

2020 Late-breaking Abstracts

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Oral Presentations

LO1: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-FINDING STUDY OF THE EFFICACY AND SAFETY OF NAMODENOSON (CF102), AN A3 ADENOSINE RECEPTOR (A3AR) AGONIST, IN TREATING NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND NON-ALCOHOLIC STEATOHEPATITIS (NASH)

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Background: Namodenoson, an A₃AR agonist, demonstrated improved liver function and pathology in a NASH preclinical model.

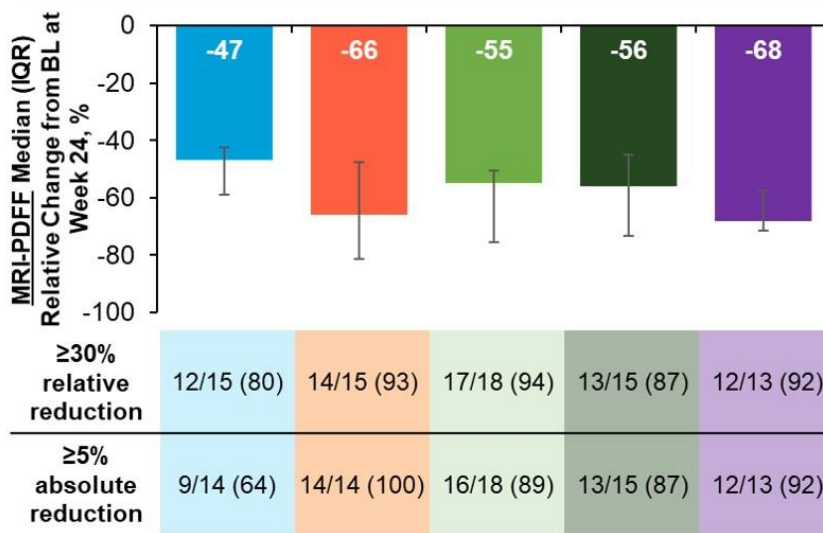
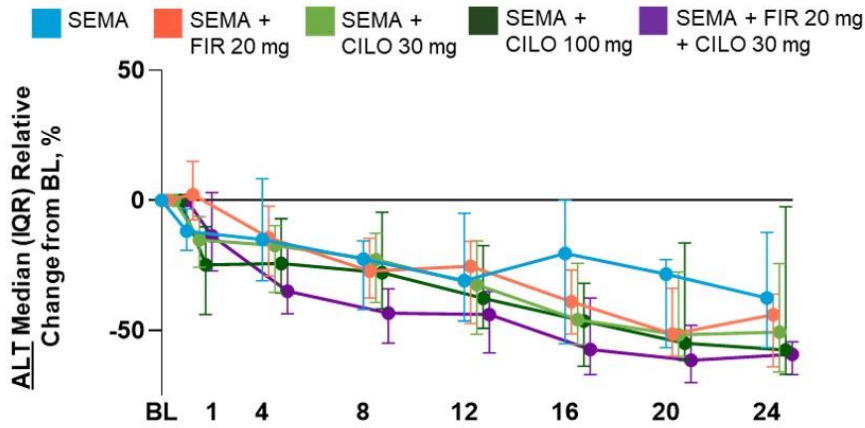
Methods: This phase 2 randomized double-blind placebo-controlled dose-finding study investigated orally administered namodenoson in patients (pts) with NAFLD and serum ALT levels ≥ 60 U/L (including a subset with NASH). Pts were randomized (1:1:1) to receive namodenoson 25 mg BID, 12.5 mg BID, or placebo for 12 wks and were followed up until wk 16. Endpoints included efficacy parameters, safety profile, and study of relevant biomarkers. **Results:** The analysis included 60 pts. ALT levels decreased consistently during the study with namodenoson treatment in a dose-dependent manner (wk 12 mean change from baseline [CFB]: -14.6, -8.7, and -4.2 U/L in the 25 mg, 12.5 mg, and placebo groups, respectively; $p=0.066$ for 25 mg vs placebo); 37%, 24%, and 10% of pts in the 25 mg, 12.5 mg, and placebo groups, respectively, achieved ALT normalization at 16 wks ($p=0.038$ for 25 mg vs placebo). AST levels also decreased throughout the study in a dose-dependent manner (wk 12 mean CFB: -8.4, -5.9, and -0.8 U/L in the 25 mg, 12.5 mg, and placebo groups,

respectively; $p=0.03$ for 25 mg vs placebo). In addition, a significant improvement in adiponectin was noted (wk 12 mean CFB: 266, 559, and -137 ng/mL for 25 mg, 12.5 mg, and placebo, respectively; $p=0.03$ for 12.5 mg vs placebo). At wk 12, a significant decrease in liver fat volume (determined by MRI-PDFF) was observed with namodenoson (mean CFB: -159, -31, and -74 cm^3 for 25 mg, 12.5 mg, and placebo, respectively; $p=0.03$ for 25 mg vs placebo). In addition, a significant decrease in Fib4-scores was noted with namodenoson (wk 12 mean CFB: -0.28, -0.09, and -0.03 for 25 mg, 12.5 mg, and placebo, respectively; $p=0.011$ for 25 mg vs placebo) suggesting an inhibitory effect of namodenoson on fibrosis progression. A consistent dose-dependent decrease in body weight was recorded in all study groups over time (wk 12 mean loss from BL: 2.1, 1.6, and 0.5 kg in the 25 mg, 12.5 mg, and placebo groups, respectively). A₃AR expression levels were stable over time in all study groups. Namodenoson was well-tolerated at both doses with no drug-emergent severe adverse events and no hepatotoxicity. **Conclusion:** A₃AR is a valid target whose levels remain stable after chronic treatment. Namodenoson at 25 mg BID is safe and more effective than 12.5 mg BID.

LO2: SAFETY AND EFFICACY OF COMBINATION THERAPIES INCLUDING SEMAGLUTIDE, CILOFEXOR, AND FIRSOCOSTAT IN PATIENTS WITH NASH

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Background: Given the biological complexity of NASH, combining therapies with complementary mechanisms may provide optimal benefit. We evaluated the safety and efficacy of semaglutide (sema), a GLP-1 receptor agonist, alone and in combination with the FXR agonist cilofexor (CILO) and/or the ACC inhibitor firsocostat (FIR), in patients with NASH. **Methods:** This phase 2 trial randomized 108 non-cirrhotic patients with NASH (F2-F3 on biopsy, or MRI-PDFF $\geq 10\%$ and liver stiffness by transient elastography [LS by TE] ≥ 7 kPa) to sema (n=21), sema+CILO 30 mg (n=22), sema+CILO 100 mg (n=22), sema+FIR 20 mg (n=22), or sema+CILO 30 mg+FIR 20 mg (n=21) for 24 weeks (W24). CILO and FIR were taken once daily and sema subcutaneously once weekly (dose escalated from 0.24 mg to 2.4 mg weekly over 16 weeks). The primary endpoint was safety; exploratory endpoints included changes in liver biochemistry, ELF, liver stiffness by TE, and MRI-PDFF between baseline (BL) and W24. Least square mean (LSmean) changes based on post-hoc ANCOVA models adjusted for BL value and diabetes status. **Results:** At BL, median (IQR) age and BMI were 54 yrs (48, 61) and 34.3 kg/m^2 (30.9, 39.4), respectively; 55% had diabetes. All regimens were well tolerated. The most common adverse events (AEs) were gastrointestinal; 5–14% discontinued any study drug due to AEs. Minimal pruritus was observed (5–10% in CILO groups only, all grade 1, no discontinuations). LSmean change in LDL from BL to W24 ranged from -9 mg/dL with sema to 7 mg/dL with sema+CILO+FIR, and 23 mg/dL with sema+CILO 100 mg; one sema+FIR-treated patient developed triglycerides ≥ 500 mg/dL. At BL, median ALT was 50 U/L (31, 82), MRI-PDFF was 17.9% (12.0, 24.3), and LS by TE was 9.3 kPa (7.7, 12.0). Greater LSmean reductions in ALT were observed with combinations vs sema at W24 (all $p<0.05$; **Fig**); reductions in AST (-26 to -11 U/L), GGT (-40 to -21 U/L), CK18 M30 (-312 to -179 U/L), and ELF (-0.59 to -0.42) were observed in all groups. From BL to W24, larger reductions in hepatic steatosis by MRI-PDFF were observed with combinations vs sema (**Fig**). At W24, LSmean reductions in liver stiffness by TE were: sema, -2.5 kPa; sema+FIR, -3.8 kPa; and sema+CILO+FIR, -3.5 kPa; a $\geq 25\%$ reduction in liver stiffness was more common with combinations (53–63%) vs sema (33%). Changes in body weight were similar between groups (-7.0 to -9.6%). **Conclusion:** In patients with NASH, combinations of sema with CILO and/or FIR were well tolerated and may provide additional benefits vs sema monotherapy.



Baseline value last available value collected on or prior to first dose date of study drug.
Data collected >30 days after last dose of any study drug excluded.

LO3: ALDAFERMIN (NGM282) PRODUCES GREATER ANTI-FIBROTIC RESPONSE IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS AND ADVANCED FIBROSIS

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Background: Liver fibrosis is the most important determinant of clinical disease progression and mortality in patients with NASH. The risk of liver-related mortality increased exponentially with each increase in the stage of fibrosis (mortality rate ratios of 16.7 for F3, 9.6 for F2 and 1.4 for F1 using F0 as a reference population; Dulai et al., 2017). Aldafermin (previously known as NGM282), an engineered FGF19 analog, significantly inhibits bile acid synthesis and regulates metabolic homeostasis. Here we report results from a pre-specified subgroup analysis in patients treated with aldafermin or placebo for 24 weeks (W24). **Methods:** 78 patients were randomized 1:2 to receive placebo (n=25) or aldafermin 1mg (n=53) SC QD at 9 US study sites. Key inclusion criteria included biopsy-proven NASH with NAS \geq 4, F2 or F3 fibrosis and absolute liver fat content (LFC) \geq 8%. Patients underwent MRI-PDFF and liver biopsies at baseline (BL) and W24. The primary endpoint was change from BL to W24 in LFC. Histological endpoints included improvement in liver fibrosis by \geq 1 stage with no worsening of NASH and resolution of NASH with no worsening of fibrosis (NASH CRN criteria). **Results:** 12 (41%) patients in the placebo group and 24 (45%) in the aldafermin group had advanced fibrosis (F3) at BL. At W24, aldafermin treatment resulted in LFC reduction in patients with F2 or F3 (Table 1). Placebo response rates in LFC reduction of \geq 30% (12% in F3 vs 38% in F2) or fibrosis improvement (0% in F3 vs 31% in F2) were lower in F3 than in F2 patients. Among F3 patients, fibrosis improvement of \geq 1-stage without NASH worsening occurred in 30% of patients receiving aldafermin compared with 0% receiving placebo, a difference of 30%. Three F3 patients achieved a \geq 2-stage fibrosis improvement vs none in placebo. Among F2 patients, fibrosis improvement without NASH worsening occurred in 44% of patients receiving aldafermin compared with 31% receiving placebo, a difference of 13%. Aldafermin produced greater reductions in fibrogenesis biomarker Pro-C3 in F3 patients than in F2 patients. **Conclusion:** Placebo response rates in LFC reduction or fibrosis improvement were lower in F3 than in F2 patients. Compared with placebo, aldafermin had greater effect in improving fibrosis in patients with NASH and advanced fibrosis (F3). These data support further studies of aldafermin in patients with NASH and advanced fibrosis.

Table 1. Baseline values and change from baseline to week 24 in key outcomes by F2 or F3 fibrosis stage

	F2 at baseline		F3 at baseline	
	PBO (n = 15)	Aldafermin 1mg (n = 29)	PBO (n = 10)	Aldafermin 1mg (n = 23)
Liver fat content				
Baseline LFC, %	20.4 (6.9)	19.2 (6.3)	15.6 (5.7)	16.5 (5.2)
Δ Absolute LFC at W24, %	-3.9 (5.9)	-8.7 (6.4)	-0.4 (3.7)	-6.7 (8.0)
% Patients with \downarrow 5% absolute	31%	74%	12%	61%
Δ Relative LFC, %	-18.4%	-42.8%	-4.3%	-34.9%
% Patients with \downarrow 30% relative	38%	74%	12%	56%
Liver histology				
% Patients achieving fibrosis improvement \geq 1-stage with no worsening of NASH	31%	44%	0%	30%
Serum parameters				
Δ Relative ALT, %	-17.0%	-54.8%	9.2%	-42.3%
Δ Relative AST, %	-10.0%	-40.1%	16.7%	-24.3%
Δ Relative Pro-C3, %	-4.0%	-22.2%	-5.0%	-33.9%

Shown are mean (SD) or % patients. LFC, liver fat content measured by MRI-PDFF.

Improvement in liver fibrosis was defined as \geq 1-stage decrease in NASH CRN fibrosis score; resolution of NASH was defined as a NAS score of 0–1 for inflammation and 0 for ballooning; no worsening of NASH was defined as no increase in NAS for ballooning, inflammation or steatosis.

LO4: EFFICACY AND SAFETY OF ODEVIXIBAT, AN ILEAL BILE ACID TRANSPORTER INHIBITOR, IN CHILDREN WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS TYPES 1 AND 2: RESULTS FROM PEDFIC 1, A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 3 TRIAL

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Background: Odevixibat, a potent, selective inhibitor of the ileal bile acid transporter (IBAT), is in development to treat cholestatic liver diseases. In this global, 24-week, phase 3 trial, the efficacy and safety of odevixibat versus placebo (PBO) was evaluated in children with progressive familial intrahepatic cholestasis (PFIC). **Methods:** Children (aged 0.5–18 years) with genetically confirmed PFIC1 or PFIC2, elevated serum bile acids (sBAs), and history of significant pruritus were randomized to oral, once-daily PBO, odevixibat 40 µg/kg/day (O-40), or odevixibat 120 µg/kg/day (O-120). The primary endpoints were change in pruritus based on a patient's proportion of positive pruritus assessments (PPAs; defined as a scratching score of ≤1 or a ≥1-point drop from baseline on Albireo observer-reported instrument) over 24 weeks and the proportion of patients with sBA response (defined as a ≥70% reduction from baseline or sBAs ≤70 µmol/L) at week 24. Safety assessments included adverse events (AEs), laboratory monitoring, and physical examinations. **Results:** In total, 62 patients were randomized (mean age: 4.3 years; female: 50%; PFIC1: 27%; PFIC2: 73%) to PBO (n=20), O-40 (n=23), or O-120 (n=19). The study met both primary endpoints, with initial effects observed at week 4. Least squares mean PPAs were 55.1% with odevixibat vs 30.1% with PBO (Table). sBA response rates were significantly higher with O-40 (43.5%; *P*=0.0006), O-120 (21.1%; *P*=0.035), and all odevixibat doses (33.3%; *P*=0.003) vs PBO (0%). Mean pruritus score change from baseline to end of treatment was -1.13 with odevixibat vs -0.25 with PBO. Mean sBAs were reduced with odevixibat (-114.3 µmol/L; -38% from baseline) vs an increase of 13.1 µmol/L with PBO. Mean treatment responses were comparable in patients with PFIC1 or PFIC2 treated with odevixibat (PPAs: 61.1% and 50.5%; percent change in sBAs: -30.4% and -42.4%, respectively). Treatment-related AE incidence was 33.3% with odevixibat and 15.0% with PBO. Treatment-related AEs of diarrhea/frequent bowel movement occurred in 9.5% of odevixibat-treated patients and 5.0% of PBO-treated patients; only 1 patient discontinued due to an AE (diarrhea, O-120 arm). No deaths or drug-related serious AEs were reported. **Conclusion:** In this study, odevixibat effectively reduced pruritus and sBAs relative to PBO and was generally well tolerated over 24 weeks in children with PFIC. Odevixibat has the potential to provide significant treatment benefits in a disease with high unmet medical needs.

Table. Proportion of Positive Pruritus Assessments^a at the Patient Level Over 24 Weeks by Treatment Group (Results for 1 of 2 Prespecified Primary Endpoints)

Proportion of Positive Pruritus Assessments	Placebo n=20	Odevixibat 40 µg/kg/day n=23	Odevixibat 120 µg/kg/day n=19	All Odevixibat n=42
Mean ^b (SE), %	30.1 (9.1)	58.3 (8.6)	51.8 (9.5)	55.1 (7.6)
Mean ^b difference (SE), %	—	28.2 (9.2)	21.7 (9.9)	25.0 (8.2)
<i>P</i> value ^c	—	0.003	0.033	0.004

^aPositive pruritus assessment is defined as a scratching score of ≤1 or at least a 1-point drop from baseline on the Albireo ObsRO instrument based on rounded baseline. ^bLeast squares mean data are shown; ANCOVA model included rounded AM and PM baseline scores as covariates, and treatment group and stratification factors (PFIC type and age category) as fixed effects. ^cDetermined by ANCOVA; two-sided, unadjusted. ANCOVA, analysis of covariance; ObsRO, observer reported; PFIC, progressive familial intrahepatic cholestasis.

LO5: PRELIMINARY ANALYSIS OF ITCH AND IMAGINE II – OUTCOME OF LONG-TERM ADMINISTRATION OF MARALIXIBAT IN CHILDREN WITH ALAGILLE SYNDROME

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Background: We reported pharmacologic inhibition of ileal bile acid transport using Maralixibat (MRX) may reduce pruritus in children with Alagille Syndrome (ALGS) in a 13-week multi-center placebo-controlled trial (ITCH;NCT02057692; *Hep. Comm.*2018;2:1184-98). We now report results of continued MRX administration up to 216 weeks in ITCH participants in IMAGINE II (NCT02117713).

Methods: Blinded dose escalation of MRX occurred during the first 4 weeks of IMAGINE II for those on placebo in ITCH. Dose optimization up to 280 µg/kg/d (for perceived anti-pruritic efficacy) occurred during weeks 5-12. As tolerated, MRX dosing was then unchanged for up to 216 weeks with monitoring of pruritus using patient report outcomes [ItchRO(observer), 0 to 4 (increasing pruritus severity), PedsQL and clinician scratch score (CSS, 0 to 4). Clinical meaningful response (CR) from baseline of ItchRO and CSS was defined as -1, while PedsQL was +5. Safety and other efficacy assessments occurred every 12 weeks. **Results:** 34 of 37 participants (mean age 7.0 yrs) in ITCH enrolled in IMAGINE II. Mean ItchRO and CSS decreased while PedsQL increased from ITCH baseline to week 48 of IMAGINE II (n=28 mean change;% participants with CR: ItchRO -1.9;80.8%, CSS -1.9;77.8%, PedsQL +10.2;53.8%) with stability of response through week 96 (n=25: ItchRO -2.2;86.4%, CSS -2.1;83.3%, PedsQL +9.7;61.1%) and beyond for an average of 92 additional weeks in selected participants (ItchRO -2.3;90.5%, CSS -2.0;80.0%, PedsQL +6.5;44.4%) (Table). At week 48 cholesterol, serum bile acids and platelets decreased, ALT and GGT increased, while total bilirubin and albumin were unchanged. Height (+0.4) and weight (+0.3) z-scores increased with 96 weeks of MRX. 7/34 (21%) participants had at least one SAE during IMAGINE II. 14 participants were withdrawn before the completion of IMAGINE II (3 caregiver withdrawal, 3 elevated ALT, 2 liver transplant, 1 each hematochezia, pancreatitis, nonadherence, progressive cholestasis, elevated total bilirubin, autoimmune hepatitis). **Conclusion:** Children with ALGS who received 48 weeks of MRX had clinically meaningful reduction in pruritus and improvement in quality of life. These changes persisted for at least 96 weeks in those who were able to continue to receive MRX. The clinical significance of increased ALT and SAEs with MRX administration is uncertain in the context of the natural history of ALGS. MRX may address a major unmet need of pruritus control in ALGS.

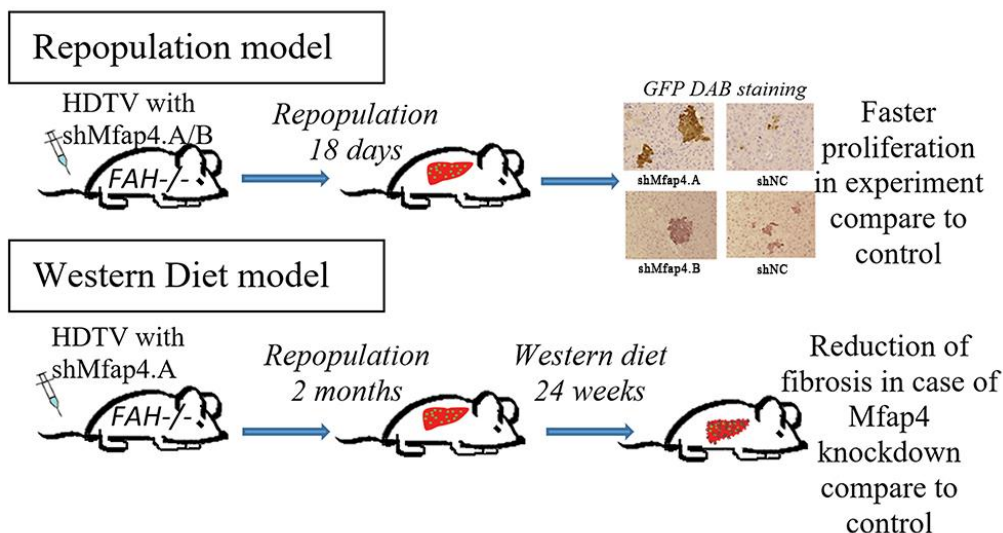
	ITCH	Change from Baseline in ITCH		
Week	-13 (Baseline)	+48	+96	EOT
N	37	28	25	25
ItchRO	2.9 (0.6)*	-1.9 (1.0)	-2.2 (1.0)	-2.3 (0.9)
CSS	3.0 (1.1)	-1.9 (1.6)	-2.1 (1.5)	-2.0 (1.5)
PedsQL	66.4 (18.7)	+10.2 (19.3)	+9.7 (18.8)	+6.5 (19.8)
Fatigue	62.8 (20.3)	+15.3 (21.3)	+17.8 (21.1)	+15.1 (20.5)
TB (mg/dL)	5.3 (6.2)	+0.1 (1.6)	-0.1 (1.9)	-0.1 (2.4)
Chol (mg/dL)	406 (314)	-30 (118)	-51 (125)	-80 (131)
SBA (μM)	216 (203)	-33 (87)	-46 (120)	-63 (88)
ALT (IU/L)	159 (87)	+47 (68)	+49 (85)	+54 (104)
GGT (IU/L)	495 (380)	+38 (178)	+90 (283)	+82 (275)
Alb (gr/dL)	4.5 (0.4)	-0.1 (0.3)	-0.1 (0.3)	-0.2 (0.3)
Plt (x10 ³)	287 (110)	-27 (64)	-44 (95)	-42 (80)
Ht z score	-1.6 (1.2)	+0.2 (0.4)	+0.4 (0.5)	+0.3 (0.5)
Wt z score	-1.3 (1.2)	+0.2 (0.5)	+0.3 (0.7)	+0.1 (0.9)

*Mean (SD) values, EOT = end of treatment

LO6: MICROFIBRIL ASSOCIATE PROTEIN 4 (Mfap4) AS A POTENTIAL REGULATOR OF LIVER REGENERATION AND DISEASE

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Background: The rising incidence of acute and chronic liver failure, which causes more than 1.3 million deaths per year worldwide (WHO, 2018), represents a major global health concern. Furthermore, liver disease is the only major cause of death still increasing year-on-year (British Liver Trust). The only curative treatment for end-stage liver diseases is liver transplantation. However, donor organs are limited. Therefore, alternative strategies to hold off or reverse end-stage liver disease are being pursued. In our research, we are pursuing strategies to enhance the liver's endogenous regenerative capacity. This will allow tissue homeostasis even under liver-damaging conditions. **Methods:** We have developed a system to conduct RNAi based in vivo functional genetic screen in any liver disease mouse model. We identified new therapeutic targets in a mouse model of chronic liver damage using repetitive doses of thioacetamide (TAA). In brief, a pool of shRNAs (targeting 250 shRNAs against 89 genes) were delivered into livers of C57Bl6 mice by hydrodynamic tail vein injections (HDTV) together with transposase sleeping beauty 13 (SB13). After stable integration, thioacetamide (TAA) treatment was given 3 times per week for 8 weeks to induce chronic liver damage associated with advanced liver fibrosis. Changes in shRNA abundance were detected by deep sequencing. We further compared the shRNA distribution to the starting pool. We identified a number of shRNAs which were consistently enriched in all animals. Targets were prioritized based on scoring of at least two independent shRNAs were enriched. For validation of therapeutic targets, we did wound healing, cell doubling, and cell proliferation assays in vitro. In vivo effects of target knockdown were tested on liver repopulation, liver regeneration after partial hepatectomy. In addition, we tested the therapeutic value in mouse models of chronic liver disease as repetitive TAA treatment and Non-Alcoholic SteatoHepatitis (NASH). **Results:** The top-scoring hit from the screen was Mfap4 with 4 independent shRNAs enriched. We validated that Mfap4 knockdown accelerates wound healing and cell doubling in vitro. Furthermore, knockdown of Mfap4 enhances liver repopulation, liver regeneration and attenuates TAA and NASH mediated pathological changes. In addition, we confirmed dysregulation of Mfap4 in two mouse models of NASH and in a local human patient cohort. We discovered that Mfap4 is potential regulator for end-stage liver diseases, validated top-scoring shRNAs against Mfap4, identified the underlying mechanism of shMfap4 mediated accelerated regeneration and disease attenuation, and observed significant reduction in fibrosis in case of Mfap4 knockdown. **Conclusion:** In vivo functional genomics can be applied to identify novel therapeutic targets for liver regeneration and disease, e.g. Mfap4. Targeting Mfap4 is enhancing liver regeneration and counteracts chronic liver disease.



