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SPECIAL ARTICLE

2025 Late Breaking Abstracts

5001 | A PHASE 2, MULTICENTER, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF PEMVIDUTIDE IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

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Background: Pemvidutide is a balanced (1:1) GLP-1/glucagon dual receptor agonist in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), alcohol use disorder (AUD), and alcohol-associated liver disease (ALD). IMPACT is a Phase 2, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3 (NCT05989711). Here, we present the results of the primary analyses of the study at 24 weeks of treatment. **Methods**: From July 27, 2023 to April 29, 2025, 212 patients were randomized 1:2:2 to receive once-weekly subcutaneous pemvidutide (1.2 mg or 1.8 mg) administered without dose titration, or placebo. The mean age was 53 yrs, the mean BMI was 39 kg/m^2, 58% were female, and 43% had type 2 diabetes. The dual primary endpoints were MASH resolution without worsening of fibrosis or $\geq$1 stage liver fibrosis improvement without worsening of MASH at 24 weeks. An ITT analysis (N = 212) was employed in which patients with missing biopsy data or who discontinued treatment early were considered non-responders. **Results:** MASH resolution without fibrosis worsening was observed in 18 [20%] of 86 patients in the placebo group, 24 [58%] of 41 patients in the 1.2 mg pemvidutide group (95% CI, 21 to 56; $p < 0.0001$), and 45 [52%] of 85 patients in the 1.8 mg pemvidutide group (95% CI, 19 to 46; $p < 0.0001$). Fibrosis improvement without worsening of MASH was observed in 24 [28%] of 86 patients in the placebo group, 13 [33%] of 41 patients in the 1.2 mg pemvidutide group (95% CI, -13 to 22; $p = 0.59$), and 30 [36%] of 85 patients in the 1.8 mg pemvidutide group (95% CI, -6 to 22; $p = 0.27$). AI-based analyses of the liver biopsies and non-invasive tests for MASH and fibrosis were statistically significant at both pemvidutide doses, consistent with an ongoing anti-fibrotic effect (Table 1). Mean weight losses were 0.5% in the placebo group vs. 4.8% ($p < 0.001$) in the 1.2 mg group and 5.8% ($p < 0.001$) in 1.8 mg group. Pemvidutide was well-tolerated despite the absence of dose titration, with discontinuations due to adverse events of 2%, 0%, and 1%, in the placebo, 1.2 mg, and 1.8 mg groups, respectively. **Conclusion:** Pemvidutide was well tolerated without dose titration and led to significant MASH resolution, weight loss, and antifibrotic activity at only 24 weeks of treatment.

Table 1. Change from baseline to week 24 in selected endpoints.

Endpoint	placebo N=86	pemvidutide 1·2 mg N=41	pemvidutide 1·8 mg N=85
MASH resolution without fibrosis worsening, % patients (SE)	19.9 (4.3)	58.2 (7.9) ****	52.1 (5.6) ****
Fibrosis improvement without worsening of MASH, % patients (SE)	27.9 (4.9)	32.6 (7.5)	35.7 (5.3)
MASH resolution and fibrosis improvement, % patients (SE)	14.4 (3.8)	24.0 (6.8)	34.1 (4.8)
Liver fat relative reduction, % (SE)	-11.4 (3.0)	-52.0 (4.2) ***	-57.7 (3.0) ***
Change in corrected T1 relaxation time, ms (SE)	-14.7 (11.9)	-124.6 (16.1) ***	-134.7 (11.9) ***
Change in alanine aminotransferase, IU/L (SE)	-10.3 (2.4)	-34.6 (3.3) ***	-34.4 (2.3) ***
Change in Pro-C3, µg/L (SE)	-2.4 (1.6)	-15.3 (2.2) ***	-14.7 (1.5) ***
Change in Enhanced Liver Fibrosis score (SE)	0.03 (0.1)	-0.6 (0.1) ***	-0.5 (0.1) ***
Change in liver stiffness measurement, kPa (SE)	-0.7 (0.5)	-3.7 (0.7) ***	-2.2 (0.5) *
Change in FAST score (SE)	-0.1 (0.03)	-0.4 (0.04) ***	-0.4 (0.02) ***
Change in FIB-4 score (SE)	-0.1 (0.05)	-0.3 (0.06) ***	-0.3 (0.04) ***
Change in area of fibrosis by PathAI Liver Explore			
Proportion of patients w/ 50% reduction	12.8	19.5	35.3 ***
Proportion of patients w/ 60% reduction	8.1	12.2	30.6 ***

Data are presented as least squares mean (SE) unless indicated otherwise. A treatment policy estimand was applied with missing outcomes due either to missing biopsies or treatment discontinuations treated as non-responders (composite estimand). One patient randomized to the placebo group received 1.2 mg pemvidutide but was included in the placebo group. The Cochran-Mantel-Haenszel test was applied to endpoints that were categorical in nature. Comparisons versus placebo were made using mixed models for repeated measures for endpoints measured at multiple time points and analysis of covariance for endpoints measured at baseline and week 24. * p <0.05, *** p <0.001, **** p <0.0001 vs. placebo.

Disclosures: Mazen Noureddin: Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor: Terns,Takeda, Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn, and ChronWell: Stock – privately held company, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharmaceuticals: Consultant, Cytodyn: Consultant, GSK: Consultant, Eli Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Terns: Consultant, Takeda: Consultant, Allergan: Principal Investigator for a Drug Study, Akero: Principal Investigator for a Drug Study, BI: Principal Investigator for a Drug Study, BMS: Principal Investigator for a Drug Study,

Gilead: Principal Investigator for a Drug Study, Galectin: Principal Investigator for a Drug Study, Genfit: Principal Investigator for a Drug Study, GSK: Principal Investigator for a Drug Study, Conatus: Principal Investigator for a Drug Study, Corcept: Principal Investigator for a Drug Study, Enanta: Principal Investigator for a Drug Study, Madrigal: Principal Investigator for a Drug Study, Novartis: Principal Investigator for a Drug Study, Novo Nordisk: Principal Investigator for a Drug Study, Shire: Principal Investigator for a Drug Study, Takeda: Principal Investigator for a Drug Study, Terns: Principal Investigator for a Drug Study, Viking: Principal Investigator for a Drug Study, Zydus: Principal Investigator for a Drug Study, Rivus Pharmaceuticals: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speaking and Teaching, Akero: Stock – privately held company, 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 Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - 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5002 | DUAL GLP-1 AND GLUCAGON RECEPTOR AGONIST, MAZDUTIDE, RESOLVED STEATOSIS IN >60% OF PARTICIPANTS WITH MASLD AND OBESITY IN A MULTICENTER, RANDOMIZED PHASE 2 TRIAL

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Background: Mazdutide (MAZ; LY3305677) is a once-weekly dual agonist of the glucagon-like peptide-1 (GLP-1) and glucagon (GCG) receptors. In this 48-week phase 2 obesity study (NCT06124807), participants with baseline liver fat content (LFC) ≥5%, as measured by MRI-PDFF, were included in the pre-specified MASLD analysis. We report changes in LFC, ALT, AST and markers of insulin sensitivity in these participants. **Methods**: Adult participants with BMI ≥30 kg/m², or BMI ≥27 kg/m² with weight-related comorbidities (non-T2D), were randomly assigned to 48 weeks of once-weekly subcutaneous MAZ (final doses of 6, 10, or 16 mg via dose escalation) or placebo (PBO) and received diet and physical activity counseling from site personnel. Endpoints were change and percent change from baseline (%CFB) in LFC, proportion of participants with ≥30%, ≥50% and ≥70% relative reduction in LFC, and proportion of participants with normal LFC (<5%) at Weeks 32 and 48. **Results:** Out of 179 participants,121 (16% of whom identified as Black or African American) with baseline LFC ≥5% were included in this MASLD analysis and were assigned to PBO (n=36) or MAZ 3/6 mg (n=22), 10 mg (n=32), or 16 mg (n=31). Baseline characteristics were balanced across arms, with mean age of 47.7 years, BMI 38.8 kg/m², LFC 13.4%, ALT 28.3 U/L, and AST 22.9 U/L. LFC was reduced in all MAZ groups versus PBO ($p<0.01$ for each comparison) at the primary endpoint of 32 weeks, with %CFB in LFC of -53.5% (SE=5.4%) in 3 mg, -67.7% (4.0%) in 10 mg, -68.8% (4.8%) in 16 mg, and -14.1% (6.7%) in PBO (**Figure**). Of these, 74.0% (SE=10.3%) in 3 mg, 84.9% (6.4%) in 10 mg, 83.4% (7.4%) in 16 mg, and 24.9% (8.7%) in PBO achieved ≥30% reduction in LFC, and normal LFC (<5%) was achieved by 50.6% (SE=10.8%) of participants in 3 mg, 69.6% (9.2%) in 10 mg, 62.7% (11.5%) in 16 mg, and 13.0% (6.3%) in PBO at Week 32. A direct correlation was observed between %CFB in LFC and %CFB in body weight (Spearman's r=0.73, $p<0.001$). Compared with PBO, MAZ doses ≥10 mg significantly reduced ALT (range: -18.3 to -18.7%) and AST (-16.8 to -19.7%), fasting insulin (range -46.5 to -53.1%), HOMA2-IR (-46.6 to -47.6%), triglycerides (-30.9 to -36.2%), and increased beta-hydroxybutyrate (97.9 to 132.6%) as a marker of glucagon action at Week 32. Similar patterns were observed at 48 weeks. **Conclusion:** In participants with obesity and baseline LFC ≥5%, MAZ resolved steatosis in >60% and >70% of participants with the highest two doses at Weeks 32 and 48, respectively. LFC reductions were associated with reductions in body weight and with improved insulin sensitivity and lipid metabolism.

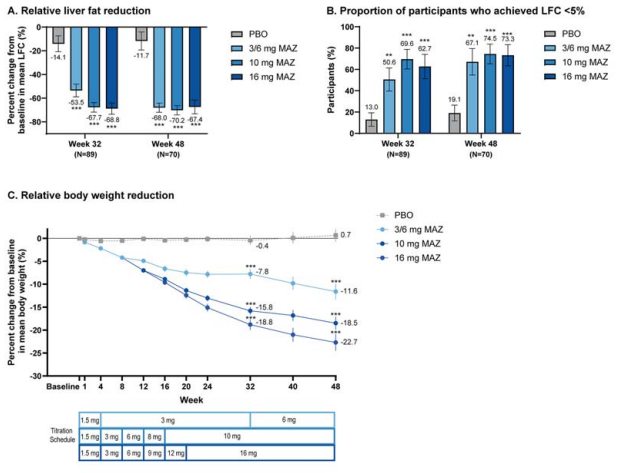

Figure. Data is for participants with baseline LFC ≥5%. Error bars represent standard error (SE). Participants assigned to 3/6 mg received 3 mg from Weeks 4 through 32 before escalating to 6 mg at Week 32. MAZ, mazdutide; PBO, placebo; LFC, liver fat content. **$p<0.01$; ***$p<0.001$.

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, Liana Billings:, Stanley Hsia: Abbvie, Inc.: Grant/Research Support, Amgen Inc.: Grant/Research Support, AstraZeneca AB: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, 89Bio, Inc.: Grant/Research Support, Biomea Fusion, Inc.: Grant/Research Support, Cidara Therapeutics, Inc.: Grant/Research Support, Corcept Therapeutics, Inc.: Grant/Research Support, Currax Pharmaceuticals: Grant/Research Support, Kowa Research Institute, Inc.: Grant/Research Support, Eli Lilly & Co.: Grant/Research Support, Madrigal Pharmacueticals, Inc.: Grant/Research Support, Merck Sharpe & Dohme LLC: Grant/Research Support, Medincell S.A.: Consultant, Moderna Tx, Inc.: Grant/Research Support, Novartis Pharmaceuticals AG: Grant/Research Support, Novo Nordisk A/G: Grant/Research Support, Regor Pharmaceuticals, Inc.: Grant/Research Support, Sanofi Pasteur Inc.: Grant/Research Support, Braintree Laboratories, Inc.: Grant/Research Support, Mylan Pharmaceuticals, Inc.: Grant/Research Support, Viking Pharmaceuticals, Inc.: Grant/Research Support, Zealand Pharma A/S: Grant/Research Support, Zydus Therapeutics, Inc.: Grant/Research Support, American Diabetes Association: Royalties or patent beneficiary, Harold Bays: Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Grant/Research Support, HighTide,: Grant/Research Support, Madrigal: Grant/Research Support, Lilly: Consultant, Novo Nordisk: Consultant, Amgen: Consultant, Pfizer: Consultant, Lilly: Grant/Research Support, Novo Nordisk: Grant/Research Support, Amgen: Grant/Research Support, Pfizer: Grant/Research Support, Olimpia Ferreira Galvao de Araujo: Eli Lilly and Co: Employee, Ann Marie Weideman: Nothing to Disclose, Lai San Tham: Eli Lilly and Company: Employee, Tamer Coskun:, Melissa Thomas: Eli Lilly and Company: Shareholder, Eli Lilly and Company: Employee, Axel Haupt: Eli Lilly and Company: Employee, Eli Lilly and Company: Stock – privately held company, Lilly: Employee, Mark Hartman:, Kieren Mather: Eli Lilly and Company: Employee

5003 | LACTULOSE AND TAI-CHI PREVENT FALLS IN PATIENTS WITH CIRRHOSIS: THE LIVESMART RANDOMIZED CONTROLLED TRIAL

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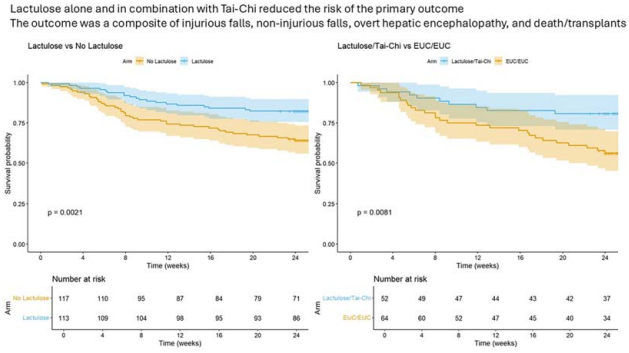
Background: Falls are common and morbid for patients with cirrhosis. Patients have identified reducing fall risk as a care priority. We sought to reduce falls by initiating lactulose and/or TeleTai-Chi. **Methods**: **Design**: We conducted a 24-week two-stage Sequential, Multiple Assignment Randomized Trial (SMART). **Setting**: Patients were enrolled at four centers in the US (Michigan, Pennsylvania, and two in Texas). **Participants**: Patients with cirrhosis and portal hypertension without prior overt hepatic encephalopathy (HE). **Interventions**: In Stage 1 (week 1-12), participants were randomized to receive either lactulose therapy or enhanced usual care (education on nutrition and falls prevention). In stage 2 (week 13-24), participants were randomized to either TeleTai-Chi or enhanced usual care (exercise education). **Main outcomes and measures**: The primary outcome was a hierarchical composite of death/transplantation, injurious falls, incident HE, and non-injurious falls, compared between study arms using an intention-to-treat win ratio (WR) with WR >1 indicating decreased event risk. **Results:** A total of 230 participants enrolled, aged 61.8 $\pm$11.3 years, 60% female, 54% with ascites, and average MELD-Na score of 9.9. The sequence of lactulose/TeleTai-Chi vs. enhanced usual care reduced injurious falls (4% vs 12%), non-injurious falls (19% vs 32%), but not overt HE (2% vs 0%) or death/transplant (0% vs 0%). Lactulose users compared to non-users experienced fewer injurious falls (3.5% vs 8.5%), non-

injurious falls (15.0% vs 26.5%), and overt HE (1.8% vs 2.6%), but not death or transplant. Sequential lactulose/TeleTai-chi reduced the risk of the primary outcome compared to usual care; WR 2.7 (95% CI: 1.3-5.5). Twelve-weeks of lactulose versus no lactulose had a favorable WR of 2.0 (95% CI: 1.1-3.7) and 12-weeks TeleTai-Chi over no TeleTai-Chi had a WR 2.3 (95% CI: 2.0-5.3). Over 24 weeks, lactulose reduced the absolute risk of the primary outcome by 18.2% (95% CI, 6.7%-29.6%) and lactulose/TeleTai-Chi by 24.2% (95% CI:7.0%-41.3%). There was no difference in adverse events between treatment groups **Conclusion:** Lactulose and TeleTai-Chi are two effective interventions to reduce falls and fall-related harms for patients with cirrhosis and portal hypertension. This is the largest trial of lactulose and the first trial of Tai-Chi for patients with cirrhosis.



Disclosures: Elliot Tapper: Madrigal: Grant/Research Support, Sumeet Asrani: Nothing to Disclose, Ethan Weinberg: PharmaIN: Consultant, BioVie: Consultant, Sequana: Consultant, Novo Nordisk: Advisor, Amgen: Consultant, Astra Zeneca: Consultant, Kezar: Consultant, Lili Zhao:, Samantha Nikirk:, Shivang Mehta: Nothing to Disclose, Neil Alexander:, Xi Chen:, Donna Evon: Nothing to Disclose, Marina Serper: Transplant Genomics: Grant/Research Support, Grifols: Grant/Research Support, Eurofins: Grant/Research Support

5004 | TOP-LINE PHASE 2 RESULTS OF DD01, A DUAL GLP-1/GLUCAGON AGONIST, LEAD TO RAPID IMPROVEMENTS IN LIVER AND METABOLIC ENDPOINTS IN PATIENTS WITH MASLD/MASH

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Background: MASH is a major public health problem, developing in the background of metabolic syndrome and obesity. DD01 is a liver-targeted dual GLP-1/glucagon receptor agonist being investigated for the treatment of MASLD/MASH. The results of 12- and 24-week assessments are presented. **Methods**: The DD01-DN-02 study is an ongoing 48-week randomized, placebo-controlled, double-blind phase 2 study (NCT06410924). Eligible subjects had ≥10% liver fat content by MRI-PDFF and either two metabolic risk factors or liver biopsy with NAS ≥4 (and at least 1 point in each component) and F1-F3 fibrosis within 6 months of enrollment. Subjects were randomized 1:1 to receive subcutaneous 40 mg DD01 or placebo weekly, with DD01 subjects receiving 20 mg doses for the first 2 weeks. The primary endpoint was ≥30% MRI-PDFF liver fat reduction from baseline at 12 weeks. **Results:** A total of 67 subjects were randomized to the DD01 group or to the placebo group. A majority (78%) had biopsy-proven MASH. The primary endpoint was met: at 12 weeks, the proportion of subjects achieving ≥30% liver fat reduction from baseline by MRI-PDFF was significantly higher in the DD01 group (75.8%) than placebo (11.8%; $p < 0.0001$). A greater proportion of patients in the DD01 group achieved ≥50% (72.7%) and ≥70% (57.6%) liver fat reduction than placebo (5.9% and 0%, respectively; $p < 0.0001$ for both). Of the subjects receiving DD01, 48.5% experienced liver fat normalization (≤5% fat), compared to 0% in those receiving placebo ($p < 0.0001$). Subjects receiving DD01 also experienced a significantly greater relative reduction in liver stiffness on MR elastography (-19.7 ± 8.1%, LSmean ± SE) relative to placebo (-7.2 ± 7.7%; $p = 0.0016$). There was a larger absolute reduction in HbA1c in the DD01 group (-0.33 ± 0.16%) than placebo (-0.19 ± 0.16%; $p < 0.05$) withing this short duration. DD01 led to a greater relative change in weight from baseline at 12 and 24 weeks (-3.8 ± 1.4% and -6.4 ± 2.3%, respectively) than placebo (-0.4 ± 1.3% and -1.8 ± 2.1%, respectively; $p < 0.0001$ for both). DD01 also led to a greater reduction in PRO-C3, ELF, liver enzymes and lipids. DD01 was generally well-tolerated. Most adverse events were GI-related, which led to discontinuation of 3 subjects in the DD01 group. **Conclusion:** The study met its primary endpoint and showed significant reductions in liver fat at 12 weeks. Also, DD01 led to improvements in markers of fibrosis, HbA1c, and weight with continued improvements evident at 24 weeks.

12-Week Endpoint	DD01 (40 mg) n=33	Placebo n=34	p-value vs placebo
Proportion of subjects achieving ≥30% liver fat reduction by MRI-PDFF, %	75.8%	11.8%	<0.0001
Proportion of subjects achieving ≥50% liver fat reduction by MRI-PDFF, %	72.7%	5.9%	<0.0001
Proportion of subjects achieving ≥70% liver fat reduction by MRI-PDFF (%)	57.6%	0%	<0.0001
Normalization: proportion of subjects with liver fat ≤5% by MRI-PDFF, %	48.5%	0%	<0.0001
Relative change in liver fat content by MRI-PDFF, % (Mean, SE)	-62.3 ± 5.4	-8.3 ± 4.4	<0.0001
Relative change in LSM by MRE, % (LS Mean, SE)	-19.7 ± 8.1	-7.2 ± 7.7	0.0016
Relative change in weight, % (LS Mean, SE)	-3.8 ± 1.4	-0.4 ± 1.3	<0.0001

LS, least squares; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction

Disclosures: Mazen Noureddin: Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor: Terns,Takeda, Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn, and ChronWell: Stock – privately held company, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharmaceuticals: Consultant, Cytodyn: Consultant, GSK: Consultant, Eli Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Terns: Consultant, Takeda: Consultant, Allergan: Principal Investigator for a Drug Study, Akero: Principal Investigator for a Drug Study, BI: Principal Investigator for a Drug Study, BMS: Principal Investigator for a Drug Study, Gilead: Principal Investigator for a Drug Study, Galectin: Principal Investigator for a Drug Study, Genfit: Principal Investigator for a Drug Study, GSK: Principal Investigator for a Drug Study, Conatus: Principal Investigator for a Drug Study, Corcept: Principal Investigator for a Drug Study, Enanta: Principal Investigator for a Drug Study, Madrigal: Principal Investigator for a Drug Study, Novartis: Principal Investigator for a Drug Study, Novo Nordisk: Principal Investigator for a Drug Study, Shire: Principal Investigator for a Drug Study, Takeda: Principal Investigator for a Drug Study, Terns: Principal Investigator for a Drug Study, Viking: Principal Investigator for a Drug Study, Zydus: Principal Investigator for a Drug Study, Rivus Pharmaceuticals: Stock – privately held company, Cytodyn: Stock - 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5005 | HU6 ORAL INVESTIGATIONAL THERAPY REDUCES LIVER FAT AND IMPROVES ADIPOSITY MARKERS IN ADULTS WITH MASH: TOPLINE RESULTS FROM A PHASE 2 RANDOMIZED PLACEBO-CONTROLLED TRIAL (M-ACCEL)

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Background: HU6 is a novel, oral, first-in-class controlled metabolic accelerator (CMA) in development for the treatment of obesity and associated cardiometabolic diseases, including MASH. This Phase 2 study (M-ACCEL) evaluated the efficacy of HU6 in reducing liver fat and improving metabolic parameters in adults with MASH. **Methods**: In total, 273 patients were randomized to receive placebo or HU6 at 150, 300, or 450 mg/d for 26 weeks in a ratio of 2:1:2:2. The study enrolled patients with MASH with a VCTE score of 7.0–15.0 kPa (targeting patients with fibrosis stages F2/F3) and an MRI-proton density fat fraction (PDFF) $\geq 8\%$. The primary endpoint was percent change from baseline in liver fat content by MRI-PDFF. Secondary endpoints included categorical liver fat reduction (decrease of $\geq 30\%$), changes in body weight, body composition, and exploratory markers of metabolic health. The primary analysis used the prespecified modified intention-to-treat population, with missing data imputed using a placebo washout multiple imputation method. **Results:** At Week 26, the primary end point was met where HU6 reduced liver fat in patients across all doses (least-squares mean difference: −29.4%, −31.2%, −27.0% for HU6 doses of 150, 300, 450 mg, respectively, vs –6.7% for placebo; $P < 0.005$ vs placebo for each). A $\geq 30\%$ liver fat reduction occurred in the majority of patients, 57%, 58%, and 50% for HU6 doses of 150, 300, 450 mg, respectively, vs 22% with placebo; $P < 0.005$ vs placebo for each. HU6 doses of 300 and 450 mg reduced body weight vs placebo ($P < 0.05$). Body fat mass was reduced with ~2:1 selectivity for visceral over subcutaneous fat at the 450-mg dose, with no change in lean or skeletal muscle mass. HU6 was generally safe and well tolerated, consistent with results of two prior Phase 2 trials. **Conclusion:** Treatment with HU6 produced clinically meaningful reductions in liver fat and visceral adiposity, a favorable safety profile, and no significant loss of lean muscle mass in adult patients with MASH, supporting further development of HU6 for MASH.

