

Entecavir is Superior to Continued Lamivudine for the Treatment of Lamivudine-refractory, HBeAg(+) Chronic Hepatitis B: Results of Phase III Study ETV-026

M Sherman¹, C Yurdaydin², J Sollano³, M Silva⁴, Z Goodman⁵, L Chen⁶, A Cross⁶, R Hindes⁶, the BEHoLD Study Group
¹Toronto General Hospital, Toronto, Canada; ²Ankara University Medical School, Ankara, Turkey; ³University of Santo Tomas, Manila, Philippines; ⁴Hospital Universitario Austral, Pilar, Argentina; ⁵Armed Forces Institute of Pathology, Washington DC, USA; ⁶Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT, USA

R.0780

Background

- Entecavir (ETV) is a potent and selective inhibitor of hepatitis B virus (HBV) polymerase
- ETV demonstrated superiority to lamivudine (LVD) in phase II and III trials in nucleoside-naïve and LVD-refractory HBeAg-positive and HBeAg-negative patients^{1,2}
- ETV 1.0 mg was selected from phase II studies for LVD-refractory patients
- Most patients treated with LVD eventually develop resistant HBV³
- Controlled clinical trials which compare continued lamivudine to other therapies in LVD-refractory HBV have not been published

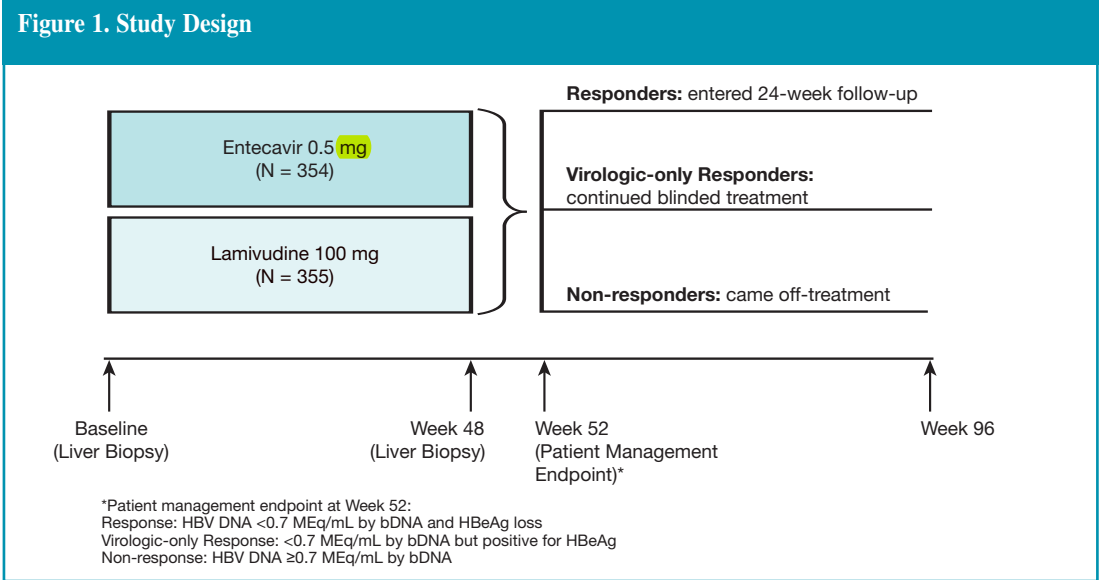
Objective

- To compare the efficacy and safety of **ETV (1.0 mg QD)** to continued **LVD (100 mg QD)** in patients with chronic hepatitis B (CHB) who were **HBeAg-positive and refractory to LVD therapy**

Methods

Study Design

- Phase III, international, double-blind, randomized (1:1) comparison of 48 weeks of therapy: ETV 1.0 mg QD (n=141); LVD 100 mg QD (n=145)**
- Patients were enrolled from 84 sites from Europe and the Middle East (28 sites), North America (28 sites), Asia (17 sites), Australia (6 sites) and South America (5 sites)
- At randomization, patients were assigned to either remain on LVD therapy or switch directly to ETV



