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Late-Breaking Abstracts

5000 | TOPLINE RESULTS FROM A 12-WEEK PHASE 2a TRIAL (DUET) EVALUATING TERN-501, A HIGHLY SELECTIVE THYROID HORMONE RECEPTOR (THR)BETA AGONIST, EITHER AS MONOTHERAPY OR IN COMBINATION WITH TERN-101, A NONSTEROIDAL FARNESOID X RECEPTOR (FXR) AGONIST, DEMONSTRATED SIGNIFICANT REDUCTIONS IN MR-BASED LIVER FAT CONTENT AND FIBROINFLAMMATION IN PATIENTS WITH PRESUMED MASH

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Background: TERN-501, a highly selective THRβ agonist with enhanced metabolic stability suitable for combination therapy, showed robust target engagement and favorable safety/PK profile in a Ph1 study. In this first MASH trial assessing efficacy and safety of a THR-β and FXR agonist combination, we evaluated TERN-501 when used alone or in combination with TERN-101, a liver directed nonsteroidal FXR agonist. **Methods:** Patients(pts) with phenotypic or prior histologic MASH were randomized to 1 of 7 treatments: once daily TERN-501(1,3,6mg), TERN-101(10mg), TERN-501(3 or 6mg) with TERN-101(10mg), or placebo. The primary endpoint was relative change in MRI-PDFF at Wk12 for TERN-501 monotherapy vs placebo. Liver fibroinflammation by cT1, sex hormone binding globulin(SHBG), lipids, MASH/fibrosis biomarkers, safety/tolerability were assessed. **Results:** Among 162 pts randomized, 55% female; 42% type2 diabetes; mean age 53yrs; BMI 38kg/m^2; LDL 94mg/dL. Mean baseline liver fat content(LFC) 18%, cT1 936ms indicated high-risk MASH population. Significant reductions in LFC were seen as early as Wk6; mean relative reduction of 27% (3mg[p=0.0036]) and 45% (6mg[p<0.0001]) TERN-501 vs 4% in placebo were seen at Wk12, meeting the primary endpoint (Table). Significantly higher %pts achieved ≥30%MRI-PDFF reduction in TERN-501 arms and ≥50% reduction at TERN-501 6mg. Significant, rapid cT1 decrease was seen at TERN-501 6mg with significantly higher %pts achieving ≥80ms reduction, recovering from at-risk MASH category. When TERN-501 was combined with TERN-101, efficacy was generally maintained or improved. TERN-501 significantly increased SHBG(marker of target engagement and predictor of histologic response in the THRβ class) and improved lipids with significant apolipoproteinB reductions in TERN-501 monotherapy arms and numeric LDL decreases in combination with TERN-101. TERN-501 was well tolerated. Treatment-related adverse event(AE) rates were similar to placebo with low overall rates(7.4%) of gastrointestinal(GI)AEs reported similarly across arms. No treatment-related cardiovascular(CV)AEs or serious AEs were reported. **Conclusion:** 12wks TERN-501 treatment significantly improved LFC and fibroinflammation in MASH pts and was well tolerated with no GI or CV AE concerns. This first placebo-controlled MASH combination trial of a THRβ and an FXR agonist met all key endpoints without additional safety findings. The compelling overall efficacy/tolerability/combinability profile of TERN-501 warrants further investigation for MASH.

Table: Effects of TERN-501 ± TERN-101 for 12 Weeks in Patients with Presumed MASH

	Placebo	Monotherapy			TERN-101 10 mg	Combination With TERN-101 10 mg	
		TERN-501 1 mg	TERN-501 3 mg	TERN-501 6 mg		TERN-501 3 mg	TERN-501 6 mg
Liver Fat Content (LFC) Measured by MRI-PDFF at Week 12							
Relative change from BL, LSM %	−4%	−15%	−27%**	−45%***	−19%	−21%*	−48%***
Patients achieving ≥30% relative reduction, %	4%	26%*	39%**	64%***	25%*	44%**	74%***
Patients achieving ≥50% relative reduction, %	0	4%	13%	41%***	13%	17%*	61%***
Patients with normalization[a] of LFC, %	0	0	4%	23%*	0	4%	9%
Liver Fibroinflammation Measured by cT1 at Week 12							
Change from BL, LSM ms	4	−28	−26	−72***	−35	−59**	−66**
Patients achieving ≥80 ms reduction, %	8%	9%	9%	32%*	29%	26%	30%
Patients shifted out of at-risk MASH[b], %	12%	35%	29%	56%**	18%	26%	54%*
Pharmacodynamic Marker at Week 12							
SHBG change from BL, LSM %	4%	17%	53%*	127%***	10%	72%**	109%***
Patient Incidence of Treatment Related[c] AEs: Overall and the AEs Occurred in >1 Patient in Any Arm							
Overall, n (%)	5 (20.8)	1 (4.3)	4 (17.4)	4 (18.2)	2 (8.3)	6 (26.1)	4 (17.4)
Pruritus, n (%)	2 (8.3)	0	1 (4.3)	2 (9.1)	1 (4.2)	4 (17.4)	2 (8.7)
Diarrhea, n (%)	1 (4.2)	1 (4.3)	2 (8.7)	1 (4.5)	1 (4.2)	1 (4.3)	0

*p<0.05, **p<0.01, ***p<0.001 vs placebo
[a]MRI-PDFF <5%
[b]cT1 >875 ms
[c]Related adverse events: Deemed by Investigator as possibly related or related to study drug
AE=adverse event; ANCOVA=analysis of covariance; BL=baseline; cT1=corrected T1; LFC=liver fat content; LSM=least squares mean from ANCOVA model; MRI-PDFF=magnetic resonance imaging proton density fat fraction; ms=millisecond; SHBG=sex hormone binding globulin.

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5001 | CONTINUOUS HOME TERLIPRESSIN INFUSION INCREASES HANDGRIP STRENGTH AND REDUCES ASCITES – A PROSPECTIVE RANDOMIZED CROSS-OVER STUDY

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Background: Sarcopenia is common in cirrhosis and has been shown to progressively deteriorate in patients waiting for liver transplant. This deterioration is independently associated with waitlist mortality. Observational data from our centre comprising 105 patients and over 13,000 patient days suggest a beneficial effect of continuous home terlipressin infusion (CTI) on ascites and muscle strength in end-stage cirrhosis with portal hypertension. This is the first prospective randomized study of CTI examining its use in this context. **Methods:** This single-centre, prospective, cross-over study randomised 30 patients with cirrhosis, ascites and sarcopenia to commence on 12 weeks of home intravenous CTI or 12 weeks of observation prior to cross-over, with each patient serving as their own control. CTI was commenced in hospital for 48 hours with subsequent discharge home for ambulatory CTI facilitated by daily nursing visits. The co-primary endpoints were change in handgrip strength and paracentesis volume. Secondary outcomes included quality of life, sarcopenia measures, renal function and biochemistry, hospitalisation events and safety. An independent safety committee provided study oversight. **Results:** The median age of participants was 62 years (IQR 57-64), median MELD-Na was 16 (12.3-20.8) and 22 (73%) were male. The co-primary endpoints were positive, with handgrip strength significantly increased in the treatment arm by a mean adjusted difference (MAD) of 3.09kg (95% CI 1.11-5.08 kg) between CTI and observation (p=0.006); representing an 11.8% increase from baseline. The volume of ascites drained decreased by a MAD of 11.39L (2.99 - 19.85, p=0.01), with 1.75 fewer episodes of paracentesis (0.925-2.59, p<0.001) on CTI over 12 weeks. Quality of life was significantly higher on CTI, with an increase in the Chronic Liver Disease Quality of life score of 0.41 points (0.23-0.59, p<0.001), with a significant improvement recorded across all measured domains. Serum creatinine decreased and urinary sodium excretion increased on CTI (both p<0.001) but serum sodium did not significantly differ between groups. There were 7 minor line-related complications but no adverse effects attributable to terlipressin; specifically no episodes of pulmonary oedema and no cardiac events. **Conclusion:** This study represents the first prospective randomised trial of continuous terlipressin infusion in end-stage cirrhosis and demonstrates a significant increase in handgrip strength and reduction in paracentesis volume. Quality of life was significantly improved and there were no serious adverse events. The increase in handgrip strength is particularly impressive in a population for whom muscle strength usually declines, and reflects the impact of portal hypertension on sarcopenia in this cohort. These findings provide a strong rationale for the use of ambulatory CTI as a bridge to liver transplant in well-selected patients with cirrhosis.

Impact of CTI on ascites and HGS over 12 weeks

	MAD	95% CI	P value
Total paracentesis volume (L)	-11.36	-19.85, -2.99	0.01
Number of episodes of paracentesis	-1.75	-2.59, -0.925	< 0.001
Change in mean non-dominant HGS (kg)	+3.09	+1.11, +5.08	0.006

MAD = mean adjusted difference, HGS = handgrip strength

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5002 | EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN THE RESPONSE TRIAL: A PHASE 3 INTERNATIONAL, RANDOMIZED, PLACEBO-CONTROLLED STUDY

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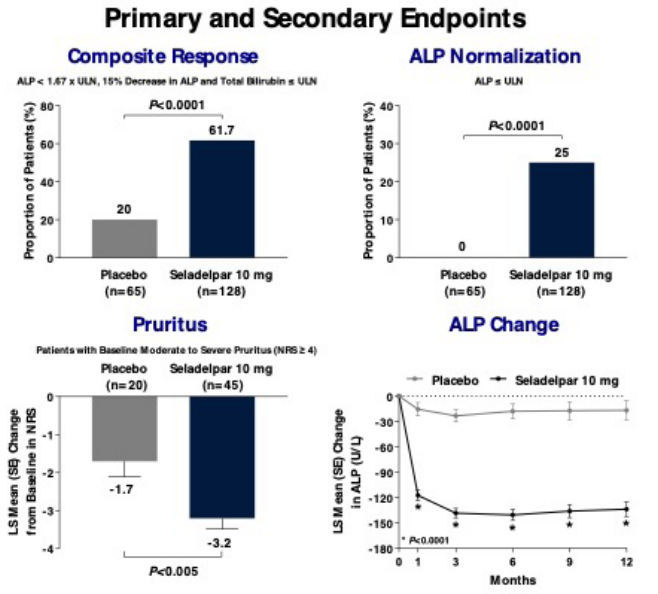
Background: Seladelpar, a potent and selective PPAR-delta agonist, has anti-cholestatic, anti-inflammatory and anti-pruritic activity. We report the results of a 12-month, placebo-controlled trial of seladelpar in patients with primary biliary cholangitis (PBC) at risk of disease progression (RESPONSE, NCT04620733). **Methods:** Eligible patients had ursodeoxycholic acid (UDCA) treatment for ≥12 months or were intolerant and had alkaline phosphatase (ALP) ≥1.67xupper-limit-of-normal (ULN) and total bilirubin (TB) ≤2xULN. Patients were randomized to receive either daily oral seladelpar 10 mg or placebo. Treatment was stratified by ALP and pruritus numerical rating scale (NRS; 0-10). The primary endpoint was a composite response of ALP <1.67xULN, ALP

decrease ≥15% and TB ≤ULN at Month 12. Key secondary endpoints were ALP normalization at Month 12 and change in NRS at Month 6. **Results:** We enrolled 193 pts (female 94.8%; mean age 56.7 years; 94% taking UDCA) with mean ALP 314.4 U/L and TB 0.76 mg/dL (13% >ULN). Patients had a baseline mean NRS of 3.0; 37.3% of patients reported moderate-to-severe itch (baseline NRS ≥4, mean NRS 6.3). At Month 12, 61.7% of patients achieved the primary composite response endpoint with seladelpar vs 20% with placebo (p<0.0001). The secondary endpoint of ALP normalization occurred in 25% of those receiving seladelpar vs 0% receiving placebo (p<0.0001). The average decrease in ALP for seladelpar was -133.9 U/L vs. -16.9 U/L for placebo (p<0.0001). Seladelpar, compared to placebo, lowered alanine aminotransferase by 23.5% vs. 6.5% and gamma-glutamyl transferase by 39.1% vs. 11.4%. The key secondary pruritus endpoint was met at Month 6 with seladelpar-treated patients with baseline NRS ≥4 reporting decreases of 3.2 vs 1.7 for placebo (p<0.005). Improvement of pruritus NRS on seladelpar was sustained through Month 12 (p<0.005). There were no treatment-related serious adverse events. Discontinuation from adverse events occurred in 3.1% of seladelpar and 4.6% of placebo patients. **Conclusion:** In this placebo-controlled pivotal trial of patients with PBC and incomplete response or intolerance to UDCA, seladelpar 10 mg for 12 months resulted in rapid, statistically significant and durable improvements in markers of cholestasis and liver injury, and improved pruritus. Seladelpar appeared overall safe and well tolerated through Month 12. The long-term safety and tolerability are being evaluated in an open-label trial (NCT03301506).



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5003 | ORAL LPCN 1148 IMPROVES SARCOPENIA AND HEPATIC ENCEPHALOPATHY IN PATIENTS WITH CIRRHOSIS

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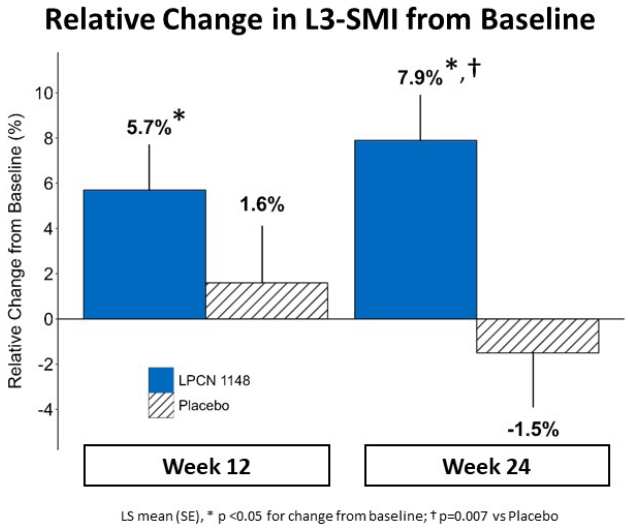
Background: Sarcopenia and anemia are highly prevalent in patients with liver cirrhosis and are associated with adverse clinical outcomes including hepatic encephalopathy (HE). Androgens are multimodal hormones which can address these conditions, however their safety and efficacy in a general population with cirrhosis have not been well established. **Methods:** In this eight-center, phase 2 trial, men with sarcopenia and cirrhosis awaiting liver transplant were randomized 1:1 to receive either oral LPCN 1148, an oral prodrug of testosterone (T), or placebo for 24 weeks (NCT04874350). Basal T level was not considered for study eligibility and participants were not asked to change diet, exercise, or background therapies including rifaximin or lactulose. The primary endpoint was the change from baseline to 24-weeks in skeletal muscle index measured by CT scan at L3 spine level (L3-SMI). **Results:** 29 participants (mean age=59 years, BMI=29 kg/m^2) were enrolled and received at least one dose of LPCN 1148 (n=15) or placebo (n=14). Baseline characteristics were similar; mean MELD and hemoglobin were 17 and 12.2 g/dL, respectively, 86% of participants had experienced ≥ 2 unique decompensation events, and 79% of participants were on therapy for HE. The primary endpoint was met, L3-SMI increased with LPCN 1148 compared to placebo (Δ 3.6±0.9 vs Δ -0.7±1.1 cm^2/m^2; p=0.007). This 3.6 cm^2/m^2 change equates to a 7.9% increase

in L3-SMI with LPCN 1148. The LPCN 1148 group experienced significantly fewer episodes of overt HE (CTCAE grade ≥2; p=0.02). Total days in hospital were 54 and 117 days for LPCN 1148 and placebo, respectively. 33% vs 0% of participants on LPCN 1148 and placebo, respectively, reported feeling "moderately" or "very much" better at 24 weeks (p=0.006). LPCN 1148 group increased Hb (Δ 1.2±0.3 vs Δ -0.1±0.3 g/dL; p=0.02) compared to placebo at Week 24. Other secondary endpoints with trends favoring LPCN 1148 include muscle quality, 6-min walk test, and Stroop test. The number and severity of treatment-emergent adverse events were similar across both arms. There were no incident cases of HCC, drug-induced liver injury, or thrombosis. **Conclusion:** LPCN 1148 is the first therapeutic intervention to both improve sarcopenia and reduce the number of overt HE episodes, in men with cirrhosis awaiting liver transplant. These results provide support for further study of LPCN 1148 for the treatment of sarcopenia and prevention of HE recurrence.



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5004 | THE MONOCLONAL ANTIBODY VIR-3434 AND siRNA VIR-2218 FOR THE TREATMENT OF CHRONIC HEPATITIS D VIRUS: PRELIMINARY RESULTS FROM THE PHASE 2 SOLSTICE TRIAL

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Background: Hepatitis D Virus (HDV) infection is an aggressive form of viral hepatitis with limited treatment options. In the Phase 2 SOLSTICE study (NCT05461170), we are investigating the efficacy and safety of VIR-2218, a small interfering ribonucleic acid (siRNA) targeting the HBx region of the HBV genome and VIR-3434, a Fc-engineered human monoclonal antibody targeting the conserved antigenic loop of HBsAg, in participants with HDV infection. **Methods:** To assess the contribution of agents, small cohorts of non-cirrhotic participants received three doses of either subcutaneous (SC) VIR-2218 200 mg (Cohort 1a) or SC VIR-3434 300 mg (Cohort 1b), administered 4 weeks apart. HDV RNA, HBsAg, PK, and safety were assessed. At Week 12, participants who did not achieve ALT normalization *and* virologic response (defined as undetectable *or* ≥ 2 $\log_{10}$ decrease in HDV RNA) when given monotherapy were eligible for combination therapy with VIR-2218 and VIR-3434 given every 4 weeks (Cohort 2c). **Results:** Preliminary results from Cohorts 1a, 1b, and 2c at Week 12 are summarized in the Table below. All participants were on nucleoside analogues (tenofovir or entecavir) with undetectable HBV DNA throughout. Twenty percent (1/5) of participants who received VIR-2218 Q4W monotherapy achieved a virologic response at Week 12. Two participants normalized ALT and one other participant (baseline HBsAg >10^4 IU/mL and HDV RNA > 10^5 IU/mL) experienced ALT increase starting at Week 12 (peaked with Grade 4 ALT elevation at Week 15). Fifty percent (3/6) of participants receiving VIR-3434 Q4W monotherapy achieved a virologic response at Week 12. No ALT elevations have been observed. PK/PD analysis suggests that Q2W VIR-3434 monotherapy could result in greater HBsAg and HDV RNA declines. Six participants (2 from Cohort 1a, 4 from Cohort 1b) transitioned to combination therapy (Cohort 2c); 5 participants

have completed 12 weeks of treatment. Virologic response was observed in 100% (5/5) of participants at Week 12; to date, no ALT elevations have been observed even in participants with HBsAg >10^4 IU/mL. Few treatment-emergent adverse events occurred across all cohorts and were all Grade 1 and 2, including myalgia, headache, and chills. **Conclusion:** After only 3 doses of VIR-2218+VIR-3434, all participants achieved HDV virologic response by Week 12. Evaluation of participants receiving VIR-3434 300mg Q2W monotherapy and *de novo* VIR-3434 and VIR-2218 combination therapy is ongoing.

SOLSTICE Preliminary Results

	Cohort 1a VIR-2218 Monotherapy (N=5)	Cohort 1b VIR-3434 Monotherapy (N=6)	Cohort 2c VIR-2218+3434 Combination Therapy (N=6[a])
Baseline Characteristics			
Age (year), Mean (SD)	47.6 (10.5)	43.2 (12.4)	41.0 (8.6)
Male, n (%)	2 (40)	3 (50)	4 (66.7)
ALT (U/L), Mean (SD)	64.4 (52.5)	59.0 (21.0)	60.3 (19.6)
HBsAg (log_{10} IU/mL), Median (IQR)	4.04 (3.17, 4.33)	4.09 (3.91, 4.30)	3.95 (3.17, 4.30)
HDV RNA (log_{10} IU/mL), Median (IQR)	5.38 (3.42, 5.69)	5.44 (3.93, 5.58)	4.70 (3.42, 5.58)
HDV genotype 1, n (%)	3 (60.0)	4 (66.7)	5 (83.3)
Week 12			
HDV Virologic Response[b], n (%)	1 (20%)	3 (50%)	5 (100%)
Reduction from Baseline in HDV RNA (log_{10} IU/mL), Median (IQR)	- 1.39 (-1.51, -1.04)	- 1.98 (-2.82, - 0.94)	- 4.29 (- 5.47, - 3.93)
HDV RNA < LLOQ[c], n (%)	1 (20%)	2 (33%)	5 (100%)
HDV RNA < LOD[d], n (%)	1 (20%)	1 (17%)	4 (80%)
Reduction from Baseline in HBsAg (log_{10} IU/mL), Median (IQR)	-1.35 (-1.52, -1.27)	-0.18 (-0.35, -0.09)	-3.88 (-4.03, -3.88)
ALT normalization[e], n (%)	2 (40%)	2 (33%)	1 (20%)
ALT (U/L), Mean (SD)	118.8 (145.5)	44.0 (19.5)	42.6 (7.5)
Grade 3/4 AE ALT Elevation, n (%)	1 (20%)[f]	0	0
Combined Endpoint[g], n (%)	0	1 (17%)	1 (20%)

[a] Cohort 2c has 6 total participants enrolled with 5 participants reaching at least 12 weeks. Baseline characteristics include the 6th participant.
[b] Undetectable or ≥ 2 log_{10} decrease in HDV RNA
[c] LLOQ = lower limit of quantification, <63 IU/mL, supplied by DDL
[d] LOD = limit of detection, <14 IU/mL, supplied by DDL
[e] ALT ≤ Upper limit of Normal (ULN): Female = 33 U/L; Male ULN = 40 U/L
[f] Baseline HBsAg was >10,000 IU/mL and HDV RNA >100,000 IU/mL. Grade 4 ALT elevation adverse event (AE) occurred at Week 15 of the study.
[g] Combined Endpoint = undetectable *or* ≥ 2 log_{10} decrease in HDV RNA + ALT normalization.

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5005 | EFRUXIFERMIN IN COMPENSATED CIRRHOSIS DUE TO NASH/MASH: RESULTS FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2b TRIAL (SYMMETRY)

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Background: NASH, or metabolic dysfunction-associated steatohepatitis (MASH), is characterized by liver steatosis and inflammation that may lead to fibrosis and cirrhosis (fibrosis stage 4, F4). FGF21 is an important regulator of whole-body metabolism and tissue-specific stress responses. Efruxifermin (EFX) is a long-acting, bivalent Fc–FGF21 analog. The SYMMETRY study assessed efficacy, safety, and tolerability of 36 weeks treatment with EFX in patients with NASH-associated cirrhosis without a history of decompensation. **Methods:** In this phase 2b, randomized, double-blind, placebo-controlled study (SYMMETRY), patients were randomly assigned (1:1:1) to once-weekly subcutaneous placebo or EFX (28 mg or 50 mg) for 96 weeks. The primary efficacy endpoint was the proportion of patients who achieved ≥1 stage improvement in fibrosis and no worsening of NASH, based on liver biopsies collected at Week 36 vs baseline. Patients are being followed for long-term safety and exploratory evaluation of efficacy through Week 96 (NCT05039450). **Results:** 181 patients were randomized and dosed (mean age, 61 yrs; 67% female; mean BMI, 36 kg/m²; 80% with type 2 diabetes, 22% with cryptogenic cirrhosis). Markers of fibrosis at baseline were consistent with NASH and cirrhosis (mean liver stiffness measurement [FibroScan], 24 kPa; mean ELF score, 11). At week 36, there was a trend toward ≥1-stage improvement in fibrosis and no worsening of NASH: 22% and 24% of patients in the EFX 28 mg and 50 mg groups, respectively, achieved the primary endpoint compared to 14% for placebo (Table). NASH resolved in 67% (*P*=.0004) and 60% (*P*=.0023) of patients in the EFX 28 mg and 50 mg groups, respectively, vs 26% for placebo. EFX was associated with significant improvements in non-invasive markers of liver injury and fibrosis, and was generally well tolerated. Most frequent drug-related adverse events (AEs) were transient, mild–moderate gastrointestinal grade-1 or -2 events; 12 subjects discontinued due to drug-related AEs. There were 21 serious AEs (not drug related, balanced among groups) and 1 death (placebo patient with pneumonia). **Conclusion:** At week 36, efruxifermin was associated with a trend toward fibrosis improvement. Patients had significant rates of NASH resolution, reductions in markers of liver injury and fibrosis,

and improvements in markers of glucose and lipid metabolism. These changes may translate to additional improvements in liver fibrosis by the end of the study (Week 96).

Table: Effects of Efruxifermin After 36 Weeks in Patients With NASH-associated Cirrhosis

	Placebo	EFX 28 mg	EFX 50 mg
Histologic Assessment (Liver Biopsy Analysis Set, N=153)			
Patients with Week 36 biopsy	**n = 57**	**n = 46**	**n = 50**
Fibrosis improvement by ≥1 stage and no worsening of NASH, n (%)	8 (14%)	10 (22%)	12 (24%)
Subset with definitive NASH at baseline	**n = 42**	**n = 36**	**n = 42**
NASH resolution, n (%)	11 (26%)	24 (67%) **	25 (60%) **
Fibrosis improvement by ≥1 stage and resolution of NASH, n (%)	4 (10%)	8 (22%)	6 (14%)
Change in Markers of Liver Injury and Fibrosis (Full Analysis Set; N=181)[1]			
Least Squares (LS) Mean Change from Baseline to Week 36	**(n=61)**	**(n=57)**	**(n=63)**
Pro-C3 (μg/L) (2nd Generation ELISA)	–16	–59 ***	–49 ***
ELF Score	+0.1	–0.2 *	–0.3 ***
Liver Stiffness (kPa) (FibroScan)	–4.3 ††	–3.6 †	–3.8 ††
ALT (U/L)	–4.9	–12.7 **	–11.4 **
AST (U/L)	–2.7	–10.1 ***	–11.7 ***
Markers of Metabolism (Full Analysis Set; N=181)[1]			
LS Mean Change From Baseline to Week 36	**(n=61)**	**(n=57)**	**(n=63)**
Adiponectin (%)	+9%	+114%***	+92% ***
Body Weight (kg)	–0.8	–0.8	–1.4 †
C-peptide (ug/L)	–0.63	–1.37 **	–1.37 **
Triglycerides (mg/dL)	–11.0	–37.0 **	–43.2 ***
Non–HDL-cholesterol (mg/dL)	–6.3	–13.3 †††	–20.5 **
Treatment-emergent Adverse Events (Safety Analysis Set; N=181)			
	n=61	**n=57**	**n=63**
Patients with any treatment-emergent AEs (TEAEs) n (%)	56 (92%)	56 (98%)	62 (98%)
Treatment-emergent serious AEs	6 (10%)	9 (16%)	6 (10%)
TEAEs leading to treatment discontinuation	2 (3%)	5 (9%)	8 (13%)
Serious AEs leading to death	1 (2%)	0 (0.0)	0 (0.0)
Patients with any study drug-related TEAEs (≥15%), n (%)	28 (46%)	35 (61%)	48 (76%)
Diarrhea, n (%)	9 (15%)	10 (18%)	19 (30%)
Nausea, n (%)	7 (12%)	11 (19%)	18 (29%)
Increased appetite, n (%)	3 (5%)	7 (12%)	17 (27%)
Injection site erythema, n (%)	5 (8%)	8 (14%)	13 (21%)
Drug-related TEAEs leading to discontinuation	1	3	8

[1] Data are presented for all patients in full analysis set, with available (non-missing) values; no imputations were performed for missing values.
* p<0.05, ** p<0.01, *** p<0.001, vs placebo; † p<0.05, †† p<0.01, ††† p<0.001, vs baseline (MMRM used for biomarkers, CMH for histology)

Disclosures:
Stephen A. Harrison – Akero: Grant/Research Support; Boehringer Ingelheim: Grant/Research Support; 89 Bio: Grant/Research Support; Axcella: Grant/Research Support; Hepion: Grant/Research Support; Gilead: Grant/Research Support; Genfit: Grant/Research Support; Genentech: Grant/Research Support; Galmed: Grant/Research Support; Galectin: Grant/Research Support; Enyo: Grant/Research Support; Cymabay: Grant/Research Support; Corcept: Grant/Research Support; Hightide: Grant/Research Support; Akero: Consultant; Viking: Grant/Research Support; Sagimet: Grant/Research Support; Poxel: Grant/Research Support; NorthSea: Grant/Research Support; NGM Bio: Grant/Research Support; Metacrine: Grant/Research Support; Madrigal: Grant/Research Support; Intercept: Grant/Research Support; Hepion: Consultant; GSK: Consultant; Gilead: Consultant; Genfit: Consultant; Echosens: Consultant; Chronic Liver Disease Foundation: Consultant; Axcella: Consultant; AstraZeneca: Consultant; Altimmune: Consultant; NGM Bio: Consultant; Medpace: Consultant; Madrigal: Consultant; Intercept: Consultant; HistoIndex: Consultant; Hightide: Consultant; Hepta Bio: Consultant; Sonic Incytes: Consultant; Sagimet: Consultant; Poxel: Consultant; Perspectum: Consultant; Novo Nordisk: Consultant; Novartis: Consultant; Northsea: Consultant; Pinnacle Clinical Research: Executive role; Viking: Consultant; Terns: Consultant; Altimmune: Grant/Research Support; AgomaAB: Consultant, Alentis: Consultant, Aligos: Consultant; Arrowhead: Advisor; Blade: Consultant, Bluejay: Consultant, BMS: Grant/Research Support; Boston: Consultant, Boxer: Consultant; BVF Partners: Advisor, Canfite: Consultant, Chronwell: Advisor; Chronwell: Stock – privately held company; Civi Biopharma: Consultant, Civi Biopharma: Grant/Research Support, Cohbar: Consultant, Conatus: Grant/Research Support , Conatus: Advisor, Fibronostics: Consultant, Forsite Labs: Consultant; Forsite Labs: Advisor; Fortress Biotech: Consultant, Fortess Biotech: Consultant, Fortess Biotech: Advisor, Galecto: Consultant; Gelesis: Consultant, GNS Healthcare: Consultant, GRI Bio: Consultant, Hepagene: Consultant; Humana: Advisor; Immuron: Grant/Research Support , Inipharma: Consultant, Innovate: Consultant, Ionis: Consultant; Kowa Research: Consultant, Merck: Consultant, MGGM: Consultant; Microba: Consultant, Neurobo: Consultant; Nutrasource: Consultant, Pathai: Advisor, Pfizer: Consultant; Pfizer: Grant/Research Support; Piper Sandler: Consultant, Prometic (now Liminal): Consultant, Ridgeline: Consultant, Second Genome: Grant/Research Support , Silverback: Consultant, Zahgen: Consultant,

5006 | EFFICACY AND SAFETY OF XALNESIRAN COMBINATION THERAPIES WITH AND WITHOUT AN IMMUNOMODULATOR IN VIROLOGICALLY-SUPPRESSED PARTICIPANTS WITH CHRONIC HEPATITIS B: PRIMARY ENDPOINT RESULTS FROM THE PHASE 2, RANDOMIZED, CONTROLLED, ADAPTIVE, OPEN-LABEL PLATFORM STUDY (PIRANGA)

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Background: PIRANGA (NCT04225715) is a phase 2 platform study designed to evaluate safety, tolerability and efficacy of new combination therapies including one or more new molecular entities in chronic hepatitis B (CHB) participants (pts) with the aim of achieving higher functional cure rates than standard of care. Here, we report the primary endpoint results of xalnesiran, a small interfering ribonucleic acid (siRNA) targeting the HBsAg coding region of the HBV genome (RO7445482, RG6346) in combination with nucleos(t)ide analogues (NUC), with or without an immunomodulator: pegylated interferon alfa-2a (Peg-IFN-α, Pegasys®), or ruzotolimod (toll-like receptor 7 agonist, RO7020531, RG7854). **Methods:** HBeAg positive or negative virologically suppressed CHB pts on established NUC therapy were randomized into the combination treatment arms (see table) or the NUC control arm for 48 weeks (wks) of treatment and 48 wks of follow-up. Randomization was stratified based on screening HBsAg level (<1000 IU/mL, ≥1000 IU/mL), with a minimum of 12 pts per arm with a screening HBsAg level <1000 IU/mL. Xalnesiran was administered subcutaneously (SC) every 4 wks for 48 wks, ruzotolimod was administered orally every other day during wks 13-24 and wks 37-48, Peg-IFN-α was administered SC weekly for 48 wks, NUC was administered daily for 48-96 wks (until NUC stopping criteria were met). The primary endpoint was the proportion of pts with HBsAg loss (<0.05 IU/mL) at 24 wks post-end of treatment (EOT). **Results:** A total of 160 pts were enrolled. The majority were male (83%), Asian (94%), with a mean (range) age of 42 (24-65) years. At baseline, 70% were HBeAg negative, 98% had normal ALT levels with a mean (SD) serum HBsAg level of 2.82 (0.92) log10 IU/ml. At 24 wks post-EOT, HBsAg loss was observed in 2/30 (6.7%), 1/30 (3.3%), 7/30 (23.3%), 4/34 (11.8%), and 0/35 (0%) pts from Arms 1-4 and the NUC control arm, respectively. All pts who achieved HBsAg loss by EOT had a baseline HBsAg level <1000 IU/mL. Xalnesiran therapy given in combination with NUC with or without an immunomodulator resulted in safety findings consistent with the individual modalities. 11 serious AEs (SAE) were reported, 10 were assessed as not related to any study drug, and 1 SAE of panic reaction was related to Peg-IFN-α. **Conclusion:** Xalnesiran combination therapies of 48 wks treatment duration were generally safe and well tolerated. Higher HBsAg loss rates were observed when xalnesiran was combined with an immunomodulator (Peg-IFN-α or ruzotolimod).