LO7: THE “KEEP IT SIMPLE AND SAFE” APPROACH TO HCV TREATMENT: PRIMARY OUTCOMES FROM THE ACTG A5360 (MINMON) STUDY

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Background: To achieve global hepatitis C virus (HCV) elimination by 2030, 80% of the ~71 million people with chronic HCV infection will need to be treated, necessitating simplification of treatment delivery and associated laboratory monitoring without compromising efficacy or safety. The COVID-19 pandemic has further highlighted the need for innovative models of health care delivery that minimize face-to-face patient-provider contact. **Methods:** ACTG A5360 is a single-arm, open-label trial to evaluate safety and efficacy of a minimal monitoring (MINMON) approach to HCV therapy in treatment-naïve persons with no evidence of decompensated cirrhosis. All participants received a single-tablet, fixed-dose regimen of sofosbuvir/velpatasvir for 12 weeks. MINMON included: (1) no genotyping; (2) all tablets dispensed at entry; (3) no on-treatment visits/labs; and (4) two remote contacts at Weeks 4 (adherence assessment) and 22 (scheduling sustained virology response [SVR] visit). Cirrhosis was classified by FIB-4. Unplanned visits for participant concerns (related/unrelated to an adverse event [AE]) were permissible. SVR is defined as HCV RNA <lower limit of quantification at least 22 weeks after treatment initiation, among those starting treatment (missing HCV RNA = non-SVR). 95% confidence intervals (CI) for SVR used Wilson's Score.

Results: 400 participants with HCV infection were enrolled from 10/2018–07/2019 at 38 sites in five countries across 4 continents; 399 initiated treatment. Median age was 47 years, 138 (35%) were cisgender women, 22 (6%) self-identified across the transgender spectrum, and 166 (42%) were White. At entry, 34 (9%) had compensated cirrhosis (FIB-4 ≥3.25) and 166 (42%) had HIV co-infection. Remote contact was successful at Weeks 4 and 22 for 394 (99%) and 335 (84%) participants, respectively. HCV RNA for SVR was available for 396 participants; 355 (89%) self-reported taking all medication in the 12-week treatment period. Overall, SVR was 95.0% (95% CI: 92.4%, 96.7%); SVR by country, biological sex, gender identity, age, cirrhosis status, HIV co-infection status and injection drug use are reported in Table. Fifteen (3.8%) participants had unplanned visits; 3 were AE related and 6 were related to abnormalities during screening. Serious AE events through Week 24 visit were reported in 14 (3.5%) participants; none were treatment related or resulted in death. **Conclusion:** In

a diverse, global patient population, the MINMON approach to HCV treatment delivery was safe and achieved SVR comparable to current standards. Wider adoption of this approach coupled with innovative case-finding strategies may facilitate HCV elimination while minimizing in-person appointments and resource use.

Baseline Characteristic		Sustained Virologic Response (n with SVR / total)	SVR % (95% Confidence Interval)
OVERALL		379/399	95.0 (92.4, 96.7)
Country	<i>United States</i>	121/131	92.4 (86.5, 95.8)
	<i>Brazil</i>	128/131	97.7 (93.5, 99.2)
	<i>South Africa</i>	12/12	100 (75.8, 100)
	<i>Thailand</i>	103/110	93.6 (87.4, 96.9)
	<i>Uganda</i>	15/15	100 (79.6, 100)
Sex at Birth	<i>Male</i>	245/260	94.2 (90.7, 96.5)
	<i>Female</i>	134/139	96.4 (91.9, 98.5)
Gender Identity	<i>Cisgender</i>	359/377	95.2 (92.6, 97.0)
	<i>Transgender Spectrum</i>	20/22	90.9 (72.2, 97.5)
Age in years	<i>20 – 29</i>	28/33	84.9 (69.1, 93.4)
	<i>30 – 39</i>	92/95	96.8 (91.1, 98.9)
	<i>40 – 49</i>	98/100	98.0 (93.0, 99.5)
	<i>50 – 59</i>	90/97	92.8 (85.9, 96.5)
	<i>60 – 69</i>	52/55	94.6 (85.2, 98.1)
	<i>70+</i>	19/19	100 (83.2, 100)
Cirrhosis status	<i>Non-cirrhotic (FIB-4 < 3.25)</i>	349/365	95.6 (93.0, 97.3)
	<i>Cirrhotic (FIB-4 ≥ 3.25)</i>	30/34	88.2 (73.4, 95.3)
HIV status	<i>Person without HIV</i>	222/233	95.3 (91.7, 97.3)
	<i>Person with HIV</i>	157/166	94.6 (90.0, 97.1)
Injection drug use status	<i>Never</i>	252/263	95.8 (92.7, 97.7)
	<i>Former</i>	116/124	93.6 (87.8, 96.7)
	<i>Current</i>	11/12	91.7 (64.6, 98.5)

Table. Sustained virologic response by select trial sample characteristics

LO8: A PHASE 2 STUDY OF PEGINTERFERON LAMBDA, LONAFARNIB, AND RITONAVIR FOR 24 WEEKS: END-OF-STUDY RESULTS FROM THE LIFT HDV STUDY.

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Background: Hepatitis Delta Virus (HDV) infection, the most aggressive form of human chronic viral hepatitis, is still without an approved FDA therapy. Separate clinical trials evaluating the prenylation inhibitor lonafarnib (LNF) boosted with ritonavir (RTV) and peginterferon lambda-1a (LMD) monotherapy have demonstrated anti-HDV activity. In a first-in-humans clinical trial, the Lambda InterFeron combination Therapy (LIFT) study evaluated the safety and antiviral effects of combination therapy with LMD/LNF/RTV in chronic HDV infected patients. **Methods:** In this phase 2 open-label study, 26 adult patients with chronic HDV and quantifiable HDV RNA in serum (lower limit of quantitation <40 IU/mL) were treated with subcutaneous LMD 180 mcg weekly and oral LNF 50 mg and RTV 100 mg twice daily for 24 weeks followed by 24 weeks of post-therapy follow-up. The primary therapeutic endpoint was a decrease of HDV RNA by >2 log from baseline at 24 weeks of therapy. Tenofovir or Entecavir was started prior to therapy. Serial assessments of safety parameters, liver tests, pharmacokinetics, histology, and virologic (HDV RNA, HBV DNA, and HBsAg) markers were obtained. **Results:** In this completed study, patients were 65% male, median age of 40 years and included Asian (54%), White (31%) and African (15%) subjects. Median baseline evaluations included: ALT (64 IU/mL), AST (47 IU/mL), Ishak Fibrosis (3), modified HAI inflammation (9), HBV DNA (<21 IU/mL) and log HDV RNA (4.7 IU/mL). During the study, 24 patients (92%) achieved a >2 log decline and 20 patients (77%) achieved

either undetectable HDV RNA levels or below the lower limit of quantification (BLOQ). By intention-to-treat analysis, at 24-weeks of therapy, the median HDV RNA decline from baseline was 3.23 log IU/mL (IQR:2.94-4.49, $p<0.0001$) with 9 patients (35%) achieving undetectable HDV RNA and 3 patients (11.5%) with HDV RNA BLOQ. Adverse events were mostly mild to moderate and included GI related side effects, weight loss, hyperbilirubinemia, and anemia. Therapy was dose reduced in 3 patients and discontinued in 4 patients. After 24-weeks of follow-up, 3 patients (11.5%) maintained a durable response with undetectable HDV RNA and normal liver enzymes. **Conclusion:** Combination therapy with LMD/LNF/RTV was safe and tolerable for up to 6 months in most patients. Along with significant anti-HDV activity, this was the first demonstration of sustained anti-HDV response with this therapeutic regimen. Preliminary analysis supports continued exploration of this regimen and that increased duration of therapy may lead to increased response rates.

LO9: HBV RNAi INHIBITOR RG6346 IN PHASE 1b-2a TRIAL WAS SAFE, WELL-TOLERATED, AND RESULTED IN SUBSTANTIAL AND DURABLE REDUCTIONS IN SERUM HBsAg LEVELS

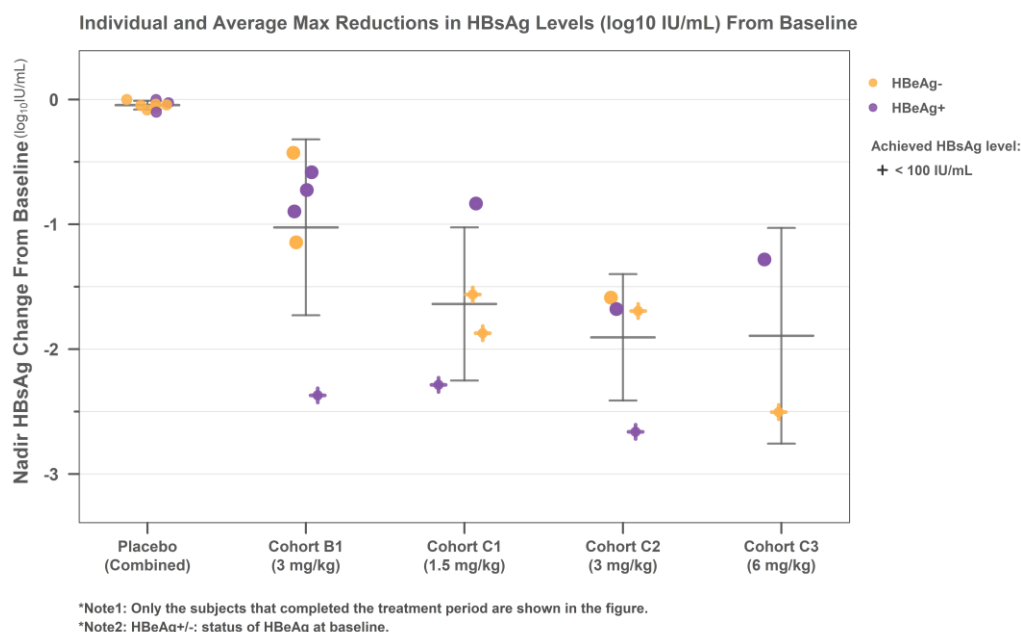
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Background: Chronic Hepatitis B (CHB) virus infection can cause progressive liver damage leading to cirrhosis and hepatocellular carcinoma. Currently CHB infection requires prolonged, often life-long, treatment with nucleos(t)ide analogs (NUCs). New treatments aim at achieving “functional cure,” i.e., durable clearance of serum HBsAg after finite therapy. RG6346 is a synthetic dsRNA conjugated to N-acetylgalactosamine that induces cleavage of mRNA encoding all forms of HBsAg in hepatocytes.

Methods: This placebo controlled study was designed in 3 parts: SAD (Group A) in healthy volunteers (HV) (n=30; RG6346:placebo=2:1; doses=0.1, 1.5, 3.0, 6.0, 12.0 mg/kg), SD (Group B) in NUC-naïve patients with immune-active CHB (n=8; RG6346:placebo=5:3; dose=3.0 mg/kg), and MAD (Group C) in CHB patients with ≥ 12 weeks of NUC suppression prior to screening (n=18; RG6346:placebo=2:1; 4 monthly doses of 1.5 (C1), 3.0 (C2), and 6.0 mg/kg (C3) per cohort. Inclusion criteria in Groups B and C were HBeAg (+) with HBsAg > 1000 IU/mL, or HBeAg (-) with HBsAg > 500 IU/mL, and for Group B, serum HBV DNA > 2000 IU/mL, and ALT ≥ 35 U/L (males) or ≥ 30 U/L (females).

Results: All doses were safe in HVs, with nearly dose proportional Cmax levels of RG6346. After 4 monthly SC doses in patients, the mean HBsAg decline from baseline was 1.39 log₁₀ IU/mL in C1, 1.80 in C2 and 1.84 in C3 at Day 112 (2/4 patients on RG6346 in C3 not yet reached Day 112). The max mean HBsAg reductions were 1.71 log₁₀ IU/mL in C1 on Day 168 (n=3), 1.88 in C2 on Day 140 (n=4), and 1.88 in C3 on Day 140 (n=2). The overall max reduction to date was 2.7 log₁₀ IU/mL (see Figure). Eighty (80) % of patients who reached at least Day-112 achieved > 1.5 log₁₀ IU/mL reduction, and 60% achieved HBsAg < 100 IU/mL regardless of HBeAg status. The longest enrolled patient in C1 maintained > 2 log₁₀ IU/ml HBsAg reduction from Day 336 through Day 448. In NUC-naïve patients, a single dose of RG6346 resulted in a mean HBsAg reduction of 1.01 log₁₀ IU/mL at Day 57. Several patients on RG6346 exhibited self-resolving ALT flares consistent with treatment-induced enhanced immune responses, as demonstrated by a decrease in viral markers and overall preserved liver function. No SAEs or dose limiting toxicities with RG6346 were observed. The most common AEs in Groups B and C were related to mild injection site reactions.

Conclusion: Treatment with RG6346 was safe and consistently induced large and durable reductions of HBsAg regardless of HBeAg status.



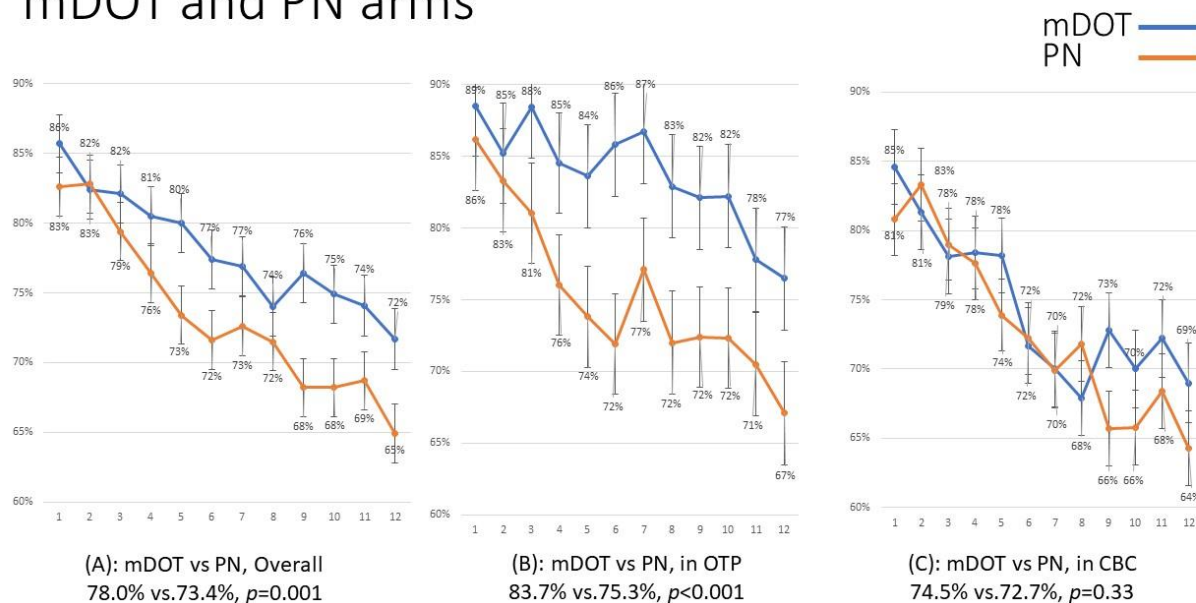
LO10: A MULTI-SITE RANDOMIZED PRAGMATIC TRIAL OF PATIENT-CENTERED MODELS OF HEPATITIS C TREATMENT FOR PEOPLE WHO INJECT DRUGS: THE HERO STUDY

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Background: While people who inject drugs (PWID) can be effectively treated for hepatitis C virus (HCV) infection with sustained virologic response (SVR) rates ranging between 63-100%, optimal models of care for achieving SVR in actively injecting PWID have not been sufficiently studied. We compared the effectiveness of two treatment models, patient navigation (PN) and modified directly observed therapy (mDOT), delivered in opioid treatment programs (OTP) and community-based clinics (CBC). **Methods:** We conducted a pragmatic randomized trial in 8 US states testing the effectiveness of PN vs. mDOT on treatment initiation, adherence (measured by electronic packs), completion, and SVR. Eligible PWID (injecting within prior 12 weeks) were randomized 1:1 to mDOT or PN and were treated with 12 weeks of sofosbuvir/velpatasvir. mDOT was delivered on-site at OTP and virtually via smartphone apps for CBC participants. We also examined associations of SVR with baseline factors, adherence and completion, using multivariable logistic regression. **Results:** 755 PWID were randomized. Mean age was 43.2 years; 96.0% had positive baseline urine toxicology results. There

were no differences between arms in initiation, completion or SVR. N=623 (82.5%) initiated treatment (mDOT 81.4%, PN 83.6%; $p=0.43$). Among those who initiated treatment (n=623), completion was 82.7% (mDOT 82.0%, PN 83.3%; $p=0.63$) and SVR was 72.2% (mDOT 71.9%, PN 72.6%; $p=0.88$). In the per-protocol analysis (n=502), SVR was 89.6% (mDOT 88.7%, PN 90.6%; $p=0.57$). Treatment completion was significantly associated with SVR (adjusted odds ratio (AOR)=9.5, $p<0.001$), as was each 10% increase in adherence (AOR=1.5, $p<0.001$). Overall adherence was 74.1% (Figure 1) and significantly higher with mDOT than PN in OTP but not CBC. Higher SVR was associated with age ≥ 40 years (AOR=1.8), Hispanic ethnicity (AOR=2.1), stable housing (AOR=2.6), and taking methadone vs. buprenorphine (AOR=2.2). Lower SVR was associated with injecting >2 times daily (AOR=0.5), ≥ 30 days injecting over last 3 months (AOR=0.7), and positive baseline urine toxicology for methamphetamine (AOR=0.5), cocaine (AOR=0.6), and opiate (AOR=0.6). **Conclusion:** In the largest trial of actively injecting PWID, both models resulted in high SVR. Although mDOT increased adherence in OTP setting, it did not increase SVR. These results demonstrate that actively injecting PWID can achieve high SVR in diverse settings with either mDOT or PN support.

Figure 1. Comparisons of Adherence between mDOT and PN arms



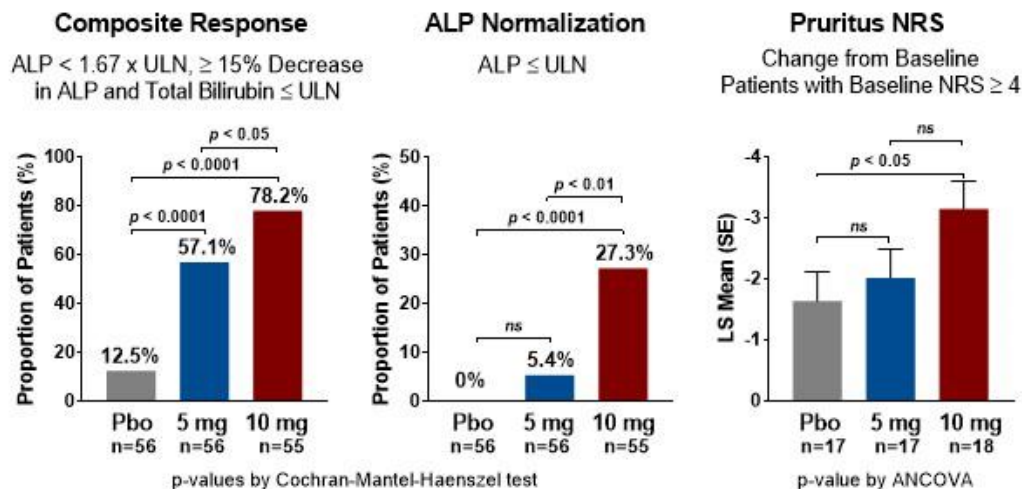
LO11: ENHANCE: SAFETY AND EFFICACY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC) - A PHASE 3 INTERNATIONAL, RANDOMIZED, PLACEBO-CONTROLLED STUDY

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Background: Seladelpar, a potent and selective PPAR-delta agonist, has anti-cholestatic, anti-inflammatory and anti-pruritic activity. We report the effects of seladelpar in a controlled trial in PBC patients (pts) at risk of progressive disease. **Methods:** Eligible pts with PBC had UDCA treatment ≥ 12 months, or were intolerant, and had alkaline phosphatase (ALP) $\geq 1.67 \times$ ULN and total bilirubin (TB) $\leq 2 \times$ ULN. Pts were randomized to seladelpar 5 or 10 mg or placebo (Pbo) orally once daily and UDCA was continued. Pruritus (0-10; numerical rating scale [NRS]) was monitored daily by e-diary. Treatment was stratified by ALP value and NRS. The primary endpoint was a composite response of ALP $< 1.67 \times$ ULN, ALP decrease $\geq 15\%$ and TB \leq ULN at Month 12. Secondary endpoints were ALP normalization at Month 12 and change in NRS at Month 6. The study terminated early due to pathology findings in a NASH study that a detailed independent review found unrelated to seladelpar. While blinded, primary and secondary endpoints were amended to Month 3. **Results:** We enrolled 265 pts (female 94%; mean age 55) with mean ALP 292 U/L and TB 0.73 mg/dL (11.7% $>$ ULN). Pts had a baseline mean NRS of 2.8; 30% of pts reported moderate to severe itch (NRS ≥ 4 ; baseline 6.2). Data were available for 237, 167 and 69 pts at Months 1, 3 and 6. Treatment with seladelpar at doses of 10 and 5 mg for 3 months resulted in significant composite responses of 78% and 57%, respectively, vs 13% in Pbo ($p < 0.0001$). ALP normalization occurred in 27% of those receiving the 10 mg dose vs 0% receiving Pbo ($p < 0.0001$). At 10 mg greater biochemical responses than 5 mg were seen at Months 1 and 6. ALT, GGT and TB decreased by up to -35%, -37%, and -15%, respectively, in the 10 mg group, but increased in the Pbo group by 2.4%, 0.1%, and 1.7%, respectively. Pts with baseline pruritus NRS ≥ 4 receiving seladelpar 10 mg saw decreases at 3 months in NRS of 3.2 vs. 1.6 in Pbo ($p < 0.03$); 39% of 10 mg vs. 6% of Pbo subjects had mild or no itch with NRS decreases ≥ 4 . No treatment-related SAEs occurred and 3 AEs led to discontinuation. The only AE in $> 10\%$ of pts was pruritus in 12.6%, 3.4%, and 11.2% in Pbo, 5 and 10 mg groups, respectively. **Conclusion:** In a randomized controlled study of the treatment of PBC, seladelpar 10 mg resulted in rapid and significant improvements in cholestasis, inflammation and pruritus. Seladelpar appeared safe and well tolerated. These results support a new Phase 3 trial of seladelpar in patients with PBC.

Primary and Secondary Endpoints at Month 3

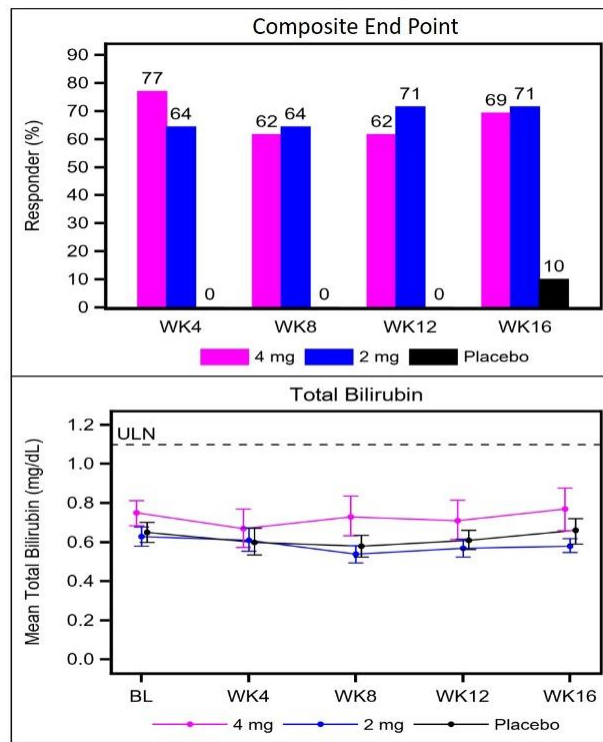
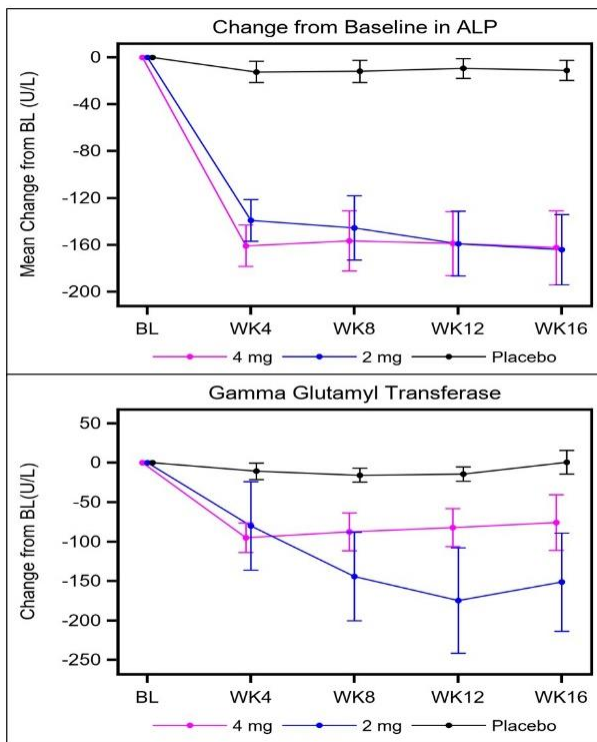


LO12: RESULTS OF PHASE 2, PROSPECTIVE, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE SAFETY, TOLERABILITY AND EFFICACY OF SAROGLITAZAR MAGNESIUM IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (EPICS)

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Background: Saroglitazar is a novel peroxisome proliferator-activated receptor (PPAR) agonist with dual agonistic properties (α/γ). Due to a strong mechanistic rationale, we aimed to test the safety and efficacy Saroglitazar in patients with primary biliary cholangitis (PBC) who did not achieve biochemical response to ursodeoxycholic acid (UDCA) or were intolerant. **Methods:** In this double-blind, phase 2 RCT, 37 PBC patients were randomized to Saroglitazar 4 mg (13 patients), Saroglitazar 2 mg (14 patients), or placebo (10 patients) daily for 16 weeks. The primary efficacy endpoint was the reduction in alkaline phosphatase (ALP) level at Week 16, based on the modified ITT analysis. Secondary end point was as a composite endpoint of ALP level <1.67 times the upper limit of the normal (ULN), with a reduction of at least 15% from baseline, and a total bilirubin level at or below the ULN at Week 16. **Results:** Baseline patient characteristics and biochemical parameters were not significantly different between the three study groups. A significant reduction of mean ALP concentration at Week 16 relative to baseline was observed in both Saroglitazar 4 mg (least-squares[LS] mean = -163.3 U/L, SE = 25.1, p < 0.001) and 2 mg (LS mean = -155.8 U/L, SE = 24.4, p < 0.001) groups, compared with Placebo (LS mean = -21.1 U/L, SE = 28.9) (Panel A). This corresponds to a mean percentage reduction of 48.9% (SE=5.5), 50.6% (SE=5.5) and 3.3% (SE=6.4) in the Saroglitazar 4 mg, Saroglitazar 2 mg and Placebo groups, respectively. Treatment with Saroglitazar resulted in a rapid reduction of ALP concentration at Week 4 and sustained. The percentage of patients with biochemical response was significantly higher in both Saroglitazar 4 mg (69%, p < 0.001) and Saroglitazar 2 mg (71%, p < 0.001) groups compared with Placebo (10%) (Panel B). The GGT levels decreased (Panel C) and total bilirubin were unchanged (Panel D) during the study. Patients with at least one treatment-emergent AE occurred in 11 (84.6%) patients in the Saroglitazar 4 mg, 12 (85.7%) in the Saroglitazar 2 mg and 8 (80%) in the placebo group. Four patients discontinued the study due to AE (3 patients in Saroglitazar 4 mg group and 1 patient in Saroglitazar 2 mg group) and 2 patients in the

Saroglitazar 2 mg group reported serious AE. Four patients (3 with 4 mg dose and 1 with 2 mg dose) had aminotransferase increases without a concomitant significant increase in total bilirubin and these were adjudicated as probable (n=3) and highly likely (n=1) drug induced liver injury (DILI) by an expert independent panel. Liver tests returned to baseline after study drug discontinuation in 3 while one patient required immune suppression for suspected overlap syndrome. **Conclusion:** Treatment with Saroglitazar for 16 weeks resulted in rapid and sustained improvements in ALP compared with placebo, with an acceptable safety profile in patients with PBC. The phase 3 trial is currently planned at 1 mg and 2 mg daily dose.



