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Virological, serological and biochemical outcomes through 3 years of entecavir treatment in nucleoside-naive Chinese chronic hepatitis B patients

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SUMMARY. Hepatitis B virus (HBV) infection has a high prevalence in China. Entecavir has shown superior efficacy over lamivudine in Chinese nucleoside-naive chronic hepatitis B (CHB) patients over 48 weeks, with continued clinical benefit to 96 weeks. The present study evaluates the long-term efficacy of entecavir in Chinese CHB patients who continued entecavir treatment for 144 weeks. Patients receiving either entecavir 0.5 mg/day (n = 258) or lamivudine 100 mg/day (n = 261) entered the initial 96-week randomized, double-blind, controlled efficacy study. Patients who did not achieve a consolidated response [HBV DNA <0.7 MEq/mL; alanine aminotransferase (ALT) <1.25 × upper limit of normal; and if hepatitis B e antigen (HBeAg) positive at baseline, loss of HBeAg for ≥24 weeks] or who experienced viral breakthrough or relapse entered a 48-week entecavir rollover study. A total of 160 patients received continuous entecavir for 144 weeks; of these, 89% had undetectable serum HBV DNA, 86% showed ALT normalization, 20% reported HBeAg loss and 8% experienced HBeAg seroconversion. The cumulative rates of HBeAg loss and seroconversion were 36% and 27% at Week 144, respectively. The development of resistance was low, with three patients up to Week 96 and an additional two patients in Weeks 96–144 showing evidence of associated genotypic mutations. Entecavir was well tolerated. Adverse event rates were similar to those in lamivudine-treated patients, but patients receiving entecavir experienced fewer ALT flares. This study demonstrates that entecavir provides durable, long-term suppression of HBV DNA and ALT normalization in Chinese CHB patients, and is associated with low rates of emerging resistance. The results are consistent with the findings using entecavir globally and in Japan.

Keywords: chronic hepatitis B, entecavir, HBeAg seroconversion, HBV DNA, hepatitis B virus, resistant mutant.

INTRODUCTION

Hepatitis B virus (HBV) infection is a serious global public health issue. Of the two billion people who are infected with HBV, more than 350 million are chronically infected and 75% of these live in Asia or the west Pacific [1]. China has one of the highest prevalences of HBV infection in the world. According to a nationwide sero-epidemiological survey between 1992 and 1995, the HBV surface antigen (HBsAg) carrier rate was 9.75% in the general population [2]. Following the success of the national HBV vaccination programme over the past 20 years, the hepatitis B surface antigen (HBsAg) carrier rate had dropped to 7.18% in 2006 [2]. However, there are an estimated 90 million chronic HBV carriers in China, of whom at least 20–30% require safe and effective treatment [3] to stop or reverse existing liver damage and prevent further disease progression. The development of antiviral nucleos(t)ide analogues is a major breakthrough in chronic hepatitis B (CHB) therapy. Currently, four nucleos(t)ide analogues have been approved in

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; bDNA, branched-chain DNA; CHB, chronic hepatitis B; CR, consolidated response; HBeAG, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOD, lower limit of detection; LOCF, last observation carried forward; NR, non-response; PCR, polymerase chain reaction; PR, partial response; SAE, serious adverse event; SD, standard deviation; SFDA, State Food and Drugs Administration; ULN, upper limit of normal.

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China for the treatment of CHB; namely, lamivudine, adefovir dipivoxil, entecavir and telbuvidine. Clinical studies have shown that entecavir is one of the most potent nucleos(t)ide analogues and that it has a favourable resistance profile [4–6]. International clinical trials and independent registrational studies in China have shown that entecavir achieved statistically superior virological and biochemical responses compared with lamivudine [7–11], and earlier and superior HBV DNA reduction compared with adefovir [12]. This article summarizes the efficacy and safety up to 3 years of entecavir treatment in nucleoside-naive Chinese CHB patients.

