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The Effect of Extracorporeal C3a Cellular Therapy in Severe Alcoholic Hepatitis-The Elad Trial

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Background: Alcoholic hepatitis (AH) results from hepatic inflammation, oxidative damage, cholestasis and apoptosis, all of which induce a vicious cycle that leads to liver and secondary organ failure associated with poor prognosis. **Study Design:** Vital Therapies' study VTI-208 was conducted in subjects with AH, using an extracorporeal hepatocellular therapy system (ELAD) containing human C3a hepatoma cells, to determine if ELAD can increase survival in AH. C3a cells express acute phase response and immune-modulatory proteins and growth factors and may provide anti-inflammatory therapy and support hepatocellular function in early stages of AH. **Inclusion/Exclusion Criteria:** Subjects >18yrs old with a clinical or histologic diagnosis of AH, bilirubin >8mg/dl, Maddrey DF >32, MELD ≤35, platelets ≥40,000, and without severe concomitant disease, uncontrolled sepsis or bleeding, hemodynamic instability or need for chronic dialysis. **Intervention:** Subjects were randomized to either 3-5 days continuous ELAD therapy plus standard of care (SOC) or to SOC alone. **Endpoint:** Overall survival (OS) assessed by Kaplan-Meier analysis. Pre-specified subgroups included subjects with MELD and age >/< baseline median. **Results:** From 2013-2015, 203 subjects were enrolled (96 ELAD and 107 SOC), at 40 sites worldwide. Comparison of baseline characteristics showed no significant differences between groups and within subgroups, including treatment with steroids or pentoxifylline. There was no significant difference in serious adverse events between groups and no unexpected serious adverse events were related to the cellular component. In an intent-to-treat (ITT) analysis, there was no significant difference in OS (52.1% vs 52.3%). Subgroup analysis showed strong trends toward improved OS in groups in which MELD or age were lower than baseline medians. The majority of subjects (n=120) presented with MELD <28 and in this group, ELAD was associated with a trend toward higher OS (71% vs 57%, p=0.077). A similar trend was seen in younger subjects (n=101) (67% vs 55%, p=0.167). Although not pre-specified, survival in subjects with a combination of MELD and age less than baseline median (n=59) was significantly better in ELAD than SOC (100% vs 73%, p=0.006) at 91 days. After 100 days, survival was fairly stable in all subject groups. **Conclusion:** There was no difference in OS between ELAD and SOC but there was a trend toward survival benefit in patients with MELD <28 or age <47 years. These data suggest ELAD may be a favorable AH treatment modality in younger patients with sufficient renal function and less severe coagulopathy. A study to confirm the survival benefit in this population is in preparation and is scheduled to start in 2016.

Disclosures:

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LB-2

A Phase 3 Double-Blind Placebo-Controlled Evaluation of Sofosbuvir/Velpatasvir Fixed Dose Combination for 12 Weeks in Naïve and Experienced Genotype 1, 2, 4, 5, 6 HCV Infected Patients with and without cirrhosis: Results of the ASTRAL-1 Study

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Introduction: Velpatasvir (VEL, GS-5816) is a pangenotypic HCV NS5A inhibitor. In Phase 2 studies, the combination of sofosbuvir (SOF) and VEL for 12 weeks resulted in high SVR12 in patients with genotype 1-6 HCV infection. This Phase 3 study evaluated treatment with a fixed dose combination of SOF/VEL for 12 weeks in patients with genotype 1, 2, 4, 5, or 6 HCV infection (ClinicalTrials.gov Identifier: NCT02201940). **Methods:** Patients with genotype 1, 2, 4, or 6 chronic HCV infection were randomized 5:1 to received SOF/VEL (400 mg /100 mg daily) or placebo for 12 weeks. Patients with genotype 5 infection were enrolled to the SOF/VEL treatment group. Patients with genotype 3 infection were evaluated in a separate study. The primary efficacy analysis was an evaluation of the superiority of SVR12 for the SOF/VEL-treated patients to a pre-specified SVR12 goal of 85%. Secondary endpoints included safety/tolerability, resistance, and additional efficacy outcomes. **Results:** 740 patients were enrolled at 81 sites in North America, Europe and Hong Kong: 60% male, 79% white, 30% IL28B CC genotype, 32% treatment-experienced (TE), and 19% compensated cirrhosis. Of the 624 patients treated with SOF/VEL, the genotype distribution was 53% GT1, 17% GT2, 19% GT4, 6% GT5 and 7% GT6. Overall SVR12 for SOF/VEL-treated patients was 99.0% (95% con-

confidence interval 97.9% to 99.6%) and the study met its primary efficacy endpoint ($p < 0.001$). SVR12 rates by HCV genotype are presented in the table. Two of 325 patients (0.6%) with genotype 1 infection, including 1 of 73 with cirrhosis, had virologic relapse: 1 genotype 1a treatment-naïve non-cirrhotic and 1 genotype 1b treatment-experienced with cirrhosis. No patients with genotype 2, 4, 5, or 6, including 48 with cirrhosis, had virologic failure. Four patients did not achieve SVR12 for non-virologic reasons (eg. lost to follow-up). Overall, the type, frequency and severity of AEs and laboratory abnormalities were similar in the SOF/VEL-treated patients compared with the 116 placebo-treated patients. Three patients discontinued treatment due to adverse events, 1 treated with SOF/VEL and 2 with placebo. One SOF/VEL-treated patient died from an unknown cause 8 days after completion of treatment. Fifteen (2.4%) SOF/VEL-treated patients and no placebo-treated patients experienced SAEs; none was assessed as related to study drug. **Conclusions:** Treatment with the once daily, all-oral, single tablet regimen of SOF/VEL for 12 weeks is well tolerated and results in high SVR12 rates in treatment-naïve and treatment-experienced genotype 1, 2, 4, 5, and 6 HCV-infected patients with and without cirrhosis.

HCV Genotype	Total (N = 624)	GT 1 (N = 328)	GT 2 (N = 104)	GT 4 (N = 116)	GT 5 (N = 35)	GT 6 (N = 41)
Cirrhosis %, (n/N)	19.4% (121/624)	22.3% (73/328)	9.6% (10/104)	23.3% (27/116)	14.3% (5/35)	14.6% (6/41)
SVR12 %, (n/N)	99.0% (618/624)	98.5% (323/328)	100.0% (104/104)	100.0% (116/116)	97.1% (34/35)	100.0% (41/41)

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LB-3

All-Oral Treatment With Daclatasvir (DCV) Plus Sofosbuvir (SOF) Plus Ribavirin (RBV) for 12 or 16 Weeks in HCV Genotype (GT) 3-Infected Patients With Advanced Fibrosis or Cirrhosis: The ALLY-3+ Phase 3 Study

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Background: HCV GT3-infected patients are a challenging population in urgent need of optimally effective therapies. In a previous study in GT3 infection (ALLY-3), 12 weeks of DCV (pangenotypic NS5A inhibitor) plus SOF (nucleoside NS5B inhibitor) achieved 96% sustained virologic response at post-treatment week 12 (SVR12) in patients without cirrhosis and 63% in patients with cirrhosis. In ALLY-3+, the efficacy and safety of DCV+SOF with RBV for 12 vs 16 weeks were evaluated in HCV GT3 patients with compensated advanced fibrosis or cirrhosis. **Methods:** Open-label, phase 3b study in HCV GT3-infected treatment-naïve or -experienced patients with compensated advanced fibrosis or cirrhosis. Patients were randomized 1:1 to receive 12 weeks vs 16 weeks of DCV (60 mg QD) + SOF (400 mg QD) + RBV (weight based), stratified by advanced fibrosis or cirrhosis status. An interim analysis of efficacy (SVR at posttreatment week 4 [SVR4]) and safety outcomes is reported. SVR12 (primary endpoint) data will be available for presentation. **Results:** 50 patients were treated (12 weeks, 24; 16 weeks, 26). Most were male (80%), white (98%), and treatment experienced (74%; 10% prior relapse on SOF+RBV); 72% had cirrhosis and 52% had HCV RNA ≥ 6 million IU/mL. Baseline characteristics were comparable between arms. Overall SVR4 by intention-to-treat analysis was 92%. In the 12- and 16-week arms, SVR4 was 88% and 96%, respectively. In the 12-week arm SVR4 was 83% in those with cirrhosis and 100% in those with advanced fibrosis; in the 16-week arm SVR4 was 94%, and 100%, respectively (Table). There were no virologic breakthroughs. Relapse occurred in 3 patients (1 in 16-week and 2 in 12-week arm). Four of 5 patients (80%) with prior relapse on SOF+RBV achieved SVR4. There was 1 death (12-week arm; not treatment-related). Treatment was well tolerated - the most common adverse events (AEs) were insomnia (30%), fatigue (26%) and headache (24%). One patient had a grade 3 hemoglobin reduction. There were no discontinuations due to AEs or treatment-related serious AEs. **Conclusion:** DCV+SOF+RBV for 12 or 16 weeks achieved high SVR4 rates of 88% and 96%, respectively, in HCV GT3-infected patients with

compensated advanced fibrosis or cirrhosis, and was generally safe and well tolerated.

n (%)	12 weeks n=24	16 weeks n=26
SVR4 ^a	21 (88)	25 (96)
in advanced fibrosis ^b	6/6 (100)	8/8 (100)
in cirrhosis ^b	15/18 (83)	17/18 (94)
Virologic breakthrough	0	0
Relapse	2 (8)	1 (4)
Death ^c	1 (4)	0

^a HCV RNA <LLOQ_{TD/TND} (next-observation-carried-backward for missing data at posttreatment week 4).
^b n/N (%); categories were based on biopsy or FibroScan data.
^c Not related to treatment.

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LB-4

High Virologic Response Rate in Egyptian HCV-Genotype 4 Patients Treated with Ravidasvir (PPI-668) and Sofosbuvir: Results of a Large Multicenter Phase 3 Registrational Trial

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BACKGROUND: Egypt has the highest prevalence of hepatitis C infection in the world, of which 90% is due to HCV genotype-4 (gt-4). Increasing HCV-related morbidity in Egypt presents an urgent need for highly curative, safe and affordable therapies. We report results from a Phase 3 registrational trial in Egyptian HCV gt-4 patients, assessing the combination

of ravidasvir (RDV), a pan-genotypic HCV NS5A inhibitor, and sofosbuvir (SOF), a nucleotide HCV NS5B polymerase inhibitor, with or without ribavirin (RBV). **METHODS:** Key inclusion criteria were age 18-65 yr, HCV gt-4 infection, serum HCV RNA >4 log₁₀ IU/mL, and absence of decompensated cirrhosis or other causes of liver disease. Patients were enrolled into 3 groups: treatment-naïve non-cirrhotic and cirrhotic, by Fibroscan & FIB-4 score (Group 1); interferon (IFN)-experienced non-cirrhotic (Group 2); and IFN-experienced cirrhotic (Group 3). Groups 1 and 2 were treated with RDV 200 mg QD + SOF 400 mg QD for 12 wk, randomized 1:1 to additional RBV (weight-based) or no RBV. Group 3 patients all received RDV+SOF+RBV and were randomized 1:1 to 12 wk vs. 16 wk of treatment. The primary endpoint is sustained virologic response (SVR), defined as serum HCV RNA below the lower limit of detection (LLD <12 IU/mL by the Abbott Real-Time™ PCR assay) at 12 wk post-treatment (SVR12). **RESULTS:** This study is fully enrolled with 300 patients (150 in Group 1, 80 in Group 2, and 70 in Group 3); 284 patients had completed treatment at the time of this abstract. Study treatment has been generally well tolerated, with one serious adverse event possibly attributed to study drug (transient episode of symptomatic bradycardia). The most common adverse events are headache and fatigue. HCV RNA decreased by ~6 logs in all groups by Wk 1, with 94% of patients HCV RNA undetectable by Wk 4. Of the 265 patients who have reached 4 wk post-treatment, 262 (99%) had RNA <LLD (SVR4); also, 236 of 242 (98%) have achieved SVR8 and 176 of 182 (97%) have achieved SVR12 to date. The addition of RBV did not improve response. The 6 treatment failures are all cirrhotic patients, one patient had only 8 weeks of treatment due to the bradycardia episode, and 5 patients relapsed after completing treatment. None of the non-cirrhotic patients have experienced a virologic relapse. Near-final SVR4, SVR8 and SVR12 data will be presented during the meeting. **Conclusions:** To our knowledge, this is the largest IFN-free clinical trial in HCV gt-4 patients. Treatment with RDV+SOF±RBV has been well-tolerated and shows high sustained response rates in a large population of Egyptian patients, regardless of previous treatment status or underlying cirrhosis.

