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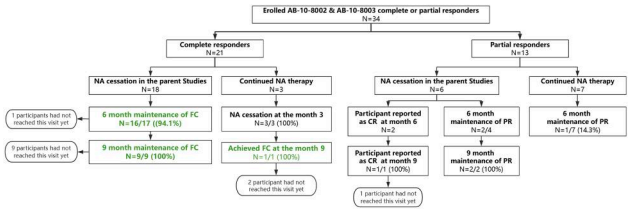
ABSTRACTS

2026 Late Breaking Abstracts

5001 | DURABILITY OF AHB-137 UP TO 9 MONTH POST END-OF-STUDIES IN NUCLEOS(T)IDE ANALOGUE TREATED PARTICIPANTS WITH CHRONIC HEPATITIS B: FIRST LONG-TERM FOLLOW-UP REPORT FROM THE AB-10-8004 STUDY

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Background: AHB-137 is an investigational unconjugated antisense oligonucleotide (ASO) targeting all HBV RNAs for the treatment of chronic hepatitis B (CHB). AB-10-8004 (NCT07146100) is a long-term follow-up Study evaluating the durability of off-treatment responses and long-term safety among participants who achieved a complete response (CR) or partial response (PR) at the end-of-study (EOS) visit of the AHB-137 Phase 2 parent Studies, AB-10-8002 (NCT06115993) and AB-10-8003 (NCT06550128). **Methods:** NA-treated participants from Studies AB-10-8002 and AB-10-8003 who achieved CR (HBsAg <0.05 IU/mL and HBV DNA $<$LLOQ [<10 IU/mL]) or PR (HBsAg 0.05 to <10 IU/mL and HBV DNA $<$LLOQ) at the end of the parent Studies were enrolled in AB-10-8004. Functional cure (FC) was defined as maintenance of CR for ≥ 24 weeks after cessation of all HBV treatment. Participants were followed for long-term durability of FC or PR, and characterization of the long-term safety profile. Participants who remained on NA therapy at entry were assessed for subsequent NA discontinuation. **Results:** A total of 34 participants from Studies AB-10-8002 and AB-10-8003 (9 and 25 participants, respectively; with 21 CR and 13 PR) were enrolled in the AB-10-8004 Study. Of the 21 with CR, 18 had already discontinued NA therapy in parent Studies. Among those FC cases with available data, 16/17 (94.1%) maintained FC at 6 months and 9/9 (100%) at 9 months in Study AB-10-8004 (12 and 15 months post NA cessation, respectively). Of the 3 participants who remained on NA therapy at entry into AB-10-8004, all discontinued NA by Month 3. Among them, one had reached Month 9 and achieved FC, while the other 2 had not yet reached Month 9 at the data cutoff date. Among the 13 participants with PR, 6 had discontinued NA therapy in parent Studies: 2 converted to CR by Month 6 (1 maintained CR through Month 9, and 1 has not yet reached Month 9), 2 maintained PR through Month 9, and 2 experienced virological rebound by Month 6. Of the remaining 7 participants with PR who stayed on NA therapy at entry of AB-10-8004, 1 maintained PR at Month 6. No participants required NA re-initiation during AB-10-8004. Overall, the long-term safety profile remained favorable, without clinical relapse, severe hepatic flares, hepatic decompensation, or new safety findings. **Conclusion:** Functional cure achieved with AHB-137 treatment is durable during long-term follow-up after treatment cessation with no severe ALT flares, HBV virologic rebound requiring NA re-initiation, or new safety signals reported. Some participants with PR subsequently converted to CR during follow-up, suggesting that response may continue to deepen after treatment cessation.



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5002 | DURABLE PGRNA LOSS IN BOTH HBEAG POSITIVE AND NEGATIVE PATIENTS TREATED WITH PBGENE-HBV SUPPORTS PATH TOWARDS VIRAL CURE

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Background: The root cause of chronic hepatitis B (CHB) infection is covalently closed circular DNA (cccDNA). cccDNA is the sole source of pregenomic RNA (pgRNA), the precursor molecule to infectious particles, HBV DNA. The persistence of cccDNA and pgRNA upstream of HBV DNA suppression by nucleoside analogue (NA) therapy drives ongoing risk of disease progression and hepatocellular carcinoma. Therefore, cccDNA elimination is key for chronic hepatitis B viral cure. PBGENE-HBV, an LNP containing ARCUS nuclease mRNA, is designed to eliminate cccDNA. ELIMINATE-B is a Phase 1b study evaluating the safety and antiviral activity of PBGENE-HBV in HBeAg-negative patients and now expanded to include HBeAg-positive patients — an important population with logarithmically higher levels of cccDNA and pgRNA. **Methods:** Multiple ascending doses of PBGENE-HBV were tested in NA-treated, CHB patients, with repeat infusions dosed at $\geq$4-week intervals. The primary endpoint was safety, defined by the frequency and severity of dose limiting toxicities (DLTs). Other endpoints included assessment of antiviral activity from blood and liver biopsy. **Results:** After PBGENE-HBV treatment, elimination and inactivation of cccDNA was confirmed in liver biopsies, and durable loss of pgRNA was demonstrated in serial blood samples (repeat measurements below the lower limit of detection, 5 copies/mL). In the first HBeAg-positive patient, treated at 0.4 mg/kg, pgRNA decreased from 5,750 copies/mL at baseline to undetectable. To date, of 11 HBeAg-negative patients with detectable pgRNA at baseline, 10 currently have undetectable pgRNA after PBGENE-HBV treatment, with 5-month average durability and ongoing follow-up. The first 6 participants with pgRNA loss have now surpassed the important 6-month durability milestone since their initial undetectable measurement. Loss of pgRNA occurred after one or two administrations at dose levels ranging from 0.4 to 0.8 mg/kg. Transcriptomic analysis from liver biopsies showed a 10-fold (1-log) reduction in cccDNA derived transcripts after 2 administrations at 0.4 mg/kg in one patient, with additional biopsy data pending.PBGENE-HBV was well-tolerated with no DLTs across 58 doses in 24 subjects, from 0.2-0.8 mg/kg. Infusion-related reactions were transient and manageable supporting a wide therapeutic window. **Conclusion:** Elimination and inactivation of cccDNA by PBGENE-HBV was confirmed by liver biopsies as well as durable loss of pgRNA in the blood. In an HBeAg positive patient, loss of pgRNA after treatment with PBGENE-HBV at 0.4 mg/kg shows elimination of cccDNA is not limited to patients with lower cccDNA burden. Safety and efficacy data support ongoing development of PBGENE-HBV as a potentially curative regimen for chronic hepatitis B.
Disclosures: Man-Fung Yuen:AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals, Immuncore: Consultant, Fujirebio Incorporation, GSK, Gilead Sciences: Consultant, Immunocore, Janssen, Precision BioSciences: Consultant, Roche, Sysmex Corporation, Tune Therapeutics: Consultant, Vir Biotechnology and Visirna Therapeutics: Consultant, AbbVie, Assembly Biosciences, Arrowhead Pharmaceuticals, Aligos Therapeutics, Arbutus Biopharma: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Immunocore, Clear B Therapeutics, GSK, Janssen: Grant/Research Support, Sysmex Corporation and Roche: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp, Aligos Therapeutics, Arbutus Biopharma: Speaking and Teaching, Precision BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy, Clear B Therapeutics, GSK, Immuncore, Janssen, Vir Biotechnology: Speaking and Teaching, Anca Streinu Cercel:, Vlad Ichim:, Emily Harrison:Precision BioSciences: Employee, James Harris:Nothing to Disclose, Keely Dulmage:, Andrew Van Cott:, Abhishek Chandiramani:, Neil Leatherbury:Precision BioSciences: Employee, Janel Lape:, Peter Balfe:

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Nothing to Disclose, Jeff Smith:, Cassandra Gorsuch: Precision BioSciences: Employee, Stanley Frankel: Precision Biosciences: Stock - publicly traded company, Precision Biosciences: Director, Oby Sogbetun:No dislosure submitted, Jane McKeating:, Mark Sulkowski: AbbVie: Advisor, Arbutus: Advisor, Aligos: Advisor, Gilead: DSMB member, Precision Biosciences: Advisor, Vir: Advisor, Vir: Grant/Research Support, GSK: Advisor, GSK: Grant/Research Support, Virion: Advisor, ImmunoCore: DSMB member, Pfizer: Advisor, Edward Gane: No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted.

5003 | TOPLINE HISTOLOGY DATA: ZABOPEGDUTIDE (DD01), A DUAL GLP-1/GLUCAGON AGONIST, DRIVES SIGNIFICANT FIBROSIS IMPROVEMENT AND MASH RESOLUTION AT 48 WEEKS

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Background: MASH is a major public health issue, with high prevalence among patients with obesity. Here, we report the 48-week results of the DD01-DN-02 study of zabopegdutide (DD01), a liver-targeted dual GLP-1/glucagon receptor agonist, in patients with MASLD/MASH (NCT06410924). **Methods:** In this 48-week double-blind, multi-center, randomized, placebo-controlled phase 2 study, patients with MASLD/MASH were randomized 1:1 to receive weekly subcutaneous zabopegdutide (40 mg following dose escalation) or placebo. Major inclusion criteria included ≥10% liver fat content by MRI-PDFF and either liver biopsy with NAS ≥4 (≥1 point per component) and F1-F3 fibrosis within 6 months of enrollment (78% of participants) or 2 metabolic risk factors. **Results:** Sixty-seven participants were randomized to the zabopegdutide (n = 33) and placebo (n = 34) groups. The study met the key 48-week histology endpoint of fibrosis improvement (≥1 stage) without worsening of MASH. In the zabopegdutide group, 8/16 (50.0%) participants met the endpoint, vs 3/19 (15.8%) in the placebo group (p = 0.03). MASH resolution without worsening of fibrosis occurred in 62.5% participants in the zabopegdutide group 5.3% participant in the placebo group (p < 0.001). In total, 37.5% of participants in the zabopegdutide group vs 5.3% of participants in the placebo group achieved both fibrosis improvement and MASH resolution (p = 0.02). Concordantly, the HistoIndex qFibrosis score, an AI histological analysis tool for quantifying liver fibrosis, was significantly reduced in the zabopegdutide arm vs placebo (p = 0.007). Additional endpoints are presented in Table 1. TEAEs occurred in 28 (84.8%) participants receiving zabopegdutide (placebo, 79.4%) and were generally gastrointestinal (n = 26) and mild or moderate in nature (n = 25) and transient. There were two participants with serious TEAEs related to the study drug in the zabopegdutide arm (one with acute cholecystitis; one with abdominal pain), and no deaths were reported. **Conclusion:** At 48 weeks, zabopegdutide met both key histologic endpoints, demonstrating significant MASH resolution without worsening of fibrosis and ≥1-stage fibrosis improvement without worsening of MASH. These histologic improvements were corroborated by favorable changes across multiple noninvasive tests, including MRI-PDFF, MRE, PRO-C3, and liver enzymes, supporting a consistent treatment effect across histologic and noninvasive measures of disease activity and fibrosis.

48-Week Endpoint Per-Protocol Analysis Set	Zabopegdutide 40 mg (n=16)	Placebo (n=19)	p-value vs placebo
≥1 stage fibrosis improvement without worsening of MASH	8 (50.0%)	3 (15.8%)	0.03
MASH resolution with no worsening of fibrosis	10 (62.5%)	1 (5.3%)	<0.001
MASH resolution and ≥1 stage fibrosis improvement	6 (37.5%)	1 (5.3%)	0.02
qFibrosis Score change from baseline			
≥1-point improvement in fibrosis, n (%)	9 (56.3%)	3 (15.8%)	0.01
Absolute change, continuous value (LS mean, SE)	-0.84 (0.31)	0.38 (0.28)	0.007
Liver fat content (MRI-PDFF) change from baseline			
Absolute change, % (LS mean, SE)	-14.2 (1.5)	-1.5 (1.3)	<0.001
Relative change, % (LS mean, SE)	-68.2 (6.7)	-7.8 (6.1)	<0.001
≥30% reduction in MRI-PDFF relative to baseline, n (%)	14 (87.5%)	2 (10.5%)	<0.001
≥50% reduction in MRI-PDFF relative to baseline, n (%)	13 (81.3%)	0	<0.001
≥70% reduction in MRI-PDFF relative to baseline, n (%)	10 (62.5%)	0	<0.001
Normalization of liver fat by MRI-PDFF (≤5%)	11 (68.8%)	0	<0.001
MRE liver stiffness change from baseline			
Absolute change, kPa (LS mean, SE)	-0.62 (0.10)	-0.14 (0.09)	0.001
Relative change, % (LS mean, SE)	-19.0 (3.4)	1.7 (3.1)	<0.001
CAP liver steatosis change from baseline			
Absolute change, dB/m (LS mean, SE)	-50.2 (12.5)	-3.6 (11.5)	0.01
Relative change, % (LS mean, SE)	-14.7 (3.8)	-0.6 (3.5)	0.01
PRO-C3 change from baseline			
Absolute change, µg/L (LS mean, SE)	-5.4 (2.0)	0.3 (1.8)	0.04
Relative change, % (LS mean, SE)	-14.6 (4.3)	3.9 (3.9)	0.004
AST change from baseline			
Absolute change, U/L (LS mean, SE)	-11.7 (2.3)	-3.2 (2.1)	0.01
Relative change, % (LS mean, SE)	-33.6 (7.4)	6.0 (6.7)	<0.001
ALT change from baseline			
Absolute change, U/L (LS mean, SE)	-22.6 (4.2)	-4.9 (3.8)	0.004
Relative change, % (LS mean, SE)	-40.8 (7.6)	-1.8 (7.0)	<0.001

Disclosures: Mazen Noureddin:Akero: Advisor, Alligos: Advisor, Altimmune: Advisor, AstraZeneca: Advisor, Boehringer Ingelheim: Advisor, Boston Pharma: Advisor, Cytodyn: Advisor, GSK: Advisor, Lilly: Advisor, Madrigal: Advisor, Merck: Advisor, Novo Nordisk: Advisor, Sagimet: Advisor, Terns: Advisor, Takeda: Advisor, Akero: Principal Investigator, Allergan: Principal Investigator, Altimmune: Principal Investigator, Boehringer Ingelheim: Principal Investigator, Bristol Myers Squibb: Principal Investigator, Boston Pharma: Principal Investigator, Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal

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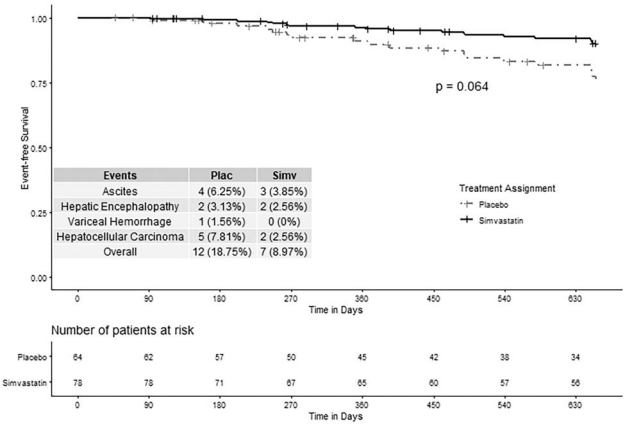
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5004 | SIMVASTATIN FOR PREVENTION OF HEPATIC DECOMPENSATION OR HEPATOCELLULAR CARCINOMA IN COMPENSATED CIRRHOSIS WITH PROBABLE CLINICALLY SIGNIFICANT PORTAL HYPERTENSION: A PHASE III RANDOMIZED TRIAL

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Background: Prospective human studies have shown that statins reduce portal hypertension and reduce death in patients with decompensated cirrhosis after variceal hemorrhage. The objective of this phase III, prospective, multi-center, double-blind, randomized clinical trial was to evaluate whether or not simvastatin reduces incident hepatic decompensation events or hepatocellular carcinoma (HCC) among patients with compensated cirrhosis at high risk for hepatic decompensation. **Methods:** This prospective randomized, double-blind, placebo-controlled trial was conducted at 11 VA medical centers.Simvastatin 40mg (SIMV) or matching placebo (PLAC) was administered for up to 2 years in patients 1) with compensated cirrhosis; 2) non-invasively assessed as highly likely to have clinically significant portal hypertension (CSPH); 3) without independent indications for statin therapy; and 4) stratified by baseline non-selective beta-blocker (NSBB) use. The primary endpoint was a composite of incident hepatic decompensation (variceal hemorrhage, ascites, encephalopathy), or hepatocellular carcinoma. **Results:** We enrolled n = 142 patients with a median age of 61 years [P25-75: 54-68], 132 men and 10 women, 105 (73.9%) White, 27 (19.0%) Black, 24 (16.9%) Hispanic, median Child-Pugh score 5 [5-6], 55 (38.7%) with cured HCV infection, 86 (60.6%) with alcohol-related liver disease, 35 (24.7%) with MASH, 49 (34.5%) on NSBB. Seventy-eight patients were randomly assigned to SIMV and 64 to PLAC. There were no statistically significant differences in baseline covariates (age, sex, race, ethnicity, etiology, NSBB use, CTP score, and MELD score) by treatment assignment. Median follow-up time was 1.96 [1.29-2.00] and 1.90 [0.87-1.99] years in the SIMV and PLAC groups, respectively. The primary endpoint occurred in 7 SIMV patients during 127.58 patient-years (PY) and 12 PLAC patients during 93.41 PY of follow-up (5.49 vs. 12.85 events per 100 PY; p = 0.083). After confirming the proportional hazards assumptions, the hazard ratio for the primary endpoint was HR = 0.41 (95% CI 0.16-1.05; p = 0.064) based on an intention-to-treat stratified Cox model. The 2-year Restricted Mean Survival Time for the primary endpoint was 1.92 ± 0.03 years for SIMV vs. 1.78 ± 0.06 years for PLAC, p = 0.043. Safety and tolerability of SIMV in this population has previously been reported and was excellent. Patient-reported outcomes will be reported separately. **Conclusion:** In this phase III randomized trial, the primary endpoint of hepatic decompensation or HCC did not differ significantly between treatment groups, although the point estimate favored simvastatin, with a 59% lower estimated hazard. These data, in the context of prior retrospective and other prospective evaluations of statin use in patients with cirrhosis, suggest a significant therapeutic benefit.



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5005 | PRIMARY ENDPOINT RESULTS OF ECLIPSE 1: A RANDOMIZED OPEN-LABEL PHASE 3 STUDY EVALUATING EFFICACY AND SAFETY OF ELEBSIRAN AND TOBEVIBART FOR CHRONIC HEPATITIS DELTA

Nancy Reau[1] Sophia Chow[2] Alina Jucov[3] Saeed Hamid[4] Zaigham Abbas[5] Marta Dobryanska[6] Elena Laura Iliescu[7] Heiner Wedemeyer[8] Pietro Lampertico[9] Carla Coffin[10] Tatyana Kushner[11] Edward Gane[12] Kaushik Agarwal[13] Todd Correll[2] Yimeng Lu[2] Richie Phan[2] Michael Chattergoon[2] Tarik Asselah[14], [1]Rush University Medical Center, [2]Vir Biotechnology, Inc., [3]Arensia Exploratory Medicine GmbH, DUüsseldorf, Germany, [4]Aga Khan University, Karachi, Pakistan, [5]Ziauddin University Hospital, [6]ARENSIA Exploratory Medicine, [7]Fundeni Clinical Institute, [8]Hannover Medical School, [9]University of Milan, [10]University of Calgary, [11]Weill Cornell Medicine, [12]University of Auckland, [13]Kings College Hospital, [14]Hôpital Beaujon

Background: Chronic hepatitis D virus (HDV) infection represents the most severe form of chronic viral hepatitis with limited treatment options. In the Phase 2 SOLSTICE study, participants receiving elebsiran and tobevibart (E+T) showed robust virologic suppression, including undetectable HDV RNA (66% at Week 48 and 88% at Week 96), reduction in hepatitis B surface antigen (HBsAg) (−3.56 $\log_{10}$ IU/mL at Week 48 and −3.87 $\log_{10}$ IU/mL at Week 96), and normalization of alanine aminotransferase (ALT) (~50% at Weeks 48 and 96). SOLSTICE demonstrated that a monthly combination regimen can achieve durable viral control, even in participants with compensated cirrhosis. The ECLIPSE registrational program comprises 3 global trials evaluating the efficacy and safety of E+T in treatment-experienced and treatment-naïve populations and the regimen was granted FDA Breakthrough Therapy Designation. ECLIPSE 1 (NCT06903338) is the first pivotal trial to report results. **Methods:** Eligible participants were non-cirrhotic or compensated cirrhotic (CPT score < 7) adults with HDV RNA ≥ 500 IU/mL and elevated ALT (< 5 × ULN) on NA therapy. Key exclusion criteria included treatment with HDV antivirals (e.g., bulevirtide or interferon-α) within 24 weeks before the first dose of E+T. Participants were randomized 2:1 to either receive treatment upon randomization with elebsiran 200 mg + tobevibart 300 mg administered subcutaneously every 4 weeks (Arm 1) or delay treatment, with initiation of E+T at Week 12 (Arm 2). The primary efficacy endpoint was the proportion of participants achieving undetectable HDV RNA defined as < lower limit of quantification (LLOQ), target not detected (TND), with ALT normalization at Week 48 for Arm 1 vs at Week 12 for Arm 2. Key secondary and exploratory endpoints included achievement of HDV RNA < LLOQ, TND, as well as changes in HBsAg. Safety and tolerability of E+T were also evaluated. **Results:** A total of 124 participants (39 sites, 10 countries) were randomized with ~55% having compensated cirrhosis; the mean baseline HDV RNA was 5.5 $\log_{10}$ IU/mL and the mean ALT was 100.1 U/L across both arms. Key baseline characteristics are summarized in the table. All Arm 1 participants completed 48 weeks of E+T; one Arm 2 participant withdrew from the study during the delayed treatment period. Complete primary efficacy and safety data will be available and analyzed prior to TLM 2026. **Conclusion:** Combination therapy with E+T represents a promising approach for the treatment of chronic HDV infection and has the potential to achieve virologic control across diverse patient populations with a once-monthly dosing regimen. The results of the ECLIPSE 1 study are anticipated to further

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characterize the efficacy and safety of elebsiran and tobevibart in a larger, geographically diverse population and evaluate the consistency of findings from earlier studies.

	Arm 1 (Immediate Treatment with Elebsiran + Tobevibart) N=83	Arm 2 (Delayed Treatment with Elebsiran + Tobevibart Starting at W12) N=41
Age*, y	43.8 ±11.6	46.4 ± 10.9
Male, n (%)	55 (66.3)	27 (65.9)
Race, n (%)		
White	41 (49.4)	24 (58.5)
Black or African American	7 (8.4)	3 (7.3)
Asian	34 (41.0)	13 (31.7)
Other	1 (1.2)	1 (2.4)
ALT*, U/L	94.0 ± 42.2	112.6 ± 65.6
HDV RNA*, log_{10} IU/mL	5.4 ± 1.2	5.7 ± 1.0
HBsAg*, log_{10} IU/mL	3.7 ± 0.6	3.7 ± 0.8
HBeAg positive, n (%)	13 (15.7)	10 (24.4)
Platelets*, 10^9/L	167.3 ± 71.8	153.1 ± 54.9
Compensated Cirrhosis^, n (%)	46 (55.4)	23 (56.1)
Liver Stiffness*, kPa	13.3 ± 5.5	13.6 ± 5.8
CPT Score*#	5.1 ± 0.2	5.1 ± 0.3
Past HDV Therapy		
Bulevirtide, n (%)	3 (3.6)	0

*mean ± SD
^cirrhosis status determined by 1) liver stiffness ≥15 and ≤25 kPa, OR 2) liver biopsy with METAVIR F4, OR 3) cirrhotic liver disease based on Investigator assessment
#applicable only for compensated cirrhotic participants

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dislosure submitted, Kaushik Agarwal:, Todd Correll:, Yimeng Lu:, Richie Phan:, Michael Chattergoon:Vir Biotechnology: Employee, Tarik Asselah:No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted, No dislosure submitted.