PATIENTS AND METHODS

Patients

Eligible patients were at least 16 and up to 65 years of age, and had a documented history of CHB infection (HBsAg positive for ≥6 months) and compensated liver disease (total bilirubin ≤2.5 mg/dL, international normalized ratio ≤1.5, albumin ≥3.0 g/dL, and no current evidence or history of variceal bleeding, hepatic encephalopathy, or ascites). Eligible patients had a serum HBV DNA level ≥3.0 MEq/mL by Quantiplex™ branched-chain (b)DNA assay (Bayer Diagnostics, Walpole, MA, USA) at screening and evidence of HBV DNA $\geq 10^5$ copies/mL by any commercial assay ≥12 weeks before screening. Patients also had a serum alanine aminotransferase (ALT) level of 1.3–10.0 times the upper limit of normal (ULN) at screening and at least once ≥12 weeks before screening. Patients with either hepatitis B e antigen (HBeAg)-positive or HBeAg-negative/HBe antibody (anti-HBe)-positive disease were eligible for inclusion in the study.

Study design

This multicentre trial was conducted at 26 sites in China, and can be divided into two stages. The first stage, a randomized (1:1) double-blind, controlled study compared entecavir (Bristol–Myers Squibb, Wallingford, CT, USA) 0.5 mg once daily to lamivudine (GlaxoSmithKline, Brentford, UK) 100 mg once daily for up to 96 weeks in patients with CHB (study 023). Response to therapy was initially assessed at Week 52, based on results obtained at Week 48. Patients achieving a consolidated response (CR) at Weeks 48–96 (HBV DNA <0.7 MEq/mL by bDNA assay, being HBeAg negative for at least 24 weeks and ALT $<1.25 \times$ ULN at Weeks 48–96 for HBeAg-positive patients; HBV DNA <0.7 MEq/mL by bDNA assay for at least 24 weeks and ALT $<1.25 \times$ ULN at Weeks 48–96 for HBeAg-negative patients) discontinued the study drug and were followed for 24 weeks. Sustained responses at 24 weeks off-treatment were also evaluated. Patients who achieved a partial response (PR) through Week 96 (HBV DNA <0.7 MEq/mL by bDNA assay but not yet meeting the criteria for a CR) were eligible to enter the second stage of the trial – an open-label rollover study (study 050). Virological non-responders (NR) at Weeks 48 and 96 (HBV DNA ≥0.7 MEq/mL by bDNA assay) discontinued the study drug at Weeks 52–96 and could either enrol in the entecavir rollover study 050 or be followed for 24 weeks post-dosing and begin marketed anti-HBV therapy as recommended by their physician.

After 96 weeks of treatment, patients who (i) did not achieve the CR criteria (PR or virological NR), (ii) experienced virological breakthrough or (iii) relapsed during the 24-week off-treatment follow-up were enrolled into the second stage (rollover study 050) and offered open-label 1.0 mg once daily entecavir until entecavir was marketed in China. A retrospective analysis evaluating the efficacy, safety and emergence of resistance in a cohort of patients who received continuous entecavir for 3 years in study 050, with a treatment gap ≤35 days during the rollover period (subsequently referred to as Year 3 cohort), is also detailed in the current report.

Efficacy parameters and assay methods

Efficacy was assessed by investigating virological (HBV DNA levels), biochemical (serum ALT) and serological (HBeAg/anti-HBe status) end-points. HBV DNA was assayed by both bDNA assay, with a lower limit of detection (LLOD) of 0.7 MEq/mL, and polymerase chain reaction (PCR) quantitative assay, with an LLOD of 300 copies/mL (57 IU/mL) (COBAS Amplicor Assay; Roche Molecular Systems, Branchburg, NJ, USA). HBeAg and anti-HBe were detected by AxSYM microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, USA).

Genotypic resistance testing (Trugene™ HBV Genotyping kit, version 1.0; Siemens Healthcare Diagnostics, Deerfield, IL, USA) was performed on available samples from patients who were treated with entecavir for at least 96 weeks and had detectable HBV DNA (≥300 copies/mL by PCR) at Weeks 96 or 144, or who had virological breakthrough while on treatment.