Arms (mITT Population)	HBsAg loss at EOT n (%)	HBsAg loss at 12 wks post-EOT n (%)	**HBsAg loss at 24 wks post-EOT n (%)**	HBsAg seroconversion at 24 wks post-EOT n (%)
Arm 1 (N=30) xalnesiran 100mg+NUC	2/30 (6.7%)	2/30 (6.7%)	**2/30 (6.7%)**	1/30 (3.3%)
Arm 2 (N=30) xalnesiran 200mg+NUC	1*/30 (3.3%)	1*/30 (3.3%)	**1*/30 (3.3%)**	0/30 (0%)
Arm 3 (N=30) xalnesiran 200mg+ Peg-IFN-α 180 µg+NUC	9/30 (30.0%)	8/30 (26.7%)	**7/30 (23.3%)**	6/30 (20.0%)
Arm 4 (N=34) xalnesiran 200mg+ ruzotolimod 150mg+NUC	6/34 (17.6%)	7/34 (20.6%)	**4/34 (11.8%)**	1/34 (2.9%)
NUC control arm (N=35)	0/35 (0%)	0/35 (0%)	**0/35 (0%)**	0/35 (0%)

*1 pt from Arm 2 had HBsAg loss at baseline.

- Modified ITT population: All pts who were randomized and received at least one dose of assigned treatment were analyzed. (Note: 1 pt randomized to the NUC control arm withdrew consent prior to Day 1 and was therefore excluded from the mITT population)
- Participants with missing or no response assessment at specified timepoint were classified as non-responders.

Disclosures:
The following people have nothing to disclose: Wenhong Zhang

5007 | EFFICACY AND SAFETY OF ELAFIBRANOR IN PRIMARY BILIARY CHOLANGITIS: RESULTS FROM THE ELATIVE™ DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PHASE 3 TRIAL

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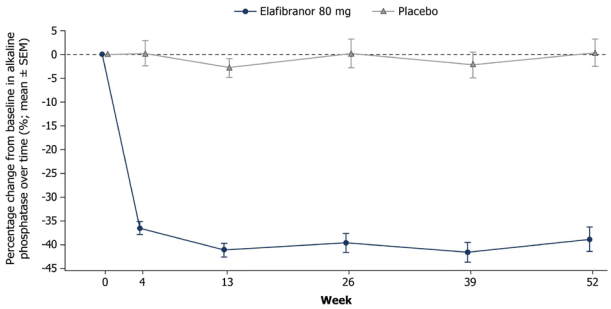
Background: Primary biliary cholangitis (PBC) is a rare autoimmune, cholestatic liver disease. Elafibranor is an oral, dual peroxisome proliferator-activated receptor-α/δ agonist. The ELATIVE™ phase 3 trial (NCT04526665) evaluated the efficacy and safety of elafibranor in patients with PBC with an inadequate response or intolerance to ursodeoxycholic acid (UDCA). **Methods:** Patients 18–75 years old with alkaline phosphatase (ALP) ≥1.67 x upper limit of normal (ULN) and total bilirubin (TB) ≤2 x ULN were randomized 2:1 to elafibranor 80 mg or placebo once daily for at least 52 weeks (W). Patients with an inadequate response to UDCA continued their stable UDCA regimen during the trial. The primary endpoint was response at W52, defined as ALP <1.67 x ULN with ≥15% reduction from baseline and TB ≤ULN, in the intent-to-treat (ITT) population. Key secondary endpoints were ALP normalization at W52 in the ITT population and, in patients with moderate-to-severe pruritus (baseline PBC Worst Itch Numeric Rating Scale [WI NRS] ≥4), change in pruritus through W52 (PBC WI NRS; daily itch averaged over each 4W period); other secondary endpoints were change from baseline through W52 in PBC-40 Itch and 5-D Itch total scores, in patients with moderate-to-severe pruritus. **Results:** Of 161 randomized patients (elafibranor: n=108; placebo: n=53), 148 (92%) completed the 52W double-blind period. Baseline characteristics were comparable between the elafibranor and placebo groups (female: 94% versus 98%; mean age: 57.5 versus 56.4 years; mean ALP: 321.3 versus 323.1 U/L; liver stiffness >10 kPa and/or bridging fibrosis or cirrhosis: 34% versus 38%). At W52, 55 (51%) patients receiving elafibranor met the primary endpoint versus 2 (4%) receiving placebo (p<0.0001). ALP normalization occurred in 16 (15%) patients receiving elafibranor, versus none receiving placebo (p=0.0019). The treatment estimate of percentage change from baseline in ALP for elafibranor versus placebo was −40.6% (95% confidence intervals: −47.8 to −33.5; p<0.0001; **Figure**); ALP reduction occurred rapidly, within 4W. In patients with moderate-to-severe pruritus, least square (LS) mean change in PBC WI-NRS through W52 was −1.9 for patients receiving elafibranor (n=44) versus −1.1 for placebo (n=22; p=0.1970). Patients receiving elafibranor had greater reductions at W52 in PBC-40 Itch (LS mean: −2.5 versus −0.1; p=0.0070) and 5-D Itch (LS mean: −4.2 versus −1.2; p=0.0199) total scores. The most common treatment-emergent adverse events (TEAEs) occurring in proportionally more patients receiving elafibranor versus placebo (>1% difference) included abdominal pain, diarrhea, nausea, and vomiting; all were mild or moderate. Serious TEAEs occurred in 10.2% and 13.2% patients receiving elafibranor and placebo, respectively. **Conclusion:** Treatment with elafibranor was well tolerated and led to significant improvement in biomarkers of cholestasis, along with improved pruritus symptoms.

Figure. Mean percentage change from baseline in ALP levels over time



No. of Patients						
Elafibranor 80 mg	108	104	107	104	102	94
Placebo	53	48	49	49	49	49

Shown is the mean percentage change from baseline in ALP levels over time. **Abbreviations:** ALP: alkaline phosphatase; SEM: standard error of the mean.

Disclosures:
Mario Reis Alvares-Da-Silva – AstraZeneca: Speaking and Teaching; Bayer: Speaking and Teaching; Biolab: Speaking and Teaching; Galectin: Speaking and Teaching; Gilead: Speaking and Teaching; Ipsen: Speaking and Teaching; Merz: Speaking and Teaching; Novartis: Speaking and Teaching; Orphan DC: Speaking and Teaching; Roche: Speaking and Teaching; AstraZeneca: Advisor; Bayer: Advisor; Biolab:

Advisor; Galectin: Advisor; Gilead: Advisor; Merz: Advisor; Novartis: Advisor; OrphanDC: Advisor; Novo Nordisk: Speaking and Teaching;

5008 | ORAL αvβ6/αVβ1 INTEGRIN INHIBITION IN PRIMARY SCLEROSING CHOLANGITIS: 12-WEEK INTERIM SAFETY AND EFFICACY ANALYSIS OF INTEGRIS-PSC, A PHASE 2a TRIAL OF BEXOTEGRAST

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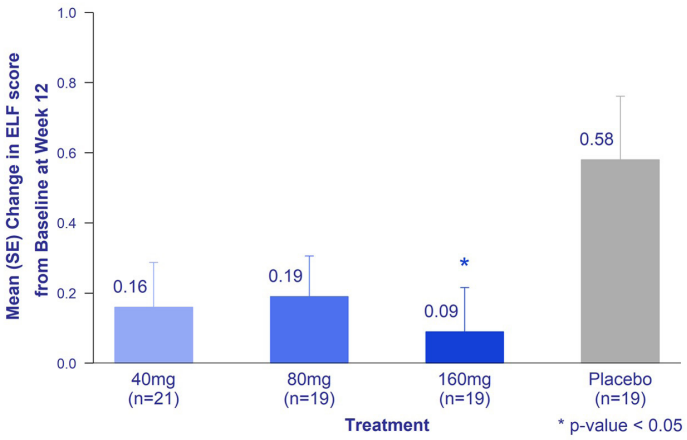
Background: There is no approved treatment for primary sclerosing cholangitis (PSC). In PSC, integrins expressed on cholangiocytes ($\alpha_v\beta_6$) and myofibroblasts ($\alpha_V\beta_1$) regulate TGF-β activity, a key driver of fibrosis. Bexotegrast (BEXO) is an oral, once-daily, inhibitor of integrins $\alpha_v\beta_6$ and $\alpha_V\beta_1$ in development for PSC. INTEGRIS-PSC is an ongoing, double-blind, dose-ranging, randomized, placebo-controlled Phase 2a study of BEXO in patients with PSC and evidence of liver fibrosis evaluating safety, tolerability, pharmacokinetics, and effects on markers of fibrosis (enhanced liver fibrosis [ELF] and N-terminal type III collagen propeptide [PRO-C3]). **Methods:** The study had a 3:1 (BEXO:placebo) randomization and stratification by ursodeoxycholic acid (UDCA) use; with doses of 40mg, 80mg or 160mg evaluated over a 12-week treatment period. A 320mg dose cohort is ongoing and will be evaluated over 24-48 weeks. Key entry criteria included: large duct PSC with stable inflammatory bowel disease, if present, and suspected liver fibrosis (without cirrhosis) as evidenced by ≥1: ELF ≥ 7.7, liver stiffness by transient elastography (TE) ≥8 kPa or magnetic resonance elastography ≥2.4 kPa or historical biopsy. **Results:** At baseline (n=85), the mean age was 45y, 75% were male and 65% on UDCA. BEXO- and placebo-treated groups were generally comparable across baseline characteristics and parameters, including (mean (SD)): ALP 264 (152) U/L, ALT 82 (63) U/L, bilirubin 0.8 (0.4) mg/dL, TE 9.0 (2.9) kPa, ELF 9.4 (0.92) and PRO-C3 47.1 (23.12) ug/mL. The incidence of treatment-emergent-adverse-events (TEAE) and study discontinuations were comparable between BEXO-treated and placebo groups. . Events of cholangitis were less frequent with BEXO than placebo (3/14). No serious TEAEs were deemed related to BEXO. At Week 12, the mean change in ELF score (figure) with 160 mg was 84% lower compared to placebo ($p<0.05$). Similar findings were observed for PRO-C3. **Conclusion:** In this 12-week interim analysis of INTEGRIS-PSC (NCT04480840), BEXO's safety and tolerability were comparable to placebo. In this fibrosis-enriched population, increases in ELF scores and PRO-C3 observed in the placebo group were attenuated by BEXO at all doses, with statistical significance observed with 160 mg at 12 weeks. This analysis supports proof of mechanism for antifibrotic activity of BEXO in at-risk PSC patients.



Disclosures:
Richard Pencek – Pliant Therapeutics: Employee;

5009 | EFFICACY AND SAFETY OF BULEVIRTIDE IN COMBINATION WITH PEGYLATED INTERFERON ALFA-2a IN PATIENTS WITH CHRONIC HEPATITIS DELTA: PRIMARY ENDPOINT RESULTS FROM A PHASE 2b OPEN-LABEL, RANDOMIZED, MULTICENTER STUDY MYR204

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Background: Bulevirtide (BLV) is a first-in-class entry inhibitor approved in the EU for the treatment of chronic HDV infection (CHD). This Phase 2 study (MYR204; NCT03852433) evaluated the safety and efficacy of BLV (2 and 10mg) with or without peginterferon alfa-2a (PegIFN) in patients with CHD and compensated liver disease. **Methods:** 174 patients with CHD were randomized (1:2:2:2) and stratified based on the absence or presence of compensated cirrhosis to receive (A) PegIFN for 48 weeks (w); (B) BLV 2mg + PegIFN or (C) BLV 10mg + PegIFN for 48w, both followed by 48w of monotherapy with BLV 2mg or 10mg, respectively; or (D) BLV 10mg for 96w. All patients were followed up for 48w after end of treatment (EOT). The primary endpoint was sustained virologic response at W24 after EOT (SVR24) defined as undetectable HDV RNA (<LLOQ, target not detected) with predefined comparison between Arms C and D. **Results:** Demographics and baseline characteristics were similar across all arms. The majority were male (71%) and White (87%) with mean age of 41 years (SD, 8.7). Overall, 35% had compensated cirrhosis, mean liver stiffness was 13.1 (7.72) kPa, mean HDV RNA was 5.3 (1.2) $\log_{10}$ IU/mL, mean alanine aminotransferase (ALT) was 114.0 (94.8) U/L, 28% were on nucleos(t)ide analogue therapy, and 48% were interferon experienced. Efficacy and safety results are shown in the table. SVR24 was achieved by 17% of Arm A, 30% of Arm B, 46% of Arm C, and 12% of Arm D (*P*=.0003; Arm C vs D). ALT normalization and composite endpoint at W24 after EOT were superior with BLV 10mg + PegIFN compared to monotherapy. HBsAg loss was only observed with the combination. The most common adverse events (AE) were leukopenia, neutropenia, thrombocytopenia, influenza-like illness, lymphopenia, and vitamin D deficiency. AEs observed in the BLV + PegIFN combination arms were similar to those with PegIFN monotherapy. BLV dose-dependent bile acid elevations were asymptomatic, and levels returned to baseline after EOT. 6 patients (3%) discontinued treatment; none were assessed as related to BLV. **Conclusion:** In patients with compensated CHD, BLV in combination with PegIFN resulted in higher rates of SVR24 and ALT normalization vs BLV or PegIFN monotherapy. Combination therapy was well tolerated with AEs consistent with PegIFN monotherapy. Longer-term off-treatment data at W48 will help define durability of finite therapy with BLV in combination with PegIFN for CHD.

Table. Efficacy and Safety at Week 24 After EOT

Number of patients, n (%)	Arm A PegIFN (n = 24)	Arm B BLV 2mg + PegIFN (n = 50)	Arm C BLV 10mg + PegIFN (n = 50)	Arm D BLV 10mg (n = 50)
SVR24	4 (16.7)	15 (30)*	23 (46)*	6 (12)
ALT normalization[1]	6 (25)	20 (40)	28 (56)*	15 (30)
Composite endpoint[2]	3 (12.5)	13 (26)*	21 (42)*	4 (8)
HBsAg loss with/without seroconversion	0	4 (8)	2 (4)	0
Treatment-emergent AEs				
Any AE	22 (92)	49 (98)	50 (100)	42 (84)
Grade 3-4 AE	13 (54)	27 (54)	30 (60)	10 (20)
AE leading to study drug D/C[3]	1 (4)	3 (6)	2 (4)	0
SAE[4]	3 (13)	3 (6)	8 (16)	2 (4)

D/C: discontinuation; HBsAg, hepatitis B surface antigen; SAE, serious adverse event.
*$P \leq .05$. Fisher's exact test was used for each comparison of binary endpoint vs Arm D (BLV 10mg monotherapy) using a significance level of .05.
[1]ALT normalization defined as ≤31 U/L for females and ≤41 U/L for males (Russian sites) or ≤34 U/L for females and ≤49 U/L for males (all other sites).
[2]Undetectable HDV RNA and ALT normalization.
[3]All AEs leading to study drug D/C occurred in first 48w.
[4]No on-treatment SAEs assessed as related to BLV.

Disclosures:
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5010 | LIVER TRANSPLANTATION FOR SEVERE ACUTE ON CHRONIC LIVER FAILURE: RESULTS OF A PROSPECTIVE NATIONAL PILOT PROGRAMME OF WAITLIST PRIORITISATION.

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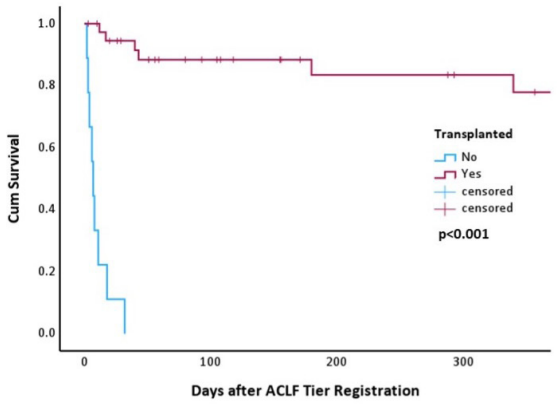
(7)University of Newcastle, Newcastle, (8)Freeman Hospital, (9)Royal Free Hospital, (10)UCL, Kent, United Kingdom, (11)Edinburgh Royal Infirmary, Edinburgh, United Kingdom, (12)UCL Institute for Liver and Digestive Health, University College of London

Background: Severe Acute on Chronic Liver Failure (ACLF) is a critical illness with very high short-term mortality and few effective treatment options. Emergency Liver Transplantation (ELT) is seldom utilised with the presumption of poor post-ELT survival and high resource use, as ACLF develops in the setting of chronic illness and sarcopenia, and the severity and progression is such that the 'window' for ELT is very short. Existing needs-based graft allocation models may underestimate mortality in ACLF resulting in delayed organ offering. We report the results of the first prospective national pilot programme of prioritised ELT for ACLF. **Methods:** A new United Kingdom national prioritisation ACLF tier was piloted across the 7 UK LT centres, with a planned interval from tier registration to ELT of 3 days. Novel inclusion and exclusion criteria and process of multidisciplinary review were developed for rapid ELT candidacy assessment. Standard UK criteria for alcohol use were applied with alcoholic hepatitis excluded. All candidates had cirrhosis and ACLF requiring critical care support with expected 28-day survival of <50%, and 50 initial registrations planned. **Results:** Forty-seven candidates were registered: median age 47 years (IQR 40-52), 55% male. 31 (66%) had been previously registered for LT and deteriorated on the standard waitlist, and 16 (34%) first presentations with ACLF. All were EASL-CLIF ACLF grade 3 and CLIF-OF score was 15 (13-16), bilirubin was 24.8 mg/dl (16.8-32) and HE grade 3 (1-4). 62% were ventilated and 87% requiring renal replacement therapy and vasopressors. 38 (81%) underwent ELT with whole grafts from brain dead donors after a wait of 3 (2-5) days; all those not transplanted died 7 (4-14) days after registration (figure 1, Log-rank p<0.001). Length of post-ELT stay: ICU 11 (6-23) days and hospital 38 (range 14-106). Post-ELT Follow-up was 164 (49-463) days with 84% survival: 1-year patient survival was 78%. Six (16%) died at 42 (16-220) days after ELT; non-survivors were more often first presentations with ACLF and those with prolonged waitlist times. **Conclusion:** In selected critically ill patients with ACLF, where no other effective therapeutic interventions exist, prioritised ELT is a practical and lifesaving intervention with relatively good survival. Post-ELT length of hospital stay is greater than elective LT but not excessive. This prioritised pathway for severe ACLF should be further validated in other regions.

Figure 1. Patient Survival after ACLF Registration.



Disclosures:
William Bernal – Versantis: Consultant; Flagship Pioneering: Consultant;

5011 | ICOSABUTATE IN NASH/MASH WITH FIBROSIS: RESULTS FROM A RANDOMISED, MULTICENTRE, DOUBLE-BLIND, PLACEBO CONTROLLED, PHASE 2b TRIAL (ICONA)

Stephen A. Harrison[1], Naim Alkhouri[2], Jacques Benun[3], Grisell Ortiz-Lasanta[4], Madhavi Rudraraju[1], Hilde H. Steineger[5], David Fraser[5], Arun J Sanyal[6] and ICONA Study Investigators , (1)Pinnacle Clinical Research, San Antonio, TX, (2)Arizona Liver Health, Phoenix, AZ, (3)Pinnacle Clinical Research, Austin, TX, (4)FDI Clinical Research, (5)Northsea Therapeutics, (6)Virginia Commonwealth University, Richmond, VA

Background: Icosabutate (ICO) is a free-fatty acid receptor (FFAR) 1 and 4 (beta-arrestin2) agonist. With tissue specific regulation of endogenous GLP-1 production, glucose stimulated insulin secretion and peripheral insulin sensitivity, FFAR1 and 4 are putative targets for the treatment of type 2 diabetes (T2D). With additional anti-inflammatory effects in liver macrophages, they may also serve as highly attractive targets for the treatment of MASH/NASH. We performed a phase 2b, 52-week, placebo-controlled trial (ICONA) testing the efficacy of ICO in NASH/MASH patients with F1-F3 fibrosis. **Methods:** 280 patients were randomized, of which 178 PP subjects met the histologic criteria (F1-3, NAS ≥4, ≥1 ballooning, ≥1 inflammation) based on a 3-member panel read. Patients were randomized 1:1:1 to receive once-daily, oral ICO 300mg, ICO 600mg or placebo for 52 weeks. The primary objective was to establish the proportion of patients with NASH/MASH resolution without worsening in fibrosis, with secondary objectives evaluating fibrosis improvement, as well as changes in markers of liver injury, glycemic parameters, lipids and safety and tolerability of ICO. A subgroup analysis

was performed in patients with T2D. **Results:** Patients (69% female; mean age 53 yrs; mean BMI 36.7 kg/m^2, 81% F2/F3, 46% T2D) were randomized to 300mg ICO (n= 57), 600mg ICO (n=62), or placebo (n=59). Although the SAP defined primary endpoint was not met, an increase in the proportion of patients achieving the more stringent endpoint that includes a ≥2 point decrease in NAS was seen in the 600mg ICO treated arm (25.8%, p=0.04) compared with placebo (11.9%) (Table). A greater treatment effect (placebo adjusted) was observed in patients with T2D, with 35.5% (p=0.007) of T2D patients treated with ICO 600 mg achieving NASH resolution and ≥2 point decrease in NAS compared to 4% in placebo. For fibrosis, 28.6% (p=0.005) and 19.4% (p=0.02) of T2D patients achieved a ≥1-stage improvement without worsening of NASH in the 300mg and 600mg arms respectively, versus none in placebo. ICO markedly improved multiple markers of liver injury, inflammation, fibrosis, glycemic control (placebo corrected ~1% decrease in HbA1c in T2D patients with HbA1c ≥6.5% without increased incidence of hypoglycaemia), atherogenic lipids and hsCRP. Both doses of ICO were well tolerated, with mild-to-moderate GI events the most frequently reported AEs. Consistent with the mechanism of action, neutral effects on both MRI-PDFF and bodyweight were seen. **Conclusion:** Icosabutate improves histology, multiple non-invasive markers of liver injury/inflammation/fibrosis, glucose, and lipid metabolism in patients with F1-F3 fibrosis due to NASH/MASH. The enhanced results in subjects with T2D support further development in this patient population, with potential for attenuation of both liver related and CV outcomes.

Histologic assessments in all patients			
Proportion of patients, n (%)	**Placebo (n=59)**	**ICO 300mg (n=57)**	**ICO 600mg (n=62)**
NASH resolution without worsening of fibrosis	13.6	19.3	25.8
NASH resolution without worsening of fibrosis and ≥2-point decrease in NAS	11.9	15.8	25.8*
≥1-stage fibrosis improvement	11.9	28.1	24.2
≥1-stage fibrosis improvement without worsening of NASH	11.9	26.3	22.6
Histologic assessments in T2D patients			
Proportion of patients, n (%)	**Placebo (n=23)**	**ICO 300mg (n=28)**	**ICO 600mg (n=31)**
NASH resolution without worsening of fibrosis	8.7	17.9	35.5*
NASH resolution without worsening of fibrosis and ≥2-point decrease in NAS	4.3	14.3	35.5**
≥1-stage fibrosis improvement without worsening of NASH	0	28.6**	19.4*
Histologic assessments in F2/F3 T2D patients			
Proportion of patients, n (%)	**Placebo (n=17)**	**ICO 300mg (n=26)**	**ICO 600mg (n=23)**
NASH resolution without worsening of fibrosis	5.6	19.2	30.4*
NASH resolution without worsening of fibrosis and ≥2-point decrease in NAS	0	15.4	30.4*
≥1-stage fibrosis improvement without worsening of NASH	0	30.8*	21.7*
Change in markers of liver injury, inflammation and fibrosis in T2D patients[1]			
Change from baseline	**Placebo (n=35)**	**ICO 300mg (n=40)**	**ICO 600mg (n=39)**
Relative change (%) in ALT	-9.6	-33§§§	-42§§§
Relative change (%) in AST	-16	-18§	-38§§§
Change in Enhanced Liver Fibrosis (ELF) Score (LS mean)	-0.04	-0.06	-0.48§§§
Change in mean in Pro-C3 (ug/L)	-2.86	-7.96§§§	-10.24§§§
Change in mean hsCRP (mg/dl)	1.4	-1.1	-2.55*
Change in HbA1c in T2D patients with ≥6.5% at baseline			
LS mean change from baseline	**Placebo (n=27)**	**ICO 300mg (n=27)**	**ICO 600mg (n=26)**
Change in HbA1c (%) absolute	0.35	-0.75*	-0.61*

Table. *p<0.05, **p<0.01 vs placebo; §p<0.05, §§§p<0.001 vs baseline. CMH test (histology). MMRN (all other endpoints), [1]All T2D subjects with baseline and 52 wk biopsies. PP analysis shown, excludes 9 subjects with protocol breach (6 related to GLP-1 therapy).

Disclosures:
The following people have nothing to disclose: David Fraser

5012-C | EIGHT-WEEK VERSUS TWELVE-WEEK OF TENOFOVIR ALAFENAMIDE TO PREVENT PERINATAL TRANSMISSION OF HEPATITIS B (TAF-PPT): A MULTICENTRE, OPEN-LABEL, NON-INFERIORITY, RANDOMIZED CONTROLLED TRIAL

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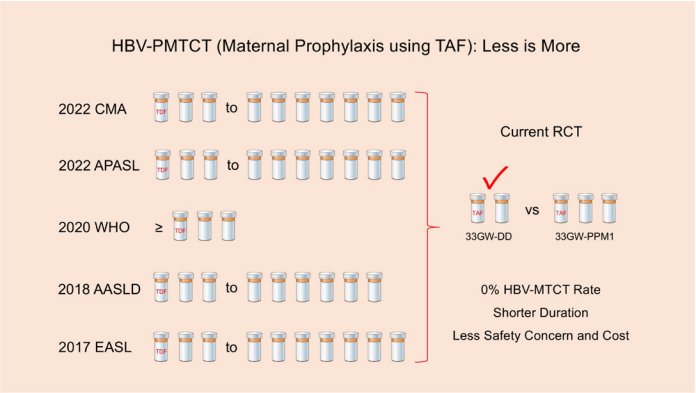
Background: Several latest international guidelines recommended 9 to 30 weeks of maternal antiviral prophylaxis to prevent mother-to-child transmission of hepatitis B virus (HBV-MTCT). We aimed to compare expected eight versus twelve weeks of tenofovir alafenamide fumarate (TAF) therapy to prevent HBV-MTCT. **Methods:** This multicentre, open-label, non-inferiority, randomized controlled trial was conducted at six Chinese referral hospitals. Eligible pregnant women with HBV DNA of 5·3-9·0 logs IU/mL received TAF from the first day of 33 gestational weeks to delivery date (33GW-DD, expected eight weeks) or to postpartum month 1 (33GW-PPM1, expected twelve weeks) were 1:1 randomly enrolled and followed until PPM6. All infants received standard immunoprophylaxis. The primary outcomes were birth defects and infants' HBV-MTCT rate at seven months of age. The secondary outcomes are safety concerns and virologic responses. This completed trial registered with ClinicalTrials.gov, number NCT04850950. **Results:** Between April 26, 2021, and June 16, 2023, 119 and 120 intention-to-treat pregnant women were enrolled, and 110 and 112 per-protocol mother-infant dyads in 33GW-DD and 33GW-PPM1 groups completed the study. At delivery, 96·5% (111/115) and 97·4% (113/116) of intention-to-treat women achieved HBV DNA <5·3 $\log_{10}$ IU/mL in two groups. No per-protocol infant had birth defect in either group (0% [0/115] versus 0% [0/116]). At PPM7, the infants' HBV-MTCT rate was similar between the two groups, both in the intention-to-treat analysis (7·6% [9/119] versus 6·7% [8/120], p=0·788) and the per-protocol analysis (0% [0/110] versus 0% [0/112]). TAF was well tolerated, and no one discontinued therapy due to adverse events; 15·1% (18/119) versus 18·3% (22/120) of women had mildly elevated alanine aminotransferase levels in two groups (p=0·507). The infants' physical and neurological development at birth and at seven months were normal in two groups. **Conclusion:** Expected eight-week TAF treatment to prevent HBV-MTCT is generally safe and effective. Future large-scale validation studies are warranted.