Poster Presentations

LP1: COVID-19 INFECTION AND INPATIENT MORTALITY AMONG PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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Background: The pandemic of COVID-19 has caused morbidity and mortality worldwide. Presence of comorbidities has been associated with adverse outcomes in COVID-19 patients. We assessed mortality of NAFLD patients admitted with COVID-19. **Methods:** Using electronic health records and chart review, we collected clinico-demographic and mortality data for adult NAFLD patients hospitalized with COVID-19 (March 13th to August 4th, 2020). Diagnosis of NAFLD was established by histology or imaging in the absence of other liver diseases. Presence of multimorbidity was assessed using Charlson's comorbidity index (CCI) and Elixhauser comorbidity index (ECI). **Results:** 256 NAFLD patients with COVID-19 were included (mean±SD age 53±15 years, 59% <55 years old, 56% male, 13% non-Hispanic white, 11% non-Hispanic black, 67% Hispanic, 6% Asian). Of NAFLD patients, 56% were obese (BMI≥ 30), 14% morbidly obese (BMI≥ 40), and 43%, 49%, and 39% had type 2 diabetes (T2DM), hypertension and hyperlipidemia, respectively. Mean CCI and ECI scores were 3.57 and 13.7, respectively. At admission, 95% of these patients had COVID-19 as the primary diagnosis, 98% had at least one symptom (>60% had fever, cough and shortness of breath). On admission, mean oxygen saturation was 92.6±7.7% and 22% had it ≤90% and 78% had interstitial pulmonary infiltrates by imaging. The crude mortality rate in NAFLD patients with COVID-19 was 10.9% (19% in March-April 2020, 9% in May 2020, and 2% in June-July 2020). The mean length of inpatient stay was 10±10 days, mean ICU use 35% and mean use of mechanical ventilation 18%. In multivariate regression analysis, earlier period of admission [odds ratio (OR) = 3.4 (1.2 - 9.4), older age (OR = 1.3 (1.1 - 1.7) per 5 years), morbid obesity (OR = 5.9 (1.5 - 23.4)), CCI ≥ 5 (OR = 4.0 (1.2 - 13.5)], and oxygen saturation ≤ 90% at admission [OR = 3.7 (1.3 - 10.4)] were independently associated with inpatient mortality (all p<0.05). By replacing CCI with ECI, the same clinical factors, including ECI, remained independent predictors of mortality. In contrast, we found no association of mortality with sex, race/ethnicity, having health insurance, or individual components of metabolic syndrome [obesity (non-morbid), T2DM, hypertension, hyperlipidemia) after adjustment for age and period of admission (all p>0.10). **Conclusion:** Multi-morbidity scores, older age, morbid obesity and low oxygen saturation in NAFLD patients with COVID-19 are associated with inpatient mortality.

LP2: SAFETY AND EFFICACY OF GLECAPREVIR/PIBRENTASVIR IN PEDIATRIC PATIENTS WITH GENOTYPES 1-6 CHRONIC HEPATITIS C VIRUS (HCV) INFECTION: PART 2 OF THE DORA STUDY

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Background: Glecaprevir (GLE) and pibrentasvir (PIB), co-formulated as G/P, is a pangenotypic, direct-acting antiviral (DAA) approved for chronic hepatitis C virus (HCV) treatment in adults and adolescents with or without compensated cirrhosis. DAA options for children remain limited; we evaluated the safety and efficacy of 8-16 weeks of G/P in HCV genotype (GT) 1-6 infected children, aged 3 - < 12 years old. **Methods:** DORA (NCT03067129) is a non-randomized, open-label, multinational study evaluating the safety and efficacy of weight-based pediatric formulations of G/P in children with chronic HCV-infection; part 1 of the DORA study evaluated the adult dose of G/P in patients 12 – 17 years of age (cohort 1). Part 2 of the DORA study evaluated chronic HCV-infected patients, aged 3 - < 12 years old, who were treatment-naïve or treatment-experienced with interferon (\pm ribavirin [RBV]), or sofosbuvir plus RBV (\pm interferon) from 2 May 2018 – 28 May 2020. Patients were divided into 3 cohorts: cohort 2 (9 – < 12 years, N = 29), cohort 3 (6 – < 9 years, N = 27), and cohort 4 (3 – < 6 years, N = 24). Following pharmacokinetic (PK) evaluation of the first 17 patients who received the initial doses, the final pediatric dosages, assigned based on body weight/age, were adjusted to 250 mg GLE + 100 mg PIB (cohort 2 or 30 kg to < 45 kg), 200 mg GLE + 80 mg PIB (cohort 3 or 20 kg to < 30 kg), and 150 mg GLE + 60 mg PIB (cohort 4 or 12 kg to < 20 kg). Patients received a pediatric granule formulation of G/P for 8, 12, or 16 weeks based on prior treatment experience, genotype, and geographical location. The primary efficacy endpoint was SVR12; adverse events (AEs) and laboratory abnormalities were assessed. **Results:** Part 2 enrolled 80 pediatric patients; most received 8 weeks of therapy (97.5%, 78/80). Baseline demographics are provided in the Table. Overall, 96.3% (77/80) of patients achieved SVR12. One patient, on the initial dose ratio, experienced virologic failure and relapsed by Post Treatment Week 4. Two patients prematurely discontinued G/P; one refused to swallow the G/P granule formulation and the other experienced a G/P-related AE of rash. The most common AEs ($\geq 10\%$) were headache (13.8%), vomiting (13.8%) and diarrhea (10%); no serious AEs or lab abnormalities were reported. The PK analyses showed similar G/P exposures compared to adults and adolescents. **Conclusion:** G/P is a safe and efficacious treatment option for children ≥ 3 years of age with chronic HCV.

Table. Baseline Demographics and Disease Characteristics

Characteristic	Cohorts 2-4 G/P N=80
Male, n (%)	36 (45.0)
Female, n (%)	44 (55.0)
White race, n (%)	55 (68.8)
Black, n (%)	3 (3.8)
Asian, n (%)	14 (17.5)
Age, median (range), years	7 (3–11)
Weight, median (range), kg	24.9 (12.7–44.3)
HCV genotype, n (%) ^a	
GT1 (%)	58 (72.5)
1a/1b subtype	37 (46.3) / 21 (26.3)
GT2 (%)	2 (2.5)
GT3 (%)	18 (22.5)
GT4 (%)	2 (2.5)
HCV RNA median (range), log ₁₀ IU/mL	6.0 (3.4–7.2)
non-cirrhotic, n (%)	80 (100)
HCV treatment-naïve, n (%)	78 (97.5)
8 weeks of treatment	78 (97.5)

^aNo patients with GT5 or GT6 infection were enrolled

LP3: RESTORATION OF IMPAIRED MITOCHONDRIAL CAPACITY IN HUMAN PRIMARY HEPATOCYTES BY INCREASING DE NOVO NAD⁺ SYNTHESIS

Jose A Chavez, Cardiovascular & Metabolism, Janssen Research & Development

Background: Mitochondrial dysfunction is associated with the early stage of nonalcoholic steatohepatitis (NASH) and promotes cell death, liver fibrogenesis, inflammation, and activation of the innate immune response. Nicotinamide adenine dinucleotide (NAD⁺) is an essential cofactor for cellular redox reactions, energy metabolism, and cellular homeostasis and maintenance of optimal NAD⁺ levels is essential for mitochondrial function. 2-amino 3-carboxymuconate 6-semialdehyde decarboxylase (ACMSD) is an enzyme that shunts liver tryptophan metabolism away from *de novo* NAD⁺ biosynthesis and inhibition of ACMSD has been shown to attenuate NAFLD in mouse models. We targeted the activity of ACMSD to evaluate the therapeutic potential of the *de novo* NAD⁺ pathway as a regulator of

mitochondrial function. **Methods:** Human primary hepatocytes and C57Bl/6N mice were infected with ACMSD shRNA silencing virus (Ad-h-ACMSD-shRNA or AAV9-msACMSD-shRNA) or treated with ACMSD inhibitors to modulate NAD⁺ levels. ¹³C-labelled tryptophan was used to evaluate *de novo* NAD⁺ biosynthesis. Quantification of NAD⁺ and isotope incorporated ¹³C-NAD⁺ as well as intermediates of the kynurenine pathway were determined using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. To induce metabolic stress and alter mitochondrial function in cells, Glucose-Lipid Treatment (GLT) conditions of 25 mM glucose and 300 μM palmitate were introduced to the cell culture media. Changes in mitochondrial respiration were evaluated using a Seahorse Bioanalyzer. **Results:** Both pharmacological inhibition and siRNA-mediated knockdown of ACMSD enhanced *de novo* NAD⁺ biosynthesis from labelled tryptophan in human primary hepatocytes. Consistent with these observations, *in vivo* administration of ACMSD inhibitors or shRNA-mediated ACMSD knockdown in mice increased hepatic *de novo* NAD⁺ concentrations. Additionally, ACMSD inhibition was able to restore impaired mitochondrial oxidative capacity in hepatocytes cultured under GLT conditions. **Conclusion:** These results demonstrated for the first time a role of ACMSD in the regulation of *de novo* NAD⁺ synthesis in human hepatocytes and suggest that restoration of NAD⁺ levels is a potential therapeutic approach to restore mitochondrial dysfunction in NASH.

LP4: RECENT TRENDS IN THE GLOBAL BURDEN OF HEPATITIS B VIRUS (HBV): 2007-2017

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Background: HBV is one of the most important causes of liver related mortality and morbidity in the world. Aim: To describe the global burden of liver complications (both primary liver cancer and cirrhosis) due to HBV from 2007 to 2017 using Global Burden of Disease (GBD) data. **Methods:** The GBD study estimation methods were used to assess incidence, deaths, and disability-adjusted life-years (DALYs) related to HBV liver complications. Results were analyzed according to 21 GBD regions as well as 195 countries and territories. **Results:** Globally, in 2017, there were 1.94 million incident cases of liver complications due HBV and associated 709,419 deaths, contributing 21.8 million DALYs. This accounted for about one third of liver complications due to all chronic liver diseases around the world. Asian regions accounted for 75.3% of these global DALYs HBV liver complications [East Asia (43.1%), South Asia (17.3%), Southeast Asia (11.5%), African regions (11.5%) and Middle East & North Africa (MENA) (4.5%), High-income Asia Pacific (2.0%), and Central Asia (1.3%)]. On the other hand, age-standardized DALYs (ASDALY) per 100,000 population due to HBV liver complications were highest in Western sub-Saharan Africa (613.58), followed by East Asia (445.09), Oceania (440.46), Southeast Asia (374.51), Central sub-Saharan Africa (370.45), Central Asia (320.58), and Eastern sub-Saharan Africa (293.31). Between 2007 and 2017, most of the regions (19 out of 21 regions) experienced improving trends (percent change <0%) in ASDALY rate for liver complications due to HBV with the steepest decrease in ASDALY rates noted for Southern sub-Saharan Africa (-37.9%) and Eastern Europe (-23.2%) while increases were noted for High-income North America (+6.1%) and Australasia (+1.6%) regions. At the country level, the steepest improvement occurred in Hungary (-44.9%), Bangladesh (-41.9%), South Africa (-40.9%), and Malawi (-40.2%) while a worsening trends were noted for Georgia (+25.5%), Iceland (+15.1%), Fiji (+11.2), Cuba (+7.7%) and United States (+6.5%). **Conclusion:** Most regions of the world show a decline in burden of HBV complications. In contrast, some countries still have some opportunities that may require policies to address these challenges related to reducing the liver complications due to HBV.

LP5: THE DISCOVERY OF A NEW CLASS OF ENDOGENOUS REACTIVE KETONES - A POTENTIAL CAUSE OF NASH AND A TREATMENT

Sean Liu, Sunrise Bio

Background: The exact cause of NASH is still unclear and currently there is no approved treatment. Bile acids (BAs) have been studied for decades on their role in the pathogenesis of NASH. Several synthetic BAs with the property of interfering endogenous BAs are currently investigated in clinical trials for NASH. However, this class of compounds are associated with dose limiting toxicities. We hypothesize the pathogenesis of NASH involves covalent binding of reactive metabolites from BAs to certain peptides, which activates immune response and cause inflammation, leading to cell damage and liver fibrosis. This study investigated the reactivity of the major Phase 1 metabolites of a series of BAs to certain peptides. Of our interests are 3-ketone BAs (3k-BAs), which are commonly considered

non-reactive BA metabolites. We further studied the ability of alkylating agents to reverse the conjugation and decrease the reactive metabolites. **Methods:** Phase 1 BA metabolites, 3k-BAs, were used to react with several peptides spontaneously in vitro. The 3k-BAs were purchased commercially [3-Oxo-7 α -hydroxy-5 β -Cholanoic Acid (3k-CDCA)] or synthesized in our lab from CA, DCA, GCA, GCDCA, GDCA, and TCDCA, respectively. The peptides were also purchased or self-made. Alkylating agents were tested for their ability to reverse peptide conjugation. LC/MS/MS in both positive and negative ion modes was used to detect and quantify 3k-BAs and their corresponding conjugates. **Results:** All seven 3k-BAs reacted with each of the peptides tested, leading to the formation of 3k-BA-peptide conjugates. Alkylating agents reversed the reaction by conjugating with 3k-BA to replace peptides from the conjugates. Differences in the rate of reaction were observed for the alkylating agents, from a complete reaction to a very limited reaction.

Conclusion:

1. This is the first to demonstrate that 3k-BAs are reactive metabolites of BAs.
2. 3k-BAs can covalently bind to certain peptides, which may play a role in NASH by incurring immune response, inflammation, and cell damage.
3. Alkylating agents, which has been studied in clinical trials for indications not related to NASH, showed ability to chemically reverse 3k-BA-peptide conjugations. Or they could directly react with 3k-BAs to prevent conjugation with peptides.
4. Mitigating the reactive metabolites of BAs by alkylating agents may provide therapeutic potential for NASH and may also help to manage the dose limiting toxicities related to the synthetic BAs.

Representative Relative Quantity of 3k-BA, 3k-BA-Peptide Conjugates and 3k-BA-Alkylating Agent Conjugates Analyzed by LC/MS

Analyte	3k-BA	3k-BA-peptide conjugates	3k-BA-alkylating agent conjugates	
	3k-CDCA	3k-CDCA-H2Oxy	3k-CDCA-MOA1	3k-CDCA-MOA2
MS Ion Mode	Positive (Unit: Million Positive Ions)			
Reaction 3k-CDCA + Oxy + DTT	1546	55	0	0
Reaction 3k-CDCA + Oxy + DTT + MOA	7	1.7	7891	7376
MS Ion Mode	Negative (Unit: Million Negative Ions)			
Reaction 3k-CDCA + Oxy + DTT	222	4.2	0.0	0.0
Reaction 3k-CDCA + Oxy + DTT + MOA	1	0.0	49	51

3k-BA = 3-ketone metabolite of bile acid; 3k-BA-alkylating agent conjugates = covalent conjugates of 3k-BA with alkylating agent; 3k-BA-peptide conjugates = covalent conjugates of 3k-BA with peptide; 3k-CDCA = 3-Oxo-7 α -hydroxy-5 β -Cholanoic Acid, 3-ketone metabolite of bile acid CDCA; 3k-CDCA-H2Oxy = covalent conjugates of 3-CDCA with peptide Oxytocine; 3k-CDCA-MOA1 = first epimer of covalent conjugates of 3k-CDCA with methoxyamine; 3k-CDCA-MOA2 = second epimer of covalent conjugates of 3k-CDCA with methoxyamine; DTT = Dithiothreitol; H2Oxy = peptide Oxytocine; MOA = alkylating agent methoxyamine; Oxy = Oxytocin, oxidized form of peptide Oxytocine.

LP6: DEVELOPMENT AND VALIDATION OF A HEPATITIS B (HBV)-SPECIFIC HEALTH-RELATED QUALITY OF LIFE INSTRUMENT: CLDQ-HBV

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Background: To understand the full impact of chronic hepatitis B (CHB) and its treatment, it is important to assess both clinical outcomes and patient-reported outcomes (PROs) such as health-related quality of life. Therefore, we developed and validated a HBV-specific PRO instrument for clinical research of patients with CHB. **Methods:** CHB patients were included from our CHB registries. Each patient included in the registry completed the original chronic liver disease questionnaire (CLDQ, 29 items). Patients also completed SF-36 and FACIT-F. The patient sample was split randomly 1:1 into training and testing groups. Using the training group, the original CLDQ items were subjected to item reduction procedure followed by exploratory factor analysis. A standard PRO instrument validation pipeline was applied to the new CLDQ-HBV using the testing group. **Results:** 1339 CHB patients were included: 48±13 years old, 60% male, 8% cirrhosis, 53% receiving oral antivirals (OAV). Using training set, ten items of CLDQ had the highest possible score returned by >50% of patients and were considered as non-relevant to HBV. Exploratory factor analysis of the remaining 19 items suggested that 95% of variance could be explained by 5 factors. Analyzing factor loadings, distribution of the items into 5 factors resulted in Emotional Function, Fatigue, Systemic Symptoms, Worry, and Sleep domains of CLDQ-HBV. The domains demonstrated good to excellent internal consistency in the testing set: Cronbach's alphas 0.70-0.90, item-to-own domain correlations >0.50 for 18/19 items. Known groups validity tests suggest that the instrument is able to discriminate between CHB patients with and without cirrhosis (all but one $p < 0.05$), with FIB-4 ≥ 3.25 vs. < 3.25 ($p < 0.05$ for Systemic symptoms), with and without history of depression or clinically overt fatigue (all $p < 0.0001$), and on vs. not on OAV (all $p < 0.05$, all but one < 0.0001). The Fatigue domain of CLDQ-HBV was highly correlated with Fatigue Scale of FACIT-F ($\rho = 0.80$); Emotional Function and Systemic Symptoms CLDQ-HBV domains also correlated with respective domains of SF-36 ($\rho > 0.6$). After 48-week follow-up, CHB patients ($N=144$) with ≥ 2.7 log 10/mL decline in HBV viral load experienced significant improvements in Fatigue, Worry and Total CLDQ-HBV scores ($p < 0.05$). **Conclusion:** The newly developed CLDQ-HBV is a HBV-specific PRO instrument developed using an established methodology with good psychometric characteristics.

LP7: MT-3995, A NOVEL NON-STEROIDAL MINERALOCORTICOID RECEPTOR ANTAGONIST, HAS BENEFICIAL EFFECTS ON THE PROGRESSION OF NON-ALCOHOLIC STEATOHEPATITIS IN CHOLINE-DEFICIENT L-AMINO ACID-DEFINED DIET-FED F344 RATS AND TRANS-FAT DIET-FED OB/OB MICE.

Naomichi Abe, Sayuka Kato, Yusuke Murata, Kohei Kikkawa and Kozo Oka, Sohyaku. Innovative Research Division, Mitsubishi Tanabe Pharma Corporation

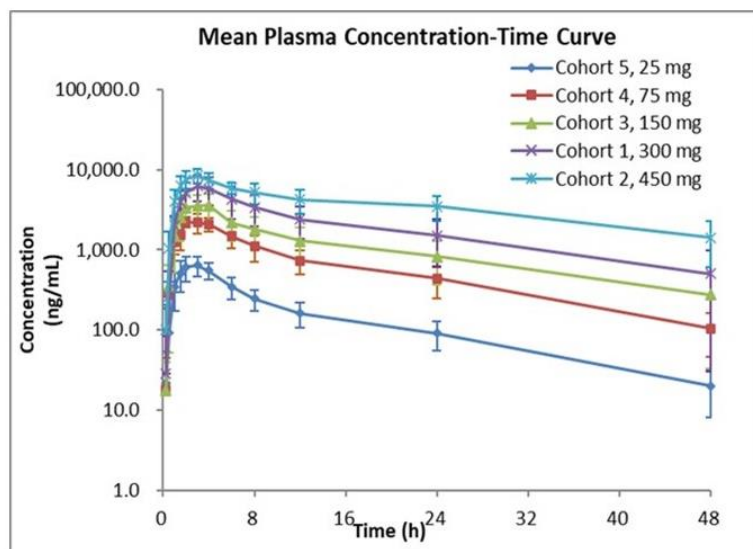
Background: Mineralocorticoid receptor (MR) activation contributes the development of cell injury and fibrosis progression in cardiovascular and renal tissues. Recently it has been reported that eplerenone, a steroidal MR antagonist, ameliorated the phenotype of nonalcoholic steatohepatitis (NASH) in several rodent models, suggesting that MR activation also plays a crucial role in the development of steatohepatitis and hepatic fibrosis. Although eplerenone has been clinically prescribed, it has a relative short biological half and drug-drug interactions with CYP3A4 inhibitors. In order to solve the issues, MT-3995 has been developed for the treatment of NASH as a highly selective and long-acting non-steroidal MR antagonist. In this study, the effect of MT-3995 on the progression of steatohepatitis and fibrosis was evaluated in choline-deficient L-amino acid-defined (CDAA) diet-fed F344 rats and trans-fat diet-fed ob/ob mice. **Methods:** The effect of MT-3995 on the progression of steatohepatitis and fibrosis was assessed by the oral administration (1, 3, and 10 mg/kg/day) for 10 weeks in CDAA diet-fed F344 rats (CDAA study), and by oral administration (3, 10, and 30 mg/kg/day) for 12 weeks in trans-fat diet-fed ob/ob mice after feeding trans-fat diet for 4 weeks (trans-fat study). As a reference substance, eplerenone (100 mg/kg/day) and obeticholic acid (10 mg/kg/day) were used in the CDAA study and trans-fat study, respectively. **Results:** In the CDAA study, the chronic treatment of MT-3995 dose-dependently decreased plasma alanine aminotransferase (ALT) levels, histological hepatic Sirius Red positive area. In the trans-fat study, histological F4/80-stained macrophage area in the liver was significantly decreased by the treatment of MT-3995. In addition, the treatment of MT-3995 in trans-fat diet-fed ob/ob mice significantly decreased plasma ALT levels and the hepatic gene expression levels of *Tnf- α* , *Mcp-1*, *Col1a1*, and *Tgfb1*, as representative genes involved in inflammation and fibrosis. **Conclusion:** We showed, for the first time, that MT-3995, a non-steroidal MR antagonist, has the beneficial effect on the development of steatohepatitis and hepatic fibrosis in rodent NASH models. MT-3995 could be a novel therapeutic approach for the treatment of NASH.

LP8: SAFETY, TOLERABILITY, AND PHARMACOKINETICS (PK) OF THE NOVEL HBV CAPSID ASSEMBLY MODULATOR ZM-H1505R IN HEALTHY SUBJECTS

Zhijun Zhang, Xiuhong Jiang, Bo Hua, Tian Xia, Gang Liu, Bo Liang and Huanming Chen, Zhimeng Biopharma

Background: Current standards of care for chronic HBV infection (CHB), which include a 48-week of subcutaneous injection of pegylated interferon or an indefinite treatment with a nucleoside/nucleotide analog HBV polymerase inhibitor, suffers from a very low cure rate. HBV capsid inhibitors belong to a new class of drug that has a potential to become a key component for future combination regimens for the treatment of CHB. ZM-H1505R is a new small-molecule HBV capsid assembly modulator with a novel pyrazole structure in development for the treatment of CHB. In PHH assay, ZM-H1505R has an EC_{50} of 12 nM in inhibiting HBV replication and an EC_{50} of 500 nM in inhibiting cccDNA formation. ZM-H1505R is active against most HBV variants that are resistant to class I or class II HBV capsid modulators. The no-observed-adverse-event-level (NOAEL) of ZM-H1505R is >1,000 mg/kg/day in rats and 300 mg/kg/day in dogs. ZM-H1505R is currently being studied in a first-in-human phase I trial to evaluate its safety, tolerability, and pharmacokinetics (PK) in healthy subjects following single and multiple ascending dose (SAD and MAD) oral administration (NCT04220801). Here we report the safety, tolerability, and pharmacokinetics of ZM-H1505R in healthy subjects after single ascending doses (Part 1). **Methods:** Study design: This is a randomized, double-blinded, placebo-controlled study. Single doses of 25, 75, 150, 300, and 450 mg of ZM-H1505R or placebo were orally administered to healthy subjects in a fasted state. Each cohort contained 8 subjects, 6 of whom received ZM-H1505R and 2 received placebo. In the case of cohort 3 (150 mg), a second dose of 150 mg was administered in the fed state after a 7-day washout period. Safety and tolerability were assessed. Pharmacokinetics analysis was conducted. **Results:** Single oral doses of 25-450 mg of ZM-H1505R were generally safe. No serious adverse events (AEs) or AEs leading to discontinuation were reported, and most AEs were Grade 1 in severity. ZM-H1505R displayed a $T_{1/2}$ of 11-18h, a linear and dose-proportional increase in plasma exposure (AUC), and a C_{24} of 162-6170 nM. High-fat food had a moderate effect on PK of ZM-H1505R, causing about 40% reduction in its plasma exposure.