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LB-5

Incidence and Determinants of Denial of DAA Treatment for Chronic HCV Infection by Insurance Type During the First 6 Months of the Modern HCV Treatment Era

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Background: The high costs of direct-acting antiviral (DAA) agents to treat chronic HCV infection have resulted in denials and delays in the receipt of these therapies. We sought to: 1) determine the incidence and determinants of denial of a DAA prescription among US chronic HCV-infected patients, according to type of insurance (US Medicaid, US Medicare, commercial insurance), and 2) ascertain the time to DAA prescription fill. **Methods:** We conducted a prospective cohort study among chronic HCV-infected patients who had a DAA prescription submitted between November 1, 2014 and April 30, 2015 to two specialty pharmacies (Burmans Specialty Pharmacy and Penn Presbyterian Medical Center) serving PA, NJ, DE, and MD. The incidence of absolute denial of the prescription, defined as no fill (even after appeal), was calculated for the overall cohort and by insurance type. Multivariable logistic regression was used to determine adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for associations between patient characteristics and absolute denial. Hypothesized determinants of absolute denial included insurance type, absence of cirrhosis, and HIV coinfection. For all approved prescriptions, we determined the time to fill, defined as the interval between the date of prescription and date of approval, by type of insurance. **Results:** Among 2,350 patients prescribed a DAA regimen (504 covered by Medicaid; 810 by Medicare; 1,036 by commercial insurance), 375 (16.0%) received an absolute denial (genotype 1: 15.2%; genotype 2: 17.7%; genotype 3: 31.6%; $p < 0.001$). The most common reasons for absolute denial were insufficient information to assess medical need (133 [35.5%]), lack of medical necessity (125 [33.3%]), and positive alcohol/drug screen (15 [4.0%]). Prescriptions were more commonly denied for patients covered by Medicaid (232 [46.0%]) than by Medicare (40 [4.9%]; $p < 0.001$) or commercial insurance (103 [9.9%]; $p < 0.001$). Among the overall cohort, Medicaid coverage (OR=8.97 [6.46-12.44]), absence of cirrhosis (OR=3.70 [2.48-5.52]), and HIV coinfection (OR=3.31 [1.28-8.56]) were independently associated with absolute denial. The median time to DAA prescription fill was longer for persons with Medicaid (23 days) than with Medicare (14 days; $p < 0.001$) or commercial insurance (14 days; $p < 0.001$). **Conclusions:** Among chronic HCV-infected patients prescribed DAA therapy, 16% were denied by their insurance carrier. For Medicaid patients, 46% were denied DAA therapy, and they had a longer time to fill than those with other insurance. Medicaid programs should seek to increase access to DAA agents for chronic HCV-infected patients.

Disclosures:

Dena M. Carbonari - Grant/Research Support: AstraZeneca

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LB-6

Emricasan (IDN-6556) administered orally for 28 days lowers portal pressure in patients with compensated cirrhosis and severe portal hypertension

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Caspases play a central role in apoptosis and inflammation. They produce hemodynamically-active, pro-inflammatory microparticles that appear to contribute to the vasodilatation that maintains and enhances portal hypertension in cirrhosis. Emricasan, a pan-caspase inhibitor, has been shown to lower portal pressure and improve survival in a murine model of portal hypertension. The aim of this study was to assess whether emricasan could lower portal pressure in patients with compensated cirrhosis. **Methods:** This proof-of-concept, multicenter, open-label study enrolled 23 subjects with compensated cirrhosis and portal hypertension (hepatic venous pressure gradient [HVPG] > 5 mmHg) at 9 U.S. sites. Emricasan (25 mg) was given orally twice a day for 28 days. HVPG measurements were standardized and a single expert read all HVPG tracings. **Results:** Median age of subjects was 59 (range 49-80) and 70% were male. Cirrhosis etiologies were mainly NASH and HCV, with 20 (87%) subjects being Child A and having median MELD score of 8 (range 6-15). 22 completed the study. Overall, there were no significant differences in median HVPG before and after emricasan (13.5 vs 13.0 mmHg, respectively). However, when patients were stratified by the recognized HVPG therapeutic threshold of 12 mmHg (indicative of more severe portal hypertension), a significant ($p < 0.003$) decrease in HVPG by 17.2% was noted only in those with an HVPG ≥ 12 mmHg, who had a mean (SD) decrease of 3.7 (4.0) mmHg. Notably, 4/12 had a $\geq 20\%$ decrease; 8/12 had a $\geq 10\%$ decrease; and in 2/12 the HVPG decreased below 12mmHg. Ten patients with HVPG < 12 mmHg had a non-significant ($p = 0.12$) mean (SD) increase of 1.9 (3.2) mmHg. Sensitivity analysis using an HVPG cutoff of 10 mmHg yielded similar results. There were no significant changes in blood pressure or heart rate. AST and ALT levels decreased significantly in the entire group and in those with an HVPG ≥ 12 mmHg. Overall, serum levels of cCK18 and caspase 3/7 (markers of microparticles and apoptosis, respectively) decreased significantly. Emricasan was well-tolerated with 1 subject discontinuing the study early for non-serious adverse events. One subject had 3 SAEs 10 days after the last emricasan dose, assessed as unrelated to treatment. **Conclusion:** Emricasan administered orally for 28 days was associated with a significant decrease in portal pressure in patients with compensated cirrhosis and severe portal hypertension. Although a hemodynamic mechanism cannot be ruled out, concomitant decreases in AST/ALT suggest an intrahepatic anti-inflammatory effect. Potential additional long-term effects due to microvascular remodeling will require further investigation.

Disclosures:

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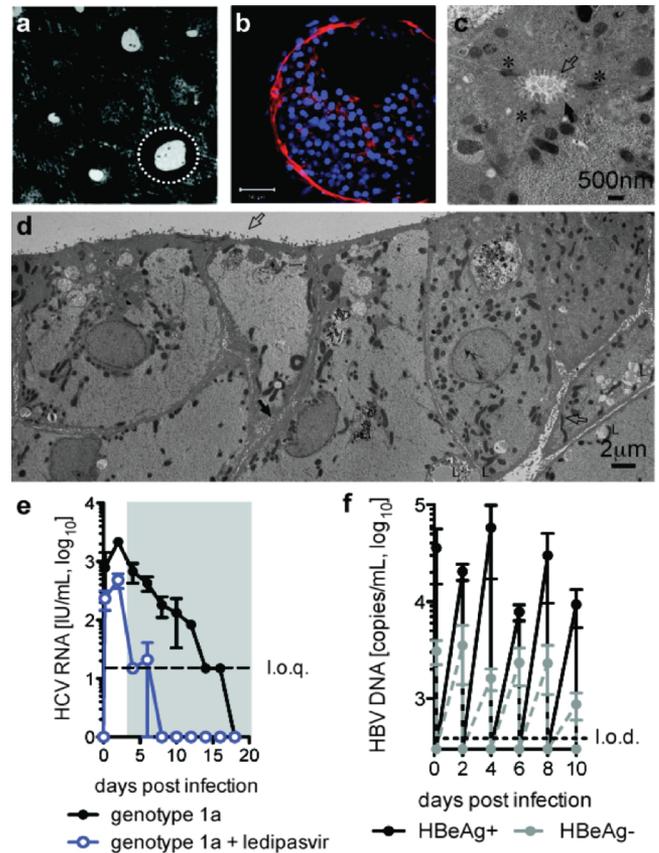
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LB-7

Microfluidic liver cultures as preclinical tool for the study of hepatitis B and C virus as well as malaria

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Liver-tropic pathogens including hepatitis B virus (HBV), hepatitis C virus (HCV) and malaria are a major health concern with more than 620 million people infected worldwide. The rapid de-differentiation of primary human hepatocytes in 2D cell culture poses significant limitations to study host-pathogen interactions and to develop novel therapies against these infectious diseases in physiological settings. Here, we describe a novel 3D microfluidic primary hepatocyte culture system permissive to HCV, HBV and malaria, which, in contrast to all other available model systems, maintains the hepatic phenotype for at least 40 days without alteration of hepatic metabolism, cell viability or degree of differentiation. Cells form functional microtissues including bile canaliculi and tight junctions. We demonstrate, for the first time, that HBV patient-derived viral isolates can successfully launch infection and maintain robust levels of replication, resulting in the production of HBV cccDNA as well as infectious progeny virus. Additionally, 3D hepatocyte cultures become susceptible to non-JFH1-derived HCV including genotype 1a patient samples. We demonstrate proof of concept data for the evaluation of novel direct-acting antivirals against HCV, including Ledipasvir and Sofosbuvir for genotypes 1 and 3 as well as Tenofovir alafenamide for HBeAg-positive and -negative HBV isolates. HBV infection induces a pro-angiogenic signature in infected hepatocytes, which is suppressed when co-culturing primary hepatocytes and Kupffer cells. Interestingly, we identify a cellular factor induced by HBV infection, which may be responsible for inactivation of Kupffer cells and the resulting lack of pro-inflammatory responses. Finally, using hepatocyte and erythrocyte co-cultures we show that malaria sporozoites can successfully invade hepatocytes, differentiate to merozoites and transition from liver to blood stage. This platform offers the unique opportunity to evaluate novel drug candidates targeting HBV cccDNA maintenance as well as the malaria liver stage, dissect host/pathogen interactions in multicellular immune networks as well as serve as a personalised medicine platform for the prediction of treatment outcomes for HCV and HBV.



Primary human hepatocytes in 3D cultures form liver-like microtissues that are susceptible to HCV and HBV patient-derived viral isolates. (a, b) Phase contrast and confocal microscopy of actin (red) and DAPI (blue) of hepatic microtissues following seeding and culture of hepatocytes. (c, d) Electron micrographs of hepatocytes in 3D cultures 20 days post seeding demonstrating hepatic microvilli (open arrow) on the basolateral growth area and within bile canaliculi (closed arrow), the formation of tight junctions (asterisk) as well as lipid droplet formation (L). (e) Longitudinal secretion of HCV RNA following infection with patient-derived HCV genotype 1a in the presence or the absence of 1mM Ledipasvir. (f) Infection of 3D hepatocyte cultures with patient-derived HBeAg-negative and -positive HBV and the longitudinal secretion of HBV DNA.

Disclosures:

Graham Cooke - Consulting: Gilead, BI, Janssen, BMS, WHO; Grant/Research Support: Gilead

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LB-8

Genetic Variation rs16937012 near the NCOA2 Gene Predicts Sustained Response to Interferon in Chronic Hepatitis B patients: the GIANT-B study

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Background & aims. Peginterferon (PegIFN) therapy leads to response in only a subset of chronic hepatitis B (CHB) patients at the cost of significant side-effects. The identification of host genetic determinants of response are therefore in demand. **Methods.** In this investigator-initiated multicentre two-stage genome-wide association study, CHB patients treated with (Peg)IFN for at least 12 weeks \pm nucleos(t)ide analogues within randomized controlled trials or as standard of care were recruited at 22 centres from Europe, Asia and North America. Patients were genotyped for >713,014 single-nucleotide polymorphisms (SNPs). Response was studied at 24 weeks off-treatment and was defined as a combined HBeAg loss with HBV DNA <2,000 IU/mL, or an HBV DNA <2,000 IU/mL for HBeAg negative patients. Patients with missing outcome or those who were re-treated after (Peg)IFN cessation were classified as non-responders. Both a discovery and a replication cohort were constructed. Here we report on the first results for the discovery cohort. **Results.** Of 1085 patients in the discovery cohort, 778 (72%) were male, and mean age was 38.8 (\pm 10.9) years. Patients were Caucasian in 35% (n=375), Asian in 62% (n=671) and African in 3% (n=35). Of Caucasian and Asian patients, 27% and 66% were HBeAg-positive, respectively. In total, 287 (27%) patients achieved the primary response (17% with HBsAg loss), of which 60 (21%) were Caucasian and 217 (76%) Asian. Adjusted for age, gender and 4 ancestry principal components, SNP rs16937012

located upstream of the NCOA2 gene region on chromosome 8 showed a suggestive association (OR=3.99, $p=1.4 \times 10^{-6}$, minor allele frequency 0.125) in Caucasians. Five other SNPs in this gene region had p-value less than 1.0×10^{-4} , including coding SNP rs1460680 in NCOA2. The association remained after additional adjustment for baseline HBeAg status, HBV DNA, ALT and the duration of IFN. These associations did not replicate in Asians ($p>0.05$ for all SNPs). In Asian patients, 2 SNPs showed a suggestive association (p -value $<1.0 \times 10^{-5}$), which remained after multivariate adjustment. **Conclusions:** A novel protein coding gene was identified as a predictor of IFN treatment response in CHB. This gene belongs to the nuclear hormone receptor superfamily which plays an important role in cell growth, development, and homeostasis by controlling expression of specific genes. This gene, and others, will be further investigated in a panel of imputed 1000 Genomes SNPs and in the replication cohort. Identification of novel genetic determinants for IFN treatment response has the potential to improve our understanding of new therapeutic options leading to functional cure of CHB.