Disclosures:
The following people have nothing to disclose: Qing-Lei Zeng

5013-C | VIR-2218 AND VIR-3434 WITH OR WITHOUT PEGYLATED INTERFERON ALFA-2a FOR THE TREATMENT OF CHRONIC HBV INFECTION: END OF TREATMENT (EOT) RESULTS AFTER 24 WEEKS OF THERAPY (MARCH STUDY PART B)

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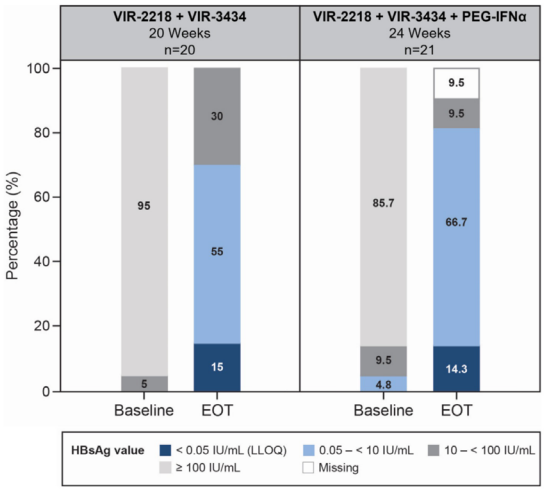
Background: There is an unmet need for a well-tolerated curative regimen for chronic hepatitis B virus (HBV) infection, which is associated with significant morbidity and mortality. VIR-2218 is an investigational small interfering ribonucleic acid (siRNA) targeting the HBx region of the HBV genome, and VIR-3434 is an investigational engineered human monoclonal antibody targeting the antigenic loop of HBsAg. We previously reported that 24 weeks of VIR-2218 + PEG-IFNα achieved HBsAg loss in 5.6% of participants at EOT. Part B of the ongoing phase 2 open-label MARCH study is evaluating the safety, tolerability, and antiviral activity of 24- and 48-week regimens of VIR-2218 and VIR-3434 with or without PEG-IFNα for the treatment of chronic HBV infection. Here, we report data through EOT for the 24-week cohorts. **Methods:** Eligible participants were adults with chronic HBV infection and any baseline HBsAg level who were on continuous NRTI therapy for ≥2 months. This preliminary analysis reflects on treatment data from cohorts evaluating VIR-2218 + VIR-3434 for 20 weeks or VIR-2218 + VIR-3434 + PEG-IFNα for 24 weeks. VIR-2218, VIR-3434, and PEG-IFNα are administered SC at 200 mg every 4 weeks (Q4W), 300 mg Q4W, and 180 µg weekly, respectively. Participants are followed for ≥48 weeks post-EOT. Primary endpoints are the proportion of participants with TEAEs, SAEs, and HBsAg loss (<0.05 IU/mL) at EOT and at 24 weeks post-EOT. **Results:** A total of 41 participants were enrolled across VIR-2218 + VIR-3434 (n=20) and VIR-2218 + VIR-3434 + PEG-IFNα (n=21); 65.9% were HBeAg-negative. The proportions of participants achieving HBsAg loss or HBsAg <10 IU/mL at EOT are presented in the **Figure**. Grade 3 or 4 TEAEs were reported in no subjects in the VIR-2218 + VIR-3434 cohort and 6/21 subjects in the VIR-2218 + VIR-3434 + PEG-IFNα cohort (all were deemed related to PEG-IFNα). One of these 6 participants in the VIR-2218 + VIR-3434 + PEG-IFNα cohort also experienced 2 PEG-IFNα-related SAEs. **Conclusion:** When administered for 20-24 weeks, VIR-2218 + VIR-3434, with and without PEG-IFNα, achieved similar HBsAg loss rates of 14.3% and 15% of participants at EOT, approximately 3 times higher than the rate previously observed for 24 weeks of VIR-2218 + PEG-IFNα. This supports an additive effect of VIR-3434. No new safety concerns were identified for the combination with PEG-IFNα. Additional cohorts evaluating 48 weeks of treatment are ongoing.

Figure: HBsAg Distribution at Baseline and End of Treatment by Cohort



Disclosures:
Kosh Agarwal – Gilead Sciences, Inc.: Speaking and Teaching; Saigmet: Consultant; Roche: Consultant; Janssen: Consultant; GSK: Consultant; Boehringer Ingelheim: Consultant; Bristol

Myers Squibb: Consultant; Arbutus: Consultant; Assembly Biosciences: Consultant; Gilead Sciences, Inc.: Consultant; Aligos: Consultant; Gilead Sciences, Inc.: Grant/Research Support; GSK: Speaking and Teaching; Janssen: Speaking and Teaching; Sobi: Speaking and Teaching; Drug Farm: Consultant;

5014-C | A PHASE II TRIAL OF FAZPILODEMAB (BFKB8488A), A FIBROBLAST GROWTH FACTOR RECEPTOR 1C/KLOTHO B AGONIST, IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

Stephen A. Harrison[1], Yixuan Zou[2], Lu Zhang[2], Ajit Dash[2], Abigail Garchitorena[2], Jill Fredrickson[2], Johnny Gutierrez[2], Kenta Yoshida[2], Yanqiu Liu[2], Rebecca Kunder[2], Maria Wilson[2] and Chin Wong[2], (1)University of Oxford, Oxford, United Kingdom, (2)Genentech, Inc.

Background: Fazpilodemab (BFKB8488A) is a bispecific antibody targeting cells expressing both fibroblast growth factor receptor 1c and Klotho β. Fazpilodemab demonstrated trends in improvement in markers of liver health in patients with type 2 diabetes mellitus and metabolic dysfunction-associated steatotic liver disease (MASLD). Here, we report results from a Phase II study (NCT04171765) of fazpilodemab in patients with MASH. **Methods:** Adult patients diagnosed with MASH were randomized to receive subcutaneous fazpilodemab (50, 75, or 100 mg) or placebo every two weeks for up to 52 weeks. The primary outcome was the proportion of patients with resolution of MASH without worsening of fibrosis at Week 52; secondary outcomes included improvement in liver histology (2-pts reduction in NAFLD activity score (NAS) with ≥1-pt reduction in lobular inflammation or hepatocellular ballooning and no worsening of fibrosis), improvement in liver fibrosis (≥1 NASH Clinical Research Network fibrosis stage improvement) without worsening of steatohepatitis (no increase in NAS for ballooning, inflammation, or steatosis), and the change in hepatic fat fraction (assessed by magnetic resonance imaging derived proton density fat fraction) at Week 52/early termination (ET). The study planned to enroll 260 patients but was discontinued early for strategic business reasons. **Results:** A total of 46 patients were enrolled (mean age 53 years, 52.2% female), among whom 27 had Week 52/ET biopsy. There was a trend for improvement favoring fazpilodemab-treated groups in the histological endpoints (Table 1). A transient improvement was observed in hepatic fat fraction between fazpilodemab-treated groups and placebo, but the treatment effect was not sustained at Week 52/ET. A trend for improvement in ALT, AST, adiponectin, and PRO-C3 was observed. Overall, 90.9% of fazpilodemab-treated patients and 69.2% of placebo-treated patients experienced ≥1 AE; 5 (10.9%) patients experienced a grade ≥3 AE. The most common AEs were nausea, COVID-19, and diarrhea. The incidence of treatment-emergent anti-drug antibodies was 21.2% (7/33) but did not appear to impact safety. **Conclusion:** In patients with MASH, fazpilodemab was adequately tolerated and demonstrated an acceptable safety profile. Improvements in liver enzymes were observed following fazpilodemab, though the early study termination and small sample size in this study limit the interpretation of clinical effect.

Table 1: Changes in histological endpoints, hepatic fat fraction, liver enzymes and biomarkers, and adverse event rates in patients treated with placebo or fazpilodemab.

Baseline value and percent change from baseline at Week 52 and/or ET, mean (SD)*								
	Placebo (n=13)		50 mg (n=11)		75 mg (n=11)		100 mg (n=11)	
	n	Value	n	Value	n	Value	n	Value
Hepatic fat fraction (%)								
Baseline	13	20.2 (6.4)	11	20.7 (6.1)	11	19.3 (4.0)	11	18.1 (7.7)
Week 16	10	-17.1 (12.9)	8	-37.9 (31.3)	9	-11.3 (52.7)	8	-52.1 (20.3)
Week 52/ET	7	-20.6 (31.1)	7	-7.1 (37.6)	7	-16.0 (64.6)	6	-21.3 (36.2)
ALT (U/L)								
Baseline	13	61.6 (29.9)	11	57.8 (24.3)	11	68.4 (52.3)	11	71.7 (39.9)
Week 16	10	-21.5 (24.4)	9	-36.0 (33.9)	9	-16.5 (27.0)	7	-52.6 (14.9)
Week 52	6	2.8 (47.4)	8	-36.7 (39.5)	8	15.1 (118.2)	4	-35.2 (27.6)
ET	5	-9.30 (54.0)	1	75.0 (NE)	2	13.1 (42.2)	5	-52.0 (19.4)
AST (U/L)								
Baseline	13	43.4 (18.8)	11	42.5 (16.3)	11	51.6 (30.0)	11	60.0 (41.9)
Week 16	10	-16.6 (30.0)	9	-38.0 (28.4)	9	-22.8 (21.2)	7	-50.9 (16.7)
Week 52	6	10.2 (47.6)	8	-37.3 (39.8)	8	21.7 (146.9)	4	-28.9 (29.4)
ET	5	-13.9 (48.2)	1	52.1 (NE)	2	-4.8 (17.9)	5	-54.6 (14.6)
Serum Adiponectin (ng/mL)								
Baseline	13	3323.1 (1748.9)	11	3036.4 (2356.4)	11	3140.0 (1012.4)	11	3790.9 (1929.5)
Week 16	10	40.1 (71.2)	9	56.6 (69.7)	9	52.1 (54.4)	7	30.4 (37.7)
Week 52	5	16.8 (43.5)	5	19.8 (19.9)	7	31.4 (44.0)	3	105.9 (199.2)
ET	5	-23.3 (21.7)	2	16.1 (52.2)	2	15.1 (64.4)	4	33.0 (52.0)
PRO-C3 (ng/mL)								
Baseline	13	44.9 (8.1)	11	49.6 (14.8)	11	51.9 (15.2)	11	47.3 (11.3)
Week 16	10	-3.8 (9.3)	9	-6.7 (18.0)	9	-18.6 (7.9)	7	-26.0 (17.4)
Week 52	6	3.1 (29.2)	6	-7.9 (37.4)	7	33.1 (132.7)	3	-14.6 (11.0)
ET	5	-11.9 (17.0)	2	4.9 (10.1)	2	-16.9 (28.5)	4	-17.5 (8.8)
Proportion of patients who experienced improvements at Week 52/ET, n (%) [95% CI]								
	Placebo (n=6)		50 mg (n=6)		75 mg (n=7)		100 mg (n=6)	
Resolution of NASH without worsening of fibrosis	1 (16.7) [0 to 54.8]		3 (37.5) [0 to 77.3]		1 (14.3) [0 to 47.4]		2 (33.3) [0 to 79.4]	
Improvement in liver histology	1 (16.7) [0 to 54.8]		3 (37.5) [0 to 77.3]		3 (42.9) [0.0 to 86.7]		2 (33.3) [0 to 79.4]	
Improvement in liver fibrosis and no worsening of steatohepatitis	1 (16.7) [0 to 54.8]		2 (25.0) [0 to 61.3]		2 (28.6) [0.0 to 69.2]		1 (16.7) [0 to 54.8]	
Proportion of patients who experienced at least one AE, n (%)								
	Placebo (n=13)		50 mg (n=11)		75 mg (n=11)		100 mg (n=11)	
Any Grade	9 (69.2)		11 (100)		9 (81.8)		10 (90.9)	
3-5 Grade	0		2 (18.2)		2 (18.2)		1 (9.1)	

*Baseline values are presented as mean (SD). All non-baseline values are presented as mean percent change from baseline (SD).
NE, not evaluable.

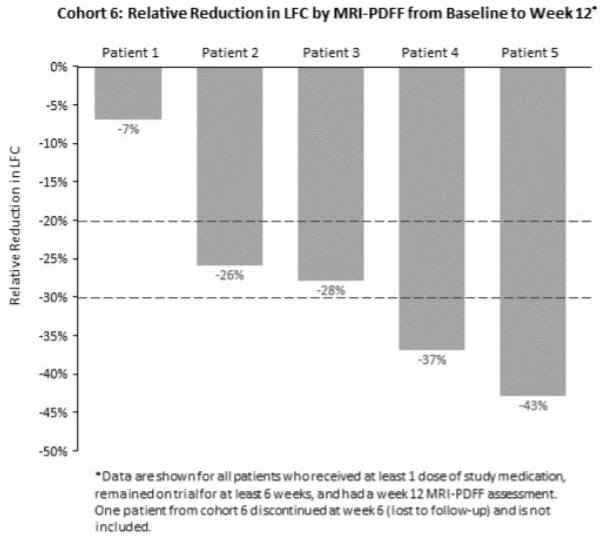
Disclosures:
Rebecca Kunder – Genentech: Stock - publicly traded company; Genentech: Employee, IGM Biosciences: Employee;

5015-C | TITLE: MIRICORILANT REDUCED LIVER FAT AND CARDIOMETABOLIC DISEASE MARKERS IN A PHASE 1b, OPEN-LABEL DOSE-FINDING STUDY IN PATIENTS WITH NON-ALCOHOLIC STEATOHEPATITIS (NASH)

Naim Alkhouri[1], Madhavi Rudraraju[2], Kris V. Kowdley[3], Mark Leibowitz[4], Jacques Benun[5], Robert A. Jenders[4], Anita Kohli[1], Mazen Noureddin[6], Rashmee Patil[7], Iulia Cristina Tudor[8], Jeffrey Botbyl[8], Joseph Custodio[8], Rafael

Mayoral Moñibas[8], Aprille Espinueva[8], Kavita Juneja[8], William Guyer[8] and Stephen A. Harrison[2], (1)Arizona Liver Health, Phoenix, AZ, (2)Pinnacle Clinical Research, San Antonio, TX, (3)Liver Institute Northwest, (4)Velocity Clinical Research, (5)Pinnacle Clinical Research, (6) Houston Methodist Hospital, Houston Research Institute, Houston, TX, (7)South Texas Research Institute, (8) Corcept Therapeutics, Inc

Background: Miricorilant has a novel mechanism of action as a nonsteroidal selective glucocorticoid receptor modulator (SGRM) with high activity in the liver. In a phase 2a trial, 4 patients (pts) with presumed NASH taking miricorilant (600 or 900 mg daily) had rapid reductions in liver fat content (LFC) of 39–74% after ~4 weeks of treatment; however, improvement was accompanied by increases in ALT and AST. No pts met Hy's Law criteria, and transaminase elevations resolved after miricorilant was discontinued (Kowdley et al. AASLD 2021). Our objective was to evaluate if significantly lower doses and intermittent dosing of miricorilant can gradually reduce LFC without a corresponding rise in liver enzymes. **Methods**: This phase 1b, open-label trial (NCT05117489) of adult pts with presumed NASH included 10 cohorts of pts who received miricorilant doses ranging from 30 to 200 mg with intermittent or daily regimens for 12 or 24 weeks. The primary endpoint was change in LFC from baseline by MRI-PDFF. **Results**: 63 pts were enrolled, with a mean age of 51.3 years, 60.3% female, mean BMI of 38.1 kg/m^2, mean LFC of 19.1%, and mean ALT of 54.3 U/L at baseline. Across all cohorts, responders (pts with ≥30% reduction in LFC from baseline) receiving intermittent miricorilant lost LFC more gradually and were less likely to have a rise in ALT >3x the upper limit of normal compared to daily dosing. Cohort 6 (100 mg miricorilant BIW for 12 weeks, n=6) had the best benefit-risk profile: at week 12, 5 pts had a mean relative reduction in LFC of −28.15% (standard deviation [SD]: 13.5), with a corresponding decline in liver enzymes (mean change from baseline: ALT, −4.0 [SD: 21.4]; AST, −6.0 [SD: 7.2]). Additionally, pts in cohort 6 had improved overall lipid profiles, glycemic markers, and fibrosis biomarkers, with mean change from baseline at week 12 of −9.8 mg/dL for LDL, −20.8 mg/dL for triglycerides, −6.8 mg/dL for fasting glucose, −5.40 mIU/L for insulin, −1.92 for HOMA-IR, and −0.19 for ELF score. No change in mean body weight occurred. Overall, TEAEs occurred in 82.5% (n=52) of pts, with the most common being headache; 4.8% (n=3) of pts had grade ≥3 TEAEs. Two serious TEAEs occurred; neither was related to miricorilant. **Conclusion**: Twice weekly 100 mg miricorilant was safe and well-tolerated and resulted in reduced LFC and improved hepatic, lipid, and glycemic markers. Based on these findings, a phase 2b study (MONARCH) of intermittent miricorilant in NASH is underway.



Disclosures:
Aprille Espinueva – Corcept Therapeutics: Employee;

5016-C | THE NOVEL THYROID HORMONE RECEPTOR BETA AGONIST VK2809 SIGNIFICANTLY REDUCES LIVER FAT IN PATIENTS WITH NASH AND FIBROSIS, RESULTS FROM THE PRIMARY ENDPOINT OF THE ONGOING PHASE 2b VOYAGE STUDY

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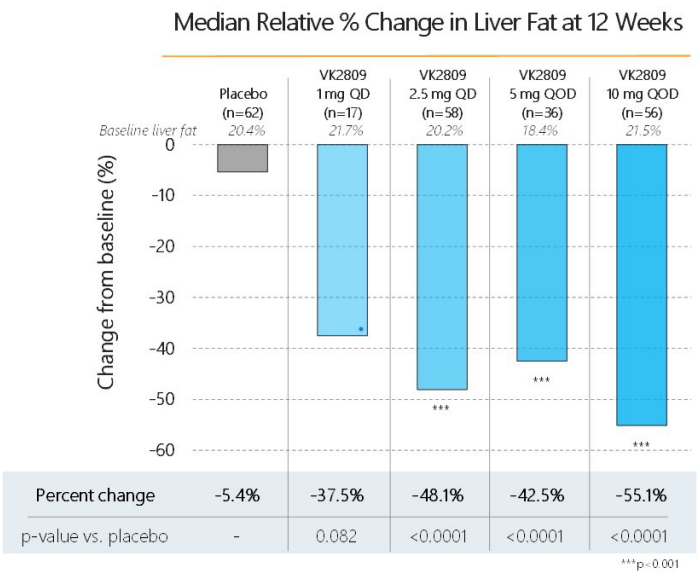
Background: Thyroid hormone is an important regulator of lipid metabolism, particularly acting via the beta isoform of the hepatic T3 receptor. VK2809 is a small molecule prodrug of a potent thyroid receptor beta agonist. VK2809 is selectively cleaved in hepatic tissues by the action of cytochrome P450 isozyme 3A4, to release a pharmacologically active metabolite. VK2809 has demonstrated robust reductions in plasma lipids, hepatic fat content, and hepatic collagen content in animal models of NASH. A prior Phase 2a study of VK2809 in patients with NAFLD demonstrated relative reductions in liver fat exceeding 50% after 12 wks of dosing. The aim of the current study is to evaluate the efficacy and safety of VK2809 in patients with biopsy-confirmed NASH and fibrosis. **Methods:** The Phase 2b VOYAGE study is a randomized, double-blind, placebo-controlled, multicenter, international trial designed to assess the efficacy, safety and tolerability of VK2809 in patients with biopsy-confirmed NASH and fibrosis. Enrollment included patients with at least 8% liver fat content as measured by MRI-PDFF, as well as F2 and F3 fibrosis. Up to 25% of patients may have F1 fibrosis provided that they possess at least one additional risk factor. The primary endpoint evaluated the change in MRI-PDFF from baseline to wk 12 in patients treated with VK2809 compared to placebo. Secondary objectives include the evaluation of histologic changes by hepatic biopsy after 52 wks of treatment. **Results:** Patients receiving VK2809 demonstrated statistically significant reductions in liver fat content relative to placebo after 12 wks of treatment. Least squares mean absolute change from baseline in MRI-PDFF was -10.9% for VK2809 10 mg QOD (p<0.0001), -8.0% for VK2809 5 mg QOD (p<0.0001), -9.9% for VK2809 2.5 mg QD (p<0.0001), -4.1% for 1 mg QD (p=0.018), and -1.4% for placebo. Median relative change from baseline in liver fat content was 55.1% for VK2809 10 mg QOD, -42.5% for VK2809 5 mg QOD, -48.1% for VK2809 2.5 mg QD, -37.5% for 1 mg QD, and -5.4% for placebo. Up to 85% of patients receiving VK2809 experienced at least a 30% relative reduction in liver fat content. Reductions in liver fat were similar between patients with F2 and F3 fibrosis, as well as among patients with and without type 2 diabetes. Patients receiving VK2809 demonstrated statistically significant reductions in LDL-C, triglycerides and the atherogenic proteins ApoB, Lp(a), and ApoC-III. The majority of treatment-related adverse events were reported as mild or moderate. Discontinuations due to adverse events were low and balanced among placebo and treatment arms. Rates of nausea, diarrhea, stool frequency, and vomiting were similar among VK2809-treated patients compared to placebo. **Conclusion:** VK2809 produced significant reductions in liver fat after 12 wks of dosing in patients with biopsy confirmed NASH and fibrosis. Dosing in the study continues and patients will be assessed by hepatic biopsy after 52 wks of treatment.



Disclosures:
Disclosure information not available at the time of publication: Brian Lian

5017-C | TRIAL OF A DEFINED BACTERIAL CONSORTIUM, VE303, TO TREAT HEPATIC ENCEPHALOPATHY

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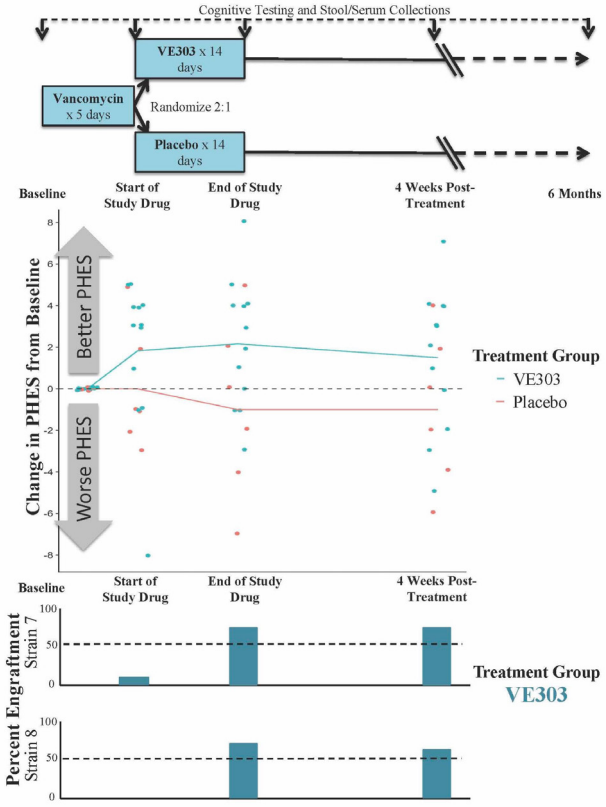
Background: Current hepatic encephalopathy (HE) therapies have limited ability to reverse HE signs and symptoms, resulting in poor quality of life, rising hospitalization rates, and mortality. Novel therapies are desperately needed and targeting the microbiome is promising. VE303 contains 8 nonpathogenic Clostridia strains, known to produce short-chain fatty acids and secondary bile acids – metabolites that may be beneficial in HE. We evaluated the safety and efficacy of VE303 to treat HE. **Methods**: We performed a phase 2A single center randomized controlled, double-blind trial of VE303 in 18 adult patients with a history of overt HE (NCT04899115). Eligible patients were taking lactulose and rifaximin, no recent systemic antibiotics, and had MELD ≤20. All patients received 5 days of vancomycin to increase VE303 strain colonization, followed by randomization to 14 days of VE303 vs placebo (2:1). The primary safety endpoint was the percentage of patients who experienced a serious adverse event (SAE) through 4 weeks post-treatment. The primary efficacy endpoint was change in psychometric HE score (PHES) from pre-vancomycin to 4 weeks post-treatment. Stool samples underwent metagenomic sequencing. **Results**: Of 19 patients enrolled, 1 withdrew prior to receiving vancomycin, and the remaining 18 patients completed study drug and were

followed for 6 months. Patients were 53% men, mean age 59 years (SD 9), 53% alcohol, 26% MASLD, and 16% MetALD cirrhosis, and mean MELD 11 (SD 4). Despite randomization, VE303 patients had more overt HE hospitalizations in the year prior to enrollment (1.5 vs 0.8) and lower baseline PHES (-6.3 vs -5.0) than placebo patients. Efficacy: Patients who received VE303 had a mean change in PHES score of +1.5 (SD 3.5) compared to -1.0 (SD 3.7) in patients who received placebo (*P* = 0.20). 67% patients who received VE303 had at least 1 point increase in PHES, compared to 33% who received placebo. Safety: 17% patients who received VE303 had at least one SAE through 4 weeks post-treatment (all overt HE hospitalizations), compared to 0% patients who received placebo. 33% patients who received VE303 had at least one overt HE hospitalization by month 6, compared to 17% patients who received placebo. These 4 VE303 patients had 3.3 overt HE hospitalizations/person in the year prior to enrollment, compared to 0 in the placebo patient. Mechanism: Shifts in the stool bacteria community structure following the treatment period did not differ between the VE303 and placebo groups. In the patients who received VE303, 2 of 8 strains engrafted in >50% of patients at the end of VE303 treatment and at 4 weeks post-treatment while none of patients who received placebo had strain engraftment. **Conclusion**: VE303 was safe, led to certain strain engraftment, and a higher percentage with improved psychometric HE scores in patients with a history of overt HE. A larger trial to verify these findings and to determine patient subgroups most likely to benefit is warranted.



Disclosures:
Patricia Pringle Bloom – Vedanta Biosciences: Grant/ Research Support; Nexilico: Consultant;

5018-C | SAFETY, TOLERABILITY, AND OUTCOMES OF SOFOSBUVIR/VELPATASVIR IN TREATMENT OF CHRONIC HEPATITIS C VIRUS DURING PREGNANCY: INTERIM RESULTS FROM THE STORC STUDY

Catherine Anne Chappell, University of Pittsburgh and STORC study team

Background: Over the past decade, hepatitis C virus (HCV) screening and detection in pregnancy has increased significantly. While AASLD/IDSA guidelines support individualization of HCV treatment in pregnancy, there are limited data to guide patient-centered discussions about risks and benefits for the maternal-infant dyad. Our objective is to present interim data from the STORC study, an international, multi-center study evaluating the safety and efficacy of sofosbuvir/velpatasvir (SOF/VEL) for HCV treatment in pregnancy. **Methods:** In this phase 4, open-label, single-arm study, pregnant individuals with HCV infection are enrolled between 20+0- and 30+0-weeks' gestation and treated with a 12-week course of SOF/VEL. HCV RNA testing is performed at screening, enrollment, 4, 8 and 12 weeks after SOF/VEL initiation, at delivery and 12 weeks after SOF/VEL completion (SVR12). The primary endpoints are SVR12 and preterm birth (defined as < 37 weeks' gestation). Infants are followed for one year with HCV RNA testing. **Results:** From July 2022 to September 2023, 32 pregnant individuals with HCV were screened and 26 were enrolled. Five were excluded due to incarceration (n=2), declined enrollment (n=1), had clinically significant drug use (n=1), or hemolytic disease of the fetus (n=1). One enrollment is pending. Median age of enrolled participants was 30.5 years (range 18, 40). All identified as women. Most identified as White (n=21, 81%), 5 (19%) identified as other races, including Black, Native American, Pacific Islander and multiracial and 3 (11.5%) identified as Hispanic. At enrollment, median HCV RNA of 5.8 (range 3.2, 6.7) $\log_{10}$ copies/mL. After initiation of SOF/VEL, undetectable HCV RNA was noted in 19/25 (76%) at 4 weeks, 19/21 (90%) at 8 weeks and 19/19 (100%) at 12 weeks of treatment (Figure). All participants had undetectable HCV RNA 15/15 (100%) at delivery and 12/12 (100%) at SVR12. Among participants who have delivered (n=19), 2 (10.5%) had a preterm birth. Median gestational age for all births was 38+0 weeks' (range 33+5, 41+1). All adverse events related to SOF/VEL were less than grade 3 and none discontinued treatment. Of 19 infants, 12 were tested for HCV RNA, and all were undetectable at 2 months and/or 6 months of age. **Conclusion:** The interim data from the STORC study provides preliminary reassurance regarding the safety and efficacy of SOF/VEL administration after 20 weeks' gestation. Recruitment for the STORC study is ongoing.

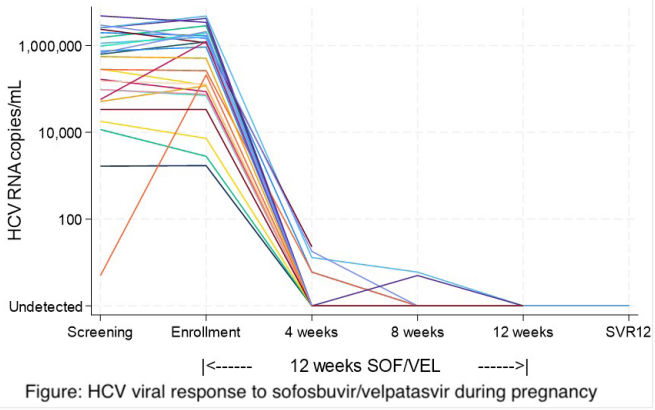


Figure: HCV viral response to sofosbuvir/velpatasvir during pregnancy

Disclosures:
Catherine Anne Chappell – Gilead Sciences: Grant/Research Support; Gilead Sciences: Advisor; Organon: Grant/Research Support;

5019-C | COMBINED EFFECT OF OBETICHOLIC ACID AND BEZAFIBRATE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND INADEQUATE RESPONSE TO OR INTOLERANCE OF URSODEOXYCHOLIC ACID: RESULTS FROM TWO PHASE 2 CLINICAL TRIALS

Cynthia Levy[1], Vaclav Hejda[2], Alexandre Louvet[3], Ziad Younes[4], Manuel Mendizabal[5], Alan Bonder[6], Heng Zou[7], Antonio Civitarese[7], Alejandra Villamil[8] and Frederik Nevens[9], (1)University of Miami School of Medicine, (2)University Hospital in Pilsen, (3)University Hospital of Lille, (4)Gastro One, Germantown, TN, (5)Hospital Universitario Austral, (6)Beth Israel Deaconess Medical Center, Boston, MA, (7)Intercept Pharmaceuticals, Inc., (8)Hepatic Autoimmunity Unit, Hospital Italiano De Buenos Aires, Buenos Aires, Argentina, (9)University Hospital KU Leuven

Background: Obeticholic acid (OCA) and bezafibrate (BZF) have each shown benefits for patients (pts) with primary biliary cholangitis (PBC). Two randomized, double-blind, active-controlled phase 2 trials (213 and 214) assessed the effects of combination OCA/BZF vs BZF monotherapy on safety/tolerability, as well as on serum biomarker levels and rates of biochemical remission. A range of doses and formulations were explored in pts with PBC who had inadequate response to or were unable to tolerate ursodeoxycholic acid (UDCA). Topline data from Study 213 and a planned interim analysis from Study 214 are presented. **Methods:** In Study 213, pts were randomized 1:1:1:1 to receive oral once-daily BZF 200 mg (B200) immediate release (IR), BZF 400 mg (B400) sustained release (SR), OCA 5 mg titrated to 10 mg at week 4 + BZF 200 mg IR (OCA/B200 IR), or OCA 5 mg titrated to 10 mg at week 4 + BZF 400 mg SR (OCA/B400 SR), all for 12 weeks. In Study 214, pts were randomized 1:1:1:1 to BZF 100 mg IR (B100 IR), BZF 400 mg IR (B400 IR), OCA 5 mg (no titration) + BZF 100 mg IR (OCA/B100 IR), or OCA 5 mg + BZF 400 mg IR (OCA/B400 IR), all for 12 weeks. Biochemical remission was defined as alkaline phosphatase (ALP), gamma-glutamyl transferase, alanine aminotransferase, and aspartate aminotransferase levels ≤ upper limits of normal (ULN), with total bilirubin (TB) ≤0.6xULN at week 12. Safety was assessed by adverse events. **Results:** Study 213 included 75 pts; Study 214's interim analysis included the first 41 of the planned 72 pts. Median dose of UDCA at baseline was 14.068 (Study 213) and 11.364 (Study 214) mg/kg/d. Independent of BZF formulation (IR vs SR), OCA/B400 showed a >60% reduction in ALP (−60.6% in 213, −65.4% in 214) and >20% reduction in TB (−24.7% in 213, −21.1% in 214); >65% of pts achieved normalization of ALP (≤ULN; 66.7% in 213, 70.0% in 214) and ≥90% achieved TB ≤0.6xULN (100% in 213, 90.0% in 214) at week 12 (Figure 1A-D). At week 12, OCA/B400 induced biochemical remission in 44.4% of pts in Study 213 and 40.0% of pts in Study 214 (Figure 1E-F). Treatment-emergent adverse events were generally balanced across cohorts in both studies; 1 pt in the OCA/B400 cohort of study 213 discontinued due to severe pruritus. The rate of new events of pruritus was lower in the OCA/B400 SR cohort of Study 213 (2/18 pts) vs preliminary data for OCA/B400 IR cohort of Study 214 (7/10 pts), likely due to the different formulations of BZF used in each study. **Conclusion:** These results suggest short-term administration of OCA/BZF was generally well tolerated and has therapeutic potential to normalize multiple serum biomarkers associated with improved clinical outcomes. Low rates of pruritus were observed in the OCA/B400 SR cohort of Study 213, which were significantly lower than those in the preliminary OCA/B400 IR cohort of Study 214 and the phase 3 POISE study. The data support progression to phase 3 development of the sustained release formulation of BZF with low doses of OCA.