Disclosures: Mazen Noureddin: Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor: Terns, Takeda, Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn, and ChronWell: Stock – privately held company, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharmaceuticals: Consultant, Cytodyn: Consultant, GSK: Consultant, Eli Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Terns: Consultant, Takeda: Consultant, Allergan: Principal Investigator for a Drug Study, Akero: Principal Investigator for a Drug Study, BI: Principal Investigator for a Drug Study, BMS: Principal Investigator for a Drug Study, Gilead: Principal Investigator for a Drug Study, Galectin: Principal Investigator for a Drug Study, Genfit: Principal Investigator for a Drug Study, GSK: Principal Investigator for a Drug Study, Conatus: Principal Investigator for a Drug Study, Corcept: Principal Investigator for a Drug Study, Enanta: Principal Investigator for a Drug Study, Madrigal: Principal Investigator for a Drug Study, Novartis: Principal Investigator for a Drug Study, Novo Nordisk: Principal Investigator for a Drug Study, Shire: Principal Investigator for a Drug Study, Takeda: Principal Investigator for a Drug Study, Terns: Principal Investigator for a Drug Study, Viking: Principal Investigator for a Drug Study, Zydus: Principal Investigator for a Drug Study, Rivus Pharmaceuticals: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speaking and Teaching, Akero: Stock – privately held company, 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 Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Conatus: Principal Investigator, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Rivus, Sagimet: Consultant, Rivus: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support, Altimmune: Grant/Research Support, Akero: Grant/Research Support, BI: Grant/Research Support, BMS: Grant/Research Support, Boston Pharma: Grant/Research Support, Conatus: Grant/Research Support,

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5006 | COTRIMOXAZOLE FOR PATIENTS WITH CIRRHOSIS AND ASCITES AND NO PRIOR SPONTANEOUS BACTERIAL PERITONITIS: THE ASEPTIC CLINICAL TRIAL (PRIMARY ANTIBIOTIC PROPHYLAXIS USING CO-TRIMOXAZOLE TO PREVENT SPONTANEOUS BACTERIAL PERITONITIS IN CIRRHOSIS)

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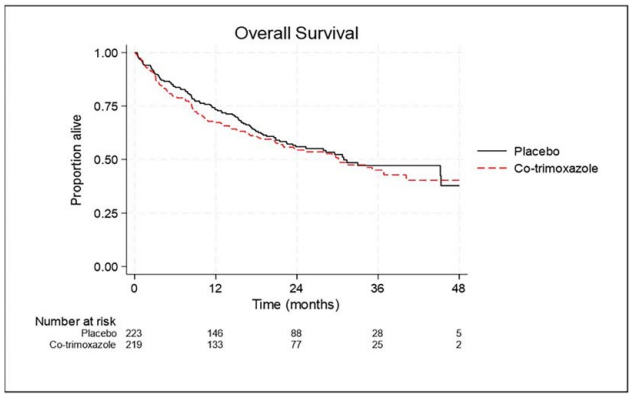
Background: Bacterial infection is a major cause of mortality in patients with cirrhosis and ascites. Secondary prophylactic antibiotic therapy has been shown to improve outcomes after an episode of spontaneous bacterial peritonitis (SBP) but primary prophylaxis to prevent a first episode remains contentious, although most cases occur in those without previous infection. Importantly prophylaxis may increase antimicrobial resistance. Whether primary prophylaxis to prevent infection using co-trimoxazole improves overall survival in these patients is unknown. **Methods**: We conducted a multicentre, placebo-controlled, double-blinded, randomised controlled trial involving patients with cirrhosis and ascites requiring diuretic treatment or paracentesis, and no current or previous episodes of SBP. Patients were randomly assigned in a 1:1 ratio to receive oral Co-trimoxazole 960 mg or an identical placebo once daily for 18 months. Follow up visits were 6 monthly thereafter with a maximum possible follow up period of 48 months, and a minimum of 18 months. The primary outcome was overall survival. **Results:** 442 patients underwent randomization at 41 hospitals in England, Scotland and Wales, 2020-2025, with alcohol the cause of cirrhosis in 84.4%. 219 patients randomised to Co-trimoxazole and 223 to placebo were included in the intention to treat analysis. Groups were matched at baseline. Overall

survival did not differ between groups with 101 (46.1%) deaths in Co-trimoxazole arm and 98 (43.9%) deaths in placebo, hazard ratio (HR) 1.10 (95% CI 0.83-1.45), p = 0.52. When adjusted for stratification factors at baseline (on transplant list, use of rifaximin, liver disease due to alcohol and active alcohol use), survival HR was 1.09 (95% CI 0.82-1.44). There was no difference in overall survival (HR 1.17, CI 0.85-1.6) nor unplanned hospital admissions (HR 1.07, CI 0.84-1.37) during trial treatment period and no difference in time to first incidence of spontaneous bacterial peritonitis (HR 1.58, CI 0.85-2.92). Predefined subgroup analyses of the 159 patients known to have an ascitic protein count ≤ 1.5g/L did not show a difference in survival between groups (HR 1.27, 95% CI 0.79-2.04). **Conclusion:** In the largest trial of primary antibiotic prophylaxis for patients with cirrhosis and ascites, use of Co-trimoxazole had no effect on overall survival. Given the increasing impact of antimicrobial resistance, our results strongly support abandoning primary prophylaxis.

Figure: Kaplan-Meier curve for overall survival. Log rank test P=0.52



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5007 | EFFICACY AND SAFETY OF LIBEVITUG (HH-003) IN PATIENTS WITH CHRONIC HEPATITIS D VIRUS INFECTION FROM AN INTERNATIONAL, MULTICENTRE, RANDOMIZED, CONTROLLED, OPEN-LABEL PHASE 2B STUDY

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Background: Libevitug (HH-003) is a human monoclonal antibody targeting the PreS1 domain of the large envelope protein of hepatitis B virus (HBV). By blocking HBV and HDV entry into hepatocytes, libevitug could lead to a profound reduction in HDV RNA and ALT levels in patients with chronic HBV/HDV infection. Libevitug is currently being evaluated in a pivotal Phase 2b study (HH003-204; NCT05861674) for treatment of chronic HDV infection. Here, we report the 48-week treatment outcomes from this ongoing study. **Methods**: Eligible patients with chronic HDV infection were stratified by cirrhosis status and country, and randomized in a 2:2:1 ratio into three groups: two libevitug dose groups receiving either 20 mg/kg or 10 mg/kg intravenously every two weeks, plus 25 mg oral tenofovir alafenamide fumarate (TAF) daily for 48 weeks followed by a 24-week follow-up period with TAF only, and a control group receiving only TAF for 48 weeks without follow-up. The primary endpoint, defined as a combined response, is the proportion of patients who, at week 24, achieve either HDV RNA below the lower limit of quantification (LLOQ) or a decrease of ≥ 2 $\log_{10}$ from baseline, together with ALT normalization. Other endpoints included the combined response at week 48, the rates of HDV RNA response and ALT normalization rates at weeks 24 and 48, changes in HDV RNA and ALT levels, and change in liver stiffness. **Results:** A total of 94 patients with abnormal baseline ALT were included in the main analysis set: 40 in libevitug 20 mg/kg group, 34 in the 10 mg/kg group, and 20 in the

control group. Baseline characteristics were generally balanced across groups with a mean age of 40.3 years, 68% males, 16% with compensated cirrhosis, mean HDV RNA 6.1 $\log_{10}$ IU/mL and mean ALT 103.8 U/L. The combined response rates at week 24 were 35.0% for the libevitug 20 mg/kg group and 32.4% for the 10 mg/kg group, increasing to 42.5% and 44.1% at week 48, respectively, which were significantly higher than that in the control group. Responses in HDV RNA, ALT and liver stiffness in the libevitug groups were also significantly greater than that in the control group. Additionally, libevitug was safe and well-tolerated, without serious adverse events (AEs) related to libevitug or AEs leading to discontinuation. **Conclusion:** Libevitug demonstrated good efficacy and safety profile in treating chronic HDV infection, with comparable results observed in both dose groups.

Table. Efficacy and safety results at weeks 24 and 48

Efficacy results at weeks 24 and 48						
n (%)	HH-003 20 mg/kg (N=40)		HH-003 10 mg/kg (N=34)		Control group (N=20)	
	Week 24	Week 48	Week 24	Week 48	Week 24	Week 48
Combined response 95% CI P Value [1]	14 (35.0%) 20.6%, 51.7% 0.0121	17 (42.5%) 27.0%, 59.7% 0.0026	11 (32.4%) 17.4%, 50.5% 0.0215	15 (44.1%) 27.2%, 62.1% 0.0022	1 (5.0%) 0.1%, 24.9% -	1 (5.0%) 0.1%, 24.9% -
HDV RNA response [2] 95% CI P Value	17 (42.5%) 27.0%, 59.1% 0.0026	24 (60.0%) 43.3%, 75.1% <0.0001	12 (35.3%) 19.8%, 53.5% 0.0188	17 (50.0%) 32.4%, 67.6% 0.0007	1(5.0%) 0.1%, 24.9% -	1(5.0%) 0.1%, 24.9% -
ALT normalization 95% CI P Value	31 (77.5%) 61.6%, 89.2% <0.0001	28 (70.0%) 53.5%, 83.4% <0.0001	20 (58.8%) 40.7%, 75.4% 0.0099	19 (55.9%) 37.9%, 72.8% 0.0012	4 (20.0%) 5.7%, 43.7% -	2 (10.0%) 1.2%, 31.7% -
Change from BL in HDV RNA levels ($\log_{10}$ IU/mL): Mean (SE) P Value	-2.00 (0.17) <0.0001	-2.53 (0.19) <0.0001	-1.70 (0.18) <0.0001	-1.95 (0.20) <0.0001	-0.38 (0.12) -	-0.49 (0.17) -
Change from BL in liver stiffness (Kpa): Mean (SE) P Value	-1.65 (0.57) 0.02	-2.3 (0.45) 0.01	-1.82 (0.37) 0.02	-1.52 (0.50) 0.23	0.17 (0.62) -	-0.45 (0.68) -
Overall safety# summary through week 48, n (%)						
TEAE	40 (95.2%)		37 (97.4%)		19 (95.0%)	
TEAE with Grade 3*	4 (9.5%)		3 (7.9%)		2 (10.0%)	
Grade 3 TEAE related to HH-003	1 (2.4%)&		0		0	
SAE related to HH-003	0		0		0	

BL=Baseline; TAF= Tenofovir alafenamide fumarate; LLOQ= Lower Limit of Quantification; CI= Confidence Interval
TEAE= Treatment Emergent Adverse Event; SE= Standard Error; SAE= Serious Adverse Event
Both HDV RNA and ALT samples were analysed in a central laboratory. HDV RNA was quantified using Robogene HDV RNA quantification kit version 2.0 (LLOQ=46.77 IU/mL), while the normal range for ALT is 0-33 U/L for female and 0-41 U/L for male.
1.Fisher's exact test was implemented in a hierarchical manner; Clopper-Pearson method was used to calculate the 95% CI.
2.HDV RNA response defined as plasma HDV RNA below the LLOQ or a decrease of ≥ 2 $\log_{10}$ from baseline.
Based on the safety set, 42 patients were in HH-003 20 mg/kg, 38 in HH-003 10 mg/kg and 20 in the control group.
& AE term: neutrophil count decreased, which was considered possibly related to HH-003; and it was transient, asymptomatic, and resolved spontaneously without intervention.
* No Grade 4 TEAEs were reported in this study.

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5008 | SAFETY AND EFFICACY OF INEBILIZUMAB IN IGG4 RELATED DISEASE IN PARTICIPANTS WITH HEPATIC, PANCREATIC, AND BILIARY INVOLVEMENT: RESULTS FROM THE PHASE 3 MITIGATE TRIAL

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Background: Pancreatic and hepatobiliary disease are frequent manifestations of IgG4 Related Disease (IgG4-RD), an immune-mediated, relapsing, fibroinflammatory disease that results in tissue damage and loss of organ function. Inebilizumab (INEB) is an anti-CD19 monoclonal antibody that results in rapid and durable B cell depletion. MITIGATE (NCT04540497) is a randomized, placebo (PBO)-controlled Phase 3 trial evaluating the safety and efficacy of INEB as a treatment for IgG4-RD. **Methods**: A post hoc subgroup analysis of MITIGATE trial results was conducted to evaluate safety and efficacy outcomes in subjects who had baseline disease activity in the pancreas, bile ducts, or liver. Eligible subjects had a history of at least 2 organs involved and had experienced an IgG4-RD flare that required glucocorticoid treatment during the screening period. Subjects were randomized 1:1 to INEB or PBO and were treated on day 1, day 15, and week 26 of the 1-year randomized controlled period (RCP). Steroids were tapered to discontinuation at the end of RCP week 8. Other immunosuppressive therapy for IgG4-RD was prohibited during the study. **Results:** Among 135 enrolled subjects, 52% had historic involvement of the pancreas, 32% of the bile ducts, and 7% liver. At study baseline, disease activity was seen in the pancreas, bile ducts, and liver in 51 (38%), 28 (21%), and 5 (4%) subjects, respectively. INEB reduced the risk of flare (primary endpoint of the study) relative to PBO in the pancreas group (HR = 0.03, nominal p = .0005). In the bile duct group, 0/13 INEB-treated and 12/15 PBO-treated subjects experienced a flare. In the liver group, 0/2 INEB-treated and 3/3 PBO-treated subjects experienced a flare. The proportion of subjects achieving flare-free, treatment-free complete remission were higher with INEB vs. PBO (odds ratios 10.8 and 35.8 for the pancreas and bile duct groups, respectively). Steroid use was substantially reduced with INEB vs. PBO in the pancreas and bile duct

groups (nominal p < .0001). CD19+ B cells peaked 3 months prior to flare, followed by increases in total IgG, IgG subclasses, and lipase levels in PBO-treated subjects experiencing on-study flares in GI organs (n = 17) (Figure 1). Safety outcomes will be presented. **Conclusion:** Analysis of IgG4-RD patients with pancreatic/hepatobiliary involvement in MITIGATE demonstrates benefit and safety of CD19-targeted B cell depletion by INEB. Organ-specific flare biomarkers were also identified in this prospective trial cohort.

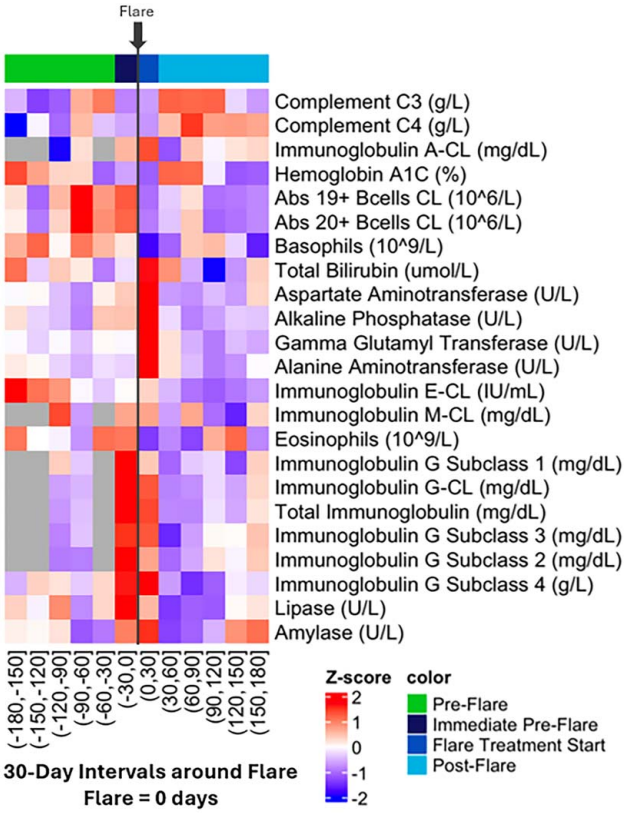

Figure 1. Row z-scored estimated marginal means (EMM) for each biomarker discretized into 30-day intervals 6 months pre- and post- flare in GI-organ involved participants receiving PBO (n=17).

Disclosures: Emma Culver: IPsen: Speaking and Teaching, Mirum: Advisor, Horizon (Amgen): Advisor, Zenus Biopharma: Advisor, GSK: Speaking and Teaching, Dr Falk Pharma: Advisor, Advance: Speaking and Teaching, Intercept: Speaking and Teaching, Jansen: Grant/Research Support, John Stone:, Arezou Khosroshahi:, Wen Zhang:, Nicolas Schleinitz:, Kazuichi Okazaki:, Yoshiya Tanaka: Chugai, UCB, Abbvie, AstraZeneca, Eli-Lilly, Behringer-Ingel: Speaking and Teaching, Matthias Lohr:, Theresa Alexander: Amgen: Employee, Kristen Clarkson:, Rong Luo: Nothing to Disclose, Melissa Rosen: Amgen: Employee, Sue Cheng: Amgen: emplyee, Daniel Cimbora:

5009 | PERFORMANCE OF A MULTI-TARGET BLOOD TEST VERSUS ULTRASOUND IN DETECTING EARLY HEPATOCELLULAR CARCINOMA: RESULTS FROM THE ALTUS PROSPECTIVE STUDY

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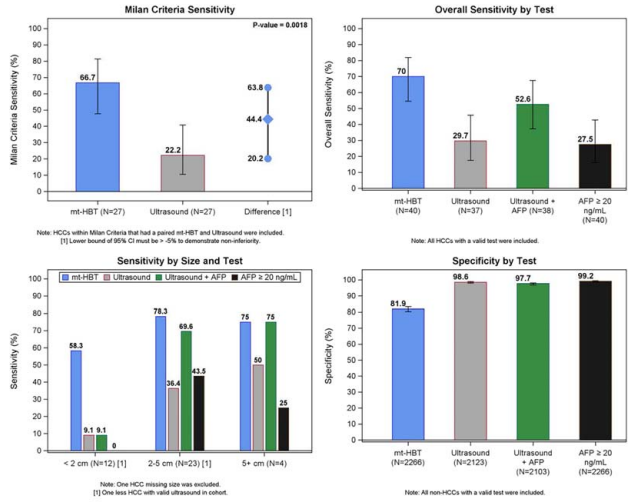
Background: Abdominal ultrasound (US) is a central component of hepatocellular carcinoma (HCC) surveillance despite suboptimal early-stage sensitivity and poor adherence. In previous studies, a multi-target HCC blood test (mt-HBT) incorporating methylated DNA markers, AFP, and patient sex showed promise in early detection of HCC. Here, we report the mt-HBT sensitivity and specificity with a prospective head-to-head comparison to US for early-stage HCC detection. **Methods**: ALTUS (NCT: 05064553) is a prospective multicenter study in the United States that enrolled adults with cirrhosis (92.9%) or chronic HBV. Participants underwent standard-of-care HCC surveillance (92.9% US, 7.1% CT/MRI) and concurrent mt-HBT testing. Reference triphasic CT/MRI was performed within 30 days. HCC was defined by central radiology adjudication of LI-RADS 5 or tumor-in-vein observations by two blinded, independent radiologists, or by pathology. Early-stage HCC was defined by Milan Criteria. The mt-HBT algorithm was locked before sample processing by a blinded central lab. The primary objectives were to assess early-stage HCC sensitivity in a non-inferiority comparison to US with sequential testing of superiority, and overall specificity. The secondary objective was to assess overall sensitivity for HCC. **Results:** Among 3089 enrolled participants, 2467 (79.9%) were evaluable (mean age, 63.1 years; 42.8% female; 20.5% Hispanic). The most common cirrhosis etiologies were MASLD (40.5%), ALD (27.2%), HCV (14.0%), and HBV (2.2%). Forty HCCs were identified, of which 28 were early-stage. Sensitivity [95% CI] for detecting early-stage HCC was higher for mt-HBT vs.US (66.7% [47.8-81.4] vs.22.2% [10.6-40.8], respectively; p = 0.002, **Figure 1**). Overall HCC sensitivity was 70.0% [54.6-81.9] for mt-HBT, 29.7% [17.5-45.8] for US, and

52.6% [37.3-67.5] for US + AFP (≥ 20 ng/mL), while mt-HBT, US, and US + AFP specificities were 81.9% [80.3-83.4], 98.6% [98.0-99.0], and 97.7% [96.9-98.2], respectively. mt-HBT sensitivities by tumor size (< 2 cm, 2-5 cm, > 5 cm) were 58.3% [32.0-80.7], 78.3% [58.1-90.3], and 75.0% [30.1.-95.4], respectively. **Conclusion:** mt-HBT achieved higher sensitivity for early-stage HCC compared to US while maintaining a clinically relevant specificity above the expert-consensus recommended threshold of 80%. mt-HBT's enhanced ability to detect very-early and early-stage HCC provides an opportunity to improve the effectiveness of HCC surveillance in at-risk patients.



AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; mt-HBT, multi-target HCC blood test

Figure 1: Sensitivity and Specificity of mt-HBT, Ultrasound, and Ultrasound + AFP for HCC Detection

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5010 | SAFETY AND PRELIMINARY EFFICACY OF GST-HG131, A FIRST-IN-CLASS ORAL HBSAG INHIBITOR IN CHRONIC HEPATITIS B – PHASE 2 TRIAL DATA

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Background: GST-HG131 is a first-in-class oral HBsAg inhibitor that suppresses HBV mRNA poly(A) tail assembly and destabilizes HBV mRNA by modulating host PAPD5/7 activity. It showed strong efficacy and safety in preclinical studies and favorable safety, tolerability, and PK in a Phase 1 trial. Preliminary Phase 2 data indicated potent HBsAg reduction. Here, we report unblinded results from the complete Phase 2 trial. **Methods**: This double-blind, randomized, placebo-controlled Phase 2 study evaluated safety and efficacy of GST-HG131 in CHB patients. Cohorts 1 and 2 (n = 10 each; 8 active, 2 placebo) received 30 mg or 60 mg BID for 28 days. Cohort 3 (n = 25) received 30 mg BID for 12 weeks. Inclusion criteria included CHB patients on nucleos(t)ide analog monotherapy for more than 6 months, with HBsAg levels between 100 and 1,500 IU/mL, and serum ALT levels below 1× ULN. The primary endpoint was change in quantitative serum HBsAg levels by the end of the study; secondary endpoints included changes in serum HBV pregenomic RNA (pgRNA), PK profiles, and safety. **Results:** GST-HG131 produced consistent, duration-dependent HBsAg declines. The 12-week 30 mg BID regimen achieved the most durable response, with mean HBsAg reduction of 0.89 $\log_{10}$ IU/mL at Day 85 versus placebo ($p < 0.001$). The maximum decrease in HBsAg level is 1.64 Log_{10} IU/mL. Notably, 76.5% of the treated patients in this group achieved HBsAg < 100 IU/mL. Treatment was well tolerated across all cohorts, with no dose-related toxicity or emerging safety signals. Most adverse events were mild or moderate. No clinically relevant abnormalities were observed in labs, vital signs, or ECGs. **Conclusion:** Oral GST-HG131 administration showed favorable safety and promising HBsAg-lowering activity in CHB patients, with the strongest effect in the 12-week regimen. These results support its further development, alone or in combination with immunomodulatory agents, toward a functional cure of CHB.

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5011 | ONCE-MONTHLY EFIMOSFERMIN ALFA FOR UP TO 48 WEEKS IN METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS WITH F2/F3 FIBROSIS: RESULTS FROM A PHASE 2, OPEN-LABEL EXTENSION STUDY

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Background: Efimosfermin alfa, a once-monthly FGF21 analogue, showed significant histologic response and improvements across liver and cardiometabolic markers with a well-tolerated safety profile in a 24-week randomized, double-blind, placebo-controlled phase 2 study in participants with biopsy-confirmed F2/F3 MASH. This open-label extension (OLE) evaluated the durability of response and safety of efimosfermin 300 mg every 4 weeks (Q4W) in participants with up to 48 weeks exposure. **Methods**: Participants completing the main study were eligible for the OLE and all received efimosfermin 300mg Q4W for up to 24 weeks (NCT04880031). The primary endpoint was safety and tolerability with histologic response and changes in non-invasive markers of liver fat, fibrosis, liver injury, and cardiometabolic markers assessed as exploratory outcomes. **Results:** Of 67 eligible participants, 33 enrolled in the OLE (15 continued efimosfermin;18 crossed over from placebo). Among those with up to 48 weeks of exposure and evaluable biopsies (n = 11), sustained or new response on fibrosis improvement ≥ 1 stage without worsening of MASH was achieved in 45.5%. MASH resolution without fibrosis occurred in 63.6% of participants, and 45.5% demonstrated both fibrosis improvement ≥ 1 stage and MASH resolution. Further reductions in fibrosis and liver injury biomarkers were observed corroborating histologic improvement, with mean (SD) changes of −20.1 (16.51)% in Pro-C3, –0.7 (0.84) in ELF, and −31.1 (24.88) U/L in ALT by end of treatment, with sustained changes in cardiometabolic markers. Placebo participants re-randomized to efimosfermin showed improvements consistent with those previously reported for 24 weeks therapy. Efimosfermin was generally well-tolerated through end of study with no new safety signals compared to those previously reported. Most adverse events (AEs) were mild or moderate with gastrointestinal events (nausea, diarrhea, and vomiting) reported most frequently and occurring within the first 24 weeks of treatment. During the OLE, one unrelated serious AE (appendicitis) was reported and no participants discontinued due to AEs. **Conclusion:** Efimosfermin 300mg Q4W showed durable response in fibrosis improvement and MASH resolution, including improvements across liver- and cardiometabolic-related markers with a well-tolerated safety profile in participants with up to 48 weeks exposure. These findings further support initiation of Phase 3 trials in 2025 to evaluate efimosfermin as a potential once-monthly treatment for MASH.

