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Histologic Assessment of Long-term Entecavir Treatment in Chronic Hepatitis B Patients

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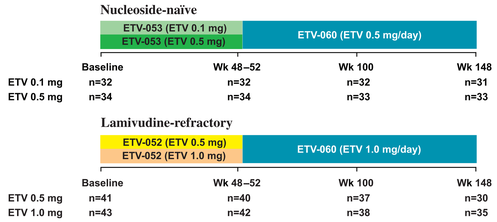
Introduction

- In large observational studies, elevated baseline HBV DNA has been demonstrated to be a significant risk factor for cirrhosis and hepatocellular carcinoma[1-3]
- HBV DNA suppression with antiviral therapy can significantly improve liver histology in HBeAg(+) patients[4]
- Entecavir (ETV) demonstrated potent suppression of HBV DNA replication and improvement in liver histology in nucleoside-naïve and lamivudine-refractory (LVDr) Japanese patients with chronic hepatitis B (CHB) (studies ETV-053 and ETV-052)[5,6]
- All patients who completed studies ETV-053 and ETV-052 could enroll in rollover study ETV-060
- We present histologic results from nucleoside-naïve and LVDr patients who received at least 3 years of ETV therapy in studies ETV-052, ETV-053 and ETV-060

Methods

Study population

- The Long-term Histology Cohorts from Japan consist of patients who:
  - were initially treated with ETV in studies ETV-053 or ETV-052
  - subsequently enrolled in ETV-060
  - had biopsies from three time points: baseline, Week 48 and Week 148



ETV-053/-052/-060: eligibility

- Eligibility criteria (ETV-053 and ETV-052)
  - CHB infection with compensated liver disease
  - HBV DNA ≥5 $\log_{10}$ copies/mL by PCR assay
  - ETV-053
    - ≤12 weeks prior treatment with anti-HBV nucleoside analogues
  - ETV-052
    - ≥24 weeks prior lamividine therapy, ongoing at the time of randomization; or
    - documented evidence of infection with HBV-carrying LVDr substitutions
  - ALT 1.3–10 x ULN
  - HBeAg(+) or HBeAg(-)
- ETV-060
  - Enrollment immediately after completion of ETV-053 or ETV-052 with no gap in dosing
  - Patients enrolling from ETV-053: ETV 0.5 mg/day for a total of up to 148 weeks (3 years) of ETV treatment
  - Patients enrolling from ETV-052: ETV 1.0 mg/day for a total of up to 148 weeks (3 years) of ETV treatment

Efficacy and resistance analyses of the Long-term Histology Cohorts from Japan

- Efficacy assessments at Week 48 (1 year) and Week 148 (3 years) included proportions of patients with:
  - histologic improvement (≥2-point decrease in Knodell necroinflammatory score)
  - improvement in fibrosis (≥1-point decrease in Knodell fibrosis score)
  - detectable HBV DNA by PCR
  - ALT normalization (ALT ≤1 x ULN)
- Resistance
  - Paired samples from baseline and all patients with HBV DNA ≥400 copies/mL at Week 148 (or last on-treatment measurement for patients discontinuing prior to Week 148) were analyzed for substitutions associated with ETV resistance
  - All patients with virologic breakthrough (≥1 $\log_{10}$ increase from nadir on two consecutive measurements) were also genotyped

Results

Table 1: Baseline Demographics and Disease Characteristics

	ETV-053/060 n=37*	ETV-052/060 n=27*
Age, mean (years)	44	44
Male, n (%)	29 (78)	24 (89)
HBeAg(+), n (%)	28 (76)	18 (67)
HBV DNA by PCR, $\log_{10}$ copies/mL, mean (SD)	7.24 (1.03)	7.87 (0.77)
ALT, IU/L, mean (SD)	155 (194)	122 (80)
Knodell HAI score, mean (SE)	9.0 (0.48)	6.2 (0.60)
Knodell fibrosis score, mean (SE)	2.5 (0.17)	2.6 (0.18)
HBV genotype C, n (%)	37 (100)	27 (100)

*Patients with biopsies at baseline, Week 48, and Week 148
HAI = histologic activity index

Resistance

- Nucleoside-naïve patients (ETV-053/060)
  - Up to Week 148, 5/37 patients had HBV DNA ≥400 copies/mL
  - One of five patients had evidence of genotypic ETVr substitutions* with virologic breakthrough. However, both Knodell necroinflammatory and fibrosis scores of this patient were improved at Week 148
- LVDr patients (ETV-052/060)
  - Up to Week 148, 14/27 patients had HBV DNA ≥400 copies/mL
  - Six of fourteen patients had evidence of genotypic ETVr substitutions*
    - Five of six patients had improvement in Knodell necroinflammatory score at Week 148
    - Knodell fibrosis scores at Week 148 were available for five of the patients: two patients showed improvement and three patients showed no worsening in fibrosis scores
- Three of six patients had virologic breakthrough up to Week 148

