dysmorphism; combined with microangiopathy of hepatic arteries, portal veins, and THV. Identification of these histopathologic features may help guide clinical management of these patients and promote further understanding of liver injury following COVID illness.

Disclosures:

Disclosure information not available at the time of publication: Judith Martinez

5030

## BIOPRINTED LIVER TISSUES IMPROVE SURVIVAL IN A MOUSE MODEL OF ACUTE LIVER FAILURE

*Christopher Dickman, Zainab A Bazzi, Oksana Nemirovsky, Stephanie Campbell, Haley Tong, Catherine Steer, Angela Dou, Reza Jalili, Simon Beyer, Tamer Mohamed, Sam Wadsworth, Spiro Getsios and Rafal Witek, Aspect Biosystems*

**Background:** Organ transplantation is a complex and invasive procedure yet remains the standard of care for severe acute and acute-on-chronic liver failure (ALF and ACLF). Due to the scarcity of donor organs many individuals will die while awaiting transplant. Transplantation of isolated hepatocytes has shown promise in pediatric patients with ALF, but it remains a challenge to demonstrate long-term viability of transplanted hepatocytes. In this study we demonstrate that by 3D bioprinting liver tissues with primary human hepatocytes (PHHs) and mesenchymal stromal cells (MSCs), we can improve the survival of mice with carbon tetrachloride (CCl<sub>4</sub>)-induced ALF. **Methods:** PHHs and CD166 positive MSCs were co-aggregated into spheroids and suspended in an alginate-based biomaterial. Bioprinted liver tissues containing 5 million PHH and 5 million MSC cells were created using Aspect Biosystems' microfluidic 3D bioprinting technology. 2 bioprinted liver tissues were implanted into the IP space of immune-competent B6 mice 1 day after CCl<sub>4</sub> injection. Blood was drawn at days 1, 2 and 7 post-surgery to test ammonia, ALT, and human albumin. Survival was recorded over 7 days. **Results:** 7 days after implantation, the survival seen in untreated control mice was 47% vs. 78% in treated mice. Mice receiving bioprinted tissues containing hepatocytes were 65% more likely to survive until the end of the experiment. Blood ammonia was elevated in mice from both groups 1 day after surgery with levels decreasing more rapidly in mice receiving a bioprinted tissue compared to sham controls. Plasma human albumin levels peaked at 25  $\mu$ g/mL on day 2 post-surgery. Mice dying before day 7 demonstrated severe liver damage as observed by gross anatomy and histology sections. Mice from both cohorts surviving to the end of the study demonstrated significant regeneration to the liver. **Conclusion:** Bioprinted liver tissues are capable of rescuing immune-competent mice from CCl<sub>4</sub>-induced liver failure without the need for systemic immune suppression. This suggests that these bioprinted tissues may be used as either a bridge to recovery or transplantation for individuals with ALF or ACLF. Furthermore, many liver diseases are caused by deficiency of the hepatocytes and therefore replacement therapy has the potential to be used with a wide variety of indications where transplantation is not an option. Further studies will examine rat and large animal models of ALF and mouse models of metabolic liver disease.

Disclosures:

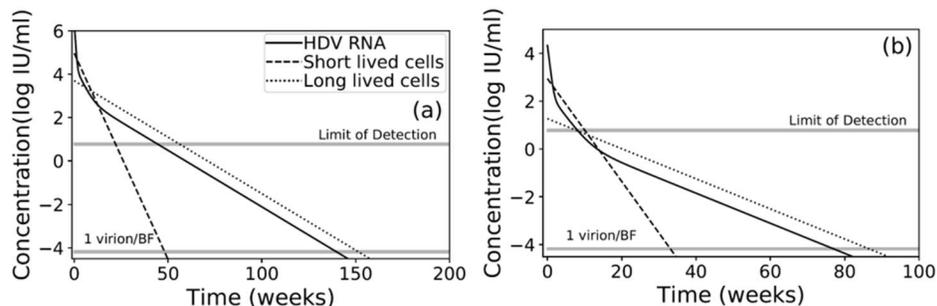
The following people have nothing to disclose: Christopher Dickman

## MODELLING HDV KINETICS UNDER ENTRY-INHIBITOR BULEVIRTIDE SUGGESTS THE EXISTENCE OF TWO HDV-INFECTED CELL POPULATIONS:IMPLICATIONS FOR RESPONSE-GUIDED THERAPY

Louis Shekhtman<sup>1,2</sup>, Scott J. Cotler<sup>1</sup>, Elisabetta Degasperi<sup>3</sup>, Maria Paola Anolli<sup>3</sup>, Sara Colonia Uceda Renteria<sup>3</sup>, Dana Sambarino<sup>3</sup>, Marta Borghi<sup>3</sup>, Riccardo Perbellini<sup>3</sup>, Floriana Facchetti<sup>3</sup>, Ferruccio Ceriotti<sup>4</sup>, Pietro Lampertico<sup>3,5</sup> and Harel Dahari<sup>1</sup>. (1)The Program for Experimental & Theoretical Modeling, Division of Hepatology, Department of Medicine, Loyola University Medical Center, Maywood, IL, USA, (2)Network Science Institute, Northeastern University, Boston, MA, USA, (3)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy, (4)Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Virology Unit, Milan, Italy, (5)CRC "a. M. and a. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

**Background:** Bulevirtide (BLV) was conditionally approved for the treatment of chronic hepatitis D virus (HDV) infection in Europe. The effect of the entry inhibitor BLV on HDV-host dynamics is in its infancy. The mechanism of action of BLV to block entry of HDV into liver cells provides a unique opportunity to understand HDV and HBV infection.

**Methods:** Participants were 18 HDV patients under nucleos(t)ide analogue treatment for hepatitis B with compensated cirrhosis and clinically significant portal hypertension who received BLV 2 mg/day (doi: 10.1016/j.jhep.2022.07.016). HDV RNA, ALT, and HBsAg were measured at baseline, weeks 4, 8 and every 8 weeks thereafter. A mathematical model was developed to account for HDV, hepatitis B surface antigen (HBsAg) and ALT dynamics during BLV treatment. **Results:** Median baseline HDV RNA, HBsAg, and ALT were 4.9 log IU/mL [interquartile, IQR:4.4-5.8], 3.7 log IU/mL [IQR:3.4-3.9] and 106 U/L [IQR:81-142], respectively. During therapy, patients fit into the following HDV kinetic patterns: monophasic, MP (n=2), biphasic, BP (n=8), BP followed by breakthrough (n=2), flat-partial response, FPR (n=3), FPR followed by decline (n=1), and non-responder, NR (n=2). ALT normalization was achieved in 14 (78%) patients at a median of 8 weeks (range:4-16) from initiation of BLV therapy. HBsAg remained at pre-treatment levels. Modeling showed that the existence of two HDV-infected cell populations: short-lived (median  $t_{1/2}$ =11 days) and long-lived (median 50 days), where the long-lived population consisted of ~1% of total HDV-infected cells could explain why most patients had a non-MP HDV decline pattern. The HDV decline under BLV was predicted to decline via 3 phases that might (Fig. 1a) or might not (Fig. 1b) be evident before the viral load is below the limit of assay detection. The latter could affect the ability to accurately predict the duration of BLV-based therapy needed to reach <1 virus copy in the entire extracellular body fluid. Moreover, modeling explained ALT normalization without a change in HBsAg based on a noncytolytic loss of HDV from infected cells, resulting in HDV-free HBsAg-infected cells that produce ALT at about a 309-fold lower rate compared to HDV-infected cells. **Conclusion:** Understanding viral-host-drug dynamics may help to develop response-guided BLV-based therapies.



**Fig. 1. Model predictions of HDV decline in two in-silico representative patients.** Model prediction to reach <1 virus copy in patients' total extracellular body fluid (BP) under combination therapy with blocking ~100% of HDV entry by BLV and drug(s) that blocks  $\epsilon$ =99% of HDV production. Limit of HDV detection in the blood (upper horizontal line); 1 virus/BF is defined as 1 virus per patients' total extracellular body fluid of 15 L (lower horizontal line).

### Disclosures:

The following people have nothing to disclose: Harel Dahari

## EFFICACY OF OBETICHOLIC ACID (OCA) VS PLACEBO AND EXTERNAL CONTROL (EC) ON CLINICAL OUTCOMES IN PRIMARY BILIARY CHOLANGITIS (PBC)

*Kris V Kowdley<sup>1</sup>, M. Alan Brookhart<sup>2</sup>, Gideon M. Hirschfield<sup>3</sup>, Charles Coombs<sup>4</sup>, Elizabeth Malecha<sup>5</sup>, Tracy Mayne<sup>5</sup>, Erik Ness<sup>5</sup>, Jing Li<sup>5</sup>, Alexander Breskin<sup>2</sup>, Nuvan Rathnayaka<sup>2</sup>, George Mells<sup>6</sup>, David Jones<sup>7</sup>, Palak J. Trivedi<sup>8,9,10,11</sup>, Bettina E. Hansen<sup>12</sup>, Rachel Smith<sup>13</sup>, James Wason<sup>14</sup>, Shaun Hiu<sup>15</sup>, Dorcas N. Kareithi<sup>15</sup>, Andrew L. Mason<sup>16</sup>, Christopher L. Bowlus<sup>17</sup>, Kate Muller<sup>18</sup>, Marco Carbone<sup>19</sup>, Marina Berenguer<sup>20</sup>, Piotr Milkiewicz<sup>21</sup>, Femi Adekunle<sup>22</sup> and Alejandra Villamil<sup>23</sup>, (1)Liver Institute Northwest, (2)Target Rwe, (3)Toronto Centre for Liver Disease, Toronto General Hospital, University of Toronto, (4)Syneos Health, (5)Intercept Pharmaceuticals, Morristown, NJ, (6)Cambridge University Hospitals NHS Foundation Trust MRC Clinical Academic Research Partner, Academic Department of Medical Genetics, University of Cambridge, (7)Population Health Sciences Institute, Newcastle upon Tyne, Newcastle University, UK, (8)National Institute for Health and Care Research Birmingham Biomedical Research Centre, Centre for Liver and Gastroenterology Research, University of Birmingham, UK, (9)Institute of Applied Health Research, University of Birmingham, UK, (10)The Liver Unit, University Hospitals Birmingham Queen Elizabeth, Birmingham UK, (11)Institute of Immunology and Immunotherapy, University of Birmingham, UK., (12)Toronto Centre for Liver Disease, Toronto General Hospital, (13)Cambridge Liver Unit, Cambridge University Hospitals NHS Foundation Trust, (14)Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, (15)Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, (16)The Applied Genomic Core, Center of Excellence for Gastrointestinal Inflammation and Immunity Research, University of Alberta, (17)University of California Davis, (18)Flinders Medical Centre, Adelaide, South Australia, (19)University of Milan-Bicocca, Monza, Italy, (20)La Fe University Hospital, Valencia, Spain, (21)Medical University of Warsaw, Warszawa, Poland, (22)Intercept Pharmaceuticals, London, UK (at the time the study was conducted), (23)Hospital Italiano De Buenos Aires, Argentina*

**Background:** COBALT is a Phase 3b/4 randomized, double-blind, PBO-controlled confirmatory trial evaluating the effect of OCA on clinical outcomes in patients (pts) with advanced PBC. The study included an EC group as a 2nd comparator arm, to mitigate challenges maintaining pts on PBO after OCA commercial availability. **Methods:** From 02/15-12/20, eligible PBC pts with serum total bilirubin  $>1$  to  $\leq 5$ x ULN and/or ALP  $>3$ x ULN were randomized 1:1 to OCA (5mg titrated to 10mg) or PBO. The primary endpoint was time to 1st occurrence of: MELD  $\geq 15$ ; hepatic decompensation (uncontrolled ascites; variceal bleed, hepatic encephalopathy); liver transplant; or death. The EC group was created from the Komodo Health claims database supplemented with national laboratory, transplant and mortality data. A random index visit was chosen from all healthcare visits at which an EC pt met COBALT eligibility criteria. Standardized morbidity ratio weights were used to balance baseline covariates. The EC primary endpoint excluded MELD (data not available in Komodo); the primary analysis was as-treated. To assess population comparability, a Komodo OCA-treated group was created and SMR-weighted against the COBALT OCA-treated arm. **Results:** COBALT randomized 168 pts to OCA, 166 pts to PBO. Almost half (44%) of OCA and 54% of PBO pts discontinued study drug; 8% and 16% initiated commercial OCA. The study was terminated in 12/21 for lack of feasibility. The ITT analysis showed no treatment effect (HR=1.01; 95% CI=0.68, 1.51). In the OCA arm, 44% of events occurred  $>90$  days after OCA discontinuation (median=13 months). There were 1050 pts in the Komodo EC. Platelet count and evidence of portal hypertension were not balanced after weighting and were included as covariates in the Cox regression. In the EC as-treated analysis, there was significantly less death, transplant and hepatic decompensation in the COBALT OCA arm vs EC (HR=0.39; 95% CI=0.22, 0.69;  $p<0.01$ ). The event rate for the OCA-treated pts in COBALT (10%) and in Komodo (11%) were equivalent. The event rate for the COBALT PBO group (8%) was significantly lower than for EC (22%). **Conclusion:** The COBALT trial did not demonstrate differences in clinical outcomes between OCA and PBO; differential drop out and treatment cross-over compromised the ITT analysis. However, the pre-specified EC as-treated analysis showed an OCA treatment effect similar to that demonstrated in previous outcomes studies and provides support for improved clinical outcomes with OCA.

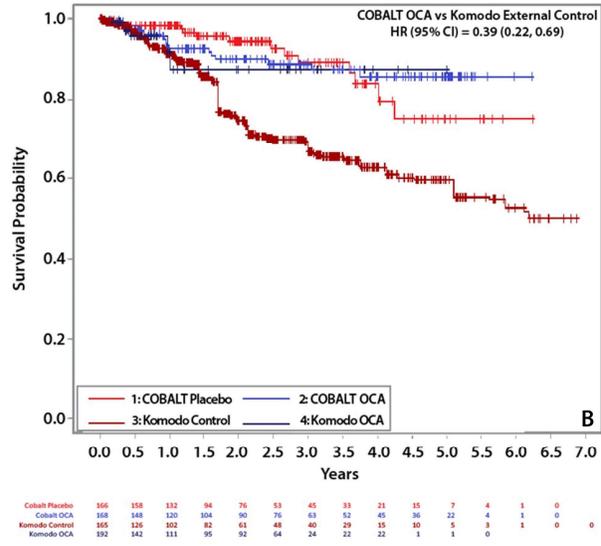
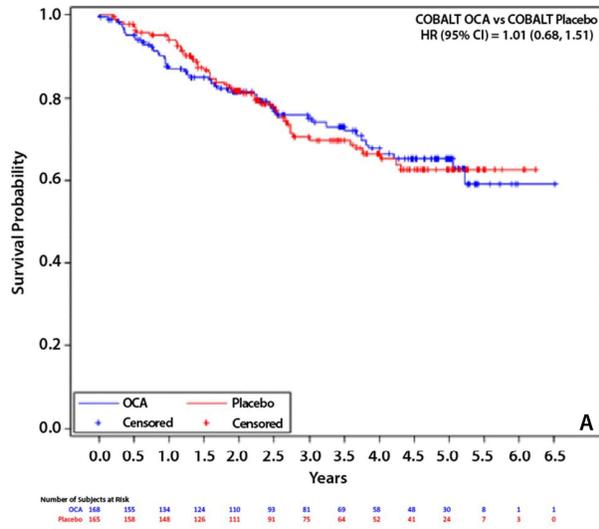


Figure 1: Kaplan Meier Survival Curves: (A) COBALT ITT OCA-treated versus Placebo; (B) As-treated COBALT OCA vs Komodo External Control (with COBALT Placebo and Komodo OCA-treated Comparators)

Disclosures:  
Erik Ness - Intercept Pharmaceuticals: Employment;

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**POTENT AND POLYFUNCTIONAL HEPATITIS B CORE (HBC)/SURFACE (HBS)-SPECIFIC CD8+ AND CD4+ T CELL RESPONSES OBSERVED IN ADULTS WITH CHRONIC HEPATITIS B (CHB) FOLLOWING TARGETED IMMUNOTHERAPY CONSISTING OF VIRAL VECTORS IN HETEROLOGOUS PRIME-BOOST REGIMEN AND ADJUVANTED HBC/HBS PROTEINS: RESULTS ON STEP B COHORT OF A PHASE I/II TRIAL**

*Kristien Swinnen<sup>1</sup>, Wen-Juei Jeng<sup>2</sup>, Manuel Romero-Gómez<sup>3</sup>, Stefan Zeuzem<sup>4</sup>, Patrick Kennedy Sr.<sup>5</sup>, Fabien Zoulim<sup>6,7</sup>, Thomas Vanwolleghem<sup>8,9</sup>, Naba Haque<sup>1</sup>, Naveen Karkada<sup>1</sup>, Bruno Salaun<sup>1</sup>, Ventsislav Vassilev<sup>1</sup> and Dorota Borys<sup>1</sup>, (1)GSK, (2)Chang Gung Memorial Hospital, (3)Universidad De Sevilla, Sevilla, Spain, (4)Department of Internal Medicine I, Goethe University Hospital, (5)Blizard Institute, Queen Mary University of London, (6)Viral Hepatitis Research Laboratory, Lyon University, Inserm, (7)Hepatology Department, Hospices Civils De Lyon, France, (8)Department of Gastroenterology and Hepatology, Antwerp University Hospital, Belgium, (9)Laboratory of Experimental Medicine and Pediatrics, University of Antwerp, Belgium*

**Background:** GSK's chronic hepatitis B-targeted immunotherapy (CHB-TI) with viral vectors in heterologous prime-boost regimen and adjuvanted recombinant Hbc and HBs proteins showed the ability to boost cell-mediated immunity (CMI) in a subgroup of adults with CHB, in a first-time-in-human clinical trial (NCT03866187). We report 2<sup>nd</sup> interim CMI results up to 14 days (D) post-dose 2 from the Step B cohort of the same trial. **Methods:** This ongoing phase I/II, randomized, single-blind, controlled trial includes 18-65-years old virally suppressed adults with CHB. In Step B, patients were randomized 2:1:1. Group B1 received heterologous prime-boost regimen of chimpanzee-derived adenovirus encoding a fusion of the human invariant chain (CD74) and hepatitis B virus (HBV) proteins (ChAd155-hI-HBV) at D1 and Modified Vaccinia Ankara virus encoding HBV proteins (MVA-HBV) at D57. Group B2 and the control group received 2 doses of Hbc-HBs/AS01<sub>B</sub> or placebo, respectively, at D1 and D57. CMI samples were collected at D1, D15, D57, D64, D71 and tested by intracellular cytokine staining to assess frequencies of Hbc-/HBs-specific CD8<sup>+</sup> and CD4<sup>+</sup> T cells, CD8<sup>+</sup> and CD4<sup>+</sup> T cell responders. **Results:** The exposed set with available CMI samples included 58 patients. Polyfunctional CMI responses were observed in ChAd-MVA recipients (group B1) in terms of Hbc- and HBs-specific CD8<sup>+</sup> T cells (up to 52.2% and 23.8% responders, respectively) and in Hbc-HBs/AS01<sub>B</sub> recipients (group B2) in terms of Hbc- and HBs-specific CD4<sup>+</sup> T cells (up to 28.6% and 9.1% responders, respectively). The prime-boost effect of the viral vectors regimen was observed for Hbc-specific CD8<sup>+</sup> T cell responses in group B1, with an increase of the mean frequency (cells/10<sup>6</sup>) in responders from 789/10<sup>6</sup> at D15 to 1589/10<sup>6</sup> at D71. In group B2, the mean frequency of Hbc-specific CD4<sup>+</sup> T cells in responders was 2019/10<sup>6</sup> at D15 but this was not sustained up to D71 (**Table**). **Conclusion:** The CMI results from Step B cohort following half of CHB-TI regimen (2/4 doses) showed that the prime-boost regimen with ChAd-MVA induced an increase in HBV-specific CD8<sup>+</sup> T cells, considered as the most critical attribute of CHB-TI, and showed a boosting effect of the MVA dose. By contrast, the Hbc-HBs/AS01<sub>B</sub> proteins only induced HBV-specific CD4<sup>+</sup> T cells, and no boosting effect of the 2<sup>nd</sup> dose was observed. These data support the ability of CHB-TI to elicit the desired immune responses in adults with CHB. Funding: GlaxoSmithKline Biologicals SA

**Table.** Number and percentage of responders for HBV-specific CD8+ and CD4+ T cells and frequencies of HBV-specific CD8+ and CD4+ T cells (exposed set with CMI samples available)

Polyfunctional*	Step B cohort	HBc-specific								HBs-specific							
		CD8 <sup>+</sup> T cells				CD4 <sup>+</sup> T cells				CD8 <sup>+</sup> T cells				CD4 <sup>+</sup> T cells			
		D15	D57	D64	D71	D15	D57	D64	D71	D15	D57	D64	D71	D15	D57	D64	D71
N	22	20	21	23	18	15	17	19	23	21	21	23	18	15	16	18	
n	1	2	10	12	1	1	3	3	-	-	5	4	1	-	-	1	
%	4.5	10.0	47.6	52.2	5.6	6.7	17.6	15.8	-	-	23.8	17.4	5.6	-	-	5.6	
Mean	-	1003	1891	1589	-	-	1042	1150	-	-	1401	990	-	-	-	-	
Min	-	979	831	830	-	-	817	1091	-	-	895	711	-	-	-	-	
Max†	789	1026	2868	3690	1273	900	1461	1215	-	-	2402	1229	1087	-	-	1074	
N	13	13	12	13	15	13	12	14	12	12	10	12	13	12	11	13	
n	-	-	-	-	4	2	3	4	-	-	-	-	1	1	1	1	
%	-	-	-	-	26.7	15.4	25.0	28.6	-	-	-	-	8.3	9.1	7.7	7.7	
Mean	-	-	-	-	2019	1526	1784	1458	-	-	-	-	-	-	-	-	
Min	-	-	-	-	846	1168	749	934	-	-	-	-	-	-	-	-	
Max†	-	-	-	-	5415	1884	3168	2149	-	-	-	-	1412	1166	1569	1569	

\*Polyfunctional CMI response is defined as T cells expressing ≥ 2 activation markers of CD40L, TNFα, IFNγ, IL2, CD137 (4-1BB), IL13 and IL17 including 21 cytokine (lower limit of quantification (LLQ) = 1000 cells/million of CD8+ or CD4+ T cells). HBV-specific CMI responder is defined as participant with post-/pre-treatment ratio in polyfunctional T cell frequencies above the maximum ratio observed in controls. D15, 14 days post-dose 1; D57, dose 2; D64, 7 days post-dose 2; D71, 14 days post-dose 2; N, number of patients with CMI results available at pre-/post-treatment at each timepoint; n, % number/percentage of responders; Mean, mean frequency in responders (cells/million); Min, minimum frequency in responders (cells/million); Max, maximum frequency in responders (last timepoints with only 1 polyfunctional CMI responder only (the maximum value is presented, cells/million)); - zero for n% or below LLQ for frequency values. Group B1: patients received ChAd155-HI-HBV (5x10<sup>9</sup> virus particles) at D1 and MVA-HBV (2x10<sup>9</sup> plaque-forming units) at D57; Group B2: patients received 2 doses of Hbc-HBs/AS01<sub>B</sub> (80-80 µg) at D1 and D57; AS01<sub>B</sub> is an Adjuvant System containing 50 µg MPL, 50 µg I05-21 and liposome.