Safety evaluation

Identification of all adverse events (AE) by clinical examination, and liver and other clinical biochemistry and haematology profiles were evaluated until the end of therapy. The severity of AE [including serious AE serious adverse event (SAE)] was coded according to World Health Organization (WHO) classification criteria [13]. Safety end-points included the proportion of patients discontinuing treatment because of AE and SAE.

Statistical analysis

For the primary efficacy end-point at 48 weeks, the target sample size of 225 patients per treatment group provided 90% power to demonstrate superiority of entecavir over

lamivudine. In the principal analysis of binary end-points, patients with a missing Week 48 measurement for an end-point were treated as having NR for that end-point. Comparisons of continuous variables used *t*-tests based on linear regression models with covariates for baseline measurement, baseline HBeAg status (positive or negative) and treatment group. *P* values were based on two-sided tests.

For the efficacy end-points at 96 weeks, confidence intervals and *P* values for differences in proportions are based on the normal approximation to the binomial distribution, with unpooled proportions used in the computation of the standard error of the difference. *P* values are based on two-sided tests.

The retrospective analysis in the Year 3 cohort assessed the proportions in response at the specified time point in relation to the total number of cohort participants having data available at that time point (cross-sectional method). This method uses all observed data, but denominators can vary by end-point as some patients might have laboratory data available for one end-point (e.g. ALT) but not for another (e.g. HBV DNA). To provide clinicians with a better understanding of the potential for serological response over time while on treatment, a cumulative analysis of HBeAg loss and HBe seroconversion using the last observation carried forward (LOCF) analysis is also provided.

A clinical trial permit was granted by the Chinese State Food and Drugs Administration (SFDA) to conduct the study. All 26 medical centres participating in the study were certified by the SFDA as clinical trial sites. Study protocol and informed consent forms were reviewed and approved by the Institutional Review Board and Independent Ethics Committee of each of the participating medical centres. All patients gave written informed consent before any study-related procedures were performed.

RESULTS

Study population

A total of 519 enrolled, screened and randomized patients received at least one dose of study drug (entecavir, $n = 258$ or lamivudine, $n = 261$). The two treatment groups were well balanced at the baseline for demographic and disease characteristics (Table 1). Overall, 86% of patients ($n = 225$ for entecavir; $n = 221$ for lamivudine) were HBeAg positive. Fifteen per cent of patients had been previously treated with interferon (IFN)-α. Mean HBV DNA levels at the baseline were higher for HBeAg-positive patients than for HBeAg-negative patients in both treatment groups. Most patients completed 52 weeks of dosing (96% for entecavir; 94% for lamivudine) and fewer entecavir-treated than lamivudine-treated patients discontinued therapy during Year 2 of the study (16 *vs* 50, respectively). A total of 160 patients with a gap in treatment ≤35 days rolled over from the previous 2-year cohort for continuing entecavir treatment (1.0 mg once daily) for up to 3 years (144 weeks). These patients were all HBeAg positive as defined by the protocol, and the baseline characteristics are shown in Table 1. An overview of the study design and patient flow through the study up to Week 144 is shown in Fig. 1.

Cumulative virological, serological and biochemical responses through 96 weeks

Virological response

Patients treated with entecavir showed a rapid reduction in HBV DNA levels. The mean reduction in HBV DNA at Week 12 (the first on-treatment HBV DNA measurement) was significantly greater for the entecavir group (−5.07 $\log_{10}$ copies/

Table 1 Demographic and baseline disease characteristics of patients treated up to Week 96 and patients in the Year 3 cohort