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Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn, and ChronWell: Stock – privately held company, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharmaceuticals: Consultant, Cytodyn: Consultant, GSK: Consultant, Eli Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Terns: Consultant, Takeda: Consultant, Allergan: Principal Investigator for a Drug Study, Akero: Principal Investigator for a Drug Study, BI: Principal Investigator for a Drug Study, BMS: Principal Investigator for a Drug Study, Gilead: Principal Investigator for a Drug Study, Galectin: Principal Investigator for a Drug Study, Genfit: Principal Investigator for a Drug Study, GSK: Principal Investigator for a Drug Study, Conatus: Principal Investigator for a Drug Study, Corcept: Principal Investigator for a Drug Study, Enanta: Principal Investigator for a Drug Study, Madrigal: Principal Investigator for a Drug Study, Novartis: Principal Investigator for a Drug Study, Novo Nordisk: Principal Investigator for a Drug Study, Shire: Principal Investigator for a Drug Study, Takeda: Principal Investigator for a Drug Study, Terns: Principal Investigator for a Drug Study, Viking: Principal Investigator for a Drug Study, Zydus: Principal Investigator for a Drug Study, Rivus Pharmaceuticals: Stock – privately held company, Cytodyn: Stock - 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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 Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Conatus: Principal Investigator, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Rivus, Sagimet: Consultant, Rivus: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support, Altimmune: Grant/Research Support, Akero: Grant/Research Support, BI: Grant/Research Support, BMS: Grant/Research Support, Boston Pharma: Grant/Research Support, Conatus: Grant/Research Support, Corcept: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Genfit: Grant/Research Support, GSK: Grant/Research Support, Kowa: Grant/Research Support, Enanta: Grant/Research Support, Madrigal: Grant/Research Support, Lilly: Grant/Research Support, Merck: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Rivus: Grant/Research Support, Shire: Grant/Research Support, Takeda: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Rivus Pharma: Stock – privately held company, Akero: Stock - publicly traded company, Zydus: Grant/Research Support, Takeda: Consultant, Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Takeda: Consultant, Kris Kowdley: Boston Scientific: Grant/Research Support, Corcept: Grant/Research Support, CymaBay: Grant/Research Support, Genfit: Grant/Research Support, Gilead: Grant/Research Support, GSK: Grant/Research Support, Hanmi: Grant/Research Support, Intercept: Grant/Research Support, Ipsen: Grant/Research Support, Janssen: Grant/Research Support, Madrigal: Grant/Research Support, Mirum: Grant/Research Support, Novo Nordisk: Grant/Research Support, NGM: Grant/Research Support, Pfizer: Grant/Research Support, Pliant Therapeutics: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Zydus: Grant/Research Support, 89bio Inc: Grant/Research Support, UpToDate: Royalties or patent beneficiary, CymaBay: Consultant, Enanta: Consultant, Genfit: Consultant, Gilead: Consultant, HighTide: Consultant, Inipharm: Consultant, Intercept: Consultant, Ipsen: Consultant, Madrigal: Consultant, Mirum: Consultant, NGM: Consultant, Pliant Therapeutics: Consultant, Pfizer: Consultant, Protagonist: Consultant, Zydus: Consultant, 89bio Inc: Consultant, AbbVie: Payment or honoraria, Gilead: Payment or honoraria, Intercept: Payment or honoraria, US Department of Justice: Payment for expert testimony, CTI: Advisor, Medpace: Advisor, Labcorp: Advisor, Worldwide Clinical Trials: Advisor, Inipharm: Stock – privately held company, Velacur: Received equipment, materials, drugs, medical writing, gifts, Boehringer Ingelheim: Grant/Research Support, Boehringer Ingelheim: Consultant, Novo Nordisk: Consultant, Akero: Grant/Research Support, Astra Zeneca: Grant/Research Support, Kowa: Grant/Research Support, Kowa: Consultant, Madrigal: Speaking and Teaching, Kelly Kutch:, Brenda Jeglinski: Nothing to Disclose, Margaret James Koziel:, Rohit Loomba: No dislosure submitted

5012 | EFFICACY OUTCOMES IN PRECIOSA SHOW NOTABLE DIFFERENCES BASED ON PATIENTS' GRADE OF ASCITES AT ENROLLMENT

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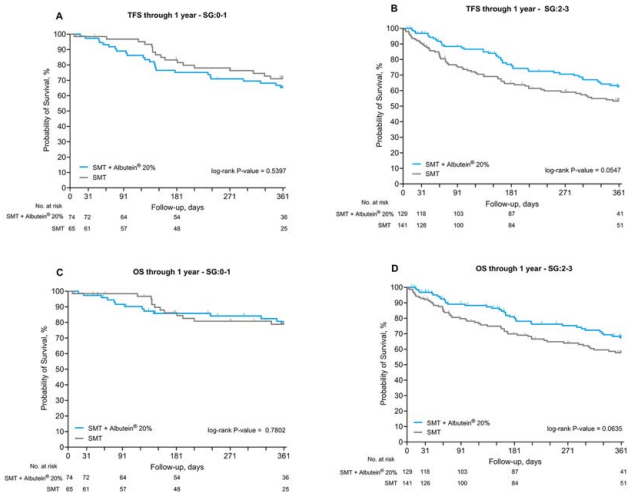
Background: PRECIOSA (NCT03451292) studied long-term Albutein® 20% (LTA) administration plus standard medical treatment (SMT) (Treatment) versus SMT alone (Control) for cirrhotic patients with existing or prior ascites and acute decompensation. This exploratory analysis compares the effect of Treatment on transplant-free survival (TFS) and overall survival (OS) for subgroups (SG) with grade 0 to 1 ascites (SG:0-1) and grade 2 to 3 ascites (SG:2-3) at enrollment. **Methods**: TFS and OS at 3 months (mo), 6 mo, and 1 year (yr) after randomization were analysed using Kaplan-Meier (KM) and Cox-Proportional-Hazard models comparing the Treatment arm to the Control arm for each SG in the Intent to Treat (ITT) population. Hazard

ratios (HR) with 95% confidence intervals (CIs) and KM survival probabilities were evaluated in the context of baseline characteristics for each SG. **Results:** SG:0-1 and SG:2-3 comprised 34% (139/410) and 66% (270/410) of the ITT population, respectively. Within SGs, baseline characteristics were similar for the Treatment and Control arms. Between SGs' Treatment arms, patients from SG:2-3 showed greater disease severity at baseline compared to SG:0-1 with higher median CLIF-C AD score (53.43 vs 50.96), higher median Child-Pugh score (9.0 vs 8.0), and lower median serum albumin (3.10 vs 3.45 g/dL), respectively. Control arms showed similar results. TFS HR [95% CI] in SG:2-3 and SG:0-1 were 0.43 [0.23, 0.81] vs 3.44 [0.73, 16.20] at 3 mo, 0.58 [0.37, 0.93] vs 1.51 [0.70, 3.27] at 6 mo, and 0.69 [0.47, 1.02] vs 1.26 [0.68, 2.33] at 1 yr, respectively. OS HR [95% CI] in SG:2-3 and SG:0-1 were 0.51 [0.26, 0.99] vs 5.22 [0.63, 43.36] at 3 mo, 0.59 [0.35, 0.99] vs 1.03 [0.41, 2.62] at 6 mo, and 0.67 [0.44, 1.03] vs 0.99 [0.46, 2.15] at 1 yr, respectively. KM TFS and OS estimates at 361 days were higher in the SG:2-3 Treatment arm vs Control arm but similar in the SG:0-1 Treatment arm vs Control arm (Figure). **Conclusion:** Patients enrolled in PRECIOSA with grade 2 to 3 ascites showed notably greater treatment benefit from LTA therapy than those with grade 0-1 ascites. Improvement in TFS and OS was observed at 3 months. This could indicate that LTA therapy is associated with positive clinical outcomes only in patients with advanced cirrhosis and moderate to severe ascites.

Figure. Kaplan-Meier curves



Disclosures: Paolo Angeli:, Jacqueline O'Leary: PharmaIn: Consultant, Genfit: Consultant, PharmaIn: Consultant, Mallinckrodt: Consultant, Giovanni Perricone: Nothing to Disclose, Wim Laleman: Cook Medical: Consultant, Boston Scientific: Grant/Research Support, CSL Behring: Consultant, Tamara Milovanovic:, Mireia Torres: Grifols: Employee, Fiona McCarthy:, Peter Nelson: Grifols: Employee, Javier Fernandez: Nothing to Disclose

5013 | COMBINATION THERAPY WITH HT-101 AND HT-102 ACHIEVES RAPID AND PROGRESSIVE HBSAG LOSS IN HBEAG-NEGATIVE, NUCLEOS(T)IDE ANALOGUES-SUPPRESSED PATIENTS: 12-WEEK INTERIM RESULTS FROM AN ONGOING MULTICENTRE, OPEN-LABEL PHASE IB/IIA STUDY

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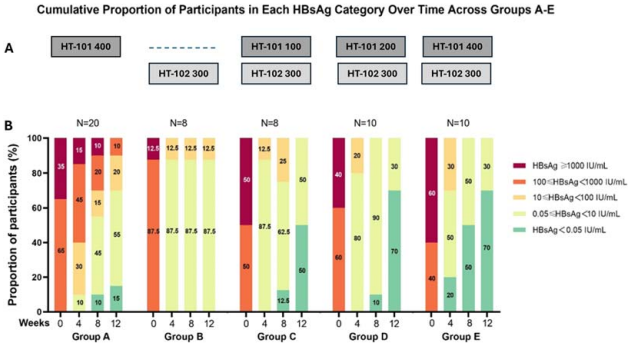
Background: HT-101 is an *N-acetylgalactosamine* (GalNAc)–conjugated small interfering ribonucleic acid (siRNA) targeting the S-region of the HBV genome that demonstrated durable reductions in hepatitis B surface antigen (HBsAg) in phase 1 study. HT-102 is a human monoclonal antibody against the antigenic loop of HBsAg that achieved rapid serum HBsAg decline in phase 1. We report interim 12-week on-treatment data from an ongoing phase Ib/IIa study in China (NCT07183306/CTR20244730) evaluating the safety and efficacy of combination treatment with HT-101 and HT-102, compared with monotherapy. **Methods**: This multicentre, open-label, partial dose-escalation study enrolled HBeAg-negative patients with stable nucleos(t)ide analogue (NA) background treatment with HBsAg 100-3,000 IU/mL. Participants were assigned to five groups: A, HT-101 400 mg; B, Sequential HT-102 300mg followed by HT-101 400 mg; C, HT-101 100mg +HT-102 300mg; D, HT-101 200mg +HT-102 300mg and E, HT-101 400mg +HT-102 300mg. HT-101 and/or HT-102 were administered subcutaneously every 4 weeks for at least 24 weeks. Follow-up planned to 48 weeks post-therapy. Primary endpoint was the incidence of treatment-emergent adverse events (TEAEs). Secondary endpoints included HBsAg kinetics, virological and pharmacodynamics markers, pharmacokinetics, and immunogenicity. **Results:** All participants (Groups A-E) completed 12 weeks of treatment with HT-101 and/or HT-102: Group A received HT-101 monotherapy, Group B received HT-102 alone, and Groups C–E received HT-101/HT102 combination therapy (Figure A). At Week 12, HBsAg seroclearance was achieved in 3/20 (15%) participants in group A, 0/8 (0%) in Group B, 4/8 (50%) in Group C, 7/10(70%) in Group D and 7/10 (70%) in Group E, respectively (Figure B). Among all subjects

with combination therapy (Groups C-E), 18/28 (64.3%) achieved HBsAg loss, notably, 2/10 (20%) participants in Group E achieved HBsAg loss as early as Week 4. Response rates were associated with baseline HBsAg levels: 13/14 (92.8%) of participants with baseline HBsAg $<1{,}000$ IU/mL achieved HBsAg loss, compared with 5/14 (35.7%) of those with baseline HBsAg $\geq 1{,}000$ IU/mL. Treatment was well-tolerated: most TEAEs being Grade 1–2 (e.g., injection site reactions). No drug-related serious AEs, grade ≥ 3 events, ALT flares, or other safety signals were observed. Pharmacokinetic profiles of HT-101 were consistent with prior phase 1 findings. Profound declines in serum HBV RNA and HBcrAg were also observed. **Conclusion:** In this ongoing phase Ib/IIa trial, combination therapy with HT-101 (up to 400 mg) and HT-102 (300 mg) in CHB patients achieved rapid serum HBsAg reduction and a high rate of HBsAg loss at treatment Week 12 with a favourable safety profile. These findings support continued development of HT-101 and HT-102 as a promising strategy toward achieving functional cure of HBV.

Figure:



Disclosures: xieer liang: Nothing to Disclose, Liang Chen:, Jianmei Lin:, Bei Zhong:, Huiqing Liang:, Wen Xie:, Yujuan Guan: Nothing to Disclose, Zhihong Liu: Nothing to Disclose, Xun Qi:, wang Dong: Nothing to Disclose, Zhipeng Zhang:, lijuan ding:, Zhiping Cui: Nothing to Disclose, Huaien Song:, Kun Yue: Nothing to Disclose, Jinlin Hou:

5014 | EFFICACY OF 24-WEEK PEGINTERFERON ALPHA-2B RETREATMENT IN INTERFERON-EXPERIENCED CHRONIC HEPATITIS B PATIENTS WITH FAVORABLE INITIAL RESPONSE

Shaowen Jiang[1] Chuanwu Zhu[2] Jia Shang[3] Li Zhu[4] Chengrun Xu[5] Yufeng Gao[6] Xuehua Sun[7] Yinong Feng[8] Haifang Cao[9] Feng Liu[10] Liguan Liu[11] Haidong Zhao[12] Liang Chen[13] Xiaoyu Hu[14] Xiulan Xue[15] Yueyong Zhu[16] Qing Xie[1], [1]Ruijin Hospital, Shanghai Jiaotong University School of Medicine, China, [2]Department of Hepatology, The Fifth People's Hospital of Suzhou, China, [3]Henan Provincial people's Hospital, China, [4]Public Health Clinical Center of Chengdu, China, [5]The 909th hospital, China, [6]The First Affiliated Hospital of Anhui Medical University, China, [7]Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, China, [8]The Third People's Hospital of Taiyuan, China, [9]Qinghai Provincial Fourth People's Hospital, China, [10]Tianjin Second People's Hospital, China, [11]The 910th Hospital of the Joint Service Support Force of the Chinese People's Liberation Army, China, [12]Xiamen chang gung hospital, China, [13]Shanghai Public Health Clinical Center, China, [14]Hospital of Chengdu University of TCM, China, [15]The First Affiliated Hospital of Xiamen University, China, [16]The First Affiliated Hospital of Fujian Medical University, China

Background: Although peginterferon alpha (PEG IFNα)-based therapy promotes HBsAg loss in patients with chronic hepatitis B (CHB), some still fail to achieve it following initial treatment. This study investigates the efficacy and safety of PEG IFNα retreatment for interferon-experienced CHB patients. **Methods**: This prospective real-world study (NCT06323681) enrolled patients who had prior interferon therapy (cessation $\geq$ 3 months) and achieved a post-treatment HBsAg decline of $\geq$ 80%, had HBsAg $\leq$ 500 IU/mL at screening and exhibited an HBsAg rebound of $\leq$ 50% of the initial treatment baseline. Patients were divided into two groups. Group A received PEG IFNα-2b (Pegbing®, Xiamen Amoytop Biotech Co., Ltd.) monotherapy or combined with nucleos(t)ide analogues (NAs), while group B received NAs alone. The treatment period was 48 weeks. Data were analyzed for those who completed 24 weeks of treatment. **Results:** 575 patients (Group A, n = 492; Group B, n = 83) were included in this analysis. At the start of initial interferon therapy, the mean HBsAg levels in groups A and B were 2873.7 and 2741.3 IU/mL, respectively, which decreased to 61.1 and 291.1 IU/mL by the end of treatment, with average reductions of 95% and 91%. At the start of current treatment, the mean HBsAg levels were 75.7 IU/mL for Group A and 143.5 IU/mL for Group B. Among those with available data, Group A achieved HBsAg loss rates of 17.0% and 35.5% at weeks 12 and 24, respectively, while Group B showed 0% at both timepoints. Among the total population reaching the treatment point, the respective rates were 13.4% and 27.2% for Group A, while Group B remained at 0% throughout (Figure 1A). In Group A, the 24-week HBsAg loss rates for intervals of 3-6, 6-12 and >12 months between the two rounds of interferon therapy were 38.9%, 33.0% and 38.1%, respectively, in the population with available data, and 30.4%, 23.8% and 30.0%, respectively, in the population who

reached the corresponding visit points. 46 patients who relapsed after obtaining HBsAg loss through initial interferon therapy were included in Group A. Among this population with available data, HBsAg loss rates at weeks 12 and 24 were 45.2% and 73.1%, respectively, and among those reaching the treatment point, the rates were 36.8% and 63.3%, respectively (Figure 1B). **Conclusion:** A significant proportion of interferon-treated patients with good initial HBsAg response, especially those who obtained HBsAg loss in initial therapy but later relapsed, achieved HBsAg loss with PEG IFNα-2b retreatment. These patients represent an ideal population for PEG IFNα-2b retreatment to early pursue functional cure.

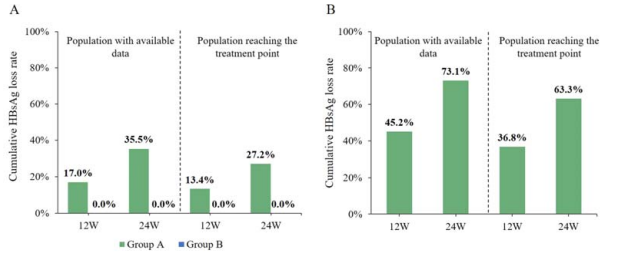


Figure 1. A: Cumulative HBsAg loss rates of different groups among all patients.
B: Cumulative HBsAg loss rates of Group A among patients who obtained HBsAg loss through initial therapy but later relapsed.

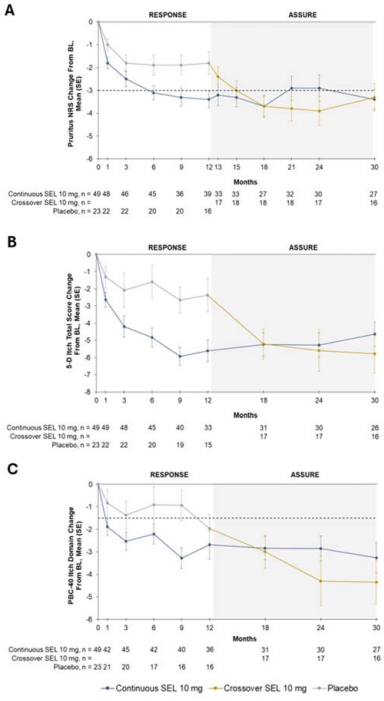
Disclosures: shaowen jiang: Nothing to Disclose, Chuanwu Zhu: Nothing to Disclose, Jia Shang:, Li Zhu:, Chengrun Xu:, Yufeng Gao:, Xuehua Sun:, Yinong Feng: Nothing to Disclose, Haifang Cao:, Feng Liu:, Liguan Liu:, Haidong Zhao: Nothing to Disclose, Liang Chen:, Xiaoyu Hu:, Xiulan Xue:, Yueyong Zhu:, Qing Xie: Nothing to Disclose

5015 | SUSTAINED AND CLINICALLY MEANINGFUL IMPROVEMENTS IN MODERATE TO SEVERE PRURITUS PATIENTS WITH PRIMARY BILIARY CHOLANGITIS TREATED WITH SELADELPAR: RESULTS FROM THE ASSURE STUDY UP TO 30 MONTHS

Gideon Hirschfield[1] Andreas Kremer[2] Cynthia Levy[3] Kris Kowdley[4] Hany Elbeshbeshy[5] Jeong Heo[6] Kyung min Kwon[7] Jie Liu[7] Caroline Burk[7] Daria Crittenden[7] Marlyn Mayo[8], [1]Toronto General Hospital, Toronto, ON, Canada, [2]University Hospital Zürich, University of Zürich, Zürich, Switzerland, [3]Miller School of Medicine, University of Miami, Miami, FL, USA, [4]Liver Institute Northwest, Seattle, WA, USA, [5]Saint Louis University School of Medicine, St. Louis, MO, USA, [6]Pusan National University and Biomedical Research Institute, Busan, Republic of Korea, [7]Gilead Sciences, Inc., Foster City, CA, USA, [8]University of Texas Southwestern, Dallas, TX, USA

Background: Pruritus affects up to 80% of patients with primary biliary cholangitis (PBC) and significantly impairs quality of life. Seladelpar (SEL), a first-in-class delpar (selective PPAR-delta agonist), is approved for second-line treatment of PBC and has shown efficacy in improving cholestasis and pruritus in the pivotal, placebo (PBO)-controlled RESPONSE study (NCT04620733). We report long-term pruritus outcomes from the RESPONSE study and interim results from its ongoing open-label extension study, ASSURE (NCT03301506), with confirmatory psychometric validation of the pruritus numeric rating scale (NRS). **Methods**: In RESPONSE, pruritus NRS was collected daily for 6 months (M), then weekly for one week each month through 12M. Upon rollover to ASSURE, NRS was collected daily for 6M and then at scheduled clinic visits. Other measures included the 5-D Itch and PBC-40. Patients with moderate to severe pruritus (NRS $\geq$4) at baseline (MSPN) were analyzed based on randomization to SEL 10 mg or PBO in RESPONSE and reported as continuous or crossover SEL 10 mg groups in ASSURE. Regression analysis and Bland-Altman plots assessed agreement between single-visit and weekly averaged NRS scores. Robust psychometric validation of NRS included reliability, convergent validity, and meaningful within-patient change analyses. Change from baseline in NRS, 5-D Itch, and PBC-40 Itch domain scores were assessed in ASSURE with a data cut off of Jan 31, 2025. **Results:** Overall, there were 49 SEL and 23 PBO MSPN patients at baseline in RESPONSE. Among them, 33 SEL and 17 PBO patients rolled over to ASSURE, and 27 and 16 patients reached 30M. Daily NRS was strongly correlated with weekly NRS (r [95% CI], 0.93 [0.90, 0.95]). Validation of the NRS demonstrated it was valid and reliable. Reduction in pruritus with SEL in RESPONSE was maintained in ASSURE up to 30M, with clinically meaningful NRS improvement observed in $\geq$50% of patients upon SEL initiation for crossover patients in ASSURE from 15M through 30M. Mean (SE) 5-D Itch total and PBC-40 Itch domain scores were reduced from baseline in continuous SEL (−4.6 [0.7]; −3.3 [0.7]) and crossover SEL (−5.8 [1.1]; −4.3 [1.0]) patients. **Conclusion:** SEL led to sustained, clinically meaningful improvement in pruritus among MSPN patients in RESPONSE and with up to 30 months of treatment. Additionally, repeated psychometric validation confirmed the reliability and validity of the NRS as an outcome measure of pruritus in PBC.

Figure. Pruritus NRS (A), 5-D Itch Scale Total (B), and PBC-40 Itch Domain (C) Score Change From BL Over 30 Months From RESPONSE to ASSURE in Patients With PBC and MSPN



n = number of evaluable patients at each time point.

MSPN was defined at RESPONSE BL.

Pruritus NRS scores ranged from 0 to 10, with higher scores indicating worse itch. A ≥3-point change, shown by the dotted line in Figure A, in the pruritus NRS score was considered clinically meaningful in RESPONSE.

Each of the 5-D Itch domains were scored from 1 to 5, and the total score ranged from 5 to 25, with higher scores indicating increased itch severity.

PBC-40 Itch domain scores ranged from 0 to 15, with higher scores indicating poorer quality of life. A meaningful response in a PBC-40 domain score was defined as a 0.5-point change from baseline per item. For the PBC-40 Itch domain, which has 3 items, a meaningful response is shown by the dotted line in Figure C.

BL, baseline; MSPN, moderate to severe pruritus (NRS ≥4) at baseline; NRS, numeric rating scale; PBC, primary biliary cholangitis; SEL, seladelpar.