Conclusion: Single doses of up to 450 mg of ZM-H1505R were safe and well tolerated in healthy subjects. The favorable safety and PK profile of ZM-H1505R supports its further evaluation in CHB patients. Evaluation of safety, tolerability, and PK characters of ZM-H1505R following multiple ascending doses in healthy subjects is ongoing (Part 2).



LP9: EFFICACY OF THE PANPPAR AGONIST LANIFIBRANOR ON THE HISTOLOGICAL ENDPOINTS NASH RESOLUTION AND FIBROSIS REGRESSION IS SIMILAR IN TYPE-2 DIABETIC AND NON-DIABETIC PATIENTS: ADDITIONAL RESULTS OF THE NATIVE PHASE 2b TRIAL IN NON-CIRRHOTIC NASH

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Background: Lanifibranor is a well-balanced agonist of the 3 PPAR isotypes with superior efficacy over single PPAR agonists in pre-clinical models of NASH and fibrosis. Lanifibranor increased HDL-cholesterol and adiponectin, while decreasing insulin resistance and triglycerides (TG), hallmarks of differential PPAR α , β/δ and γ activation in a 4-week phase 2a study in diabetic patients. Diabetic patients are at risk of more severe NASH and fibrosis and treatment response can be different compared to non-diabetics. **Methods:** We here report the results of lanifibranor in the diabetic subpopulation of the NATIVE trial, a phase 2b double-blind randomised-controlled trial of lanifibranor in patients with biopsy proven, non-cirrhrotic NASH, with a SAF activity score of 3-4. Patients were randomised 1:1:1 to receive placebo, 800 or 1200 mg of lanifibranor for 24 weeks and stratified according to diabetes status as defined by the Investigator. **Results:** Among 247 randomised and treated patients (Full Analysis Set), 103 had type 2 diabetes (T2DM): mean age 56 y, mean BMI 33.1 kg/m², 60% females, 81% F2-3 and 82% NAFLD Activity Score ≥ 6 . 83% of patients were on metformin, 22% on sulfonylureas, 29% on statins. 144 patients were non-diabetics, age 52 y, BMI 32.7 kg/m², 57 % females, 73% F2-3 and 67% NAS ≥ 6 . Results on the primary and key secondary histological endpoints are listed in the Table. The percentage of responders was similar in T2DM and non-diabetic patients and there was no interaction between treatment effect and diabetes. In the 103 T2DM patients, there was a reduction in fasting glycaemia starting at week 4 (lowest median decrease among both doses: 0.7 mmol/L) and HbA1c starting at week 14 (lowest median decrease: 0.5%) and confirmed at all different time points onwards for both doses. Similarly, median HDL-c increase was $> 8\%$ on all time points and median TG decrease was $> 20\%$ on all time points from week 4 onwards, for both lanifibranor doses. **Conclusion:** In the T2DM subpopulation of NATIVE, lanifibranor produced major improvements in key histological endpoints (including both resolution of NASH and regression of fibrosis) after 24 weeks of treatment similar to non-diabetic patients. Furthermore, clinically significant improvements in glucose and lipid metabolism were already observed after 4 weeks. Lanifibranor is hence a promising drug for NASH treatment in both non-diabetic and diabetic patients.

Treatment Group	Placebo	800 mg	1200 mg
N diabetics/non-diabetics	35/46	33/50	35/48
Histological Endpoint	Percentage of responders in diabetics/non-diabetics		
Reduction of 2 points of the SAF Activity score without worsening of fibrosis (primary endpoint)	28.6/26.1	45.5/38.0	51.4/47.9
Resolution of NASH (CRN-Inflammation = 0 or 1 and CRN-Ballooning =0) without worsening of fibrosis	14.3/21.7	33.3/32.0	42.9/45.8
Improvement of fibrosis (-1 point CRN-F) with no worsening of NASH	22.9/23.9	30.3/26.0	45.7/39.6
Resolution of NASH and improvement of fibrosis	2.9/10.9	24.2/18.0	28.6/33.3

LP10: IMPACT OF COVID-19 ON HEPATITIS C SCREENINGS IN AMBULATORY CLINICS AND EMERGENCY DEPARTMENT

Ms. Vicki Shah, PA, Hepatology, Rush University Medical Center

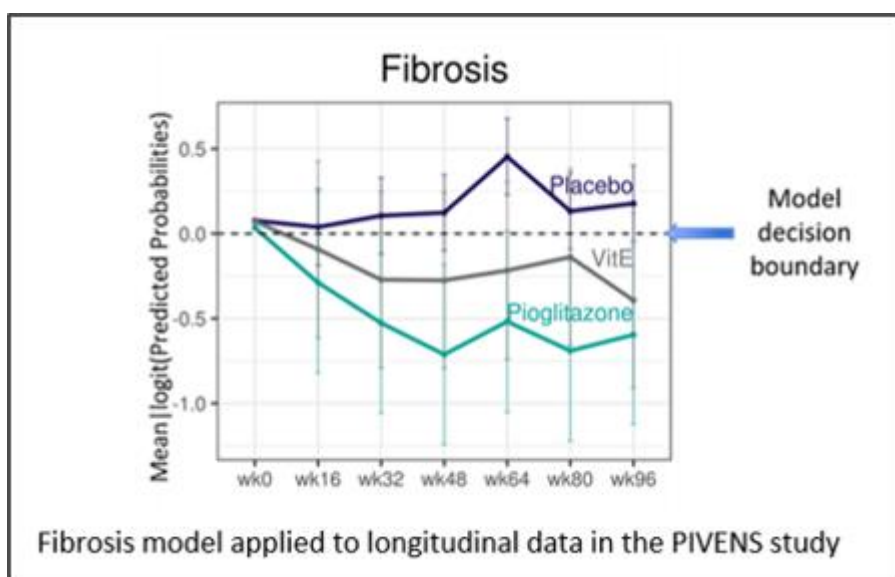
Background: With the emergence of COVID-19, healthcare systems were strained. Healthcare resources were reallocated and in many areas persons were encouraged to stay-at-home resulting in a disruption of care for other disease processes. The World Health Organization (WHO) has a goal of eliminating hepatitis C virus (HCV) by 2030. The biggest barrier to HCV elimination is identifying infected individuals and linking them to care. Both of these steps have been interrupted during this pandemic. We sought to determine the impact of the COVID-19 pandemic on HCV testing and linkage to care. **Methods:** In October 2016, a best practice advisory for HCV screening was placed in the electronic medical record (EMR) for the CDC defined birth cohort 1945-1965 without previous HCV diagnosis or prior HCV antibody testing at our institution. A retrospective review of the number of HCV screenings completed from July 2019 to July 2020 completed across all primary care clinics, obstetric and gynecology clinics, gastroenterology clinic, and the emergency department was performed. The primary outcome was to determine if there was significant impact on HCV Ab testing due to closures of outpatient clinics, redeployment of providers to COVID impacted departments, and transition to virtual visits. **Results:** From July 2019 to July 2020, 7,167 patients were tested for HCV antibodies. Of those patients, 298 tested positive for HCV antibody and 127 patients had confirmed infection by reflex to HCV RNA Quantitative. The average number of patients screened for HCV in ambulatory clinics from July 2019 to February 2020 was 431 patients per month. There was a significant drop in HCV screenings in the ambulatory setting from March 2020 to June 2020, with only 221 patients tested in March, 38 in April, 110 in May, and 231 in June. This correlated with the closures of in-person outpatient clinics during COVID-19 restrictions. The decreasing trend was not seen in the emergency department with an average of 291 patients tested per month as the overall patient census was the same or higher during the COVID-19 spring surge. **Conclusion:** There are several barriers to the identification of HCV-infected persons and the HCV care cascade. The impact of COVID-19 has added another obstacle to the elimination of hepatitis C. The number of patients screened for HCV has decreased across outpatient clinics which can ultimately lead to delay in HCV treatment with the resultant increased incidence of cirrhosis and hepatocellular carcinoma or transmission to others. At our institution, the number of patients screened in the ambulatory clinics has not yet returned to numbers seen prior to the COVID-19 pandemic. The COVID-19 pandemic has disrupted routine healthcare and instilled fear in patients concerned about exposures from seeking care at a medical center. The full impact on access to screening, treatment, and care for hepatitis C remains to be seen.

LP11: A LIQUID LIVER BIOPSY: SERUM PROTEIN PATTERNS OF LIVER STEATOSIS, INFLAMMATION, HEPATOCYTE BALLOONING AND FIBROSIS IN NAFLD AND NASH

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Background: The definitive diagnostic test for Nonalcoholic steatohepatitis (NASH) is liver biopsy, which carries risks and cannot be used for frequent monitoring. There is no single noninvasive method that can accurately and simultaneously capture steatosis, inflammation, hepatocyte ballooning and fibrosis, the four major pathologic components assessed by biopsy. Each of these is relevant to the multiple mechanisms targeted in drug in development for NASH. We show that large scale proteomics has promise as an alternative

to liver biopsies in clinical trials or longitudinal studies of NASH. **Methods:** Using modified-aptamer proteomics, we scanned ~5000 proteins in each of 2852 serum samples from the NASH CRN, including 636 participants from a natural history cohort and longitudinal samples from the PIVENS (pioglitazone, vitamin E and placebo) and the FLINT (obeticholic acid and placebo) clinical trials for a total of ~15 million protein measurements. Liver biopsy results were modeled with measured proteins using machine learning methods independently for each biopsy component in the natural history cohort and 50% of FLINT and PIVENS [half baseline, half end of study] and validated in the other 50% of FLINT and PIVENS samples not used for model training. **Results:** Results for the 4 protein models in training/validation were: fibrosis (AUC 0.92/0.85); steatosis (AUC 0.95/0.79), inflammation (AUC 0.83/0.72), and ballooning (AUC 0.87/0.83). A concurrent positive score for steatosis, inflammation and ballooning predicted the biopsy diagnosis of NASH with an accuracy of 73%. When applied longitudinally, model scores improved in the active groups vs. placebo and differential pharmacodynamic effects were evident on each model component. For example, the fibrosis model predicted a decline in fibrosis over time in the two treatment arms across the 96 week trial, while the placebo arm stayed relatively constant (Figure). **Conclusion:** Serum protein scanning is the first technique to capture four components of the liver biopsy individually and noninvasively. The four models were sufficiently sensitive and precise to characterize the time-course and extent of three drug mechanisms. Concurrent positive results from the protein models had performance characteristics of “rule-out” tests for pathologists’ diagnosis of NASH. These tests may assist in new drug development and medical intervention decisions.



LP12: IMPROVING DIAGNOSIS OF CIRRHOSIS IN PATIENTS WITH NAFLD BY COMBINING LIVER STIFFNESS MEASUREMENT BY VIBRATION-CONTROLLED TRANSIENT ELASTOGRAPHY AND ROUTINE BIOMARKERS: A GLOBAL DERIVATION AND VALIDATION STUDY

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Background: Currently available noninvasive tests, including FIB-4 and liver stiffness measurement (LSM) by VCTE (FibroScan), are highly effective in excluding cirrhosis yet their ability to rule in cirrhosis is more modest. Our objective was to develop and validate a new score (F4 score), combining LSM with routine clinical parameters to identify cirrhosis in NAFLD patients, with optimized positive predictive value (PPV) and reduced number of cases with indeterminate results. **Methods:** This multi-national, retrospective study included 7 cohorts of adults with suspected NAFLD who underwent liver biopsy (LB), LSM by VCTE, and phlebotomy in either routine clinical practice or during screening for clinical trials. The population was randomly divided into a training set (TS; 2/3 of pool), on which the best fitting logistic regression model was built, and an internal validation set (VS; 1/3 of pool), on which performance and goodness of fit of the model were assessed. An additional cohort from 8 US centers was used as an external VS (NASH CRN). Cut-offs with 85% sensitivity and 95% specificity in the TS were derived to rule out and rule in cirrhosis, respectively. **Results:** 2719 patients were included (TS, n=1434; internal VS, n=700; external VS, n=585). The optimal new F4 score combined LSM, AST/ALT ratio, platelets, gender, and presence of diabetes mellitus. Calibration plots for both the internal and external VS did not show misspecification of the model. For the diagnosis of cirrhosis, the AUCs of the F4 score in the TS, internal VS, and external VS were 0.91, 0.89, and 0.93, respectively. In the external VS, the F4 score outperformed LSM and FIB-4 in terms of AUC, percentage of patients with indeterminate results, sensitivity, and PPV to rule-in cirrhosis, while maintaining equivalent performance characteristics to exclude cirrhosis (Table). **Conclusion:** A novel noninvasive score including LSM by VCTE and routine clinical parameters improves the identification of cirrhosis among patients with NAFLD and may reduce the necessity of liver biopsy in this patient population.

	Training Set	Internal VS	External VS		
N	1434	700	585		
F4 prevalence	23%*	23%*	13%		
Test	F4 score	F4 score	FIB4	VCTE	F4 score
AUROC [95% CI]	0.91 [0.89-0.92]	0.89 [0.87-0.92]	0.83 [0.79-0.88]	0.89 [0.86-0.93]	0.93** [0.91-0.96]
Rule-out cut-off Test < 85% Se	0.25	1.39	3.25	0.25	0.25
Percentage of patients	67%	68%	56%	71%	77%
Se/Sp	0.85/0.82	0.79/0.83	0.87/0.63	0.87/0.79	0.87/0.86
NPV/PPV	0.98/0.35*	0.97/0.34 *	0.97/0.25	0.98/0.38	0.98/0.49
Indeterminate « grey » zone 85%Se < Test ≤ 95%Sp	0.25 - 0.57	1.39 - 3.25	12.1 - 23.2	0.25 - 0.57	0.25 - 0.57
Percentage of patients	17%	16%	36%	21%	13%
Rule-in cut-off Test > 95%Sp	0.57	3.25	23.2	0.57	0.57
Percentage of patients	17%	16%	8%	8%	10%
Se/Sp	0.55/0.95	0.53/0.96	0.35/0.96	0.41/0.97	0.55/0.97
NPV/PPV	0.95/0.55	0.95/0.58	0.91/0.58	0.92/0.69	0.94/0.72

* PPV and NPV were adjusted on a prevalence of F4 = 10% (Standard prevalence in liver tertiary care center)

**On external VS, F4 score AUC significantly outperforms VCTE and FIB4

LP13: IS REDEFINING NAFLD AS MAFLD MEANINGFUL?: RESULTS FROM A PROSPECTIVE, COMMUNITY-BASED COHORT FOLLOW-UP STUDY

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Background: The term “non-alcoholic fatty liver disease (NAFLD)”, which only excludes unsafe alcohol use, does not seem to wholly reflect metabolic dysfunction in fatty liver. Metabolic (dysfunction)-associated fatty liver disease “MAFLD” is a recently suggested alternative. We compared baseline anthropometric/metabolic traits, and outcomes after 7 years of follow-up in NAFLD and MAFLD.

Methods: In an ongoing, community-based, cohort study, participants (aged 35-64 years) were selected in 2007 from a suburban community in Sri Lanka, using stratified random sampling. Screening was by structured-interview, anthropometry, liver ultrasonography, and biochemical/serological tests. They were reassessed in 2014 to evaluate new onset metabolic and cardiovascular events (CVEs). NAFLD was diagnosed on ultrasound criteria for fatty liver, safe alcohol use and absence of Hepatitis B and C markers. MAFLD was diagnosed on the proposed, consensus recommendation: fatty liver with overweight/obesity, presence of diabetes mellitus or evidence of metabolic dysregulation. Baseline characteristics, and metabolic outcomes and CVEs after 7-years were compared in NAFLD and MAFLD vs healthy controls (no fatty liver, no unsafe alcohol use, no metabolic abnormalities) from the same population cohort. **Results:** Of 2985 recruited in 2007, 940 (31.5%) had NAFLD [617 (65.6%) women; mean-age 52.9 (SD-7.2) years], 990 (33.1%) had MAFLD [610 (61.6%) women; mean-age 52.8 (SD-7.4) years] and 362 (12.1%) were healthy controls. When compared to NAFLD, MAFLD captured an additional 2.9% individuals of the population (fatty liver with metabolic abnormality and/or alcohol use), and lost 1.3% (NAFLD with no obesity or metabolic abnormality). At baseline, anthropometric and metabolic traits were similar in NAFLD and MAFLD, but were

significantly worse in both groups compared to controls (Table). After 7-years, the odds of having new-onset metabolic traits were similar in NAFLD and MAFLD. The odds of having fatal/non-fatal CVEs were also similar in the two groups, but were significantly higher compared to controls, after adjusting for age, sex and respective baseline (Table). **Conclusion:** In this study, individuals with NAFLD and MAFLD had worse metabolic traits than controls at baseline, and similar outcomes after 7 years. Other than to increase the “captive” population by a small proportion (<2%), redefining NAFLD as MAFLD did not seem meaningful, and should await larger, longer-term longitudinal studies.

Table. NAFLD and MAFLD vs controls with baseline characteristics (2007) and metabolic and cardiovascular outcomes at follow-up (2014)

Prevalence in 2007	Controls (no fatty liver, DM, BMI<23, given metabolic derangement, alcohol) N = 362	NAFLD (2/3 criteria for fatty liver + without alcohol) N = 940	NAFLD vs controls P value	MAFLD (2/3 criteria for fatty liver + given metabolic abnormalities) N = 990	MAFLD vs controls P value
General obesity	0/362 (0.0%)	644/936 (68.8%)	<0.001	699/989 (70.7%)	<0.001
Central obesity	9/362 (2.5%)	792/940 (84.3%)	<0.001	850/990 (85.9%)	<0.001
DM	0/362 (0.0%)	275/939 (29.3%)	<0.001	293/989 (29.6%)	<0.001
HTN	54/362 (14.9%)	525/940 (55.9%)	<0.001	567/990 (57.3%)	<0.001
Raised TG	19/362 (5.2%)	449/940 (47.8%)	<0.001	483/990 (48.8%)	<0.001
Low HDL	50/362 (13.8%)	310/940 (33.0%)	<0.001	318/990 (32.1%)	<0.001
Outcomes in 2014	Controls N = 255	NAFLD N = 708	NAFLD vs controls [OR (95% CI)]	MAFLD N = 735	MAFLD vs controls [OR (95% CI)]
Incident general obesity	9/254 (3.5%)	53/705 (7.5%)	10.3 (4.8 – 22.3)	57/735 (7.8%)	11.5 (5.4 – 24.5)
Incident central obesity	39/254 (15.4%)	37/708 (5.2%)	3.7 (2.1 – 6.6)	44/735 (6.0%)	5.7 (3.1 – 10.3)
Incident DM	31/243 (12.8%)	203/689 (29.5%)	4.5 (3.0 – 6.9)	216/716 (30.2%)	4.7 (3.1 – 7.2)
Incident HTN	36/255 (14.1%)	109/708 (15.4%)	2.6 (1.7 – 4.1)	111/735 (15.1%)	2.7 (1.7 – 4.1)
Incident TG	68/245 (27.8%)	145/695 (20.9%)	1.5 (1.1 – 2.2)	153/723 (21.2%)	1.6 (1.1 – 2.3)
Incident low HDL	68/248 (27.4%)	246/695 (35.4%)	2.4 (1.6 – 3.7)	250/723 (34.6%)	2.5 (1.7 – 3.8)
CVD events	4/255 (1.6%)	43/708 (6.1%)	3.9 (1.4 – 11.2)	50/735 (6.8%)	4.5 (1.6 – 12.8)

LP14: ARO-AAT REDUCES SERUM AND INTRA-HEPATIC Z-AAT PROTEIN IN PIZZ ALPHA-1 ANTITRYPSIN DEFICIENT PATIENTS WITH LIVER DISEASE LEADING TO IMPROVEMENTS IN CLINICALLY RELEVANT LIVER BIOMARKERS

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Background: Homozygous PiZZ alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant genetic disorder causing pulmonary and liver disease in children and adults. Wild type alpha-1 antitrypsin (AAT) is synthesized by hepatocytes and secreted into circulation to protect the lung during inflammation by inhibition of neutrophil proteases. The mutant Z protein (Z-AAT) misfolds and is retained in the hepatocyte rather than secreted. This triggers liver injury which can lead to cirrhosis and the reduced serum activity can lead to lung injury. Intracellular proteolysis pathways are activated in the hepatocyte to reduce Z-AAT accumulation, but liver injury still results in some individuals. ARO-AAT is a hepatocyte targeted RNAi therapeutic designed to silence expression of Z-AAT mRNA leading to reduced Z-AAT protein synthesis. Herein, we report initial results from Cohort 1 in the AROAAT2002 phase 2 clinical trial. **Methods:** 4 PiZZ AATD patients with liver fibrosis were enrolled to receive open label ARO-AAT 200 mg by subcutaneous injection at Weeks 1, 4 and 16. Patients underwent liver biopsy at Screening and Week 24. Assessments include safety (e.g. AEs, labs, spirometry and DLCO), serum and intra-

hepatic Z-AAT, serum biomarkers of liver injury and fibrogenesis (e.g. ALT, GGT, Pro-C3) and transient elastography (FibroScan). **Results:** At Week 24, serum and total intra-hepatic Z-AAT decreased by 86-93% and 72-95% respectively. Three of four patients demonstrated reductions in intra-hepatic Z-AAT polymer at Week 24 with a range of 68-97%. All four patients showed reductions in ALT and GGT from baseline to Week 24 ranging from 36-66% and 43-58% respectively. Liver stiffness (FibroScan) improved in all patients, with 3 of 4 patients demonstrating >20% reductions at Week 24. Three of 4 patients demonstrated reductions in the fibrogenesis biomarker Pro-C3 ranging from 31-51% at Week 24. One SAE (EBV related myocarditis) was reported. No clinically meaningful changes in FEV1 were observed. **Conclusion:** ARO-AAT is the first investigational therapeutic to demonstrate reductions in intra-hepatic Z-AAT in humans. The associated improvement in clinically relevant biomarkers of liver disease is consistent with pre-clinical studies showing that Z-AAT accumulation is the causative factor in AATD liver disease. These data confirm that when Z-AAT synthesis is halted, endogenous proteolysis can clear accumulated Z-AAT with associated improvements in liver health.

Table 1. Relative change from baseline to week 24

Pharmacodynamic Response	Subject			
	001	003	004	005
Δ Serum Z-AAT	-92.3%	-93.1%	-86.7%	-85.8%
Total liver Z-AAT baseline*,	33.9	15.2	35.2	146
Δ nmol/total protein,	-26.6,	-14.4,	-25.4,	-107.2,
Δ %	-78.6%	-95.1%	-72.2%	-73.4%
Monomer liver Z-AAT baseline*	16.8	13.6	33.3	33.5
Δ nmol/total protein,	-15.1	-12.9	-28.9	-27.2
Δ %	-89.8%	94.9%	86.8%	81.2%
Δ Polymer liver Z-AAT*	-11.6	-1.5	3.5	-80
Δ ALT	-66.4%	-54.9%	-35.7%	-50.0%
Δ GGT	-42.6%	-43.2%	-57.7%	-55.3%
Δ FibroScan	-25.8%	-22.4%	-0.8%	-20.9%
Δ Pro-C3, ng/mL	-19.7	0.9	-6.9	-8.4

*nmol/total protein

LP15: HAPLOTYPE NUMBER AT BASELINE IS HIGHLY PREDICTIVE OF HEPATITIS B VIRUS (HBV) FUNCTIONAL CURE ON TDF ANTIVIRAL THERAPY

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Background: In chronic hepatitis HBeAg positive patients treated with Tenofovir (Gilead GS-US-174-0103 study), 78/147 (genotype A, B, C, and D) patients (53%) became hepatitis B e antigen (HBeAg) negative by week 228 and 13/40 (32.5%) genotype A2 patients and 5/32 (15.6%) genotype D1 patients exhibited hepatitis B surface antigen (HBsAg) loss by week 192. We investigated if haplotype number (HN) in individual patients was predictive of HBsAg loss in the same setting. **Methods:** In chronic hepatitis HBeAg positive patients treated with Tenofovir (Gilead GS-US-174-0103 study), 78/147 (genotype A, B, C, and D) patients (53%) became hepatitis B e antigen (HBeAg) negative by week 228 and 13/40 (32.5%) genotype A2 patients and 5/32 (15.6%) genotype D1 patients exhibited hepatitis B surface antigen (HBsAg) loss by week 192. We investigated if haplotype number (HN) in individual patients was predictive of HBsAg loss in the

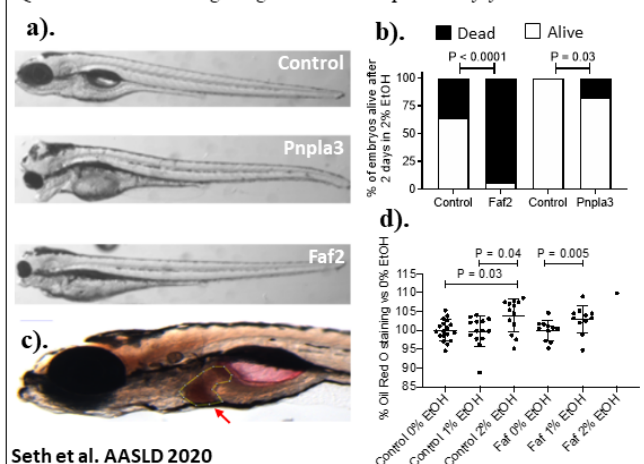
same setting. **Results:** MLR analysis using single factors (number of haplotypes (HN), HBsAg and HBeAg titres, viral load (VL), age, ALT level, and BCP variants A1762T & G1764A) showed that HN (25th centile range, 1 or 2 haplotypes) was the single best dichotomous clinical predictor of HBsAg loss following treatment at baseline. Patients within one or two haplotypes had a 28-fold and a 32-fold higher odds ratio of losing HBsAg in A2 and D1 genotype patients, respectively. The predictive AUC value was 0.81 ($P = 0.0017$) for genotype A2 and 0.84 ($P = 0.0158$) for genotype D1. The addition of HBsAg or HBeAg titres to the dichotomous HN category in the MLR modelling increased the odds ratio for HBsAg loss in genotype A2 patients from 28 to 39 ($p = 0.00633$), and from 28 to 48 ($p = 0.00102$) respectively. **Conclusion:** In conclusion, haplotype number at baseline was strongly predictive of HBsAg loss on TDF treatment. This finding suggests HBV full genome deep sequencing prior to the initiation of TDF therapy, may identify patients who are likely to achieve functional cure (HBsAg loss) without additional therapeutic interventions and warrants further validation in additional datasets.