Disclosures:

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LB-9

ARC-520 produces deep and durable knockdown of viral antigens and DNA in a phase II study in patients with chronic hepatitis B

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Chronic hepatitis B (CHB) has become an important target for drug development. ARC-520 (ARC), the first RNA interference-based drug to reach patients (pts), targets ccc-DNA-derived mRNA; herein we report results in CHB. **Methods:** 58 CHB pts (48 ARC, 10 placebo (PL), mean age 41 yrs (range 23-59) were included. 38 pts were HBeAg-neg and 20 HBeAg-pos. At entry, 32 of 38 HBeAg-neg and 14 of 20 HBeAg-pos had taken entecavir (ETV) for mean of 5 yrs (range 2-8) and were on ETV throughout the study. 12 treatment naïve pts (6 HBeAg-neg, 6 HBeAg-pos) started on ETV during the trial. All pts received a single dose IV of ARC or PL (6 HBeAg-pos received a divided dose of ARC separated by 2 wks) and had viral parameter knockdown (KD) measured over 85 days [qHBsAg, HB core-related antigen (qHBcrAg) and viral DNA in all, qHBeAg in HBeAg-pos]. Doses were 1-4 mg/kg in HBeAg-neg. All HBeAg-pos received 4 mg/kg. 15 pts are continuing in follow-up. **Results:** ARC therapy was well tolerated - 23% reported a mild or mod adverse event (AE) with no AE rated serious, severe, drug-related or causing withdrawal from the trial. Viral DNA was below level of quantitation in all chronic ETV pts at study entry. Naïve pts reduced viral DNA up to 4.3 log (mean 2.2 log) after ARC and ETV. ARC reduced viral antigens with qHBeAg best KD of 1.7 log (mean max 1.2 log) following a single 4 mg/kg dose. In naïve pts, best qHBsAg KD of 1.9 log (mean max 1.1 log) in HBeAg-pos and 0.7 log (mean max 0.2 log) in HBeAg-neg were observed. qHBcrAg showed a dose response in HBeAg-neg with best KD at 1 mg/kg of 0.18 log (mean max 0.15 log) and 1.1 log (mean max 0.9 log) with 4 mg/kg. HBeAg-pos showed best KD of 1.1 log (mean max 0.92 log). The qHBsAg dose response was less deep in chronic ETV pts with best observed reduction of 0.3 log (mean max 0.2 log) observed at 1 mg/kg vs 0.5 log (mean max 0.4 log) at 4 mg/kg in HBeAg-neg. Best qHBsAg KD in chronic ETV treated HBeAg-pos was 0.7 log (mean max 0.3 log). Divided doses at 4 mg/kg did not increase antigen KD. Duration of qHBsAg KD was typically 8 wks with 2 distinct KD patterns of qHBsAg seen: an immediate, direct ARC antiviral effect (~70% of pts) and a delayed response several weeks after treatment (~30% of pts). **Conclusions:** 1) These findings are consistent with more cccDNA-driven antigen production in HBeAg-pos. 2) ARC was well tolerated 3) ARC effectively inhibited cccDNA-derived mRNA with protein KD up to 1.9 logs (99%) observed 4) These variations in viral protein KD are consistent with ARC data in chimps and previously reported chronic ETV reductions in pts for cccDNA 5) Chronic ARC studies aimed at producing HBsAg seroclearance are underway.

Disclosures:

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LB-10

Phase 1b Efficacy and Safety of NVR 3-778, a First-In-Class HBV Core Inhibitor, in HBeAg-Positive Patients with Chronic HBV Infection

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Background: Current therapies for chronic hepatitis B (CHB) can suppress HBV replication but long-term therapy is required in most patients. HBV Core (capsid) protein plays multiple roles in HBV persistence. NVR 3-778 is an HBV core inhibitor which can potentially inhibit viral assembly, HBV genome replication, cccDNA replenishment, and hepatic reinfection cycles. We report clinical proof-of-concept data for NVR 3-778 from a multicenter Phase 1b trial in patients with CHB. **Methods:** Safety and efficacy were assessed in 4 dosing cohorts of adults with chronic HBV infection. Patients were 18-65 yrs., predominantly male, and HBeAg-positive with serum HBV DNA > 20,000 IU/mL. ALT levels could be normal or elevated to less than 7 times upper limit of normal. Patients were randomized to NVR 3-778 capsules (10 patients/cohort in first 2 cohorts, 8/cohort in last 2 cohorts) or placebo (2 patients/cohort) for 28 days. The first 3 cohorts received NVR 3-778 doses of 100, 200, or 400 mg QD, and the 4th cohort received 600 mg BD. Safety evaluations included adverse events (AEs) and safety-related clinical labs. **Results:** A total of 44 patients were enrolled in the 4 cohorts; 36 received active NVR 3-778 treatment. Safety and tolerability of NVR 3-778 were satisfactory for all cohorts, with no treatment-related discontinuations or serious adverse

events (SAEs). AEs and lab abnormalities were generally mild and not related to study drug. A patient in the 100 mg cohort developed a rash involving the hands and feet that was considered to be serious. No other study patients developed a significant rash. Small HBV DNA reductions were apparent with 200 mg and 400 mg QD dose cohorts. With tripling of the daily dose to 1200 mg (600 mg BD) the mean 28-day reduction in serum HBV DNA levels increased substantially to 1.72 log₁₀ (range 1.06-3.71 log₁₀ IU/mL). PK results indicated multi-micromolar concentrations of NVR 3-778 supporting QD or BD dosing, with dose-related increases in drug levels. The study is advancing to evaluation of a combination of NVR 3-778 and peg-interferon. A higher dose will be tested to define a maximal-effect dose for NVR 3-778, and a nucleoside combination regimen will be tested later. **Conclusions:** NVR 3-778 was well-tolerated in patients with CHB. 600 mg BD dosing achieved significant reductions in HBV DNA. When used alone or in combination with current HBV antivirals, NVR 3-778 may contribute substantial efficacy by unique Core-related mechanisms, toward a goal of increased durable response rates in HBV patients.

Disclosures:

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LB-11

Phase I/IIa study of TT-034, a DNA-directed RNA interference agent (ddRNAi) delivered as a single administration for the treatment of subjects with chronic hepatitis C virus (HCV)

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Background: Designed to treat HCV, TT-034 is an RNAi therapeutic comprised of a recombinant DNA that is delivered intravenously using an Adeno-Associated Virus capsid (AAV8) for transduction of hepatocytes. Once inside, TT-034 uses the cell's transcriptional machinery to drive long term expression of three independent short hairpin RNAs (shRNAs) to simultaneously target three well-conserved regions of the HCV RNA genome, including the 5' UTR (shRNA6) and NS5B (shRNA19 and shRNA22). In non-human primate (NHP) studies, clinically relevant doses of TT-034 transduced nearly 100% of hepatocytes and resulted in persistent shRNA expression for 180 days (the length of the study). Intended as a one-time treatment, the dosing with TT-034 is the first time a non-withdrawable RNAi therapeutic has been used in man. **Methods:** This ongoing, first-in-man, Phase I/IIa open label dose-escalating trial is enrolling chronic HCV genotype 1 patients without cirrhosis. Patients

receive a single intravenous infusion of TT-034 at one of 5 dose levels. A liver biopsy, collected 21 days post dosing, is used to assess hepatic TT-034 DNA levels and shRNA expression.

Results: To date, seven subjects have received a single dose of TT-034 at either 4.00E10, 1.25E11, or 4.00E11 vg/kg. Additional subjects will be enrolled in dose cohorts of 1.25E12 or 4.00E12 vg/kg. There have been no treatment-related SAEs in the study to date. Once administered, TT-034 clears from serum within the first week post dosing. No long term TT-034 shedding has been detected in the urine, stool, semen, or sputum. TT-034 DNA levels in liver biopsies are measured by QCR and are similar to those reported in NHP models. Patients administered the lowest dose resulted in 0.01 or 0.02 copies of the TT-034 genome per cell, the equivalent of 1 or 2 % hepatocyte transduction. At a dose of 1.25E11 vg/kg, substantially higher levels were detected in the hepatic tissues from the three subjects, yielding 0.48, 3.65 and 10.44 copies of TT-034 DNA per cell respectively. The first subject dosed with 4.00E11 vg/kg demonstrated 17.74 copies per cell, indicating that a significant portion of the hepatocytes may have been transduced. QPCR analyses of RNA isolated from the biopsies confirmed concomitant, dose dependent expression of anti-HCV shRNAs. Copy numbers of shRNA6, shRNA19 and shRNA22 were measured at 66, 2032, and 99 copies per cell respectively in the subject dosed with 4.00E11 vg/kg. **Conclusion:** Initial doses of TT-034 are well tolerated in human subjects infected with HCV. At higher doses, substantial portions of hepatocytes are transduced and result in concurrent dose-dependent expression of anti-HCV shRNAs.

Disclosures:

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LB-12

C-SWIFT Retreatment (Part B): 12 weeks of Elbasvir/ Grazoprevir with Sofosbuvir and Ribavirin Successfully Treated GT1-infected Subjects who Failed Short-Duration All-Oral Therapy

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PURPOSE: Therapies to retreat patients who have failed prior all-oral, direct-acting antiviral (DAA) therapies have not been defined. The purpose of this study was to assess a retreatment regimen for patients who had failed therapy with elbasvir/grazoprevir (EBR/GZR, a potent NS3/4A protease inhibitor + NS5A inhibitor fixed-dose combination) + sofosbuvir (SOF).

METHOD: G1-infected patients who relapsed after therapy with EBR/GZR + SOF for 4, 6 or 8 weeks were offered retreatment with 12 weeks of EBR/GZR + SOF + ribavirin (RBV). The primary endpoint was the proportion of patients achieving HCV RNA <15 IU/mL 12 weeks after end of treatment (SVR12). Population sequencing was used to detect resistance-associated variants (RAVs) in NS3, NS5A and NS5B. **RESULTS:** Of 29 eligible patients, 25 enrolled (17/20, 7/8 and 1/1 who failed prior 4, 6 or 8 weeks of treatment respectively): 88% (22/25) with G1a infection, 20% (5/25) with cirrhosis; baseline viral load at retreatment mean 6.6 log₁₀ IU/mL (range: 4.3-7.4 log₁₀ IU/mL). Of the 22 G1a patients, 12 (55%), 15 (68%) or 0% failed with NS5A RAVs, NS3 RAVs or NS5B RAVs, respectively, in Part A. At the start of retreatment, 45% (10/22), 59% (13/22) or 0% of G1a patients had NS5A RAVs, NS3 RAVs, or NS5B RAVs, respectively. NS5A RAVs (>5-fold potency shift to EBR shown by underlining) included M28T (2/10), M28V (2/10), Q30H/K/R (5/10), L31M (1/10), Y93H/N (3/10) while NS3 RAVs included V36M (1/22), Q80K (12/22), S122G (2/22), D168E (1/22; >5-fold resistant to GZR), and I170V (1/22). No RAVs were present in the 3 G1b-infected patients. Two patients were lost to follow-up after Treatment Day 3 and Week 4 at which time viral load was 363 IU/mL and undetectable, respectively. All patients who completed treatment (100%, 23/23) achieved SVR4. Final SVR12 results will be presented. No patient discontinued due to AEs or laboratory abnormalities. The single AE occurring in >10% of patients was fatigue (12%). **CONCLUSION:** In a population of patients who failed short-duration therapy with DAAs and were enriched for G1a infection and presence of NS3 and NS5A RAVs, including 2 class RAVs, a 12 week regimen of GZR/EBR + SOF + RBV showed strong antiviral activity and high SVR4 rates.

