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5000 | SOFOSBUVIR/VELPATASVIR PLUS RIBAVIRIN AND SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR FOR 12 WEEKS FOR THE TREATMENT OF HCV PATIENTS WITH GT3B, COMPENSATED CIRRHOSIS: RESULTS FROM A MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY IN CHINA

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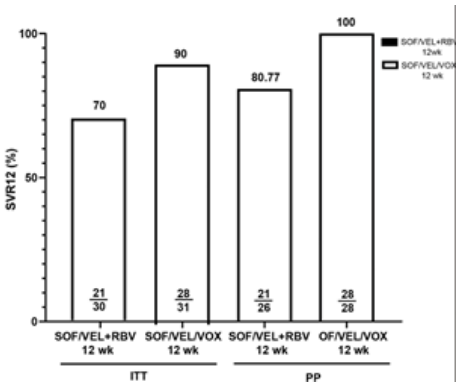
Background: Genotype (GT) 3b represents more than 50% of patients with GT3 hepatitis C virus (HCV) infection in China, while GT3a predominates in most other countries. The sustained virological response (SVR) rate among patients with GT3b is lower than that observed in patients with GT3a infection, particularly among patients with cirrhosis. However, the current treatment recommendations for patients with GT3 are based on clinical data generated in regions where GT3a predominates. **Methods:** This multicenter, randomized, open-label study aims to evaluate the efficacy and safety of sofosbuvir (SOF)/velpatasvir (VEL) plus ribavirin (RBV) (Arm A) and SOF/VEL/voxilaprevir (VOX) (Arm B) for 12 weeks in treatment-naive (no previous direct-acting antiviral [DAA] therapy) HCV patients with GT3b, and compensated cirrhosis in China. The primary endpoint was SVR at 12 weeks after the end of treatment (SVR12). **Results:** The study was conducted from 14 September 2022 to 12 April 2024 at seven centers in China. Of the 64 patients screened, 61 were enrolled and received at least one dose of study drug. 30 (49%) and 31 (51%) received SOF/VEL plus RBV or SOF/VEL/VOX for 12 weeks, respectively. In 7 patients who didn't complete the follow-up (Arm A, 4 patients & Arm B, 3 patients), 1 patient withdrew consent and 6 patients lost follow-up. 54 have completed follow-up at 12 weeks after the end of treatment (Arm A, 26 patients & Arm B, 28 patients). Of the 61 patients enrolled, 47 (77%) were men, 37 (61%) were drug abusers, and the mean age was 51.1±7.3 years. The median ALT was 95 (59, 124) U/L and the median HCV RNA was 6.5 (5.9, 6.9) log IU/mL. Baseline characteristics were generally balanced across the treatment arms (all $p > 0.05$). SVR12 was achieved by 49 patients, the total rates of SVR12 were 80% (49 0f 61) and 91% (49 of 54) in intention to treat (ITT) and per protocol (PP) populations, respectively. The SVR12 rates were significantly lower in Arm A than those in Arm B in both ITT (70% & 90%, $p = 0.046$) and PP (81% & 100%, $p = 0.021$) populations. 5 patients who failed in achieving SVR12 were all in Arm A, among whom 3 experienced post-treatment virological relapse and 2 patients had on-treatment virological failure. 4 patients experienced adverse event (AE), none of which was assessed as related to study drugs. **Conclusion:** Compared to SOF/VEL plus RBV treatment, 12 weeks of SOF/VEL/VOX treatment achieved a significantly higher SVR12 rate in treatment-naive (no previous DAA therapy) patients with GT3b, compensated cirrhosis in China (NCT05467826).



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5001 | TRANSARTERIAL CHEMOEMBOLIZATION (TACE) WITH OR WITHOUT LENVATINIB (LEN) PLUS PEMBROLIZUMAB (PEMBRO) FOR INTERMEDIATE-STAGE HEPATOCELLULAR CARCINOMA (HCC): PHASE 3 LEAP-012 STUDY

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Background: TACE remains standard of care for intermediate-stage HCC. We present results from LEAP-012, a randomized, multicenter, double-blind, phase 3 trial evaluating len plus pembro plus TACE vs placebo (pbo) plus TACE in intermediate-stage HCC. **Methods:** Eligible patients (pts) with HCC not amenable to curative treatment and Child-Pugh class A, no portal vein invasion, and ECOG PS ≤1 were randomized 1:1 to len 12 mg (body weight ≥60 kg) or 8 mg (body weight <60 kg) QD PO plus pembro 400 mg Q6W IV or to pbo PO plus IV for ≤2 years; len/oral pbo alone continued until PD or discontinuation. The first TACE occurred 2-4 wk after the start of systemic therapy (≤2 treatments/tumor [4 total]). Randomization was stratified by study site, AFP, ECOG PS, ALBI grade, and tumor burden. Primary end points were PFS per RECIST v1.1 by BICR and OS; secondary end points included ORR, DOR, disease control, and time to progression (TTP) per RECIST v1.1 by BICR. HR and 95% CIs were estimated using a stratified Cox proportional hazards model with the Efron method of tie handling. The data cutoff for this first interim analysis was Jan 30, 2024. **Results:** 480 pts were randomized (237, len plus pembro; 243, pbo PO plus IV); all pts received TACE. Median study follow-up was 25.6 mo (range, 12.6-43.5). PFS was significantly improved for len plus pembro vs pbo (286 events; HR, 0.66, 95% CI, 0.51-0.84; $P = 0.0002$; significance threshold, $P = 0.025$); median PFS was 14.6 mo (95% CI, 12.6-16.7) vs 10.0 mo (95% CI, 8.1-12.2). OS was immature and the significance threshold was not met (151 events [information fraction, 47%]; HR, 0.80; 95% CI, 0.57-1.11; $P = 0.0867$; significance threshold, $P = 0.0012$). TTP was improved with len plus pembro (median 16.6 vs 10.3 mo; HR, 0.59; 95% CI, 0.46-0.77). Safety and subsequent therapy data are shown in the Table. **Conclusion:** LEAP-012 met the PFS primary end point. Len plus pembro plus TACE showed a statistically significant, clinically meaningful improvement in PFS and an early trend toward improvement in OS vs pbo plus

TACE in pts with intermediate-stage HCC; data were consistent across subgroups. The AE profile was consistent with known safety profiles of len, pembro, and TACE; no new safety signals were uncovered. OS will be retested in future analyses.

n (%)	Len + pembro + TACE n = 237	Pbo + TACE n = 241
Treatment-related AEs	234 (98.7)	204 (84.6)
Grade 3-5	169 (71.3)	76 (31.5)
Led to discontinuation of both drugs	20 (8.4)	3 (1.2)
Immune-mediated AEs and infusion reactions	113 (47.7)	29 (12.0)
Grade 3-5	21 (8.9)	4 (1.7)
Led to discontinuation of both drugs	6 (2.5)	0
Received high-dose[a] systemic corticosteroids	12 (5.1)	3 (1.2)
Received subsequent anticancer therapy	114 (48.1)	142 (58.4)
Systemic therapies	54 (22.8)	76 (31.3)
Locoregional therapies	84 (35.4)	104 (42.8)
[a]High-dose was defined as ≥40 mg/day prednisone or equivalent.		

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5002 | IMPACT OF MELD 3.0 FOR LIVER TRANSPLANT ALLOCATION

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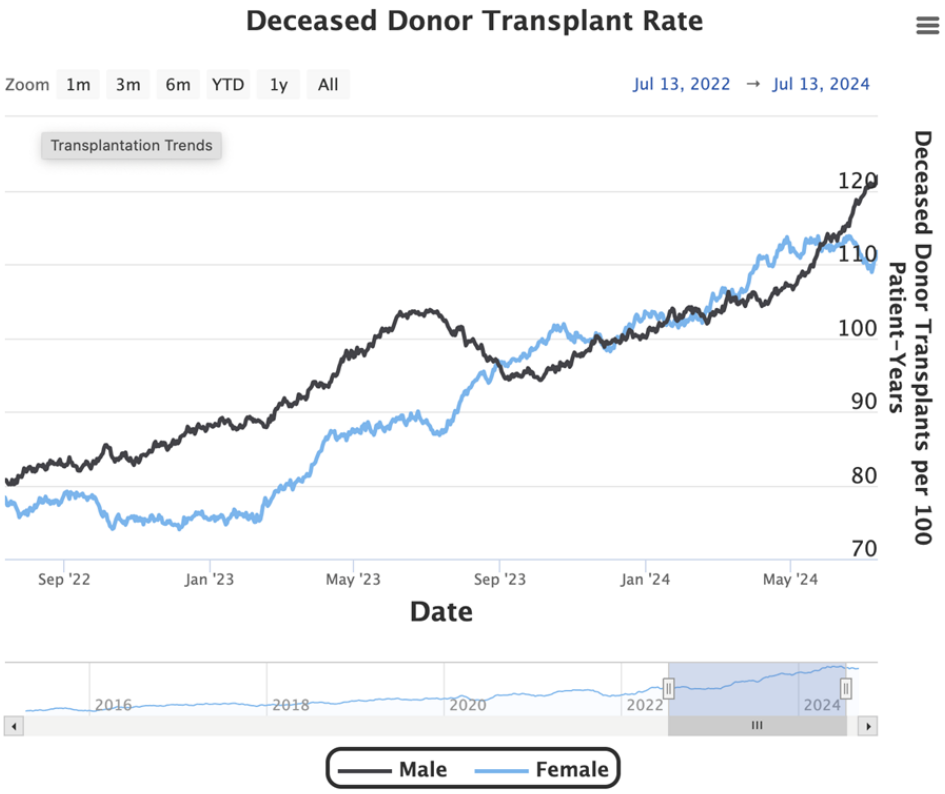
Background: Patients with chronic liver disease awaiting liver transplantation in the United States are prioritized by their medical urgency as represented by the Model for End-Stage Liver Disease (MELD). On July 13, 2023, the OPTN updated MELD-Na to MELD 3.0 for liver transplant candidates on the waitlist aged 12 years or older. We examined the impact of MELD 3.0 in reducing sex- based disparities in waiting list mortality and access to transplant. Key words: MELD 3.0, sex disparity Learning Objective: Understand the impact that the MELD 3.0 policy had on the sex disparity and equalizing transplant rates between sexes in the US liver allocation system after 1 year. **Methods:** Using OPTN data, we identified liver transplant candidates and recipients aged 12 years or older without exception and evaluated their waiting list outcomes during equivalent 6-month time periods before and after policy implementation (MELD-Na: 1/11- 7/12/2023 vs MELD 3.0: 7/13/2023-1/11/2024). The probability of 90-day waiting list dropout (removal for death or too sick) pre- and post- policy by Cox regression, with censoring at liver transplantation, 90 days, or end of policy era. Using the SRTR Donation and Transplant System Explorer, which includes more recent data, the trend in deceased donor transplant rate for 1 year pre and post implementation was visualized using a 90-day rolling window, stratified by sex. **Results:** There were 10,203 candidates newly registered and 9,357 transplant recipients. In the 6-month analysis, women were more likely to

be listed and transplanted post-policy, representing 43.3% of new registrations (vs 40.5% pre-policy, p=0.005), and 41.8% of transplants (vs 37.0% pre-policy, p<0.001). For women, the probability of 90-day waiting list dropout decreased from 18.5% pre-policy to 9.1% post-policy; for men, this decreased from 13.5% to 8.2%. In the time trend analysis, deceased donor transplant rates between sexes equalized after the implementation of MELD 3.0 (Figure). The median allocation MELD score at transplant decreased from 28 to 27 post-policy, but remained higher for females (29) compared to males (26). **Conclusion:** After the implementation of MELD 3.0, waitlist mortality and transplant rates for women more closely approximate the rates for men, suggesting that MELD 3.0 has successfully mitigated some disparities in waiting list outcomes and transplant access. Analysis of the policy impact after 1 year with 90-day follow-up (through October 2024) will be presented at TLM.



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5003 | MITOCHONDRIAL INJURY DURING NORMOTHERMIC MACHINE PERFUSION PREDICTS OUTCOMES AND COSTS AFTER LIVER TRANSPLANTATION – THE FIRST ANALYSIS IN 300 HUMAN LIVERS WITH PROSPECTIVE VALIDATION

Chase Wehrle[1] Chunbao Jiao[2] Keyue Sun[2] Khaled Ali[2] Mingyi Zhang[2] Beatrice Cazzaniga[2] Sangeeta Satish[2] Muhammed Nadeem[2] Qiang Liu[2] Yuki Miyazaki[2] Mazhar Khalil[2] Alejandro Pita[2] Jaekeun Kim[2] Shyamasree Datta[2] Bijan Eghtesad[2] Federico Aucejo[2] Choon Kwon[2] Masato Fujiki[2] Antonio Pinna[3] Robert Fairchild[2] Charles Miller[2] David Meierhofer[4] Koji Hashimoto[2] Andrea Schlegel[2]

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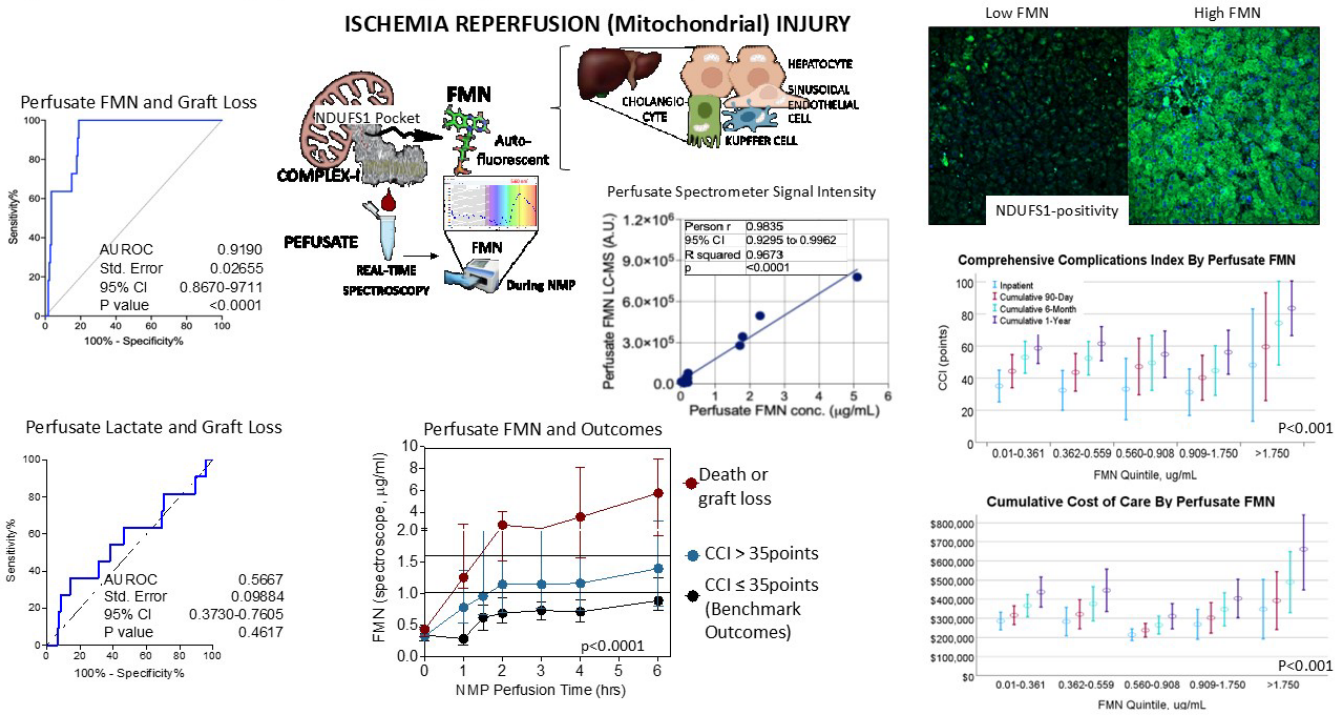
Background: Robust data on current viability markers (i.e., perfusate lactate, bile flow and biliary chemistry) on graft loss and complications during Normothermic Machine Perfusion (NMP) are lacking. This is the first systematic analysis of the role of mitochondrial Flavin-mononucleotide (FMN) perfusate-release during NMP.

Methods: All transplants with endischemic NMP (OrganOx-MetraÒ) at our center were included. Donor and recipient risk factors were analyzed along with posttransplant complications and costs and current viability tests. ROC-curve, multivariate cox-regression and mixed-effects models were performed for graft loss and complications. Spectroscopic FMN levels were confirmed with liquid chromatography-mass spectrometry (LC-MS). Tissue from FMN-low vs. -high grafts were assessed with anti-NDUFS1 fluorescence- immunohistochemistry to quantify mitochondrial complex 1 injury. **Results:** Two-hundred human livers underwent NMP (10/2022-12/2023) in the discovery cohort resulting in 188 liver transplantations (DBD:132; DCD:56). Overall 1-year graft & recipient survival were 94% & 94.7% (141&142/150). Four grafts were lost due to primary- non-function or ischemic cholangiopathy. Three additional recipients had clinically-relevant non-anastomotic-biliary-strictures requiring multiple interventions. Graft loss was predicted best by perfusate FMN (>1700 samples; c-statistic AUC 0-4hrs NMP: 0.92, 95%CI:0.8670-0.9711, p<0.0001) versus traditional viability markers. Spectroscopic FMN measurement was confirmed with LC-MS (Pearson R=0.9835, 95%CI0.9295-0.9962). High FMN grafts demonstrate significant complex 1 damage using NDUFS-1 immunofluorescence staining [Fig1]. Youden's index for predicting graft-related graft loss was FMN>1.75ug/mL, which predicted overall complications, biliary stricturing, and graft loss. Recipients of livers with perfusate FMN beyond 1mg/mL/kg and 2mg/mL/kg experienced increasing comprehensive complication index, graft loss, and medical costs (all p<0.001) within six-months. Forty-four percent of transplant-related cost variation was explained by FMN in the top quintile [Fig1]. 123 livers were perfused with prospective FMN testing resulting in 108 (88%) transplants with no instances of graft-related graft loss or NAS, despite greater traditionally-measured graft risk in this era. Transplant in the FMN-era was independently associated with improved graft survival on time-to-event Cox regression (HR=6.821, 95%CI 1.247-37.300). **Conclusion:** This is the first analysis of mitochondrial biomarkers during NMP, allowing a more objective interpretation of liver quality on a subcellular level, when compared to donor-derived data and "traditional viability parameters". Perfusate FMN predicted graft loss, cumulative complications and transplant costs. Preliminary validation results confirm prospective utility with reasonable graft discard.

Figure 1: Mitochondrial Injury Markers during NMP predict Graft loss, Complications and Costs after Liver Transplantation



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Fujiki: Nothing to Disclose, Antonio Pinna: Nothing to Disclose, Robert Fairchild: Nothing to Disclose, Charles Miller: Nothing to Disclose, David Meierhofer: Nothing to Disclose, Koji Hashimoto: Nothing to Disclose, Andrea Schlegel: Nothing to Disclose

5004 | BEXOTEGRAST, AN ORAL INHIBITOR OF A_VB_6 AND AVB1 INTEGRINS, WAS SHOWN TO IMPROVE MARKERS AND SYMPTOMS OF CHOLESTASIS AND STABILIZED MARKERS OF LIVER FIBROSIS IN PARTICIPANTS WITH PRIMARY SCLEROSING CHOLANGITIS: WEEK 24 RESULTS FROM THE PHASE 2 INTEGRIS-PSC TRIAL

Kris Kowdley[1] Palak Trivedi[2] Bertus Eksteen[3] Bilal Hameed[4] Catherine Vincent[5] Tianyan Chen[6] Aparna Goel[7] K. Gautham Reddy[8] Eric Orman[9] Deepak Joshi[10] Eric Lefebvre[11] Johanna Schaub[11] Mahru An[11] Annie Clark[11] Chris Barnes[11] Richard Pencek[11] Douglas Thorburn[12] Aldo Montano-Loza[13] Christoph Schramm[14] Christopher Bowlus[15] Michael Trauner[16] Cynthia Levy[17] Gideon Hirschfield[18]

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Background: Transforming growth factor-beta (TGF-β) signaling activated by αvβ6 and αvβ1 integrins drives liver fibrosis in primary sclerosing cholangitis (PSC). Bexotegrast (BEXO) is an oral, once-daily, dual-selective inhibitor of these integrins and is in development for treatment of PSC. We report the long-term safety and exploratory efficacy outcomes from a Phase 2, double-blind, randomized controlled trial of BEXO in PSC (INTEGRIS-PSC study, NCT04480840). **Methods:** Participants (pts) with PSC and suspected liver fibrosis were randomized 3:1 to BEXO across 4 dose levels (40, 80, 160 mg or placebo (PBO) for 12 weeks (wks); 320 mg or PBO for ≥24 and up to 48 wks) or PBO. Safety and exploratory efficacy results through Wk 12 were reported previously.[1] This final Wk 24 analysis evaluated the safety and tolerability of BEXO 320 mg vs PBO and exploratory efficacy endpoints of enhanced liver fibrosis (ELF) score, alkaline phosphatase (ALP) values, liver stiffness (LS) by transient elastography, Itch Numeric Rating Scale (NRS) and optional gadoxetate contrast–enhanced MRI parameters. **Results:** A total of 36 pts received BEXO 320 mg (n=27) or PBO (n=9) for up to 40 wks. Treatment-emergent adverse events (TEAEs) were generally similar between BEXO- and PBO-treated pts from Wks 12 to 40; TEAEs of pruritus and cholangitis were observed less frequently with BEXO (11.1% and 3.7%) than PBO (22.2% and 11.1%). Changes in Itch NRS from baseline (BL) to Wk 24 were consistent with TEAE findings. No serious TEAEs related to study drug were reported. At Wk 24, ALP values were significantly lowered from BL with BEXO vs increased with PBO ($P<0.05$; Table); similar changes in gamma-glutamyl transferase were observed. No change in LS from BL to Wk 24 was observed with BEXO but it increased with PBO. The ELF score was stable from Wk 12 to Wk 24 in pts treated with BEXO 320 mg. From Wk 12 to 24, liver MRI demonstrated a continued increase in peak enhancement and decrease in time to arrival in common bile duct with BEXO. **Conclusion:** BEXO 320 mg was generally well tolerated for up to 40 wks of treatment. BEXO was shown to improve ALP and symptoms associated with cholestasis and, in exploratory analyses, demonstrated potential antifibrotic activity suggesting disease stabilization as evidenced by LS, ELF and MRI. This study supports the targeting of integrin-mediated TGF-β activation as a potential therapeutic approach for PSC. Further studies on the use of BEXO in PSC are warranted. **Reference:** 1. Trauner M, et al. Poster presented at: EASL; June 5-8, 2024, Milan, Italy. Poster LB-039.

Table. Markers of Cholestasis and Antifibrotic Activity Among Participants Receiving Bexotegrast Through Week 24.

	Baseline		Change at Week 12		Change at Week 24	
	Placebo (n=9)	320 mg (n=27)	Placebo (n=9)	320 mg (n=27)	Placebo (n=9)	320 mg (n=27)
Liver stiffness by transient elastography, median (IQR), kPa	7.4 (7.2, 10.1)	9.0 (5.6, 10.7)	–	–	1.5 (−0.4, 2.3)	0 (−1.5, 1.6)
ALP, mean (SD), U/L	318.6 (282.7)	190.6 (91.3)	–	–	34.4 (56.6)	−26.1 (66.6)*
GGT, mean (SD), U/L	263.0 (249.8)	210.2 (211.9)	–	–	46.1 (120.5)	−53.5 (131.9)
Itch NRS score, mean (SD)	0.9 (1.05)	0.9 (1.77)	–	–	1.0 (1.1)	0 (1.7)
ELF score, mean (SD)	9.5 (0.93)	9.0 (0.84)	0.08 (0.55)	0.19 (0.59)	0.14 (0.58)	0.19 (0.76)
Gadoxetate time to arrival in the common bile duct, mean (SD) [n], sec[a]	NA	566.6 (271.1) [10]	NA	−22.2 (196.0) [10]	NA	−113.5 (240.4) [8]
Whole liver relative enhancement, mean (SD) [n], %[a]		72.2 (29.0) [10]		0.8 (12.5) [10]		4.0 (11.8) [8]

ALP, alkaline phosphatase; BL, baseline; ELF, enhanced liver fibrosis; kPa, kilopascal; NRS, Numerical Rating Scale.
[a] Data for placebo were not summarized due to only 2 placebo participants having data available in the sub-study.
*P<0.05.

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5005 | CM-101 IMPROVED FIBROSIS BIOMARKERS IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS: THE PHASE 2 SPRING STUDY

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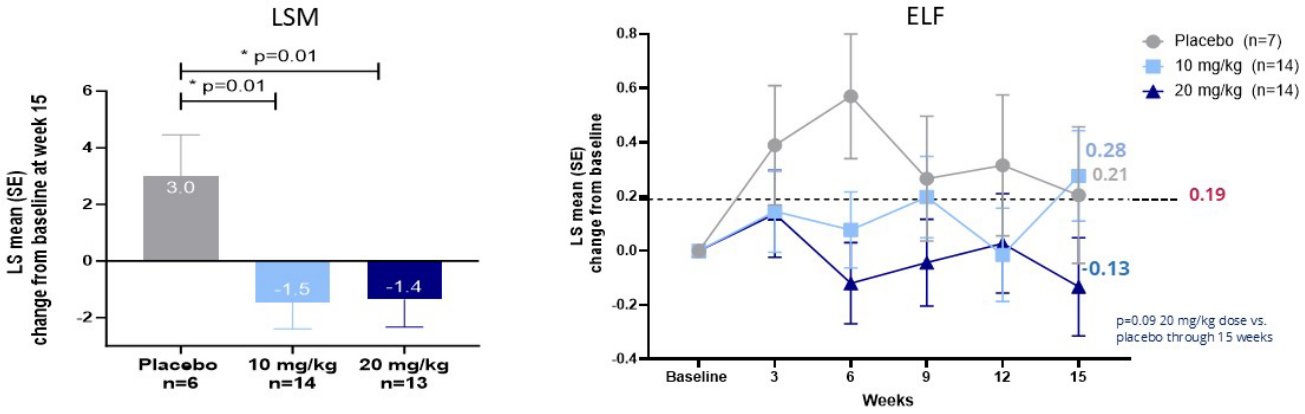
Background: In pre-clinical cholestatic models, CM-101, an anti-CCL24 monoclonal antibody, exhibits anti-inflammatory and anti- fibrotic activity. We evaluated safety, tolerability, and biological activity of CM-101 in patients with primary sclerosing cholangitis (PSC). **Methods:** This double-blind (DB), randomized, placebo

(PBO)-controlled study (NCT04595825) enrolled patients with large duct PSC and ALP >1.5XULN to either IV CM-101 10 mg/kg, 20 mg/kg or PBO every 3 weeks for 15 weeks (5 total doses). The primary endpoint was safety and tolerability. Secondary endpoints included change from baseline to week 15 in liver stiffness measurement (LSM) by vibration-controlled trainsient elastography, enhanced liver fibrosis (ELF) score, liver tests and itch. Biological activity was analyzed in a prespecified subgroup with LSM > 8.7kPa at baseline. **Results:** 76 patients received at least one dose of study treatment (PBO n=20, CM-101 n=56). Baseline characteristics were similar across the groups; mean age 45+/-13 years, 61% male, 62% IBD, and 63% UDCA. 66 patients (PBO n=16, CM-101 10mg/kg n=22, CM-101 20mg/kg n =28) completed the DB period, received all 5 doses, and had both a baseline and at least 1 post-dose measurement of ALP and ELF. Treatment-emergent-adverse-events (TEAEs) were comparable between CM-101 (82%) and placebo (75%). The most common TEAEs were fatigue, headache, and pruritus. Serious TEAEs occurred in 3 patients (1 placebo, 2 CM-101), none were treatment related. CM-101 20mg/kg-treated patients had consistent reductions in AST, ALT, GGT, ALP and total bilirubin compared to CM-101 10mg/kg and PBO patients. Other biomarkers (PRO-C3, IL-6, and TGFβ) showed dose dependent improvements. CM-101- treated patients had reductions in the 5D-itch score from baseline compared to PBO patients. Among those with LSM > 8.7 kPa at baseline (Figure 1), CM-101 10mg/kg and 20mg/kg-treated patients had a reduction in mean LSM compared with PBO patients (p=0.01 in both groups). In this subgroup, a majority of the CM-101 20mg/kg treated patients had ELF scores that did not increase > 0.19, a threshold predictive of worse clinical-outcomes (Muir et al. Hepatology 2019). **Conclusion:** Safety and tolerability of CM-101 was similar to PBO. CM-101 exhibited anti-fibrotic, anti-inflammatory and anti- cholestatic activity in patients with PSC. CM-101 20mg/kg showed reductions in LSM and ELF scores in patients with moderate/advanced PSC. These results support the evaluation of CM-101 in a phase 3 study.