	Up to week 96		Year 3 entecavir cohort
Characteristic	Entecavir 0.5 mg ($n = 258$)	Lamivudine 100 mg ($n = 261$)	Entecavir 1.0 mg ($n = 160$)
Male, *n* (%)	211 (82)	217 (83)	135 (84)
Mean (SD) age, years	30 (9)	30 (9)	30 (9)
HBeAg positive, *n* (%)	225 (87)	221 (85)	160 (100)
HBeAg negative, *n* (%)	33 (13)	40 (15)	0 (0)
HBV DNA $\log_{10}$ copies/mL (by PCR, mean ± SD)			
All patients	8.64 ± 0.99	8.48 ± 1.12	8.83 ± 0.86
HBeAg positive	8.77 ± 0.86	8.65 ± 1.0	8.83 ± 0.86
HBeAg negative	7.70 ± 1.28	7.59 ± 1.33	–
Serum ALT, IU/L (mean ± SD)			
All patients	196 ± 140	198 ± 180	179 ± 117
HBeAg positive	191 ± 135	204 ± 192	179 ± 117
HBeAg negative	225 ± 169	164 ± 83	–

HBeAg, hepatitis B e antigen.

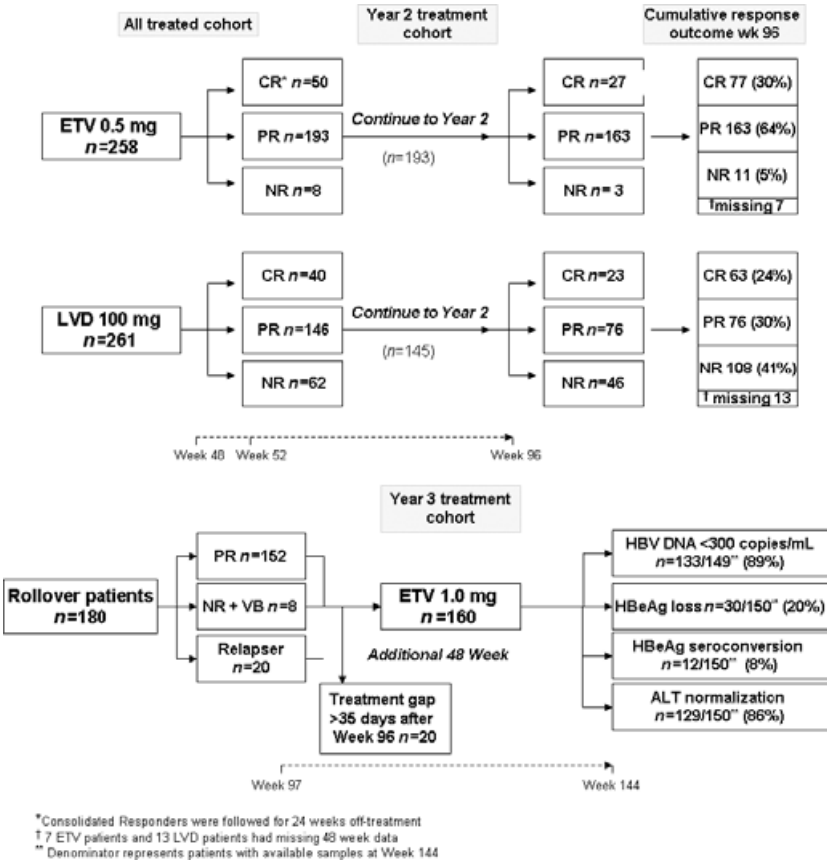

Fig. 1 Study design and protocol-defined outcome through 3 years. Patients entered the second year of treatment at Week 52, based on the results of Week 48 HBV DNA by bDNA assay and hepatitis B e antigen (HBeAg) status. Only partial responders (PR) continued blinded therapy into the second year. Patients entered the third year of treatment at Week 96, based on the results of Week 96 HBV DNA by bDNA assay and HBeAg status. Consolidated responder (CR) HBV DNA level <0.7 MEq/mL and HBeAg negative; PR HBV DNA level <0.7 MEq/mL and HBeAg positive; non-responder (NR) HBV DNA level ≥0.7 MEq/mL. Viral breakthrough (VB) patients. PR HBV DNA <0.7 MEq/mL by bDNA assay, but not yet meeting the criteria for a CR. ETV, entecavir; LVD, lamivudine.