- Genotypic and phenotypic HBV resistance was monitored by analysis of random samples from ETV-treated patients at baseline and Week 48, and samples from all patients with virologic rebound (≥1.0 log₁₀ increase in HBV DNA from baseline)

Key Inclusion Criteria

- Age ≥16 years**
- Refractory to LVD therapy defined as:
 - Persistently detectable HBV DNA (bDNA) after ≥36 weeks of LVD therapy, OR
 - Breakthrough viremia while receiving LVD, OR
 - Recurrence of HBV viremia after LVD discontinuation that persists when LVD is resumed, OR
 - Documented genotypic LVD resistance and HBV viremia while receiving LVD
- Documented HBV viremia ≥4 weeks prior to screening by any commercial assay or >1.5x10⁶ copies/mL (PCR)
- HBV DNA ≥3 MEq/mL (bDNA) at screening**
- HBsAg-positive for ≥24 weeks prior to screening**
- HBeAg-positive
- Serum ALT 1.3-10 x ULN**
- Evidence of CHB on biopsy** during screening or ≤52 weeks prior to randomization
- Compensated liver disease due to CHB
- No co-infection with HIV, HCV or HDV**

Study Endpoints at Week 48*

- Co-primary efficacy endpoints:
 - Histological Improvement: ≥2-point decrease in Knodell necroinflammatory score and no worsening of fibrosis (worsening: ≥1-point increase in the Knodell fibrosis score) compared with baseline
 - Composite endpoint: undetectable serum HBV DNA by bDNA (<0.7 MEq/mL) and ALT <1.25 x ULN
- Secondary efficacy endpoints included:
 - Improvement (≥1-point decrease from baseline) in Ishak fibrosis
 - Undetectable serum HBV DNA by bDNA (<0.7 MEq/mL)
 - Undetectable serum HBV DNA by PCR (<300 copies/mL)
 - Mean log₁₀ reduction from baseline in HBV DNA levels by PCR
 - Seroconversion (loss of HBeAg and appearance of anti-HBe)
 - ALT normalization (≤1.0 x ULN)
 - HBV resistance
- Primary safety endpoint
 - Proportion of patients who discontinued treatment due to adverse events

*Efficacy results are reported through Week 48 (data cut-off: March 10, 2004) and cumulative safety data are reported for patients who received ≥1 dose of study therapy through June 1, 2004