RAV Class present at start of retreatment ¹	% (n/m) with HCV RNA <15 IU/mL		
	Treatment Week 4	End of Treatment	SVR4
No RAVs (n=13) ²	92% (12/13)	100% (12/12)	100% (12/12)
NS3 or NS5A RAVs (n=9) ³	63% (5/8)	100% (8/8)	100% (8/8)
NS3 and NS5A RAVs (n=3)	100% (3/3)	100% (3/3)	100% (3/3)

1: RAVs excluding Q80K; 2: one LTFU after TW4; 3: one LTFU at day 3

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LB-13

Sofosbuvir/Velpatasvir Fixed Dose Combination For The Treatment Of HCV In Patients With Decompensated liver Disease: The Phase 3 ASTRAL-4 Study

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Introduction: HCV-infected patients with decompensated liver disease have significant morbidity and mortality with limited HCV treatment options. Velpatasvir (VEL, formerly GS-5816), is a pangenotypic HCV NS5A inhibitor that has demonstrated high SVR rates in patients with genotypes 1-6 HCV infection when used in combination with sofosbuvir (SOF). This Phase 3 study evaluated the safety and efficacy of the fixed dose combination (FDC) of SOF/VEL in HCV infected patients with decompensated liver disease. **Methods:** Genotype (GT) 1, 2, 3, 4 or 6 HCV infected patients with CPT-B cirrhosis were randomized 1:1:1 to receive SOF/VEL (400 mg /100 mg) daily for 12 weeks, SOF/VEL + weight based RBV for 12 weeks, or SOF/VEL for 24 weeks. Patients with prior liver transplant or hepatocellular carcinoma were excluded. **Results:** Of the 267 patients randomized and treated, the majority were treatment experienced (55 %), white (90%), males (70%), with IL28B non-CC (77%). Patients had genotype 1(78% overall, 60% 1a), 2 (4.5%), 3 (15%), 4 (3%) or 6 (<1%) HCV infection. The median CPT score was 8 (range 5-10) and median MELD score was (range 6-24). The SVR12 rates by GT are shown in table 1. SOF/VEL+RBV for 12 weeks resulted in high SVR rates with relapse occurring in 1 (1%) GT1 and 1 (8%) GT3 subjects respectively. A second GT3 patient in the SOF/VEL+RBV 12 Week group had on-treatment breakthrough with pharmacokinetic data consistent with nonadherence. There were no genotype 2, 4 and 6 virologic failures across all treatment arms. Among patients who achieved SVR, 47% and 56% had improvements in CPT and MELD scores by week 12 post EOT largely driven by increases in albumin and decreases in bilirubin. The most common adverse events were fatigue, headache, nausea and (anemia in the RBV containing arm with a median Hgb decrease of 1.4 g/dL). Overall 9 patients discontinued SOF/VEL due to adverse events. A total of 47 (18%) patients experienced serious adverse events (SAEs) with the most common being hepatic encephalopathy and sepsis; only 1 patient had SAEs assessed as related to SOF/VEL There were 9 deaths: sepsis (3); liver failure (2); cardiopulmonary arrest (2); myocardial infarction (1) and respiratory failure (1); none were assessed as related to study drug. **Conclusions:** In HCV infected patients with decompensated liver disease, SOF/VEL+RBV for 12 weeks resulted in an overall SVR rate of 94.3% with high individual SVR rates across all HCV genotypes and

resulted in early improvements in liver function. This regimen was well tolerated with AEs consistent with clinical sequelae of decompensated liver disease and RBV.

Virologic Outcome By Genotype

	Total (All GTs)	GT-1	GT-2	GT-3	GT-4	GT-6
SOF/VEL 12 Week Group						
SVR12	75/90 (83.3%)	60/68 (88.2%)	4/4 (100.0%)	7/14 (50.0%)	4/4 (100.0%)	NA
Virologic Failure	11/90 (12.2%)	5/68 (7.4%)	0/4	6/14 (42.9%)	0/4	—
Other	4/90 (4.4%)	3/68 (4.4%)	0/4	1/14 (7.1%)	0/4	—
SOF/VEL+RBV 12 Week Group						
SVR12	82/87 (94.3%)	65/68 (95.6%)	4/4 (100.0%)	11/13 (84.6%)	2/2 (100.0%)	NA
Virologic Failure	3/87 (3.4%)	1/68 (1.5%)	0/4	2/13 (15.4%)	0/2	—
Other	2/87 (2.3%)	2/68 (2.9%)	0/4	0/13	0/2	—
SOF/VEL 24 Week Group						
SVR12	77/90 (85.6%)	65/71 (91.5%)	3/4 (75.0%)	6/12 (50.0%)	2/2 (100.0%)	1/1 (100.0%)
Virologic Failure	8/90 (8.9%)	3/71 (4.2%)	0/4	5/12 (41.7%)	0/2	0/1
Other	5/90 (5.6%)	3/71 (4.2%)	1/4 (25.0%)	1/12 (8.3%)	0/2	0/1

Other = subject who did not achieve SVR and did not meet virologic failure criteria.

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LB-14

100% SVR4 in HCV Genotype 1 Non-Cirrhotic Treatment-Naïve or -Experienced Patients With the Combination of ABT-493 and ABT-530 for 8 Weeks (SURVEYOR-I)

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Introduction: Next-generation HCV direct-acting antivirals (DAAs) ABT-493, an NS3/4A protease inhibitor identified by AbbVie and Enanta, and ABT-530, an NS5A inhibitor, demonstrated potent pangenotypic in vitro antiviral activity, with a high barrier to resistance and maintenance of activity against common resistance-associated variants. In Part 1 of the SURVEYOR-I study, ABT-493 and ABT-530 co-administered for 12 weeks showed high sustained virologic response (SVR) rates and was well tolerated in non-cirrhotic patients with HCV genotype 1 (GT1) infection. We present here the efficacy and safety data from Part 2 of the SURVEYOR-I study, which evaluates the combination of ABT-493 and ABT-530 administered for 8 weeks in non-cirrhotic patients with GT1 infection. **Methods:** Treatment-naïve or pegylated interferon treatment-experienced patients received once-daily ABT-493 300 mg + ABT-530 120 mg for 8 weeks. SVR at post-treatment week 4 (SVR4; HCV RNA measured using COBAS TaqMan® RT-PCR [lower limit of detection of 15 IU/mL and lower limit of quantitation of 25 IU/mL]) and safety data are reported. **Results:** 34 patients were enrolled: 56% male, 97% white, 71% GT1a, 68% non-CC IL28B, 15% had an F3 fibrosis stage at baseline, and 15% were treatment experienced. The median (range) HCV RNA log₁₀ IU/mL was 6.5 (2.9–7.5) at baseline, and 38% of patients had HCV RNA ≥ 6,000,000 IU/mL. All 34 (100%) patients achieved SVR4. SVR at post-treatment week 12 (SVR12) data will be available for presentation. One patient discontinued the study prematurely at treatment week 4 (with HCV RNA <15 IU/mL) due to the serious adverse event (AE) of adenocarcinoma, which was assessed as not related to treatment with study drugs. There were no additional serious or severe AEs reported. The most frequent AEs observed in >10% of patients were fatigue (21%) and diarrhea (12%). **Conclusions:** The combination of highly potent next generation HCV DAAs, ABT-493 and ABT-530, was well tolerated and achieved 100% SVR4 in all patients regardless of baseline viral load or presence or absence of prior treatment history.

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LB-15

Phase 2, Randomized, Open-Label Clinical Trials of the Efficacy and Safety of Grazoprevir and MK-3682 (NS5B Polymerase Inhibitor) with Either Elbasvir or MK-8408 (NS5A Inhibitor) in Patients with Chronic HCV GT1, 2 or 3 Infection (Part A of C-CREST-1 & 2)

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PURPOSE/BACKGROUND: To evaluate the safety and efficacy of all-oral therapy for HCV using combinations of 3 direct-acting antiviral drugs: grazoprevir, an NS3/4A protease inhibitor; MK-3682, an NS5B polymerase inhibitor, and either elbasvir or MK-8408, which are NS5A inhibitors.

METHODS: In Part A of 2 ongoing randomized, dose-ranging, parallel-group, multicenter, open-label Phase 2 trials, 93 GT1 (46 GT1a, 47 GT1b), 61 GT2, and 86 GT3-infected treatment-naïve, non-cirrhotic patients with chronic HCV infection were dosed once-daily for 8 weeks duration with one of 4 regimens including grazoprevir (100 mg), MK-3682 (300 mg or 450 mg), and either elbasvir (50 mg) or MK-8408 (60 mg).

RESULTS: GT1: Across treatment arms, 45/46 (98%) GT1a and 46/47 (98%) GT1b patients achieved sustained virologic response 12 weeks after end of study therapy (SVR12). In the 2 relapsers, population sequencing did not detect NS3, NS5B, or NS5A resistance associated variants (RAVs) conferring ≥ 5 -fold potency shifts at baseline or following relapse. **GT2:** The grazoprevir/MK-3682 (450 mg)/MK-8408 regimen was highly effective, with SVR12 among 15/16 (94%) of GT2-infected patients, but regimens containing the 300 mg dose of MK-3682 and/or elbasvir resulted in lower efficacy (SVR12 in 29/45 (64%) GT2 patients; 60-71% across the 3 arms). Relapses were more common among patients who harbored an L31M/I NS5A variant at baseline. No treatment-emergent RAVs were observed. **GT3:** Across arms, SVR12 was achieved among

78/86 (91%) of GT3-infected patients; response was comparable across arms (86-95%). Eight GT3 patients relapsed. SVR12 was lower among GT3-infected patients who harbored an NS5A A30K, L31M, or Y93H RAV at baseline compared with patients without these RAVs at baseline (5/11 [45%] vs 72/74 [97%], respectively). Two of 8 GT3 relapsers acquired NS5A Y93H. All 240 patients completed the full 8 weeks of dosing. All regimens were generally well tolerated, and no cardiac or renal safety signals were identified. The most frequent study drug-related AEs in >5% of all patients were headache, fatigue, nausea, diarrhea, flatulence and insomnia. There were no drug-related serious adverse events and no patients discontinued due to adverse events. **CONCLUSIONS:** An 8-week regimen of grazoprevir/MK-3682 (450 mg)/MK-8408 was highly effective and well-tolerated in GT1, 2, and 3-infected treatment-naïve, non-cirrhotic patients. The results of Part A support further evaluation of this 3-drug combination among a diverse population of HCV-infected patients, including those with additional HCV genotypes, cirrhosis, prior treatment, and HIV/HCV-co-infection.

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LB-16

High Rates of SVR in Patients with HCV Genotype 2 or 3 Infection Treated with Ombitasvir/Paritaprevir/r and Sofosbuvir with or without Ribavirin

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Background: Few interferon-free treatments are approved for hepatitis C virus (HCV) genotype (GT) 2 and 3 infection. Among the approved treatment options, sustained virologic response rates 12 weeks post-treatment (SVR12) are lower in patients with cirrhosis or with prior treatment failure. We investigated the safety and efficacy of ombitasvir/paritaprevir (identified by AbbVie and Enanta)/ritonavir (OBV/PTV/r) plus sofosbuvir (SOF) in patients with GT2 or GT3 infection without cirrhosis. **Methods:** In this phase 2, open-label, multicenter study, patients with GT3 infection were randomized to receive OBV/PTV/r (25/150/100 mg once daily) plus SOF (400 mg once daily) with or without weight-based ribavirin (RBV) for 12 weeks. Patients were stratified by prior treatment status and IL28B genotype (CC vs non-CC). Patients with GT2 infection all received OBV/PTV/r plus SOF with RBV for 8 weeks. Efficacy was assessed by SVR12 defined as HCV RNA <25 IU/mL. Safety was assessed in all patients receiving at least 1 dose of study drugs. **Results:** Twenty patients with GT3 infection, including 8 with prior treatment failure, were randomized to receive OBV/PTV/r + SOF without RBV (N = 11) or with RBV (N = 9). One patient discontinued OBV/PTV/r + SOF + RBV treatment after 1 week due to non-serious events of viral flu-like symptoms and emesis. All other patients were HCV RNA suppressed <25 IU/mL by treatment week 2 and through the end of treatment. As of September 17 there have been no relapses; SVR12 was achieved in 7/7 (100%) GT3 patients treated for 12 weeks with OBV/PTV/r + SOF, and in 7/8 (88%) GT3 patients treated with OBV/PTV/r + SOF + RBV for 12 weeks. Ten patients with GT2 infection, including 2 with treatment experience, received 8 weeks of treatment with OBV/PTV/r + SOF + RBV, and 10/10 (100%) were HCV RNA suppressed at the end of treatment. As of September 17, all remain suppressed through post-treatment week 2 (10/10, 100%) and SVR at post-treatment week 4 was achieved in 9/9 (100%). Among the 30 patients in the study, 1 serious adverse event (pneumonia) was reported and not considered related to study drugs. **Conclusions:** The investigational combination of OBV/PTV/r with SOF for 12 weeks may be a promising IFN and RBV-free treatment option for patients with GT3 infection. This combination plus RBV for 8 weeks also appears highly effective in patients with GT2 infection. Complete SVR12 data will be presented.

