

Free Paper Session III

#049

Durability of response to peginterferon alfa-2a (40KD) (PEGASYS®) in Asian patients with HBeAg-positive chronic hepatitis B: 12 month follow-up data from a large, randomized study
 GEORGE KK LAU,¹ TEERHA PIRATVISUTH,² SATAWAT THONGSAWAT,³ SEUNG-WOON PAIK,⁴ MICHAEL W FRIED,⁵ KANG-XIAN LUO,⁶ EDWARD GANE,⁷ PATRICK MARCELLIN,⁸ MATEI POPESCU,⁹ JIAN WU¹⁰

¹Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, China, ²Songklanagarind Hospital, Prince of Songkla University, Hat Yai, Thailand, ³Department of Internal Medicine, Chiang Mai University, Chiang Mai, Thailand, ⁴Department of Gastroenterology, Samsung Medical Center, Seoul, Republic of Korea, ⁵University of North Carolina Liver Program, University of North Carolina, Chapel Hill, NC, USA, ⁶Department of Infectious Diseases, Nangfang Hospital, Guangzhou, China, ⁷Gastroenterology Department, Middlemore Hospital, Otahuhu, New Zealand, ⁸Service d'Hépatologie, Hôpital Beaujon, University of Paris, Clichy, France, ⁹Roche, Basel, Switzerland, ¹⁰Roche, Dee Why, Australia

Background and Aims In patients with HBeAg-positive CHB, treatment with peginterferon alfa-2a (PEGASYS) +/- lamivudine achieved significantly higher rates of response 6 months post-treatment versus lamivudine alone (Lau et al. *NEJM* 2005). Durability of PEGASYS in Asian patients participating in a long-term follow-up study (LT-study) was evaluated.

Patients and Methods In the original study, patients received PEGASYS 180µg once-weekly for 48 weeks and were assessed 6 months post-treatment. Patients were offered participation in the LT-study and assessed 12 months post-treatment to see whether the response to PEGASYS treatment (HBeAg seroconversion) was durable.

Results Of those Asian patients treated with PEGASYS alone in the original study, 73/238 (31%) achieved HBeAg seroconversion 6 months post-treatment. Response rates were similar in Asian patients infected with genotypes B and C (30% and 32%, respectively). A total of 150 Asian patients participated in the LT-study, of whom 39% achieved HBeAg seroconversion 6 months post-treatment. Of the patients with HBeAg response 6 months post-treatment, 83% kept their response 12 months post-treatment, while 10 patients had seroreversion or no data. Of the 92 patients without HBeAg response 6 months post-treatment, 13% achieved HBeAg seroconversion at week 96. Thus, among patients participating in the LT-study 40% (60/150) had HBeAg-seroconversion 12 months post-treatment.

#050

Asian patients with HBeAg-negative chronic hepatitis B respond well to peginterferon alfa-2a (40KD) (PEGASYS®) treatment

JI-DONG JIA,¹ TEERHA PIRATVISUTH,² GEORGE KK LAU,³ KANG-XIAN LUO,⁴ RUI JIN,⁴ ZHI-MENG LU,⁵ PATRICK MARCELLIN,⁶ MATEI POPESCU,⁷ PETER BUTTON⁸

¹Liver Research Centre, Beijing Friendship Hospital, Beijing, China, ²Songklanagarind Hospital, Prince of Songkla University, Hat Yai, Thailand, ³Department of Medicine, Queen Mary Hospital, University of Hong Kong, Hong Kong, China, ⁴Beijing You An Hospital, Beijing, China, ⁵Department of

Infectious Diseases, Ruijin Hospital, Shanghai, China, ⁶Service d'Hépatologie, Hôpital Beaujon, University of Paris, Clichy, France, ⁷Roche, Basel, Switzerland, ⁸Roche, Dee Why, Australia

Background and Aims Asian patients have traditionally been considered to respond poorly to interferon-based treatment. We explored the effect of peginterferon alfa-2a (PEGASYS) in Asian patients with HBeAg-negative CHB enrolled in a large randomized clinical trial investigating the response to PEGASYS +/- lamivudine versus lamivudine (Marcellin et al. *NEJM* 2004).

Patients and Methods 177 patients with HBeAg-negative CHB received 48 weeks of PEGASYS (180µg once-weekly) + placebo. Patients were assessed 24 weeks post-treatment.