LP16: NOVEL FAF2 ASSOCIATED WITH RISK OF CIRRHOSIS IN HIGH-RISK DRINKERS: GROWING EVIDENCE OF LIPID GENETICS IN ALCOHOL-RELATED LIVER INJURY USING ZEBRAFISH MODEL

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Background: Recent literature reveals several single nucleotide polymorphisms (SNPs), that alter the risk of alcohol-related cirrhosis (AC). Many of these SNPs are located in genes involved in lipid droplet/biology. Our multinational GenomALC Consortium performed genome-wide association study (GWAS) in heavy chronic drinkers ($\geq 80g$ (men)/ $50g$ (women) of alcohol/day for ≥ 10 years) with alcohol-related cirrhosis (cases) and equivalent alcohol exposure but no evidence of liver disease (controls), and meta-GWAS in GenomALC, UK Biobank and summary data from published study (Buch et al *Nat Genet* 2015). We identified a new protective association for AC at rs374702773 in *Fas Associated Factor family member 2* (FAF2, del(T) allele) ($OR=0.61$, $p\text{-value}=2.56 \times 10^{-8}$) using conditional analysis accounting for the *PNPLA3* and *HSD17B13* loci in GenomALC (Schwantes-An et al, *Hepatology* 2020). Meta-analysis confirmed genome-wide significance for the newly identified FAF2 locus, as well as *PNPLA3*, *HSD17B13*, *SERPINA1* and *SUGP1/TM6SF2*. Gene enrichment analysis using top 15 significant genes showed a significant enrichment for lipid droplet organization (>100 -fold, $FDR=3.42 \times 10^{-3}$). GeneOntology pathway analysis identified lipid droplets as the target for several identified genes, implicating lipid droplets in the biological pathway(s) underlying AC. Our findings add to the growing evidence of lipid genetics in AC. **Methods:** *In vivo* zebrafish model of acute alcohol-induced liver injury (1-2% alcohol in water, 24 hours) was established. Zebrafish was used as liver development and function are well conserved between humans and zebrafish, especially for studying fatty liver diseases. Using Crispr-Cas9 genome editing, available orthologs of novel and known genes (*faf2*, *pnpla3*) were depleted in 5-day post fertilization (dpf) zebrafish embryos. Embryo morphology, oil red O staining, survival and imaging were investigated. **Results:** Alcohol exposure induced significant lipid accumulation in the livers of zebrafish. Knockdown using orthologs of novel and known genes (*faf2*, *pnpla3*) increased susceptibility to acute alcohol toxicity by increasing lipid deposits and reduced survival following high dose alcohol exposure (Figure 1). **Conclusion:** The new locus at FAF2 associated with reduced risk of AC in heavy drinkers is involved in lipid biology. Functional studies in the zebrafish implicate *faf2* role in steatosis.

Figure 1. Zebrafish model of alcohol-induced liver injury to study lipid biology. a). Embryo morphology of F0 Crispr-Cas9 generated *pnp1a3* and *faf2* mutants. b). Survival of F0 mutants following exposure to high dose 2% alcohol. c). Oil Red O staining of 6dpf embryo and d). Quantification following range of alcohol exposure in *faf2* mutants.



LP17: TRANSCRIPTIONAL LANDSCAPE OF HEPATOCELLULAR CARCINOMA REVEALS THAT PATIENT ANCESTRY INFLUENCES PATTERNS OF EXPRESSION

Rachel Zayas, Research and Development, Aged Diagnostics

Background: The global incidence of hepatocellular carcinoma (HCC) has increased threefold in the last 30 years. In the United States, individuals with ancestry from Asia and sub-Saharan Africa have a significantly higher risk of developing HCC. However, the molecular mechanisms by which HCC disparities occurs remain largely unknown. **Methods:** We applied advanced bioinformatics analysis tools towards the identification of genomic drivers of HCC disparities in patients of distinct ancestries (geographic origins). We used samples of resected liver tissue data from the TCGA, and open-source software tools HiSTAT, StringTie, and Ballgown to map next generation sequencing (NGS) reads from both DNA and RNA, assemble transcripts, and quantify gene abundance. We then mapped differential genes/transcripts to known biomarkers and targets of systemic HCC therapeutics. **Results:** We found 4 overlapping transcripts between each ancestry group: FCN2, FCN3, COLEC10, and GDF2. However, we also found that multiple genes are expressed in an ancestry-specific manner. Our models also revealed that both current and emerging biomarkers fail to capture heterogeneity between patients of different origins. Finally, we have determined that first-line treatment, such as Sorafenib, may be better suited for Asian patients, while Lenvatinib may exhibit better efficacy for Caucasian patients. **Conclusion:** In conclusion, we have outlined that the pathways involved in early hepatocarcinogenesis may occur in an ancestry-specific manner and that these distinct phenotypes should be taken into account during biomarker development.

LP18: CM-101 DEMONSTRATES REDUCTION IN SERUM FIBROTIC BIOMARKERS IN A PHASE 1b RANDOMIZED, CONTROLLED MULTIPLE DOSE TRIAL IN NAFLD PATIENTS

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Background: CCL24 is a chemokine involved in liver inflammation and fibrosis. Blocking CCL24 attenuates liver fibroblast activation in vitro and fibrosis in animal models. Therefore, CCL24 is a potential candidate as an anti-fibrotic therapeutic target. CM-101, a novel fully humanized CCL24 blocking monoclonal antibody alleviated animal liver fibrosis and was well tolerable in humans. **Methods:** This controlled randomized single-center Phase 1b trial assessed safety, tolerability, PK and exploratory pharmacodynamics of multiple CM-101 administrations in 16 NAFLD patients with normal liver enzymes. Patients received five CM-101 treatments (every 3 weeks), either

IV 2.5mg/kg (6 vs. 2 matching placebo cases) or SC 5mg/kg (6 vs. 2) and had a post treatment follow-up of 42 days. **Results:** The mean age was 49.5±10.8 years (56% males) with similar demographics and laboratory parameters in study groups. CM-101 was well tolerated in both doses; without death or severe adverse events (SAE). One non-drug related SAE reported in the SC dose group (meningioma) that led to early patient discontinuations. Mild to moderate drug related AE's were reported; lacking injection site reactions. Following CM-101 treatment, percent reductions of fibrotic biomarkers from baseline was noted, Pro-C3 -4.5%, Pro-C4 -11.8%, PIIINP -4.7%, TIMP1 -10.5% and TIMP2 -4.4%. Placebo patients demonstrated 0.7, 0.14, 5.0, 8.2 and 9.3 mean percent increase from baseline, respectively. These changes were accompanied by improvement in liver stiffness measured by FibroScan™. **Conclusion:** 12 weeks treatment with CM-101 was safe and well tolerated. Although low disease burden patients recruited, repeated CM-101 administration showed early signals of anti-fibrotic activity by serum biomarkers and elastography. These advantages support CM-101 anti-fibrotic activity mediated by CCL24 blockage. Further analysis of CM-101 anti-fibrotic effect will be provided at the meeting. Further studies in PSC and NASH are planned.

LP19: LONG-TERM EFFICACY AND SAFETY OF ODEVIXIBAT, AN ILEAL BILE ACID TRANSPORTER INHIBITOR IN CHILDREN WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: INTERIM RESULTS FROM PEDFIC 2, AN OPEN-LABEL PHASE 3 TRIAL

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Background: PEDFIC 2 (P2) is an ongoing, phase 3, open-label extension study evaluating long-term efficacy and safety of odevixibat in patients with progressive familial intrahepatic cholestasis (PFIC). **Methods:** Patients with genetically confirmed PFIC, elevated serum bile acids (sBAs), and history of significant pruritus were treated with odevixibat 120 µg/kg/day. There are 3 groups described here: patients with PFIC1 or 2 who were treated with odevixibat in the 24-week PEDFIC 1 (P1) study (n=34), defined as "P1O"; those treated with placebo in P1 (n=19); and new patients enrolled in P2 with any form of PFIC (n=16). These latter 2 groups were combined and are defined as "treatment naïve" (TN). This interim analysis includes data to July 15, 2020 and focuses on data collected after 24 weeks of treatment in P2. Key efficacy measures were change in pruritus over time using the PRUcision instrument, change in sBAs, growth, hepatic parameters, and safety. **Results:** Sixty nine patients were analyzed (mean age: 5.3 y; PFIC1: 26.1%; PFIC2: 65.2%; PFIC3: 7.2%; other [1 patient with MYO5B variant]: 1.4%). sBAs (µmol/L) dropped from 251.8 to 85.1 (P1 baseline to P2 week 24; $P<0.0001$) for P1O (48 weeks for most patients) and from 248.3 to 173.6 for TN over the course of P2 (Table). Monthly pruritus scores dropped from 3.0 to 1.4 ($P<0.0001$) for P1O and from 2.8 to 1.8 for TN. Height Z scores improved from -1.6 to -0.5 and -2.0 to -1.6 for P1O and TN, respectively. Weight Z scores in P1O normalized over 48 weeks (-0.9 to 0.2). Similar treatment effects were observed across all PFIC subtypes examined. Odevixibat was well tolerated, with diarrhea occurring in 10.1%. Most treatment-emergent adverse events (TEAEs) were mild to moderate; 2 patients discontinued due to TEAEs (1 patient with cholestasis; 1 with pruritus, splenomegaly, hypophagia, weight decreased, and jaundice). No deaths or drug-related serious AEs were reported. **Conclusion:** Data from this ongoing, long-term study demonstrate the continued effect of odevixibat over 48 weeks on key parameters like sBA, pruritus, growth, and hepatic parameters. Importantly, average sBAs in patients treated for 48 weeks fell below the published NAPPED threshold for PFIC2 disease modification, and efficacy was seen across all PFIC subtypes studied, with an acceptable safety and tolerability profile. Therefore, odevixibat has the potential to provide long-term treatment benefits in patients with PFIC.

Mean Data	PEDFIC 1 Baseline	PEDFIC 2 Baseline	PEDFIC 2 Week 24
Serum bile acids (μmol/L)			
P1O	251.8	127.4	85.1
TN		248.3	173.6
Pruritus scores (average of AM and PM scores)			
P1O	3.0	2.0	1.4
TN		2.8	1.8
Height Z score			
P1O	-1.6	-1.5	-0.5
TN		-2.0	-1.6
Weight Z score			
P1O	-0.9	-0.7	0.2
TN		-1.2	-0.9
Serum alanine aminotransferase (U/L)			
P1O	114.5	73.9	53.8
TN		70.6	81.6
Total serum bilirubin (mg/dL)			
P1O	3.1	1.7	0.9
TN		2.8	2.0

P1O, PEDFIC 2 participants who received odevixibat (combined 120 and 40 μg/kg/day dose groups) in the preceding PEDFIC 1 study (n=34). TN, PEDFIC 2 participants who received placebo in the preceding PEDFIC 1 study (n=19) plus patients enrolled in PEDFIC 2 cohort 2 (n=16).

LP20: Hsd17b13 DEFICIENCY PROTECTS MICE FROM ADVANCED HEPATIC FIBROSIS

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Background: Loss-of-function variants in 17-beta hydroxysteroid dehydrogenase 13 (HSD17B13) are genetically associated with decreased severity and fibrosis in NASH and alcohol-associated liver disease. Several antisense oligonucleotide approaches are being developed as therapies, despite no experimental evidence to date to support a causal role for HSD17B13. In fact, a mouse model of Hsd17b13 knockout did not show any protection using several obesogenic diets, although these conditions induce mild fibrosis at most. The aim of this study was to test the role of HSD17B13 in an in vivo model that mimics advanced human NASH-like hepatic fibrosis.

Methods: Hsd17b13 whole-body knockout (KO, n=13) male mice and wild-type littermate controls (WT, n=14) were fed choline-deficient, L-amino acid-defined, high-fat diet (CDAA-HFD) for 12 weeks. Hepatic histology and the liver lipidome were analyzed at sacrifice.

Results: KO mice had significantly higher body weight throughout the feeding period compared to WT (p<0.05), and 24% higher fat mass at sacrifice (p=0.005). There was no difference in liver weight or liver enzyme levels. CDAA-HFD induced marked histological hepatic steatosis and inflammation in both genotypes, with significantly greater steatosis in KO (p<0.0001). Marked fibrosis induced by CDAA-HFD was significantly decreased in KO, as demonstrated by sirius red staining (p=0.046) and collagen content quantification (33% decrease, p=0.003). Consistently, hepatic expression of fibrosis-related genes (Col1a1 and Col1a2) was significantly decreased in KO mice. Liver lipidomics revealed a distinct profile; consistent with the histological findings, KO mice had significantly elevated triglycerides and diglycerides with a concomitant decrease in several bioactive lipid species. **Conclusion:** We show for the first time that Hsd17b13 deficiency can protect mice from diet-induced fibrosis, possibly by modulating hepatic lipid composition. In line with the validated human genetic findings, we have provided the first experimental evidence to support ongoing development of HSD17B13-directed therapies.

LP21: HEPATOCYTE TARGETED THERAPY TO ENHANCE EFFICACY AND SAFETY OF DRUGS FOR LIVER DISEASES

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Background: Hepatocytes are the major liver cell-types predominantly implicated in many liver disorders including NASH. Although many drugs administered systemically accumulate in the liver, the delivery to hepatocytes is hampered by their rapid sequestration by macrophages and Kupffer cells making uptake and retention in hepatocytes a challenge. To overcome this challenge, we developed a novel hepatocyte targeted hydroxyl dendrimer (htHD) therapeutic to enable selective targeting of farnesoid X receptor agonists (FXRa) to hepatocytes through the asialoglycoprotein receptor (ASGP-R) mediated uptake after systemic administration, enhancing the drug

efficacy and reducing the dose and off-site toxicity. **Methods:** Cy5 labelled htHD and htHD-FXRa were synthesized and characterized. Binding and uptake were studied *in vitro* in human hepatocytes (HepG2) culture. *In vivo* hepatocyte targeting and uptake was evaluated using immunofluorescence confocal microscopy. *In vivo* efficacy of htHD-FXRa was evaluated in mice with a NASH (STAM™) model. Upon development of fatty liver disease (6 weeks), the mice were randomized into 4 groups of 8 mice and treated for 3 weeks (G1: saline QOD IP; G2: free FXRa (30 mg/kg) daily PO; G3: htHD-FXRa low dose (FXRa: 6 mg/kg), QOD IP; and G4: htHD-FXR agonist - high dose (FXRa: 30 mg/kg) QOD IP). Mice were sacrificed and the efficacy was evaluated using histology (NAFLD activity score, fibrosis area, liver ballooning) and biochemistry (ALT and liver triglyceride levels from blood). htHD-Cy5 was administered at 6 weeks or 9 weeks as a single administration and mice will be sacrificed 24 hr later for evaluation of hepatocyte targeting. **Results:** *In vitro* studies demonstrate binding and uptake via ASGP-R mediated endocytosis in human hepatocytes. Confocal imaging of mice liver tissues demonstrates that systemic htHDs target and are internalized by hepatocytes via ASGP-R. Immunohistochemistry analysis of liver tissues demonstrates that htHD-FXRa therapy decreases NAFLD score, liver fibrosis and hepatocyte ballooning significantly compared to free FXRa and vehicle control ($p < 0.05$, $n=8$). Low dose htHD-FXRa treatment showed significant reduction in stenosis score whereas high dose demonstrates improved reduction in fibrosis score compared to free FXRa group. Biochemical analysis suggests that htHD-FXRa treatment may improve liver function. **Conclusion:** Selective targeting of FXRa to hepatocytes improves functional outcomes in a NASH model. This targeted approach may significantly reduce systemic off-target toxicity observed with current FXRa compounds. Previous studies with HDs demonstrated a sustained localization within the target cells for up to 1 month. Future studies will evaluate the potential for htHD-FXRa therapy as infrequently as once per month and investigate oral administration. Overall, the htHD approach provides a platform for developing a wide range of drugs to treat liver diseases.

LP22: PROPORTION AND DETERMINANTS OF HCV REINFECTION DETECTED AT INCARCERATION AMONG PEOPLE IN PRISONS FROM CATALONIA, SPAIN. SUBANALYSIS OF THE RE-HCV STUDY

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Background: Since 2015, over 1000 people with hepatitis C in Catalan prisons have been treated with direct-acting antivirals and >95% obtained a sustained virological response (SVR). However, some got reinfected and infected others, which is an obstacle to HCV elimination. We aimed to assess how many cases of viremic HCV infection at incarceration were due to reinfection and to identify its determinants. **Methods:** Re-HCV is a prospective study of HCV infection and reinfection in the eight Catalan prisons. Data from a cohort of people with detectable HCV-RNA at incarceration (January 2019 to August 2020) is presented. Socio-demographic, clinical, therapeutic data was collected. An epidemiological questionnaire was filled by participants regarding drug consumption and sexual practices inside and outside prison. Proportions were compared between reinfected and non-reinfected cases, and determinants of reinfection were identified by multivariate logistic regression analysis. HCV isolates from prisons were sequenced and phylogenetically analysed for epidemiological relatedness with those from harm reduction centers (HepC detect II study). **Results:** Among the 14,776 people entering prison and tested for HCV-RNA, 307(2.1%) were viremic and 294 (95.8%) accepted to participate in the study; 37 (12.6%) of them were classified as reinfections. HIV coinfection and homelessness were more frequent in those reinfected (50.0% vs 29.7%, $p=0.051$; and 38.5% vs 12.1%, $p<0.01$, respectively). Drug consumption practices inside the prison significantly related to reinfection were: a) intravenous drug use (48.0% vs 27.9%, $p=0.058$) and b) sharing of needles (60.0% vs 28.8%, $p=0.023$); and those outside the prison were: a) sharing of syringes (65.4% vs 41.3%, $p=0.019$), b) sharing of needles (61.5% vs 40.3%; $p=0.036$) c) sharing of pre-prepared drugs (69.2% vs 49.8%, $p=0.045$), and d) practicing front-backloading (50.0% vs 29.1%, $p=0.043$). Multivariate analysis confirmed the independent predictive value of sharing needles in prison (OR=3.3, 95% CI: 1.03-10.58). Evidence of epidemiological relatedness between certain HCV isolates from prisons and harm reduction centers was found. **Conclusion:** Reinfection is common in people entering Catalan prisons, and is mostly associated with sharing needles in prison during previous imprisonments. In order to avoid the potential spread of HCV infection within prisons and achieve microelimination in this setting, it is necessary to strengthen harm reduction programs inside and outside prisons.

LP23: RESOLVE-IT PHASE 3 TRIAL OF ELAFIBRANOR IN NASH: FINAL RESULTS OF THE WEEK 72 INTERIM SURROGATE EFFICACY ANALYSIS

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Background: NASH is a major cause of liver related mortality for which there are no approved drugs. A phase 2B trial of a PPAR α/δ agonist elafibranor (Ela) showed histological improvement in those with NASH, high disease activity and F2/3 fibrosis. We here report the interim results of the Phase 3 RESOLVE-IT trial of Ela in this population. **Methods:** In this multicenter, randomized, double-blind, placebo (Pbo)-controlled study, adult patients with NASH, non-alcoholic fatty liver disease activity score (NAS) ≥ 4 and fibrosis stages F1–F3, were randomized (2:1) to receive Ela 120 mg/day or Pbo. The primary endpoint for the planned surrogate efficacy analysis at week 72 was NASH resolution without worsening of fibrosis in patients with F2/3. Other histological and biochemical markers of NASH and fibrosis and safety were also evaluated. **Results:** Surrogate efficacy was assessed in 1070 patients [Ela n=717, Pbo n=353; mean age 55; 50% with type 2 diabetes (T2D); 61% male]. The primary endpoint assessed by intention to treat was not met. 138 (19.2%) patients in the Ela group and 52 (14.7%) patients in the Pbo group achieved resolution of NASH without worsening of fibrosis ($p=0.066$). The estimate of the between treatment groups difference in response rates was 4.3% (99% CI: -1.7, 10.4%). Sensitivity and other analyses of NASH histological features did not significantly modify the overall results. The response rates for the key secondary endpoint, fibrosis improvement of ≥ 1 stage, were 24.5% and 22.4% for patients who received Ela and Pbo, respectively (N.S.). There were no significant changes in insulin resistance or glucose parameters, but a significant difference was achieved for reduction in non HDL-cholesterol and triglycerides, as well as for the hepatic markers ALT, GGT, but not for AST (Table 1). There was significant reduction in inflammatory markers haptoglobin and fibrinogen. There was no significant difference in liver stiffness measured by VCTE. No significant histological benefit was shown in pre-specified sub-populations, but favorable trends were observed for T2D, NAS ≥ 6 and HbA1c $>6.0\%$. Treatment with Ela was generally well tolerated. **Conclusion:** Ela 120 mg daily for 72 weeks did not achieve resolution of NASH without worsening of fibrosis in adult patients with NASH and significant fibrosis. Despite absence of safety signals, the RESOLVE-IT trial was discontinued due to the limited effect of Ela on surrogate efficacy endpoints.

	Elafibranor-120 mg (N=717)		Placebo (N=353)		Treatment effect vs Pbo LSmean (95%CI)	Raw P Value*
	Baseline Mean (SD)	Change W72 vs Baseline LSmean (95%CI)	Baseline Mean (SD)	Change W72 vs Baseline LSmean (95%CI)		
ALT (U/L)	71.2 (48.2)	-14.9 (-17.6, -12.2)	70.0 (49.2)	-6.2 (-10.0, -2.4)	-8.7 (-13.3, -4.1)	<0.001
AST (U/L)	51.5 (31.8)	-3.9 (-5.8, -1.9)	50.0 (29.6)	-2.8 (-5.6, 0.0)	-1.1 (-4.5, 2.4)	0.544
GGT (U/L)	88.0 (104.6)	-24.4 (-28.5, -20.4)	73.4 (69.0)	-1.7 (-7.4, 4.0)	-22.7 (-29.7, -15.8)	<0.001
HbA1C (%) –Diabetic	6.96 (1.07)	0.03 (-0.19, 0.25)	7.06 (1.14)	-0.01 (-0.24, 0.23)	0.03 (-0.14, 0.20)	0.702
HOMA-IR –non diabetic	8.85 (11.09)	-0.79 (-2.98, 1.40)	9.47 (15.77)	-0.93 (-3.35, 1.49)	0.14 (-1.71, 1.99)	0.881
Triglycerides (mg/dL)	188 (123)	-42 (-48, -35)	200 (240)	-13 (-22, -4)	-28 (-39, -17)	<0.001
Non-HDL Chol (mg/dL)	140 (46)	-17 (-19, -15)	138 (46)	-10 (-14, -8)	-7 (-10, -3)	<0.001
LDL-Chol (mg/dL)	104 (39)	-10 (-11, -8)	101 (36)	-9 (-11, -6)	-1 (-4, 2)	0.412
HDL-Chol (mg/dL)	47 (14)	-2 (-2, -1)	46 (12)	-2 (-3, -1)	1 (-0.0, 2)	0.188
Fibrinogen (mg/dL)	383 (106)	-30 (-36, -24)	382 (100)	0 (-8, 9)	-30 (-40, -20)	<0.001
Haptoglobin (mg/dL)	133.5 (60.6)	-13.5 (-16.1, -10.9)	131.9 (59.9)	3.5 (-0.2, 7.2)	-17.0 (-21.5, -12.5)	<0.001
* Data analyzed using a repeated measures analysis of covariance (ANCOVA) model with fixed terms for treatment, type 2 diabetes (yes, no), gender (male, female), fibrosis stage (F2, F3), baseline endpoint specific value, time-point and treatment by time-point interaction. P values not corrected for multiple testing.						
	Baseline Median (min, max)	Change W72 vs Baseline Median (min, max)	Baseline Median (min, max)	Change W72 vs Baseline Median (min, max)	Treatment effect vs Pbo Estimate (95%CI)	Raw P Value**
Liver Stiffness (kPa)	9.7 (2, 75)	-0.4 (-62, 59)	9.9 (0, 72)	-0.4 (-49, 45)	-0.14 (-0.91, 0.62)	0.608
**Data analyzed using a non parametric analysis of covariance with fixed terms for treatment, type 2 diabetes, gender, fibrosis stage and baseline Fibroscan measurement. P values not corrected for multiple testing.						

LP24: NONINVASIVE TESTS FOR DETECTION OF BIOPSY-PROVEN CIRRHOSIS IN CHRONIC HEPATITIS D INFECTED PATIENTS ARE SUBOPTIMAL

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Background: Non-invasive tests for assessment of liver fibrosis have largely replaced liver biopsy for disease staging in several chronic liver diseases. However, the utility of these tests in chronic Hepatitis Delta Virus (HDV) infection has not yet been established. The aim of the present analysis was to evaluate and compare the diagnostic accuracy of liver stiffness and serum-based markers for diagnosis of biopsy proven cirrhosis in HDV. **Methods:** We prospectively evaluated a cohort of 100 patients who enrolled in the on-going Phase 3 HDV D-LIVR trial (NCT03719313). At baseline, liver stiffness measurement (LSM) and/or FibroTest® were performed, and alanine aminotransferase (ALT), aspartate aminotransferase (AST) and platelet counts were obtained and used for calculation of AST to ALT ratio (AAR), AST to platelet ratio index (APRI) and Fibrosis-4 index (FIB-4). All patients underwent percutaneous liver biopsy within 45 days from non-invasive testing. Sensitivity, specificity, positive and negative predictive values for detection of cirrhosis were calculated based on cut-offs predefined in the literature. Receiver operator curve (ROC) analysis was employed for evaluation of the discriminant

capacity of the different tests for diagnosis of cirrhosis. **Results:** The majority of patients were male (66%), median age of 45.6 (19-69) with 36% cirrhotic proven by biopsy. Mean baseline values included ALT 110 U/L (27-500), AST 79 U/L (20-429) and platelet counts $175 \times 10^9/L$ (79-493). The sensitivity and negative predictive values for detection of cirrhosis were 48.4 and 77.5% for FibroTest®, 45% and 70% for LSM, 38% and 73.8% for FIB-4, 76.5% and 80.0% for APRI and 11.8 and 67.7% for AAR, respectively. Correct classification of cirrhotics vs non-cirrhotics was best achieved by FibroTest® (74.5%), followed by FIB-4 (72%), AAR (67%), APRI (58%) and LSM (54%). Area under the ROC was highest for FIB-4 (0.74, Standard error [S.E], 0.05), followed by FibroTest® (0.73, S.E 0.06), LSM (0.71, S.E 0.06), APRI (0.69, S.E 0.06) and AAR (0.67, S.E 0.06). No statistical significance was found between ROCs for the different tests.