Disclosures: Gideon Hirschfield: Intercept: Consultant, Intercept: Consultant, GSK: Consultant, GSK: Consultant, CymaBay: Consultant, CymaBay: Consultant, Ipsen: Consultant, Ipsen: Consultant, Falk: Consultant, Falk: Consultant, Pliant: Consultant, Pliant: Consultant, Mirum: Consultant, Mirum: Consultant, Advanz: Consultant, Advanz: Consultant, Chemomab: Consultant, Chemomab: Consultant, Gilead: Consultant, Gilead: Consultant, Kowa: Consultant, Kowa: Consultant, Kezar: Consultant, Intercept: Consultant, Intercept: Consultant, GSK: Consultant, GSK: Consultant, CymaBay: Consultant, CymaBay: Consultant, Ipsen: Consultant, Ipsen: Consultant, Falk: Consultant, Falk: Consultant, Pliant: Consultant, Pliant: Consultant, Mirum: Consultant, Mirum: Consultant, Advanz: Consultant, Advanz: Consultant, Chemomab: Consultant, Chemomab: Consultant, Gilead: Consultant, Gilead: Consultant, Kowa: Consultant, Kowa: Consultant, Kezar: Consultant, Andreas Kremer: Abbvie: Advisor, Abbvie: Consultant, Advanz: Advisor, Advanz: Consultant, Alentis: Advisor, AlphaSigma: Consultant, AlphaSigma: Speaking and Teaching, AstraZeneca: Advisor, Avior: Advisor, Bayer: Advisor, CymaBay: Advisor, Escient: Advisor, Falk: Consultant, Falk: Speaker, Gilead: Consultant, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GSK: Consultant, GSK: Speaking and Teaching, GSK: Advisor, Intercept: Consultant, Intercept: Grant/Research Support, Intercept: Speaking and Teaching, Ipsen: Consultant, Ipsen: Speaking and Teaching, Mirum: Consultant, Mirum: Advisor, Mirum: Speaking and Teaching, MSD: Consultant, MSD: Speaking and Teaching, MSD: Advisor, Roche: Consultant, Roche: Grant/Research Support, Roche: Speaking and Teaching, Takeda: Consultant, Takeda: Advisor, Takeda: Advisor, Viofor: Advisor, Viofor: Speaking and Teaching, Viofor: Advisor, Astellas: Consultant, BMS: Consultant, Böhringer-Ingelheim: Consultant, Curatis: Consultant, Novo Nordisk: Consultant, Rectify Pharma: Consultant, Advanz: Speaking and Teaching, AOP Orphan,: Speaking and Teaching, Johnson & Johnson,: Speaking and Teaching, Abbvie: Advisor, Advanz Pharma: Advisor, Alentis Therapeutics: Advisor, Alfasigma: Advisor, Astellas: Advisor, AstraZeneca: Advisor, Attovia Therapeutics: Advisor, Avior Bio: Advisor, Bayer: Advisor, Bristol Mysers Squibb: Advisor, Böhringer-Ingelheim: Advisor, Curatis: Advisor, CymaBay: Advisor, Dr. Falk Pharma: Advisor, Gilead Sciences: Advisor, GSK: Advisor, Ipsen: Advisor, Mirum Pharmaceuticals: Advisor, Mirum Pharmaceuticals: Advisor, Merck Sharp & Dohme: Advisor, Novo Nordisk: Advisor, Roche: Advisor, Takeda: Advisor, Abbvie: Speaking and Teaching, Advanz Pharma: Speaking and Teaching, Bayer: Speaking and Teaching, Bristol Myers Squibb: Speaking and Teaching, CymaBay Therapeutics: Speaking and Teaching, Falk Foundation: Speaking and Teaching, Gilead Sciences: Speaking and Teaching, GSK: Speaking and Teaching, Ipsen: Speaking and Teaching, Johnson & Johnson: Speaking and Teaching, Medscape: Speaking and Teaching, Mirum Pharmaceuticals: Speaking and Teaching, Merck Sharp & Dohme: Speaking and Teaching, Novartis: Speaking and Teaching, Roche: Speaking and Teaching, Viofor: Speaking and Teaching, Gilead Sciences: Grant/Research Support, Intercept Pharmaceuticals: Grant/Research Support, Roche: Grant/Research Support, Abbvie: Advisor, Abbvie: Consultant, Advanz: Advisor, Advanz: Consultant, Alentis: Advisor, AlphaSigma: Consultant, AlphaSigma: Speaking and Teaching, AstraZeneca: Advisor, Avior: Advisor, Bayer: Advisor, CymaBay: Advisor, Escient: Advisor, Falk: Consultant, Falk: Speaker, Gilead: Consultant, Gilead: Speaking and Teaching, Gilead: Grant/Research Support, GSK: Consultant, GSK: Speaking and Teaching, GSK: Advisor, Intercept: Consultant, Intercept: Grant/Research Support, Intercept: Speaking and Teaching, Ipsen: Consultant, Ipsen: Speaking and Teaching, Mirum: Consultant, Mirum: Advisor, Mirum: Speaking and Teaching, MSD: Consultant, MSD: Speaking and Teaching, MSD: Advisor, Roche: Consultant, Roche: Grant/Research Support, Roche: Speaking and Teaching, Takeda: Consultant, Takeda: Advisor, Takeda: Advisor, Viofor: Advisor, Viofor: Speaking and

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5016 | LONG-TERM TREATMENT WITH ELAFIBRANOR LEADS TO BIOCHEMICAL AND SYMPTOMATIC IMPROVEMENTS FOR AT LEAST 3 YEARS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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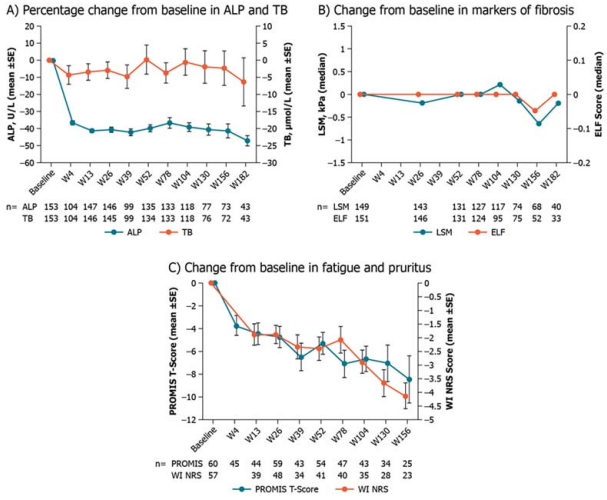
Background: Elafibranor (ELA), a PPARα/PPARδ agonist, is approved as second-line treatment in patients (pts) with primary biliary cholangitis (PBC) based on phase III ELATIVE® trial results (NCT04526665). We present findings through >3 years of ELA treatment in the ongoing ELATIVE® open-label extension (OLE). **Methods**: Pts who completed the ELATIVE® double-blind period (DBP) could enter the OLE and receive ELA 80 mg daily. For pts who received placebo (PBO) in the DBP, baseline (BL) was set as the last non-missing value before the first OLE ELA dose; for pts who received ELA in the DBP, BL was at DBP start. Endpoints included biochemical response (alkaline phosphatase [ALP] <1.67x upper limit of normal [ULN], with ≥15% reduction from BL, and total bilirubin [TB] ≤ULN), ALP normalization, and change in ALP, TB, albumin, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), liver stiffness measurement (LSM), and enhanced liver fibrosis (ELF) score. Changes in fatigue (PROMIS Fatigue Short Form 7a T-score) and pruritus (Worst-Itch Numeric Rating Scale [WI NRS]) were assessed in pts with moderate-to-severe (mod-to-sev) fatigue (PROMIS T-Score ≥60) or mod-to-sev pruritus (PBC WI NRS ≥4) at BL, respectively. Results presented descriptively. Safety outcomes reported from OLE start, up to data cut-off (DCO; May 2025). **Results:** At DBP DCO, 153 pts had received ELA; 108 received ELA and 45 received PBO. 138 pts entered the OLE; 115 pts remained in May 2025. Through Week (W)182, biochemical response rates were sustained (W182: 72.1%; 31/43). The proportion of pts with normal ALP remained consistent (W182:

18.6%; 8/43). The effect of ELA treatment on ALP was seen as early as W4, and was sustained and reproducible in pts crossing from PBO (Figure A); at all timepoints beyond W52, over 60% of pts had reductions of ≥40% from BL (W182: 67.4%; mean change in ALP: −47.1%). Markers of hepatic function including TB (Figure A) and albumin remained unchanged; GGT and ALT decreased. Markers of fibrosis (LSM and ELF) were stable with ELA (Figure B). Improvement in PROMIS T-scores was seen at W4 with ELA and sustained to W156 in pts with BL mod-to-sev fatigue (n = 25; mean [SD] −8.5 [10.3]); similar results were observed for pruritus (WI NRS in pts with BL mod-to-sev pruritus: n = 23; mean [SD] −4.1 [2.3]; Figure C). No new safety signals were identified; no new cases of rhabdomyolysis, myalgia, or treatment-related creatinine phosphokinase (CPK) elevations were observed. **Conclusion:** In the ongoing ELATIVE® OLE, ELA has led to rapid, sustained, and reproducible responses in clinically relevant biomarkers of cholestasis and fibrosis, suggesting potential for slowing disease progression. Positive effects on cholestasis, sustained improvement in pruritus and fatigue, stabilization of markers of fibrosis, and a consistent safety profile confirm ELA's suitability for long-term PBC treatment.

Figure. Change from baseline in (A) ALP and TB, (B) markers of fibrosis, and (C) fatigue and pruritus with elafibranor treatment



ITT analysis set. Data for all patients treated with elafibranor 80 mg. ALP: alkaline phosphatase; ELF: enhanced liver fibrosis; ITT: intention-to-treat; LSM: liver stiffness measurement; PROMIS: Patient-Reported Outcomes Measurement Information System; SE: standard error; TB: total bilirubin; WI NRS: Worst-Itch Numeric Rating Scale; W: week.

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5017 | PBGENE-HBV, A FIRST-IN-CLASS GENE EDITING THERAPY FOR CHRONIC HEPATITIS B, DEMONSTRATES SAFETY AND ANTIVIRAL ACTIVITY IN EARLY COHORTS

Man-Fung Yuen[1] Alina Jucov[2] Edward Gane[3] Emily Harrison[4] Andrew Van Cott[4] Abhishek Chandiramani[4] Neil Leatherbury[4] John Fry[4] Jeff Smith[4] Cassie Gorsuch[4] Stanley Frankel[4] Mark Sulkowski[5], [1]Queen Mary Hospital, The University of Hong Kong, Hong Kong, [2]ARENSIA Research Clinic, Chisinau, Moldova, State University of Medicine and Pharmacy, Moldova, [3]New Zealand Clinical Research, [4]Precision BioSciences Inc., [5]Johns Hopkins Bayview Medical Center, Johns Hopkins University & Medicine

Background: PBGENE-HBV is a first-in-class gene editing therapy designed to eliminate cccDNA and inactivate integrated HBV DNA, targeting the root cause of chronic infection with the goal of achieving complete cure. ELIMINATE-B is an ongoing global, multicenter, first-in-human Phase 1 study evaluating safety and antiviral activity of PBGENE-HBV. PBGENE-HBV is composed of an mRNA that encodes an ARCUS nuclease formulated in a lipid nanoparticle. ARCUS nucleases are single-component gene editors that can be engineered for optimal safety, leveraging the unique 3' DNA overhangs generated by ARCUS cuts. **Methods**: Multiple ascending doses were tested in HBeAg-negative patients controlled on nucleos(t)ide analogs with three infusions dosed at $\geq$8-week intervals. Primary endpoints were safety and tolerability. A dose limiting toxicity (DLT) was defined as any clinically significant, organ-specific, treatment-emergent adverse event (AE) $\geq$ Grade 3 that does not decrease to $\leq$ Grade 2 within 7 days and is related to study medication. **Results:** In the first cohort of 3 participants, 3 doses of 0.2 mg/kg PBGENE-HBV were well-tolerated with no DLTs, serious adverse events (SAEs), or AEs above grade 2. Declines in HBsAg levels were observed in all 3 participants with maximal reductions from baseline ranging from 47% (0.36 log) to 69% (0.51 log), and one participant had a sustained HBsAg reduction 7 months after initial treatment. HBV DNA remained below the LOQ (10 IU/mL) in all 3 participants. The other two participants in Cohort 1 demonstrated antiviral response after each dose administration and eventually returned to baseline levels of HBsAg. Additional cohorts evaluating 0.4 mg/kg (n = 4) and 0.8 mg/kg (n = 1) have been initiated. One participant did not complete dosing due to a transient, reversible infusion-related reaction that resolved within minutes of initiating dosing. In the remaining 4 participants dosed at 0.4 and 0.8 mg/kg, who received two or one dose(s), respectively, there were no DLTs or SAEs at four weeks after the latest administration. Across all patients dosed at all dose levels, AST and ALT levels remained $<$3x the upper limit of normal and there were no clinically significant laboratory abnormalities related to treatment, including transaminases and platelets. Analyses of HBsAg decline are ongoing. **Conclusion:** This is the first clinical proof of concept for a gene-editing approach designed to eliminate cccDNA, the root cause of chronic hepatitis B infection. Initial safety and antiviral data support continued evaluation of PBGENE-HBV to identify the optimal dose level, dose interval, and number of doses required to ultimately result in complete cure.

Disclosures: Man-Fung Yuen: AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals: Consultant, Fujirebio Incorporation, GlaxoSmithKline, 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: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Immunocore: Grant/Research Support, Sysmex Corporation and Roche: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Roche, Sysmex Corp: Speaking and Teaching, Precision BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy, Alina Jucov:, Edward Gane: Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Aligos Therapeutics: Advisor, Aligos Therapeutics: Advisor, Assembly Biosciences: Advisor, Assembly Biosciences: Advisor, AbbVie: Speaking and Teaching, AbbVie: Speaking and Teaching, Intellia Therapeutics: Advisor, Intellia Therapeutics: Advisor, Tune Therapeutics: Consultant, Tune Therapeutics: Consultant, Precision Bio: Advisor, Precision Bio: Advisor, Virion Therapeutics: Advisor, Virion Therapeutics: Advisor, Gilead Sciences: Advisor, Gilead Sciences: Advisor, GSK: Advisor, GSK: Advisor, AusperBio: Advisor, Emily Harrison: Precision BioSciences: Employee, Andrew Van Cott: Becton Dickinson: Employee, Precision Biosciences, Inc.: Employee, Abhishek Chandiramani: Precision Biosciences: Employee, Neil Leatherbury:, John Fry: Nothing to Disclose, Jeff Smith:, Cassie Gorsuch: Precision BioSciences: Employee, Stanley Frankel: Precision Biosciences: Stock - publicly traded company, Precision Biosciences: Director, Mark Sulkowski:

5018 | A BLOOD-BASED COMBINED METHYLATION AND AFP TEST FOR EARLY DETECTION OF HEPATOCELLULAR CARCINOMA IN AT-RISK POPULATION: VALIDATION AND PERFORMANCE

Neehar Parikh[1] Chun-Chi Liu[2] Matthew Demaio[3] Angela Yeh[4] Mary Stackpole[5] Shuo Li[4] Wenyuan Li[4] Xianghong Zhou[6] Xiaohui Ni[7] Anna Lok[1] Steven-Huy Han[4], [1]University of Michigan Medical Center, [2]EarlyDiagnostics Inc, Agoura Hills, CA, USA, [3]University of Michigan, Ann Arbor, MI, [4]University of California at Los Angeles, Los Angeles, CA, USA, [5]EarlyDiagnostics Inc., Agoura Hills, CA, USA, [6]University of California at Los Angeles, Los Angeles, CA, [7]EarlyDiagnostics, Inc., Agoura Hills, CA, USA

Background: Conventional surveillance methods for hepatocellular carcinoma (HCC), such as abdominal ultrasound (US) plus alpha-fetoprotein (AFP) testing, have suboptimal performance for early detection and poor adherence. We evaluated a novel, blood-based assay that integrates cell-free DNA (cfDNA) methylation profiling with serum AFP to improve HCC detection in high-risk populations. **Methods**: From 9/1/2023 to 4/30/2025, a prospective cohort of 135 individuals with treatment-naïve HCC and 167 at risk for HCC was enrolled at the University of Michigan and UCLA. Additionally, retrospective samples from 46 patients with HCC and 32 at-risk individuals meeting the same inclusion criteria were included. Methylation risk scores were generated using a blood-based cfDNA methylation assay, and serum AFP levels were obtained from clinical records. A logistic regression model was used to integrate the methylation and AFP biomarkers for HCC detection. Test performance was evaluated using sensitivity, specificity, and area under the receiver operating characteristic (ROC) curve (AUC). **Results:** The combined methylation + AFP test achieved an AUC of 0.94 (95 CI%, 0.92-0.96) for detecting HCC in at-risk individuals, significantly outperforming both methylation alone (AUC 0.92, 95% CI, 0.89-0.95; P = 0.001) and AFP alone (AUC 0.83, 95% CI, 0.79-0.87; $P < 0.0001$) (Fig. 1). In patients with early-stage HCC (within Milan Criteria), the combined test achieved an AUC of 0.90 (95% CI, 0.86-0.94), also outperforming methylation alone (AUC 0.88, 95% CI, 0.83-0.92; P = 0.030) and AFP alone (AUC 0.81, 95% CI, 0.76-0.86; $P < 0.0001$). The addition of AFP enhanced the detection of early-stage HCC, while the benefit was less pronounced in late-stage disease. At 92% specificity, the combined test demonstrated a sensitivity of 73% (95% CI, 64%-80%) for early-stage HCC, compared to 62% (95% CI, 52%-71%) for methylation alone and 52% (95% CI, 43%-62%) for AFP alone. The combined test consistently improved sensitivity across all demographic and etiologic subgroups, including patients with metabolic-dysfunction associated steatotic liver disease. **Conclusion:** These results support the use of a combined cfDNA methylation and AFP test to enhance the accuracy of HCC detection in at-risk groups. This blood-based approach offers improved sensitivity for early-stage disease and broader applicability across diverse patient subgroups and may serve as a valuable complement to current surveillance strategies.

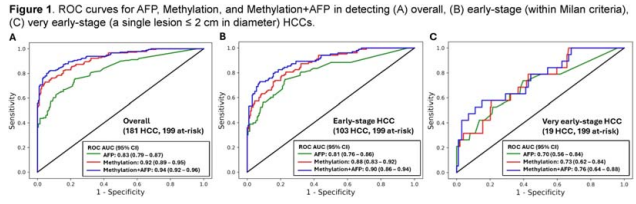

Figure 1. ROC curves for AFP, Methylation, and Methylation+AFP in detecting (A) overall, (B) early-stage (within Milan criteria), (C) very early-stage (a single lesion ≤ 2 cm in diameter) HCCs.

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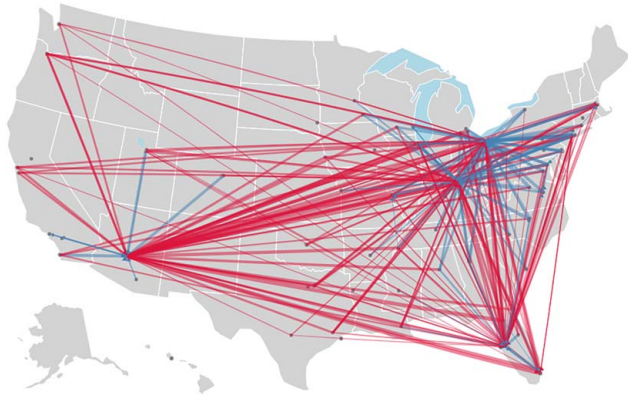
5019 | NATIONAL PATTERNS OF ALLOCATION OUT OF SEQUENCE (AOOS) IN LIVER TRANSPLANTATION

David Lee[1] Sidian Lin[2] Soroush Saghafian[3], [1]Beth Israel Deaconess Medical Center, [2]Harard Kennedy School, [3]Harvard Kennedy School

Background: Allocation out of sequence (AOOS) when organs are “offered or accepted, or transplanted into a transplant candidate or potential transplant recipient that deviates from the match sequence and is not consistent with OPTN policy”, bypassing candidates at transplant centers. AOOS has recently drawn scrutiny from HRSA and OPTN due to concerns of fairness, transparency, and rising non-use. Despite this, little is known about national patterns of AOOS bypass, which centers are “winners” versus “losers,” and how flows of organs between centers shape utilization. **Methods**: We analyzed the Standard Transplant and Recipient datafile* for all liver offer-level data from 2022-2024. AOOS donors were identified using OPTN bypass codes (861, 862, 863, 887) with text mining for “expedited placement/open offer” (code 799). For each donor, we defined a bypass flow as an instance where one center was bypassed and another ultimately accepted the organ. Flows were aggregated to quantify frequency, directionality, and geography. OPO-level AOOS rates were computed, and centers were categorized as net beneficiaries or net bypassed based on standardized net AOOS gain (accepted minus bypassed offers, adjusted for transplant volume). **Results**: During this three year window, a total of 3,644 donors were identified as AOOS, generating more than 1,500,000 bypass codes and 7,000 distinct bypass flows. AOOS occurred in 10 of the 11 OPTN regions, confirming that it is a national rather than a regional phenomenon. A small number of centers were disproportionately advantaged: 11 centers accounted for over half of all bypass inflows – and these centers were distinct for having significantly higher volume. By contrast, some high-volume centers were among the top bypassed centers, including 7 of the 11 recipient centers. At the OPO level, initiation of AOOS varied widely (3.5%–40.2%), with 15 among 57 OPOs responsible for half of all AOOS cases. Geographic mapping demonstrated regional asymmetries in bypass flows, with certain centers consistently receiving organs across long distances. **Conclusion**: AOOS in liver transplantation is widespread, and appears to advantage a small subset of centers, which could introduce systematic disparities in access. These findings echo HRSA concerns that AOOS may undermine equity and transparency in allocation. Characterizing bypass flows offers a novel lens to evaluate who benefits and who loses in AOOS. Future work should assess whether AOOS improves organ utilization, and develop policy solutions that preserve rescue of hard-to-place organs while ensuring fairness across centers.



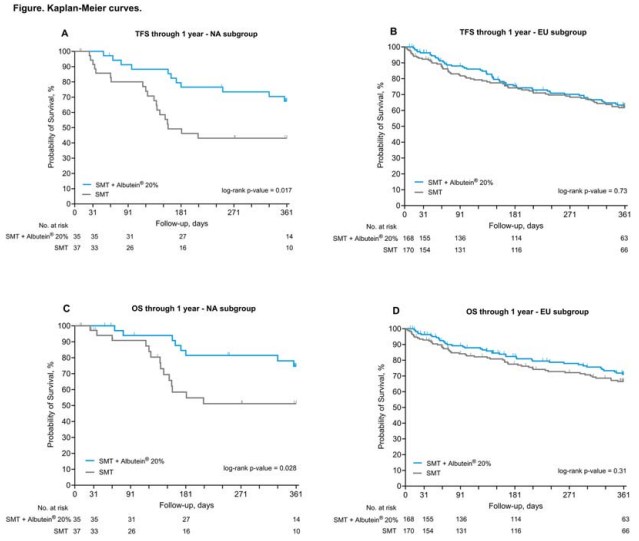
Disclosures: David Lee: Grifols: Advisor, Sidian Lin: Nothing to Disclose, Soroush Saghafian:

5020 | EFFICACY OUTCOMES IN PRECIOSA SHOW NOTABLE REGIONAL DIFFERENCES: COMPARISON OF THE NORTH AMERICAN AND EUROPEAN SUBGROUPS

Jacqueline O'Leary[1] Jasmohan Bajaj[2] Syed Naqvi[3] Nikolaos Pyrsopoulos[4] K Rajender Reddy[5] Florence Wong[6] Giovanni Perricone[7] Mireia Torres[8] Fiona McCarthy[8] Tarek Hassanein[9] Peter Nelson[8] Paolo Angeli[10] Javier Fernandez[11], [1]University of Texas Southwestern and Dallas VA Medical Center, [2]Hunter

Holmes McGuire VA Medical Center, [3]University of Missouri Hospital, [4]Rutgers-New Jersey Medical School, [5]University of Pennsylvania, [6]University of Toronto, [7]ASST Grande Ospedale Metropolitano Niguarda, [8]Grifols, [9]Southern California GI & Liver Centers, [10]University of Padova, [11]EF Clif, EASL-CLIF Consortium and Grifols Chair; Hospital Clínic, IDIBAPS and CIBERehd

Background: PRECIOSA (NCT03451292) is the first prospective randomized controlled trial to study long-term albumin (LTA) therapy in patients with cirrhosis with current or prior ascites and acute decompensation from North America (NA) and Europe (EU). We present exploratory analyses comparing the effect of LTA on transplant-free survival (TFS) and overall survival (OS) for the NA and EU subgroups (SGs). **Methods**: TFS and OS at 6 months (mo) and 1 year (yr) after randomization were analysed by Kaplan-Meier (KM) and Cox-Proportional-Hazard models comparing Treatment (standard medical treatment [SMT] plus LTA with Albutein® 20%) to Control (SMT alone) for each SG in the Intent to Treat (ITT) population. Hazard ratios (HR) and KM survival probabilities were interpreted in the context of baseline characteristics, compliance with LTA, and change in serum albumin (ALB) concentration. **Results**: The NA and EU SGs comprised 18% (72/410) and 82% (338/410) of the ITT population, respectively. Baseline characteristics were similar within and between SGs' Treatment and Control arms. Overall compliance with LTA was 83% in the NA Treatment arm vs 91% in the EU Treatment arm. During 1 yr of treatment, median ALB increased to >4.0 g/dL by mo 2 in both NA and EU Treatment arms. Median ALB increased to >3.5 g/dL by mo 2 in the EU Control arm but remained <3.5 g/dL in the NA Control arm. TFS HR [95% confidence interval (CI)] in the NA and EU SGs were 0.38 [0.16, 0.88] vs 0.90 [0.58, 1.40] at 6 mo and 0.42 [0.20, 0.88] vs 0.94 [0.65, 1.34] at 1 yr, respectively. OS HR [95% CI] in the NA and EU SGs were 0.41 [0.15, 1.08] vs 0.75 [0.46, 1.24] at 6 mo and 0.41 [0.17, 0.98] vs 0.81 [0.54, 1.22] at 1 yr, respectively. KM TFS estimate at 361 days was notably higher in the NA Treatment vs Control arm (67% vs 43%, $p=0.017$) but similar in EU (63% vs 62%, $p=0.73$) (Figure). Likewise, KM OS estimate at 361 days was notably higher in the NA Treatment vs Control arm (75% vs 51%, $p=0.028$) but similar in EU (71% vs 66%, $p=0.31$). **Conclusion**: In the NA SG, where median ALB increased to normal range in the Treatment arm but not the Control arm, LTA plus SMT produced marked improvements in 6-mo and 1-yr TFS and OS compared to SMT alone. In the EU SG, where median ALB increased to normal range in both Treatment and Control arms, little differences were observed. These findings could suggest that LTA therapy confers a clinical benefit in NA patients with decompensated cirrhosis and ascites.