Results Of the 177 patients, 108 (61%) were of Asian origin. Almost all the Asian patients (97%) were infected with genotypes B or C (42 patients with B, 63 with C, one with D and two other). The rate of combined response (ALT normalization and HBV DNA <20,000 cp/ml) in Asian patients treated with PEGASYS was 45% (49/108), which was higher than that observed in the overall ITT population (36%). Response to PEGASYS was equally good in Asian patients infected with HBV genotype B (43%) and genotype C (49%). HBV DNA suppression of <400 cp/ml was achieved in 26% of Asian patients compared with 19% in the overall ITT population. A total of three (3%) Asian patients treated with PEGASYS achieved HBsAg seroconversion after only 6 months of follow-up.

Conclusions Asian patients responded favorably to PEGASYS treatment; 45% of Asian patients had a virological and biochemical response which was sustained 24 weeks after the end of treatment. Response rates were similar in patients infected with genotypes B or C.

#051

Modeling clinical benefits of suppressing viral replication in HBeAg-negative chronic hepatitis B (CHB) patients: a number-needed-to-treat (NNT) analysis of entecavir and adefovir

UCHENNA ILOEJE,¹ YONG YUAN,² KENNETH KLESCZEWSKI,¹ JOEL HAY³

¹Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, USA, ²Bristol-Myers Squibb Pharmaceutical Research Institute, Plainsboro, New Jersey, USA, ³University of Southern California, Los Angeles, California, USA

Background Treatment success in HBeAg-negative CHB patients is often measured by viral suppression and ALT normalization. We estimated the clinical value of entecavir versus adefovir in this population using estimates of disease progression based upon observed viral suppression from randomized clinical trials.

Methods Data on CHB progression by level of viral replication from a large-scale epidemiology study were matched to two randomized clinical trials: BMS AI-463027, and GS 438 with open-label extension to 5-years. Projected liver complications over 10-years were based on a hypothetical cohort of 1000 patients on either entecavir or adefovir for 5-years continuously. We assumed no incremental benefit for entecavir beyond 1-year of therapy and adefovir results from the latest 5-year analyses were used (Hadzyannis 2005). NNT was calculated as the reciprocal of the projected absolute-risk reduction at 10-years.

Results Of the entecavir-treated subjects, 96% had viral suppression (HBV DNA <1000 copies/mL) after 48-weeks' therapy, compared to 67% of adefovir-treated subjects after 5-years' therapy. Of the 1000 hypothetical patients, projected number of events were: entecavir 29 HCC, 80 cirrhosis and 88 with >1 liver event; and adefovir 75 HCC, 157 cirrhosis and 178 with >1 liver event. Projected

risk of any liver complication over 10-years was 8.8% and 17.8% for entecavir and adefovir, respectively, resulting in an NNT of 11 patients needing treatment with entecavir, rather than adefovir, to prevent one liver complication in 10-years.

Conclusions Results of this model suggest a favorable benefit profile for entecavir in patients with HBeAg-negative CHB.

#052

Entecavir (ETV) treatment through 96 weeks results in substantial virologic and biochemical improvement and HBeAg seroconversion in HBeAg(+) chronic hepatitis B (CHB) patients (study ETV-022)

TING-TSUNG CHANG,¹ YOU-CHEN CHAO,¹ JOSE SOLLANO,² KWANG-HYUB HAN,³ CHING-LUNG LAI,⁴ JUDY LAO-TAN,⁵ NURUL AKBAR,⁶ JIN ZHU,⁷ ANNE CROSS,⁷ HELENA BRETT-SMITH,⁷ BOON-LEONG NEO⁸

¹Tri-Service General Hospital, Taipei, Taiwan, ²Section of Gastroenterology, University of Santo Tomas, Manila, Philippines, ³Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, ⁴Queen Mary Hospital, Hong Kong, China, ⁵Cebu Doctors Hospital, Cebu, Philippines, ⁶Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia, ⁷Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, USA, ⁸Bristol-Myers Squibb Pharmaceutical Research Institute, Singapore

Background ETV demonstrated superior virologic, histologic and biochemical benefit compared to lamivudine (LVD) after 48-weeks of therapy in HBeAg(+) CHB patients. Efficacy and safety data through Week-96 are presented here.