Disclosures:

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LB-17

Failure with All-oral DAA Regimens: Real-world experience from the TRIO Network

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BACKGROUND: DAA therapies ledipasvir/sofosbuvir (LDV/SOF) and ombitasvir/paritaprevir/ritonavir+dasabuvir (VKP) have yielded SVR12 rates over 95% in clinical trials. Given the remarkable efficacy in clinical trials, understanding factors associated with treatment failure in clinical practice remains challenging due to the relatively few patients who do not achieve an SVR. **AIM:** The purpose of this study is to examine a large real-world population to assess the characteristics of patients with genotype 1 HCV who failed 12 week LDV/SOF, VKP or other all-oral DAA therapies. **METHODS:** Data were collected from providers and specialty pharmacies through Trio Health's Innervation Platform, a cloud-based disease management program. All genotype 1 HCV patients who initiated treatment with 12 week LDV/SOF, VKP or simeprevir + sofosbuvir (SMV+SOF)-based regimens between Oct 2014 and Mar 2015 were included in the analysis (n = 1225). **RESULTS:** Overall SVR12 rate from this heterogeneous population was 97% (1190/1225). By regimen, rates were 97% (1128/1159) for LDV/SOF+/-RBV, 95% (37/39) for VKP+/-RBV and 93% (25/27) for SMV+SOF+/-RBV. Of the 35 patients that did not achieve SVR, 6 discontinued treatment and 29 completed therapy and were virological failures. In the virological failures, treatment site (academic versus community practice), age, race, genotype subtype, viral load and presence of HIV coinfection (100% SVR, n = 90) or post-transplant (100% SVR, n = 40) were not associated with treatment failure. Positive association with virological failure in real life was male (80% in failures versus 58% in SVR, p=0.011), cirrhosis (60% in failures versus 27% in SVR, p<0.001), platelets less than 100,000/ml (41% in failures versus 10% in SVR, p<0.001) and prior treatment failure (60% in failures versus 40% in SVR, p=0.016). **SUMMARY:** Overall SVR in real world genotype 1 HCV patients is 97% across regimens and patient characteristics with cirrhosis, thrombocytopenia and prior treatment failure representing the most difficult to treat patients. Treatment discontinuation is not a major issue with any all oral DAA therapy

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LB-18

Daclatasvir and Asunaprevir in Non-Japanese Asian Patients With Chronic HCV Genotype 1b Infection who are Ineligible for or Intolerant to Interferon-alfa Therapies With or Without Ribavirin: Phase 3 SVR12 Interim Results

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Purpose The all-oral combination of daclatasvir (DCV; pangenotypic NS5A inhibitor) and asunaprevir (ASV; NS3 protease inhibitor) has been shown to be effective and well tolerated in Japanese patients with chronic HCV genotype (GT) 1b infection. This phase 3, single-arm, open-label study investigated the efficacy and safety of DCV + ASV in non-Japanese Asian patients with chronic HCV GT 1b infection who are ineligible for or intolerant to interferon-alfa therapies with or without ribavirin (IFN ± RBV). **Methods** Patients received DCV 60 mg (tablet) once daily + ASV 100 mg (soft capsule) twice daily for 24 weeks. Enrollment of patients with compensated cirrhosis was capped at 40%. The primary endpoint was sustained virologic response at post-treatment (PT) Week 24 (SVR24); interim (secondary) efficacy (SVR12) and safety analyses, conducted at PT Week 12, are reported here. **Results** In total, 159 patients received DCV + ASV treatment; the majority were Chinese (89%), female (65%), aged (65 years (82%), non-cirrhotic (67%), *IL28B* CC (60%), and had HCV RNA levels ≥800,000 IU/mL (91%). HCV RNA was undetectable in 86% of patients by treatment Week 4. SVR12 was achieved by 145 patients

(91%, 95% CI 85.7–95.1) and was unaffected by cirrhosis status, gender, age, baseline HCV RNA level, *IL28B* genotype, and IFN ineligibility/intolerance status; SVR12 was achieved by 47 of 52 (90%, 95% CI 79.0–96.8) and 98 of 107 (92%, 95% CI 84.6–96.1) patients with and without cirrhosis, respectively. SVR12 was higher in patients without baseline NS5A (L31M or Y93H) resistance-associated variants (RAVs) (n=137/139 [99%]), regardless of the presence (n=43/44 [98%]) or absence (n=94/95 [99%]) of cirrhosis. SVR12 was lower in patients with baseline NS5A RAVs (n=8/19 [42%]). All deaths (n=1/159 [0.6%]), serious adverse events (AEs) (n=5/159 [3.1%]) and grade 4 laboratory abnormalities (n=3/159 [1.9%]) that occurred on-treatment were considered to be unrelated to the study drugs; two patients experienced AEs leading to discontinuation (increase in bilirubin; anemia and increase in LDH). AEs in >5% of patients were: platelet count decrease, upper respiratory tract infection, ALT increase, absolute neutrophil count decrease, monocyte decrease, white blood cell decrease, thrombocytopenia and pruritus. Safety parameters were comparable in patients with and without cirrhosis. **Conclusions** The all-oral combination of DCV + ASV achieved a high SVR12 rate of 91%, rising to 99% in patients without baseline NS5A RAVs. This regimen was generally well tolerated in IFN ± RBV ineligible/intolerant non-Japanese Asian HCV GT 1b patients with or without cirrhosis.

Disclosures:

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LB-19

Prevalence of Direct Acting Antiviral (DAA) Resistance in the Department of Veterans Affairs (VA)

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Purpose: Determine prevalence of DAA resistance mutations (DRM) in a convenience sample of specimens from patients treated for HCV infection in VA. **Methods:** Plasma samples collected for clinical care were sent to the VA Public Health Reference Laboratory. HCV RNA was extracted from plasma, and then RT-PCR amplified for the NS3, NS5A, and NS5B genes using genotype-specific primers. Sanger sequencing was performed on amplicons, and sequences aligned to genotype-specific reference strains using Geneious software, and DRMs were identified based on publically available information. Only those genes included in the physician orders were evaluated, thus all 3 genes were not tested in all samples. Data on HCV genotype and VA, but not outside VA treatment history, were collected. Baseline samples in patients experiencing DAA regimen failure were not available for comparison of pre-existing mutations. **Results:** 224 unique patient samples were

received from 26 VA medical centers from February-August 2015 and 220 (98%) yielded reportable results. Genotypes tested were: GT1a (150), GT1b (40), GT3a (20), GT2b (6), GT4a (3), GT2a (1). DRMs found overall are described in Table 1. Fourteen patients had DRMs in 2 or more genes. VA treatment history was known for 176 (80%) patient samples and of these, 25 were baseline samples from those who had only received peg-interferon/ribavirin. In those that were treatment naïve (and had no prior DAA exposure) 31/52 (60%) had one or more DRMs. In samples from treatment-experienced patients with prior DAA exposure 57/99 (58%) had one or more DRMs, with simeprevir/sofosbuvir (SIM/SOF, n=22) and ledipasvir/sofosbuvir (LED/SOF, n=20) being the most common regimens prescribed. Of those who failed SIM/SOF as their first VA regimen, NS3 DRMs included Q80K (12), R155K (10) and D168V (4), and one NS5B L159F (1). Of those who failed LED/SOF as their first VA regimen, NS5A DRMs included: Q30R/H/E (7), Y93H/C/N (6), M28V (1) and H58D (1). One primary regimen failure of ombitasvir/paritaprevir/ritonavir/dasabuvir included NS5A DRMs M28V and Q30R. **Conclusion:** In VA specimens tested for HCV DRMs, numerous patients were found to have preexisting or post treatment HCV DRMs after regimen failure. Genotypic resistance testing may be helpful to guide initial and subsequent DAA regimens.

Table 1. Total Tested (# with DRM, %)

NS3	NS5A	NS5B
124 (57, 46%)	96 (41, 43%)	107 (6, 6%)
Mutations Found* (#)		
Q80K (54)	Q30R/H/L/E (20)	S556G/R (6)
R155K/Q (22)	Y93H (18)	M414T (1)
D168V/A/E (9)	L31M/V (14)	L159F (1)
V36M (3)	M28V/T (8)	S282T (1)
V55A (3)	Y93N/S/C (7)	
T54S/A (2)	K24R (2)	
	H58D (2)	

Disclosures:

Mark A. Winters - Independent Contractor: Eiger Biopharmaceuticals

Timothy R. Morgan - Grant/Research Support: Merck, Abbvie, Genentech, Gilead, Bristol Myers Squibb

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LB-20

Retreatment of HCV Genotype 1 DAA-failures with Ombitasvir/Paritaprevir/r, Dasabuvir, and Sofosbuvir

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Background: Retreatment options for HCV patients who fail treatment with direct-acting antiviral (DAA) regimens are not yet clearly defined. Resistance-associated variants in NS5A have been shown to persist up to 96 weeks post-treatment; thus, patients who fail regimens with NS5A inhibitors are likely to require a multi-targeted approach to retreat infection. We evaluated the safety and efficacy of ombitasvir/paritaprevir (identified by AbbVie and Enanta)/ritonavir (OBV/PTV/r) and

dasabuvir (DSV) plus sofosbuvir (SOF) in DAA-experienced patients with HCV genotype (GT) 1 infection. **Methods:** Patients with GT1 infection without cirrhosis were to receive OBV/PTV/r + DSV + SOF for 12 weeks; ribavirin (RBV) was added for patients with GT1a infection without cirrhosis. GT1a-infected patients with cirrhosis received 24 weeks of OBV/PTV/r + DSV + SOF + RBV. Enrolled patients must have had history of previous DAA treatment failure without discontinuation for reasons other than virologic failure. Efficacy was assessed by sustained virologic response (SVR), defined as an HCV RNA <25 IU/mL. Safety was assessed in all patients receiving at least 1 dose of study drugs. **Results:** Twenty-two DAA-experienced patients were enrolled including 20 with GT1a infection and 6 with compensated cirrhosis. Prior DAAs included in the previous failed treatment regimens were OBV/PTV/r + DSV (n = 14), OBV/PTV/r (n = 2), telaprevir (n = 2), SOF (n = 2), simeprevir/samatasvir (n = 1), and simeprevir + SOF (n = 1). One GT1a patient without cirrhosis had treatment extended to 24 weeks in response to having an HCV RNA >25 IU/mL at treatment week 4. As of September 1, SVR4 was achieved in 15/15 (100%) patients treated for 12 weeks. Among patients receiving 24 weeks of treatment, 7/7 are virally suppressed below the lower limit of detection while on treatment. Two patients experienced serious adverse events (pneumonia and cellulitis), neither assessed as being related to study drugs. The patient with pneumonia discontinued study drug at week 10 and HCV RNA remains undetectable. **Conclusions:** The multi-targeted regimen of OBV/PTV/r + DSV ± RBV in combination with SOF appears to be a promising retreatment strategy for patients who fail DAA-containing HCV regimens, including those containing an NS5A inhibitor. Baseline resistance and available SVR12 data will be presented.

Disclosures:

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LB-21

Preclinical characterization of CC-31244, a pan-genotypic, potent non-nucleoside NS5B polymerase inhibitor for the treatment of chronic hepatitis C

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Purpose/Background: NS5B non-nucleoside inhibitors are a distinct class of direct acting agents (DAA) for the treatment of HCV. We designed and characterized a novel, pan-genotypic NNI inhibitor (CC-31244), which is targeted for use in combination DAA therapies. We present here our recent preclinical study results, including *in vitro* characterization of CC-31244, drug resistance profiles, and pharmacokinetic data. **Methods:** NS5B polymerases (GT1-6) and drug resistant NS5B polymerases were purified for protein crystallization and IC₅₀ determination. NS5B polymerase cocrystals were diffracted to 1.7 – 2.2 Å. Antiviral activity was determined using HCV replicon and chimeric replicon assays. Safety pharmacology and pharmacokinetic profiles of CC-31244 were determined. **Results:** CC-31244 showed pan-genotypic activity against genotypes 1a–6a. In HCV replicon assays, the EC₅₀ values of CC-31244 against replicons from genotypes 1a, 1b, and 2a, and chimeric 1b replicons encoding NS5B from genotypes 3a, 4a, or 5a ranged from 2-26 nM. High resolution X-ray data have confirmed that CC-31244 binds to a highly conserved drug binding pocket, NNI-4, and extends to the highly conserved active site of the NS5B polymerase. CC-31244 showed excellent activity against the NNI-4 drug resistant variants including S365T and N316Y. HCV replicons with reduced susceptibility to CC-31244 have been selected in cell culture for GT1b. Reduced susceptibility to CC-31244 was associated with the NS5B amino acid substitution C445F. Site-directed mutagenesis of the C445F substitution conferred 8-fold increased EC₅₀ to CC-31244. CC-31244 showed no cytotoxicity, no inhibition in hERG, and no mitochondrial toxicity. CC-31244 did not inhibit CYP450 isozymes, and showed no significant drug-drug interactions or genotoxicity. Rat PK of CC-31244 showed a favorable PK profile (44% oral bioavailability), and the drug exposure level in the rat liver at 4 hours post-dose was >1,000x the drug level measured in a genotype 1b replicon EC₅₀. **Conclusion:** A pan-genotypic NNI lead, CC-31244, demonstrated potent HCV antiviral activity, *in vitro* safety and a good pharmacokinetic profile. Given this favorable preclinical activity and safety profile, CC-31244 has been selected to advance to Phase 1 clinical studies in 2016.