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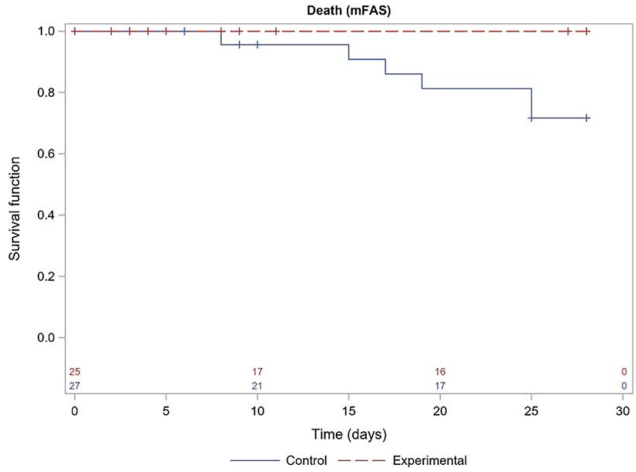
5021 | SHORT-TERM HUMAN ALBUMIN THERAPY IMPROVES SERUM SODIUM CONCENTRATION AND REDUCES MORTALITY IN PATIENTS WITH CIRRHOSIS AND DILUTIONAL HYPONATREMIA

Adrià Juanola[1] María Moreta[2] Cristina Sole[3] Martina Pérez-Guasch[2] Jordi Gratacós Ginès[4] Anna Soria[2] Berta Cuyas[5] Marta Martín-Llahí[6] Ann Ma[2] Enrico Pompili[2] Maria Amorós[7] Anna Cruceta[7] Sonia Diestro[2] Gemma Domenech[2] José Ríos[8] Jordi Sánchez[3] Nuria Fabrellas[9] Isabel Graupera[2] Elisa Pose[2] Pere Gines[10], [1]Hospital Clinic i Provincial de Barcelona, [2]Hospital Clínic de Barcelona, [3]Parc Tauli Hospital Universitari, [4]Hospital Clinic de Barcelona, [5]Hospital de la Santa Creu i Sant Pau, [6]Hospital de Sant Joan Despí Moisès Broggi, [7]CTU, Hospital Clínic de Barcelona, [8]Universitat Autònoma de Barcelona, UAB, [9]University of

Barcelona, UB, [10]Hospital Clinic de Barcelona, Idibaps, Ciberehd, UB

Background: Dilutional hyponatremia is common in decompensated cirrhosis and associated with high morbidity and mortality. Currently, there is no effective treatment available, and therapy is based on fluid restriction and diuretic withdrawal. Findings from small cohorts and retrospective studies suggest that intravenous(IV) human albumin(HA) administration may be effective in improving serum sodium concentration, but definitive data from specific randomized controlled trials (RCT) is lacking. We therefore aimed at investigating the effects of IV HA therapy in hospitalized patients with decompensated cirrhosis and dilutional hyponatremia in a RCT. **Methods**: We performed a multicenter, open-label, RCT in patients with cirrhosis and dilutional hyponatremia. Patients with serum sodium $\leq$133mEq/L were randomized 1:1 to receive either IV HA for a maximum of 10 days (1g/kg the first day, followed by 40g/day) plus standard of care (SoC; fluid restriction and diuretic withdrawal) or SoC alone. Primary outcome was resolution of hyponatremia as defined by an increase in serum sodium $\geq$ 5mEq/L with a final value > 130mEq/L. Secondary outcomes included frequency of resolution of hyponatremia plus partial resolution (increase in serum sodium $\geq$ 5 mEq/L irrespective of the final value of serum sodium), incidence of liver-related complications and survival. **Results**: 52 patients (median age 61 years, male 69% and alcohol-related cirrhosis 73%) were randomly assigned to receive either iv HA (n = 25) plus SoC or SoC alone (n = 27). The median MELD score at inclusion was 17(14–21), and the median serum sodium was 128mEq/L(123–131), with 17 patients (33%) showing severe hyponatremia (< 125mEq/L). Resolution of hyponatremia was achieved in 12 patients (48%) in the HA group compared with only 4 patients (15%) in the SoC group [RR 3.39(95%CI 1.27–9.05), p = 0.015]. If partial resolution (increase $\geq$ 5 mEq/L with a final value < 130mEq/L) was also considered, improvement/resolution of hyponatremia was observed in 17 patients(68%) from the HA group versus 5 patients (19%) in the SoC group [RR 3.65(95%CI 1.58–8.40), p = 0.002]. Mortality at 28 days was lower in the HA group vs the SoC group (0 vs 5 patients, log-rank p = 0.022) (Figure). The incidence of AKI was lower in the HA group (6 patients, 24%) compared with the SoC group (15patients, 56%) [HR 0.374 (95%CI 0.150–0.929), p = 0.034]. There were two episodes of respiratory failure probably related to the use of HA, that improved with treatment and IV HA withdrawal. **Conclusion**: In patients with cirrhosis and dilutional hyponatremia, short-term administration of IV HA is associated with higher rates of hyponatremia resolution, as well as lower mortality and a reduced incidence of AKI compared to standard treatment with fluid restriction and diuretic withdrawal. Intravenous albumin appears beneficial in the treatment of dilutional hyponatremia in cirrhosis



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5022 | HIGH PROPORTION OF PARTICIPANTS ACHIEVED SUSTAINED COMPLETE RESPONSE 24 WEEKS AFTER END OF AHB-137 TREATMENT IN HBEAG NEGATIVE CHRONIC HEPATITIS B PARTICIPANTS ON NA THERAPY: POOLED ANALYSIS OF TWO PHASE 2 STUDIES IN CHINA

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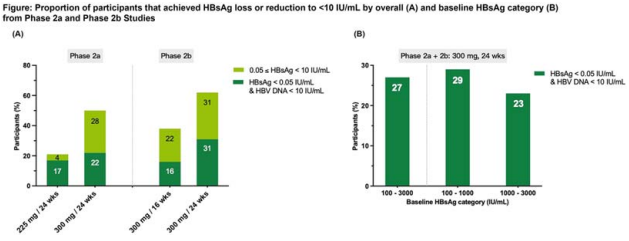
Background: AHB-137, an unconjugated antisense oligonucleotide (ASO), has shown promising efficacy with a favorable safety profile in HBeAg negative chronic hepatitis B (CHB) participants on nucleos(t)ide analogue (NA) therapy in Phase 2a (NCT06115993) and Phase 2b (NCT06550128) studies. Here, we report the pooled Week 48 results of the two Phase 2 studies (24 weeks after end of AHB-137 [EOT]). **Methods**: HBeAg-negative CHB participants (N = 119) on stable NA therapy with baseline HBsAg > 100-3,000 IU/mL and HBV DNA < 100 IU/mL were included. In Phase 2a, participants received weekly AHB-137 (300 mg or 225 mg) for 24 weeks. In Phase 2b, participants received AHB-137 300 mg for 24 weeks or placebo for 8 weeks followed by AHB-137 300 mg for 16 weeks. After EOT, participants continued NA monotherapy for 24 weeks. At Week 48, participants entered an additional 24-week follow-up period in which they either continued or discontinued NA treatment per NA discontinuation criteria, where discontinuation required the participant to have achieved complete response [CR], defined as HBsAg < 0.05 IU/mL and HBV DNA < 10 IU/mL. **Results**: At 24 weeks after EOT (Week 48), higher CR rates were observed with higher dose (300 mg) and longer treatment duration (24 weeks): 22% (7/32) in the 300 mg arm vs. 17% (4/23) in the 225 mg arm (Phase 2a), and 31% (10/32) with 24 weeks treatment vs. 16% (5/32) with 16 weeks treatment (Phase 2b). All 26 participants who achieved sustained CR at Week 48 discontinued NA therapy. Among those treated for 24-weeks with 300 mg AHB-137, 26.6% (17/64) achieved sustained CR at Week 48, with comparable response rates across baseline HBsAg strata (≤ 1000 IU/mL: 28.9% [11/38]; > 1000 IU/mL: 23.1% [6/26]). Of these responders, 82.4% (14/17) attained anti-HBs ≥ 10 IU/L. Partial response (PR; HBsAg ≥ 0.05 to < 10 IU/mL and HBV DNA < 10 IU/mL) was achieved in 29.7% (19/64) of the participants. TEAEs occurred primarily during the AHB-137 treatment period. No treatment-related SAEs were reported, and no AEs led to treatment discontinuation, early discontinuation, or death. **Conclusion**: AHB-137 treatment achieved robust and sustained antiviral responses (including CR and PR) 24 weeks after EOT in HBeAg-negative CHB participants, with the highest rates observed with the 24-week 300 mg regimen. Efficacy was consistent across baseline HBsAg strata. AHB-137 was well-tolerated, with no new safety signals identified during the 24 weeks after AHB-137 treatment. These results support the continued development of AHB-137 for CHB functional cure.



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5023 | EFFICACY OF LOW-DOSE ALBUMIN INFUSION IN PATIENTS OF DECOMPENSATED CIRRHOSIS WITH ACUTE KIDNEY INJURY

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Background: Acute kidney injury (AKI) is common in patients with decompensated cirrhosis(DC), frequently treated with volume explanation with 20% Human Albumin infusion for initial 48 hours, however studies evaluating the dose and duration of albumin infusion are limited and controversial. Also, human albumin infusion is associated with significant risk of volume overload, allergic reactions and has cost constraints. Current study evaluate the efficacy and safety of low-dose albumin (0.25-0.3 g/kg/d for 48 hours) in patients with DC and AKI. **Methods**: Patients with decompensated cirrhosis with AKI admitted in tertiary care centre from Sept 2022 to Aug 2025 were screened and enrolled after excluding Chronic kidney disease, Hepatocellular Carcinoma, respiratory or circulatory failure and patients on maintenance Albumin therapy. Enrolled patients received intravenous 20% Human Albumin (100 ml) for 2 consecutive days. Response to albumin was defined as reduction of serum creatinine to within 0.3 mg/dl of the baseline value. Patients who did not respond in 48 hours were further evaluated for aetiology of AKI and administered with vasoconstrictors. Baseline demographic, clinical, biochemical data with response to albumin at 48 hours and adverse events and mortality outcomes were noted.

Results: A total of 252 patients (215 [83%] males, mean age 46.5 ± 11.3 years) were enrolled. Alcohol was the most common aetiology (62.6%), followed by hepatitis C (12.3%). Median MELD-Na was 28.46 ± 7.07, and 182 patients (72.2%) were in Child–Pugh C. Mean S. Cr on enrolment was 2.71 ± 1.24 mg/dL. AKI resolution was noted in 116 (44.7%) patients: 59 patients (23.4%) after 24 hours and 57 patients (22.6%) after 48 hours of Albumin therapy. Clinically significant volume overload was observed in 2 patients (0.7%). Mean duration of hospital stay was 7.98 ± 4.63 days. In hospital mortality was observed in 65 patients (25.7%). **Conclusion**: Low-dose albumin (0.25-0.3 g/kg/d for 48 hours) is safe and effective method of volume repletion for AKI in decompensated cirrhosis patients

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5024 | EFRUXIFERMIN REDUCED FIBROSIS AND SEPTA AREA BY QUANTITATIVE DIGITAL PATHOLOGY IN PARTICIPANTS WITH COMPENSATED CIRRHOSIS DUE TO MASH: RESULTS FROM THE 96-WEEK, PLACEBO-CONTROLLED, PHASE 2B SYMMETRY TRIAL

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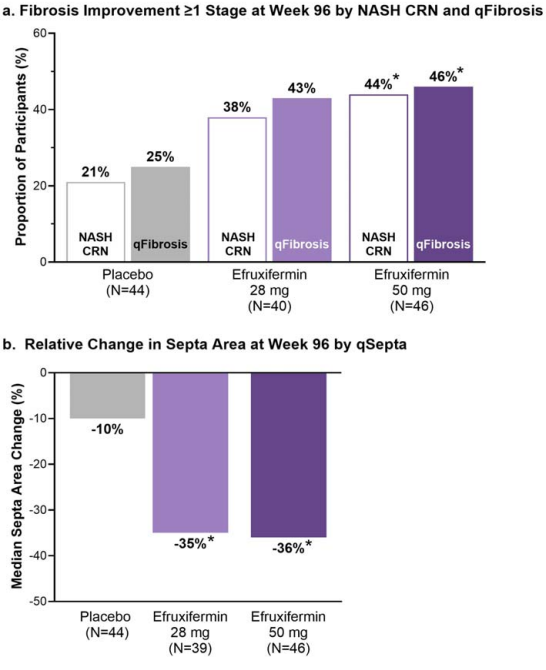
Background: Efruxifermin improved liver fibrosis by conventional pathology (NASH CRN) in the 96-week SYMMETRY trial in participants with MASH and compensated cirrhosis (F4c) (NCT05039450). This post hoc analysis used AI-based digital pathology to evaluate the impact of efruxifermin on overall fibrosis burden and septa area, cardinal features of cirrhosis. **Methods**: SYMMETRY was a phase 2b, randomized, placebo-controlled, double-blind trial that included 181 participants with MASH and biopsy-confirmed compensated cirrhosis. Unstained liver biopsies were available at baseline, week 36, and week 96 for 130 participants (placebo n = 44, efruxifermin 28 mg n = 40, efruxifermin 50 mg n = 46). Biopsies were imaged using second harmonic generation/two-photon excitation fluorescence microscopy and analyzed by: 1) qFibrosis for continuous and categorical fibrosis changes, and 2) qSepta for changes in septa morphology, specifically septa area. **Results**: A significantly greater proportion of participants in the efruxifermin 50 mg group had ≥1-stage fibrosis improvement by qFibrosis vs placebo (46% for efruxifermin 50 mg vs 25% for placebo, $p < 0.05$), consistent with NASH CRN fibrosis stage (Figure). Increased septa area at baseline was associated with higher CSPH risk category (based on Baveno VII criteria). Efruxifermin resulted in a greater reduction from baseline to week 96 in median septa area vs placebo (-35% and -36% for efruxifermin 28 mg and 50 mg vs -10% for placebo, both $p < 0.05$). In addition, a greater proportion of participants in the efruxifermin groups than in placebo had decreased septa area, while more participants in the placebo group than the efruxifermin groups had increased septa area at week 96. In those with ³1-stage fibrosis improvement (NASH CRN responders), septa area decreased to a similar extent in all treatment groups (median change -34% to -42%). Strikingly, septa area was also reduced in NASH CRN non-responders treated with efruxifermin (-24% to -25%), but not with placebo (14%). **Conclusion**: In participants with F4c, AI-based digital pathology assessment confirmed previously demonstrated histological fibrosis improvements with efruxifermin at week 96. Efruxifermin reduced septa area, which was associated with disease severity, independent of categorical histological fibrosis response. Digital analysis of septa area, which may detect more subtle changes in fibrosis, demonstrated a broad antifibrotic effect of efruxifermin in participants with MASH and F4c that may yield clinically meaningful improvements in liver outcomes.

Figure. a. Fibrosis improvement ≥1 stage at week 96 evaluated by NASH CRN criteria and digital pathology (qFibrosis). b. Septa area change (median) at week 96 evaluated by digital pathology (qSepta). *p<0.05 vs placebo within analysis method (NASH CRN or digital pathology).



Disclosures: Mary Rinella: akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, akero: Consultant, akero: Consultant, akero: Consultant, 89Bio: Consultant, 89Bio: Consultant, 89Bio: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Boehringer Ingelheim: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Cytodyn: Consultant, Echosens: Consultant, Echosens: Consultant, Echosens: Consultant, Histoindex: Consultant, Histoindex: Consultant, Histoindex: Consultant, Intercept: Consultant, Intercept: Consultant, Intercept: Consultant, Madrigal: Consultant, Madrigal: Consultant, Madrigal: Consultant, GSK: Consultant, GSK: Consultant, GSK: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Novo Nordisk: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Eli Lilly: Consultant, Takeda: Consultant, Takeda: Consultant, Takeda: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sagimet: Consultant, Sonic Incytes: Consultant, NGM Bio: Consultant, Yukti Choudhury:, Galvin Gan: HistoIndex Pte Ltd: Employee, Elaine Chng: Nothing to Disclose, Cynthia Behling:, Doreen Chan: Akero Therapeutics: Employee, Akero Therapeutics: Stock - 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Conatus: Principal Investigator, Corcept: Principal Investigator, Galectin: Principal Investigator, Genfit: Principal Investigator, GSK: Principal Investigator, Kowa: Principal Investigator, Enanta: Principal Investigator, Madrigal: Principal Investigator, Lilly: Principal Investigator, Merck: Principal Investigator, Novartis: Principal Investigator, Novo Nordisk: Principal Investigator, Rivus: Principal Investigator, Shire: Principal Investigator, Takeda: Principal Investigator, Terns: Principal Investigator, Viking: Principal Investigator, Zydus: Principal Investigator, Rivus: Stock – privately held company, Cytodyn: Stock - publicly traded company, ChronWell: Stock – privately held company, Madrigal: Speakers bureau, Conatus: Principal Investigator, Gilead Sciences: Principal Investigator, Akero: Consultant, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharma: Consultant, Curve bioscience: Consultant, Cytodyn: Consultant, GSK: Consultant, Histoindex: Consultant, Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Rivus, Sagimet: Consultant, Rivus: Consultant, Sagimet: Consultant, Terns: Consultant, Allergan: Grant/Research Support, Altimmune: Grant/Research Support, Akero: Grant/Research Support, BI: Grant/Research Support, BMS: Grant/Research Support, Boston Pharma: Grant/Research Support, Conatus: Grant/Research Support, Corcept: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Genfit: Grant/Research Support, GSK: Grant/Research Support, Kowa: Grant/Research Support, Enanta: Grant/Research Support, Madrigal: Grant/Research Support, Lilly: Grant/Research Support, Merck: Grant/Research Support, Novartis: Grant/Research Support, Novo Nordisk: Grant/Research Support, Rivus: Grant/Research Support, Shire: Grant/Research Support, Takeda: Grant/Research Support, Terns: Grant/Research Support, Viking: Grant/Research Support, Rivus Pharma: Stock – privately held company, Akero: Stock - publicly traded company, Zydus: Grant/Research Support, Takeda: Consultant, Madrigal: Speaking and Teaching, Novo Nordisk: Speaking and Teaching, Takeda: Consultant

5025 | REDUCTION OF LIVER FIBROSIS BY AI-BASED DIGITAL PATHOLOGY ANALYSIS: RESULTS FROM THE PEMVIDUTIDE PHASE 2 IMPACT TRIAL

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Background: Pemvidutide is a GLP-1/glucagon dual receptor agonist in development for the treatment of metabolic dysfunction-associated steatohepatitis (MASH), alcohol use disorder (AUD), and alcohol-associated liver disease (ALD). IMPACT is a Phase 2, randomized, placebo-controlled, double-blind trial in patients with biopsy-confirmed MASH and fibrosis stage F2 or F3 (NCT05989711). Liver Explore™ is an artificial intelligence (AI) algorithm that provides granular quantification of fibrosis subtypes beyond the categorical grades provided by conventional NASH Clinical Research Network (CRN) staging. Here, we present the results of a Liver Explore™ assessment of IMPACT liver biopsies at 24 weeks. **Methods**: From July 2023 to April 2025, 212 subjects were randomized 1:2:2 to once-weekly subcutaneous pemvidutide [1.2 mg (N = 41) or 1.8 mg (N = 85)], without dose titration, or placebo (N = 86). Biopsies were assessed by NASH CRN staging and quantified for the proportionate areas of total, early (periportal and perisinusoidal), and advanced fibrosis (bridging and nodular), adjusted for steatosis area, by Liver Explore™. Liver Explore™ is for research use only, not for use in diagnostic procedures. Patients with missing biopsy data or who discontinued treatment early were considered non-responders (ITT analysis). **Results**: AI-based continuous analyses showed significant, dose-dependent improvements across the 1.2 mg and 1.8 mg pemvidutide doses. The absolute change from baseline in the proportionate area of pathologic fibrosis at 1.2 mg was -0.40% ($p = 0.039$ vs. placebo), -0.69% at 1.8 mg ($p < 0.001$ vs. placebo), and +0.38% for placebo. In a responder analysis, 31% of patients in the 1.8 mg group achieved a 60% relative reduction in the area of total fibrosis (Odds Ratio (OR), 5.0; $p = 0.0003$; Figure 1). Subcomponent fibrosis analyses revealed a significant proportion of patients had reductions in early fibrosis at both doses, with 24% of patients in the 1.2 mg group (OR, 3.2; $p = 0.017$) and 34% of patients in the 1.8 mg group achieving a 60% relative decrease (OR, 5.0; $p < 0.0001$) versus 9% of placebo patients. Importantly, 27% of patients in the 1.8 mg group had a 60% relative reduction in advanced fibrosis (OR, 3.2; $p = 0.0063$) compared to 11% of placebo patients. **Conclusion**: Pemvidutide significantly reduced the AI-quantified total fibrosis burden at 24 weeks, with effects in the early and advanced fibrosis compartments. Future studies should evaluate the relationship of continuous fibrosis improvement to outcomes.

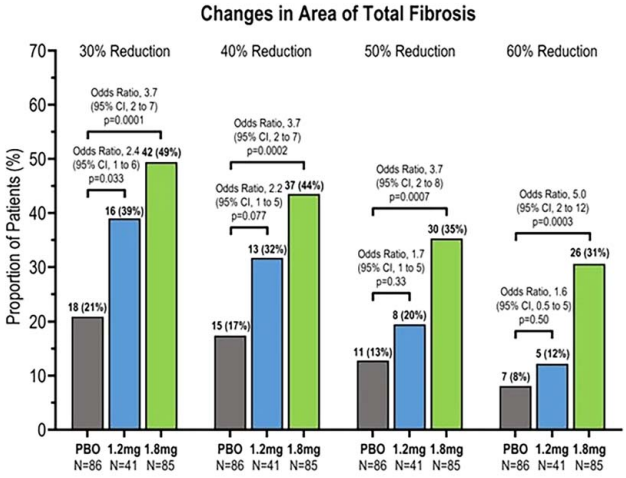

Figure 1. The change in the proportion of biopsy sample with pathological liver fibrosis from baseline to week 24 per Liver Explore™ artificial intelligence-based digital pathology tool, with statistical comparisons by Cochran-Mantel-Haenszel test. PBO, placebo.