Methods Patients were randomized and treated with ETV 0.5 mg QD (n = 354) or LVD 100 mg QD (n = 355) for 48-weeks. Responders (HBVDNA < 0.7 MEq/mL by bDNA and HBeAg-loss) and Non-responders (HBVDNA ≥ 0.7 MEq/mL) discontinued therapy at Week-48. Virologic responders (HBVDNA < 0.7 MEq/mL and HBeAg(+)) continued into year-2 (ETV n = 243; LVD n = 164) and received blinded treatment up to Week-96. Virologic responders who became Responders or Non-responders during the year-2 dosing discontinued therapy.

Results Overall, 313/354 (88%) ETV patients and 179/355 (50%) LVD achieved Response or Virologic response through week-96. By week-96, 31% of ETV-treated patients vs 26% of LVD-treated patients had achieved Response. By week-96, the cumulative proportion of patients achieving confirmed HBVDNA < 300 copies/mL by PCR was significantly higher (p < 0.0001) for the ETV- (80%) than for the LVD-treated group (39%). The cumulative proportion of patients achieving confirmed ALT normalization (≤1.0 × ULN) was

higher for the ETV-treated group (87%) than for the LVD-treated group (79%) (p = 0.0056). 31% ETV vs 25% LVD patients achieved confirmed HBeAg seroconversion. The safety profile of ETV was comparable to LVD.

Conclusions Continuing through year-2, ETV was superior to LVD in achieving undetectable HBVDNA (<300 copies/mL) and ALT normalization. The frequency of achieving a Response was higher in the ETV- than LVD-treated group. The safety profile of ETV was comparable to LVD through year-2.

#053

Maximal early HBV suppression in telbivudine-treated hepatitis B patients is associated with optimal virologic and clinical efficacy at one year

EDWARD GANE,¹ CHING LUNG LAI,² CW HSU,² SATAWAT THONGSAWAT,³ YUMIN WANG,⁴ Y CHEN,⁵ NANCY LEUNG,⁶ XIA-QIU ZHOU,⁷ YOUNG MYOUNG MOON,⁸ YOU CHEN CHAO,⁹ STEFAN ZEUZEM,¹⁰ ANUCHIT CHUTAPUTTI,¹¹ DOUNG JOON KIM,¹² GEORGE CHAO,¹³ NATHANIEL BROWN,¹³ THE GLOBE STUDY GROUP¹³

¹Middlemore Hospital, ²Chang Gung University and Memorial Hospital, ³Chiang Mai University, ⁴Military Medical University, ⁵Zhejiang University College of Medicine, ⁶Alice Ho Miu Ling Nethersole Hospital, ⁷Ruijin Hospital, Shanghai Second Medical University, ⁸Severance Hospital, ⁹Tri-Service General Hospital, ¹⁰Universitaetsklinik des Saarlandes, ¹¹Phramongkutklao Hospital, ¹²Chuncheon Sacred Heart Hospital, ¹³Idenix Pharmaceuticals

Background The large (1367 patient) database from the GLOBE trial of telbivudine vs lamivudine allows detailed assessment of links between early virologic response and subsequent clinical outcomes.

Methods Efficacy outcomes at 1 year were assessed in relation to HBV DNA levels achieved at Week 24, for the overall study population and by treatment.

Results All clinical and virologic efficacy responses at 1 year were proportional to HBV DNA level at Week 24. Positive predictive values were high for patients who were PCR-negative at Week 24: at 1 year, 36% of this group achieved HBeAg seroconversion, and <1% developed resistance. For patients with HBV DNA >4 log₁₀ at Week 24, the negative-predictive value for failure to HBeAg seroconvert was 93%.

Conclusions Maximal early reduction of HBV DNA levels is associated with optimal 1-year efficacy. Observed relationships between early viral response and subsequent efficacy may be useful in optimizing patient management.

Serum HBV DNA at W24(cp/mL)		PCR-neg			<3 log ₁₀			3–4 log ₁₀			>4 log ₁₀		
		Total	LdT	Lam	Total	LdT	Lam	Total	LdT	Lam	Total	LdT	Lam
HBeAg +	n	349	203	146	120	57	63	162	83	79	272	107	165
	HBeAg seroconv (%)	41	39	45	26	30	23	13	10	17	4	2	6
	ALT normalized (%)	90	90	91	89	91	88	80	75	85	54	54	54
	PCR-negative (%)	90	95	84	70	77	62	30	36	24	5	8	3
	Resistance (%)	1	1	2	3	0	7	8	5	10	11	7	13
HBeAg–	n	335	178	157	38	18	20	40	16	24	30	10	20
	ALT normalized (%)	83	79	88	74	76	71	63	50	71	36	30	39
	PCR-negative (%)	93	96	90	66	72	60	38	63	21	10	20	5
	Resistance (%)	<1	0	1	9	6	13	18	7	25	32	20	39

