

A 1-Year Trial of Telbivudine, Lamivudine, and the Combination in Patients With Hepatitis B e Antigen–Positive Chronic Hepatitis B

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Background & Aims: A previous 4-week trial of telbivudine in patients with chronic hepatitis B indicated marked antiviral effects with good tolerability, leading to the present 1-year phase 2b trial. **Methods:** This randomized, double-blind, multicenter trial evaluated the efficacy and safety of telbivudine 400 or 600 mg/day and telbivudine 400 or 600 mg/day plus lamivudine 100 mg/day (Comb400 and Comb600) compared with lamivudine 100 mg/day in hepatitis B e antigen (HBeAg)-positive adults with compensated chronic hepatitis B. **Results:** A total of 104 patients were randomized 1:1:1:1 among the 5 groups. Median reductions in serum hepatitis B virus (HBV) DNA levels at week 52 (\log_{10} copies/mL) were as follows: lamivudine, 4.66; telbivudine 400 mg, 6.43; telbivudine 600 mg, 6.09; Comb400, 6.40; and Comb600, 6.05. At week 52, telbivudine monotherapy showed a significantly greater mean reduction in HBV DNA levels (6.01 vs 4.57 \log_{10} copies/mL; $P < .05$), clearance of polymerase chain reaction–detectable HBV DNA (61% vs 32%; $P < .05$), and normalization of alanine aminotransferase levels (86% vs 63%; $P < .05$) compared with lamivudine monotherapy, with proportionally greater HBeAg seroconversion (31% vs 22%) and less viral breakthrough (4.5% vs 15.8%) ($P = \text{NS}$ for both). Combination treatment was not better than telbivudine alone. All treatments were well tolerated. In exploratory scientific analyses, clinical efficacy at 1 year appeared related to reduction in HBV DNA levels in the first 6 months of treatment. **Conclusions:** Patients with chronic hepatitis B treated with telbivudine exhibited significantly greater virologic and biochemical responses compared with lamivudine. Results with the combination regimens were similar to those obtained with telbivudine alone. These data support the ongoing phase 3 evaluation of telbivudine for treatment of patients with chronic hepatitis B.

Despite recent advances in vaccination and treatment, chronic hepatitis B virus (HBV) infection remains a major cause of severe liver-related morbidity and premature mortality and comprises a challenging global public health problem. Worldwide, it is estimated that about 50 million new HBV infections occur annually and approximately 350–400 million people are chronically infected.^{1–3}

Published epidemiologic and clinical studies indicate that persistent high-level HBV replication, signaled by serologic detectability of hepatitis B e antigen (HBeAg) and/or high levels of circulating HBV DNA, is a dominant factor contributing to the risk of progressive necro-inflammatory liver injury in individuals chronically infected with HBV.^{4,5} High-level HBV replication is a major risk factor for progression to end-stage complications such as decompensated cirrhosis and hepatocellular carcinoma.^{6–9} Correspondingly, long-lasting suppression of HBV replication with effective antiviral therapy has been linked to a reduced risk of further disease progression and end-stage sequelae.¹⁰ Hence, the goal of antiviral therapy for chronic hepatitis B is to provide prolonged suppression of HBV replication to abrogate progression of liver injury and improve patients' long-term prognoses.^{1,2,11} Unfortunately, many patients fail to develop durable responses to the currently available therapies due to suboptimal efficacy, poor tolerability, and/or the emergence of resistance.

Abbreviations used in this paper: AUCMB, area under the curve minus baseline; Comb400, telbivudine 400 mg plus lamivudine 100 mg; Comb600, telbivudine 600 mg plus lamivudine 100 mg; PCR, polymerase chain reaction.

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Published guidelines for the management of patients with chronic hepatitis B suggest that suppression of viral load to $<5 \log_{10}$ copies/mL is associated with clinical improvement and is therefore an important treatment objective.^{2,11} However, recent reports suggest that the likelihood of achieving clinically important treatment end points can be increased by suppressing HBV replication to even lower levels early in the course of therapy. With lamivudine, the highest rates of HBeAg seroconversion and the lowest rates of drug resistance were observed in the subgroup of patients who achieved serum HBV DNA levels $<3-4 \log_{10}$ copies/mL in the first 6 months after initiation of lamivudine therapy.^{12,13} These findings suggest that early antiviral effect is linked to clinical efficacy, and maximizing early HBV suppression may therefore be an important objective for antiviral treatment in patients with hepatitis B.