Disclosures: Vlad Ratziu: Novo-Nordisk: Consultant, Boehringer-Ingelheim: Consultant, Madrigal: Consultant, Akero: Consultant, 89Bio: Consultant, Sagimet: Consultant, 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, Naim Alkhouri: Madrigal: Speaking and Teaching, Novo Nordisk: Consulting, Novo Nordisk: Grant/Research Support, Corcept: Grant/Research Support, Echosens: Speaking and Teaching, Perspectum: Consultant, Cima: Consultant, Fibronostics: Consultant, 89Bio: Grant/Research Support, Inventiva: Grant/Research Support, Merck: Grant/Research Support, Pfizer: Grant/Research Support, Ipsen: Speaking and Teaching, Intercept: Speaking and Teaching, Madrigal: Consulting, Research Funding, Novo Nordisk: Consulting, Research Funding, Inventiva: Research Funding, Boehringer Ingelheim: Consulting, Research Funding, Corcept: Research Funding, Ipsen: Consulting, Research Funding, Gliead: Consulting, Research Funding, Speaking, Perspectum: Consulting, Research Funding, Cima: Advisor, 89Bio: Consulting, Research Funding, Arbutus: Grant/Research Support, GSK: Grant/Research Support, Regeneron: Grant/Research Support, AstraZeneka: Grant/Research Support, Madrigal: Grant/Research Support, Akero: Grant/Research Support, Boehringer Ingelheim: Grant/Research Support, Eli Lilly: Grant/Research Support, Gilead: Grant/Research Support, Galectin: Grant/Research Support, Boston Pharma: Grant/Research Support, 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, Julio Gutierrez: Altimmune: Consultant, AbbVie: Speaking and Teaching, Gilead: Speaking and Teaching, Alexion: Speaking and Teaching, Exelixis: Speaking and Teaching, Madrigal: Consultant, Intercept: Speaking and Teaching, Livivos: Stock – privately held company, Surozen: Advisor, Escient: DSMB Chairman, Shaheen Tomah: Altimmune: Employee, Altimmune: Stock - publicly traded company, Christina Jayson: PathAI: Stock – privately held company, PathAI: Employee, Ylaine Gerardin: PathAI: Employee, Alyson Warr: PathAI: Employee, Kelonia Therapeutics: Employee, John Suschak: No dislosure submitted, Scot Roberts: Altimmune: Executive role, Sarah Browne:, Rachel Garner: Altimmune Inc.: Employee, Scott Harris: Altimmune: Employee, Mazen Noureddin: Itimmune, BI, Cytodyn, 89BIO, GSK, Madrigal, Merck, Novo Nor: Terns,Takeda, Zydus., Allergan, Akero, BI, BMS, Gilead, Galectin, Zydus GSK: Terns, Corcept, Takeda, Madrigal, Novartis, Novo Nordisk, Rivus Pharma, Cytodyn, and ChronWell: Stock – privately held company, Altimmune: Consultant, Alligos: Consultant, AstraZeneca: Consultant, BI: Consultant, Boston Pharmaceuticals: Consultant, Cytodyn: Consultant, GSK: Consultant, Eli Lilly: Consultant, Madrigal: Consultant, Merck: Consultant, Novo Nordisk: Consultant, Terns: Consultant, Takeda: Consultant, Allergan: Principal Investigator for a Drug Study, Akero: Principal Investigator for a Drug Study, BI: Principal Investigator for a Drug Study, BMS: Principal Investigator for a Drug Study, Gilead: Principal Investigator for a Drug Study, Galectin: Principal Investigator for a Drug Study, Genfit: Principal Investigator for a Drug

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5026 | SAFETY, PHARMACOKINETICS, AND ANTIVIRAL ACTIVITY OF THE NEXT-GENERATION HEPATITIS B CAPSID ASSEMBLY MODULATOR ABI-4334 IN PATIENTS WITH HBEAG-NEGATIVE CHRONIC HEPATITIS B INFECTION NOT SUPPRESSED ON NUCLEOSIDE ANALOGUES: RESULTS FROM A RANDOMIZED, BLINDED, PHASE 1B STUDY

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Background: ABI-4334-102 (NCT06384131) is a randomized, blinded, multiple-dose escalation study assessing the safety, pharmacokinetics (PK), and antiviral activity of the next-generation capsid assembly modulator (CAM) ABI-4334 (4334) in patients (pts) with chronic HBV infection. **Methods**: Two cohorts were enrolled evaluating 150 mg and 400 mg 4334. In each cohort up to 10 pts were randomized 4:1 to receive 4334 or placebo (PBO) once-daily (QD) for 28 days. Eligible pts were male or female, aged 18–65 years, HBeAg-positive (HBV DNA $\geq 2x10^4$ IU/mL) or -negative (HBV DNA $\geq 2x10^3$ IU/mL), off antiviral therapy and non-cirrhotic with Fibroscan $<$ 9kPa or Metavir F0–F2. Safety was assessed by physical examination, adverse events (AEs) and lab parameters. PK and viral biomarkers (including HBV DNA) were assessed throughout. Here, we report safety, PK, and antiviral activity. **Results**: Overall, 15/20 pts enrolled were HBeAg-negative therefore results are summarized for this subgroup. Baseline (BL) demographics and HBV characteristics were balanced across treatments. Treatment was well tolerated, with no serious AEs or AEs leading to study drug discontinuation. Treatment-emergent (TE)AEs were reported in 9/13 and 1/2 4334 and PBO recipients respectively; most were Grade 1/2. Two Grade 3 TE lab abnormalities were observed, 1 ALT elevation in a 150 mg 4334 recipient (considered related to treatment) and 1 total bilirubin elevation in a PBO recipient; both returned

to BL levels with continued study drug administration. The mean change from BL in HBV DNA at Day 28 was -2.7 and –3.1 log_{10} IU/mL for 150 mg and 400 mg 4334 recipients, respectively. No change in HBsAg was observed during treatment. The mean Day 28 C_{max}, C_{min}, AUC_{24} and $t_{1/2}$ were 723.1 ng/mL, 93.3 ng/mL, 5161 h*ng/mL, and 27.5 h for 150 mg 4334, and 3080 ng/mL, 403.7 ng/mL, 23140 h*ng/mL, and 17.5 h for 400 mg 4334. **Conclusion**: 4334 was safe and well tolerated at doses up to 400 mg QD for 28 days. Most TEAEs and lab abnormalities were mild to moderate (Grade 1 or 2). No serious AEs or study drug discontinuations occurred due to treatment. Increased in vitro potency of 4334 relative to first-generation CAMs was reflected in multi-log declines in HBV DNA. Safety and PK data from the 400 mg cohort continue to support QD oral dosing, achieving exposures in greater excess of those anticipated to inhibit cccDNA formation. The findings strongly support continued development of 4334 as part of combination regimens with agents of complementary mechanisms of action.

HBeAg Negative Patients	150 mg 4334 (n = 6)	400 mg 4334 (n = 7)	PBO (n = 2)
BL Characteristics			
Age; years; mean (SD)	48 (4.3)	50 (7.5)	45 (9.9)
Male; n/N (%)	3 (50.0)	4 (57.1)	2 (100.0)
Race, White; n (%)	5 (83.3)	7 (100.0)	1 (50.0)
HBV genotype D; n (%)	4 (66.7)	6 (85.7)	2 (100.0)
HBV DNA (log_{10} IU/mL); mean (SD)	5.2 (2.45)	4.4 (1.04)	4.2 (1.27)
HBsAg (log_{10} IU/mL); mean (SD)	3.8 (0.79)	3.5 (0.40)	3.4 (0.18)
ALT; mean (SD) U/L	42 (24.0)	73 (97.3)	63 (53.7)
Pts with any TEAE; n (%)	4 (66.7)	5 (71.4)	1 (50.0)
Pts with Grade 3 or 4 TEAE	1 (16.7)	0	0
Pts with any serious AE; n (%)	0	0	0
Pts with any AE leading to study drug discontinuation; n (%)	0	0	0
HBV DNA change from BL at Day 28 (log_{10} IU/mL); mean (SD)[a]	-2.7 (0.58)	-3.1 (0.59)	-0.1 (0.20)
HBV pgRNA change from BL at Day 28 (log_{10} U/mL); mean (SD)[b]	-1.1 (1.52)	-0.6 (1.09)	0.3 (0.36)
HBsAg change from BL at Day 28 (log_{10} IU/mL); mean (SD)	-0.1 (0.11)	0.0 (0.06)	0.0 (0.05)

[a]HBV DNA values <lower limit of quantification (10 IU/mL; 1.0 log_{10} IU/mL) were imputed as 5 IU/mL (0.69 log_{10} IU/mL) for calculation of change from BL; [b]Overall, 9/15 (60.0%) of subjects had HBV pgRNA <LLOQ at BL; 4334, ABI-4334; BL, baseline; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; PBO, placebo; pt, patient; SD, standard deviation; TEAE, treatment-emergent adverse event

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5027 | EFFECTS OF ZIBOTENTAN AND DAPAGLIFLOZIN IN PATIENTS WITH CIRRHOSIS AND CLINICALLY SIGNIFICANT PORTAL HYPERTENSION: A RANDOMIZED PLACEBO-CONTROLLED 16-WEEK STUDY

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Background: Endothelin-1 is a strong vasoconstrictor causing intrahepatic vasoconstriction after liver injury, and endothelin A receptor antagonists (ET_ARAs) have been shown in preclinical studies to reduce intrahepatic resistance. We hypothesized that zibotentan, an ET_ARA, could potentially reduce hepatic venous pressure gradient (HVPG) but may also cause fluid retention. Since sodium-glucose co-transporter 2 inhibitors (SGLT2i) may normalize extracellular water volume, we examined effects of different doses of zibotentan (zibo), combined with 10 mg dapagliflozin (dapa) on HVPG. **Methods**: Patients with HVPG >10 mmHg and compensated or decompensated cirrhosis (MELD <15 and Child Pugh score <10) were randomized to receive 5 mg zibo/dapa (n = 36), 2.5 mg zibo/dapa (n = 34), 1 mg zibo/dapa (n = 34), dapa monotherapy (n = 34) or placebo (n = 35) in a 16-week double-blind study. The primary endpoint was absolute change in HVPG from baseline to week 6. Secondary endpoints included changes in body weight and composition, loop diuretic use, systolic and diastolic blood pressures. Analyses were 2-sided and are presented with 90% CI.

Results: Out of 177 randomized participants, 173 were treated and 154 completed 6 weeks of treatment. The mean age was 61 years (52% males), 26% were decompensated and 67% were on non-selective beta blockers. The main etiologies were ALD (58%) and MASLD (33%), with mean (SD) MELD and Child-Pugh scores of 8.4 (2.2) and 5.3 (0.6), respectively. Mean (SD) baseline HVPG was 16.2 (3.8) mmHg. There was no placebo-corrected effect on HVPG in any active treatment arm (**Table**). Prespecified subgroup and sensitivity analyses resulted in similar results. Measures of fluid retention (e.g., extracellular water volume and BNP) were numerically worse and fluid retention events were more frequent with the higher zibo dose. In contrast, dapa monotherapy increased hematocrit and resulted in fewer fluid retention events than placebo. Numbers of SAEs were similar across all treatment groups. There were no deaths, DILI events, or increased risks for orthostatic hypotension. **Conclusion**: Six weeks of treatment with different zibo doses in combination with dapa did not reduce HVPG, possibly because any effect on intrahepatic vasoconstriction was counteracted by plasma volume expansion. Dapa monotherapy has promising effects on fluid retention in cirrhosis. This work is dedicated to the memory of late Dr. Jaume Bosch for his invaluable contributions to the field and this study.

Absolute change in HVPG (mmHg) from baseline to week 6.

		Comparison of treatment groups	
Group	**n**	**Estimate and 90% CI**	**p-value**
Placebo	35	-	-
Dapa 10 mg	34	0.81 (-0.30, 1.92)	0.885
Zibo/Dapa 1 mg/10 mg	34	-0.10 (-1.26, 1.05)	0.442
Zibo/Dapa 2.5 mg/10 mg	34	1.39 (0.27, 2.52)	0.979
Zibo/Dapa 5 mg/10 mg	36	0.35 (-0.86, 1.57)	0.683

The analysis is performed using ANCOVA and includes treatment group as fixed categorical factor and baseline HVPG as continuous covariate and the absolute change in HVPG is the dependent variable. Missing HVPG values at week 6 in each arm are imputed using multiple imputation, except for missing due to terminal events. The estimate in a treatment group is least squares means.

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5028 | 1-YEAR CHANGE IN ENHANCED LIVER FIBROSIS (ELF) PREDICTS LIVER-RELATED CLINICAL EVENTS IN PATIENTS WITH METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS

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Background: The U.S. Food and Drug Administration recently called for more evidence to enable the use of non-invasive tests as alternatives to liver biopsy as a reasonably likely surrogate endpoint (RLSE) in MASH clinical trials. Although histological endpoints have been historically used in MASH clinical trials, due to safety, accuracy, and cost concerns associated with biopsy, an alternative non-invasive option is desirable. While the Enhanced Liver Fibrosis (ELF) Test was granted FDA de novo marketing authorization for prognostic use in patients with advanced fibrosis due to MASH, RLSE validation requires data demonstrating that changes in ELF scores are associated with changes in clinical outcome risk. Therefore, we aimed to determine if serial changes in ELF scores are associated with a differentiated risk of liver-related events (LREs) in support of use of the ELF Test as an RLSE. **Methods**: Data were pooled from 5 large placebo-controlled trials in patients with MASH and advanced fibrosis (NCT01672866, NCT01672879, NCT024629967, NCT03053050, NCT03053063). Patients were excluded if they were missing histology or ELF at baseline or at 1 year. Patients were stratified by baseline ELF (lower LRE risk: <9.80, mid risk: ≥ 9.80 to <11.30, higher risk: ≥ 11.30) and 1-year change in ELF, either by category (i.e., different risk category at 1 year versus baseline) or

magnitude (↓0.50, stable, ↑0.50). For comparison, parallel risk strata based on histological stage at baseline (F3, F4) and 1 year (F0-F2, F3, F4) were also evaluated. Liver-related events were a composite endpoint of clinical manifestations of decompensation, (qualification for) transplant, and liver-related death, based on the first event per patient. Outcomes were measured concurrently, but patients with events within 1 year were excluded if ELF and histological assessment were not recorded at the 1-year time point. Event risk (%), likelihood ratio (LR) and events per 1000 years of patient follow-up (LRE/1000 PY) were calculated with 95% confidence intervals. **Results**: A total of 2071 participants, with a median follow-up time of 16.5 months, were included in this study. 88 study participants had liver-related events during the follow-up period. After baseline adjustment, groups with worsening ELF were associated with a higher incidence of LREs while groups with improving ELF were associated with fewer LREs. Trends were consistent for event risk, iLR and LRE/1000 PY. Histology underestimated risk compared to the highest ELF strata. **Conclusion**: Our results indicate that risk strata defined by serial changes in ELF are associated with differences in clinical outcome risk. Serial measurement of ELF may be useful to identify patients experiencing MASH improvement or worsening and holds promise as a reasonably likely surrogate endpoint to potentially replace histology in clinical trials.

Measurement at Baseline	Measurement at 1 Year	N	LREs (N)	Risk of LREs (95% CI)	Interval Likelihood Ratio (95% CI)	LRE Incidence per 1000 PY (95% CI)
ELF Score (categorical change)						
≥11.30	≥11.30	282	41	14.5% (10.6%, 19.2%)	3.83 (2.98, 4.94)	112.5 (79.6, 148.2)
	≥9.80 to <11.30	105	5	4.8% (1.6%, 10.8%)	1.13 (0.47, 2.70)	29.2 (5.8, 58.4)
	<9.80	4	0	0.0% (0.0%, 60.2%)	0.00	0.0
≥9.80 to <11.30	≥11.30	180	16	8.9% (5.2%, 14.0%)	2.20 (1.38, 3.51)	62.0 (34.9, 93.1)
	≥9.80 to <11.30	742	17	2.3% (1.3%, 3.6%)	0.53 (0.34, 0.81)	15.3 (8.1, 23.4)
	<9.80	149	1	0.7% (0.0%, 3.7%)	0.15 (0.02, 1.08)	4.2 (0.0, 12.7)
<9.80	≥11.30	4	0	0.0% (0.0%, 60.2%)	0.00	0.0
	≥9.80 to <11.30	194	7	3.6% (1.5%, 7.3%)	0.84 (0.41, 1.74)	24.2 (6.9, 44.9)
	<9.80	411	1	0.2% (0.0%, 1.3%)	0.05 (0.01, 0.39)	1.4 (0.0, 4.3)
ELF Score (magnitude change)						
≥11.30	Δ ≥0.5	81	13	16.0% (8.8%, 25.9%)	4.31 (2.48, 7.49)	124.0 (57.2, 200.2)
	Δ >−0.5 to <0.5	201	26	12.9% (8.6%, 18.4%)	3.35 (2.35, 4.76)	98.8 (64.6, 136.7)
	Δ ≤−0.5	108	7	6.5% (2.6%, 12.9%)	1.56 (0.75, 3.26)	40.4 (11.5, 75.0)
≥9.80 to <11.30	Δ ≥0.5	284	18	6.3% (3.8%, 9.8%)	1.52 (0.99, 2.34)	42.3 (23.5, 63.4)
	Δ >−0.5 to <0.5	619	14	2.3% (1.2%, 3.8%)	0.52 (0.32, 0.85)	15.3 (7.7, 24.1)
	Δ ≤−0.5	169	2	1.2% (0.1%, 4.2%)	0.27 (0.07, 1.07)	7.5 (0.0, 18.7)
<9.80	Δ ≥0.5	225	6	2.7% (1.0%, 5.7%)	0.62 (0.28, 1.35)	17.4 (5.8, 32.0)
	Δ >−0.5 to <0.5	317	1	0.3% (0.0%, 1.7%)	0.07 (0.01, 0.50)	1.9 (0.0, 5.7)
	Δ ≤−0.5	67	1	1.5% (0.0%, 8.0%)	0.34 (0.05, 2.43)	8.8 (0.0, 26.3)
NASH CRN						
F4	F4	965	76	7.9% (6.3%, 9.8%)	1.93 (1.75, 2.12)	52.1 (40.5, 64.5)
	F3	165	6	3.6% (1.3%, 7.7%)	0.85 (0.39, 1.87)	25.6 (8.5, 46.9)
	<F3	8	0	0.0% (0.0%, 36.9%)	0.00	0.0
F3	F4	148	2	1.4% (0.2%, 4.8%)	0.31 (0.08, 1.23)	14.9 (-0.0, 37.2)
	F3	643	4	0.6% (0.2%, 1.6%)	0.14 (0.05, 0.37)	3.8 (0.9, 7.6)
	<F3	142	0	0.0% (0.0%, 2.6%)	0.00	0.0
Overall						
---	---	2071	88	4.2% (3.4%, 5.2%)	---	28.1 (22.3, 32.2)

LREs: liver-related events; PY: person years; Δ: change from baseline to 1 year (applicable to ELF analysis only)

Disclosures: Matthew Gee: Siemens Healthineers: Employee, Edward De Vol: Nothing to Disclose, William Rosenberg:, Jordan Feld: AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, AbbVie: Advisor, AbbVie, Bluejays, Gilead, Janssen, GSK, Roche, VIR Roche: Consultant, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Altimmune, AbbVie, Gilead, Jannsen, GSK, Roche, VIR Bio: Grant/Research Support, Bluejay: Advisor, Gilead: Advisor, GlaxoSmithKline: Advisor, Precision Biosciences: Advisor, Arbutus: Advisor, Astra Zeneca: Advisor, Roche: Advisor, Vir: Advisor, Orphalan: Advisor, Pfizer: Advisor, Abbvie: Grant/Research Support, Gilead: Grant/Research Support, GlaxoSmithKline: Grant/Research Support, Atea: Advisor, Atea: Grant/Research Support, Roche: Grant/Research Support, Vir: Grant/Research Support, Keyur Patel: Novo-Nordisk: Consultant, Gilead Sciences: Consultant, Merck: Consultant, Resalis: Advisor, Boehringer Ingelheim: Advisor, Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Eli Lilly, Echosens, Abbott, Promed, Genfit, Satellite Bio,: Consultant, Corcept, Arrowhead, Boston Pharmaceuticals, Variant,: Consultant, Cascade, 89 Bio, AstraZeneca, Alnylam, Regeneron: Consultant, Boehringer Ingelheim Bristol Myers Squibb, Genetech, Gilead: Consultant, Histoindex,

Janssen, Lipocine, Madrigal, Merck, GSK,: Consultant, Niovartis, Akero, Novo Nordisk, Path AI, Pfizer, Poxel: Consultant, Salix, Myovant, Median Technologies, Sequana, Surrozen: Consultant, Takeda, Terns, Zydus: Consultant, AstraZeneca, Bristol Myers Squibb, Gilead, Intercept: His institution has received grants from:, Mallinckrodt, Merck, Ocelot, Novartis, Salix: His institution has received grants from:, UpToDate, Elsevier: Royalties or patent beneficiary, Durect, Genfit, Tiziana, Inverage: Stock – privately held company

5029 | SAFETY AND HBSAG REDUCTION IN PATIENTS WITH CHRONIC HEPATITIS B TREATED BY A LENTIVIRAL VECTOR THERAPEUTIC VACCINE (J-51): AN INVESTIGATOR-INITIATED PILOT TRIAL

Jieyu Song[1] Yumeng Zhang[1] Jingjing Shen[2] Kun Wang[2] Rongrong Wei[2] Chunyan Shen[2] Wenjuan Wang[2] Mingmei Chu[3] Fang Zhou[3] Xiao Liang[3] Linshu Zhang[3] Chao Qiu[1] Hong Wu[2] Wenhong Zhang[1] Qiran Zhang[1], [1]Department of Infectious Diseases, Huashan Hospital, Fudan University, [2]Changzhi People's Hospital, [3]Jinwei Biotechnology

Background: Functional cure for chronic hepatitis B (CHB) remains a major unmet medical need, necessitating innovative therapeutic strategies. J-51 is a novel non-integrating lentiviral vector-based therapeutic vaccine designed to restore potent and sustained HBV-specific T-cell immunity. This investigator-initiated trial aimed to evaluate the safety of J-51 and to identify an optimal vaccination regimen. **Methods**: In this first-in-human, open-label, investigator-initiated pilot trial, adults with HBeAg-negative CHB, normal ALT levels, and HBsAg <5000 IU/mL were enrolled. Participants received intramuscular administrations of J-51 across two parts: an initial exploratory part for safety, dosing, and regimen optimization (Part 1), followed by a dose-escalation part for further safety and efficacy evaluation (Part 2). The primary endpoints were serious adverse event and HBsAg response (defined as achieving a >0.5 $\log_{10}$ IU/mL HBsAg reduction from baseline) at any timepoint during follow-up. **Results**: Seven patients were enrolled in this safety and dose-exploration study. J-51 exhibited a favorable safety and tolerability profile across all dose levels (up to $2\times10_9$ TU), with no serious adverse events reported. Preliminary efficacy assessments showed that three out of six eligible patients (50%) achieved a serum HBsAg response. Notably, one patient in the 1×10^9 TU cohort achieved HBsAg seroclearance (HBsAg <0.05 IU/mL) by Week 52. Responders were generally characterized by low baseline HBsAg levels (<120 IU/mL). **Conclusion**: J-51, a first-in-class lentiviral vector-based therapeutic vaccine, was well-tolerated and induced sustained HBsAg reduction. These results support the continued development of J-51 as an immunotherapeutic intervention aimed at functional cure for CHB and justify further investigation in larger clinical trials.

Figure 1

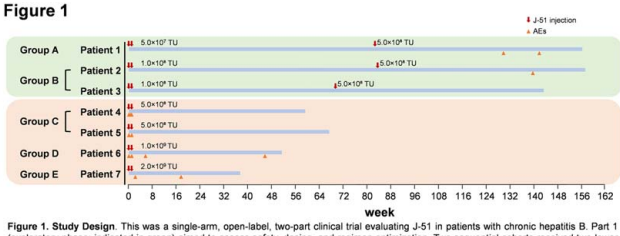

Figure 1. Study Design. This was a single-arm, open-label, two-part clinical trial evaluating J-51 in patients with chronic hepatitis B. Part 1 (exploratory phase; indicated in green) aimed to assess safety, dosing, and regimen optimization. Two sequential cohorts received two lower priming doses (Group A: 5.0×10^7 TU; Group B: 1.0×10^8 TU) on Days 1 and 8, followed by a higher booster dose (5.0×10^8 TU) administered no earlier than week 24. Part 2 (dose-escalation phase; indicated in orange) involved three cohorts receiving three fixed doses without a booster (Group C: 5.0×10^8 TU; Group D: 1.0×10^9 TU; Group E: 2.0×10^9 TU) on Days 1 and 8. After screening and vaccination, all patients entered a follow-up period for safety and efficacy evaluations lasting at least 24 weeks, with an optional extended follow-up. All adverse events were plotted relative to the time of vaccination for each participant, visually highlighting the transient and non-dose-related characteristics of most events. TU denotes transduction units.