mL) than for the lamivudine group (−4.53 $\log_{10}$ copies/mL; $P < 0.001$). The mean reduction in HBV DNA was also greater for entecavir-treated patients at Week 48 (−5.90 $\log_{10}$ copies/mL) than for lamivudine-treated patients (−4.33 $\log_{10}$ copies/mL; $P < 0.001$). At Week 48, significantly more entecavir-treated patients than lamivudine-treated patients had HBV DNA <300 copies/mL by PCR (76% *vs* 43%, $P < 0.001$). The cumulative proportion of patients with HBV DNA <300 copies/mL was significantly greater among the entecavir-treated patients (79%; 204/258) than the lamivudine-treated patients (46%; 121/261) through 96 weeks ($P < 0.001$).

Biochemical response

The proportion of patients with normalization of serum ALT levels (≤1.0 × ULN) at Week 48 was 90% in the entecavir group *vs* 78% in the lamivudine group ($P = 0.0003$). Up to 96 weeks, the cumulative proportion with confirmed ALT normalization was higher among entecavir-treated patients than among lamivudine-treated patients, with 96% (248/258) and 92% (241/261) of patients achieving this, respectively ($P = 0.06$).

Serological response

Among patients who were HBeAg positive at the baseline, entecavir was comparable to lamivudine for the proportion of patients achieving HBeAg loss (entecavir, 18%; lamivudine, 20%) and HBeAg seroconversion (entecavir, 15%; lamivudine, 18%) at Week 48. The cumulative proportion with confirmed loss of HBeAg through 96 weeks was 27% for both treatment groups (entecavir, $n = 61/225$; lamivudine, $n = 59/221$). The cumulative confirmed proportion of patients achieving HBeAg seroconversion was 21% in the entecavir group ($n = 48/225$) and 23% in the lamivudine group ($n = 51/221$; P = NS for both comparisons). No patients achieved HBsAg loss throughout the duration of the trial.

The cumulative virological, serological and biochemical responses through 96 weeks are presented in Table 2.

Protocol-defined outcomes through 2 years

At Week 48, 50 (19%) entecavir-treated patients and 40 (15%) lamivudine-treated patients achieved a CR. During year 2 of therapy, an additional 27 entecavir-treated patients and 23 lamivudine-treated patients achieved the protocol-defined CR. Over the first 96 weeks, 29.8% (77/258) patients on entecavir (50 at Week 48, plus 27 during Year 2) had a CR, compared with 24.1% (63/261) patients on lamivudine (40 at Week 48, plus 23 during Year 2). More patients in the entecavir group than in the lamivudine group achieved a PR (entecavir, 61%; lamivudine, 30%). Fewer entecavir-treated patients (4%; 11/258) than lamivudine-treated patients (41%; 108/261) were deemed to be non-responders throughout the 96 weeks of treatment.

Sustained response

During the 96 weeks of treatment, of all entecavir-treated patients with a CR, 99% (76/77) had HBV DNA <300 copies/mL, 95% (73/77) had ALT normalization, and 80% (36/45) of HBeAg-positive patients achieved HBeAg seroconversion. These results were sustained in 24%, 85% and 78% of patients, respectively, at the end of the 24-week follow-up. In comparison, of the lamivudine-treated patients with a CR, 86% (54/63) had HBV DNA <300 copies/mL, 98% (62/63) had ALT normalization and 90% (27/30) of HBeAg-positive patients achieved HBeAg seroconversion. These results were sustained in 17%, 63% and 78% of patients, respectively, at the end of the follow-up.

Virological, serological and biochemical responses in the Year 3 treatment cohort

Of the 149 patients in the Year 3 cohort with available samples at Year 3, 133 (89%) had an undetectable viral load (HBV DNA <300 copies/mL) by Week 144 (Fig. 2). Of the patients with available serum samples, 129/150 (86%) had achieved normalization of ALT levels (≤1.0 × ULN) by Week 144 (Fig. 2). Thirty patients (20%) lost HBeAg and 12/150 (8%) experienced HBeAg seroconversion by Week 144. Of all entecavir-treated patients, cumulative 3-year rates of HBeAg loss and HBeAg seroconversion were 36% (80/225) and 27% (60/225) at 144 weeks, respectively (Fig. 3).