Telbivudine (β -L-2'-deoxythymidine) is an orally bioavailable L-nucleoside with potent and specific anti-HBV activity in vitro and in the woodchuck hepadnavirus model, and a favorable preclinical toxicologic profile.^{14,15} A placebo-controlled dose-escalation trial of telbivudine in adults with chronic hepatitis B investigated once-daily dosages of 25–800 mg for a 4-week treatment period with 12 weeks of follow-up.¹⁶ The results of this trial indicated excellent tolerability and potent dose-related antiviral activity; after 4 weeks of treatment, reductions in serum HBV DNA levels from baseline averaged 3.4–3.8 \log_{10} copies/mL for the 2 highest dosages of telbivudine tested (400 and 800 mg/day). *Emax* modeling of the dose-response data from the phase 1/2 trial confirmed that dosages of telbivudine in the range of 400–800 mg/day maximize antiviral effects.¹⁶

Based on the encouraging phase 1/2 trial results, a larger, longer-duration trial of telbivudine was undertaken and is the subject of this report. The objective of this international phase 2b trial was to gain a 1-year controlled assessment of the antiviral efficacy and safety of 2 different dosages of telbivudine (400 and 600 mg/day), taken alone or in combination with lamivudine (100 mg/day), with a concurrent comparison with standard lamivudine monotherapy.

Patients and Methods

Study Design

This international, multicenter, double-blind, randomized phase 2b trial investigated 5 antiviral treatment regimens for 1 year (52 weeks) in adults with HBeAg-positive chronic hepatitis B and compensated liver disease (Figure 1). Eligible patients were randomized (1:1:1:1:1) among the following 5 daily oral treatment regimens: telbivudine 400 mg, telbivudine 600 mg, telbivudine 400 mg plus lamivudine 100

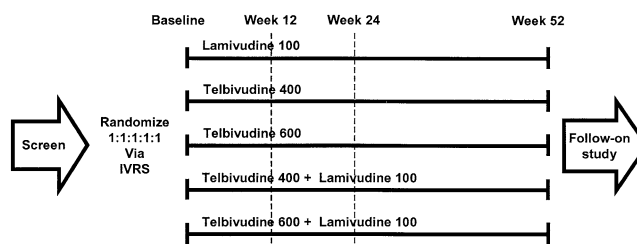


Figure 1. Study design. Patients were randomized 1:1:1:1:1 among the 5 treatment groups and treated for 12 months as shown. Interim data analyses were completed at weeks 12 and 24, with the final analysis at week 52. Patients who completed 52 weeks of treatment were offered participation in a 2-year follow-on study.

mg (Comb400), telbivudine 600 mg plus lamivudine 100 mg (Comb600), or lamivudine 100 mg.

The selected dosages of telbivudine (400 and 600 mg/day) were based on the results of the completed phase 1/2 dose-escalation trial.¹⁶ *Emax* modeling of the phase 1/2 data indicated that the 4-week antiviral effect achieved with an 800-mg/day dose of telbivudine is about 0.3 \log_{10} greater than the antiviral effect of 400-mg/day dosing. However, a 600-mg/day dosage was predicted to have nearly the same antiviral effect as the 800-mg/day dosage while affording a more convenient tablet size. Therefore, telbivudine dosage levels of 400 mg/day and 600 mg/day were selected for further evaluation in the present trial. The dosage of lamivudine (100 mg/day) is the regulatory-approved dose for hepatitis B. Telbivudine tablets were produced by Idenix Pharmaceuticals Inc (Cambridge, MA); lamivudine and matching placebo were generously supplied by GlaxoSmithKline (Research Triangle Park, NC). Blinded study drug was supplied to patients in bottles containing telbivudine tablets (200 mg) or matching placebo and, separately, lamivudine tablets (100 mg) or matching placebo. The first dose of study drug was taken at baseline, and then the study drug was taken by mouth once daily for 52 weeks, with evaluations at baseline and weeks 1, 4, 8, 12, 16, 24, 32, 40, 48, and 52 (study completion). Patients who completed the study were offered participation in a 2-year follow-on trial. Patients who elected not to participate in the follow-on study or who discontinued early were to undergo posttreatment safety evaluations for 4 months.

This clinical trial was conducted internationally under Investigational New Drug authorization #60,459 from the US Food and Drug Administration, together with local regulatory approvals. The trial protocol was approved by institutional review boards at all clinical centers, and all patients gave written informed consent for their participation in the study, in accord with Good Clinical Practice standards and the Declarations of Helsinki.

Patient Population

Eligible patients were enrolled from 16 clinical centers in 5 countries (Hong Kong SAR, Singapore, United States, Canada, and France). The first patient was enrolled on November 8, 2001, and the last patient completed the study on September 2, 2003.