5006 | HEPATIC FAT REDUCTION, LIPID-LOWERING EFFECTS, AND SAFETY OF THYBETADOR (CS060380), A NEXT-GENERATION THR-N2 AGONIST, IN MASH: A PHASE 2A, RANDOMIZED TRIAL

Jiangao Fan[1] Junping Shi[2] Qi Zheng[3] Hua Bian[4] Liang Hong[5] Chuanwu Zhu[6] Huiqing Liang[7] Yue Wang[8] Xiangwei Hua[8] Rong Deng[8] Li Tang[8] Hualing Pan[8] Gaihong Wang[8] Julia Yang[8] Zhenwei Zhang[8] Peter Wang[8] H.Eric Xu[8], [1]Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, [2]The Affiliated Hospital of Hangzhou Normal University, [3]The First Affiliated Hospital of Fujian Medical University, [4]Zhongshan Hospital Affiliated with Fudan University, [5]Wenzhou Medical University Third Affiliated Hospital, [6]The Fifth People's Hospital of Suzhou, [7]Xiamen Hospital of T.C.M, [8]Cascade Pharmaceuticals, Inc

Background: Metabolic dysfunction-associated steatohepatitis (MASH) represents an urgent global therapeutic need with limited approved treatment options. This study evaluated Thybetador (CS060380), an oral, liver-targeted thyroid hormone receptor beta (THR-β) agonist with high potency and greater than 100-fold selectivity for THR-β over THR-α relative to triiodothyronine (T3). **Methods:** This phase 2a, randomized, double-blind, placebo-controlled study enrolled 120 adults with MASH (biopsy-confirmed or MRI-PDFF ≥10%). Participants received daily oral doses of Thybetador (0.25 mg, 0.5 mg, 1 mg, or 2 mg) or pooled placebo for 84 days. The primary endpoint was the percentage change in liver fat (MRI-PDFF) to Day 84; secondary endpoints included SHBG, lipid parameters, and safety through Day 98. **Results:** Thybetador demonstrated robust target engagement, as evidenced by dose-dependent increases in serum SHBG that peaked at a mean change of 505.2% in the 2 mg cohort ($P < 0.0001$). For the primary endpoint, Thybetador produced substantial reductions in hepatic fat; in the full analysis set (FAS), the 2 mg dose achieved a 72.6% reduction in liver fat, while in the per-protocol set (PPS), the peak reduction was 75.5% versus 4.6% with placebo ($P < 0.0001$). Furthermore, 83% to 100% of treated participants achieved the ≥30% MRI-PDFF responder threshold in the PPS. Beyond hepatic fat reduction, Thybetador 2 mg improved systemic cardiometbolic risk markers by Day 84, reducing serum LDL-C by 32.3%, ApoB by 38.2%, the ApoB/ApoA ratio by 32.3%, lipoprotein(a) by 46.4% and triglycerides by 64.4% (placebo-adjusted). At the Day 98 follow-up, circulating lipid levels trended back toward baseline, consistent with a reversible pharmacological effect. Furthermore, a higher proportion of participants achieved a ≥17 U/L reduction in ALT at Day 84 with Thybetador 0.25 mg and 0.5 mg compared with placebo. No serious adverse events, deaths, or cases meeting Hy's Law criteria for drug-induced liver injury were reported, and no treatment-emergent adverse events led to drug discontinuation. Transient elevations in ALT and AST peaked around Day 14, consistent with on-target metabolic activity; these resolved toward baseline by Day 84 and fell slightly below baseline by Day 98. No clinical thyroid axis toxicity was observed. The incidence of gastrointestinal adverse events, including diarrhea and nausea, was low and comparable between the Thybetador and placebo groups. **Conclusion:** Over 12 weeks of treatment, Thybetador achieved profound, rapid, and exceptional reductions in liver fat and significantly improved systemic atherogenic and metabolic lipid markers. Coupled with a favorable safety and tolerability profile, including a low incidence of gastrointestinal adverse events, these findings support the continued clinical development of Thybetador as a leading metabolic therapy.

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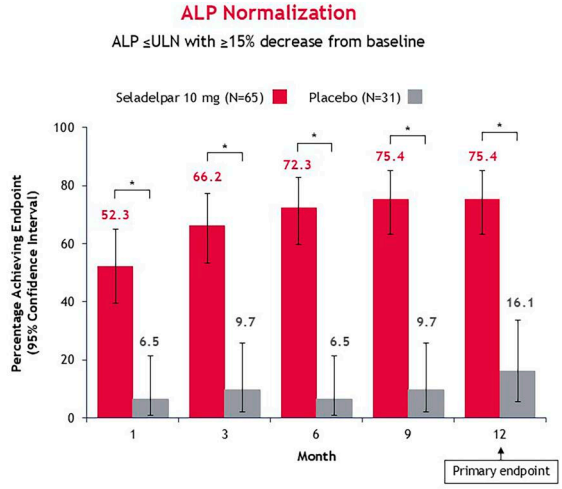
5007 | SELADELPAR FOR ALKALINE PHOSPHATASE NORMALIZATION IN PRIMARY BILIARY CHOLANGITIS: RESULTS FROM THE IDEAL PHASE III RANDOMIZED-CONTROLLED TRIAL

Cynthia Levy[1] Susheela Carroll[2] Kris Kowdley[3] Christopher Bowlus[4] Ira Jacobson[5] Marlyn Mayo[6] Sonal Kumar[7] Stuart Gordon[8] Hin Hin Ko[9] Mitchell Shiffman[10] Ziad Younes[11] Yan Zhou[2] Mark Sheng[2] Anna Zagorska[2] Daria Crittenden[2], [1]Miller School of Medicine, University of Miami, Miami, FL, USA, [2]Gilead Sciences, Inc., Foster City, CA, USA, [3]Liver Institute Northwest, Seattle, WA, USA, [4]University of California Davis School of Medicine, Sacramento, CA, USA, [5]Division of Gastroenterology and Hepatology, NYU Grossman School of Medicine, New York, NY, USA,

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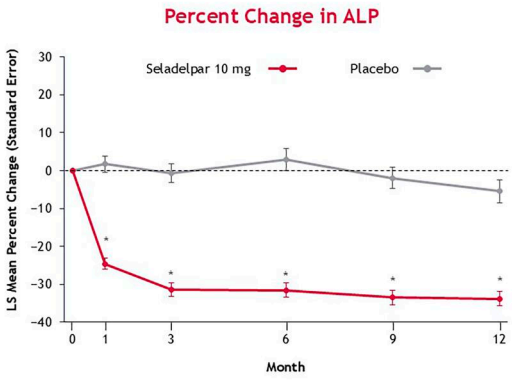
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Background: Alkaline phosphatase (ALP) is a key biomarker in primary biliary cholangitis (PBC). Historically, ALP level > 1.67× the upper limit of normal (ULN) has been a threshold for escalation to second-line therapy, and patients (pts) with values above this threshold have been evaluated in registrational studies. However, it is increasingly appreciated that any ALP elevation may increase risk of disease progression. Seladelpar (SEL) is a first-in-class delpar (selective peroxisome proliferator-activator receptor delta agonist) approved for second-line treatment of PBC. For the first time, we report the results from the IDEAL trial (NCT06060665), which evaluated the effect of SEL in pts with ALP between 1–1.67× ULN. **Methods:** In this phase III, double-blind trial, pts receiving ursodeoxycholic acid (UDCA) or intolerant to UDCA with ALP > 1 and < 1.67× ULN were randomized 2:1 to receive once-daily SEL 10 mg or placebo (PBO) for 12 months. The primary endpoint was ALP normalization defined as a composite of ALP ≤ ULN and a ≥ 15% decrease from baseline (BL) at Month (M) 12. Secondary endpoints included the ALP normalization composite endpoint, ALP ≤ ULN, and ALP changes from BL at each timepoint. Exploratory endpoints included changes in other markers of cholestasis and liver injury. Safety was also assessed. **Results:** Overall, 96 pts were randomized (SEL: 65, PBO: 31). At BL, 93.8% were female, with a mean age of 61 years, mean (SD) ALP of 153 (22.7) U/L, and mean (SD) total bilirubin (TB) of 0.62 (0.20) mg/dL. At M12, ALP normalization based on the composite endpoint was achieved in 75.4% of pts receiving SEL versus 16.1% receiving PBO, with a stratum-adjusted treatment difference of 61.3% (P < 0.0001); higher response rates were seen with SEL versus PBO at all timepoints (**Figure**). Greater decreases in ALP were observed with SEL versus PBO as early as M1 and over the treatment period, with M12 least squares (LS) mean percent changes from BL of −33.8% and −5.4% (P < 0.0001), respectively (**Figure**). TB was reduced with SEL at M6 but was similar to PBO at M12. At M12, the LS mean change from BL in alanine aminotransferase was −22.5% and −5.6% (P < 0.01) in the SEL and PBO groups, respectively. The LS mean change from BL in gamma-glutamyl transferase was −29.9% and −4.4% (P = 0.0001), respectively. Adverse event incidence was generally similar between SEL and PBO groups; serious adverse events occurred in 3.1% and 12.9% of pts, respectively, and none were deemed related to trial drug. **Conclusion:** In pts with PBC and ALP between 1–1.67× ULN, SEL led to a significantly higher proportion of pts achieving ALP normalization, with rapid and sustained ALP reductions and no new safety concerns. These results help inform treatment decisions for an understudied population and demonstrate biochemical normalization as a feasible goal.



* Indicates P<0.0001. A two-sided P value was provided for the primary endpoint based on the Cochran-Mantel-Haenszel test, and all other P values provided are nominal. Treatment differences are stratum-adjusted. The ULN for ALP is 116 U/L.

Number of responders/ patients in full analysis set	34/65	2/31	43/65	3/31	47/65	2/31	49/65	3/31	49/65	5/31
ALP ≤ULN, n (%)	35 (53.8)	4 (12.9)	46 (70.8)	4 (12.9)	48 (73.8)	4 (12.9)	50 (76.9)	6 (19.4)	50 (76.9)	5 (16.1)
≥15% decrease in ALP, n (%)	52 (80.0)	2 (6.5)	58 (89.2)	4 (12.9)	56 (86.2)	2 (6.5)	56 (86.2)	5 (16.1)	57 (87.7)	10 (32.3)
Treatment difference, % (95% confidence interval)	47.9 (32.2 to 63.6)		58.5 (42.7 to 74.4)		67.4 (52.6 to 82.1)		67.0 (51.6 to 82.3)		61.3 (44.9 to 77.7)	



* indicates P<0.0001.

Number of patients						
Seladelpar 10 mg	65	62	63	63	61	62
Placebo	31	30	30	28	27	26

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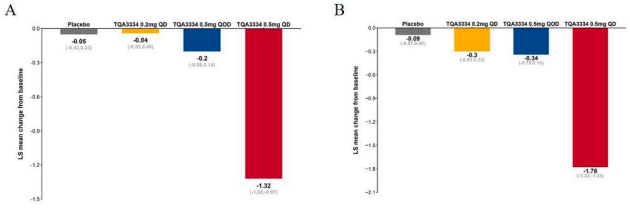
5008 | EFFICACY AND SAFETY OF AN ORAL TLR7 AGONIST THROUGH 48 WEEKS IN NAS-TREATED CHRONIC HBV INFECTION: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II TRIAL

Peng Hu[1] Hong Tang[2] Xiaobo Lu[3] Yingli He[4] Bing Zhao[5] Guoxin Hu[6] Hong Peng[7] Cunli Nong[8] Liang Hong[9] Fang Yang[10] Xudong Hu[11] Jiawei Geng[12] Zheng Wang[13] Ding Yu[14] Miaoxia Liu[14] Jianing Wang[14], [1]The First Affiliated Hospital of Chongqing Medical University, [2]West China Hospital of Sichuan University, [3]The First Affiliated Hospital of Xinjiang Medical University, [4]The First Affiliated Hospital of Xi'an Jiaotong University, [5]Pu'er People's Hospital, [6]Peking University Shenzhen Hospital, [7]Guizhou Provincial People's Hospital, [8]Liuzhou Workers' Hospital, [9]Ruian People's Hospital, [10]The Sixth People's Hospital of Shenyang, [11]Wuhan Jinyintan Hospital, [12]The First People's Hospital of Yunnan Province, [13]Wuxi Fifth People's Hospital, [14]Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

Background: Chronic HBV infection remains a major global health challenge. Current therapies (interferons and NAs) have limited efficacy in reducing/clearing HBsAg. TQ-A3334, a TLR7 agonist, activates innate and adaptive immunity. This study evaluated TQ-A3334 combined with NAs in reducing HBsAg in NAs-treated chronic HBV subjects. **Methods:** NAs-treated CHB subjects (18–65 years, HBsAg 100–5000 IU/mL, HBeAg-negative/positive) were enrolled. Subjects were sequentially assigned to low-dose (0.2 mg QD, n = 16), medium-dose (0.5 mg QOD, n = 32), and high-dose (0.5 mg QD, n = 33) groups. Within each group, subjects were randomized 3:1 to TQ-A3334 or placebo. All received TQ-A3334/placebo + NAs for 48 weeks, then NAs alone for 24 weeks. After 48 weeks, eligible subjects discontinued NAs and were followed for 48 more weeks. **Results:** Mean age of 81 enrolled subjects: 43.9 years; 61.73% male. Low-dose, medium-dose, high-dose, and placebo groups had 12, 24, 24, and 21 subjects. Baseline mean HBsAg (log10 IU/mL): 3.01, 2.95, 2.78, 2.88. HBeAg positivity:

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16.67%, 25.00%, 16.67%, 4.76%. At week 24, mean HBsAg change (log10 IU/mL): low-dose −0.0352, medium-dose −0.2069, high-dose −1.3244, placebo −0.0534. High-dose vs. placebo: p < 0.0001. At week 48, mean HBsAg change (log10 IU/mL):low-dose −0.3041, medium-dose −0.3372, high-dose −1.7786, placebo −0.0880; High-dose vs. placebo: p < 0.0001; High-dose achieved HBsAg seroclearance in 20.83% (5/24) subjects and seroconversion in 16.67% (4/24) subjects; no other groups reached these. HBeAg seroclearance: medium-dose 16.67% (1/6), high-dose 25% (1/4). In subjects with baseline HBsAg < 1000 IU/mL, high-dose reduced HBsAg by 2.079 log10 IU/mL, with HBsAg loss in 26.32% (5/19) and seroconversion in 21.05% (4/19). In those with baseline HBsAg < 500 IU/mL, high-dose reduced HBsAg by 2.31 log10 IU/mL, with HBsAg loss in 40% (4/10) and seroconversion in 30% (3/10). TQ-A3334 was well tolerated. Most AEs were Grade 1/2. Grade 3 TEAEs were neutrophil count decreased, WBC decreased, lymphocyte counts decreased, ALT increased, and hypertriglyceridemia. No grade 4/5 AEs. All AEs were reversible/manageable. **Conclusion:** In NAs-treated subjects with chronic HBV infection, TQ-A3334 0.5mg QD combined with NAs substantially reduced HBsAg levels and even achieved HBsAg seroclearance or seroconversion in some subjects, with greater efficacy observed in those with lower baseline HBsAg levels.



Mean HBsAg decline from baseline at week 24 (A) and week 48 (B) in each group

Disclosures: Peng Hu:Nothing to Disclose, Hong Tang:, Xiaobo Lu:, Yingli He:, Bing Zhao:, Guoxin Hu:, Hong Peng:, Cunli Nong:, Liang Hong:, Fang Yang:, Xudong Hu:, Jiawei Geng:, Zheng Wang:, Ding Yu:, Miaoxia Liu:, Jianing Wang:Chia Tai Tianqing Pharmaceutical Group Co., Ltd.: Employee.

5009 | EFFICACY AND SAFETY OF SEQUENTIAL BRII-179, ELEBSIRAN, AND PEGYLATED INTERFERON ALFA THERAPY IN CHRONIC HEPATITIS B VIRUS INFECTION: END-OF-TREATMENT AND FOLLOW-UP RESULTS FROM THE PHASE 2 ENRICH STUDY

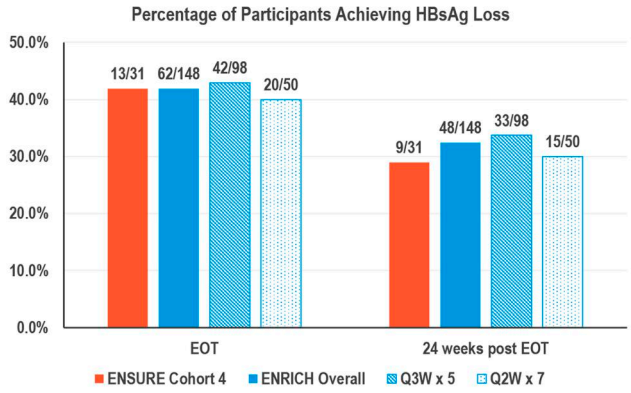
Jinlin Hou[1] Jianmei Lin[2] Qing Xie[3] Jianping Li[4] Xuejiao Liao[5] Qianguo Mao[6] Li Zhu[7] Fangfang Lv[8] Jiming Zhang[9] Xinyue Chen[10] Wen Xie[11] Honglian Bai[12] Xie-Er Liang[1] Chong Zhu[13] Alex Tian[13] Qing Zhu[14] Haifeng Cao[13] David Margolis[14], [1]Nanfang Hospital, Southern Medical University, [2]Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, [3]Ruijin Hospital, [4]Guangzhou Eighth People's Hospital, Guangzhou Medical University, [5]Shenzhen Third People's Hospital, [6]Xiamen Hospital of Traditional Chinese Medicine, [7]Public Health Clinical Medical Center of Chengdu, [8]Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, [9]Huashan Hospital Affiliated to Fudan University, [10]Beijing YouAn Hospital, Capital Medical University, [11]Beijing Ditan Hospital, Capital Medical University, [12]The First People's Hospital of Foshan, [13]Brii Biosciences (Beijing) Co. Limited, [14]Brii Biosciences, Inc.

Background: Previous ENSURE Cohort 4 (NCT05970289) demonstrated that BRII-179-experienced participants achieved higher functional cure rates after receiving elebsiran and pegylated interferon alfa (PEG-IFNα), especially among anti-HBs responders, suggesting that BRII-179 may play an important role in achieving durable immunological control of HBV. A Phase 2b ENRICH Study (NCT06491563) aims to validate the priming effect of BRII-179 followed by elebsiran + PEG-IFNα. End-of-treatment (EOT) and 24 weeks post EOT results are summarized. **Methods:** Virologically suppressed non-cirrhotic participants with chronic HBV infection on nucleos(t)ide analogues, with screening HBsAg > 100 and ≤ 3,000 IU/mL and anti-HBs < LLOQ (2 IU/L), were eligible. All participants received a 12-week BRII-179 prime treatment: 40 mcg BRII-179 for 5 doses administered once every 3 weeks (Q3W) or for 7 doses once every 2 weeks (Q2W). Starting from Week 16, all participants received 48-week combination treatment of elebsiran and PEG-IFNα and were followed for another 24 weeks post EOT. **Results:** A total of 148 participants were enrolled and completed BRII-179 prime treatment (Q3W: n = 98, Q2W: n = 50). At EOT, 41.9% (62/148) of the participants achieved HBsAg loss, with similar HBsAg loss rates across different BRII-179 dosing schedules (5 doses Q3W: 42.9% [42/98]; 7 doses Q2W: 40.0% [20/50]). Subgroup analyses showed that participants with higher baseline HBsAg levels (1,000-3,000 IU/mL) achieved clinically meaningful HBsAg loss rates at EOT: 33.0% (13/39) and 28.6% (4/14) with BRII-179 Q3W and Q2W regimens, respectively. Durable HBsAg loss up to 24 weeks post EOT was achieved in 32.4% (48/148) among the overall population, and 38.9% (37/95) and 20.8% (11/53) among participants with baseline HBsAg 100-1,000 and 1,000-3,000 IU/mL, respectively. BRII-179 followed by elebsiran and PEG-IFNα were generally safety and tolerated. The majority of treatment-related adverse events were consistent with the known side effects of PEG-IFNα and had

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recovered or resolved within 24 weeks after treatment completion. **Conclusion:** BRII-179 followed by elebsiran and PEG-IFNα achieved clinically meaningful rates of HBsAg loss at EOT (41.9%) and through 24 weeks post EOT (32.4%), in particular among subgroups with higher baseline HBsAg levels. HBsAg loss durability was maintained in a meaningful proportion of participants through 24 weeks post EOT. These results were consistent with the HBsAg loss rate observed in ENSURE Cohort 4, 41.9% at EOT and 29.0% through 24 weeks post EOT (Wong et al., AASLD 2025), supporting BRII-179 priming as a potential strategy to enhance functional cure responses in chronic HBV infection.

Figure. Percentage of participants achieving HBsAg loss among the overall population and grouped by BRII-179 dose regimens



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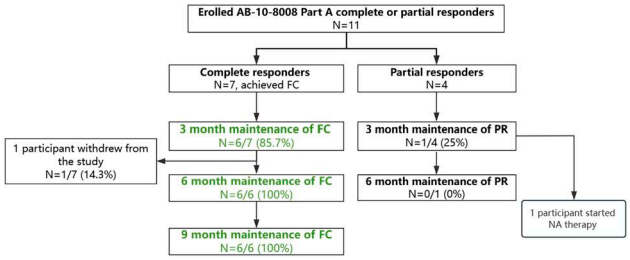
5010 | DURABILITY OF FUNCTIONAL CURE TO AHB-137 MONOTHERAPY IN TREATMENT-NAC/VE PARTICIPANTS WITH CHRONIC HEPATITIS B: LONG-TERM FOLLOW-UP RESULTS OF THE AB-10-8004 STUDY

Yunqing Qiu[1] Zhihong Liu[2] Dazhi Zhang[3] Haibin Gao[4] Yujuan Guan[5] Guohong Ge[6] Youwen Tan[7] Qian Zhou[1] Shan Zhong[3] Lvfeng Yao[4] Ying Zhu[5] Chunyan Ye[6] Xingbei Zhou[7] Cuiting Jiang[8] Kaili Zhang[8] Mingyue Chen[8] Yeming Pan[8] Hanze Zhang[8] Chen Yang[8] Miao Wang[8] Hao Wang[8] Chengyong Yang[8] Chengyong Yang[9] Guofeng Cheng[8] Guofeng Cheng[9] Jinlin Hou[2] Junqi Niu[10], [1]The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China, [2]Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China, [3]The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China, [4]Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, Fujian, China, [5]Guangzhou Eighth People's Hospital, Guangzhou Medical University, Guangzhou, Guangdong, China, [6]The Third People's Hospital of Changzhou, Changzhou, Jiangsu, China, [7]The Third People's Hospital of Zhenjiang, Zhenjiang, Jiangsu, China, [8]Ausper Biopharma Co. Ltd., Hangzhou, China, [9]Ausperbio Therapeutics Inc., Foster City, CA, United States, [10]The First Hospital of Jilin University, Changchun, Jilin, China

Background: AHB-137 is an investigational unconjugated antisense oligonucleotide (ASO) targeting all HBV RNAs for the treatment of chronic hepatitis B (CHB). The long-term follow-up Study AB-10-8004 (NCT07146100) evaluated the durability of off-treatment responses and long-term safety in treatment-naïve participants who achieved a complete response (CR) or partial response (PR) after 16 weeks of AHB-137 monotherapy and a 24-weeks follow-up without HBV treatment in the Phase 2 parent Study AB-10-8008 (Part A, NCT06829329). **Methods:** Treatment-naïve participants from AB-10-8008 Part A who achieved CR (HBsAg < 0.05 IU/mL and HBV DNA < LLOQ [< 10 IU/mL]) or PR (HBsAg 0.05 to < 10 IU/mL and HBV DNA < LLOQ) at the end of the parent study were enrolled in AB-10-8004. Participants were treated with AHB-137 monotherapy without NA treatment; thus functional cure (FC) was defined as maintenance of CR for ≥ 24 weeks after cessation of AHB-137, without initiation of other HBV treatment. Participants were followed for long-term durability of HBsAg and HBV DNA suppression and characterization of the long-term safety profile of AHB-137. **Results:** A total of 11 participants from Study AB-10-8008 (including 7 CR and 4 PR) were enrolled in AB-10-8004 Study. Among the 7 CR participants, 6/7 (85.7%) remained in FC at Month 3 of AB-10-8004 (9 months after AHB-137 cessation). All 6 participants remaining under follow-up maintained FC through Month 9, (15 months after AHB-137 cessation). One CR participant experienced HBsAg and HBV DNA rebound by Month 3 and withdrew from the Study. Among the 4 PR participants, 1 maintained PR at Month 3; no participant maintained PR at Months 6. One participant experienced virologic relapses and initiated NA therapy, no ALT elevation was observed. Overall, the long-term safety profile remained favorable. No clinical

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relapse was observed. No severe hepatic flares, hepatic decompensation, or treatment-related late-onset adverse events were reported during follow-up. **Conclusion:** Complete responses following 16 weeks of AHB-137 monotherapy showed durable off-treatment maintenance after AHB-137 cessation, whereas partial responses were less durable. The long-term safety profile remained favorable, with no clinical relapse, severe hepatic flares, or hepatic decompensation observed. This data further supports the development of AHB-137 in treatment-naïve CHB patients.