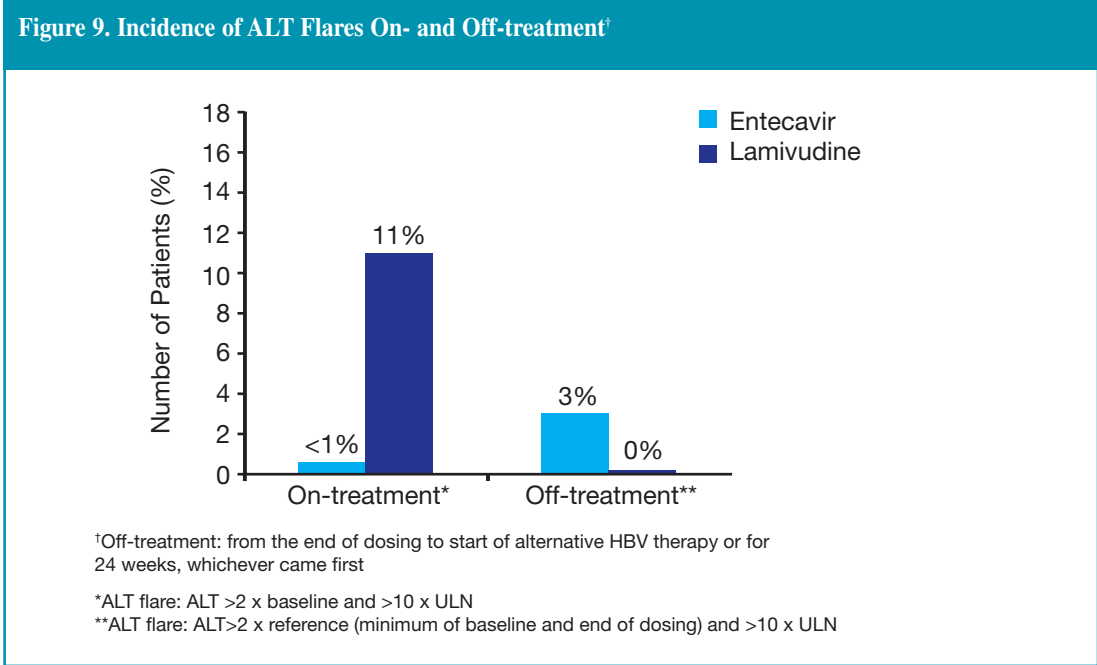
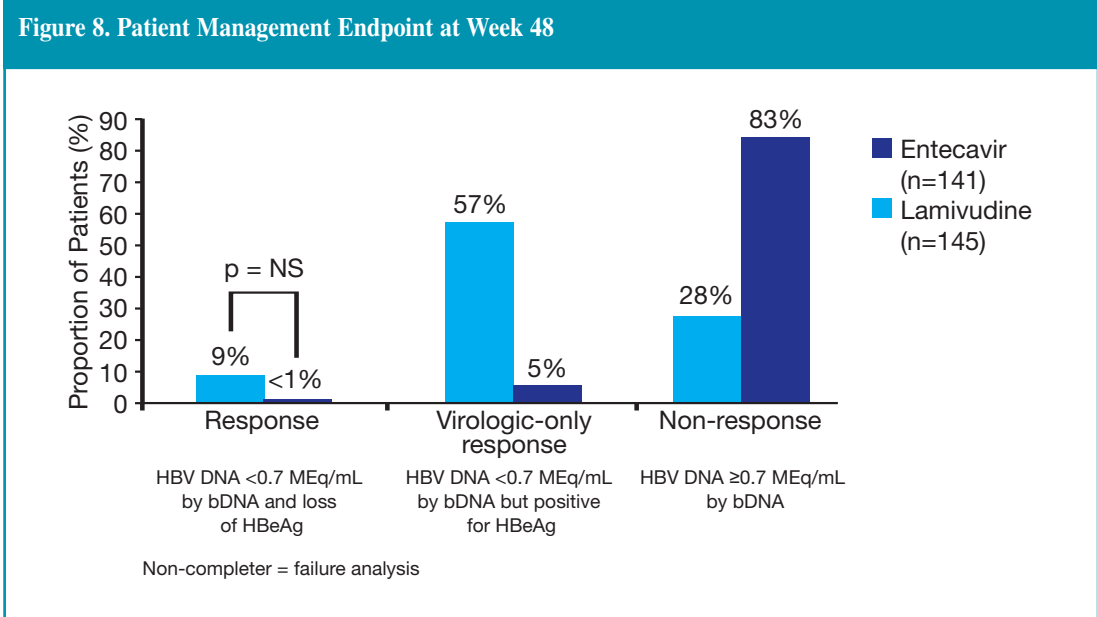
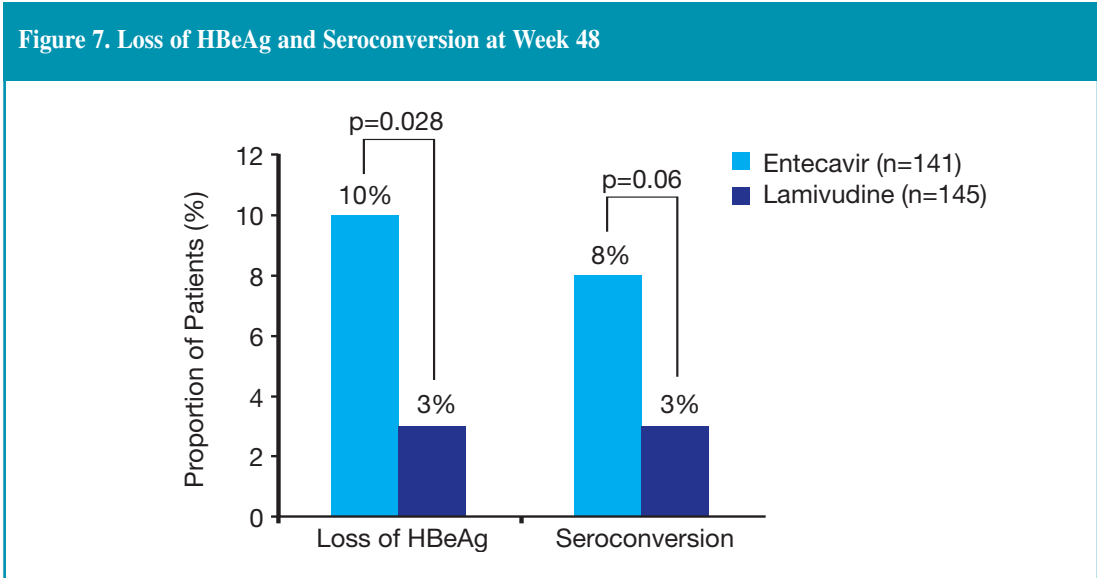