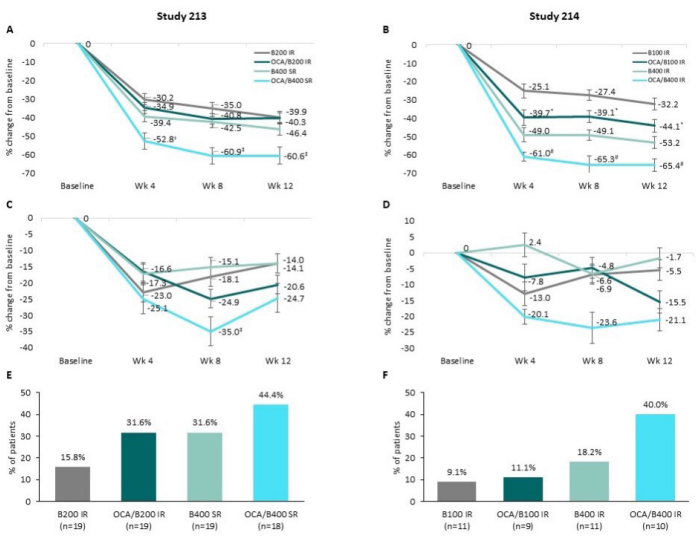


Figure 1. Effect of BZF monotherapy and OCA + BZF combination therapy in studies 213 and 214 on percentage change from baseline in ALP (**A-B**) and TB (**C-D**), as well as biochemical remission† (**E-F**) in patients with PBC at week 12

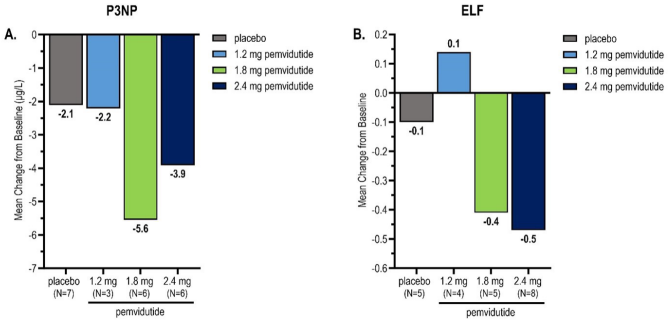
†Biochemical remission was defined as ALP, GGT, ALT, and AST levels ≤ULN, with TB ≤0.6xULN.
‡p<0.05 for OCA/B400 SR compared to B400 SR.
*p<0.05 for OCA/B100 IR compared to B100 IR.
#p<0.05 for OCA/B400 IR compared to B400 IR.
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; B100, bezafibrate 100 mg; B200, bezafibrate 200 mg; B400, bezafibrate 400 mg; BZF, bezafibrate; GGT, gamma-glutamyl transferase; IR, immediate release; OCA, obeticholic acid; PBC, primary biliary cholangitis; SR, sustained release; TB, total bilirubin; ULN, upper limit of normal.

Disclosures:
Antonio Civitarese – Intercept Pharmaceuticals, Inc.: Employee;

5020-C | PEMVIDUTIDE-INDUCED LIVER FAT REDUCTION IN SUBJECTS WITH NONALCOHOLIC FATTY LIVER DISEASE CORRELATE WITH IMPROVEMENTS IN NON-INVASIVE MARKERS OF INFLAMMATION AND FIBROSIS: RESULTS OF A 24-WEEK MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL

Stephen A. Harrison[1], Shaheen Tomah[2], John J Suschak[2], Jonathan Kasper[2], M. Scot Roberts[2], M Scott Harris[2] and Sarah K Browne[2], (1)Pinnacle Clinical Research, San Diego, CA, (2)Altimmune, Inc.

Background: Pemvidutide is a long-acting, balanced GLP-1/glucagon (GCG) dual receptor agonist under development for the treatment of NASH and obesity. We previously reported that pemvidutide 1.8 mg weekly (QW) led to a 7 reduction in liver fat content (LFC) by MRI-PDFF after 24 weeks of treatment. This analysis examined the correlations between these changes in LFC with changes in non-invasive markers of inflammation and fibrosis. **Methods:** 64 subjects with nonalcoholic fatty liver disease (NAFLD), defined as LFC ≥10% by MRI-PDFF, were randomized in a 1:1:1:1 ratio to receive 1.2 mg, 1.8 mg, 2.4 mg pemvidutide, or placebo QW for 24 weeks. Subjects with baseline serum alanine aminotransferase (ALT) >75 IU/L or evidence of significant liver stiffness (Fibroscan ≥10 kPa) were excluded. Assessments included changes in LFC, MRI-based corrected T1 (cT1) imaging, ALT, Enhanced Liver Fibrosis test (ELF), and the procollagen type III N-terminal peptide (P3NP) component of PRO-C3. **Results:** Median baseline body mass index (BMI), LFC, cT1, ALT, P3NP, and ELF were 36.8 kg/m^2, 20.6%, 906.5 ms, 31.0 IU/L, 8 µg/L, and 8.7 respectively. Across the entire study population, reductions in LFC correlated with reductions in cT1 (R^2: 0.7; p<0.0001) and serum ALT (R^2: 0.3; p<0.0001). In subgroup analyses of subjects receiving pemvidutide 1.8 mg QW with suspected fibrosis, defined as baseline P3NP and ELF in the upper tertiles of the study population (mean 10.5 µg/L and 9.4, respectively), P3NP decreased by 5.6 µg/L (-46.5%) versus 2.1 µg/L (-13%) in placebo, respectively, corresponding to a decrease in ELF of 0.4 (4.3%) in 1.8 mg vs. 0.1 (1.1%) decrease in placebo. **Conclusion:** Pemvidutide administered 1.8 mg QW for 24 weeks, without dose titration, led to rapid and potent reductions in LFC that strongly correlated with improvements in non-invasive biomarkers of inflammation and fibrosis. These findings are expected to predict meaningful histopathological improvement in NASH.



Disclosures:
Jonathan Kasper – Altimmune, Inc.: Employee;

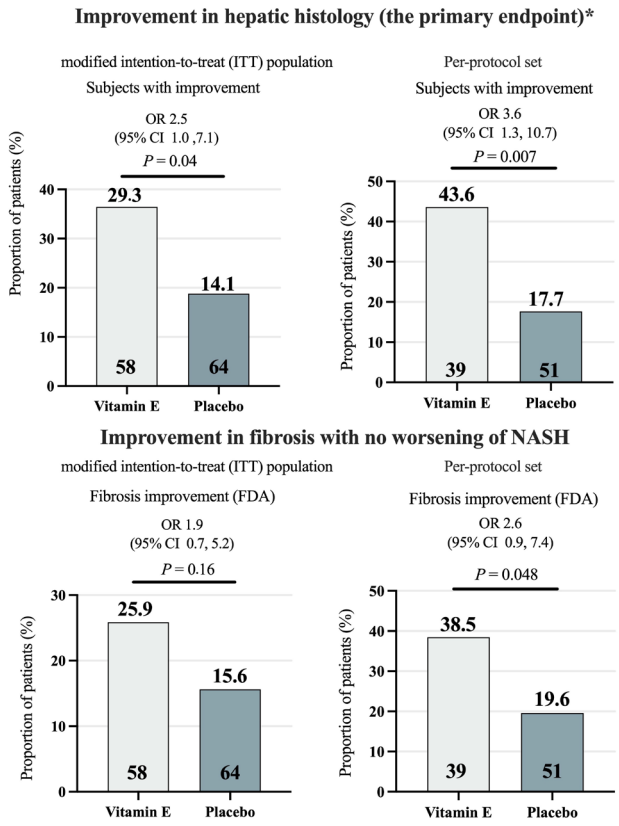
5021-C | VITAMIN E (300mg) VERSUS PLACEBO IN THE TREATMENT OF NONALCOHOLIC STEATOHEPATITIS: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Yu Song[1], Ming-Hua Zheng[2], Huiping Sheng[3], Jing Wang[4], YongFeng Yang[5], Xiaoling Chi[6], Jinjun Chen[7], Fangping He[7], Xiaotang Fan[8], Yuqiang Mi[9], Jing Zhang[10], Bingyuan Wang[11], Lang Bai[12], Wen Xie[13], Bihui Zhong[14], Yee Hui Yeo[15], Jie Li[16], Shufei Zang[17] and Junping Shi[18], (1)Hangzhou Normal University Affiliated Hospital, (2) Mafld Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, (3)Department of Infectious Diseases, General Hospital of Ningxia Medical University, (4)The Affiliated Traditional Chinese Medicine Hospital of Southwest Medical University, (5)The Second Hospital of Nanjing, (6) Guangdong Provincial Hospital of Chinese Medicine, (7)

Nanfang Hospital, Southern Medical University, (8)The First Affiliated Hospital of Xinjiang Medical University, (9)Tianjin Second People's Hospital, (10)Beijing Youan Hospital, Capital Medical University, Beijing, China, (11) The First Hospital of China Medical University, (12)West China Hospital, Sichuan University, Chengdu, China, (13) Beijing Ditan Hospital, Capital Medical University, Beijing, China, (14)The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, (15)Cedars-Sinai Medical Center, Los Angeles, CA, (16)Nanjing Drum Tower Hospital, (17)Shanghai Fifth People's Hospital, (18)The Affiliated Hospital of Hangzhou Normal University, Hangzhou, Zhejiang, China

Background: Despite the proven efficacy of long-term high-dose vitamin E (800IU) for the treatment of nondiabetic patients with nonalcoholic steatohepatitis (NASH), potential risks hinder its application. The efficacy and safety of a lower dose of vitamin E for NASH treatment is unclear. **Methods:** This was a multicenter, randomized, double-blind, placebo-controlled study of nondiabetic patients with biopsy-proven NASH. Patients were randomly assigned in a 1:1 ratio to receive oral vitamin E (300mg about 450 IU) or placebo. The primary outcome was an improvement in hepatic histology. The exploratory secondary endpoint was improvement in liver fibrosis by at least one stage and no worsening of NASH. The analyses of end points were performed in a modified intention-to-treat (ITT) population and also in a per-protocol set (PPS). Safety analysis was performed in all the patients. **Results:** A total of 124 patients were randomly assigned to receive vitamin E (58 patients) or placebo (66 patients). In the modified ITT population, 29.3% of those who received vitamin E demonstrated an improvement in histology (43.6% in PPS) compared with 14.1% (17.7% in PPS) in the placebo group (p = 0.040 in modified ITT, p = 0.0071 in PPS). An improvement in the exploratory secondary endpoint was observed in 25.9% (38.5% in PPS) of the vitamin E group and 15.6% (19.6% in PPS) of the placebo group (p = 0.16 in modified ITT, p = 0.048 in PPS). Serious adverse events were reported in a similar proportion of patients across groups but were not considered to be related to treatment. **Conclusion:** Oral vitamin E administered at a dose of 300mg daily resulted in a significantly higher histologic improvement in nondiabetic NASH patients and was safe and well tolerated for NASH treatment. ClincialTrials.gov number, NCT02962297.

Figure 2. Primary endpoints and confirmatory secondary endpoints in mITT and PPS.



Primary endpoint was improvement in hepatic histology after 96 weeks of treatment. The definition of histologic improvement was based on the following criteria: improvement in either NAS by at least 2 points or in post-treatment NAS by 3 points or less; at least 1 point improvement in score for ballooning or inflammation; and no worsening of fibrosis stage. The confirmatory secondary endpoint was an improvement in liver fibrosis by ⩾ 1 stage and no worsening of steatohepatitis (defined as no increase in NAS for steatosis, inflammation, or ballooning). NAS = nonalcoholic fatty liver disease activity score.

Disclosures:
The following people have nothing to disclose: Junping Shi

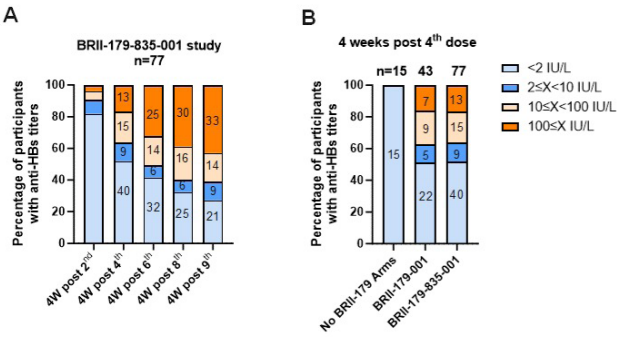
5022-C | BRII-179 INDUCED DISTINCT ANTI-HBS ANTIBODY RESPONSES IN CHRONIC HEPATITIS B PARTICIPANTS WITH DIVERSE UNDERLYING IMPAIRMENT OF HUMORAL IMMUNITY

Yun Ji[1], Nina Le Bert[2], Haiyan Ma[3], Ariel Lee[3], Chong Zhu[4], Ying Tan[5], Weihong Liu[4], Jianxiang Lv[4], Dong Li[4], Xiaofei Chen[4], Antonio Bertoletti[2] and Qing Zhu[6], (1)Brii Biosciences Inc., Germantown, MD, (2)Duke-Nus Medical School, Singapore, (3)Hyris/TCD Limited, Singapore, (4) Brii Biosciences Limited, China, (5)Brii Bioscience Limited, China, (6)Brii Biosciences Limited, Rockville, MD

Background: BRII-179 (VBI-2601), a therapeutic vaccine consisting of 3 HBV surface antigens (PreS1, PreS2, and S), was demonstrated to be safe and well tolerated. It induced significant T and B cell immune responses in chronic hepatitis B (CHB) participants when administered alone[1] or in combination with an HBV-targeted small interfering RNA, BRII-835 (VIR-2218)[2]. **Methods:** Ninety participants on nucleos(t)ide analogue (NA) therapy were randomized (1:2:2) in a phase 2 study to receive 9 doses of 100mg BRII-835 subcutaneously either alone or in combination with 9 doses of 40μg BRII-179 intramuscularly with or without IFN-α co-adjuvant (BRII-179-835-001 study). Peripheral blood mononuclear cells from 49 participants were collected at 6 time points and evaluated in expanded ELISpot assays. Serum anti-HBs were quantified during study period. The immune responses were analyzed and compared to the responses induced by 4 doses of BRII-179 alone in a previous phase 1b BRII-179-001 study[1]. **Results:** HBsAg-specific T cell response was detected in the BRII-835 alone group. However, both the magnitude and breadth of this response were significantly improved in BRII-179 and BRII-835 combination group and are comparable to the response induced by BRII-179 treatment alone[1]. Robust anti-HBs antibody responses were observed only in the combination group, with 43% of participants achieving titer >=100 IU/L. Notably, higher levels of anti-HBs antibody appeared to be associated with elevated T cell responses. The kinetics of antibody responses from the BRII-179 and BRII-835 combination study were similar to those found in the BRII-179 monotherapy study[1] (Figure). Interestingly, even after 9 doses of BRII-179, approximately 40% of participants exhibited no or minimal anti-HBs response with titers <10 IU/L. **Conclusion:** In CHB participants on NA therapy, BRII-179 (therapeutic vaccine), alone or in combination with BRII-835 (siRNA), induced substantial anti-HBs antibody responses in some CHB participants, suggesting that the anti-HBV humoral immunity of certain participants is impaired to mount effective antibody responses. Several studies including the recently presented VIR-2218 (BRII-835)/PEG-IFN-α combination study demonstrated that strong anti-HBs antibody responses were associated with sustained HBsAg seroclearance. Immune profiling by BRII-179 has the potential to select participants with optimal intrinsic humoral immunity and increases likelihood of achieving functional cure. **Reference**

1. Ma et al. Therapeutic vaccine BRII-179 restores HBV-specific immune responses in patients with chronic HBV in a phase Ib/IIa study. JHEP Rep. 2021 Sep 8;3(6):100361

2. Yuen MF et al. Preliminary safety and efficacy of the combination therapy of BRII 835 (VIR 2218) and BRII 179 (VBI 2601) treating chronic HBV infection. APASL 2023.



Kinetics of anti-HBs titers in BRII-179-835-001 study and comparison with BRII-179-001 study. (A) Distribution of maximum anti-HBs titers in participants receiving 9 doses of BRII-179 over time in BRII-179-835-001 study. (B) Distribution of maximum anti-HBs titers in participants evaluated at 4 weeks post receiving 4 doses of BRII-179. "No BRII-179 Arms" includes all participants receiving no BRII-179 treatment in BRII-179-001 study and BRII-179-835-001 study. "BRII-179-001" and "BRII-179-835-001" columns include subjects receiving BRII-179 treatment from each study respectively.

Disclosures:
The following people have nothing to disclose: Nina Le Bert

5023-C | CHARACTERIZATION OF HDV RNA KINETIC PATTERNS DURING TREATMENT: THE D-LIVR PHASE 3 STUDY

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Background: HDV rebound was observed in patients treated with Lonafarnib (LNF). We analyzed viral kinetic data from the D-LIVR study to assess HDV kinetic patterns and to compare rates of rebound between patients treated with lonafarnib (LNF)-containing regimens and pegylated interferon α-2a (pegIFN) alone. **Methods:** The D-LIVR study randomized patients with HDV viremia and HBV DNA<20 IU/ml to 48 weeks of placebo, LNF+ritonavir (RTV), LNF+RTV+pegIFN, or pegIFN. Participants who completed treatment without early discontinuation were included in this study. Three participants were excluded from analysis due to insufficient data. The analysis focused on on-treatment viral kinetic data and did not include post-treatment time points. HDV measurements

fluctuated in the placebo group with 95% no more than 1.6 log below baseline viral load. Thus, non-responders (NR) during antiviral treatment were defined as participants who did not have >1.6 log HDV decline. A viral rebound was defined as >1 log increase in HDV from nadir in 2 consecutive samples. **Results:** Three HDV kinetic patterns were identified under LNF±pegIFN treatment: nonresponders (NR) consistent responders (CR) who did not rebound, and responders with rebound (Table 1). Rebound rates were high (>50%) and similar between participants treated with LNF with or without pegIFN. There was a non-significant (p=0.12) trend toward a higher rate of rebound in the LNF groups compared to the pegIFN alone group. Time to rebound was similar among the three treatment groups. However, while HDV levels returned to baseline levels by the end of treatment (EOT) in participants who rebounded under LNF+RTV alone, HDV levels were significantly lower than baseline at EOT with pegIFN-based treatments (Table 1). The CR rate was about 40% in the pegIFN and LNF+RTV+PegIFN groups, while significantly (p<0.011) fewer participants who received LNF+RTV alone had CR (24%). About half of CR in all three treatment groups reached LLoQ by EOT. There were similar frequencies of NR in the PegIFN and LNF+RTV treatment groups (20 and 22%, respectively), while there were significantly (p<0.0001) fewer NR in the LNF+RTV+PegIFN group (5%). **Conclusion:** On-treatment HDV rebound was frequent among D-LIVR recipients who received LNF containing regimens or pegIFN alone, although the rebound magnitude was significantly less for PegIFN-containing regimens. HDV RNA levels fluctuated by up to 1.6 log in the placebo group, which will need to be considered in future viral kinetic studies of HDV. Further analysis of the effects of dose reduction/interruptions on viral kinetics is needed.

	PegIFN	LNF + RTV	LNF+RTV+PegIFN
Completed treatment, N (%)	41	142	102
Non-responders (NR*)	8 (20%)	31 (22%)	5 (5%)[&]
Responders with Rebound	16 (39%)	77 (53%)	56 (54%)
Consistent Responders	17 (41%)	34 (24%)[#]	41 (40%)
Responders with Rebound			
Decline (from baseline) at rebound [mean±SD log IU/ml)]	2.4±1.0	2.5±0.7	3.2±0.9
Time of Rebound [mean±std weeks]	20.0±12.0	18.4±9.9	18.6±9.7
Reached LLoQ at time of rebound [N (%)]	7 (44%)	22 (29%)	19 (34%)
Reached TND at time of rebound [N (%)]	2 (12%)	4 (5%)	7 (12%)
Decline (from baseline) at EOT [mean±SD log IU/ml)	1.7±1.6	0.2±1.2*	0.9±1.2
Consistent Responders			
Decline (from baseline) at EOT [mean±SD log IU/ml]	3.1±1.5	2.6±1.1	3.2±1.3
Reached LLoQ [N (%)]	8 (47%)	17 (50%)	24 (59%)
Reached TND [N (%)]	5 (29%)	5 (15%)	15 (37%)

Table 1. Summary of HDV RNA kinetic patterns under treatment. &, Significantly (p< 0.0001) different than monotherapy treatment; #, Significantly (p<0.011) different from other treatment groups; *, Significantly (p<0.001) different from PegIFN treatment groups; NR, based on the analysis of the Placebo group, a kinetic non-response was defined as less than 1.6 log IU/ml decline from baseline during treatment; EOT, end of therapy (week 48); LLoQ, lower limit of quantification (<40 IU/ml); TND, target not detected (<4 IU/ml); LNF, lonafarnib; RTV, ritonavir; PegIFN, pegylated interferon α-2a; SD, standard deviation.

Disclosures:
The following people have nothing to disclose: Harel Dahari

5024-C | PRIME EDITING PRECISELY CORRECTS PREVALENT MUTATIONS OBSERVED IN GLYCOGEN STORAGE DISEASE TYPE 1b (GSD1b) PATIENTS

Jonathon Winnay, Chris Hart, Harpreet Turna, Daphne Collias, Celia Chang, Sascha Hernandez, Serge Kyrychenko, Matt Roy, Seth Alexander, Rowshon Alam, Pei Ge, John Hadcock, Vivian Choi and Jeremy Stuart Duffield, Prime Medicine

Background: GSD1b is an autosomal recessive disorder caused by mutations in the *SLC37A4* gene encoding the glucose 6-phosphate translocase (G6PT) which is required for normal glucose-6-phosphate metabolism, including hepatic glycogenolysis. Patients exhibit multiple clinical manifestations including severe hypoglycemia resulting in seizures and cognitive impairment. Without an approved treatment for GSD1b, patients maintain metabolic control with a special diet and with medications that alleviate secondary complications such as neutropenia. The most prevalent mutations include p.G339C and/or p.L348fs, observed in ~50% of patients. A gene editing approach to correct the mutations in the affected cells to restore G6PT function would directly address the underlying genetic cause of the disease. **Methods:** Prime Editing (PE) is a next generation gene editing technology that can precisely correct more than 90% of all pathogenic human mutations without the need for double strand breaks (DSBs), minimal byproducts at the edit site, off-target activity and risk of chromosomal alterations or genotoxicity sometimes observed with CRISPR-based editing. We have generated LNP-RNA PE candidates that are lipid nanoparticles (LNP) formulated with an engineered mRNA that encodes the Prime Editor and the Prime Editor guide RNA (pegRNA), with the aim to edit the mutated *SLC37A4* gene in hepatocytes. **Results:** Comprehensive high-throughput screening for pegRNA identified initial hits that correct either the p.G339C or p.L348fs mutation. Initial PE lead assessment in primary hepatocytes isolated from humanized mice in which the mouse *Slc37a4* gene was replaced with the human gene harboring either the G339C or L348fs mutations, or in iPSC-derived hepatocytes, resulted in editing efficiencies up to 80% *in vitro*. A similar assessment was performed in vivo following intravenous delivery of the LNP-RNA PE candidates to humanized mice. Genomic correction of the L348fs mutation was observed in whole liver at an average correction rate of 47% (total liver alleles) and an associated correction of *SLC37A4* transcripts and protein expression. **Conclusion:** These results demonstrate efficient LNP-mediated delivery of Prime Editing cargo to the liver and that Prime Editing can efficiently and precisely correct pathogenic mutations causing GSD1b at rates exceeding those believed to reverse manifestations of disease. Updated results including new non-human primate data will be provided at the time of the meeting.

Disclosures:
Jonathon Winnay – Prime Medicine: Employee;

5025-C | ARTIFICIAL INTELLIGENCE-BASED MEASUREMENT OF NASH HISTOLOGY (AIM-NASH) RECAPITULATES PRIMARY RESULTS FROM PHASE 3 STUDY OF RESMETIROM FOR TREATMENT OF NASH/MASH

Janani S. Iyer[1], Pierre Bedossa[2], Cynthia D. Guy[3], Brian Hartman Baker[1], Darren Fahy[1], Tayla Parker-Shen[1], Darshit Makawana[1], Jonathan Glickman[1], Dominic Labriola[4], Andrew H. Beck[1], Rebecca A. Taub[4] and Stephen A. Harrison[5], (1)Pathai, Inc., (2)Hopital Beaujon, (3)Duke University, Durham, NC, (4)Madrigal Pharmaceuticals, (5)Pinnacle Clinical Research, San Antonio, TX

Background: Histologic endpoint assessment in clinical trials for non-alcoholic steatohepatitis/metabolic dysfunction-associated steatohepatitis (NASH/MASH) has historically been complicated by pathologist variability in interpreting the NASH Clinical Research Network (CRN) scoring guidelines. Artificial intelligence (AI)-powered digital pathology promises to address this challenge by providing accurate, repeatable, and reproducible scoring of NASH/MASH histologic features, thereby reducing the impact of rater variability on trial outcomes. Here, we test the ability of one such tool - namely, AI-based Measurement of NASH Histology (AIM-NASH) - to detect drug-induced histologic change in a recently completed Ph3 trial of resmetirom for treatment of NASH/MASH. **Methods:** Participants were randomized into the MAESTRO-NASH Ph3 trial (NCT03900429) if they met the following histologic inclusion criteria: 1) NAFLD Activity Score (NAS) ≥ 4 with a grade of at least one for each of steatosis, ballooning, and lobular inflammation (LI); and 2) NASH CRN fibrosis stage 1-3. The primary endpoints were: 1) NASH resolution, defined as ballooning grade 0, LI grade 0 or 1, and at least a 2-point reduction in NAS with no worsening of fibrosis; and 2) ≥1-stage reduction in fibrosis with no worsening of NAS. Participants with paired Baseline and End-of-Study (Week 52) biopsies were assessed by the study's two central pathologists (CP; Harrison et al. 2023) and by AIM-NASH, an AI-powered NASH CRN scoring tool that has been previously described (N=782 and N=777, respectively). A Cochran-Mantel-Haenszel (CMH) test stratified for Type 2 Diabetes status and baseline fibrosis stage was used to assess statistical significance. **Results:** **Table 1** displays response rates per treatment arm as measured by CP or AIM-NASH. Both CP and AIM-NASH showed a clear dose effect on histologic response. Placebo response rates measured by CP vs. AIM-NASH for both primary endpoints were numerically similar. The difference in response rates between treated and placebo subjects was statistically significant for both the 80mg and 100mg treatment groups, as measured by both CP and AIM-NASH. All treatment vs. placebo response rate differences detected by CP vs. AIM-NASH were numerically similar. **Conclusion:** AI-powered digital pathology recapitulated all primary endpoint results that were achieved by the central readers in a successful Ph3 study of resmetirom for treatment of NASH/MASH, while also detecting a clear dose response. These results complement similar AIM-NASH results achieved in the corresponding Ph2 study of resmetirom (Harrison et al. 2022). Importantly, the AIM-NASH workflow is highly repeatable and reproducible (Harrison et al. 2023); this, in combination with the fact that AIM-NASH accurately detects histologic response, inspires confidence in the potential future utility of AI-assist histologic scoring in NASH/MASH clinical trials.

Table 1. Treatment vs. Placebo response rates measured by the study's central pathologists (CP) vs. AIM-NASH per endpoint in a Phase 3 study of resmetirom for treatment of NASH/MASH.