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5011 | SAROGLITAZAR MAGNESIUM ACHIEVES RESOLUTION OF STEATOHEPATITIS WITHOUT WORSENING FIBROSIS IN PATIENTS WITH MASH: RESULTS OF A RANDOMIZED, PLACEBO-CONTROLLED PHASE 2B TRIAL (EVIDENCES X)

Naga Chalasani[1] Don Lazas[2] Paola Casciato[3] Nomita Kim[4] Beatriz Ameigeiras[5] Marcela De Sousa Coelho[6] Oscar Cummings[7] Nehal Parikh[8] Nihal Shaikh[9] Deven Parmar[9] Arun Sanyal[10], [1]Indiana University Medical Center, [2]Digestive Health Research, [3]Hospital Italiano de Buenos Aires, [4]IMA Clinical Research, [5]Hospital Ramos Mejía-CABA, [6]Hospital General de Agudos Dr. José María Ramos Mejía, [7]Indiana University School of Medicine, [8]Zydus Lifesciences Ltd, [9]Zydus Therapeutics Inc, [10]Virginia Commonwealth University

Background: Saroglitazar is a predominantly PPAR-α agonist with moderate PPAR-γ activity that improves metabolic and hepatic abnormalities associated with metabolic dysfunction-associated steatohepatitis (MASH). We evaluated the efficacy and safety of saroglitazar in adults with MASH in a randomized Phase 2b trial. **Methods:** In this multicenter, double-blind, placebo-controlled trial (NCT05011305), adults with MASH were randomized to saroglitazar magnesium 4 mg (n = 64), saroglitazar magnesium 2 mg (n = 63), or placebo (n = 62) once daily for 52 weeks. The primary histologic endpoint was resolution of steatohepatitis without worsening of liver fibrosis at end of treatment. A secondary histologic endpoint was ≥ 1-stage improvement in fibrosis without worsening of NAFLD Activity Score (NAS). Analyses used the intention-to-treat population with missing-at-random methodology and were stratified by baseline diabetes status. **Results:** Among 189 randomized participants, mean age was 56 years, approximately 61% were women, and mean BMI was approximately 35 kg/m²; 59% had type 2 diabetes. Baseline demographic and clinical characteristics were balanced across groups. Steatohepatitis resolution without worsening fibrosis occurred in 39.1% with saroglitazar magnesium 4 mg, 32.4% with 2 mg, and 13.7% with placebo. Treatment differences versus placebo were 24.9% (95% CI 9.5–40.3; P = 0.002) for 4 mg and 16.5% (95% CI 1.3–31.6; P = 0.033) for 2 mg. Fibrosis improvement without worsening NAS occurred in 34.8%, 22.8%, and 24.6%, respectively; differences versus placebo were 10.2% (95% CI −6.3–26.6; P = 0.230) and −0.9% (95% CI −16.7–14.9; P = 0.209). However, compared with placebo, saroglitazar magnesium 4 mg demonstrated favorable improvements in non-invasive assessments of liver fibrosis, with a treatment difference of −9.50 ng/mL (95% CI: −15.3, −3.7) for Pro-C3, −0.35 (95% CI: −0.5, −0.2) for APRI, −0.30 (95% CI: −0.5, −0.1) for FIB-4, and −0.53(95% CI: −1.0,−0.1) for ADAPT. Saroglitazar magnesium 4 mg also produced clinically meaningful improvements in liver enzymes, lipid and glycemic parameters, and insulin resistance. Treatment was well tolerated, without significant weight gain or a drug-induced liver injury signal. **Conclusion:** In this randomized Phase 2b trial, saroglitazar achieved the primary histologic endpoint of MASH resolution without worsening fibrosis, with the greatest effect observed with 4 mg. It did not meet the secondary end point of histological improvement in liver fibrosis but the positive effects of saroglitazar 4 mg on non-invasive fibrosis markers are encouraging.

Disclosures: Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus,

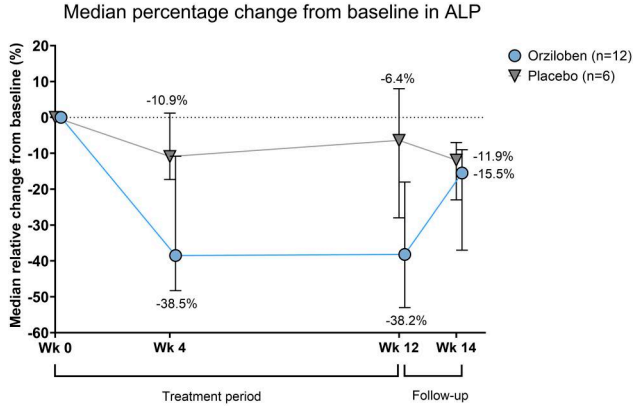
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5012 | PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF ORZILOBEN (NST-6179) IN ADULTS WITH INTESTINAL FAILURE-ASSOCIATED LIVER DISEASE (IFALD)

David Fraser[1] Manpreet Mundi[2], [1]Northsea Therapeutics, [2]Mayo Clinic, Rochester MN, United States

Background: IFALD is a rare and serious liver disease in patients with chronic intestinal failure, with no approved treatments. Orziloben is an investigational, oral, fully synthetic medium-chain fatty acid analogue targeting cholestasis, inflammation, and fibrosis. **Methods:** This Phase 2 trial (NCT05919680) randomized 33 adults with IFALD receiving parenteral nutrition across international academic centers. Eligible patients had persistent (≥ 6 months) elevation of ≥ 1 predefined IFALD criteria: ALP, GGT, ALT, or AST ≥ 1.5 x ULN, or total bilirubin > ULN. Key exclusion criteria included severe hepatic injury (total bilirubin > 2.5 mg/dL, ALP ≥ 10 x ULN, ALT or AST ≥ 5 x ULN). Patients were randomized 2:1 to receive orziloben 800 mg QD or placebo for 4 weeks in Part A, or orziloben 1200 mg QD or placebo for 12 weeks in Part B. Safety, tolerability, and changes from baseline to end-of-treatment in non-invasive biomarkers of cholestasis and liver injury were evaluated. **Results:** In Part B, 24 patients were randomized (58% female; mean age 46 yrs), of which 18 (orziloben n = 12; placebo n = 6) completed the 12-week treatment period without any major protocol deviations. At baseline, patients presented with a predominantly cholestatic phenotype; 92% had baseline levels ≥ 1.5 x ULN for ALP and/or GGT, compared to 46% for ALT and 33% for AST. Orziloben led to pronounced, sustained reductions in cholestatic biomarkers at weeks 4 and 12. For ALP, median (IQR) percent change from baseline for orziloben (n = 12) vs. placebo (n = 6) was −38.5% (−48.3, −10.8) vs. −10.9% (−17.3, 1.2) at week 4 and −38.2% (−53.0, −17.6) vs. −6.4% (−26.3, 7.7) at week 12 (LS mean differences vs. placebo: −21.5% [90% CI: −38.6, −4.5] at week 4 and −21.0% [90% CI: −44.4, 2.4] at week 12), with reversal toward baseline following discontinuation of orziloben (week 14) (see Figure). GGT changes were −31.0% (−57.6, −5.7) vs. −15.8% (−22.1, −10.5) at week 4 and −39.1% (−53.9, −15.8) vs. 0.7% (−11.2, 22.9) at week 12; total bilirubin changes were −36.3% (−50.0, −29.7) vs. −13.1% (−29.2, −6.7) at week 4 and −27.8% (−50.0, −4.9) vs. −7.1% (−29.2, 8.3) at week 12. At baseline, elevated bilirubin (≥ 1 × ULN) was present in three patients in the orziloben group and two in the placebo group, with median reductions of −50 % and −14.6 % at Week 12, respectively. In patients with baseline ALP ≥ 1.5 x ULN, 82% (9/11) of orziloben treated patients achieved a composite ALP response (≥ 30% reduction with no bilirubin worsening) at week 12 versus 20% (1/5) for placebo. No notable difference in safety or tolerability parameters were observed between the treatment and placebo arms. **Conclusion:** Orziloben demonstrated rapid and sustained improvements in cholestatic liver injury, highlighted by marked reductions in ALP, GGT, and bilirubin. These findings support the further development of orziloben as a promising oral therapy for the treatment of IFALD.



Disclosures: David Fraser: Nothing to Disclose, Manpreet Mundi: Northsea: Grant/Research Support, Nestle: Grant/Research Support, VectivBio: Grant/Research Support, Fresenius Kabi: Advisor, NovoNordisk: Advisor, Baxter: Advisor, Nutrishare: Advisor, Otsuka: Advisor.

5013 | EFFICACY AND SAFETY OF PEMVIDUTIDE IN THE TREATMENT OF ADULTS WITH ALCOHOL USE DISORDER: RESULTS FROM RECLAIM, A 24-WEEK PHASE 2 RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

Henry Kranzler[1] Shaheen Tomah[2] W. Kyle Simmons[3] Stephanie O'Malley[4] Joseph Schacht[5] Xiaoxi Li[2]

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Background: Chronic excessive alcohol use is associated with significant morbidity and mortality and can lead to alcohol-associated liver disease (ALD), a leading indication for liver transplantation. There is a pressing unmet need for novel pharmacotherapies that simultaneously reduce chronic alcohol consumption and ameliorate alcohol-related liver injury. Pemvidutide is an investigational balanced 1:1 glucagon/glucagon-like peptide-1 (GLP-1) dual receptor agonist under development for the treatment of metabolic dysfunction-associated steato-hepatitis, ALD, and alcohol use disorder (AUD). While GLP-1 activity promotes satiety and weight loss, glucagon activity confers direct hepatic benefits, lowering liver fat, inflammation, and fibrosis. GLP-1 receptor agonists may also down-regulate central pathways implicated in AUD. This study assessed the safety and efficacy of pemvidutide in reducing heavy drinking among adult patients with AUD. **Methods:** RECLAIM (NCT06987513) was a Phase 2, multi-center, randomized, double-blind, placebo-controlled trial in treatment-seeking patients with moderate-to-severe AUD as per DSM-5, and BMI $\geq$25 kg/m². Patients were randomized 1:1 to receive pemvidutide 2.4 mg or placebo (PBO) once weekly for 24 weeks. The primary endpoint was change from baseline in heavy drinking days (HDDs)/week measured using the timeline follow-back (TLFB). Key secondary endpoints included two FDA-qualified self-reported measures of alcohol use (proportion of patients with a $\geq$2-level reduction in World Health Organization Risk Drinking Level [WHO-RDL] or zero HDDs), and serum phosphatidylethanol (PEth) levels, an alcohol biomarker. Adverse events (AEs) and discontinuation rates were reported. **Results:** At week 24, patients treated with pemvidutide (n = 50) achieved statistically significant improvements in primary and key secondary endpoints compared with PBO (n = 50). Treatment with pemvidutide led to significantly greater reductions in HDDs/week (-4.20 vs. -2.75; p = 0.0014) and PEth levels (p < 0.0001) and higher response rates of a 2-level reduction in WHO-RDL (p = 0.0049) and zero HDDs (p = 0.0066) than PBO. AEs were primarily mild-to-moderate gastrointestinal events, and treatment discontinuation rates were similar between pemvidutide and PBO (20% vs 22%). **Conclusion:** RECLAIM met its primary endpoint, with pemvidutide demonstrating significantly greater reduction in HDDs/week than placebo among patients with moderate-to-severe AUD. Patients treated with pemvidutide showed consistent significant improvements across key secondary endpoints, including self-reported and objective measures of alcohol use. Together with its generally favorable safety profile, these findings support further evaluation of pemvidutide as a potential novel treatment for AUD in a pivotal phase 3 trial of both heavy alcohol consumption and the early or advanced liver disease associated with it.

24-Week Primary and Key Secondary Efficacy Endpoints

Outcome Endpoints	Placebo (N=50)	Pemvidutide 2.4 mg (N=50)	Treatment Difference or OR (95% CI)*	p-value
HDDs/week,** LSM change from baseline	-2.75 (-3.44 to -2.07)	-4.20 (-4.92 to -3.49)	Diff = -1.45 (-2.32 to -0.58)	0.0014
≥2-level Reduction in WHO-RDL,*** (% [n/N[a]])	34.8 [16/46]	64.4 [29/45]	OR = 3.31 (1.4 to 7.7)	0.0049
Zero HDDs,*** (% [n/N[a]])	17.4 [8/46]	42.2 [19/45]	OR = 3.84 (1.4 to 10.4)	0.0066
Serum PEth Level,** LSM change from baseline (ng/mL)	22.0 (-41.9 to 85.8)	-153.4 (-218.8 to 87.9)	Diff = -175.4 (-259.6 to -91.1)	< 0.0001

*Expressed as odds ratios for categorical endpoints and least-squares mean (LSM) differences for continuous endpoints;
**Presented as model-estimated LSM using a Mixed Model for Repeated Measures (MMRM) model;
***Presented as percentages and counts using the Cochran-Mantel-Haenszel (CMH) test;
[a]Denominator for the proportion is the number of subjects who have non-missing outcome data
HDDs, heavy drinking days; LSM, Least-squares mean; OR, odds ratio; PEth, phosphatidylethanol; WHO-RDL, World Health Organization Risk Drinking Level.

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5014 | DR10624, A FIRST-IN-CLASS, FGF21 RECEPTOR/GLUCAGON RECEPTOR/GLP-1 RECEPTOR TRIPLE AGONIST, RAPIDLY AND SIGNIFICANTLY REDUCED LIVER FAT AND FIBROSIS MARKERS, AND IMPROVED LIVER FUNCTIONS AND LIPID PROFILES, IN PATIENTS WITH MASLD/MASH: RESULTS OF A RANDOMIZED PHASE 2 TRIAL.

Yongliang Fang[1] Vincent Wong[2] Junping Shi[3] Xiaoying Li[4] Yueyong Zhu[5] Xiqing Guo[6] Ming-Hua Zheng[7] Jinjun Chen[8] Jie Li[9] Hua Ye[10] Jiansheng Zhu[11] Xujing Liang[12] Junmin Jiang[13] Zijian Luan[14] Ge Li[14] Kaile Zhou[14] Junfang Xu[15] Yulong Gan[1] Yanshan Huang[1], [1]Zhejiang Doer Biologics Co., Ltd., [2]The Chinese University of Hong Kong, [3]The Affiliated Hospital of Hangzhou Normal University, [4]Zhongshan Hospital, Fudan University, [5]The First Affiliated Hospital of Fujian Medical University, [6]Chongqing University Three

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Gorges Hospital, [7]The First Affiliated Hospital of Wenzhou Medical University, [8]Nanfang Hospital, Southern Medical University, [9]Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, [10]Ningbo Medical Center Lihuili Hospital, [11]Taizhou Hospital of Zhejiang Province, [12]The First Affiliated Hospital of Jinan University, [13]Guangdong Provincial Hospital of Chinese Medicine, [14]Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd., [15]Huadong Medicine Co., Ltd.

Background: DR10624 is a first-in-class long-acting triple agonist targeting FGF21 receptor, glucagon receptor, and GLP-1 receptor, being investigated for the treatment of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH). The DR10624-201 study is a Phase 2, multicenter, randomized, placebo-controlled, double-blind study in patients with MASLD/MASH (NCT07024212). Here, we present the efficacy and safety results of the Phase 2 study. **Methods:** Adult participants with BMI 25-40 kg/m², liver fat content (LFC) ≥10% assessed by MRI-PDFF, and liver stiffness (LSM) 8-14.9 kPa assessed by FibroScan®, were randomized in a 4:1 ratio to receive subcutaneous injections of DR10624 (12.5 mg, 25 mg, 50 mg, and 75 mg) or placebo weekly for 12 weeks. The primary endpoint was relative percent change (%) of LFC from baseline to week 12. Secondary endpoints included changes in liver enzymes, fibrosis markers, lipid profiles, and safety. **Results:** A total of 110 subjects were enrolled in the study (mean age 39.5 years, BMI 31.7 kg/m², LFC 19.0%, LSM 9.9 kPa). Significant reductions from baseline in least squares (LS) mean LFC were observed across all DR10624 dose groups, compared with placebo at Week 12: Placebo (n = 19): −18.0%; 12.5 mg (n = 19): −58.8% (p < 0.001); 25 mg (n = 18): −72.7% (p < 0.001); 50 mg (n = 18): −80.3% (p < 0.001); 75 mg (n = 18): −78.4% (p < 0.001). Responder analysis showed that 60.8%, 88.9%, 94.1%, 94.3%, and 5.3% of subjects in 12.5 mg, 25 mg, 50 mg, 75 mg, and placebo groups, respectively, achieved ≥50% reduction in LFC; and 33.4%, 55.6%, 87.7%, 70.1%, and 0.0% of subjects in 12.5 mg, 25 mg, 50 mg, 75 mg, and placebo groups, respectively, achieved ≥70% reduction in LFC after 12-week treatment of DR10624. In addition, LFC normalization (< 5%) was achieved by 23.9% in 12.5 mg, 66.7% in 25 mg, 81.8% in 50 mg, and 69.8% in 75 mg, and 0.0% in placebo. Moreover, a ≥ 30% reduction in LSM was observed in 38.1%, 70.4%, 56.2%, 59.8%, and 27.3% of subjects in the 12.5 mg, 25 mg, 50 mg, 75 mg, and placebo groups, respectively. Compared with placebo, 12-week treatment with DR10624 led to reduction in ALT, AST, and fibrosis markers (FIB-4 and FAST), and improvement in lipid profiles (reduced TG, TC, non-HDL-C, LDL-C, VLDL-C, and ApoB, and increased HDL-C), and metabolic parameters (increased adiponectin and reduced body weight and uric acid). DR10624 was well tolerated. The most common adverse effects were gastrointestinal events and injection site reactions. **Conclusion:** Treatment with DR10624 resulted in a rapid and significant reduction in liver fat, along with improvements in liver stiffness, liver enzymes, fibrosis markers, lipid profiles, and metabolic parameters in patients with MASLD/MASH. These robust Phase 2 data support further development of DR10624 as an innovative and promising therapeutic option for MASH.

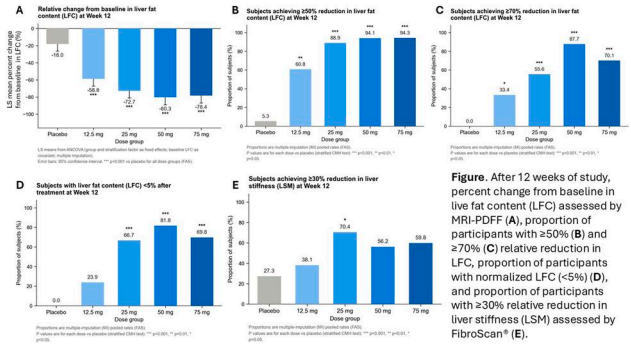


Figure. After 12 weeks of study, percent change from baseline in live fat content (LFC) assessed by MRI-PDFF (**A**), proportion of participants with ≥50% (**B**) and ≥70% (**C**) relative reduction in LFC, proportion of participants with normalized LFC (<5%) (**D**), and proportion of participants with ≥30% relative reduction in liver stiffness (LSM) assessed by FibroScan® (**E**).

Disclosures: Yongliang Fang:Nothing to Disclose, Vincent Wong:Abbott: Speaking and Teaching, AbbVie: Advisor, AbbVie: Speaking and Teaching, Boehringer Ingelheim: Advisor, Echosens: Advisor, Echosens: Speaking and Teaching, Gilead Sciences: Advisor, Gilead Sciences: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Novo Nordisk: Advisor, Pfizer: Advisor, TARGET PharmaSolutions: Advisor, Illuminatio Medical Technology: Stock - privately held company, Eli Lilly: Consultant, Merck: Consultant, Altimmune: Consultant, AstraZeneca: Consultant, Roche Diagnostics: Consultant, Furui: Consultant, Junping Shi: Nothing to Disclose, Xiaoying Li: Nothing to Disclose, Yueyong Zhu:, Xiqing Guo:, Ming-Hua Zheng:Nothing to Disclose, Jinjun Chen:, Jie Li: Nothing to Disclose, Hua Ye:, Jiansheng Zhu:, Xujing Liang:, Junmin Jiang:, Zijian Luan:Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd.: Employee, Ge Li: Name of Ineligble Company: Employee, Kaile Zhou: Hangzhou Zhongmei Huadong Pharmaceutical Co., Ltd: Employee, Junfang Xu: Nothing to Disclose, Yulong Gan: Nothing to Disclose, Yanshan Huang: Nothing to Disclose.

5015 | A PHASE 2B RANDOMIZED PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF EFINOPEGDUTIDE IN ADULTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS AND STAGE 2-3 FIBROSIS

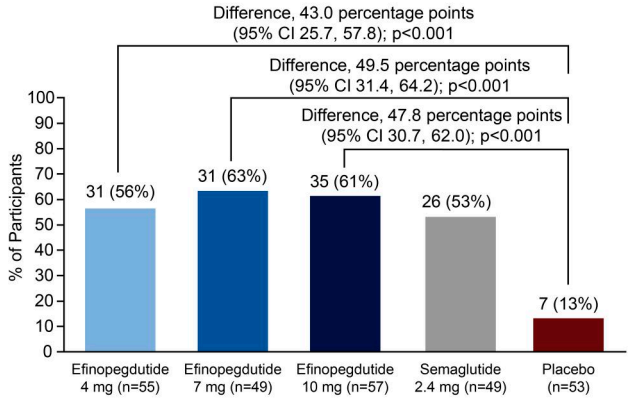
Jörn Schattenberg[1] Eric Lawitz[2] R. Ravi Shankar[3] Vincent Wong[4] Sven Francque[5] Keyur Patel[6] Luca

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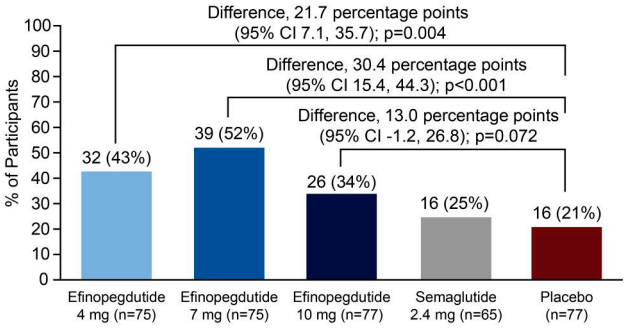
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Background: Efinopegdutide is a once-weekly GLP-1/glucagon receptor co-agonist (~2:1 relative receptor potency balance) under development for metabolic dysfunction-associated steatohepatitis (MASH). **Methods:** This phase 2b study enrolled adults with biopsy-proven MASH and F2/F3 fibrosis, randomized 1:1:1:1:1 to receive once-weekly subcutaneous efinopegdutide (4, 7 or 10 mg), placebo, or open-label semaglutide 2.4 mg. The baseline biopsy was assessed centrally on two occasions (Read 1 & Read 2). Read 1 was performed by a single pathologist to assess eligibility during screening and Read 2 was performed by a 3-pathologist panel at the time of the end-of-treatment (EOT) biopsy read to assess response. The primary endpoint (MASH resolution without worsening of fibrosis at week 52) was assessed in the mITT1 population (restricted to participants with baseline NAS ≥ 3 and >0 in each component on Read 2). The key secondary endpoint (fibrosis improvement ≥ 1-stage without worsening of steatohepatitis at week 52) was assessed in the mITT2 population (restricted to participants with baseline F1-F4 on Read 2). Missing EOT biopsies were considered non-responses. **Results:** 381 participants were randomized and received ≥ 1 dose. Baseline characteristics were similar across groups; 239 [63%] had F2 and 142 [37%] had F3. At week 52, MASH resolution without worsening of fibrosis occurred in 31 [56%] (4 mg), 31 [63%] (7 mg), and 35 [61%] (10 mg) participants receiving efinopegdutide vs 7 [13%] receiving placebo (difference vs placebo: 43.0 percentage-points [95% CI 25.7–57.8; $p<0.001$] for 4 mg, 49.5 percentage-points [95% CI 31.4–64.2; $p<0.001$] for 7 mg, and 47.8 percentage points [95% CI 30.7–62.0; $p<0.001$] for 10 mg]); 26 [53%] receiving semaglutide achieved this. Fibrosis improvement ≥ 1-stage without worsening of steatohepatitis occurred in 32 [43%] (4 mg), 39 [52%] (7 mg), and 26 [34%] (10 mg) participants receiving efinopegdutide vs 16 [21%] receiving placebo (difference vs placebo: 21.7 percentage-points [95% CI 7.1–35.7; $p=0.004$] for 4 mg, 30.4 percentage-points [95% CI 15.4–44.3; $p<0.001$] for 7 mg, and 13.0 percentage-points [95% CI −1.2–26.8; $p=0.072$] for 10 mg); 16 [25%] receiving semaglutide achieved this. Gastrointestinal adverse events (AEs) were the most frequently reported with the highest rates seen with 10 mg. AE-related discontinuations occurred more frequently among participants receiving efinopegdutide 10 mg (9 [11%]) compared to the other efinopegdutide groups (range: 3% to 4%) or placebo (1 [1%]); 1 [1%] receiving semaglutide discontinued study intervention due to an AE. **Conclusion:** Efinopegdutide significantly increased MASH resolution without worsening of fibrosis compared with placebo. The 7 mg dose demonstrated the most favorable benefit-risk profile, improving fibrosis by ≥ 1-stage without worsening steatohepatitis in ~50% of participants at 1 year.

