

fining potential relapsers. It is well known that the enhancement of Th1 response is closely related to HCV clearance. Dendritic cells (DC) are potent antigen presenting cells that regulate Th1/Th2 differentiation, which are numerically and functionally impaired in HCV infection. However, little is known whether the restoration of DC function contributes to a successful outcome in the combination therapy. We thus aimed to evaluate the feasibility of blood DC frequencies and their function for the predictors of relapse. Methods: Twenty-five CHC patients with HCV genotype 1 and high titer were enrolled in this study. They received 48 weeks of PEG-IFN α 2b and ribavirin and their virological response was determined at week 12 of therapy and 24 weeks after its completion. During the treatment, frequencies of myeloid DC (MDC) and plasmacytoid DC (PDC) and their changes from the beginning of the therapy were determined by means of flow cytometric analyses. The ability of patient DC to stimulate allogeneic CD4+ T cells was assessed at the end and after the therapy by determining the ratio of DC-primed T cell proliferation to those in healthy counterparts. Results: Among 25 patients who completed 48-week treatment, 11 patients achieved sustained virological response (SVR), 11 were transient response (TR) and 3 were non-response (NR), respectively. In comparison between the SVR and TR groups, MDC and PDC frequencies did not differ throughout the therapy. By tracing the changes from the beginning to week 12, MDC frequency was not different between the groups. In contrast, the PDC frequency significantly declined in TR group ($p < 0.05$), whereas those in SVR did not. At week 48 and thereafter, allostimulatory capacity of DC in TR was sustained to be lower than those in SVR patients ($p < 0.05$). Even in patients who once attained negative serum HCVRNA at week 12, PDC decrease and impaired DC function were more significant in TR than in SVR ($p < 0.05$). Negative predictive value of DC function at week 48 for SVR was 100%, when DC-primed CD4 T cell proliferation ratio was less than 0.7. Conclusions: The early decline of PDC frequency and sustained DC dysfunction at the end of treatment are served as predictors of relapse in 48 weeks of PEG-IFN α 2b and ribavirin therapy.

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TWO-YEAR RESULTS FROM THE GLOBE TRIAL IN PATIENTS WITH HEPATITIS B: GREATER CLINICAL AND ANTIVIRAL EFFICACY FOR TELBIVUDINE (LDT) VS. LAMIVUDINE Ching-Lung Lai¹, Edward Gane², Chao-Wei Hsu³, Satawat Thongsawat⁴, Yumin Wang⁵, Yagang Chen⁶, Elizabeth J. Heathcote⁷, Jens Rasenack⁸, Natalie Bzowej⁹, Nikolai Naoumov¹⁰, Stefan Zeuzem¹¹, Adrian Di Bisceglie¹², George C. Chao¹³, Barbara A. Fieldman Constance¹³, Nathaniel A. Brown¹³, Study Group Globe¹³; ¹University of Hong Kong, Hong Kong; ²Middlemore Hospital, Auckland, New Zealand; ³Chang Gung University and Memorial Hospital, Taipei, Taiwan; ⁴Chiang Mai University, Chiang Mai, Thailand; ⁵Military Medical University, Chongqing, China; ⁶Zhejiang University College of Medicine, Hangzhou, China; ⁷Toronto Western Hospital, Toronto, ON, Canada; ⁸Albert Ludwigs Universität, Freiburg, Germany; ⁹Sutter Health, San Francisco, CA; ¹⁰University College, London, United Kingdom; ¹¹Saarland University Hospital, Homburg, Germany; ¹²Saint Louis University, St. Louis, MO; ¹³Idenix Pharmaceuticals, Cambridge, MA

Background: First-year results from the GLOBE trial, reported in 2005, indicated superior efficacy for telbivudine vs. lamivudine on all measures of direct antiviral efficacy and on several key clinical efficacy measures. Here we report the 2-year results from this large trial. Methods: The GLOBE study is a randomized, blinded Phase III trial comparing telbivudine (600 mg/d PO) vs standard lamivudine (Lam) treatment (100 mg/d PO) for 2 years, in an intent-to-treat population of 1,367 patients (pts) with chronic hepatitis B recruited from 20 countries. Key entry criteria were HBsAg+, HBV DNA >6 log₁₀ copies/mL by COBAS Amplicor PCR assay, ALT 1.3-10 xULN, and compensated liver disease. Patients were pre-stratified for HBeAg status (+/-) and ALT < or > 2.5 xULN. Follow-up liver biopsies were performed at 1 year but were