#054

Polymorphisms of MxA and OAS1 might be associated with outcomes of hepatitis B virus infection

XINXIN ZHANG,^{1,2} XIAOFEI KONG,^{1,2}
ZHITAO YANG,^{1,2} ZHIMENG LU,^{1,2} JIEHONG JIANG,¹
DONGHUA ZHANG,^{1,2} QIMING GONG,¹
DENGDI JIN,^{1,2} SHENYING ZHANG^{1,2}

¹Department of Infectious Diseases, Rui Jin Hospital, Shanghai, China, ²Pole Sino-Francaise de recherche en science vivant et genomes, Shanghai, China

Interferons play important roles in inhibiting the hepatitis B virus replication and imposing great immune pressure for clearing the viral infection. SNPs (Single Nucleotide Polymorphisms) of genes involved in the interferon pathway should be intriguing candidate markers for studying the association with the clinical outcomes of HBV infection. Our study was intended to investigate these potential associations. 253 subjects of self-limited HBV infection and 308 patients with persistent HBV infection from Chinese HAN ethnic were enrolled. The genotypes of 6 SNPs in 4 genes, including interferon alpha receptor-1, interferon gamma receptor 2, OAS1, and MxA, which were related with anti-viral effects of interferons, were detected by the allele specific PCR and RFLP. As the multiplicative logistic model was used to exclude the influence of age and sex, the distribution of CC genotype of MxA-123 is less frequent in the self-limited HBV infection group than that of persistent HBV infection (OR = 1.65, 95% CI: 1.22–2.22, $p = 0.001$). As the dominant/recessive logistic model was used, the dominant C allele at the position -123 of the promoter MxA was observed significantly associated with persistent HBV infection (OR = 2.44, 95% CI 1.218–2.222, $p = 0.02$), meanwhile, the dominant A allele of MxA-123 was associated with self-limited HBV infection (OR = 0.56, 95% CI: 0.385–0.824, $p = 0.003$). The individuals with the dominant G allele of OAS1 3'UTR A/G polymorphism had less liabilities to persistent HBV infection (OR = 0.37, 95% CI 0.164–0.814, $p = 0.014$). These results implied for the first time that the polymorphism of these genes might be associated with outcomes of HBV infection. The combination of other SNPs in interferon pathway should be studies extensively to find more SNPs with clinical promise.

#055

48 Weeks pegylated interferon alfa-2a is superior to 24 weeks of pegylated interferon alfa-2b in achieving HBeAg seroconversion in chronic hepatitis B infection

LAWRENCE SW LAI,¹ TANG-TAT FUNG,²
SIK-TO LAI,³ JAK YIU,³ POLLY LAM,⁴
HAI-YING ZHANG,^{5,6} WAI-MAN WONG,⁷
CHUNG-MAU LO,^{6,8} SHEUNG-TAT FAN,^{6,8}
CHEE-KIN HUI,^{5,6} NANCY LEUNG,⁹
GEORGE KK LAU^{5,6}

¹Department of Medicine, Caritas Medical Centre, Hong Kong SAR, China, ²Department of Medicine, Kwong Wah Hospital, Hong Kong SAR, China, ³Department of Medicine, Princess Margaret Hospital, Hong Kong SAR, China, ⁴Department of Pathology, Queen Elizabeth Hospital, The University of Hong Kong, Hong Kong SAR, China, ⁵Department of Medicine, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China, ⁶Centre For The Study of Liver Diseases, The University of Hong Kong, Hong Kong SAR, China, ⁷St. Paul's Hospital, Hong Kong SAR, China, ⁸Department of Surgery, Queen Mary Hospital, The University of Hong Kong, Hong Kong SAR, China, ⁹Department of Medicine, Alice Ho Miu Ling Nethersole Hospital, Hong Kong SAR, China

Background/Aim Although 48-week therapy with pegylated-interferons has been shown to be effective for the treatment of chronic hepatitis B virus (HBV) infection, the efficacy of a shorter duration of therapy with pegylated interferons is unknown.