Figure 1: In patients with moderate/ advanced disease (baseline LSM >8.7kPa), LSM and ELF significantly improved in CM-101 treated patients compared to placebo treated patients



Disclosures: Christopher Bowlus: Consultant: Cymabay, ChemoMab, GlaxoSmithKline, Hanmi, Invea Therapeutics, Ipsen, NGM Bio, Pliant Therapeutics, Grant/Research Support: Calliditas, ChemoMab, COUR Phamaceuticals, Cymabay, Gilead, GlaxoSmithKline, Hanmi, Intercept, Ipsen, Mirum, Novartis, NovoNordisk, Pliant Therapeutics, Viking, Zydus, Stephen Barclay: Gilead: Speaking and Teaching, Ipsen: Travel support to attend conference, Falk: Speaking and Teaching, Falk: Advisor, Deepak Joshi: Nothing to Disclose, Maria Carlota Londono: Advanz: Consultant, Advanz: Speaking and Teaching, Ipsen: Consultant, GSK: Consultant, Cymabay: Speaking and Teaching, Parvez Mantry: Nothing to Disclose, Rifaat Safadi: Nothing to Disclose, Revital Aricha: Nothing to Disclose, Chris Cirillo: Nothing to Disclose, Matthew Frankel: Chemomab: Employee, John Lawler: Chemomab: Employee, Ilan Vaknin: Nothing to Disclose, Adi Mor: Nothing to Disclose, Douglas Thorburn: Nothing to Disclose

5006 | TAPERING DOSE OF CORTICOSTEROID IS SAFER AND AS EFFECTIVE AS A FIXED DOSE OF CORTICOSTEROIDS IN PATIENTS WITH SEVERE ALCOHOL-ASSOCIATED HEPATITIS – A MULTICENTER OPEN-LABEL RANDOMIZED CONTROLLED TRIAL (STASH TRIAL)

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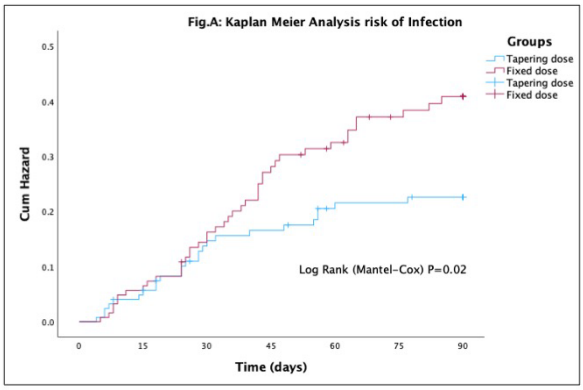
Background: Infections are a major concern in patients with severe alcohol-associated hepatitis (SAH) who receive corticosteroid therapy. The recommended dose of corticosteroids is largely arbitrary, with no large-scale randomized controlled studies (RCT) evaluating the optimal dose, which we aimed to assess. **Methods:** In an open-label multicenter RCT, patients with SAH (MELD ³21) were centrally randomized to receive either a fixed dose of 40 mg prednisolone daily for 4 weeks (Gr. A) or tapering dose starting at 40 mg reduced by 10 mg weekly over 4 weeks (Gr. B). The primary objective was to compare the incidence of mortality, infections, drug-related adverse events, and hospitalizations until day 90. **Results:** A total of 254 patients (age: 41.1±8.2 years; MELD: 25.6±3.9; Men: 98.4%; Index episode of SAH: 92.1%) were included from four Indian and one Canadian centre. Sixty-six percent in Gr. A and 55% in Gr. B received prophylactic antibiotics during corticosteroid therapy (P=0.07). The proportion of steroid responders (defined as Lille's score < 0.45) was similar in both groups (Gr.A:80.3% vs. Gr.B:82.5%; P=0.64). The average daily dose of corticosteroid was 40.8±4.6 mg/day in Gr. A compared to 28.4±6.1 mg/day in Gr. B. (P<0.001). The duration of corticosteroid therapy was similar in both groups (22.1±9.1 days in Gr. A vs. 23±8.8 days in Gr. B). The incidence of drug-related adverse events was higher in Gr. A (52%) than in Gr. B (36.2%; P=0.01). Most common adverse events included infection, hyperglycemia and hematochezia. The incidence of infection at day 90 was 33.1% (95%CI, 23.8-44.7) in Gr.A compared to 19.7% (95%CI, 16.1-37) in Gr. B (P=0.02) (Fig. A). The most common site of infection was the lung (28.3%), followed by the urinary tract (22.4%) in both groups. Other common adverse events, including hyperglycemia (Gr. A: 7.1% vs. Gr. B:3.9%) and hematochezia (Gr.A: 6.3% vs. Gr.B:4.7%), were similar among both groups. On Kaplan Meier analysis, survival was 83.5% (95%CI, 68.3-100) in Gr. A compared to 86.6% (95%CI, 71.1-100) in Gr. B (P=0.5) at day 90 (Fig.B). Four (3.1%) in Gr. A and three (2.4%) in Gr. B underwent living donor liver transplantation by day 90. The proportion of patients developing acute kidney injury (26.8% in Gr.A vs. 18.9% in Gr.B; P=0.13), acute variceal bleed (3.1% in each group), hepatic encephalopathy (Gr.A: 11.8% vs. Gr.B: 6.3%; P=0.12) were similar. Fifty-six patients in Gr. A and 42 patients in Gr. B required hospitalization within 90 days (P=0.07). (Table 1) By day 90, 13.4% in Gr. A and 12.6% in Gr. B had relapse (P=0.85) **Conclusion:** Tapering dose of corticosteroids is safer and equally effective than a fixed conventional dose of corticosteroids in patients with SAH. (*CTRI/2023/03/050521)*



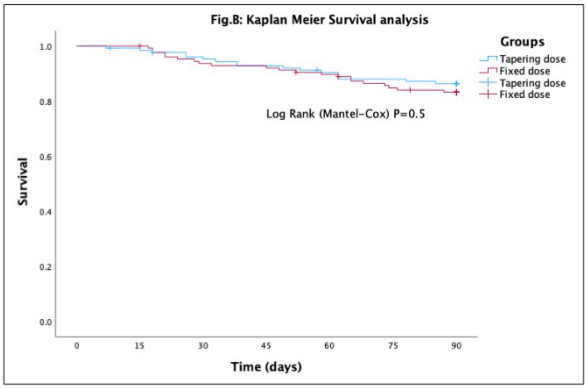


Table 1: outcomes in each group

Outcomes at day 90	Gr. A (Fixed=127)	Gr. B (Tapering=127)	P
All AE	59.8%	48.8%	0.07
Drug Related AE	52%	36.2%	0.01
Infections	33.1%	19.7%	0.01
Liver related outcomes			
Hepatic encephalopathy	11.8%	6.3%	0.12
AVB	3.1%	3.1%	1
AKI	26.8%	18.9%	0.13
Readmissions	44.1%	33.1%	0.07
Death	15.7%	12.6%	0.87
LDLT	3.1%	2.4%	
Loss to follow up	0.8%	0.8%	
Alive	80.3%	84.3%	

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5007 | TOBEVIBART (VIR-3434) AND ELEBSIRAN (VIR-2218) WITH OR WITHOUT PEGYLATED INTERFERON ALFA-2A FOR THE TREATMENT OF CHRONIC HBV INFECTION: END OF TREATMENT RESULTS AFTER 48 WEEKS OF THERAPY (MARCH STUDY)

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Background: Tobevibart (VIR-3434) is an investigational engineered human monoclonal antibody targeting the conserved antigenic loop of HBsAg, and elebsiran (VIR-2218) is an investigational siRNA targeting the HBx region of the HBV genome. Part B of the Phase 2 MARCH study is evaluating 24- and 48-week regimens of tobevibart and elebsiran with or without pegylated interferon alfa-2a (IFN) for the treatment of chronic HBV infection. Available end of treatment (EOT) data are reported for the 48-week regimens. **Methods:** Participants received 44-48 weeks of tobevibart monotherapy, tobevibart + elebsiran, or tobevibart + elebsiran + IFN. Tobevibart, elebsiran, and IFN were administered at 300 mg every 4 weeks (Q4W), 200 mg Q4W, and 180 µg weekly, respectively. Primary endpoints included treatment-emergent adverse events (TEAEs), serious TEAEs, and HBsAg seroclearance at EOT. Secondary endpoints included anti-HBs seroconversion. Participants will also be monitored for post-treatment responses. **Results:** All participants in the tobevibart (n=20) and tobevibart +

elebsiran (n=51) cohorts, and 27/50 of those in the tobevibart + elebsiran + IFN cohort, have completed EOT. HBsAg seroclearance at EOT was achieved in 0/20 (0%), 8/51 (15.7%), and 6/27 (22.2%) participants receiving tobevibart, tobevibart + elebsiran, or tobevibart + elebsiran + IFN, respectively. Higher HBsAg seroclearance rates were observed in participants with lower baseline HBsAg. Among those with baseline HBsAg < 1,000 IU/mL, HBsAg seroclearance at EOT was achieved in 7/18 (38.9%) and 5/11 (45.5%) participants receiving tobevibart + elebsiran or tobevibart + elebsiran + IFN, respectively (Table). TEAEs were most commonly grade 1-2, and grade ≥3 TEAEs were reported in 0, 2 (3.9%), and 9 (33.3%) participants receiving tobevibart, tobevibart + elebsiran, or tobevibart + elebsiran + IFN, respectively. Study drug-related serious TEAEs were reported in 2 participants receiving tobevibart + elebsiran + IFN: one event of leukopenia considered related to IFN, and one event of hepatitis considered related to tobevibart, elebsiran, and IFN (both events improved without sequelae). **Conclusion:** The combination of tobevibart + elebsiran, with or without IFN, achieved HBsAg loss and seroconversion at EOT, particularly in participants with lower baseline HBsAg. No new safety concerns were identified, and TEAEs were generally mild- moderate. These data and the overall risk benefit-profile support continued clinical development for chronic HBV infection.

Table: HBsAg Seroclearance and Seroconversion at EOT by Cohort

	Tobevibart 44 Weeks N=20	Tobevibart + Elebsiran[1] 44 Weeks N=51	Tobevibart + Elebsiran + IFN[2] 48 Weeks N=27
HBsAg Seroclearance at EOT, n (%)			
Overall	0	8 (15.7)	6 (22.2)
Baseline HBsAg < 1,000 vs. ≥ 1,000 IU/mL			
< 1,000 IU/mL	0/6	7/18 (38.9)	5/11 (45.5)
≥ 1,000 IU/mL	0/14	1/33 (3.0)	1/16 (6.3)
Baseline HBsAg < 3,000 vs. ≥ 3,000 IU/mL			
< 3,000 IU/mL	0/12	8/32 (25.0)	5/11 (45.5)
≥ 3,000 IU/mL	0/8	0/19	1/16 (6.3)
HBsAg Seroclearance and Anti-HBs Seroconversion at EOT, n (%)			
Overall	0	4 (7.8)	6 (22.2)
Baseline HBsAg < 1,000 vs. ≥ 1,000 IU/mL			
< 1,000 IU/mL	0/6	3/18 (16.7)	5/11 (45.5)
≥ 1,000 IU/mL	0/14	1/33 (3.0)	1/16 (6.3)
Baseline HBsAg < 3,000 vs. ≥ 3,000 IU/mL			
< 3,000 IU/mL	0/12	4/32 (12.5)	5/11 (45.5)
≥ 3,000 IU/mL	0/8	0/19	1/16 (6.3)

1. Baseline HBsAg range of those achieving HBsAg seroclearance: 0.42 to 1,277 IU/mL
2. Baseline HBsAg range of those achieving HBsAg seroclearance: 29 to 6,449 IU/mL
HBsAg seroclearance defined as HBsAg < 0.05 IU/mL (lower limit of quantification).
Anti-HBs seroconversion defined as anti-HBs level ≥ 10 mIU/mL.
HBsAg was quantified using the Abbott Architect or Roche Cobas.
Anti-HBs levels were determined via Roche Elecsys Anti-HBs kit on the cobas8000 e801 module; a tobevibart-binding blocker was added to samples prior to analysis, preventing assay interference by tobevibart.

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5008 | EFFICACY AND SAFETY OF ELEBSIRAN (BRII-835) AND PEGYLATED INTERFERON ALFA-2A (PEG-IFNA) COMBINATION THERAPY VS PEG- IFNA IN VIROLOGICALLY SUPPRESSED PARTICIPANTS WITH CHRONIC HEPATITIS B VIRUS (HBV) INFECTION: PRELIMINARY RESULTS FROM AN ONGOING PHASE 2, RANDOMIZED, OPEN-LABEL STUDY (ENSURE)

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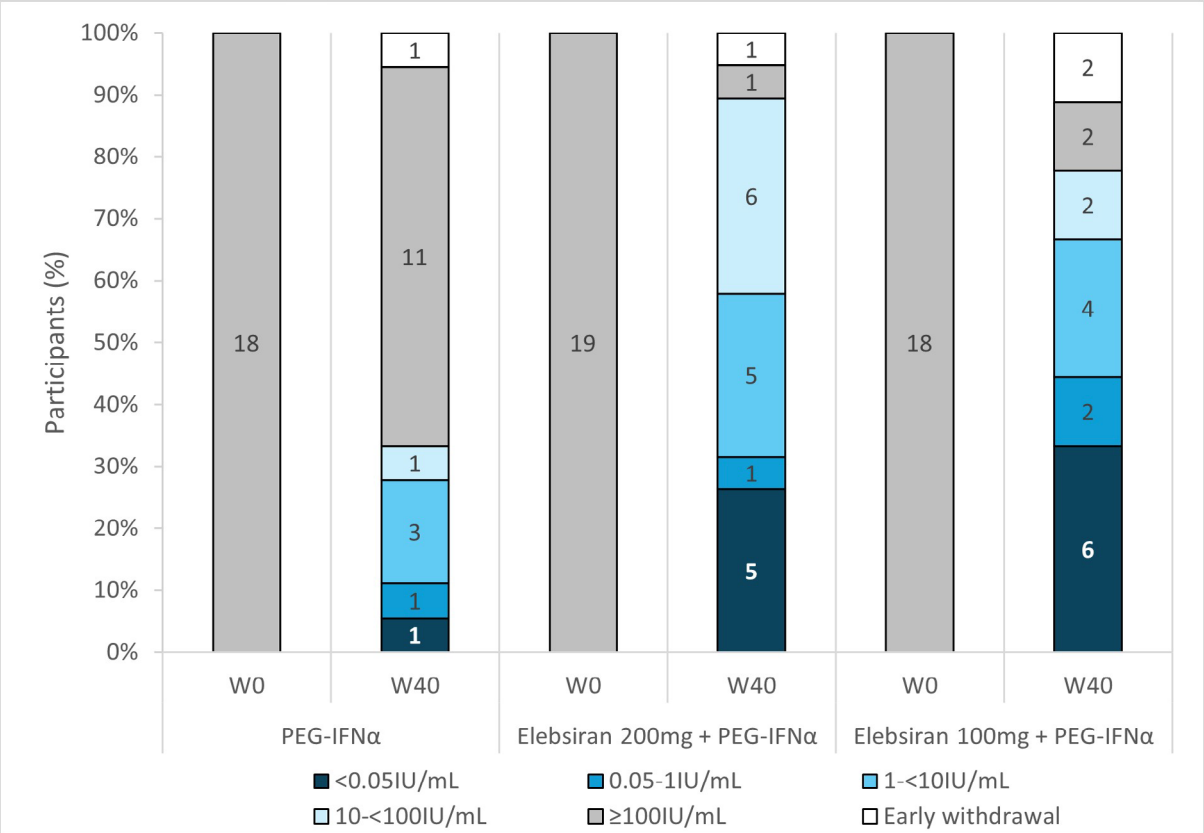
Background: Previous studies demonstrated potentially improved HBsAg loss rate can be achieved by combination treatment with GalNAc conjugated, HBV targeting, small interfering ribonucleic acids (siRNAs) including elebsiran (BRII-835, VIR-2218) and PEG- IFNα in patients with chronic HBV infection. However, these studies did not include PEG-IFNα-only control arms. The ENSURE study (BRII-835-002, NCT05970289) is an ongoing phase 2, randomized, PEG-IFNα controlled study to delineate the contribution of elebsiran and PEG-IFNα, respectively, to the loss of HBsAg and durability of curative outcomes. **Methods:** Virologically suppressed non-cirrhotic participants with chronic HBV infection on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy, with screening HBsAg > 100 and ≤ 3,000 IU/mL, were randomized at a ratio of 1:1:1 to one of the three cohorts: PEG- IFNα alone, elebsiran 200mg + PEG-IFNα, or elebsiran 100mg + PEG-IFNα. Elebsiran and PEG-IFNα were administered subcutaneously every 4 weeks (Q4W) and weekly for 48 weeks, respectively. NRTI was given daily until NRTI stopping criteria were met at Week(W) 72. Preliminary W40 on-treatment data was summarized. **Results:** A total of 55 participants were enrolled. The baseline characteristics were generally well balanced across the cohorts. Elebsiran in combination with PEG-IFNα was generally safe and tolerated. The majority of participants reported at least one treatment emergent adverse event (TEAE), most being grade 1 or 2 in severity. The incidence of TEAEs was comparable across cohorts, and most TEAEs were consistent with the known side effects of PEG-IFNα. Three serious adverse events were reported; 2 were related to PEG-IFNα and none were considered as related to elebsiran. At W40, HBsAg loss was observed in 5/19 (26.3%) and 6/18

(33.3%) participants from elebsiran 200mg or 100mg plus PEG-IFNα cohorts respectively, compared with 1/18 (5.6%) in the PEG-IFNα alone cohort (Figure). 8/12 (66.7%) participants achieving HBsAg loss had HBsAg seroconversion by W40. Greater HBsAg reduction was observed in elebsiran plus PEG-IFNα cohorts compared to the PEG-IFNα alone cohort (approximately -2.4 log10IU/mL vs -0.9 log10IU/mL). **Conclusion:** Elebsiran and PEG-IFNα combination therapy up to 40 weeks was generally safe and tolerated. Compared with PEG-IFNα alone, the addition of elebsiran at 200mg or 100mg Q4W resulted in greater HBsAg loss and HBsAg reduction during treatment, supporting the added benefit of siRNA. The evaluation of 48-week treatment and follow-up is ongoing.



Disclosures: Jidong Jia: No Relevant Financial Relationships, Bingliang Lin: Nothing to Disclose, Peng Hu: Nothing to Disclose, Qing Xie: Nothing to Disclose, Mark Douglas: Gilead Sciences: Advisor, GSK: Speaking and Teaching, Roche Diagnostics: Speaking and Teaching, GSK: Advisor, Gilead Sciences: Grant/Research Support, Fangfang Lv: Nothing to Disclose, Won Young Tak: Nothing to Disclose, Ke Cao: Brii Biosciences (Beijing) Co. Limited: Employee, Chong Zhu: Brii Biosciences: Employee, Weihong Liu: Brii Bioscience: Employee, Jianxiang Lv: Nothing to Disclose, Xiaofei Chen: *Briibiosciences: Employee, David Margolis: Nothing to Disclose, Qing Zhu: Nothing to Disclose

5009 | VTP-300 COMBINED WITH LOW-DOSE NIVOLUMAB IS ASSOCIATED WITH HBSAG LOSS IN CERTAIN CHRONIC HEPATITIS B PARTICIPANTS WITH HBSAG LESS THAN 200 IU/ML: RESULTS FROM A PHASE 2B OPEN-LABEL STUDY

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Background: Current antiviral therapies for chronic hepatitis B virus (CHB) infection are effective in controlling HBV replication but functional cure (FC) remains elusive. VTP-300 is an antigen-specific investigational immunotherapy that has been shown to induce sustained CD8+ T cell responses to HBV, and is considered a potential component of functional cure. We report interim safety and efficacy data from the ongoing, fully enrolled HBV003 study. **Methods:** This is an open-label Phase 2b trial (NCT05343481) enrolling participants with CHB, on nucleo(s)tide analogues (NUCs) for at least six months before screening, with an HBV-DNA viral load of ≤1000 IU/mL and HBsAg between ≥10 IU/mL and ≤4,000 IU/mL, subsequently amended to include only participants with HBsAg <200 IU/mL at screening. Safety data, immunology data, and HBV marker data are collected throughout the study. The primary endpoint is the percentage of participants with a greater than 1 log HBsAg reduction at least 6 months after initiation of therapy. Secondary endpoints and additional analyses include safety and reactogenicity, the loss of HBsAg and HBsAb seroconversion. **Results:** This study fully enrolled with 121 participants in August 2024, of whom 70 (58%) had HBsAg ≤200 IU/mL at screening. At the 2024 AASLD meeting, we expect to report interim data on 92 participants who will have reached D169 (NUC discontinuation), and 65 participants who will have completed the study. Current interim data at D169, show HBsAg declines of >1 log were observed in 23% of participants with HBsAg screening levels ≤200 IU/mL. Currently, eight participants achieved undetectable HBsAg levels. Notably, three of whom have remained off NUCs for periods exceeding 6 months thus reaching the definition of functional cure. HBsAb seroconversion has been observed in 3 participants with undetectable HBsAg. VTP-300 and Low Dose nivolumab (LDN) continue to be generally well-tolerated. **Conclusion:** VTP-300, a novel antigen-specific investigational immunotherapy administered in combination with LDN, has been generally well-tolerated throughout the course of this study. Emerging efficacy data, particularly the loss of HBsAg and HBsAb seroconversion in participants with baseline HBsAg <200 IU/mL are very encouraging.

Disclosures: Chun Jen Liu: No Relevant Financial Relationships, Anchalee Avihingsanon: Gilead Science, ViiV/GSK, Roche, MSD,: Grant/Research Support, Gilead Science: travel support to present abstract, Wan Long Chuang: Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, BMS: Speaking and Teaching, Vaccitech: Consultant, PharmaEssentia: Consultant, Apinya Leerapun: Nothing to Disclose, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol- Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Has not ended, Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals, Has not ended, Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics, Has not ended, Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc, Has not ended, Consultant relationship with Immunocore, Janssen, Precision BioSciences, Has not ended, Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Has not ended, Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore, Has not ended, Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Has not ended, Consultant relationship with Vir Biotechnology and Visirna Therapeutics, Has not ended, Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics, Has not ended, Grant/Research Support relationship with

Sysmex Corporation and Roche, Has not ended, Radka Kolenovska: Barinthus Biotherapeuitcs Ltd.: Employee, Bethan Jones: Barinthus Biotherapeutics: Employee, Dereck Tait: Nothing to Disclose, Leon Hooftman: Nothing to Disclose

5010 | SAFETY AND EFFICACY OF REP 2139-MG IN HEPATITIS D PATIENTS: REPORTING OF EXTENDED FOLLOW-UP DATA FROM THE INTERNATIONAL COMPASSIONATE USE PROGRAM

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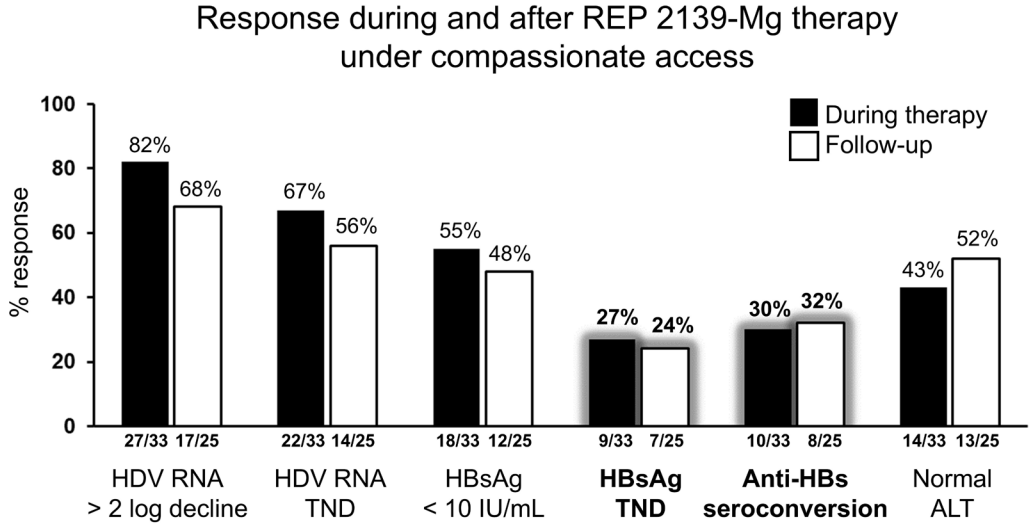
Background: REP 2139 blocks HDV replication, HBV subviral particle assembly and HDV envelopment. The real-life safety and efficacy of REP 2139-Mg in patients with chronic HBV / HDV co-infection with advanced liver disease is being evaluated under at international compassionate use program (NCT05683548). **Methods:** REP 2139-Mg (250 mg qW SC) for 48 weeks was added to existing NUC therapy. Safety / liver function were monitored weekly. Virologic response (quantitative HBsAg, anti-HBs, HBV-DNA, HDV-RNA) was assessed every 4 weeks. REP 2139-Mg dose increases and/or combination with pegIFN (45-180µg qW SC) were guided by virologic response. PegIFN was added in 17 patients. **Results:** Most of the 33 patients (21-69 y.o, 27 cirrhotic, 6 decompensated) had failed previous therapy (n=24 pegIFN; n=20 bulevirtide; n=2 lonarfarnib). At submission, 31 patients have entered follow-up on NUC monotherapy. REP 2139-Mg was halted early in 6 patients [liver transplant (n=2), lost-to-follow-up (n=1), variceal bleeding (n=1), problematic IV access (n=2)] and extended > 48 weeks in 6 patients (60-80 weeks) to improve antiviral response. REP 2139-Mg was well tolerated no REP 2139-related SAE were observed. At lerast one or more transient grade 1 injection site reactions occurred in n=22 (67%) of patients. ALT elevation occurred in 20 patients (14 with pegIFN). Non-response to REP 2139 250mg SC was rescued with 250mg IV or 500mg (SC or IV) and or dose extension in 8/33 patients. At the end of REP 2139-Mg therapy, ALT normalization and 2 log10 HDV RNA decline were achieved in 14/33 (43%) and 27/33 (82%) patients, respectively; HDV RNA negativity was achieved in 22/33 (67%). HBsAg became < 10 IU/mL in 18/33 (55%) with HBsAg loss in 9/33 (27%). Anti-HBs seroconversion occurred in 10/33 (30%). In 25 patients completing therapy with available follow-up (median 24 weeks), ALT remains normal in 13/25 (52%). HDV RNA decline > 2 log10 persists in 17/25 (68%) with HDV RNA negativity in 14/25 (56%). This included patients with HDV genotypes 1, 5 and 7. HBsAg <10 IU/mL persists in 12/25 (48%) and HBsAg loss in 6/25 (24%) with anti-HBs seroconversion in 8/25 (32%). HBsAg loss is maintained in 2 patients with decompensated cirrhosis who

did not receive pegIFN (at 31 and 64 wks of follow-up). Three patients have had all therapy removed for 26, 32 and 60 weeks; all maintain normal ALT with undetectable HBV DNA, HDV RNA and HBsAg and anti-HBsAg seroconversion. In one cirrhotic patient, liver stiffness decreased from a baseline of 18.7 kPa to 7.9 kPa at 60 weeks of treatment free follow-up. **Conclusion:** REP 2139-Mg is safe and well tolerated in HDV patients with advanced liver disease and can lead to HDV cure and HBV functional cure. REP 2139-Mg treatment can lead to HDV cure (including in the presence of HBsAg) and HBV functional cure independently of pegIFN.



Disclosures: Christiane Stern: Consultant: Echosens, Speaking/Teaching: Gilead, Hologic, Stocks - privately held: Gilead, Marc Bourliere: Nothing to Disclose, Veronique Loustaud-Ratti: GILEAD: Consultant, abbvie: Speaking and Teaching, GSK: Consultant, Cihan Yurdaydin: Nothing to Disclose, Giuseppina Brancaccio: Nothing to Disclose, Mathias Jachs: Nothing to Disclose, Thomas Reiberger: Nothing to Disclose, Edouard Bardou-Jacquet: gilead: Speaking and Teaching, abbvie: Speaking and Teaching, orphalan: Speaking and Teaching, astellas: Speaking and Teaching, sanofi: Speaking and Teaching, Sophie Metivier: Nothing to Disclose, Laurent Alric: MSD, Abbvie, Sanofi: Speaking and Teaching, Lea Colombain: Nothing to Disclose, Magdalena Meszaros: Nothing to Disclose, Philippe Mathurin: Nothing to Disclose, David Yardeni: Nothing to Disclose, Ohad Etzion: Nothing to Disclose, Christoph Neumann-Haefelin: Nothing to Disclose, Mark Douglas: Gilead Sciences: Advisor, GSK: Speaking and Teaching, Roche Diagnostics: Speaking and Teaching, GSK: Advisor, Gilead Sciences: Grant/ Research Support, Sébastien Poulin: Nothing to Disclose, Segolene Brichler: Nothing to Disclose, Emmanuel Gordien: Gilead: Eurobio, Eurobio: Consultant, Gilead: Eurobio, Eurobio, Gilead: Consultant, Stephane Chevaliez: Nothing to Disclose, Michel Bazinet: Nothing to Disclose, OLGA METIN: Nothing to Disclose, Giovanni Geata: Nothing to Disclose, Alessandro Vitale: Nothing to Disclose, valentina svicher: Nothing to Disclose, Umberto Cillo: Nothing to Disclose, Michael Schwarz: Nothing to Disclose, Souad Ben Ali: Nothing to Disclose, Jose Ursic Bedoya: Nothing to Disclose, Sandrine Francois: Nothing to Disclose, Furkan Kaysin: Nothing to Disclose, Cecilia De Freitas: Nothing to Disclose, Laurence Lecomte: Nothing to Disclose, Anita Levacher: Nothing to Disclose, Oceane Camou: Nothing to Disclose, Kimberly Lemoine: Nothing to Disclose, Christopher Morvan: Nothing to Disclose, Athenais Gerber: Nothing to Disclose, Vincent Mackiewicz: Nothing to Disclose, Jocelyn Schramko: Nothing to Disclose, Kindness Bondezi: Nothing to Disclose, Marie-Eve Baril: Nothing to Disclose, Carla Osiowy: Nothing to Disclose, Andrew Vaillant: Replicor Inc.: Employee, Replicor Inc.: Stock - privately held company

5011 | HBSAG LOSS AND SEROCONVERSION IN HBEAG-NEGATIVE CHRONIC HEPATITIS B SUBJECTS ON NA THERAPY AFTER AHB-137 TREATMENT: PRELIMINARY DATA FROM AN ONGOING MULTICENTER, RANDOMIZED, OPEN-LABEL PHASE IIA STUDY

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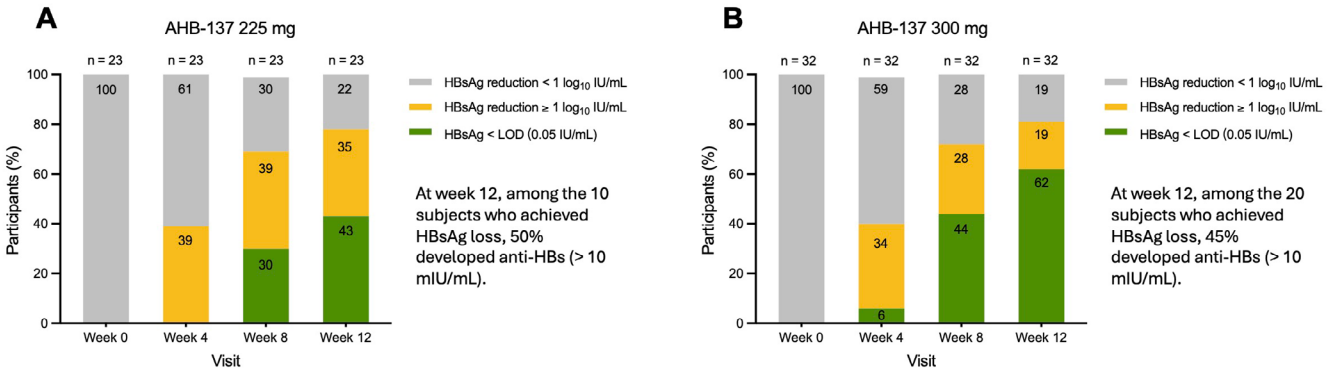
Background: AHB-137 is an antisense oligonucleotide (ASO) that has previously demonstrated good tolerability and strong antiviral activity following up to 4 weeks of dosing in phase 1a/1b clinical studies. Here, we present the initial results of a 24-week treatment with AHB-137 in subjects with chronic hepatitis B (CHB) from an ongoing phase IIa study in China. **Methods:** HBeAg-negative CHB subjects, with baseline HBsAg > 100 to 3,000 IU/mL (inclusive) and under stable nucleos(t)ide analogue (NA) treatment, were enrolled in the multicenter, randomized, open-label phase IIa study (NCT06115993). Subjects were randomized to receive subcutaneous doses of either 300 mg or 225 mg of AHB-137 weekly, with two loading doses on Days 4 and 11. Following the 24-week treatment, a 24-week follow-up with NA therapy alone and an additional 24-week follow-up post NA cessation was scheduled. The primary outcome is the proportion of subjects achieving HBsAg loss (HBsAg < limit of detection (0.05 IU/ml) and HBV DNA < lower limit of quantification (10 IU/ml)), at the conclusion of the 24-week AHB-137 treatment. **Results:** To date, all subjects have completed at least 12 weeks of AHB-137 treatment. Serum HBsAg levels were rapidly reduced by AHB-137 treatment. At Week 12, 62% (20/32) of subjects in the 300 mg arm and 43% (10/23) in the 225 mg arm achieved HBsAg loss, which primarily occurred within the initial 8-week treatment (44% and 30% respectively; see figure). Furthermore, in the 300 mg arm, 50% (7/14) of subjects with baseline HBsAg > 1,000 IU/mL ≤ 3,000 IU/ml achieved HBsAg loss. Among the 30 subjects who achieved HBsAg loss, 47% have experienced seroconversion (detection of anti-HBsAg antibodies > 10 mIU/mL) by Week 12. There were no serious adverse events (SAEs) or drug discontinuations. The most common treatment-related AEs (TRAEs) were Grade 1-2, including injection site reactions, pyrexia, and laboratory abnormalities. Grade 3 TRAEs included ALT increased, AST increased, and transient lymphocyte counts decreased. No Grade 4 TRAEs were observed. Notably, ALT increase and on-treatment normalization was highly associated with HBsAg loss. **Conclusion:** In this ongoing phase IIa trial, AHB137 was well tolerated. AHB-137 treatment led to rapid HBsAg loss within 12 weeks in 62% of subjects at a dose of 300 mg. Furthermore, nearly half of the subjects with HBsAg loss had seroconversion. Current data support further development of AHB-137 for HBV functional cure.

Figure: Cumulative proportion of subjects within each HBsAg categories over time in the 225mg (A) and 300 mg (B) AHB-137 arms.



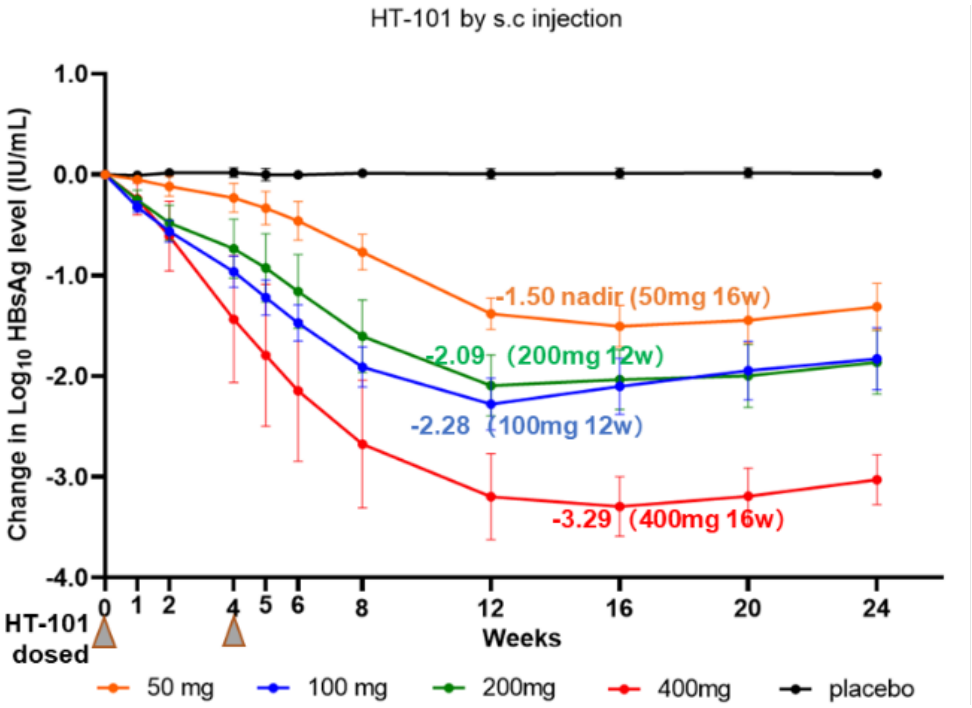
Disclosures: Yanhua Ding: No Relevant Financial Relationships, Xian Yu: Nothing to Disclose, Xieer Liang: Nothing to Disclose, Hong Ren: Nothing to Disclose, Chongyuan Xu: Nothing to Disclose, Wen Wang: Nothing to Disclose, Zhihong Liu: Nothing to Disclose, Yi Yang: Nothing to Disclose, Hong Zhang: Nothing to Disclose, Jinlin Hou: Nothing to Disclose, Shan Zhong: Nothing to Disclose, Hong Chen: Nothing to Disclose, Yilei Wen: Nothing to Disclose, Tingting Lu: Nothing to Disclose, Xiao Qiu: Nothing to Disclose, Lidan Wang: Nothing to Disclose, Di Zhao: Nothing to Disclose, Chen Yang: Nothing to Disclose, Miao Wang: Nothing to Disclose, Chris Yang: Nothing to Disclose, Guofeng Cheng: Nothing to Disclose, Junqi Niu: Nothing to Disclose

5012 | ROBUST HEPATITIS B SURFACE ANTIGEN REDUCTION BY HT-101 IN CHRONIC HEPATITIS B PATIENTS: RESULTS FROM A PHASE IB STUDY

Dong Shanzhong Wang Zhang[1]

[1]*hepa thera*

Background: HT-101 is an N-acetylgalactosamine (GalNAc) –conjugated small interfering ribonucleic acid (siRNA) targeting hepatitis B virus. Preclinical studies exhibited a promising potential for the treatment of chronic hepatitis B virus (HBV) infection. Here we reported the phase 1b study results to evaluate the safety, tolerability, pharmacokinetics and antiviral activity of HT-101 in chronic HBV infection participants with nucleos(t)ide reverse transcriptase inhibitor (NRTI) treatment (CTR2022854/ChiCTR2200066547). **Methods:** This was a randomized, double-blind, placebo-controlled, multiple ascending doses study of HT-101 administered via subcutaneous (SC) injection to chronic hepatitis B patients who received continuous NRTI therapy for ≥ 6 months. Participants with non-cirrhosis (<F3) were restricted with HBsAg 200-5,000 IU/mL at screening. Participants received two SC HT-101 injections, 4 weeks apart, of 50, 100, 200 or 400 mg. At each dose level, eight participants were randomly assigned to HT-101 or placebo (6:2 ratio). Follow-up was carried out for 24 weeks post dose. Written informed consent was obtained prior to study procedures. **Results:** The administration of multiple SC doses of HT-101 for up to 400 mg in CHB subjects demonstrated a favourable safety profile and was well tolerated. No subjects dosed HT-101 discontinued due to an adverse event (AE), no serious adverse events (SAE) nor death were reported. No ALT flare was observed. Demographic and baseline characteristics were generally well balanced across treatment groups. Reductions in HBsAg with time were observed across all HT-101 groups regardless of baseline HBeAg status or HBsAg level. Higher doses associated with greater reduction and maximum mean reduction at 3.29 log in 400mg group(Figure) and all 6 subjects achieved <10 IU/ml from w16 to w24. In 100&200mg group, most subjects (11/12) achieved <100 IU/ml from w12 to w24. In 50mg group most subjects (5/6) remained over 1log HBsAg reduction at w24. The durability of HBsAg response after two doses of HT-101 lasted post-treatment 20 weeks without obvious rebound. Other viral parameters (HBV DNA, RNA, HBcrAg, HBeAg) above LLOQ at baseline improved. Plasma PK parameters (AUC, Cmax,Tmax,T1/2) was consistent in CHB patients with healthy volunteers. Urine PK parameters were similar between healthy and CHB subjects in 50-400 mg. The mean percentage excreted in urine up to 48 hours was 13.3% ~30.9%. The recovery rate reached the plateau at 24h after dose. **Conclusion:** Two monthly doses of HT-101 administered SC were well safe and tolerated with a favourable pharmacokinetics profile in Chinese patients with chronic HBV infection. Dose-dependent significant reductions from baseline in serum HBsAg levels were achieved through up to 20 weeks post last dose. These data support the continued development of HT-101 for treatment of chronic HBV infection.