Disclosures:

Stefan Zeuzem - BioMarin: Consulting; Gilead Sciences: Consulting; GSK: Consulting; Novo Nordisk: Consulting; MSD: Consulting; Sobi: Consulting; Abbvie: Speaking and Teaching; BioMarin: Speaking and Teaching; Gilead Sciences: Speaking and Teaching; Janssen: Speaking and Teaching; MSD: Speaking and Teaching; Gilead Sciences: Expert testimony;

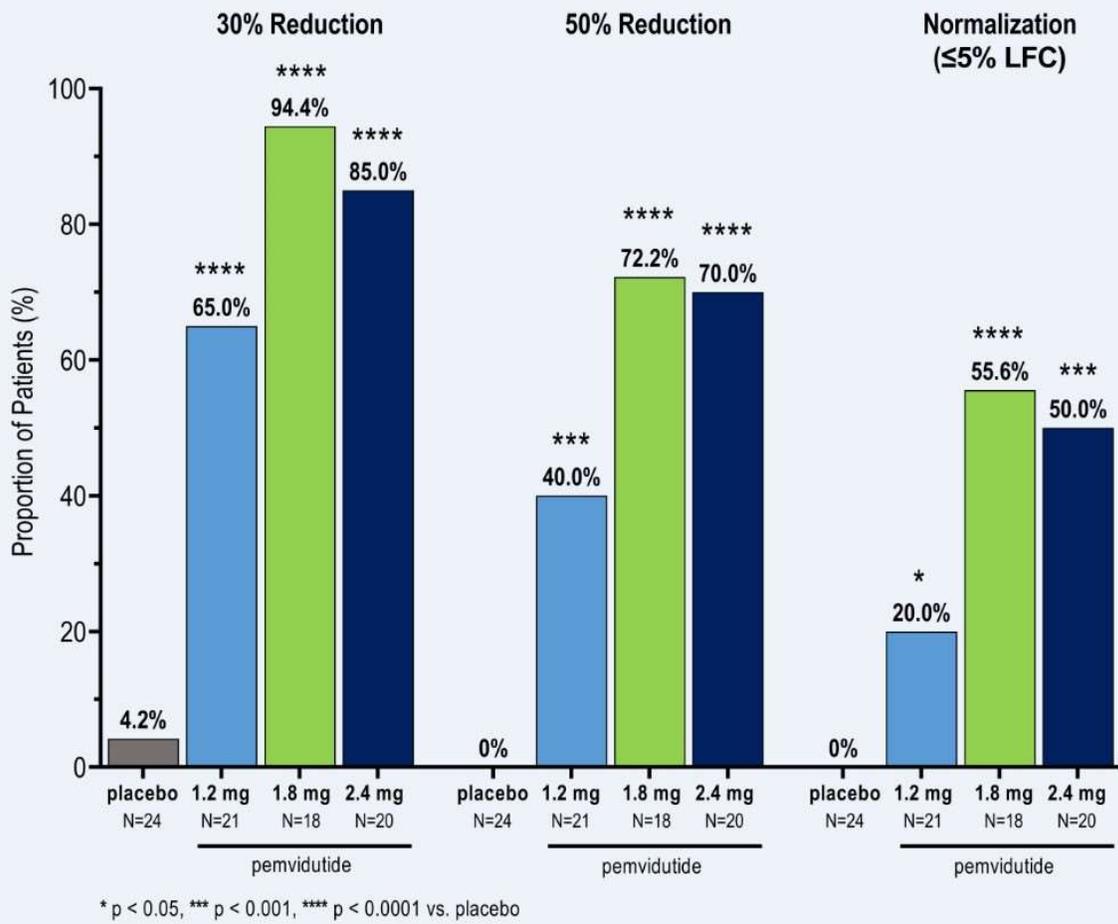
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**EFFECTS OF A BALANCED GPL-1/GLUCAGON RECEPTOR DUAL AGONIST ON REDUCTION OF LIVER FAT AND WEIGHT LOSS: RESULTS OF A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL IN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE**

*Stephen A Harrison<sup>1</sup>, John Suschak<sup>2</sup>, M. Scot Roberts<sup>2</sup>, Jay Yang<sup>2</sup>, Liang He<sup>2</sup>, Bertrand Georges<sup>2</sup>, Lakisha Rodwell-Green<sup>2</sup>, Randy Brown<sup>2</sup>, Shaheen Tomah<sup>2</sup>, M. Scott Harris<sup>2</sup> and Sarah Browne<sup>2</sup>, (1)Pinnacle Research, (2)Altimmune, Inc.*

**Background:** Pemvidutide is a long-acting GLP-1/glucagon dual receptor agonist under development for treatment of NASH and obesity. The 1:1 balanced ratio combining the reduced caloric intake effects of GLP-1 receptor agonism and the lipometabolic effects of glucagon receptor agonism are hypothesized to optimize efficacy and tolerability. This study assessed the efficacy and safety of pemvidutide on liver fat content (LFC) and body weight reduction in patients with NAFLD. **Methods:** Subjects with BMI  $\geq$  28.0 kg/m<sup>2</sup> and baseline ALT  $\leq$  75 IU/L were randomized 1:1:1:1 to 1.2mg, 1.8mg, 2.4mg pemvidutide, or placebo weekly for 12 weeks. No dose titration was used with the 1.2mg or 1.8mg doses; a short 4-week titration was used to reach a weekly dose of 2.4mg for 8 weeks. Primary and secondary efficacy endpoints were the reductions in LFC by MRI-PDFF and % body weight loss from baseline after 12 weeks of treatment. The trial was conducted without adjunctive diet and exercise interventions. **Results:** Ninety-four patients were randomized and treated at 13 US sites. Mean baseline BMI, LFC, and ALT were approximately 36 kg/m<sup>2</sup>, 22%, and 36.5 IU/L, respectively. Twenty-seven (29%) participants had type 2 diabetes (T2D), and 71 (75.5%) were of Hispanic ethnicity. The primary and secondary endpoints were met in all pemvidutide treatment groups. At the 1.8mg dose, mean LFC reduction was 68.5% ( $p < .001$ ), with 94.4% achieving a 30% reduction ( $p < .0001$ ), 72.2% a 50% reduction ( $p < .0001$ ), and 55.6% achieving normalization of LFC, defined as  $\leq$  5% LFC ( $p < .0001$ ) (**Figure 1**). Mean weight losses of 4.9% (4.7% placebo-adjusted) were achieved in subjects without T2D (1.8mg group) ( $p < .001$ ) and 4.4% (3.9% placebo-adjusted) in subjects with T2D (2.4mg group) ( $p < .001$ ). In subjects with baseline alanine aminotransferase (ALT)  $\leq$  30 IU/L, mean serum ALT declined by  $> 17$  IU/L at all doses and 27.0 IU/L at 2.4 mg ( $p < .05$ ). Pemvidutide was safe and well-tolerated with mild and transient gastrointestinal (GI) adverse events most common. Two subjects discontinued treatment due to GI intolerance (one each at 1.8mg and 2.4mg doses). No ALT elevations  $\geq 3$ X the upper limit of normal were observed; glycemic control was maintained. **Conclusion:** The rapid and potent reductions in LFC and body weight without dose titration support evaluation of pemvidutide as a potential treatment for NASH and obesity.

Figure 1: Reduction in liver fat content by MRI-PDF at Week 12 - Responder Analysis



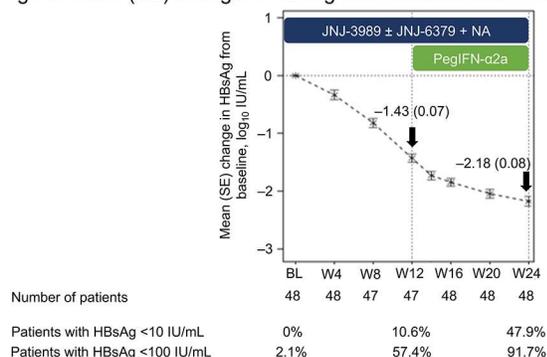
Disclosures:  
Sarah Browne - Altimmune, Inc.: Employment;

## EFFICACY AND SAFETY OF siRNA JNJ-73763989, CAPSID ASSEMBLY MODULATOR JNJ-56136379, NUCLEOS(T)IDE ANALOG (NA), AND PEGYLATED INTERFERON ALPHA-2a (PEGIFN- $\hat{I}\pm 2a$ ) FOR TREATMENT OF CHRONIC HEPATITIS B (CHB): WEEK 24 RESULTS FROM THE PHASE 2 PENGUIN STUDY

Edward John Gane<sup>1</sup>, Ewa Janczewska<sup>2</sup>, Tetsuo Takehara<sup>3</sup>, Wan-Long Chuang<sup>4</sup>, Cheng-Yuan Peng<sup>5</sup>, Maria Hlebowicz<sup>6</sup>, Yasuhiro Asahina<sup>7</sup>, Ting-Tsung Chang<sup>8</sup>, Ronald Kalmeijer<sup>9</sup>, John Jezorwski<sup>9</sup>, Oliver Lenz<sup>10</sup>, Thomas N. Kakuda<sup>9</sup>, Thierry Verbinnen<sup>10</sup>, Nonko Pehlivanov<sup>9</sup>, Zacharias Anastasiou<sup>11</sup> and Michael Biermer<sup>10</sup>, (1)New Zealand Liver Transplant Unit, University of Auckland, (2)Faculty of Health Sciences, Medical University of Silesia, (3)Osaka University Graduate School of Medicine, (4)Kaohsiung Medical University Hospital, Kaohsiung, Taiwan, (5)Center for Digestive Medicine, China Medical University Hospital, (6)Department of Family Medicine and Infectious Diseases, University of Warmia and Mazury in Olsztyn, (7)Department of Gastroenterology and Hepatology, Tokyo Medical Dental University, (8)Department of Internal Medicine, National Cheng Kung University Medical College, (9)Janssen Research & Development, LLC, (10)Janssen Pharmaceutica NV, (11)Janssen-Cilag Pharmaceutical

**Background:** The phase 2, open-label, single-arm, multicenter PENGUIN study (NCT04667104) assessed the efficacy and safety of treatment with JNJ-3989, JNJ-6379, NA, and PegIFN- $\hat{I}\pm 2a$  in virologically suppressed (VS), hepatitis B e antigen positive (HBeAg+) or negative (HBeAg-) CHB patients with hepatitis B surface antigen (HBsAg) >100 IU/mL. Here, we present the results up to end of treatment (Week 24 [W24]). **Methods:** Patients on NA received JNJ-3989 and JNJ-6379 (some did not start/discontinued due to protocol amendment) for 24 weeks with PegIFN- $\hat{I}\pm 2a$  added during the final 12 weeks of treatment. The primary endpoint was the proportion of patients with HBsAg reduction from baseline (BL) of  $\hat{a}\% \hat{\neq} 2 \log_{10}$  IU/mL at W24. Changes in viral markers from BL and the proportion of patients meeting NA stopping criteria (HBsAg <10 IU/mL, HBeAg-, HBV DNA <lower limit of quantitation [LLOQ], and alanine transaminase <3 $\hat{A}$ — upper limit of normal) at W24 were also assessed. **Results:** A total of 48 HBeAg+ (n=11) and HBeAg- (n=37) VS CHB patients were enrolled. Thirty-one (64.6%) patients met the primary endpoint of HBsAg reduction  $\hat{a}\% \hat{\neq} 2 \log_{10}$  IU/mL at W24, and 1 (2.1%) patient achieved seroclearance (HBsAg <0.05 IU/mL). JNJ-3989 $\hat{A}\pm$ JNJ-6379+NA resulted in mean (SE) HBsAg changes from BL (3.27 [0.09]  $\log_{10}$  IU/mL) of -1.43 (0.07)  $\log_{10}$  IU/mL at W12 and -2.18 (0.08)  $\log_{10}$  IU/mL at W24 (**Figure**). Forty-four (91.7%) and 23 (47.9%) patients had HBsAg <100 and <10 IU/mL at W24, respectively. For HBeAg+ patients, mean (SE) changes in HBeAg were -0.68 (0.09)  $\log_{10}$  IU/mL at W12 and -0.72 (0.11)  $\log_{10}$  IU/mL at W24. Of 11 HBeAg+ patients, 4 (36.4%) and 3 (27.3%) reached HBeAg seroclearance at W12 and W24, respectively. At W24, 15 (31.3%) patients met predefined NA stopping criteria. Of all patients not meeting NA criteria, 76.0% failed to attain HBsAg <10 IU/mL; of HBeAg+ patients, missing HBeAg seroclearance was the leading reason (72.7%). All treatments were safe and well tolerated; adverse events (AEs) and laboratory abnormalities from W12 to W24 were in line with the known safety profile of PegIFN- $\hat{I}\pm 2a$ . There were no serious AEs, and only 1 AE (grade 4 neutropenia) led to discontinuation of PegIFN- $\hat{I}\pm 2a$ . **Conclusion:** Addition of JNJ-3989 $\hat{A}\pm$ JNJ-6379 and PegIFN- $\hat{I}\pm 2a$  to NA was generally safe and well tolerated in PENGUIN and resulted in profound HBsAg reduction and a high proportion of patients achieving HBsAg <100 IU/mL at W24. The additional antiviral effect of PegIFN- $\hat{I}\pm 2a$  in this regimen needs further evaluation.

Figure: Mean (SE) change in HBsAg from baseline over time.



### Disclosures:

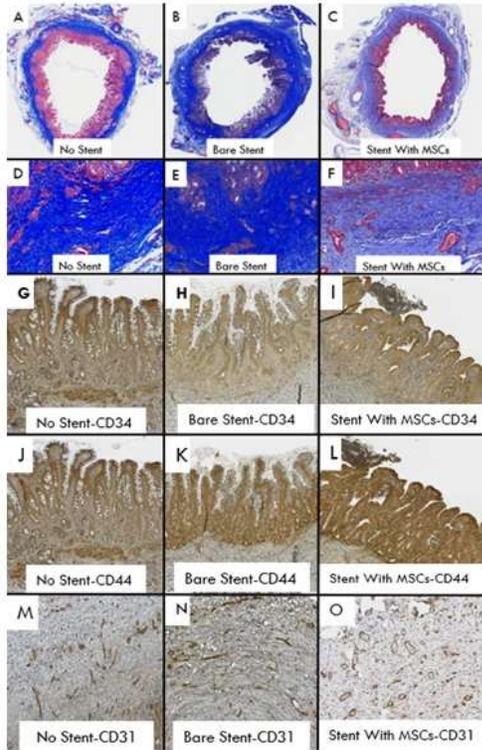
Disclosure information not available at the time of publication: Tetsuo Takehara

5036

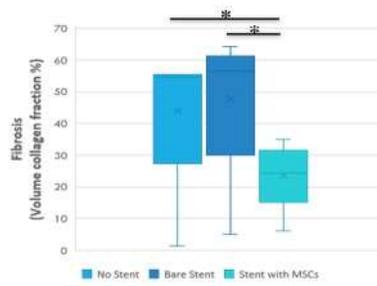
## BIODEGRADABLE BILIARY STENTS COATED WITH MESENCHYMAL STROMAL CELLS IN A PORCINE CHOLEDOCHOJEJUNOSTOMY MODEL

*Seyed Mohammad Hosseiniasl<sup>1</sup>, Philipp Felgendreff<sup>2</sup>, Mohammad Tharwat<sup>3</sup>, Bruce Amiot<sup>4</sup>, Anan Abu Rmilah<sup>4</sup>, Anna Minshew<sup>4</sup>, Xiaoye Sun<sup>5</sup>, Bormschlegl Alexander<sup>5</sup>, Nidhi Jalan-Sakrikar<sup>5,6</sup>, Michele Smart<sup>5</sup>, Allan Dietz<sup>7</sup>, Robert C. Huebert, M.D.<sup>8</sup> and Scott L. Nyberg<sup>4</sup>, (1)Abdominal Transplant Surgery, Mayo Clinic, (2)University Hospital Jena, (3)Zagazig University, (4)William J. Von Liebig Center for Transplantation and Clinical Regeneration, Mayo Clinic, Rochester, Minnesota, USA, (5)Mayo Clinic, (6)Division of Gastroenterology and Hepatology, Mayo Clinic Rochester, (7)Department of Laboratory Medicine and Pathology, Mayo Clinic, (8)Division of Gastroenterology and Hepatology, Mayo Clinic*

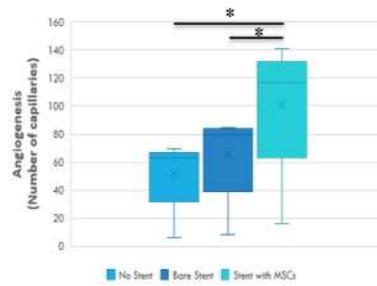
**Background:** Roux en y anastomosis is a preferred method of biliary reconstruction in liver transplantation that involves living donors or pediatric patients. However, biliary stricture is a frequent and serious complication accounting for up to 40 percent of biliary complications in these patients. Previously, we demonstrated that extraluminal delivery of Mesenchymal Stromal Cells (MSCs) decreased fibrosis and increased neoangiogenesis in a porcine model of duct-to-duct biliary anastomosis. In this study, we used a porcine model of Roux en y anastomosis to evaluate the beneficial impact of a novel intraluminal MSC delivery system. **Methods:** Nine animals were divided into 3 groups: no stent (Group 1), bare stent (Group 2) and stent coated with MSCs (Group 3). All animal husbandry and procedures were performed in accordance with the guidelines set forth by the Mayo Foundation Animal Care and Use Committee. All animals underwent cholecystectomy with roux en y choledochojejunostomy. Two animals per group were followed for 4 weeks and 1 animal per group was followed for 8 weeks. Cholangiograms and blood were sampled at baseline and the end of study. Biliary tissue was collected and examined by Masson's Trichrome staining and immunohistochemical (IHC) staining for MSC markers (CD34 and CD44) and for neo-angiogenesis (CD31). **Results:** Two of three animals in Group 1 developed an anastomotic site stricture. No strictures were observed in animals of Group 2 or Group 3. CD34 and CD44 staining showed that MSCs engrafted successfully at the anastomotic site by intraluminal delivery (Group 3). Furthermore, biliary tissue from Group 3 showed significantly less fibrosis and increased angiogenesis compared with the other groups. **Conclusion:** Intraluminal delivery of MSCs resulted in successful biliary engraftment of MSCs as well as reduced fibrosis and increased neo-angiogenesis.



A to F - Trichrome staining of Bile duct at the anastomotic site; G to L - IHC staining of bile duct at the anastomotic site for CD34 and CD44. The strongest staining is in the epithelium of Group 3 (Stent with MSCs) in favor of engraftment of MSC; M, N, O - IHC staining of bile duct at the anastomotic site for CD31.



The graph shows the quantified fibrosis fraction. There is a significant difference between Group 3 (Stent with MSCs) and the other groups



Quantification of capillaries number is suggestive of significant difference of neo-angiogenesis between Group 3 (Stent with MSCs) and the other groups.

**Disclosures:**

The following people have nothing to disclose: Seyed Mohammad Hosseiniasl

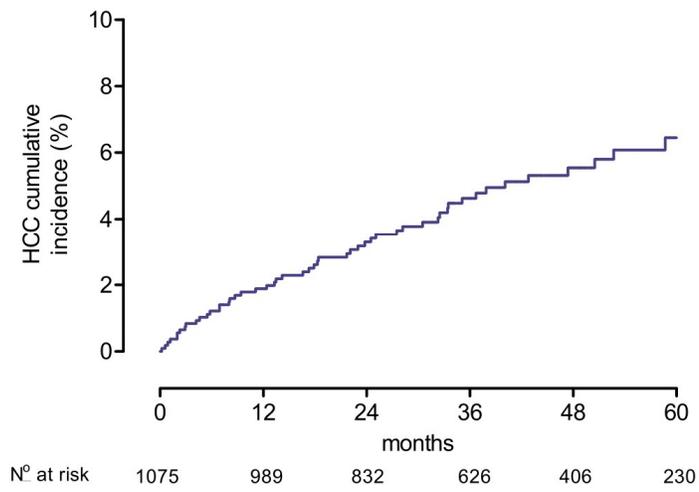
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### INCIDENCE AND RISK FACTORS FOR HEPATOCELLULAR CARCINOMA IN PATIENTS WITH CHRONIC HEPATITIS C TREATED WITH DIRECT-ACTING ANTIVIRALS (DAAS).

*Cassia Leal<sup>1,2</sup>, Rosangela Teixeira<sup>3</sup>, Renata M. Perez<sup>4</sup>, Carmem Ferguson Theodoro<sup>2</sup>, Thaís Guaranãj<sup>2</sup>, Jorge Paulo Strogoff De Mattos<sup>5</sup>, Tatiana Guimarães Noronha<sup>6</sup>, Paulo De Tarso Aparecida Pinto<sup>1</sup> and Solange Artimos Oliveira<sup>5</sup>, (1)Gastroenterology and Hepatology, Hospital Federal Dos Servidores Do Estado Do Rio De Janeiro, (2)Gastroenterology and Hepatology Unit, Fluminense Federal University, (3)Universidade Federal De Minas Gerais, (4)Hepatology, University Hospital Clementino Fraga Filho - Ufrj, (5)Clinical Medicine Department, Fluminense Federal University, (6)Departamento Materno Infantil, Fluminense Federal University*

**Background:** The cure of hepatitis C virus (HCV) infection with direct antiviral agents (DAAs) is remarkable. However, conflicting data regarding the incidence of hepatocellular carcinoma (HCC) after DAAs still remains. We investigated the incidence and risk factors to HCC in a large cohort of patients treated with DAAs followed up for five years.