Method We retrospectively compared the efficacy of 48 weeks treatment with pegylated-interferon-alfa-2a to a 24-week regime with pegylated-interferon-alfa-2b in 53 hepatitis B e antigen (HBeAg) positive Chinese patients. Sustained virological response (SVR) was defined as HBeAg seroconversion and HBV DNA less than 10^5 copies/ml at 24 weeks after the end-of-therapy (EFU).

Results Twenty-nine patients were treated with 48 weeks of pegylated-interferon-alfa-2a and 24 patients with 24 weeks of pegylated-interferon-alfa-2b. The baseline characteristics were comparable between the 2 groups. At the end-of-therapy, 9 of the 29 patients (31.0%) treated with 48 weeks of pegylated-interferon-alfa-2a compared with 2 of the 24 patients (8.3%) treated with 24 weeks of pegylated-interferon-alfa-2b had HBeAg seroconversion and HBV DNA less than 10^5 copies/ml ($p = 0.09$). At the EFU, 10 of the 29 patients (34.5%) treated with 48 weeks of pegylated-interferon-alfa-2a compared with 2 of the 24 patients (8.3%) treated with 24 weeks of pegylated-interferon-alfa-2b had SVR ($p = 0.04$). There was no withdrawals from treatment in both groups. Adverse events were comparable between the 2 groups.

Conclusion A 48-week course of pegylated-interferon may be associated with a higher SVR when compared with 24-week of pegylated-interferon-alfa-2b.

#056

Comparison of serum HBsAg level and intrahepatic HBsAg distribution in patients infected with genotype B and C

JINJUN CHEN,¹ JINLIN HOU,¹ SHIWU MA,¹
ZHANHUI WANG,¹ YOUFU ZHU,¹ KANGXIAN LUO¹

¹Nikolai V Naoumov Hepatology Unit and Department of Infectious Diseases Nanfang Hospital, Southern Medical University, Guangzhou

Backgrounds HBsAg titer is high in most HBsAg carriers and old generation assays could not measure it accurately. A true quantitative correlation between serum HBsAg and other parameters cannot be concluded previously.

Aims To observe the correlations of HBsAg in serum and liver with other parameters and affects of HBV genotypes (B/C) on HBsAg level in chronic hepatitis B patients, and changes of HBsAg in serum and liver during peginterferon- α -2a treatment.

Methods Sera matched with liver biopsy samples were collected from 50 HBeAg+ and 40 HBeAg- patients without antiviral treatments. Sera from 11 HBeAg+ and 14 HBeAg- patients treated with peginterferon- α -2a were collected at baseline, week12, week24, week48 and week72; liver biopsies were performed at baseline and end of treatment (week48). Serum HBsAg titers were quantified with Abbott Architect HBsAg assay and HBV antigens in liver were determined by immunostain.

Results Serum HBsAg, HBV DNA, proportions of hepatocytes with HBeAg+ nucleus or cytoplasm were greater in HBeAg+ patients than in HBeAg-, HBsAg in liver was not different between two groups. Serum HBsAg level was correlated with HBV DNA ($rs = 0.524$, $p = 0.000$) and proportions of hepatocytes with HBeAg+ nucleus ($rs = 0.455$, $p = 0.001$) in HBeAg+ patients. In HBeAg- group, serum HBsAg had correlation with HBV DNA ($rs = 0.349$, $p = 0.029$) and proportions of HBsAg+ hepatocytes ($r = 0.349$, $p = 0.027$), not with proportions of hepatocytes with HBeAg+ nucleus. Proportions of HBsAg+ hepatocytes were greater in genotype C patients than genotype B in both HBeAg positive ($p = 0.000$) and negative group ($p = 0.012$), HBV DNA in genotype C patients was lower in HBeAg+ group ($p = 0.010$) than in genotype B and no dif-

ference in HBsAg- group ($p = 0.670$). HBsAg declined significantly under peginterferon- α -2a at week12, week24 and week48 compared to baseline (change median, -0.25, -0.58, -0.50 log 10 IU/ml, respectively). Changes of serum HBsAg (week48 vs. baseline) had correlations with changes of proportions of HBsAg+ hepatocytes and that of HBcAg+ nucleus.

Conclusions Serum HBsAg level is associated with HBV replication and can be reduced by peginterferon- α -2a. The overexpression of HBsAg in hepatocyte in patients with HBV genotype C might suggest that there was different export process of HBsAg from hepatocyte between the two genotypes.

#057

The expression of extra cellular matrix genes in hepatic oval cells were similar to hepatic stellate cells (HSCs): an origin of HSCx?