	Placebo		80 mg		100 mg	
	AIM-NASH (N=273)	CP (N=276)	AIM-NASH (N=257)	CP (N=258)	AIM-NASH (N=247)	CP (N=248)
NASH resolution responders at Wk52						
Response rate (%)	9.5	11.2	23.7	31.8	32.4	38.7
Difference from placebo (%) (95% CI)	N/A	N/A	14.0 (7.8, 20.3)	20.9 (14.6, 27.1)	23.9 (17.2, 30.7)	28.5 (22.1, 34.9)
P-value	N/A	N/A	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Fibrosis responders at Wk52						
Response rate (%)	15.8	16.3	23.3	29.7	30.4	33.5
Difference from placebo (%) (95% CI)	N/A	N/A	8.02 (1.3, 14.7)	13.6 (7.3, 19.9)	15.31 (8.1, 22.5)	17.2 (10.8, 23.6)
P-value	N/A	N/A	**0.0199**	**<0.0001**	**<0.0001**	**<0.0001**

Disclosures:
Janani S. Iyer – PathAI, Inc.: Employee;

5026-C | LIVER FUNCTION MEASURED BY HEPQUANT DUO PREDICTS THE LIKELIHOOD FOR LARGE ESOPHAGEAL VARICES IN CHILD-PUGH A CIRRHOSIS

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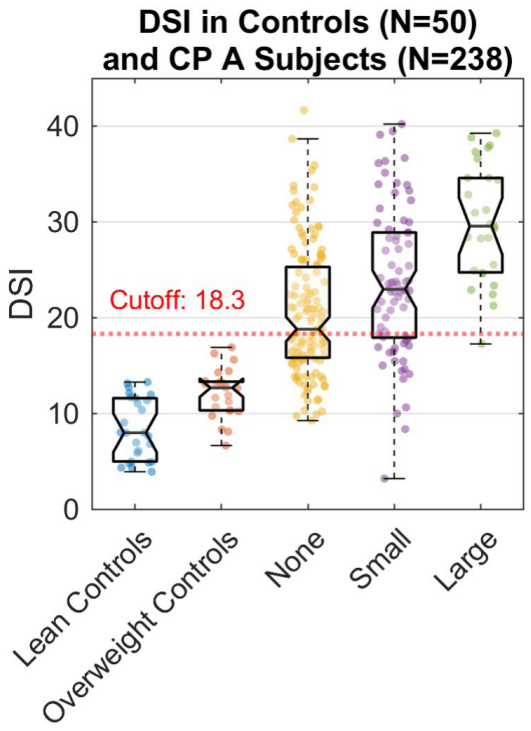
Background: Endoscopy (EGD) is indicated in patients with cirrhosis to check for large esophageal varices (LEVs) which need treatment. But the prevalence of LEVs in Child-Pugh (CP) A cirrhosis is only 10%. Liver stiffness (<20 kPa) plus platelet count (>150 nL^{-1}) is useful to "rule out" LEVs, but operator dependency, technical factors, obesity, and MASH can compromise the accuracy of transient elastography, and non-hepatic factors can affect platelet count. For these reasons we evaluated the disease severity index (DSI) score from the HepQuant DuO test to rule out LEVs in CP A cirrhosis. **Methods:** The validation dataset was comprised of 238 US subjects with CP A cirrhosis who had been participants in the SHUNT-V study. Fifty percent of subjects had MASH, 24% had hepatitis C, 18% had alcoholic liver disease, 85% had BMI >25 kg m^{-2}, and 64% had BMI >30 kg m^{-2}. Exclusions were known large esophageal varices, prior treatment of varices, history of variceal bleeding, refractory ascites, refractory encephalopathy, CP C cirrhosis, or prior liver transplantation. DSI was determined from serum concentrations of d4-cholate, 20 and 60 minutes after its oral administration. DSI from lean and overweight controls (HepQuant internal data) were plotted alongside subjects with no, small, or large esophageal varices.

Diagnostic performance for ruling out LEVs was evaluated at the prespecified cutoff of DSI <18.3 based on the sensitivity (≥95%) of the HepQuant SHUNT test in the HALT-C quantitative liver function test (QLFT) ancillary study. **Results:** The AUROC for DSI was 0.81 (95% CI: 0.72–0.87). The distribution of DSI in subjects with no, small, or large varices is shown in Figure 1. Applying the DSI <18.3 cutoff resulted in 96% (81–100%) sensitivity, 39% (33–46%) specificity, NLR 0.09 (0.01–0.65), and Miss Rate 3.7%. DSI <18.3 would have prevented 35.3% of unnecessary EGDs. DSI captured all but one LEV case, 96.2% of treated esophageal varices, all cases with red wale signs, all cases with large gastric varices, and all cases with severe portal hypertensive gastropathy. **Conclusion:** The DSI score from the HepQuant DuO test predicts the likelihood of LEVs and other endoscopic findings of portal hypertension across a wide spectrum of patient characteristics and disease etiologies. The HepQuant DuO test represents a simple-to-administer, noninvasive test of liver function and physiology that can aid in the decision to avoid endoscopic screening for varices in CP A cirrhosis.



Disclosures:
Michael P. McRae – HepQuant LLC: Consultant;

5027-C | HUMAN PXR SIGNALING PROMOTES ETHANOL-INDUCED HEPATOTOXICITY IN FEMALES

Malvin Ofosu-Boateng[1], Sora Choi[2], Elizabeth Twum[1], Daniel Okuwdili Nnamani[1], Lidya H Gebreyesus[1] and Maxwell Gyamfi[1], (1)The University of Tennessee Health Science Center, Memphis, TN, (2)North Carolina Central University

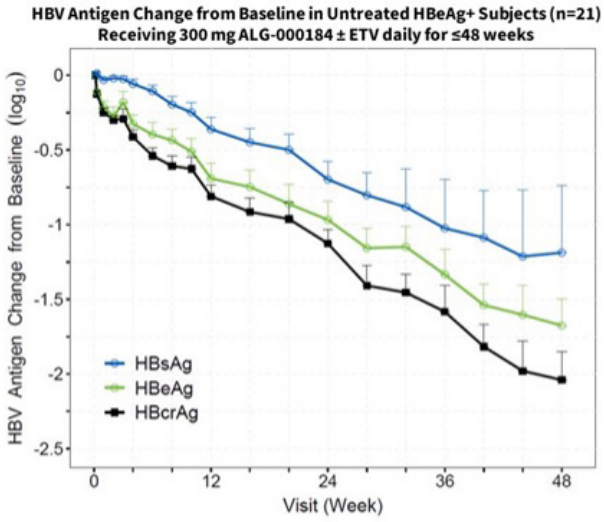
Background: Alcohol-associated liver disease (ALD) develops from excessive alcohol use and is more severe in both human and rodent females than their male counterparts. Women alcoholics also have higher death rate than men. The pregnane X receptor (PXR), a xenobiotic nuclear receptor important for defense against toxic agents has been implicated in ALD but the underlying mechanisms are unknown, and differences in ligand specificity between the mouse and the human *PXR* genes necessitate the use of mice bearing the human *PXR* gene to investigate the impact of this gene in the sexual dimorphism of ALD in humans. **Methods:** Male and female C57BL/6NTac (wild type, WT) and humanized PXR (hPXR) mice were paired-fed control diets or fed 5% ethanol (EtOH)-containing diet for 10 days followed by a single dose of EtOH (5 g/kg, 20% EtOH solution) and examined for hepatotoxicity, liver histopathology, and protein expression, hepatic transcriptomic profiling, and bioinformatic analyses to identify PXR targets in EtOH-induced sexual dimorphism. Gene expression in alcoholic liver samples and tissue microarrays (TMA) were also evaluated. **Results:** EtOH produced a more severe hepatotoxicity in female hPXR mice than male hPXR or male and female WT mice (with the mouse *Pxr* gene). Microarray analyses revealed that 442 genes were uniquely regulated by EtOH in the female hPXR mice by EtOH with more pathway changes than either male mouse strain or female WT mice. qRT-PCR confirmed that the EtOH-induced hepatotoxicity in female hPXR mice was associated with upregulation of the hepatic mRNA levels of peroxisome proliferator-activated receptor γ (*Pparγ*) (1.9-fold), its target genes, *Fsp27/Cidec* (31-fold) and the liver-specific *Fsp27β (*66-fold*)*. Hepatic mRNA and protein levels of the constitutive androstane receptor (CAR)/PXR target gene, *Cyp2b10,* implicated in EtOH-induced hepatotoxicity and ROS generation was also significantly increased in EtOH-fed female hPXR mice. Furthermore, hepatic mRNA levels of the lipid droplet-associated protein which promotes steatosis cell death-inducing DNA fragmentation factor alpha-like effector C (CIDEC), *were* significantly elevated in female, but not male alcoholic patients compared to normal livers. Moreover, TMA results revealed higher CYP2B6 and PXR1 expression in steatohepatitis patients with a history of alcohol use. **Conclusion:** Together, these data identify the hPXR-transgenic mice as a promising in vivo animal model to study human sexual dimorphism in EtOH-induced hepatotoxicity.

Disclosures:
The following people have nothing to disclose: Malvin Ofosu-Boateng

5028-C | LONG-TERM DOSING WITH THE CAPSID ASSEMBLY MODULATOR ALG-000184 RESULTS IN MULTI-LOG REDUCTIONS OF DNA, RNA, HBSAG, HBEAG AND HBCRAG IN UNTREATED HBEAG POSITIVE CHRONIC HEPATITIS B SUBJECTS

Man-Fung Yuen[1], Edward J Gane[2], Kosh Agarwal[3], Hua Yan Ding[4], Alina Jucov[5], Min Wu[6], Kha Le[6], Maida Maderazo[6], Christopher Westland[6], Lawrence M. Blatt[6], Leonid N. Beigelman[6], Sushmita Chanda[6], Tse-I Lin[6], Matthew McClure[6] and Jinlin Hou[7], (1)State Key Laboratory of Liver Research, the University of Hong Kong, Hong Kong, China, (2)Auckland Clinical Studies Limited, (3)Institute of Liver Studies, King's College Hospital, London, United Kingdom, (4)First Hospital of Jilin University, (5)Arensia Exploratory Medicine Gmbh, Dusseldorf, Germany, (6)Aligos Therapeutics, Inc., (7) Nanfang Hospital, Southern Medical University

Background: Chronic hepatitis B (CHB) treatment is challenging due to persistence of intrahepatic cccDNA, which acts as the template for hepatitis B virus (HBV) replication and transcription of viral proteins. ALG-000184 is a prodrug of ALG-001075, a potent capsid assembly modulator-empty (CAM-E) that, in vitro, inhibits viral replication (1st mode of action (MOA)) and cccDNA establishment (2nd MOA). **Methods:** ALG-000184-201 is a multi-part, multi-center, double-blind, randomized, placebo-controlled study (NCT04536337). We previously reported favorable results from cohorts receiving ALG-000184 alone x 28 days and ALG-000184 + entecavir (ETV) x ≤32 weeks with no safety concerns and multi-$\log_{10}$ reductions in viral DNA, RNA and HBsAg. Here we report emerging safety and antiviral activity data in ongoing CHB cohorts following additional dosing with ALG-000184 ± ETV. **Results:** Safety and antiviral activity data are available in HBeAg+ subjects dosed x ≤48 weeks with 300mg ALG-000184 alone (n=10, ex-China sites) or with ETV (n=11, China sites). Subjects were predominantly HBV genotype C (52%) and B (43%), Asian (95%) and male (57%) with a mean age of 33.8 years. At baseline, mean values of CHB markers were: HBV DNA 8.0 $\log_{10}$ IU/mL, HBV RNA 6.0 $\log_{10}$ copies/mL, HBcrAg 8.3 $\log_{10}$ U/mL, HBeAg 2.9 $\log_{10}$ U/mL and HBsAg 4.4 $\log_{10}$ IU/mL. Profound reductions in all viral markers were observed during treatment, including mean reductions at Week 48 of 6.7 and 4.6 $\log_{10}$ for HBV DNA and RNA, respectively, as well as 1.2-2.0 $\log_{10}$ mean declines in HBsAg, HBeAg and HBcrAg (Figure). No viral breakthrough, measured by HBV DNA, has been observed with ALG-000184 monotherapy. ALG-000184 has been well tolerated with no serious adverse events (AEs) and no discontinuations due to AEs. All treatment emergent AEs (TEAEs) were Grade 1 or 2 in severity except 4 subjects who experienced Grade 3 TEAEs of transaminase elevations (n=4) and Grade 4 neutropenia (n=1). All transaminase elevation events were associated with HBV DNA, RNA and antigen declines and have resolved or are improving with continued dosing; none were assessed by the study's safety committee as being related to study drug toxicity. **Conclusion:** Sustained dosing with 300mg ALG-000184 ± ETV broadly suppresses production of HBV viral markers, indicating it may potently inhibit cccDNA formation and has the potential to become a cornerstone therapy for treating CHB. Longer dosing in these and additional cohorts is ongoing.



N at each visit:

HBsAg	21	19	17	7	5
HBeAg	21	19	13	7	5
HBcrAg	21	19	17	7	5

Disclosures:
The following people have nothing to disclose: Min Wu

5029-C | A NOVEL SERUM DIAGNOSTIC SIGNATURE FOR LIVER FIBROSIS AND "AT RISK" MASH VALIDATED IN A POPULATION-SCALE SCREENING

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Background: Non-invasive identification of liver fibrosis in Metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic-associated steatohepatitis (MASH) is a major unmet clinical need. **Methods:** 1,350 serum samples from 4 patient cohorts with biopsy-proven MASLD were obtained from hospitals in Europe (2 were used as derivation cohort, and 2 as independent validation cohorts). An additional real-world patient cohort with serum samples collected as part of standard clinical routine by Maccabi Health, within the Israeli Multi-OMICS screening study (IMOSS-500K), included 184 patients with cirrhosis (based on ICD9 code and Liver Forum definition[1]) that were identified among ~30,000 MASLD patients between 2021-2023. All samples were analyzed with a proprietary high-throughput mass-spectrometry based metabolomics, lipidomics, and proteomics, detecting tens of thousands of biomarker ions per sample. Logistic regression was used to identify a serum signature in the derivation cohorts, and the diagnostic performance for different fibrosis stages and "at-risk" MASH was evaluated. Significance between competing methods was evaluated using Delong method. **Results:** We developed two novel scores for diagnosing liver fibrosis and "at-risk" MASH, based on the serum concentration of 3 proteins. The scores show high diagnostic performance for identifying significant fibrosis, advanced fibrosis, cirrhosis and "at-risk" MASH, which could not be improved by adding other metabolites, lipids, or protein biomarkers. The method significantly outperforms commonly used clinical scores (FIB-4, BARD, NFS), commercial blood-tests (FibroTest, ELF), and Fibroscan®-based panels (Table 1). Finally, the method was validated via a real-world patient cohort in which it significantly outperformed existing clinical scores in screening for patients with cirrhosis (AUC of 0.83 vs 0.75, 0.53, 0.72 for FIB-4, BARD and NFS, respectively). Notably, across tested cohorts, the advantage of our method was further emphasized when focusing on patients with an indefinite FIB-4 range, i.e., 1.3<FIB-4<2.67 (e.g., for MAFLD population cirrhosis screening study: AUC of 0.87 vs 0.67, 0.47, 0.62 for FIB-4, BARD and NFS, respectively). **Conclusion:** We identified a novel protein molecular signature for liver fibrosis and "at-risk" MASH, outperforming existing blood-based diagnostic methods and Fibroscan®-based panels, and having consistent performance across different cohorts.

Significant fibrosis (≥ F2)			
	Derivation cohort (Puerta de Hierro and Marqués de Valdecilla) Cases = 160, Controls = 196	Hospital Validation cohort 1 (HUVR) Cases = 133, Controls = 107	Hospital Validation cohort 2 (UZA) Cases = 147, Controls = 362
MetaSight	**0.83**	**0.82**	**0.80**
FIB4	0.76*	0.67**	0.75*
BARD	0.63**	0.68**	0.59**
NFS	0.72**	0.65**	0.57*
Fibroscan® (VCTE)	0.74	0.81	NA
Fibroscan® (FAST)	0.75*	0.65**	NA
FibroTest	0.73*	NA	NA
ELF	NA	0.76	NA
Advanced fibrosis (≥ F3)			
	Derivation cohort (Puerta de Hierro and Marqués de Valdecilla) Cases = 105, Controls = 251	Hospital Validation cohort 1 (HUVR) Cases = 101, Controls = 139	Hospital Validation cohort 2 (UZA) Cases = 83, Controls = 426
MetaSight	**0.86**	**0.83**	**0.87**
FIB4	0.80*	0.67**	0.83
BARD	0.66**	0.67**	0.67**
NFS	0.78**	0.68**	0.6*
Fibroscan® (VCTE)	0.7	0.81	NA
Fibroscan® (Agile 3+)	0.82	0.84	NA
FibroTest	0.79	NA	NA
ELF	NA	0.78	NA
Cirrhosis (≥ F4)[1]			
	Derivation cohort (Puerta de Hierro and Marqués de Valdecilla) Cases = 40, Controls = 316	Hospital Validation cohort 1 (HUVR) Cases = 32, Controls = 208	Hospital Validation cohort 2 (UZA) Cases = 26, Controls = 483
MetaSight	**0.96**	**0.85**	**0.97**
FIB4	0.88**	0.68**	0.97
BARD	0.74**	0.66**	0.81**
NFS	0.82**	0.74	NA
Fibroscan® (VCTE)	0.7	0.79	NA
Fibroscan® (Agile 4)	0.90*	0.82	NA
FibroTest	0.89*	NA	NA
ELF	NA	0.75*	NA
"at-risk" MASH (NAFLD Activity Score ≥ 4 and ≥ F2)			
	Derivation cohort (Puerta de Hierro and Marqués de Valdecilla) Cases = 77, Controls = 193	Hospital Validation cohort 1 (HUVR) Cases = 80, Controls = 158	Hospital Validation cohort 2 (UZA) Cases = 69, Controls = 262
MetaSight	**0.78**	**0.78**	**0.71**
FIB4	0.65**	0.59**	0.61*
BARD	0.56*	0.59**	0.55**
NFS	0.61**	0.55**	0.58*
Fibroscan® (VCTE)	0.74	0.76	NA
Fibroscan® (FAST)	0.73	0.72*	NA
FibroTest	0.64*	NA	NA
ELF	NA	0.72	NA

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5030-C | ESTIMATING PREVALENCE OF HEPATITIS C VIRUS INFECTION IN THE UNITED STATES, 2017–2020

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Background: Hepatitis C virus (HCV) infection is the most common bloodborne illness in the United States; however, disease burden is challenging to measure. The National Health and Nutrition Examination Survey (NHANES) underestimates the true prevalence of HCV infection because it excludes or underrepresents certain populations with high prevalence (e.g., incarcerated persons, unsheltered/unhoused persons, persons who inject drugs [PWID]). By accounting for populations inadequately represented in NHANES, we aimed to estimate the national prevalence of HCV infection among US adults during 2017–2020. **Methods:** Two models were created to estimate national hepatitis C prevalence. The first approach (Hofmeister) replicated previous methodology by

supplementing the hepatitis C prevalence estimate among the US noninstitutionalized civilian population from NHANES with a systematic literature review and meta-analysis of hepatitis C prevalence among four populations not included in the NHANES sampling frame: incarcerated people, unsheltered/unhoused people, active-duty military personnel, and nursing home residents. In the second approach (PWID adjustment), we developed a model to account for underrepresentation of PWID in NHANES by incorporating estimated number of adult PWID in the United States (n=3,694,500), assuming PWID were distributed among the non-institutionalized, incarcerated, and unsheltered/unhoused populations, and applying PWID-specific HCV prevalence estimates to these groups. **Results:** Using the Hofmeister methodology, we estimated an HCV RNA prevalence of 1.0% (95% CI: 0.5%-1.4%) among US adults in 2017-2020, corresponding to 2,463,700 (95% CI: 1,321,700-3,629,400) current HCV infections. Using the PWID adjustment model, we estimated an HCV RNA prevalence of 1.6% (95% CI: 0.9%-2.2%), corresponding to 4,043,200 (95% CI: 2,401,800-5,607,100) current HCV infections. **Conclusion:** Despite years of an effective cure, estimated prevalence of hepatitis C in 2017–2020 remains unchanged from 2013–2016 when using comparable methodology. When accounting for increased injection drug use in the United States, estimated prevalence of hepatitis C is substantially higher than previously reported. National action is urgently needed to expand testing, increase access to treatment, and improve surveillance among medically underserved populations to support hepatitis C elimination goals.

TABLE. Estimated Hepatitis C RNA Prevalence among Adults 18+ Years of Age, United States

Methodology	Years	N	n	95% CI		%	95% CI	
Hofmeister et al. 2018[1]	*2013-2016*	*244,869,800*	*2,386,100*	*1,983,900*	*2,807,800*	*1.0*	*0.8*	*1.1*
Hofmeister methodology	*2017-2020*	*254,207,169*	*2,463,700*	*1,321,700*	*3,629,400*	*1.0*	*0.5*	*1.4*
Non-institutionalized		249,177,857	2,229,600	1,081,700	3,399,100	0.9	0.4	1.4
Incarcerated		2,086,600	201,900	138,300	266,500	9.7	6.6	12.8
Unsheltered/unhoused		212,090	23,700	8,700	38,300	11.2	4.1	18.1
Active-duty military		1,326,200	200	100	400	0.02	0.01	0.03
NH residents		1,404,422	8,100	4,300	12,000	0.6	0.3	0.9
PWID adjustment model	*2017-2020*	*254,207,169*	*4,043,200*	*2,401,800*	*5,607,100*	*1.6*	*0.9*	*2.2*
Non-institutionalized		249,177,857	3,721,700	2,094,300	5,299,500	1.5	0.8	2.1
Incarcerated		2,086,600	277,300	220,200	335,600	13.3	10.6	16.1
Unsheltered/unhoused		212,090	28,800	14,900	42,400	13.6	7.0	20.0
Active-duty military		1,326,200	200	100	400	0.02	0.01	0.03
NH residents		1,404,422	8,100	4,300	12,000	0.6	0.3	0.9

Abbreviations: PWID, persons who inject drugs; NH, nursing home

Notes: PWID adjustment model assumes 10.6% of incarcerated[2,3] and 7.4% of unsheltered/unhoused[3,4] are people who inject drugs. The non-institutionalized estimates for 2017-2020 utilize NHANES data from 2017-March 2020 because the COVID-19 pandemic interrupted the survey cycle.

[1]Hofmeister MG, Rosenthal EM, Barker LK, Rosenberg ES, Barranco MA, Hall EW, Edlin BR, Mermin J, Ward JW, Ryerson AB. Estimating Prevalence of Hepatitis C Virus Infection in the United States, 2013-2016. Hepatology. 2019 Mar;69(3):1020-1031. doi: 10.1002/hep.30297.

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Disclosures:

Eric Hall – Merck & Co: Independent contractor (including contracted research);

5031-C | PHASE 2 INTERIM RESULTS: BRII-179 (VBI-2601), A PROTEIN-BASED HBV THERAPEUTIC VACCINE, INDUCED ROBUST HBSAB RESPONSES THAT ARE STRONGLY ASSOCIATED WITH INCREASED HBsAg LOSS IN SUBJECTS RECEIVING PEG-IFNα TREATMENT

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Background: BRII-179, a novel recombinant therapeutic vaccine expressing the Pre-S1/Pre-S2/S HBV surface antigens, has previously been demonstrated to induce HBV specific B-cell and T-cell immune responses in patients with chronic hepatitis B (CHB). This randomized, double-blind, placebo-controlled phase 2 study is evaluating the safety and efficacy of BRII-179 as an add-on therapy in CHB patients receiving PEG-IFNα and nucleos(t)ide reverse transcriptase inhibitors (NrtI) therapy. **Methods:** HBeAg negative CHB patients treated with ≥12 months of NrtI and 24-28 doses of PEG-IFNα and predefined partially response with HBsAg levels ≥0.05 and <100 IU/mL were randomized 1:1. The patients received BRII-179 or placebo every 3 weeks for 7 doses over 18 weeks and continued PEG-IFNα for 24 weeks. The primary endpoint was HBsAg loss at Week 24 (end of treatment, EOT). Eligible patients with sustained HBsAg loss at 12-24 weeks post EOT (Week 36-48) would discontinue NrtI and be monitored for another 48 weeks. The interim Week 24/36 data summarized here were unblinded at the cohort level and additional data will be analyzed at Week 48 and end-of-study. **Results:** 57 Chinese patients were randomized to each cohort (n=114). BRII-179/PEG-IFNα combination was generally safe and tolerated with AEs similar to those observed with PEG-IFNα or BRII-179 as previously reported. Most ≥Grade 3 AEs were PEG-IFNα related lab abnormalities. A higher HBsAg loss rate was observed at Week 24 in patients treated with BRII-179/PEG-IFNα than placebo/PEG-IFNα in Full Analysis Set (FAS) (26.3% vs. 19.3%) and per protocol analysis set (PPS) (32.6% vs. 21.6%). At Week 36 (12 weeks EOT follow-up), the difference in HBsAg loss rate between two cohorts were 24.6% vs. 14.0% in FAS and 31.8% vs. 14.9% in PPS. Patients treated with BRII-179/PEG-IFNα also had significantly higher HBsAg seroconversion rate (15.8% vs.

1.8%, p=0.0163) than placebo/PEG-IFNα at Week 24 (FAS) and had more patients with maximum HBsAb titer ≥10 and ≥100 IU/L by Week 24 and 36. In a multivariate logistic regression, maximum HBsAb titer 10-100 IU/L (p=0.0015) and ≥100 IU/L (p=0.0004) were strongly associated with HBsAg loss at Week 36 compared with HBsAb <10 IU/L. **Conclusion:** BRII-179/PEG-IFNα combination was generally safe and tolerated. The addition of BRII-179 induced robust immune responses that may improve the rate and duration of HBsAg loss in CHB patients who receive PEG-IFNα treatment, thereby significantly increasing the CHB functional cure rate.

Table: Key efficacy results at Week 24 and Week 36, FAS and PPS

	BRII-179 + PEG-IFNα	Placebo + PEG-IFNα	BRII-179 + PEG-IFNα	Placebo + PEG-IFNα
	At Week 24		At Week 36	
HBsAg Loss - FAS	15/57 (26.3%)	11/57 (19.3%)	14/57 (24.6%)	8/57 (14.0%)
HBsAg Loss - PPS	15/46 (32.6%)	11/51 (21.6%)	14/44 (31.8%)	7/47 (14.9%)
HBsAg seroconversion - FAS	9/57 (15.8%)*	1/57 (1.8%)	10/57 (17.5%)	4/57 (7.0%)
HBsAg seroconversion - PPS	9/46 (19.6%)**	1/51 (2.0%)	10/44 (22.7%)	4/47 (8.5%)
FAS: HBsAb# ≥10 IU/L	23/57 (40.3%)***	3/57 (5.3%)	26/57 (45.6%)***	7/57 (12.3%)
HBsAb# ≥ 100 IU/L	10/57 (17.5%)**	1/57 (1.8%)	11/57 (19.3%)*	2/57 (3.5%)
PPS: HBsAb# ≥10 IU/L	20/46 (43.5%)***	3/51 (5.9%)	22/44 (50.0%)***	7/47 (14.9%)
HBsAb# ≥100 IU/L	9/46 (19.6%)**	1/51 (2.0%)	10/44 (22.7%)*	2/47 (4.3%)

FAS: Full analysis set; PPS: Per protocol set;
HBsAg loss: HBsAg changing from positive (≥0.05 IU/mL) at baseline to negative (<LLOQ 0.05 IU/mL) at any postbaseline visit;
HBsAg Seroconversion: HBsAg changing from positive (≥0.05 IU/mL) at baseline to negative (<LLOQ 0.05 IU/mL) and HBsAb changing from negative (<10.0 IU/L) at baseline to positive (≥ 10.0 IU/L) at any postbaseline visit;
* Fisher's Exact Test was used to compare difference between two treatment groups without considering stratification factor HBsAg level at screening using 2-sided test. Statistically significant differences were marked as *p<0.05, **p<0.01, and ***p<0.001;
# maximum HBsAb post-baseline up to Week 24 or Week 36 are presented.

Disclosures:
Yiwen Liu – Brii Biosciences Limited, China: Employee;

5032-C | HEPATIC FUNCTIONAL IMPROVEMENT DETECTED BY HEPQUANT DUO WITHIN 120 DAYS OF TREATMENT WITH RENCOFILSTAT (RCF) IN MASH SUBJECTS WITH ≥ F3 FIBROSIS

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Background: Rencofilstat (RCF) is an antifibrotic cyclophilin inhibitor targeting MASH-related fibrosis. In MASH, liver dysfunction and altered portal physiology precede clinical complications. HepQuant DuO is a non-invasive, blood-based test of liver function, portal circulation, and portal-systemic shunting. In this study, DuO quantified effects of RCF on liver function and physiology. **Methods:** Seventy subjects with MASH and AGILE 3+ >0.53 (≥F3 fibrosis) were randomized 1:1:1 into 3 RCF treatment arms (75, 150, 225 mg/day) and underwent HepQuant SHUNT tests at baseline and Days 60 and 120. Subjects were administered 40 mg of labeled cholate (CA) orally, and blood CA concentrations analyzed at 20 and 60 min for the following DuO parameters: systemic and portal hepatic filtration rates (HFRs), disease severity index (DSI), hepatic reserve (HR), portal systemic shunt (SHUNT%), and risk of clinical events per person-year (RISK ACE). Changes from baseline to 60 and 120 days were analyzed, and numerous other MASH non-invasive assessments were also collected. **Results:** Baseline characteristics revealed an advanced MASH population (Agile 3+ 0.73 ± 0.15). At baseline, 30.4% of subjects had significant hepatic functional impairment (DSI >18.3), 37.7% had increased portal-systemic shunting (SHUNT% >27%), and 23.2% had both. DuO results with 225 mg RCF (Table 1) revealed significant reductions after 60 and 120 days in DSI (−1.34, p=0.022; −1.61, p=0.019) and SHUNT% (–2.24%, p=0.043; –2.28%, p=0.094) in paired analysis. Improved liver function (reduction of ≥2 DSI units) occurred in 10/18 subjects (55.6%) in the 225 mg RCF group after 120 days (p=0.055). DuO test parameters improved most in subjects with higher baseline DSI, and there was a clear dose response in many of the MASH non-invasive assessments. Subjects with the most impaired hepatic function at baseline showed the greatest improvement in response to RCF. **Conclusion:** RCF (225 mg) was associated with improvements in hepatic function and portal-systemic shunting. Subjects with the most impaired hepatic function at baseline showed the greatest improvements, suggesting a positive effect of RCF in MASH subjects with advanced fibrosis. These results demonstrate the successful use of HepQuant DuO to assess hepatic function and the promise of RCF as a potential MASH treatment in advanced fibrosis.