**Methods:** 1075 HCV patients > 18 years were treated with DAAs from 2015 to 2019 and followed until 2022. Ultrasonography was performed before DAAs (upper limit 6 months) and each 6 months thereafter. **Results:** 51/1075 (4,74%) developed HCC in the median follow up of 40.3 (IQR 25.5-57.7) months: 26/51 (51%) male, mean age 60 (IQR 54-66) years, AFP 12,2 (IQR 6.1-18.8) ng/mL, 47/51(92.1%) cirrhotic (78.7% CP A and 21.3% CP B), 8/51 (15,7%) without RVS. 13/51 (25,5%) had liver nodules before DAA (17% non-characterized). Overall incidence of HCC was 1.46/100 PY (95% CI = 1.09-1.91), being 2.31/100 PY (95% CI = 1.70-3.06), 0.45/100 PY (95% CI = 0.09-1.32) and 0.20/100 patient-years (95% CI 0.01-1.01) in F4, F3 and F2, respectively. The cumulative incidence of HCC was 1.7%, 3.1%, 4.3%, 5.0% and 5.9% after 1, 2, 3, 4 and 5 years, respectively. According to BCLC, liver tumors were classified as follows: 0 (8/51, 15.6%) A (26/51, 51%) B (11/51, 21.6%), C (5/51, 9.8%) and D (1/51, 2%). The main risk factors to HCC were non-characterized nodule, cirrhosis, liver stiffness > 14 kPa, AFP > 10 ng/mL and non-SVR. **Conclusion:** The HCV treatment with DAAs reduced the risk of HCC. However, the HCC still occurred, justifying the screening after cure of patients with advanced liver fibrosis, which favored early diagnosis in more than 50% of patients who developed the tumor. Some risk factors were predictable and can be identified to benefit patients with the early diagnosis.



Disclosures:  
The following people have nothing to disclose: Cassia Leal

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**PERSONALIZED YTTRIUM-90 TUMOR DOSE: AN INDEPENDENT PREDICTOR OF OVERALL SURVIVAL IN PATIENTS WITH SURGICALLY UNRESECTABLE HEPATOCELLULAR CARCINOMA**

*Nima Kokabi<sup>1</sup>, Howard Dabbous<sup>2</sup>, Anand Shah<sup>3</sup>, Alex Villalobos<sup>1</sup>, David Brandon<sup>4</sup> and David Schuster<sup>4</sup>, (1)Radiology and Imaging Sciences, Division of Interventional Radiology and Image-Guided Medicine, Emory University School of Medicine, (2)Radiology and Imaging Sciences, Emory University School of Medicine, (3)Medicine, Division of Digestive Diseases, Emory University School of Medicine, (4)Radiology and Imaging Sciences, Division of Nuclear Medicine and Molecular Imaging, Emory University School of Medicine*

**Background:** Personal dosimetry has been shown to improve overall survival (OS) in patients with hepatocellular carcinoma (HCC) treated with glass Yttrium-90 radioembolization (Y90-RE). The aim of this study was to evaluate personalized tumor dose (TD) as a predictor of OS in patients with surgically unresectable HCC treated with resin Y90-RE. **Methods:** This was a prospective single-arm clinical trial (NCT04172714) with the primary aim of evaluating the efficacy of scout activity (15 mCi) of resin Y90 for personalized treatment planning. The secondary aim of the study was to evaluate personalized dosimetry as a predictor of OS in HCC. Partition dosimetry model was used with the goal of tumor dose (TD) >200 Gy and non-tumoral liver dose (NTLD) <70 Gy for non-segmental therapies. Single compartment dose of 200 Gy was used for segmentectomies. Prescribed Y90 activity minus scout activity was administered for therapeutic Y90 followed by Y90-PET/CT. Sureplan<sup>®</sup> (MIM Software, Cleveland, OH) was used for dosimetry analysis. OS was measured from Y90 using Kaplan-Meier estimation. Log-rank was used as a univariate analysis (UVA) for potential predictors of OS including cumulative (scout + therapeutic) mean Y90 TD, and baseline clinical factors. Multivariate analysis (MVA) with Cox logistic regression was then performed to determine independent predictors of OS. **Results:** Overall, N=30 patients with treatment naïve HCC with 33 tumors (19 segmental and 14 non-segmental) were included in the study. Majority of patients (24(80%)) were Child-Pugh (CP) A with 16 (53%) Barcelona Liver Cancer Clinic stage A, 10 (33%) stage B and 4 (13%) stage C, respectively. Mean Y90 tumor dose was 493 Gy (SD: 343 Gy). One patient died before the 3-month imaging follow-up with 24/29 (83%) having objective response (OR) and 21/29 (72%) with complete response (CR) at 3-mo post Y90 by modified Response Evaluation Criteria in Solid Tumors. Median follow-up since enrollment into the study was 22.5 months. At the time of the analysis, 20 patients remained alive. Mean OS was 24.9 months for the entire cohort. A total of 5 patients underwent orthotopic liver transplantation post Y90 and were excluded from survival analysis to eliminate survival benefit from the transplantation. Mean OS for the remainder of the cohort was 23.8 months. Mean tumor dose >250 Gy resulted in prolonged mean OS of 26.2 months vs. 16 months for others (p=0.003). Additionally, Albumin-bilirubin grade, CP-score, OR and CR were found to be predictors of prolonged OS on UVA (p's <0.05). On MVA, mean TD >250 Gy was the only independent predictor of OS (Hazard Ratio: 0.013, p=0.032). **Conclusion:** In patients with treatment naïve, surgically unresectable, HCC treated with resin Y90 radioembolization, mean TD >250 Gy appears to be an independent predictor of prolonged overall survival.

Disclosures:

Nima Kokabi - Sirtex medical Ltd: Consulting; Sirtex Medical Ltd: Grant/Research Support; Sirtex Medical Ltd: Speaking and Teaching; Balt USA: Consulting;

**NONALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND HEPATIC FIBROSIS IN ADULT NON-DIABETIC AND PRE-DIABETIC UNITED STATES POPULATION**

James M. Paik<sup>1</sup>, Katherine Elizabeth Eberly<sup>2</sup>, Ameeta Kumar<sup>3</sup>, Austin Wentworth Henry<sup>4</sup>, Pegah Golabi<sup>4</sup> and Zobair M. Younossi<sup>5</sup>, (1)Medicine Service Line, Inova Health System, (2)Betty and Guy Beatty Center for Integrated Research, Inova Health System, (3)Center for Liver Disease, Department of Medicine, Falls Church, VA, United States, Inova Health System, (4)Betty and Guy Beatty Center for Integrated Research, Inova Health System, Falls Church, VA, United States, (5)Center for Liver Disease, Department of Medicine, Inova Fairfax Medical Campus

**Background:** Although NAFLD is common among diabetics, it can also be observed among non-diabetics. Our aim was to assess the prevalence of NAFLD and associated significant fibrosis (SF) in adult non-diabetic US population. **Methods:** Data from National Health and Nutrition Examination Survey (NHANES 2017-2018) was utilized. NAFLD was determined by transient elastography (TE) with a controlled attenuation parameter (CAP) of  $\geq 285$  dB/m without other causes of liver disease or excessive alcohol use. SF was defined by liver stiffness measurement (LSM)  $>8.0$  kPa. Insulin resistance (IR) was defined by Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) score of  $\geq 2.0$ . **Results:** 2,000 NHANES adults ( $\geq 18$  years) were included [mean age 46.6 years; 48.9% male; 61.8% White, 10.4% Black, 10.2% Mexican American, 7.02% Hispanic, and 5.6% Asian; 35.5% NAFLD; and 16.8% diabetes]. Of adults without diabetes, 29.0% had NAFLD and 45.4% had a normal HOMA-IR. The prevalence of NAFLD among non-diabetics without IR (prediabetics) was 10.7%. The prevalence of NAFLD among non-diabetics with IR was 44.2%. Compared to non-diabetics with IR, non-diabetics without IR were less likely to be Mexican American (6.7 vs. 12.6%), have unhealthy diets (48.0 vs. 58.6%), be physically inactive (35.3 vs. 45.7%), have central obesity (27.7 vs. 70.8%), hypertension (25.1 vs. 46.0%), hyperlipidemia (45.7 vs. 70.5%), and high C-reactive protein (CRP) (26.8 vs. 50.8%); all p-values  $<.001$ . In non-diabetics, a model adjusted for central obesity, hypertension, hyperlipidemia, and high CRP showed that HOMA-IR is significantly associated with increased risk of NAFLD (odds ratio [OR]=1.34, 95% confidence interval: 1.19-1.50). Among pre-diabetics with NAFLD (non-diabetics with IR), the prevalence of SF was 12.8%; among non-diabetics with NAFLD without IR, the prevalence was 2.7% ( $p<.001$ ). In adjusted model (sociodemographic confounders and hypertension), HOMA-IR was associated with increased risk of SF (OR=1.06, 1.01-1.12). After adjustment for hyperlipidemia, high CRP, or central obesity, the model shifted towards non-significant, suggesting that the association of HOMA-IR and SF among this group may be partially mediated by hyperlipidemia, high CRP, or central obesity. Also, the independent predictors of SF among NAFLD patients without diabetes were hyperlipidemia (OR=4.45, 1.14-17.42) and high CRP (OR=3.71, 1.25-10.99). **Conclusion:** NAFLD can be observed among non-diabetics (both pre-diabetics and non-diabetics without IR). The prevalence rates for NAFLD and SF are higher when IR is present.

**Disclosures:**

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**TARGETING GPX4-MEDIATED FERROPTOSIS ALLEVIATES LIVER INJURY IN A RAT MODEL OF INTESTINAL FAILURE-ASSOCIATED LIVER DISEASE**

*Siyang Cheng*<sup>1</sup>, *Lu Jiang*<sup>2</sup>, *Ying Wang*<sup>3</sup> and *Wei Cai*<sup>3</sup>, (1)1665 Kongjiang Road, Yangpu District, 1665 Kongjiang Road, Yangpu District, (2)University of Kansas Medical Center, (3)Xinhua Hospital

**Background:** Intestinal failure-associated liver disease (IFALD) is a common complication of long-term parenteral nutrition (PN) associated with significant morbidity and mortality. Ferroptosis, an iron-dependent regulated cell death, plays an important role in a series of liver diseases, while little is known about its role in IFALD. We aimed to investigate the pathogenic role of ferroptosis in IFALD and the underlying mechanisms. **Methods:** RNA sequencing was performed in pediatric patients with IFALD and non-IFALD controls. For animal models, four-week-old Sprague Dawley rats received total parenteral nutrition (TPN) or 0.9% saline for 7 days after a central venous catheter (CVC) was inserted into the superior vena cava. Liproxstatin-1 was used to inhibit ferroptosis at the dose of 10mg/kg for 7 days. Ferroptosis level and the beneficial effects of ferroptosis inhibitor were evaluated in livers. Serum and liver bile acid composition were evaluated after ferroptosis inhibition. The regulatory roles of microRNAs on ferroptosis were investigated by miRNA sequencing and in HepG2 cell line. **Results:** RNA sequencing showed upregulation of genes and pathways associated with ferroptosis in pediatric patients with IFALD. Iron accumulation was detected in livers from TPN rats, which was inhibited by liproxstatin-1. Hepatic steatosis induced by TPN administration was alleviated by liproxstatin-1 through downregulating fatty acid synthesis and uptake. TPN rats showed an altered liver bile acid profile compared to controls, while was restored after ferroptosis inhibition. miRNA sequencing identified mir-431 as the mostly upregulated miRNA in TPN group and was negatively correlated with glutathione peroxidases 4 (GPX4) expression in liver. In vitro studies showed that mir-431 induced ferroptosis by downregulating GPX4 in HepG2 cells. **Conclusion:** Ferroptosis plays a pathogenic role in the development of IFALD, inhibition of which could potentially alleviate the disease. Further studies are needed to explore the applications of ferroptosis inhibitors in clinic.

Disclosures:

The following people have nothing to disclose: Siyang Cheng

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## **NIMBLE 1.2: REPEATABILITY OF MRI BIOMARKERS IN NONALCOHOLIC FATTY LIVER DISEASE**

*Kathryn Fowler<sup>1</sup>, Sudhakar K. Venkatesh<sup>2</sup>, Nancy Obuchowski<sup>3</sup>, Michael S. Middleton<sup>4</sup>, Jun Chen<sup>5</sup>, Kay Pepin<sup>6</sup>, Jessica Magnuson<sup>2</sup>, Kathy Brown<sup>7</sup>, Danielle Batakis<sup>8</sup>, Walter Henderson<sup>8</sup>, Sudha S Shankar<sup>9</sup>, Helen Heymann<sup>10</sup>, Tania Kamphaus<sup>11</sup>, Roberto Calle<sup>12</sup>, Arun J Sanyal<sup>13</sup>, Rohit Loomba<sup>14</sup>, Richard L. Ehman<sup>6</sup>, Claude B. Sirlin<sup>4</sup> and Sarah Sherlock<sup>12</sup>, (1)Radiology, University of California San Diego, (2)Mayo, (3)Biostatistics, Cleveland Clinic, (4)Department of Radiology, University of California, San Diego, (5)Radiology, Mayo Clinic Rochester, (6)Department of Radiology, Mayo Clinic, (7)Radiology, Mayo, (8)Radiology, UCSD, (9)Astra Zeneca, (10)Nih, (11)Fnih, (12)Pfizer, (13)Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, (14)University of California San Diego*

**Background:** NIMBLE is a multi-stakeholder, public-private partnership effort to standardize, compare, validate, and advance the regulatory qualification of imaging and soluble biomarkers to diagnose and stage nonalcoholic fatty liver disease (NAFLD). Herein, we report the primary outcome results of the NIMBLE 1.2 MRI biomarker study to determine 'different-day, same-scanner' repeatability coefficient (RC<sub>diff-day</sub>) of liver MRI biomarkers in a relevant patient population. **Methods:** Adults with NAFLD across a spectrum of FIB-4 levels were prospectively block enrolled at a single academic clinical site. A standardized protocol was implemented on six MRI scanners from three vendors at two field strengths (1.5T and 3T). Scanners were qualified by a central site. Participants underwent up to seven MRI exams across 2 visits  $\hat{\alpha}$  7 days apart. The primary objective was to estimate the RC<sub>diff-day</sub> of MRI-PDFF, 2D and 3D MR elastography (MRE)-stiffness, and visceral adipose tissue (VAT) volume, pooling 1.5T and 3T data. An interim analysis (IA) was planned after the first 12 participants completed both scanning visits with chi-square and statistical modeling to estimate 95% confidence intervals of RC<sub>diff-day</sub> for each biomarker. Secondary analyses were performed after excluding participants with clinically-evident cirrhosis as they were no longer considered 'at risk' for cirrhotic nonalcoholic steatohepatitis. **Results:** A decision was made to discontinue enrollment after completion of IA. During the IA period a further five participants enrolled and underwent MRI. As a result, 17 participants [mean age 58 yrs, 10 females, mean BMI 33 (28-44) kg/m<sup>2</sup>; FIB-4 mean 3.0 (0.5-7.0)] completed the study protocol and were included in the primary analysis (full analysis set). Two participants with evident cirrhosis were excluded from the secondary analyses. Pooled RC<sub>diff-day</sub> are shown in **Table 1**. RC<sub>diff-day</sub> was 3% (primary analysis) or 3% (secondary analysis) for VAT, 9-11% (primary) or 9-10% (secondary) for magnitude and complex MRI-PDFF, 24% (primary) or 24% (secondary) for 2D MRE-stiffness, and 20% (primary) or 18% (secondary) for 3D MRE-stiffness. **Conclusion:** For longitudinal measurements acquired at either 1.5 or 3T on the same platform, differences of at least 3% for VAT, 9-11% for MRI-PDFF, and 20-24% for MRE stiffness may constitute real change, not attributable to measurement error. These results may help inform future clinical trial design incorporating MR-based assessments.

Biomarker	Mean	wSD (wCV <sup>†</sup> )	RC <sub>diff-day</sub>	%RC <sub>diff-day</sub> point estimate, primary analysis	%RC <sub>diff-day</sub> point estimate, secondary analysis	95% confidence interval, primary analysis	Secondary Analysis 95% confidence interval
VAT (liters)	6.60	0.08	0.22	3.3%	3.4%	2.6%, 4.3%	2.7%, 4.6%
2D MRE Stiffness pooled (kPa)	3.15	0.27	0.75	24%	23.8%	19.0%, 31.3%	19.0%, 31.5%
3D MRE Stiffness pooled (kPa)	2.63	0.07 <sup>†</sup>	Not applicable	19.7%	17.7%	15.8%, 26.2%	14.0%, 23.9%
Magnitude PDFF (%)	13.19	0.43	1.19	9.1%	8.9%	7.3%, 12.2%	7.1%, 11.9%
Complex PDFF (%)	14.16	0.56	1.56	11.0%	10.2%	8.9%, 14.6%	8.1%, 13.6%

**Table 1.** Primary outcome data for each biomarker pooling 1.5T and 3T data across the final sample (N=17) using 32 measurements, and in the secondary analysis (N=15) using 29 measurements after excluding two participants with clinically-evident cirrhosis. VAT-visceral adipose tissue, wSD-within subject standard deviation, wCV-within subject coefficient of variation, RC-repeatability coefficient, MRE-magnetic resonance elastography, PDFF-proton density fat fraction. The upper bounds of the confidence interval were calculated using pivotal chi square distribution with degrees of freedom equal to the number of observations. The selection of wSD versus wCV was determined based on the relationship between measurement variance and measurement magnitude; wCV was reported if measurement variance was proportional to measurement magnitude.

† - TBA

Disclosures:

Kathryn Fowler - Bayer: Advisory Committee or Review Panel; GE: Consulting; Quantix Bio: Board Membership;

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## THE NOVEL GALECTIN-3 INHIBITOR GB1211 REDUCES INFLAMMATION & FIBROSIS IN A RABBIT HIGH FAT DIET MODEL OF NASH & FIBROSIS

Robert Slack<sup>1</sup>, Paolo Comeglio<sup>2</sup>, Sandra Filippi<sup>2</sup>, Giulia Guarnieri<sup>3</sup>, Ilaria Cellai<sup>3</sup>, Luciano Adorini<sup>4</sup>, Annamaria Morelli<sup>3</sup>, Linda Vignozzi<sup>5</sup> and Mario Maggi<sup>3</sup>, (1)Galecto Biotech AB, (2)Department of Experimental and Clinical Biochemical Sciences "Mario Serio", University of Florence, (3)University of Florence, (4)Istituto Nazionale Biostrutture e Biosistemi, (5)Sexual Medicine and Andrology, University of Florence

**Background:** Galectin-3 (Gal-3) is a pro-fibrotic  $\beta$ -galactoside binding lectin highly expressed in fibrotic liver<sup>1</sup> & implicated in hepatic fibrosis<sup>2</sup>. GB1211 is a novel orally active Gal-3 small molecule inhibitor<sup>3</sup> that has high affinity for Gal-3 (human  $K_D=25nM$ ; rabbit  $K_D=12nM$ ) & high oral bioavailability in rabbits & man. In this study the efficacy of GB1211 was investigated in a high fat diet (HFD) rabbit model of non-alcoholic steatohepatitis (NASH)<sup>4</sup>. **Methods:** Male New Zealand White rabbits were individually caged under standard conditions in a temperature & humidity-controlled room on a 12h light/darkness cycle. After 1 week of regular diet (RD), rabbits were randomly assigned to 4 different groups (n=3/group): RD/vehicle, RD/30mg/kg GB1211, HFD/vehicle & HFD/30 mg/kg GB1211 (vehicle/GB1211 *p.o.* dosed therapeutically *q.d.* 5 days from week 11) for 12 weeks. Liver inflammation, steatosis, ballooning, and fibrosis was measured via blood metabolic markers (glucose, cholesterol, triglycerides & transaminases), histomorphological analysis (Masson's trichome, Giemsa, oil red O & picrosirius red (PSR)), second generation harmonics (SHG collagen content) & fibrotic gene signature. Plasma concentrations of GB1211 were determined by LC-MS. **Results:** Inflammation score, steatosis (binomial score & % area oil red O), ballooning score & fibrosis (% PSR, SHG) were all significantly increased from RD to HFD vehicle groups. GB1211 significantly reduced all measures of inflammation & fibrosis compared with the HFD/vehicle group. There were also trends for reduction in fibrotic & Gal-3 mechanistic genes (COL1A1, COL3A1, SNAI2, LGALS3, PAI-1). GB1211 reached steady state free plasma concentrations at  $C_{min}$  of  $40 \times K_D$  when dosed *q.d.* for 4 days. **Conclusion:** GB1211 normalized inflammation & fibrosis in a HFD rabbit model of NASH & liver fibrosis following less than a week of dosing. This data supports the current ongoing phase 2b study investigating GB1211 in liver cirrhosis patients (NCT05009680). <sup>1</sup>Gudowska et al., (2015). *Ann Clin Lab Sci*, 45, 669-673. <sup>2</sup>Henderson et al., (2006) *Proc Natl Acad Sci USA*, 103, 5060-5065. <sup>3</sup>Zetterberg et al., (2022) *J Med Chem*, (in press). <sup>4</sup>Comeglio et al., (2018) *J Endocrinol*, 238, 107-127.

