

# Entecavir Therapy for up to 96 Weeks in Patients With HBeAg-Positive Chronic Hepatitis B

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## Introduction:

Chronic hepatitis B (CHB) is one of the most common infectious diseases in Taiwan, affecting approximately three million people. More than one-half of reported cases of hepatocellular carcinoma (HCC) and reported cases of cirrhosis are caused by chronic hepatitis B. An estimated 400 million people worldwide are chronically infected with hepatitis B virus (HBV). HCC and cirrhosis, in turn, result in approximately one million deaths each year. A goal of treatment for CHB is to suppress HBV replication, thus decreasing the hepatic necroinflammatory response and arresting or reversing progression of liver disease. Entecavir is a potent inhibitor of HBV DNA polymerase. Entecavir demonstrated superior histologic, virologic, and biochemical responses to lamivudine at 48 weeks in nucleoside-naïve patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B. The efficacy and safety of entecavir in HBeAg-positive patients was evaluated in a large randomized international clinical trial. The present analysis investigates the efficacy and cumulative safety of entecavir versus lamivudine for up to 96 weeks of blinded treatment.



## Methods:

The efficacy and safety of entecavir in patients with HBeAg-positive chronic hepatitis B were established in a double-blind, international study in which patients were randomized to entecavir 0.5 mg/day or lamivudine 100 mg/day. 709 HBeAg-positive CHB patients were randomized to entecavir 0.5 mg (n = 354) or lamivudine 100 mg (n = 355) once daily. At week 52, protocol defined virologic responders could continue blinded treatment for up to 96 weeks. Patients continuing in year 2 (entecavir, n = 243; lamivudine, n = 164) were assessed for serum hepatitis B virus (HBV) DNA, alanine aminotransferase (ALT) normalization, HBeAg seroconversion, and safety. Cumulative confirmed proportions of all treated patients who achieved these responses were also analyzed.

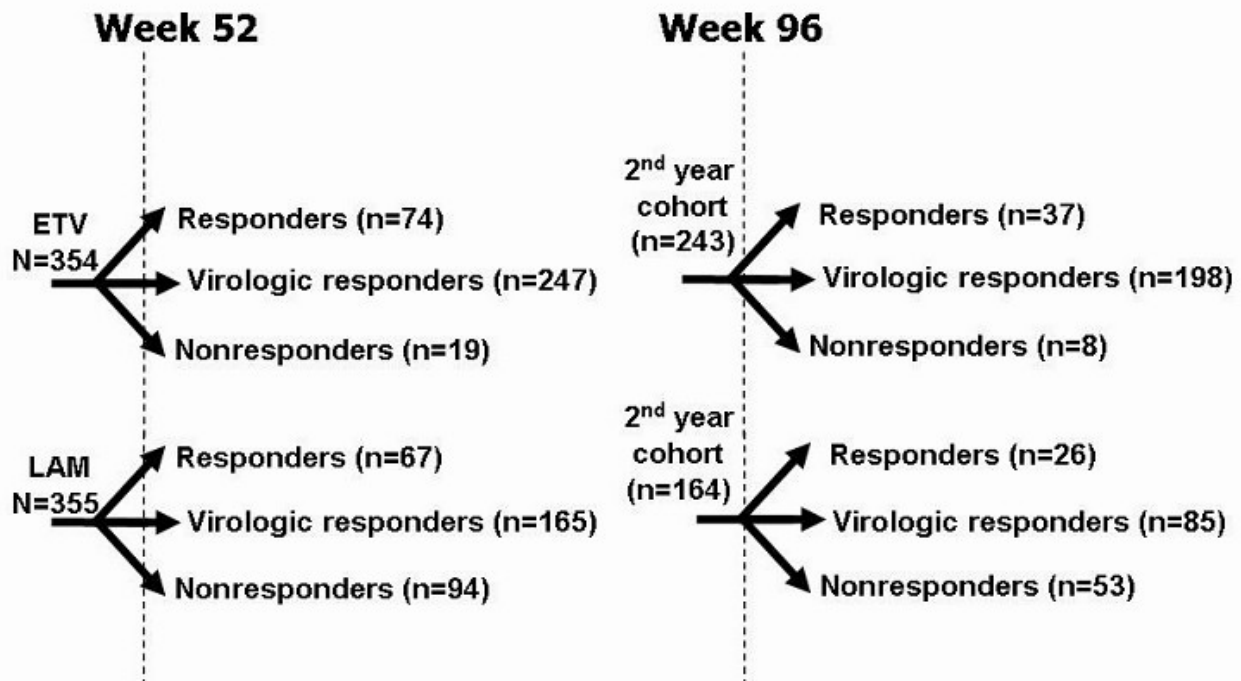
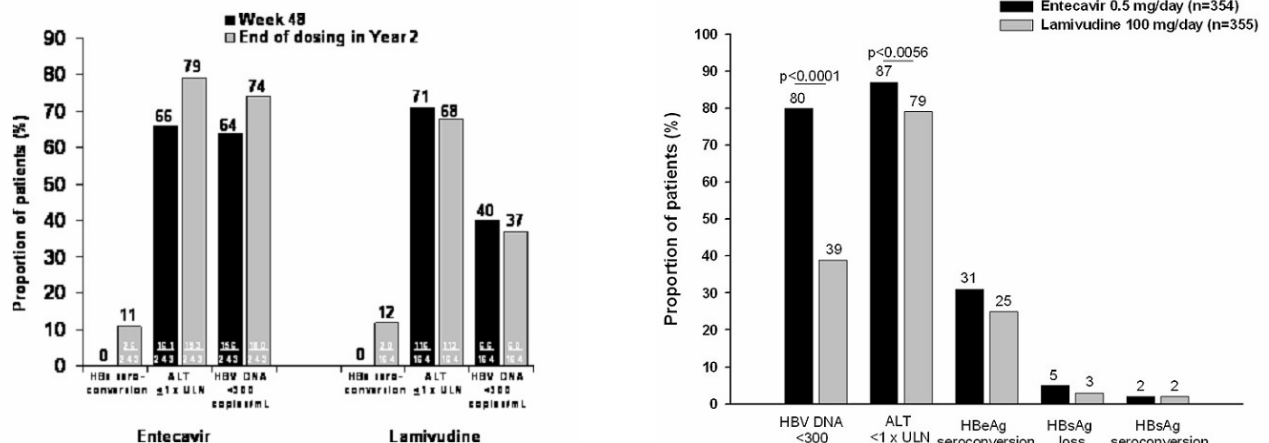