Disclosures: Dong Shanzhong Wang Zhang: No Relevant Financial Relationships

5013 | ALG-055009, A NOVEL THYROID HORMONE RECEPTOR BETA (THR-β) AGONIST, WAS WELL-TOLERATED WITH SIGNIFICANT REDUCTIONS IN LIVER FAT AT WEEK 12 IN NON-CIRRHOTIC MASH PATIENTS IN THE ONGOING RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2A HERALD STUDY

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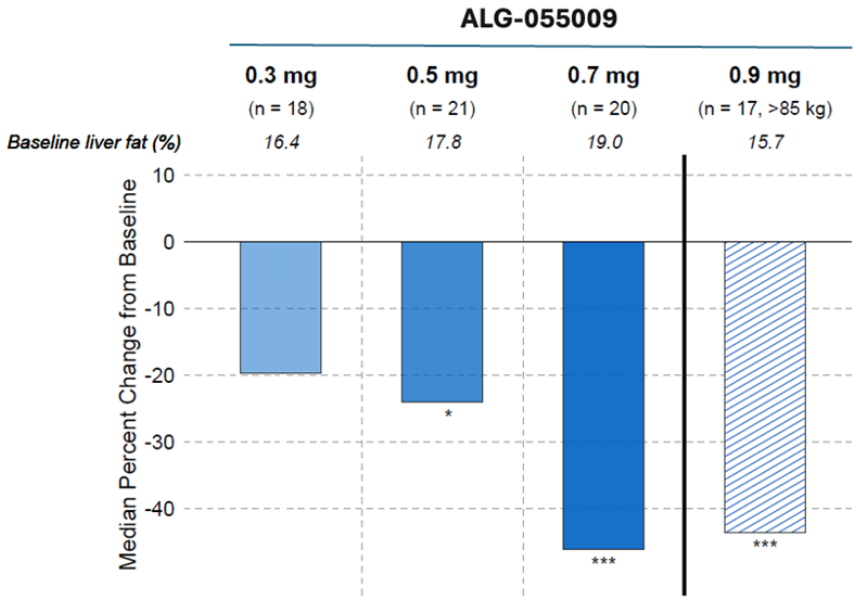
Background: THR-β agonists reduce atherogenic lipids, decrease hepatic fat, and improve liver histology in MASH. ALG-055009, a novel next generation THR-β agonist with β selectivity and in vitro potency exceeding that of first generation THR-β drugs, demonstrated favorable Ph1 safety, pharmacokinetic (PK) and pharmacodynamic (PD) effects in healthy volunteers/hyperlipidemic subjects. Ph2a HERALD (NCT06342947) is a randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, PK and PD of ALG-055009 in non-cirrhotic adults with presumed MASH and F1-F3 fibrosis. Primary analysis results following completion of treatment in this Ph2a study are reported here. **Methods:** In this Ph2a randomized, double-blind, placebo-controlled study, 102 subjects (~20/arm) were randomized to receive 0.3, 0.5, 0.7 or 0.9 mg ALG-055009 or placebo, orally once daily for 12 weeks. Only subjects with body weight >85 kg were enrolled in the 0.9 mg arm, with no weight restrictions for other arms. The primary endpoint was relative change from baseline in liver fat by MRI-PDFF at Week 12. Levels of lipid/lipoproteins, sex hormone binding globulin (SHBG), MASH/fibrosis biomarkers and safety/tolerability were assessed. **Results:** Baseline characteristics were generally similar across arms: 62% female, mean age 50 yrs, mean BMI 39 kg/m^2, 46% Type 2 diabetes. ALG-055009 dose groups met the primary endpoint, with statistically significant placebo-adjusted median relative reductions in liver fat of up to 46.2% at Week 12 with a dose response between 0.3-0.7 mg (Figure). Up to 70% of subjects achieved ≥30% relative reduction in liver fat compared to baseline, with no apparent differences in liver fat reduction in subjects with or without stable GLP-1 agonist use. Significant reductions in atherogenic lipids, including LDL-C, lipoprotein (a) and apolipoprotein

B and dose-dependent increases in SHBG were observed. The majority of treatment emergent adverse events (TEAEs) were mild to moderate, with one discontinuation due to worsening insomnia in a subject with pre-existing insomnia. No clinically meaningful findings in laboratory tests, ECGs, vital signs, physical exams or clinical evidence of hypo/hyperthyroidism were observed. Incidence of gastrointestinal (GI)-related TEAEs were similar in ALG-055009 dose groups compared to placebo, including a lower incidence of diarrhea for ALG-055009 vs. placebo. **Conclusion:** 12 weeks of once daily ALG-055009 treatment in MASH subjects met the primary endpoint, demonstrating significant reductions in liver fat and was well-tolerated, with rates of GI-related TEAEs similar to placebo. This supports evaluation of longer durations of ALG-055009 and its effects on liver histology.



Note: Data from MRI-PDFF analysis dataset, defined as all randomized subjects who have MRI-PDFF measurements available at both baseline and Week 12; median % change in placebo was +7.2%; *p<0.05 ***p<0.001. Only subjects weighing >85 kg were enrolled in the 0.9 mg dose group, no body weight restrictions were implemented in other dose groups.

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Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Guy Neff: Nothing to Disclose, Antonio Bianco: Nothing to Disclose, Eveline Bruinstroop: Nothing to Disclose, Stanley Wang: Aligos Therapeutics: Employee, Kha Le: Nothing to Disclose, Megan Fitzgerald: Aligos Therapeutics, Inc.: Employee, Min Wu: Nothing to Disclose, Ifong Kan-Eng: Nothing to Disclose, Genevieve Harrington: Aligos Therapeutics: Employee, Melissa San Nicolas: Nothing to Disclose, Chris Burnett: Nothing to Disclose, Jen Rito: Aligos Therapeutics, Inc.: Employee, Doug Clark: Nothing to Disclose, Naqvi Mohammed: aligos therapeutics: Employee, Meenakshi Venkatraman: Nothing to Disclose, Tse-I Lin: Nothing to Disclose, Sushmita Chanda: Nothing to Disclose, Lawrence Blatt: Nothing to Disclose, Christos Mantzoros: Nothing to Disclose

5014 | IMPACT OF PNPLA3 RS738409 VARIANT ON THE RESPONSE TO TIRZEPATIDE VERSUS PLACEBO FOR THE TREATMENT OF NON-CIRRHOTIC MASH

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Background: Tirzepatide (TZP) is a long-acting GIP/GLP-1 receptor agonist. The SYNERGY-NASH trial (NCT04166773; Loomba et al NEJM 2024) randomized 190 patients with biopsy-confirmed MASH, stage 2/3 fibrosis, and NAS ≥4 to receive QW sc TZP (5, 10 or 15 mg) or placebo (PBO) for 52 weeks. The *PNPLA3* rs738409 variant (CG and GG genotypes) is associated with a higher risk of major adverse liver outcomes. In this post hoc analysis, we explored the relationship between *PNPLA3* genotype and TZP vs PBO treatment response for histological endpoints, liver fat (MRI-PDFF) and body weight. **Methods:** Changes in endpoints for TZP (pooled doses) vs PBO within genotype groups were analyzed by Cochran-Mantel-Haenszel test and ANCOVA. To test if TZP treatment responses differed by genotype, the Breslow-Day test for homogeneity was used for binary endpoints and an interaction term between treatment and genotype was tested for continuous endpoints. **Results:** *PNPLA3* genotype data were available for 131 participants (33 CC, 65 CG, 33 GG). Hispanic/Latino ethnicity was more common in CG (54%) and GG (71%) than in CC (15%). Baseline mean ALT and AST were higher in GG (72.7, 56.9 U/L) than in CC (54.7, 44.2 U/L). Baseline mean MRI-PDFF, NAS, NIS4®, FAST, VCTE liver stiffness, FIB-4, Pro-C3 and ELF, and the proportion of F2 vs F3 fibrosis did not differ significantly by genotype. Significantly more participants achieved MASH resolution without worsening of fibrosis with TZP vs PBO in the overall population, CC, CG and CG+GG combined (Table); the PBO-corrected treatment effect of TZP was significantly higher with CC vs CG+GG combined (p=0.033). Fibrosis improvement by ≥1 stage without worsening of MASH was significantly more common with TZP vs PBO for the overall population, CG and CG+GG but an effect of genotype to influence the TZP treatment effect on fibrosis was not apparent (p>0.8). There was no significant impact of genotype on reductions in liver fat (p>0.6) or body weight (p>0.4). The small sample size is a limitation. **Conclusion:** TZP had beneficial effects on MASH disease activity, fibrosis, liver fat and body weight across all 3 *PNPLA3* genotypes. The TZP treatment effect for MASH resolution was greater in those with the CC genotype compared to those who are G-allele carriers. Fibrosis improvement and reductions in liver fat or body weight were similar across genotypes. These data suggest that the G- risk allele may be related to MASH independently of its effect on liver fat.

Effect of PNPLA3 genotype on tirzepatide vs placebo treatment response for histological endpoints, liver fat (MRI-PDFF) and body weight.

PNPLA3 genotype	MASH resolution TZP pooled (n/N, %)	MASH resolution Placebo (n/N, %)	Fibrosis improvement TZP pooled (n/N, %)	Fibrosis improvement Placebo (n/N, %)	≥30% decrease in MRI-PDFF TZP pooled (n/N, %)	≥30% decrease in MRI-PDFF Placebo (n/N, %)	LS mean difference between TZP (pooled) and placebo for change from baseline in MRI-PDFF (% [95% CI])	LS mean difference between TZP (pooled) and placebo for percent change from baseline in body weight (% [95% CI])
CC	17/18 (94)***	0/8 (0)	13/18 (72)	3/8 (38)	15/18 (83)*	2/6 (33)	-7.3 (-13.2, -1.3)*	-11.3 (-18.5, -4.3)**
CG	26/43 (60)**	2 /13 (15)	27/43 (63)*	4/13 (31)	26/32 (81)*	4/9 (44)	-5.4 (-10.3, -0.6)*	-14.3 (-20.1, -8.6)***
GG	12/22 (55)	0/2 (0)	9/22 (41)	0/2 (0)	11/15 (73)*	0/2 (0)	-10.3 (-19.7, -1.0)*	-18.0 (-31.2, -4.8)**
CG+GG	38/65 (58)**	2/15 (13)	36/65 (55)*	4/15 (27)	37/47 (79)**	4/11 (36)	-6.6 (-10.8, -2.4)**	-15.0 (-20.2, -9.8)***
All	55/83 (66)***	2/23 (9)	49/83 (59)*	7/23 (30)	52/65 (80)***	6/17 (35)	-6.7 (-10.1, -3.4)***	-13.5 (-17.6, -9.4)***

*p<0.05; **P<0.01; ***P<0.001 for comparison vs. placebo. N=total number with measure; n=participants achieving the endpoint.
Abbreviations: LS, least squares; MRI, magnetic resonance imaging; PDFF, proton density fat fraction; TZP, tirzepatide

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5015 | EFFICACY AND SAFETY OF ERVOGASTAT, A DIACYLGLYCEROL ACYLTRANSFERASE-2 INHIBITOR (DGAT2I), ALONE OR IN COMBINATION WITH CLESACOSTAT, AN ACETYL-COENZYME A CARBOXYLASE INHIBITOR (ACCI), IN ADULTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS WITH F2–F3 FIBROSIS

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Background: Small molecule inhibitors of the terminal step in intrahepatic triglyceride synthesis (diacylglycerol acyltransferase-2 inhibitor [DGAT2i] PF-06865571/ervogastat [E]) and upstream blockade of de novo lipogenesis via an acetyl-coenzyme A carboxylase inhibitor (ACCi, PF-05221304/clesacostat [C]) have shown promise in reducing hepatic steatosis in early clinical trials. Increased circulating triglycerides, a mechanistic consequence of hepatic ACCi, have been shown to be downregulated by DGAT2i coadministration. Hence, E alone and E+C are potential therapeutic options for metabolic dysfunction-associated steatohepatitis (MASH). **Methods:** This phase 2 study assessed the efficacy and safety of E alone and E+C in adult patients with biopsy-confirmed MASH and fibrosis stage (F) 2 or 3. Patients were randomized to receive placebo, one of four doses of E (25–300 mg twice daily [BID]), or one of two dose levels of E+C (E150+C5 or E300+C10 mg BID) for 48 weeks. The composite primary endpoint was the proportion of patients achieving MASH resolution without worsening of fibrosis, or improvement in fibrosis by ≥1 stage without worsening of MASH, or both, at Week 48. Secondary endpoints included improvements in different responder definitions, percent change in liver fat, and assessment of safety, including fasting lipids (Week 48). **Results:** Of the 255 patients randomized and dosed, median age was 58 years, 61% had T2DM, and 65% had F3 at baseline. For the composite primary endpoint, all active doses had greater response than placebo with both dose levels of E+C significantly outperforming placebo. Furthermore, E and E+C had a robust effect on MASH resolution without worsening of fibrosis. While the fibrosis-based component of the histological primary endpoint was not met by any active dose (likely due to a large placebo response and limited sample size), changes in non-invasive biomarkers demonstrated anti-fibrotic activity (Table). Both E and E+C were generally well tolerated; the majority of adverse events (AEs) were mild in severity and AE frequency was comparable between placebo and all active doses. However, E+C (though not E alone) resulted in undesirable sustained increases in serum triglycerides, ApoC3, and direct VLDL- C (Table). **Conclusion:** The data from this study contribute to the growing body of evidence supporting the efficacy of these novel therapies in MASH and support larger, longer trials to further assess the efficacy and safety of E and E+C.

Table. Efficacy and safety outcomes at Week 48, unless otherwise stated

Treatment arm (number randomized and dosed)	Placebo, E alone, or E+C (mg BID)						
	Placebo (N=34)	E25 (N=35)	E75 (N=48)	E150 (N=42)	E150 + C5 (N=35)	E300 (N=31)	E300 + C10 (N=30)
Efficacy-related elements							
% with resolution of MASH without worsening fibrosis or % with fibrosis improvement by ≥1 stage without worsening MASH or both[a]	38%	46%	52%	50%	66%*	45%	63%*
% with resolution of MASH without worsening fibrosis[a]	9%	31%*	46%*	31%*	63%*	42%*	57%*
% with fibrosis improvement by ≥1 stage without worsening MASH[a]	35%	29%	21%	33%	37%	13%	40%
% with fibrosis improvement by ≥2 stages without worsening MASH[a]	3%	11%	6%	12%	20%*	6%	20%*
% with resolution of MASH without worsening fibrosis and fibrosis improvement by ≥1 stage without worsening MASH[a]	6%	14%	15%	14%	34%*	10%	33%*
Liver fat (MRI-PDFF substudy)[b]	-6.3 (-27.2, 20.7)	-43.2* (-55.1, -28.1)	-41.3* (-51.7, -28.7)	-60.3* (-68.4, -50.1)	-69.6* (-76.2, -61.1)	-49.8* (-62.0, -33.5)	-68.7* (-76.5, -58.4)
Median stiffness (VCTE)[b]	-9.46 (-18.02, -0.01)	-11.97 (-20.33, -2.75)	-28.38* (-34.11, -22.15)	-22.32* (-29.13, -14.86)	-26.19* (-33.09, -18.57)	-18.77 (-27.39, -9.14)	-30.05* (-37.18, -22.12)
ELF score[b]	1.18 (-0.48, 2.87)	-1.85* (-3.49, -0.18)	-2.24* (-3.64, -0.83)	-3.71* (-5.25, -2.14)	-2.05* (-3.72, -0.34)	-3.26* (-5.03, -1.45)	-3.83* (-5.51, -2.11)
Safety-related elements							
Premature withdrawal from study (26/255 [10.2%]), n	2	4	3	7	3	5	2
Discontinued study due to AEs, n	0	2	2	2	2	2	0
ALT[b]	-7.2 (-16.9, 3.7)	-45.9* (-51.5, -39.7)	-46.7* (-51.5, -41.4)	-45.5* (-50.8, -39.7)	-60.0* (-64.1, -55.5)	-48.7* (-54.5, -42.3)	-59.1* (-63.6, -54.1)
AST[b]	-6.0 (-15.2, 4.1)	-38.7* (-44.5, -32.2)	-42.0* (-46.8, -36.7)	-37.7* (-43.3, -31.6)	-50.8* (-55.4, -45.6)	-43.6* (-49.5, -37.1)	-51.3* (-56.4, -45.8)
Fasting serum triglycerides[b]	0.3 (-9.6, 11.3)	4.3 (-5.8, 15.4)	4.4 (-4.4, 13.9)	4.7 (-4.7, 15.0)	29.7* (17.4, 43.4)	5.7 (-5.3, 18.1)	50.2* (34.7, 67.5)
Fasting direct VLDL-C[b]	37.55 (7.58, 75.87)	18.43 (-6.50, 50.01)	-14.36 (-29.53, 4.08)	13.57 (-8.38, 40.77)	88.99 (50.24, 137.74)	51.28 (16.42, 96.60)	101.84* (56.64, 160.09)
Fasting ApoC3[b]	5.62 (-3.09, 15.11)	2.43 (-5.96, 11.57)	5.49 (-1.79, 13.32)	8.45 (0.26, 17.31)	28.54* (18.32, 39.64)	12.58 (2.50, 23.66)	39.10* (27.09, 52.25)

Across endpoints, number of patients/arm differ based on the number of patients with non-missing data in the full analysis set or safety analysis set.
[a]Proportion of responders was defined by NASH-CRN; patients with missing on-treatment biopsy at Week 48 were counted as nonresponders; values with * denote doses that separate from placebo with ≥95% certainty (one-sided), as estimated from a logistic regression model with treatment and baseline F2/F3 as a factor.
[b]Log-transformed relative changes from baseline were modeled using a mixed model repeated measures with treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline F2/F3 as a factor and baseline value as a covariate; values were back-transformed from the log scale and percent change = 100*(relative change-1); reported as least-square means (90% CI) for percent change from baseline at Week 48 for all parameters except ELF score, which is presented at Week 50 due to an aberrant Week 48 result for placebo; values with * denote doses that separate from placebo with ≥95% certainty (one-sided).

AE, adverse event; ALT, alanine aminotransferase; ApoC3, apolipoprotein C-III; AST, aspartate aminotransferase; BID, twice daily; C, clesacostat; CI, confidence interval; E, ervogastat; ELF, enhanced liver fibrosis score; F, fibrosis stage; MASH, metabolic dysfunction-associated steatohepatitis; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; N, number of patients randomized and dosed in each treatment group; n, number of patients with event; NASH-CRN, nonalcoholic steatohepatitis clinical research network; VCTE, vibration-controlled transient elastography; VLDL-C, very low-density lipoprotein cholesterol.

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5016 | RESULTS FROM THE 52 WEEK PHASE 2B VOYAGE TRIAL OF VK2809 IN PATIENTS WITH BIOPSY-CONFIRMED NON-ALCOHOLIC STEATOHEPATITIS AND FIBROSIS: A RANDOMIZED, PLACEBO-CONTROLLED TRIAL

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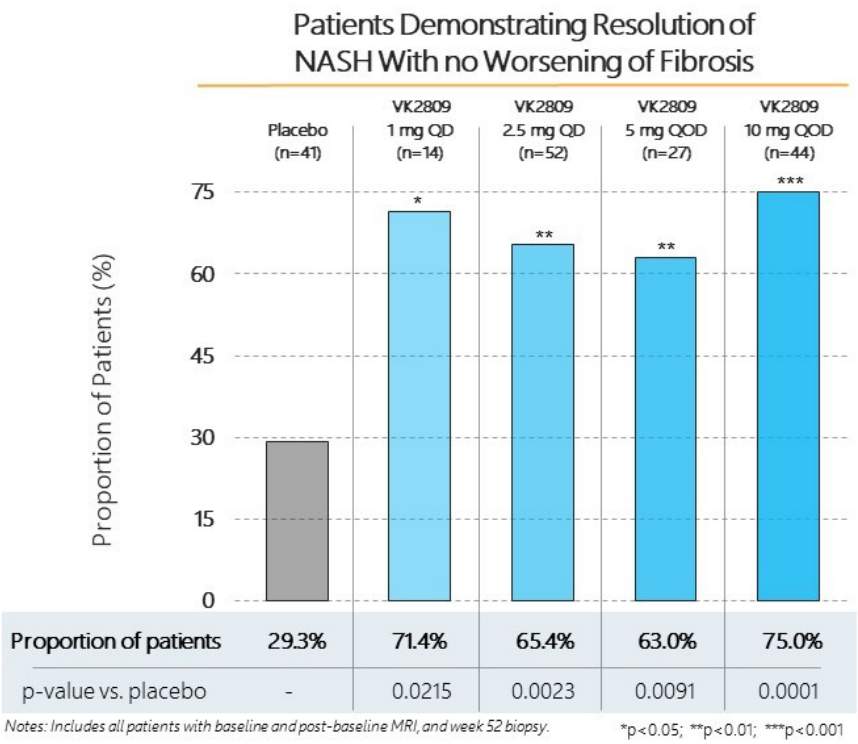
Background: VK2809 is a small molecule prodrug of a potent thyroid beta receptor agonist that is selectively cleaved in hepatic tissue by the action of cytochrome P450 isozyme 3A4, to release a pharmacologically active metabolite. In animal models, VK2809 has demonstrated reductions in cholesterol, liver fat and fibrosis. A prior 12 week Phase 2a study demonstrated mean reductions in hepatic fat of up to 60%, improvement of plasma lipid levels, and encouraging safety and tolerability. We report herein the results from a Phase 2b trial of VK2809 in patients with biopsy-confirmed NASH and fibrosis. The aim of this study was to examine the safety and efficacy of oral VK2809 in reducing NASH and fibrosis following 52 weeks of dosing. **Methods:** This was a multi-center, randomized, double-blind, placebo-controlled, Phase 2b trial to evaluate the efficacy, safety, and tolerability of VK2809 versus placebo in patients with MASH and fibrosis. Patients with biopsy-confirmed steatohepatitis, fibrosis stage 1, 2 or 3, and liver fat content ≥8% by MRI-PDFF were randomized to receive oral VK2809 at doses of 1.0 mg, 2.5 mg, 5.0 mg, 10 mg, or placebo for 52 weeks. **Results:** A total of 178 patients received a baseline and post-baseline MRI, as well as a week 52 liver-biopsy. Patients receiving VK2809 demonstrated statistically significant improvements in NASH resolution, fibrosis, and the combination of both after 52 weeks. NASH resolution ranged from 63% for the 5 mg QoD cohort (p=0.009) to 75% for the 10 mg QoD cohort (p=0.0001), compared to 29% for placebo. The proportion of patients demonstrating a ≥1 point reduction in fibrosis with no worsening of NASH ranged from 44% for the 2.5 mg QD cohort (p=ns) to approximately 57% for the 10 mg QoD cohort (p<0.05) compared with 34% for placebo. The proportion of patients experiencing both resolution of NASH and a ≥1 point reduction in fibrosis was also significantly greater for VK2809 cohorts (44% combined, p<0.01) compared with placebo (19.5%). Approximately 88% of VK2809 treated patients demonstrated ≥30% mean relative reductions in liver fat content, compared with 27% for placebo (p<0.0001). VK2809 was well tolerated over 52 weeks of treatment; drug-related TEAEs were similar among VK2809 treated patients (29%) compared with placebo (34%). After 52 weeks VK2809 treatment also resulted in significant reductions in plasma lipids, including LDL-C, triglycerides, Lp(a), ApoB, and ApoC-III. **Conclusion:** Treatment of biopsy-confirmed NASH with oral VK2809 for 52 weeks resulted in clinically significant improvement in NASH resolution, fibrosis, and the combination of both endpoints. VK2809 appeared to improve not only liver disease risk but also cardiovascular risk in patients with NASH related fibrosis.



Disclosures: Brian Lian: Viking Therapeutics Inc.: Employee, Rohit Loomba: Consultant relationship with Bristol Myers Squibb, Research grant relationship with Merck, Consultant relationship with Terns Pharmaceuticals, Consultant relationship with Theratechnologies and Viking Therapeutics, Stock options relationship with 89bio, Stock options relationship with Sagimet Biosciences, Research grant relationship with Arrowhead Pharmaceuticals, Research grant relationship with AstraZeneca, Co-founder relationship with LipoNexus, Inc., Research grant relationship with Terns Pharmaceuticals, Research grant relationship with Sonic Incytes, Research grant relationship with Pfizer, Research grant relationship with Novo Nordisk, Research grant relationship with NGM Biopharmaceuticals, Consultant relationship with Sagimet Biosciences, Research grant relationship with Madrigal Pharmaceuticals, Research grant relationship with Janssen, Inc., Research grant relationship with Ionis, Research grant relationship with Inventiva, Research grant relationship with Intercept, Research grant relationship with Hanmi, Research grant relationship with Gilead, Research grant relationship with Galmed Pharmaceuticals, Research grant relationship with Galectin Therapeutics, Research grant relationship with Eli Lilly, Research grant relationship with Bristol Myers Squibb, Research grant relationship with Boehringer Ingelheim, Consultant relationship with Inipharma, Consultant relationship with Aardvark Therapeutics, Consultant relationship with AstraZeneca, Consultant relationship with Arrowhead Pharmaceuticals, Consultant relationship with 89bio, Consultant relationship with Amgen, Consultant relationship with CohBar, Consultant relationship with Eli Lilly, Consultant relationship with Galmed Pharmaceuticals, Consultant relationship with Gilead, Consultant relationship with Glympse Bio, Consultant relationship with Hightide, Consultant relationship with Alnylam/Regeneron, Consultant relationship with Intercept, Consultant relationship with Inventiva, Consultant relationship with Ionis, Consultant relationship with Janssen, Inc., Consultant relationship with Altimmune, Consultant relationship with Eli Lilly and Company, Consultant relationship with Madrigal Pharmaceuticals, Consultant relationship with Merck, Metacrine, Inc., Consultant relationship with NGM Biopharmaceuticals, Consultant relationship with Novartis, Consultant relationship with Novo Nordisk, Consultant relationship with Pfizer, Manuel Rodriguez: Gilead Sciences: Speaking and Teaching, Madrigal Pharmaceuticals: Speaking and Teaching, Muhammad Sheikh: Nothing to Disclose, Stephen Harrison: Nothing to Disclose, Madhavi Rudraraju: Nothing to Disclose, Alexander White: Nothing to Disclose, Elizabeth Maley: Nothing to Disclose, Eric Lawitz: Nothing to Disclose, Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting,

Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, William Sanchez: Nothing to Disclose, Joel Neutel: Nothing to Disclose, Carmen Margaritescu: Nothing to Disclose, Summer Ji: Nothing to Disclose, William Hoye: Nothing to Disclose, Geoffrey Barker: Nothing to Disclose, Becky Steele: Nothing to Disclose, Marianne Mancini: Nothing to Disclose

5017 | ONCE-MONTHLY EFIMOSFERMIN ALFA (BOS-580) IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS WITH F2/F3 FIBROSIS: RESULTS FROM A 24 WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 TRIAL

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Background: In a Phase 2a multiple dose/ regimen study[1], efimosfermin alfa (BOS-580), a FGF21 analogue, significantly improved liver steatosis, markers of liver injury and fibrosis in subjects with phenotypic metabolic dysfunction-associated steatohepatitis (MASH). A Phase 2, randomized, double-blind, placebo-controlled study was conducted in subjects with biopsy-confirmed MASH and F2/F3 fibrosis and NAS ≥4. **Methods:** Subjects (N=84) were randomized 1:1 to receive once-monthly efimosfermin 300mg or placebo for 24 weeks. The primary endpoint was safety and tolerability. Exploratory objectives included the proportion of subjects achieving fibrosis improvement ≥1 stage without worsening of MASH, MASH resolution without worsening of fibrosis, ≥2 point improvement in the NAS score, and a composite endpoint of fibrosis improvement ≥1 stage and MASH resolution (NCT04880031). **Results:** Subjects (52.4% female; mean age 54 yrs; mean BMI 37.3 kg/m^2; mean HFF 20.6%) were administered efimosfermin 300mg (n=43), or placebo (n=41). 43% had F3 fibrosis and 57% had type 2 diabetes. In the biopsy analysis set, a significantly higher proportion of subjects treated with efimosfermin 300mg (n=34) achieved improvement in fibrosis without worsening of MASH (45.2% v. 20.6%, p=0.038), and resolution of MASH without worsening of fibrosis (67.7% v. 29.4%, p=0.002) compared to placebo (n=31, Table 1). Additionally, a significantly higher proportion of subjects achieved MASH improvement with ≥2 point improvement in the NAS score without worsening of fibrosis (67.7% v. 20.6%, p<0.001). The proportion of subjects who achieved the composite endpoint of ≥1 stage fibrosis improvement and MASH resolution was 38.7% for efimosfermin 300mg and 17.6% for placebo (p=0.066). In both groups, the most frequent treatment-related adverse events (AEs) were mild to moderate gastrointestinal events of nausea, diarrhea and vomiting. Overall, discontinuations were balanced with only 2 efimosfermin subjects who discontinued due to low-grade AEs. There was only 1 treatment-related grade 3 serious AE. **Conclusion:** Once-monthly efimosfermin significantly improved both regulatory key endpoints including MASH resolution and fibrosis improvement at 24 weeks in subjects with F2/F3 fibrosis due to MASH. In this study, efimosfermin was generally well-tolerated with a low rate of discontinuations due to AEs. These data support further development of once-monthly efimosfermin for the treatment of MASH-related fibrosis.

