Poster Number 960

Evaluation of Long-term Entecavir Treatment in Stable Chronic Hepatitis B Patients Switched from Lamivudine Therapy

Tatsuya Ide[1], Michio Sata[1], Michiko Shindo[2], Kazuaki Chayama[3], Joji Toyota[4], Satoshi Mochida[5], Eiichi Tomita[6], Hiroshi Yatsuhashi[7], Norio Hayashi[8], Hiroki Ishikawa[9], Taku Seriu[10], Masao Omata[11]

[1]Division of Gastroenterology, Department of Medicine, Kurume University School of Medicine, Fukuoka, Japan; [2]Division of Liver Disease, Department of Internal Medicine, Akashi Municipal Hospital, Hyogo, Japan; [3]Department of Medicine and Molecular Science, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan; [4]Department of Gastroenterology, Sapporo Kosei General Hospital, Hokkaido, Japan; [5]Department of Gastroenterology and Hepatology, Saitama Medical University, Saitama, Japan; [6]Department of Gastroenterology, Gifu Municipal Hospital, Gifu, Japan; [7]Clinical Research Center, National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan; [8]Department of Gastroenterology and Hepatology, Osaka University Graduate School of Medicine, Osaka, Japan; [9]Research and Development, Bristol-Myers K.K., Tokyo, Japan; [10]Research and Development, Bristol-Myers Squibb, Princeton, NJ, USA; [11]Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

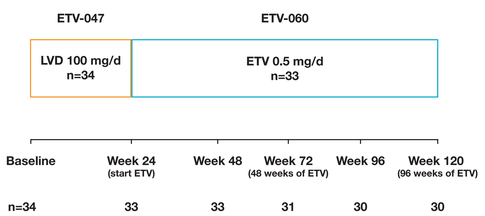
Introduction

- The goal of chronic hepatitis B (CHB) treatment is to achieve sustained suppression of HBV DNA and remission of liver disease[1]
- Long-term treatment of CHB patients with lamivudine (LVD) is associated with the development of resistance and loss of clinical benefit[2]
- Current Japanese CHB treatment guidelines recommend that patients should be switched to entecavir (ETV) 0.5 mg daily if they have received less than 3 years of LVD therapy, have HBV DNA <400 copies/mL and no breakthrough hepatitis or YMDD mutations
- ETV 0.5 mg daily for 24 weeks demonstrated superior HBV DNA reduction compared to LVD 100 mg daily in phase 2 study ETV-047 in Japan[3]
- After completing ETV-047, all patients could enroll in open-label ETV rollover study ETV-060
- We report long-term efficacy, safety and resistance for patients who were switched from LVD to ETV therapy

Methods

Study population

- Thirty-four patients in ETV-047 received LVD 100 mg daily
- Thirty-three LVD-treated patients from ETV-047 entered ETV-060 and received ETV 0.5 mg daily



- Eligibility criteria (study ETV-047)
  - CHB infection with compensated liver disease
  - HBV DNA ≥7.6 $\log_{10}$ copies/mL by PCR assay
  - ≤12 weeks of prior treatment with anti-HBV nucleoside analogues
  - Alanine transaminase (ALT) 1.25–10 x ULN
  - HBeAg(+) or HBeAg(-)
- Study ETV-060
  - Patients enrolled immediately after completion of ETV-047 with no gap in dosing

Analyses through Week 120 (96 weeks of ETV)

Efficacy

- Efficacy assessments evaluated proportions of patients who had available samples (Non-completer=Missing) at Weeks 24, 48, 72, 96 and 120 for the following parameters:
  - HBV DNA by PCR assay
  - ALT normalization (ALT ≤1.0 x ULN)
  - HBe seroconversion among HBeAg(+) patients

Resistance

- Paired samples from all patients with HBV DNA ≥400 copies/mL at Week 96 (72 weeks of ETV), Week 120 (96 weeks of ETV) or last on-treatment measurement (for patients discontinuing prior to Week 120) were analyzed for substitutions associated with ETV or LVD resistance
- All patients with virologic breakthrough (≥1 $\log_{10}$ increase from nadir on two consecutive measurements) were also genotyped