Disclosures:

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The following people have nothing to disclose: Irina Jacobson, Michael Feese, Hong Xiao, Lothar Uher, Biing Lin, Emiliano J. Sanchez, Robert J. Tomkiewicz, Judy Pattassery, Sam Lee

LB-22

Prevalence and Impact of Baseline NSA Resistance Associated Variants (RAVs) on the Efficacy of Elbasvir/ Grazoprevir (EBR/GZR) Against GT1a Infection

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Background and Aims: A 12-week EBR/GZR regimen (no ribavirin [RBV]) is highly effective in GT1a patients. Virologic failure (VF) occur mainly among patients in whom population sequencing at baseline (BL) identified substitutions at NS5A resistance-associated positions 28, 30, 31, 58, or 93 that reduce EBR potency ≥ 5 -fold *in vitro* (5XRAVs). In GT1a patients who received 16 weeks of GZR/EBR+RBV, no VFs were observed despite the presence of 5XRAVs. We assessed the association between presence of BL NS5A RAVs and SVR12 using a more sensitive next generation sequencing (NGS) assay on BL samples from treatment-naïve (TN) or experienced (TE) GT1a patients in Phase 3 trials. **Methods:** NGS (Illumina MiSeq) deep sequencing was performed on BL samples from 355/362 and 54/55 subjects who received 12 weeks of EBR/GZR (no RBV) or 16 weeks of EBR/GZR+RBV, respectively, in Phase 3 trials and had BL NS5A results. Using NGS sensitivity thresholds (ST) from 20% to 1% (i.e., the fraction of virus sequences bearing RAVs, with maximum sensitivity at 1%), the prevalence of BL NS5A RAVs and their impact on efficacy were assessed. Specific BL RAVs that predicted failure were defined. **Results:** 12 week/no RBV: 335/355 (94%) achieved SVR12; 20 had VF, of whom 16 were patients with BL 5XRAVs. Compared with the 1% ST, a 20% ST conferred much greater specificity/minimally less sensitivity in identifying VFs (Table). The 20% ST missed only one BL5XRAV patient with VF, while at 1% ST, 20 more patients with BL 5XRAVs were identified but only one had VF. Only BL substitutions at positions 30, 31, 58 were associated with VF. At the 20% ST, patients with such RAVs constituted only 5.6% of the overall TN/TE GT1a population. In patients without these BL RAVs, including hard-to-cure patients (e.g., TE cirrhotics), a 12 week/no RBV regimen resulted in 99% SVR12. 16 week/RBV: All patients with BL NS5A RAVs achieved SVR12. **Conclusion:** Among GT1a patients, baseline NGS (20% ST) identifies a small group of patients harboring NS5A RAVs that reduce the efficacy of a 12 week/no RBV EBR/GZR regimen. The 12 week/no RBV regimen yielded a 99% SVR12 in patients lacking these BL RAVs. The impact of such RAVs on efficacy was no longer seen among patients given 16 weeks of EBR/GZR+RBV.

ST	BL NS5A RAV	SVR12 (No BL RAVs)	SVR12 (With BL RAVs)	%Patients with BL RAVs	% NS5A Associated VFs Identified
EBR/GZR 12 weeks					
1%	5XRAV	307/311 (99%)	28/44 (64%)	12.4%	16/16 (100%)
20%	5XRAV	326/331 (98%)	9/24 (38%)	7.0%	15/16 (94%)
20%	RAV at position 30,31,58	330/335 (99%)	5/20 (25%)	5.6%	15/16 (94%)
EBR/GZR+RBV 16 weeks					
1%	5XRAV	45/45 (100%)	9/9 (100%)	16.7%	-
20%	5XRAV	50/50 (100%)	4/4 (100%)	7.4%	-
20%	RAV at position 30,31,58	51/51 (100%)	3/3 (100%)	5.6%	-

Disclosures:

Ira M. Jacobson - Consulting: AbbVie, Achillion, Alnylam, Bristol Myers Squibb, Enanta, Gilead, Janssen, Merck; Grant/Research Support: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck, Tobira; Speaking and Teaching: AbbVie, Bristol Myers Squibb, Gilead, Janssen

Ernest Asante-Appiah - Employment: Merck

Todd A. Black - Employment: Merck
 Anita Y. Howe - Employment: Merck Research Laboratory
 Janice Wahl - Employment: Merck & Co.,
 Michael Robertson - Employment: Merck; Stock Shareholder: Merck
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 Melissa Shaughnessy - Employment: Merck & Co., Inc.; Stock Shareholder: Merck & Co., Inc.
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LB-23

Complete cure after three weeks of all-oral triple-direct acting antiviral (DAA) regimens in non-cirrhotic chronic hepatitis C genotype 1b Chinese subjects (SODAPI STUDY)

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Background/Purpose: DAAs have a high cure rate and favorable tolerability in persons infected with hepatitis C virus (HCV). However, shorter courses could improve adherence, affordability and increase DAAs accessibility. We postulated that the addition of an NS3 protease inhibitor to dual NS5A-NS5B (nucleoside) inhibitors would enhance antiviral efficacy and reduce treatment duration to 3 weeks (wks) in individuals with a rapid virologic response (RVR) defined as plasma HCV RNA < 500 IU/mL by day 2. **Methods:** In this pilot, response guided therapy (RGT), open-label study, 26 non-cirrhotic Chinese subjects with chronic hepatitis C GT 1b [median age = 34 yr (21-66), male = 6, median BMI = 21.7 (15.9-32.1), baseline mean HCV RNA log₁₀ IU/ml = 6.55 (4.09-7.34)] were randomized to receive at the approved doses either: sofosbuvir, ledipasvir and asunaprevir (group 1, n = 12), sofosbuvir, daclatasvir and simeprevir (group 2, n = 6) or sofosbuvir, daclatasvir and asunaprevir (group 3, n = 8). Subjects who achieved RVR were maintained on their respective regimen for a total of 3 wks while others continued for 8-12 wks. Plasma HCV RNA was measured (Lower limit of quantification 25 IU/mL) at 0, 1, 2, 4, 8, 24 and 48 h after dosing, then weekly during treatment and monthly post-treatment until 12 wks. The primary endpoint was the proportion of subjects with plasma HCV RNA below the limit of detection 12 wks (SVR12) after treatment completion. **Results:** RVR was achieved in 18 (66.7%) subjects (6/12, 6/6, 6/8 for group 1, 2, 3 respectively, p = 0.06). Baseline viral load was lower in subjects with RVR as compared to those without RVR (log₁₀ IU/mL 5.96 vs. 7.00, p < 0.0001). The median time to achieve plasma HCV RNA < 25 IU/mL (limit of detection) was shorter in group 1 as

compared to group 3 (p = 0.01). All 18 subjects who had RVR and 3 weeks DAAs achieved SVR12. There were no discontinuations or significant adverse events reported. **Conclusions:** This proof-of-concept SODAPI study explored RGT to shorten the duration of HCV treatment. The results strongly suggest that administration of potent triple regimens containing NS3, NS5A and NS5B HCV-inhibitors leads to RVR (plasma HCV RNA < 500 IU/mL) within 2 days in two-thirds of non-cirrhotic HCV GT 1b-infected subjects. 100% of subjects with RVR and had treatment for 3 wks, achieved SVR12, with excellent adherence and tolerability. Future studies exploring this RGT concept are recommended to reduce duration of therapy, cut drug costs, and to significantly improve accessibility and adherence. (ClinicalTrials.gov number NCT02470858)

Disclosures:

George K. Lau - Consulting: Roche, Novartis, Roche, Novartis, Roche, Novartis, Roche, Novartis

Jinlin Hou - Consulting: Roche, GSK, Novartis, BMS; Grant/Research Support: Roche, GSK, Novartis

Alan S. Perelson - Consulting: Bristol-Myers Squibb, Achillion Pharmaceuticals, Gilead; Stock Shareholder: Pfizer, Merck, Glaxo

Raymond F. Schinazi - Board Membership: Cocrysal Pharma, Inc.; Stock Shareholder: Cocrysal Pharma, Inc.

The following people have nothing to disclose: Yves Benhamou, Guofeng Chen, Jin Li, Qing Shao, Dong Ji, Fan Li, Bing Li, Jialiang Liu, Jian Sun, Cheng Wang, Jing Chen, Vanessa Wu, April Wong, Lei Po, Chris Wong, Stella Tsui Ying Tsang, Wang Yudong, Ruian Ke

LB-24

Cell Specific and Contradicting Functions of miR-615-5p and miR-155 in both Natural Killer cells and their Target Hepatocytes in Hepatocellular Carcinoma.

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Hepatocellular carcinoma (HCC) is a complex challenging disease, highly endemic in Egypt, and not amenable to traditional treatment. Consequently, an urge has developed for new strategies shifted towards boosting the body's immune system to harness HCC progression. Previous literature unraveled the critical role of Insulin-like Growth Factor (IGF) axis as a primary gate-keeper in HCC initiation as well as a paradigmatic immunity modulator. Natural Killer (NK) cells are the native sentinels of the innate immune system against tumors in humans, reported to be mediated by IGF system and a class of non-coding RNAs known as microRNAs. In-silico analysis showed that IGF-1R is potentially regulated by miR-615-5p and miR-155. Therefore, this study aimed at investigating the impact of both miRNAs on the IGF-axis and hence on NK signaling and function in HCC patients and Huh7 cells for the first time as a proposed triad for an efficient immunotherapy. Huh7 cells were cultured and NK cells were isolated from 50 HCC patients. Both cell types were transfected by miRNAs of interest using lipofection. Total RNA was extracted and quantified using qRT-PCR. The cytotoxicity of NK cells was measured by LDH Cytotoxicity Assay using Huh7 as target cells. miR-615-5p and miR-155 are significantly upregulated in NK cells of HCC patients compared to healthy controls. Ectopic expression of miR-615-5p in the effector NK cells and the target Huh7 cells, repressed IGF-1R and its mediator STAT3, opposing to miR-155 which induced IGF-1R and STAT3. The impact of both miRNAs inducing opposing effects on the IGF-axis was then studied in NK cells. miR-615-5p reduced NKG2D, TNF- α and perforin expression level, while miR-155 over expressed the pleiotropic TNF- α only. In

Huh7 cells, the tumor suppressor miR-615-5p repressed mTOR and inhibited NKG2D ligand (ULBP2) halting NK cell recognition ability, in converse, the oncomiR miR-155 elevated mTOR and upregulated ULBP2. Consistent with the previous results, miR-615-5p and miR-155 over-expressing NK cells displayed significantly lower and higher cytotoxicity respectively against Huh7 cells compared with the mock untransfected NK cells. In conclusion, miR-615-5p and miR-155 have contradicting roles in NK cells compared to its target hepatocytes by targeting IGF-1R. Therefore miR-155 might be a potential miRNA enhancing NK cell cytotoxicity, while miR-615-5p is preferentially utilized in target hepatocytes as a tumor suppressor. This provides a novel insight, paving the road for correction of NK functional impairment and eventually an efficient immunotherapy.

Disclosures:

Imam Waked - Advisory Committees or Review Panels: Janssen; Speaking and Teaching: Hoffman L Roche, Merck, BMS, Gilead, AbbVie

The following people have nothing to disclose: Mai A. Rahmoon, Rana A. Youness, Asmaa Gomaa, Gamal Esmat, Hend M. El Tayebi, Ahmed I. Abdelaziz

LB-25

Eomes^{hi} Tbet^{lo} CD56^{bright} natural killer cells: a functionally distinct liver resident population

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Natural Killer (NK) cells are innate lymphocytes crucial for anti-viral and tumour immunity. NK cells are enriched in human liver, accounting for 30-50% of lymphocytes compared to 5-10% in peripheral blood (PB). We have previously demonstrated the presence of haematopoietic precursors in the adult human liver. We believe these are capable of differentiating into mature NK cells in situ. NK cell development is a complex process; however the transcription factors EOMES and T-BET have been identified as key regulators of this process. We aimed to characterise the phenotype, function and transcription factor usage of hepatic NK cells in liver perfusate. During transplantation, Wisconsin preservative-perfused donor livers (n=18) were flushed with saline and mononuclear cells from this perfusate and matched blood samples were assessed by flow cytometry for activatory and inhibitory receptors NKG2C, NKG2D, NKp44, NKp46, NKG2A, intracellular perforin and granzyme B and the transcription factors, TBET and EOMES. NK cell function was assessed by CD107a and IFN- γ expression in response to MHC class I deficient target cells. Over 40% of liver lymphoid cells were NK cells (25.7-67.1%). CD56^{bright} NK cells are enriched in liver perfusate (41.3 \pm 9.7%) compared to PB (10.8 \pm 3.7%). These cells showed increased expression of activatory receptors NKG2D (p=0.001), NKp46 (p=0.006) and NKp44 (p=0.004). Hepatic NK cells differ in expression of cytotoxic molecules, with reduced Granzyme B and increased Perforin in CD56^{bright} liver NK cells (p=0.03). Hepatic CD56^{bright} cells show greater CD107a expression than CD56^{dim} cells in response to target cells (p=0.0006). Hepatic CD56^{bright} NK cells show increased expression of EOMES and reduced TBET. This EOMES^{hi} TBET^{lo} phenotype was absent from PB NK cells. The majority of these cells express CXCR6, a chemokine receptor associated with tissue residency. We believe these cells may develop locally from populations of NK cell precursors (0.57 \pm 0.27%). In this study we describe a unique hepatic population of EOMES^{hi} TBET^{lo} CD56^{bright} NK cells which are phenotypically distinct from peripheral blood and show enhanced cytotoxicity. We believe these cells gener-

ate from local lymphoid precursors and continue to differentiate after transplantation.