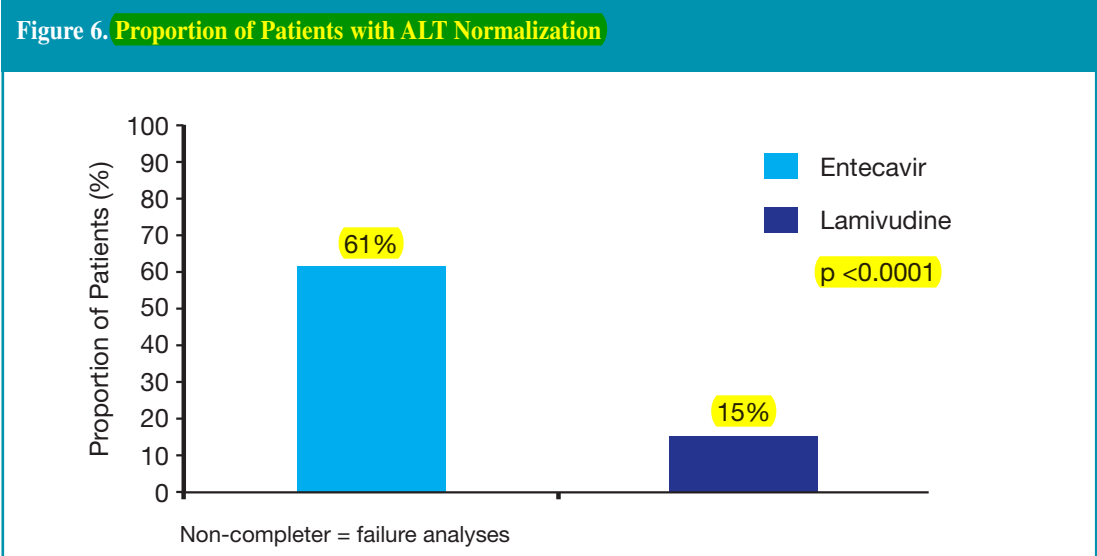
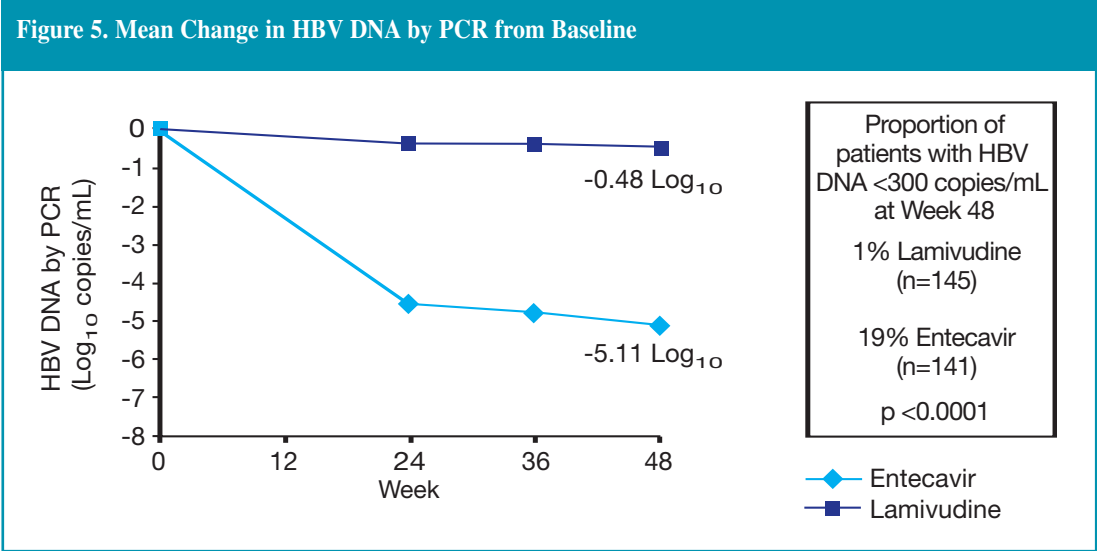