Table 1: Once-monthly efimosfermin (BOS-580) treatment effects at 24 weeks in biopsy-confirmed MASH with F2/F3 fibrosis

Proportion of subjects, n (%)	Placebo (N=34)	Efimosfermin 300mg (N=31)	p-value (vs placebo)
Fibrosis improvement ≥1 stage without worsening of MASH	7 (20.6%)	14 (45.2%)	0.038
MASH resolution without worsening of fibrosis	10 (29.4%)	21 (67.7%)	0.002
MASH resolution with ≥2 points improvement in the NAS score without worsening of fibrosis	7 (20.6%)	21 (67.7%)	<0.001
NAS score improvement ≥2 points	16 (47.1%)	26 (83.9%)	0.002
Fibrosis improvement ≥1 stage and MASH resolution	6 (17.6%)	12 (38.7%)	0.066
Cochran-Mantel-Haenszel test stratified by baseline fibrosis stage Source data: Biopsy analysis set			

[1]Loomba 2023, JHep Reports (EASL 2023)

Disclosures: Mazen Noureddin: Principal Investigator for a Drug Study relationship with Takeda, Principal Investigator for a Drug Study relationship with Terns, Stock - privately held company relationship with ChronWell, Stock - publicly traded company relationship with Cytodyn, Stock - privately held company relationship with Rivus Pharmaceuticals, Principal Investigator for a Drug Study relationship with Zydus, Principal Investigator for a Drug Study relationship with Viking, Consultant relationship with Cytodyn, Principal Investigator for a Drug Study relationship with BI, Principal Investigator for a Drug Study relationship with BMS, Consultant relationship with Altimmune, Consultant relationship with Alligos, Consultant relationship with AstraZeneca, Consultant relationship with BI, Consultant relationship with Boston Pharmaceuticals, Principal Investigator for a Drug Study relationship with Conatus, Consultant relationship with GSK, Consultant relationship with Eli Lilly, Principal Investigator for a Drug Study relationship with Gilead, Principal Investigator for a Drug Study relationship with Galectin, Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor, Consultant relationship with Merck, Principal Investigator for a Drug Study relationship with GSK, Principal Investigator for a Drug Study relationship with Genfit, Consultant relationship with Madrigal, Kris Kowdley: Boston Scientific: Grant/Research Support, Corcept: Grant/Research Support, CymaBay: Grant/Research Support, Genfit: Grant/Research Support, Gilead: Grant/Research Support, GSK: Grant/Research Support, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Ipsen: Grant/Research Support, Janssen: Grant/Research Support, Madrigal: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordisk: Grant/Research Support, NGM: Grant/Research Support, Pfizer: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Zydus: Grant/Research Support, 89bio Inc: Grant/Research Support, UpToDate: Royalties or patent beneficiary, CymaBay: Consultant, Enanta: Consultant, Genfit: Consultant, Gilead: Consultant, HighTide: Consultant, Inipharm: Consultant, Intercept: Consultant, Ipsen: Consultant, Madrigal: Consultant, Mirum: Consultant, NGM: Consultant, Pliant Therapeutics: Consultant, Pfizer: Consultant, Protagonist: Consultant, Zydus: Consultant, 89bio Inc: Consultant, AbbVie: Payment or honoraria, Gilead: Payment or honoraria, Intercept: Payment or honoraria, US Department of Justice: Payment for expert testimony, CTI: Advisor, Medpace: Advisor, Labcorp: Advisor, Worldwide Clinical Trials: Advisor, Inipharm: Stock - privately held company, Velacur: Received equipment, materials, drugs, medical writing, gifts, Alicia Clawson: Boston Pharmaceuticals: Employee, Tatjana Odrljin: Nothing to Disclose, Matthew Bryant: Boston Pharmaceuticals: Employee, Boston Pharmaceuticals: Stock - privately held company, Boston Pharmaceuticals: Executive role, Brenda Jeglinski: Nothing to Disclose, Margaret Koziel: Nothing to Disclose, Rohit Loomba: Eli Lilly and Company: Consultant, 89bio: Consultant, Aardvark Therapeutics: Consultant, Altimmune: Consultant, Alnylam/Regeneron: Consultant, Amgen: Consultant, Arrowhead Pharmaceuticals: Consultant, AstraZeneca: Consultant, Bristol Myers Squibb: Consultant, CohBar: Consultant, Eli Lilly: Consultant, Galmed Pharmaceuticals: Consultant, Gilead: Consultant, Glympse Bio: Consultant, Hightide: Consultant, Inipharma: Consultant, Intercept: Consultant, Inventiva: Consultant, Ionis: Consultant, Janssen, Inc.: Consultant,

Madrigal Pharmaceuticals: Consultant, Merck, Metacrine, Inc.: Consultant, NGM Biopharmaceuticals: Consultant, Novartis: Consultant, Novo Nordisk: Consultant, Pfizer: Consultant, Sagimet Biosciences: Consultant, Terns Pharmaceuticals: Consultant, Theratechnologies and Viking Therapeutics: Consultant, 89bio: Stock options, Sagimet Biosciences: Stock options, Arrowhead Pharmaceuticals: Research grant, AstraZeneca: Research grant, Boehringer Ingelheim: Research grant, Bristol Myers Squibb: Research grant, Eli Lilly: Research grant, Galectin Therapeutics: Research grant, Galmed Pharmaceuticals: Research grant, Gilead: Research grant, Hanmi: Research grant, Intercept: Research grant, Inventiva: Research grant, Ionis: Research grant, Janssen, Inc.: Research grant, Madrigal Pharmaceuticals: Research grant, Merck: Research grant, NGM Biopharmaceuticals: Research grant, Novo Nordisk: Research grant, Pfizer: Research grant, Sonic Incytes: Research grant, Terns Pharmaceuticals: Research grant, LipoNexus, Inc.: Co-founder

5018 | PHASE 3 ESSENCE TRIAL: SEMAGLUTIDE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)

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Background: Semaglutide, a glucagon-like peptide-1 receptor agonist, is a candidate for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). Semaglutide is being investigated for its potential to treat MASH in the phase 3 ESSENCE trial. **Methods:** ESSENCE, an ongoing multi-center, phase 3 randomized, double-blind, placebo-controlled outcome trial involving 1200 participants with biopsy-defined MASH and fibrosis stage F2/F3, randomized participants 2:1 to once-weekly subcutaneous semaglutide 2.4 mg or placebo for 240 weeks. A planned interim analysis at week 72 of the first 800 participants evaluated the trial's primary endpoints: resolution of steatohepatitis with no worsening of liver fibrosis, and improvement in liver fibrosis with no worsening of steatohepatitis. **Results:** Among the 800 participants (semaglutide [n=534; 169 F2, 365 F3] or placebo [n=266; 81 F2, 185 F3]), mean (standard deviation [SD]) age was 56.0 (11.6) years and body mass index was 34.6 (7.2) kg/m2. Most participants were White (67.5%), female (57.1%) and 55.9% had type 2 diabetes at baseline; 250 (31.3%) participants had F2 and 550 (68.8%) had F3. Resolution of steatohepatitis with no worsening of fibrosis was achieved by 62.9% of participants in the semaglutide group vs 34.1% receiving placebo, with an estimated difference in responder proportions (EDP) of 28.9% (95% CI, 21.3 to 36.5; P<0.0001). Improvement in liver fibrosis with no worsening of steatohepatitis was achieved by 37.0% (semaglutide) and 22.5% (placebo) (EDP, 14.4%; 95% CI, 7.5 to 21.4; P<0.0001), while 32.8% (semaglutide) and 16.2% (placebo) achieved combined resolution of steatohepatitis with improvement in liver fibrosis (EDP, 16.6%; 95% CI, 10.2 to 22.9; P<0.0001). There were improvements in liver enzymes and non-invasive fibrosis markers. As expected, improvements in body weight and cardiometabolic parameters were also observed. The incidence of serious adverse events in the safety analysis set was similar in both arms. **Conclusion:** In participants with MASH and moderate to advanced liver fibrosis, semaglutide 2.4 mg once-weekly demonstrated superiority vs placebo for improvement of histological activity and fibrosis markers, thus meeting both primary endpoints after 72 weeks of treatment. In addition, semaglutide improved MASH injury and fibrosis biomarkers and cardiometabolic features.

Disclosures: Philip Newsome: Consultant: Novo Nordisk, Boehringer Ingelheim, Madrigal, 89Bio, Sagimet, Zydus, Speaking/Teaching: Abbot, Echosens, Eli Lilly, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk (<5K), Pfizer (<5K), 89 Bio (<5K),: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex

(<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Iris Kliers: Nothing to Disclose, Laura Østergaard: Nothing to Disclose, Michelle Long: Novo Nordisk A/S: stock, Mette Kjær: Novo Nordisk A/S: Employee and stock owner, Anna MG Cali: Novo Nordisk: Shareholder, Elisabetta Bugianesi: Nothing to Disclose, Mary Rinella: Consultant relationship with Sagimet, Consultant relationship with Takeda, Consultant relationship with Eli Lilly, Consultant relationship with Novo Nordisk, Consultant relationship with GSK, Consultant relationship with Madrigal, Consultant relationship with Intercept, Consultant relationship with Boehringer Ingelheim, Consultant relationship with 89Bio, Consultant relationship with akero, Consultant relationship with Histoindex, Consultant relationship with Cytodyn, Consultant relationship with Echosens, Michael Roden: Astra Zeneca: Speaking and Teaching, Echosens: Advisor, Boehringer Ingelheim: Grant/Research Support, Madrigal: Speaking and Teaching, MSD: Speaking and Teaching, Lilly: Advisor, Novo Nordisk: Advisor, Vlad Ratziu: Nothing to Disclose

5019 | SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF ECC4703, A HIGHLY SELECTIVE LIVER TARGETING THYROID HORMONE RECEPTOR-BETA (THR-B) FULL AGONIST FOR MASH

Samuel Pak[1] Laurie Butcher[2] Xuefeng Sun[3] Xiaoliang Pan[3] Bo Zhu[3] Haihui Liu[3] Wengang Chen[2] Jianfeng Xu[3] Jingye Zhou[2] Jianfeng Xu[2]

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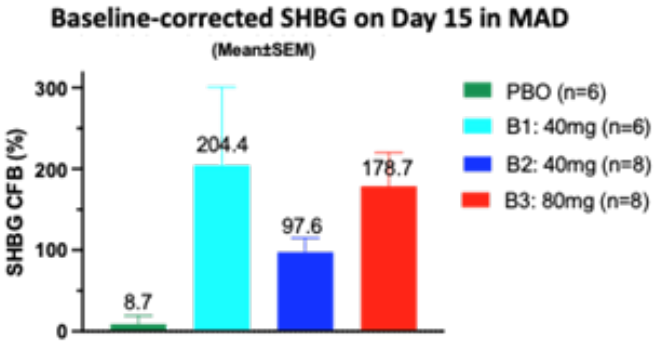
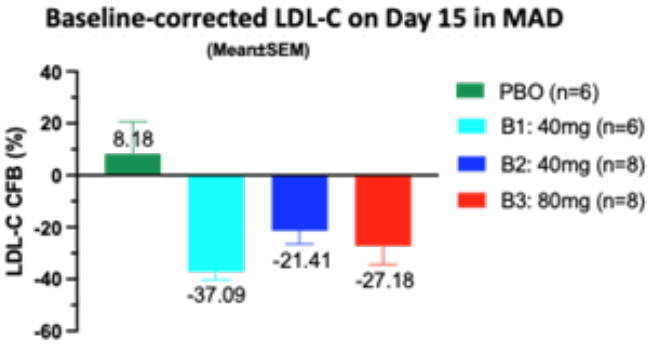
Background: ECC4703, a novel THR-β full agonist developed by Eccogene, has shown superior max agonism compared to Resmetirom in preclinical studies. ECC4703 has also demonstrated robust efficacy in preclinical animal model of MASH. This first-in-human (FIH) study aimed to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of ECC4703. Two MAD cohorts of the studies enrolled subjects with elevated low-density lipoprotein cholesterol (LDL-C) which is a common co-morbidity of MASLD, and LDL-C reduction was evaluated as a key pharmacodynamic endpoint of the study. **Methods:** This study was designed as a randomized, double-blind, placebo-controlled investigation of single ascending doses (SAD) and multiple ascending doses (MAD) of ECC4703. In the SAD phase, a total of 38 healthy participants were randomized (6:2) to receive ECC4703 of 1 mg to 320 mg or placebo. In the MAD phase, a cohort of 8 healthy participants was randomized (6:2) to receive multiple doses of 40 mg of ECC4703 or placebo once daily for 14 days. Subsequently, two cohorts of subjects with elevated LDL-C levels were randomized (8:2) to receive 40 mg or 80 mg of ECC4703 or placebo for 14 days. **Results:** No serious adverse events (SAEs) or deaths were reported during the study. No incidence of diarrhea or pruritis was observed. Overall, ECC4703 was well tolerated across all dose levels in both single and repeat dosing, with no evident trends of dose- related adverse events. The exposures of ECC4703 showed a linear profile in the SAD phase and a geometric mean half-life ranging from 10.7 to 15.8 hours in the MAD phase. Following 14-day repeat doses of ECC4703, there were an approximate 30-45% placebo- corrected reduction in LDL-C and an approximate 89-196% placebo-corrected increase in sex hormone binding globulin (SHBG). Additionally, placebo-corrected reduction in ApoB (23-28%), total cholesterol (12-24%), and triglycerides (14-21%) were observed. **Conclusion:** ECC4703, a differentiated THR-β full agonist, exhibited a favorable safety and tolerability profile in this FIH study. The observed pharmacodynamic biomarker changes indicate clear target engagement. ECC4703 effectively lowered a panel of atherogenic lipids, with significant LDL reduction observed over 14 days of treatment.





Disclosures: Samuel Pak: Nothing to Disclose, Laurie Butcher: Eccogene, Inc: Employee, Xuefeng Sun: Nothing to Disclose, Xiaoliang Pan: Nothing to Disclose, Bo Zhu: Nothing to Disclose, Haihui Liu: Nothing to Disclose, Wengang Chen: Nothing to Disclose, Jianfeng Xu: Eccogene (Shanghai) Co., Ltd.: Employee, Jingye Zhou: Nothing to Disclose, Jianfeng Xu: Nothing to Disclose

5020 | SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF ECC0509, A SSAO INHIBITOR FOR MASH

Jianfeng Xu[1] Angela Rowland[2] Xuefeng Sun[3] Laurie Butcher[1] Xiaoliang Pan[3] Haihui Liu[3] Wengang Chen[1] Jingye Zhou[1] Jianfeng Xu[3]

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Background: ECC0509, a novel peripherally distributed Semicarbazide-sensitive amine oxidase (SSAO) inhibitor, has demonstrated efficacy in preclinical model of MASH. This first-in-human (FIH) study investigated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single ascending doses (SAD) and multiple ascending doses (MAD) of ECC0509 administered orally in healthy participants. **Methods:** It was a randomized, double-blind, placebo-controlled FIH study. A total of 89 healthy participants, 48 participants in SAD and 41 participants in MAD, were randomized (6:2 in SAD; 8:2 in MAD) to receive 6 single doses from 1 mg to 60 mg or placebo, or 4 multiple doses from 3 mg to 60 mg once daily for 14 days in MAD. **Results:** ECC0509 was well tolerated in the study with no death reported. All adverse events (AEs) in SAD and most AEs in MAD were mild in severity. No participants were discontinued due to AEs related to the investigational product (IP). One participant in MAD experienced SAEs within one occurrence, which were determined by the Investigator and sponsor to be unrelated to the IP. PK data showed a linear and dose-proportional increase in exposures with Tmax of 2 to 4 h, and T1/2 of 3 to 4.5 h in both SAD and MAD. Pharmacodynamic data showed a rapid and roughly 90% to 100% decrease in plasma SSAO activity ³3 mg in MAD. Additionally, a dose-dependent increase in plasma methylamine concentration was observed, with the maximal increase at ³30 mg in MAD. **Conclusion:** This FIH study of ECC0509 demonstrated a desirable safety and tolerability profile. Plasma SSAO activity was nearly completely inhibited by low doses of ECC0509, whereas plasma methylamine increased dose-dependently. Overall, these data support the continued development of ECC0509 as a potential oral once-daily therapy for patients with MASH.

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5021 | EFRUXIFERMIN SIGNIFICANTLY REDUCED PROPORTION OF SUBJECTS WITH AT-RISK MASH AND LED TO NEAR-COMPLETE HISTOLOGICAL DISEASE REVERSAL AT WEEK 96 IN THE HARMONY STUDY

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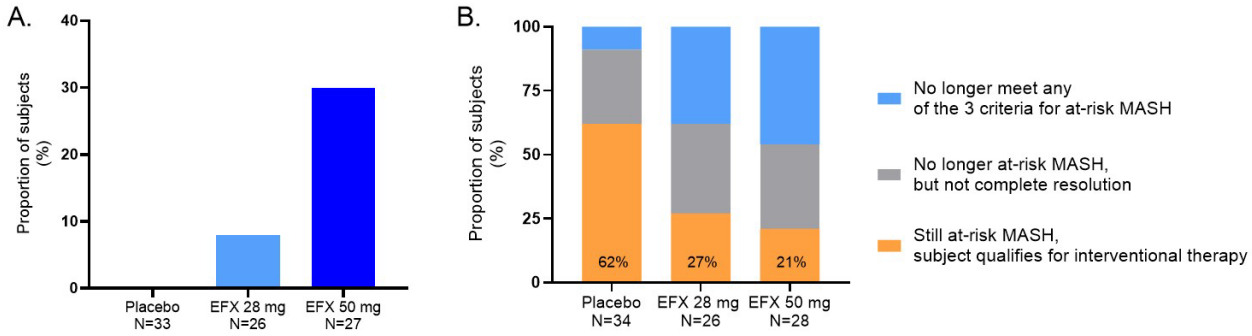
Background: The phase 2b HARMONY study evaluated the efficacy and safety of efruxifermin (EFX) in subjects with metabolic dysfunction-associated steatohepatitis (MASH), fibrosis stage 2 or 3 (F2–F3). After 24 weeks of treatment, a significant proportion of EFX-treated subjects met the primary endpoint of ≥1 stage improvement in fibrosis with no worsening of MASH, with a sustained, expanded, and deepened response after continued treatment to 96 weeks. Here we further characterize the extent of histopathologic response by evaluating multiple stringent composite endpoints which evaluate the extent of disease reversal. **Methods:** Subjects with MASH and F2-F3 fibrosis, all of whom had features consistent with the definition of "at risk of progression" (definite steatohepatitis [≥1 in each component of NAS], NAS ≥4, and fibrosis stage ≥2) were randomly assigned 1:1:1 to receive placebo, EFX 28 mg, or EFX 50 mg once weekly for 96 weeks. Liver biopsies and liver fat content (LFC) by MRI-PDFF were assessed at Baseline, Week 24, and Week 96. Histological changes were characterized by NASH CRN scoring, and by digital pathology using second harmonic generation/two-photon excitation fluorescence (SHG/TPEF) microscopy coupled with artificial intelligence-based quantitation (HistoIndex Pte Ltd). **Results:** A near-complete reversal of disease, evident as MASH resolution, F≤1 and normalization (≤5%) of LFC[1], was observed in 8 of 27 (30%) subjects on EFX 50 mg compared to none for placebo (Fig. 1A). Likewise, almost half, 13 of 28 (46%) subjects on EFX 50 mg resolved all three criteria for at-risk MASH, compared to 3 of 34 subjects (9%) on placebo. Of those treated with placebo, a majority of subjects (21 of 34 [62%]) remained at-risk MASH[1], compared to only 6 of 28 (21%) of those who received EFX 50 mg (Fig. 1B). The extent of reversal of disease was also evident in the deepening of fibrosis response, with a 10-fold higher proportion of EFX-treated subjects than placebo experiencing ≥2 stage-improvement without worsening of MASH that was consistent across fibrosis stages at Baseline. The pattern of histological response based on NASH CRN scoring was corroborated by digital pathology scoring of fibrosis (HistoIndex qFibrosis). [1]Rinella, Mary E.et al AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 77(5):p 1797-1835, May 2023. DOI: 10.1097/HEP.0000000000000323 **Conclusion:** In subjects with F2–F3 fibrosis, 96 weeks of treatment with EFX(the longest duration in MASH trials) resulted in near- complete disease reversal, with fewer subjects remaining classified as having at-risk MASH. This study demonstrates that extended treatment with EFX can significantly improve liver health, positioning efruxifermin as a potential cornerstone therapy for MASH.

Figure 1

A. Proportion of subjects with near-complete reversal of disease, i.e. fibrosis improved to F≤1 **plus** MASH resolution **plus** normalization of hepatic fat (≤5%) at Week 96
B. Extent of disease reversal as indicated by being "at-risk MASH" at Week 96



Data for (A) from subjects with both Baseline and Week 96 liver biopsies and available hepatic fat data; Data of (B) from subjects with both Baseline and Week 96 liver biopsies

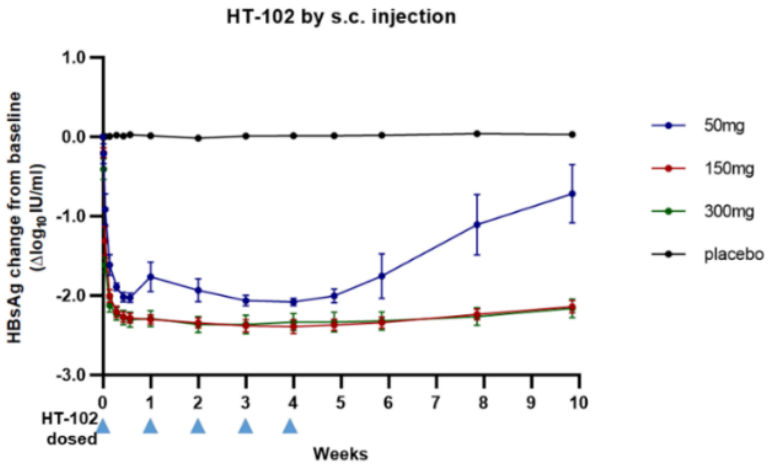
Disclosures: Mazen Noureddin: Principal Investigator for a Drug Study relationship with Takeda, Principal Investigator for a Drug Study relationship with Terns, Stock - privately held company relationship with ChronWell, Stock - publicly traded company relationship with Cytodyn, Stock - privately held company relationship with Rivus Pharmaceuticals, Principal Investigator for a Drug Study relationship with Zydus, Principal Investigator for a Drug Study relationship with Viking, Consultant relationship with Cytodyn, Principal Investigator for a Drug Study relationship with BI, Principal Investigator for a Drug Study relationship with BMS, Consultant relationship with Altimmune, Consultant relationship with Alligos, Consultant relationship with AstraZeneca, Consultant relationship with BI, Consultant relationship with Boston Pharmaceuticals, Principal Investigator for a Drug Study relationship with Conatus, Consultant relationship with GSK, Consultant relationship with Eli Lilly, Principal Investigator for a Drug Study relationship with Gilead, Principal Investigator for a Drug Study relationship with Galectin, Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor, Consultant relationship with Merck, Principal Investigator for a Drug Study relationship with GSK, Principal Investigator for a Drug Study relationship with Genfit, Consultant relationship with Madrigal, Cindy Behling: Pacific Rim Pathology Lab: Employee, Novo Nordisk: Consultant, Pathology Institute: Consultant, boehringer ingleheim: Consultant, akero: Independent Contractor, Pierre Bedossa: Nothing to Disclose, Lan Shao: Nothing to Disclose, Elaine Chng: Nothing to Disclose, Yukti Choudhury: Nothing to Disclose, Dean Tai: Histoindex.com: Employee, Doreen Chan: Akero Therapeutics: Employee, Erica Fong: Akero Therapeutics: Employee, Brittany De Temple: Akero Therapeutics, Inc.: Employee, Matt Minerva: Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Mark Burch: Nothing to Disclose, Kimberly Barrett: Akero Therapeutics, Inc.: Employee, Reshma Shringarpure: Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Erik Tillman: Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Timothy Rolph: Nothing to Disclose, Andrew Cheng: Akero Therapeutics: Employee, Kitty Yale: Akero Therapeutics: Employee, Stephen Harrison: Nothing to Disclose

5022 | RAPID HEPATITIS B SURFACE ANTIGEN DECLINE IN CHRONIC HEPATITIS B VIRUS INFECTION: RESULTS FROM A PHASE IB STUDY EVALUATING MULTIPLE ASCENDING DOSES OF HT-102, A NEUTRALIZING ANTIBODY AGAINST HEPATITIS B SURFACE ANTIGEN IN CHRONIC HEPATITIS B PATIENTS

Dong Shanzhong Wang Zhang[1]

[1]*hepa thera*

Background: HT-102 is a human monoclonal antibody targeting the conserved antigenic loop of hepatitis B surface antigen (HBsAg) with the potential to functions as 1) inhibition of hepatitis B virus (HBV) entry into cells, 2) elimination of virions and sub-viral particles for the treatment of chronic HBV infection. Single dose of HT-102 up to 600 mg were well tolerated in healthy subjects. Here, we reported phase I b data in subjects with chronic HBV infection(ChiCTR2300072837) **Methods:** This was a randomized, double-blind, placebo-controlled, multiple ascending doses study of HT-102 administered via subcutaneous (SC) injection to subjects with chronic HBV infection. The study enrolled subjects who were on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy≥2 months and had HBsAg 200-3000 IU/ml with hepatitis B e antigen (HBeAg) negative at screening. Eligible patients were assigned to 50mg, 150mg, or 300mg group to receive 5 SC HT-102 doses, every week for 4 weeks. Eight subjects per cohort were randomized (6:2) to receive HT-102 or placebo. All patients received NRTI treatment throughout the study. Patients were followed-up to Day 70 after the first HT-102 or placebo dosed. **Results:** Twenty-four subjects were randomized to receive 5 SC doses of HT-102 with 50mg, 150mg, 300mg or placebo. Demographic and baseline characteristics were well balanced across all cohorts. The administration of multiple SC doses of HT-102 for up to 300mg in CHB subjects demonstrated a favourable safety profile and was well tolerated. No subjects dosed HT-102 discontinued due to an adverse event (AE), no serious adverse events (SAE) nor death were reported. All adverse event (AE)s were grade 1 or 2. No subjects developed clinical or laboratory evidence of immune complex disease. All subjects achieved a > 2 log10 IU/mL decline at nadir and rapidly achieved within approximately 1-week post-dose across 3 cohorts. Most subjects (11/12) in 150mg and 300mg group achieved <10 IU/ml and remained at Week10. (Figure). Pharmacokinetic parameters (Cmax and AUC0-last) basically increased with dose escalation both in CHB patients. The mean peak time (Tmax) ranged from 71.08 to 107.98 h and half-life (t1/2) ranged approximately from 10.1 to 16.1 days in CHB patients, both shorter than in HV, which suggestive of target-mediated drug disposition in CHB patients. All samples for ADA test is negative except one sample in 300 mg group tested ADA positive with titer 1.0 at week 10 and negative for further Nab test. **Conclusion:** Multiple doses of HT-102 in 50-300mg were associated with rapid HBsAg reductions in the CHB patients and slight greater HBsAg decline with longer sustained duration was observed in 150mg or 300mg group. HT-102 is generally well tolerated in CHB patients with NRTI with good pharmacokinetics profile. The early data support further evaluation of HT-102 as a potential functional cure for patients with chronic HBV infection.



Disclosures: Dong Shanzhong Wang Zhang: No Relevant Financial Relationships

5023 | DIMENSION ANALYSIS OF EQ-5D IN PATIENTS WITH ACUTE HEPATIC PORPHYRIA CATEGORIZED BY ANNUALIZED ATTACK RATE TO ASSESS ANY RELATIONSHIP WITH SYMPTOMS OCCURRING BETWEEN ATTACK

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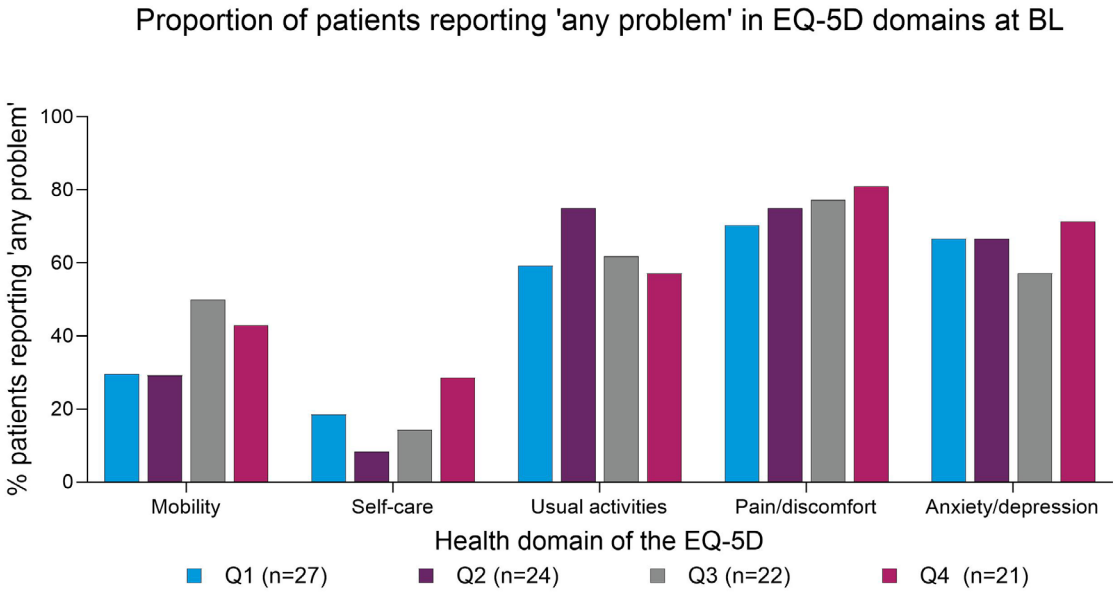
Background: Patients with acute hepatic porphyria (AHP) experience acute attacks, characterized by pain, neurological symptoms, and altered mental status. Although AHP severity is typically measured by attack frequency, it is becoming accepted by the scientific community that patients with AHP also have chronic symptoms that may affect patients between acute attacks. In this analysis, we seek to understand the relationship between the annualized rates of attacks (AAR) requiring hospitalization, urgent care, or intravenous hemin administration, and the burden of symptoms occurring between attacks, as assessed by the EQ-5D survey (which measures the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). **Methods:** In the phase 3 ENVISION trial, patients with AHP aged ≥12 years and with an AAR ≥4 completed the EQ-5D survey to describe their health that day at baseline (BL; assessment period: study day −60 to −1). BL EQ-5D scores were considered a proxy for chronic disevase burden because patients were unlikely to be experiencing an acute attack at/near the time of survey completion. Patients in the givosiran and placebo groups were pooled and categorized into quartiles by historical AAR. The relationship between EQ-5D dimension scores at BL and historical AAR was determined by Spearman correlation coefficients (ρ) and logistic regression. **Results:** Among 94 patients (mean [standard deviation] age 38.8 [11.4] years; 89.4% female), the median (range) historical AAR was 8 (0–46) and 52% of patients reported prior chronic symptoms between attacks. When reporting ‘any problems’, the most frequent dimension was pain/discomfort (75.5%), the least frequent dimension was self-care (17.2%), and the affected distributions for each dimension were generally similar across AAR quartiles (Figure). No correlations were observed between EQ-5D scores and AAR for any dimension (ρ=−0.01 to 0.12). There was no significant difference in the odds of reporting a problem in any EQ-5D dimension between any AAR quartiles. **Conclusion:** These results may suggest that patients with AHP experience chronic symptoms such as pain/discomfort and anxiety/depression that are not associated with attacks or predicted by historical AAR. The chronic impact of AHP should be assessed regularly to guide management decisions. Additional research is needed to characterize disease burden in patients with lower AARs who, to date, have not been included in clinical trials.



BL, baseline; Q, quartile

Disclosures: Susana Monroy-Santoyo: Consultant: Alnylam Pharmaceuticals, AstraZeneca, Recordati Rare Diseases, Stenhal Pharma, Advisor: Alnylam Pharmaceuticals, AstraZeneca, Speaking/Teaching: Alnylam Pharmaceuticals, AstraZeneca, Recordati Rare Diseases, Ultragenyx Pharmaceutical, Stendhal Pharma, Manish Thapar: Alnylam Pharmaceuticals: Consultant, Disc Medicine: Consultant, Mitsubishi Tanabe: Consultant, Recordati Rare Diseases: Consultant, Susana Monroy: ALNYLAM PHARMACEUTICALS: Speaking and Teaching, ASTRA ZENECA: Speaking and Teaching, Weiming Du: Nothing to Disclose, Teresa Kauf: Alnylam, Inc: Employee, Mural Oncology: Stock - publicly traded company, Alkermes, Inc: Stock - publicly traded company, Marianne Sweetser: Alnylam Pharmaceuticals: I am an employee and also own stock/stock options., Jamie Weiss: Alnylam Pharmaceuticals: Stockholder, Alnylam Pharmaceuticals: Employee, Paolo Ventura: Alnylam pharmaceuticals: Advisor, Bruce Wang: Nothing to Disclose

5024 | SAFETY AND EFFICACY OF GST-HG141, A NOVEL HBV CAPSID ASSEMBLY MODULATOR, IN PHASE 2 STUDY FOR TREATMENT OF CHB PATIENTS WITH LOW-LEVEL VIREMIA

Chong Wang[1] Fei Kong[1] Jinlin Hou[2] Guicheng Wu[3] Zhijun Su[4] Zhenguo Liu[5] Bei Zhong[6] Qin Ning[7] Guoqiang Zhang[8] George Zhang[9] John Mao[9] Tianxiang Zhang[9] Wenqiang Wu[9] Wenhao Yan[9] Xiuping Yan[9] Guoping Li[9] Dachuan Cai[10] Haibing Gao[11] YANHANG GAO[1] Junqi Niu[1]

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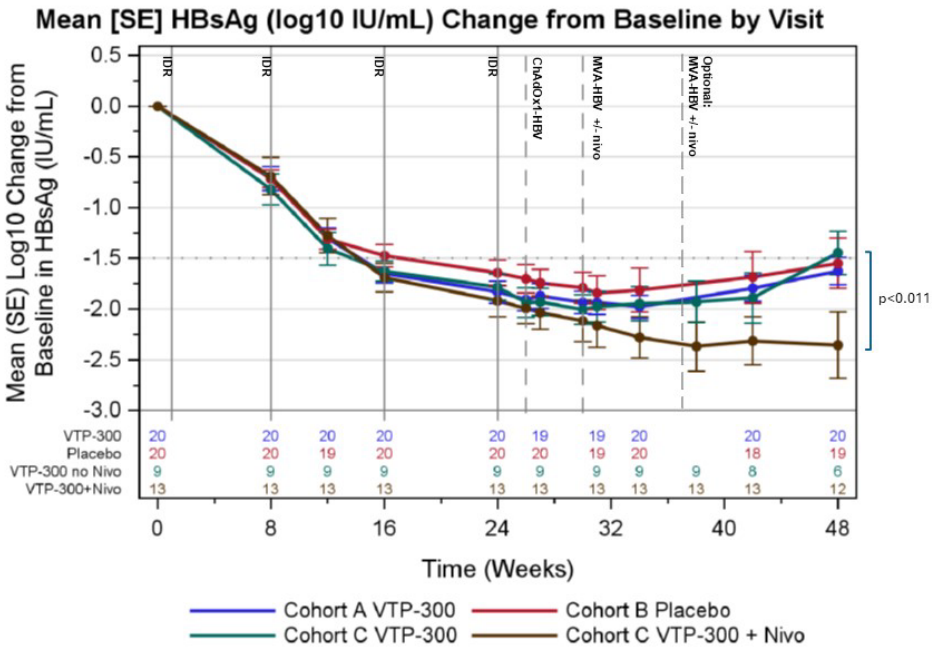
Background: Chronic hepatitis B (CHB) remains a major global health problem despite currently available treatment options such as nucleos(t)ide analogues (NAs) and PEGylated interferons. A significant portion of CHB patients (15-40%) does not respond adequately to NA treatment and suffers from low-level viremia (LLV) after prolonged treatment, which can potentially lead to cirrhosis, liver failure, or hepatocellular carcinoma. Novel therapeutic approaches with different MOAs are urgently needed to combat LLV in CHB patients. GST-HG141 is a novel HBV capsid assembly modulator (CAM) that previously demonstrated excellent safety and anti-viral efficacy in preclinical and Ph1a/1b clinical studies. Here, we report the recent Ph2 data in CHB patients with LLV. **Methods:** The Ph2 study was a double-blind, randomized, placebo-controlled, multi-center trial designed to evaluate efficacy and safety of GST-HG141 in CHB patients with LLV. The study enrolled a total of 90 patients from 10 research centers in China who had been treated with antiviral therapy (NAs) for 1-3 years, and whose serum HBV DNA levels remained between 20 to 2000 IU/mL, with ALT levels ≤5×ULN. Eligible subjects were randomly assigned to 3 groups (30 each): a low-dose GST-HG141 group (50 mg), a high-dose group (100 mg), and a placebo group in a 1:1:1 ratio for a treatment period of 24 weeks. The primary endpoint was the change from baseline in HBV DNA levels at each visit, as well as percentage of patients who achieved HBV DNA seronegativity by the end of treatment. **Results:** GST-HG141 demonstrated strong efficacy in reducing serum HBV DNA levels in CHB patients with LLV. A greater than 80% complete suppression rate was achieved in the treated groups compared to a ~30% suppression rate in the placebo group with continued NAs treatment. GST-HG141 showed a rapid onset of effect in reducing HBV DNA and pgRNA levels, with the maximum effect achieved within 2 weeks of treatment. The efficacy was maintained and stable throughout the study. The reduction in HBV DNA and pgRNA exceeded 1 log, indicating strong suppression of HBV replication and potential depletion of cellular cccDNA levels. GST- HG141 demonstrated good safety and tolerability in the study. **Conclusion:** GST-HG141, administered orally at 50 and 100 mg BID, was safe, well-tolerated, and demonstrated strong efficacy in CHB patients with LLV. These results warrant its further development for treating CHB patients with LLV.