Safety

- Safety was assessed throughout the treatment period

Results

Table 1: Demographics and Baseline Characteristics

	ETV-047/-060 LVD to ETV switch cohort (n=33)
Age, mean (years)	42.7
Male, n (%)	27 (82)
Japanese, n (%)	33 (100)
HBeAg(+), n (%)	30 (91)
HBV DNA by PCR, mean, $\log_{10}$ copies/mL (SD)	7.9 (0.80)
ALT, mean, IU/L (SD)	184.8 (132.9)
HBV genotype C, n (%)	29 (88)

Figure 1: Mean HBV DNA ($\log_{10}$ copies/mL) through Week 120 (96 weeks of ETV)

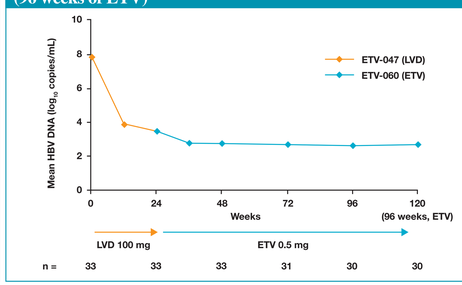
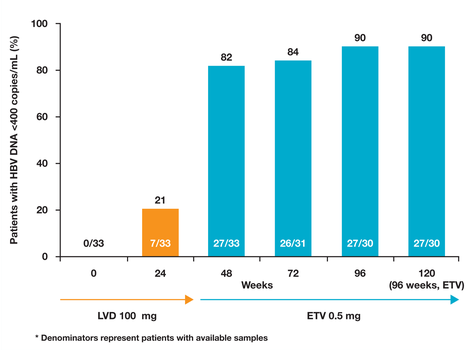
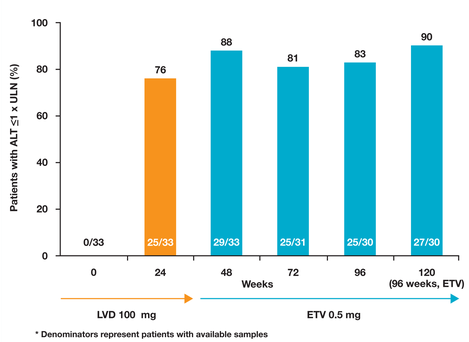


Figure 2: Proportion of Patients with HBV DNA <400 copies/mL*



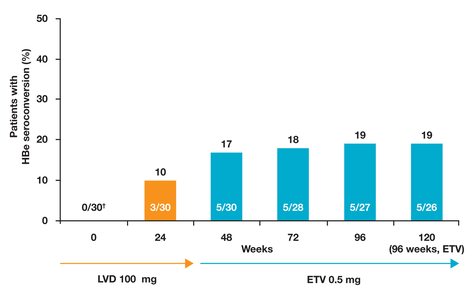
* Denominators represent patients with available samples

Figure 3: Proportion of Patients with ALT ≤1 x ULN*



* Denominators represent patients with available samples

Figure 4: Proportion of Patients with HBe Seroconversion*



* Denominators represent patients with available samples; † Thirty patients were HBeAg(+) at baseline

Resistance

Of 33 treated patients, 4 had HBV DNA ≥400 copies/mL during ETV-060

- One patient discontinued at Week 68 (44 weeks of ETV)
  - Testing of isolates revealed no substitutions associated with ETV resistance
- Three patients had HBV DNA ≥400 copies/mL at Week 120 (96 weeks of ETV)
  - Two of three had samples available for resistance testing
  - Neither (0/2) demonstrated substitutions associated with ETV resistance

Safety

Table 2: Summary of Safety

On-treatment (ETV-060)	n (%) ETV-047/-060 LVD to ETV switch cohort (n=33)
Any adverse events	33 (100)
Clinical adverse events	33 (100)
Laboratory adverse events	33 (100)
Grade 3/4 clinical adverse events	1 (3)
Grade 3/4 laboratory adverse events	5 (15)
Clinical serious adverse events*	2 (6.1)
Discontinuations due to adverse events†	1 (3)
Deaths	0 (0)
ALT flares‡	1 (3)

* Clinical serious adverse events were Meniere's disease (1 patient) and subcutaneous abscess (1 patient)
† One patient discontinued treatment because of depression
‡ ALT >2 x baseline and >10 x ULN; ALT flare occurred in one patient at Week 18 of ETV therapy, and was not associated with a change in HBV DNA