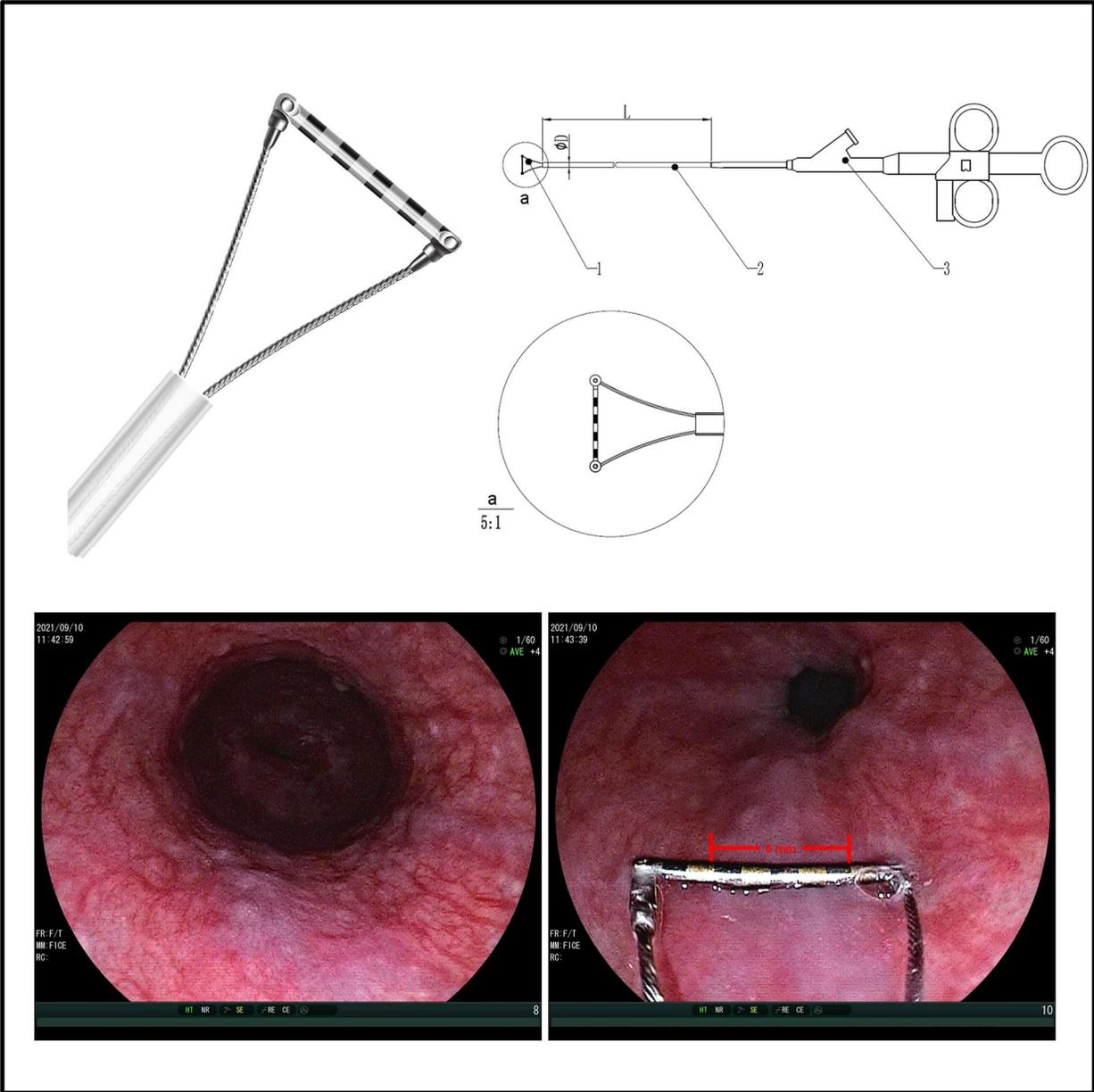
Disclosures:

Robert Slack - Galecto Biotech AB: Employment; Galecto Biotech AB: Stock Shareholder;

## ENDOSCOPIC RULER FOR VARIX SIZE MEASUREMENT (CHESS2005): A PROSPECTIVE MULTICENTER STUDY

*Yifei Huang<sup>1,2</sup>, Shengjuan Hu<sup>3</sup>, Yang Bo<sup>3</sup>, Yiling Li<sup>4</sup>, Yanhong Deng<sup>3</sup>, Jianping Hu<sup>5</sup>, Shaoqi Yang<sup>6</sup>, Qian Shen<sup>7</sup>, Mark Edward McAlindon<sup>8</sup>, Ruichun Shi<sup>9</sup>, Xiaoqin Li<sup>10</sup>, Tiejing Song<sup>11</sup>, Hailong Qi<sup>12</sup>, Taiwei Jiao<sup>4</sup>, Mengyuan Liu<sup>4</sup>, Fang He<sup>6</sup>, Jun Zhu<sup>10</sup>, Bin Ma<sup>5</sup>, Xiaobing Yu<sup>3</sup>, Jianyang Guo<sup>3</sup>, Yuehua Yu<sup>5</sup>, Haijiang Yong<sup>9</sup>, Wentun Yao<sup>5</sup>, Ting Ye<sup>5</sup>, Hua Wang<sup>10</sup>, Wenfu Dong<sup>10</sup>, Jianguo Liu<sup>13</sup>, Qiang Wei<sup>13</sup>, Jing Tian<sup>13</sup>, Haoxiang He<sup>14</sup>, Changhui He<sup>14</sup>, Xavier Dray<sup>15</sup> and Xiaolong Qi<sup>1</sup>, (1)Center of Portal Hypertension, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, (2)The First Hospital of Lanzhou University, (3)People's Hospital of Ningxia Hui Autonomous Region (Ningxia Medical University Affiliated People's Hospital of Autonomous Region), (4)Department of Gastroenterology, The First Affiliated Hospital of China Medical University, (5)Department of Gastroenterology, Yinchuan First People's Hospital, (6)Department of Gastroenterology, Ningxia Medical University General Hospital, (7)Department of Gastroenterology, Yinchuan Second People's Hospital, (8)Academic Department of Gastroenterology and Hepatology, Sheffield Teaching Hospitals NHS Trust, (9)Department of Gastroenterology, Wuzhong People's Hospital, (10)Department of Gastroenterology, The Fifth People's Hospital of Ningxia Hui Autonomous Region, (11)Department of Second Gastroenterology, The Sixth People's Hospital of Shenyang, Shenyang, (12)Department of Gastroenterology, Shizuishan Second People's Hospital, (13)Department of Gastroenterology, Zhongwei People's Hospital, (14)Shanghai Alton Medical Devices Co., Ltd, (15)Centre for Digestive Endoscopy, Saint-Antoine Hospital, Aphp*

**Background:** Oesophageal varices (OV) screening by Esophagogastroduodenoscopy (EGD) is generally performed by endoscopists with different levels of experience, and the operator assesses the size of OV according to subjectivity in the procedure. We developed a novel endoscopic device, named as Endoscopic Ruler, for objective measurement of varix size. This study aimed to evaluate the feasibility and safety of Endoscopic Ruler, assess the agreement on diagnosing large OV (varix size  $\geq 5$ mm) between endoscopists and Endoscopic Ruler and interobserver reliability on detecting large OV by Endoscopic Ruler. **Methods:** This study was a prospective, multicenter, pilot trial (CHESS2005, ClinicalTrials.gov identifier: NCT04639323), in which we consecutively recruited cirrhotic patients from 11 hospitals in China between November 2020 and April 2022. All patients underwent EGD with Endoscopic Ruler. Endoscopic Ruler consists of three parts: tip, sheath and operating handle. Endoscopic Ruler is divided into ten millimeters. There are ten black and white grids and the width of each grid is 1mm (Figure 1). Empirical interpretation of OV by endoscopists was prior to measurement of Endoscopic Ruler and the results would be recorded by a specific recorder at individual centers. The primary outcome was the success of measurement of varix size by Endoscopic Ruler: from Endoscopic Ruler being sent into the region of interest, the largest OV being measured, to Endoscopic Ruler being drawn out. Secondary outcomes were safety, operation time of Endoscopic Ruler, agreement on diagnosing large OV between empirical reading of endoscopists and objective measurement of Endoscopic Ruler and interobserver reliability on diagnosing large OV using Endoscopic Ruler. **Results:** A total of 120 eligible patients (mean age 54.02 years; male 59.17 %) were involved in final analysis. Hepatitis B virus infection was the main etiology of cirrhosis (n= 82, 68.33%). The number of patients of Child-Pugh class A, B, and C were 43 (35.83%), 59 (49.17%), 18 (15.00%), respectively. EGD with Endoscopic Ruler were successfully performed in all 120 patients (100%), with no adverse events related to EGD and Endoscopic Ruler (n= 0, 0%). The median operation time of Endoscopic Ruler was 3.00 (interquartile range 3.00) minutes. The kappa score between endoscopists and Endoscopic Ruler on diagnosis of large OV was 0.52 (95% confidence interval: 0.31-0.73), demonstrating a moderate agreement. The overall kappa score on detecting OV using Endoscopic Ruler among the six independent and blinded observers was 0.77 (95% confidence interval: 0.61-0.93), demonstrating a substantial agreement. **Conclusion:** The results suggested that Endoscopic Ruler was feasible and safe for measurement of varix size. Endoscopic Ruler might help promote the quantitative 2-grade classification system of OV in clinical practice.



Disclosures:  
The following people have nothing to disclose: Xiaolong Qi

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## HIGH EXPRESSION OF CIRCULATING EXOSOMAL PD-L1 CONTRIBUTES TO IMMUNE ESCAPE IN HEPATOCELLULAR CARCINOMA AND IMMUNE CLEARANCE OF CHRONIC HEPATITIS B

*Tongjing Xing, Hui Shao, Yongzhi Tang, Qiupeng Wang, Zhenyu Yang, Hongwei Wu and Xiaoqing Lin, Taizhou Hospital of Zhejiang Province Affiliated to Wenzhou Medical University*

**Background:** To investigate the expression of programmed death ligand-1 (PD-L1) in circulating exosomes, and to define the role of exosomal PD-L1 in promoting immune escape mechanism during chronic hepatitis B infection (CHB) and related liver diseases. **Methods:** Circulating exosomes were isolated from patient samples using exosome isolation kits and identified by NanoSight and transmission electron microscopy. The levels of PD-L1 expressed in exosomes were detected by ELISA. CD8<sup>+</sup>T cells were sorted and cytotoxicity test assessed by flow cytometry. PD-L1 protein expression in hepatocellular carcinoma (HCC) and normal adjacent tissues were detected by immunohistochemistry. **Results:** Circulating exosomal PD-L1 levels were significantly higher in patients with liver cirrhosis and HCC than in patients with CHB ( $F = 4.76$ ,  $P < 0.05$ ). Compared with patients receiving isotype blocking antibody, levels of CD107a on CD8<sup>+</sup>T cells significantly increased in patients with HCC receiving anti-PD-L1 antibody ( $t = 3.51$ ,  $P < 0.05$ ). Levels of CD107a on CD8<sup>+</sup>T cells in patients with CHB receiving PD-L1 blocking antibody was significantly lower than in patients receiving isotype blocking antibody ( $t = 4.96$ ,  $P < 0.01$ ). In experiments assessing the immune response, we observed marginally higher levels of IFN- $\gamma$  in cell culture supernatants in the PD-L1 blocking antibody group compared to the isotype blocking antibody group ( $t = 2.43$ ,  $P = 0.07$ ). Levels of TNF- $\alpha$  in cell culture supernatants of the PD-L1 blocking antibody group were significantly higher than in the isotype blocking antibody group ( $t = 5.92$ ,  $P < 0.01$ ). Compared with adjacent tissues, the levels of PD-L1 protein expression in HCC tissues were slightly higher; however, no significant difference between the two groups was observed ( $t = 1.34$ ,  $P > 0.05$ ). **Conclusion:** PD-L1 blockade in exosomes can promote the cytotoxic function of CD8<sup>+</sup>T cells and may inhibit immune evasion mechanisms commonly observed during the progression of HCC. Strikingly, we found that blocking PD-L1 in exosomes reduced the cytotoxic function of CD8<sup>+</sup>T cells in patients with CHB while enhancing the production of proinflammatory cytokines. This study could provide potential biomarkers for guided anti-viral therapy of CHB patients and immunotherapy in HCC patients.

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## CHARACTERISTICS OF CHRONIC HEPATITIS B PATIENTS ENROLLED IN A 20-YEAR, REAL-WORLD STUDY OF TREATMENT PATTERNS IN A US HEALTH CARE DELIVERY SYSTEM

Mark A. Schmidt<sup>1</sup>, Yihe Daida<sup>2</sup>, Sacha Satram<sup>3</sup>, Ana Gabriela Rosales<sup>1</sup>, Andre Arizpe<sup>3</sup>, Vaidehi Thanawala<sup>3</sup>, Carolina Reyes<sup>3</sup> and Norah Terrault<sup>4</sup>, (1)Center for Health Research, Kaiser Permanente Northwest, (2)Center for Integrated Health Care Research, Kaiser Permanente Hawaii, (3)Vir Biotechnology, (4)Division of Gastrointestinal and Liver Diseases, University of Southern California

**Background:** Chronic hepatitis B (CHB) infection is an important public health concern due to its worldwide prevalence and potential for severe complications, including cirrhosis, hepatocellular carcinoma, and death. CHB treatment is intended to reduce these complications and is recommended for those at highest risk, such as by elevated HBV DNA and markers of liver inflammation. The objective of this analysis was to compare baseline cohort characteristics for treated and untreated CHB patients in routine clinical practice. **Methods:** This retrospective, observational analysis utilized electronic health records from Kaiser Permanente Northwest and Hawaii integrated health care delivery systems. Patients were included if they had  $\geq 2$  positive laboratory results, or 1 positive laboratory result and 1 diagnostic code for CHB, separated by  $> 6$  months, during the study period from January 1, 2000 - December 31, 2020. Treated patients were defined as those receiving at least a 60-day consecutive course of either nucleos(t)ide analogs (NA) or interferon alpha (IFN) after cohort entry. **Results:** Out of 3,716 patients diagnosed with CHB, 1,276 (34%) received treatment and 2,440 (66%) did not. The proportion treated remained steady throughout the study period. Of the treated cohort, 1,207 (95%) received an NA, while 69 (5%) received IFN. Compared to untreated patients, treated patients were more likely to be male (63% vs 45%,  $p < 0.0001$ ), older (71% vs. 56%  $\geq 40$  years,  $p < 0.0001$ ), overweight or obese (41% vs. 38%,  $p = 0.036$ ), and have a higher comorbidity burden ( $p < 0.0001$ ). Treated patients were also more likely to be HBeAg+ and had higher HBV DNA and ALT levels and mean FIB4 score compared to untreated patients ( $p < 0.0001$ ) at baseline. At baseline, patients treated with IFN were on average 9 years younger ( $p < 0.0001$ ), had a lower comorbidity burden ( $p = 0.0141$ ), were more likely to be HBeAg+, and had higher HBV DNA and ALT levels and lower mean FIB4 score compared to patients treated with NRTI ( $p < 0.0001$ ). **Conclusion:** Although we observed a higher proportion of CHB patients receiving treatment than previously reported, two-thirds were still not treated. Among treated CHB patients, those receiving NA were older, sicker, and had significantly worse clinical characteristics than those receiving IFN. These points suggest considerable unmet needs in understanding the role of treatment recommendations for CHB patients at risk of disease progression.

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## EFFICACY OF THERAPEUTIC VACCINATION WITH LENTIVIRAL VECTOR FOR CHRONIC HEPATITIS B IN HBV PERSISTENT MICE AND INTERIM RESULTS FOR TWO PATIENTS

Yumeng Zhang<sup>1</sup>, Maryline Mancini-Bourguin<sup>2</sup>, Zongying Li<sup>3</sup>, Yanmin Wan<sup>1</sup>, Jieyu Song<sup>1</sup>, Yiqi Yu<sup>1</sup>, Wangfang Jiang<sup>3</sup>, Didier Santucci<sup>4</sup>, Wenhong Zhang<sup>1</sup>, Christian Brechot<sup>5</sup>, Pierre Charneau<sup>2</sup>, Hong Wu<sup>6</sup> and Chao Qiu<sup>1</sup>, (1)Department of Infectious Disease, Huashan Hospital, Fudan University, (2)Pasteur-Theravectys Joint Lab, Institut Pasteur, (3)Department of Laboratory Medicine, Changzhi People's Hospital, (4)Jinwei Biotechnology, (5)Theravectys S.a., (6)Department of Infectious Disease, Changzhi People's Hospital

**Background:** Immunotherapy for treatment of hepatitis B virus (HBV) chronic infection has not yet demonstrated sufficient efficacy. We developed a non-integrative lentiviral vectored therapeutic vaccine for chronic hepatitis B and tested its therapeutic potential in HBV carrier mice and an exploratory investigator-initiated trial of inactive carriers. **Methods:** Lentiviral vectors (LV) encoding Core, preS1, or large HBs (LHBs) proteins of HBV were evaluated for their immunogenicity in HBV naïve mice and therapeutic efficacy in a proof-of-concept murine model of chronic HBV infection. Two HBV chronic patients received two doses of  $5 \times 10^7$  IU or  $1 \times 10^8$  IU of LV-LHBs on day 0 and day 7, respectively. Endpoints: safety, LHBs-specific T cell response, and serum HBsAg quantification through 24 weeks after immunization. **Results:** In mouse models, LV-LHBs was the most promising in eliciting robust antigen-specific T cell and in significantly reducing the levels of serum HBsAg and viral load. By the 34-week observation period, 6 out of 10 (60%) HBV persistent mice achieved serum HBsAg loss and the HBV-positive hepatocytes were significantly depleted from the liver, strongly supporting further test in clinical use. In two HBV carriers, a considerable transient increase in the number of peripheral LHBs-specific T cells was observed, accompanied by sustained HBsAg reduction of  $0.31 \log_{10}$  IU/ml and  $0.46 \log_{10}$  IU/ml from baseline to nadir. **Conclusion:** This study demonstrates that lentiviral vectored therapeutic vaccine for chronic HBV infection can overcome HBV-specific T cell tolerance and downsize the HBV-positive hepatocytes, leading to a sustained loss or reduction in serum HBsAg. It paves the way for larger clinical studies.

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Chao Qiu - Jinwei Biotechnology, Shanghai, China: Dr. Qiu is a scientific consultant and holds stock in Jinwei Biotechnology, he is one of the inventors of the lentiviral vector HBV vaccine;

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**HEPATITIS B VIRAL CONTROL MAINTAINED DURING EXTENDED FOLLOW UP OF HBeAg-CHRONIC HEPATITIS B (CHB) SUBJECTS WHO DISCONTINUED NUCLEOS(T)IDE ANALOGUE (NA) THERAPY AFTER COMPLETION OF AB-729 TREATMENT, AND IN HBeAg+ SUBJECTS STILL ON NA THERAPY**

*Man-Fung Yuen<sup>1</sup>, Jacinta A. Holmes<sup>2</sup>, Simone I. Strasser<sup>3</sup>, Apinya Leerapun<sup>4</sup>, Wattana Sukeepaisarnjaroen<sup>5</sup>, Pisit Tangkijvanich<sup>6</sup>, Varun Sharma<sup>7</sup>, Elina Medvedeva<sup>7</sup>, Emily P Thi<sup>8</sup>, Gaston R. Picchio<sup>7</sup>, Timothy Eley<sup>7</sup> and Karen Sims<sup>7</sup>, (1)Department of Medicine, The University of Hong Kong, (2)Gastroenterology, St. Vincent's Hospital, Melbourne, Australia, (3)A.W. Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Sydney NSW, Australia, (4)Chiang Mai University, Chiang Mai, Thailand, (5)Srinagarind Hospital, Khon Kaen University, Thailand, (6)Center of Excellence in Hepatitis and Liver Cancer, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand, (7)Clinical Development, Arbutus Biopharma, Warminster, PA USA, (8)Research/Discovery, Arbutus Biopharma, Warminster, PA USA*

**Background:** AB-729 is a GalNAc-conjugated single trigger siRNA therapeutic that targets all HBV RNA transcripts, resulting in suppression of viral replication and all viral antigens. AB-729 is currently in Phase 2 clinical development in combination with other agents for the treatment of CHB. Study AB-729-001 assessed different regimens of AB-729 for 48 weeks (W) in combination with ongoing NA therapy. Here we report early follow-up (FU) data for all subjects from the dedicated HBeAg+ Cohort K (all have completed the AB-729 treatment period), and extended FU data for the 9 subjects from other study Cohorts who elected to stop NA therapy at least 6 months after their last dose of AB-729 as part of an optional NA discontinuation (d/c) period. **Methods:** Cohort K is a dedicated HBeAg+ cohort (N=7) dosed with AB-729 90mg every 8W for 48W. Two of 7 subjects received 5 of the planned 6 AB-729 doses due to drug supply, and all subjects are now in the FU period. All subjects in the AB-729-001 study who received AB-729 for 48W are assessed for eligibility for NA d/c at least 24W after their last dose of AB-729. NA d/c criteria include ALT <2 $\times$ ULN, HBeAg-, HBV DNA undetectable, and HBsAg <100 IU/mL on 2 consecutive visits. Safety and virologic assessments (including HBV DNA, HBsAg, HBV RNA, HBcrAg, HBeAg) are assessed every 4W during Cohort K dosing and post-treatment FU, and every 2-4W after NA d/c. **Results:** In Cohort K, the mean (SE) log<sub>10</sub> change from baseline in HBsAg was -2.51 (0.57) IU/mL at W48 and -2.26 (0.68) IU/mL at FU W12 (N=5 each), with 2 of these subjects achieving HBsAg levels below the limit of quantitation (BLQ) at W44 and at FU W12 (pre-treatment HBsAg levels were 600.1 IU/mL and 545.2 IU/mL, respectively). No Cohort K subjects have met NA d/c criteria to date. Nine subjects from Cohorts E, F, G, and I elected to stop NAs; baseline characteristics of these subjects have been reported previously. To date, all 9 subjects have completed between 16W and 40W of FU off all HBV therapy. Key HBV DNA and HBsAg values are shown in the **Table**. One subject restarted NA per Investigator request after the NA d/c FU W20 visit when HBV DNA reached 4670 IU/mL; the subject was asymptomatic and ALT remained normal. No subjects have met the protocol-defined NA restart criteria. At the last available timepoint, all HBV DNA levels are <1000 IU/mL and HBsAg levels remain well below pre-study levels for all subjects. **Conclusion:** AB-729 treatment leads to marked HBsAg declines in HBeAg+ subjects, with 2 subjects achieving HBsAg BLQ. NA d/c after NA+AB-729 treatment in HBeAg- subjects who achieve HBsAg <100 IU/mL is well-tolerated and results in sustained low HBV DNA and HBsAg levels up to 40 weeks off all therapy, suggestive of new viral set points via immune control.