Disclosures:

The following people have nothing to disclose: Cathal Harmon, Ronan Fahey, Sarah Whelan, Diarmaid D. Houlihan, Justin Geoghegan, Cliona O'Farrelly

LB-26

The Italian Compassionate use of Sofosbuvir (ITACOPS) in patients with HCV-related cirrhosis waitlisted for liver transplantation: virological and clinical outcomes from a national real-life experience.

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Background/aims. Sofosbuvir/Ribavirin (SOF/R) can prevent HCV recurrence after liver transplantation (LT) in patients with compensated cirrhosis and hepatocellular carcinoma (HCC). This study aimed to assess the real-life efficacy and safety of SOF/R in waitlisted patients within the frame of a national compassionate program endorsed by the Italian Drug Agency (AIFA). **Methods.** Patients with decompensated cirrhosis (Child B and C) and/or HCC within Milan criteria waitlisted for LT were enrolled to receive daily SOF/R until LT or for a maximum of 48 weeks. **Results.** 216 patients (115 without and 101 with HCC) with at least one follow-up visit were included in the present preliminary analysis. Median age was 55 years (25-70), while 74% were male. Genotypes were 1a (16%) 1b (47%), 2 (7%), 3 (22%) and 4 (8%). Basal median MELD and Child-Pugh (C-P) scores were 13 (6-24) and 8 (5-12), respectively. Of the 88 transplanted patients, 56 patients stopped treatment at LT: up to now, 4% of those with HCV-RNA negative for >4 weeks relapsed after LT as compared to 36% of those negative for <4 weeks. In 32 patients, physicians decided to continue treatment after LT (bridge therapy) because still viremic or HCV-RNA negative for <4 weeks at transplant: up to now, 6% of patients relapsed after stopping therapy. In the pre-transplant treatment phase, median time to HCV-RNA clearance was 4 weeks (2-24), while only 2 patients presented a virological failure (1 non-responder and 1 breakthrough). MELD and C-P scores showed a trend to a progressive improvement during treatment in the whole population. However, at 24 weeks of treatment, while mean MELD and C-P scores did not differ from baseline in patients with MELD <15 (n=40) or C-P <8 (n=37), a significant decrease was observed in those with MELD \geq 15 (n=54) or C-P \geq 8 (n=56). In this latter group, MELD improved by at least 3 points in 35% of patients, reaching a value below 15 in 40%, and C-P by 3 points in 28%. 9 patients died during treatment for complications of cirrhosis (7 pts) or related to LT (2 pts). The most frequent adverse event related to treatment was the R-induced anemia, while no severe adverse events could be directly attributed to SOF.

Conclusions. These real-life data indicate that waitlisted patients: 1. SOF/R appears to be safe and effective in preventing viral recurrence after LT also in decompensated cirrhosis, and 2. viral clearance is associated to a significant improvement of liver function within months in a proportion of patients with advanced cirrhosis. If strengthened and confirmed longer, this latter finding may lead to inactivation and even delisting of some of these patients without HCC.

Disclosures:

Paola Carrai - Consulting: Gilead

Paolo Caraceni - Advisory Committees or Review Panels: GSK; Consulting: BMS; Grant/Research Support: Grifols; Speaking and Teaching: Baxter, Kedrion

The following people have nothing to disclose: Silvia Martini, Maria F. Donato, Chiara Mazzarelli, Maria Rendina, Daniela Fili', Alice Gianstefani, Ubaldo Visco Comandini, Stefano Faggioli, Pierluigi Russo, Sandra Petraglia, Simona Montilla, Luca Pani

LB-27

The Italian Compassionate use of Sofosbuvir (ITACOPS) in patients with recurrent HCV hepatitis after liver transplantation: virological and clinical outcomes and safety from a national real-life experience

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Background/aims. New IFN-free regimens have the highest expectations of care in recurrent hepatitis C (RHC) after liver transplantation (LT). This study aimed to evaluate the virological and clinical efficacy of the combination of Sofosbuvir and Ribavirin (SOF/R) for 24 weeks in treating RHC within the frame of a compassionate program endorsed by the Italian Drug Agency (AIFA). **Methods.** Patients with RHC and METAVIR F3-F4 were prospectively enrolled and received daily SOF (400 mg) plus R (400-1200 mg) for 24 weeks. Clinical and virological data were collected at baseline and at regular intervals. Serum HCV-RNA undetectable by Real Time PCR 24 weeks after the start of treatment and 4 and 12 weeks thereafter defined end of treatment viral response (EOT), sustained viral response at 4 (SVR 4) and at 12 (SVR 12) weeks. **Results.** This preliminary analysis refers to 330 patients (252 males, median age 61 years) out of 609 that completed 24 weeks of therapy and had data on SVR 4. HCV genotype frequencies were: 1a (19%), 1b (58%), 2 (5%), 3 (14%) and 4 (4%). Median (range) basal HCV-RNA was 1.8×10^3 IU/ml (38- 1×10^8). Two hundred five (77%) patients failed previous treatments and 210 (69%) had cirrhosis. Tacrolimus or cyclosporin was used in 58.5% and 41.5% of patients. In cirrhotics, basal median (range) Child-

Pugh (CP) and MELD scores were 5 (5-10) and 9 (7-20). EOT was achieved in 329/330 (99.7%) and SVR 4 in 284/330 (86.3%) patients. SVR 12, available in a subgroup of 207 patients, was achieved in 201 (97.1%) of them. No significant differences in SVR4 were observed between HCV genotype 1 Vs other genotypes (83.3% Vs 88.1%, $p=0.95$) or using median daily R ≤ 500 mg (91% Vs 85%, $p=0.12$). A significant better SVR4 rate was observed in patients with METAVIR F3 compared to those with F4 (93.5% Vs 85.3%, $p=0.033$) and in cirrhotics with CP score of 5 Vs CP >5 (92.7% Vs 76.4%, $p=0.002$). Compared to baseline, a significant difference in mean CP score values 4 weeks after the end of treatment was observed between patients with and without SVR4 (from 5.98 to 5.65 Vs 6.74 to 8.91, $p=0.018$). At multivariate analysis, in the whole population the only independent predictor of SVR4 failure was METAVIR F4 (O.R. 6.58, C.I. 1.48-29.3, $p=0.002$) while in cirrhotics was CP score >5 (O.R. 11.8, C.I. 2.57-53.8, $p<0.001$). In 29% of patients the R-induced anemia was treated by EPO. No significant drug interactions and no deaths related to antivirals were reported. **Conclusions.** This large real-life study indicates that SOF/R combination therapy for 24 weeks is a very effective and tolerated treatment for RHC, particularly in patients with less severe RHC or in those with CP5 cirrhosis.

Disclosures:

Paola Carrai - Consulting: Gilead

Paolo Angeli - Advisory Committees or Review Panels: Sequana Medical

Sherrie Bhoori - Speaking and Teaching: Bayer, BTG

The following people have nothing to disclose: Maria Cristina Morelli, Maria Rosa Tamè, Ilaria Lenci, Patrizia Burra, Roberto Ganga, Giada Pietrosi, Rosa Maria Iemmolo, Francesco Paolo Russo, Guido Piai, Carmine Coppola, Simona Montilla, Pierluigi Russo, Sandra Petraglia, Luca Pani, Silvia Martini, Pierluigi Toniutto

LB-28

Efficacy and Tolerability of a 12 week Course of Sofosbuvir-based HCV Antiviral Therapy without Ribavirin for Treatment of Recurrent HCV Genotype 1 Infection after Liver Transplantation

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Aims: To evaluate sustained viral responses (SVR) and potential adverse events in patients with recurrent hepatitis C (HCV) infection after liver transplantation (LT) who underwent 12 weeks (wks) of therapy with either simeprevir/sofosbuvir (SIM/SOF) or ledipasvir/sofosbuvir (LDV/SOF) without ribavirin (RBV) x 12 wks. **Background:** Recurrent HCV infection after LT has been associated with accelerated rates of liver allograft fibrosis & reduced response rates to conventional antiviral therapy. Treatment with new direct acting antiviral medications has resulted in the ability to treat earlier in the post-LT course with greater efficacy & tolerability than ever before. However, given the unique characteristics of this immunosuppressed population, the current clinical guidelines (AASLD-IDSA) continue to recommend treating patients with recurrent HCV genotype 1 (G1) infection with regimens that contain ribavirin when treating for 12 wks or extending therapy to 24 wks in those intolerant to RBV. Previously, the use of RBV as part of the antiviral regimen has been associated with anemia and the potential to worsen renal function in the setting of nephrotoxic immunosuppression. **Methods:** We examined the results of 66 LT recipients having documented recurrent HCV G1 infection who were treated with either SIM/SOF or LDV/SOF for 12 wks without RBV. Although fatigue and headache were reported,

none of the patients had to interrupt or discontinue therapy due to adverse events. **Conclusions:** We observed excellent responses when treating LT patients with recurrent HCV GT1 using combinations of SIM/SOF or LDV/SOF without ribavirin for 12 wks. Given the improved tolerability of these treatment regimens, most patients were able to initiate antiviral therapy earlier in their post-LT course, prior to the development of more advanced fibrosis. These response rates are comparable or better than those previously reported in this unique patient population. Further corroboration of these data may result in the elimination of the need for RBV in 12 wk treatment regimens or for extended duration (24 wk) antiviral therapy in post-LT patients.

	SIM/SOF	LDV/SOF
Total patients (N)	48	18
Rx experienced	35	10
Stage 3 - 4 fibrosis	10	0
GT1a	38	10
Viral load > 6,000,000 IU/mL	11	6
Viral relapse	3	0
SVR (%)	45 (94%)	18 (100%)

Disclosures:

The following people have nothing to disclose: Molly S. Hassett, Heather O'Dell, David S. Raiford, Christie B. Truscott, Chan Y. Chung, Natasha J. Schneider, Andrew Scanga, Roman Perri, Michael K. Porayko

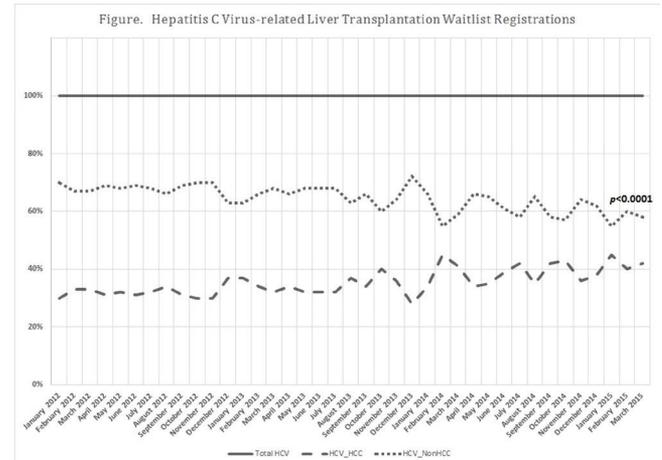
LB-29

Decline in Hepatitis C Virus-related Liver Transplantation Waitlist Registrations among Patients without Hepatocellular Carcinoma: Early Effect of Direct-Acting Antivirals?