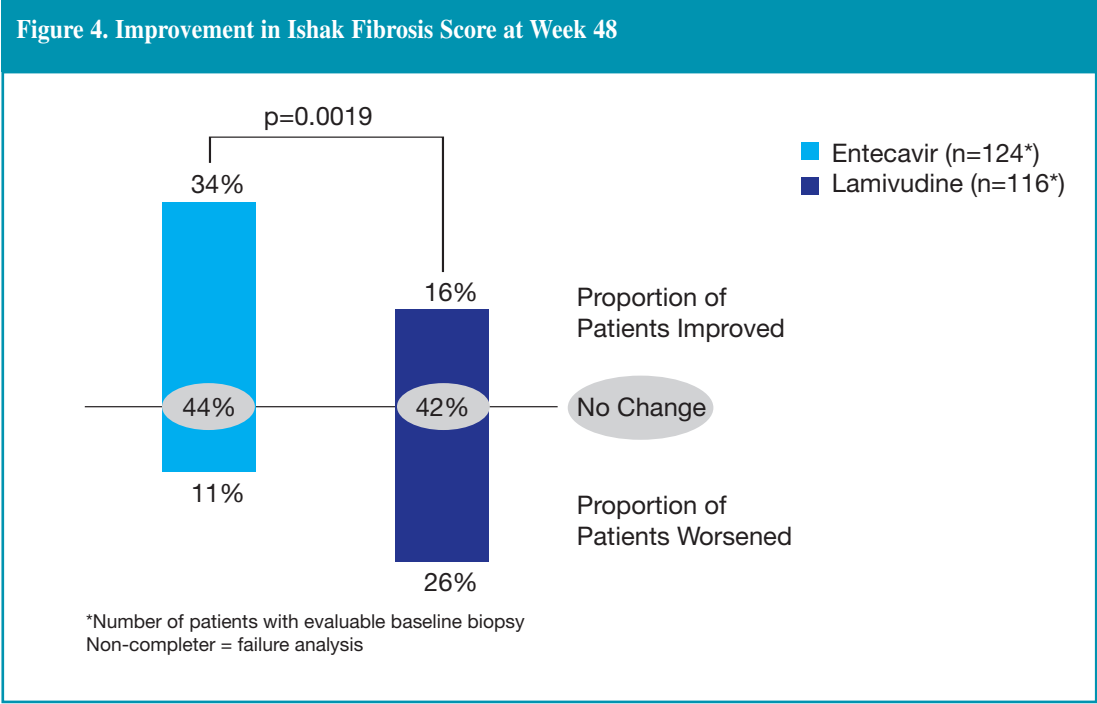
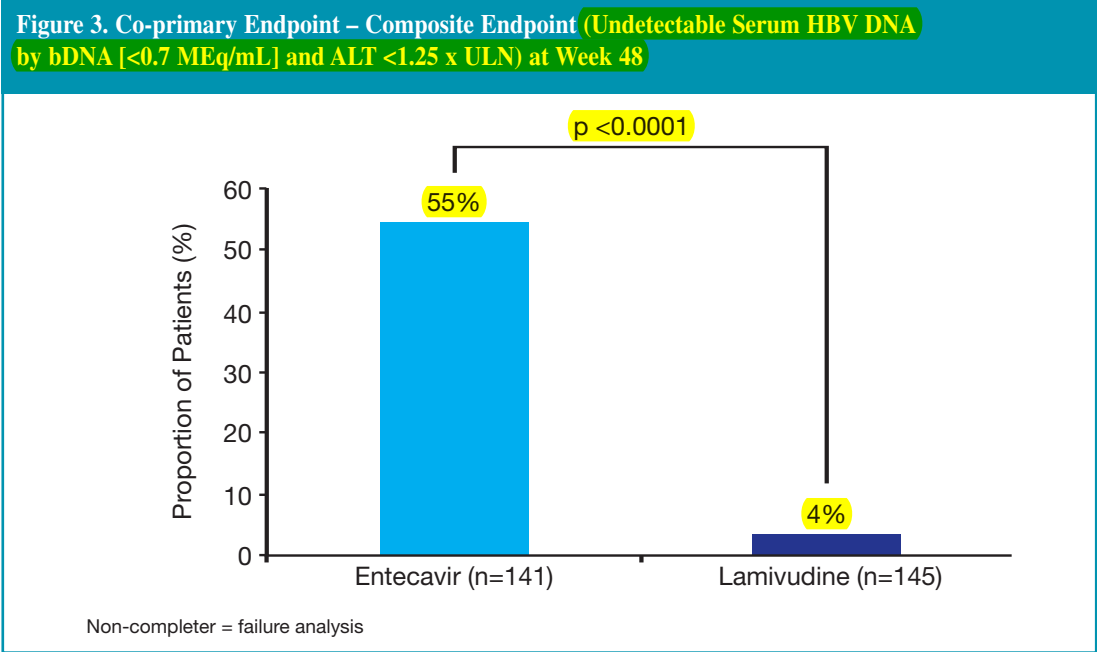
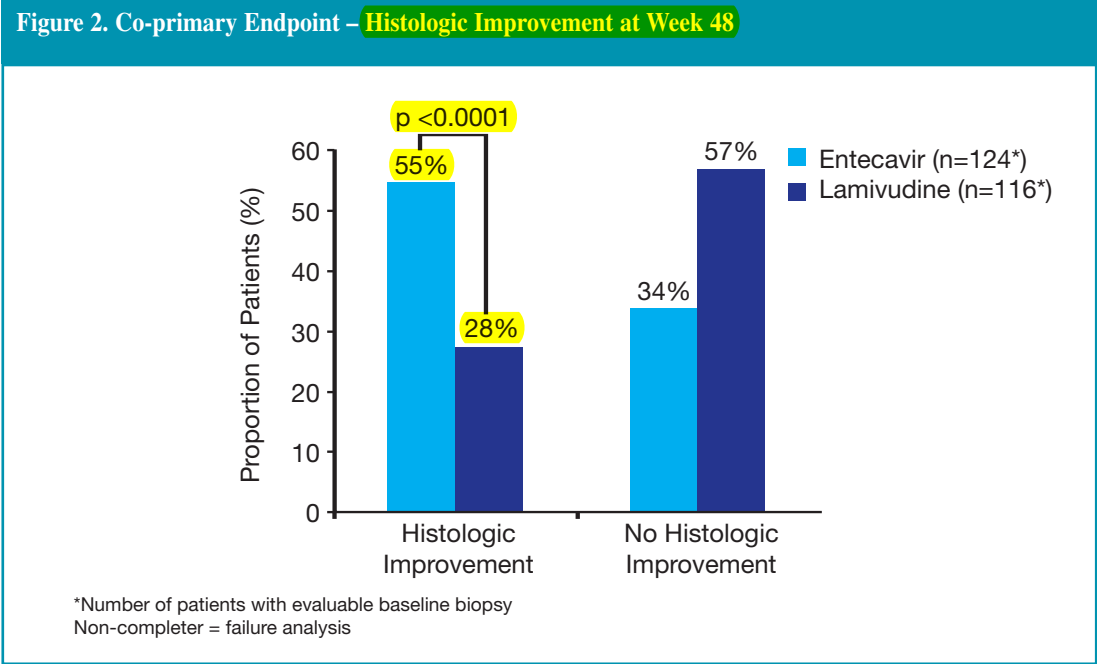
Results