HBV genotypic resistance to entecavir

Over the first 96 weeks of entecavir treatment, 77 patients had a CR and stopped treatment as predefined by the study protocol. Among the Year 3 cohort patients for whom resistance evaluation was feasible (142 through Week 96, and 118 through Week 144), three cases of genotypic resistance were identified through Week 96 and two additional cases were found through Week 144. All of these five patients had the lamivudine resistant rtM204I/V and rtL180M substitutions, plus additional entecavir resistant substitutions: rtT184A/I/P/L in the three patients up to Week 96 and one additional patient through Week 144; and both rtT184A/I/P/L and rtS202G substitutions in the remaining patient through Week 144. These data result in a genotypic resistance rate of 1.4% (3/219) through Week 96 and 2.6% (5/195) through Week 144. However, because not all cohort participants had stored samples available for testing, these rates are necessarily approximate.

Safety

Safety findings for the first 2 years of the study have been published elsewhere [10,11]. In general, the safety of entecavir was comparable with that of lamivudine. During the third year of treatment, entecavir's safety profile was consistent with previously reported findings from Years 1 to 2. Of the 160 patients in the Year 3 cohort, 55 reported a Grade 1–2 AE. No Grade 3 or 4 AEs, or associated deaths, were reported, and no further ALT flares were detected during treatment. No patient discontinued treatment due to an AE (Table 3).

DISCUSSION

The results show that entecavir is superior to lamivudine in achieving virological and biochemical responses in Chinese nucleoside-naive CHB patients through 96 weeks of

Table 2 Cumulative confirmed proportion of patients achieving virological, serological and biochemical end-points through Week 96

	Entecavir	Lamivudine	*P*-value
HBV DNA <300 copies/mL (PCR*), *n* (%)	204/258 (79)	121/261 (46)	<0.0001
ALT normalization (≤1 × ULN), *n* (%)	248/258 (96)	241/261 (92)	0.06
HBeAg loss, *n* (%)	61/225 (27)	59/221 (27)	NS
HBeAg seroconversion, *n* (%)	48/225 (21)	51/221 (23)	NS

HBeAg, hepatitis B e antigen; ULN, Upper Limit of Normal. *Lower Limit of Detection 300 copies/mL.

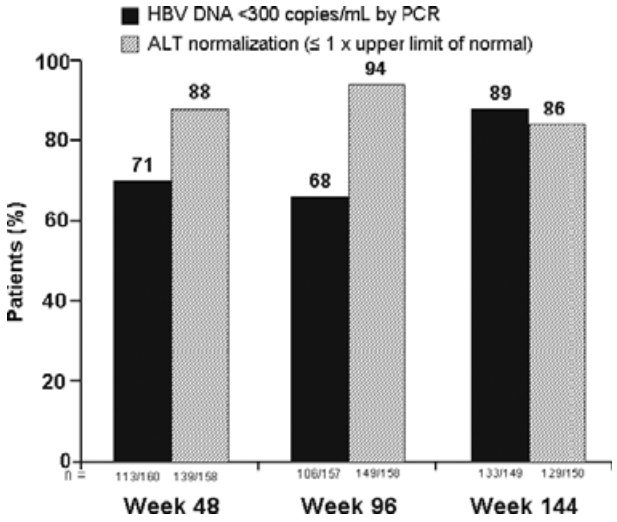

Fig. 2 Proportion of Year 3 cohort patients with virological and biochemical responses at Weeks 48, 96 and 144.