Disclosures: Chong Wang: Nothing to Disclose, Fei Kong: Nothing to Disclose, Jinlin Hou: Nothing to Disclose, Guicheng Wu: Nothing to Disclose, Zhijun Su: Nothing to Disclose, Zhenguo Liu: Nothing to Disclose, Bei Zhong: Nothing to Disclose, Qin Ning: Nothing to Disclose, Guoqiang Zhang: Nothing to Disclose, George Zhang: Nothing to Disclose, John Mao: Nothing to Disclose, Tianxiang Zhang: Nothing to Disclose, Wenqiang Wu: Nothing to Disclose, Wenhao Yan: Nothing to Disclose, Xiuping Yan: Nothing to Disclose, Guoping Li: Nothing to Disclose, Dachuan Cai: Nothing to Disclose, Haibing Gao: Nothing to Disclose, YANHANG GAO: Nothing to Disclose, Junqi Niu: No Relevant Financial Relationships

5025 | PRELIMINARY ANTIVIRAL EFFICACY AND SAFETY OF REPEAT DOSING OF IMDUSIRAN (AB-729) FOLLOWED BY VTP-300 WITH OR WITHOUT NIVOLUMAB IN VIRALLY-SUPPRESSED, NON-CIRRHOTIC SUBJECTS WITH CHRONIC HEPATITIS B (CHB)

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Background: Reaching functional cure of CHB likely requires suppression of viral replication, reduction of HBsAg and stimulation of host HBV-specific immunity. Imdusiran (IDR) is a GalNAc-conjugated single trigger siRNA therapeutic and VTP-300 is an HBV- specific immunotherapeutic consisting of a chimpanzee adenoviral vector (ChAdOx1-HBV) dose followed by a Modified Vaccinia Ankara (MVA-HBV) dose delivering HBV antigens. IM-PROVE II is an ongoing Phase 2a study assessing the safety, pharmacodynamics and immunogenicity of repeat doses of IDR followed by VTP-300 (Group A), placebo (Group B) or VTP-300+/-low dose nivolumab (LDN; Group C) in nucleos(t)ide analogue (NA) suppressed CHB subjects. Results from Groups A and B have been reported previously. Preliminary data up to Week(W)48 from Group C is reported here. **Methods:** CHB subjects in

Group C with HBsAg ≥100 but <5000 IU/mL received 4 doses of IDR 60 mg every 8 weeks. At W26 and 30, VTP-300 was given and in addition, at W30, eligible subjects received LDN 0.3 mg/kg if they did not have risk factors for immune related thyroiditis. Subjects could receive a 2nd MVA-HBV dose+/-LDN at W38 if their HBsAg was >10 IU/mL at W34. Subjects were eligible for NA discontinuation based on W48 data. Safety, HBV parameters and immunology samples were assessed at multiple timepoints. HBsAg was assessed via Diasorin Liaison XL assay (lower limit of quantitation [LLOQ] = 0.05 IU/mL) and results <LLOQ were analyzed by Abbott HBsAg Next Qualitative assay (high sensitivity; cutoff = 0.005 IU/mL). **Results:** Of the 22 subjects in Group C, 68% were male and 91% were Asian. 13 subjects received IDR+VTP-300+LDN and 9 received IDR+VTP-300 alone. Baseline mean HBsAg was 1104.7 IU/mL (IDR+VTP-300 +LDN) and 1295.6 IU/mL (IDR+VTP-300 only). Preliminary mean (SE) HBsAg declines by Group are shown (Figure 1). Subjects receiving IDR+VTP-300+LDN had a significantly greater mean log10 decline of HBsAg at W48 than the other groups (-0.79 [95% CI -1.37, -0.21], p<0.011). At W48, 3 subjects who received IDR+VTP-300+LDN had HBsAg <LLOQ; 2 of the 3 subjects were tested via Next Assay and were negative. Their baseline and W24 HBsAg values were <500 and <3 IU/mL respectively. There have been no Serious Adverse Events (SAEs), Grade 3 or 4 AEs or treatment discontinuations. **Conclusion:** Preliminary data suggest that repeat dosing of IDR followed by VTP-300 and nivolumab was well-tolerated and contributed to deeper HBsAg reductions, w/ 3 subjects reaching HBsAg <LLOQ, compared to VTP-300 alone. Additional on-treatment data will be presented.

Disclosures: Grace Wong: Consultant relationship with AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen, Advisor relationship with GSK, Independent Contractor relationship with Gilead Sciences, Grant/Research Support relationship with Gilead Sciences, Speaking and Teaching relationship with Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi, Advisor relationship with Janssen, Advisor relationship with AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen, Speaking and Teaching relationship with Gilead Sciences, Speaking and Teaching relationship with GSK, Speaking and Teaching relationship with Abbott, Grant/Research Support relationship with Gilead Sciences, Speaking and Teaching relationship with Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi, Advisor relationship with AstraZeneca, Speaking and Teaching relationship with Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche, Advisor relationship with AstraZeneca, Gilead Sciences, GSK and Janssen, Advisor relationship with Gilead Sciences, Speaking and Teaching relationship with AbbVie, Consultant relationship with AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical, Man-Fung Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Has not ended, Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals, Has not ended, Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics, Has not ended, Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc, Has not ended, Consultant relationship with Immunocore, Janssen, Precision BioSciences, Has not ended, Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Has not ended, Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore, Has not ended, Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Has not ended, Consultant relationship with Vir Biotechnology and Visirna Therapeutics, Has not ended, Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics, Has not ended, Grant/Research Support relationship with Sysmex Corporation and Roche, Has not ended, Patrick Kennedy: Nothing to Disclose, Ashley Brown: Nothing to Disclose, Chi-Yi Chen: Nothing to Disclose, Gin-Ho Lo: Nothing to Disclose, Pei-yuan Su: Nothing to Disclose, Sheng-Shun Yang: Nothing to Disclose, Kosh Agarwal: Nothing to Disclose, Deana Antoniello: Nothing to Disclose, Elina Medvedeva: Nothing to Disclose, Emily Thi: Arbutus Biopharma: Employee and holds shares in Arbutus Biopharma, Christine Espiritu: Arbutus Biopharma Corp: Employee, Christina Iott: Nothing to Disclose, Ingrid Graves: Arbutus Biopharma: Employee, Arbutus Biopharma: Stock - publicly traded company, Sharie Ganchua: Arbutus Biopharma Inc.: Employee, Sanjana Kangabam: Nothing to Disclose, Timothy Eley: Arbutus Biopharma: Employee, Arbutus Biopharma: Stock - publicly traded company, Tom Evans: Nothing to Disclose, Bethan Jones: Barinthus Biotherapeutics: Employee, Leon Hooftman: Nothing to Disclose, Mark Anderson: Abbott Laboratories: Employee, Abbott Laboratories: Stock - publicly traded company, Tiffany Fortney: Abbott Laboratories: Employee, Gavin Cloherty: Abbott: Shareholder, Abbott: Head of Infectious Disease Research, Gaston Picchio: Nothing to Disclose, Karen Sims: Arbutus Biopharma: Employee, Arbutus Biopharma: Stock - publicly traded company, Tilly Varughese: Arbutus Biopharma: Employee

5026 | SCG101 TCR-T CELL THERAPY ACHIEVES RAPID AND SUSTAINED HBSAG REDUCTION WITH >40% HBSAG LOSS IN HBV-RELATED HEPATOCELLULAR CARCINOMA PATIENTS

Shunda Du[1] Huichuan Sun[2] Jinlin Hou[3] Xiaowu Huang[2] Jiuwei Cui[4] Nanya Wang[4] Xiujuan Qu[5] Cheng Huang[2] Chongyuan Xu[3] Xueshuai Wan[1] Hongyan Liu[3] Naifei Chen[4] Zan Teng[5] Karin Wisskirchen[6] Xiaorui Wang[6] Ke Zhang[6] Ulrike Protzer[7] Shukui Qin[8] Jia Fan[2]

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Background: SCG101, a first-in-class autologous T cell receptor (TCR)-T cell therapy targeting hepatitis B virus (HBV), utilizes a natural, high-affinity TCR and is being evaluated for its safety and efficacy in patients with HBV-related hepatocellular carcinoma (HCC) in a Phase I investigational new drug (IND) study (NCT06617000). Here, we summarize the antiviral outcomes of the trial. **Methods:** The trial enrolled 12 HLA-A*02:01(+), serum HBsAg(+), and HBV-DNA≤1000 IU/mL patients with advanced HBV-related HCC (BCLC B/C, Child-Pugh≤7, INR≤2, total bilirubin≤2×ULN) who had received ≥ 2 prior systemic anti-cancer therapies, including anti-PD-(L)1. Patients received a single intravenous infusion of SCG101 at $5x10^7$ or $1x10^8$ cells/kg after lymphodepletion. Key outcomes reported here are safety/tolerability and changes in HBV markers. **Results:** Of the 12 patients, 11 were on antiviral treatment before and throughout the study, and all had underlying liver cirrhosis. Baseline liver biopsies from all patients showed no detectable HBcAg, suggesting that a substantial part of HBsAg was derived from integrated HBV-DNA. Following SCG101 infusion, all patients achieved a 1.0~4.6 log10 drop of serum HBsAg within the first month, which persisted below 100 IU/mL for up to 1 year. Five patients (42%) achieved a HBsAg loss. The $1x10^8$ cells/kg group showed a trend of faster HBsAg decline compared with $5x10^7$ cells/kg group. SCG101 was well-tolerated. The most common treatment-related adverse events included elevated liver enzymes, cytokine release syndrome, and cytopenia. One patient experienced a dose-limiting toxicity of grade 3 acute kidney injury, which resolved within 8 days with supportive care. One serious adverse reaction of disseminated intravascular coagulation was reported in 1 patient on day 2 post-infusion, from which the patient recovered within 14 days without sequelae. Transient alanine aminotransferase (ALT) elevations (Grade ≥3 in 9/12 patients, lasting 3~9 days) correlated with HBsAg reduction was observed, suggesting on-target activity. Ten patients had HBV-DNA below LOD at baseline; 8 of them maintained HBV- DNA suppression throughout the study, and 2 exhibited a transient elevation for 2-3 days post-infusion, which may have resulted from the killing of HBV+ hepatocytes and the subsequent release of HBV-DNA-containing capsids and integration fragments. Among the 2 patients with detectable baseline HBV-DNA, one achieved suppression post-infusion, while the other experienced a 0.9log10 increase. **Conclusion:** SCG101 demonstrated a rapid and sustained serum HBsAg reduction in advanced HBV-HCC patients that can be attributed to its cytolytic activity targeting hepatocytes and HCC cells with integrated HBV-DNA. The sustained reduction in HBsAg, along with the >40% HBsAg loss observed in this difficult-to-treat population, demonstrates SCG101's potential to be a curative treatment option for chronic HBV infection.

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5027 | NIS2+® IMPROVES SECONDARY RISK ASSESSMENT FOR REFERRING PATIENTS AT RISK FOR OR WITH ESTABLISHED MASLD TO SPECIALISTS

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Background: With Rezdiffra™ approved in the US for treating patients (pts) with MASH and fibrosis (F) stage 2-3, there is an increased need for an efficient non-invasive clinical pathway to detect and refer pts with MASH eligible for hepatology care. We aimed to assess and compare the performance of NIS2+®, a blood-based test for at-risk MASH (NAS≥4; F≥2) detection, with ELF and VCTE for referring pts with FIB-4 in the intermediate risk zone (IRZ) to specialists. **Methods:** Pts screened for potential inclusion in the RESOLVE-IT phase 3 trial with availability of liver biopsy (LB), FIB-4, and both NIS2+® and ELF if FIB-4 was in IRZ [1.3 if ≤65y or 2.0 if >65y; 2.67] were selected (cohort A, N=3472). Diagnostic performances (AUC, Sen, Spe, PPV, NPV) were derived for at-risk MASH, MASH F2-3 and F≥3. The prognostic performance of NIS2+®, ELF and VCTE was compared in a subcohort of pts (cohort B, N=272) with MASH, NAS≥4, F1-3 and FIB-4 in IRZ at baseline, and an end of treatment LB. Thresholds indicative of pts referral to specialists were: NIS2+® ≥0.68, ELF ≥9.8 and VCTE ≥8kPa. **Results:** In cohort A, 29% of pts had F3, 5% F4. Using FIB-4 in first line, 51% of pts with F3 and 28% of pts with F4 were ruled-out, while only 19% of pts with F3 and 32% of pts with F4 were ruled-in. Among pts with FIB-4 in IRZ (9%, n=690), 65% had at-risk MASH, 62% had MASH F2-3 and 54% had F≥3. In this population, NIS2+® showed a significantly higher AUC than ELF for at-risk MASH (0.80 vs 0.68, p<0.0001) and for MASH F2-3 (0.73 vs 0.60, p<0.0001), but lower than ELF for F≥3 (0.64 vs 0.74, p=0.0001). NIS2+® referred pts with a higher Sen and PPV than ELF for at-risk MASH (Sen: 0.72 vs 0.60, p<0.0001; PPV: 0.83 vs 0.77, p=0.007) and for MASH F2-3 (Sen: 0.69 vs 0.56, p<0.0001; PPV: 0.76 vs 0.69, p=0.0012). In cohort B, mean follow-up was 17 months. As secondary risk assessment, meeting the NIS2+® threshold was significantly correlated with subsequent fibrosis change (p<0.0001), with only 19% NIS2+® positives in pts who improved fibrosis by 2-3 stages to 86% in pts who experienced a 2-stage progression (Fig). Meeting the VCTE threshold showed a smaller but significant (p=0.03) correlation with fibrosis change, while referring pts with ELF did not (p=0.29). **Conclusion:** NIS2+® as a second line test in pts with FIB-4 in the IRZ surpassed ELF and VCTE by accurately targeting pts who could benefit from emerging treatments and/or those with high risk of fibrosis progression. NIS2+® could thus optimize the referral pathway in secondary care.

Fig: Correlation between the proportion of patients meeting the tests' threshold for referral at baseline and the evolution of fibrosis during follow-up (N=272).

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5028 | GOLEXANOLONE DOES NOT REQUIRE DOSE ADJUSTMENT AND IS WELL TOLERATED BY PBC PATIENTS WITH CENTRAL FATIGUE AT PLASMA LEVELS SHOWN TO IMPROVE NEUROPSYCHIATRIC PERFORMANCE IN CLD

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Background: Current PBC therapies (UDCA, FXR & PPAR agonists) reduce risk of disease progression but have no impact on the fatigue and cognitive symptoms which adversely impact quality of life. Neurosteroids such as allopregnanolone (ALLO) have been shown to be elevated in PBC patients with cognitive symptoms. Golexanolone (GOLEX) is a novel oral GABAA receptor-modulating steroid antagonist that shows promise for cognitive and sleep disorders due to neuroinflammation and allosteric over-activation of GABAA receptors by ALLO. It restores cognitive impairment, motor coordination and fatigue in animal models of HE and cholestasis; dose-dependently mitigates sedation and impaired saccadic eye velocity induced by iv ALLO in healthy adults (HAs) and improved measures of cognitive performance, vigilance and sleepiness in C-P A/B cirrhotics with covert HE (CHE). **Methods:** Safety and PK were analyzed in Part A of the ongoing randomized, double-blind, placebo-controlled study of GOLEX in PBC patients. 1 male/7 female subjects with non-cirrhotic or C-P A cirrhotic PBC on stable SoC Rx with clinically significant fatigue and cognitive symptoms by PBC-40 at baseline were randomized to 40 mg GOLEX (n=6) or placebo (n=2) BID for 5 days **Results:** After 5 days' dosing to steady-state, mean exposure in PBC patients assessed as AUCt (h*ng/mL) and Cmax (ng/mL)[CV%] (3654 [CV 12.3%]; 490.7 [CV 26.8%]) was similar to that previously reported in patients with C-P A/B cirrhosis and CHE (3463 [34.1%]; 459.8 [47.9%]) and less than in HAs dosed with 50mg BIDx5 days (5034 [27.3%]; 895.1 [28.0%], respectively). Inter-subject variability in exposure was low (CV 12.3%); mean terminal T1/2 was 12.98 h, mean CLss/F and Vz/F were 10.95 L/h and 205 L, respectively, and geometric mean accumulation ratios for Cmax and AUC from day 1 to day 5 were 0.93 and 1.7, respectively. 40mg BID was well tolerated with generally mild AEs and no SAEs. **Conclusion:** GOLEX dosing in PBC patients sufficient to produce drug levels above those which reverse the brain inhibitory effects of iv ALLO and improve cognitive measures in cirrhotics with CHE appears well tolerated and exhibits predictable PK similar to that in cirrhotics with CHE. This, plus the recent finding that ALLO levels are elevated and associated with cognitive symptom severity in PBC patients, suggest that GOLEX shows promise as a therapeutic for fatigue with cognitive symptoms in patients with PBC and potentially other liver and CNS disorders.

Disclosures: David Jones: Consultant: Ipsen, Advanz, Intercept, GlaxoSmithKline, Stephen Ryder: Nothing to Disclose, Adina Olaru: Nothing to Disclose, Géza Lakner: Nothing to Disclose, Lindsay Crate: Nothing to Disclose, Rachel Scott: Nothing to Disclose, Lakshmi Aneesh: Nothing to Disclose, Rita Danko: Nothing to Disclose, Nikolett Berki: Nothing to Disclose, Istvan Lang: Nothing to Disclose, Mo Christie: Nothing to Disclose, Ivan Dobromyslov: Nothing to Disclose, Dora Burik: Nothing to Disclose, Johan Bylund: Nothing to Disclose, Roberto Camerini: Umecrine Cognition: Consultant, Maria Mansson: Nothing to Disclose, Charlotta Bjork: Umecrine Cognition: Employee, Umecrine Cognition: Consultant, Eva Bredberg: Nothing to Disclose, Anders Karlsson: Nothing to Disclose, Magnus Doverskog: Nothing to Disclose, Bruce Scharschmidt: Umecrine Cognition: Member, Board of Directors, Ocelot Bio: Consultant, Camp4: Advisor, Poseida Therapeutics: Consultant, JCare: Consultant

5029 | POSITIVE CLINICAL AND IMMUNE RESPONSES FOLLOWING A SINGLE DOSE OF VRON-0200: INTERIM RESULTS FROM A PHASE1B STUDY FOR HBV FUNCTIONAL CURE IN CHRONIC HBV-INFECTED PATIENTS

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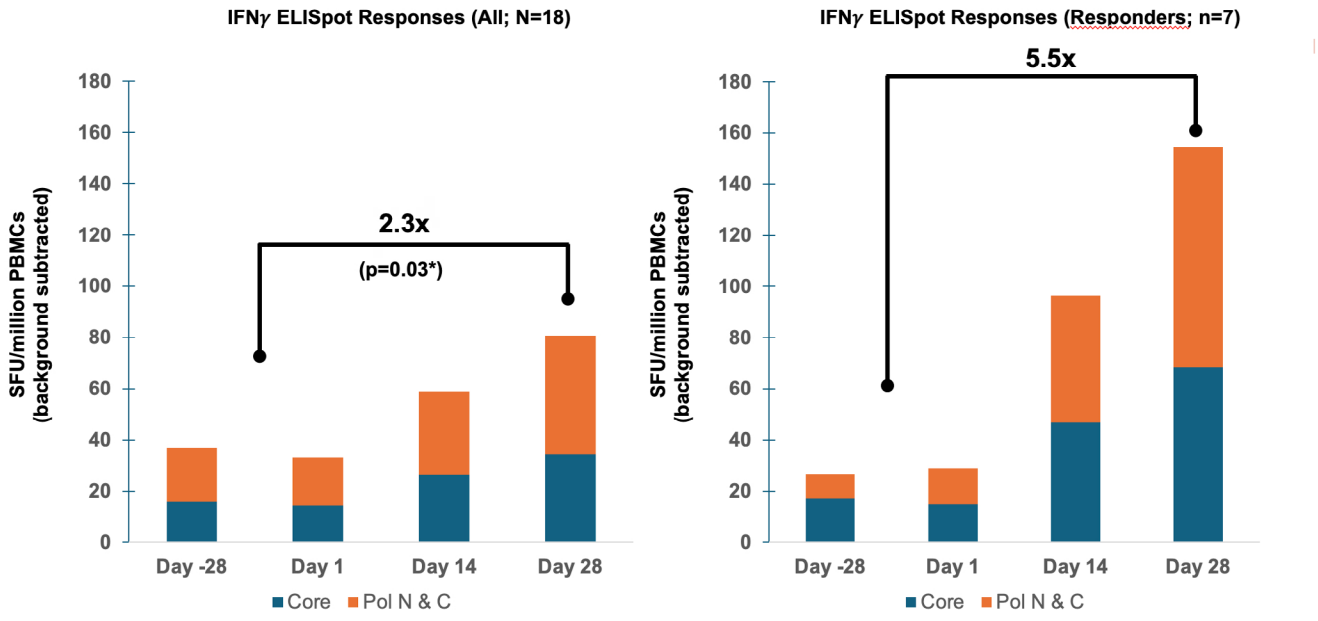
Background: VRON-0200 is a therapeutic vaccine for CHB functional cure that expresses a genetically encoded checkpoint modifier, fused with HBV core and pol (but not S) antigens, designed to enhance, broaden, and prolong $CD8^+$ T cell responses. Here, we report immunogenicity, HBsAg and safety data, in patients (pts) who received a single dose of VRON-0200. **Methods:** CHB, virally suppressed pts, with HBsAg <500IU/mL, are randomized to receive i.m. VRON-0200 $1x10^{10}$vp (Cohort 1) or $5x10^{10}$vp (Cohort 2). Cohort 1a/2a receives a prime, followed by a heterologous boost, on D91; Cohort 1b/2b receives prime only. Assessments include safety, virologic, and immunologic. T cell frequencies are assessed pre-tx (2 timepts) and at multiple post-tx timepts, via IFN-ɣ ELISpot (LLOD<30 SFU/1e6) from PBMCs using 3 peptide pools (core & pol representing the vaccine peptides, and S antigen peptides). Responders are defined as 2 consecutive core plus pol ELISpot values at D28 above the avg of the 2 pre-tx values. A one-sided paired t-test assessed if there was a difference between pre-tx and D28 values. D91 response was defined as pts with a core plus pol ELISpot value above the avg of the 2 pre-tx values. Changes in HBsAg were evaluated in pts with D91 results. **Results:** 18 pts are included, 13 - Cohort 1 and 5 - Cohort 2: 83% male, 83% Asian, mean age, 47yrs, median baseline(BL) HBsAg, 200 IU/mL (range:16–623). As of Sept.6, 2024, there are 3,321 pt safety days, with 18 AEs(14 - Grade 1; 4 - Grade 2) in 10 patients reported, and no SAEs, and no study discontinuations.18 and 11 pts have ELISpot results through D28 and 91, respectively. At BL, the majority of pts (n=11; 61%) had both pre-tx ELISpot values to both core and pol below LLOD. At D28, responses to core and pol significantly increased 2.3-fold (Figure); among responders (n=7; 39%), responses increased 5.5-fold. 8/11 pts (73%) had a response at D91. At D91, 3 pts had -2.2, -0.5, and -0.4log_{10}IU/mL HBsAg declines. **Conclusion:** A single i.m. dose of VRON-0200 was safe, well tolerated, and significantly increased HBV-specific T cell responses. Although VRON-0200 does not target S, HBsAg declines were observed at D91. These data support the continued study of VRON-0200 as a simple, easy-to-administer, IFN-sparing immunotherapy, alone, or in combination, for HBV functional cure. Immunologic, clinical, and safety analyses are ongoing.

Figure: IFNγ ELISpot Responses to a Single IM Dose of VRON-0200



*One-sided paired t-test

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5031 | A MULTICENTER, SINGLE-ARM PROSPECTIVE PHASE 3 STUDY TO EVALUATE SAFETY AND EFFICACY OF GLECAPREVIR/PIBRENTASVIR 8-WEEK TREATMENT IN ADULTS WITH ACUTE HEPATITIS C VIRUS INFECTION

Josep M Llibre[1] Patrick Lank[2] Michael Miller[2] Linda Fredrick[2] Anne Welhaven[2] Dimitri Semizarov[2] John Marcinak[2] Stuart Gordon[3] Juhi Moon[4] Axel Baumgarten[5] Kimberly Workowski[6]

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Background: In the US, the estimated number of acute hepatitis C virus (HCV) infections in 2022 was 67,400, 2× higher than in 2015. For the WHO HCV elimination goal to be achieved, it is critical to link patients with acute HCV to care early to prevent further transmission. Current AASLD and EASL guidelines recommend treating acute HCV without delay. Glecaprevir (GLE)/pibrentasvir (PIB) is currently approved for chronic HCV treatment. This phase 3b single-arm study examined efficacy and safety of GLE/PIB in adults with acute HCV. **Methods:** An 8-week regimen of GLE/PIB was studied in adults with acute/recent HCV infection (Table 1) who had not previously been treated for the current infection. Results based on a data cutoff of July 15, 2024 are presented herein. Efficacy endpoints included the proportion of subjects achieving sustained virologic response at 12 weeks after the last actual study drug dose (SVR12), based on plasma HCV RNA below the lower limit of quantification, in the ITT set of all subjects receiving ≥1 study drug dose (primary endpoint) and in the modified ITT set excluding those who did not achieve SVR12 for reasons other than virologic failure (mITT-VF, key secondary endpoint). Safety endpoints included alanine aminotransferase (ALT) and total bilirubin elevations from baseline during treatment, treatment-emergent (TE) hepatic decompensation, TE serious adverse events (TESAEs), and TEAEs leading to GLE/PIB discontinuation. **Results:** A total of 286 subjects were enrolled and treated (median age, 43.0 years; median HCV RNA, 5.37 log10 IU/mL), 14.0% had a history of illicit injection drug use within 12 months prior to treatment, and 50.0% had HIV co-infection (HIV-1 RNA <20 copies/mL, 84.2%). For subjects with available SVR12 data at the data cutoff, SVR12 was achieved by 96.1% (244/255) and 99.6% (245/246; note: confirmation of reinfection in one subject pending at data cutoff) in the ITT and mITT-VF set, respectively. None of the 286 subjects had ALT >3× upper limit of normal (ULN) that had worsened from baseline, post-nadir ALT >3× ULN + total bilirubin >2× ULN, hepatic decompensation, or a TEAE leading to GLE/PIB discontinuation. TESAEs were experienced by 10 subjects (3.5%), none considered related to GLE/PIB. ALT was normal at the final treatment visit for 95.0% (133/140) of subjects who had baseline ALT >3× ULN. **Conclusion:** Initial results of this study indicate that 8-week treatment with GLE/PIB was safe in subjects with acute HCV infection and resulted in high rates of SVR12.

Table 1. Study Protocol Eligibility Criteria for Acute/Recent HCV Infection	
Physician diagnosis of acute HCV infection	
AND	
Quantifiable HCV RNA at screening	
AND	
At least one of	Negative anti-HCV antibody, HCV RNA, and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 8-month period prior to screening
	Negative anti-HCV antibody, HCV RNA, and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen all within an 11-month period prior to screening AND Risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen
	Clinical signs and symptoms compatible with acute hepatitis (ALT >5×ULN and/or jaundice) in the absence of a history of chronic liver disease or other cause of acute hepatitis and positive HCV RNA or HCV core antigen all within an 8-month period prior to screening AND Risk behavior for HCV infection within 6 months prior to positive HCV RNA or HCV core antigen
	Negative anti-HCV antibody with a positive HCV RNA or HCV core antigen within a 5-month period prior to screening

ALT, alanine aminotransferase; HCV, hepatitis C virus; RNA, ribonucleic acid; ULN, upper limit of normal.