not repeated at 2 years. Results: Treatment groups were well-matched at Baseline. Efficacy data (ITT) at Week 104 are shown below. At 2 years, LdT was superior to Lam for the primary efficacy measure (Therapeutic Response; HBV DNA <5 log₁₀ with HBeAg loss or ALT normalization) and for all direct measures of antiviral efficacy in both HBeAg+ and HBeAg- pts. HBeAg loss was significantly better for LdT for the subgroup of pts recommended for treatment by AASLD and Asia-Pacific guidelines, i.e. baseline ALT \geq 2xULN. ALT normalization was proportionally greater for LdT in both HBeAg+ and HBeAg- pts ($p=0.08$). Treatment failure was significantly more common with Lam in both groups. Ongoing analyses of genotypic resistance will be available at the meeting. Both study drugs were generally well-tolerated, with similar patterns of clinical adverse events. Conclusions: During 2 years of treatment, telbivudine produced significantly greater antiviral efficacy than lamivudine and was associated with greater and better-maintained clinical efficacy, in HBeAg+ and HBeAg- patients with chronic hepatitis B.

Response	HBeAg Positive		HBeAg Negative	
	LdT	Lam	LdT	Lam
n †	458	463	222	224
Mean log ₁₀ HBV DNA ↓	-5.7*	-4.4	-5.0*	-4.2
% PCR negative	54*	38	79*	53
% ALT normalization	67	61	75	67
% Therapeutic Response	61*	47	74*	62
% HBeAg loss	34	29	-	-
% HBeAg loss (baseline ALT \geq 2 xULN)	40*	32	-	-
% HBeAg seroconversion	29	24	-	-
% Primary Treatment Failure‡	4*	12	0*	3

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Ching-Lung Lai - Scientific Advisor: Idenix Pharmaceuticals
Stefan Zeuzem - Scientific advisor: Idenix/Novartis
Adrian Di Bisceglie - Scientific Advisor: Idenix
George C. Chao - Employee: Idenix Pharmaceuticals
Barbara A. Fieldman Constance - Employee: Idenix Pharmaceuticals
Nathaniel A. Brown - Employee: Idenix Pharmaceuticals

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COMBINATION OF TELAPREVIR (VX-950) AND PEG-IFN-ALFA SUPPRESSES BOTH WILD-TYPE VIRUS AND RESISTANCE VARIANTS IN HCV GENOTYPE 1-INFECTED PATIENTS IN A 14-DAY PHASE 1B STUDY Tara Kieffer¹, Christoph Sarrazin², Janice Miller¹, Stella Traver², Yi Zhou¹, Doug Bartels¹, Brian Hanzelka¹, Ute Müh¹, Chao Lin¹, Henk Reesink³, Ann Kwong¹, Stefan Zeuzem²; ¹Infectious Diseases, Vertex Pharmaceuticals Inc., Cambridge, MA; ²Internal Medicine, Universitätsklinikum des Saarlandes, Homburg, Germany; ³Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, Netherlands

Background: Telaprevir (VX-950) is an orally-active HCV protease inhibitor that profoundly reduced plasma HCV RNA in genotype 1 patients during 14 days of dosing alone (median 4.4-log₁₀ decline in optimal dose group) and in combination with peg-IFN-alfa (peg-IFN) (median 5.5-log₁₀ decline). Using a highly sensitive sequencing assay that detects minor populations of viral variants ($\geq 5\%$), mutations were identified in a previous clinical study that conferred low-level (V36M/A, T54A, or R155K/T) or high-level resistance (A156V/T and 36/155) in vitro. These variants were sensitive to IFN in the HCV replicon system. We now report a detailed kinetic analysis of these variants in a second study of 14 days of dosing with telaprevir (750 mg q8h) alone (n=8) or in combination with peg-IFN (n=8). Methods: Plasma HCV RNA was isolated at days 4, 8, 12, and 14 during dosing and 7-10 days after dosing. The NS3 protease domain cDNA was amplified by nested RT-PCR, cloned and sequenced with a lower limit of detection (LLD) of 100 IU/mL. Sequence changes were analyzed from about 75 clones/patient/time point. Results: In patients dosed with telaprevir/peg-IFN, wild-type virus was detected at