Figure 2

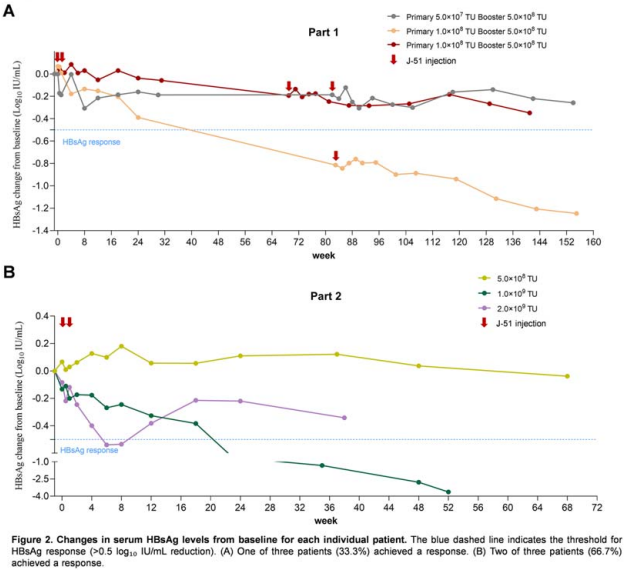

Figure 2. Changes in serum HBsAg levels from baseline for each individual patient. The blue dashed line indicates the threshold for HBsAg response (>0.5 $\log_{10}$ IU/mL reduction). (A) One of three patients (33.3%) achieved a response. (B) Two of three patients (66.7%) achieved a response.

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5030 | ELAFIBRANOR-ASSOCIATED CHANGES IN PROTEINS LINKED TO MITOCHONDRIAL FUNCTION CORRELATE WITH FATIGUE IMPROVEMENT: PROTEOMIC RESULTS FROM THE ELATIVE® TRIAL

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Antunes[3] George Harb[3] Marwan Sleiman[2] Hugo Gomes da Silva[2] Andrew Mason[4], [1]Liver Unit, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada, [2]Ipsen, Paris, France, [3]Ipsen, Cambridge, MA, USA, [4]CEGIIR, University of Alberta, Edmonton, AB, Canada

Background: Fatigue, a common, debilitating symptom in patients (pts) with primary biliary cholangitis (PBC), has poorly understood pathophysiology. Elafibranor (ELA), a peroxisome proliferator-activated receptor (PPAR)α/δ agonist approved for PBC second-line treatment, has shown clinically meaningful improvements in fatigue. Expression levels of ten proteins associated with a potential role in fatigue or mitochondrial function were found to be impacted in pts treated with ELA (ATAD3B, BAX, CA14, CA5A, ECI1, GRPEL1, HPD, KYNU, MECR, SOD2).[1] Here, we examine the relationship between changes in expression of these proteins and fatigue severity with ELA. **Methods**: Serum samples were collected from pts in the phase III ELATIVE® trial (NCT04526665) at baseline (BL) and Week (W)52 and analyzed using the Olink® Explore HT proteomic panel. Spearman correlations were evaluated between Patient-Reported Outcome (PRO) Measurement Information System (PROMIS) Fatigue Short Form 7a (PFSF 7a), PBC-40 Fatigue domain (PBC-40 F), and expression levels of the ten proteins impacted by ELA treatment. Analyses were conducted in the overall population and in pts with BL moderate-to-severe (mod–sev) fatigue (PFSF 7a T-score ≥ 60 or PBC-40 F score ≥ 29). Proteins are reported by the names of their encoding genes. P values were not controlled for multiplicity. **Results**: Of 161 pts in ELATIVE®, samples were included from 119; 46 and 63 had BL mod–sev fatigue according to PFSF 7a and PBC-40 F, respectively. At BL, in the overall population, significant, moderate-to-strong correlations were observed between the expression of all proteins ($r = 0.29–0.89$; $p < 0.05$). In pts with BL mod–sev fatigue according to both PROs, expression of CA5A, ECI1, GRPEL1, KYNU, MECR, and SOD2 were significantly correlated with fatigue at BL ($r = 0.25–0.39$, $p < 0.05$). Of these pts treated with ELA (BL mod–sev fatigue: PFSF 7a: $n = 33$; PBC-40 F: $n = 41$), moderate-to-strong correlations ($r = 0.27–0.88$) were observed between expression changes from BL (CfB) to W52 of all proteins, which were all significant ($p < 0.05$) except for CA5A and ATAD3B, and MECR and CA14. In the 33 ELA-treated pts with BL mod–sev fatigue according to PFSF 7a, significant correlations between CfB to W52 in BAX, ECI1, GRPEL1, HPD, KYNU, MECR, and SOD2 expression and PFSF 7a were observed ($r = 0.35–0.54$, $p < 0.05$). CfB to W52 in SOD2 and PBC-40 F were significantly correlated in the 41 pts with BL mod–sev fatigue according to PBC-40 F ($r = 0.32$; $p < 0.05$). **Conclusion**: ELA treatment led to expression changes of proteins linked to fatigue or mitochondrial function, significantly correlated with each other and with fatigue improvement. This suggests that PPARα/δ agonism beneficially impacts fatigue-associated pathways linked to mitochondrial function, providing a foundation for further research into the mechanistic contribution of PPARα/δ agonism to fatigue improvement in PBC.

Reference: 1. Swain MG, et al. EASL 2025: Poster LBP-025.

Disclosures: Mark Swain: Gilead, Ipsen, Novo Nordisk, Advanz, Abbott: Advisor, GSK, Mirum, Boehringer Ingelheim: Advisor, Gilead, BMS, GSK, Cymabay, Intercept, Kowa: Grant/Research Support, Novo Nordisk, Pfizer, Ancella, Merck, Galectin: Grant/Research Support, Calliditas, Ipsen, Madrigal, Roche, Altimmune: Grant/Research Support, 89Bio, Inventiva, Boehringer Ingelheim: Grant/Research Support, Gilead: Speaking and Teaching, Ipsen: Speaking and Teaching, Maria del Pilar Schneider: IPSEN INNOVATION: Employee and shareholder of Ipsen, Pascale Plas: IPSEN: Employee, Jacquie Maignel: IPSEN: Employee, IPSEN: Stock – privately held company, Aurélie Martin: Nothing to Disclose, Lola Lecru: Nothing to Disclose, Nuno Antunes: Ipsen: Employee, Ipsen: Stock - publicly traded company, George Harb:, Marwan Sleiman:, Hugo Gomes da Silva:, Andrew Mason: No dislosure submitted

5031 | DISEASE CONTROL AS EVIDENCED BY LONGITUDINAL TRANSIENT ELASTOGRAPHY MEASUREMENTS IN THE ASSURE STUDY: 36 MONTHS OF TREATMENT WITH SELADELPAR IS ASSOCIATED WITH STABLE OR IMPROVED LIVER STIFFNESS IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS

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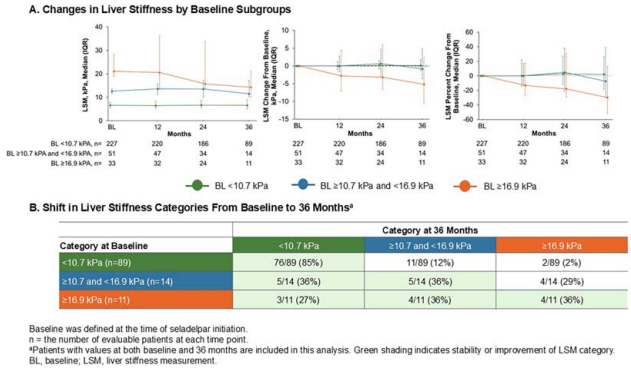
Blizard Institute, Queen Mary University of London, London, UK, [10]Seoul National University Bundang Hospital, Seoul National University, Seongnam, Korea, [11]Gilead Sciences, Inc., Foster City, CA, USA, [12]Echosens, Paris, France, [13]Miller School of Medicine, University of Miami, Miami, FL, USA

Background: Seladelpar (SEL) is a first-in-class delpar (PPAR-delta agonist) indicated for the treatment of primary biliary cholangitis (PBC) combined with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients intolerant to UDCA. While SEL's efficacy in improving cholestatic markers is well established, its impact on liver stiffness measurements (LSMs), which typically worsen over time in PBC, remains underexplored. We report longitudinal LSM data in patients treated with SEL for up to 36 months (M) in an interim analysis of the ongoing, open-label Phase 3 ASSURE study (NCT03301506). **Methods**: Patients enrolled in ASSURE from the placebo-controlled Phase 3 RESPONSE trial (NCT04620733) or earlier legacy SEL studies. LSM assessed by vibration-controlled transient elastography (FibroScan) was collected as an exploratory endpoint with local reads. This analysis included on-treatment LSM from patients with ≥ 1 post-baseline measurement, excluding values with a confirmed IQR/LSM ratio $>30\%$. Baseline was defined at the time of SEL initiation. Patients were stratified by baseline LSM categories: <10.7, ≥ 10.7 and <16.9, and ≥ 16.9 kPa. LSM changes were assessed at 12M, 24M, and 36M, with category shifts assessed at 36M. Due to the non-normal distribution of LSM values, medians were reported. Data cutoff: Jan 31, 2025. **Results**: A total of 311 patients were included in the analysis. LSM values at 36M were available in 114 patients. The overall median (IQR) LSM at baseline was 7.5 (5.9, 11.1) kPa. The median change in LSM was −0.2 (−1.7, 1.8) kPa, with a percent change of −2.9% (−22.8%, 25.9%). In patients with baseline LSM of <10.7 kPa, ≥ 10.7 and <16.9 kPa, or ≥ 16.9 kPa, median changes in LSM to 36M were +0.1 (−1.3, 1.8) kPa, −0.9 (−3.6, 4.8) kPa, and −5.2 (−10.6, 2.4) kPa, respectively (**Fig A**). Similarly, median percent changes from baseline were +2.0% (−18.3, 26.1), −7.4% (−29.5, 38.7), and −29.7% (−51.5, 12.7). For category shifts, most patients (97/114 [85%]) were stable or improved at 36M (**Fig B**). Patients whose LSM worsened by 30% or more from baseline were younger ($P<0.05$), with otherwise comparable characteristics. **Conclusion**: In this interim analysis, most patients maintained or improved their LSM category over 36M of SEL treatment. In the group at the highest risk for progression (≥ 16.9 kPa), there was a trend towards improvement with SEL.



B. Shift in Liver Stiffness Categories From Baseline to 36 Months[a]

Category at Baseline	Category at 36 Months: <10.7 kPa	≥10.7 and <16.9 kPa	≥16.9 kPa
<10.7 kPa (n=89)	76/89 (85%)	11/89 (12%)	2/89 (2%)
≥10.7 and <16.9 kPa (n=14)	5/14 (36%)	5/14 (36%)	4/14 (29%)
≥16.9 kPa (n=11)	3/11 (27%)	4/11 (36%)	4/11 (36%)

Baseline was defined at the time of seladelpar initiation.
n = the number of evaluable patients at each time point.
[a]Patients with values at both baseline and 36 months are included in this analysis. Green shading indicates stability or improvement of LSM category.
BL, baseline; LSM, liver stiffness measurement.

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5032 | NORMALIZATION OF HEPATIC COPPER LEVEL DETECTED BY ^{64}CU PET IMAGING IN MICE TREATED WITH PRIME EDITOR THAT PRECISELY CORRECTED *ATP7B* P.H1069Q MUTATION CAUSING WILSON DISEASE

David Waterman[1] Tiernan O'Malley[1] Shivangi Modi[1] Michelle O'Connor[1] Celia Chang[1] Weiyi Li[1] Luis Santos[1] Rowshon Alam[1] Jacob Stewart-Ornstein[1] Seth Alexander[1] Jon Winnay[1] Andrea De Erkenez[1] Jonathan Levy[1] Andrew Anzalone[1] Vivian Choi[1], [1]Prime Medicine

Background: Wilson disease (WD) is a monogenic disorder caused by *ATP7B* loss-of-function mutations,

leading to toxic copper accumulation and disrupted copper homeostasis. Current therapies are life-long, burdensome, and non-curative. Direct correction of WD causative mutations at their endogenous genomic loci in the liver offers a disease-modifying approach that could restore native gene regulation, ATP7B protein function and copper homeostasis, leading to improved organ function. Prime Editing enables precise correction of pathogenic *ATP7B* mutations back to the wild-type sequence without double-strand DNA breaks or bystander edits, including the prevalent p.H1069Q and p.R778L mutations, which together account for >40% of WD alleles in the US, EU and East Asia and Pacific region. **Methods**: We developed PM577a, a liver-targeted LNP-formulated Prime Editor (PE) designed to precisely correct the *ATP7B* p.H1069Q mutation. **Results**: In hepatocyte models containing the mutation, PM577a achieved efficient gene correction *in vitro*. In the humanized *ATP7B* p.H1069Q mouse model, PM577a demonstrated dose-dependent, precise editing exceeding 80% in hepatocytes, with durable correction accompanied by >75% reduction in hepatic copper. Furthermore, copper homeostasis in treated humanized mutant mice was rescued to wild-type mice levels as demonstrated by radiocopper challenge and positron emission tomography (PET), which was developed as a translational biomarker to bridge to study effects in human clinical studies. In nonhuman primates, a single dose of an *ATP7B* PE yielded stable editing >1 year post treatment, demonstrating long-term durability of edits at the endogenous locus. As a key safety measure, no off-target editing was detected across human hepatocytes and WD patient-derived cells. In addition, we are also advancing a PE targeting the *ATP7B* p.R778L mutation. Early *in vitro* and *in vivo* studies confirm robust correction of R778L alleles, supporting future expansion of Prime Editing therapies to patients with prevalent WD mutations. **Conclusion**: In conclusion, PM577a is a first-in-class Prime Editing therapeutic that is well tolerated with robust correction of the *ATP7B* p.H1069Q mutation, normalization of copper metabolism, and durable efficacy. Together, these efforts highlight the potential of Prime Editing as a disease-modifying gene editing therapy for Wilson disease patients. IND-enabling studies for PM577a are underway.

Disclosures: David Waterman: Prime Medicine Inc: Emp, Tiernan O'Malley: Prime Medicine: Employee, Shivangi Modi:, Michelle O'Connor:, Celia Chang:, Weiyi Li: Nothing to Disclose, Luis Santos:, Rowshon Alam: Nothing to Disclose, Jacob Stewart-Ornstein:, Seth Alexander: Prime Medicine: Employee and Shareholder of Prime Medicine, Jon Winnay:, Andrea De Erkenez:, Jonathan Levy:, Andrew Anzalone:, Vivian Choi: Prime Medicine: Employee

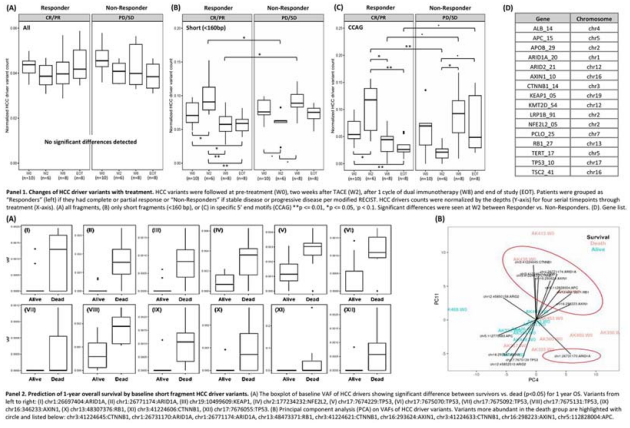
5033 | ABSTRACT WITHDRAWN

5034 | ctDNA DYNAMICS AS AN EARLY PREDICTOR OF TREATMENT RESPONSE AND SURVIVAL IN INTERMEDIATE-STAGE HEPATOCELLULAR CARCINOMA TREATED WITH TACE AND DURVALUMAB / TREMELIMUMAB

Amy Kim[1] Cinee Liu[2] Harry Luu[3] Boqun Zhu[3] Selena Lin[4] Zhili Wang[4] Mark Yarchoan[1] Marina Baretti[1] Won Jin Ho[3] Claire Brookmeyer[3] James Hamilton[5] Robert Liddell[3] Christos Georgiades[3] Kelvin Hong[3] Ana De Jesus Acosta[3] Ying-Hsiu Su[2], [1]Johns Hopkins School of Medicine, [2]Baruch S. Blumberg Institute, [3]Johns Hopkins University School of Medicine, [4]JBS Science, [5]Johns Hopkins University

Background: Intermediate-stage hepatocellular carcinoma (HCC) is a therapeutic challenge, with transarterial chemoembolization (TACE) plus immunotherapy emerging as a promising strategy. Circulating tumor DNA (ctDNA) has been studied in early-stage disease, but biomarkers for treatment response and prognosis in intermediate-stage HCC remain lacking. This study evaluates ctDNA dynamics—integrating mutation profiles, fragment size (<160 bp), and HCC-preferential end motifs—as predictors of overall response rate (ORR) and 1-year overall survival (OS) in patients with BCLC stage B disease. **Methods**: We used serial blood samples from a Phase II clinical trial (NCT03638141) involving 20 patients with intermediate-stage HCC (BCLC B) who underwent TACE followed by dual immune checkpoint blockade with durvalumab and tremelimumab initiated 2 weeks after TACE. Plasma samples were collected at baseline, Week 2 (W2, post-TACE), Week 8 (W8, after one cycle of immunotherapy), and end of treatment (EOT). ctDNA driver mutations were analyzed using a 16-HCC-targeted gene panel by NGS with fragment size filtering (<160 bp) and HCC-preferential end motifs (eg CCAG) to enhance tumor-specific detection. Variant allele frequencies (VAFs) were assessed for association with 1-year OS, and ctDNA dynamics were stratified by treatment response (PR/CR vs. PD/SD) per mRECIST. Principal component analysis (PCA) explored mutation profiles related to survival outcomes. **Results**: Among the 20 patients, the ORR was 55% (11/20). Initial unfiltered ctDNA analysis could not distinguish responders (PR/CR) from non-responders (PD/SD). However, fragment size filtering (<160 bp) revealed distinct

ctDNA dynamics between the groups (Panel 1B). Responders showed a significant rise in ctDNA at W2, likely due to TACE-induced tumor cell death, followed by declines at EOT, coinciding with radiographic regression. In contrast, non-responders showed transient decreases in ctDNA at W2, with no further changes by EOT, reflecting limited tumor regression. Incorporating HCC-preferential end motifs (e.g., CCAG) improved early identification of treatment response, similar to size-based filtration (Panel 1C). Baseline ctDNA VAFs were significantly associated with 1-year OS ($p < 0.05$), with mutations in TP53, ARID1A, KEAP1, and NFE2L2 enriched in non-survivors, suggesting aggressive tumor biology (Panel 2A). PCA further stratified survival groups, identifying CTNNB1, ARID1A, RB1, AXIN1, and APC mutations as primary drivers of poor prognosis. **Conclusion**: Early ctDNA dynamics, refined by size filtering and end motifs, may provide robust biomarkers of treatment response detectable within 2 weeks of TACE. This approach identifies responders to TACE-immunotherapy before radiographic assessment. Baseline ctDNA also reveals mutations linked to overall survival, supporting its role in risk stratification and outcome prediction in intermediate-stage HCC.



Panel 1. Changes of HCC driver variants with treatment. HCC variants were followed at pre-treatment (W0), two weeks after TACE (W2), after 1 cycle of dual immunotherapy (W8) and end of study (EOT). Patients were grouped as "Responders" (left) if they had complete or partial response or "Non-Responders" if stable disease or progressive disease per modified RECIST. HCC drivers counts were normalized by the depths (Y axis) for four serial timepoints through treatment (X-axis). (A) all fragments, (B) only short fragments (<160 bp), or (C) in specific 5' end motifs (CCAG) **p <= 0.01, *p <= 0.05, p < 0.1. Significant differences were seen at W2 between Responder vs. Non-Responders. (D). Gene list.

Panel 2. Prediction of 1-year overall survival by baseline short fragment HCC driver variants. (A) The boxplot of baseline VAF of HCC drivers showing significant difference between survivors vs. dead (p<0.05) for 1 year OS. Variants from left to right: (I) chr1:26697404:ARID1A, (II) chr1:26771174:ARID1A, (III) chr19:10499609:KEAP1, (IV) chr2:177234232:NFE2L2, (V) chr17:7674229:TP53, (VI) chr17:7675070:TP53, (VII) chr17:7675092:TP53, (VIII) chr17:7675131:TP53, (IX) chr16:346233:AXIN1, (X) chr13:48307376:RB1, (XI) chr5:41224606:CTNNB1, (XII) chr17:7676055:TP53. (B) Principal component analysis (PCA) on VAFs of HCC driver variants. Variants more abundant in the death group are highlighted with circle and listed below: chr3:41224645:CTNNB1, chr1:26731170:ARID1A, chr1:26771174:ARID1A, chr13:48473371:RB1, chr3:41224621:CTNNB1, chr16:293624:AXIN1, chr3:41223633:CTNNB1, chr16:298223:AXIN1, chr5:112828004:APC.

Disclosures: Amy Kim: AstraZeneca: Speaking and Teaching, Cinee Liu:, Harry Luu: Nothing to Disclose, Boqun Zhu: Nothing to Disclose, Selena Lin: Nothing to Disclose, Zhili Wang:, Mark Yarchoan: Genentech: Grant/Research Support, Genentech: Consultant, Exelixis: Consultant, Incyte: Grant/Research Support, Astrazeneca: Consultant, Lantheus: Consultant, Adventris: Cofounder with equity, Marina Baretti:, Won Jin Ho:, Claire Brookmeyer: Nothing to Disclose, James Hamilton: orphalan pharmaceuticals: Advisor, Robert Liddell: Nothing to Disclose, Christos Georgiades: Nothing to Disclose, Kelvin Hong:, Ana De Jesus Acosta: Nothing to Disclose, Ying-Hsiu Su: Nothing to Disclose

5035 | HbA_{1c}-INDEPENDENT BENEFITS OF SEMAGLUTIDE ON LIVER HISTOLOGY AND NON-INVASIVE TESTS IN PARTICIPANTS WITH BIOPSY-DEFINED MASH: INSIGHTS FROM POST-HOC ANALYSIS OF THE ESSENCE TRIAL PART 1

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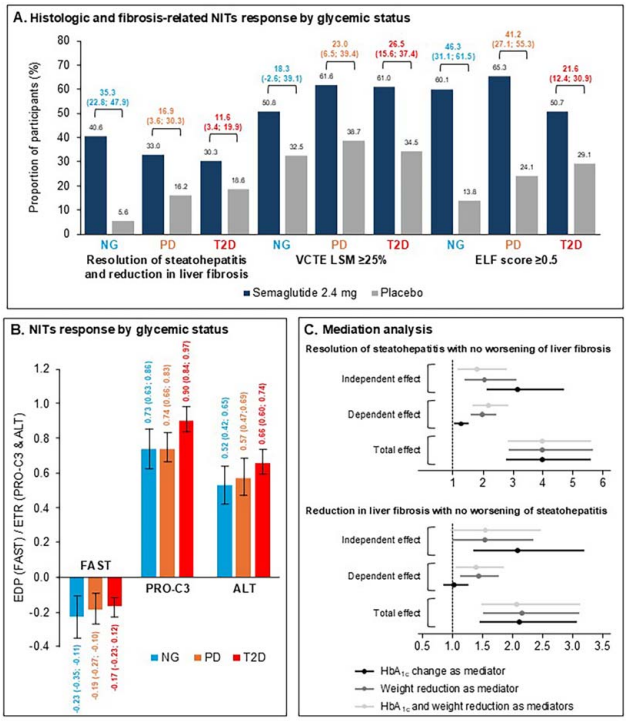
Background: Glycemic dysregulation predicts liver disease severity, highlighting complexities in managing metabolic dysfunction–associated steatohepatitis (MASH) and diabetes. This post hoc analysis of the ESSENCE trial (NCT04822181) assessed the effects of baseline (BL) glycemia on histology and non-invasive tests (NIT), and HbA_{1c} change on histology with semaglutide 2.4 mg treatment vs placebo. **Methods:** To assess the impact of BL glycemia, participants were stratified into three groups: Normoglycemia (investigator-assessed [I-A] non-type 2 diabetes [T2D] and BL $HbA_{1c} \leq 5.6\%$); prediabetes (IA T2D and BL HbA_{1c} 5.7–6.4%); T2D (IA T2D and BL $HbA_{1c} \geq 6.5\%$). Proportions of participants achieving response at 72 weeks were evaluated, defined as histologic resolution of steatohepatitis and reduction in liver fibrosis, $\geq 25\%$ decrease from BL in liver stiffness measurement by vibration-controlled transient elastography (VCTE LSM) and ≥ 0.5 units decrease from BL in enhanced liver fibrosis (ELF) score. Changes in FibroScan-AST (FAST) score, alanine aminotransferase (ALT) and N-terminal propeptide of type III collagen (PRO-C3) were assessed as continuous endpoints. Mediation analysis assessed the effects of change in HbA_{1c} on resolution of steatohepatitis with no worsening of liver fibrosis, and reduction in liver fibrosis with no worsening of steatohepatitis with treatment as exposure and HbA_{1c} change from BL to week 72 as

mediator. Responder proportions for these endpoints were previously reported[1]. **Results:** Across nearly all BL glycemia groups, differences in responder proportions favoured semaglutide for histology and NITs (**Figure, A**). Semaglutide showed positive effects on FAST score, PRO-C3 and ALT across all glycemia groups (**Figure, B**). Total effects of semaglutide (odds ratio [95% confidence interval]) for resolution of steatohepatitis with no worsening of liver fibrosis, and reduction in liver fibrosis with no worsening of steatohepatitis were 4.0 (2.8–5.6) and 2.1 (1.5–3.1), respectively (**Figure, C**). The corresponding HbA_{1c} change-independent effects were 3.2 (2.1–4.7) and 2.1 (1.4–3.2), whilst HbA_{1c} change-dependent effects were 1.3 (1.0–1.5) and 1.0 (0.8–1.3). **Conclusion:** Semaglutide demonstrated histologic improvements independent of changes in HbA_{1c} during treatment. Irrespective of BL glycemic status, semaglutide showed better histologic and NIT responses vs placebo. **Reference**: [1]Bugianesi E, et al. Presentation at EASD; Sep 15–19, 2025, Vienna, Austria.