A. MASH resolution without worsening of fibrosis (mITT1, missing as failure)



B. Fibrosis improvement ≥1-stage without worsening of steatohepatitis (mITT2, missing as failure)



Disclosures: Jörn Schattenberg:Akero: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Ipsen: Consultant, Inventiva Pharma: Consultant, Madrigal: Consultant, Northsea Therapeutics: Consultant, Novo Nordisk: Consultant, Roche: Consultant, Siemens Healthineers: Consultant, Boehringer Ingelheim: Advisor, AGED diagnostics: Stock - privately held company, Hepta Bio: Stock - privately held company, Novo Nordisk: Speaking and Teaching, Madrigal: Stock - publicly traded company, MedPublico GmbH: Speaking and Teaching, Eli Lilly: Advisor, Altimmune: Consultant, Astra Zeneca: Consultant, Gilead Science: Consultant, Merck: Consultant, MSD Sharp & Dohme GmbH:

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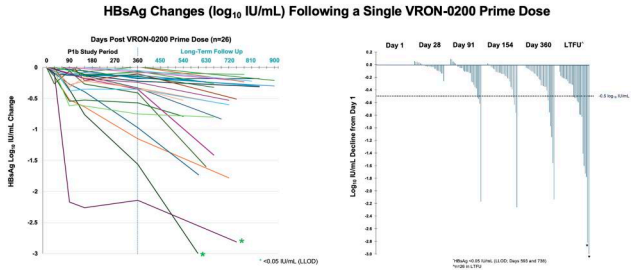
5016 | A SINGLE VRON-0200 DOSE ALONE PRODUCED DURABLE AND/OR CONTINUING HBSAG DECLINES, WITHOUT REBOUND, FOR MORE THAN TWO YEARS: COMPLETE LONG-TERM FOLLOW-UP RESULTS

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Background: New HBV functional cure(FC) treatments have been limited by rapid off treatment HBsAg rebound and responses predominantly in patients with low BL HBsAg levels. Immune modulators/therapeutic vaccines are considered important to improving FC responses. VRON-0200 is a checkpoint modifier-containing therapeutic vaccine targeting HBV core and pol(but not S) antigens that has shown a favorable safety profile, immunogenicity, and sustained HBsAg declines following a single i.m. dose (Gane and Wong, Lancet Microbe,2026). Here we report the complete HBsAg long-term follow up(LTFU) results out to 2+ years, and viral biomarkers, for all VRON-0200 alone treated patients. **Methods:** CHB pts, NUC-suppressed with HBsAg < 500IU/mL were randomized to receive i.m. VRON-0200 prime on D1, w/wo VRON-0200 boost on D91(Groups 1 and 2; Combination Group 3 not included in this analysis). An elective LTFU was implemented to collect additional HBsAg data after end of study(EOS; D360). HBsAg (ELISA; LLOD $\leq$ 0.05 IU/mL), HBV DNA(LLOD $\leq$ 40 cps/mL), pgRNA(LLOD $\leq$ 10 cps/mL), HBcrAg(LLOD $\leq$ 1000 U/mL), and HBsAb(ELISA; detectable at $\geq$ 10 IU/mL) were measured. HBsAg results post EOS, during LTFU, and viral biomarkers through D360 are reported. **Results:** 27 pts were enrolled: 22(81%) male, 24(89%)Asian, median age, 46yrs, 26(96%) HBeAg neg, and median BL HBsAg, 177IU/mL (range:10–623). HBsAg levels during LTFU were available for 26 pts, with a median of 720 days (range:524-909) post VRON-0200 prime dosing. At LTFU, no pt had HBsAg rebound;25(96%) pts had continued HBsAg declines(12 pts > 100 IU/mL at BL declined to < 100IU/mL), 8 pts declined to < 10IU/mL and 2 pts experienced HBsAg loss. 14(54%) pts had $\geq$ 0.5log$_{10}$ decline from BL, including 6 pts with a $\geq$ 1.4 log$_{10}$ decline(Figure). A boost dose did not improve HBsAg declines. HBV DNA remained ND in all pts throughout the study; at BL and D360: pgRNA TND in 23(85%) and 25(93%), HBsAb negative in 27

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(100%) and 27(100%), and HBcrAg LLOD in 13(48%) and 15(56%) respectively. **Conclusion:** LTFU in NUC-suppressed pts who received a prime dose of VRON-0200 were observed to have durable and/or continued HBsAg declines out to 2+ years, without HBsAg rebound. More than half of pts had a $\geq 0.5\log_{10}$ decline from BL, and 2 patients experienced HBsAg loss. In addition, 19/26(73%) pts had HBsAg levels at LTFU that would qualify for NUC discontinuation (< 100IU/mL). As a result, a single VRON-0200 dose alone may be sufficient for some pts and might improve FC responses by preventing HBsAg rebound when used in combination treatments, and/or immunologically lowering HBsAg levels prior to ARV dosing(e.g., > 1000IU/mL to < 1000IU/mL) where higher FC rates have been demonstrated. A Phase 2B SPARK-B trial is in development and will assess FC, with NUC discontinuation, and higher BL HBsAg levels, when VRON-0200 is used alone, and in combination treatments.



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5017 | ELEBSIRAN PLUS BRII-179 AND PEGINTERFERON ALFA ACHIEVE GREATER HBSAG LOSS AND ENHANCED IMMUNE RESPONSES COMPARED WITH PEGINTERFERON ALFA ALONE IN VIROLOGICALLY SUPPRESSED CHRONIC HEPATITIS B: RESULTS FROM THE PHASE 2 ENHANCE PART A-1

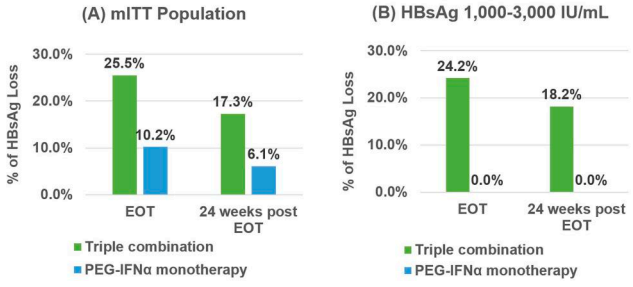
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Background: Achieving hepatitis B virus (HBV) functional cure remains challenging, particularly in patients with high HBsAg levels. Previous Phase 2 studies demonstrated that either siRNA elebsiran or therapeutic vaccine BRII-179, when combined with peginterferon alfa (PEG-IFNα), improved functional cure rate compared with PEG-IFNα monotherapy. ENHANCE Part A-1 was designed to evaluate whether concurrent viral antigen suppression and immune restoration through a triple regimen of elebsiran, BRII-179, and PEG-IFNα could further enhance antiviral outcomes. **Methods:** In this randomized, double-blind, active-controlled Phase 2 study (NCT06650852), virologically suppressed, non-cirrhotic participants who had chronic HBV infection, with HBsAg levels > 100, ≤ 3000 IU/mL and anti-HBs < 10 IU/L were randomized 2:1 to receive 13 monthly doses of elebsiran plus 48 weeks of PEG-IFNα with 10 monthly doses of BRII-179 add-on (triple therapy group) or PEG-IFNα monotherapy for 48 weeks. Participants were stratified by HBsAg levels at screening. The primary endpoint was HBsAg loss (< LLOQ) at Week 48 (EOT). Follow-up continued

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through 24 weeks post-EOT. **Results:** A total of 147 participants were randomized (triple, n = 98; PEG-IFNα, n = 49). At EOT, a significantly greater proportion of participants achieved HBsAg loss in the triple therapy group than in the PEG-IFNα monotherapy group (25.5% [25/98] vs 10.2% [5/49], p = 0.0301). Higher HBsAg loss rates with triple therapy were observed in participants with baseline HBsAg > 1000 IU/mL (24.2% [8/33] vs 0% [0/18], p = 0.0389). Triple therapy was also associated with enhanced anti-HBs responses. At EOT, 40.8% (40/98) of participants receiving triple therapy achieved anti-HBs levels ≥ 100 IU/L, compared with minimal anti-HBs responses in the PEG-IFNα monotherapy group. Among participants in the triple therapy group who achieved anti-HBs levels ≥ 100 IU/L, 50% also achieved HBsAg loss at EOT. At 24 weeks post-EOT, HBsAg loss was maintained in 17.3% (17/98) of all participants receiving triple therapy and in 18.2% (6/33) of those with baseline HBsAg > 1000 IU/mL (Figure), maintenance of HBsAg loss through Week 72 was more frequent in those with anti-HBs levels ≥ 100 IU/L than in those with anti-HBs < 100 IU/L at EOT (80% vs 20%). The safety profile of the triple regimen was generally comparable with the PEG-IFNα monotherapy, with no new safety signals identified. **Conclusion:** Elebsiran, BRII-179, and PEG-IFNα triple therapy was generally safe and demonstrated greater HBsAg loss rate than PEG-IFNα monotherapy. The benefit of triple therapy over PEG-IFNα monotherapy observed among participants with baseline HBsAg levels > 1000 IU/mL, together with robust anti-HBs induction and durable post-treatment response in a subset of participants, providing further support for the therapeutic potential of combining viral antigen suppression with immune modulation as a strategy to improve HBV functional cure.

Figure. Percentage of participants achieving HBsAg loss among modified Intent-To-Treat (mITT) population (A) and participants with baseline HBsAg 1,000-3,000 IU/mL (B)



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5018 | RNA EDITING FOR THE TREATMENT OF ALPHA-1 ANTITRYPSIN DEFICIENCY (AATD): INTERIM RESULTS FROM RESTORAATION-2

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Background: Severe alpha-1 antitrypsin deficiency (AATD) is most commonly caused by homozygous SERPINA1 Pi*ZZ variants. It results in hepatocellular accumulation of misfolded Z-AAT polymers predisposing to progressive liver disease, and inadequate circulating AAT increasing the risk of lung damage from unopposed neutrophil elastase. Current augmentation therapy increases plasma AAT but does not correct hepatic Z-AAT production and accumulation nor associated liver disease. WVE-006 is the prototypical GalNAc-conjugated RNA editing oligonucleotide that converts Z-AAT to functional wild-type M-AAT. Here we present the most recent first-in-human data showing its ability to increase lung-protective M-AAT while reducing the pathogenic hepatic Z-AAT burden. **Methods:** RestorAATion-2 (NCT06405633) is an ongoing phase 1/2a study of single- and multiple-ascending subcutaneous doses of WVE-006 (200, 400, 600 mg; n = 8/cohort) in Pi*ZZ participants. Following a single dose and 12-week follow-up, participants received biweekly (200 mg) or monthly (400, 600 mg) dosing for 12 weeks followed by 12 weeks of observation. Serum M-AAT, Z-AAT, and total (M + Z) AAT were quantified by LC-MS to assess RNA editing, restoration of functional AAT production, and reduction of mutant Z-AAT. **Results:** WVE-006 was generally well tolerated; all adverse events were mild to moderate, with no serious adverse events. Single doses of 200, 400, and 600 mg produced M-AAT levels representing 44%, 48%, and 52% of total AAT, and reductions of 47%, 50% and 59% in Z-AAT, respectively, consistent with

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target engagement and hepatocyte RNA editing. In the 200 and 400 mg multiple-dose cohorts, serum M-AAT reached 64%, and 59% of total serum AAT, accompanied by Z-AAT reductions of 71% and 68%, respectively. Following a single 200 mg dose, total endogenous AAT rose to >20 μM during an acute phase response, with two additional acute phase responses in the 400 mg multiple-dose cohort resulting in rises of total endogenous AAT by 58% and 60%. **Conclusion:** These interim data provide first-in-human proof of mechanism for therapeutic RNA editing, demonstrating production of functional M-AAT, substantial reduction of mutant Z-AAT, and endogenous upregulation of total AAT during stress in Pi*ZZ individuals. By directly editing hepatocyte SERPINA1 mRNA, WVE-006 may address both AATD-associated lung and liver disease and paves the way for targeted correction of single nucleotide-based mutations.

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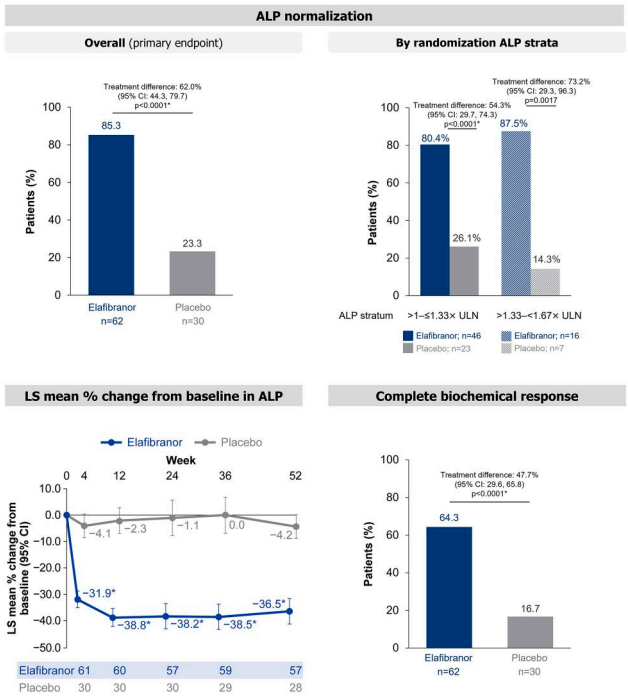
5019 | ELAFIBRANOR TO NORMALIZE ALKALINE PHOSPHATASE IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS AND INCOMPLETE RESPONSE TO URSODEOXYCHOLIC ACID: RESULTS FROM THE PHASE III RANDOMIZED CONTROLLED ELSPIRE TRIAL

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Background: Inadequate treatment response in primary biliary cholangitis (PBC) is commonly defined as ALP $\geq$1.67× upper limit of normal (ULN). As such, registrational clinical trials have included patients (pts) with screening ALP $\geq$1.67× ULN, excluding pts with ALP >1–<1.67× ULN. As ALP >ULN is associated with active disease, ALP normalization, associated with better complication-free survival, is an increasingly favored treatment target. Pts with ALP >ULN, even if <1.67× ULN, may therefore benefit from ALP reduction. Elafibranor (ELA), a peroxisome proliferator-activated receptor (PPAR)-α/δ agonist approved for PBC second-line treatment, has shown significant biochemical efficacy in pts with ALP $\geq$1.67× ULN. ELA has not been investigated in pts with ALP >1–<1.67× ULN. Here, we report results from the phase III randomized, placebo-controlled ELSPIRE trial (NCT06383403), evaluating the effect of ELA in pts with PBC, ALP >1–<1.67× ULN, and incomplete response/intolerance to ursodeoxycholic acid (UDCA). **Methods:** Pts with PBC and ALP >1–<1.67× ULN were randomized 2:1 to ELA 80 mg or placebo (PBO). The primary endpoint was ALP $\leq$ULN at Week (Wk) 52 (multiple imputation; missing at random assumption; 2-sided $p<0.05$ significance). Secondary endpoints (with descriptive p-values) included least squares (LS) mean % change from baseline (CfB) in ALP to Wk 52, complete biochemical response (normal total bilirubin, ALP, AST, ALT, albumin, and INR) at Wk 52, and ELA safety over the study period. **Results:** Of 92 randomized pts (ELA: 62; PBO: 30), 85 (92.4%) completed Wk 52 (ELA: 57; PBO: 28). Mean (SD) age was 60.2 (10.0) years; 92.4% were female. At randomization, 69 (75.0%) had ALP >1–$\leq$1.33× ULN, 23 (25.0%) had ALP >1.33–<1.67× ULN, and 89 (96.7%) had concurrent UDCA treatment. At Wk 52, significantly more pts had ALP $\leq$ULN with ELA (85.3%) vs PBO (23.3%); difference: 62.0% (95% CI: 44.3, 79.7; $p<0.0001$). Similar differences were seen in pts with randomization ALP >1–$\leq$1.33× ULN (ELA: 80.4%, PBO: 26.1%; $p<0.0001$) and ALP >1.33–<1.67× ULN (ELA: 87.5%, PBO: 14.3%; $p=0.0017$; **Figure**). Significantly greater LS mean % CfB in ALP at Wk 52 was seen with ELA (–36.5%) vs PBO (–4.2%; $p<0.0001$). At Wk 52, 64.3% of pts with ELA vs 16.7% with PBO achieved complete biochemical response ($p<0.0001$; **Figure**). Treatment-emergent adverse events (AEs) were observed in 79.0% of pts with ELA vs 70.0% with PBO, mostly mild/moderate. Serious AEs were observed in 3 (4.8%) pts with ELA (none treatment-related; no deaths) and 4 (13.3%) with PBO, with no DILI. There were no new safety signals. **Conclusion:** In ELSPIRE, the primary endpoint of ALP normalization was achieved in a significantly higher proportion of pts with PBC and ALP >1–<1.67× ULN with 1 year of ELA vs PBO, with rapid and sustained reductions in ALP and no new safety signals. These results support the potential of second-line ELA treatment alongside UDCA to achieve ALP normalization in these pts.

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Figure. ALP normalization at Week 52, least squares mean % change from baseline in ALP to Week 52, and complete biochemical response at Week 52



Intent-to-treat set. *p<0.0001. ULN for ALP: 120 U/L. ALP normalization (overall, primary endpoint) and complete biochemical response analyses used ALP-stratified CMH testing, with multiple imputation (MAR assumption) for missing values. ALP normalization analyses within randomization ALP strata used Fisher's Exact tests, with nearest prior value for missing data. LS mean % change from baseline was calculated using an MMRM including baseline, treatment, visit and treatment by visit interaction as fixed effects. Complete biochemical response was defined as normal total bilirubin, ALP, AST, ALT, albumin, and INR. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMH: Cochran-Mantel-Haenszel; ELA: elafibranor; INR: International Normalized Ratio; LS: least squares; MAR: missing at random; MMRM: mixed model for repeated measures; PBO: placebo; ULN: upper limit of normal.

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5020 | ESSENTIAL AMINO ACID SUPPLEMENTATION REDUCES HEPATIC FAT IN ADOLESCENTS WITH MASLD AND OBESITYB

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Background: Pediatric metabolic dysfunction-associated steatotic liver disease (**MASLD**) is the most common chronic liver disease in youth, affecting nearly 40% of those with obesity. Hepatic steatosis is the hallmark of MASLD, with risk of progression to steatohepatitis and extrahepatic complications. However, treatment for pediatric MASLD is limited to lifestyle changes. Our group previously demonstrated that essential amino acid supplementation (**EAA**) decreases hepatic fat (**HF**) in elderly adults and improves hepatic function in adults with alcoholic liver disease. We sought to determine if EAA reduces HF in adolescents with MASLD and obesity. **Methods:** Adolescents with MASLD and obesity (age 13-18 years, HF $\geq$ 5% by MRI-PDFF, BMI $\geq$ 85th percentile for age and sex) were included from two clinical cohorts. Participants in a recently completed phase 3, double-blind, randomized placebo-controlled trial (NCT05935826, IND169103) received 8 weeks of twice-daily EAA (AMS2392, Amino Co., Lewes, DE) or placebo. Participants from a prior phase 3, double-blind, randomized placebo-controlled cross-over trial with 4-week twice-daily EAA intervention with the same formulation in adolescents with obesity and polyendocrine metabolic ovarian syndrome (NCT03717935) were included if HF was $\geq$ 5%. Baseline and post-intervention assessments for both studies were 8 weeks apart and included hepatic MRI, DXA, fasting blood collection, and anthropometric measurements. The primary outcome for both trials and this analysis was change in HF. Secondary outcomes included ALT, AST, metabolic biomarkers, and body composition. Between group HF change differences were evaluated with an intent-to-treat linear mixed-effects model (LMM) adjusted for study, age, sex, and BMI. A power variance structure was used to account for increasing residual variability with higher fitted HF. Absolute and relative changes in secondary outcomes were compared using Welch's t-tests. Data are presented as mean ± SD; $p < 0.05$ was considered significant. **Results:** Thirty-one adolescents (EAA n = 19 [8 male, 11 female], BMI 36.0 ± 6.3 kg/m^2, age 15.3 ± 1.5 years; placebo n = 12 [7 male, 5 female], BMI 36.5 ± 4.1 kg/m^2, age 16.0 ± 1.9 years) were included. EAA had an absolute HF reduction of -1.5 ± 3.6%, compared with an increase of 0.99 ± 3.1% in placebo (LMM between-group difference in change = −1.90%; 95% CI = −3.64 to −0.16; Group x Timepoint p = 0.033). Relative ALT decreased with EAA and increased with placebo (−22.1 ± 22.2% vs 4.6 ± 21.3%, respectively, p = 0.003). No between-group differences were observed in changes in AST, fasting insulin, glucose, TG, and BMI or body fat. **Conclusion:** Following 4 or 8 weeks of twice-daily EAA supplementation, adolescents with MASLD and obesity had reductions in hepatic fat and ALT compared with placebo, consistent with improvement in hepatocellular injury. Evaluation of liver stiffness is needed to determine if EAA improves additional hepatic outcomes.

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5021 | SUSTAINED HIGH LOSS OF HBSAG 36 WEEKS POST-TREATMENT WITH A COMBINATION OF HT-101 PLUS HT-102 IN HBEAG-NEGATIVE, NUCLEOS(T)IDE ANALOGUE-SUPPRESSED CHRONIC HEPATITIS B

Xieer Liang[1] Liang Chen[2] Jianmei Lin[3] Bei Zhong[4] Huiqing Liang[5] Wen Xie[6] Yujuan Guan[7] Zhihong Liu[1] Xun QI[8] Wang Dong[9] Zhipeng Zhang[9] Yachun Qin[9] Kai Wu[9] Jinlin Hou[1], [1]Nanfang Hospital, Southern Medical University, [2]Shanghai Public Health Clinical Centre, [3]Sichuan Provincial People's Hospital, [4]Qingyuan People's Hospital, [5]Xiamen Traditional Chinese Medicine Hospital, [6]Beijing Ditan Hospital, [7]Guangzhou Eighth People's Hospital, [8]Shanghai Public Health Centre, [9]Hepa Thera Biotech Company

Background: HT-101 is a GalNAc-conjugated small interfering RNA targeting the HBV S region that demonstrated durable HBsAg reductions in phase I. HT-102 is a human monoclonal antibody targeting the HBsAg antigenic loop that produced rapid declines in serum HBsAg in phase I. We report Week 60 (36 weeks post-treatment) results from a phase Ib/IIa study in China (NCT07183306/CTR20244730) evaluating HT-101 plus HT-102 combination therapy and monotherapy in patients with chronic hepatitis B (CHB). **Methods:** This multicenter, open-label, partially dose-escalating study enrolled HBeAg-negative patients with CHB receiving stable nucleos(t)ide analogue (NA) therapy and screening HBsAg levels of 100–3,000 IU/mL. Study treatments were administered subcutaneously every 4 weeks. Group A received HT-101 400 mg for 24 weeks, with treatment extended through Week 48 for participants without HBsAg loss at Week 24. Group B received HT-102 300 mg for 24 weeks followed by HT-101 400 mg for 24 weeks. Groups C–E received HT-102 300 mg plus HT-101 100 mg, 200 mg, or 400 mg, respectively, for 24 weeks. Eligible patients discontinued NAs at Week36. The primary endpoint was the incidence of treatment-emergent adverse events (TEAEs). **Results:** All participants completed the Week 60 visit (Figure 1). Among participants in the combination groups (C–E; n = 28), 22/28 (79%) achieved HBsAg loss at end of treatment (EOT; Week 24), and 8/28 (29%) maintained HBsAg loss through Week 60. Sustained HBsAg loss was observed in 5/14 (36%) participants with baseline HBsAg < 1,000 IU/mL and 3/14 (21%) with baseline HBsAg ≥ 1,000 IU/m. In Group E, 4/10 (40%) participants maintained HBsAg loss through Week 60, including 2/6 (33%) participants with baseline HBsAg ≥ 1,000 IU/mL. In Group A, 4/20 (20%) participants achieved HBsAg loss at Week 24, and 3/20 (15%) maintained HBsAg loss through Week 60. HT-101 treatment was extended to 48 weeks in the remaining 16/20 cases in Group A and 2/16 (13%) achieved HBsAg loss by Week 60. In Group B, no participant achieved HBsAg loss at Week 24 following HT-102 monotherapy, whereas 4/8 (50%) achieved HBsAg loss at Week 48 after subsequent HT-101 treatment; at Week 60, HBsAg had rebounded in all participants but remained < 1 IU/mL. Most TEAEs were Grade 1–2; one Grade 3 treatment-related injection-site reaction was reported. No drug-related serious adverse events or ALT flares occurred. **Conclusion:** Combination of HT-101 plus HT-102 induced high rates of on-treatment HBsAg loss and sustained off-treatment HBsAg loss through Week 60 in HBeAg-negative, NA-suppressed CHB. HT-101 monotherapy also achieved sustained off-treatment HBsAg loss in some cases, with additional HBsAg loss observed following treatment extension. The highest sustained HBsAg loss rate was observed with HT-101 400 mg plus HT-102 300 mg (40%). These findings support further evaluation of HT-101 plus HT-102 as a finite-treatment combination regimen toward functional cure in CHB.