**Table:**

Timepoint	HBV parameter (IU/mL)	Pre-Study HBV DNA- (NA Suppressed)					Pre-Study HBV DNA+			
		Subject 46	Subject 52	Subject 51	Subject 53	Subject 61	Subject 56	Subject 59	Subject 58	Subject 60
Pre-study baseline	HBV DNA	TND	TND	TND	TND	TND	212,490	560	5840	9990
Pre-NA DC	HBV DNA	<LLOQ	<LLOQ	TND	TND	<LLOQ	<LLOQ	TND	<LLOQ	<LLOQ
NA DC FU W4	HBV DNA	<LLOQ	10	N/A <sup>#</sup>	10	TND	N/A <sup>#</sup>	TND	10	TND
NA DC FU W12	HBV DNA	10	30	<LLOQ	140	<LLOQ	4100 <sup>†</sup>	TND	970	<LLOQ
NA DC FU W24	HBV DNA	<LLOQ	50	80	20 <sup>*</sup>	90				
NA DC FU W36	HBV DNA	90	350	150						
Pre-study baseline	HBsAg	1392	1888	6765	2368	2021	277.3	1338	1397	1128
Pre-NA DC	HBsAg	10.53	3.95	64.9	69.06	3.99	8.4	17.31	31.09	1.24
NA DC FU W4	HBsAg	23.04	2.93	N/A <sup>#</sup>	90.69	4.18	N/A <sup>#</sup>	3.63	41.29	2.47
NA DC FU W12	HBsAg	33.12	6.61	113.5	128.7	7.16	8.56	6.78	65.06	5.45
NA DC FU W24	HBsAg	41.22	14.43	161.2	180.1 <sup>*</sup>	29.79				
NA DC FU W36	HBsAg	76.99	27.29	139.3						

HBV DNA lower limit of quantitation (LLOQ) = 10 IU/mL (Abbott Realtime HBV viral load assay); HBsAg LLOQ = 0.07 IU/mL (Roche Elecsys HBsAg II quant II), TND = target not detected. <sup>#</sup>missed visits due to COVID-19; <sup>\*</sup>post-NA restart; <sup>†</sup>W16 HBV DNA = 440 IU/mL

Disclosures:

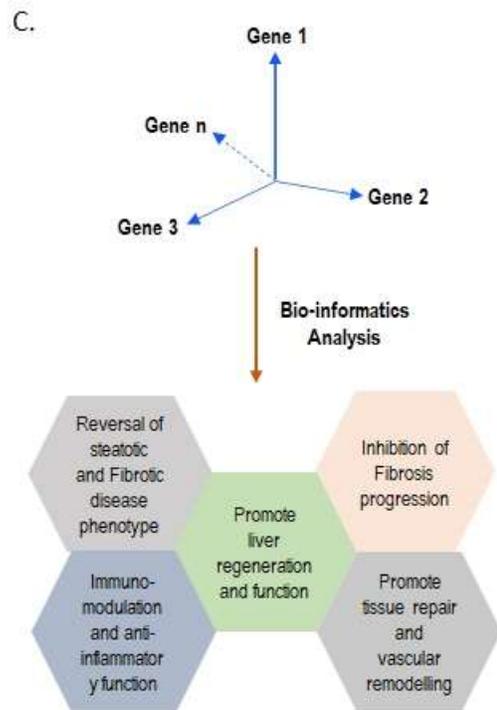
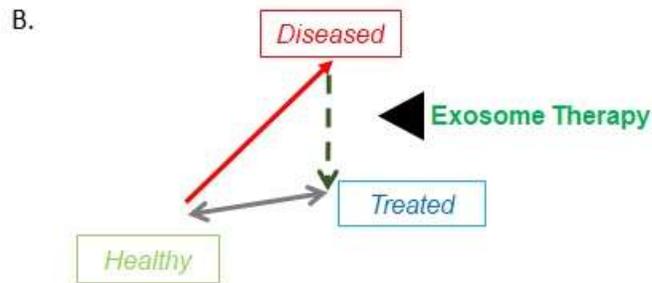
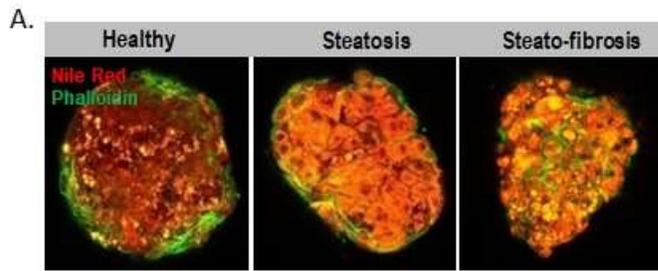
Karen Sims - Arbutus Biopharma: Employment; Arbutus Biopharma: Stock Shareholder;

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## EXOSOME THERAPY REVERSES NASH ASSOCIATED PATHOLOGY: FINDINGS FROM HUMAN LIVER ORGANOIDS

*Wenson David Rajan<sup>1</sup>, Nisha Rajendran<sup>1</sup>, Ajith V Kamath<sup>1</sup>, Sonal Asthana<sup>1,2</sup>, Arun Chandru<sup>1</sup> and Tuhin Bhowmick<sup>1</sup>, (1)Pandorum Technologies Pvt. Ltd., (2)Integrated Liver Care, Aster CMI Hospital Bangalore*

**Background:** Progression of steatosis to steatohepatitis and fibrosis involves complex interplay and activation of different cell types including hepatocytes, Kupffer cells and stellate cells, thus developing a therapeutic target much difficult. Mesenchymal stem cell (MSCs) are stromal cells that can self-renew and differentiate into multi-lineage population. MSCs are known to possess excellent immunomodulatory and tissue regenerative properties owing to secretion of paracrine signaling factors including exosomes, growth factors and cytokines. Exosome are cell-free nanovesicles rich in cell modulatory proteins, mRNA and miRNAs. In recent times, therapeutic potential of exosomes in treating various inflammatory and fibrotic diseases are steadily increasing with the number of pre-clinical and clinical trials being currently carried out. **Methods:** In our study, we had demonstrated a novel NASH model using multi-lineage primary hepatic spheroid consisting of primary human hepatocytes and hepatic stellate cells. Using quantitative microscopy and transcriptomic/bioinformatics-based readouts, we had demonstrated the NASH organoid model recapitulated the steato-fibrotic gene-signatures similar to human NAFLD/NASH liver. Exosomes derived from naïve and pathway primed MSCs were used to treat the NASH induced organoids along with some of the promising investigational drugs such as HGF, Saroglitazar and Obeticholic acid. **Results:** Differential gene expression and pathway enrichment analysis showed pathways relevant to human NASH pathology such as PPAR signaling pathway, fatty acid metabolism, NF- $\kappa$ B signalling, Hippo signalling, ECM-receptor/TGF $\beta$  signalling were found to be differentially regulated in the NASH organoids. Ingenuity pathway analysis performed on the transcriptomic data from the NASH organoid showed significant similarities with the publicly available human NASH patient data. We had demonstrated the pathway-specific priming of producer MSCs enhances the therapeutically relevant cargoes in the secretome and exosomes including HGF, VEGF etc. when compared to naïve exosomes. Quantitative microscopy analysis showed a significant reduction in the Col1 and alpha-SMA expression in the NASH organoids treated with exosomes. We observed increased albumin secretion in the NASH organoids treated with primed exosomes when compared to naïve exosomes and investigational drugs. We found primed exosomes are more potent in reversing the NASH associated pathology closer to healthy organoids with the genes related to fibrosis, liver metabolism (Xenobiotics, fatty acid) being altered to a healthy state. **Conclusion:** Taken together, we had demonstrated using human organoid NASH model that exosome-based therapy as a promising therapeutic strategy to reverse NASH associated pathology and reverse hepatic metabolic dysfunction.



**A.** Steato-fibrotic liver spheroids recapitulating fat accumulation and fibrotic phenotype. **B.** Schematic of tissue-state change from Healthy to Diseased upon disease induction and reversal state upon treatment with various drug candidates. The distance between the healthy and treated state determines the efficacy of the drug molecule. **C.** Induction of gene expression space, post-treatment with MSC derived exosome on NASH liver organoids and functional pathways that mediates NASH disease reversal and liver regeneration

Disclosures:

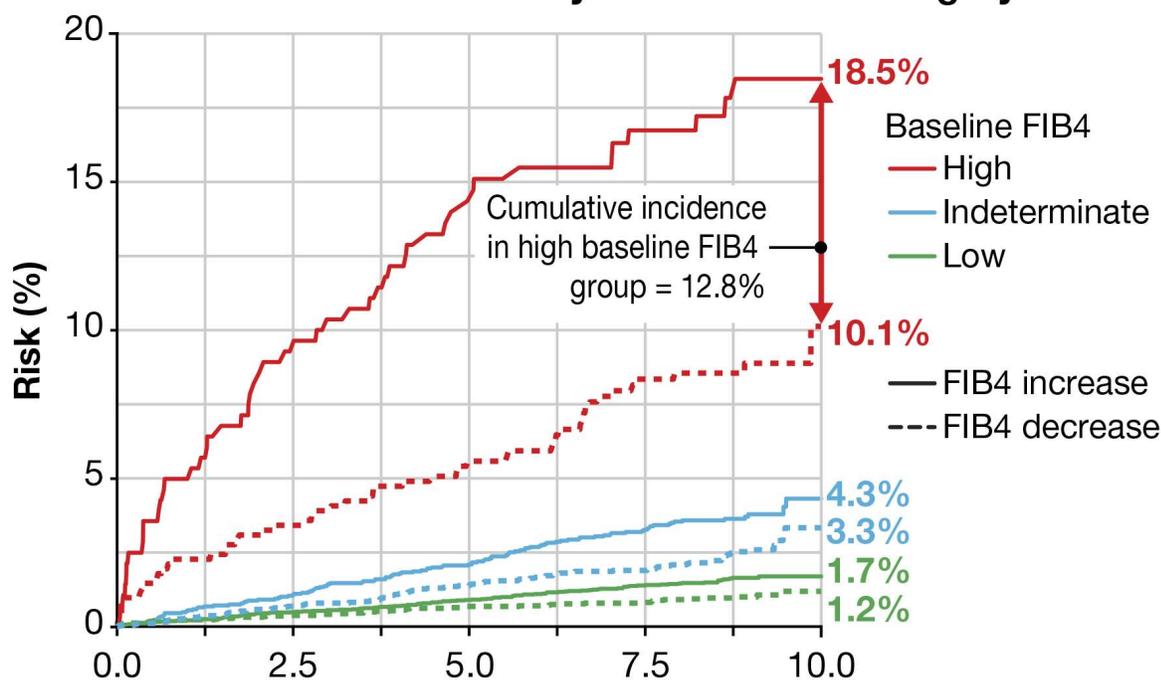
The following people have nothing to disclose: Wenson David Rajan

## CHANGE IN FIBROSIS-4 INDEX (FIB4) OVER TIME IS ASSOCIATED WITH SUBSEQUENT RISK OF LIVER EVENTS, CARDIOVASCULAR EVENTS, AND ALL-CAUSE MORTALITY IN PATIENTS WITH OBESITY AND/OR TYPE 2 DIABETES (T2D)

Quentin M. Anstee<sup>1,2</sup>, Tina L. Berentzen<sup>3</sup>, Louise M. Nitze<sup>3</sup>, Maximilian Jara<sup>3</sup>, Anders Jensen<sup>3</sup>, Mette S. Kjær<sup>3</sup>, Kamal K. Mangla<sup>3</sup>, Jens M. Tarp<sup>3</sup> and Kamlesh Khunti<sup>4</sup>, (1)Translational & Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK, (2)Newcastle Nihl Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Trust, Newcastle upon Tyne, UK, (3)Novo Nordisk A/S, Søborg, Denmark, (4)Diabetes Research Centre, University of Leicester, Leicester General Hospital, Leicester, UK

**Background:** Tools to monitor patients with NASH and assess their risk of morbidity and mortality are lacking. We evaluated the association of 12-month changes in FIB4 ( $\Delta$ FIB4) with the risk of developing severe NASH-related clinical events. **Methods:** We conducted a longitudinal cohort study using data from the UK Clinical Practice Research Datalink linked with Hospital Episodes Statistics and Office for National Statistics data. Patients were aged  $\geq 18$  years; had obesity and/or T2D;  $\geq 2$  FIB4 measurements; and no alcohol-related disorders, chronic liver diseases other than NAFLD, or prescriptions of drugs inducing liver disease. We calculated  $\Delta$ FIB4 using score at baseline and after 12 ( $\pm 3$ ) months. Patients were followed from second measurement until time of first liver event; time of first cardiovascular (CV) event (hospitalization/death); all-cause mortality; database migration; 10 years' follow-up; or 1 Jan 2020, whichever was first. Cumulative incidence and HRs were estimated with Aalen-Johanson and Cox proportional hazards models. **Results:** There were 466 liver events among 20,443 included patients. Risk of an incident liver event after 10 years in patients with high baseline FIB4 ( $>2.67$ ) was 12.8%, but 18.5% and 10.1% for patients whose FIB4 increased or decreased in the 12 months from baseline (**Figure**). Patients with an indeterminate (1.30-2.67) or low baseline FIB4 ( $<1.30$ ) also showed increased risk with increasing FIB4 and vice versa (**Figure**). In Cox models adjusted for sex, age, and baseline FIB4,  $\Delta$ FIB4 was positively associated with the risk of a liver event, with the association depending on baseline FIB4. Thus, compared with patients with low baseline FIB4 and no change in FIB4 (reference), the HR (95% confidence interval) was 24.27 (16.98, 34.68) for those with high baseline FIB4 and a 1-unit FIB4 increase, and 10.90 (7.90, 15.05) for those with high baseline FIB4 and a 1-unit decrease. Compared with the reference, those with indeterminate and low baseline FIB4 and 1-unit FIB4 increase/decrease also had significantly higher/lower risk. Similar results were seen for CV events and mortality, though the association with CV events was attenuated after adjustment for age. **Conclusion:** In patients with obesity and/or T2D, a 12-month increase/decrease in FIB4 was associated with higher/lower risk of a NASH-related clinical event across all three FIB4 baseline groups, highlighting the monitoring potential of FIB4 to identify patients at risk of severe events.

### Cumulative incidence for liver events according to a 12-month increase or decrease in FIB4 by baseline FIB4 category



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**PRECLINICAL CHARACTERIZATION OF A NOVEL LIVER-FOCUSED SMALL MOLECULE EFFICIENTLY INHIBITING HEPATITIS B VIRUS BY ACTIVATING TYPE I INTERFERON SIGNALING**

Ariel Tang, Lida Guo, Xiang Xu, Nuruddin Unchwaniwala, Lewyn Li, Carl Li, Michael Shen, Jiaxin Yu, Hassan Pajouhesh, Marc P. Windisch, Michel Perron, Michael A. Walker, William Delaney, Min Zhong and Ken Zhang, Assembly Biosciences

**Background:** Chronic HBV infection (cHBV) affects ~296 million patients worldwide. Nucleos(t)ide reverse transcriptase inhibitors reduce HBV DNA, but treatment is indefinite. Pegylated interferon alpha (PEG-IFN- $\alpha$ ), which has immunomodulatory and antiviral activities, leads to HBsAg clearance (functional cure) in a subset of patients. However, poor tolerability limits its clinical use. Here we describe the preclinical profile of a novel class of orally bioavailable small molecules that inhibit HBV and engage the immune system through activating IFN signaling pathways. **Methods:** EC<sub>50</sub>s for HBV and hepatitis C virus (HCV) inhibition were measured in infected primary human hepatocytes (PHHs) by HBeAg ELISA and Huh-7 replicon cells by luciferase reporter, respectively. IC<sub>50</sub>s for interferon-sensitive response element (ISRE) reporter activity were measured in HEK293 cells. Interferon stimulated gene (ISG) induction was assessed by RT-qPCR and RNA hybridization (NanoString) in mouse liver (*in vivo*) and PHHs (*in vitro*), respectively. Compound exposure time to induce antiviral effects was evaluated in HCV replicon cells. JAK-1 dependency was assessed with JAK-1-specific inhibitors and STAT-1 phosphorylation assessed by Western blot. Pharmacokinetic (PK) and pharmacodynamic (PD) experiments were performed in mice. **Results:** Structurally differentiated compounds were selected for potency and PK/PD profiling. All compounds inhibited HBV (EC<sub>50</sub> 0.8-5  $\mu$ M), HCV (EC<sub>50</sub> 0.03-0.2  $\mu$ M), and induced ISRE reporter activity (IC<sub>50</sub> 2-9  $\mu$ M). A JAK-1 inhibitor prevented antiviral effects and STAT-1 phosphorylation. *In vitro*, only 15 minutes of compound exposure was required to inhibit HCV replication, whereas 24 hours of compound exposure was required to achieve the same effect with IFN- $\alpha$ . The magnitude of ISG induction by small molecules was comparable to IFN- $\alpha$  in PHHs and mouse liver. Compounds showed good absorption in rodents (F=19-105% in mice and 69-124% in rats) with enhanced liver exposure (7-12-fold greater than plasma) and a range of terminal half-lives (1.6-32.5 hr). **Conclusion:** We have identified a novel class of small molecules that are orally bioavailable, activate type I IFN signaling, and efficiently inhibit HBV and HCV. Lead optimization is ongoing with the objective of nominating a development candidate with liver-focused exposure for evaluation for treatment of cHBV.

Disclosures:

Michel Perron - Assembly Biosciences: Employment; Assembly Biosciences: Stock Shareholder;

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## EFRUXIFERMIN, A BIVALENT FC-FGF21 ANALOG, DEMONSTRATES IMPROVED BIOPHYSICAL AND PHARMACOLOGICAL ENGAGEMENT WITH LIVE CELLS COMPARED TO MONOVALENT FGF21 ANALOGS

Erik J Tillman<sup>1</sup>, Sina Bondza<sup>2</sup>, Louben Dorval<sup>1</sup>, Anna Boström<sup>1</sup> and Timothy P Rolph<sup>1</sup>, (1)Akerø Therapeutics, (2)Ridgeview Instruments, AB

**Background:** Efruxifermin (EFX) is a long-acting Fc-FGF21 fusion protein currently in Ph2b clinical trials for treatment of advanced (F2/F3) liver fibrosis and compensated cirrhosis (F4) due to non-alcoholic steatohepatitis (NASH). Unlike monovalent analogs of FGF21, one molecule of EFX comprises two molecules of an FGF21 variant. We hypothesized this could result in greater affinity for FGF21's receptors on the cell surface compared to monovalent FGF21 analogs, potentially leading to more potent, durable, and effective agonism. One of FGF21's two receptors, Î²-Klotho, forms a high-affinity interaction with the C-terminus of FGF21. Subsequently, the N-terminus binds to one of FGFR1c, 2c, or 3c forming a multimeric complex required to mediate intracellular signaling. A greater number of theoretical binding interactions for bivalent EFX than for monovalent FGF21 analogs would be expected to result in different pharmacological properties. **Methods:** Bivalent EFX, comprising an Fc-RGE dimer, was compared with either a monomeric variant of FGF21, termed RGE (L98R, P171G, A180E), or another monovalent RGE variant fused to an Fc-dimer termed ¾ EFX. The LigandTracer® assay was used to follow association and dissociation of monovalent or bivalent FGF21 analogs with the surface of live HEK293 cells overexpressing Î²-Klotho and FGFR1c. These cells also incorporate an FGF21-dependent luciferase reporter enabling biopotency of each type of FGF21 analog to be measured. **Results:** Addition of an Fc-dimer to the N-terminus slightly reduces affinity of RGE for the surface of cells, yet potency is reduced over 10-fold (¾ EFX vs RGE; Table 1). This loss of potency is likely due to steric hindrance between the Fc-dimer and FGFR1c. On the other hand, addition of a second RGE variant to ¾ EFX (forming EFX) completely overcomes hindrance by the Fc-dimer, with >100-fold higher affinity than for monovalent RGE or ¾ EFX analogs. This restoration and potentiation of binding affinity is also associated with higher potency than that of RGE (Table 1). **Conclusion:** EFX's bivalent-FGF21 structure, with two RGE variants per molecule, results in much stronger affinity-predominantly because of more stable binding, i.e. slower dissociation-which translates into greater potency compared to the monovalent FGF21 analogs RGE and ¾ EFX. This is likely due to avidity effects due to bivalent EFX having more high- and low-affinity interactions with the surface of target cells than monovalent FGF21 analogs.

Table 1. Characteristics of monovalent and bivalent FGF21 analogs

	RGE <sub>monomer</sub>	FC <sub>dimer</sub> - RGE <sub>monomer</sub> (¾ EFX)	FC <sub>dimer</sub> - RGE <sub>dimer</sub> (EFX)
FGF21 receptor hindrance	none	N-terminus linked to IgG1 Fc	N-terminus linked to IgG1 Fc
mol. FGF21 / mol. analog	1	1	2
Number of potential interaction points with cell surface	2	2	4
# of high-affinity interaction points (KLB-mediated)	1	1	2
# of low-affinity interaction points (FGFR-mediated)	1	1	2
K <sub>D</sub> (affinity) on live cells	3 nM	5.4 nM	0.018 nM
EC <sub>50</sub> (potency), cell-based bioassay	0.52 nM	7.93 nM	0.24 nM

Disclosures:

Erik J Tillman - Akerø Therapeutics: Employment; Akerø Therapeutics: Patent Held/Filed; Akerø Therapeutics: Stock Shareholder;

## NAFLD PATHOBIOLOGY IN AFRICAN-AMERICAN PATIENTS IN THE WASHINGTON DC AREA

Somiranjana Ghosh<sup>1</sup>, Tanmoy Mondal<sup>1</sup>, Christopher A Loffredo<sup>2</sup>, Coleman I. Smith<sup>3</sup>, Ruth Quartey<sup>4</sup>, Gemeyel Moses<sup>5</sup>, Charles D Howell<sup>6</sup> and Gail Nunlee-Bland<sup>7</sup>, (1)Pediatrics & Child Health, Howard University, (2)Department of Oncology, Georgetown University, (3)Medstar Georgetown University Hospital, (4)Viral Hepatitis Center, Howard University, (5)College of Medicine, Howard University, (6)Howard University Hospital, (7)Diabetes Treatment Clinic, Howard University

**Background:** Non-alcoholic fatty liver disease (NAFLD) is progressively becoming the most common chronic liver condition worldwide and is of concern among African Americans (AA) in the United States due to health disparities. This pilot study aims to assess differential gene expression to identify signature genes and their pathways for the first time among AA individuals with NAFLD in the Washington DC area. **Methods:** AA NAFLD patients (n=23; mean age: 40.4±11.4) were recruited from the Georgetown University Liver Transplantation Unit, in comparison to healthy AA controls (n=24; mean age: 48.18±7.26) from the same region. Their sociodemographic, lifestyle exposures, and medical background information analysis were performed, coupled with Ingenuity Pathway Analysis (IPA<sup>®</sup>) to divulge the major disease pathways. The Chi-square test was applied to see if there was a statistically significant relationship between the study variables. **Results:** Compared to controls, NAFLD subjects report a history of hypertension (*p*-value <0.001). However, BMI, Obesity, smoking, stroke, and other comorbidities were similar between the groups. The transcriptome analysis of differentially expressed genes (n=21,448) revealed that 67.4% and 32.5% were significantly (*p*-value <0.05) up- and downregulated, respectively. *TNFRSF9* and *CASP5* (apoptosis) are the signature genes that were upregulated, while the downregulation of *TGFB1* (Cell proliferation, differentiation, and growth) was also noteworthy. The IPA analysis showed *Hepatic Fibrosis Signaling*, *Hepatic Fibrosis*, and *Hepatic Cholestasis* were the top canonical pathways (*p*-values <0.0001) and their corresponding bio-functions were *Proliferation of hepatic satellite cells*, *Progressive hepatic fibrosis*, and *Acute-Chronic Liver failure* (Figure -1). Finally, we noted that *Liver Inflammation* and *Liver Cirrhosis* were also prominent pathways that were overexpressed in the NAFLD cases compared to controls. **Conclusion:** Our results begin to fill knowledge gaps on which genes and functional pathways are dysregulated in AA patients with NAFLD. The outcome of the current results will help us to understand disease mechanisms and establish molecular classifiers to identify future risks in this vulnerable population, suggesting that further studies and other ethnic groups would be of interest.