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5032 | HIGHER ATTENDANCE IN COMMUNITY COMPARED TO HOSPITAL SETTINGS FOR TRANSIENT ELASTOGRAPHY IN THE PROSPECTIVE MULTICENTER PRIMARY CARE-BASED PRELUDE-1 STUDY THAT EVALUATES INTEGRATING THE FIB4 SCORE INTO THE TYPE 2 DIABETES ANNUAL REVIEW: AN INTERIM ANALYSIS

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Background: Type 2 diabetes mellitus (T2DM) is an independent risk factor for progressive metabolic dysfunction associated steatotic liver disease (MASLD). Non-invasive tests for fibrosis are used to risk-stratify patients, determine referral to secondary care and increase rates of early detection of advanced liver disease. Guidelines recommend a calculated score (e.g. FIB4) followed by a second-tier test such as vibration controlled transient elastography (VCTE). However, uptake and implementation of guidance remain suboptimal. Possible explanations include unfamiliarity with FIB4 in primary care practices (PCP) or barriers to attendance for VCTE for patients with positive results. PRELUDE-1 is a prospective feasibility and acceptability study that assesses the implementation of a community fibrosis assessment pathway embedded into the NHS Diabetes Annual Review in the United Kingdom. Here we present an interim analysis of the referral and attendance rates for VCTE by location of the scan. **Methods:** In PRELUDE-1, the FIB4 score was included in routine tests taken at T2DM annual review in ten PCPs across London and Bristol that care for 7703 people with type 2 diabetes. Patients with FIB4³1.3 were invited for VCTE either in the community (at their PCP) or in secondary care (hospital scan) depending on which PCP they were based at. Patients with a liver stiffness (LS)³8.0kPa were referred to specialist hepatology outpatient services. Patients with a score <8.0kPa were returned to primary care for advice on lifestyle

and future testing. Fisher's exact test was used to compare community and hospital scanning cohorts. **Results:** In this interim analysis 895 patients with a positive FIB4 had been referred from ten PCPs for VCTE (63.2% male, 36.8% female): 497 patients from community scanning PCPs and 398 patients from hospital scanning PCPs. 383/497 (77%) patients from community scanning PCPs attended for VCTE, compared with 266/398 (66%) patients who were offered a hospital scan ($p<0.01$). Fewer community scanned patients had LS³8.0kPa compared to those scanned in hospital, 24% (91/383) and 32% (84/266) respectively ($p<0.05$). **Conclusion:** Implementation of fibrosis assessment into a primary care-based T2DM Annual Review is feasible in this interim analysis of a prospective, multicenter comparative study. Patients are more likely to attend for elastography if this is offered in a community primary care setting than in a hospital albeit with slightly lower rates of at-risk VCTE scores. Trial registration number: ISRCTN14585543

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5033 | ENTECAVIR PLUS FUZHENG HUAYU COMPOUND REDUCE THE RISK OF PORTAL HYPERTENSION AND DECOMPENSATION IN PATIENTS WITH HEPATITIS B VIRUS-RELATED CIRRHOSIS

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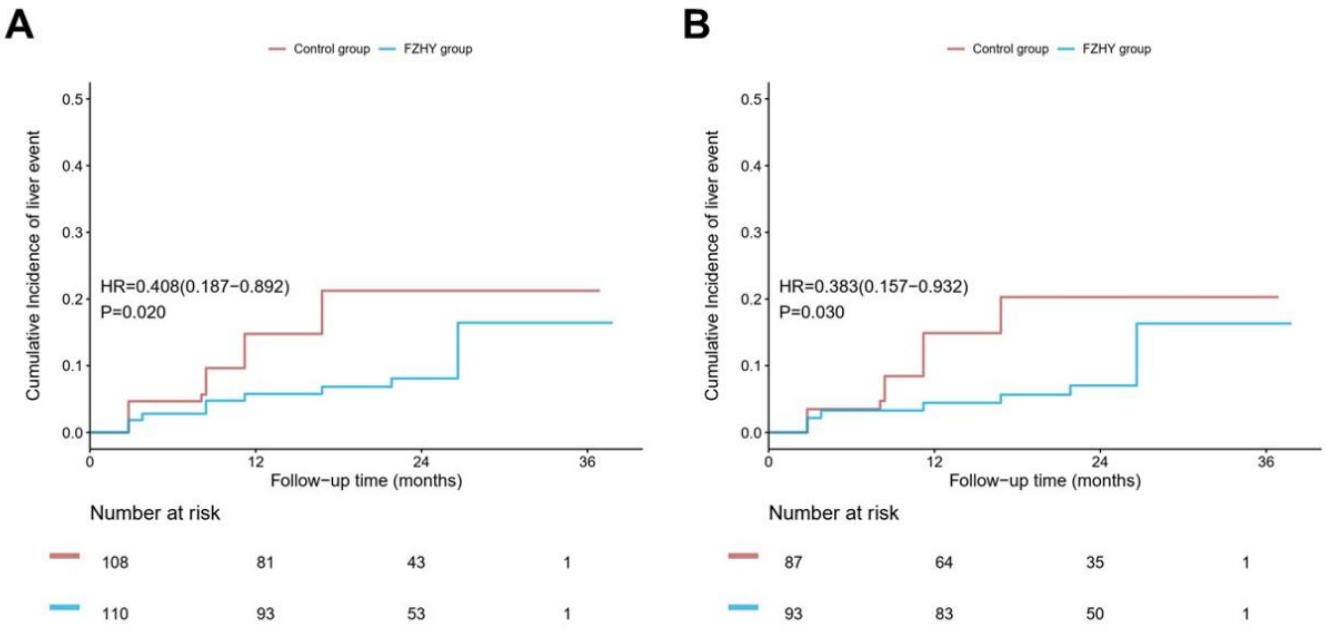
Background: The effect of this non-cardiovascular medication on portal hypertension and the consequent complications needs further investigation. Fuzheng Huayu, a patent herbal product, has shown promise in in vitro, animal, and human studies for liver fibrosis and cirrhosis. This present multicenter prospective study aimed to assess whether Fuzheng Huayu could prevent portal hypertension and decompensation in patients with hepatitis B virus-related cirrhosis. **Methods:** A prospective cohort study with data from two randomized controlled clinical trials (Trial registration number: NCT 02945982; NCT 02945956) was conducted at 7 hospitals in China. Patients with hepatitis B virus-related cirrhosis were enrolled from October 2017 to March 2021. The primary endpoint was a composite of the liver events and the individual components including variceal bleeding, ascites, overt hepatic encephalopathy and hepatocellular carcinoma. **Results:** A total of 218 (Fuzheng Huayu group:110 and control group: 108; mean age, 51.5 years; 66.5% male; median follow-up time, 23.1 months) were included in the primary analysis. The occurrence of liver events was less in the Fuzheng Huayu group than control group for both the full analysis set (HR = 0.408 [0.187-0.892], P = 0.020, Figure 1A) and the per protocol set (HR = 0.383 [0.157-0.932], P = 0.030, Figure 1B]. Among the individual components of liver events, the incidence of ascites was significantly lower in Fuzheng Huayu group than the control group (1.8% vs 9.3%, P = 0.016). While there were no significant differences about the incidences of other complications including variceal bleeding, overt hepatic encephalopathy and hepatocellular carcinoma between the Fuzheng Huayu and control group (4.5% vs 7.4%, P = 0.372; 0% vs 0%, -; 1.8% vs 2.8%, P = 0.636, respectively). In addition, the rate of varices regression was significantly higher in the Fuzheng Huayu group (27.3% vs 10.2%, P = 0.005). **Conclusion:** In patients with hepatitis B virus-related cirrhosis, the Chinese patent medicine Fuzheng Huayu, as an adjunctive therapy to antiviral entecavir and cirrhosis guideline-directed treatments significantly reduced the risk of portal hypertension and decompensation events specifically referring to cirrhotic ascites. Further research is needed to investigate the long-term efficacy and the mechanism of action of this prevention.



Disclosures: Yanan Guo: No Relevant Financial Relationships, Li Du: Nothing to Disclose

5034 | THE INTERIM SAFETY, TOLERABILITY, AND EFFICACY RESULTS OF A PHASE 2A STUDY OF CANOCAPAVIR, A CAPSID ASSEMBLY MODULATOR, FOR THE TREATMENT OF THE ETV-TREATED CHRONIC HEPATITIS B PATIENTS

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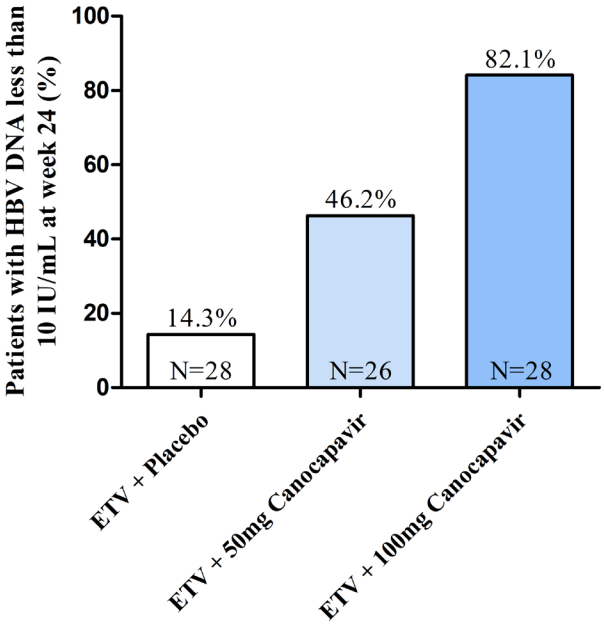
Background: Canocapavir is a hepatitis B virus (HBV) capsid assembly modulator with a novel pyrazole chemical structure. It showed a desired pharmacokinetics and safety profile in Phase 1 study. The Phase 2a study of Canocapavir (NCT05484466) is ongoing to evaluate its safety, tolerability, and efficacy in Entecavir (ETV)-treated chronic hepatitis B (CHB) patients and its interim analysis has been conducted. **Methods:** Non-cirrhotic, ETV-treated CHB patients with HBV DNA levels < 2000 IU/mL but ≥ 50 IU/mL were randomized to 50 mg or 100 mg Canocapavir once daily or matching placebo. Treatment was stratified by hepatitis B e antigen (HBeAg) status. After 48 weeks of treatment, all subjects are set to continue taking ETV as monotherapy for a 12-week follow-up. The primary efficacy endpoint is the percentage of subjects who achieved a complete virologic response (CVR), as measured by a serum HBV DNA level of ≤ 10 IU/mL, at the end of the 24-week. **Results:** 83 subjects have been dosed with one subject excluded from Full Analysis Set due to no valid post-dose efficacy data. The demographic characteristics of 82 subjects (FAS) were median age 40.6 years; male 64.6 %; HBeAg positive 76.8 %. 71 subjects (85.5%) reported a total of 329 TEAEs and 70 TEAEs (21.3%) were considered to be related to Canocapavir/placebo. Most TEAEs were mild (CTCAE 5.0 Grade 1, 226/329, 68.7%) or moderate (CTCAE 5.0 Grade 2, 98/329, 29.8%) in severity. There were 5 SAEs, 2 from the 100 mg cohort and 3 from the placebo, and all SAEs were considered to be not related or unlikely related. No case of ALT flare was observed. At week 24, the percentages of patients with HBV DNA levels ≤ 10 IU/ml were 14.3% (4/28), 46.2% (12/26), and 82.1% (23/28) in the placebo, 50 mg, and 100 mg cohorts, respectively. The 100 mg cohort exhibited the most rapid decline in HBV DNA, attaining CVR with a median of 3.07 weeks. At week 24, a dose-dependent decline in HBV RNA was observed, i.e., the median values of the change from baseline are -0.1139, -1.5247, and -2.4401 Log10 copies/mL for placebo, 50 mg, and 100 mg cohorts, respectively. One patient of 50 mg cohort exhibited HBeAg seroconversion. **Conclusion:** Current results indicate that adjunctive treatment of Canocapavir with ETV was generally well tolerated and effectively reduced HBV DNA to less than 10 IU/mL. Canocapavir enhanced viral suppression when combined with ETV. These findings support the further development of Canocapavir for the treatment of CHB.

Figure: Canocapavir Enhances HBV DNA Suppression In ETV-treated Chronic Hepatitis B Patients



Disclosures: Tian XIA: Nothing to Disclose, Junqi Niu: No Relevant Financial Relationships, Shiffman Yuen: Speaking and Teaching relationship with Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Has not ended, Consultant relationship with Clear B Therapeutics, Dicerna Pharmaceuticals, Has not ended, Consultant relationship with AbbVie, Abbott Diagnotics, Aligos Therapeutics, Has not ended, Consultant relationship with Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc, Has not ended, Consultant relationship with Immunocore, Janssen, Precision BioSciences, Has not ended, Consultant relationship with Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Has not ended, Grant/Research Support relationship with Fujirebio Incorporation, Gilead Sciences, Immunocore, Has not ended, Grant/Research Support relationship with AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Has not ended, Consultant relationship with Vir Biotechnology and Visirna Therapeutics, Has not ended, Consultant relationship with Roche, Sysmex Corporation, Tune Therapeutics, Has not ended, Grant/Research Support relationship with Sysmex Corporation and Roche, Has not ended, Bin He: Nothing to Disclose, Zhihong Lu: Nothing to Disclose, Huanming Chen: Nothing to Disclose

5035 | SAFETY AND PRELIMINARY EFFICACY OF GST-HG131, AN ORALLY BIOAVAILABLE SMALL MOLECULE HBSAG INHIBITOR FOR THE TREATMENT OF CHRONIC HEPATITIS B – PH2 COHORT 1 DATA

Yuming Guo[1] Geore Zhang[2] John Mao[2] Zhe Xu[1] Yuanyuan Li[1] Tianxiang Zhang[2] Yonggang Li[1] Fanping Meng[1] Junliang Fu[1] Xin Zhang[1] Yongqian Cheng[1] Dong Ji[1] Yingjie Ji[1] Wenqiang Wu[3] Wenhao Yan[2] Xiuping Yan[2] Guoping Li[2] Fu-Sheng Wang[1]

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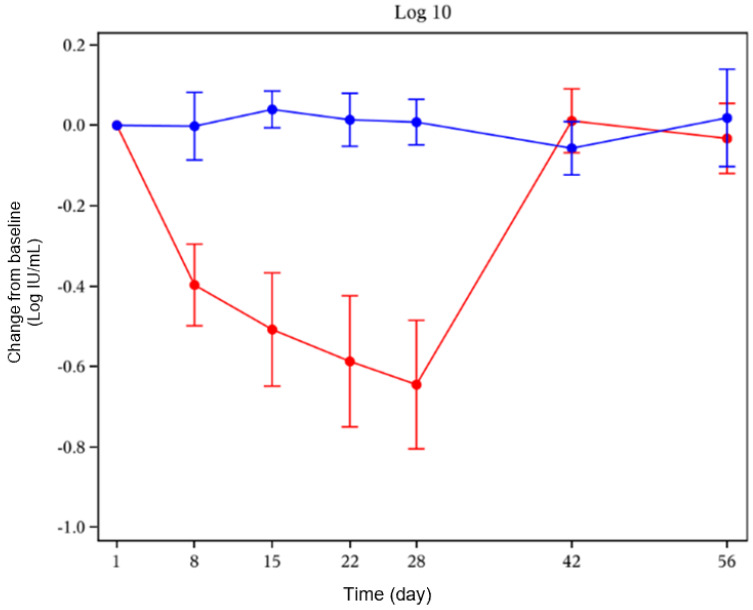
Background: GST-HG131 is a potent and selective HBsAg inhibitor that targets HBV mRNA poly(A) tail assembly and mRNA stability by modulating host PAPD5/7 activities. GST-HG131 has previously demonstrated excellent efficacy and safety in preclinical studies, as well as good safety, tolerability, and pharmacokinetic (PK) profiles in a Phase 1 study in healthy volunteers. Here, we report the unblinded data from the Phase 2 clinical development for the treatment of chronic hepatitis B (CHB). **Methods:** This double-blind, randomized, placebo-controlled,

single-center Phase 2 trial was designed to evaluate the safety and preliminary efficacy of orally administered GST-HG131 in CHB patients, and included three cohorts. Cohorts 1 and 2 each enrolled 10 patients (8 in the treatment group and 2 in the placebo group) for a 28-day treatment period, with doses of 30 mg (Cohort 1) or 60 mg (Cohort 2), administered orally twice daily. Cohort 3 involves a 12-week treatment period at 30 mg BID. Inclusion criteria were CHB patients who had been on nucleos(t)ide analog monotherapy for more than 6 months, with HBsAg levels between 100 and 1,500 IU/mL, and serum ALT levels below 1×ULN. The primary endpoint was the change in serum HBsAg levels and the percentage of patients who achieved HBsAg seronegativity by the end of treatment. **Results:** All eight patients in the treatment group experienced a rapid decrease in HBsAg levels, with the lowest levels observed at visit 7 (day 28) after the final dose. Seven patients showed a significant reduction in HBsAg levels (>50%), with the largest decrease being 1.1 $\log_{10}$ IU/mL. HBsAg levels returned to baseline two weeks after discontinuation of the drug. In the two subjects who received placebo controls, no changes in serum HBsAg levels were observed. Most treatment-emergent adverse events (TEAEs) were classified as CTCAE grade 1 in severity. The incidence of grade 2 TEAEs was 20% (2/10), with no grade 3 or higher TEAEs, no serious adverse events (SAEs), and no adverse events (AEs) leading to dose reduction, drug discontinuation, withdrawal from the study, or death. **Conclusion:** Oral administration of GST-HG131 at 30 mg BID in CHB patients was well-tolerated, with no serious toxicities or safety concerns observed. HBsAg levels decreased rapidly in all treated patients, supporting further development of GST-HG131 as a potential treatment for CHB.

Effect of GST-HG131 on Serum HBsAg Levels in Ph IIa Study



Disclosures: Yuming Guo: No Relevant Financial Relationships, Geore Zhang: Nothing to Disclose, John Mao: Nothing to Disclose, Zhe Xu: Nothing to Disclose, Yuanyuan Li: Nothing to Disclose, Tianxiang Zhang: Nothing to Disclose, Yonggang Li: Nothing to Disclose, Fanping Meng: Nothing to Disclose, Junliang Fu: Nothing to Disclose, Xin Zhang: Nothing to Disclose, Yongqian Cheng: Nothing to Disclose, Dong Ji: Nothing to Disclose, Yingjie Ji: Nothing to Disclose, Wenqiang Wu: Nothing to Disclose, Wenhao Yan: Nothing to Disclose, Xiuping Yan: Nothing to Disclose, Guoping Li: Nothing to Disclose, Fu-Sheng Wang: Nothing to Disclose

5036 | IM-PROVE I: IMDUSIRAN IN COMBINATION WITH SHORT COURSES OF PEGYLATED INTERFERON ALFA-2A IN VIRALLY SUPPRESSED, HBEAG- NEGATIVE SUBJECTS WITH CHRONIC HBV (CHB) INFECTION LEADS TO FUNCTIONAL CURE

Man-Fung Yuen[1] Jeong Heo[2] Ronald Nahass[3] Grace Wong[4] Tatiana Burda[5] Eugene Schiff[6] Tsung-Hui Hu[7] Tuan Nguyen[8] Chi-Yi Chen[9] Young-Suk Lim[10] Stuart Gordon[11] Jacinta Holmes[12] Wan-Long Chuang[13] Naim Alkhouri[14] Anita Kohli[14] Kalyan Ram Bhamidimarri[15] Kevin Gray[16] Emily Thi[16] Elina Medvedeva[16] Timothy Eley[16] Christine Espiritu[16] Sharie Ganchua[16] Christina Iott[16] Mark Anderson[17] Tiffany Fortney[17] Gavin Cloherty[17] Gaston Picchio[16] Karen Sims[16]

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Background: Functional cure (FC, defined as sustained HBV DNA and HBsAg loss 24 weeks after cessation of all treatment) requires suppression of viral replication, reduction of HBsAg and enhancement of HBV-specific immunity. Imdusiran (IDR/AB-729) is a GalNAc-conjugated single trigger siRNA that targets all HBV RNA transcripts including HBx, reduces all viral antigens including HBsAg, and stimulates anti-HBV immunity. Pegylated interferon alfa-2a (IFN) is an approved HBV therapeutic with antiviral and immunomodulatory effects. IM-PROVE I is an ongoing Phase 2a study assessing 24 weeks (W) of IDR to maximally reduce HBsAg followed by 12 or 24 weeks of IFN ± additional IDR doses. All available post-treatment follow-up data through the FC timepoint is presented. **Methods:** Forty-three HBeAg-negative CHB subjects on nucleos(t)ide analogue (NA) therapy received IDR 60 mg every 8W for 24W (4 doses) during the lead-in phase. After W24, subjects were randomized to 1 of 4 cohorts: A1 (24W IFN + 2 IDR doses + NA; N=12), A2 (24W IFN + NA; N=13), B1 (12W IFN + 1 IDR dose + NA; N=8) or B2 (12W IFN + NA; N=10). After completing IFN ± IDR treatment (EOT), subjects continued NA therapy for an additional 24W (24W post-EOT) and then stopped NA therapy per protocol criteria. Safety, antiviral and immunologic assessments were obtained. HBsAg was assessed via Roche Cobas Elecsys HBsAg II assay (lower limit of quantitation [LLOQ] = 0.05 IU/mL) and results ≤LLOQ were analyzed by Abbott HBsAg Next assay (sensitivity cutoff = 0.005 IU/mL). **Results:** Baseline (BL) characteristics and a favorable tolerability profile were described previously. Subjects achieving HBsAg loss (≤LLOQ by Roche assay) are summarized in the Table. In A1/A2 subjects with BL HBsAg <1000 IU/mL, sustained HBsAg loss at W24 post-EOT was 67% (4/6) in A1 and 29% (2/7) in A2. Five of these 6 subjects have reached the FC timepoint; 4 achieved FC and remain anti-HBs positive (18.1 – 72.4 mIU/mL) and Next assay negative, resulting in a FC rate of 40% (2/5) in A1 and 29% (2/7) in A2 in subjects with BL HBsAg <1000 IU/mL. The remaining A1 subject has completed 18W off therapy and remains HBV DNA and HBsAg <LLOQ and anti-HBs positive. One B2 subject also achieved FC and remained Next assay negative at study completion. **Conclusion:** Imdusiran plus 24W of IFN was well tolerated and led to FC in 4 subjects to date, with 1 more subject approaching FC at 18W off all therapy. Subjects with BL HBsAg <1000 IU/mL responded more favorably to the treatment regimens, with FC rates of up to 40%. The additional 2 doses of IDR administered during the 24W IFN treatment may improve FC rates.

Table: HBsAg loss at key timepoints

HBsAg loss (≤0.05 IU/mL)	Cohort A1 N=12	Cohort A2 N=13	Cohort B1 N=8	Cohort B2 N=10
EOT:				
All	4/12 (33%)	3/13 (23%)	0	0
BL HBsAg <1000	4/6 (67%)	2/7 (29%)	0	0
24W post-EOT:				
All	4/12 (33%)	2/13 (15%)	0	0
BL HBsAg <1000	4/6 (67%)	2/7 (29%)	0	0
Functional Cure:				
All	2/11* (18%)	2/13 (15%)	0	1/10 (10%)
BL HBsAg <1000	2/5* (40%)	2/7 (29%)	0	0

BL=baseline; EOT=end of IFN treatment; FC=functional cure; W=week
*1 subject has not reached FC timepoint but has sustained HBV DNA and HBsAg loss at W18

Disclosures: Man-Fung Yuen: Consultant: AbbVie, Abbott Diagnotics, Aligos Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc,Clear B Therapeutics, Dicerna Pharmaceuticals, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Precision BioSciences, Roche, Sysmex Corporation, Tune Therapeutics, Vir Biotechnology and Visirna Therapeutics, Grant/Research Support: AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Fujirebio Incorporation, Gilead Sciences, Immunocore, Sysmex Corporation and Roche, Speaking/Teaching: Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Jeong Heo: Gilead: Grant/Research Support, Roche: Speaking and Teaching, Roche: Speaking and Teaching, Yuhan: Speaking and Teaching, Abbvie: Speaking and Teaching, AstraZeneca: Advisor, Oncolys Japan: Grant/Research Support, Surrozen: Advisor, MedVir: Advisor, Ronald Nahass: Nothing to Disclose, Grace Wong: AstraZeneca: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Janssen: Advisor, GSK: Advisor, GSK: Speaking and Teaching, Abbott: Speaking and Teaching, AbbVie: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen,: Advisor, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, Gilead Sciences: Grant/Research Support, AstraZeneca, Gilead Sciences, GlaxoSmithKline and Janssen: Consultant, Abbott, AbbVie, Ascletis, Bristol-Myers Squibb, Echosens, Gi: Speaking and Teaching, AstraZeneca, Gilead Sciences, GlaxoSmithKline Pharmaceutical: Consultant, Gilead Sciences: Independent Contractor, AstraZeneca, Gilead Sciences, GSK and Janssen,: Advisor, Abbott, AbbVie, BMS, Gilead Sciences, GSK, Janssen, Roche: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Tatiana Burda: Nothing to Disclose, Eugene Schiff: Nothing to Disclose, Tsung-Hui Hu: Nothing to Disclose, Tuan Nguyen: Nothing to Disclose, Chi-Yi Chen: Nothing to Disclose, Young-Suk Lim: Nothing to Disclose, Stuart Gordon: Nothing to Disclose, Jacinta Holmes: Nothing to Disclose, Wan-Long Chuang: Gilead: Speaking and Teaching, AbbVie: Speaking and Teaching, BMS: Speaking and Teaching, Vaccitech: Consultant, PharmaEssentia: Consultant, Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Anita Kohli: Nothing to Disclose, Kalyan Ram Bhamidimarri: orphalan: Advisor, ipsen: Advisor, egenesis: Advisor, mallinckrodt: Advisor, albireo: Advisor, Kevin Gray: Nothing to Disclose, Emily Thi: Arbutus Biopharma: Employee and holds shares in Arbutus Biopharma, Elina Medvedeva: Nothing to Disclose, Timothy Eley: Arbutus Biopharma: Employee, Arbutus Biopharma: Stock - publicly traded company, Christine Espiritu: Arbutus Biopharma Corp: Employee, Sharie Ganchua: Arbutus Biopharma Inc.: Employee, Christina Iott: Nothing to Disclose, Mark Anderson: Abbott Laboratories: Employee, Abbott Laboratories: Stock - publicly traded

company, Tiffany Fortney: Abbott Laboratories: Employee, Gavin Cloherty: Abbott: Shareholder, Abbott: Head of Infectious Disease Research, Gaston Picchio: Nothing to Disclose, Karen Sims: Arbutus Biopharma: Employee, Arbutus Biopharma: Stock - publicly traded company

5037 | ESSENTIAL PHOSPHOLIPIDS EFFICACY IN IMPROVING HEPATIC STEATOSIS IN PATIENTS WITH MASLD ASSOCIATED WITH TYPE 2 DIABETES MELLITUS AND/OR HYPERLIPIDEMIA AND/OR OBESITY – A RANDOMIZED AND CONTROLLED, DOUBLE-BLIND, PHASE IV STUDY

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Background: Metabolic dysfunction-associated steatotic liver disease (MASLD), previously known as non-alcoholic fatty liver disease is associated with comorbidities such as obesity, diabetes, and dyslipidemia and impose an increased risk of cirrhosis, hepatocellular carcinoma, cardiometabolic diseases and extrahepatic cancers. Although essential phospholipids (EPLs) have been shown to be effective for treatment of MASLD, its efficacy when added to standard of care (SoC) was less explored. We evaluated the efficacy and safety of EPLs in patients with MASLD and the associated comorbidities. **Methods:** In this phase IV, multicenter, double-blinded trial, 193 participants were randomized 1:1 to receive either EPLs (Essentiale®) 1800 mg/day (N=82) or placebo (N=83) orally in combination with SoC treatment for 6 months with a follow-up at 3, 6 and 9-month. Participants were eligible if they had steatosis (S1–S3 score) and fibrosis (F1−F3 score), based on transient elastography measurements, and at least one cardiometabolic comorbidity. The primary endpoint was the change in steatosis from baseline to 6 months, measured by controlled attenuation parameter (CAP) score. The secondary endpoint was a change in quality of life [measured by the validated Chronic Liver Disease Questionnaire (CLDQ-MASLD/MASH)]. A mixed-effects model with repeated measures was used for statistical analysis. **Results**: Baseline characteristics of the participants are presented in Table 1. EPLs treatment resulted in a significant reduction in hepatic steatosis (CAP score) from baseline to 6 months compared to placebo (LS mean difference (LSMD) [95%CI]; p-value) (-14.81 [-27.9 to -1.72]; 0.0269). Moreover, a statistically significant reduction in CAP score was reported with EPLs vs placebo treatment at month 3 (-16.11 [- 27.27 to -4.96]; 0.0049) and post-treatment at month 9 (-15.19 [-28.29 to -2.09]; 0.0234). Overall, CLDQ-MASLD/MASH score was numerically improved in EPLs group compared to placebo (LSM: 0.44 vs 0.28; LSMD: 0.17; [p=0.2445]) and CLDQ-MASLD/MASH fatigue subscore improved significantly with EPLs than placebo at month 6 (LSM: 0.58 vs 0.27; LSMD: 0.31; [p=0.0229]). No treatment emergent serious adverse events (SAEs) were reported. **Conclusion:** Treatment with EPLs demonstrated clear superiority in reducing hepatic steatosis compared to placebo in patients with MASLD and associated comorbidities. The significant improvement in steatosis reduction was sustained through 9 months post-treatment, highlight its long-term efficacy when added to SoC. The treatment was well tolerated with no SAEs, making EPLs a promising option for early intervention of MASLD.

Table 1: Baseline disease characteristics according to treatment randomization (mITT population)

	EPLs arm (N=82)	Placebo arm (N=83)
Age (years), Mean (SD)	53.7 (12.13)	52.0 (10.81)
SEX n (%)		
Male	41 (50.0)	49 (59.0)
MASLD, n (%)		
Type 2 diabetes	5 (6.1)	2 (2.4)
Hyperlipidemia	39 (47.6)	40 (48.2)
Obesity (BMI ≥30 kg/m^2)	64 (78.0)	71 (85.5)
BMI category (kg/m^2), n (%)		
Lean (<18.5 to <25)	3 (3.7)	2 (2.4)
Overweight (25 to <30)	15 (18.3)	10 (12.0)
Obese (≥30)	64 (78.0)	71 (85.5)
CAP (dB/m), n (%)		
S0: CAP score is <248	0	0
S1: CAP score is ≥248 and <268	6 (7.3)	6 (7.2)
S2: CAP score is ≥268 and <280	8 (9.8)	9 (10.8)
S3: CAP score is ≥280	68 (82.9)	68 (81.9)
Liver stiffness measurement (kPa), n (%)		
F1: Mild fibrosis (≤7)	50 (61.0)	52 (62.7)
F2: Moderate fibrosis (7.1–8.8)	18 (22.0)	19 (22.9)
F3: Severe fibrosis (8.9–11.6)	7 (8.5)	11 (13.3)
F4: Cirrhosis or advanced fibrosis (>11.6)	7 (8.5)	1 (1.2)

BMI, body mass index; CAP, controlled attenuation parameter; mITT, modified intent-to-treat; MASLD, metabolic dysfunction-associated steatotic liver disease; SD, standard deviation.

Disclosures: Norbert Stefan: Advisor: Eli Lilly, GlaxoSmithKline, Grant/Research Support: Opella, Speaking/ Teaching: Sanofi, Pfizer, AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Eli Lilly, GlaxoSmithKline, Marek Hartleb: Nothing to Disclose, Branko Popovic: Nothing to Disclose, Rafael Varona: Nothing to Disclose, Beatrice Bois-de-Fer: Nothing to Disclose, Guillaume Blanchard: Nothing to Disclose, Münevver Demir: Nothing to Disclose

5038 | VOLIXIBAT FOR CHOLESTATIC PRURITUS IN PRIMARY BILIARY CHOLANGITIS: AN ADAPTIVE, RANDOMIZED, PLACEBO-CONTROLLED PHASE 2B TRIAL (VANTAGE): INTERIM RESULTS

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Background: Cholestatic pruritus (CP) is a debilitating symptom of primary biliary cholangitis (PBC) which greatly impacts overall quality of life. Elevated serum bile acids (sBAs) have been implicated to play a role in CP. Volixibat (VLX) is an ileal bile acid transporter inhibitor (IBATi) which blocks the enterohepatic recirculation of bile acids, leading to reductions in sBA. Here we present the interim analysis (IA) for VANTAGE which evaluated two doses of VLX for efficacy and safety in PBC. **Methods:** VANTAGE is a 28-week randomized, multicenter, double-blind, placebo (PBO)-controlled Phase 2b study in adults with PBC and CP. The study has an adaptive design with a dose selection period with an IA (1:1:1 randomization, VLX 20mg, 80mg or PBO BID) and a pivotal period (1:1 randomization, selected dose or PBO BID), where efficacy and safety of the selected dose will be confirmed. The primary efficacy endpoint is the mean change in Adult ItchRO score (0-10 pruritus scale) from Baseline through Week 28 in participants with moderate-to-severe pruritus. The PBC-40 assessment scale was a key secondary endpoint. The IA was conducted when approximately 12 participants per treatment arm completed Week 16 or prematurely discontinued study drug. **Results:** A total of 30 participants with moderate-to-severe pruritus were randomized (20mg VLX=10; 80mg VLX=10; PBO=10). Mean Baseline ItchRO scores were balanced between groups. Volixibat treatment led to rapid reductions in ItchRO with the VLX combined dose group achieving a statistically significant -3.82-point reduction from Baseline ($p<0.0001$) and a placebo-adjusted response of −2.32 ($p=0.0026$). Each VLX dose achieved statistically significant and similar responses. Overall, 75% of participants who received VLX achieved ≥50% reduction in sBA. The PBC-40 showed numerical improvement in VLX versus PBO with statistically significant improvements in fatigue ($p=0.027$; two-sided t-test). No new safety signals were observed, with a similar incidence of adverse events between VLX treatment groups. The most common adverse event in the VLX groups was diarrhea; all were mild in severity; 1 patient discontinued therapy due to mild diarrhea. **Conclusion:** Volixibat led to early and significant reductions in PBC-associated cholestatic pruritus and

fatigue, with no new safety signals observed. Given similar results between VLX doses, the 20 mg BID dose was selected for Part 2 of VANTAGE, constituting a new promising therapy to address important symptoms in PBC.