Figure-1A Proportion of Participants with Sustained HBsAg Loss from End of Treatment Following 24 Weeks Treatment

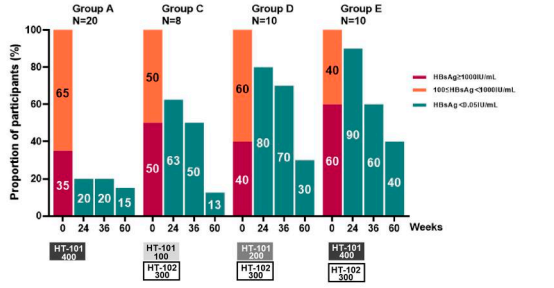
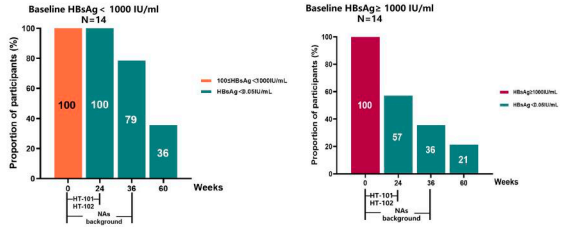


Figure-1B Subgroup Analysis by Baseline HBsAg Levels in Combo groups (C, D, and E)



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5022 | PEGINTERFERON ALFA-2B PROVIDES DUAL BENEFITS OF REDUCING HCC DEVELOPMENT AND FACILITATING HBSAG LOSS IN NA-TREATED CHB PATIENTS AT INTERMEDIATE-TO-HIGH RISK OF HCC: EVIDENCE FROM 5-YEAR DATA OF THE PARADISE STUDY

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Background: Up to 80% of hepatocellular carcinoma (HCC) is caused by chronic hepatitis B (CHB) in China. Although nucleos(t)ide analogues (NAs) therapy reduces the risk of HCC in CHB patients, the residual risk of HCC remains high, particularly in high-risk individuals. This study aimed to investigate whether peginterferon alfa-2b (PegIFNα-2b) add-on to NAs can further reduce the risk of HCC compared with NA monotherapy in NA-treated CHB patients with intermediate-to-high risk of HCC. **Methods:** In this multi-center randomized controlled trial "PARADISE study" (NCT05671315), CHB patients with intermediate to high risk of HCC, who had undetectable HBV DNA after more than 24-week NAs pretreatment, were recruited, randomized to NAs group or PegIFNα+NAs group at a ratio of 1:2, and followed up for 240 weeks. NAs group continued NAs monotherapy, while PegIFNα+NAs group received PegIFNα-2b add-on NAs therapy for 48 weeks, then switched to NAs monotherapy. Changes in HBV serological markers and the cumulative incidence of HCC at week 240 were compared between the groups. **Results:** A total of 196 CHB patients were included in this analysis, comprising 68 in the NAs group and 128 in the PegIFNα+NAs group. Among them, 55 and 103 patients, respectively, completed the 240-week follow-up. Baseline characteristics were comparable between the two groups. Over 240 weeks of follow-up, the cumulative incidence of HCC was markedly lower in PegIFNα+NAs group than NAs group (1.0% vs. 8.9%, HR = 5.62, P = 0.013; Fig.1A). Notably, among CHB patients characterized by male sex, age > 40 years, or a family history of HCC, PegIFNα add-on therapy still demonstrated significant advantages in reducing HCC (all P < 0.05). Compared with NAs group, PegIFNα+NAs group exhibited numerically lower HBsAg levels at week 240 (1.89 ± 1.54 vs. 2.32 ± 1.00 log10 IU/mL) and a relatively greater decline of HBsAg from baseline (1.07 ± 1.13 vs. 0.66 ± 0.73 log10 IU/mL). The rates of HBsAg loss at week 240 were significantly higher in PegIFNα+NAs group than NAs group (25.2% vs. 3.6%, P = 0.001; Fig.1B). None of the patients who achieved HBsAg loss prior to week 96 experienced HBsAg relapse throughout the follow-up. Multivariate analysis demonstrated that NAs therapy (vs. PegIFNα add-on therapy, HR = 5.19, P = 0.019) and older age (HR = 1.11, P = 0.046) were independently associated with an increased risk of HCC. **Conclusion:** PegIFNα-2b add-on NAs therapy is superior to NAs monotherapy in reducing HCC risk and facilitating sustained HBsAg loss among NA-treated, virologically suppressed CHB patients with intermediate-to-high risk of HCC.

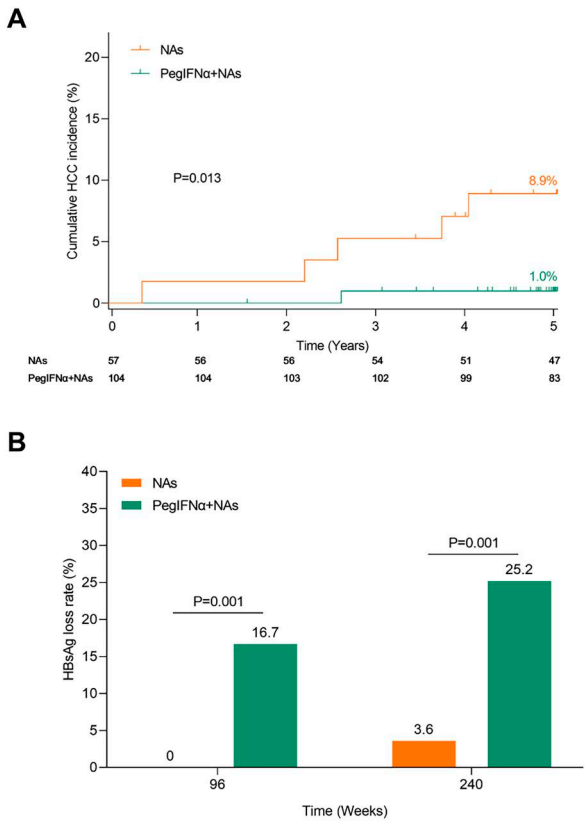


Figure 1. The cumulative HCC incidence (A) and the rates of HBsAg loss (B) between the NAs group and PegIFNα+NAs group

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5023 | LIVER FUNCTION TRAJECTORY, POST-PROGRESSION OUTCOMES, AND SAFETY IN THE PHASE 3 EMERALD-3 STUDY OF TREMELIMUMAB (T) + DURVALUMAB (D) B1 LENVATINIB (L) + TRANSARTERIAL CHEMOEMBOLIZATION (TACE) IN PARTICIPANTS (PTS) WITH EMBOLIZATION-ELIGIBLE HEPATOCELLULAR CARCINOMA (EEHCC)

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Background: EMERALD-3 met its primary endpoint. Favorable OS trends were seen for STRIDE ± L + TACE vs TACE in eeHCC. Preserved liver function in HCC treatment is associated with better outcomes and allows subsequent treatment (Tx) post progression. We report *post-hoc* exploratory analyses of liver function trajectory, post-progression outcomes, and safety by baseline (BL) liver function in EMERALD-3. **Methods:** Pts (≥ 18 y) with eeHCC were randomized 1:1:1 to STRIDE (T 300 mg + D 1500 mg on Day 1 then D 1500 mg every 4 weeks) + L (8 or 12 mg once daily) + TACE; STRIDE + TACE; or TACE until reaching 175 pts/arm, then 1:1 until STRIDE + L + TACE and TACE reached ~275 pts/arm. Pts were stratified by region, prior palliative embolization, and BL tumor burden. The primary endpoint was PFS for STRIDE + L + TACE vs TACE. Key secondary endpoints were OS for STRIDE + L + TACE vs TACE; PFS and OS for STRIDE + TACE vs TACE. PFS2 for STRIDE ± L + TACE vs TACE was a secondary endpoint. Adverse events (AEs) were recorded throughout the study, with causality determined by the investigator. All hepatic and hemorrhagic Standardised MedDRA Queries (SMQs) were presented as other significant AEs. This *post-hoc* exploratory analysis assessed outcomes by BL albumin-bilirubin (ALBI) grade (1 vs 2/3). **Results:** As of Feb 23, 2026, mean ALBI and Child-Pugh scores remained stable over the Tx period across arms, in the safety analysis set (SAS). In the full analysis set (FAS), median OS (95% CI) was 44.6 months (39.5–not calculable [NC]) for STRIDE + L + TACE vs 39.2 months (34.7–NC) for TACE in pts with ALBI Grade (Gr) 1 (HR 0.86 [95% CI 0.60–1.22]); and 28.5 months (20.7–34.3) vs 22.1 months (17.4–33.3), respectively, in pts with ALBI Gr 2/3 (HR 0.88 [0.60–1.28]). Median OS was NC (37.8–NC) for STRIDE + TACE vs 39.2 months (28.0–NC) for TACE in pts with ALBI Gr 1 (HR 0.57 [95% CI 0.36–0.90]); and 27.9 months (17.8–NC) vs 20.4 months (16.6–30.1), respectively, in pts with ALBI Gr 2/3 (HR 0.81 [0.52–1.26]). STRIDE ± L + TACE numerically improved median time to next treatment and PFS2 vs TACE across BL ALBI grades (Table). In the FAS, subsequent Tx use was 43% (ALBI Gr 1) and 46% (ALBI Gr 2/3) for STRIDE + L + TACE; 50% and 53% for STRIDE + TACE; and 72% and 68% for TACE. Within Tx arms, rates of max. Gr 3/4 Tx-related AEs were similar across BL ALBI grade. Any-grade AEs of hepatic disorders per SMQ were more common with STRIDE-based regimens + TACE vs TACE alone, irrespective of BL ALBI grade. The most common hepatic disorder SMQ category was liver-related investigations, signs, and symptoms. **Conclusion:** STRIDE ± L + TACE showed clinically relevant improvements in post-progression and survival outcomes vs TACE, with stable liver function over the Tx period and comparable safety across BL ALBI grades within each arm. No new hepatic safety signal was identified in addition to the previously known safety profile of the STRIDE regimen. These findings support a STRIDE-based regimen + TACE as a potential new Tx option for eeHCC.

Table. Efficacy and safety outcomes by BL ALBI grade

FAS

	ALBI Grade 1				ALBI Grade 2/3			
	STRIDE+L+TACE (n=188)	TACE (n=183)	STRIDE+TACE (n=105)	TACE (n=111)*	STRIDE+L+TACE (n=105)	TACE (n=109)	STRIDE+TACE (n=70)	TACE (n=64)*
TTNT								
HR (95% CI)	0.56 (0.43–0.72)		0.46 (0.33–0.64)		0.57 (0.41–0.77)		0.55 (0.38–0.80)	
Median, months (95% CI)	21.1 (18.5–27.3)	10.6 (8.7–12.8)	20.3 (15.6–33.7)	9.2 (7.2–11.3)	14.0 (10.8–20.4)	7.3 (5.5–9.2)	13.4 (8.4–17.6)	6.0 (4.6–8.9)
PFS2								
HR (95% CI)	0.70 (0.51–0.95)		0.53 (0.36–0.79)		0.74 (0.52–1.05)		0.69 (0.46–1.05)	
Median, months (95% CI)	39.5 (34.0–NC)	25.8 (21.6–NC)	NC (37.8–NC)	23.9 (17.4–38.4)	24.5 (18.8–34.1)	17.4 (14.6–25.2)	24.7 (15.8–32.5)	17.1 (13.3–22.1)

*Of the first 175 pts randomized to the TACE arm

SAS

	ALBI Grade 1			ALBI Grade 2/3		
	STRIDE+L+TACE (n=188)	STRIDE+TACE (n=105)	TACE (n=183)	STRIDE+L+TACE (n=105)	STRIDE+TACE (n=70)	TACE (n=109)
Tx-related AEs with a max. Grade 3/4, n (%)	115 (62)	49 (47)	32 (18)	65 (64)	36 (51)	22 (20)
AEs leading to interruption of any study investigational product, n (%)	149 (81)	48 (46)	NA	92 (90)	29 (41)	NA
AEs leading to discontinuation of any study investigational product, n (%)	35 (20)	21 (20)	NA	47 (46)	15 (21)	NA
AEs of hepatic disorders per SMQ by max. grade, n (%)	99 (54)	53 (50)	49 (27)	63 (64)	43 (61)	37 (34)
Grade 1	24 (13)	12 (11)	21 (12)	7 (7)	8 (11)	6 (6)
Grade 2	34 (18)	21 (20)	13 (7)	21 (21)	18 (26)	20 (18)
Grade 3	35 (19)	19 (18)	15 (8)	31 (30)	15 (21)	11 (10)
Grade 4	5 (3)	1 (1)	0	3 (3)	0	0
Grade 5	1 (1)[†]	0	0	3 (3)[‡]	2 (3)[§]	0
Liver-related investigations, signs, and symptoms per SMQ by max. grade, n (%)	80 (43)	42 (40)	43 (24)	44 (43)	34 (49)	24 (22)
Grade 1	24 (13)	12 (11)	19 (10)	4 (4)	9 (13)	7 (6)
Grade 2	31 (17)	17 (16)	11 (6)	20 (20)	15 (21)	12 (11)
Grade 3	23 (12)	13 (12)	13 (7)	19 (19)	10 (14)	5 (5)
Grade 4	2 (1)	0	0	1 (1)	0	0
Grade 5	0	0	0	0	0	0

FAS includes all randomized pts. SAS includes all pts who received at least one dose of investigational product.
AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. MedDRA version 28.1 was used.
[†]Hepatic failure (possibly related to durvalumab treatment). [‡]Hepatic failure (n=2) and hepatorenal syndrome (n=1). [§]Hepatic cirrhosis (n=1) and hepatic failure (n=1).
AE, adverse event; ALBI, albumin-bilirubin; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; L, lenvatinib; MedDRA, Medical Dictionary for Regulatory Activities; NA, not applicable; NC, not calculable; PFS2, time from randomization to second progression; pts, participants; SAS, safety analysis set; SMQ, Standardised MedDRA Query; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TACE, transarterial chemoembolization; TTNT, time to next treatment; Tx, treatment.

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and Teaching, Abbvie: Speaking and Teaching, AstraZeneca: Advisor, Oncolys Japan: Grant/Research Support, Surrozen: Advisor, MedVir: Advisor, Masatoshi Kudo:, Ghassan Abou-Alfa: Abbvie, Agenus, Amgen, Arcus, Astra Zeneca, Atara, Beigene, BioNtech, BMS, Coherus, Digestive Care, Grant/Research Support, Abbvie, Ability Pharma, Agenus, Alligator Biosciences, Amgen, Astellas, Arcus, Astra Zeneca, Autem, Consultant, Zhenggang Ren, Joseph Erinjeri:, Riccardo Lencioni, Yasuaki Arai, José Francisco Escobar Penagos: Nothing to Disclose, I-Cheng Lee: AstraZeneca: Speaking and Teaching, AstraZeneca: Advisor, Roche: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, Eisai: Speaking and Teaching, Eisai: Advisor, Fengmei Wang, Weidong Jia:, Vincenzo Mazzaferro, Arthur Gregory Lui, Christoph Roderburg: Nothing to Disclose, Mehmet Akce: BMS: Consultant, AstraZeneca: Consultant, BioNTech: Consultant, Boehringer Ingelheim: Consultant, Partner Therapeutics: Consultant, Daiichi: Consultant, Taiho: Consultant, Incyte: Consultant, Sri Harsha Tekumalla, Lucy Clark: Nothing to Disclose, Sajid Ali, Jia Fan.

5024 | PREDICTING FUNCTIONAL CURE RESPONSE WITH BEPIROVIRSEN IN PATIENTS WITH BASELINE HBSAG LEVELS < 100 IU/ML

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Background: The B-Well Phase 3 trials showed that a 24-week course of bepirovirsen (BPV), an antisense oligonucleotide, resulted in 19–20% functional cure (FC) rate in nucleos(t)ide analog (NA)-treated participants with chronic hepatitis B virus (HBV) infection and baseline hepatitis B surface antigen (HBsAg) levels 100–3000 IU/mL.[1] FC rates increased to 25–28% among those with HBsAg levels ≤1000 IU/mL. As healthcare providers and patients with baseline HBsAg <100 IU/mL may consider treatment with BPV, characterizing the FC rate achievable within this population is therefore of clinical importance. Here, we used model-based extrapolation to predict FC in participants with baseline HBsAg <100 IU/mL based on available clinical data from the B-Well studies and the real-world Everest study (pegylated interferon).[2] **Methods:** The ability of several predictive models to capture the inverse relationship between baseline HBsAg and FC observed in the B-Well studies (n = 1194) was evaluated. Unlike the B-Well studies, the real-world Everest study reported data in the baseline HBsAg <100 IU/mL range (n = 2067) and showed a similar inverse relationship between baseline HBsAg and the FC-related clinical endpoint of HBsAg loss rate at end of treatment; Everest was therefore used as an external benchmark for the ability of models to predict FC in this range. Models were also fitted to the ≥100 IU/mL subgroup of Everest and predictions were compared against observed <100 IU/mL data, allowing best predictive models to be selected. A final model was selected based on ability to capture B-Well data and ability to predict held-out Everest data in the baseline HBsAg <100 IU/mL range, and model parsimony. **Results:** FC rate in the B-Well studies increased monotonically as baseline HBsAg decreased. In the NA-treated population with baseline HBsAg <100 IU/mL, the final model predicted mean FC rates of approximately 46–53% with 24 weeks of BPV treatment, reflecting variation in assumed baseline HBsAg levels within this range. These predictions are consistent with the monotonic trend observed in B-Well, exceeding the 40% FC rate seen in the 100–200 IU/mL subgroup. The lower bound of the model's 95% confidence interval suggests FC of at least 34% in the baseline HBsAg <100 IU/mL population. **Conclusion:** Model-based extrapolation supports clinically meaningful FC benefit of at least 34% (with an estimated mean of 46–53%) in response to 24 weeks of BPV treatment in a NA-treated population with baseline HBsAg levels <100 IU/mL.

References: [1] Hou J et al. *N Engl J Med* 2026;394(24):2395–2406 [2] Xie C et al. *Clin Gastroenterol Hepatol* 2026:S1542-3565(26)00057-1 **Funding:** GSK (202009/NCT05630807; 219288/NCT05630820)[for the B-Well Study Group].

Disclosures: Dominic Whittaker: Nothing to Disclose, Rajat Desikan:, Marissa Renardy: GSK: Employee, Melanie Paff: GSK: Stock - publicly traded company, GSK: Employee, Dickens Theodore:, Ahmed Nader: GSK: Employee.

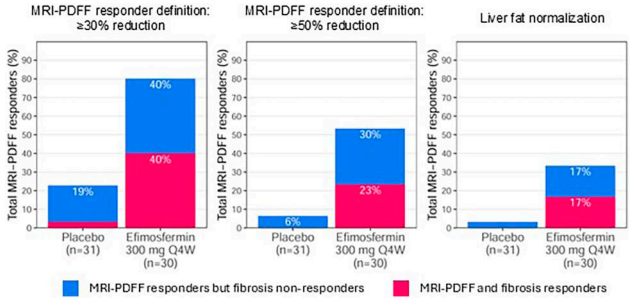
5025 | LIVER FAT REDUCTION FOLLOWING ONCE-MONTHLY EFIMOSFERMIN ALFA TREATMENT IS ASSOCIATED WITH HISTOLOGICAL FIBROSIS IMPROVEMENT IN PARTICIPANTS WITH MASH AND STAGE F2/F3 FIBROSIS

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Background: Previous studies have shown that a ≥30% relative reduction from baseline in liver fat,

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measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF), is associated with resolution of metabolic dysfunction-associated steatohepatitis (MASH) and is commonly referred to as an MRI-PDFF response. Data evaluating whether a ≥50% reduction in liver fat content, as measured by MRI-PDFF, is associated with fibrosis improvement in MASH remain limited. Efimosfermin alfa, a once-monthly (Q4W) FGF21 analog, led to improvements in fibrosis versus placebo at 24 weeks in participants (pts) with MASH with stage 2/3 fibrosis (F2/3) in a Phase 2 study (NCT04880031). In this post-hoc analysis, we evaluated the associations of ≥30% and ≥50% relative MRI-PDFF reductions (≥50%, super-response), normalization of liver fat content (absolute MRI-PDFF ≤5%), and fibrosis response among pts with F2/3 MASH treated with efimosfermin 300 mg versus placebo. **Methods:** Pts willing/able to undergo liver biopsy with body mass index ≥25 kg/m^2 and MRI-PDFF ≥8% were included in this analysis. In total, 37 pts had F2 fibrosis (placebo: n = 20; 300 mg: n = 17) and 28 had F3 fibrosis (placebo: n = 14; 300 mg: n = 14) at baseline. Changes in MRI-PDFF from baseline to Week 28 were assessed. The main histologic outcome was ≥1-stage improvement in fibrosis without worsening of MASH. **Results:** Efimosfermin 300 mg demonstrated significantly greater reductions in MRI-PDFF compared with placebo, with an absolute reduction (placebo-adjusted) of −8.1% (95% CI, −11.0 to −5.1; p < 0.001) and a relative reduction of −34% (95% CI, −47 to −20; p < 0.001) at Week 28. Based on pooled analysis of 300 mg and placebo, relative MRI-PDFF declines of 30% and 50%, respectively, were associated with fibrosis responses of 32% (95% CI, 21 to 45) and 36% (95% CI, 23 to 51). Fibrosis response in those who achieved <30% decline in MRI-PDFF versus those who achieved a ≥30% decline in MRI-PDFF relative to baseline was 23% versus 42%, respectively (OR = 2.3; 95% CI, 0.7 to 8.5). The rate of fibrosis response in those who achieved <50% decline in MRI-PDFF versus those who achieved a ≥50% decline in MRI-PDFF (MRI-PDFF super-responders) relative to baseline was 30% versus 39%, respectively (OR = 1.5; 95% CI, 0.4 to 5.3). The rate of fibrosis response in those who did not achieve normalization of liver fat versus those who did (MRI-PDFF ≤5% at the end of treatment) was 30% versus 45%, respectively (OR = 1.9; 95% CI, 0.4 to 8.9). For all MRI-PDFF responder definitions, the proportion of MRI-PDFF responders who were also fibrosis responders was higher with efimosfermin 300 mg than with placebo (Figure 1). **Conclusion:** Reductions in MRI-PDFF of ≥30% and ≥50% were associated with fibrosis improvement. Most pts treated with efimosfermin achieved an MRI-PDFF reduction ≥30%, with some achieving liver fat normalization. The results support evaluation of efimosfermin in F2/F3 MASH in longer-duration Phase 3 trials.