Panel A. Numbers shown above the bars represent EDP (95% CI). Panel B. Numbers shown above the bars represent ETR (95% CI) for PRO-C3 and ALT. Numbers shown below the bars represent EDP (95% CI) for FAST score. Vertical bars indicate 95% CIs. Panel C. Mediation analysis assessed the effects of change in HbA_{1c} on histology using treatment as exposure and HbA_{1c} change from baseline to week 72 as mediator. The total change, HbA_{1c} change-independent and HbA_{1c} change-dependent effect sizes are calculated as odds ratios. Data are also presented for weight reduction and HbA_{1c} change combined with weight reduction as mediators. ALT, alanine aminotransferase; CI,confidence interval; EDP, estimated difference in responder proportions; ELF, Enhanced Liver Fibrosis; ETR, estimated treatment ratio; FAST, FibroScan-AST; LSM, liver stiffness measurement; NG, normoglycemia; PD, prediabetes; PRO-C3, N-terminal propeptide of type III collagen; T2D, type 2 diabetes; VCTE, vibration-controlled transient elastography.

Disclosures: Arun Sanyal: Genfit, Akarna, Tiziana, Durect, Inversago, Hemoshear, North: Stock - publicly traded company, Astra Zeneca (<5K), Terns (<5K), Merck (<5K),: Consultant, Boehringer Ingelheim (5-10K), Lilly (5-10K), Novartis (<5K),: Consultant, Novo Nordisk: Consultant, Regeneron (<5K), Alnylam (<5K), Akero (<5K),: Consultant, Tern (<5K), Histoindex (<5K), Corcept (<5K),: Consultant, Path AI (<5K), Genfit (<5K), Mediar (<5K),: Consultant, Satellite Bio (<5K), Echosens (<5K), Abbott (<5K),: Consultant, Promed (<5K), Glaxo Smith Kline (~11K), Arrowhead (<5K): Consultant, Zydus (>60K), Boston Pharmaceutical (<5K), Myovent (<5K),: Consultant, Variant (<5K), Cascade (<5K), Northsea (<5K): Consultant, Gilead, Salix, Tobira, Bristol Myers, Shire,. Intercept,: Institution has received grants from above companies, Merck, Astra Zenca, Mallinckrodt, Novartis: Institution has received grants from above companies, UpToDate, Elseiver: Royalties or patent beneficiary, Sanyal Bio: Employee, Histoindex: Advisor, pliant: Consultant, chemomab: Consultant, Aligos: Consultant, Avant Sante: Advisor, Takeda: Consultant, Eli Lilly: Advisor, 89Bio: Advisor, Boston Pharma: Advisor, GSK: Advisor, Akero: Advisor, Eli Lilly, Echosens, Abbott, Promed, Genfit, Satellite Bio,: Consultant, Corcept, Arrowhead, Boston Pharmaceuticals, Variant,: Consultant, Cascade, 89 Bio, AstraZeneca, Alnylam, Regeneron: Consultant, Boehringer Ingelheim Bristol Myers Squibb, Genetech, Gilead: Consultant, Histoindex, Janssen, Lipocine, Madrigal, Merck, GSK,: Consultant, Niovartis, Akero, Novo Nordisk, Path AI, Pfizer, Poxel: Consultant, Salix, Myovant, Median Technologies, Sequana, Surrozen: Consultant, Takeda, Terns, Zydus: Consultant, AstraZeneca, Bristol Myers Squibb, Gilead, Intercept: His institution has received grants from:, Mallinckrodt, Merck, Ocelot, Novartis, Salix: His institution has received grants from:, UpToDate, Elsevier: Royalties or patent beneficiary, Durect, Genfit, Tiziana, Inverage: Stock – privately held company, Elisabetta Bugianesi: Nothing to Disclose, M.T. Arias-Loste: Nothing to Disclose, L. Castera:, Nathalie Eklöf: Novo Nordisk A/S: Employee, W. Kim: Nothing to Disclose, Niels Krarup: Novo Nordisk: Employee, Bernhard Ludvik: Nothing to Disclose, P. Newsome:, V. Ratziu:, M. Rinella:, A. Trifan:, Thea Vestergaard: Novo Nordisk: Employee, Michael Roden: Astra Zeneca: Speaking and Teaching, Boehringer Ingelheim: Grant/Research Support, Echosens: Advisor, Eli LIlly: Speaking and Teaching, Madrigal: Speaking and Teaching, MSD Merck: Advisor, Novo: Consultant, Synlab: Speaking and Teaching, Target RWE: Advisor

5036 | CHRONIC HEPATITIS B VIRUS INFECTED PARTICIPANTS RESPONDING TO PRIOR BRII-179 TREATMENT ACHIEVED HIGHER RATE OF SUSTAINED HEPATITIS B VIRUS SURFACE ANTIGEN LOSS ON ELEBSIRAN PLUS PEGYLATED INTERFERON ALFA: FOLLOW-UP DATA FROM ENSURE STUDY

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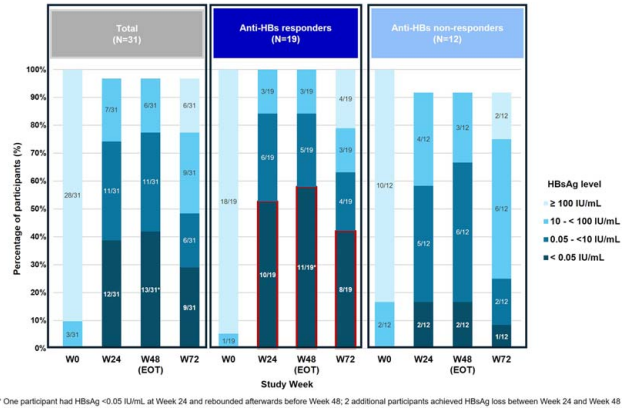
Background: In a previously completed phase (ph) 2 study (NCT04749368), therapeutic vaccine BRII-179 induced robust hepatitis B virus (HBV) specific immune responses in approximately 60% of participants. We proposed that patients who were able to generate HBV surface antibody (anti-HBs) following BRII-179 treatment, might have a less impaired intrinsic immune profile and be more responsive to curative therapies. Preliminary end of treatment (EOT) data from the ENSURE study (NCT05970289) have been published. Here, we summarize 24 weeks post EOT follow-up results, focusing on sustained HBV surface antigen (HBsAg) loss. **Methods**: Eligible participants who completed BRII-179 and elebsiran in a previous study were enrolled into this open-label ph2 ENSURE study. Participants received elebsiran 100 mg plus pegylated interferon alfa (PEG-IFNα) over a 48-week treatment period and were followed for 24 weeks after EOT. The participants with sustained HBsAg loss at 24 weeks post EOT will discontinue nucleos(t)ide analogues and enter another 24 weeks of follow-up. Participants were categorized as BRII-179 anti-HBs responders or non-responders based on peak anti-HBs titer $\geq$ 10 IU/L or $<$ 10 IU/L in the previous study. **Results**: 31 participants were enrolled, with 19 BRII-179 anti-HBs responders and 12 non-responders. Median [range] HBsAg at baseline was numerically higher in anti-HBs responders (520 [34-2165] IU/mL including one $<$100 IU/mL) than in non-responders (185 [51-672] IU/mL including two $<$100 IU/mL). At 24 weeks post EOT, 9/31 participants achieved HBsAg loss, with a notably higher rate in anti-HBs responders (8/19, 42.1%) than non-responders (1/12, 8.3%) (Figure). Although all participants with sustained HBsAg loss had HBsAg $<$ 1500 IU/mL at baseline of this ENSURE study, 4/8 (50.0%) from anti-HBs responders had baseline HBsAg ranging from 1514-3086 IU/mL when enrolled in the previous study, suggesting that BRII-179 may induce anti-HBs responses regardless of baseline HBsAg level. Elebsiran + PEG-IFNα was generally safe and well tolerated. The majority of adverse events were consistent with the known side effects of PEG-IFNα and recovered after EOT. **Conclusion**: The participants who developed anti-HBs responses following BRII-179 treatment exhibited a substantially higher rate of sustained HBsAg loss when treated with elebsiran plus PEG-IFNα. These data suggest that BRII-179-induced immune responses may help to identify and select a patient population more likely to benefit from curative treatments. Confirmatory studies are ongoing.



Disclosures: Ke Cao: Brii Biosciences (Beijing) Co. Limited: Employee, Grace Lai-Hung Wong: Advisory committee member: AstraZeneca, Barinthus Bio: Consultant, Abbott, AbbVie, Bristol-Myers Squibb, Echosens, Ferring,: Speaking and Teaching, Gilead Sciences, GlaxoSmithKline, Janssen, and Roche: Speaking and Teaching, Gilead Sciences, GlaxoSmithKline, Janssen and Virion: Consultant, Gilead Sciences: Grant/Research Support, Apinya Leerapun:, YOUNG-SUK LIM: Nothing to Disclose, PISIT TANGKIJVANICH:, Mark Douglas: Gilead Sciences: Advisor, GSK: Speaking and Teaching, Roche Diagnostics: Speaking and Teaching, GSK: Advisor, Gilead Sciences: Grant/Research Support, Suparat Khemnark:, Witsarut Manasirisuk: Nothing to Disclose, Teerha Piratvisuth: Sysmex: Grant/Research Support, GSK: Grant/Research Support, ROCHE: Speaking and Teaching, EISAI: Speaking and Teaching, ASTRAZENECA: Speaking and Teaching, NOVOTECH: Grant/Research Support, JANSSEN: Grant/Research Support, Martin Weltman: Ipsen: Advisor, Chiesi: Speaking and Teaching, Gilead: Advisor, Falk: Speaking and Teaching, Chong Zhu: Brii Biosciences: Employee, Alex Tian:, Xiaofei Chen: *Briibiosciences: Employee, David Margolis:, Qing Zhu: Nothing to Disclose, Man-Fung Yuen: AbbVie, Abbott Diagnotics, Aligos Therapeutics: Consultant, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosc: Consultant, Clear B Therapeutics, Dicerna Pharmaceuticals: Consultant, Fujirebio Incorporation, GlaxoSmithKline, 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: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Immunocore: Grant/Research Support, Sysmex Corporation and Roche: Grant/Research Support, Fujirebio Incorporation, Gilead Sciences, Roche,

Sysmex Corp: Speaking and Teaching, Precision BioSciences: consultancy, Ausperbio: consultancy, IntergerBio: consultancy, Tune Therapeutics: consultancy

5037 | REAL-WORLD EXPERIENCE OF SELADELPAR AMONG PATIENTS WITH PRIMARY BILIARY CHOLANGITIS INCLUDING PATIENTS SWITCHED FROM OBETICHOLIC ACID

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Background: Primary biliary cholangitis (PBC) is a progressive autoimmune liver disease. Obeticholic acid (OCA) was recently withdrawn from the US creating a therapeutic gap. Seladelpar (SEL), approved in 2024 for patients with PBC and an inadequate response or intolerance to ursodeoxycholic acid (UDCA), offers a new treatment option. This study aims to characterize the real-world experiences of patients switching from OCA to SEL vs adding on to UDCA or monotherapy use. **Methods**: Patients with PBC who received $>=1$ prescription and $>=30$ days of supply for SEL were identified in the HealthVerity database with laboratory data from LabCorp and Quest. Baseline (BL) characteristics and laboratories were assessed using the most recent tests during the 12 months preceding the SEL initiation. SEL treatment duration was determined in patients switched from OCA within 3 months of SEL (OCA-switch) or starting SEL as add on to UDCA or as monotherapy without use of UDCA, OCA, fenofibrate, or elafibranor for $>$ 3 months prior to SEL (SEL-2L), using all available data as of 13 Jun 2025. Biochemical response was assessed using the most recent available lab data. Safety labs were assessed based on the most recent tests available within 90 days prior to SEL initiation vs within 90 days after any SEL treatment. **Results**: A total of 396 PBC patients initiated SEL including 130 OCA-switch and 266 SEL-2L patients. The 2 groups had comparable sex distribution (88% vs 91% female) and mean age (59 vs 58 years) at the time of SEL initiation. Cirrhosis was observed in 11.5% and 18.5% of OCA-switch and SEL-2L patients, respectively. In OCA-switch group, the mean duration of prior OCA treatment was 788 days; mean time between last OCA use and the initiation of SEL was 8 days. Mean duration of SEL treatment was 119 days in the OCA-switch group and 98 days in SEL-2L. In patients switching from OCA, mean alkaline phosphatase (ALP) decreased from 235 U/L at BL to 171 U/L. In the SEL-2L group, ALP decreased from 290 U/L at BL to 194 U/L. ALP $<1.67\times$ULN was observed in 55% at BL and 83% post SEL in OCA-switch patients and, similarly, 53% at BL and 74% post SEL in SEL-2L patients. Safety labs within 90 days prior to SEL initiation vs after were generally similar between the groups. 93% of patients maintained continuous SEL treatment from initiation until the end of the observation period. **Conclusion**: These real-world experiences suggest SEL may be an effective and safe alternative for patients switching from OCA and as a second-line therapy. Given the relatively short SEL observation period, further evaluation with extended follow-up is warranted.

Table 1. Baseline characteristics, biochemical results, and safety labs of patients with PBC who switch from obeticholic acid to seladelpar, or add seladelpar on to ursodeoxycholic acid or monotherapy use

	OCA to SEL switch group (OCA-switch, N=130)		SEL +/- UDCA group (SEL-2L, N=266)	
Baseline characteristics				
Mean age (SD)	58.8 (11.9)		58.3 (10.8)	
Female, n (%)	114 (87.7)		241 (90.6)	
Duration of PBC, years, mean (SD)	5.6 (2.9)		3.3 (2.9)	
Cirrhosis, n (%)	15 (11.5)		49 (18.4)	
Autoimmune hepatitis, n (%)	10 (7.7)		24 (9.0)	
MASH, n (%)	6 (4.6)		19 (7.1)	
MASLD, n (%)	33 (25.4)		85 (32.0)	
UDCA use, n (%)	112 (86.2)		221 (83.1)	
Duration of UDCA use prior to SEL, days, mean (SD)	924 (950)		874 (829)	
Duration of OCA use, days, mean (SD)	788 (827)		-	
Duration of SEL use, days, mean (SD)	119 (68)		98 (64)	
Interval between last OCA treatment and SEL initiation, days, mean (SD)	8 (18)		-	
Biochemical Results (where available*)	**Prior to SEL**	**After SEL**	**Prior to SEL**	**After SEL**
ALP [U/L], mean (SD)	234.9 (94.1)	171.0 (73.2)	289.9 (223.5)	194.3 (147.2)
ALP level ≥1.67xULN, n (%)	19 (45.2)	5 (16.7)	47 (47.5)	14 (25.5)
ALP level <1.67xULN, n (%)	23 (54.8.)	25 (83.3)	52 (52.5)	41 (74.5)
ALP ≤1xULN, n (%)	4 (9.6)	9 (30.0)	10 (10.1)	17 (30.9)
TB [mg/dL], mean (SD)	0.6 (0.2)	0.6 (0.3)	0.8 (0.7)	0.6 (0.4)
TB >1xULN, n (%)	1 (2.6)	1 (3.3)	10 (10.1)	6 (11.1)
ALT [U/L], mean (SD)	46.3 (36.1)	44.3 (36.8)	47.9 (50.4)	35.8 (23.3)
ALT >1xULN, n (%)	22 (56.4)	15 (50.0)	52 (52.5)	26 (47.3)
AST [U/L], mean (SD)	39.3 (20.7)	43.1 (23.9)	45.1 (30.1)	39.1 (22.0)
AST >1xULN, n (%)	16 (41.0)	16 (53.3)	44 (44.4)	20 (36.4)
GGT [U/L], mean (SD)	98.8 (78.0)	121.5 (72.7)	211.1 (342.0)	101.2 (103.5)
GGT >1 x ULN, n (%)	8 (57.1)	6 (54.5)	29 (69.0)	9 (50.0)
Safety Labs (where available*)				
ALT or AST > 3x ULN, n (%)	2 (1.5)	2 (1.5)	7 (2.6)	2 (0.8)
eGFR (mL/min/1.73 m2), Mean (SD)	90.6 (18.6)	88.8 (20.2)	91.4 (17.4)	91.7 (17.7)
Creatine Kinase >1xULN, n (%)	1 (0.8)	0 (0.0)	4 (1.5)	4 (1.5)

* Not all patients had labs available; percentages are presented as the percentage based on number of total patients with available biochemical results

MASH: metabolic dysfunction-associated steatohepatitis; MASLD: metabolic dysfunction-associated steatotic liver disease; UDCA: ursodeoxycholic acid; OCA: obeticholic acid; ALP: alkaline phosphatase; TB: total bilirubin; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; eGFR: estimated glomerular filtration rate

Disclosures: Christopher Bowlus: No dislosure submitted, Stuart Gordon:, Theo Beltran: Gilead Sciences: Consultant, Gilead Sciences: Consultant, Rongjun Shen: Gilead Sciences: Employee, Fang Xia: Gilead Sciences: Employee, Nirali Kotowsky: Gilead: Employee, GSK: Employee, Daria Crittenden:, Catherine Frenette: Gilead Sciences, Inc.: Employee, Gilead Sciences, Inc.: Stock - publicly traded company, Grace Chee: Gilead Sciences: Employee, Steve Gao: Nothing to Disclose

5038 | A REAL-WORLD, MULTICENTER, PHASE 4 STUDY TO EVALUATE THE SAFETY AND EFFICACY OF SAROGLITAZAR 4 MG IN INDIAN PATIENTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE AND ASSOCIATED METABOLIC COMORBIDITIES

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Background: Non-alcoholic fatty liver disease (NAFLD) has emerged as a major global health challenge, with prevalence estimates ranging from 13% to 32% worldwide and up to 28% in Asian populations, including India. Closely associated with obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia, NAFLD is now recognized as the hepatic component of the metabolic syndrome. Saroglitazar, a dual PPAR α/γ agonist, is approved in India for the treatment of NAFLD and non-cirrhotic NASH. While clinical trials have demonstrated its efficacy, real-world data reflecting day-to-day clinical use remain limited. This real-world evidence (RWE) Phase 4 study was initiated to evaluate the safety and effectiveness of Saroglitazar 4 mg in Indian patients with NAFLD and metabolic comorbidities under routine practice conditions. **Methods**: This is an ongoing, prospective, open-label, multicenter, single-arm real-world evidence (RWE) study conducted across India, with a planned enrollment of 1500 patients. Adults with NAFLD and at least one metabolic comorbidity (obesity, T2DM, dyslipidemia, or metabolic syndrome) were eligible if they had liver stiffness measurement (LSM) ≥ 8 kPa and/or serum ALT ≥ 45 U/L at screening (or FIB-4 score > 1.3 if LSM < 8 kPa). All patients received Saroglitazar 4 mg once daily for 52 weeks. Efficacy endpoints included changes in LSM, ALT, and AST from baseline to Weeks 24 and 52. Safety was assessed based on the frequency, severity, and relatedness of treatment-emergent adverse events (TEAEs). **Results**: As of the 20 June 2025 data cut-off, 1315 patients were screened and 1000 enrolled. The mean age was 45.2 $\pm$ 11.4 years, mean BMI was 30.2 $\pm$ 4.8 kg/m², and 69.7% were male. A total of 636 patients completed the Week 24 visit and 290 completed Week 52. Treatment with Saroglitazar 4 mg once daily led to consistent and statistically significant improvements in hepatic and biochemical parameters. At Week 24, liver stiffness (LSM) reduced from 10.2 to 8.0 kPa (mean change: –2.13; $p < 0.001$), ALT from 60.2 to 38.9 U/L (–21.3; $p < 0.001$), and AST from 49.6 to 38.8 U/L (–10.8; $p < 0.001$). These improvements were sustained at Week 52, with LSM declining further to 7.02 kPa, ALT to 36.0 U/L, and AST to 34.7 U/L (all $p < 0.001$). A total of 113 TEAEs were reported among 90 patients (9.0%), most of which were mild (94) or moderate (17) in severity; only 2 events were severe. Two serious adverse events occurred but were not attributed to Saroglitazar, and all TEAEs were resolved without long-term consequences. **Conclusion**: This interim analysis from a large, real-world evidence (RWE) Phase 4 study demonstrates that Saroglitazar 4 mg provides sustained improvements in liver stiffness and transaminase levels over 52 weeks in Indian patients with NAFLD and metabolic comorbidities. The treatment was well tolerated, with no new safety concerns. These findings support the use of Saroglitazar in routine clinical practice for the management of NAFLD in high-risk populations.

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UpToDate, Elsevier: Royalties or patent beneficiary, Durect, Genfit, Tiziana, Inverage: Stock – privately held company, Bhargav Darji: Nothing to Disclose

5039 | ABCB11 mRNA THERAPY FOR THE TREATMENT OF PROGRESSIVE FAMILIAL INTRAHEPATIC CHOLESTASIS TYPE 2 (PFIC2)

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Background: Progressive familial intrahepatic cholestasis type 2 (PFIC2) is an autosomal recessive liver disease caused by loss-of-function mutations in ABCB11, encoding the bile salt export pump (BSEP). BSEP deficiency leads to intrahepatic cholestasis with jaundice, pruritus, failure to thrive, and progression to liver failure and hepatocellular carcinoma in childhood. Current treatment options for PFIC2 have limited efficacy and are associated with numerous adverse effects. Liver transplantation remains the only curative therapy but carries substantial risk and morbidity. Conventional protein replacement is not feasible due to delivery barriers, and viral gene therapy faces hurdles in vector packaging limit, pre-existing neutralizing antibodies, and potential genotoxicity. We aimed to develop mRNA-based therapy for PFIC2. **Methods**: We engineered chemically modified, codon-optimized human ABCB11 (hABCB11) mRNA and formulated it in liver-directed lipid nanoparticles (LNPs). The therapeutic activity of hABCB11 mRNA was evaluated in transfected cells and in Abcb11−/− mice. Key endpoints included BSEP protein expression, bile acid-transporting activity, serum bile acids, liver enzymes, bilirubin, hepatic bile acids content, liver histopathology, and survival. hABCB11 variants generated by multi-species sequence alignment analysis and targeting consensus residues were screened for improved therapeutic activity. **Results**: hABCB11 mRNA led to robust BSEP expression and significant increase in bile acid transporting activity in transfected cells. Intravenous administration of hABCB11-mRNA-LNP in Abcb11-/- mice resulted in strong and sustained BSEP protein expression in liver and improved disease biomarkers, including reduction in serum bile acids levels. Repeat dosing of ABCB11-mRNA-LNP caused a sustained reduction in serum bile acid and liver enzymes, accompanied by a significant improvement in liver pathology. Screening top consensus residues-targeted hABCB11 variants led to identification of novel variants with improved therapeutic activity. **Conclusion**: These findings provide preclinical proof-of-concept that systemic delivery of ABCB11 mRNA-LNP restores BSEP function and improves biochemical and histopathological abnormalities of PFIC2 conditions. Protein engineering identified novel hABCB11 variants with enhanced potency, supporting further development of these optimized constructs.

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