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Background: Hepatitis C virus (HCV) infection is the leading indication for liver transplantation (LT) in the U.S. In late 2013, the U.S. Food and Drug Administration (FDA) first approved second-generation direct-acting antiviral (DAA) agents for the treatment of HCV infection – simeprevir on November 22, 2013, and sofosbuvir on December 6, 2013. DAA therapy has been prioritized in patients with HCV-related cirrhosis in an effort to retard clinical progression and induce regression of hepatic histologic damage. Our study aims to analyze the impact of DAA therapy on new waitlist registrations (NWR) for LT in the setting of HCV-related cirrhosis. **Methods:** Utilizing the most up-to-date United Network for Organ Sharing data through March 31, 2015 available as of Sept. 2015, we evaluated HCV-specific NWR trends for 15 months prior to and following the FDA approval of DAA agents. We excluded November and December 2013 from our analysis. We compared the mean of NWR for LT between Aug. 2012 and Oct. 2013 to the mean of NWR for LT between Jan. 2014 and Mar. 2015 among HCV patients without hepatocellular carcinoma (HCC) using the unpaired *t*-test. **Results:** From Aug. 2012 to Mar. 2015, the range for NWR for all indications of LT varied from 740 to 976 each month. The proportion of all NWR for LT represented by HCV patients declined 23.0% (34.8% in Aug. 2012 and 26.8% in Mar. 2015). Moreover, the proportion

of all NWR for LT represented by HCV patients without HCC declined 33.0% (23.0% in Aug. 2012 and 15.4% in Mar. 2015). There was a statistically significant decline in NWR for LT in non-HCC HCV patients from Jan. 2014 to Mar. 2015 (mean, 153 per month) compared to Aug. 2012 to Oct. 2013 (mean, 188 per month) (mean difference 35.0, 95% confidence interval [19.7, 50.2], *p*<0.0001). Among HCV-related NWR for LT, the proportion of patients without HCC declined 12.5% (66.3% in Aug. 2012 and 58.0% in Mar. 2015) (Figure). Numerically, while the absolute number of NWR for HCC HCV LT remained stable, NWR for non-HCC HCV LT declined significantly, resulting in the rising percentage for HCC HCV noted in the Figure. **Conclusions:** We report a statistically significant downtrend in NWR for LT among HCV patients without HCC following the introduction of second-generation DAA agents. Our study is limited by its retrospective design.



Disclosures:

Stevan A. Gonzalez - Consulting: AbbVie; Speaking and Teaching: Gilead, Salix, AbbVie

Zobair M. Younossi - Advisory Committees or Review Panels: Salix, Janssen, Vertex; Consulting: Gilead, Enterome, Coneatus

Aijaz Ahmed - Consulting: Bristol-Myers Squibb, Gilead Sciences Inc., Roche, AbbVie, Salix Pharmaceuticals, Janssen pharmaceuticals, Vertex Pharmaceuticals, Three Rivers Pharmaceuticals; Grant/Research Support: Gilead Sciences Inc.

The following people have nothing to disclose: Ryan B. Perumpail, Robert J. Wong, Channa R. Jayasekera, Jeffrey S. Glenn

LB-30

A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Lusutrombopag for Thrombocytopenia in Patients with Chronic Liver Disease Undergoing Elective Invasive Procedures in Japan (L-PLUS 1)

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Purpose: Thrombocytopenia is common in patients (pts) with chronic liver disease (CLD). These pts often receive platelet transfusions as standard therapy in preparation for invasive procedures. Lusutrombopag (LUSU), an oral thrombopoietin receptor agonist, upregulates platelet production. This multi-center study evaluated the efficacy and safety of LUSU versus (vs) placebo (PBO) in thrombocytopenic pts with CLD undergoing elective invasive procedures. **Methods:** Pts with CLD

who had a platelet count (PTC) $<50,000/\mu\text{L}$ and a planned invasive procedure were randomized (1:1) to receive a LUSU 3-mg tablet or matching PBO once daily for up to 7 days. Platelet transfusion was required for all pts with a preoperative PTC $<50,000/\mu\text{L}$. The primary endpoint was the proportion of pts who required no preoperative platelet transfusion. Key secondary endpoints were the proportion of responders (pts who attained a PTC $\geq 50,000/\mu\text{L}$ with a $\geq 20,000/\mu\text{L}$ increase from baseline) and duration of PTC increase. **Results:** Of 97 pts randomized, 96 (48 in each treatment arm) received LUSU or PBO. Baseline characteristics were balanced in the 2 arms. Mean baseline PTC was $40,400/\mu\text{L}$. Common invasive procedures included percutaneous liver ablation (42.7%), transcatheter arterial chemoembolization (25.0%), and endoscopic variceal ligation (14.6%). The proportion of pts who required no preoperative platelet transfusion was significantly greater with LUSU (79.2% [38/48 pts]) than with PBO (12.5% [6/48 pts]) ($P<0.0001$). The proportion of responders was significantly greater with LUSU (77.1% [37/48 pts]) than with PBO (6.3% [3/48 pts]) ($P<0.0001$). The number of days (d) (median) on which the PTC was $\geq 50,000/\mu\text{L}$ was significantly greater with LUSU (22.1 d without platelet transfusion) than with PBO (3.3 d with platelet transfusion) ($P<0.0001$). Adverse events (AEs) were reported for 93.8% (45/48) of LUSU-treated pts and 100% (48/48) of PBO-treated pts. Frequently reported AEs ($>20\%$) in both arms were postoperative fever (LUSU, 39.6%; PBO, 56.3%), procedural pain (45.8%; 41.7%), procedural hypertension (41.7%; 37.5%), and increased AST (22.9%; 31.3%). Increased ALT also was a frequent AE in PBO-treated pts (20.8%). The incidence of bleeding-related AEs was lower in the LUSU arm (14.6%) than in the PBO arm (27.1%). Protocol-required CT/MRI revealed 1 thromboembolic event of the portal venous system in each arm, neither of which was related to PTC. No pts died or discontinued due to an AE. **Conclusions:** LUSU was an efficacious and well tolerated alternative to platelet transfusion in thrombocytopenic pts with CLD undergoing elective invasive procedures. A global Phase 3 (L-PLUS 2) study is ongoing.

Disclosures:

Namiki Izumi - Speaking and Teaching: MSD Co., Beyer Co., Daiichi Sankyo Co., Gilead, Shionogi Co.

Yukio Osaki - Speaking and Teaching: Sumitomo Dainippon Pharma Co., Ltd., Otsuka Pharma Co., Ltd., Bristol-Myers Squibb, Gilead Sciences Inc., GE Healthcare Japan, Bayer Yakuin, Ltd, Hitachi Aloka Medical, Ltd., MSD Co., Inc., AJINOMOTO PHARMACEUTICALS CO.,LTD., Wako Pure Chemical Industries, Ltd

Mineo Kurokawa - Advisory Committees or Review Panels: Shionogi, Kyowa Hakko Kirin, Celgene, MSD; Grant/Research Support: Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, Kyowa Hakko Kirin, Teijin Pharma, Nippon Shinyaku, Astellas Pharma, Bristol-Myers Squibb, Asahikasei Pharma, Eli Lilly Japan, MSD; Speaking and Teaching: MSD

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The following people have nothing to disclose: Kazuhide Yamamoto, Katsuki Tanaka

LB-31

Cysteamine Bitartrate Delayed-Release (DR) for the Treatment of Nonalcoholic Fatty Liver Disease (NAFLD) in Children (CyNCh) Trial

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Objective: NAFLD, the most common cause of chronic liver disease in children, lacks an approved treatment. Treatment of pediatric NAFLD with cysteamine decreased ALT and AST and increased adiponectin in a 6 month pilot study. Based on this preliminary evidence, the CyNCh trial compared cysteamine bitartrate DR (CyB) to placebo for the treatment of NAFLD in children using liver histology as the primary outcome. **Methods:** CyNCh was a multicenter, double-masked, randomized, placebo-controlled, phase IIb clinical trial conducted by the NIDDK NASH CRN from June 2012 to August 2015. Children ages 8-17 y with a NAFLD Activity Score (NAS) ≥ 4 were randomly assigned 1:1 (stratified by center and weight stratum) to receive twice daily oral CyB (300 mg if ≤ 65 kg, 375 mg if >65 -80 kg or 450 mg if >80 kg) or matching placebo for 52 weeks. The primary outcome was improvement in liver histology, defined as a decrease in NAS ≥ 2 points without worsening of fibrosis; children without follow-up biopsies were counted as unimproved in the intention-to-treat (ITT) analyses. All participants received standardized lifestyle advice. **Results:** 169 children were randomly assigned to receive CyB (n=88) or placebo (n=81). The mean (SD) age was 13.7 (2.7) and 70% were boys. Follow-up liver biopsy was obtained in 81% (71/88) of children taking CyB and 93% (75/81) of children taking placebo (p=0.03). There was no significant difference in the rates of histologic improvement between groups (CyB 28% (25/88) vs placebo 22% (18/81); relative improvement ratio=1.3, 95% CI: 0.8-2.1, p=0.34). ITT analyses of 4 individual histologic features showed no significant (Bonferroni p<0.0125 required) differences between CyB and placebo comparing initial to end-of-treatment improvement in steatosis (30% vs 41%, p=0.15), ballooning (19% vs 26%, p=0.29), lobular inflammation (36% vs 21%, p=0.03), or fibrosis (28% vs 28%, p=0.98). Children receiving CyB had a greater mean (SD) change in ALT (-53 [88] vs -8 [77] U/L, p=0.02) and AST (-31 [52] vs -4 [36] U/L, p=0.008) compared to placebo. Reductions in aminotransferases with CyB treatment occurred within the first 4 weeks and were sustained through 52 weeks of treatment. Serum lipids, cholesterol, and insulin sensitivity were unchanged. There was no difference in adverse events for children taking CyB compared to placebo. **Conclusion:** One year of treatment with cysteamine bitartrate DR was safe, but did not improve liver histology in children with NAFLD compared to placebo. In contrast, there were substantial and

rapid improvements in liver enzymes with CyB treatment. Lessons learned in CyNCh should guide future clinical trials for pediatric NAFLD.

Disclosures:

Joel E. Lavine - Advisory Committees or Review Panels: Janssen; Consulting: Prestige Brands, Pfizer

Brent A. Neuschwander-Tetri - Advisory Committees or Review Panels: Nimbus Therapeutics, Bristol Myers Squibb, Janssen, Mitsubishi Tanabe, Conatus, Scholar Rock, Zafgen, Pfizer, Novartis, Galmed

Sarah E. Barlow - Stock Shareholder: Dyax Corporation

Jean P. Mollenst - Grant/Research Support: scherring, roche, vertex, raptor, abbvie; Speaking and Teaching: vindico

Philip Rosenthal - Advisory Committees or Review Panels: Abbvie, Retrophin; Consulting: Gilead; Grant/Research Support: Gilead, Abbvie, Vertex, BMS, Roche/Genetech

Karen F. Murray - Grant/Research Support: Gilead, Vertex; Stock Shareholder: Merck

Elizabeth M. Brunt - Consulting: Synageva; Independent Contractor: Rottapharm

The following people have nothing to disclose: Jeffrey B. Schwimmer, Laura Wilson, Stavra A. Xanthakos, Miriam B. Vos, Peter F. Whittington, Ajay K. Jain, David E. Kleiner, Mark L. Van Natta, Jeanne M. Clark, James Tonascia, Edward Doo

tors (cholesterol, triglyceride, FFA, HOMA-IR, and BMI) were not affected by the treatment of HL tablet or placebo. There was no drug related safety issues during the study. **[Conclusion]** Despite the short-term treatment only for 12 weeks, HL tablet has shown effectiveness on the reduction of hepatic fat content by MRS without any negative lipid profile, BMI change and adverse effects. Larger extended trials are warranted to assess the long-term efficacy of HL tablet. (ClinicalTrials.gov number, NCT02491905.)

Disclosures:

The following people have nothing to disclose: Yeon Kim, Sung Woon Hong, Mi Hyung Lim, Jong Hwan Lim, Sung Hum Yeon, Yang Hyun Baek, Yong Kyun Cho, Joo Hyun Sohn

LB-32

A new botanical drug, HL tablet, reduces significantly hepatic fat by MR spectroscopy in patients with nonalcoholic fatty liver disease: a placebo-controlled, randomized, Phase II clinical trial

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[Background] The demand of new drugs for nonalcoholic fatty liver disease (NAFLD) is increasing worldwide. *Magnolia officinalis* is a traditional herbal medicine that has been used to treat various liver diseases. HL tablet is a new botanical drug extracted from *magnolia officinalis*. This study is aimed to evaluate the effect and safety of HL tablet in the treatment of patients with NAFLD. **[Methods]** A placebo-controlled, parallel, multi-center, randomized, double-masked, Phase II clinical trial: 74 patients with NAFLD diagnosed by ultrasonic examination were given HL tablets of low dose group (100mg/day), high dose group (300mg/day), or placebo by equal chance (1:1:1) twice daily for 12 weeks. Safety analysis set, full analysis set and per protocol set was analyzed in 73, 68, and 60 subjects, respectively. The primary endpoint was pre and post-treatment variation of hepatic fat content by magnetic resonance spectroscopy (MRS). Secondary endpoints included pre and post-treatment variation of serum AST, ALT, cholesterol, triglyceride, free fatty acid (FFA), homeostasis model assessment-estimated insulin resistance (HOMA-IR), and body mass index (BMI). **[Results]** Compared with placebo group, HL significantly reduced the mean hepatic fat content by MRS in a dose-dependent manner (mean change, high dose vs. placebo, -1.71 vs. +0.63, $p=0.0328$; variation rate compared to baseline, high dose: $-12.14\% \pm 23.46$, low dose: $-3.21\% \pm 31.98$, and placebo: $7.56\% \pm 43.98$). Serum AST and ALT had shown its tendency to decrease in the groups of HL tablet. Other fac-