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5026 | HISTOLOGICAL INJURY AND HBSAG CLEARANCE WITH PEGINTERFERON ALFA-2B-BASED THERAPY IN HBV DNA-NEGATIVE INACTIVE HBSAG CARRIERS: RESULTS FROM THE STARHB COHORT

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Background: Undetectable HBV DNA may not indicate histological quiescence in inactive HBsAg carriers (IHCs). We evaluated the histological burden and week-48 HBsAg clearance with peginterferon alfa-2b (PEG-IFNα-2b) in this population. **Methods:** STARHB is an ongoing, multicenter, real-world cohort study of IHCs. In a histopathological substudy, 231 treatment-naïve patients underwent liver biopsy. Evident hepatic injury (EHI) was defined as necroinflammation grade ≥2 and/or fibrosis stage ≥2. The treatment-effectiveness analysis included participants who, as of September 7, 2026, had reached week 48 according to their enrollment date and had either completed week-48 follow-up or achieved HBsAg clearance before week 48. Patients with undetectable baseline HBV DNA (<20 IU/mL) were grouped as PEG-IFNα-2b monotherapy, PEG-IFNα-2b plus a nucleos(t)ide analogue (NUC), NUC monotherapy, or no treatment. HBsAg clearance was defined as HBsAg <0.05 IU/mL. **Results:** A total of 5,573 participants were eligible for the week-48 analysis, of whom 3,580 (64.2%) had undetectable baseline HBV DNA (<20 IU/mL) and 1,993 had detectable baseline HBV DNA (≥20 IU/mL). Among participants with undetectable baseline HBV DNA, 1,657 received PEG-IFNα-2b monotherapy, 1,736 received PEG-IFNα-2b plus a nucleos(t)ide analogue (NUC), 146 received NUC monotherapy. Among participants with undetectable baseline HBV DNA, 43.9% (1,491/3,393) of those receiving PEG-IFNα-2b-based therapy achieved HBsAg clearance by week 48, compared with 8.2% of those receiving NUC monotherapy (P<0.001). Among participants with detectable baseline HBV DNA, 45.0% (846/1,882) of those receiving PEG-IFNα-2b-based therapy achieved HBsAg clearance by week 48. HBsAg clearance rates with PEG-IFNα-2b-based therapy were comparable between participants with undetectable and detectable baseline HBV DNA (43.9% vs 45.0%; P=0.32). Among the 231 patients who underwent liver biopsy, 35.9% had EHI. EHI was more frequent in HBV DNA-negative than HBV DNA-positive patients (44.6% vs 31.1%; P=0.04), predominantly because of a higher prevalence of fibrosis stage ≥2 (42.2% vs 21.6%; P<0.001). **Conclusion:** HBV DNA negativity did not exclude clinically relevant histological injury, particularly significant fibrosis, in IHCs. Meanwhile, PEG-IFNα-2b-based therapy was associated with a high week-48 HBsAg clearance rate. These findings support risk stratification and further evaluation of PEG-IFNα-2b therapy in appropriately selected HBV DNA-negative IHCs.

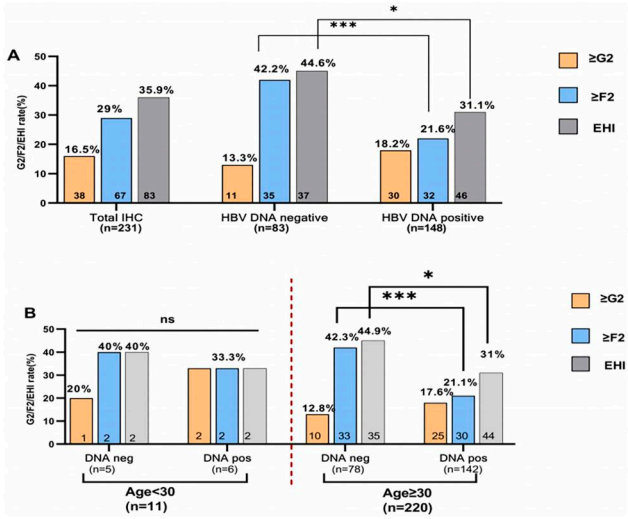


Fig. 1 Overall liver tissue pathology of IHC patients according to the age(above 30 years old or not) and HBV DNA grouping: (A) all patients according to the HBV DNA group; (B) all patients grouped by age(above 30 years old or not) and HBV DNA positivity. Note: G: inflammation stage; F: fibrosis stage; EHI (G≥2 and/or F≥2), *: P<0.05; ***: P<0.001 ns: non significantly

Disclosures: Shan Ren:Nothing to Disclose, Jing Zhao, Sujun Zheng, Bingliang Lin, Yongfang Jiang, Qingfa Ruan:, YAN HUANG, Yilan Zeng, Geng Jiawei, Haifang Cao, Wenhua Zhang, Ying Guo, Xiaorong Mao, Zhiliang Gao, Tianyuan Shi, Yueyong Zhu, Zujiang Yu, Xiaoping Wu, Qing Mao, Xiulan Xue, Xinyue Chen.

5027 | A CLINICAL TRIAL TO EVALUATE THE SAFETY, TOLERABILITY, AND PRELIMINARY EFFICACY OF CG-BM1 ALLOGENEIC HUMAN BONE MARROW MESENCHYMAL STEM CELL INJECTION IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

Jun-feng Chen[1] Xuezhong Lei[2] Xiaowei Xu[3] Yingli He[4] Hui Wang[5] Sunxing Yan[6] Yongyu Mei[7] Liping Zeng[6] Ziying Lei[7] Peng Xiang[8] Bingliang Lin[1], [1]The Third Affiliated Hospital, Sun Yat-sen University,Guangzhou, China, [2]West China Hospital, Sichuan University, [3]The First Affiliated Hospital, Zhejiang University School of

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Background: Acute-on-chronic liver failure (ACLF) carries a high short-term mortality. Mesenchymal stem cell (MSC) therapy has shown promise in improving outcomes, but no commercial MSC product is yet available for routine use. CG-BM1 is an allogeneic human bone marrow-derived MSC product. This trial assessed its safety, tolerability, and preliminary efficacy in ACLF patients. **Methods:** The study comprised two phases. Phase I was an open-label, dose-escalation "3 +3" design evaluating single intravenous doses of 1 x 10^6, 2 x 10^6, and 4 x 10^6 cells/kg. Phase II was a multicenter, randomized, double-blind, placebo-controlled trial in which 90 patients were allocated 1:1:1 to receive four weekly infusions of CG-BM1 at 1 x 10^6 (Group A) or 2 x 10^6 cells/kg (Group B), or placebo (Group C), plus conventional therapy. Co-primary endpoints were dose-limiting toxicity (Phase I) and 90-day transplant-free survival (Phase II). (NCT06740149) **Results:** In Phase I, 10 patients completed infusion without dose-limiting toxicity; the 180-day survival rate was 70%, with only mild rash and fever. In Phase II, 46 serious adverse events occurred in 33 patients; three were treatment-related (two in Group B: fever and rash; one in placebo: rash). In the full analysis set, 90-/180-day transplant-free survival rates for Groups A, B, and C were 79.4%/68.0%, 81.0%/77.0%, and 75.1%/67.6% (all P>0.05). Treatment groups showed a trend toward faster HBV-ACLF grade improvement; by Day 28, grade reduction rates were 50%, 53%, and 30%, respectively. In patients receiving artificial liver support, corresponding 90-day rates were 83.0%, 83.9%, and 68.6%, and 180-day rates 69.1%, 78.3%, and 62.9% (all P > 0.05). Per-protocol analyses yielded similar findings. **Conclusion:** CG-BM1 was safe and well-tolerated across all tested doses. Although the medium dose (2 x 10^6 cells/kg) showed a numerically better survival trend, no comparisons reached statistical significance. These results warrant confirmation in a larger Phase III trial.
Disclosures: Jun-feng Chen:Nothing to Disclose, Xuezhong Lei, Xiaowei Xu, Yingli He, Hui Wang, Sunxing Yan, Yongyu Mei, Liping Zeng, Ziying Lei, Peng Xiang, Bingliang Lin.

5028 | EFFICACY AND SAFETY OF THE COMBINATION THERAPY OF PEMAFIBRATE AND TOFOGLIFLOZIN (K-001) VERSUS PLACEBO IN PATIENTS WITH NONCIRRHOTIC MASH WITH LIVER FIBROSIS: PHASE 2B, INTERNATIONAL, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, 48-WEEK STUDY - PEMASH TRIAL

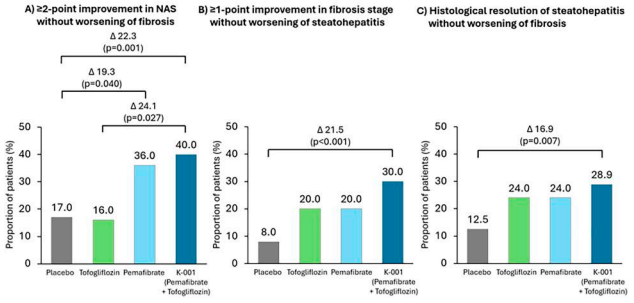
Rohit Loomba[1] Ryohei Tanigawa[2] Hideki Suganami[2] Andrey Belous[3] Atsushi Nakajima[4], [1]University of California, San Diego, [2]Kowa Company, [3]Kowa Pharma Development, [4]International University of Health and Welfare

Background: Pemafibrate and tofogliflozin are expected to attenuate inflammation and fibrosis associated with MASH, and may work synergistically. Pemafibrate, a selective PPAR α modulator, reduces de novo triglyceride synthesis and increases β-oxidation, potentially attenuating MASH progression; however, this effect may be partially offset by compensatory de novo lipogenesis driven by excess glucose, which tofogliflozin, SGLT2 inhibitor, may reduce by increasing urinary glucose excretion. K-001, a combination of extended-release pemafibrate 0.4 mg and tofogliflozin 20 mg, has the potential to attenuate disease progression and prevent worsening of fibrosis in MASH. We evaluated safety and efficacy of K-001 in an international, randomized, placebo-controlled, double-blind, Phase 2b study in patients with noncirrhotic MASH with liver fibrosis; NCT05327127. **Methods:** Patients with NAFLD activity score (NAS) $\geq$ 4 (at least 1 in each component), NASH CRN fibrosis stage F1-F3, and type 2 diabetes or fasting plasma glucose $\geq$ 90 mg/dL were assigned 3:1:1:3 to receive placebo, tofogliflozin 20 mg, pemafibrate 0.4 mg, or K-001, orally, once daily for 48 weeks. Primary endpoint was a $\geq$ 2-point improvement in NAS without worsening of fibrosis at Week 48. **Results:** 228 eligible patients were randomly assigned to receive placebo (n = 88), tofogliflozin (n = 25), pemafibrate (n = 25), and K-001 (n = 90) for 48 weeks. Mean baseline liver stiffness measurement was 10.9 kPa, controlled attenuation parameter was 337.9 dB/m, AST was 44.6 U/L, and ALT was 59.4 U/L. Mean NAS was 4.8, and 36% and 49% of patients had F2 and F3, respectively. The primary

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endpoint was achieved by 17% of patients in the placebo, 16% in tofogliflozin, 36% in pemafibrate, and 40% in K-001 groups ($p = 0.949$, 0.040, and 0.001 vs. placebo, respectively). Key secondary endpoints of ≥ 1-point improvement in fibrosis stage without worsening of steatohepatitis at Week 48 was statistically and significantly better with K-001 versus placebo and numerically higher compared to mono-therapy [with 8%, 20%, 20% and 30% of patients in the placebo, tofogliflozin, pemafibrate, and K-001 groups, respectively ($p = 0.098$, $p = 0.094$, and $p < 0.01$ vs. placebo)], similarly histological resolution of steatohepatitis without worsening of fibrosis at Week 48 was both statistically and clinically significant between K-001 versus placebo [achieved by 13%, 24%, 24%, and 29%, respectively ($p = 0.007$ for K-001 vs. placebo)]. Therefore, K-001 met all three histologic endpoints versus placebo. No major safety concerns or new safety signals were identified. **Conclusion:** K-001 (a combination of pemafibrate 0.4 mg and tofogliflozin 20 mg) was well tolerated over 48 weeks and demonstrated significant improvements in both fibrosis and MASH resolution compared with placebo. The observed trends towards synergistic action of the two components support further development of K-001 in Phase 3 trials.

Figure: Proportion of patients who achieved the primary A) and the key secondary endpoints B) and C) at Week 48



Disclosures: 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, Cascade Pharmaceuticals: Consultant, Eccogene: Consultant, HeptaBio: Consultant, Metavi: Consultant, Neurobo: Consultant, Novo Nordisk: Consultant, Sourcebio: Consultant, Roche: Consultant, Roche: Consultant, Takeda: Consultant, GSK: Grant/Research Support, Roche: Grant/Research Support, TensorBio: Grant/Research Support, Aarrowhead Pharmaceuticals: Consultant, Boehringer-Ingelheim: Consultant, Altimmune: Grant/Research Support, Eccogene: Grant/Research Support, Heptabio: Grant/Research Support, 89 bio: Grant/Research Support, Takeda: Grant/Research Support, Ryohei Tanigawa:Kowa Company, Ltd.: Employee, Hideki Suganami:Nothing to Disclose, Andrey Belous:Kowa Pharma Development, Inc: Employee, Hana Pharmaceuticals: Consultant, Atsushi Nakajima: Nothing to Disclose.

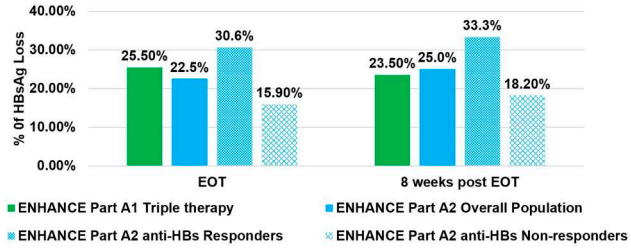
5029 | IMMUNE PRIMING WITH BRII-179 AND ELEBSIRAN ENABLES SHORTENED PEGYLATED INTERFERON ALFA TREATMENT WHILE MAINTAINING HBSAG LOSS IN PARTICIPANTS WITH CHRONIC HBV INFECTION: RESULTS FROM ENHANCE PART A2

Jidong Jia[1] Zhiliang Gao[2] Jianmei Lin[3] Jianping Li[4] Huiying Rao[5] Libo Yan[6] Guoxin Hu[7] Fangfang Lv[8] Jiming Zhang[9] Xinyue Chen[10] Wen Xie[11] Ming Yang[12] Yiwen Liu[13] Alex Tian[13] Qing Zhu[14] Haifeng Cao[13] David Margolis[14], [1]Beijing Friendship Hospital, Capital Medical University, [2]The Third Affiliated Hospital, Sun YAT SEN University, [3]Sichuan Provincial People's Hospital, [4]Guangzhou Eighth People's Hospital, [5]Peking University People's Hospital, [6]West China Hospital of Sichuan University, [7]Peking University Shenzhen Hospital, [8]Sir Run Run Shaw Hospital, [9]Huashan Hospital, Fudan University, [10]Beijing YouAn Hospital, Capital Medical University, [11]Beijing Ditan Hospital, Capital Medical University, [12]Beijing Tsinghua Changgung Hospital, [13]Brii Biosciences (Beijing) Co. Limited, [14]Brii Biosciences, Inc.

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Background: In the completed Phase 2 ENSURE study, participants previously treated with siRNA elebsiran and therapeutic vaccine BRII-179 achieved substantially higher functional cure rates following subsequent elebsiran plus pegylated interferon alfa (PEG-IFNα), compared with BRII-179/elebsiran-naïve participants. Notably, on-treatment HBsAg loss at Week 24 in the primed individuals exceeded the Week 48 end-of-treatment (EOT) response observed in naïve participants, suggesting that priming with BRII-179/elebsiran may potentiate responsiveness to PEG-IFNα and potentially allow for a shorter PEG-IFNα treatment duration. ENHANCE Part A2 was designed to evaluate this hypothesis. **Methods:** The phase 2 ENHANCE study (NCT06650852) includes a randomized, double-blind, active-controlled A-1 part that assessing concurrent elebsiran/BRII-179/PEG-IFNα triple combination and an open-label A2 assessing sequential combination of 24-week BRII-179/elebsiran priming followed by 24-week of elebsiran/PEG-IFNα treatment. In Part A2, virologically suppressed, non-cirrhotic participants with chronic HBV infection who had HBsAg levels > 100 and ≤ 3000 IU/mL and anti-HBs < 2 IU/L at baseline were enrolled. The primary endpoint was HBsAg loss (< LLOQ) at Week 48 (EOT). This analysis includes data available through Week 56 (8 weeks post EOT). **Results:** Eighty participants were enrolled in Part A2. At EOT, 36.3% of participants achieved HBsAg < 1 IU/mL, including 22.5% who achieved HBsAg loss. Higher HBsAg loss rates were observed among individuals with baseline HBsAg ≤ 1000 IU/mL (34.4% vs 14.6%). At the end of the 24-week priming phase, anti-HBs levels reached ≥ 10 IU/L and ≥ 100 IU/L in 45.0% and 21.3% participants, respectively. Anti-HBs responder (≥ 10 IU/L) demonstrated markedly higher HBsAg loss rates at EOT than non-responders (30.6% vs 15.9%). Importantly, at 8 weeks post-EOT, HBsAg loss rate went up further to 25.0% in the overall population or 33.3% among anti-HBs responders. Compared with the triple therapy group in Part A1, in which PEG-IFNα was administered for 48 weeks (EOT HBsAg loss rate 25.5%), interferon-associated adverse events (AEs), including platelet count decreased, red blood cell count decreased, pyrexia, weight decreased, and alopecia, were observed less frequently and consistent with the shorter course of PEG-IFNα therapy. **Conclusion:** A 24-week BRII-179/elebsiran priming strategy enabled a 50% reduction in PEG-IFNα exposure and less frequent AEs associated with PEG-IFNα while maintaining HBsAg loss rates comparable to those treated with 48 weeks of BRII-179/elebsiran/PEG-IFNα triple combination. Participants who developed anti-HBs responses following priming experienced substantially higher HBsAg loss rates, supporting anti-HBs induction as a marker of immune restoration and a potential predictor of responsiveness to subsequent PEG-IFNα-based combination therapy for HBV functional cure.

Figure. Percentage of participants achieving HBsAg loss in the ENHANCE Study at EOT and 8 weeks post EOT



EOT: end-of-treatment
Note: In ENHANCE Part A2, anti-HBs responders = anti-HBs ≥ 10 IU/L at Week 24, anti-HBs non-responders = anti-HBs < 10 IU/L at Week 24. In ENHANCE Part A1, participants received 48 weeks of elebsiran plus PEG-IFNα, with 10 monthly doses of BRII-179 add-on from Week 12 to Week 48. In Part A2, participants received monthly elebsiran plus BRII-179 during a 24-week priming phase, followed by elebsiran plus PEG-IFNα for an additional 24 weeks.

Disclosures: Jidong Jia:Nothing to Disclose, Zhiliang Gao:, Jianmei Lin:, Jianping Li:, Huiying Rao:, Libo Yan:, Guoxin Hu:, Fangfang Lv:, Jiming Zhang:, Xinyue Chen:, Wen Xie:Nothing to Disclose, Ming Yang:, Yiwen Liu:Brii Biosciences: Employee, Alex Tian:Nothing to Disclose, Qing Zhu:, Haifeng Cao:, David Margolis:BRII Biosciences: Stock Holder.

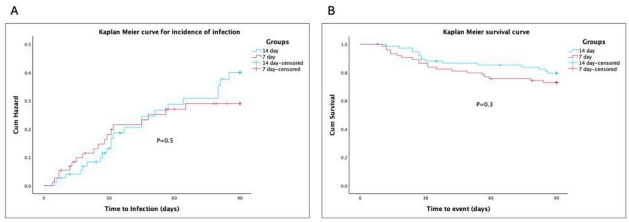
5030 | SEVEN OR FOURTEEN DAYS OF CORTICOSTEROIDS FOR SEVERE ALCOHOL-ASSOCIATED HEPATITIS: A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED, MULTICENTER STUDY (STASH II)

Anand Kulkarni[1] Karan Kumar[2] Akash Roy[3] Madhumita Premkumar[4] Dibyalochan Praharaj[5] Suprabhat Giri[6] Harshith Kadnur[7] Shantan Venishetty[7] Manasa Alla[7] Sowmya T R[7] Mithun Sharma[7] Vivek Saraswat[8] Padaki Nagaraja Rao[7] Mahesh Goenka[9] Nageshwar Reddy[7] K Rajender Reddy[10], [1]Asian Institute of Gastroenterology, [2]Mahatma Gandhi Medical College, [3]Apollo Hospitals, [4]Postgraduate Institute of Medical Education & Research, [5]Kalinga Institute of Medical Sciences, [6]Kalinga Institute of Medical Sciences, Orissa, [7]AIG Hospitals, [8]Mahatma Gandhi University of Medical Sciences and Technology, [9]Apollo Multispeciality hospitals, Kolkata, [10]University of Pennsylvania

Background: We have previously reported that rapid tapering of corticosteroids over four weeks reduces infections in patients with severe alcohol-associated hepatitis (AAH). In this study, we aimed to assess whether a shorter duration of therapy is associated with a reduced infection rate without compromising efficacy. **Methods:** In this double-blind randomized study, patients with AAH (NIAAA criteria) were randomized to receive seven-day prednisolone

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(40mg/day) followed by placebo for next 7 days or 14-day prednisolone (40mg/day) based on the Lille score across five centers in India. The primary objective was the infection rate at day 90. The secondary objectives were mortality at day 90, the proportion of patients achieving MELD < 17 at day 90, and adverse events including acute kidney injury (AKI) at day 90. **Results:** 151 patients with severe AAH (age: 41 years; men: 99.3%; MELD: 25.2; mDF: 80.61; biopsy-proven AAH: 51%) were randomized: 76 to the 14-day arm and 75 to the 7-day arm. The cumulative dose of prednisolone was 458.4 mg in the 14-day arm compared with 271.1 mg in the 7-day arm ($P < 0.001$). Seventy-seven percent in 14 days and 80.6% in 7 days responded to corticosteroids (Lille < 0.45). In the Kaplan-Meier analysis, the incidence of infection was 28.9% (22/76; 95% CI, 19.1-40.5) in the 14-day group compared with 24% (18/75; 95% CI, 14.9-35.2; $P = 0.5$) in the 7-day group. (Figure A) Similarly, the mortality was 19.7% (15/76; 95% CI, 11.5-30.4) in the 14-day group compared with 26.6% (20/75; 95% CI, 17.1-38.1; $P = 0.3$) in the 7-day group (Figure B). A similar proportion of patients achieved MELD < 17 at 90 days in both groups. Eighty-three percent in the 14-day group and 84% in the 7-day group developed adverse events ($P = 1$). The incidence of AKI was 15.8% (12/76) in the 14-day group compared to 25.3% (19/75) in the 7-day group ($P = 0.16$). **Conclusion:** Seven-day and fourteen-day corticosteroid therapy had similar infection and mortality rates and was equally effective in patients with severe AAH. (NCT06919458)



Disclosures: Anand Kulkarni:Nothing to Disclose, Karan Kumar:Nothing to Disclose, Akash Roy:Nothing to Disclose, Madhumita Premkumar:Nothing to Disclose, Dibyalochan Praharaj:Nothing to Disclose, Suprabhat Giri:Nothing to Disclose, Harshith Kadnur: Nothing to Disclose, Shantan Venishetty:, Manasa Alla:Nothing to Disclose, Sowmya T R:, Mithun Sharma:Nothing to Disclose, Vivek Saraswat:Nothing to Disclose, Padaki Nagaraja Rao:, Mahesh Goenka:, Nageshwar Reddy:Nothing to Disclose, K Rajender Reddy:BD (Becton, Dickinson and Company): Consultant, GSK: Grant/Research Support, Exact Sciences: Grant/Research Support, GSK: Grant/Research Support, Camurus: Grant/Research Support, B and D Instruments: Grant/Research Support, Sequana: Grant/Research Support, Grifols: Grant/Research Support, Pfizer: DSMB, Arbutus: DSMB, Mirum: DSMB, Vir Bio: DSMB, N Chroma Bio: DSMB, B and D Instruments: Advisor, Organ Ox: Consultant, Gastroenterology: Associate Editor, Current Hepatology Reports: Co-Editor in Chief, Up To Date: Royalties or patent beneficiary.