Key inclusion criteria were as follows: male or female, aged 18–65 years; clinical history compatible with chronic hepatitis B; hepatitis B surface antigen (HBsAg) seropositive for ≥ 6 months; HBeAg seropositive at screening; serum HBV DNA level $> 6 \log_{10}$ copies/mL; and serum alanine aminotransferase (ALT) level 1.3–10 times the upper limit of normal. Key exclusion criteria were as follows: prior treatment with anti-HBV nucleosides or nucleotides; interferon treatment within the preceding 12 months; coinfection with human immunodeficiency virus, hepatitis C virus, or hepatitis delta virus; other known primary or secondary causes of liver disease; history or signs of hepatic decompensation; history of pancreatitis; concurrent medical conditions that might confound safety or efficacy assessments during the study; history of alcohol or illicit substance abuse within the preceding 2 years; hemoglobin < 11 g/dL for men and < 10 g/dL for women; absolute neutrophil count $< 1,500/\text{mm}^3$; platelet count $< 80,000/\text{mm}^3$; serum creatinine level > 1.5 mg/dL; bilirubin level > 2.0 mg/dL; albumin level < 3.4 g/dL; or prothrombin time prolonged > 3 seconds despite administration of vitamin K.

Efficacy and Safety End Points

The primary goals of this trial were to identify which investigational treatment regimen produced the greatest antiviral effect and to compare the antiviral effects of the investigational treatment regimens with lamivudine. The primary measure of antiviral effect was reduction in serum HBV DNA levels from baseline. Serum HBV DNA was assessed quantitatively by the COBAS Amplicor HBV Monitor polymerase chain reaction (PCR) assay, with an estimated lower limit of detection of 200 HBV genome copies/mL (Roche Molecular Systems, Branchburg, NJ). Reductions in serum HBV DNA levels from baseline were analyzed in several ways: area under the curve minus baseline (AUCMB), which provides a cumulative average measure of reduction in HBV DNA levels over time; absolute reductions in HBV DNA levels from baseline in \log_{10} copies/mL; and proportions of patients achieving HBV DNA levels < 5 , < 4 , or $< 3 \log_{10}$ copies/mL or nondetectable levels (< 200 copies/mL). AUCMB analyses were conducted from baseline to week 52 and from week 1 to week 12. Samples below the assay limit of quantitation were assigned a value of 100 copies/mL for data analysis.

Secondary efficacy parameters included normalization of serum ALT levels, serum HBeAg loss and seroconversion (HBeAg loss with gain of detectable antibody against HBeAg), and serum HBsAg loss and seroconversion. Two composite serologic end points were also assessed. First, virologic response was defined as HBeAg loss and HBV DNA level $< 5 \log_{10}$ copies/mL, as in the recent National Institutes of Health Workshop and American Association for the Study of Liver Diseases recommendations.^{2,17,18} A second composite serologic end point, therapeutic response, was defined as HBV DNA level $< 5 \log_{10}$ copies/mL coupled with HBeAg loss or normalization of ALT levels; this composite efficacy measure captures viral suppression (here assessed at the American As-

sociation for the Study of Liver Diseases—recommended level of $5 \log_{10}$ copies/mL) linked with either of the 2 types of clinical benefit achievable with nucleoside therapy in patients with hepatitis B, that is, clearance of HBeAg or normalization of ALT levels.

Virologic breakthrough was defined in 2 ways. For patients who achieved reductions in HBV DNA levels to $< 5 \log_{10}$ copies/mL on 2 or more successive visits, virologic breakthrough was defined as an on-treatment increase in HBV DNA levels to $> 5 \log_{10}$ copies/mL on 2 or more visits, including the last visit. For patients who did not achieve suppression of HBV DNA levels to $< 5 \log_{10}$ copies/mL, virologic breakthrough was defined as an on-treatment increase in HBV DNA levels to within 1 \log_{10} of the baseline value on 2 or more visits, including the last visit.

Safety assessments included evaluation at each study visit of clinical adverse events, vital signs, and symptom-targeted physical examinations, together with clinical laboratory monitoring of complete blood counts, serum chemistries (ALT, aspartate aminotransferase, bilirubin, total protein, albumin, blood urea nitrogen, creatinine, amylase, lipase, creatinine kinase), periodic testing of prothrombin times and serum β -human chorionic gonadotropin levels (as a pregnancy test for women), and periodic urinalyses. Laboratory testing for this study was performed at an independent reference laboratory (Quintiles Laboratories, Ltd, Smyrna, GA, with affiliated regional laboratories in Asia and Europe).