Conclusion: Accuracy of commercial and routine lab-based non-invasive tests for diagnosis of cirrhosis in HDV is suboptimal. Liver biopsy is currently the most reliable method for detection of cirrhosis in this population.

Non-invasive Test	Cutoffs for Cirrhosis	Subjects with Cirrhosis n (%)	Subjects without Cirrhosis n (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	Correctly Classified n (%)
Fibrotest	> 0.74	15/31 (48.4)	8/63 (12.7)	48.4 (30.2 - 66.9)	87.3 (76.5 - 94.4)	65.22 (42.73, 83.62)	77.46 (66.00, 86.54)	70/94 (74.5)
	≤ 0.74	16/31 (51.6)	55/63 (87.3)					
Fibroscan	>13 kPa	14/31 (45.2)	10/50 (20.0)	45.2 (27.3 - 64.0)	80.0 (66.3 - 90.0)	58.33 (36.64, 77.89)	70.18 (56.60, 81.57)	54/81 (66.7)
	≤ 13 kPa	17/31 (54.8)	40/50 (80.0)					
APRI (AST to platelet ratio index)	> 1	26/34 (76.5)	34/66 (51.5)	76.5 (58.8 - 89.3)	48.5 (36.0 - 61.1)	43.33 (30.59, 56.76)	80.00 (64.35, 90.95)	58/100 (58.0)
	≤ 1	8/34 (23.5)	32/66 (48.5)					
FIB-4	> 3.25	13/34 (38.2)	7/66 (10.6)	38.2 (22.2 - 56.4)	89.4 (79.4 - 95.6)	65.00 (40.78, 84.61)	73.75 (62.71, 82.96)	72/100 (72.0)
	≤ 3.25	21/34 (61.8)	59/66 (89.4)					
AAR (AST to ALT ratio)	> 1	4/34 (11.8)	3/66 (4.5)	11.8 (3.3 - 27.5)	95.5 (87.3 - 99.1)	57.14 (18.41, 90.10)	67.74 (57.25, 77.07)	67/100 (67.0)
	≤ 1	30/34 (88.2)	63/66 (95.5)					

LP25: DCD IN PEDIATRIC TRANSPLANTATION: KING'S COLLEGE HOSPITAL 20 YEARS EXPERIENCE

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Background: Liver grafts from donation after circulatory death donors are increasingly accepted as extension of the organ pool for transplant. There is little data on the outcome of liver transplant with DCD grafts in children. The objective of this study was to assess the outcome of pediatric liver transplantation with DCD grafts compared to DBD donors. **Methods:** Liver transplants performed in recipients <16 years were included. Patient and graft survival and complication rates were compared between DCD and DBD recipients. **Results:** Between 2001 and 2018, 677 liver transplants were performed in children. Of these, 118 patients with a minimum follow-up of 24 months were selected: 44 DCD and 74 DBD. The median follow-up was 93 months (2–219 months) for the DCD group and 103 months (0.1–232 months) for DBD. The median DWIT of DCD grafts was 23 minutes (8–43 minutes). DCD recipients received more organs from pediatric donors age <16 years ($p=0.032$), and were more likely to receive whole grafts (64%) while DBD recipients were transplanted predominantly with LLS (73%, $p=0.0002$). The total cold ischemia time was lower for DCD compared to DBD, and DCD grafts had higher AST levels postoperatively compared to DCD which had higher bilirubin. All other variables were comparable between the 2 groups. Patient survival rate was similar for recipients of DCD and DBD grafts at 6-months (93.1% DCD, 93.2% DBD). At 5- and 10-years DCD outcomes were better than DBD ($p=0.0016$). Graft survival rate was 91% at 1-year in DCD, compared to 93% in the DBD. At 10-years, graft survival was 89% in recipients of DCD versus 85% in DBD ($p=0.015$). Graft loss occurred in 4/44 (10%) recipients of DCD grafts and in 10/74 (13.5%) recipients of DBD grafts. In DCD recipients 1 case of graft failure occurred within 3 months due to hepatic artery thrombosis, another developed late HAT, 1 patient had cholangiopathy and the fourth had graft dysfunction. All 4 patients underwent retransplantation and they are all still alive. In the DCD group, the DWIT exceeded 30 minutes in 4 patients and half of these lost their grafts. The rate of complications within the first year after transplantation was not different between the 2 groups. PNF did not occur in either groups in this series. Arterial thrombosis occurred in 2/44 (4.5%) of DCD grafts and 5/74 (6.7%) of DBD grafts. DBD recipients had higher rate of PTLT and de novo AIH. The rate of retransplantation was lower in the DCD group (9.1% vs 13.5%). 3/44 (6.8%) recipients of DCD grafts and 13/74 (17.6%) DBD recipients died. **Conclusion:** DCD grafts transplanted in children showed excellent graft and

patient outcomes in the long term with a low incidence of complications. Careful donor selection and short donor WIT(<30 minutes) and CIT are important considerations in utilizing DCD grafts for children. This data confirms that liver reduction with DCD grafts is feasible and associated with good longterm outcomes. Splitting should be considered if CIT for both grafts can be kept <8hours.

LP26: ASSESSMENT OF THE MECHANISM FOR REMDESIVIR-ASSOCIATED CLINICAL ALT ELEVATIONS USING DILISYM QUANTITATIVE SYSTEMS TOXICOLOGY MODELING

Dr. Kyunghye Yang¹, Dr. Brett A. Howell¹, Joy Feng², Darius Babusis², Tomas Cihlar² and Dr. Scott Q. Siler¹, (1)Dilysym Services Inc., (2)Gilead

Background: Remdesivir (RDV), a monophosphoramidate prodrug of a nucleoside analog, has been granted Emergency Use Authorization for the treatment of hospitalized COVID-19 patients. In a Ph1 clinical study in healthy volunteers treated with the 150 mg daily dose of RDV for 7 or 14 days (higher than the current clinical dose), reversible low grade elevations of serum ALT and AST were observed at 5-25 days after the first dose in 8 out of 16 individuals. The underlying potential mechanisms of observed liver signals were investigated leveraging DILIsym®, a quantitative systems toxicology (QST) modeling platform. **Methods:** A physiologically-based pharmacokinetic (PBPK) model of RDV and its metabolites (i.e., GS-441524 and phosphorylated metabolites) was developed within DILIsym. In vitro mechanistic toxicity assays were performed to assess the potential for RDV to induce oxidative stress, inhibit bile acid transporters, and induce mitochondrial toxicity. Hepatotoxicity responses to RDV in humans were simulated in DILIsym by combining in vivo exposure predicted by a PBPK model and mechanistic toxicity parameters derived from in vitro data. Previously constructed human simulated populations (SimPops™) that incorporate variability in hepatotoxicity pathways were employed for population analyses. **Results:** The DILIsym PBPK sub-model reasonably reproduced clinical PK profile; simulated AUC and C_{max} values were within 25% of clinical data. Combining mechanistic DILI assay results with PBPK-predicted liver concentrations for RDV and its metabolites, DILIsym predicted no systemic ALT elevations or liver ATP reductions for the RDV multiple dose treatment (1-hr IV infusion of 150 mg QD for 2 weeks) in SimPops (Figure 1). Dose escalation simulations showed that a dose 10-fold above the current clinical dose was required to elicit ALT elevations and liver ATP reductions (Figure 1). **Conclusion:** Clinically-observed reversible ALT increases following multiple dose treatment with 150mg of RDV for 7 or 14 days are unlikely to be due to mitochondrial ETC or bile acid transport inhibition, indicating potentially alternative mechanisms.

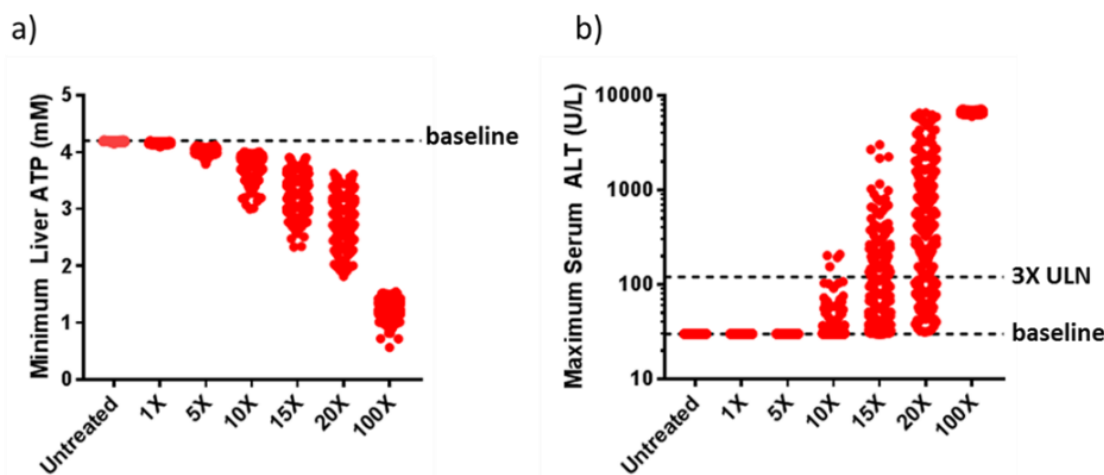


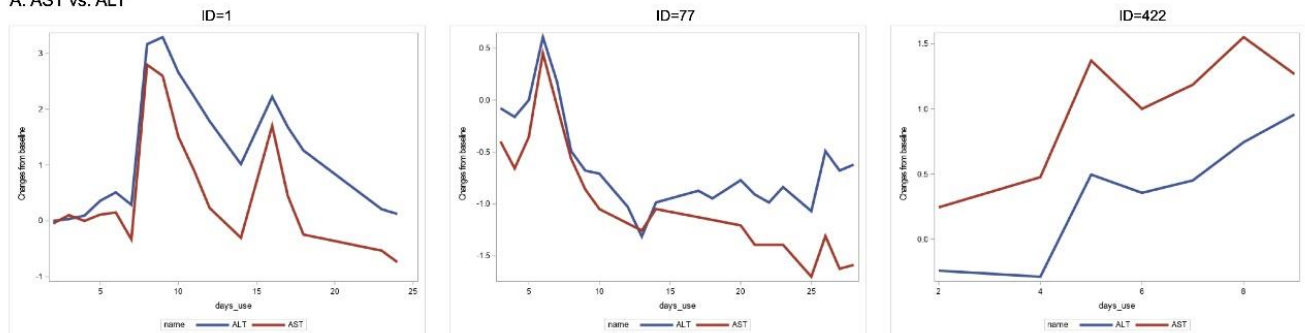
Figure 1. Simulated minimum liver ATP (a) and peak plasma ALT (b) in the human SimPops v4A-1 (n=285) without treatment or after 1 hr IV infusion of Remdesivir QD for 2 weeks at various dose levels: 150 mg (1X clinical dose), 750 mg (5X clinical dose), 1500 mg (10X clinical dose), 2250 mg (15X clinical dose), 3000 mg (20X clinical dose), and 15000 mg (100X clinical dose). Each symbol represents a simulated individual. The ALT upper limit of normal (ULN) in DILIsym is 40 U/L.

LP27: LIVER INJURY DURING COVID-19: PRIMARY OR SECONDARY?

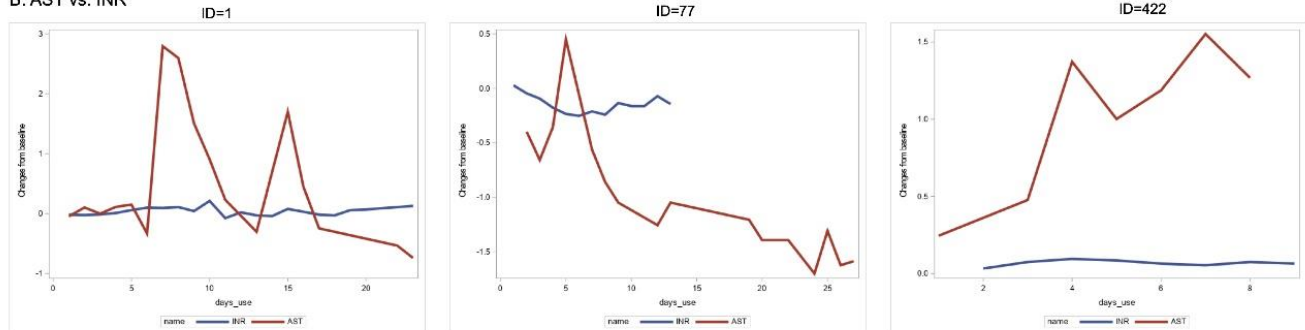
Dr. Michael Chew^{1,2}, Zeyu Tang³, Christopher Radcliffe³, Natty Doilicho³, Dennis L Caruana³, Maria Ciarleglio⁴, Yanhong Deng⁴ and Dr. Guadalupe Garcia-Tsao, MD, FAASLD^{1,2}, (1)Digestive Diseases, Yale University School of Medicine, (2)VA-Connecticut Healthcare System, West Haven, CT, USA, (3)Yale University School of Medicine, (4)Yale Center for Analytical Sciences, Yale School of Public Health

Background: It is known that COVID-19 is associated with abnormalities in liver enzymes (mostly increases in AST and ALT). It is uncertain whether these abnormalities represent liver injury from the SARS-CoV-2 virus and can result in liver failure and death or whether these abnormalities are secondary to concomitant processes, specifically, ischemia, drug-induced liver injury, inflammatory state and/or hypercoagulable state. We hypothesize that the liver injury observed in COVID-19 is likely a secondary event, not associated with liver failure or with a higher mortality. **Methods:** 836 consecutive patients hospitalized from April 1 through April 30, 2020 with COVID-19 were included in the study. Results of blood tests, clinical status and medications used were obtained at admission and throughout hospitalization. Severe COVID-19 was defined as pressors + intubation; ischemia was defined as vasopressor use; hyper-inflammatory state as CRP >100mg/dL or ferritin >1000ng/mL; and hypercoagulability as development of venous thromboembolism (VTE), D-dimer >5mg/dL, or fibrinogen >700mg/dL at any time during hospitalization. **Results:** Compared with patients with non-severe COVID-19, patients with severe COVID-19 (n=138) had higher median admission AST (U/L) [52 vs. 37, $p < 0.001$] and ALT (U/L) [35 vs. 24, $p < 0.001$], peak AST [89 vs. 37, $p < 0.001$] and ALT [57 vs. 24, $p < 0.001$], lower albumin (g/dL) [3.3 vs. 3.6, $p < 0.001$] but no difference in bilirubin (mg/dL) (0.56 vs. 0.49, $p = 0.14$) or INR (1.12 vs. 1.05, $p = 0.18$). Median time to peak AST was 3 (IQR 1-6) days after admission. Longitudinal random mixed-effects regression models showed that throughout hospitalization changes in log AST and log ALT were significantly correlated ($R = 0.89$), while changes in log AST did not correlate with changes in log INR ($R = 0.10$) (Figure). 105 patients had AST >5X ULN (upper limit of normal) at any time during hospitalization. Multivariate logistic regression showed that ischemia (OR 3.9 [2.4-6.3]) and tocilizumab use (OR 3.5 [1.8-6.6]) were independent predictors of AST >5X ULN, while hypercoagulability and inflammation were not. 138 (16.5%) patients died during hospitalization. Multivariate logistic regression showed that ischemia was independently associated with death (OR 3.4 [2.2-5.4]), while AST >5X ULN was not (OR 1.4 [0.8-2.5]). **Conclusion:** Abnormal liver enzyme abnormalities known to be associated with COVID-19 are secondary to other insults, mostly ischemia or drug-induced liver injury, and do not lead to liver insufficiency or death.

A. AST vs. ALT



B. AST vs. INR



LP28: BILE DUCT INJURY AND SEVERE CHOLESTASIS IN PATIENTS RECOVERING FROM SEVERE COVID-19: A NOVEL ENTITY OF COVID-ASSOCIATED CHOLANGIOPATHY

Dr. Saamia Faruqi¹, Dr. Fidelis Okoli¹, Dr. Sonja K. Olsen¹, Dr. David M. Feldman¹, Dr. Harmit S Kalia¹, Dr. Sooah Kim², Dr. James Park¹, Dr. Carmen M Stanca¹, Dr. Viviana Figueroa Diaz¹, Dr. Suparna A Sarkar³, Dr. Shani Fruchter⁴, Sarah Yuan¹, Dr. Krishna Shanbhogue², Dr. Neil D. Theise³ and Dr. Ira M. Jacobson¹, (1)Department of Medicine, NYU Grossman School of Medicine, (2)Department of Radiology, NYU Grossman School of Medicine, (3)Department of Pathology, NYU Grossman School of Medicine, (4)Department of Surgery, NYU Grossman School of Medicine

Background: In COVID-19 patients, there are reports of abnormal liver tests, mainly varying levels of abnormality in serum aminotransferases, with no disease specific lesions on biopsy. We have observed a syndrome in patients recovering from severe COVID-19 characterized by marked elevations in serum alkaline phosphatase (ALP) and inflammation of the biliary tract on imaging, frequently with strictures similar to secondary sclerosing cholangitis (SSC) as previously described in critically ill patients. We describe a syndrome of cholangiopathy seen in patients recovering from severe COVID-19, including biochemical, radiographic, and histologic features, clinical course, and associations with other manifestations of COVID-19. **Methods:** We studied patients with COVID-19 on whom the Hepatology service was consulted for abnormal liver tests, choosing those with ALP > 3xULN and/or abnormalities in the biliary tract on MRCP. Baseline features, clinical course, and lab data were recorded in a REDcap database. **Results:** 12 patients met criteria; mean age was 58 years, 11 males. 8 had history of hypertension, 3 diabetes. During their initial hospitalization, 12 had pneumonia, 11 ARDS and mechanical ventilation, 3 ECMO. 10 had sepsis requiring pressors and 8 required dialysis. 8 had new thromboembolic events requiring therapeutic anticoagulation, while 4 others received only DVT prophylaxis. At the time of consultation, median time since admission was 121 days. Mean peak laboratory values were: ALP 1789 IU/L (971-2544), ALT 714 U/L (242-2171), total bilirubin 12 mg/dl (0.7-35), creatinine 6.0 mg/dL (0.4-13.0), INR 2.29 (1.0-6.6), CRP 362 mg/L (277-477). 7 patients had peak D-dimers >10,000 ng/ml DDU. 10 (83%) had abnormal MRCP findings: 9 had beading of intrahepatic ducts; 9 had peribiliary diffusion high signal; 6 had bile duct wall thickening and enhancement of the common hepatic duct/common bile duct/intrahepatic biliary tree (Figure). Liver biopsy findings in 4 patients showed acute and/or chronic large duct obstruction, none showed bile duct injury/loss, i.e. changes compatible with SSC after radiographic correlation. CD61 immunostain shows widespread stain of platelets/exosomes with small sinusoidal aggregates, but no intravascular thrombi were seen. Biochemical resolution or regression of biliary strictures has not yet been documented. **Conclusion:** Patients with severe COVID-19 may develop cholestatic liver injury associated with biliary tract inflammation and/or strictures as a late complication. While this may reflect SSC post-critical illness, other pathogenetic mechanisms require study, e.g. ischemia related to COVID-19-associated thrombosis or direct biliary epithelial viral infection. Cholangiopathy is an important complication of SARS-CoV-2 infection requiring further study on natural history and potential therapeutic interventions.



Figure: MRCP image revealing mild irregular intrahepatic biliary dilatation with alternating segments of narrowing of the ducts ('beaded' appearance)

LP29: VANISHING BILE DUCT SYNDROME SECONDARY TO COVID-19: A CASE REPORT

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Background: While the coronavirus disease 2019 (COVID-19) is recognized as a respiratory illness, emerging studies indicate that COVID-19 also impacts the liver, which expresses the angiotensin-converting enzyme 2 (ACE2) receptor targeted by the virus. The typical pattern of injury seen is a transient elevation of liver enzymes in a hepatocellular pattern. The mechanisms of injury appear to be multifactorial, including drug-induced liver injury, direct cytotoxicity by SARS-CoV-2, and severe ischemia in the setting of acute respiratory failure. However, there have been no reports of progression of COVID-19 related liver injury to vanishing bile duct syndrome (VBDS) and secondary sclerosing cholangitis (SSC). **Methods:** We report the first case of a young, healthy patient with severe COVID-19 progressing to VBD and SSC following a prolonged hospitalization. **Results:** A 35-year-old man with diabetes was admitted with acute respiratory failure due to COVID-19. Upon admission, his liver tests were normal. His 3-month hospital course involved an ICU stay, requiring pressors and prolonged ventilatory support. He received multiple medications including azithromycin, hydroxychloroquine, remdesivir and antibiotics. Prior to discharge, his bilirubin was normal, but his liver enzymes were mildly elevated (alkaline phosphatase: 600 IU/L). Approximately 1 month later, he developed pruritus, with a total bilirubin of 2.5 mg/dL but a normal magnetic resonance cholangiopancreatography (MRCP). Over the next few weeks, his pruritus and jaundice worsened, and he was transferred to our center for a transplant evaluation with total bilirubin 21.1 mg/dL, direct bilirubin 13.8 mg/dL, alanine transaminase 40 U/L, aspartate transaminase 38 U/L, alkaline phosphatase 285 IU/L and normal albumin and INR. Repeat MRCP now showed diffuse irregularity and distension of the intrahepatic biliary system, consistent with sclerosing cholangitis. Liver biopsy revealed cholestatic liver injury with ductopenia, suggestive of VBDS. There was no improvement in his symptoms or liver tests, in spite of using ursodeoxycholic acid, cholestyramine, naltrexone and sertraline. **Conclusion:** To our knowledge this is the first case report of chronic and severe COVID-19 liver injury, prompting transplant evaluation. It appears that the critical illness associated with severe hypoxia, along with the direct viral cytotoxicity to the ACE2R-expressing cholangiocytes and use of various medications resulted in progressive and irreversible bile duct damage, leading to the VBDS and SSC. The transplant community must remain vigilant during this pandemic, as there is more to come from COVID-19.

LP30: BILE DUCT INJURY AND SEVERE CHOLESTASIS IN PATIENTS RECOVERING FROM SEVERE COVID-19: A NOVEL ENTITY OF COVID-ASSOCIATED-CHOLANGIOPATHY

Dr. Saamia Faruqi¹, Dr. Fidelis Okoli¹, Dr. Sonja K. Olsen¹, Dr. David M. Feldman¹, Dr. Harmit S Kalia¹, Dr. Sooah Kim², Dr. James Park¹, Dr. Carmen M Stanca¹, Dr. Viviana Figueroa Diaz¹, Dr. Suparna A Sarkar³, Dr. Shani Fruchter⁴, Sarah Yuan¹, Dr. Krishna Shanbhogue², Dr. Neil D. Theise³ and Dr. Ira M. Jacobson¹, (1)Department of Medicine, NYU Grossman School of Medicine, (2)Department of Radiology, NYU Grossman School of Medicine, (3)Department of Pathology, NYU Grossman School of Medicine, (4)Department of Surgery, NYU Grossman School of Medicine

Background: In COVID-19 patients, there are reports of abnormal liver tests, mainly varying levels of abnormality in serum aminotransferases, with no disease specific lesions on biopsy. We have observed a syndrome in patients recovering from severe COVID-19 characterized by marked elevations in serum alkaline phosphatase (ALP) and inflammation of the biliary tract on imaging, frequently with strictures similar to secondary sclerosing cholangitis (SSC) as previously described in critically ill patients. We describe a syndrome of cholangiopathy seen in patients recovering from severe COVID-19, including biochemical, radiographic, and histologic features, clinical course, and associations with other manifestations of COVID-19. **Methods:** We studied patients with COVID-19 on whom the Hepatology service was consulted for abnormal liver tests, choosing those with ALP > 3xULN and/or abnormalities in the biliary tract on MRCP. Baseline features, clinical course, and lab data were recorded in a REDcap database. **Results:** 12 patients met criteria; mean age was 58 years, 11 males. 8 had history of hypertension, 3 diabetes. During their initial hospitalization, 12 had pneumonia, 11 ARDS and mechanical ventilation, 3 ECMO. 10 had sepsis requiring pressors and 8 required dialysis. 8 had new thromboembolic events requiring therapeutic anticoagulation, while 4 others received only DVT prophylaxis. At the time of consultation, median time since admission was 121 days. Mean peak laboratory values were: ALP 1789 IU/L (971-2544), ALT 714 U/L (242-2171), total bilirubin 12 mg/dl (0.7-35), creatinine 6.0 mg/dL (0.4-13.0), INR 2.29 (1.0-6.6), CRP 362 mg/L (277-477). 7 patients had peak D-dimers >10,000 ng/ml DDU. 10 (83%) had abnormal MRCP findings: 9 had beading of intrahepatic ducts; 9 had peribiliary diffusion high signal; 6 had bile duct wall thickening and enhancement of the common hepatic duct/common bile duct/intrahepatic biliary tree (Figure). Liver biopsy findings in 4 patients showed acute and/or chronic large duct obstruction, none showed bile duct injury/loss, i.e. changes compatible with SSC after radiographic correlation. CD61 immunostain shows widespread stain of platelets/exosomes with small sinusoidal aggregates, but no intravascular thrombi were seen. Biochemical resolution or regression of biliary strictures has not yet been documented. **Conclusion:** Patients with severe COVID-19 may develop cholestatic liver injury associated with biliary tract inflammation and/or strictures as a late complication. While this may reflect SSC post-critical illness, other pathogenetic mechanisms require study, e.g.

ischemia related to COVID-19-associated thrombosis or direct biliary epithelial viral infection. Cholangiopathy is an important complication of SARS-CoV-2 infection requiring further study on natural history and potential therapeutic interventions.