DuO Results in the 225 mg/day Rencofilstat Arm

Parameter	Base		60 Days		120 Days	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
DSI	23	16.44 (3.30)	21	14.98 (4.08)**	18	14.79 (3.35)**
SHUNT (%)	23	24.98 (4.91)	21	22.52 (5.28)**	18	23.15 (4.60)*
Hepatic Reserve (%)	23	87.64 (7.45)	21	90.77 (8.45)**	18	91.60 (7.49)**
Portal HFR (mL/min/kg)	23	16.52 (5.50)	21	20.44 (11.81)*	18	18.83 (5.19)*
Systemic HFR (mL/min/kg)	23	3.91 (0.55)	21	4.09 (0.70)**	18	4.17 (0.63)**
RISK ACE† (predicted events per 100 person-years)	23	2.41	21	2.07****	18	1.92****

Change from baseline, by paired t-test: *p<0.10; **p<0.05; ***p<0.01; ****p<0.001

† RISK ACE from Poisson regression; units are events per 100 patient-years, value represents RISK ACE at day 60 or 120 (Model D) minus RISK ACE at baseline (Model A)

Disclosures:
Todd Hobbs – Hepion Pharmaceuticals Inc: Employee;

5033-C | EXTRA-CORPOREAL LIVER CROSS-CIRCULATION CORRECTS THE BIOCHEMICAL AND CLINICAL HALLMARKS OF ACUTE LIVER FAILURE IN A PORCINE MODEL

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Background: Although various liver support systems have been trialled in acute liver failure (ALF), none have replaced the complex roles of an intact liver. Normothermic machine perfusion (NMP) is an organ preservation technique developed for liver transplantation, in which the graft is supplied with blood at body-temperature. During NMP, livers maintain activity across the full spectrum of hepatic function. Extra-corporeal liver cross-circulation (ELC) exchanges the systemic circulation of a patient with the perfusate of an auxiliary liver undergoing NMP. The goal is to provide temporary liver support, and bridge patients to recovery or transplant. **Methods:** 12 anaesthetised pigs (51-70kg) underwent complete hepatic inflow devascularisation (porto-caval shunting and hepatic artery ligation) to induce ALF. Control and intervention pigs received intensive medical therapy including inotropic support, and were observed up to 25 hours post-devascularisation. Auxiliary livers were procured from anaesthetised donor pigs (57-69kg) and reperfused on an OrganOx *metra* NMP device, modified to enable ELC. Intervention pigs commenced ELC via veno-venous bypass 1-hour post-devascularisation. **Results:** The target exchange rate of 400mL/min was achieved in all cases. Auxiliary livers maintained physiological hepatic artery (280±160mL/min), portal vein (1030±130mL/min) flows, and bile production (10.3±3.8mL/hr). ELC provided effective detoxification, excretory, synthetic and metabolic regulatory function (table 1). This translated into improved clinical parameters (table 1). ELC corrected haemodynamic instability; attenuated the hyperdynamic circulation exhibited by controls; reduced vasopressor requirement; and improved renal function. Controls demonstrated a profound fall in bi-spectral index, a measure of cerebral activity correlated with grade of hepatic encephalopathy. This was completely prevented by ELC. **Conclusion:** ELC successfully replaces hepatic function and improves prognostically-significant clinical parameters in a porcine model. 35% of potential donor livers do not proceed to transplantation. This provides a ready supply of grafts for ELC. The generation of human-compatible porcine livers through CRISPR gene editing holds promise as an alternative source of grafts in the future. Modern perfusion technology has made multi-day ELC feasible, enabling a treatment duration consistent with meaningful clinical benefit. As a result, the clinical translation of ELC is now a realistic prospect.

Table 1

Evidence of effective liver support across multiple domains

	Domain	Parameter (final value, unless specified)	Control (n=6) (mean (range))	Intervention (n=6) (mean (range))	p-value
Hepatic Function	Detoxification	Ammonia (umol/L)*	8690 (2460 - 27200)	314 (212 - 388)	0.044
	Excretion	Bilirubin (mg/dL)	1.13 (0.7 - 1.70)	0.4 (0.3 - 0.4)	<0.001
	Synthetic	Prothrombin time (secs)	28.8 (24.5 - 33.9)	12.3 (11.9 - 13.5)	<0.001
	Metabolic regulation	Percentage of time normoglycaemic (%)‡	25 (14.4 - 42.0)	65.8 (40.6 - 100)	0.003
		Total supplementary glucose dose (g)	643 (347 - 1005)	67 (0 - 210)	<0.001
		Lactate (mmol/L)	8.74 (2.25 - 20.00)	1.24 (0.71 - 2.10)	0.025
Clinical Feature	Haemodynamic stability	Heart rate (bpm)	140 (96 - 190)	74 (63 - 95)	<0.001
		Mean arterial pressure (mmHg)	53 (38 - 69)	72 (62 - 76)	<0.001
	Hyperdynamic circulation	Pulse pressure (mmHg)	82 (55 - 130)	50 (38 - 62)	<0.001
		Systemic vascular resistance (dynes s/cm^5)†	783 (447 - 1017)	1480 (1080 - 1943)	0.009
		Cardiac output (L/min)‡	5.90 (4.34 - 8.93)	3.21 (2.57 - 3.63)	0.006
	Vasopressor requirement	Noradrenaline dose (ug/kg/min)	0.79 (0.11 - 2.05)	0 (0 - 0)	<0.001
	Hepatic encephalopathy	Bi-spectral index	0 (0 - 0)	37 (13 - 75)	0.003
	Renal function	Percentage of time oligo-anuric (%)§	22.4 (9.4 - 43.9)	0.4 (0 - 2.2)	0.002
		Creatinine (mg/dL)	4.05 (3.50 - 4.70)	2.47 (2.20 - 2.90)	0.007
		Number of interventions for hyperkalaemia¶	5 (1 - 7)	0 (0 - 1)	0.005

Note.
Statistical analysis:
- multiple time-points sampled per experiment: two-way repeated measures anova
- single sample per experiment, parametric data: two-tailed Student's T-test
- single sample per experiment, non-parametric data: Mann Whitney U test.
* Systemic ammonia immediately post-porto-caval anastomosis and pre-hepatic artery ligation: 264 (164 - 357) umol/L.
‡ Normoglycaemia: 3.5 - 6.0 mmol/L.
† Initial systemic vascular resistance: 1535 (1211 - 1973) dynes s/cm^5.
‡ Initial cardiac output: 3.73 (2.79 - 4.78) L/min.
§ Oligo-anuria: urine output < 0.5mL/kg/hr.
¶ Hyperkalaemia treatment threshold: potassium > 6.5 mmol/L.

Disclosures:
Alexander Sagar – OrganOx Ltd: Consultant;

5034-C | IMPROVEMENTS OF EFFICACY AND SAFETY PROFILES OF TENOFOVIR AMIBUFENAMIDE IN CHRONIC HEPATITIS B PATIENTS WITH MAINTAINED VIROLOGICAL RESPONSE OR LOW-LEVEL VIREMIA

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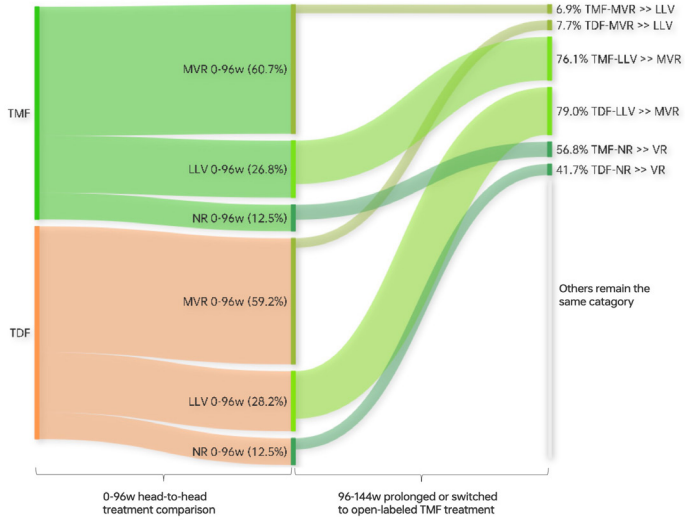
Background: Tenofovir amibufenamide (TMF) is a latest approved prodrug of tenofovir. In a phase 3 randomized, double-blind, active-controlled study, TMF has provided a non-inferior efficacy and better safety profile to that of tenofovir disoproxil fumarate (TDF) for 96 weeks in chronic hepatitis B patients. **Methods:** From week 96 to 144, all patients received open-labeled TMF treatment. Virological response (VR) was defined as HBV DNA levels <20 IU/mL, while the upper limit of normal alanine aminotransferase (ALT) was defined as 35 U/L for males and 25 U/L for females. **Results:** A total of 593 patients in the TMF group and 287 patients in the TDF group completed the study (including those discontinued prematurely due to primary non-response or virological breakthrough). At week 96, 60.7% of patients in the TMF group were classified as having maintained VR (MVR, defined as VR persisted once developed), 26.8% had low-level viremia (LLV, defined as VR developed with any episode of quantifiable HBV DNA hereafter), and 12.5% showed no response (NR). Similar virological outcomes were observed in the TDF group, but the corresponding ALT normalization rates were significantly higher in the TMF group than those in the TDF group (82.2% vs. 73.9%, 71.6% vs. 63.8%, and 54.8% vs. 42.9% in the subgroups of TMF vs. TDF, respectively). From week 96 to 144, less than 8.0% of patients with MVR in TDF and TMF groups (Figure 1) experienced LLV, nearly 80.0% with LLV developed MVR thereafter. In the NR subgroups, a numerically higher percentage of NR patients from the TMF group transformed to either MVR or LLV compared to the TDF group. The switching from TDF to TMF treatment has markedly improved the ALT normalization rates, with an increase of 11.4% (p<0.001), 12.7% (p<0.001), 7.0% and 7.1% in the entire group, MVR, LLV and NR subgroups, respectively. Simultaneously, switching to TMF treatment also led in significant improvements in safety profiles that the bone mineral density has increased by 0.8%, 0.6%, 0.7% in the hip, femur neck, and spine, respectively, while the mean estimated glomerular filtration rate (calculated by non-indexed CKD-EPI equation) increased by 2.3 ml/min. **Conclusion:** By re-classifying patients into MVR, LLV or NR subgroups, TMF treatment still provided similar virological suppression and better ALT normalization rates compared to TDF. Switching from TDF to TMF significantly improved the ALT normalization rates and also the safety profiles.

Firgure 1
The incidences of patients with maintained virological response (MVR), low level viremia (LLV) and non-response (NR) at week 96 and week 144.



Disclosures:
The following people have nothing to disclose: Qinglong Jin

5035-C | LANIFIBRANOR REVERSES INSULIN RESISTANCE AND IMPROVES GLUCOSE AND LIPID METABOLISM IN PATIENTS WITH TYPE 2 DIABETES (T2D) AND METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE (MASLD)

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Background: Lanifibranor, a pan-PPAR agonist, improves steatohepatitis and fibrosis in patients with NASH (Phase 2b NATIVE trial), but the mechanism of the effects warrant further study. Insulin resistance (IR) has a central role in the cardiometabolic health of patients with MASLD. Here we assess the effect of lanifibranor on IR in liver, muscle and adipose tissue in relation to intrahepatic triglyceride (IHTG)

content. **Methods:** In this single-center study, 38 patients with T2D and MASLD were randomized 1:1 to lanifibranor 800 mg or placebo o.d. for 24 weeks. Primary endpoint was IHTG change quantified by ^{1}H-MRS from baseline to end of treatment (EOT). Secondary endpoints included: a) proportion of patients with ≥ 30% decrease in IHTG; b) with steatosis resolution (≤5.5% IHTG); c) change in hepatic, muscle and adipose tissue IR using the euglycemic insulin clamp with stable 6-6D$_2$-glucose and indirect calorimetry; d) changes in HbA1c and lipid profile. (NCT03459079). **Results:** Patient characteristics of Full Analysis Set [FAS]): mean±SD age: 60±9 years, HbA1c: 6.9±0.7%, weight: 97±17 kg, BMI: 34±6 kg/m^2, 37% male; 87% Caucasian; IHTG content: 19.6±7.1%; 28 completers, 14 per arm). Lanifibranor compared to placebo significantly lowered IHTG at EOT (FAS -44% vs. -12%, respectively; least squares [LS] means difference -31%, 95% CI -51 to -12%; completers -50% vs. -16%; both p<0.01 (Table 1). At EOT, more patients reached ≥30% IHTG reduction with lanifibranor compared to placebo (FAS 65% vs. 22%; completers 79% vs. 29%; both p<0.01), and steatosis resolution (FAS 25% vs. 0%; p<0.05). Lanifibranor significantly improved hepatic and peripheral IR (i.e., fasting hepatic glucose production, hepatic IR index, and insulin-stimulated muscle glucose disposal; Table 1). Secondary metabolic endpoints also improved: fasting plasma insulin/glucose concentration and HOMA-IR; HbA1c; plasma HDL-C, >2-fold adiponectin increase (p<0.001; Table 1). Compared to placebo, lanifibranor caused modest weight gain (+2.7%), and in 1 patient mild edema. Adverse events were mild (GI side effects, hemoglobin decrease) and drug-related TEAE leading to discontinuation were balanced between groups (3 on lanifibranor, 2 on placebo). **Conclusion:** Lanifibranor treatment significantly improves hepatic and peripheral insulin sensitivity, resulting in improved glucose and lipid metabolism and IHTG reduction, confirming its cardiometabolic benefits. Treatment with lanifibranor was well tolerated.

TABLE 1: Summary of efficacy of lanifibranor in patients with type 2 diabetes after 24 weeks of treatment.

	FAS N=38				Completers N=28			
	Adjusted LS Mean [95% CI]		*Adjusted LS Mean difference [95% CI]*	*p-value*	*Adjusted LS Mean [95% CI]*		*Adjusted LS Mean difference [95% CI*]	*p-value*
	Lanifibranor N=20	Placebo N=18	Lanifibranor *versus* Placebo		Lanifibranor N=14	Placebo N=14	Lanifibranor *versus* Placebo	
Primary endpoint								
Relative change from baseline (%) in IHTG	-44 [-57;-31]	-12 [-26;2]	-31 [-51;-12]	0.002 [1]	-50 [-64;-36]	-16 [-30;-3]	-33 [-53;-14]	0.002 [1]
Secondary continuous endpoints								
Relative change from baseline in:								
Fasting hepatic glucose production (%)	-8 [-13;-4]	4 [-1;9]	-13 [-20;-6]	<0.001 [1]	-12 [-19;-5]*	4 [-2;11]	-16 [-26;-7]	0.001 [1]
Hepatic IR index (%)	-26 [-37;-14]	-7 [-19;4]	-18 [-34;-2]	0.03 [1]	-39 [-54;-24]*	-10 [-24;3]	-29 [-49;-9]	0.007 [1]
Insulin-stimulated muscle glucose disposal (%)	30 [13;46]	0 [-17;18]	29 [5;54]	0.02 [1]	45 [23;67]*	0 [-22;23]	45 [12;77]	0.009 [1]
Absolute change from baseline in:								
Fasting plasma insulin (µU/mL)	-3.1 [-5.5;-0.8]	-0.0 [-2.5;2.5]	-3.1 [-6.5;0.3]	0.07 [1]	-4.3 [-7.5;-1.2]	-0.1 [-3.3;3.1]	-4.2 [-8.7;0.3]	0.07 [1]
Fasting plasma glucose (mg/dL)	-17.2 [-27.4;-7.0]	2.4 [-8.4;13.2]	-19.6 [-34.5;-4.7]	0.01 [2]	-19.4 [-31.3;-7.4]	-3.5 [-15.5;8.4]	-15.8 [-32.8;1.1]	0.07 [2]
HOMA-IR	-1.6 [-2.5;-0.7]	-0.1 [-1.1;0.8]	-1.5 [-2.8;-0.2]	0.03 [1]	-2.4 [-3.7;-1.1]	-0.3 [-1.5;0.9]	-2.1 [-3.8;-0.3]	0.02 [1]
ADIPO-IR	-2.7 [-4.3;-1.2]	-0.7 [-2.4;0.9]	-2.0 [-4.2;0.3]	0.08 [1]	-3.9 [-5.9;-1.9]	-0.9 [-2.9;1.1]	-3.0 [-5.8;-0.20]	0.04 [1]
HbA1c (%)	-0.7 [-1.0;-0.5]	-0.1 [-0.3;0.2]	-0.6 [-1.0;-0.5]	<0.001 [2]	-0.9 [-1.2;-0.7]	-0.2 [-0.5;0.0]	-0.7 [-1.1;-0.4]	<0.001 [2]
Plasma HDL-C (mg/dL)	7.6 [4.4;10.7]	0.9 [-2.4;4.3]	6.6 [2.0;11.3]	0.006 [2]	6.3 [2.6;10.1]	-0.3 [-4.0;3.5]	6.6 [1.3;11.9]	0.016 [2]
Fold change in Adiponectin	2.4 [2.0;2.7]	1.0 [0.6;1.4]	1.4 [0.9;1.9]	<0.001 [2]	2.7 [2.3;3.1]	1.0 [0.6;1.4]	1.7 [1.2;2.4]	<0.001 [2]
Secondary categorical endpoints	*% [95%CI]*		*p-value*		*% [95%CI]*		*p-value*	
	Lanifibranor	Placebo	Lanifibranor *versus* Placebo		Lanifibranor	Placebo	Lanifibranor *versus* Placebo	
≥30% reduction in IHTG	65 [41;85]	22 [6;48]	0.008 [3]		79 [49;95]	29 [8;58]	0.008 [3]	
Steatosis resolution (IHTG ≤ 5.5%)	25 [9;49]	0 [0;19]	0.046 [4]		21 [5;51]	0 [0;23]	0.048 [4]	

CI=Confidence Interval, FAS=Full Analysis Set, HDL= High Density Lipoprotein, IHTG=IntraHepatic TriGlyceride, IR=Insulin Resistance. In the FAS, missing data were imputed by baseline data.
* N=12, 2 patients were excluded from the analysis because samples were unreliable due to hemolysis.
[1] p-value from an Analysis of Covariance (ANCOVA), including treatment and baseline data as covariates.
[2] p-value from a Mixed Model Repeated Measures (MMRM), including visit as repeated variable, and treatment and baseline data as covariates.
[3] p-value from a Chi² test. [4] p-value from a Fisher exact test.

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5036-C | PRELIMINARY PHARMACODYNAMICS AND SAFETY OF REPEAT DOSING OF IMDUSIRAN (AB-729) FOLLOWED BY VTP-300 OR PLACEBO IN VIRALLY-SUPPRESSED, NON-CIRRHOTIC SUBJECTS WITH CHRONIC HEPATITIS B (CHB)

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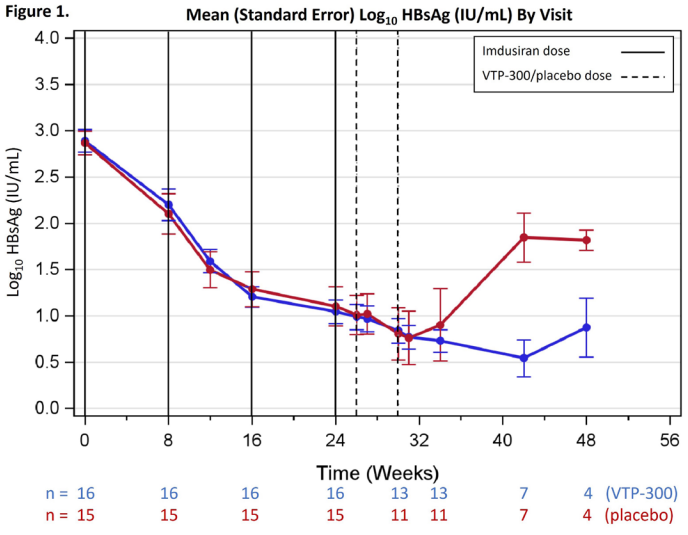
Background: Functional cure of CHB requires suppression of viral replication, reduction of HBsAg and stimulation of host HBV-specific immunity. Imdusiran (AB-729) is a GalNAc-conjugated single trigger siRNA therapeutic that targets all HBV RNA transcripts and suppresses viral replication and all viral antigens. In prior studies, 24 weeks of imdusiran treatment led to -1.5 to -2.0 log$_{10}$ mean declines from baseline in HBsAg and appears to stimulate HBV-specific immune responses in some subjects. VTP-300 is an HBV-specific immunotherapeutic consisting of a chimpanzee adenoviral vector (ChAdOx1-HBV) dose and a Modified Vaccinia Ankara (MVA-HBV) dose both encoding the inactivated polymerase, core, and the entire S region from a consensus genotype C HBV virus. In a prior study, VTP-300 induced HBV-specific CD4+ and CD8+ T cells and lowered HBsAg in a subset of patients with baseline HBsAg levels below 100 IU/mL. Study AB-729-202 is an ongoing, randomized, double-blinded Phase 2a study assessing the safety, pharmacodynamics and immunogenicity

of repeat doses of imdusiran followed by VTP-300 or placebo in nucleos(t)ide analogue (NA) suppressed, non-cirrhotic CHB subjects. **Methods:** CHB subjects on stable NA therapy with HBsAg ≥100 but <5000 IU/mL received imdusiran 60 mg every 8 weeks for 4 doses. At Week 24, subjects were randomized 1:1 to receive VTP-300 or placebo at Weeks 26 and 30. Subjects could receive a second MVA-HBV/placebo dose at Week 38 if they had a >0.5 $\log_{10}$ HBsAg reduction between Weeks 26 and 34. Subjects were assessed for NA discontinuation eligibility based on Week 48 data. Safety data, HBV parameters and immunology samples were collected at multiple timepoints. The study is ongoing. **Results:** Of the 40 subjects enrolled to date, 70% were male, 92.5% were Asians, and 35% were HBeAg positive. Baseline mean (SE) HBsAg was 1129.1 (±162.07) IU/mL, and at Week 24 the mean (SE) HBsAg decline from baseline was -1.81 (±0.09) $\log_{10}$ IU/mL (N=31). To date, 13 subjects have received active VTP-300 (Group A) and 11 have received placebo (Group B). Preliminary mean (SE) HBsAg declines by Group are shown in **Figure 1**. Subjects receiving VTP-300 appear to maintain lower HBsAg levels post-imdusiran than those receiving placebo. At Week 48, 100% of subjects who received VTP-300 have maintained HBsAg <100 IU/mL vs 75% of placebo subjects. One HBeAg+ subject (Group B) reached HBsAg below the lower limit of quantitation at Week 36. Five of 8 subjects completing Week 48 have stopped NA treatment with no adverse events (AEs) or ALT elevations. There have been no Serious Adverse Events, Grade 3 or 4 AEs or treatment discontinuations. **Conclusion:** Preliminary data suggest that repeat dosing of imdusiran for 24 weeks followed by VTP-300 was well-tolerated and may contribute to prolonged HBsAg reductions compared to placebo. Additional on-treatment and follow-up data including HBV parameters and immunology data will be presented.

Figure 1.



Disclosures:
Karen D. Sims – Arbutus Biopharma: Employee; Arbutus Biopharma: Stock - publicly traded company; Arbutus Biopharma: Executive role;

5037-C | PEGINTERFERON-A-2b PROVIDES DUAL BENEFITS OF REDUCING HCC DEVELOPMENT AND FACILITATING HBsAg LOSS FOR NA-TREATED CHB PATIENTS WITH INTERMEDIATE TO HIGH RISK OF HCC: INTERIM ANALYSES OF PARADISE STUDY

Shaowen Jiang[1], Simin Guo[1], Haiguang Xin[1], Jie Xu[2], Yi Li[3], Yilan Zeng[4], Yuan Guo[5], Lijuan Ouyang[6], Chuanwu Zhu[7], Weifeng Zhao[8], Qin Zhang[9], Qing Guo[1] and Qing Xie[1], (1)Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, (2)Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, (3) Anhui Provincial Hospital, (4)Public Health Clinical Center of Chengdu, Chengdu, Sichuan 610041, China, (5)The Affiliated Hospital of Qingdao University, (6)Xiamen Hospital of Traditional Chinese Medicine, Xiamen, China, (7)The Affiliated Infectious Diseases Hospital of Soochow University, Suzhou, Jiangsu, China., (8)Xinxiang Medical University Third Hospital, (9)Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Up to 80% of hepatocellular carcinoma (HCC) is caused by chronic hepatitis B (CHB) in China. Nucleos(t)ide analogs (NAs) treatment can reduce but cannot completely eliminate HCC risk in CHB patients. This study is to investigate whether peginterferon-α-2b (IFN) add-on NAs can further reduce HCC risk compared with NAs monotherapy in NAs-treated virologically suppressed CHB patients. **Methods:** In this multi-center randomized controlled trial "PARADISE study" (NCT05671315), CHB patients with intermediate to high risk of HCC, who had undetectable HBV DNA after more than 24-week NAs pretreatment, were recruited, randomized to two groups at a ratio of 1:2 and followed up for 240 weeks. NAs group continued NAs monotherapy, while IFN+NAs group received IFN add-on NAs therapy for 48 weeks, then switched to NAs monotherapy. The changes of HBV serological markers at week 48 and the 96-week cumulative incidences of HCC were compared between groups. **Results:** A total of 196 CHB patients were included in the interim analyses based on 96-week follow-up data (68 in NAs group, 128 in IFN+NAs group). There was no significant difference between groups in baseline characteristics. As of week 96, three patients developed HCC in NAs group, whereas no HCC case occurred in IFN+NAs group. The 96-week cumulative incidence of HCC was markedly lower in IFN+NAs group than NAs group (0% *vs.* 4.5%, log-rank test p<0.05) (Fig.1). Compared with NAs group, IFN+NAs group had a significantly lower level of HBsAg at week 48 (1.553±1.884 *vs.* 2.885±0.714 log10 IU/ml, p<0.001) and a notably greater HBsAg decline from baseline to week 48 (1.242±1.333 *vs.* 0.095±0.333 log10 IU/ml, p<0.001). Rates of HBsAg loss and HBsAg seroconversion at week 48 were much higher in IFN+NAs group than NAs group (21.9% *vs.* 0%, p<0.001; 18.0% *vs.* 0%, p<0.001). For HBeAg-positive

patients (24 *vs.*57 in NAs *vs.*IFN+NAs group), IFN+NAs group had a significantly higher rate of HBeAg loss at week 48 (43.9% *vs.* 16.7%, p<0.05), but the difference in HBeAg seroconversion rate between the two groups did not reach a statistical significance (19.3% *vs.* 8.3%, p>0.05) (Fig.2). **Conclusion:** IFN add-on NAs therapy is superior to NAs monotherapy in reducing HCC risk and facilitating HBsAg loss among NA-treated virologically suppressed CHB patients with intermediate to high risk of HCC.

Fig.1

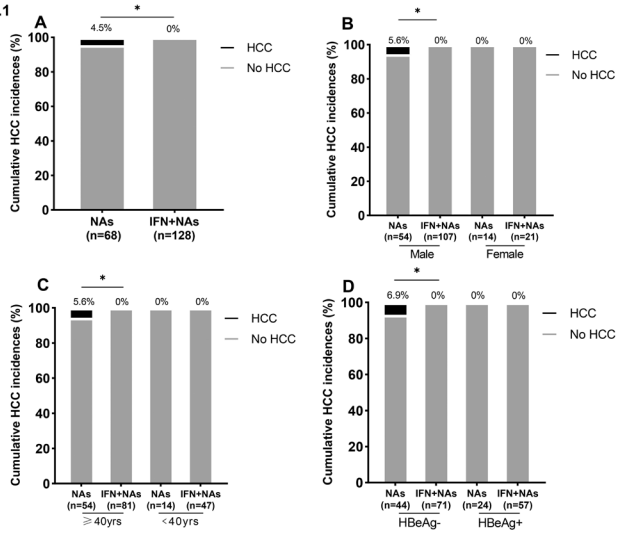
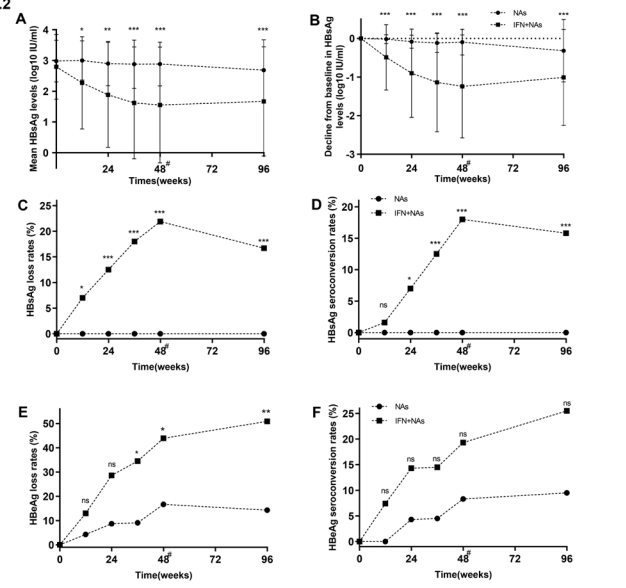


Fig.2



Disclosures:
The following people have nothing to disclose: Shaowen Jiang

5038-C | SAFETY, PHARMACOKINETICS AND PHARMACODYNAMICS OF A NOVEL GLP-1/FGF21 DUAL AGONIST HEC88473 IN TYPE 2 DIABETES PATIENTS WITH NONALCOHOLIC FATTY LIVER DISEASE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 1b/2a MULTIPLE-ASCENDING-DOSE STUDY

Lin Xiang[1], Hua Yan Ding[1], Jiangyu Yan[2], Lin Luo[2], Hong Zhang[1], Can Xie[2], Yu Yu Peng[2], Hong Chen[1], Qian Qian Li[1], Xiao Ping Li[2], Yu Lei Zhuang[2] and Linfeng Guo[2], (1) First Hospital of Jilin University, (2)Sunshine Lake Pharma Co., Ltd

Background: HEC88473, a novel GLP-1/FGF21 dual agonist developed by Sunshine Lake Pharma Co., Ltd, has shown superior therapeutic efficacy to single-targeted analogues in preclinical type 2 diabetes mellitus (T2DM), obesity and non-alcoholic steatohepatitis (NASH) animal models. In this clinical study, we aimed to assess the safety, pharmacokinetics and pharmacodynamics of HEC88473 in T2DM subjects combined with nonalcoholic fatty liver disease (NAFLD). **Methods:** This study was a randomized, double-blind, placebo-controlled, multiple-ascending-dose phase 1b/2a trial (Chinese Drug Trial Identifier: CTR20211088). A total of 60 T2DM subjects with NAFLD were randomized (10:2) to receive HEC88473 of 5.1mg, 15.3mg, 30.6mg, 45.9mg, 68.0mg or placebo via weekly subcutaneous injection for 5 weeks. MRI proton-density fat fraction was used to quantify the liver fat content (LFC, %) of the patients. **Results:** After 5 weeks of treatment with HEC8847, LFC, gamma-glutamyl transpeptidase, triglycerides, total cholesterol, and low-density lipoprotein cholesterol all showed decline trends compared with the placebo group. Mean relative changes from baseline to D38 in LFC were -25.60%, -37.06%, -47.21% (p=0.0167), -44.00% (p=0.0232), -46.54% (p=0.0167) in the 5.1mg, 15.3mg, 30.6mg, 45.9mg and 68.0mg cohort respectively, compared with -15.05% in placebo. If only patients with baseline LFC>8% were taken into account, 2/4(50%), 3/6(50%), 5/6(83.3%), 5/7(71.4%), and 5/5(100%) of patients in each HEC88473 cohort respectively versus 1/4(25%) in placebo, achieved a ≥30% mean relative decreases in LFC. Adiponectin levels increased in a dose-dependent manner, with Mean relative increase from baseline to D29 reached up to 77.46% (p<0.0001) for patients receiving HEC88473, compared with -0.05% for placebo. Mean change from baseline to D38 in HbA1c levels were up to -1.10% for patients receiving HEC88473, compared with -0.31% for placebo. HEC88473 was generally safe and well tolerated. Most adverse events (AEs) were mild-to-moderate in severity, no drug-related severe AE or death occurred. The most frequently reported AEs were gastrointestinal disorders (29 (48.3%)). **Conclusion:** To our knowledge, this study presents the first clinical safety and proof of concept data for the

GLP-1/FGF21 dual agonist class. Five weeks treatment with HEC88473 was safe and well tolerated and associated with clinically meaningful reductions in LFC as well as HbA1c levels in T2MD patients combined with NAFLD.