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5039 | TOLEROGENIC TREATMENT WITH CNP-104 RESULTS IN REGULATION TH17 CELLS SLOWING PROGRESSION OF PBC ON LIVER STIFFNESS

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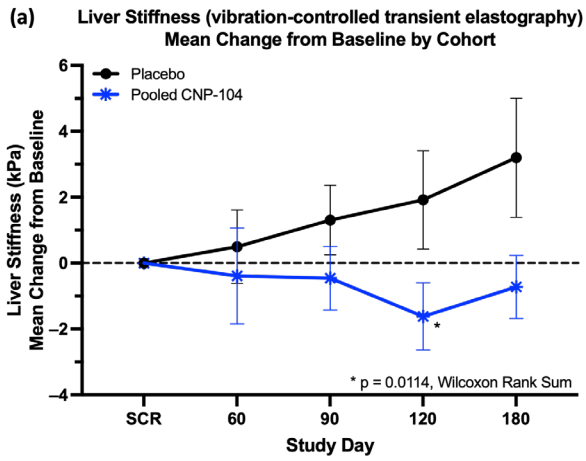
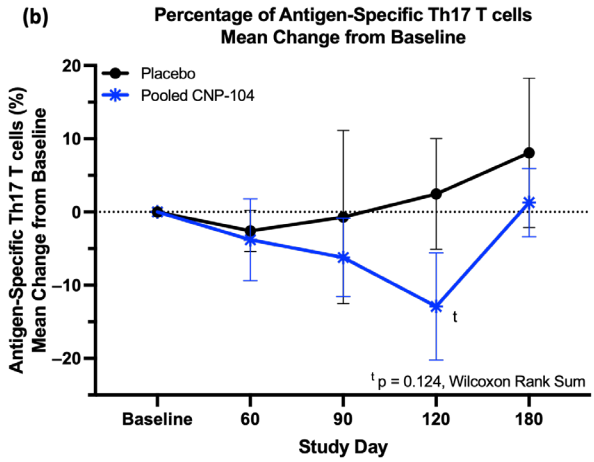
Background: Primary biliary cholangitis (PBC) is an archetypal autoimmune disease in which the E2 subunit of the mitochondrial pyruvate dehydrogenase complex (PDC-E2) is the dominant autoantigen. Evidence suggests that the lipoic acid-containing epitope is essential for loss of tolerance and initiation of biliary disease. Hitherto treatment of PBC has been non-specific and not directed at attempts to restore immune tolerance. CNP-104 is a tolerogenic nanoparticle encapsulating the PDC-E2 antigen which we hypothesize is capable of restoring tolerance in pathogenic T cells. **Methods:** To address the potential role of CNP-104, we conducted a Phase 2a First-in-Human randomized controlled trial in patients with PBC (and an ALP > 1.5 x ULN) after treatment with ursodeoxycholic acid and/or obeticholic acid. Subjects were randomized 2:1 to receive two loading doses of CNP-104 or placebo (PBO) 1 week apart and were followed for 120 days to assess safety and treatment durability. The 42 subjects enrolled, 41 dosed (25 CNP-104; 16 PBO), were largely female (92.9%) with mean baseline ALP of 319 and 338 U/L (CNP-104 or PBO respectively). **Results:** No important safety risks were identified. All 38 drug-related AE in 8 subjects receiving CNP-104 were mild. There were no drug-related SAEs and no deaths. There were no biochemical deviations, on hematology, coagulation, liver, and renal assessments. Subjects receiving CNP-104 had a reduction in the percentage of antigen-specific Th17 T cells compared to PBO at Day 120 (Fig 1A). ALP was not different between groups. But liver stiffness by vibration-controlled transient elastography at Day 120 was statistically significantly different between treatment arms with an increase in the PBO cohort and stability in CNP-104 (Fig 1B). Four subjects consented to a liver biopsy (3 CNP-104; 1 PBO) which suggested a reduction in PanCK+ and CD3–CD4+ cells in CNP-104, markers of ductal pathology. Limitations: This RCT is limited by its small size and data variability. **Conclusion:** CNP-104 had a favorable safety profile with all drug-related treatment-emergent AE being mild. Trending reductions in PBC-relevant T cell populations and corresponding effects on liver stiffness suggest effects on mechanism of action translate to clinical benefits. These data support future studies with this unique therapeutic platform to treat PBC, with focus on dosing and defining subjects likely to respond.



total n	D60	D90	D120	D180
Placebo	13	7	9	7
Pooled CNP-104	17	17	14	12



total n	D60	D90	D120	D180
Placebo	16	16	15	13
Pooled CNP-104	22	24	23	20

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5040 | COMBINATION THERAPY OF LANIFIBRANOR WITH EMPAGLIFLOZIN: METABOLIC IMPROVEMENT IN PATIENTS WITH METABOLIC DYSFUNCTION- ASSOCIATED STEATOHEPATITIS (MASH) AND TYPE-2 DIABETES (T2D)

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Background: The broad disease biology of MASH, from upstream insulin resistance to progressive liver fibrosis, underlies the concept that many patients may benefit from tailored, complementary combination therapy. We compared therapeutic effects of lanifibranor alone and the combination of lanifibranor with an SGLT2 inhibitor versus placebo in the prospective proof-of-concept study LEGEND. **Methods:** The LEGEND trial enrolled 39 patients (33 completers) with MASH and T2D, randomized 1:1:1 to Lanifibranor (L, n=12 patients/12 completers), Lanifibranor with Empagliflozin (L+E, n=13/12) and Placebo (P, n=14/9) for a treatment duration of 24 weeks. MASH was diagnosed per historical liver biopsy or MRI imaging (cT1 or cT1+PDFF). Change in HbA1c from baseline (BL) to end-of-treatment (EOT) was the primary efficacy endpoint. Secondary and exploratory endpoints included liver enzymes, markers of inflammation, fibrosis, lipid and glucose metabolism; MRI-based imaging: hepatic steatosis

(PDFF), MASH composite disease activity and fibrosis (cT1), visceral (VAT) and subcutaneous (SAT) adipose tissue, spleen and liver volumes; vital signs and safety were evaluated. **Results:** Both L and L+E met the primary endpoint of HbA1c improvement versus P (both p<0.001, FAS); 50% in both active arms reached HbA1c < 6.5% at EOT, with 58% and 80% HbA1c decrease ≥1% for L and L+E versus 0% for P, respectively. Liver tests (ALT, AST, GGT), fibrosis markers (TIMP-1, P3NP, Pro-C3), insulin, HOMA-IR, hs-CRP, ferritin, glycemia, lipid profile (HDL-C, Triglycerides) improved with L and L+E treatment, and adiponectin increased by a mean of 3-fold in both L (p=0.009) and L+E (p=0.004) arms compared to no increase for P. Patients had mean weight increase of 3.6% with L at EOT, while mean weight remained unchanged in the L+E and P arms. The ratio VAT/SAT shifted favorably toward SAT for both L and L+E compared to P (-5% and -18% vs +2%, respectively). Significant improvements of hepatic steatosis and composite MASH activity + fibrosis were observed for both L and L+E with mean relative MRI-PDFF changes of -49% (p=0.005) and -41% (p=0.02) and mean absolute cT1 changes of -82 and -85 ms (both p=0.06) respectively. Spleen and liver volumes decreased with L and L+E compared to placebo. L and L+E were safe and well tolerated. **Conclusion:** The combination of lanifibranor with an SGLT2 inhibitor has comparable beneficial effects to Lanifibranor alone on noninvasive hepatic and cardiometabolic markers of MASH, including a shift toward subcutaneous adipose tissue, without observed weight gain. The combination is safe and well tolerated.

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5041 | LONG-TERM EFFICACY AND SAFETY OF ELAFIBRANOR IN PRIMARY BILIARY CHOLANGITIS: INTERIM RESULTS FROM THE OPEN-LABEL EXTENSION OF THE ELATIVE® TRIAL UP TO 3 YEARS

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Background: Elafibranor (ELA) significantly improved biomarkers of cholestasis at Week (W)52 in patients (pts) with primary biliary cholangitis (PBC) in the phase III ELATIVE® trial (NCT04526665). We report up to 3-year interim results from the ongoing ELATIVE® open-label extension (OLE). **Methods:** Pts completing the ELATIVE®

double-blind period (DBP) were eligible to enter the OLE receiving ELA 80 mg daily. For pts who received placebo (PBO) in the DBP, baseline (BL) was set as the last non-missing value before the first OLE ELA dose; for pts who received ELA in the DBP, BL was the DBP start. Endpoints reported include biochemical response (alkaline phosphatase [ALP] <1.67xULN, with ≥15% reduction from BL and total bilirubin [TB] ≤ULN), ALP normalization, change in liver stiffness measurement (LSM) and enhanced liver fibrosis (ELF) score, and change in pruritus (PBC Worst Itch Numeric Rating Scale [WI-NRS], PBC-40 Itch, and 5-D Itch) in those with moderate-to-severe pruritus at BL (PBC WI-NRS ≥4). Results presented descriptively; safety analyses evaluated events in the OLE. **Results:** At data cutoff (June 2024), 153 pts had received ELA; 108 received ELA and 45 received PBO in the DBP. 138 pts entered the OLE. Pts receiving continuous ELA had data up to W156. At BL for each group, pts crossing over from PBO had increased mean ALP and TB vs pts receiving continuous ELA (335.8 U/L vs 321.3 U/L; 0.64 mg/dL vs 0.57 mg/dL). In pts receiving continuous ELA, 34/61 (56%) at W104 and 11/13 (85%) at W156 had biochemical response; ALP normalization occurred in 8/61 (13%) at W104 and 5/13 (39%) at W156. In pts crossing over from PBO, 21/41 (51%) had biochemical response and 9/41 (22%) had ALP normalization at W52. LSM and ELF scores showed a trend for stability in pts receiving continuous ELA for ≥104 weeks (median change from BL in LSM: W104: −0.2 kPa [n=48], W156: −0.5 kPa [n=11]; ELF: W104: 0.0 [n=41], W156: −0.6 [n=9]). Improvement in pruritus was sustained in pts with moderate-to-severe pruritus at BL receiving continuous ELA (mean change from BL in PBC WI-NRS: W104: −3.1 [n=21], W156: −4.4 [n=5]; PBC-40 Itch: W104: −3.0 [n=22], W156: −4.6 [n=5]; 5-D Itch: W104: −5.0 [n=22], W156: −7.0 [n=5]). No new safety signals were identified. **Conclusion:** In the ongoing ELATIVE® OLE, ELA led to sustained improvements in biomarkers of cholestasis and pruritus and stabilization of fibrosis up to W156, and remained well tolerated. Pts crossing over from PBO had similar results at W52 to those who received ELA in the DBP.

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5042 | IMPACT OF ELAFIBRANOR ON FATIGUE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: INTERIM RESULTS FROM THE LONG-TERM OPEN- LABEL EXTENSION OF THE ELATIVE® TRIAL

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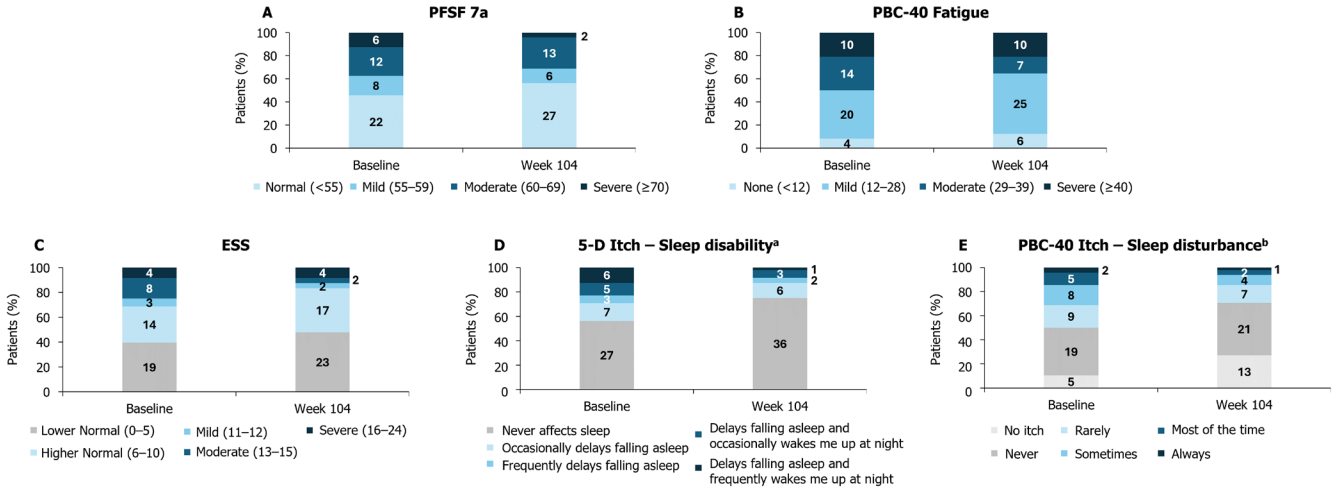
Background: Fatigue is a common symptom in primary biliary cholangitis (PBC); 20% of patients (pts) report significant or life-altering fatigue. Elafibranor (ELA) significantly improved cholestasis biomarkers in pts with PBC in the phase III ELATIVE® trial (NCT04526665). We report long-term data on pt-reported outcomes (PROs) for fatigue and sleep from an interim analysis of the ongoing ELATIVE® open-label extension (OLE). **Methods:** Pts completing the ELATIVE® double-blind period (DBP) were eligible to enter the OLE receiving ELA 80 mg daily. Fatigue and sleep were assessed via the PRO Measurement Information System (PROMIS) Fatigue Short Form 7a (PFSF 7a), PBC-40 Fatigue domain, Epworth Sleepiness Scale (ESS), and sleep questions of the PBC-40 Itch domain and 5-D Itch scale. Pts randomized to ELA in the DBP, without an intercurrent event, without missing data at baseline (BL) and the timepoint of interest were included in the analyses; no pts receiving placebo were included. Changes in fatigue/sleepiness were summarized from BL to Week (W)104 and W130, with respect to available minimal clinically important differences (MCID) and categorical changes. **Results:** At data cutoff (June 2024), 48 pts had data available at BL and W104. At BL, 18/48 (38%) pts had moderate-to-severe fatigue (PFSF 7a total score ≥60). At W104, 10/18 (56%) pts had a ≥3-point (MCID) improvement, with 33/48 (69%) pts describing normal/mild fatigue (Figure). At BL, 24/48 (50%) pts had ≥moderate fatigue according to the PBC-40 Fatigue domain (total score ≥29); 12/24 (50%) had an improvement ≥5 (MCID) and 31/48 (65%) reported none/mild fatigue at W104 (Figure). Excessive daytime sleepiness (ESS total score ≥10) was observed in 16/48 (33%) pts at BL. At W104, 11/16 (69%) pts had a ≥2-point (MCID) improvement, with 40/48 (83%) pts having normal sleepiness. From BL to W104, there was a 50% decrease in pts with moderate-to-severe sleepiness (12 to 6 pts; Figure). For sleep questions of the 5-D Itch scale and PBC-40 Itch domain, 16/48 (33%) and 24/48 (50%) pts, respectively, achieved any improvement from BL to W104; categorical changes are shown in the Figure. Trends were sustained and further improved in the 26 pts with data to W130. **Conclusion:** Long-term treatment with ELA in the ongoing ELATIVE® OLE resulted in clinically meaningful improvements in fatigue and sleep in pts with PBC. These common, debilitating symptoms of PBC have historically been challenging to effectively manage.

Figure. Proportion of patients in different categories of fatigue and sleep PROs at baseline and Week 104



n=48. Data labels inserted in the colour coded bars represent the number of patients in each category. [a]The sleep disability question of the 5-D Itch scale asks patients to rate the impact of their itching on sleep over the last 2 weeks; [b]The Sleep disturbance question of the PBC 40 Itch domain asks patients to rate how often itching disturbed their sleep in the last 4 weeks. PFSF 7a: Patient Reported Outcomes Measurement Information System Fatigue Short Form 7a; PRO: patient-reported outcome; ESS: Epworth Sleepiness Scale; PBC: primary biliary cholangitis.

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5043 | EFFICACY AND SAFETY OF XALNESIRAN IN COMBINATION WITH THE CHECKPOINT INHIBITOR PD-L1 LNA IN VIROLOGICALLY SUPPRESSED PARTICIPANTS WITH CHRONIC HEPATITIS B: RESULTS FROM THE PIRANGA PHASE 2, RANDOMIZED, CONTROLLED, ADAPTIVE, OPEN-LABEL PLATFORM STUDY

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Background: Piranga (NCT04225715) is a phase 2 platform study designed to evaluate the efficacy and safety of finite duration therapies to achieve functional cure in virologically suppressed chronic hepatitis B (CHB) participants (pts). Here, we report the primary endpoint results of xalnesiran (RO7445482), a GalNAc-conjugated small interfering ribonucleic acid (siRNA) targeting HBsAg transcripts, in combination with PD-L1 LNA (RO7191863), a GalNAc-conjugated locked nucleic acid inhibiting the expression of the programmed death-ligand 1. **Methods:** Virologically suppressed CHB pts on nucleos(t)ide analogue (NA) therapy for at least 12 months were randomized to two arms: concurrent or sequential. In both arms, xalnesiran was administered every 4 weeks from week (w)1 to w24. PD-L1 LNA was administered weekly for 12 weeks: either from w13 to w24 (concurrent arm) or from w25 to w36 (sequential arm). NA therapy continued in all pts during the treatment period and until NA stopping criteria were met at the end of treatment (EOT) or during the follow-up period. The primary endpoint was the proportion of pts with HBsAg loss at w24 post-EOT. Secondary endpoints included changes in viral markers and safety. **Results:** A total of 33 and 31 pts were enrolled in the concurrent and sequential arms, respectively. Across both arms, the mean (SD) age was 49.3 (8.6) years and the majority of pts were male (75.0%), Asian (68.8%), and HBeAg-negative at baseline (78.1%). At EOT, HBsAg loss had occurred in 2 (6.1%) and 4 (13.3%) pts in the concurrent and sequential arms, respectively, with no cases of seroconversion. At the primary endpoint, HBsAg loss was sustained in only 2 pts from the sequential arm. All pts with HBsAg loss had a baseline HBsAg < 200 IU/mL. The mean HBsAg reductions in the concurrent and sequential arms were, respectively, 2.12 and 2.08 log10 IU/mL at EOT and 1.30 and 1.46 log10 IU/mL at w24 post-EOT. Adverse events (AEs) were primarily of Grade 1 or 2, with no serious AEs reported. Maximum ALT elevations of DAIDS Grade 2 and 3 were observed in 22 (34.4%) and 3 (4.7%) of all 64 pts, respectively. All ALT elevations were associated with preserved liver synthetic and excretory functions, and resolved without sequelae. **Conclusion:** The combination of xalnesiran with the checkpoint inhibitor PD-L1 LNA, either concurrently or sequentially, achieved limited efficacy on HBsAg loss and its durability. Xalnesiran with PD-L1 LNA was generally safe and well-tolerated.

HBsAg loss and change from baseline in HBsAg in the two treatment arms with xalnesiran and PD-L1 LNA (concurrent and sequential) compared to the NA control arm

Treatment arm (enrolled participants, n)	Concurrent (33)	Sequential (31)	NA control* (36)
xalnesiran† 200 mg SC Q4W **PD-L1 LNA**‡ 2.0 mg/kg SC QW	w1 to w24 w13 to w24	w1 to w24 w25 to w36	N/A N/A
baseline			
mITT participants, n§	33	30	35
HBsAg, mean (SD)	2.90 (0.76)	2.76 (1.11)	2.76 (1.00)
HBsAg, range	1.54, 4.27	-0.43, 4.28	0.12, 4.44
w24 (EOT for concurrent arm)			
n	33	30	34
HBsAg loss, n (%)	2 (6.1%)	2 (6.7%)	0
HBsAg CFB, mean (SD)	-2.12 (0.73)	-1.80 (0.49)	-0.08 (0.16)
HBsAg CFB, range	-3.53, -0.61	-2.61, -0.84	-0.57, 0.14
w36 (EOT for sequential arm)			
n	N/A	30	33
HBsAg loss, n (%)	N/A	4 (13.3%)	0
HBsAg CFB, mean (SD)	N/A	-2.08 (0.63)	-0.08 (0.13)
HBsAg CFB, range	N/A	-3.31, -0.87	-0.59, 0.13
w24 post-EOT			
n	32	30	29
HBsAg loss, n (%)	0	2 (6.7%)	0
HBsAg CFB, mean (SD)	-1.3 (0.70)	-1.46 (0.74)	-0.19 (0.35)
HBsAg CFB, range	-2.79, -0.23	-4.02, -0.35	-1.77, 0.06

CFB: change from baseline; EOT: end of treatment; GalNAc: N-acetylgalactosamine; HBsAg: Hepatitis B s antigen expressed in log_{10} IU/mL; HBsAg loss: HBsAg < 0.05 IU/mL; LNA: Locked Nucleic Acid; mITT: modified intent-to-treat; N/A: Not applicable; NA: nucleos(t)ide analogues; PD-L1: programmed death-ligand 1; Q4W: every 4 weeks; QW: weekly; SC: subcutaneous; SD: standard deviation; siRNA: small interfering ribonucleic acid; w: week

* The NA control arm is the common comparator to all arms in the Piranga platform study. Results from the NA control arm are published in Hou J, *et al*. Efficacy and safety of xalnesiran with and without an immunomodulator in virologically suppressed participants with chronic hepatitis B: end of study results from the phase 2, randomized, controlled, adaptive, open-label platform study (PIRANGA). European Association for the Study of Liver Diseases Meeting 2024, 5-8 June 2024, Milan, Italy. Journal of Hepatology, Volume 80, S26.

† Xalnesiran (RO7445482) is a GalNAc-conjugated siRNA targeting HBsAg transcripts.

‡ PD-L1 LNA (RO7191863) is a GalNAc-conjugated LNA inhibiting PD-L1 expression.

§ All primary and secondary efficacy analyses used the modified intent-to-treat (mITT) population comprising all participants who were randomized and received at least one dose of each drug from the assigned treatment. Participants with missing data were classified as non-responders for the calculation of the HBsAg loss rate.

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Yang: Nothing to Disclose, Edward Gane: Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Precision Bio: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, GSK: Advisor, Gemma Attley: Hoffmann-La Roche Inc: Employee, Maria Teresa Catanese: Nothing to Disclose, Farouk Chughlay: Roche: Employee, Anna Maria Geretti: Roche Pharma: Previous employee (2017-2023), Gregory Hooper: Roche Products Limited: Employee, Rémi Kazma: Hoffmann - La Roche: Employee, Hoffmann - La Roche: Stock - publicly traded company, Novartis: Stock - publicly traded company, Alcon: Stock - publicly traded company, Sandoz: Stock - publicly traded company, Yukun Liang: Nothing to Disclose, Sijie Lu: Nothing to Disclose, Ruchi Upmanyu: Roche: Employee, Yun Xu: Nothing to Disclose, Wen Zhang: Nothing to Disclose, Man-Fung Yuen: Consultant: AbbVie, Abbott Diagnotics, Aligos Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc,Clear B Therapeutics, Dicerna Pharmaceuticals, Fujirebio Incorporation, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Precision BioSciences, Roche, Sysmex Corporation, Tune Therapeutics, Vir Biotechnology and Visirna Therapeutics, Grant/Research Support: AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Fujirebio Incorporation, Gilead Sciences, Immunocore, Sysmex Corporation and Roche, Speaking/Teaching: Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp

5044 | LONG-TERM EFFICACY AND SAFETY OF OPEN-LABEL SELADELPAR TREATMENT IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: POOLED INTERIM RESULTS FOR UP TO 3 YEARS FROM THE ASSURE STUDY

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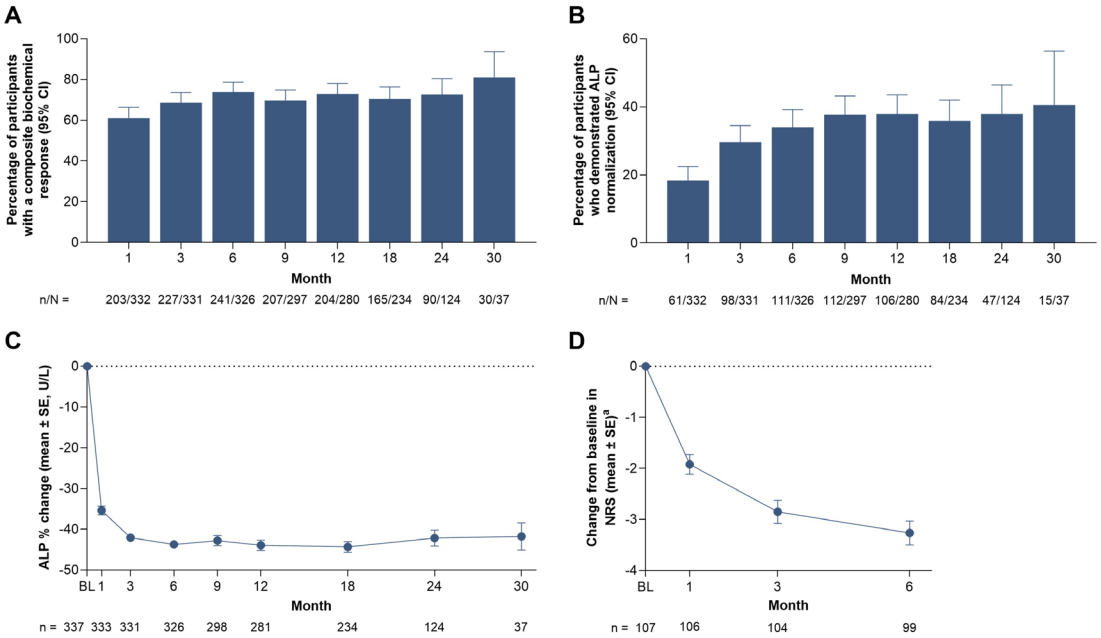
Background: ASSURE (NCT03301506) is an ongoing, open-label, long-term, Phase 3 trial of seladelpar—a novel delpar (selective PPARδ agonist)—in patients (pts) with primary biliary cholangitis rolling over from the Phase 3, placebo-controlled, registrational RESPONSE trial (NCT04620733) or with prior participation in legacy trials (Phase 3 ENHANCE [NCT03602560], CB8025-21629 [NCT02955602], CB8025-31731 [NCT03301506], CB8025-21838 [NCT04950764]). The parent studies required an inadequate response or intolerance to first-line ursodeoxycholic acid. Here, we report pooled interim efficacy and safety for all pts in ASSURE. **Methods:** Using a data cutoff of January 31, 2024, pt exposure to seladelpar in ASSURE (including exposure in pts who were randomized to the active treatment arm in RESPONSE) was analyzed. Key efficacy endpoints included composite biochemical response (CBR; alkaline phosphatase [ALP] <1.67× upper limit of normal [ULN], ALP decrease ≥15%, and total bilirubin [TB] ≤ULN) and ALP normalization. Pruritus was recorded using a numeric rating scale (NRS; 0–10) collected daily through month (M) 6; change from baseline (BL) was assessed through M6 in pts with moderate-to-severe pruritus (NRS ≥4) at BL. Exposure-adjusted adverse events (AEs) were calculated for each year on study as incidence per 100 pt-years. BL was based on first exposure to seladelpar in ASSURE or RESPONSE. **Results:** 337 pts received 10-mg seladelpar daily. 34 pts reached 30M on study; 90 pts had ≥24M of seladelpar exposure. At BL, the mean (SD) age was 58.1 (9.7) years, 318/337 (94%) pts were female, mean (SD) ALP was 287.5 (128.4) U/L, mean (SD) TB was 0.75 (0.34) mg/dL, and 55/337 (16%) had cirrhosis. At M12, M24, and M30, 204/280 evaluable pts (73%), 90/124 (73%), and 30/37 (81%) met the CBR endpoint, respectively, and ALP normalized in 106/280 (38%), 47/124 (38%), and 15/37 (41%) pts, respectively. In the pruritus NRS, mean (SE) change from BL at 6M was −3.3 (0.24) among 99 evaluable pts. Outcomes are in Figure 1. Exposure-adjusted AEs were observed in 86, 70, and 63 pts per 100 pt-years at M12, M24, and M36, respectively. There were no treatment-related serious AEs. **Conclusion:** By M30 of the long-term ASSURE study, seladelpar resulted in a durable and sustained biochemical response in 81% of pts, with an ALP normalization rate of 41%, and robust improvement in pruritus. Seladelpar continues to appear safe and well tolerated, with no new safety signals or change in frequency of AEs with up to 3 years of exposure.

Figure 1. (A) Composite Biochemical Response Rate Through Month 30, **(B)** ALP Normalization Through Month 30, **(C)** ALP Percentage Change From BL Through Month 30, and **(D)** Pruritus NRS Change From BL Through Month 6



Data cutoff: January 31, 2024.
ALP, alkaline phosphatase; BL, baseline; NRS, numeric rating scale.
[a]The pruritus NRS ranged from 0 (no itch) to 10 (worst itch imaginable).

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relationship with Pliant Therapeutics, Has not ended, Grant/Research Support relationship with Gilead, Has not ended, Grant/Research Support relationship with Calliditas, Has not ended, Grant/Research Support relationship with GSK Pharmaceuticals, Has not ended, Consultant relationship with GSK Pharmaceuticals, Has not ended, Consultant relationship with Pliant Therapeutics, Has not ended, Maria Carlota Londono: Advanz: Consultant, Advanz: Speaking and Teaching, Ipsen: Consultant, GSK: Consultant, Cymabay: Speaking and Teaching, Gideon Consultant relationship with Mirum, Has not ended, Consultant relationship with Advanz, Has not ended, Consultant relationship with Chemomab, Has not ended, Consultant relationship with Gilead, Has not ended, Consultant relationship with Kowa, Has not ended, Consultant relationship with Intercept, Has not ended, Consultant relationship with Pliant, Has not ended, Consultant relationship with Falk, Has not ended, Consultant relationship with GSK, Has not ended, Consultant relationship with Ipsen, Has not ended, Consultant relationship with CymaBay, Has not ended, Aliya Gulamhusein: Advanz: Consultant, Cymabay: Consultant, Daria Crittenden: Gilead Sciences, Inc: Employee, CymaBay Therapeutics, Inc.: Employee, Shuqiong Zhuo: Nothing to Disclose, Carrie Heusner: Nothing to Disclose, Cynthia Levy: Consultant relationship with Cymabay, Has ended, Advisor relationship with COur, Has ended, Grant/Research Support relationship with GSK, Has not ended, Grant/Research Support relationship with Ipsen, Has not ended, Consultant relationship with Ipsen, Has ended, Grant/Research Support relationship with Mirum, Has not ended, Consultant relationship with Mirum, Has ended, Grant/Research Support relationship with Zydus, Has not ended, Grant/Research Support relationship with Gilead, Has not ended, Consultant relationship with Gilead, Has ended, Grant/Research Support relationship with Escient, Has not ended, Grant/Research Support relationship with Kowa, Has not ended, Consultant relationship with Kowa, Has ended, Grant/Research Support relationship with Genfit, Has ended, Consultant relationship with Chemomab, Has ended, Consultant relationship with GSK, Has ended, Consultant relationship with Calliditas, Has ended, Grant/Research Support relationship with Calliditas, Has not ended, Consultant relationship with Intercept, Has ended, Grant/Research Support relationship with Cymabay, Has not ended, Grant/Research Support relationship with Intercept, Has not ended

5045 | SUSTAINED, LONG-TERM EFFICACY AND SAFETY OF ODEVIXIBAT IN PATIENTS WITH PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS: RESULTS FROM THE PEDFIC2 PHASE 3, OPEN-LABEL EXTENSION STUDY

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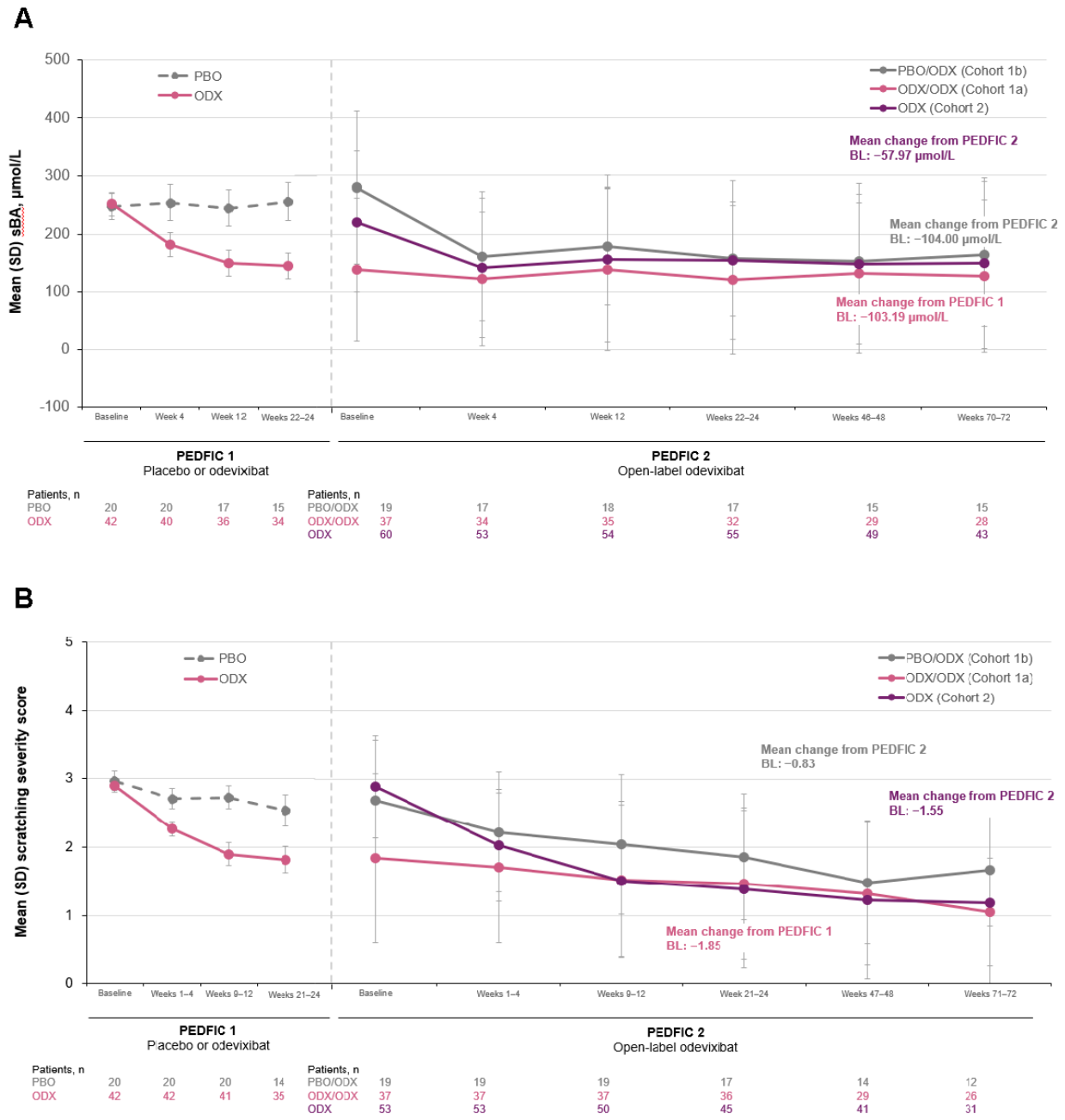
Background: Odevixibat (ODX) effectively reduced serum bile acids (sBA) and pruritus and was well tolerated vs placebo (PBO) in patients with progressive familial intrahepatic cholestasis (PFIC) in PEDFIC 1 (NCT03566238), a 24-week, randomized, double-blind, placebo-controlled, phase 3 study. PEDFIC 2 (NCT03659916) was an open-label, phase 3 extension study; we present data from the longest follow-up with ODX to date. **Methods:** PEDFIC 2 enrolled patients with PFIC 1/2 who completed PEDFIC 1 with ODX (Cohort 1a) or PBO (Cohort 1b), or from an additional cohort (Cohort 2; any age and PFIC subtype). All patients received 120 µg/kg/day ODX. Primary endpoints: change from baseline (BL) in sBAs and positive pruritus assessments (PPAs) at week 72. **Results:** 116 patients received ODX in PEDFIC 2: 37 in Cohort 1a (ODX/ODX), 19 in Cohort 1b (PBO[MS1] [SW2] /ODX), and 60 in Cohort 2. Median age was 3.7 years (range, 0.3–26.0); 56% of patients had PFIC2 (BSEP deficiency), 31% PFIC1 (FIC-1 deficiency), 6% PFIC3 (MDR3 deficiency), 3% PFIC 4/6 (TJP2/MYO5B deficiency), and 3% episodic PFIC. 83/116 (72%) patients completed 72- weeks' treatment, with 61 (53%) having received ≥96 weeks (median treatment duration: 98.9 weeks [range, 4.3–248.7]). For all cohorts, sBA levels and pruritus reduced rapidly at ODX initiation, with improvements sustained for patients who remained on ODX (Fig). Frequency of patients with PPA[MS3] [SW4] s was 55% in Cohort 1 and 77% in Cohort 2 at week 72. 11 patients with PFIC other than PFIC1/2 showed high rates of sBA (91%) and pruritus (90%) response at week 72; 2/4 patients with episodic PFIC showed good response to ODX. For patients with longer follow-up (max 4.5 years), sBA and pruritus improvements were sustained with continued treatment, as well as improvements in growth, sleep, and quality of life vs BL. 19 patients underwent surgical intervention; 1 surgical biliary diversion (SBD) followed by liver transplantation (LT), 15 LT and 3 SBD. Estimated surgery-free survival and native liver survival (NLS) [MS5] [SW6] rates in Cohorts 1 and 2 were ≥76% and ≥77% at week 72, respectively. Most AEs were mild/moderate in severity; most common were gastrointestinal (n=20/116; 17.2%), mostly diarrhea (n=14/116; 12.1%). There were 2 ODX-related SAEs (both diarrhea); 1 led to treatment interruption and 1 to discontinuation of ODX. **Conclusion:** In patients with PFIC on long-term ODX [MS1] treatment, we observed sustained clinically meaningful improvements in sBA and pruritus across PFIC subtypes. A high proportion of patients had NLS, and treatment was well tolerated.