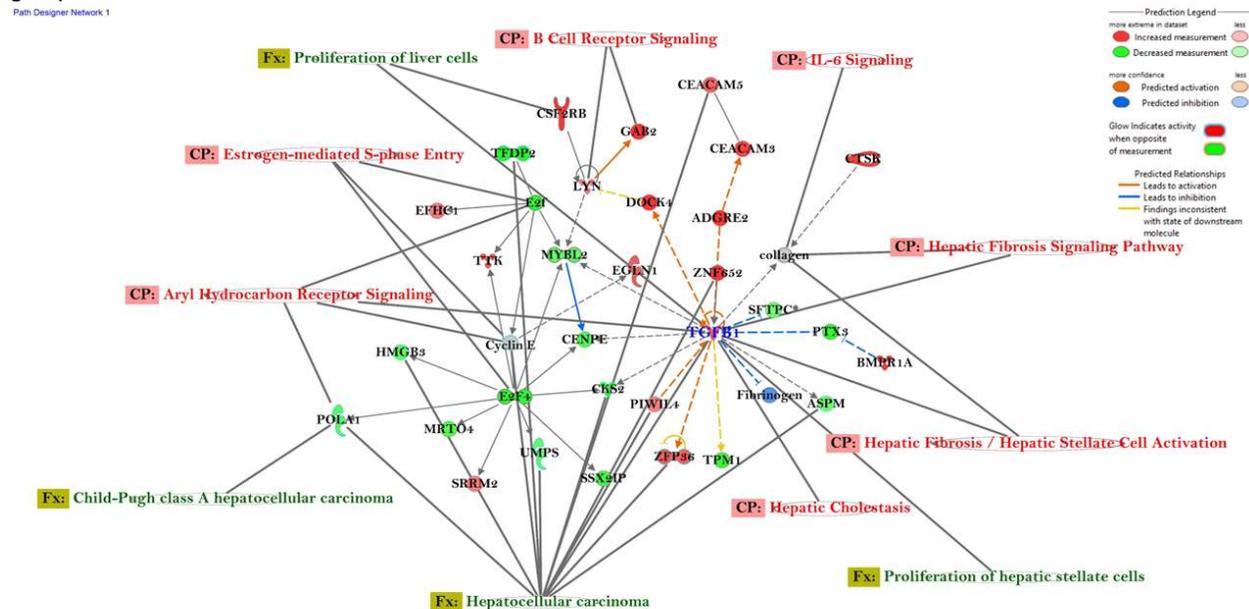


Figure 1. Connectivity of differentially expressed genes in the important signaling pathways in the NAFLD subjects, relative to controls, depicting the connectivity between differentially expressed genes (those with  $\geq 2$ -fold change, *t*-test, *p* <0.05).

### Disclosures:

Somiranjana Ghosh - Howard University: Employment;

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## COVID-19 HOSPITALIZATIONS AMONG LIVER TRANSPLANT RECIPIENTS: MULTICENTER STUDY OF CLINICAL OUTCOMES IN THE UNITED STATES

*Robert L. Gottlieb*<sup>1,2,3,4</sup>, *Aastha Chandak*<sup>5</sup>, *Linda Chen*<sup>6</sup>, *Heng Jiang*<sup>5</sup>, *Kyung Min Kwon*<sup>6</sup>, *Catherine Frenette*<sup>6</sup> and *Essy Mozaffari*<sup>6</sup>, (1)Center for Advanced Heart & Lung Disease, Baylor University Medical Center Dallas, (2)Baylor Scott and White Research Institute, (3)Internal Medicine, Texas a&m Health Science Center, (4)Internal Medicine, TCU School of Medicine, (5)Certara, (6)Gilead Sciences, Inc.

**Background:** AASLD issued an FAQ in May 2022 highlighting the impact of COVID-19 on liver transplant recipients. The objective of this study is to examine the characteristics, treatments, and outcomes of liver transplant recipients hospitalized with COVID-19. **Methods:** We identified a heterogeneous cohort of liver transplant recipients who underwent liver transplant procedures, experienced liver transplant complications, or had liver transplant-related visit between Jan 2019-Mar 2022 in the Premier Healthcare US Database. Among these patients, we identified subsequent COVID-19 hospitalization between Apr 2020-Mar 2022. Demographics, comorbidities, COVID-19 severity defined as oxygenation requirements during hospitalization, COVID-19 medications, immunosuppression medications, and inpatient all-cause mortality were examined. **Results:** 1,977 liver transplant recipients were hospitalized for COVID-19 in 481 hospitals of varying size, type, and location (Table). The average age was 61 years (SD=14), 59% male, 69% white, and 23% Hispanic. Key recorded comorbidities included: 77% hypertension, 61% renal disease, 40% diabetes with chronic complications, and 38% diabetes without chronic complications. On admission, 5% received invasive mechanical ventilation (IMV/ECMO), 10% high-flow/non-invasive ventilation (HFO/NIV), and 17% low-flow oxygen (LFO). During the entire hospitalization, 17% received IMV/ECMO, 12% HFO/NIV, 18% LFO as maximal oxygen support. Key COVID-19 medications documented were: 55% dexamethasone, 35% remdesivir, and 23% corticosteroids other than dexamethasone. Additionally, calcineurin inhibitors (CNI) were documented for majority of the patients (84%) and mycophenolate for 39%. Few were reported to receive mTOR (6%) or azathioprine (1%). 32% were admitted to ICU during hospital stay and inpatient all-cause mortality rate was 18%. **Conclusion:** This study captures COVID-19 hospitalizations among liver transplant recipients over two years of the pandemic, across geographically representative institutions in the US. Inpatient all-cause mortality rate in this high risk population is higher compared to the general population (16%) per our previous analyses of COVID-19 hospitalizations. Although corticosteroids are prescribed for COVID-19 with hypoxemia or for transplant, dexamethasone is not typically used for liver transplant immunosuppression; its use in the majority confirms a principal COVID-19-related hospitalization.

**Table. Characteristics, treatments, and outcomes of liver transplant recipients hospitalized with COVID-19**

		Study cohort
<b># of Patients<sup>1</sup></b>		<b>n=1977</b>
<b># of Hospitals</b>		<b>n=481</b>
<b>Demographics and Patient Characteristics</b>		
<b>Age, years</b>	Mean [SD]	61 [14]
	<18	1%
<b>Age Group, years</b>	18-49	14%
	50-64	37%
	65+	48%
<b>Gender</b>	Male	59%
	Female	41%
<b>Race</b>	White	69%
	Black	12%
	Other	19%
<b>Ethnicity</b>	Hispanic	23%
	Medicare	63%
<b>Primary Payor</b>	Commercial	20%
	Medicaid	13%
	Other Payor	3%
<b>Comorbidities</b>	Hypertension	77%
	Renal disease	61%
	Diabetes with chronic complications	40%
	Diabetes without chronic complications	38%
	Obesity	24%
	Congestive heart failure	19%
	Chronic pulmonary disease	17%
	Moderate or severe liver disease	12%
	Myocardial infarction	8%
<b>Hospital Characteristics</b>		
<b>Bed Size</b>	500+	50%
	300-499	23%
	<300	27%
<b>Teaching Status</b>	Teaching Hospital	62%
<b>Census Region</b>	South	43%
	Midwest	20%
	Northeast	19%
	West	18%
<b>Clinical Treatment and Outcomes</b>		
<b>Oxygenation support upon admission (first two days of hospitalization)</b>	IMV/ECMO	5%
	HFO/NIV	10%
	LFO	17%
	NSOc	68%
<b>Maximum oxygenation support (highest level needed during hospitalization)</b>	IMV/ECMO	17%
	HFO/NIV	12%
	LFO	18%
	NSOc	54%
<b>COVID-19 medications recommended by NIH for hospitalized adults<sup>2</sup>, %</b>	Any Dexamethasone	55%
	Any Remdesivir	35%
	Remdesivir+Dexamethasone	24%
	Dexamethasone monotherapy	27%
	Remdesivir monotherapy	8%
	Tocilizumab	4%
	Remdesivir+Dexamethasone+Baricitinib/Tocilizumab	3%
	Baricitinib	2%
	Dexamethasone and Tocilizumab	1%
<b>Other medications by class, %</b>	Anticoagulants	44%
	Corticosteroids (not including Dexamethasone)	23%
	Convalescent plasma	8%
<b>Immunosuppression medications, %</b>	CNI	84%
	Mycophenolate	39%
	mTOR	6%
	Azathioprine	1%
<b>LOS</b>	Median [IQR]	7.0 [4.0 ; 14.0]
<b>ICU use, %</b>		32%
<b>ICU LOS</b>	Median [IQR]	6.0 [2.0 ; 14.0]
<b>Mortality, %</b>		18%

IMV/ECMO= invasive mechanical ventilation/extracorporeal membrane oxygenation; HFO/NIV=high-flow/non-invasive ventilation; LFO=low-flow oxygen; NSOc=no supplemental oxygen charges; CNI: calcineurin inhibitors; LOS: length of stay; ICU: intensive care unit; SD: standard deviation; IQR: interquartile range

<sup>1</sup>This study included a heterogenous cohort of adult liver transplant recipients who underwent liver transplant procedures (ICD-10-PCS: 0FY00Z0, 0FY00Z1, 0FY00Z2; CPT: 47135), experienced liver transplant complications (ICD-10: T86.4x) or had liver transplant-related visit (ICD-10: Z94.4) between Jan 2019-Mar 2022 and subsequent COVID-19 hospitalization (ICD-10: U07.1) between Apr 2020-Mar 2022.

<sup>2</sup>NIH: Therapeutic Management of Hospitalized Adults With COVID-19 (updated August 8, 2022) <https://www.covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-hospitalized-adults/>

**Disclosures:**

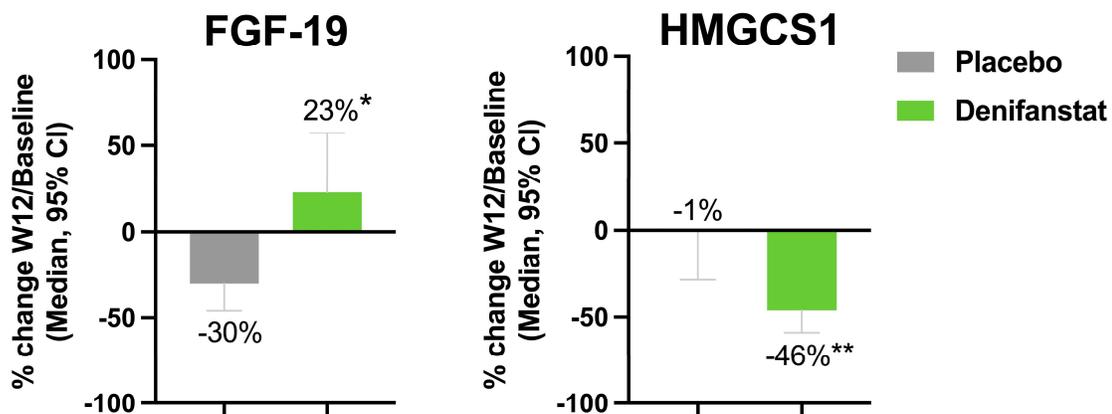
Aastha Chandak - Certara: Employment; Certara: Stock Shareholder;

## SERUM PROTEOMIC PROFILING REVEALS THAT THE FATTY ACID SYNTHASE (FASN) INHIBITOR DENIFANSTAT PROVIDES METABOLIC BENEFITS VIA INCREASING FIBROBLAST GROWTH FACTOR 19 (FGF-19) AND DECREASING 3-HYDROXY-3-METHYLGLUTARYL-COA SYNTHASE 1 (HMGCS1) IN NASH PATIENTS

Wen-Wei Tsai<sup>1</sup>, Katharine Grimmer<sup>1</sup>, Althea Zetter<sup>1</sup>, William Beckwith<sup>2</sup>, Penn Whitley<sup>3</sup>, Eduardo Bruno Martins<sup>1</sup>, George Kemble<sup>1</sup>, Stephen A Harrison<sup>4</sup>, Rohit Loomba<sup>5</sup> and Marie O'Farrell<sup>1</sup>, (1)Sagimet Biosciences, Inc, (2)Somalogic Operating Co., Inc., (3)Boulder Bioconsulting, Inc, (4)Pinnacle Clinical Research Center, (5)University of California San Diego

**Background:** Denifanstat is a first-in-class specific FASN inhibitor currently in Ph2b for NASH in the FASCINATE-2 study. In the Ph2a FASCINATE-1 study, 50mg denifanstat significantly reduced liver fat and decreased NASH-associated biomarkers, including ALT, PRO-C3 and LDL-C. To determine the impact of denifanstat-mediated DNL inhibition on metabolic effects in NASH patients, a comprehensive serum proteomic analysis was performed. **Methods:** Baseline and week 12 serum samples from FASCINATE-1 (placebo n=30 and denifanstat 50mg n=31) were profiled for ~7000 protein analytes by the multiplexed aptamer-based proteomic technology (SomaScan assay, SomaLogic). These chemically modified aptamers form complex three-dimensional shapes which bind to epitopes on their target protein and the amount of the available protein epitope is read out on a DNA microarray with complementary sequences. Microarray signal was normalized using the Cyclic Loess method and linear regression models were fit to each aptamer. **Results:** Quality control and lower limit of detection (LOD) analyses indicate consistent signal distribution and normal sensitivity for all samples, with fewer than 1% of aptamers below LOD. Differential expression analysis revealed that denifanstat treatment and diabetes were two key factors related to changes in serum protein levels. Pathway analyses of differential expression proteins showed that denifanstat downregulated amino acid processes and catabolic oxidation pathways, and altered several pathways associated with immune response. Among differentially expressed proteins, FGF-19 was increased by denifanstat (denifanstat 23% vs. placebo -30%, p<0.05, Figure 1), suggesting that denifanstat may play a role in regulating bile acid synthesis, glucose and lipid metabolism through FGF-19/FGFR4 signaling. Interestingly, HMGCS1 was detected in serum and was decreased by denifanstat (denifanstat -46% vs. placebo -1%, p<0.01, Figure 1), concomitant with reduced circulating cholesterol and LDL-C, suggesting that denifanstat decreased HMGCS1 proteins in the liver, thereby reducing cholesterol synthesis. **Conclusion:** Serum proteomic profiling suggests that denifanstat provides additional metabolic effects on top of the demonstrated reduction in liver fat, and inflammation and fibrosis biomarkers in NASH patients. Denifanstat increased FGF-19 secretion and decreased HMGCS1, thereby inhibiting cholesterol synthesis. These findings further support FASN inhibition as a promising therapeutic approach in NASH.

Figure 1



Disclosures:

Disclosure information not available at the time of publication: Katharine Grimmer

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## THE BISPECIFIC ANTI-FGFR1/KLB AGONIST ANTIBODY bFKB1 ATTENUATES NON-ALCOHOLIC STEATOHEPATITIS AND ATHEROSCLEROSIS IN LDLR<sup>-/-</sup>.LEIDEN MICE

Jos A Inia<sup>1,2,3</sup>, Joline Attema<sup>1</sup>, Christa De Ruiter<sup>1</sup>, Martien P.M. Caspers<sup>4</sup>, Lars Verschuren<sup>4</sup>, Maria Wilson<sup>5</sup>, Hans Princen<sup>1</sup>, Mark Chen<sup>5</sup> and Martine Morrison<sup>1</sup>, (1)Department of Metabolic Health Research, The Netherlands Organisation for Applied Scientific Research (TNO), (2)Department of Cardiology, Leiden University Medical Center, (3)Eindhoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, (4)Department of Microbiology and Systems Biology, The Netherlands Organisation for Applied Scientific Research (TNO), (5)Genentech, Inc.

**Background:** Fibroblast growth factor 21 (FGF21) is an endocrine factor that has an important role in regulating whole-body metabolic organ homeostasis and energy balance through heterodimeric receptor complexes comprising FGFR1-3c and  $\text{Klotho}$ . It is considered a promising target for the treatment of obesity-associated metabolic diseases such as NASH and atherosclerosis. Here, we evaluated the effects of a bispecific anti-FGFR1/KLB agonist antibody (bFKB1), specifically targeting FGFR1c, in a translational preclinical model of obesity-associated NASH and atherosclerosis, to investigate its therapeutic potential against these diseases. **Methods:** Ldlr<sup>-/-</sup>.Leiden mice were fed a high-fat diet (HFD) for 20 weeks, after which one group was treated with an isotype control antibody and one group with the bFKB1 antibody for 12 weeks. Effects on NASH and atherosclerosis were assessed histopathologically and biochemically (including D<sub>2</sub>O analysis for new collagen formation in liver). Underlying mechanisms of the bFKB1 treatment were investigated by hepatic transcriptomics analysis (NGS). **Results:** bFKB1 lowered body weight and adipose tissue mass without reducing food intake. It lowered plasma insulin and plasma total cholesterol and triglycerides. bFKB1 lowered plasma ALT and reduced liver weight. Liver steatosis (with reduced triglycerides, cholesteryl esters and free cholesterol), inflammation (number of inflammatory cell clusters and hepatic IL-1 $\beta$  protein) and NAS score were reduced. Histological measurement of fibrosis was not significantly affected by the treatment, while new collagen formation was significantly inhibited by bFKB1. In line with this, hepatic inflammatory and profibrotic transcriptional programs were broadly inactivated by the treatment. In the vasculature, bFKB1 had anti-atherogenic effects, lowering total atherosclerotic lesion area in the aortic root. This atherosclerosis-lowering effect of bFKB1 was attributable to a reduction in the severe type V lesions. **Conclusion:** The bispecific anti-FGFR1/KLB agonist antibody has strong metabolic effects in HFD-fed Ldlr<sup>-/-</sup>.Leiden mice. These beneficial effects are associated with a reduction in liver steatosis and inflammation as well as atherosclerosis. Liver fibrosis was not affected within the treatment period studied, but analysis of new collagen formation and profibrotic transcriptional programs indicate that the treatment may have antifibrotic potential in a longer treatment duration in line with recent clinical results of FGF21 mimetic class of molecules.

Disclosures:

The following people have nothing to disclose: Martine Morrison

## ANALYSIS OF BIOCHEMICAL AND IMMUNOLOGICAL ALTERATIONS IN DISEASE CONTROL GROUP VS DISEASE PROGRESSION GROUP AFTER HEPATITIS B VIRUS (HBV)-SPECIFIC T-CELL RECEPTOR (TCR) T CELL THERAPY FOR PRIMARY HBV-RELATED HEPATOCELLULAR CARCINOMA

Fanping Meng<sup>1</sup>, Jinfang Zhao<sup>1</sup>, Anthony Tanoto Tan<sup>2</sup>, Wei Hu<sup>1</sup>, Siâ€Yu Wang<sup>1</sup>, Jiehua Jin<sup>1</sup>, Juan Wu<sup>1</sup>, Yuanyuan Li<sup>3</sup>, Lei Shi<sup>1</sup>, Jun-Liang Fu<sup>1</sup>, Shuangjie Yu<sup>1</sup>, Yingjuan Shen<sup>1</sup>, Limin Liu<sup>1</sup>, Junqing Luan<sup>1</sup>, Ming Shi<sup>1</sup>, Yunbo Xie<sup>1</sup>, Chunâ€Bao Zhou<sup>1</sup>, Regina Wong<sup>4</sup>, Lu-En Wai<sup>4,5</sup>, Sarene Koh<sup>4,5</sup>, Antonio Bertolotti<sup>2,5</sup>, Tingting Tina Wang<sup>4</sup>, Ji-Yuan Zhang<sup>1</sup> and Fu-Sheng Wang<sup>1</sup>, (1)The Fifth Medical Center of Chinese PLA General Hospital, National Clinical Research Centre for Infectious Diseases, (2)Emerging Infectious Diseases, Duke-Nus Medical School, (3)Department of Liver Diseases, Fifth Medical Center of Chinese PLA General Hospital, (4)Lion TCR Pte Ltd, (5)Agency for Science, Technology and Research (A\*STAR)

**Background:** Adoptive T cell immunotherapy has revolutionized blood cancer treatment, however its efficacy in solid tumor remains limited. LioCyx-M, autologous T cells transiently modified with *in-vitro* transcribed mRNA encoding HBV-specific TCR, is a potential treatment against advanced HBV-related HCC as demonstrated previously [1, 2]. Here, we report the updated OS data and determine the association between clinical response with treatment-induced immunological alterations. **Methods:** In an open-label, phase 1 dose-escalation study (NCT03899415), eligible patients were enrolled to receive of LioCyx-M dosed at  $1\text{A}—10^4$ cells/kg,  $1\text{A}—10^5$ cells/kg,  $1\text{A}—10^6$ cells/kg,  $5\text{A}—10^6$ cells/kg bodyweight in the first treatment cycle by weekly intravenous administration. If there were no drug associated toxicities, patients continued to receive weekly administration at  $5 \times 10^6$ cells/kg BW. Tumor response as per RECIST1.1 were assessed, with ongoing survival follow-up. Baseline and post-treatment peripheral blood were collected longitudinally for the analysis of both HBV-related and immunological biomarkers and were compared between Disease Progression Group (PD or SD lasting <3 months) (N=3) and Disease Control Group (Remaining N=5). **Results:** As of 18 Jan 2022, median OS was 33.1 months (range:2.5 to 40.9 months). Disease Control Group showed larger degree of reversible localized liver inflammation, measured by changes in ALT levels post treatment, suggesting the on-target effects of LioCyx-M. In addition to tumor shrinkage, larger anti-viral response shown by reduction in serum HBsAg during treatment phase were also observed in Disease Control Group (4/5) as compared to Disease Progression Group (1/3). Importantly, Disease Control Group (4/5) also displayed activation of proliferative T-cell compartment (Ki67+CD39+CD8+CD4+) and/or elevations of serum inflammatory chemokines, CXCL9 and CXCL10. This is suggestive of the activation of secondary immune responses resulting in a durable efficacy of these functionally short-lived HBV-specific TCR-T cells, which could explain the longer OS in this group of patients. In contrast, Disease Progression Group (0/3) did not display any detectable peripheral blood immunological alterations. **Conclusion:** These data collectively depict the differential liver function, viral and immune alterations in patient with and without clinical response, highlighting the importance of secondary immune response activation via the cancer-immunity cycle for durable anti-tumor effects of LioCyx-M. 1) Meng et al. Immunotherapy of HBV-related advanced hepatocellular carcinoma with short-term HBV-specific TCR expressed T cells: results of dose escalation, phase I trial. *Hepatol Int* 2021.15(6):1402-12 2) Tan et al. Immunological alterations after immunotherapy with short lived HBV-TCR T cells associates with long-term treatment response in HBV-HCC. *Hepatol Commun* 2022.6(4):841-854