5031 | A SERUM PROTEOMIC SCORE OUTPERFORMS EXISTING BLOOD-BASED TESTS FOR IDENTIFYING AT-RISK MASH AND PREDICTING LIVER-RELATED OUTCOMES

Joseph Pickrell[1] Joshua Backman[1] Christopher Gillies[1] Olukayode Sosina[1] Niek Verweij[1] George Hindy[1] Sarah Murphy[1] Nadia Rana[1] Aris Baris[1] Candice Laubach[2] Naga Chalasani[3] Tae-Hwi Schwantes-An[3] Goncalo Abecasis[1], [1]Regeneron Genetics Center, [2]Geisinger Health System, [3]Indiana University School of Medicine

Background: Metabolic dysfunction associated steatohepatitis (MASH) is estimated to affect 5% of US adults, with rates expected to climb over the coming decades. Recently approved therapies for MASH are indicated for non-cirrhotic patients with stage F2 or F3 fibrosis. Liver biopsy remains the gold standard for diagnosing F2 or F3 fibrosis, but accurate blood-based non-invasive tests will be needed for effective population-scale identification and treatment of MASH. We evaluated whether a serum/plasma proteomic score could improve identification of at-risk MASH and prediction of liver-related outcomes. **Methods:** We performed the Olink Explore HT assay to measure serum levels of 5,416 proteins in over 63k participants from the Geisinger Health System (GHS) DiscovEHR cohort. We trained a penalized regression model to predict 10-year incident liver fibrosis or cirrhosis and evaluated the model in three independent settings: (1) in UK Biobank ($n = 52{,}320$ patients with electronic health records and $n = 11{,}179$ patients with liver assessments through MRI imaging), (2) 294 GHS bariatric surgery patients, and (3) in the NASH Clinical Research Network (NASH CRN, 2,384 adult samples with baseline biopsy). Performance was benchmarked against FIB-4, ELF, and other published blood-based NITs to assess ability to identify MASH cases with stage $\geq$F2 fibrosis and to predict MASH-related outcomes (cirrhosis, hepatocellular carcinoma, decompensation, transplant). **Results:** The proteomic model predicted 10-year risk of incident liver fibrosis or cirrhosis more accurately than any clinical biomarker-based score derived in the same held-out GHS population (AUROC = 0.82, AUPRC = 0.20). Performance replicated in the UK Biobank (AUROC = 0.91, AUPRC = 0.20; 0.2% event rate), where the

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score also tracked with liver fat and fibro-inflammation on MRI performed an average of 12 years after blood sampling. The score correlated with fibrosis stage and with histologic features of MASH in both GHS and NASH-CRN. When tests were calibrated to identify 90% of MASH cases, the proteomic score had a false positive rate of 11%, far exceeding the performance of FIB-4, ELF, NIS4, and FibroMeter. The proteomic score was comparable to biopsy-based staging at predicting the rates of future cirrhosis and additional downstream complications such as hepatocellular carcinoma, ascites, esophageal varices, and hepatic encephalopathy. For example, the rate of developing cirrhosis within 6 years was 9.3% in the 259 patients at risk through F2/F3 stage biopsies and 10.6% in the 226 patients with the highest proteomic risk scores. **Conclusion:** A plasma proteomic score identifies at-risk MASH more accurately than currently available NITs and predicts liver-related outcomes with prognostic ability comparable to liver biopsy. These results support development of a blood-based test for risk stratification and treatment-eligibility assessment in MASH.

Disclosures: Joseph Pickrell:Regeneron: Employee, Joshua Backman:, Christopher Gillies:Regeneron: Own Stock, Olukayode Sosina:, Niek Verweij:, George Hindy:, Sarah Murphy:, Nadia Rana:, Aris Baris:, Candice Laubach:, Naga Chalasani:Madrigal, Eccogene, Insitro, Boston Pharma, Chugai: Consultant, Zydus, GSK, Akero, Plaint, Altimmune: Consultant, Exact Sciences: Grant/Research Support, NIH: Grant/Research Support, Heligenics: Board member, investor, Avant Sante: Board member, investor, Ipsen, Biomea Fusion, Pfizer, Merck: Consultant, Tae-Hwi Schwantes-An:Nothing to Disclose, Goncalo Abecasis.

5032 | FIRST-IN-PERSON EVIDENCE OF *IN VIVO* AXIOMER RNA EDITING OF NTCP FOR THE TREATMENT OF CHOLESTASIS: PROOF OF CONCEPT DATA FROM THE AX-0810 PHASE 1 TRIAL

Robert Bart Takkenberg[1] Gideon Hirschfield[2] Henkjan Verkade[3] Golnar Karimian[4] Eva Coll-de la Rubia[4] Nicole Cnubben[4] Galja Pletikapic[4] Sjef de Kimpe[4] Lianne Stevens[4] Walter Boiten[4] Max Lagraauw[4] Agathe Plichta[4] Gerard Platenburg[4] Cristina Lopez Lopez[4], [1]Amsterdam University Medical Centers, [2]Toronto General Hospital, [3]University Medical Center Groningen, [4]ProQR Therapeutics

Background: Intrahepatic accumulation of bile acids (BA) is a key driver of cholestatic liver disease, with limited disease-modifying options. Sodium taurocholate cotransporting polypeptide (NTCP; *SLC10A1*) mediating most hepatic conjugated-BA uptake, is a novel therapeutic target. AX-0810 is a first-in-class GalNAc-conjugated Axiomer RNA editing oligonucleotide that selectively reduces NTCP-mediated BA uptake via site-specific editing of *SLC10A1* mRNA while preserving other NTCP functions. By lowering intrahepatic BA toxicity, AX-0810 leverages a mechanism supported by human NTCP loss-of-function, causing hypercholanemia without pruritus or liver dysfunction. **Methods:** In this randomized, double-blind, placebo-controlled, multiple-ascending-dose Phase 1, healthy participants received subcutaneous AX-0810 at 3 or 6 mg/kg (4 doses over 4 weeks; 12-week follow-up). Objectives were safety, tolerability, pharmacokinetics, and pharmacodynamic assessed via plasma total and conjugated BA and an oral tauro-ursodeoxycholic acid (TUDCA) challenge. Thyroid hormones were monitored to assess non-BA NTCP-mediated transport. **Results:** The analysis included 22 healthy participants (mean age of 40.6 [26-55] yo, 21M/1F; placebo, n = 6; AX-0810 3 mg/kg, n = 8; 6 mg/kg, n = 8). AX-0810 was well tolerated, with no serious or severe adverse events (AEs), discontinuations, or clinically meaningful changes in liver function, bilirubin, thyroid hormones, vitamin D, or pruritus. Treatment-related AEs were limited to mild injection-site reactions. Pharmacokinetics indicated an estimated hepatic half-life of 8 weeks. At week 5, AX-0810 produced concordant, dose-dependent changes across BA biomarkers, consistent with NTCP target engagement. Following challenge, plasma TUDCA (Cmax, µmol/L) increased by 34% and 61% from baseline at 3 and 6 mg/kg, respectively. Plasma conjugated BA exposure (AUC0-12h, µmol/L·h) increased by 95% and 136%, and total BA (Cmax, µmol/L) increased by 5- and 8-fold at 3 and 6 mg/kg, respectively. Urinary conjugated BA excretion (AUC0-24h, nmol/L·h) increased by 87% and 138%, respectively, versus placebo, indicating enhanced renal BA elimination. AX-0810 was also associated with dose dependent higher plasma level of GCDCA (post-hoc Pearson correlation, r = 0.56, p = 0.007) and TCDCA (r = 0.48, p = 0.024) associated with lower sulfated (r = -0.42, p = 0.052) and secondary BAs (r = -0.37, p = 0.086). **Conclusion:** In this first-in-person study of Axiomer in vivo RNA editing, AX-0810 showed favorable safety, pharmacokinetic and dose-dependent pharmacodynamic evidence of NTCP target engagement. Changes in circulating and urinary conjugated

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BAs were consistent with reduced NTCP-mediated hepatic BA uptake. Our data represents the first reported clinical proof-of-concept for RNA editing-mediated NTCP modulation and supports development of Axiomer RNA editing as a novel treatment for cholestatic liver disease.

Table. Changes in Bile Acids biomarkers following AX-0810 or placebo treatment

	Placebo	3 mg/kg	6mg/kg
Plasma Total Bile Acids [CFB, Cmax (µmol/L)]	+4-fold	+5-fold	+8-fold (p<0.05 vs. placebo)
TUDCA Clearance [CFB, Cmax (µmol/L)]	+0.9-fold	+1.3-fold (+34% vs. placebo)	+1.5-fold (+61% vs. placebo, p<0.05)
Plasma Conjugated Bile Acids [CFB, AUC0-12h (µmol/L·h)]	-11.3	+7.6 (+95% vs. placebo)	+16.4 (+136% vs. placebo, p<0.05)
GCDCA (% median at week 5, t=0)	29.6	29.4	41.2
TCDCA (% median at week 5, t=0)	2.0	3.1	5.7
Sulfated BAs (% median at week 5, t=0)	30.2	26.0	14.3
Secondary BAs (% median at week 5, t=0)	20.4	23.5	11.3
Urine Conjugated Bile Acids [AUC0-24h (nmol/L·h)]	48.1	90.0 (+87% vs. placebo)	114.4 (+138% vs. placebo, p<0.05)

All 6mg/kg data showed p<0.05, post hoc vs. placebo.

Disclosures: Robert Bart Takkenberg: No dislosure submitted, Gideon Hirschfield: Intercept: Consultant, GSK: Consultant, CymaBay: Consultant, Ipsen: Consultant, Falk: Consultant, Pliant: Consultant, Mirum: Consultant, Advanz: Consultant, Chemomab: Consultant, Gilead: Consultant, Kowa: Consultant, Henkjan Verkade: Mirum: Grant/Research Support, Mirum: Consultant, Mirum: Speaking and Teaching, Ipsen / Albireo: Consultant, Ipsen / Albireo: Grant/Research Support, Ipsen / Albireo: Speaking and Teaching, Intercept: Consultant, Vertex: Consultant, ProQR: Consultant, Rectify: Grant/Research Support, Golnar Karimian:proqr: Employee, Galapagos: Employee, Eva Coll-de la Rubia:, Nicole Cnubben: Nothing to Disclose, Galja Pletikapic:Nothing to Disclose, Sjef de Kimpe: Nothing to Disclose, Lianne Stevens:, Walter Boiten: ProQR: Employee, Max Lagraauw:, Agathe Plichta:Nothing to Disclose, Gerard Platenburg: Nothing to Disclose, Cristina Lopez Lopez:Nothing to Disclose.

5033 | ELAFIBRANOR IMPROVES BIOCHEMICAL MARKERS AND SYMPTOM BURDEN IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN REAL-WORLD PRACTICE: SIX-MONTH, PRIMARY ENDPOINT RESULTS FROM THE GLOBAL PHASE IV ELFINITY STUDY

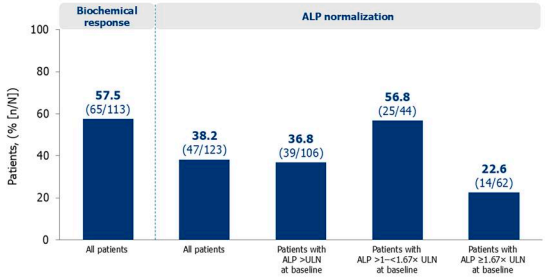
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Background: Elafibranor (ELA) is a dual peroxisome proliferator-activated receptor α/δ agonist approved as a second-line (2L) treatment for primary biliary cholangitis (PBC). Here, we present Month (M)6 data from the ongoing, prospective, global, non-interventional phase IV ELFINITY study (NCT06447168) assessing the real-world effectiveness and safety of ELA. **Methods:** ELFINITY will recruit ~424 patients (pts) receiving ELA 80 mg/day in real-world settings, prospectively followed for up to 5 years. The primary endpoint is the rate of biochemical response (ALP < 1.67× upper limit of normal [ULN] with ≥ 15% reduction from baseline [BL], and TB ≤ ULN) at M6. ALP normalization, ALP category (≤ 1, > 1– < 1.67, ≥ 1.67– < 3, ≥ 3× ULN) shifts, and ALP change from BL (CfB) are reported. Symptoms were assessed using pt-reported outcome (PRO) instruments (completion optional). Moderate-to-severe (mod–sev) fatigue was defined as PBC-40 Fatigue ≥ 29 or PROMIS Fatigue Short Form 13a (PFSF-13a) ≥ 60, and mod–sev pruritus as Worst-Itch Numeric Rating Scale (WI NRS) ≥ 4, PBC-40 Itch ≥ 9, or 5-D Itch ≥ 12. Pts with BL mod–sev symptoms achieving minimum clinically important differences (MCID; PBC-40 Fatigue ≥ 5, PFSF-13a ≥ 3, WI NRS ≥ 3, PBC-40 Itch ≥ 1.5, 5-D Itch ≥ 4.5) are reported at M6.Pts receiving ≥ 1 dose were assessed. For biochemical response/ALP normalization, predefined estimand strategies addressed intercurrent events and missing M6 assessments; all other data are observed. **Results:** As of May 2026, 259 pts were enrolled and 253 received ≥ 1 ELA dose. Of pts with BL data, mean (SD) age was 60.1 (10.6) years, 89.3% were female, and 60.2% (112/186) had ALP ≥ 1.67× ULN. At M6, 65/113 (57.5%; 95% CI: 48.4–66.6) pts had biochemical response to ELA. Response rates were 51.6% (32/62) in pts with BL ALP ≥ 1.67× ULN, 44.4% (12/27) in pts with BL advanced disease (LSM > 10 kPa/Nakanuma score ≥ 2), and 61.8% (34/55) in pts switching within 3 months from other 2L therapies. ALP normalization rates were 36.8% (39/106) in pts with BL ALP > ULN, and 56.8% (25/44) in pts with BL ALP > 1– < 1.67× ULN (Figure). By M6, among pts with BL and M6 data (n = 77), 49 (63.6%) improved by ≥ 1 ALP category, 26 (33.8%) maintained the same category, and 2 (2.6%) worsened by one ALP category. Mean (SD) ALP CfB to M6 was –0.8 (0.7)× ULN. In pts with mod–sev fatigue at BL and non-missing M6 data, 11/26 (42.3%) and 5/13 (38.5%) had improvements ≥ MCID in PBC-40 Fatigue and PFSF-13a at M6, respectively. In pts with mod–sev pruritus at BL and non-missing M6 data, 6/8 (75.0%), 6/8 (75.0%), and 5/19 (26.3%) had ≥ MCID in WI NRS, PBC-40 Itch, and 5-D Itch at M6, respectively. By data cut-off, 78/253 (30.8%) pts had TEAEs, and 12 (4.7%) had serious TEAEs of which one led to discontinuation. No single TEAE preferred term occurred in ≥ 5% of pts. **Conclusion:** These M6 findings suggest that ELA is associated with rapid improvements in biochemical markers and symptom burden and has generally been well tolerated in routine clinical practice for PBC.

Figure. Biochemical response and ALP normalization at Month 6



Biochemical response defined as ALP <1.67× ULN with ≥15% reduction from BL, and TB ≤ULN. Data based on the composite strategy imputing non-response for patients who experienced intercurrent events (ICEs; intake of investigational drug, intake of rescue therapy for PBC, liver-related events, study discontinuation for AE, lack of effectiveness, or death for any cause) prior to Month 6, or based on the hypothetical strategy imputing by the last available assessment for patients who experienced ICEs (study discontinuation for other reasons than the above ones) prior to Month 6. Missing response not due to an ICE is imputed using the closest non-missing assessment before or after (+/– 3 months) the theoretical Month 6 date. ALP: alkaline phosphatase; BL: baseline; ICE: intercurrent event; TB: total bilirubin; ULN: upper limit of normal.

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5034 | REGENERATIVE MACROPHAGE THERAPY (RMT) IN END-STAGE LIVER DISEASE: EARLY RESULTS FROM THE EMERALD/ OPAL TRIALS

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Background: Treatment of patients with decompensated cirrhosis is limited to management of complications or liver transplantation. The MATCH trial demonstrated the safety and potential efficacy of autologous monocyte-derived regenerative macrophages in compensated cirrhosis, with outcomes followed for 4 years (Brennan et al. Cell Stem Cell 2026). The EMERALD phase 1/2 trial aims to extend these findings by evaluating phenotypically similar macrophages further engineered with mRNA encoding IL-10 and MMP-9 to enhance anti-inflammatory and anti-fibrotic effects, respectively (RTX001), in patients with more advanced cirrhosis. **Methods:** Two single-arm trials were conducted: OPAL (observational study, serving as an external control) and EMERALD (interventional study), using primarily the same study sites (UK/Spain) and

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inclusion/exclusion criteria. Patients with steatotic liver disease (MASLD, Met-ALD, ALD) were recruited based on a recent hepatic decompensation event requiring hospitalization or recent-onset refractory ascites. Once clinically stable, EMERALD patients received filgrastim (G-CSF) mobilization and underwent apheresis to collect monocytes, which were cultured to differentiate into regenerative macrophages and then electroporated with single-stranded mRNA encoding human IL-10 and MMP-9. Patients received up to four doses of 10^8 RTX001 cells via peripheral IV infusion. OPAL external-control patients received standard of care and were followed for a similar duration. This report describes the first 6 months following the first RTX001 dose in EMERALD (n = 9/15 enrolled), with a corresponding follow-up period in OPAL (n = 21). **Results:** The two groups were balanced for gender (67% male), age (mean OPAL 60 years, EMERALD 58 years), and MASLD status (OPAL 29%, EMERALD 33%). No infusion-related serious adverse events (SAEs) or reactions, severe treatment-emergent AEs, macrophage activation syndrome, immune effector cell-associated neurotoxicity syndrome, or cytokine release syndrome occurred . Non-hepatic SAE rates were similar between treated patients (33%) and external controls (38%) in the first 6 months following the first dose (or equivalent period in controls). The relative risk of experiencing a major clinical event (death/liver transplantation/protocol-defined hepatic decompensation) was 42% lower in RTX001-treated patients (2/9 (22%)) than patients in the control arm (8/21 (38%). Preliminary longitudinal pharmacodynamic plasma biomarker analyses suggest a rapid anti-fibrotic effect in RTX001-treated patients. **Conclusion:** These initial data confirm that RMT is safe and shows an early signal of efficacy at 6 months following RTX001 treatment, similar to the 4-year data from the MATCH trial of non-engineered RMT, but in a higher-risk population. Both studies are fully accrued and progressing towards the final 2-year post-treatment evaluation.

Numbers of patients experiencing major AEs or a major clinical event (most severe event per patient)

	Numbers of patients experiencing major clinical event or major AE	
	OPAL (ext Control), n=21 (%)	EMERALD (RTX001), n = 9 (%)
Hepatic Decompensation	4 (19%)	1 (11%)
Liver Transplant	2 (9.5%)	0
Death (all cause)	2 (9.5%)	1 (11%)
Total	8 (38%)	2 (22%)
Transplant or death	4 (19%)	1 (11%)
Non-Hepatic SAEs	8 (38%)	3 (33%)
Treatment related severe AEs	NA	0
Infusion related SAEs	NA	0
MAS, ICANS, CRS	NA	0

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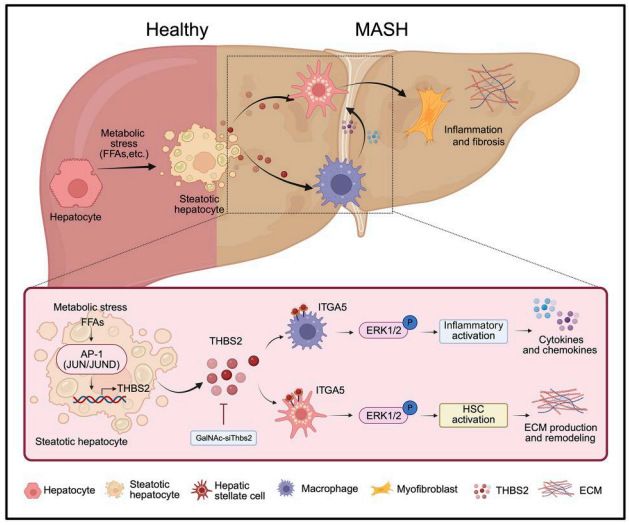
5035 | HEPATOCYTE THBS2 COUPLES METABOLIC STRESS TO IMMUNE-STROMAL REMODELING THROUGH ITGA5 IN MASH

Qiuyu Wang[1], [1]Zhongshan Hospital, Fudan University

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is characterized by persistent immune activation and stromal remodeling, yet how hepatocyte stress is translated into remodeling of the hepatic microenvironment remains unclear. We sought to identify disease-relevant extracellular signals linking hepatocyte metabolic stress to immune and stromal reprogramming. **Methods:** Human and murine transcriptomic and secretome datasets were integrated with protein-level validation and cell type-specific genetic models. Hepatocyte- and hepatic stellate cell-specific Thbs2 genetic models, single-nucleus RNA sequencing, biochemical interaction studies, and complementary loss-of-function approaches were used to define the cellular source and downstream signaling of THBS2. Myeloid-specific Itga5 deletion was used to

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determine the in vivo requirement for ITGA5 in THBS2-driven liver injury and fibrosis. Hepatocyte-targeted GalNAc-conjugated siRNA was used to evaluate the therapeutic effects of Thbs2 silencing during MASH progression and regression. **Results:** We identified thrombospondin-2 (THBS2) as a stress-responsive matricellular signal associated with MASH progression. Although Thbs2 transcripts were enriched in non-parenchymal cells, protein-level analyses and cell type-specific genetic models identified stressed hepatocytes as a major disease-relevant source of THBS2 protein in vivo. Lipotoxic stress induced hepatocyte THBS2, with AP-1 signaling involving JUN and JUND contributing to this response.Secreted THBS2 engaged integrin α5 (ITGA5) on macrophages and hepatic stellate cells to promote inflammatory and fibrogenic programs. Single-nucleus transcriptomics showed that loss of hepatocyte-derived THBS2 suppressed disease-associated macrophage states and shifted stellate cells toward quiescence. Biochemical studies demonstrated direct THBS2–ITGA5 interaction, which was impaired by disruption of the THBS2 RGD motif. ITGA5 blockade or silencing attenuated THBS2-induced inflammatory and fibrogenic responses in macrophages and hepatic stellate cells. Importantly, myeloid-specific deletion of Itga5 markedly attenuated THBS2-driven inflammation, liver injury, and fibrosis despite sustained hepatocyte THBS2 overexpression, establishing an in vivo requirement for myeloid ITGA5 in this signaling axis.Finally, hepatocyte-targeted GalNAc-siRNA silencing of Thbs2 attenuated disease progression and enhanced regression of established inflammatory and fibrotic pathology. **Conclusion:** Together, these findings define a hepatocyte-derived THBS2–ITGA5 signaling circuit through which metabolic stress is translated into immune–stromal remodeling and identify THBS2 as a therapeutically tractable target in MASH.



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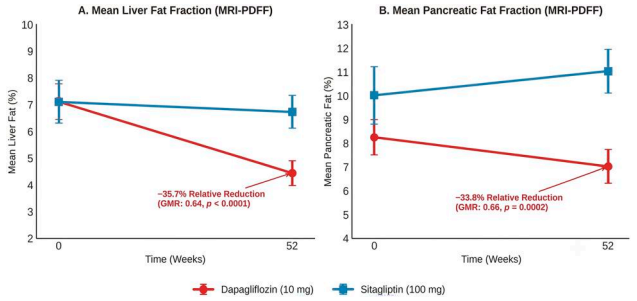
5036 | EFFECT OF DAPAGLIFLOZIN VERSUS SITAGLIPTIN ON ECTOPIC FAT PARTITIONING AND BODY COMPOSITION IN LIVER TRANSPLANT RECIPIENTS WITH DIABETES: THE DAPA-LIT RANDOMISED CONTROLLED TRIAL

Mohammad Kuchay[1] Narendra Choudhary[1] Sonal Krishan[1] Mitali Mishra[1] Parjeet Kaur[1] Surender[1] Tamanna Gandhi[1] Lavi Kashyap[1] Manish Singh[1] Neeraj Saraf[1] Swapnil Dhampalwar[1] Arvinder Soin[1], [1]Medanta The Medicity

Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors are increasingly prescribed off-label for managing diabetes in liver transplant recipients. However, their impact on ectopic fat partitioning and body composition in liver transplant recipients remain poorly characterized. We aimed to evaluate the 52-week effects of dapagliflozin versus sitagliptin on ectopic fat accumulation and body composition in liver transplant recipients with diabetes. **Methods:** In this RCT, 100 adult liver transplant recipients with diabetes were randomly assigned (1:1) to receive either dapagliflozin (10 mg/day) or sitagliptin (100 mg/day) under glycaemic equipoise. The primary outcome was the baseline-adjusted difference in 52-week liver fat fraction (LFF). Secondary outcomes included changes in pancreatic fat fraction (PFF), and body composition metrics (total body mass, total fat mass, body fat percentage, lean mass, bone mineral content [BMC]), and handgrip strength. LFF and PFF were quantified using MRI proton density fat fraction (MRI-PDFF), body composition was assessed via dual-energy X-ray absorptiometry (DEXA), and handgrip strength using a Jamar dynamometer. Log-transformed analysis of covariance (ANCOVA) was used to estimate geometric mean ratios (GMRs) for fat factions (LFF and PFF), while linear ANCOVA was used for absolute changes in fat fractions and body composition matrics. **Results:** In the primary intention-to-treat log-ANCOVA analysis, dapagliflozin achieved a 35.7% relative reduction in 52-week LFF compared with sitagliptin (GMR 0.643 [95% CI 0.527 to 0.785], $p < 0.0001$; absolute difference: -2.00 percentage points [95% CI -3.08 to -0.92], $p = 0.0003$). For secondary outcomes, dapagliflozin demonstrated a 33.5% relative reduction in 52-week PFF compared with sitagliptin (GMR 0.665 [95% CI 0.538 to 0.821], $p = 0.0002$; absolute difference -2.78 percentage points [95% CI -4.65 to -0.90], $p = 0.0037$). Compared with sitagliptin, dapagliflozin significantly reduced total body mass (adjusted difference: -3.38 kg [95% CI -5.54, -1.22], $p = 0.003$), total fat mass (-1.98 kg [95% CI -3.84, -0.13], $p = 0.037$), and body fat percentage (-2.52% [95% CI -4.07, -0.97], $p =$

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0.002). Total lean mass, BMC, and handgrip strength were preserved without significant between-group differences. Safety evaluations noted uncomplicated genital and urinary tract infections in four patients receiving dapagliflozin (leading to two drug discontinuations) and one patient receiving sitagliptin. Two deaths occurred in the sitagliptin arm, both judged unrelated to study medication. **Conclusion:** In liver transplant recipients with diabetes, dapagliflozin treatment superiorly optimized ectopic fat partitioning by reducing graft hepatic and pancreatic steatosis compared with sitagliptin. Dapagliflozin selectively reduced total body mass and body fat while preserving lean mass, muscle strength, and bone mineral content.