day 4, and either wild-type or resistant virus was observed at day 8 in 4 of 8 patients with HCV RNA levels above the LLD. Viral levels continued to decline in all patients. All 8 patients began standard therapy (peg-IFN/RBV) and their HCV RNA levels were undetectable 3 months after the 14-day study period. Among patients dosed with telaprevir alone, four patients had a breakthrough or plateau response. In these patients, R155 and A156V/T variants were detectable by day 8, and the V36(M/A)/R155(K/T) variant predominated by day 14. Four other patients dosed with telaprevir alone all had a continuous decline in HCV RNA levels. Two of these patients had A156V/T uncovered by day 8, while the other two had levels below LLD. Conclusions: The rapid and dramatic antiviral response to telaprevir reflects a sharp reduction in wild-type virus. Viral variants were uncovered as wild-type virus was cleared. HCV RNA levels can decline in patients receiving telaprevir monotherapy, even in those with detectable A156V/T variant. Viral rebound with monotherapy appears to result from the presence of V36(M/A)/R155(K/T); this could be due to greater fitness of this variant compared to A156V/T. The combination of telaprevir and peg-IFN suppressed resistant variants, indicating that these variants are fully sensitive to peg-IFN.

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 Yi Zhou - Employee/Stock: Vertex Pharmaceuticals
 Doug Bartels - Employee/Stock: Vertex Pharmaceuticals
 Brian Hanzelka - Employee/Stock: Vertex Pharmaceuticals
 Ute Müh - Employee/Stock: Vertex Pharmaceuticals
 Chao Lin - Employee/Stock: Vertex Pharmaceuticals
 Henk Reesink - Consultant: Schering-Plough; Consultant: Chiron; Grant/Research Support: Schering-Plough; Grant/Research Support: Chrion; Grant/Research Support: Roche; Grant/Research Support: Vertex
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VALOPICITABINE (NM283) PLUS PEG-INTERFERON IN TREATMENT-NAÏVE HEPATITIS C PATIENTS WITH HCV GENOTYPE-1 INFECTION: HCV RNA CLEARANCE DURING 24 WEEKS OF TREATMENT Eric Lawitz¹, Tuan Nguyen², Ziad Younes³, John Santoro⁴, Norman Gitlin⁵, David McEniry⁶, Richard Chasen⁷, John Goff⁸, Steven Knox⁹, Kristin Kleber⁹, Bruce Belanger⁹, Nathaniel A. Brown⁹, Douglas Dieterich¹⁰, Investigator Group The 006⁹; ¹Alamo Medical Research, San Antonio, TX; ²Tuan Nguyen, M.D., San Diego, CA; ³Gastroenterology Center of the Mid-South, Germantown, TX; ⁴AGA Clinical Research Assoc., Egg Harbor, NJ; ⁵Atlanta Gastroenterology Associates/Emory University, Atlanta, GA; ⁶Northwest Medical Specialties, Tacoma, WA; ⁷Maryland Digestive Disease Research, Laurel, MD; ⁸Rocky Mountain Gastroenterology, Lakewood, CO; ⁹Idenix Pharmaceuticals, Cambridge, MA; ¹⁰Mt. Sinai School of Medicine, New York, NY

Background: Valopicitabine (NM283) showed dose-related anti-HCV activity, alone and combined with pegylated interferon (NM283/pegIFN) in trials of patients with hepatitis C (HCV genotype 1). In this ongoing Phase IIb trial, Week 4 (W4) data from treatment-naïve patients showed significantly greater HCV RNA reductions with NM283/pegIFN compared to pegIFN alone (Dieterich, EASL 2006). Here we report longer term results from this trial. **Methods:** Enrolled pts have hepatitis C (HCV-1), HCV RNA $\geq 5 \log_{10}$ IU/mL by TaqMan™ PCR, ALT $< 5 \times$ ULN, compensated liver disease, and no prior treatment. Pts were randomized into 5 treatment groups: (A) pegIFN alone QW to W4, with NM283 added in W5 (dose ramped from 400 to 800 mg/d), with both drugs continued thereafter (B) NM283 200 mg/d + pegIFN (C) NM283 ramped 400 to 800 mg/d in 1st wk, + pegIFN (D) NM283 800 mg/d, + pegIFN (E) NM283 800 mg/d, + pegIFN. PegIFN- $\alpha 2a$ is dosed 180 μ g QW starting Day 8 (Groups A-D) or Day 1 (Group E). Serum HCV RNA is assessed by the TaqMan™ real-time PCR assay, with PCR-nondetectability reported here at the historically-