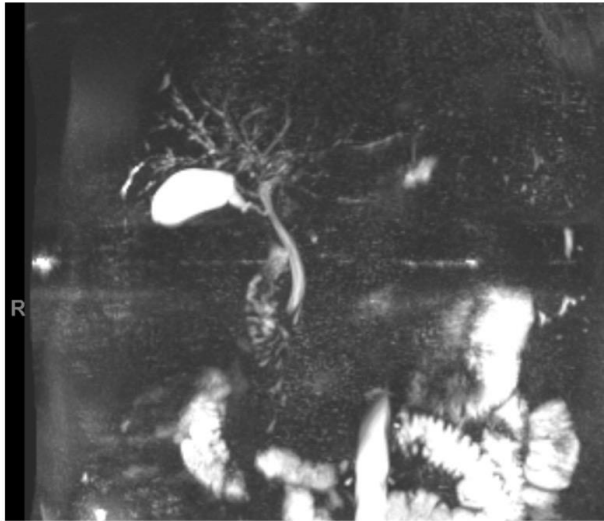


Figure: MRCP image revealing mild irregular intrahepatic biliary dilatation with alternating segments of narrowing of the ducts ('beaded' appearance')

LP31: ABSTRACT WITHDRAWN

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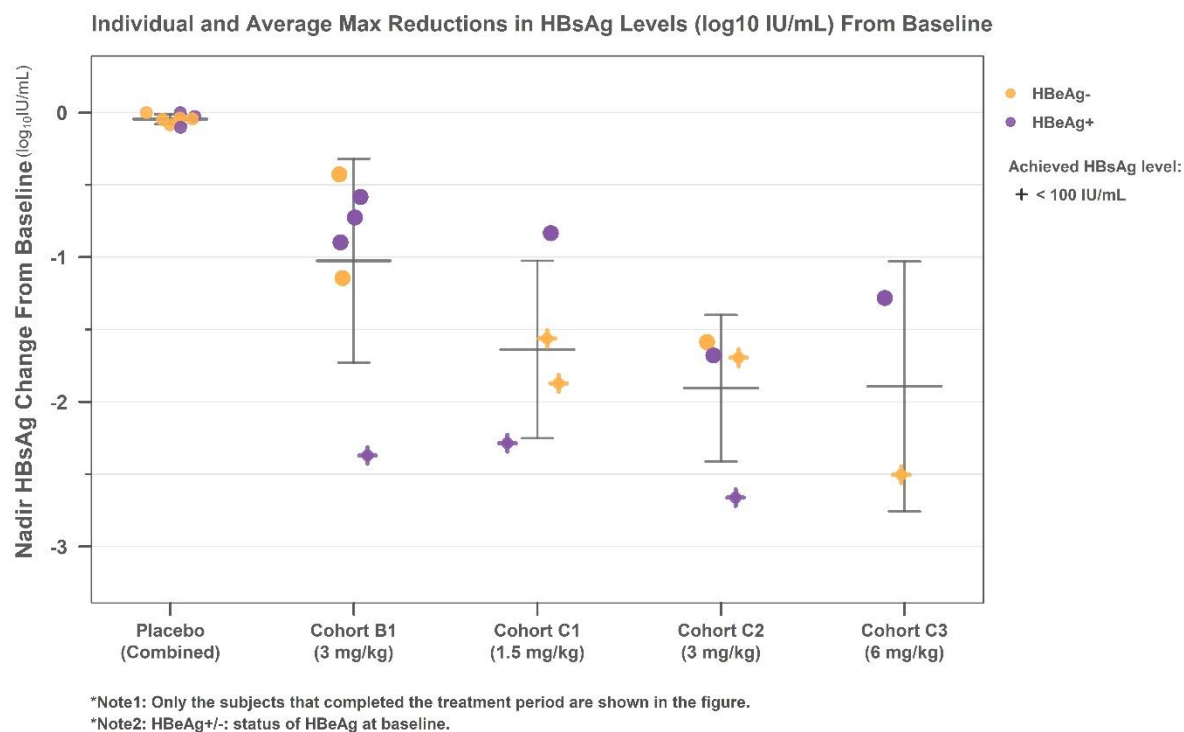
LP32: HBV RNAi INHIBITOR RG6346 IN PHASE 1b-2a TRIAL WAS SAFE, WELLTOLERATED, AND RESULTED IN SUBSTANTIAL AND DURABLE REDUCTIONS IN SERUM HBsAg LEVELS

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Background: Chronic Hepatitis B (CHB) virus infection can cause progressive liver damage leading to cirrhosis and hepatocellular carcinoma. Currently CHB infection requires prolonged, often life-long, treatment with nucleos(t)ide analogs (NUCs). New treatments aim at achieving "functional cure," i.e., durable clearance of serum HBsAg after finite therapy. RG6346 is a synthetic dsRNA conjugated to *N*-acetylgalactosamine that induces cleavage of mRNA encoding all forms of HBsAg in hepatocytes. **Methods:** This placebo controlled study was designed in 3 parts: SAD (Group A) in healthy volunteers (HV) (n=30; RG6346:placebo=2:1; doses=0.1, 1.5, 3.0, 6.0, 12.0 mg/kg), SD (Group B) in NUC-naïve patients with immune-active CHB (n=8; RG6346:placebo=5:3; dose=3.0 mg/kg), and MAD (Group C) in CHB patients with ≥ 12 weeks of NUC suppression prior to screening (n=18; RG6346:placebo=2:1; 4 monthly doses of 1.5 (C1), 3.0 (C2), and 6.0 mg/kg (C3) per cohort. Inclusion criteria in Groups B and C were HBeAg (+) with HBsAg > 1000 IU/mL, or HBeAg (-) with HBsAg > 500 IU/mL, and for Group B, serum HBV DNA > 2000 IU/mL, and ALT ≥ 35 U/L (males) or ≥ 30 U/L (females).

Results: All doses were safe in HVs, with nearly dose proportional C_{max} levels of RG6346. After 4 monthly SC doses in patients, the mean HBsAg decline from baseline was 1.39 log₁₀ IU/mL in C1, 1.80 in C2 and 1.84 in C3 at Day 112 (2/4 patients on RG6346 in C3 not yet reached Day 112). The max mean HBsAg reductions were 1.71 log₁₀ IU/mL in C1 on Day 168 (n=3), 1.88 in C2 on Day 140 (n=4), and 1.88 in C3 on Day 140 (n=2). The overall max reduction to date was 2.7 log₁₀ IU/mL (see Figure). Eighty (80) % of patients who

reached at least Day-112 achieved $> 1.5 \log_{10}$ IU/mL reduction, and 60% achieved HBsAg < 100 IU/mL regardless of HBeAg status. The longest enrolled patient in C1 maintained $> 2 \log_{10}$ IU/ml HBsAg reduction from Day 336 through Day 448. In NUC-naïve patients, a single dose of RG6346 resulted in a mean HBsAg reduction of $1.01 \log_{10}$ IU/mL at Day 57. Several patients on RG6346 exhibited self-resolving ALT flares consistent with treatment-induced enhanced immune responses, as demonstrated by a decrease in viral markers and overall preserved liver function. No SAEs or dose limiting toxicities with RG6346 were observed. The most common AEs in Groups B and C were related to mild injection site reactions. **Conclusion:** Treatment with RG6346 was safe and consistently induced large and durable reductions of HBsAg regardless of HBeAg status.



LP33: HEPATITIS C PREVALENCE AND INFLUENTIAL FACTORS ON TESTING BEHAVIOR AMONG HIV HIGH-RISK MSM IN CHINA: A GSN-DELIVERED CROSS-SECTIONAL STUDY

Mr. Fei Yu, Medical Affairs, Danlan Beijing Media Limited

Background: Men who have sex with men (MSM) are a high-risk population for the acquisition of HCV infection across the world. The prevalence of HCV in Chinese MSM varies, with estimates ranging from 0.6% to 4.8%. This population prevalence mostly relies on passive, hospital-based reporting systems in China and as such, it is widely perceived that there is underreporting of the true prevalence of HCV. This study aims to investigate HCV prevalence, testing uptake and factors associated with HCV testing among HIV high-risk MSM through Blued, a geosocial networking application (GSN) with more than 20 million MSM users in China. **Methods:** A cross-sectional survey was delivered through Blued in Beijing and Chengdu, the capital and so-called “gay capital” in China, from Dec. 20, 2019 to Jan. 15, 2020. Information of demographics, sexual behaviors, substance use, HCV knowledge, testing history and willingness are collected through a self-administered questionnaire. Participants who meet either one of the following criteria are identified as “HIV high-risk”: in recent 6 months, 1) have had condomless anal sex, 2) had HIV+ partner(s), 3) had more than one sex partners, 4) diagnosed with STD, or 5) used substance. Chi-square analysis and multivariate logistic regression were used. **Results:** A total of 1203 HIV high-risk MSM were recruited. 22.3% (268/1203) participants had tested for HCV, among which 7.1% (19/268) were reported to be infected with HCV, including 9 HIV/HCV co-infection cases. On multivariate analysis, factors significantly associated with HCV testing behavior are (OR_{adjusted}:3.61, CI:2.55~5.09) and ever having invasive examination (OR_{adjusted}:1.41, CI:1.02~1.95). **Conclusion:** HCV prevalence

among MSM, especially MSM at high-risk of contracting HIV in China has long been underestimated. Systematic and comprehensive interventions are desperately needed to prevent HCV transmission among MSM in China.

LP34: BIO89-100 DEMONSTRATED ROBUST REDUCTIONS IN LIVER MRI-PDFF, FAVORABLE TOLERABILITY AND POTENTIAL FOR EVERY 2 WEEKS (Q2W) DOSING IN A PHASE 1b/2a PLACEBO-CONTROLLED, DOUBLE-BLIND, MULTIPLE ASCENDING DOSE STUDY IN NASH

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Background: FGF21 is an endogenous hormone that regulates carbohydrate, lipid and energy metabolism. FGF21 analogs improve liver and metabolic abnormalities in non-alcoholic steatohepatitis (NASH). BIO89-100 is a long-acting glycoPEGylated FGF21, with promising tolerability and pharmacodynamic effects, and potential for Q2W dosing. **Methods:** This Phase 1b/2a trial enrolled 81 subjects with liver fat $\geq 10\%$ by MRI-PDFF, and either biopsy-proven NASH or phenotypic NASH [PNASH; central obesity with type 2 diabetes mellitus or evidence of liver injury - ALT or fibroscan vibration controlled transient elastography (VCTE) score above defined thresholds]. Subjects were randomized in cohorts to 12 weeks of treatment at one of 6 BIO89-100 doses [3, 9, 18 or 27 mg weekly (QW); 18 or 36 mg Q2W] or placebo. Key endpoints were safety, tolerability, pharmacokinetics, and change in MRI-PDFF and liver and metabolic markers. **Results:** Baseline characteristics were generally similar between pooled BIO89-100 vs. pooled placebo groups, and between NASH vs. PNASH subjects. At week 13, all BIO89-100 dose groups showed significant absolute and relative reductions in MRI-PDFF (Table 1). Up to 88% of BIO89-100 subjects achieved $\geq 30\%$ MRI-PDFF reduction vs. baseline ($p < 0.001$). Significant decreases in ALT vs. placebo were observed with BIO89-100, that were maximal with 27 mg QW (30 U/L decrease from baseline, $p < 0.001$), and also prominent in the subgroup ($n = 17$) with baseline ALT > 45 U/L (35 U/L decrease from baseline, $p < 0.05$). Reductions in ProC3, a fibrosis marker, were also noted. Metabolic benefits of BIO89-100 included a favorable effect on lipids, with significant reductions in triglycerides (TG; up to 28% in overall population, up to 49% in the subgroup ($n = 15$) with baseline TG ≥ 200 mg/mL); non-HDL cholesterol and LDL-C (up to 15% and 16%, respectively), and increased adiponectin (up to +61%). BIO89-100 had a favorable tolerability profile. There were no deaths or related serious adverse events; one BIO89-100-treated subject discontinued due to a related adverse event (AE; localized skin rash). Mild increased appetite (15.9% in pooled BIO89-100) was the most common AE. The frequency of gastrointestinal (GI) AEs compared favorably to placebo; diarrhea (BIO89-100 12.7%; placebo 22.2%) and nausea (BIO89-100 7.9%; placebo 16.7%) were the only GI AEs in $\geq 5\%$ BIO89-100-treated subjects. There were no hypersensitivity reactions, tremor, or adverse effects on blood pressure or heart rate. **Conclusion:** In subjects with NASH, BIO89-100 led to robust, significant and clinically meaningful reductions in liver fat assessed by MRI-PDFF and ALT, with concurrent metabolic benefits. These effects were observed in both QW and Q2W dosing, with a good safety and tolerability profile. The favorable clinical profile of BIO89-100 supports further development in NASH.

Table 1. MRI-PDFF Summary

Measure	Placebo (n= 19)	BIO89-100 Weekly (QW)				BIO89-100 Once every two weeks (Q2W)	
		3mg (n= 6)	9mg (n= 12)	18mg (n= 11)	27mg (n= 10)	18 mg (n= 14)	36 mg (n= 9)
Relative change in MRI-PDFF vs. baseline	+10%	-37%**	-50%**	-36%**	-60%**	-43%**	-50%**
Relative reduction in MRI-PDFF vs. placebo		-47%**	-59%**	-46%**	-70%**	-53%**	-60%**
Absolute change in MRI-PDFF vs. baseline	+1.4%	-7.5%*	-10%**	-7.5%**	-13.5%**	-9.0%**	-9.7%**
Proportion of subjects with $\geq 30\%$ relative reduction in MRI-PDFF	0%	60%*	82%**	60%**	86%**	69%**	88%**

* $p < 0.01$; ** $p < 0.001$ vs. placebo. n based on subjects randomized. Least square mean based on MRI analysis set (N=75) and responder based on subjects with MRI at Week 13. Levels of liver fat in the BIO89-100 and placebo groups at baseline were 21.2% (on a pooled basis) and 21.8%, respectively. Baseline liver fat levels and changes in liver fat were similar in biopsy-confirmed NASH and phenotypical NASH subjects.

LP35: AUTOMATED DETECTION OF IMMUNE CELLS IN LIVER TISSUE BASED ON A COMBINATION OF HANDCRAFTED AND DEEP-LEARNING APPROACH

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Background: Recent years have seen a growing interest in the role of immune cells in the pathogenesis of NAFLD and NASH. The methods for automatic detection of immune cells have evolved from traditional handcrafting (morphology, color and texture features) to deep learning techniques. Deep learning-based techniques outperform handcrafted methods but suffers from the limited availability of large-scale expert annotated datasets to train appropriate models. Our approach combining handcrafted and learned-based techniques may overcome the limited availability of annotated datasets to create fast and accurate cell detection and counting software. **Methods:** C57Bl6/J mice were fed an AMLN (amylin liver NASH) diet to develop a mild to moderate fibrotic NASH phenotype. Among the cells of the immune system, contribution of T-cells and B-cells were specifically selected to further characterize the mechanisms driving immune cell infiltration into the liver. We extracted, under guidance from expert pathologists, accurate handcrafted features from liver tissue sections stained with immunohistochemical markers (CD3+ and CD19+) for T-cells and B-cells respectively. These features allowed us to automatically define a set of 1900 image patches containing regions of interest. These regions of interest were fed to an Autoencoder neural network (U-Net). Evaluation of our algorithm was performed using manually annotated cells (~100 k cells) and compared with both handcrafted (HC) and deep learning (DL) techniques. We used the weighted linear Cohen's Kappa score to evaluate the agreement between pathologists and our algorithm. **Results:** A poor agreement was observed between manually annotated cells and HC technique (K = 0.43 and 0.44). DL technique showed a better agreement than HC technique (K = 0.61 and 0.58). In comparison, our combined approach showed excellent accuracy in predicting immune T and B cells (K = 0.74 and 0.70). **Conclusion:** Combination of HC and DL techniques shows the highest level of agreement with the expert annotations and better performances as compared to HC or DL techniques alone. In addition to significantly reducing time required to generate training dataset, our approach is reader independent and increase both the volume and the diversity of the dataset. Such high-quality dataset is more meaningful for DL neural network to automatically extract new features to solve cell detection task. This framework is now ready to use for high-throughput cell detection in samples from pre-clinical studies.

	Number of annotations (use for evaluation)	(HC) Handcrafted features	(DL) Learned features	(HC+DL) Combined approach
		Kappa	Kappa	Kappa
CD3+T	70168	0.43	0.61	0.74
CD19+B	37971	0.44	0.58	0.70

LP36: EFFECT OF THE PANPPAR AGONIST LANIFIBRANOR ON PLASMA BIOMARKERS OF LIVER NECRO-INFLAMMATION AND FIBROSIS IN NON-CIRRHOTIC NASH PATIENTS: ADDITIONAL RESULTS OF THE NATIVE PHASE 2b TRIAL.

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Background: Lanifibranor is a well-balanced agonist of the 3 PPAR isotypes with anti-inflammatory and anti-fibrotic effects in pre-clinical models of NASH. The NATIVE phase 2b trial in non-cirrhotic NASH patients demonstrated beneficial effects of lanifibranor treatment on several histological endpoints including NASH resolution and improvement of fibrosis. We report here the effects of lanifibranor on plasma biomarkers of liver necro-inflammation and fibrosis measured during the NATIVE trial. **Methods:** NATIVE is a phase 2b double-blind randomised-controlled trial of lanifibranor in patients with biopsy proven, non-cirrhotic NASH, with a SAF activity score of 3-4. Patients were randomised 1:1:1 to receive placebo (Pbo), 800 or 1200 mg of lanifibranor for 24 weeks. Blood samples were taken at baseline and week 24. The following biomarkers were measured: the collagen neo-epitope Pro-C3 (Nordic Bioscience using ELISA), MMP2 and TIMP1 (BARC using Mesoscale and CMIA, respectively), Hs-CRP and ferritin (BARC using turbidimetry and ECLIA, respectively) and CK18-M30 (BARC using ELISA). For each biomarker, the patients with values available pre-treatment (baseline) and post-treatment (week 24) were considered. The two doses of lanifibranor were pooled in the treatment group. Mean values at baseline and week 24, mean absolute change, mean and median relative changes from baseline at week 24 were described in the placebo and treatment groups. Relative changes in treatment group vs. placebo were compared using Student t test or Wilcoxon signed rank test. **Results:** Relative to Pbo, lanifibranor produced significantly greater reductions from baseline to week24 of Pro-C3 in the overall study cohort and amongst those with baseline Pro-C3 levels >14ug/L, (indicative of advanced fibrosis, Bril et al. Diabetes care, 2019), TIMP1/MMP2 ratio (depicting the inhibition of matrix remodeling process – fibrogenesis/fibrolysis), CK18-M30 as apoptotic marker, ferritin and Hs-CRP as inflammatory markers. The comparison of the relative changes in the lanifibranor-treated patients vs. the placebo-treated patients was statistically significant for all the biomarkers. **Conclusion:** Consistent with the histological data from the NATIVE study showing a decrease in the activity and fibrosis of the SAF score, the plasma markers of inflammation - ferritin and Hs-CRP, apoptosis - CK18-M30, and fibrosis - ro-C3, TMP1/MMP2, all show a statistically significant reduction in the lanifibranor treatment group compared to the placebo group.

	Lanifibranor treatment						Placebo						P-value*
	N	Mean at baseline	Mean at Week 24	Mean absolute change	Mean relative change (%)	Median relative change (%)	N	Mean at baseline	Mean at Week 24	Mean absolute change	Mean relative change (%)	Median relative change (%)	
PRO-C3 (ug/L)	137	17.5	14.5	-3.0	-9.1	-13.9	69	15.8	15.4	-0.3	1.1	-4.1	p= 0.005
PRO-C3 > 14 (ug/L)	79	22.0	16.4	-5.6	-20.5	-20.5	28	23.1	22.0	-1.1	-2.3	-12.8	p= 0.017
TIMP1/MMP2 ratio	135	3.4	2.7	-0.7	-16.8	-22.5	66	3.5	3.4	-0.1	2.6	-4.6	p < 0.001
Cytokeratin M30 (pmol/L)	135	954.9	564.7	-390.2	-22.2	-41.1	69	701.6	710.0	8.5	16.9	0.5	p < 0.001
Ferritin (ug/L)	145	240.4	167.6	-72.7	-18.0	-29.4	73	267.0	263.2	-3.8	2.4	-9.1	p < 0.001
Hs-CRP (mg/L) - High Sensitivity	146	5.1	3.3	-1.8	-2.9	-35.5	72	4.1	4.6	0.5	43.1	13.0	p < 0.001

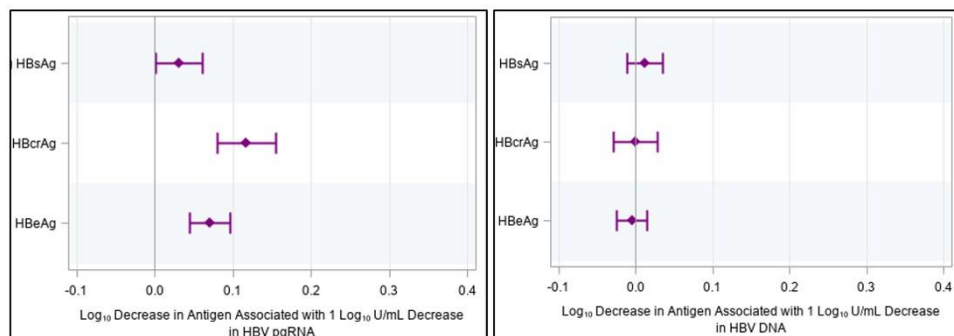
* Comparisons of placebo median change vs. lanifibranor median change assessed using Wilcoxon test

LP37: CHANGES IN VIRAL ANTIGENS ARE MORE STRONGLY ASSOCIATED WITH HBV pgRNA THAN HBV DNA IN STUDIES OF VEBICORVIR AND NRTI IN TREATMENT-NAIVE PATIENTS WITH CHRONIC HBV INFECTION

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Background: HBV pregenomic RNA (pgRNA) plays an integral role in viral replication and provides an indirect assessment of the level of cccDNA transcriptional activity and number of productively infected cells. The presence of pgRNA is associated with persistent viral infection and with a higher risk of relapse following cessation of nucleos(t)ide reverse transcriptase inhibitor therapy. To better understand the correlations of changes in levels of HBV pgRNA and HBV DNA with those of antigens, post-hoc statistical analyses were performed using clinical data from studies of vebicorvir (VBR; ABI-H0731), a first-generation core inhibitor, and entecavir in treatment-naive patients. **Methods:** Available clinical data were evaluated from 25 patients through 72 weeks of treatment in the Phase 2 studies Study 202 (NCT03577171) and Study 211 (NCT03780543), including HBV pgRNA (in-house assay, LLOQ=135 U/mL), HBV DNA (COBAS, LLOQ=20 IU/mL), HBeAg (Abbott, LLOQ=0.11 IU/mL), HBcrAg (FujiRebio, LLOQ=1 kU/mL) and HBsAg (Abbott, LLOQ=0.05 IU/mL). An initial correlation analysis with a Pearson's coefficient was performed, followed by an analysis with a mixed-effects model for repeated measures (MMRM) using log₁₀ change from baseline in each of the viral antigens as the response variable and log₁₀ baseline levels of viral antigen, change from baseline in log₁₀ pgRNA, change from baseline in log₁₀ DNA and study visit as covariates. **Results:** The Pearson's correlation coefficients with viral antigens were greater with pgRNA compared to DNA: pgRNA v HBeAg $r=0.72$, pgRNA v HBcrAg $r=0.76$, pgRNA v HBsAg $r=0.54$, DNA v HBeAg $r=0.43$, DNA v HBcrAg $r=0.47$, DNA v HBsAg $r=0.43$ (all $p<0.001$). The associations between pgRNA and DNA with viral antigens using the MMRM are shown in Figure 1. Reductions in pgRNA predicted reductions in HBeAg ($p<0.0001$), HBcrAg ($p<0.0001$) and HBsAg ($p=0.045$). In contrast, reductions in DNA did not significantly predict reductions in HBeAg, HBcrAg or HBsAg. **Conclusion:** Data from the ongoing Phase 2 clinical studies with VBR analyzed by two distinct statistical approaches show that the changes in viral antigens are more strongly associated with the change in HBV pgRNA than HBV DNA. The correlations between HBV pgRNA and HBeAg and HBcrAg were higher than with HBsAg, likely due to variable levels of HBsAg derived from integrants rather than cccDNA. These results demonstrate the importance of HBV pgRNA as a key biomarker for chronic HBV infection.

Figure 1: Associations of changes in HBV pgRNA and HBV DNA with viral antigens using the mixed-effects model for repeated measures (all available data through 72 weeks of treatment)



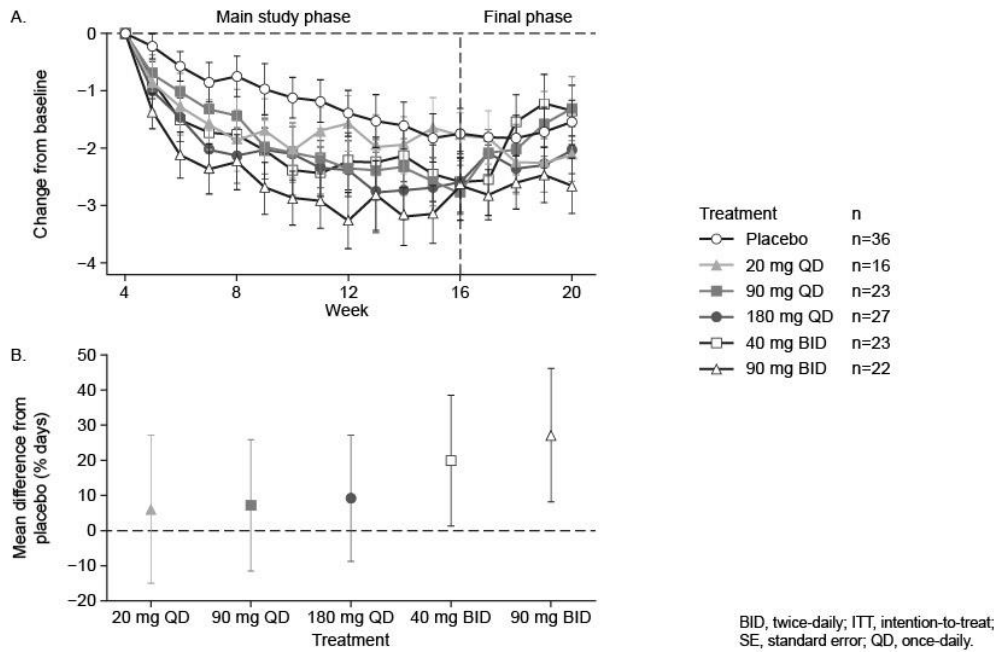
Note: Parameter estimates are the coefficients of the changes in log₁₀ HBV pgRNA and HBV DNA with 95% confidence intervals based on the MMRM model.