Disclosures:

The following people have nothing to disclose: Yuanyuan Li

5057

**MECHANISTIC PK/PD MODELING AND SIMULATION OF BEPIROVIRSEN PK, HBsAg AND ALT CHANGES FROM PHASE 2b STUDY TO INFORM PHASE 3 STUDY DESIGN AND DOSE SELECTION: B-CLEAR STUDY**

*Amir Youssef<sup>1</sup>, Mohamed Ismail<sup>2</sup>, Donald E. Mager<sup>2,3</sup>, Andrew Santulli<sup>2</sup>, Mindy Magee<sup>1</sup>, Dickens Theodore<sup>4</sup>, Melanie Paff<sup>5</sup> and Ahmed Nader<sup>1</sup>, (1)Clinical Pharmacology Modeling and Simulation, GSK, Collegeville, PA, USA, (2)Enhanced Pharmacodynamics LLC, Buffalo, NY, USA, (3)Department of Pharmaceutical Sciences, University at Buffalo, SUNY, Buffalo, NY, USA, (4)Development Clinical Sciences Hepatology/GI, GSK, Durham, NC, USA, (5)Medicine Development Leaders, GSK, Collegeville, PA, USA*

**Background:** Bepirovirsen (BPV; GSK3228836) reduced serum hepatitis B surface antigen (HBsAg) in participants (pts) with chronic hepatitis B infection in Phase 2 studies. Transient increases in alanine transaminase (ALT) were often observed after, or in parallel to, decreases in HBsAg. A mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model was developed to simultaneously capture the time course of HBsAg and ALT changes observed in BPV Phase 2 studies (Youssef A et al. Presented at EASL 2022 [abstract 3592]). In this work, the model was used to simulate HBsAg responses to inform Phase 3 study design, dose regimen, and patient population selection. **Methods:** The model was used to simulate BPV exposures and HBsAg levels for a range of dosing regimens (300 mg weekly and 300 mg weekly with dose reduction to 150 mg weekly), with and without loading doses in the first 2 weeks of treatment, and for dosing durations of 12 and 24 weeks. Simulations of end of treatment (EOT; Week 12 or 24) and end of study (EOS; 48 weeks post BPV treatment) responses (HBsAg <lower limit of detection [LLOD]) were completed for different subpopulations based on significant covariates (eg, low baseline HBsAg [ $<3000$  IU/mL]). A sustained response HBsAg threshold of 0.000015 IU/mL reliably predicting EOS responses was identified, and used to simulate responses under potential Phase 3 study designs. **Results:** Baseline HBsAg was a significant predictor of response to BPV treatment. In simulations, pts with low baseline HBsAg were more likely to achieve HBsAg <LLOD following administration of BPV compared with the overall population (range of predicted responses for pts with low baseline HBsAg: 34.8%-44.7% at EOT and 15.5%-19.2% at EOS; range of predicted responses for overall population: 23.3%-30.4% at EOT and 9.7%-12.3% at EOS) across different BPV dose regimens (Table). Similar response rates were predicted with and without loading doses. A higher proportion of pts were predicted to achieve a response with 24- versus 12-week BPV treatment (44.6% vs 34.8% at EOT and 19.1% vs 15.5% at EOS) in the low baseline HBsAg population (Table). **Conclusion:** These modeling and simulation results support enrollment of pts with low baseline HBsAg in Phase 3 studies to maximize the benefit of BPV treatment. Simulation results will also be used to support BPV dose selection for the Phase 3 studies. Funding: GSK (218363)

Table: Summary of simulation-based HBsAg response by dose regimen

Bepirovirsen dosing regimen	Population	Outcome	Participants with HBsAg response (%)	
			EOT	EOS
300 mg weekly x 24 weeks with loading dose on Day 4 and 11	Overall	HBsAg <LLOD	30.4	12.3
	Baseline HBsAg 35% <3000 IU/mL, 65% <1000 IU/mL*	HBsAg <LLOD	44.7	19.2
300 mg weekly x 24 weeks without loading dose	Overall	HBsAg <LLOD	30.3	12.2
	Baseline HBsAg 35% <3000 IU/mL, 65% <1000 IU/mL*	HBsAg <LLOD	44.6	19.1
300 mg weekly x 12 weeks, without loading dose	Overall	HBsAg <LLOD	23.3	9.7
	Baseline HBsAg 35% <3000 IU/mL, 65% <1000 IU/mL*	HBsAg <LLOD	34.8	15.5
300 mg weekly x 12 weeks, then 150 mg weekly x 12 weeks (without loading dose)	Overall	HBsAg <LLOD	26.1	11.0
	Baseline HBsAg 35% <3000 IU/mL, 65% <1000 IU/mL*	HBsAg <LLOD	39.3	17.5

\*Phase 3 population simulated to include only patients with baseline HBsAg <3000 IU/mL, with 65% of them below 1000 IU/mL. HBsAg LLOD = 0.05 IU/mL.

EOT, end of bepirovirsen treatment (Week 12 or Week 24); EOS, end of study (48 weeks post end of bepirovirsen treatment: Week 60 or Week 72); HBsAg, hepatitis B surface antigen; LLOD, lower limit of detection.

**Disclosures:**

Ahmed Nader - GSK: Employment; GSK: Stock Shareholder;

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## Î<sup>2</sup>-CATENIN ACTIVATION PROMOTES B-CELL EXCLUSION IN THE HEPATOCELLULAR CARCINOMA MICROENVIRONMENT

*Brandon Michael Lehrich<sup>1</sup>, Evan Delgado<sup>1</sup>, Junyan Tao<sup>1</sup>, Silvia Liu<sup>2,3</sup>, Aatur Singhi<sup>1,3</sup> and Satdarshan (Paul) S Monga<sup>1,2,3</sup>, (1)Department of Pathology, University of Pittsburgh, School of Medicine and University of Pittsburgh Medical Center, (2)Department of Pathology, University of Pittsburgh School of Medicine, (3)Pittsburgh Liver Research Center, University of Pittsburgh, School of Medicine and University of Pittsburgh Medical Center*

**Background:** Current immunotherapeutic approaches for hepatocellular carcinoma (HCC) are focused on T-cell specific immune checkpoint inhibitors (ICIs). Work in other cancer models have linked ICI response to B-cell signaling in the tumor microenvironment. Our group and others have demonstrated that Î<sup>2</sup>-catenin-mutated HCCs promote resistance to ICIs. Here, we investigated if Î<sup>2</sup>-catenin-mutation in HCCs may play a role in B-cell exclusion and impact subsequent response to ICIs. **Methods:** Public HCC datasets were assessed for mutations in the Î<sup>2</sup>-catenin gene, CTNNB1, and B-cell related gene signatures. Our clinically relevant mouse HCC models of T41A-CTNNB1/G31A-NFE2L2, S45Y-CTNNB1/hMET, and MYC/hMet treated with and without anti-PD-1 therapy, were assessed for the presence or absence of B-cells by immunohistochemistry (IHC). Next, the influence of Î<sup>2</sup>-catenin suppression on B-cells was explored using an antisense technology in HCC models. **Results:** Overall, 26% of HCC cases in The Cancer Genome Atlas (TCGA) showed CTNNB1 mutations. Ingenuity pathway analysis of TCGA RNA-sequencing data demonstrated that multiple pathways in B-cells were significantly altered in CTNNB1 mutated vs non-mutated cases. Similarly, comparing these two cohorts, differentially expressed genes were overlapped with a publicly available B-cell signature which revealed 130 overlapping genes, of which 101 were downregulated, including MS4A1 (which encodes for CD20). In our murine HCC models, we also noticed decreases in CD20+ immune cells on IHC in both Î<sup>2</sup>-catenin-driven models compared to MYC/hMET model. Additionally, we noted no differences in B-cell numbers following anti-PD-1 treatment in Î<sup>2</sup>-catenin-driven models. Moreover, using an antisense oligonucleotide to suppress Î<sup>2</sup>-catenin in HCC models increased CD20+ immune cell infiltration in the tumor microenvironment and simultaneously significantly reduced tumor burden. **Conclusion:** Î<sup>2</sup>-Catenin-driven HCC may drive a B-cell exclusionary phenotype. Future directed studies aim to elucidate the mechanism of B-cell signaling in ameliorating tumor burden following Î<sup>2</sup>-Catenin inhibition in conjunction with anti-PD-1 therapy in CTNNB1-mutated HCC.

Disclosures:

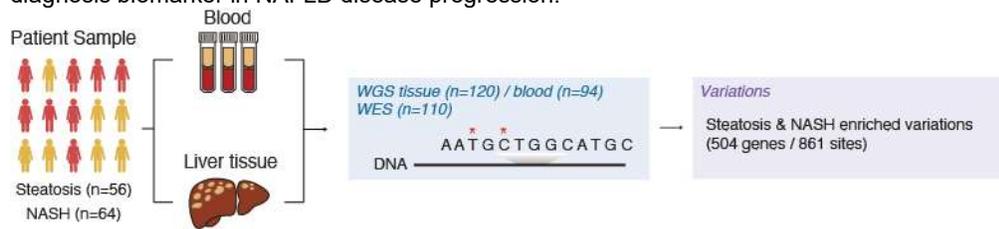
The following people have nothing to disclose: Brandon Michael Lehrich

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## DISCOVERY OF NAFLD-ASSOCIATED SOMATIC VARIANT FEATURES THROUGH OPTIMIZED CALLING PIPELINE FOR WHOLE GENOME SEQUENCING

*Sungju Jung, Sumin Yoon, Suhyang Han, Sunyoung Jang, Chaeun Oh, Kyung Hyun Ryu and Jong Hoon Park, Sookmyung Women's University*

**Background:** Non-alcoholic fatty liver disease (NAFLD) is a metabolic associated disease in which fat accumulates in the liver regardless of alcohol intake and includes NAFL and nonalcoholic steatohepatitis (NASH). Since NASH could ultimately cause cirrhosis and liver cancer, identification of molecular marker that could detect NAFLD is valuable in diagnosis and treatment for NAFLD patients. Although several studies have been conducted on germline variation in NAFLD, understanding of somatic variations related with NAFLD is still lacking. This study is aimed to find NAFLD-associated somatic variation that has possibility of direct effect, through NGS sequencing data analysis in NAFLD patient. **Methods:** Whole genome sequencing (WGS) and whole exome sequencing (WES) were performed with 120 biopsy-proven liver tissues from NAFLD patients, that comprising 56 steatosis and 64 NASH patients. Through basic sequencing data processing, raw sequence data converted to sequence alignment data. Then aligned data were used to call variants by genome analysis tool kit (GATK) Mutect2. To identify liver tissue-specific and somatic variants in NAFLD, optimized calling pipeline was established. In this pipeline, blood WGS data was used to exclude germline variations, and population common variant pool was used to eliminate population common characteristics. **Results:** Our somatic variant calling approach provided 861 somatic variation sites associated with 504 genes which related in NAFLD-progression. Of 504 somatic variation genes, *CD209*, *AZGP1*, *TNFRSF14*, *SERPINA3* and *ALMS1* were related to macrophage activator, inflammatory mediator and fibrosis suggesting that our 504 somatic variation genes are associated with NAFLD biological function and potential for NAFLD diagnosis marker. Among 504 genes, representatively, *CLEC4M* and *TUBA4A* showed significantly decreased expression level in altered group. These results suggested that genomic variation was related to transcriptional dysregulation that contribute to changes in biological functions result in disease progression. **Conclusion:** We established optimized tissue-specific somatic variation calling pipeline, and identified 504 NAFLD-associated somatic variation genes, suggesting the potential diagnosis biomarker in NAFLD disease progression.



Disclosures:

The following people have nothing to disclose: Sungju Jung

## IMPLEMENTING FIBROSCAN DEVICES IN PRIMARY CARE AT THREE U.S. HEALTH SYSTEMS TO INFORM REFERRALS TO HEPATOLOGY

Parvez S. Mantry<sup>1</sup>, Holly Lofton<sup>2,3</sup>, Viviana Figueroa Diaz<sup>2</sup>, Kristi Abbott<sup>4</sup> and Douglas T Dieterich<sup>5</sup>, (1)The Liver Institute, Methodist Dallas Medical Center, (2)Department of Medicine, NYU Grossman School of Medicine, (3)Department of Surgery, NYU Grossman School of Medicine, (4)Nashnet, (5)Division of Liver Diseases, Icahn School of Medicine at Mount Sinai

**Background:** Nonalcoholic fatty liver disease (NAFLD) affects 30% of the global population. Noninvasive tests (NITs) are needed to risk stratify patients and inform referrals in primary care. From 2019-2022, three U.S. health systems, Methodist Health System, NYU Langone Health, and Mount Sinai Health System, evaluated the utility of implementing FibroScan devices and training personnel in primary care to identify patients suspected of nonalcoholic steatohepatitis (NASH) and refer to hepatology. **Methods:** 1-2 FibroScan devices were placed in primary care or bariatric clinics at each system. Inclusion criteria was  $\geq 1$  of the following: liver biopsy within 1-year, fatty liver on imaging,  $\geq 7.0$  kPa, CAP score  $>240$  dB/m within 3 months, type 2 diabetes (T2D), or BMI $>30$ . Chi Square tests were used to analyze relationships between baseline demographic and lab value data and outcomes of interest. Regression analysis will be conducted for variables of significance. 19 records were excluded due to incomplete data entry. **Results:** Of the 488 patients, 56% were female, and 44% were male. 56% were white, 9% were black, 7% were Asian, 0.2% were Native American, and 29% were unknown/chose not to report. 48% were non-Hispanic, 28% were Hispanic, and 13% were unknown/chose not to report. 46% of enrollees had a BMI $>30$ , 31% had a history of T2D, and 12% had history of liver disease. Patients with T2D were 5.5 times more likely to have severe fibrosis than those without, and patients with BMI $>30$  were more likely to have fatty liver on imaging, VCTE Cap Score  $>240$  dB/m, and VCTE liver stiffness  $>7$ kPa. Those with  $>7$ kPa had significantly higher BMI's, A1C's, NAFLD Fibrosis scores, AST, and ALT, and significantly lower platelet counts. Patients with APRI scores  $>0.7$  had higher AST, ALT, and NAFLD fibrosis scores as well as lower white blood cells, neutrophils, and platelets. Hispanics were 6 times more likely to have fatty liver on imaging compared to non-Hispanics ( $p=0.001$ , CI:1.33-30.4). FibroScan results are largely consistent with FIB-4 and biopsy data. Screening identified 268 (61%) patients with low fibrosis who could continue to be managed in primary care. 173 (39%) patients with moderate to advanced fibrosis were identified and required specialist care. Patients and providers noted the colocation of FibroScan devices within primary care contributed to improved continuity of care and patient experience. **Conclusion:** This study has validated the utility of using FibroScan devices in primary care to direct referrals to hepatology and enhance the patient experience. Improved access to VCTE and other NITs is essential to avoid unnecessary, potentially costly referrals and improve early identification of patients with advanced liver fibrosis at risk for complications.

Diagnostic	Number Included in Analysis	Low fibrosis	Moderate/ Indeterminate fibrosis	Advanced fibrosis
<b>FibroScan</b> Cut Offs: Low fibrosis: $<7$ kPa; Moderate fibrosis: 7 – 14kPa; advanced fibrosis $>14$ kPa	441	268 (61%)	125 (28%)	48 (11%)
<b>FIB-4</b> Cut offs: Low fibrosis: $<1.3$ ; Indeterminate fibrosis: 1.3 – 2.66; advanced fibrosis $\geq 2.67$	419	243 (58%)	130 (31%)	46 (19%)
<b>Liver Biopsy*</b>	81	41 (51%)	26 (32%)	14 (17%)

\*Note: Results reported for patients with available liver biopsy data (n=81).

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The following people have nothing to disclose: Kristi Abbott

5061

## ELIMINATION OF WNTLESS FROM HEPATIC STELLATE CELLS IMPACTS ENDOTHELIAL CELL ZONATION AND IMPROVES METABOLIC FITNESS IN MICE

*Anya Singh-Varma<sup>1</sup>, Leon Min<sup>1</sup>, Shikai Hu<sup>1</sup>, Silvia Liu<sup>1</sup>, Minakshi Poddar<sup>1</sup>, Sucha Singh<sup>1</sup>, Aaron W Bell<sup>2</sup> and Satdarshan (Paul) S Monga<sup>1,3</sup>*, (1)Department of Pathology, University of Pittsburgh School of Medicine, (2)University of Pittsburgh Medical Center, (3)Department of Medicine, University of Pittsburgh Medical Center

**Background:** The liver, a main regulator of physiologic homeostasis, is histologically organized into metabolic zones defined by specific gene expression and function of all cells along the portal triad-central vein axis. This process of zonation allows for efficient division of labor. Pericentral venous and sinusoidal endothelial cells (ECs) in zone-3 of the liver lobule are known to secrete key Wnts which have been thoroughly implicated in regulating hepatic zonation and function. However, ECs are not the sole source of Wnts in the liver. Less understood is the role of Wnts secreted from hepatic stellate cells (HSCs) in liver pathophysiology. Here we investigated the global role of Wnt from HSCs by characterizing mice that are unable to secrete Wnt proteins from HSCs. **Methods:** Male and female HSC-specific Wntless (Wls) knockout (KO) mice were generated by interbreeding Wls-floxed mice and lecithin retinol acyl-transferase-driven Cre transgenic mice. Bulk RNA sequencing and immunohistochemistry (IHC) were performed to identify any changes in expression between KO and control animals. Metabolic cage studies and mixed meal gavage assessed for metabolic homeostasis. **Results:** Preliminary results show no difference in ALT, AST, and LW/BW ratio between HSC-Wls-KO mice and control at baseline. Analysis of differentially expressed genes (DEG) in control and KO groups with FDR=5% and fold change greater than or equal to 1.5 revealed 17 common up- and 9 common downregulated genes amongst male and female mice. Strikingly, qPCR confirmed fatty acid binding protein 4 (Fabp4), a DEG expressed by ECs, to be 3-fold higher in the HSC-Wls-KO mice ( $p<0.001$ ). IHC showed pericentral EC expression of Fabp4 in control mice but a panzonal EC expression in the HSC-Wls-KO mice, suggesting an altered zonation of ECs. Metabolic cage data found KO mice to have greater lean-to-fat mass body composition ( $p<0.05$ ). Furthermore, total energy expenditure was greater in KO mice and total activity level was less in KO mice ( $p<0.01$ ). KO mice also had less body weight following mixed meal gavage ( $p<0.01$ ). Interestingly, serum glucose and triglyceride levels were equivalent to controls. **Conclusion:** Abrogation of HSC Wnt signaling disrupts the pericentral EC zonation of Fabp4 and simultaneously alters the metabolic phenotype such that KO mice demonstrate leaner body mass with no alteration in serum lipids. Our study suggests that HSC Wnts act on ECs and altering this relationship leads to favorable metabolic phenotype.

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## SINGLE CELL ASSESSMENT REVEALS HETEROGENEITY OF LIVER RESIDENT MACROPHAGES ASSOCIATED WITH FIBROTIC LIVER INJURY

*Shawna Cooper*<sup>1,2</sup>, *Bushra Arif*<sup>2</sup>, *Nidhi Jalan-Sakrikar*<sup>3</sup>, *Mandy Wong*<sup>2</sup>, *Sofia Jerez Ortega*<sup>2</sup>, *Usman Yaqoob*<sup>3</sup>, *Tejasav S Sehwat*<sup>2</sup>, *Enis Kostallari*<sup>1,2</sup>, *Sheng Cao*<sup>2</sup> and *Vijay Shah*<sup>2</sup>, (1)Biochemistry and Molecular Biology, Mayo Clinic, (2)Division of Gastroenterology and Hepatology, Mayo Clinic Rochester, (3)Mayo Clinic

**Background:** Infiltration of monocyte-derived macrophages (macs) into the Kupffer cell (KC) niche is known, but phenotype and functional differences during fibrotic injury are not fully understood. The purpose of this study was to investigate the differences between infiltrating vs KC marker expressing liver macs at single cell resolution to identify unique subpopulations and targets that potentially contribute to fibrotic injury. We hypothesize that mac heterogeneity will be significantly increased during liver injury and reveal pro-fibrotic targets. **Methods:** Mouse liver fibrosis was induced with CCl<sub>4</sub> and livers sectioned for immunohistochemistry (IHC) or single cell suspension for 10X Genomics single cell RNA sequencing (scRNAseq). Data were analyzed via Seurat v4.0.6 with manual cell annotation. After differential gene expression (DEG), cells were filtered into subpopulations by genes of interest and DEG rerun with Ingenuity pathway analysis (IPA). Top DEGs of interest were validated via IHC on CCl<sub>4</sub> mice and human cirrhosis liver sections. **Results:** Approximately 300 macs were identified from each group by scRNAseq. DEG revealed increased mono marker *Irgam* (log<sub>2</sub>FC 1.84) and *Ccr2* (log<sub>2</sub>FC 1.06), while KC markers *Clec4F* (log<sub>2</sub>FC -2.55) and *Vsig4* (log<sub>2</sub>FC -1.52) were reduced, suggestive of a large proportion of CCl<sub>4</sub> macs as infiltrating mono derived macs versus liver resident KC. The top increased DEG between CCl<sub>4</sub> and healthy was *Marco*, a cell surface scavenger receptor notable for recent reports as an anti-inflammatory marker (avglog<sub>2</sub>FC 3.60, p < 3.55e-17). *Trem2*, a "scar or lipid associated" mac marker significantly increased in CCl<sub>4</sub> versus control (log<sub>2</sub>FC 1.71 p < 1.62e-11); but bioinformatic filtering by *Marco*<sup>+/+</sup>, *Trem2*<sup>+/+</sup>, or *Irgam*<sup>+/+</sup> revealed that this was only within the monocyte-derived (*Irgam*<sup>+</sup>), *Marco*<sup>-</sup> macs. IPA confirmed inflammatory pathway downregulation in CCl<sub>4</sub> *Marco*<sup>+</sup> cells. IHC of mouse liver sections confirmed increased *Marco*<sup>+</sup> macs with CCl<sub>4</sub> (p < 0.003) and disruption of the healthy diffuse distribution of *Marco*<sup>+/+</sup> macs. *Marco*<sup>+</sup> macs concentrated in the uninvolved parenchyma and *Marco*<sup>-</sup> *Clec4f*<sup>+</sup> macs infiltrated fibrotic regions. This distribution was confirmed by IHC of human cirrhotic liver sections. **Conclusion:** CCl<sub>4</sub>-induced fibrotic liver injury increases mac heterogeneity and alters subset spatial distribution. IPA confirmed downregulation of inflammatory pathways in *Marco*<sup>+</sup> cells, agreeing with recent literature, but the distinction between *Trem2*<sup>+</sup> and *Marco*<sup>+</sup> populations in CCl<sub>4</sub> injury is notable. Subset functional characterization during fibrotic injury is ongoing.