Table 1. Baseline Patient Demographic		
	Entecavir n=141	Lamivudine n=145
Males (%)	74	77
Age (years): Mean (SD)	38 (15)	40 (14)
Race:		
White (%)	59	64
Asian (%)	40	34
Other (%)	<1	1
Region:		
Europe (%)	22	17
Asia (%)	44	50
South America (%)	9	26
North America (%)	25	1

Table 2. Baseline Disease Characteristics		
	Entecavir n=141	Lamivudine n=145
HBV DNA by PCR (log ₁₀ copies/mL): Mean (SD)	9.48 (1.81)	9.24 (1.56)
ALT (U/L): Mean (SD)	123.9	131.9
Detectable Lamivudine Mutations (%)	84	86
HBV Subtype:	n=124	n=116
A (%)	32	35
B (%)	26	22
C (%)	19	19
D (%)	16	12
F (%)	3	6
Other/Missing (%)	0	0

Table 3. Baseline Histology		
	Entecavir n=141*	Lamivudine n=145*
Knodell Necroinflammatory Score (0–18)		
Median	7.0	7.0
Mean (SE)	6.5 (0.28)	6.5 (0.30)
SD	3.23	3.42
Knodell Fibrosis Score (0–4)		
Median	1.0	1.0
Mean (SE)	1.7 (0.10)	1.8 (0.10)
SD	1.19	1.18
Cirrhosis by Knodell (%) (score=4)	10	6
Ishak Fibrosis Score (0–6)		
Median	2.0	2.0
Mean (SE)	2.3 (0.13)	2.2 (0.12)
SD	1.50	1.41
Cirrhosis by Ishak (%) (Score=6)	6	4