LP38: GLIMMER TRIAL- A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED STUDY OF LINERIXIBAT, AN INHIBITOR OF THE ILEAL BILE ACID TRANSPORTER, IN THE TREATMENT OF CHOLESTATIC PRURITUS IN PRIMARY BILIARY CHOLANGITIS (PBC)

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Background: Linerixibat is a minimally absorbed oral small molecule inhibitor of the human ileal bile acid transporter. The trial assessed dose response and tolerability of linerixibat compared to placebo in adults with cholestatic pruritus in PBC. **Methods:** PBC patients with pruritus (≥ 3 on 0–10 Numeric Rating Scale [NRS]) were randomized to linerixibat (20 mg/90 mg/180 mg QD and 40 mg/90 mg BID) or placebo for 12 weeks, followed by single-blind placebo. Stable anti-itch therapy was permitted. Subjects graded their itch twice daily using NRS with worst daily itch scores averaged over the 7 days preceding randomization/baseline and compared to the last 7 days of treatment. Response was classified as ≥ 2 -point improvement. **Results:** The study enrolled 147 patients (linerixibat, 111; placebo, 36). Rapid itch relief, particularly in BID dosing groups, with return of itch after treatment withdrawal was seen for linerixibat. (Figure 1a). Change from baseline in mean worst daily itch was -2.86 95% CI, (-3.76, -1.95) for 40 mg BID and -2.25 (-3.19, -1.32) for 90 mg BID. A high placebo response was seen throughout the treatment period (-1.73 [-2.44, -1.01]). A statistically significant itch reduction ($p=0.037$) was observed relative to placebo in the 40 mg BID arm in the sub-set of subjects with baseline NRS ≥ 4 . Percentage of itch responder days also favored BID dosing, with a mean increase of 20% for 40 mg BID and 27% for 90 mg BID relative to placebo (Figure 1b). Compared to placebo, a rapid, dose response in target engagement biomarkers was evident at Week 4 and was maintained during the dosing interval (LS mean change from baseline: 40mg BID C4 55.39ng/ml 95% CI (40.76, 70.03), FGF19 -73.03pg/ml (-121.98, -24.07); 90 mg BID C4 40.38ng/ml (25.46, 55.29), FGF19 -53.60pg/ml (-105.16, -2.04). All arms including placebo showed significant improvement from baseline in the itch domain of PBC-40 but only 40 mg BID demonstrated significant improvements in the PBC-40 social and emotional domains ($p=0.0016$ and $p=0.0025$, respectively). 10% of patients withdrew due to drug-related adverse events. The only on-treatment drug-related AE in $>10\%$ of patients was diarrhea, consistent with fecal elimination of bile acids. **Conclusion:** 12 weeks twice-daily linerixibat demonstrated rapid, significant improvement in itch and improved quality of life domains with expected pharmacologic effects. Targeting bile acid reuptake may provide relief for PBC patients with cholestatic pruritus.

Figure 1: Mean (\pm SE) for the observed weekly change from baseline in mean worst daily itch score (A) and mean difference (\pm SE) from placebo in percentage responder days in worst daily itch during 84 days treatment for each linerixibat dose (response defined as ≥ 2 point improvement in itch from baseline) (B); ITT population



LP39: THE IMPACT OF INITIAL TREATMENT MODALITY AND TREATMENT INTERVAL ON SURVIVAL OUTCOMES OF HEPATOCELLULAR CARCINOMA PATIENTS

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Background: For the treatment of HCC, various factors such as tumor stage, liver function and performance status should be taken into consideration. Since repeated treatments damage not only cancer cells but also normal hepatocytes. The selection of a treatment with a long interval between the first and second treatments may reduce the deterioration of liver functions, and affect the survival rates. Thus, this study aims to analyze the interval between treatments according to first treatment methods and to investigate whether the interval between the first and second treatments affect the survival rates independently. **Methods:** Among the 10,740 patients with HCC extracted randomly from the 2008–2014 national cohort of the Korean Central Cancer Registry, we selected the patients who had undergone the second treatment. Firstly, BCLC stages were further categorized according to CTP groups, and the interval between the first and second treatments was examined according to the first treatment method. Next, the factors independently affecting the survival rates such as the first treatment method, the interval between treatments, and BCLC stage were evaluated through the Cox proportional hazards regression analysis. **Results:** A total of 3832 patients received the first treatment followed by the second treatment. The treatment method was divided into 4 groups, surgical treatment, locoregional therapy, transarterial therapy, chemotherapy and radiation therapy. First, in the BCLC stage 0 and Child-Pugh Class A patient group, there was no significant difference between 19.1 months in the surgical treatment group and 18.3 months in the locoregional therapy group. Interestingly, in the BCLC stage A and Child-Pugh Class A patient group, 17.4 months in locoregional therapy group was superior to surgical treatment group, which had a treatment interval of 14.7 months. In addition, the BCLC stage C and Child-Pugh Class A patients showed longer treatment interval in the locoregional treatment group, which had a treatment interval of 13 months, compared to the surgical treatment group, which had a treatment interval of 10.5 months. Compared to the patients who received locoregional therapy, the treatment interval in the patients who received surgical treatment tended to be slightly decreased according to higher BCLC stage, and this trend was also observed in Child-Pugh Class B patients. The Cox proportional hazards regression analysis showed that factors independently affecting the survival rates were the interval between treatments (HR 0.98; $p < 0.001$), the type of the first treatment, BCLC & CTP stages, AFP, tumor size, tumor number, age and sex. **Conclusion:** In this

study, it was shown that the longer interval between the first and second treatments led to the higher survival rates independently. Therefore, in the treatment of HCC, it is considered important to select a treatment method that can increase the interval between treatments.

LP40: CD40 AGONISTS BOOST IFN-INDUCED SIGNALING PATHWAY AND SUBSEQUENT ANTI-HBV RESPONSE IN VITRO AND IN VIVO

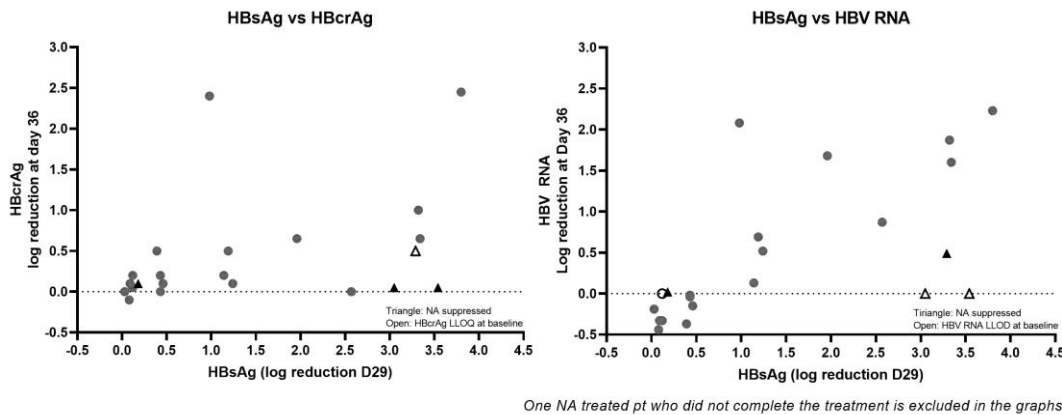
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Background: There is a continued need for improved therapeutics for chronic hepatitis B. **Methods:** In this light, the combination of CD40 agonism and IFN-I stimulation was explored on HBV infection both *in vitro* and *in vivo*. **Results:** *In vitro* CD40L boosts the anti-viral effect of IFN-I on HBV-infected primary human hepatocytes with a decrease of HBeAg and pgRNA. This combination also increased the release of the IFN-responsive protein CXCL10, but not the inflammatory protein IL-8. The combination boosted other Interferon Stimulating Genes, such as CXCL9, CXCL11 or ISG20, a key player in innate anti-viral immunity. Furthermore, in comparison to single agents, the co-administration of CD40L and IFN β to AAV/HBV-infected mice led to a significant reduction of viral parameters including circulating HBV DNA, HBeAg and HBsAg as well as pgRNA and HBV DNA in the liver. Importantly, *ex vivo* treatment of either human or murine whole blood cells with CD40L and IFN-I did not significantly induce inflammatory markers. **Conclusion:** Together, these results show the combination of CD40L and IFN-I has potent anti-HBV activity *in vitro* and *in vivo* with minimal inflammation. Such a combination may have an important therapeutic effect in chronic hepatitis B patients.

LP41: SHORT TERM THERAPY WITH GSK3228836 IN CHRONIC HEPATITIS B (CHB) PATIENTS RESULTS IN REDUCTIONS IN HBcRAG AND HBV RNA: PHASE 2a, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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Background: GSK3228836 (GSK836; formerly known as ISIS 505358) is a 2'-MOE modified antisense oligonucleotide targeting all HBV RNAs that has demonstrated rapid reductions in HBsAg and HBV DNA during four weeks of therapy in CHB patients (Ionis sponsored, GSK funded ISIS CS-3 Study, NCT02981602). The aim of the analysis was to evaluate the effect of GSK836 treatment on serum HBV RNA and HBcRag. **Methods:** All patients (pts) were HBsAg positive ≥ 6 month and HBsAg > 50 IU/mL at screening. Nucleos(tide) analog (NA)-naïve patients had HBV DNA $\geq 2 \times 10^3$ IU/mL. NA-treated patients had HBV DNA ≤ 100 IU/mL. Both HBeAg positive and negative patients were eligible. GSK836 (150mg and 300 mg) or placebo was administered subcutaneously on Days 1, 4, 8, 11, 15, and 22. Comparison between GSK836 and placebo in HBV DNA and HBsAg were performed for each dose level, using an analysis of covariance (ANCOVA) model. Sera collected at Days 1, 8, 15, 23, 36, 85, 113, and 211 were used for analyses of HBcRag (Lumipulse platform [Fujirebio]) and HBV RNA (Quantitative PCR assay run on a Roche LC480). Summaries of HBV RNA and HBcRag were post-hoc. **Results:** For NA-naïve pts receiving GSK836 at 150mg (n=6) and 300 mg (n=12), respectively, HBsAg mean \pm SD changes in log₁₀ IU/mL were -0.504 ± 0.5656 (p=0.245 vs Pbo) and -1.556 ± 1.3787 (p=0.001 vs Pbo) at Day 29. Three pts (all 300mg) had HBsAg reductions > 3.0 log₁₀ IU/mL, with two pts also having levels reduced to $< \text{LLOQ}$. Of the 18 NA-naïve patients receiving 150mg or 300mg GSK836, nine pts had > 0.5 log IU/mL reduction in HBsAg at Day 29. Of these, 8/9 and 5/9 pts also had a > 0.5 log reduction in HBV RNA and HBcRag at Day 36, respectively. For NA-treated pts, mean HBsAg log₁₀ IU/mL \pm SD change from baseline was -1.986 ± 1.7986 for GSK836 (300mg, n=5) and -0.008 for placebo (Pbo, n=2) at Day 29. In NA-treated pts, 3/5 had HBsAg reductions > 3.0 log₁₀ IU/mL at Day 29; with two pts reaching $< \text{LLOQ}$ during treatment or Day 36. All three NA-treated pts with HBsAg declines > 3.0 log₁₀ IU/mL had low baseline levels of HBV RNA and HBcRag. **Conclusion:** Clinically significant reductions of HBsAg levels were observed with 4-week GSK836 treatment in CHB pts. The majority of NA-naïve pts with > 0.5 log IU/mL reductions in HBsAg had concomitant reductions in HBV RNA and to a lesser extent, HBcRag, confirming that GSK836 is able to reduce other viral markers.

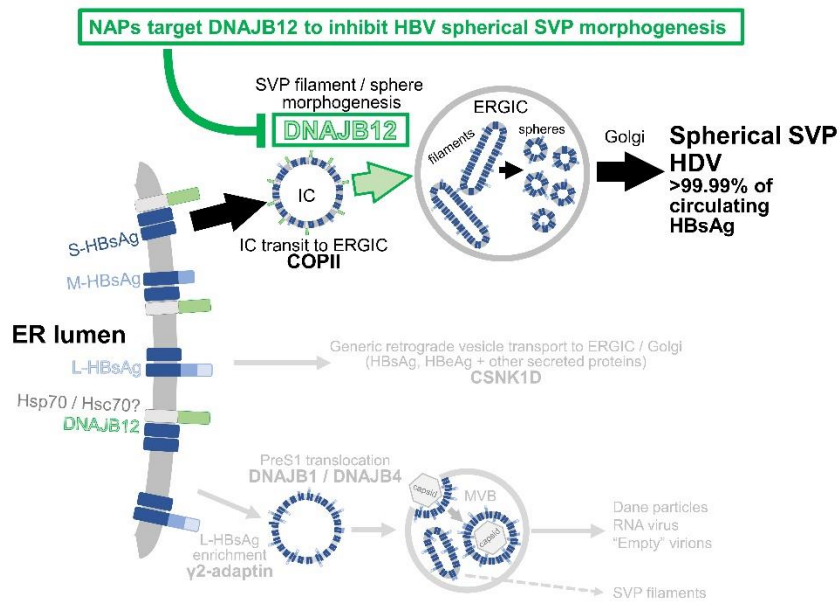


LP42: THE HSP40 CHAPERONE DNAJB12 IS INVOLVED IN THE MORPHOGENESIS OF HBV SPHERICAL SUBVIRAL PARTICLES AND IS SELECTIVELY TARGETED BY NUCLEIC ACID POLYMERS

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Background: Nucleic acid polymers (NAPs) inhibit the assembly and secretion of HBV spherical subviral particles (SVP) without affecting the secretion of HBeAg or Dane particles. Given that > 99.99% of circulating HBsAg is derived from spherical SVP, the importance of HBsAg loss in achieving functional cure of HBV and the high rates of HBsAg loss and functional cure uniquely accompanying NAP-based therapy, the host target(s) of NAPs has been a topic of great interest. Recent validation of the *in vivo* and clinical effects of NAP effects in HepG2.2.15 cells (Blanchet *et al.*, Antiviral Res. 2019;164:97-105, Boulon *et al.*, Antiviral Res. 2020;180:104853) identifies a suitable model system for NAP target identification. **Methods:** A differential-interactome screen of HepG2.2.15 lysate used biotinylated NAPs which bracket the size and phosphorothioation (PS) dependent structure activity relationship of NAPs (Blanchet *et al.*, *ibid*). These NAPs included the clinically active 40mer PS REP 2139 and its inactive analogs: the 40mer phosphodiester REP 2147 and the short PS (20mer) REP 2179. MS/MS analysis (three experiments per NAP) identified NAP-bound proteins. DNA / RNA binding proteins or proteins with interaction selectivity ratio < 2 were excluded. Selected candidates had the greatest significant ($p < 0.05$) selective interaction ratio between REP 2139 / REP 2147 (PS-dependent) and REP 2139 / REP 2179 (size-dependent). Candidates were validated by shRNA-mediated knockdown effects on HBsAg and HBeAg secretion. Reproducibility ($n=3$) of validation experiments was recently confirmed.

Results: No interactions with viral proteins were detected. Knockdown of candidate targets in HepG2.2.15 cells revealed two targets involved in HBsAg secretion: the Hsp40 chaperone DNAJB12 and casein kinase 1 isoform delta (CSNK1D), involved in retrograde vesicle transport. Knockdown of DNAJB12 resulted in the strongest inhibition of HBsAg secretion with no effect on HBeAg. Knockdown of CSNK1D induced milder inhibition of both HBsAg and HBeAg secretion (inconsistent with NAP activity *in vitro* and in humans). No selective interactions were observed with other Hsp40 family DNAJ members, including DNAJB1 and DNAJB4 involved in regulating preS1 membrane topology during Dane particle morphogenesis. **Conclusion:** The selective inhibition of spherical SVP assembly by NAPs is a result of the inhibition of DNAJB12-mediated chaperone functions required for spherical SVP assembly. NAP interaction with CSNK1D does not appear to be physiological but may reflect an interaction which can occur *in vitro* under experimental conditions which do not mimic normal intracellular NAP trafficking.



LP43: SINGLE-MOLECULE AND HISTOPATHOLOGICAL EVALUATION OF SARS-COV-2 IN THE LIVER REVEALS SINUSOIDAL VIRAL AGGREGATES AND ABSENCE OF PARENCHYMAL INFECTION

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Background: Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become one of the greatest threats to public health within this century. Much of the variety of patient symptoms and diversity of disease progression remains to be understood. One aspect of COVID-19 that has emerged in several large cohort studies is the high frequency (>50%) of abnormal liver function tests (elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels) in affected patients. Despite these findings, investigations for the presence of SARS-CoV-2 in liver tissue of patients remain limited. Thus, we aimed to examine if SARS-CoV-2 may affect liver function through direct parenchymal infection or have an alternative role in eliciting liver abnormalities. **Methods:** We evaluated liver histology from a cohort of 35 deceased patients who had tested positive for SARS-CoV-2. To assess viral presence in the liver of patients with severe and ultimately fatal cases of COVID-19, we applied single-molecule fluorescence in situ hybridization (smFISH), immunofluorescence (IF), and immunohistochemical analyses. **Results:** Angiotensin-converting enzyme 2 (ACE2) expressed in cholangiocytes has been proposed as a mechanism by which cells within the liver of patients with COVID-19 may become infected by SARS-CoV-2. While variable expression of ACE2 in cholangiocytes was confirmed, direct parenchymal infection by SARS-CoV-2 was not identified in either hepatocytes or cholangiocytes in any of the liver samples evaluated. Rather, in 2/35 patients, viral RNA molecules were robustly identified in distinct focal aggregates within hepatic sinusoids. While the assay also identified rare single viral RNA molecules in the sinusoids of 14/35 patients, evidence of substantial viral aggregation was infrequent (<6%). Finally, we identified that these distinct regions of viral aggregation in the liver, which were confirmed by immunohistochemistry for the SARS-CoV-2 nucleocapsid protein, were also frequently accompanied by platelet aggregates (identified by CD61 positivity) clearly indicating sinusoidal microthrombi. **Conclusion:** Our work demonstrates the absence of SARS-CoV-2 infection in hepatic parenchymal tissue and confirms variable ACE2 expression in cholangiocytes. Further, our results uncover low levels of circulating RNA viral molecules in liver sinusoids, and dramatically highlights rare and distinct regions of viral aggregates within microthrombi in hepatic sinusoids. These results suggest that elevated ALTs may not be due to direct viral infection of hepatic cells with SARS-CoV-2, but may be explained by the immune and endothelial complications of COVID-19.

LP44: GENOMIC AND TRANSCRIPTOMIC CHARACTERIZATION OF YAP1-DRIVEN HEPATOBLASTOMA DURING THERAPEUTIC DIFFERENTIATION

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Background: Hepatoblastoma (HB) is primary pediatric liver cancer, occurring predominantly in children under five and disproportionately impacting those born with genetic abnormalities. While surgical resection and chemotherapy are often effective in controlling local disease, metastatic hepatoblastoma has a relatively poor prognosis. While systemic therapy has limited success in curbing HB progression, the low mutational burden of this pediatric malignancy makes it an ideal candidate for targeted therapy. Previous studies have implicated the YAP1 transcription cofactor in driving liver carcinogenesis and regeneration. Recently, we designed an inducible murine HB model that successfully recapitulates tumor formation, maintenance and regression. Here, we present further analysis of chromatin accessibility and gene expression in this model to identify DNA regulatory elements with key roles in HB tumorigenesis. Finally, we provide mechanistic context to these elements by profiling YAP1, H3K27Ac and H3K4me1 DNA binding in HB tumors. **Methods:** Transcription factor (TF) footprinting and transcript isoform usage analyses were performed on our previously published ATAC-seq and RNA-seq datasets, respectively, in YAP1-induced HB, YAP1-withdrawal regression timepoints, and in normal liver tissues. CUT&TAG was used for YAP1 and histone variant profiling. Additional characterization of candidate *cis*-regulatory DNA elements was completed, in part, using tissue-specific sequencing datasets available from ENCODE3 and SCREEN. **Results:** Putative HB-driving DNA regulatory elements were screened by differential chromatin accessibility ($n \approx 10^6$ loci). We then isolated elements within or near genes exhibiting absolute changes in expression or isoform switch (247 switches observed in 182 distinct genes). HB-specific TF footprints ($n = 552$ motifs), K27Ac, K4me1 and YAP1 profiles were superimposed on candidate elements to further assess potential regulatory function. Finally, we generated a curated list of YAP1-dependent and independent TFs and their target genes/elements in HB. **Conclusion:** Here, we provide extensive genomic and transcriptomic characterization of a YAP1-driven murine HB model. Integrated analysis of gene expression, chromatin accessibility, YAP1-binding and epigenetic landscapes have allowed us to substantially refine regulatory proteins and DNA elements with a potentially outsized effect on HB tumorigenesis. This heavily curated dataset establishes a network of known and novel HB tumor drivers that will contribute to both mechanistic insight and therapeutic approach.

LP45: AMINO ACID SUBSTITUTIONS IN THE INHIBITOR BINDING POCKET OF HBV CORE PROTEIN CONFER DIFFERENTIAL CHANGES IN SUSCEPTIBILITY TO THREE GENERATIONS OF HBV CORE INHIBITORS

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Background: Core inhibitors are a novel class of HBV direct-acting antivirals with the potential to increase on-treatment responses and cure rates after finite treatment. All core inhibitors bind to the same highly conserved pocket on core protein; data indicate that amino acid substitutions in this region can confer reduced sensitivity. Here we describe the in vitro resistance profiles of vebicorvir (VBR; ABI-H0731), ABI-H2158 (2158), and ABI-H3733 (3733), 3 generations of structurally distinct core inhibitors with increasing in vitro potency against encapsidation of viral RNA and delivery of existing nucleocapsids to establish cccDNA. VBR, 2158, and 3733 are in clinical development with VBR & 2158 currently in combination studies with nucleos(t)ide reverse transcriptase inhibitors (NrtIs). **Methods:** Huh7-Lunet cells were transiently transfected with plasmids encoding wild-type HBV or HBV encoding core protein substitutions previously reported in the literature. Transfected cells were treated with VBR, 2158, 3733 or entecavir (ETV) for 1 week after which the amount of replicating HBV DNA in the cells was evaluated by qPCR. **Results:** VBR, 2158, 3733, and ETV had EC₅₀s of 146, 10, 4, and 2 nM against wild-type HBV, respectively. The 1st generation core inhibitor VBR had a >10-fold loss of activity against the D29G, T33N, T109I, T109M, and Y118F substitutions (Table 1); these substitutions had reduced replicative capacity (9-61% of wild-type) and are present in <1% of sequences in public databases. In contrast, 2158, a 2nd generation inhibitor, and 3733, a 3rd generation inhibitor, had improved resistance profiles with >10-fold resistance to only the T33N. For all three inhibitors, there were substitutions that conferred lower (<10-fold) shifts in EC₅₀; importantly, these substitutions differed between inhibitors. No core protein substitutions conferred reduced susceptibility to ETV (all EC₅₀s <2.5-fold of wild-type). **Conclusion:** Although all HBV core inhibitors are known to bind the same pocket, specific amino acid substitutions in the region confer differential changes in the resistance profile of structurally distinct small molecules suggesting that specific interactions between the protein and the inhibitors modulate drug susceptibility. ETV retains activity against all tested core protein mutations suggesting that combination therapy with NrtIs may prevent viral breakthrough due to pre-existence or potential emergence of core protein substitutions.

Table 1: Susceptibility of HBV Core Protein Containing Amino Acid Substitutions to Core Inhibitors and the Nrti Entecavir

Core Protein Substitutions	Replication Capacity (%WT)	Fold Change in EC ₅₀ vs Wild-type			
		VBR (1 st Gen) WT EC ₅₀ = 146 nM	2158 (2 nd Gen) WT EC ₅₀ = 10 nM	3733 (3 rd Gen) WT EC ₅₀ = 4 nM	Entecavir WT EC ₅₀ = 2 nM
P25A	122%	1.2	2.9	1.9	1.5
D29G	19%	20.2	9.3	2.1	0.3
T33N	61%	20.9	245	442	1.8
Y38C	92%	1.5	0.8	0.7	0.6
Y38F	55%	3.3	0.6	1.1	2.4
I105L	73%	0.3	0.8	0.9	0.2
I105T	52%	2.2	4.0	7.0	0.4
T109I	52%	>68.4	0.4	0.8	1.0
T109M	29%	>68.4	2.7	0.6	0.8
I116L	88%	0.4	0.8	0.4	0.4
Y118F	9%	14.2	1.5	7.6	0.8

LP46: RANDOMIZED TRIAL OF LOSARTAN FOR PEDIATRIC NONALCOHOLIC FATTY LIVER DISEASE (NAFLD).

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Background: To date, no pharmaceutical treatment for pediatric nonalcoholic fatty liver disease (NAFLD) has been identified. Losartan, an angiotensin II receptor blocker approved for treatment of high blood pressure in children, has been proposed as a treatment for NAFLD due to its anti-fibrotic effects. It was hypothesized that 24 weeks of losartan would reduce severity of NAFLD as measured by non-invasive surrogate biomarkers. **Methods:** We conducted a multicenter, double masked, placebo controlled, randomized clinical trial of children with histologically confirmed NAFLD from October 2018 thru March 2020 at 8 pediatric sites in the Nonalcoholic Steatohepatitis Clinical Research Network. Inclusion criteria were age 8-17 years, histologic NAFLD activity score (NAS) ≥ 3 , and serum alanine aminotransferase (ALT) ≥ 50 IU/L at screening. Children received 100 mg losartan orally once per day or placebo for 24 weeks. The primary outcome was change in ALT level from baseline to 24 weeks. Treatment effects were assessed using linear regression of change on baseline value and treatment group. **Results:** 43 patients were randomized to the losartan group and 40 to the placebo group. The study planned to recruit 110 patients. However, the trial was stopped after a futility analysis following an enrollment pause due to the COVID-19 pandemic. Baseline characteristics were similar between groups. There was no significant difference between groups for 24-week change in ALT, the primary outcome (change -5.3 U/L for losartan (n=33), -6.3 U/L for placebo (n=34) with an adjusted mean difference of 1.1 U/L, 95% CI=(-30.6, 32.7); p=0.95. Change in aspartate aminotransferase and gamma-glutamyl transferase also did not differ between groups, although there was a significant decrease in alkaline phosphatase in the losartan group (adjusted mean difference of -23.4 U/L, 95% CI=(-41.5, -5.3); p=0.01). Systolic blood pressure decreased in the losartan group while the placebo group increased with a mean adjusted difference between groups of -7.5 mmHg, 95% CI=(-12.2, -2.8); p=0.002. Based on pill counts, 71% of patients taking losartan



and 75% taking placebo had at least 80% compliance. Adverse events were similar between the two groups. **Conclusion:** In this randomized trial, we found that losartan for 24 weeks did not reduce ALT in children with NAFLD compared to placebo. Despite good compliance, change in liver biomarkers over time were similar between the two groups.