Disclosures:
The following people have nothing to disclose: Lin Xiang

5039-C | PRETREATMENT SERUM BILE ACID COMPOSITION IN PATIENTS WITH BILE SALT EXPORT PUMP DEFICIENCY IS STRONGLY ASSOCIATED WITH TREATMENT RESPONSE TO ILEAL BILE ACID TRANSPORTER INHIBITION BY ODEVIXIBAT

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Background: Bile salt export pump (BSEP) deficiency (ie, PFIC2) is a rare genetic liver disease characterized by defective secretion of bile acids (BAs). Odevixibat, an ileal bile acid transporter inhibitor (IBATi), inhibits the reabsorption of conjugated BAs and effectively reduced the total concentration of serum BAs (sBAs) in a proportion of patients with PFIC2 (Thompson et al. *Lancet Gastroenterol Hepatol*. 2022;7:830−42). It has so far been impossible, however, to predict the responsiveness to an IBATi in patients with PFIC2. We tested the hypothesis that the sBA composition before treatment is associated with future responsiveness to an IBATi in patients with PFIC2. **Methods:** We included 41 patients with PFIC2 who were treated with odevixibat in the PEDFIC 1 trial (n=29) or the rollover PEDFIC 2 trial (n=12). We analyzed the pretreatment sBA composition. Concentrations of individual sBAs were measured by liquid chromatography-tandem mass spectrometry. Relative contributions per sBA were calculated by dividing the individual BA concentration by the total concentration of sBAs from which ursodeoxycholic acid (UDCA) concentration was subtracted. We compared pretreatment sBA composition in patients who, upon treatment, were sBA responders (ie, had an sBA reduction ≥70% or a total sBA concentration ≤70 µmol/L after 24 weeks; Rs) with sBA nonresponders (ie, did not meet sBA responder criteria; NRs). **Results:** In pretreatment serum samples, total sBA and UDCA concentrations were similar between Rs and NRs (median [range]: total sBA: Rs, 237 µmol/L [51−646 µmol/L]; NRs, 279 µmol/L [100−628 µmol/L]; *P*=0.40; UDCA: Rs, 56 µmol/L [0.1−196 µmol/L]; NRs, 77 µmol/L [0.1−201 µmol/L]; *P*=0.86). However, Rs had higher percentages of unconjugated cholic acid (CA) (median [range]: 0.04% [0.01%–0.4%]) and chenodeoxycholic acid (CDCA) (0.03% [0.01%–0.7%]) compared with NRs (CA: 0.02% [0.01%–0.05%]; *P*=0.03; CDCA: 0.02% [0.01%–0.05%]; *P*=0.01). The absolute concentration of CA + CDCA was higher in Rs (0.14 µmol/L [0.07−0.34 µmol/L]) compared with NRs (0.09 µmol/L [0.06−0.18 µmol/L]; *P*=0.004). Receiver operating characteristic curve analysis for CA percentage, CDCA percentage, and absolute concentration of CA + CDCA revealed an area under the curve of 0.70 (95% CI: 0.52, 0.87; *P*=0.03), 0.73 (95% CI: 0.56, 0.90; *P*=0.01), and 0.76 (95% CI: 0.61, 0.92; *P*=0.004), respectively. When a patient did or did not meet at least 1 of the 3 optimal thresholds, 36 of 41 patients with PFIC2 (87.8%) were correctly classified as Rs or NRs, respectively (sensitivity: 89.5%; specificity; 86.4%; Table). **Conclusion:** Pretreatment unconjugated sBA levels are strongly associated with responsiveness to IBATi treatment by odevixibat in patients with BSEP deficiency. These observations strongly suggest that IBATi treatment responsiveness can be predicted and requires a minimal threshold of residual biliary BA secretion.

Table: Contingency Table Classified by Whether Patients With BSEP Deficiency Met At Least 1 of 3 Unconjugated Bile Acid Thresholds Before Treatment and by Subsequent Treatment Response to Odevixibat

	Responsiveness to IBATi (Odevixibat)	
	R[a]	NR[b]
Pretreatment sBA Composition		
Meeting ≥1 of 3 unconjugated BA thresholds[c]	17	3
Not meeting any unconjugated BA threshold[c]	2	19

Sensitivity=89.5%; Specificity=86.4%; Positive Predictive Value=85%; Negative Predictive Value=90.5%.
[a]sBAs reduced ≥70% or a total sBA concentration ≤70 µmol/L after 24 weeks; [b]Did not meet sBA responder criteria; [c]Thresholds were: unconjugated CA percentage (≥0.03406%), unconjugated CDCA percentage (≥0.0283%), and unconjugated CA concentration + unconjugated CDCA concentration (≥0.1209 µmol/L). BA, bile acid; BSEP, bile salt export pump; CA, cholic acid; CDCA, chenodeoxycholic acid; IBATi, ileal bile acid transporter inhibitor; NR, nonresponder; R, responder; sBA, serum bile acid.

Disclosures:
The following people have nothing to disclose: Mark Nomden

5040-C | PRECLINICAL EFFICACY AND SAFETY OF ARCUS-POL NUCLEASES FOR CHRONIC HEPATITIS B: A POTENTIALLY CURATIVE STRATEGY

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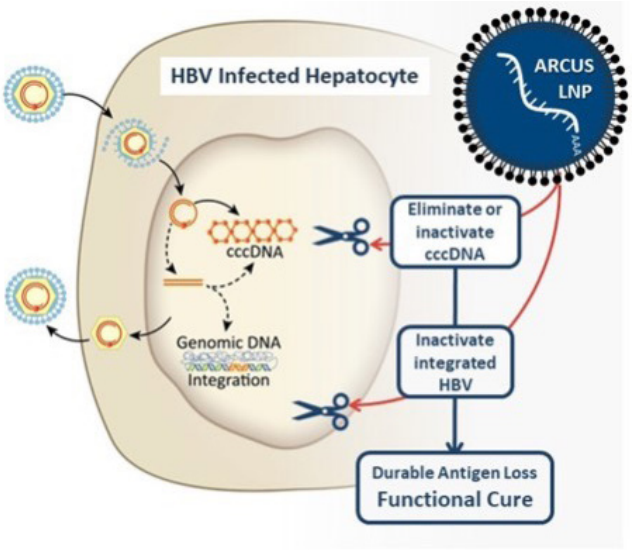
Neil Leatherbury[1], Janel Lape[1], Jeff Smith[1] and Cassandra L Gorsuch[1], (1)Precision Biosciences, (2)Acuitas Therapeutics

Background: Gene editing with ARCUS nucleases is a potentially curative approach for chronic hepatitis B (CHB) capable of eliminating or inactivating hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) and integrated HBV DNA. We previously demonstrated that ARCUS-POL nucleases engineered to recognize a conserved target sequence in the HBV polymerase gene durably reduce HBV surface antigen (HBsAg) *in vitro* and *in vivo*. The previously described ARCUS-POL nuclease, construct, and formulation were each optimized for increased activity and safety (ARCUS-POL v.2), then further engineered to enhance specificity for the HBV target site (ARCUS-POL v.3). The efficacy and safety of ARCUS-POL v.2 and v.3 were tested in preclinical models. **Methods:** To evaluate efficacy of ARCUS-POL v.2 in non-human primates (NHP), animals were dosed with a cccDNA-surrogate AAV containing the HBV target sequence then two administrations of 0.5, 1.0 or 2.0 mg/kg ARCUS-POL v.2 mRNA encapsulated in lipid nanoparticles (LNPs). The activity and specificity of ARCUS-POL v.2 and v.3 were evaluated side by side in a liver cell line with integrated HBV DNA and an AAV-surrogate mouse model similar to the AAV-surrogate NHP study. ARCUS-POL v.3 was further tested in HBV-infected primary human hepatocytes (PHH) and a transgenic HBV mouse model. **Results:** In NHPs, the optimized ARCUS-POL v.2 was well tolerated and resulted in cccDNA-surrogate elimination and editing, achieving 99% total inactivation at the highest dose and >90% at all dose levels. Compared to ARCUS-POL v.2, the v.3 variant showed enhanced specificity, eliminating editing at off-target sites, with similar HBsAg reductions in a HepG2 cell line with integrated HBV DNA. In a cccDNA-surrogate mouse model, treatment with ARCUS-POL v.2 or v.3 resulted in high levels of viral inactivation and durable reduction of serum HBsAg. In HBV-infected PHH, ARCUS-POL v.3 reduced HBsAg, HBeAg, HBV DNA, and HBV RNA and eliminated or inactivated the majority of cccDNA. Finally, ARCUS-POL v.3 edited integrated HBV DNA and durably reduced HBsAg, HBeAg, HBV DNA, and HBV RNA in a transgenic mouse model. **Conclusion:** The fully optimized ARCUS-POL v.3 eliminates or inactivates both cccDNA and integrated HBV DNA resulting in durable reductions in HBsAg with high levels of specificity for the target HBV DNA sequence, and this approach represents a potentially curative therapy for CHB.



Disclosures:
Cassandra L Gorsuch – Precision BioSciences: Employee;

5041-C | PHI-PROTECTED GPT-4 ACHIEVES 93.4% OVERALL ACCURACY IN NATURAL LANGUAGE PROCESSING OF LONGITUDINAL HEPATOCELLULAR CARCINOMA IMAGING REPORTS

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Background: Publicly available large language models (LLMs), such as ChatGPT, cannot be used with protected health information (PHI). LLMs deployed in PHI-protected environments are now becoming available, but they have not been extensively tested with actual clinical data. HCC imaging, which is systematically reported using LI-RADs, provides an ideal demonstration case for LLM-enabled natural language processing of unstructured text. **Methods:** We compared the performance of "Versa," the PHI-compatible implementation of Microsoft Azure OpenAI GPT-4 API at UCSF, versus manual chart review in extracting data elements from HCC imaging reports. We manually tagged 8 distinct data elements (maximum LI-RADs for any lesions, number of lesions, size of largest lesion, sum of diameters, macrovascular invasion, extrahepatic metastases, prior locoregional treatment, and imaging adequacy) from 1,101 longitudinal pre- and post-locoregional treatment imaging reports for 753 patient enrolled in the FrAILT study at UCSF. We iteratively developed a "few-shot" prompt (one with a training example) was used in the GPT-4 "system" role for extraction. We calculated performance metrics (accuracy, precision, recall, and F1) to compare GPT-4

versus manual chart review. **Results:** The performance metrics are presented in Table 1. Processing of 1,101 reports took ~2 hours. GPT-4's overall accuracy was 0.934 (95%CI 0.928-0.939) across the 8 parameters. Accuracy rates were higher for binary classification tasks, such as extrahepatic metastases (0.989, 95%CI 0.980-0.994), imaging adequacy (0.965, 95%CI 0.952-0.974), macrovascular invasion (0.936, 95%CI 0.919-0.948), and previous locoregional treatment (0.910, 95%CI 0.891-0.926). For more complex operations such as identification of maximum tumor diameter and sum of tumor diameters, accuracy decreased to 0.920 (95%CI 0.902-0.944) and 0.886 (95%CI 0.866-0.903), respectively. Precision, recall, and F1 statistics varied significantly based on the classification type and number of positive events (Table 1). **Conclusion:** This is one of the first studies to utilize a PHI-protected LLM for clinical research in hepatology. GPT-4 achieved superior accuracy for extracting data from HCC imaging reports. While iterative prompt development ("prompt engineering") was necessary, this process did not require extensive technical knowledge. GPT-4's ability to process both pre- and post-treatment scans indicate that it can follow complex instructions. This use-case illustrates the potential for PHI-protected versions of commercially available general-purpose LLMs to augment clinical research in liver diseases.

Table 1 – Performance metrics of "Versa" GPT-4 versus manual chart review

	Accuracy	Binary Event Rate (if applicable)	Precision	Recall	F1
Max LIRADs Rating	0.944 (0.928-0.955)		0.946 (0.931-0.958)*	0.944 (0.928-0.955)*	0.944 (0.930-0.956)*
Number of Tumors	0.922 (0.903-0.936)		0.924 (0.906-0.938)*	0.922 (0.905-0.937)*	0.922 (0.904-0.938)*
Maximum Tumor Diameter	0.920 (0.902-0.944)		0.934 (0.914-0.944)*	0.920 (0.902-0.935)*	0.924 (0.907-0.937)*
Sum of Tumor Diameters	0.886 (0.866-0.903)		0.907 (0.881-0.918)*	0.886 (0.866-0.904)*	0.892 (0.871-0.908)*
Macrovascular Invasion (Binary)	0.936 (0.919-0.948)	0.005	0.054 (0.013-0.109)	0.800 (0.333-1.000)	0.101 (0.026-0.195)
Extrahepatic Metastases (Binary)	0.989 (0.980-0.994)	0.006	0.308 (0.071-0.600)	0.571 (0.143-1.000)	0.400 (0.125-0.667)
Previous LRT (Binary)	0.910 (0.891-0.926)	0.761	0.924 (0.907-0.942)	0.961 (0.947-0.973)	0.942 (0.931-0.953)
Inadequate Study (Binary)	0.965 (0.952-0.974)	0.052	0.655 (0.528-0.780)	0.667 (0.546-0.788)	0.661 (0.553-0.755)
Overall Accuracy	0.934 (0.928-0.939)				

*Weighted statistics given as these were multi-level classifications

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5042-C | ECONOMIC AND SOCIAL BURDEN OF MASLD IN THE UNITED STATES

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Background: MASLD & MASH represent a large and growing burden in the U.S. & better estimates of economic and social burden is needed to develop effective national strategies. In the last 5 years, several clinical and cohort studies in the US have provided more refined estimates of the burden allowing us to develop better forecasts. **Methods:** A Markov model was used to estimate MASLD/ MASH incidence & prevalence by disease stage between 2015-2045. Annual follow up costs for diagnosed F2–F4, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC) & liver transplantation (LT) was collected from literature & applied to the forecasted population pool after applying a 3% discount rate. Disability utilities for DC, HCC and LT were also collected & only applied to those aged 18-65 to estimate the societal impact. Life expectancy was calculated using all cause, liver related & excess mortality in this population. The impact of treatment was estimated by changes in progression rate. **Results:** in 2022, an estimate 26 million people had MASH in the U.S., forecasted to grow to 40 million by 2045. MASLD is estimated to cost the U.S. health system $13.2B annually. In 2023 this increased to $16.8B. MASH related disability adjusted life years will increase from 124K to 260K life years between 2023 & 2045. The impact of GLP-1 and SGLT-2 drugs was muted (only 4K DC, 1K HCC & 2.2K LRD averted between 2024-2044) even if treatment increased to 18% in all diagnosed MASH cases. These drugs are shown to reduce steatosis but so far have not shown a lack of fibrosis progression. On the other hand, any medication that can reduce fibrosis progression by 70% can avert 253-287K DC, 26-30K HCC, 163-186K LRD, 327-373K DALYs depending on treatment restrictions (between 2023-2045). **Conclusion:** MASH represent a large and growing burden in the U.S and the associated healthcare costs are expected to increase if there is no action. Interventions like diagnosis and treatment (when available) can have a large impact on future disease and societal burden.

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5043-C | EFFICACY AND SAFETY OF A NOVEL NUCLEOSIDE ANALOGUE HEPENOFOVIR FOR THE TREATMENT OF CHRONIC HEPATITIS B VIRUS INFECTION: INTERIM RESULTS FROM THE PHASE IC/IIb STUDY

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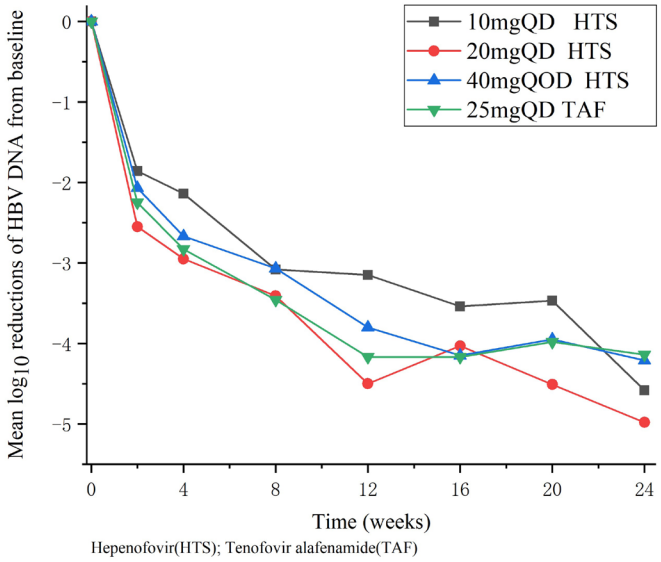
Background: Hepenofovir (HTS), an oral liver-targeting prodrug of tenofovir developed using the HepDirect technology, is for the potential first line treatment of Chronic hepatitis B, which is developed by Xi'an Xintong Pharmaceutical Research Co., Ltd. In this clinical study, we aimed to assess the safety,

antiviral activity, and pharmacokinetics of Hepenofovir and an active control cohort of Tenofovir alafenamide(TAF) in CHB patients. **Methods:** In the Phase Ic/IIb, randomized, open labeled active-controlled study, a total of 48 CHB patients were randomized to receive HTS of 10mgQD, 20mgQD, 40mgQOD, or TAF 25mgQD for 48 weeks. The primary end point of the study was assessed via the decreases of HBV DNA levels, the rate of the HBV DNA reached undetectable (20 IU/mL), the changes of HBsAg and HBeAg and ALT normalization from baseline. **Results:** At week 12, the mean reductions of HBV DNA in HTS cohorts at 10mg(N=8), 20mg(N=10), 40mg (N=9) and TAF at 25mg(N=10) were -3.15, -4.50, -3.80 and -4.17 $\log_{10}$IU/mL, respectively; the rates of HBV DNA reached undetectable were 12.5%, 30%, 44.4% and 30%; the changes of HBsAg were -0.34, -0.18, -0.17 and -0.05 $\log_{10}$IU/mL, respectively (4 subjects with HTS experienced significant decrease, which were -1.12, -1.05, -0.89, and -0.93 $\log_{10}$IU/mL, respectively); the mean reductions of HBeAg were -0.19, -0.59, -0.64 and -0.22 $\log_{10}$IU/mL; and ALT normalization rates were 50%, 70%, 66.7% and 60%, respectively. At week 24, the mean reductions of HBV DNA in HTS cohorts at 10mg(N=4), 20mg(N=4), 40mg(N=6) and TAF at 25mg(N=4) were -4.58, -4.98, -4.21 and -4.14 $\log_{10}$ IU/mL; the rates of HBV DNA reached undetectable were 25%, 25%, 66.7% and 25%, respectively; the mean reductions of HBsAg were -0.70, -0.25, -0.10 and -0.14 $\log_{10}$IU/mL (in HTS cohort, one subject experienced a significant reduction of HBsAg: -1.76 $\log_{10}$IU/mL); the mean reductions of HBeAg were -1.08, -1.02, -0.82 and -0.30 $\log_{10}$IU/mL; and ALT normalization rates were 100%, 50%, 83.3% and 50%, respectively. Most adverse events (AEs) were mild-to-moderate in severity. No SAEs were observed, and no discontinuations were reported due to AEs, The most common AEs were the elevation of ALT/AST, all of which were considered as good flare. **Conclusion:** HTS was generally safe and well tolerated; the mean reductions of HBV DNA and the rates of HBV DNA reached to undetectable were dose-dependent, and were superior to those in TAF cohort. The mean reductions of HBsAg /HBeAg and ALT normalization rates were more favorable than those in TAF cohort.



Hepenofovir(HTS); Tenofovir alafenamide(TAF)

Disclosures:
The following people have nothing to disclose: Jing Zhou

5044-C | ANTIVIRAL AND ANTITUMOR EFFECT OF NOVEL HBsAg-SPECIFIC TCR T CELL THERAPY (SCG101) IN PATIENTS WITH HBV-RELATED HEPATOCELLULAR CARCINOMA

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Background: Hepatitis B virus (HBV) infection accounts for 75-80% of virus-associated hepatocellular carcinoma (HCC). HBV DNA integration into the host cell genome may trigger carcinogenesis and result in expression of HBV antigens, mainly HBsAg. HBsAg-positive cells can be effectively targeted by T cells grafted with HBsAg-specific T-cell receptors. SCG101, a first-in-class autologous HBsAg-specific TCR-T cell therapy, uses a high avidity TCR, that showed profound anti-viral and anti-tumor activity in preclinical studies. Here, we present the evaluation of SCG101 in subjects with HBV-related HCC in an investigator-initiated trial. **Methods:** The trial enrolled six HLA-A*02:01(+), HBsAg(+), HBeAg(-) subjects with advanced HBV-related HCC, BCLC B/C stage, who had received one to three prior systemic therapies and at least 12 months of nucleoside analogue treatment. All subjects received a single dose of 5x10e7 or 1x10e8 cells/kg of SCG101 TCR-T cells intravenously after lymphodepletion with cyclophosphamide-fludarabine. Safety, pharmacokinetics, antiviral, and antitumor activities were evaluated. **Results:** Following infusion, SCG101 TCR-T cells showed significant dose-dependent proliferation and persisted during the study period. Antiviral and/or antitumor activities were observed in all six subjects treated with SCG101. Serum HBsAg dropped in all six subjects, with 4/6 >1 $\log_{10}$. Transient ALT elevation correlating with HBsAg reduction was observed in all subjects, indicating on target activity of SCG101. Tumor control was observed in all 4 patients with >1 $\log_{10}$ serum HBsAg reduction, with two patients showing partial response and two stable disease as per mRECIST criteria. Patients with less than 1 $\log_{10}$ reduction in serum HBsAg showed no tumor response. Until data cut-off date (end of Aug 2023), the medium overall survival was not reached. The treatment was well-tolerated, no dose-limiting toxicity or neurotoxicity was observed. **Conclusion:** SCG101, as a single agent, demonstrated significant antiviral and antitumor activity in subjects with HBV-related HCC. The persistence of TCR T cells, reduction of serum HBsAg, and tumor response proved on-target activity of SCG101. A

phase I/II clinical trial to systematically evaluate the safety and efficacy of SCG101 has been initiated.

Disclosures:
Xiaorui Wang – SCG Cell Therapy: Employee;

5045-C | NUCLEOS(T)IDE ANALOGUE DISCONTINUATION OUTCOMES IN CHRONIC HEPATITIS B PARTICIPANTS TREATED WITH XALNESIRAN COMBINATION THERAPIES WITH AND WITHOUT AN IMMUNOMODULATOR: INTERIM RESULTS FROM THE PHASE 2, RANDOMIZED, CONTROLLED, ADAPTIVE, OPEN-LABEL PLATFORM STUDY (PIRANGA)

Edward J Gane[1], Qing Xie[2], Wenhong Zhang[3], Junqi Niu[4], Hong Tang[5], Luis Enrique Morano Amado[6], Sheng-Shun Yang[7], Cheng Yuan Peng[8], Xieer Liang[9], Cynthia Wat[10], Cong Cheng[11], Katerina Glavini[12], Sudip Das[13], Qingyan Bo[14], Yan Huang[11], Vedran Pavlovic[13], Nelson Guerreiro[12], Ethan Chen[15], Miriam Triyatni[12], Bernadette Surujbally[13], Ruchi Upmanyu[13] and Jinlin Hou[9], (1) Auckland Clinical Studies Limited, (2)Ruijin Hospital Shanghai Jiaotong University School of Medicine, (3) Huashan Hospital, Fudan University School of Medicine, Shanghai, China, (4)The First Hospital of Jilin University, (5)West China Hospital, Sichuan University, (6)Alvaro Cunqueiro University Hospital, Health Research Institute South Galicia, (7)Taichung Veterans General Hospital, (8) China Medical University Hospital, (9)Nanfang Hospital, Southern Medical University, (10)Former Employee of Roche Products Ltd, (11)China Innovation Center of Roche, (12)Roche Innovation Centre Basel, (13)Roche Products Ltd, (14)Former Employee of China Innovation Center of Roche, (15)Roche (China) Holding Ltd

Background: There is a lack of consensus on Nucleos(t)ide analogues (NUC) discontinuation and restarting criteria in clinical trials exploring novel finite duration regimens for chronic hepatitis B (CHB). Here, we report the criteria and the associated outcomes from xalnesiran (a small interfering ribonucleic acid targeting the HBsAg coding region of the HBV genome, RO7445482, RG6346) combination therapies in the PIRANGA phase 2 platform study (NCT04225715, please refer to Abstract #48375). **Methods:** Virologically-suppressed CHB participants (pts) on established NUC therapy were randomized into the combination treatment arms (see table) or the NUC control arm for 48 weeks (wks) of treatment and 48 wks of follow-up. Pts who completed the treatment period were required to stop NUC therapy if the end-of-treatment (EOT) or any subsequent follow-up visits showed: ALT<1.25baseline value, AND HBV DNA<20 IU/mL, AND negative HBeAg, AND HBsAg loss or HBsAg<100 IU/mL with ≥1 log10 IU/mL decline from baseline. Pts who discontinued NUC therapy were required to be followed up every 2 weeks for the first 12 weeks, and 4 weekly thereafter. In addition, pts with HBV DNA levels >20 and >2,000 IU/mL were required to be followed up every 2 weeks and weekly. NUC therapy should have been restarted if: HBV DNA>20,000 IU/mL; OR HBV DNA>2,000 IU/mL and ALT>1.5upper limit of normal (ULN); OR HBV DNA>2,000 IU/mL and ALT≤1.5ULN and if retest within 7 days confirmed HBV DNA>2,000 IU/mL; OR clinically significant signs of decreasing liver function (based on laboratory findings or clinical assessments). **Results:** By primary analysis cutoff date, 55/124 (44.3%) pts met NUC stopping criteria across xalnesiran combination arms, of which 36 stopped NUC. 14/36 (38.9%) pts experienced virological relapse (HBV DNA> 2000 IU/mL), with maximum HBV DNA of <4, 4 to 5, and 6 to 7log10IU/mL in 5, 7, and 2 pts, respectively. In 6/14 (42.9%) pts liver enzymes were elevated, and maximum ALT was <2ULN, 6-8ULN, and 23ULN in 3, 2, and 1 pts, respectively. 13/14 (92.8%) pts restarted NUC per protocol and all 13 pts achieved virological suppression (and ALT normalization, if applicable). HBsAg loss at 24 wks post-EOT was observed in 14/124 (11.3%) pts, of which 10 met NUC stopping criteria. Only 1 pt had HBsAg loss after NUC discontinuation. **Conclusion:** NUC discontinuation in xalnesiran combination arms was safely managed with close monitoring and pre-specified stopping/restarting criteria.

Arms (mITT Population)	Met NUC stopping criteria n (%)	Stopped NUC per protocol[1] n (%)	HBsAg loss at 24 wks post-EOT n (%)	HBsAg loss at 24 wks post-EOT AND met NUC stopping criteria [2] n (%)	Virological relapse n (%)
Arm 1 (N=30) xalnesiran 100mg+NUC	11/30 (36.7%)	7/30 (23.3%)	2/30 (6.7%)	0/30 (0%)	5/30 (16.7%)
Arm 2 (N=30) xalnesiran 200mg+NUC	13/30 (43.3%)	6/30 (20%)	1/30 (3.3%)	1/30 (3.3%)	1/30 (3.3%)
Arm 3 (N=30) xalnesiran 200mg+ Peg-IFN-α 180 µg+NUC	11/30 (36.7%)	8/30 (26.7%)	7/30 (23.3%)	6/30 (20.0%)	2/30 (6.7%)
Arm 4 (N=34) xalnesiran 200m+ ruzotolimod 150mg+NUC	20/34 (58.8%)	15/34 (44.1%)	4/34 (11.7%)	3/34 (8.8%)	6/34 (17.6%)
NUC control arm[3] (N=35)	5/35 (14.3%)	2/35 (5.7%)	0/35 (0%)	0/35 (0%)	2/35 (5.7%)

Peg-IFN-α, Pegylated interferon alfa-2a (Pegasys®); ruzotolimod, toll-like receptor 7 agonist (RO7020531, RG7854)
mITT, modified intention-to-treat (all randomized pts who received at least one dose of assigned treatment)

[1] 17 pts continued NUC therapy despite meeting the NUC stopping criteria (e.g. withdrawal of consent, refusal to stop NUC therapy and other logistic issues)
[2] 4 pts who achieved HBsAg loss at 24 wks post-EOT but failed to meet the NUC stopping criteria due to ALT >1.25 xbaseline, with 1 pt also remaining HBeAg positive.
[3] 5 pts from NUC control arm met the earlier version of the NUC stopping criteria (HBsAg<100 IU/mL), but all 5 pts didn't meet the latest version of the NUC stopping criteria (HBsAg loss or, HBsAg<100 IU/mL and ≥1 log10 IU/mL decline from baseline); 3 of the 5 pts refused to stop NUC.

Disclosures:
Cong Cheng – China Innovation Center of Roche: Employee;

5046-C | EVIDENCE OF DURABLE RESPONSE TO BEPIROVIRSEN IN B-CLEAR NOT-ON-NA RESPONDERS: B-SURE SECOND REPORT

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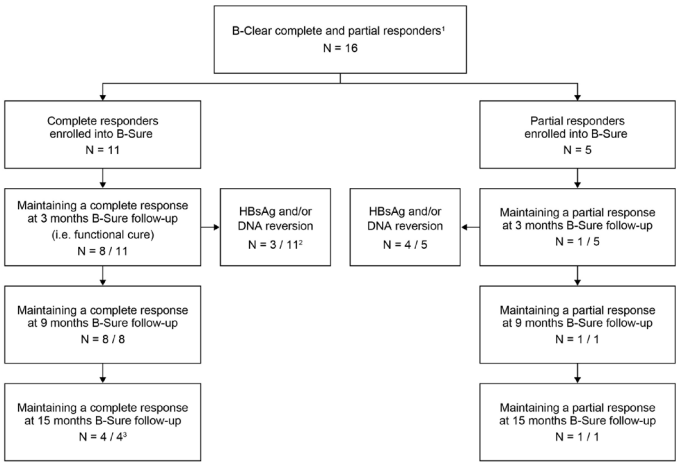
Background: Bepirovirsen (BPV) is an investigational, unconjugated antisense oligonucleotide, currently in Phase 3, for the treatment of chronic hepatitis B virus (HBV) infection. Data from a Phase 2b study (B-Clear; NCT04449029) indicated that a subset of participants (pts) achieved a response at the end of BPV treatment, which was sustained for 24 weeks. This occurred in pts on and not on background nucleos(t)ide analog (NA) therapy (On-NA and Not-on-NA). Pts who achieved a complete (CR) or partial (PR) response at the end of B-Clear were eligible for this long-term durability study (B-Sure; NCT04954859; ongoing). Here we present further data on the durability of response for B-Clear Not-on-NA complete responders (CRs) and partial responders (PRs) who entered B-Sure. **Methods:** CR was defined as hepatitis B surface antigen (HBsAg) <0.05 IU/mL and HBV DNA <lower limit of quantification (LLOQ), and PR as HBsAg <100 IU/mL and HBV DNA <LLOQ. Following entry into B-Sure, pts will be assessed at baseline and at months 3, 9, 15, 21, 27 and 33. Pts maintaining a CR at month 3 (i.e., at least 9 months off BPV), were considered to have achieved functional cure (FC). Adverse events were recorded, with physical examinations and blood tests performed at each visit for safety/efficacy, including time from achieving response in B-Clear to loss of response in B-Sure. **Results:** 11 CRs and 5 PRs were enrolled into B-Sure; all were ongoing at the time of this analysis. One parent study non-responder was also enrolled (see Figure). 11/17 (65%) were male, with a mean age of 44.1 years; 8/17 (47%) were of Asian race; 5/17 (29%) had a duration of HBV of ≥20 years; all were HBeAg negative and 9/17 (53%) had HBsAg ≤1000 IU/mL at B-Clear baseline. For CR pts, at 3 months of B-Sure follow-up, 8/11 (73%) pts maintained a CR, thus achieving FC. All 8 pts maintained FC at 9 months of B-Sure. Of these 8, 4 had Month 15 data (i.e., at least 21 months off BPV), and all 4 maintained FC. For PR pts, only 1/5 pts maintained a PR at 3 months of B-Sure. This was maintained through to 15 months of follow-up, but the pt had not experienced HBsAg seroclearance. There were no safety signals that suggested a latent adverse drug effect following use of BPV, and none of the pts started on NA treatment. **Conclusion:** These data provide further evidence of the durability of functional cure observed with BPV, particularly in those pts who achieved a complete response. **Funding:** GSK (Study 206882)

Figure. Participant flow diagram and treatment response for Not-on-NA-controlled participants in B-Sure



[1]1 non-responder from B-Clear was enrolled into B-Sure as a complete responder; this participant is excluded from the flow diagram.
[2]1 participant subsequently had seroclearance by Month 15.
[3]Only 4 of the 8 CRs at 9 months had reached the 15-month follow-up timepoint at the data cut.