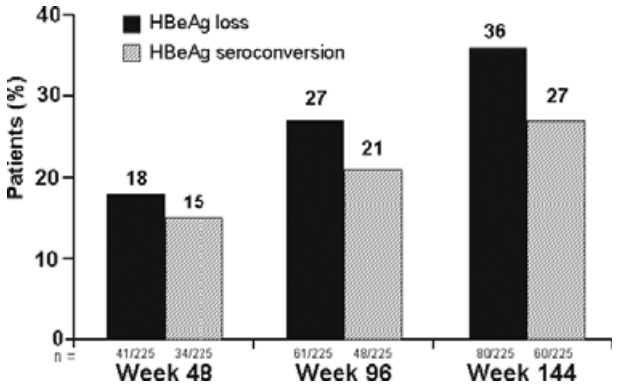

Fig. 3 Cumulative proportion of entecavir-treated hepatitis B e antigen (HBeAg)-positive patients (n = 225) with HBeAg loss and HBeAg seroconversion through 144 weeks.

treatment. The proportion of patients achieving an undetectable viral load (HBV DNA <300 copies/mL) was maintained among subjects treated with entecavir throughout Year 2. In total, 76% of entecavir-treated patients at Week 48 and 79% (cumulative) through Week 96 had HBV DNA <300 copies/mL. In comparison, 43% of lamivudine-treated patients at Week 48 and 46% (cumulative) through Week 96 achieved HBV DNA <300 copies/mL. Furthermore, in those patients who failed to meet criteria for discontinuing therapy during the first 96 weeks of treatment, continuous treatment with entecavir up to 144 weeks was able to maintain undetectable HBV DNA levels (<300 copies/mL) with minimal resistance. The proportion of patients achieving HBeAg loss and HBe seroconversion was similar between entecavir- and lamivudine-treated patients during the first 96 weeks of this study; however, incremental HBeAg loss and HBe seroconversion continued to occur in a proportion of patients over longer term entecavir treatment (144 weeks).

Treatment was well tolerated throughout 3 years of therapy, with comparable safety profiles between entecavir and lamivudine. Fewer ALT flares (on and off treatment) were observed with entecavir than with lamivudine. Most ALT flares during treatment with entecavir were associated with reductions in HBV DNA. In contrast, 44% of ALT flares that occurred with use of lamivudine were associated with increased HBV DNA.

Chronic hepatitis B is highly prevalent in China. The results of entecavir trials performed in China are encouraging as they have demonstrated superior efficacy of entecavir compared with lamivudine in Chinese patients, with comparable safety and tolerability [8,10,11]. Persistently elevated HBV DNA levels increase the risk of development of cirrhosis and hepatocellular carcinoma in persons with CHB [14], and this relationship remains consistent when both baseline and follow-up HBV DNA and ALT values are taken into consideration [15]. Treatment guidelines cite the suppression of HBV replication as the primary goal of therapy [16–18]. For HBeAg-negative patients who cannot, and most HBeAg-positive patients who do not, achieve HBeAg seroconversion, prolonged antiviral therapy is often necessary. However, one of the major challenges associated with long-term treatment is the development of resistance. For example, 70% of patients treated with lamivudine develop resistance and lose the benefit of therapy over 3 years of treatment [19]. The rates of resistance are lower with newer agents. Among patients treated with adefovir for 240 weeks, 30% were reported to have acquired resistance mutations [20]. The rate of resistance to telbivudine in HBeAg-positive patients is reported to be 5% after 48 weeks and 25% after 2 years of continuous treatment [21,22]. Of the available nucleos(t)ide analogues in China, the lowest rates of resistance are associated with entecavir (1.2% through 5 years of treatment) due to its high potency and high genetic barrier to resistance [5].

