

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 $\alpha$ 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 HCV RNA 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 $\alpha$ 2b and ribavirin therapy.

#### Disclosures:

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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

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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 log<sub>10</sub> 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 log<sub>10</sub> 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 <sub>10</sub> 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

#### Disclosures:

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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

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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-log<sub>10</sub> decline in optimal dose group) and in combination with peg-IFN-alfa (peg-IFN) (median 5.5-log<sub>10</sub> 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