Disclosures:
Robert Elston – GSK: Employee; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans);

5047-C | EVIDENCE OF DURABLE RESPONSE TO BEPIROVIRSEN IN B-CLEAR ON-NA RESPONDERS: B-SURE SECOND REPORT

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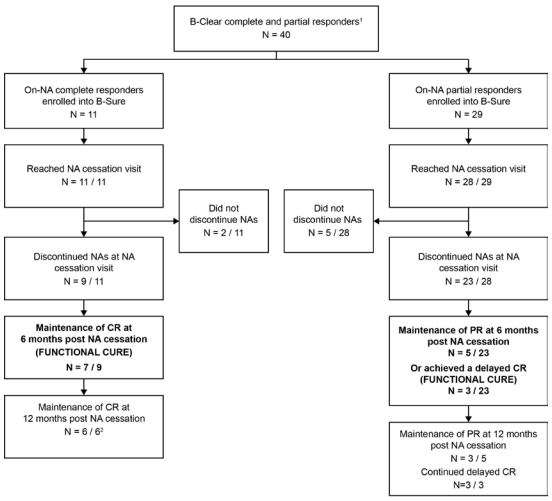
Queen Mary Hospital, the University of Hong Kong, Hong Kong, China, (10)GSK, (11)Phastar

Background: Bepirovirsen (BPV) is an investigational unconjugated antisense oligonucleotide, currently in Phase 3, for the treatment of chronic hepatitis B virus (HBV) infection. Data from a Phase 2b study (B-Clear; NCT04449029) indicated that a subset of participants (pts) achieved a response at the end of BPV treatment, which was sustained for 24 weeks. This occurred in pts on and not on nucleos(t)ide analog (NA) therapy (On-NA and Not-on-NA). Pts who had a complete (CR) or partial (PR) response at the end of the B-Clear study were eligible for this long-term durability study (B-Sure; NCT04954859; ongoing). Here we present further data on the durability of response for B-Clear On-NA complete responders (CRs) and partial responders (PRs) who entered B-Sure. **Methods:** CR was defined as hepatitis B surface antigen (HBsAg) <0.05 IU/mL and HBV DNA <lower limit of quantification (LLOQ), and PR as HBsAg <100 IU/mL and HBV DNA <LLOQ. If eligible, pts discontinued NA treatment 3 months into B-Sure (at least 9 months from their last BPV dose) and were followed to determine the durability of response off all HBV therapy. Adverse events were recorded, with physical examinations and blood tests performed each visit for safety/efficacy, including time from NA cessation to loss of response. **Results:** 11 CRs and 29 PRs were enrolled into B-Sure; 4 parent study non-responders were also enrolled (Figure). 33/44 (75%) were male, with a mean age of 53.8 years and 24/44 (55%) were of Asian race. At entry into B-Clear, the majority of pts were HBeAg negative (77%), 19/44 (43%) had a duration of HBV of ≥20 years and 32/44 (73%) had HBsAg ≤1000 IU/mL. For CR pts, 9/11 (82%) discontinued NAs 3 months after rollover into B-Sure; 7/9 (78%) maintained a CR to 6 months post NA cessation, thus achieving functional cure. For PR pts, 23 pts discontinued NAs 3 months after rollover into B-Sure. 8/23 (35%) of PR pts either maintained PR status (5/23) or had achieved and maintained a CR (3/23) 6 months post NA cessation (i.e. functional cure). None of the 9 CRs who discontinued NAs had restarted NA therapy by 9 months post NA cessation. Of the PRs who discontinued NAs, 8 had restarted NAs within 6 months post NA cessation due to virological breakthrough. 5 of the pts who discontinued NAs had an ALT >2xULN. **Conclusion:** These data provide further evidence of the durability of functional cure observed with BPV, particularly in those pts who achieved a complete response. **Funding:** GSK (Study 206882)

Figure: Participant flow diagram and treatment response for NA-controlled participants in B-Sure



[1]4 non-responders from B-Clear were enrolled into B-Sure as a partial responders; these participants are excluded from the flow diagram.
[2]1 of the 7 CRs at month 12 had not reached the 12-month follow-up timepoint and therefore no data are available.

Disclosures:
GSK: Employee; GSK: Stock - publicly traded company (excluding mutual/index funds or pension plans)

5048-C | LONG-TERM MAINTENANCE OF RESPONSE AND IMPROVED LIVER HEALTH WITH MARALIXIBAT IN PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS (PFIC): 2-YEAR DATA FROM THE MARCH-ON STUDY

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Aires, Buenos Aires, Argentina, (12)Hannover Medical School, Hannover, Germany, (13)Hospital Papa Giovanni XXIII, Bergamo, Italy, (14)Medical University of South Carolina, Charleston, SC, (15)Hôpital Des Enfants – CHU Toulouse, Toulouse, France, (16)Koc University School of Medicine, Istanbul, Turkey, (17)Children's Hospital Los Angeles, Los Angeles, California, (18)University of Alberta, Alberta Canada, (19)University of Texas Health Science Center at San Antonio, (20)Kk Women's and Children's Hospital, Singapore, (21)Medical University of Vienna, Vienna, Austria, (22)Mirum Pharmaceuticals, Inc., Foster City, CA, (23)Cleveland Clinic Children's, Cleveland, Ohio, (24)Adventhealth for Children and Adventhealth Transplant Institute, Orlando, FL, (25)Medstar Georgetown Transplant Institute, Medstar Georgetown University Hospital, Washington DC, (26)Birmingham Women and Children's Hospital, Birmingham, United Kingdom, (27) Hopital Femme Mere Enfant, Hospices Civils De Lyon, Lyon, France, (28)New York University Grossman School of Medicine, New York, New York, (29)Institute of Liver Studies, King's College Hospital, London, United Kingdom

Background: Progressive familial intrahepatic cholestasis (PFIC) is a group of genetic disorders resulting in disrupted bile composition, cholestasis, and pruritus. Maralixibat (MRX) is a minimally absorbed ileal bile acid transporter inhibitor which prevents enterohepatic bile acid recirculation. In the 26-week placebo-controlled MARCH Phase 3 study, MRX at 570 µg/kg BID demonstrated significant improvements in pruritus, serum bile acids (sBA), total bilirubin (TB) and growth in patients across the broadest range of PFIC types studied to date. We report on long-term maintenance of effect of up to 2 years of treatment with MRX in MARCH-ON, an open-label, long-term extension study of MARCH. **Methods:** Long-term maintenance of response was assessed for patients who were originally randomized to receive MRX in MARCH and continued with treatment in MARCH-ON (MRX-MRX group: n=33; BSEP [n=14], FIC1 [n=7], MDR3 [4], TJP2 [6], MYO5B [2]), and for patients who received placebo (PBO) in the MARCH study and switched to open-label MRX in MARCH-ON (PBO-MRX group: n=27; BSEP [n=14], FIC1 [n=6], MDR3 [n=5], TJP2 [n=1], MYO5B [n=1]). Assessments included: pruritus, sBA, TB, growth z-scores, and incidence of treatment-emergent adverse events (TEAEs). Baseline (BL) was defined as the start of MRX for each group. **Results:** For the MRX-MRX group, the median (min, max) time on MRX was 638 days (108, 1023). 13 of 33 patients reached Week 104 at time of analysis. Significant improvements observed in the first 26 weeks of the MARCH study were sustained through Week 104 in MARCH-ON for pruritus (-2.03, p<0.0001), sBA (-166 µmol/L, p=0.003), TB (-1.6 mg/dL, p=0.02), and growth (height z-score: +0.40, p=0.046; weight z-score: +0.52, p=0.01). In the PBO-MRX group, the median time on MRX was 475 days (72, 720). 18 of 27 patients reached Week 52 of MRX treatment at time of analysis. Significant improvements through Week 52 for pruritus (-1.1, p=0.0001), sBA (-71 µmol/L, p=0.03), and growth (height z-score: +0.37, p=0.01; weight z-score: +0.32, p=0.03) were in line with observations from the initial MARCH MRX group. Additionally, numeric reductions in TB (-0.4 mg/dL; p=0.7) were observed. No new safety signals were identified. The most common TEAEs were GI-related with diarrhea (50%) being mostly mild and transient. **Conclusion:** Significant and sustained improvements in pruritus, sBA, TB, and growth are observed with up to 2 years of MRX treatment across the broadest range of genetic PFIC types studied to date. These data suggest overall improved liver health with MRX treatment which can be maintained long-term.

Disclosures:
The following people have nothing to disclose: Adib Moukarzel

5049-C | SAFETY AND EFFICACY OF EFRUXIFERMIN IN COMBINATION WITH A GLP-1 RECEPTOR AGONIST (GLP-1RA) IN PATIENTS WITH NASH/MASH AND T2D: A RANDOMIZED, PLACEBO-CONTROLLED STUDY (COHORT D)

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Background: Many patients with nonalcoholic steatohepatitis (NASH), or metabolic dysfunction-associated steatohepatitis (MASH), have type 2 diabetes (T2D), which is increasingly treated with glucagon-like peptide-1 receptor agonists (GLP-1RA). Efruxifermin (EFX) is an Fc–FGF21 analog that reduced liver fat content (LFC), improved liver histology, reduced markers of liver injury and fibrosis, and improved glucose and lipid metabolism in patients with NASH, with or without T2D. EFX appears well tolerated; the most frequent adverse events (AEs) are mild or moderate gastrointestinal events. The aim of this study (Cohort D) was to determine if EFX added to an existing stable dose of a GLP-1RA is tolerated in patients with NASH and T2D, and if there is potential for greater clinical efficacy. **Methods:** Patients with NASH, fibrosis stages 1–3 (F1–F3), and T2D on stable GLP-1RA therapy were randomized 2:1 to receive once-weekly EFX or placebo for 12 weeks. The primary objective was to evaluate the safety and tolerability of EFX combined with a GLP-1RA. Secondary objectives were to

determine effects on LFC, markers of liver injury and fibrosis, markers of glucose and lipid metabolism, and body weight. **Results:** Patients (N=31; 58% female; mean 57 yrs and 99 kg) received either 50 mg EFX (n=21) or placebo (n=10). At baseline, most patients were taking once-weekly semaglutide (48%; median dose, 1 mg) or dulaglutide (45%; 3 mg), with a few on once-daily liraglutide (7%; 1.5 mg). Most patients (68%) had been on these treatments for >1 yr. The most frequent drug-related AEs were mild or moderate diarrhea, nausea, or increased appetite. One patient on EFX discontinued due to an AE of nausea, and 1 patient withdrew consent. Addition of EFX increased the proportion of patients with normal LFC (≤5% on MRI-PDFF) after 12 weeks to almost 90% vs 10% for GLP-1RA alone (Table). EFX also improved markers of liver injury and fibrosis, as well as glucose and lipid metabolism over GLP-1RA alone, while maintaining weight loss. **Conclusion:** The tolerability of combined EFX and GLP-1RA treatment appears to be comparable to that of either drug alone. EFX provided clear benefits over GLP-1RA alone, normalizing LFC in most patients and further reducing markers of liver injury and fibrosis, while improving overall metabolic health through its action as an insulin sensitizer. The combination offers potential to accelerate resolution of steatohepatitis and reversal of fibrosis among the many patients with NASH and T2D.

Table. Summary of Week 12 Changes

Frequent treatment-emergent AEs (TEAEs)	**Placebo (N=10)**	**EFX 50mg (N=21)**
Drug-related serious AE (SAE)	0	0
Drug-related TEAE leading to discontinuation	0	1 (5%)
Most frequent (≥15%) drug-related TEAEs	**Placebo (N=10)**	**EFX 50mg (N=21)**
Diarrhea	3 (30%)	4 (19%)
Nausea	1 (10%)	7 (33%)
Increased appetite	0	5 (24%)
Decreased appetite	2 (20%)	3 (14%)
Liver fat at week 12	**Placebo (N=10)**	**EFX 50mg (N=16)**
Hepatic fat fraction (MRI-PDFF) (%), LS mean relative change from baseline	–10	–65 ***
Proportion of patients who achieved normalization of liver fat at week 12, n (%)	1 (10%)	14 (88%)
LS mean absolute change from baseline, unless otherwise indicated	**Placebo (N=10)**	**EFX 50mg (N=21)**
Pro-C3 (µg/L)	–2.7	–5.2 ††
ELF score	+0.1	–0.6 **
Liver stiffness (kPa) (FibroScan)	–1.1	–3.0 †††
FAST score	+0.04	–0.16 ***
ALT (U/L)	–1.0	–10 *
AST (U/L)	+1.5	–5.3 *
HbA1c (%, absolute)	–0.2	–0.5 †††
Insulin (%)	–13	–26
C-peptide (%)	–3.5	–22 †
Adiponectin (%)	+16	+129 ***
Triglycerides (%)	–4.1	–42 ***
Non-HDL cholesterol (%)	–6.8	–19 †††
Apolipoprotein B (%)	–4.5	–21 *
LDL cholesterol (%)	-6.1	–8.0
HDL cholesterol (%)	+2.5	+38 ***
Body weight (kg)	–0.8	–1.2

** p<0.01, *** p<0.001 vs placebo; † p<0.05, †† p<0.01, ††† p<0.001 vs baseline (ANCOVA for liver fat analysis; MMRM for biomarker analysis); MRI-PDFF, magnetic resonance imaging proton density fat fraction

Note: Two SAEs in the EFX group were not drug related: post-procedural hemorrhage and uterine cancer. The drug-related TEAE that led to study discontinuation was nausea.

Disclosures:
Juan Pablo Frias – 89Bio: Grant/Research Support; Akero: Grant/Research Suppor; Akero: Consultant; 89Bio: Consultant; Eli Lilly: Grant/Research Support; Eli Lilly: Consultant; Eli Lilly: Speaking and Teaching; Novo Nordisk: Grant/Research Support; Novo Nordisk: Consultant; Novo Nordisk: Speaking and Teaching; Madrigal: Grant/Research Support; Echosens: Speaking and Teaching; Pfizer: Grant/Research Support; Pfizer: Consultant; Novartis: Grant/Research Support; Merck: Grant/Research Support; Merck: Consultant; Merck: Speaking and Teaching; Altimmune: Grant/Research Support; Altimmune: Consultant;

5050-C | THE NECROPTOSIS MEDIATOR, RECEPTOR-INTERACTING PROTEIN KINASE 3 (RIPK3), IS INDEPENDENTLY ASSOCIATED WITH TRANSPLANT-FREE SURVIVAL IN ACUTE LIVER FAILURE

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Background: Acute liver failure (ALF) is associated with significant mortality. Prognostication and liver transplant (LT) allocation are on the basis of clinical scores; mechanistic biomarkers are an unmet clinical need to improve prognostication and facilitate drug development. Necroptosis is a programmed, pro-inflammatory, mode of cell death mediated by RIPK1, RIPK3 and mixed lineage kinase domain-like (MLKL). We aimed to determine the association of circulating RIPK3 and MLKL levels with 21-transplant free survival (TFS) in ALF patients. **Methods:** Nested cohort study of 176 ALF patients from the US US ALFSG registry from 01/2006-12/2018. RIPK3 and total MLKL were measured using enzyme-linked immunosorbent assay (Biorbyt Ltd, UK). Multivariable logistic regression was performed to determine if these markers were associated with 21-day transplant-free survivors after adjusting for clinically significant covariates. **Results:** Of n=176 ALF patients (APAP n=152, DILI n=24), n=86 were alive at day 21 without LT (ALF TFS) while 90 had either died (n=89) or required LT (n=1). During first 7 days of admission, ALF TFS patients were less likely to require organ support (ventilation 50% vs 92%, vasopressors 28% vs 74%, renal replacement therapy (34% vs 59%; p< 0.001 for all comparisons. ALF TFS patients had significantly lower rates of high grade coma (54% vs 90%; p< 0.001) and MELD scores (29 vs. 35, p< 0.001) on admission. ALF TFS patients on admission had significantly lower serum RIPK3 (6.79 vs. 10.25 ng/ml, p<0.001) and MLKL (38.39 vs. 44.48 ng/ml, p<0.001) compared with non-survivors (Fig 1). Using multivariable logistic regression, after adjusting for known associations (acetaminophen etiology) and significant covariates (Model 1: vasopressors, mechanical ventilation and MELD; Model 2 vasopressors, high coma grade, MELD), increased admission

serum RIPK3 levels in both models (Model 1: Odds Ratio (OR) 0.88 (0.88-0.99, p=0.013) and Model 2 OR 0.93(0.88-0.99, p=0.014) were independently associated with significantly decreased 21-day TFS. Area under the receiver operating curve (AUROC) for Model 1 and 2 were 0.802 and 0.788 respectively. After performing similar modelling, MLKL was not significantly associated with 21-day TFS on multivariable analysis (p>0.5 for both). **Conclusion:** Circulating levels of the necroptosis mediator RIPK3 are independently associated with TFS in ALF. These data are consistent with the protective effect of RIPK3 inhibition noted in murine models of APAP-ALF (Ramachandran et al., 2013). MLKL was not an independent predictor of outcome; this may reflect MLKL-independent activation of inflammasome signaling by RIPK3 (Lawlor et al., 2015). These data support validation studies of RIPK3 as a mechanistic biomarker in ALF, and further translational work of necroptosis inhibition as a treatment modality.

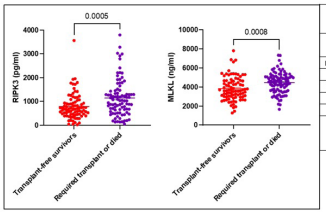

Figure 1. Admission (day 1) levels of circulating RIPK3 (left panel) and MLKL (right panel)

Covariate	Unadjusted (n=.176)		Adjusted Model 1 (N=169), AUROC=0.802			Adjusted Model 2 (N=164), AUROC=0.788		
	OR (95% CI)	P	In Model	OR (95% CI)	P-value	In Model	OR (95% CI)	P-value
RIPK3(per ng)	**0.92(0.87,0.97)**	**0.001**	**Yes**	**0.93 (0.88,0.99)**	**0.013**	**Yes**	**0.93 (0.88,0.99)**	**0.014**
APAP	1.15(0.49,2.73)	0.75	Yes	1.79 (0.63,5.08)	0.27	Yes	1.39 (0.50,3.86)	0.52
Vasopressors	0.31(0.16,0.62)	<0.001	Yes	0.67(0.29,1.54)	0.35	Yes	0.59 (0.26,1.34)	0.21
MELD	0.90(0.86,0.94)	<0.001	Yes	0.90 (0.86,0.94)	<0.001	Yes	0.90 (0.86,0.95)	<0.001
Ventilation	0.25(0.14,0.48)	<0.001	Yes	0.25(0.11,0.56)	<0.001	No		
HE Grade 3/4	0.40(0.21,0.74)	0.003	No			Yes	0.45 (0.21,0.95)	0.035

Table 1. Multivariable analysis of 176 ALF patients to determine independent associations with 21-day transplant-free survival.

Disclosures:
The following people have nothing to disclose: Constantine J. Karvellas

5051-C | INTERIM ANALYSIS OF FASCINATE-2 A PHASE 2b RANDOMIZED, PLACEBO CONTROLLED TRIAL DEMONSTRATES DENIFANSTAT REDUCES CIRCULATING SATURATED DIACYLGLYCEROLS AND TRIACYLGLYCEROLS, MARKERS OF LIPOTOXICITY

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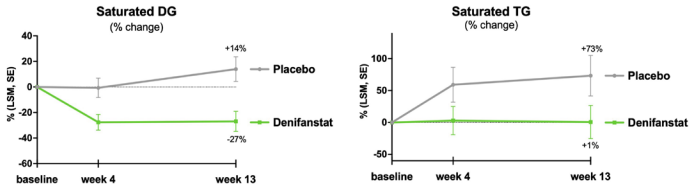
Background: Denifanstat is a fatty acid synthase inhibitor currently in Ph2b for NASH (FASCINATE-2, NCT04906421). In the completed 12 week FASCINATE-1 trial, patients with NAFLD treated with denifanstat showed significant reductions in liver fat content and inflammatory and fibrosis biomarkers, including ALT, PRO-C3 and LDL-C. Increased DNL results in increased saturated lipids and ceramides, markers of lipotoxicity. An interim analysis (IA) of lipidomics was performed in FASCINATE-2 to examine if denifanstat can reverse lipid mediators of lipotoxicity by reducing saturated diacylglycerols (DG) and triacylglycerols (TG) and increasing PUFA content at week 13, prior to week 52 liver biopsy. **Methods:** NASH patients with biopsy confirmed F2-F3 fibrosis and NAFLD Activity Score ≥4 were enrolled in FASCINATE-2 for 52 weeks treatment. The first 52 patients on study for 26 weeks with baseline ≥8% liver fat by MRI-PDFF were included in the IA. Comprehensive lipidomic analysis was performed for baseline, wk4 and wk13 plasma samples. **Results:** The week 26 IA showed a significant relative reduction of liver fat compared to baseline in denifanstat (50mg, QD)-treated patients compared to placebo (-34.1% vs. -1.5%, p<0.002). 67% of denifanstat-treated patients reduced their liver fat by ≥30% and approximately half of these decreased liver fat by ≥50%. Lipidomic analysis showed a rapid reduction of plasma tripalmitin at wk4 (-37% vs. +24% placebo), a marker of target engagement, and further reduction at wk13 (-42% vs. +22% placebo), confirming inhibition of FASN. Total DG and TG were not changed by denifanstat at wk4 or wk13; however, saturated DG (-27% vs. +14% placebo at wk13) and saturated TG (+1% vs. +73% placebo at wk13) were significantly and favorably altered (Figure 1). In contrast, both polyunsaturated DG and TG were increased by denifanstat (+20% vs. -2% placebo and +35% vs. +3% placebo, respectively). C16- and C22-ceramides were also decreased with denifanstat treatment (-12% vs. +4% placebo and -9% vs. 0% placebo, respectively). **Conclusion:** Denifanstat showed strong improvement of key disease markers in FASCINATE-1 and FASCINATE-2 IA. Lipidomic results confirm that denifanstat changed circulating lipid compositions rather than altering total lipids. Reduction of saturated DG/TG and ceramides and increased incorporation of PUFA in DG/TG has potential to reduce lipotoxic drive and reduce cardiovascular risk in denifanstat-treated NASH. This concordance of non-invasive metrics together with previously demonstrated biomarker changes suggest that denifanstat will have a positive impact on histological endpoints.

Figure 1



Disclosures:
Wen-Wei Tsai – Sagimet Biosciences: Employee; Sagimet Biosciences: Stock - publicly traded company (excluding mutual/index funds or pension plans);

5052-C | HBsAg LOSS IN CHRONIC HEPATITIS B PATIENTS AFTER 24-WEEK TREATMENT WITH SUBCUTANEOUSLY ADMINISTERED PD-L1 ANTIBODY ASC22 (ENVAFOLIMAB): INTERIM RESULTS FROM A PHASE IIb EXTENSION COHORT

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Background: Data from the previously completed Phase IIb study indicated that in 1.0 mg/kg ASC22 Q2W cohort (n=48, per protocol), more HBsAg reduction was observed in chronic hepatitis B (CHB) patients with lower baseline HBsAg. Among 48 patients, 7 of them had baseline HBsAg <= 100 IU/mL and 3 patients (3/7, 42.9%) achieved sustained HBsAg loss (< 0.05 IU/mL) after 24-week treatment and 24-week follow-up, indicating functional cure. Building upon this promising outcome, we initiated an extension cohort of 49 patients with baseline HBsAg ≤100 IU/ml to explore sustained HBsAg loss in this specific population. **Methods:** ASC22 expansion cohort enrolled 49 patients with baseline HBsAg ≤100 IU/ml. At a ratio of 4:1, patients are subcutaneously administered with1.0 mg/kg ASC22 Q2W (ASC22 cohort, n=40) or placebo (n=9) for 24-week treatment in background Nucleot(s)ide Analogues (NAs). After treatment, follow-up period is 24 weeks. Patients who achieve HBsAg loss at completion of 24-week treatment of ASC22 are expected to discontinue background NAs for the follow-up. The primary efficacy endpoint is HBsAg reduction. Interim analysis was conducted when approximately 50% of enrolled patients completed 24-week treatment of ASC22 or placebo. **Results:** 25 patients completed 24-week treatment (19 in ASC22 cohort and 6 in placebo cohort). In ASC22 cohort at week 24, 4 (4/19, 21.1%) patients achieved HBsAg loss. ALT or AST flares (defined as ALT/AST >2X ULN and >3X baseline level) were observed in ASC22 cohort (2/19) only, which were associated with more significant HBsAg reduction from baseline (-1.86 $\log_{10}$ IU/mL). pgRNA, HBcrAg, HBcAb, INFgamma and IL-2 were measured at baseline and weeks 4, 8, 12, 16, 20 and 24. ASC22 was generally safe and well tolerated. Most of ASC22 drug related adverse effects (AEs) were Grade 1 or 2. A patient with HBsAg loss experienced a grade 3 ALT and AST elevation. There were 2 patients experienced ASC22 drug related AEs, included ALT/AST elevation and hyperthyroidism, leading to discontinuation of the investigational drug. One Grade 3 SAE of coronary atherosclerotic heart disease was considered as possibly unrelated to the study drug. **Conclusion:** ASC22 monotherapy with background NAs showed statistically significant HBsAg reduction and 21.1% (4/19) HBsAg loss after 24-week treatment. Together with the acceptable safety profile and convenient subcutaneous injections, ASC22 demonstrated potential as a promising immune-therapy for CHB.

Table 1. HBsAg reduction from baseline at the end of 24-week treatment

HBsAg reduction	1.0mg/kg ASC22 (N=19)	PBO (N=6)
HBsAg loss, n(%)	4(21.1%)	0
≥1 log10 IU/mL, n(%)	8(42.1%)	0
≥0.5 log10 IU/mL, n(%)	11(57.9%)	0
≥0.3 log10 IU/mL, n(%)	12(63.2%)	1(16.7%)

Disclosures:
Jinzi Jason Wu – Ascletis BioScience Co., Ltd.: Stock - publicly traded company (excluding mutual/index funds or pension plans);

5053-C | SAFETY AND TOLERABILITY OF CONTINUOUS INFUSION TERLIPRESSIN (BIV201) IN PATIENTS WITH DECOMPENSATED CIRRHOSIS AND REFRACTORY ASCITES: A PHASE 2, RANDOMIZED, CONTROLLED, OPEN-LABEL STUDY

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Background: The standard of care (SOC) for diuretic-resistant ascites due to cirrhosis includes regular large-volume therapeutic paracentesis (TP) and/or transjugular intrahepatic portosystemic shunt (TIPS), but TP provides only temporary relief, while TIPS may lead to medical complications. Terlipressin, an analog of vasopressin, improves renal function in patients with decompensated cirrhosis. In a recent 6-month, exploratory, phase 2b, open-label, randomized, controlled trial, BIV201 (terlipressin administered as a continuous infusion by a small ambulatory pump) plus SOC was associated with significantly reduced ascites accumulation and its associated symptoms compared with SOC alone. Here we report the safety profile of BIV201 from the trial. **Methods:** Fifteen adult patients with diuretic-resistant ascites due to decompensated cirrhosis who had undergone 3 to 9 TPs within the previous 60 days were enrolled and randomized 2:1 to receive either continuous infusion of BIV201 (3 mg/day; dose-adjusted to 2-4 mg/day) for two 28-day cycles plus SOC, separated by an up to 56-day washout period, or SOC alone, for a total of 180 days, followed by a 180-day, long-term follow-up phase. Adverse events (AEs), treatment-emergent AEs (TEAEs), discontinuations, and deaths were recorded. **Results:** Patients (N=15) had a mean age of 61.3 years; mean MELD-Na score was 15.4 [range: 10-26], and the mean Child-Turcotte-Pugh score was 9 [range: 7-12]. Five (50%) patients in the BIV201 group completed both 28-day infusion cycles; 5 patients discontinued early during treatment: 1 for inconvenience, 2 for unrelated TEAEs, and 2 for asymptomatic hyponatremia considered related to BIV201. There was a total of 383 outpatient days of BIV201 infusion for the 10 patients randomized to BIV201 plus SOC. The incidence of serious TEAEs was similar in both groups with 3 of 20 events in the BIV201 group occurring during BIV201 infusion, only 1 of which was considered related to BIV201 (asymptomatic hyponatremia). Other non-serious treatment-related TEAEs were headache (1) and asymptomatic hyponatremia (2). Hyponatremia was considered likely due to an interaction between gabapentenoids and V2 effects of terlipressin. **Conclusion:** BIV201 plus SOC was well tolerated in this phase 2b clinical trial. Episodes of hyponatremia can be easily monitored and managed. Furthermore, the exclusion of gabapentenoids use during treatment with BIV201 may help mitigate the risk of hyponatremia in patients.

Overall Summary of TEAEs

	BIV201 and SOC (N=10) n (%) m	SOC Only (N=5) n (%) m	Total (N=15) n (%) m
Subjects with at least one TEAE	10 (100.0%) 123	5 (100.0%) 57	15 (100.0%) 180
Subjects with at least one related TEAE	3 (30.0%) 4	0 0	3 (20.0%) 4
Subjects with at least one TEAE with CTCAE grade ≥3	8 (80.0%) 24	4 (80.0%) 13	12 (80.0%) 37
Subjects with at least one related TEAE with CTCAE grade ≥3	2 (20.0%) 2	0 0	2 (13.3%) 2
Subjects with at least one serious TEAE	7 (70.0%) 20	4 (80.0%) 10	11 (73.3%) 30
Subjects with at least one serious related TEAE	1 (10.0%) 1	0 0	1 (6.7%) 1
Subjects with at least one TEAE leading to discontinuation of study drug	4 (40.0%) 6	0 0	4 (26.7%) 6
Subjects with at least one TEAE requiring dose adjustment	1 (10.0%) 1	0 0	1 (6.7%) 1
Subjects with TEAE leading to death	1 (10.0%) 1	1 (20.0%) 1	2 (13.3%) 2

CTCAE = Common Terminology Criteria for Adverse Events; n = number of subjects; m = number of events; SOC = standard of care; TEAE = treatment-emergent adverse event.

Disclosures:
Penelope Markham – BioVie, Inc.: Employee;