PING WANG,¹ ZHONG-YU YAN,¹ MIN CONG,¹ SHUZHEN TANG,¹ BAO-EN WANG,¹ JIDONG JIA,¹ HONG YOU¹

¹Liver Reserach Center, Beijing Friendship Hospital, Capital University of Medical Sciences

Background Hepatic oval cells, the liver progenitor cells, can be activated and may differentiate to hepatocytes and bile duct cells during the regeneration process after liver injury. In the regeneration region, the existence of hepatic oval cells was always accompanied by hepatic stellate cells. As progenitor cells, whether hepatic oval cells could differentiate towards hepatic stellate cells is till unknown.

Methods Rat hepatic oval cells were isolated by collagenase/proteinase treatment and Percoll density gradient from rat fed with choline-deficient diet supplemented with 0.1% ethionine. Immunohistochemistry, reverse transcriptase-polymerase chain reaction (RT-PCR), Western blot and flurescence activated cell sorter (FACS) were used to identify hepatic oval cells. Gene expressions were analyzed by RT-PCR and Western blot in these primary cultures rat hepatic oval cells and hepatic stellate cell-T6 (HSC-T6)

Results More than 90 percent isolated cells were positive for liver progenitor cell marker OV-6 and c-kit. In addition, these cells expressed hepatocyte markers (albumin and alfa-fetaprotein) and bile duct cell markers (γ -glutamyl transferase, cytokeratin-19, BD1 and BD2). Interestingly, these hepatic oval cells also expressed collagen type 1, collagen type III, connective tissue growth factor (CTGF), matrix metalloproteinase MMP-2, MMP-13 and their tissue inhibitor TIMP-1, which were expressed in HSC-T6. The gene transaction level of CTGF, MMP-2 and MMP-13 were even higher in hepatic oval cells than in HSC-T6. While compared with HSC-T6, oval cells expressed less TIMP-1, collagen type I and type III.

Conclusion These results suggested that hepatic oval cells showed many key phenotypic characteristics of hepatic stellate cells. In combination with the close relationship between hepatic oval cells and hepatic stellate cells, there exists the possibility that hepatic oval cells may be an origin of hepatic stellate cells.

#058

Pradefovir, a prodrug of PMEA, demonstrated an excellent liver-targeting property in rats and humans

CHIN-CHUNG LIN,¹ CHRISTINE XU,¹ LI-TAIN YEH¹

Background Pradefovir (PDV) is a CYP3A4-activated prodrug of PMEA with a better safety profile than Adefovir dipivoxil (ADV), an esterase-activated prodrug of PMEA in rats.

Aim To evaluate the liver-targeting property of PDV in rats and humans.

Methods Rats received an oral dose (30 mg/kg) of either [¹⁴C]PDV or [¹⁴C]ADV. At 2, 4, and 24 hr after dosing, whole body

autoradiograms were analyzed qualitatively for localization of radioactivity and quantitatively by densitometry. In addition, plasma samples were also analyzed for PMEA using a validated LC-MS/MS method. In a phase 2 study, HBV patients received 10 mg of ADV or PDV once daily for 24 weeks. At week 24, serum samples were collected and analyzed for PMEA and HBV titers.

Results In rats, plasma PMEA AUC and liver radioactivity AUC was 1,370 ng.hr/mL and 14,012 nCi.hr/g, respectively, after PDV dosing, and 3,680 ng.hr/mL and 889 nCi.hr/g, respectively, after ADV dosing. The liver to plasma ratio was 10.2 after PDV dosing and 0.242 after ADV dosing. In humans, plasma PMEA AUC was 82.3 ng.hr/mL after PDV dosing and 298 ng.hr/mL after ADV dosing. HBV log decline was 4.3 after PDV dosing and 3.7 after ADV dosing.

Conclusions (1) In rats, ratio of liver to plasma after PDV dosing was 42x that after ADV dosing, indicating excellent liver-targeting of PDV in rats. (2) In humans, PDV dosing yielded much lower plasma PMEA levels whereas it produced greater decline in HBV DNA, suggesting a good liver-targeting property.