The results from this analysis are consistent with those from other long-term studies in patients receiving continuous entecavir for a period of 3 or 4 years. Of 146 HBeAg-positive, nucleoside-naive patients treated for at least 4 years with entecavir (0.5 mg once daily up to Week 96, then 1.0 mg once daily up to Week 192), 91% had undetectable HBV DNA (<300 copies/mL), 86% had normalization of ALT levels, and an additional 41% of patients lost HBeAg with 16% HBe seroconversion [8]. Entecavir was also found to be safe, with a consistent profile through 4 years [8]. In a study of Japanese nucleoside-naive patients treated with entecavir 0.5 mg once daily for 3 years, 87% achieved HBV DNA <400 copies/mL, 91% achieved ALT normalization, and the cumulative probability of entecavir resistance was 1.7% [7]. The data presented here support other clinical studies in demonstrating that entecavir is one of the most potent anti-HBV compounds with a favourable resistance profile in nucleoside-naive patients.

Table 3 Cumulative safety data through 96 weeks on treatment and data from the Year 3 cohort

Adverse event (AE)	Cumulative through 96 weeks: Entecavir, *n* (%) (*n* = 258)	Cumulative through 96 weeks: Lamivudine, *n* (%) (*n* = 261)	Year 3 cohort: Entecavir, *n* (%) (*n* = 160)
Any AE	166 (64)	156 (60)	55 (34)
Grade 3 or 4 AE	18 (7)	23 (9)	0 (0)
Serious AE	9 (3)	16 (6)	1 (<1)
Discontinuation due to AE	1 (<1)	3 (1)	0 (0)
On-treatment ALT flare*	11 (4)	18 (7)	0 (0)
Off-treatment ALT flare†	4 (5)‡	8 (10)‡	–

ULN, Upper Limit of Normal. *On-treatment ALT flare: ALT >2 × baseline and >10 × ULN; †off-treatment ALT flare: ALT >2 × reference and >10 × ULN (reference is minimum of baseline laboratory value and last laboratory value at end-of-dosing); ‡entecavir off-treatment, *n* = 88; lamivudine off-treatment, *n* = 78.

There are two points in the study design that could impact the interpretation of data and need to be considered. First, as defined in the protocol, in order to observe sustained response, patients who achieved a CR during the first 2 years discontinued treatment. The remaining patients were those who achieved viral suppression but did not achieve HBeAg seroconversion, or subjects who did not achieve timely viral suppression, and as such comprise a special group of patients that may not be representative of general hepatitis B patients. Based on experience with other antiviral agents, it is known that early viral suppression predicts better treatment outcomes and lower resistance rates. Therefore, entecavir resistance monitoring in this study focussed on patients who had a higher risk of developing resistance than the general patient population. Second, the dose of entecavir was increased from 0.5 mg once daily in study 023 to 1.0 mg once daily in study 050, as previously lamivudine-treated patients were also enrolled in study 050. This could potentially have helped improve the reported clinical efficacy, and further data are needed to understand the long-term efficacy of entecavir 0.5 mg once daily. The Japanese long-term data mentioned above used 0.5 mg once daily throughout the 3 years of study, and the results are consistent with the current findings.

In conclusion, entecavir provides safe, potent and durable suppression of HBV replication for a period of 3 years in nucleoside-naive Chinese CHB patients. Among those patients treated with entecavir, the proportion with undetectable HBV DNA levels was increased and maintained up to Year 2 of treatment. For patients unable to achieve a CR and requiring maintained viral suppression, ongoing 1 mg once daily entecavir therapy led to continued viral suppression and incremental HBeAg seroconversion with minimal emergence of resistance through 3 years. These findings demonstrate that continued long-term treatment with entecavir provides additional clinical benefits. Together, the combined data from this study support the use of entecavir as a first-line nucleoside analogue for the treatment of CHB patients.

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STATEMENT OF INTERESTS

Authors' declaration of personal interests:

(i) G. B. Yao served as a global advisory board member for Bristol–Myers Squibb in 2003–2006.

Declaration of funding interests:

(i) This study was funded in full by Bristol–Myers Squibb. (ii) Initial data analyses were undertaken by Dong Xu who is an employee of Bristol–Myers Squibb. (iii) Writing support was provided by Jesse Quigley-Jones of MediTech Media Asia Pacific Pte Ltd and funded by Bristol–Myers Squibb.

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