Figure 1. Management of patients through 96 weeks of treatment. Fourteen entecavir recipients and 29 lamivudine recipients had missing 48 week data.

**Results:**

Among the 243 entecavir and 164 lamivudine virologic responders (HBV DNA <0.7 MEq/mL but no loss of HBeAg) who continued treatment into a second year, 74% and 37% respectively, achieved a serum HBV DNA <300 copies/mL, and 79% and 68% respectively, normalized ALT levels at end of dosing in year 2. Similar proportions of entecavir-treated and lamivudine-treated patients achieved HBeAg seroconversion (11% vs 12%, respectively).

A significantly higher percentage of entecavir-treated patients than lamivudine-treated patients achieved cumulative confirmed HBV DNA <300 copies/mL (80% vs. 39%, respectively,  $p < 0.0001$ ), and cumulative confirmed normalization of ALT (87% vs. 79%, respectively,  $p < 0.0056$ ). The proportion of patients experiencing HBeAg seroconversion (31% vs. 25%, respectively), HBsAg loss (5% vs. 3%, respectively) and HBsAg seroconversion (2% in both groups) did not differ significantly between the two treatment groups. Through 96 weeks, no patient experienced virologic breakthrough due to entecavir resistance. The safety profile was comparable in both groups.



**Figure 2. Outcomes in patients with a ‘virologic response’ at 48 weeks (HBV DNA <0.7 MEq/mL without loss of HBeAg) who continued treatment in year 2.**

**Figure 3. Cumulative confirmed proportions of all-treated patients who achieved undetectable HBV DNA (<300 copies/mL), normalization of serum ALT or a serologic end point through 96 weeks of treatment.**

## **Discussion:**

The cumulative confirmed results of this study show that extended treatment with entecavir provided continued viral suppression and normalization of ALT levels through 96 weeks. In contrast, the proportions of lamivudine-treated patients achieving these end points decreased over the course of the study. Continued monitoring for resistance in year 2 among those with detectable HBV DNA levels or virologic breakthrough confirmed that entecavir resistance through 96 weeks is rare. Over this 2-year experience, entecavir maintained a safety and tolerability profile that was comparable to that for lamivudine. Nonetheless, discontinuation of treatment among patients who achieved a protocol-defined response at 48 weeks resulted in more than 77% of entecavir-treated patients sustaining HBe seroconversion for 6 months off-treatment. Given the maintained suppression and low rates of resistance with prolonged therapy, entecavir represents an important advance in the management of CHB in nucleoside-naive HBeAg-positive patients.

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