*Patients with adequate baseline biopsy



- 1/141 (<1%) patients treated with ETV had an on-treatment ALT flare
 - This flare occurred on Day 29 of therapy and was associated with ≥2 log₁₀ reduction in HBV DNA by bDNA
- 16/145 (11%) patients treated with LVD had an on-treatment ALT flare
 - All 16 flares were associated with stable or rising HBV DNA

Table 4. Cumulative Safety Profile On-treatment		
	Entecavir n=141	Lamivudine n=145
Any adverse event	120 (85)	117 (81)
Serious adverse event	14 (10)	11 (8)
Discontinuation due to adverse event	2 (1)	10 (7)
Deaths (On-study*)	1(<1)	2(1)

*On-study = on-treatment and during 24 week follow-up. No deaths were attributable to the study medication

Table 5. Most Frequent Adverse Events (≥10%) On-treatment		
	Entecavir n=141	Lamivudine n=145
Upper Respiratory Tract Infection	26 (18)	16 (11)
Headache	25 (18)	24 (17)
Fatigue	19 (13)	16 (11)
Cough	17 (12)	14 (10)
Upper Abdominal Pain	12 (9)	19 (13)
Nausea	11 (8)	14 (10)
Nasopharyngitis	14 (10)	14 (10)
Alanine aminotransferase increased	5 (4)	16 (11)

Conclusions

- LVD-refractory patients who were switched directly to entecavir experienced significant improvement in their disease after 48 weeks:
 - Improvement in Knodell necroinflammatory score (≥2 points) and no worsening in Knodell fibrosis
 - Improvement in fibrosis (Ishak score)
 - Composite Endpoint (undetectable HBV DNA by bDNA and ALT <1.25 x ULN)
 - HBV DNA reduction by both bDNA and PCR assays**
 - ALT normalization
 - HBeAg loss
 - Complete virologic response (undetectable HBV DNA by bDNA and HBeAg loss)
- ETV was well tolerated and has a safety profile comparable to LVD**
- LVD-refractory patients continuing on LVD experienced more ALT flares on-treatment than ETV-treated patients
- Confirmed virologic rebound due to ETV resistance was observed in a single LVD-refractory patient (<1%)

References

- Chang TT et al. Hepatology 2004;40(4.Suppl.1):193A
- Shouval D et al. Hepatology 2004;40(4.Suppl.1):728A
- Conjeevaram H, Lok A. J Hepatology 2003;38:S90–S103