Disclosures:

The following people have nothing to disclose: Shawna Cooper

5063

## A FIRST-IN-PATIENT PHASE IB STUDY OF A HEPATITIS B VIRUS (HBV) NEUTRALIZING ANTIBODY HH-003 IN TREATMENT NA<sup>-</sup>VE PARTICIPANTS WITH HBEAG-POSITIVE CHRONIC HBV INFECTION

Yue Hu<sup>1</sup>, Yingshuo Huang<sup>2</sup>, Guangming Li<sup>3</sup>, Shuang Li<sup>3</sup>, Zong Zhang<sup>4</sup>, Jingbo Wang<sup>4</sup>, Zuxiong Huang<sup>5</sup>, Ling Zheng<sup>5</sup>, Wen Xie<sup>6</sup>, Yunqing Qiu<sup>7</sup>, Xiaorong Mao<sup>8</sup>, Ting Wang<sup>8</sup>, Huiguo Ding<sup>9</sup>, Meixia Wang<sup>9</sup>, Hongxin Piao<sup>10</sup>, Pan Chen<sup>11</sup>, Long Xiao<sup>11</sup>, Yumei Gu<sup>11</sup>, Yin Zhang<sup>11</sup>, Yonghe Qi<sup>11</sup>, Hong You<sup>2</sup>, Jianhua Sui<sup>12</sup>, Wenhui Li<sup>12</sup>, Junqi Niu<sup>1</sup>, Yanhua Ding<sup>1</sup> and Jidong Jia<sup>2</sup>, (1)The First Hospital of Jilin University, Changchun, China, (2)Beijing Friendship Hospital, Capital Medical University, Beijing, China, (3)Henan Infectious Disease Hospital, Zhengzhou, China, (4)Shandong Public Health Clinical Center, Jinan, China, (5)Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, China, (6)Beijing Ditan Hospital, Capital Medical University, Beijing, China, (7)The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China, (8)The First Hospital of Lanzhou University, Lanzhou, China, (9)Beijing Youan Hospital, Capital Medical University, Beijing, China, (10)Yanbian University Hospital, Yanji, China, (11)Huahui Health Ltd. Beijing, China, (12)National Institute of Biological Sciences, Beijing, China

**Background:** HH-003 is a human monoclonal antibody targeting the pre-S1 domain of the HBV large envelope protein. It blocks the engagement of preS1 with sodium taurocholate co-transporting polypeptide (NTCP), the cellular receptor for HBV/HDV. HH-003 neutralizes HBV/HDV with high potency, effectively blocking viral infection and re-infection of hepatocytes; it has also demonstrated antibody-Fc-dependent immunological effector functions to clear HBV virions and/or virus-infected hepatocytes in preclinical studies. The objectives of this study were to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of HH-003. **Methods:** This study is a randomized, double-blind, and placebo-controlled study. A total of 67 treatment na<sup>-</sup>ve HBeAg-positive participants including subgroup-1 (Immune-tolerant (n=34)) and subgroup-2 (Immune-active (n=33)) were enrolled and randomized (6:2 within each dose cohort for both subgroups). Each subgroup included (3, 10, 20, and 40 mg/kg) to receive HH-003 or placebo intravenously bi-weekly at Day 0, Day 14, and Day 28, with 12 weeks of follow-up. **Results:** HH-003 treatment-emergent adverse events (AE) were mostly mild. There were no treatment-related serious AEs or AEs leading to treatment discontinuation. Forty (78.4 %, 40/51) and ten (62.5%, 10/16) participants experienced on-treatment adverse events in the HH-003 and placebo groups, respectively. The incidence of treatment-related AEs was 52.9% and 50% in the HH-003 and placebo groups, respectively. HH-003 exposure increased in a dose-dependent manner, and the elimination half-life ranged from 5.6 to 13.7 days. Subgroup-1 and subgroup-2 participants' baseline mean HBV DNA levels (log<sub>10</sub> IU/mL) were 8.2 $\pm$ 0.35 and 8.1 $\pm$ 0.54, respectively; mean ALT (U/L) levels were 26.30 $\pm$ 11.69 and 123.06 $\pm$ 67.07, respectively. A decrease in HBV DNA and viral antigens from baseline was observed across all dose cohorts in subgroup-2 at 4 weeks after HH-003 treatment, but not in subgroup-1. In particular, for the 20mg/kg dose cohort in subgroup 2, the HBV DNA level declined by >1 log<sub>10</sub> in 50% of participants and HBsAg declined by 0.54-1.1 log<sub>10</sub> (the base line levels ranging from 3.88 to 4.32 log<sub>10</sub> IU/mL) in 66.7% of participants at 4 weeks after treatment. **Conclusion:** HH-003 was safe and well-tolerated, and demonstrated a dose-dependent PK profile in the treatment na<sup>-</sup>ve, HBeAg-positive CHB participants. Three doses of 20 mg/kg of HH-003 resulted in optimum dose exposure and antiviral activity in immune active participants.

Disclosures:

The following people have nothing to disclose: Yonghe Qi

**EVALUATION OF THE VEBICORVIR, NRTI AND AB-729 COMBINATION IN VIROLOGICALLY SUPPRESSED PATIENTS WITH HBEAG NEGATIVE CHRONIC HEPATITIS B VIRUS INFECTION: INTERIM ANALYSIS FROM AN OPEN LABEL PHASE 2 STUDY**

*Jacob George<sup>1</sup>, Diana Stefanova-Petrova<sup>2</sup>, Krasimir Antonov<sup>3</sup>, Zina Valaydon<sup>4</sup>, Scott Davison<sup>5</sup>, Scott Fung<sup>6</sup>, Fei Chen<sup>7</sup>, Curtis Cooper<sup>8</sup>, Stuart Roberts<sup>9</sup>, Marie-Louise Vachon<sup>10</sup>, Carla S. Coffin<sup>11</sup>, Brian Conway<sup>12</sup>, Gail Matthews<sup>13</sup>, Mariana Radicheva<sup>14</sup>, Steven J Knox<sup>15</sup>, Ran Yan<sup>15</sup>, Emily P Thi<sup>16</sup>, Calvin Chan<sup>15</sup>, Jieming Liu<sup>15</sup>, Katie Zomorodi<sup>15</sup>, Timothy Eley<sup>16</sup>, Michele Anderson<sup>15</sup>, Karen Sims<sup>16</sup>, Luisa M Stamm<sup>15</sup>, Gaston R. Picchio<sup>16</sup>, Grace Wang<sup>15</sup>, Rozalina Balabanska<sup>17</sup>, Gerry MacQuillan<sup>18</sup> and Magdy Elkhatab<sup>19</sup>, (1)Westmead Hospital, Westmead, New South Wales, Australia, (2)Diagnostic Consultative Center Aleksandrovska, Sofia, Bulgaria, (3)University Multiprofile Hospital for Active Treatment St Ivan Rilski, Sofia, Bulgaria, (4)Footscray Hospital, Footscray, Victoria, Australia, (5)Liverpool Hospital, Liverpool, New South Wales, Australia, (6)Toronto General Hospital, Toronto, Ontario, Canada, (7)Saint George Hospital, Kogarah, New South Wales, Australia, (8)Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, (9)The Alfred, Melbourne, Victoria, Australia, (10)Centre Hospitalier Universitaire De Qu bec - Universit  Laval, Qu bec, Qu bec, Canada, (11)Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada, (12)Vancouver Infectious Diseases Centre, Vancouver, British Columbia, Canada, (13)St Vincent's Hospital Sydney, Darlinghurst, New South Wales, Australia, (14)Nov Rehabilitatsionen Tsentar Eood, Stara, Bulgaria, (15)Assembly Biosciences, South San Francisco, CA, USA, (16)Arbutus Biopharma, Warminster, PA, USA, (17)Acibadem City Clinic Tokuda Hospital, Sofia, Bulgaria, (18)Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia, (19)Toronto Liver Center, Toronto, Ontario, Canada*

**Background:** Vebicorvir (VBR), a 1<sup>st</sup>-generation core inhibitor, plus a nucleos(t)ide reverse transcriptase inhibitor (Nrti) resulted in deeper viral suppression compared to continued Nrti alone in virologically suppressed (VS) eAg negative chronic (c)HBV patients (pts). AB-729, a single trigger GalNac-siRNA which targets all HBV RNA transcripts demonstrated mean 1.8-2 log<sub>10</sub> sAg reductions in VS cHBV pts. ABI-H0731-204 (NCT04820686) is an open-label study assessing safety and efficacy of VBR+AB-729+Nrti in VS eAg negative pts. Here we report interim results. **Methods:** Sixty-five VS eAg negative pts were randomised to receive VBR+AB-729+Nrti (n=32), VBR+Nrti (n=16) or AB-729+Nrti (n=17) for 48 wks. VBR was given orally 300 mg QD and AB-729 as a 60 mg SC injection Q8Wks. At Wk 48, pts with ALT<2xULN + DNA<LLOQ + sAg<100 IU/mL were to discontinue all treatment with all other pts continuing Nrti alone during follow-up. Outcomes assessed included the virological markers sAg, DNA, RNA, and crAg, with adverse events (AE) and standard lab parameters for safety. **Results:** Baseline characteristics were similar across treatment arms; overall, mean (SD) age was 41 (6.1) years, 43/65 (66%) male, 37/65 (57%) Asian, mean (SD) time on current Nrti 6.1 (3.61) years. At Baseline, HBV DNA was <LLOQ in all pts with mean (SD) HBV RNA, sAg, and ALT of 1.3 (0.77) log<sub>10</sub> U/mL, 3.3 (0.57) log<sub>10</sub> IU/mL and 28 (17.4) U/L, respectively. Treatments were well-tolerated. The proportions of pts with treatment emergent (TE) AEs were 26/32 (81%), 11/16 (69%) and 11/17 (65%) for VBR+AB-729+Nrti, VBR+Nrti, AB-729+Nrti, respectively. TEAEs leading to early discontinuation occurred in 2 pts (pancytopenia/rash), 1 pt (rash) and 1 pt (ALT elevation) receiving VBR+AB-729+Nrti, VBR+Nrti and AB-729+Nrti, respectively. A serious AE of COVID-19 infection (unrelated to study drugs) was reported in a VBR+AB-729+Nrti recipient. No deaths were reported. Table 1 summarises sAg responses at key study visits. At the time of analysis, 3/4 (75%), 0/1 and 2/2 (100%) pts with Wk 48 data met criteria to stop all treatment in VBR+AB-729+Nrti, VBR+Nrti and AB-729+Nrti recipients, respectively. No pts had sAg loss or seroconversion. Similar trends in viral parameters were observed between VBR+AB-729+Nrti and AB-729+Nrti. **Conclusion:** All regimens were safe and well tolerated. Interim data indicate that adding VBR to AB-729+Nrti does not result in greater on-treatment improvements in markers of active HBV infection as compared to AB-729+Nrti.

**Table 1: HBsAg Response by Study Visit**

		VBR+AB-729+NrtI	VBR+NrtI	AB-729+NrtI
Baseline	Mean (SD) (log <sub>10</sub> IU/mL)	3.4 (0.57)	3.3 (0.62)	3.3 (0.56)
	n/N (%) <100 IU/mL	0/32	0/16	0/17
	n/N (%) <10 IU/mL	0/32	0/16	0/17
Wk 12	Mean (SD) CFB (log <sub>10</sub> IU/mL)	-1.2 (0.65)	0.0 (0.07)	-1.1 (0.51)
	n/N (%) <100 IU/mL	13/29 (44.8%)	0/15	7/16 (43.8%)
	n/N (%) <10 IU/mL	3/29 (10.3%)	0/15	0/16
Wk 24	Mean (SD) CFB (log <sub>10</sub> IU/mL)	-1.6 (0.57)	0.0 (0.06)	-1.8 (0.30)
	n/N (%) <100 IU/mL	9/18 (50.0%)	0/10	7/9 (77.8%)
	n/N (%) <10 IU/mL	3/18 (16.7%)	0/10	0/9
Wk 48	Mean (SD) CFB (log <sub>10</sub> IU/mL)	-2.3 (0.36)	0.0 (NA)	-2.2 (0.35)
	n/N (%) <100 IU/mL	4/4 (100%)	0/1	2/2 (100%)
	n/N (%) <10 IU/mL	1/4 (25.0%)	0/1	1/2 (50.0%)
Follow-up Wk 4	Mean (SD) CFB (log <sub>10</sub> IU/mL)	-1.8 (1.24)	0.0 (NA)	-2.0 (0.04)
	n/N (%) <100 IU/mL	1/3 (33.3%)	0/1	2/2 (100%)
	n/N (%) <10 IU/mL	1/3 (33.3%)	0/1	1/2 (50.0%)

HBsAg measured by Abbott Architect (LLOQ=0.05 IU/mL)

CFB = Change From Baseline; NA = Not Applicable

All subjects at Follow-up Wk 4 were taking NrtI at time of visit

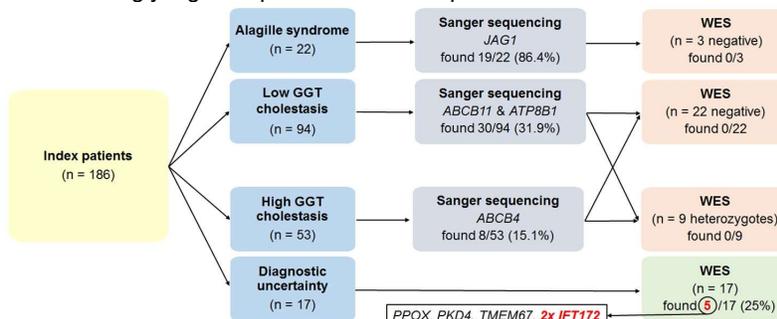
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## DIAGNOSTIC OUTCOME STUDY OF EXOME SEQUENCING IN GENETIC CHOLESTASIS REVEALS IFT172 VARIANTS IN ASSOCIATION WITH NON-SYNDROMIC LIVER DISEASE

Magdaléna Neřoldová<sup>1</sup>, Elzbieta Ciara<sup>2</sup>, Janka Slatinská<sup>1</sup>, Sona Franková<sup>3,4</sup>, Petra Lišková<sup>5</sup>, Radana Kotalová<sup>6</sup>, Janka Globinová<sup>7</sup>, Markéta Šafaříková<sup>5</sup>, Lucie Pfeiferová<sup>8</sup>, Hana Zůnová<sup>6</sup>, Lenka Mrázová<sup>5</sup>, Viktor Stránecký<sup>5</sup>, Ondřej Fabián<sup>1</sup>, Eva Sticová<sup>1</sup>, Daniela Skanderová<sup>9</sup>, Jan Šperl<sup>1</sup>, Marta Kalousová<sup>5</sup>, Tomáš Zima<sup>5</sup>, Milan Macek<sup>6</sup>, Prof. Joanna Pawłowska<sup>10</sup>, Alex Knisely<sup>11</sup>, Stanislav Kmoč<sup>5</sup>, Prof. Milan Jirsa<sup>12</sup> and Joanna Pawłowska, Janka Slatinská, Soňa Fraňková, Petra Lišková, Radana Kotalová, Janka Globinová, Markéta Šafaříková, Lucie Pfeiferová, Hana Zůnová, Lenka Mrázová, Viktor Stránecký, Ondřej Fabián, Eva Sticová, Daniela Skanderová, Jan Šperl, Marta Kalou, (1)Institute for Clinical and Experimental Medicine, (2)Children's Memorial Health Institute: Warsaw, PL, (3)Institute for Clinical and Experimental Medicine, (4)Department of Hepatogastroenterology, Institute for Clinical and Experimental Medicine, (5)Charles University and General University Hospital in Prague, (6)Charles University and Faculty Hospital Motol, (7)Hospital Poprad, (8)University of Chemistry and Technology in Prague, (9)Palacky Univerzity Olomouc and Faculty Hospital, (10)Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland, (11)Institut Für Pathologie, Medizinische Universität Graz, Graz, Austria, (12)Ikem

**Background:** Gene defects contribute to the aetiology of intrahepatic cholestasis. We explored the outcome of whole-exome sequencing (WES) for molecular diagnosis in patients with intrahepatic cholestasis, including those with a clinical phenotype suggesting *JAG1* / *NOTCH2* disease. **Methods:** Both pediatric and adult patients with cholestatic liver disease or a history of cholestasis of unknown aetiology were eligible. Patients with extrahepatic bile duct obstruction and those fed only parenterally were excluded. WES was performed in 34 patients without diagnostic variants in *JAG1*, *ABCB11*, *ATP8B1*, or *ABCB4* demonstrable by Sanger sequencing and in 17 patients recruited from tertiary-care institutions in Central Europe for cholestasis of undefined etiology. Nasal smear mRNA was analysed to address variant pathogenicity. **Results:** WES revealed biallelic variants in 3 ciliopathy genes, a heterozygous known variant in *PPOX*, and the hitherto unreported homozygous splice site variant c.65-2A>T in *F11R*. Extrahepatic genetic diseases were diagnosed in 3 families. Whereas phenotypes of probands with variant *PKHD1*, *TMEM67*, and *PPOX* accorded with those earlier reported, the association of the *F11R* c.65-2A>T variant with liver disease remains unclear. Two patients harbored biallelic variants in *IFT172*, a gene implicated in short rib thoracic dysplasia 10. In one, a 26-year-old homozygote for rs780205001 c.167A>C (p.Lys56Thr) was followed for glycogenosis-mimicking liver disease since age 4y, with chronic cholestasis and nephronophthisis requiring kidney transplantation manifest in adulthood. A second, an 18-year-old carried three novel heterozygous variants classified as pathogenic (c.2070del / p.Met690Ilefs\*11) or of uncertain significance (c.157T>A / p.Phe53Ile and c.164C>G / p.Thr55Ser, located in *cis*) and presented with an 8mo cholestatic episode in early infancy followed by lifelong mild hyperbilirubinemia and proteinuria without deterioration of kidney function. Neither patient has any skeletal malformations. **Conclusion:** Our findings confirm the clinical utility of WES in patients with suspected genetic cholestasis. Our observation of two patients with *IFT172* variants that were associated with early onset non-syndromic isolated liver disease - parenchymal liver injury with massive glycogen deposition or intrahepatic cholestasis - extends the current list of hepatic ciliopathies.



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The following people have nothing to disclose: Magdaléna Neřoldová

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**TREATMENT WITH GLECAPREVIR AND PIBRENTASVIR IS SAFE AND EFFECTIVE IN ITALIAN PATIENTS WITH CHRONIC HEPATITIS C AGED 75 YEARS OR OLDER: A MULTICENTER STUDY**

*Nicola Pugliese, Division of Internal Medicine and Hepatology, Department of Gastroenterology, Irccs Humanitas Research Hospital, Rozzano (MI), Italy, Vincenzo Calvaruso, Department of Gastroenterology and Hepatology, University of Palermo, Palermo, Italy, Mario Masarone, Università Di Salerno; Department of Medicine and Surgery "Scuola medica Salernitana", University of Salerno, Roberta D'Ambrosio, Division of Gastroenterology and Hepatology, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Sara Battistella, Università Di Padova, Anna Licata, University of Palermo, Palermo, Italy, Marcello Persico, Department of Medicine, Surgery and Odontostomatology, University of Salerno, Maria Paola Anolli, Foundation Irccs Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy, Francesco Paolo Russo, Department of Surgery, Oncology and Gastroenterology, University of Padova; Padova University, Marco Distefano, Ospedale Umberto I°, Salvatore Petta, Department of Gastroenterology and Hepatology, Di.Bi.M.I.S University of Palermo, Vito Di Marco, Department of Gastroenterology and Hepatology, Di.Bi.M.I.S. University of Palermo, Italy and Alessio Aghemo, Department of Biomedical Sciences, Humanitas University, Milan, Italy*

**Background:** Glecaprevir and Pibrentasvir (G/P) determines high rates of sustained virologic response (SVR) with optimal safety profile in patients with chronic hepatitis C virus (HCV) infection. The efficacy and safety of G/P in Caucasian patients aged 75 years and older has not been widely analyzed yet. **Methods:** This is a multicenter real-world study enrolling all consecutive patients 75 years and older who received G/P between October 2017 and January 2022 at 5 referral centers in Italy. SVR was analyzed by Intention to Treat (ITT) and Per Protocol analysis (PP). **Results:** 570 patients met the inclusion criteria and were analyzed: mean age was 80 (75-97) years, 356 were females (62.4%), 52% (298/570) had HCV-1 and 44% (251/570) had HCV-2. 94 (16.5%) patients had advanced liver fibrosis following non-invasive methods. 463 (81%) patients were taking at least 1 concomitant drug, with 144 (25%) taking ≥5 concomitant drugs. G/P was given for 8 weeks in 488 patients (86%). During treatment 48 patients (8%) reported side effects, with 10 (2%) patients discontinuing treatment prematurely. Two patients developed treatment unrelated serious adverse events. Overall the SVR rate was 97.9% (558/570) by ITT analysis and 99.6% (558/560) by PP analysis. SVR rates remained consistently high among subgroup analysis stratified by genotype, treatment duration, fibrosis stage and concomitant medications. **Conclusion:** Treatment with G/P achieved 97.9% SVR rates in HCV patients older than 75 years of age. Safety was optimal with only 2% of patients discontinuing early.

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