used Amplicor™ PCR quantitation limit and the TaqMan™ limit. **Results:** The study is fully enrolled with 173 pts. Final W12 HCV RNA results and interim W24 results (with data presently available for 96/173 pts) are shown below. Compared to prior W4 results, W12 and W24 data show a convergence of anti-HCV efficacy across treatment groups due to continued viral clearance to PCR-nondetectable levels in most pts in all groups. Early virologic response ($\geq 2 \log_{10}$ drop in HCV RNA at W12) was observed in 82-92% of pts. Treatment B (with NM283 200 mg/d) has been generally well-tolerated. GI side effects were more common and were occasionally severe at the 800 mg/d NM283 dosing level (arms C-E). After a protocol amendment pts are continuing NM283 at the 200 or 400 mg/d levels (with weekly pegIFN) with improved tolerance to date. Final W24 results will be available at the meeting. **Conclusions:** At doses as low as 200 mg/d, valopicitabine plus pegIFN markedly suppresses viremia in treatment-naïve patients with HCV-1 infection. By W24, most patients have achieved PCR-nondetectable HCV RNA by the sensitive TaqMan assay.

Treatment Group	Mean \downarrow from Baseline (log ₁₀ IU/mL)				Amplicor™ negative <600 IU/mL (%)		TaqMan™ negative <20 IU/mL (%)	
	n	Week 12	n	Week 24	Week 12	Week 24	Week 12	Week 24
A	34	-4.11	18	-4.50	68	83	59	61
B	34	-3.86	20	-4.44	68	75	44	70
C	34	-4.11	20	-4.48	74	80	44	65
D	36	-4.57	18	-4.71	81	83	67	72
E	35	-4.04	20	-4.06	69	60	54	50

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 Bruce Belanger - Employee: Idenix Pharmaceuticals
 Nathaniel A. Brown - Employee: Idenix Pharmaceuticals
 Investigator Group The 006 - Employee: Idenix Pharmaceuticals
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INHIBITORY ACTIVITY OF THE 2,4-DIAMINO-6-[2-(PHOSPHONOMETHOXY)ETHOXY]-PYRIMIDINE (PMEO) AGAINST WILD TYPE AND DRUG RESISTANT MUTANTS OF HBV Marie-Noelle Brunelle¹, Julie Lucifora¹, Stephanie Villet¹, Johan Neyts², Christian Trepo¹, Fabien Zoulim¹; ¹INSERM U271, Lyon, France; ²Rega institute for Medical Research, Leuven, Belgium

Background/Aim. Successive anti-human hepatitis B virus (HBV) therapy with nucleoside analogs leads to the emergence of resistant HBV strains harboring complex pattern of mutations within HBV polymerase gene. The development of new HBV inhibitors is thus needed. The 2,4-diamino-6-[2-(phosphonomethoxy)ethoxy]-pyrimidine (PMEO), a novel acyclic pyrimidine nucleoside phosphonate analog, was shown to have an anti-HBV effect comparable to adefovir (ADV) in hepatoma cells expressing permanently wild-type (wt) or lamivudine-resistant (LAM-R) HBV. In this study, we investigated the cross-resistance profile of multiple-resistant HBV strains against PMEO in comparison to LAM, ADV, entecavir (ETV) and tenofovir (TDF). **Methods.** The anti-HBV activity of the drugs was evaluated after transfection of Huh7 cells with HBV genomes cloned in a pTriex-HBV vector. These genomes are from a) laboratory HBV strains [wt, LAM-R (L180M/M204V), ADV-R (N236T) or LAM+ADV-R (L180M/M204V/N236T)], b) the viral quasispecies of a chronically infected patient failing successive therapy with LAM and LAM+ADV (patient 1) [wt, LAM-R (L180M/M204V; L180M/A181V) or LAM+ADV-R (V173L/L180M/A181V; V173L/L180M/A181V/M204V; V173L/L180M/A181V/N236T; V173L/L180M/A181V/M204V/N236T)], c) a chronically infected patient failing successive therapy with LAM and ETV (patient 2) [wt, LAM-R (V173L/L180M/M204V) or ETV-R (L180M/M204V/S202G)]. Drugs were administered daily from day 4 to day 9 post transfection. Cells were lysed at day 9 for analysis of intracellular viral DNA by Southern Blot hybridization.