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5037 | HP515, A SELECTIVE AND POTENT THR-N2 AGONIST, MARKEDLY REDUCES LIVER FAT AND ATHEROGENIC LIPIDS IN MASLD PATIENTS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2A TRIAL

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Background: HP515 is a highly selective and potent thyroid hormone receptor beta (THR-N2) agonist designed to improve hepatic lipid metabolism. This phase 2a study was aimed to evaluate the efficacy and safety of HP515 in Asian patients with metabolic dysfunction associated steatotic liver disease (MASLD). **Methods:** This was a randomized, double-blind, placebo-controlled phase 2a study conducted at 30 Chinese centers. Patients with liver fat content (LFC) b %10% by MRI-PDFF and elevated LDL-C were randomized based on body weight at baseline (< 80 kg at a ratio of 2:2:1 to receive HP515 40 mg, 50 mg, or placebo, or b %80 kg at a ratio of 2:1 to receive HP515 60 mg or placebo, respectively) to receive oral study drugs once daily for 12 weeks. The primary endpoint was relative percentage change from baseline in LFC by MRI-PDFF at week 12. Secondary endpoints included proportions of patients achieving b %30 or b %50% LFC reduction, lipid and pharmacodynamic parameters, and safety. **Results:** In total, 99 patients were randomly assigned to HP515 40 mg (n = 20), 50 mg (n = 21), 60 mg (n = 32) or placebo (n = 26) groups. Baseline characteristics except bodyweight were generally comparable across treatment groups. Specifically baseline LFC by MRI-PDFF was 18.6%, 17.9%, 18.2%, and 18.1%, respectively. At week 12, ANCOVA-adjusted LS mean percentage changes in LFC were -52.4%, -43.9%, and -61.5% with HP515 40, 50, and 60 mg, respectively, versus -5.0% with placebo. Placebo-adjusted LS mean differences were -47.3% (95% CI -67.7 to -26.9), -38.9% (-60.1 to -17.6), and -56.5% (-74.2 to -38.8) for HP515 40, 50 and 60 mg, respectively (all P < 0.001). b %50% LFC reduction was achieved by 65.0%, 66.7%, and 68.8% of patients receiving HP515 40, 50, and 60 mg, respectively, versus 3.8% with placebo (all p < 0.001 vs placebo). Furthermore, HP515 treatment also produced highly significant (P < 0.001 vs respective placebo) decreases in LDL-C, sd-LDL-C, ApoB, triglyceride, and total cholesterol levels. SHBG level was however markedly increased, indicating hepatic THR-N2 receptor target engagement. AE occurred in 90%, 67%, 81% or 73% of patients in HP515 40, 50, and 60 mg or placebo groups, respectively. No SAE, treatment-related grade b %3 AE, or AE leading to permanent discontinuation occurred. Diarrhea was the most frequent treatment-related AE, which was transient (mainly in weeks 2-4) and mild (most cases grades 1-2) with no need for treatment. No clinically relevant changes in liver and thyroid function, heart rate, QTc, or bone-turnover markers were observed during the study. **Conclusion:** A 12-week oral treatment of HP515 significantly reduced liver fat level with 60% patients achieving a b %50% reduction. Additionally, HP515 treatment markedly improved atherogenic lipid profiles and was generally well tolerated, supporting further clinical studies to develop HP515 as a better option for the treatment of MASLD

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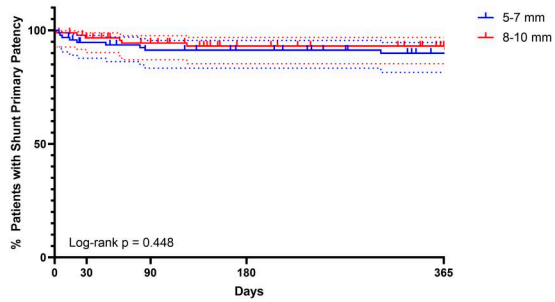
Disclosures: Ming Yang:, Huiying Rao:, Fei Lan: Nothing to Disclose, Xiuqin Jia: No dislosure submitted, Yangming Guo: Nothing to Disclose, Zheng Yao:, Ling Chen:, Shuang Li: Nothing to Disclose, Xinghai Li:, Yuanwei Chen:, Simon Li: Nothing to Disclose, Lai Wei.

5038 | SMALL-DIAMETER TIPS WITH GORE® VIATORR® TIPS WITH CONTROLLED EXPANSION: 12-MONTH PATENCY ACCORDING TO DILATION DIAMETER IN THE VTR 21-09 PROSPECTIVE MULTICENTER REGISTRY

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Background: VIATORR CX 6-10 mm stent-grafts have recently become available for TIPS. Until now, it was common to underdilate (< 8 mm) the 8-10 mm VIATORR CX. We report the 12-month analysis of VTR 21-09 that characterizes the performance of underdilated vs standard diameter devices. **Methods:** VTR 21-09 is a prospective, multicenter, single-arm registry of the GORE® VIATORR® TIPS Endoprosthesis with Controlled Expansion (8-10 mm) at seven European centers. The primary endpoint, 12-month primary patency (freedom from reintervention for thrombotic occlusion or significant stenosis), was estimated by Kaplan-Meier analysis. Secondary endpoints included technical success, immediate post-TIPS portosystemic gradient (PSG) reduction and shunt-related reintervention. Outcomes were compared by final dilation diameter (small-diameter 5-7 mm vs standard 8-10 mm). Device-related serious adverse events are pending site adjudication. **Results:** A total of 195 patients underwent attempted TIPS-procedure (variceal bleeding 92, ascites 80, other 23). Technical success was 97.9% (191/195), while all failures were due to inability to access the portal vein. Mean age was 61.1 ± 11.4 years, 73.2% were male, MELD 12 ± 4, Child-Pugh B 53.6%. Mean PSG decreased from 19.0 ± 5.9 to 9.8 ± 4.1 mmHg. Within 12 months, 41 patients discontinued follow up, including 19 deaths and 8 transplants; 133/150 (88.7%) completed the 12-month visit.Patients were stratified by the final dilation diameter, which was 5-7 mm (small-TIPS) in 95 patients (5 mm [10.5%], 6 mm [67.4%], 7 mm [22.1%]), and 8-10 mm (standard-TIPS) in 94 (8 mm [86.2%], 9 mm [1.1%], 10 mm [12.8%]). Indications were similarly distributed between groups (VB 50.5% vs 45.7%, ascites 41.1% vs 38.3%, other 8.4% vs 16.0%), as were median MELD (11 vs 12; range 6-25) and prior overt HE (14.0% vs 14.1%). Post-TIPS PSG was higher with small than with standard-TIPS (11.6 ± 3.9 vs 8.0 ± 3.6 mmHg; p < 0.001). PSG < 12 mmHg was achieved in 48.4% in smaller diameter group versus 85.1% (p < 0.001).Total freedom from shunt-related intervention was 84.0% (95% CI 77.7-88.7%) (among patients with final balloon diameter: planned expansion n = 15 (5 vs 10), reduction n = 3 (2 vs 1), planned revision n = 9 (6 vs 3); intentional shunt occlusion due to shunt-related complications: 5 (4 vs 1)). Patency was restored in 12 patients. Overall Kaplan-Meier primary patency at 12 months was 91.6% (95% CI 86.4-94.8%). Small and standard subgroups had similar primary patency (90.0% vs 93.1%; 9 vs 6 events; log-rank p = 0.45; Figure 1). 12-month patency at 6 mm (n = 64) was 90.2% (95% CI 79.3-95.5%). No device-related deaths occurred. **Conclusion:** The VIATORR CX endoprosthesis achieved high technical success, substantial PSG reduction and high 12-month primary patency. Small-diameter was associated with higher immediate post-TIPS PSG but no significant difference in patency. These prospective data provide a benchmark for the recently introduced VIATORR CX 6-10 mm.

Figure 1. Kaplan-Meier estimates of primary shunt patency at 12 months according to final dilation diameter (5-7 mm vs 8-10 mm), with number of patients at risk.



Numbers of patients at risk	0	30	90	180	365
5-7 mm	95	86	81	76	64
8-10 mm	94	88	80	67	56

Disclosures: Filippo Schepis:Nothing to Disclose, Dario Saltini:Nothing to Disclose, Cristian Caporali:, Filippo Sciano:, Francesco Vizzutti:, Rosario La Delfa:Nothing to Disclose, Silvia Aspite:Nothing to Disclose, Lucia Ragozzino:, Juan Carlos García-Pagán:Mallinckrodt: Grants or contracts, COOK Medical: Honoraria for lectures, presentations, speakers bureaus, GORE Medical: Honoraria for lectures, presentations, speakers bureaus, AstraZeneca: Grants or contracts, Anna Baiges Aznar:Nothing to Disclose, Virginia Hernandez-Gea: COOK MEDICAL: Advisor, GORE MEDICAL: Speaking

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5039 | CHRONIC HEPATITIS B, ANTIVIRAL TREATMENT, AND THE RISK OF DEMENTIA AND PARKINSON'S DISEASE: A NATIONWIDE FRENCH COHORT STUDY

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Background: The association between chronic hepatitis B virus (HBV) infection and neurodegenerative diseases remains poorly understood. Several studies have suggested an association between HBV infection and Parkinson's disease, although effect sizes have varied across populations, while evidence for dementia remains scarce and inconclusive. Whether antiviral treatment modifies this risk in chronic HBV infection specifically remains unclear. We aimed to assess the association between chronic HBV infection, stratified by antiviral treatment status, and the incidence of dementia and Parkinson's disease in a nationwide French population-based cohort, accounting for established risk factors. **Methods:** We conducted two parallel nationwide cohort analyses using the French national health data system (SNDS), covering approximately 98% of the French population (~64 million individuals in 2015). For each outcome, a population at risk was identified in 2015, excluding individuals with a prior history of the outcome, and followed from 2016 to 2025 for incident events. An a priori set of risk factors was defined for each outcome using a directed acyclic graph (DAG). HBV-infected patients were classified as treated or untreated based on antiviral therapy (tenofovir disoproxil or entecavir) received at baseline (2010–2015). A 1:10 age- and sex-matched cohort (HBV vs. general population) was used to fit cause-specific Cox models, adjusted for the DAG-derived covariate sets, with a three-level exposure variable (general population as reference, untreated HBV, treated HBV) and deaths from other causes treated as censored competing events. Robustness was assessed using inverse probability of treatment weighting (IPTW). **Results:** For dementia, untreated HBV patients had a modestly increased hazard compared with the general population (HR 1.09, 95% CI 1.00–1.19; p = 0.041), while no significant association was observed among treated patients (HR 0.86, 95% CI 0.74–1.01; p = 0.056). For Parkinson's disease, untreated HBV patients showed a significantly increased hazard (HR 1.19, 95% CI 1.08–1.31; p < 0.001), whereas treated patients showed no association with disease risk (HR 0.99, 95% CI 0.84–1.16; p = 0.854). IPTW analyses were consistent, with the treatment-associated reduction in dementia risk reaching significance (HR 0.82, 95% CI 0.69–0.98; p = 0.026). **Conclusion:** Untreated chronic HBV infection was associated with an increased hazard of neurodegenerative disease, notably Parkinson's disease and, to a lesser extent, dementia, whereas no excess risk was observed among treated patients, with a possible protective signal for dementia. These findings suggest untreated chronic HBV infection increases the hazard of neurodegenerative disease relative to the general population, an excess attenuated by antiviral therapy.

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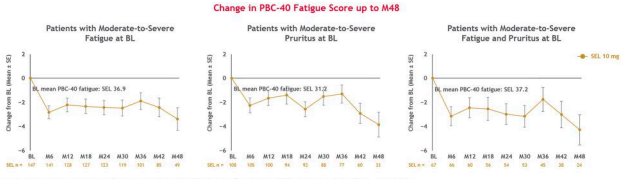
5040 | CLINICALLY MEANINGFUL FATIGUE IMPROVEMENT WITH SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS: DATA FROM THE OPEN-LABEL ASSURE STUDY

Alan Bonder[1] Andreas Kremer[2] Marlyn Mayo[3] K. Gautham Reddy[4] David E.J. Jones[5] Kyung min Kwon[6] Peyvand Amini[6] Caroline Burk[6] Jie Liu[6] Daria Crittenden[6] Gideon Hirschfield[7], [1]Beth Israel Deaconess Medical Center, Boston, MA, USA, [2]University Hospital Zürich, University of Zürich, Zürich, Switzerland, [3]University of Texas Southwestern, Dallas, TX, USA, [4]University of Chicago Medicine, Chicago, IL, USA, [5]Newcastle University, Newcastle, UK, [6]Gilead Sciences, Inc., Foster City, CA, USA, [7]Toronto General Hospital, Toronto, Canada

Background: Fatigue is a common symptom of primary biliary cholangitis (PBC), impairing quality of life. Pivotal phase 3 studies for approved second-line treatments seladelpar (SEL) and elafibranor (RESPONSE and ELATIVE, respectively) were not specifically designed to assess this multifactorial symptom. SEL significantly improved pruritus in RESPONSE, while fatigue measures suggested improvement at Months (M) 6 and 12. However, long-

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term data remain limited. Here we explore effects of SEL on fatigue from the open-label ASSURE study (NCT03301506) with data up to 4 years. **Methods:** ASSURE is an ongoing, open-label study of SEL 10 mg. Patients were enrolled from RESPONSE or prior SEL legacy trials. All patients in ASSURE were pooled with baseline (BL) defined as SEL initiation in RESPONSE or ASSURE. Three groups were defined at BL: moderate-to-severe fatigue (PBC-40 fatigue ≥ 29), moderate-to-severe pruritus (Numerical Rating Scale [NRS] ≥ 4), and moderate-to-severe pruritus and fatigue (PBC-40 fatigue ≥ 29 and NRS ≥ 4). Changes in fatigue score over time and rates of clinically meaningful fatigue improvement (PBC-40 fatigue score improvement ≥ 5) were assessed among evaluable patients up to M48 in this interim analysis. For PBC-40 fatigue score, sleep disturbance (PBC-40 item "itching disturbed my sleep"), and pruritus NRS, associations at BL and for change from BL at M48 were determined in the overall population using Spearman correlation. Data cutoff date: Jan 31, 2026. **Results:** Among 337 patients enrolled, 147 (44%) had moderate-to-severe fatigue, 108 (32%) had moderate-to-severe pruritus, and 67 (20%) had moderate-to-severe pruritus and fatigue. Mean PBC-40 fatigue score at BL reflected high symptom burden in these groups (36.9, 31.2, and 37.2, respectively). The moderate-to-severe fatigue group experienced sustained decline in PBC-40 fatigue score with similar findings in the other two groups (Figure). Clinically meaningful fatigue improvement was achieved in 35-46% of patients across groups at M48, with the highest rates observed in the group with both moderate-to-severe fatigue and pruritus at BL. Correlations were weak or moderate between fatigue and pruritus scores ($r = 0.38$ and $r = 0.35$ at BL and for change at M48, respectively; both $p < 0.05$) and fatigue and sleep scores ($r = 0.42$ and $r = 0.24$; both $p < 0.05$); strong correlations were observed between pruritus and sleep scores ($r = 0.82$ and $r = 0.62$; both $p < 0.05$). **Conclusion:** Sustained fatigue improvement was observed in symptomatic patients with PBC receiving open-label SEL with clinically meaningful improvements observed in more than one third of patients at 4 years of treatment, including those with moderate-to-severe fatigue, pruritus, or both. Correlations across fatigue, pruritus, and sleep disturbance highlight the interrelated nature of these symptoms and support the multifactorial nature of fatigue in PBC, including contributions from pruritus-related burden.



BL, baseline; M, month; NRS, Numerical Rating Scale; PBC, primary biliary cholangitis; SEL, seladelpar.

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5041 | ELBASVIRB IS PREDICTED TO INHIBIT IRREVERSIBLE ELASTIC FIBER FORMATION IN EXTRACELLULAR MATRIX IN LIVER FIBROSIS BY BLOCKING ADAMTS-LIKE PROTEIN 2

Rathan Duggirala[1] Sofia Jerez[1] Milan Darji[1] Usman Yaqoob[1] Sheng Cao[1] Vijay Shah[1], [1]Mayo Clinic Rochester

Background: Hepatic stellate cells (HSCs) are the primary source of extracellular matrix (ECM) in liver fibrosis. Although liver fibrosis can regress at early stages, it may progress to an irreversible state. The ECM components that contribute to this irreversibility remain poorly defined. ADAMTS-like protein 2 (ATL2) is an ECM component that, in the liver, is secreted almost exclusively by HSCs and is highly expressed during fibrosis. However, its role in ECM accumulation and the irreversibility of liver fibrosis remains unknown. In this study, we analyze the role of ATL2 in the establishment of irreversible liver fibrosis. **Methods:** Expression levels of ATL2 and ECM components Fibrillin-1 (FBN1) and Elastin (TE) were analyzed in vitro using human primary HSCs treated with TGFβ, with or without ATL2 silencing, and in vivo, using carbon tetrachloride (CCl4)-induced fibrosis model. In silico analysis with AlphaFold3 was used to predict 3D models of interactions between ATL2, FBN1, and TE. Molecular dynamics (MD) simulations in GROMACS were used to assess conformational stability and structural integrity. Protein-protein docking simulations were then performed in HADDOCK3 to characterize the binding interfaces and energetic affinities of the complex. The ZINC20 database was screened for compounds targeting the predicted interface, and the strongest candidate was selected to be evaluated in HSC cultures in vitro. **Results:** Gene expression analysis and IF revealed increased ATL2, FBN1, and TE expression in CCl2/4-treated mice and in TGFβ-treated human HSCs, which was reversed with ATL2 silencing. The predicted models for ATL2, FBN1 and TE binding exhibited confidence scores >90%. ATL2 interacted strongly with specific FBN1 domains but showed no direct interaction with TE. MD simulations indicated that ATL2 reduced FBN1 conformational entropy. Docking suggested that this stabilization favors TE deposition and the assembly of stable elastic fibers. Ensemble visualization of the ATL2-FBN1-TE complex revealed the ATL2-FBN1 interface as the most suitable target for halting the progression of liver fibrosis. Docking 1600+ FDA-approved drugs from the ZINC20 database with ATL2 revealed Elbasvir as a potential ATL2-FBN1 binding inhibitor. **Conclusion:** Our findings identify ATL2 as a key regulator for ECM stabilization in liver fibrosis. ATL2 binding to FBN1 reduces conformational flexibility and may facilitate the formation of highly stable elastic fibers, contributing to fibrosis irreversibility. The FDA-approved drug Elbasvir was identified as a potential agent to disrupt the ATL2–FBN1 interaction, thereby positioning this protein complex as a therapeutic target for fibrosis regression. **Disclosures:** Rathan Duggirala:Nothing to Disclose, Sofia Jerez:, Milan Darji:No dislosure submitted, Usman Yaqoob:Nothing to Disclose, Sheng Cao:, Vijay Shah: Boehringer Ingelheim: Consultant, GSK: Consultant, GENFIT SA: Consultant, Intercept Pharmaceuticals, Inc.: Advisor, Korro Bio, Inc.: Consultant, Novo Nordisk A/S: Consultant, Resolution Therapeutics, Ltd.: Advisor, Seal Rock Therapeutics, Ltd.: Consultant, Surrozen: Advisor, Dexcel Pharma Technologies, Ltd.: Consultant, Dimension Inx.: Advisor, Enveda: Consultant, Ochre Bio: Consultant, Satellite Biosciences, Inc.: Consultant.

5042 | EFFICACY AND SAFETY OF BRELOVITUG MONOTHERAPY FOR CHRONIC HEPATITIS D: PRIMARY 24-WEEK RESULTS FROM THE PHASE 3 AZURE-1 STUDY

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Background: Chronic Hepatitis D (CHD) is the most aggressive form of viral hepatitis, and current therapeutic options are limited. Brelovitug (BJT-778) is an investigational fully human monoclonal antibody that targets Hepatitis B surface antigen (HBsAg). Brelovitug is being evaluated in AZURE-1 (NCT06907290), a global, randomized, Phase 2b/3 study compared to delayed treatment (DT) in adults with CHD. Here we present the primary efficacy and safety results from the AZURE-1 phase 3 study. **Methods:** Participants across 29 sites in 11 countries were randomized 2:2:1 to brelovitug 300 mg subcutaneous (SC) once weekly (QW) self-administered at home, 900 mg SC every 4 weeks (Q4W) administered in clinic, or DT for 24 weeks followed by 300mg QW. Key eligibility criteria included HDV RNA > 500 IU/mL, ALT > upper limit of normal (ULN), and Child–Turcotte–Pugh (CTP) Score < 7; Participants with HIV co-infection or compensated cirrhosis including those with clinically significant portal hypertension (CSPH) were eligible. No eligibility restrictions were imposed for liver stiffness, bilirubin, albumin, INR or upper ALT threshold. The primary endpoint was a combined response defined as a virologic response (HDV RNA ≥ 2 log10 IU/mL reduction or **Results:** A total of 153 participants were randomized; 59 to 300 mg QW, 65 to 900 mg Q4W, and 29 to DT. Mean (SD) age overall was 46 (12.1) years, 89 (58%) were White, 49 (32%) were Asian, 103 (67%) were male, and 63 (41%) had cirrhosis. Mean (SD) baseline HDV RNA was 5.7 (1.06) $\log_{10}$ IU/mL and ALT was 125 (97.4) U/L, including 28 (18%) with ALT ≥ 5X ULN. 31 (20%) had at least probable CSPH and 12/63 (19%) with cirrhosis had a pre-treatment CTP score ≥ 6.The primary endpoint was achieved in 56% (33/59) p < 0.0001, 45% (29/65) p < 0.0001, and 0% (0/29) for the 300mg, 900mg, and DT groups, respectively. See virologic and ALT responses listed in Table 1. The mean change (SD) from baseline in HDV RNA level at Week 24 was -3.4 (1.18) and -3.4 (1.26) in the 300 mg and 900 mg groups, respectively. The most common adverse event reported was injection site reaction. Injection site reactions were mild to moderate in severity and reported in 6 (10%) and 12 (18%) in the 300 mg and 900 mg groups, respectively. Flu-like illness was reported in 3 (5%) of participants in the 300 mg and 7 (11%) in the 900 mg group. There were no treatment-related SAEs, Grade ≥ 3 AEs, or AEs leading to study discontinuation. **Conclusion:** In this phase 3 trial of individuals with CHD, brelovitug met the primary endpoint, demonstrating significant improvements in HDV RNA and ALT at Week 24 and was safe and well-tolerated. Evaluation of long-term efficacy and safety through Week 96 is ongoing. Additional phase 3 studies for brelovitug in CHD are in progress.

Table 1. Efficacy of Brelovitug in Participants with CHD at Week 24

Response[a]	300 mg QW (n=59) n (%)	900 mg Q4W (n=65) n (%)	Delayed Treatment (n=29) n (%)
Primary endpoint[b] (Virologic response + ALT normalization)	33 (56%) P<0.0001	29 (45%) P<0.0001	0
Virologic response (HDV RNA ≥2 $\log_{10}$ reduction or TND)	51 (86%)	55(85%)	0
ALT normalization	37 (63%)	35 (54%)	0
HDV RNA <LLOQ	15 (25%)	17 (26%)	0
HDV RNA undetectable (TND)	10 (17%)	11 (17%)	0

[a]HDV RNA levels were assessed using an RT-qPCR assay (Victorian Infectious Disease Reference Laboratory, Melbourne) in which LLOQ was 10 IU/mL and LOD was 5 IU/mL. [b]P values compare each treatment group against delayed treatment using a stratum-adjusted Miettinen Nurminen test..

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