Table 3: Most Frequent (≥15%) Clinical Adverse Events

On-treatment (ETV-060)	n (%) ETV-047/-060 LVD to ETV switch cohort (n=33)
Nasopharyngitis	25 (76)
Diarrhea	7 (21)
Back pain	6 (18)
Influenza	6 (18)
Rhinitis (allergic)	5 (15)

Summary of Results

- Switching CHB patients from LVD to long-term ETV therapy resulted in the following:
  - Additional suppression of HBV DNA replication
    - Proportion of patients with HBV DNA <400 copies/mL increased from 21% to 90% after 72 weeks of ETV and was maintained through 96 weeks of ETV
  - Increasing proportions of patients achieving ALT ≤1 x ULN
- No evidence of resistance emergence during 96 weeks of ETV treatment
- ETV was well tolerated during long-term treatment

Conclusion

- CHB patients switched from LVD to long-term ETV achieve increased rates of virologic suppression, with no evidence of resistance through 2 years of ETV treatment

References

1. Lok AS and McMahon BJ. Hepatology 2007;45:507-39.
2. Lai CL, Dienstag J, Schiff E, et al. Clin Infect Dis 2003;36:687-96.
3. Shindo M, Chayama K, Toyota J, et al. J Clin Virol 2006;36 (Suppl 2):S94.

Study Group

Investigators: J Toyota: Sappro Kosei Hospital, T Hasebe: Yoshida Hospital, S Kawanishi: Inazumi Koen Hospital, K Suzuki: Iwate Medical University, Y Ueno: Tohoku University, S Mochida: Saitama Medical University, O Yokosuka: Chiba University, N Izumi: Musashino Red Cross Hospital, H Saito: Keio University, N Masaki: International Medical Center, K Tatemoto: Tokyo Women's Medical University, Y Arakawa: Nihon University, H Kumada: Toranomon Hospital, Y Matsuda: Niigata University, S Okada: Yamanashi University, E Tanaka: Shinsyu University, Y Katano: Nagoya University, E Orito: Nagoya City University, S Kakumu: Aichi Medical School, N Hirashima: Chyukyo Hospital, E Tomita: Gifu Municipal Hospital, T Kumada: Ogaki Municipal Hospital , T Okanoue: Kyoto Prefectural University, N Hayashi: Osaka University, K Katayama: Osaka Koseinenkin Hospital, M Kato: Osaka National Hospital,Y Yoshihara: Osaka Rosai Hospital, T Hijioka: Osaka Minami National Hospital, M Shindo: Akashi Municipal Hospital, K Sakaguchi: Okayama University, G Yamada: Kawasaki Hospital, K Chayama: Hiroshima University, K Hino: Yamaguchi University, N Horiike: Ehime University, S Sakisaka: Fukuoka University, R Kumashiro: Kurume University, K Hamasaki: Nagasaki University, H Yatsuhashi: Nagasaki Medical Center, M Seike: Oita University, H Sasaki: Kumamoto University, K Hayashi: Miyazaki University, S Fijioka: Okayama Saiseikai General Hospital, K Takaguchi: Kagawa Prefectural Central Hospital, H Ikeda: Kurashiki Central Hospital, M Miyake: Tsuyama Central Hospital, Y Araki: Hiroshima City Hospital, K Fujio: Fukuyama City Hospital, M Ando: Mitoyo General Hospital.

Coordinating Committee: K Suzuki: Iwate Medical University, O Yokosuka: Chiba University, H Kumada: Toranomon Hospital, T Okanoue: Kyoto Prefectural University, N Hayashi: Osaka University, Y Shiratori: Okayama University, M Sata: Kurume University, H Tsubouchi: Kagoshima University.

Efficacy and Safety Committee: K Kiyosawa: Shinsyu University, C Sato: Tokyo Medical and Dental University, K Tanikawa: International Institute for Liver Research.

Biopsy Reading Committee: F Imazeki: Chiba University, M Moriyama: Nihon University, M Kage: Kurume University.

Medical Expert: M Omata: University of Tokyo.

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: Tatsuya Ide, Michio Sata, Michiko Shindo, Kazuaki Chayama, Joji Toyota, Satoshi Mochida, Eiichi Tomita, Hiroshi Yatsuhashi and Norio Hayashi.

59th Annual Meeting of the American Association for the Study of Liver Diseases. Presented October 31 – November 4, 2008.

Bristol-Myers Squibb Company