Figure: Mean sBA (A) and pruritus scores (B) through PEDFIC 2 week 72



Notes: Week 72 was the prespecified primary endpoint for PEDFIC2. Study is limited through results only being reported for patients who remain on treatment, with patient numbers decreasing over time.

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5046 | IMPACT OF GIVOSIRAN TREATMENT ON SYMPTOMS BETWEEN ACUTE ATTACKS OF ACUTE HEPATIC PORPHYRIA AS ASSESSED BY DIMENSION- LEVEL ANALYSIS OF EQ-5D DATA FROM THE ENVISION STUDY

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Background: Acute hepatic porphyria (AHP) is a group of rare inherited disorders of heme metabolism characterized by acute neurovisceral attacks and chronic symptoms. Givosiran is a small interfering RNA approved for AHP treatment. In the phase 3, randomized, double-blind, placebo-controlled ENVISION trial (NCT03338816), givosiran led to sustained reductions in annualized attack rate (AAR) and, in an open-label extension study, improved health-related quality of life (HRQoL). This post hoc analysis evaluated givosiran treatment effect on symptoms assessed using the EQ-5D survey, which measures the dimensions of mobility, self- care, usual activities, pain/discomfort, and anxiety/depression. **Methods:** Patients were randomized to subcutaneous monthly givosiran or placebo in a 6-month double-blind period, and completed the EQ-5D at baseline (BL) and month 6 (6M). Changes in EQ-5D dimension scores at 6M from BL were characterized as stable, improved, or worsened and compared descriptively; ≥2 step improvement was also captured to evaluate greater changes in QoL. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using the Mantel–Haenszel chi squared test. **Results:** The study included 94 patients (givosiran, n=48; placebo, n=46; majority female [89.4%]) with a mean (standard deviation [SD]) age of 38.8 (11.4) years. The mean (SD) historical AAR was 11.4 (9.1). At BL, 52.1% of patients reported prior chronic symptoms, 62.8% had no mobility limitations and 82.8% had no self-care limitations. At 6M, over 30% of givosiran treated patients reported 'any improvements' in usual activities (31.9%), anxiety/depression (31.9%), and pain/discomfort (33.3%). Odds of reporting an improvement of ≥2 steps were higher in the givosiran group than in the placebo group across all 5 dimensions (OR 1.3-3.0). The strongest trends towards givosiran were observed for pain/discomfort (OR [95% CI] 2.5 [0.2-26.6]) and mobility (OR [95% CI] 3.0 [0.2-39.6]). The proportion of patients receiving givosiran reporting moderate/extreme problems was lower at 6M than at BL for all dimensions (decreases 6.7-31.3%). **Conclusion:** AHP symptoms occurring between attacks and their impact on HRQoL reflect the burden of disease beyond acute attacks. This analysis suggests that givosiran is associated with improvements across EQ-5D dimensions, particularly pain/discomfort and anxiety/depression. Additional research is needed to fully understand the impact of givosiran on AHP symptoms between attacks.

Disclosures: Manish Thapar: Consultant: Alnylam Pharmaceuticals, Recordarti Rare Diseases, Disc Medicine, Mistubishi Tanabe, Bruce Wang: Nothing to Disclose, Susana Monroy: ALNYLAM PHARMACEUTICALS: Speaking and Teaching, ASTRA ZENECA: Speaking and Teaching, Weiming Du: Nothing to Disclose, Teresa

Kauf: Alnylam, Inc: Employee, Mural Oncology: Stock - publicly traded company, Alkermes, Inc: Stock - publicly traded company, Marianne Sweetser: Alnylam Pharmaceuticals: I am an employee and also own stock/stock options., Jamie Weiss: Alnylam Pharmaceuticals: Stockholder, Alnylam Pharmaceuticals: Employee , Paolo Ventura: Alnylam pharmaceuticals: Advisor, Manisha Balwani: Alnylam Pharmaceuticals: Also, consulting fees, advisory board fees and lecture fees, Recordati Rare Diseases: Advisor, Mitsubishi Tanabe: Advisor, Alexion: Advisor, Genzyme/Sanofi: Advisor, Takeda: Advisor

5047 | AI AND DIGITAL-BASED PATHOLOGY CORROBORATE REDUCTION IN FIBROSIS OBSERVED BY CONVENTIONAL PATHOLOGY WITH EFRUXIFERMIN TREATMENT OF PATIENTS WITH F2-F3 MASH IN THE HARMONY STUDY

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Background: Efruxifermin (EFX), a bivalent Fc-FGF21 fusion protein, demonstrated significant improvement in fibrosis by conventional pathology in the HARMONY trial (NCT04767529) for both 28mg and 50mg groups. This was associated with significantly reduced hepatic fat content reflected by significant improvement in key secondary endpoints including resolution of MASH and the composite of fibrosis improvement and MASH resolution. This post-hoc analysis investigates the fibrosis changes across liver zones, utilizing Second Harmonic Generation/Two-Photon Excitation Fluorescence (SHG/TPEF) microscopy and HistoIndex's proprietary qFibrosis scoring, and concurrence with conventional pathologist consensus scoring. **Methods:** 108 paired, unstained biopsies available at baseline (BL) and week 24 (W24) were analyzed by SHG/TPEF imaging coupled to qFibrosis scoring. The analysis of fibrotic structures, which incorporated a correction to account for the significant reduction in hepatic fat observed with EFX treatment, included a detailed zonal analysis across the following defined hepatic zones: portal, peri-portal (zone 1), peri-sinusoidal (zone 2), central, and peri-central (zone 3). **Results:** Steatosis-corrected qFibrosis stage revealed improvements in W24 fibrosis for 60% and 66% of subjects in the 28mg and 50mg EFX groups respectively, versus 18% for placebo. Among subjects with F2 or F3 fibrosis at BL, significant reductions in fibrotic area were noted primarily in the peri-portal (zone 1) and peri-sinusoidal (zone 2) regions. This was most evident in F3 subjects who had significantly less fibrosis in zones 1 and 2 after 24 weeks treatment with either 28mg or 50mg EFX, compared to placebo. The quantitative regression of fibrosis in these two zones was evident in subjects whether or not improvements in fibrosis had been seen by conventional pathologist staging, highlighting the consistency and sensitivity of AI-enhanced imaging in detecting subtle but significant reductions in fibrosis for EFX-treated subjects. **Conclusion:** Detailed zonal analysis provided by digital pathology tools like qFibrosis offers valuable insights into specific patterns of fibrosis reduction associated with EFX treatment of subjects with F2 and F3 MASH.

Figure 1A. Fibrosis Improvement ≥1-stage at Week 24

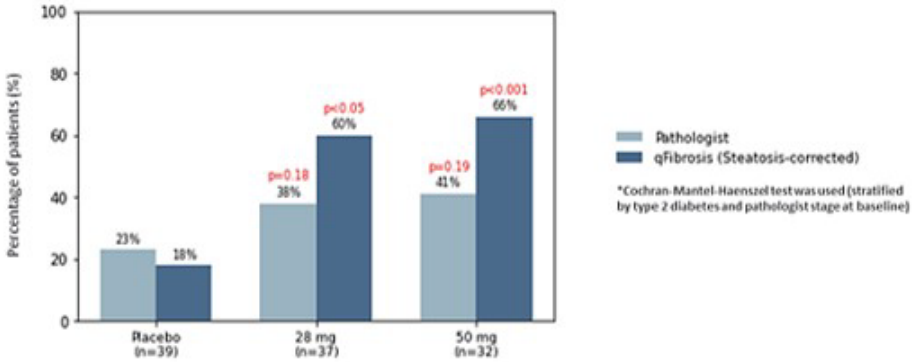
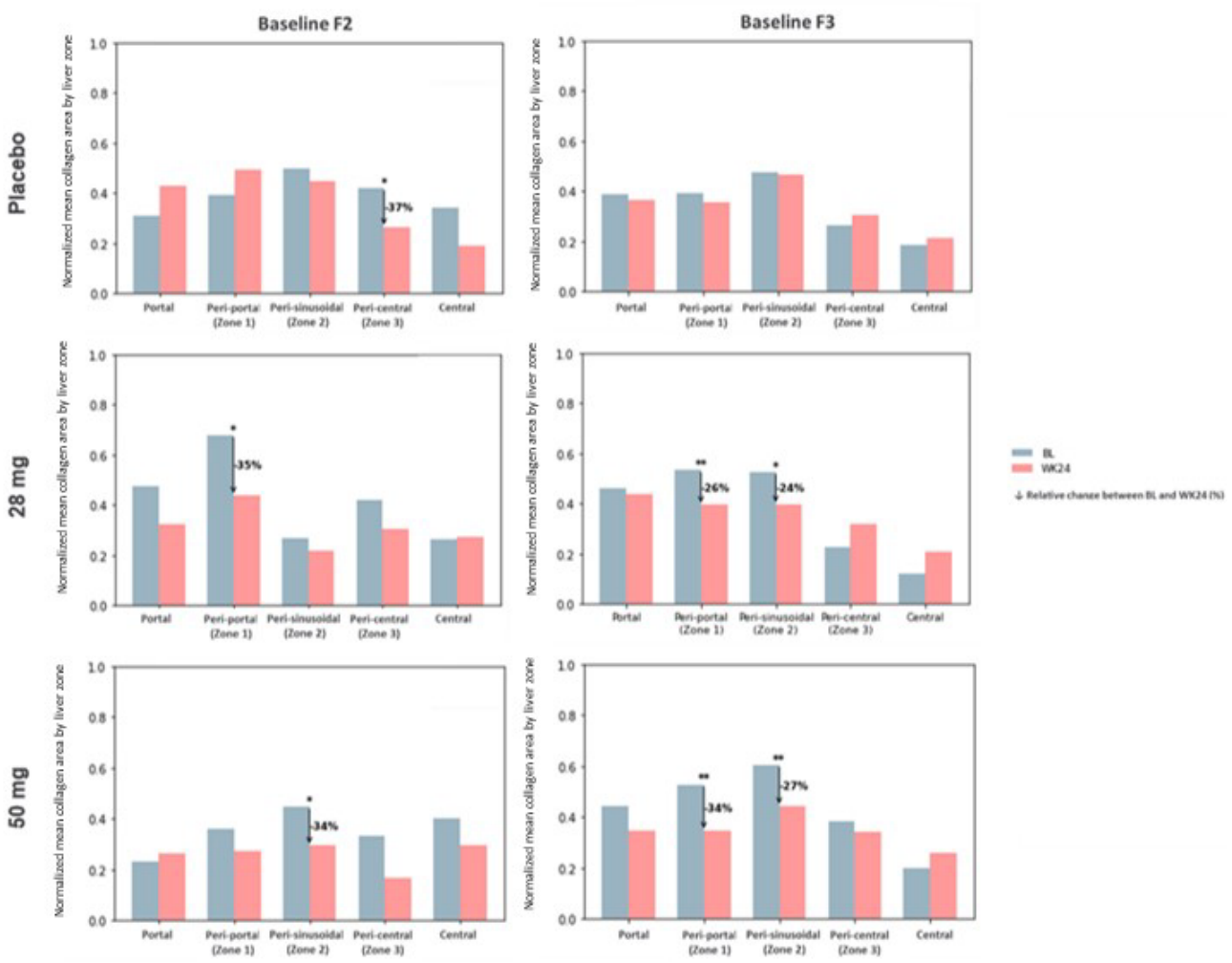


Figure 1B. Change in fibrosis from BL to Week 24 for different zones of the liver



Disclosures: Mazen Noureddin: Principal Investigator for a Drug Study relationship with Takeda, Principal Investigator for a Drug Study relationship with Terns, Stock - privately held company relationship with ChronWell, Stock - publicly traded company relationship with Cytodyn, Stock - privately held company relationship with Rivus Pharmaceuticals, Principal Investigator for a Drug Study relationship with Zydus, Principal Investigator for a Drug Study relationship with Viking, Consultant relationship with Cytodyn, Principal Investigator for a Drug Study relationship with BI, Principal Investigator for a Drug Study relationship with BMS, Consultant relationship with Altimmune, Consultant relationship with Alligos, Consultant relationship with AstraZeneca, Consultant relationship with BI, Consultant relationship with Boston Pharmaceuticals, Principal Investigator for a Drug Study relationship with Conatus, Consultant relationship with GSK, Consultant relationship with Eli Lilly, Principal Investigator for a Drug Study relationship with Gilead, Principal Investigator for a Drug Study relationship with Galectin, Terns,Takeda, Zydus. relationship with Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor, Consultant relationship with Merck, Principal Investigator for a Drug Study relationship with GSK, Principal Investigator for a Drug Study relationship with Genfit, Consultant relationship with Madrigal, Dean Tai: Histoindex. com: Employee, Elaine Chng: Nothing to Disclose, Yukti Choudhury: Nothing to Disclose, Cindy Behling: Pacific Rim Pathology Lab: Employee, Novo Nordisk: Consultant, Pathology Institute: Consultant, boehringer ingleheim: Consultant, akero: Independent Contractor, Pierre Bedossa: Nothing to Disclose, Lan Shao: Nothing to Disclose, Doreen Chan: Akero Therapeutics: Employee, Jimmie Zhang: Akero Therapeutics: Employee, Erica Fong: Akero Therapeutics: Employee, Brittany De Temple: Akero Therapeutics, Inc.: Employee, Matt Minerva: Akero Therapeutics: Employee, Akero Therapeutics: Stock - publicly traded company, Mark Burch: Nothing to Disclose, Kimberly Barrett: Akero Therapeutics, Inc.: Employee, Reshma Shringarpure: Akero Therapeutics:

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5048 | EVALUATION OF INTESTINAL MICROBIOTA TRANSPLANTATION ON THE OUTCOMES OF SEVERE ALCOHOL-ASSOCIATED HEPATITIS: A PARALLEL ARM OPEN-LABEL STUDY

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Background: Steroid therapy has been the mainstay treatment of patients with severe alcoholic hepatitis (SAH) for the past 50 years. However, many patients are ineligible or non-responders to treatment with steroid and it may not improve long-term outcomes. In this study, we aim to examine the outcomes of intestinal microbiome transplant (IMT) in patients with SAH. **Methods:** Under IRB approval from Baylor College of Medicine, we conducted a nonrandomized parallel arm design study in patients with SAH (MELD 20-30, DF >32) selected following NIAAA AH consortia. Patients in the IMT arm, received oral lyophilized capsules containing microbiota suspension (PRIM-DJ2727) from healthy donors 30 grams every day for a week followed by once weekly for 3 weeks. Patients who choose not to be in the IMT arm, received the standard of care treatment. However, patients treated with steroids were excluded from the study. All patients in both arms were monitored at baseline, 1-week, 4-weeks, 12-weeks. Repeated measurement analyses and mixed linear model were performed to assess the changes in the prognostic scores and related parameters over 12 weeks of follow-up. **Results:** Total of 20 patients were enrolled (10 in the IMT arm and 10 in the control arm), M:F 13:7. Majority was white (85.7%) with mean age (±SD) 45.1 years (±11.1). IMT played a significant role in the observed age, gender- adjusted variation of the mean values of the prognostic parameters over 12 weeks (Table 1); P values were <.001, .001, .03, and .02 for Albumin, PT, BUN, and MELD score respectively. Four patients in the IMT group were transplanted following institutional policy; median time to transplant 29 days (21-78), none died. In the control group, 5 were transplanted, one died, median time 72 days (26-187), p=.5. The percentage change of the median values from baseline to week 12 significantly improved among IMT group as compared to the control group for total bilirubin (P=.02), albumin (P=.02), PT (P=.02), INR (P=.02), BUN (P=.001), and MELD score (P=.02). There was no significant difference in the median Lille score at day 7 between IMT and control arms, P=.65. IMT was well tolerated, none had discontinuation of therapy, and none had any clinically significant adverse event related to IMT. **Conclusion:** Early analyses suggest that IMT has a favorable outcome on the prognosis in patients with SAH and is safe. A longer follow up with a larger sample size is needed to define the outcome further.

Table 1: Mean ± Standard Deviation (SD) of liver parameters over the study period

Liver Function	Baseline Mean (±SD)		Week-1 Mean (±SD)		Week-4 Mean (±SD)		Week-12 Mean (±SD)	
	Controls	IMT	Controls	IMT	Controls	IMT	Controls	IMT
Total Bilirubin	13.9±6.7	17.8±7.3	12.9±8.3	16.4±7.0	16.6±14.7	7.5±6.3	6.8±4.6	1.9±1.6
Albumin	2.4±0.7	2.5±.5	2.2±.5	2.7±.4	2.6±0.7	3.1±0.8	2.8±0.4	4.0±0.7
PT	21.7±4.8	19.9±3.2	24.6±6.2	19.1±2.7	24.1±7.4	18.7±4.3	20.9±6.9	14.1±1.9
INR	1.9±0.6	1.8±0.4	2.3±0.8	1.7±0.3	2.2±0.9	1.6±0.5	1.8±0.8	1.2±0.1
Creatinine	0.85±0.20	0.71±0.13	0.84±0.24	0.96±0.48	1.0±0.31	0.8±0.22	0.96±0.39	0.72±0.13
BUN	13.6±7.4	8.9±4.6	14.7±12.9	11.2±7.3	12.1±6.2	9±6.6	10.3±4.0	10.2±3.0
MELD	23.4±3.6	23.9±2.7	25.1±4.7	24.3±5.2	25.1±7.3	18.1±6.6	19.8±5.9	10.6±3.6

Unit Measure: Total Bilirubin (mg/dL); Albumin (g/dL); PT (seconds)

Disclosures: Megha Bhongade: Nothing to Disclose, Islam Mohamed: Nothing to Disclose, Mohamad Ali Ibrahim: Nothing to Disclose, Mahmoud Hashim: Nothing to Disclose, Zhi-Dong Jiang: Nothing to Disclose, Herbert DuPont: Ferring Pharmaceuticals: attended Live Biotherapeutic Products Scientific Summit, Manal Hassan: Nothing to Disclose, Prasun Jalal: Speaking/Teaching: AbbVie, Madrigal

5049 | LONG-TERM HDV VIROLOGIC RESPONSE AND ABSENCE OF LIVER-RELATED EVENTS FOLLOWING FINITE TREATMENT WITH LONAFARNIB: LONG- TERM FOLLOW-UP OF LOWR 1 AND 2 STUDIES

Devrim Müge Özarı Gülnar[1] Cihan Yurdaydin[1] Genco Gencdal[1] Müjdat Zeybel[1] Jeffrey Glenn[2]

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Background: Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis. The oral farnesyl transferase inhibitor lonafarnib (LNF) inhibits virion assembly and possesses immunomodulatory properties. This study's aim was to assess if treatment with a finite course of LNF-based therapy can prevent hard clinical endpoints through achieving a durable viral response. **Methods:** In LOWR 1 and 2 studies, a total of 76 patients received 17 different LNF-based regimens for 5 to 48 wks. Long-term follow- up (LTFU) data was available on 61 patients. The end of follow-up was set to either the last date of data collection (June 2024), or the date of liver-related death/liver transplantation, the starting date of another anti-HDV therapy, or loss to follow-up, whichever occurred first. Long-term virologic response (LTVR) was defined as undetectable HDV RNA or a ³ 2 log decline of HDVRNA compared to baseline that persisted during LTFU. Cumulative probabilities of hepatocellular carcinoma, decompensation, mortality/liver transplantation, or any event occurrence were estimated by the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate logistic regression models with forward Wald deletion were used to estimate the effect of various baseline and on and off treatment parameters on clinical outcome measures. **Results:** LTFU was a median 89 (2-123) months and was available in 61 patients. 7 patients had LTVR, either as a result of on treatment response that persisted, or a post-treatment beneficial flare. Four of the 7 patients also cleared HBsAg. None of the 7 patients with LTVR developed a clinical event whereas 17 out of 54 patients without LTVR developed a liver-related complication (p=0.07). By multivariate analysis end of treatment serum albumin level was the only independent predictor of developing a liver-related event on LTFU (HR: 0.720, 95% CI; 0.531-0.977, p=0.035); however, age, post-treatment month 6 AST and baseline Fib-4 Score displayed a trend for significance in predicting a clinical event (p values of 0.057, 0.057 and 0.09, respectively). **Conclusion:** Liver disease severity may predict liver-related events during long-term follow-up. Finite treatment with LNF can result in a LTVR, either as a result of on treatment response that persists post treatment, or a post-treatment beneficial flare. LTVR following a finite course of LNF-based therapy is associated with excellent long-term outcomes.

Disclosures: Devrim Müge Özarı Gülnar: Nothing to Disclose, Cihan Yurdaydin: Advisor: Roche, Eiger Biopharma, Grant/Research Support: Gilead, Genco Gencdal: Nothing to Disclose, Müjdat Zeybel: Nothing to Disclose, Jeffrey Glenn: Nothing to Disclose

5050 | A NOVEL MECHANISTIC VIRAL DYNAMICS MODELING (MVDM) FRAMEWORK TO CHARACTERIZE AND PREDICT THE EFFECT OF COMBINATION THERAPIES IN CHRONIC HEPATITIS B: MODELING OF THE PIRANGA PHASE 2, RANDOMIZED, CONTROLLED, ADAPTIVE, OPEN-LABEL PLATFORM STUDY

Annabelle Lemenuel-Diot[1] Selma El Messaoudi[2] Jérémie Guedj[2] Sylvie Retout[1] Franziska Schaedeli-Stark[1] Amine Ait-Ali[1] Nelson Guerreiro[1] Sijie Lu[3] Farouk Chughlay[1] Claire McGeown[1] Rémi Kazma[1]

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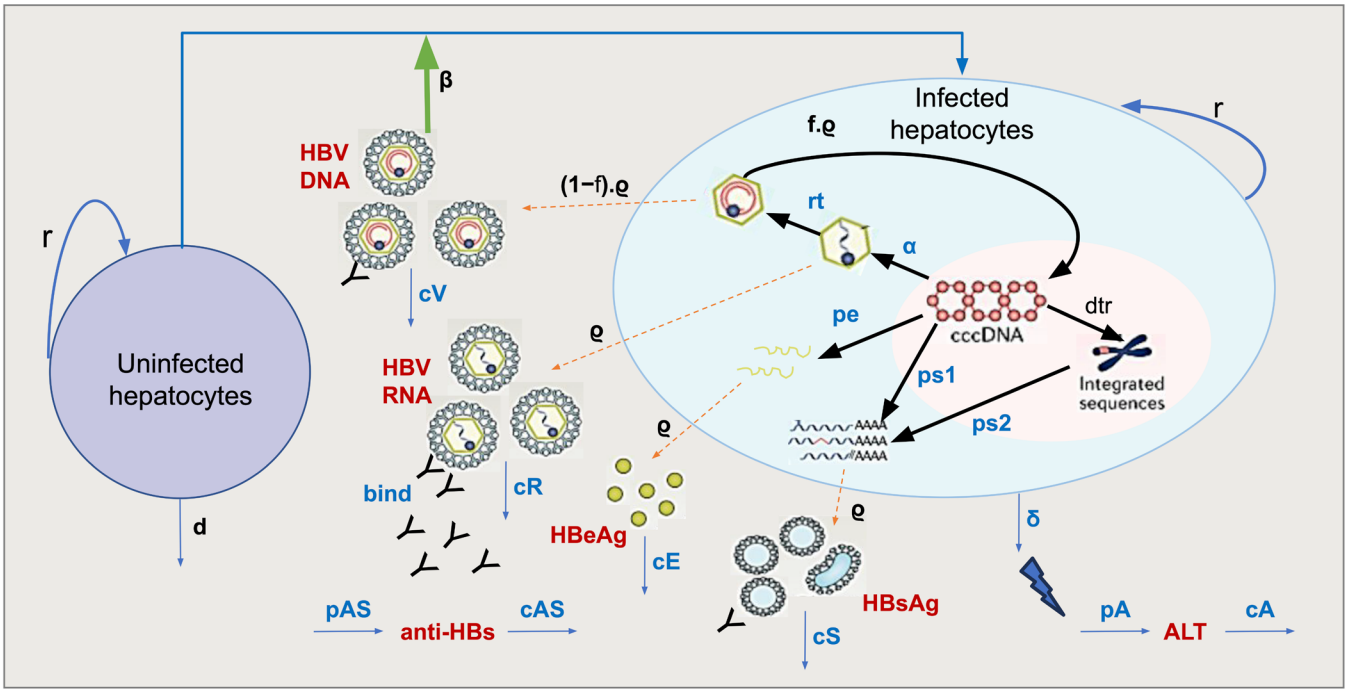
Background: Existing mechanistic models of chronic hepatitis B infection (CHB) focus on a subset of biomarkers that do not capture the full complexity of CHB processes. Therefore, these models cannot adequately describe the various modes of action of novel therapeutics aiming to achieve functional cure in patients with CHB. To address

this gap, the complexity of the HBV viral life cycle has been incorporated into a novel mechanistic viral dynamics modeling (MVDM) framework. **Methods:** Leveraging the Piranga Phase 2 platform study (NCT04225715), the MVDM framework (see figure) was developed to fit jointly the dynamics of the full pharmacokinetic and biomarker datasets. Data originated from 188 nucleos(t)ide analogue-treated participants randomized into one of 6 arms with different combination regimens of xalnesiran, a GalNAc-conjugated small interfering RNA targeting HBsAg transcripts, with or without an immunomodulator (ruzotolimod, pegylated interferon α, or PD-L1 LNA). This MVDM framework included a pool of infected hepatocytes producing viral transcripts at different rates, either from cccDNA (ps1), or from integrated HBV sequences (ps2). The death rate of infected hepatocytes (δ) was modelled primarily using ALT data. The effect of each molecule and the impact of participants' characteristics were estimated via a model selection process. Using the MVDM framework, simulations predicted the in silico performance of changes to the dose, duration, or regimen of the different combinations of molecules tested in Piranga. **Results:** The effect of xalnesiran was estimated as an inhibition of HBsAg production from both origins (ps1 and ps2) and an acceleration of hepatocytes death rate (δ). Furthermore, the model estimated the add-on effect of each immunomodulator mainly through an enhancement of the δ parameter and, specifically for pegylated interferon α, an increase in anti-HBs. Model simulations using the MVDM framework did not predict any substantial increase in rates of HBsAg loss (HBsAg < 0.05 IU/mL) when simulating changes to the dose, duration, or regimen of the different combinations of molecules tested in Piranga. **Conclusion:** This novel MVDM framework improves the characterization of the complex long-term dynamics of viral parameters during and after treatment with different combination regimens. Optimization of such combinations can therefore be supported by the model, paving the way to potential in silico efficacy prediction of new anti-HBV agents.

Schematic representation of the Mechanistic Viral Dynamic Modelling (MVDM) framework for chronic hepatitis B infection



Parameters in red are biomarkers, which were quantitatively measured during the treatment (24 to 48 weeks) and follow-up (48 weeks) periods of the Piranga Phase 2 platform study. Parameters in blue are estimated from the data and parameters in black are fixed.

Acronyms of viral biomarkers and particles: cccDNA: covalently closed circular DNA; HBV (DNA) RNA, hepatitis B (deoxy)ribonucleic acid; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis B surface antigen; anti-HBs: Anti hepatitis B surface antigen; ALT, Alanine aminotransferase

Acronyms of model parameters: α, transcription rate; β, infectivity rate; pe, production rate of HBeAg; ps1, production rate of HBsAg from cccDNA; ps2, production rate of HBsAg from integrated sequences; pA, production rate of ALT; pAS, production rate of Anti-HBs; dtr, rate of HBV sequence integration; rt, reverse transcription rate; δ, loss rate of infected cells; ϱ, extracellular export rate; cE, clearance of HBeAg; cR, clearance of HBV RNA; cS, clearance of HBsAg; cV, clearance of virions; cAS, clearance of anti-HBs; cA, clearance of ALT; d, loss rate of uninfected cells; f, recycling fraction; r, proliferation rate

Disclosures: Annabelle Lemenuel-Diot: No Relevant Financial Relationships, Selma El Messaoudi: Nothing to Disclose, Jérémie Guedj: Nothing to Disclose, Sylvie Retout: Nothing to Disclose, Franziska Schaedeli-Stark: Nothing to Disclose, Amine Ait-Ali: Nothing to Disclose, Nelson Guerreiro: F. Hoffmann-La Roche: Employee, Sijie Lu: Nothing to Disclose, Farouk Chughlay: Roche: Employee, Claire McGeown: Nothing to Disclose, Rémi Kazma: Hoffmann - La Roche: Employee, Hoffmann - La Roche: Stock - publicly traded company, Novartis: Stock - publicly traded company, Alcon: Stock - publicly traded company, Sandoz: Stock - publicly traded company

5051 | CLINICAL PERFORMANCE EVALUATION OF THE XPERT® HCV TEST AT POINT OF CARE IN A MULTI-SITE PROSPECTIVE CLINICAL STUDY

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Background: The United States Centers for Disease Control and Prevention recommended testing algorithm for the diagnosis of current HCV infection is two-step, with HCV antibody testing first. To diagnose individuals with active HCV infection, patients with a positive HCV antibody test result need to be tested with an FDA-approved molecular test. This limits diagnosis and linkage to care to individuals with a subsequent positive HCV RNA test result. Testing is typically done at a referral laboratory, which may affect lost to follow-up. Decentralization of diagnosis and treatment based on “test-and-treat” strategies for individuals with or without HCV antibodies, in point of care settings, could help improve continuity of care in populations at-risk and/or symptomatic for HCV infection. **Methods:** This multi-site, prospective study evaluated the clinical performance of the Xpert HCV test (Xpert HCV) using K2- EDTA fingerstick (FS) blood from adult individuals at risk and/or symptomatic for HCV infection, irrespective of HCV antibody status. FS specimens were tested on Xpert HCV by untrained users using the GeneXpert® Xpress System. Serum obtained from paired venous blood was tested on an FDA-approved HCV antibody test and an FDA-approved HCV RNA NAAT by trained users in a central laboratory. The clinical performance of Xpert HCV was determined relative to patient infected status (PIS) based on the HCV RNA NAAT and the HCV antibody test results. **Results:** A total of 1279 participants were enrolled in the study, with 1012 deemed eligible for inclusion. The majority (63.6%) of the study population were between 22 and 60 years of age. Approximately 28.9% of individuals reported a history of HCV infection; 43.1% reported a history of injection drug use and 15.4% were HIV-positive. Moreover, 92.2% of the study population reported at-risk factors and 36.8% were categorized as symptomatic for HCV infection. Xpert HCV showed good performance relative to PIS for detecting HCV RNA in the study population, with a negative percent agreement of 99.8% (95% CI: 99.2 – 99.9) and a positive percent agreement of 93.4% (95% CI: 87.6 – 96.6). **Conclusion:** The overall performance of Xpert HCV was deemed clinically acceptable, since it showed good ability to detect HCV RNA in individuals with active HCV infection. It also enables obtaining results in a single patient visit, that could result in a decrease in lost to follow-up and an increased number of individuals that receive timely treatment.

Disclosures: Gail Louw: Employee: Cepheid, Sarah Brown: Cepheid: Employee, Wei Zhang: Cepheid: Employee, Laura Spelmink: Nothing to Disclose, Marika Kleman: Nothing to Disclose, Suzette Chance: Cepheid: Employee, Scott Campbell: Cepheid: Employee