* ETV resistance substitutions = LVDr (M204V/I ± L180M) + substitution at one of the following residues: T184, S202 or M250

Figure 1: Distribution of Knodell Necroinflammatory Scores at Baseline, Week 48 and Week 148

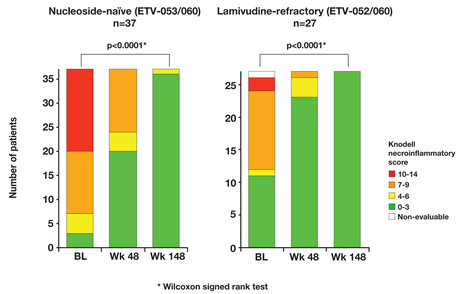


Figure 2: Histologic Improvement through Week 148

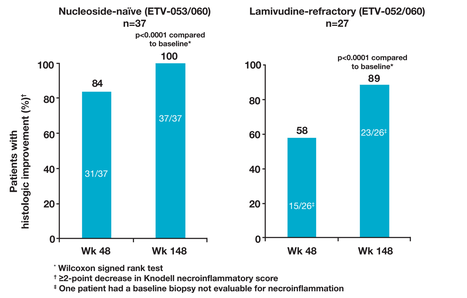


Table 2: Histologic, Virologic and Biochemical Endpoints at Week 148

	ETV-053/060 n=37	ETV-052/060 n=27
Mean change from baseline in Knodell HAI score (SE)	–7.3 (0.45)	–4.9 (0.57) (n=26)
Mean change from baseline in Knodell fibrosis score (SE)	–0.8 (0.17) (n=36)	–0.5 (0.20) (n=25)
HBV DNA <400 copies/mL, n (%)	35 (95)	15 (56)
Mean change from baseline in HBV DNA by PCR, $\log_{10}$ copies/mL (SE)	–4.6 (0.17)	–4.1 (0.33)
ALT ≤1 x ULN, n (%)	33/35 (94)	24/25 (92)

Figure 3: Distribution of Knodell Fibrosis Scores at Baseline, Week 48 and Week 148

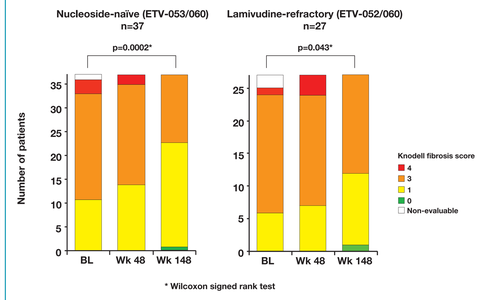


Figure 4: Improvement in Knodell Fibrosis Score through Week 148

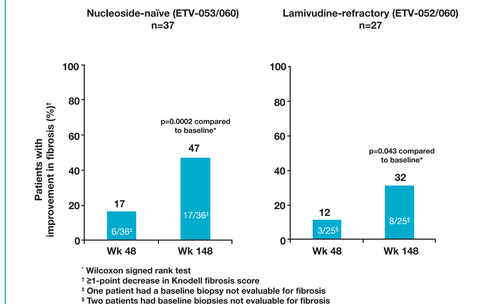


Table 3: Mean platelet count and Albumin through Week 148

	Baseline	Week 48	Week 148
Nucleoside-naïve (ETV-053/060)			
Mean albumin, g/dL (SD)	4.33 (0.36)	4.53 (0.31)	4.57 (0.27)
Mean platelet count, 10^4/μL (SD)	14.65 (4.63)	16.00 (4.14)	17.66 (5.09)
LVD-refractory (ETV-052/060)			
Mean albumin, g/dL (SD)	4.46 (0.27)	4.53 (0.30)	4.55 (0.31)
Mean platelet count, 10^4/μL (SD)	16.14 (5.29)	16.66 (5.84)	17.87 (6.25)

Summary of Results

- Three years of ETV treatment resulted in histologic improvement in 100% of nucleoside-naïve and 89% of LVDr patients
- Treatment with ETV beyond 48 weeks resulted in further improvement in fibrosis scores in both naïve and LVDr patients
- High proportions of both naïve and LVDr patients achieved HBV DNA suppression and ALT normalization during 3 years of ETV

Conclusion

- The results from these cohorts demonstrate that long-term continuous treatment with ETV results in durable suppression of HBV replication and significant histologic improvement in nucleoside-naïve and LVDr patients

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Study Group

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Disclosures

Masao Omata – Global Advisory Board Member: Bristol-Myers Squibb.

Hiroki Ishikawa and Taku Seriu – Bristol-Myers Squibb employees.

The following people have nothing to disclose: Yoshiaki Katano, Hiromitsu Kumada, Haruhiko Kobashi, Joji Toyota, Osamu Yokosuka, Koichi Takaguchi, Masayoshi Kage, Mitsuhiko Moriyama and Fumio Imazeki.

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