#059

In vitro assessment of a novel porcine liver slice-filled bioartificial liver (BAL) for dialysis of liver failure patients

HOLGER BEHRING,¹ JENNIFER TAM,¹ YOUNG PARK,¹ HYOUNG YUN,¹ ANDY DO,¹ BRAD GRAY,¹ DELAI ZHAO,¹ CHARLES GROPPER,¹ JAEHO JUNG,¹ ROBERT GISH,² BRENDAN MCGUIRE,³ ANGELA PANOSKALTSIS-MORTARI,⁴ GEORGE LAU,⁵ YOUNG-SUK LIM,⁶ HAN CHU LEE,⁶ DONG-JIN SUH,⁶ SUNG-SOO PARK¹
¹HepaHope, Inc., ²California Pacific Medical Center, ³University of Alabama, ⁴University of Minnesota, ⁵Hong Kong University, ⁶University of Ulsan

Due to the large number of patients who die annually from acute liver failure worldwide, the BAL has been identified as a medical need. With efficient toxin removal and biochemical function, the new Hepa-Hope BAL is designed to treat such patients. The BAL contains porcine liver slices with multiple, native cell types in well-preserved structures that allow high capacity and efficient removal of toxins in acute hepatic failure patients. Several 6 hour exposure *in vitro* BAL studies designed to mimic *in vivo* treatment conditions were conducted to evaluate: 1) ammonia and drug clearance, 2) stability tests under shipping conditions, 3) effects of human anti-GAL on porcine slices, and 4) potential for porcine endogenous retrovirus (PERV) infection. Studies examining ammonia clearance demonstrated an 88% clearance of ~1000 μ g/dL (~590 μ M) ammonia in 2 L human plasma (circulation rate ~6 L/hour). Clearance of nine drugs commonly administered to liver failure patients (Diazepam, Dopamine, Fentanyl, etc.) indicated a varied metabolism profile, with clearance ranging from 15 to 58% of initial dose. The BAL retained functionality (assessed by ammonia/drug clearance) and histological integrity (by light microscopy) after shipping periods lasting up to 15 hours. Perfusion with human plasma did not appear to adversely affect BAL function, and minimal staining of anti-GAL antibodies was seen after perfusion. Samples of plasma were also studied for PERV infection; results are pending at the time of this abstract's submission.

Conclusion The favorable pre-clinical *in vitro* results have led to *in vivo* studies designed to further characterize this BAL.

#060

Short-term cardiotrophin-1 (CT-1) rescues marginal cirrhotic liver remnant after major hepatectomy without increasing the risk of tumor recurrenceZHEN FAN YANG,¹ CHI KEUNG LAU,¹PATRICIA NGAI,¹ DAVID WING YUEN HO,¹KA HO TAM,¹ CHI TAT LAM,¹RONNIE TUNG-PING POON,¹ SHEUNG TAT FAN¹¹Department of Surgery, The University of Hong Kong

Background Hepatic resection is not applicable to the majority of hepatocellular carcinoma (HCC) patients due to insufficient liver function reserve. Cardiotrophin-1 (CT-1), a member of the interleukin-6 family, has demonstrated protective and pro-proliferative effects in the myocytes and hepatocytes.

Aim The present study aimed to investigate the potential role of CT-1 in rescuing marginal cirrhotic liver remnant in a rat orthotopic HCC model.

Materials and Methods Liver cirrhosis was induced by subcutaneous injection of CCL4 for 8 weeks. The rat orthotopic HCC model

was generated by injecting HCC cells into the left lobe of the liver. Animals received the following treatments: 1) hepatectomy only, n = 6; 2) CT-1 (2 µg/kg) intraportal vein injection (i.pv) right after hepatectomy, n = 6; 3) CT-1 (2 µg/kg) i.pv right after hepatectomy, and 1 µg/kg intraperitoneal injection (i.p) 24 hr after hepatectomy, n = 6; 4) CT-1 (2 µg/kg) i.p 24 hr before hepatectomy, n = 6; 5) CT-1 (2 µg/kg) i.p 24 hr before hepatectomy, and 1 µg/kg i.p 24 hr after hepatectomy, n = 6.

Results The double-dose CT-1 significantly improved animal survival, and all the surviving animals did not present with tumor recurrence. CT-1 administration decreased the plasma AST and ALT levels, augmented the number of Ki-67⁺ and gp130⁺ cells, and restored the ATP levels. CT-1 culture enhanced the viability of primarily isolated hepatocytes. CT-1 treatment increased the expression of Akt and PI3K in the liver remnant.

Conclusions A short-term administration of CT-1 could improve animal survival after major hepatectomy, through promoting cell proliferation and restoring cell survival.