After screening, eligible patients were enrolled and randomized via a central randomization scheme using an interactive voice response system, with the system linked to the study drug supply vendor for dispensing of blinded study medications to the study sites. Treatment assignments remained double blinded for the duration of the study.

Sample Size, Randomization, and Statistical Analyses

Preliminary (12-week) data from this study were to be used for planning phase 3 trials with global regulatory bodies. Therefore, sample size calculations were based on postulated reductions in serum HBV DNA levels at week 12 using the AUCMB method described previously between week 1 and week 12, with test assumptions extrapolated from the earlier phase 1/2 study. A factorial design feature in the statistical analysis plan allowed comparisons of the combined telbivudine monotherapy and combined combination groups under certain circumstances. Specifically, if the effects of the dose of telbivudine (400 vs 600 mg) and the effects of combination therapy versus monotherapy were found to be independent of each other (which subsequently proved to be the case), the 2 telbivudine monotherapy groups and the 2 combination groups could be combined for further statistical analysis of response by treatment type. Thus, it was estimated that with a total of 100 patients (20 per treatment group), the study allowed detection of a $0.33 \log_{10}$ difference in reduction of HBV DNA levels between treatment types (lamivudine vs telbivudine vs combination) and detection of a $0.5 \log_{10}$ difference in reduction of

Table 1. Patient Baseline Demographics and Disease Characteristics

	Lamivudine 100 mg/day	Telbivudine 400 mg/day	Telbivudine 600 mg/day	Telbivudine 400 mg/day + lamivudine 100 mg/day	Telbivudine 600 mg/day + lamivudine 100 mg/day
n	19	22	22	21	20
Median (range) age at screening (y)	34 (18–61)	41 (22–68)	40 (19–60)	30 (19–51)	33 (21–53)
Mean (range) weight (kg)	69 (45–86)	70 (51–96)	70 (53–120)	66 (42–105)	74 (57–105)
Ethnicity (%)					
Asian	84	86	86	90	80
White	16	9	5	10	5
Other	0	5	9	0	15
Sex (% male)	74	77	82	71	100
Median (range) serum HBV DNA (log ₁₀ copies/mL)	9.3 (6.6–12.9)	8.9 (6.3–12.9)	9.0 (6.3–13.3)	9.3 (5.9–12.8)	9.7 (6.4–13.2)
Median (range) serum ALT (U/L)	122 (62–309)	130 (35–400)	130 (61–325)	152 (52–323)	132 (32–1657)
Prior use of interferon alfa (%)	5	9	0	0	5

NOTE. All patients were HBsAg and HBeAg positive at screening. The upper limit of normal for serum ALT was 48 U/L for men and 37 U/L for women. There were no statistically significant differences between groups in any baseline demographic, clinical, or virologic parameters.

HBV DNA levels between individual treatment groups, with 80% power at a 2-sided significance level of $\alpha = .05$.

A centralized randomization process was used for all sites. Patients were stratified by serum ALT level (above or below 2.5 times the upper limit of normal), and sequential blocks of 5 were used to randomize eligible patients among the 5 treatment groups, implemented using the central interactive voice response system.

Further Data Analyses

After study completion, further analyses were undertaken to explore potential scientific relationships between early antiviral response and clinically important efficacy outcomes. Data from 103 treated patients (one patient who withdrew at week 4 was excluded) were pooled, regardless of treatment arm. Patients were then categorized according to their serum HBV DNA level at week 24: undetectable (<200 copies/mL), detectable but <3 log₁₀ copies/mL, from 3 to 4 log₁₀ copies/mL, and >4 log₁₀ copies/mL, similar to the categorical analysis previously reported for resistance to lamivudine.¹² One-year (week 52) clinical and virologic efficacy outcomes were then assessed for patients in these 4 week-24 viral load categories.

Results

Enrolled Patient Population and Patient Disposition

A total of 107 patients were randomized in this study. Three patients withdrew before baseline (first day of treatment). The 104 enrolled patients with postbaseline data comprise the intention-to-treat population for the study, for which the primary study analyses were conducted. Enrolled patients were mostly men and ranged in age from 18 to 68 years (Table 1). Demographics across the 5 treatment groups were comparable with respect to sex, age, race, height, weight, duration of

HBV infection, baseline HBV DNA levels, baseline ALT levels, baseline hepatitis B serology, and prior use of interferon (Table 1). Baseline levels of HBV DNA were relatively high across treatment groups, with an overall mean of 9.20 log₁₀ copies/mL. Of the 104 patients, 5 discontinued prematurely and 99 completed the study. Reasons for premature study discontinuation for the 5 patients included noncompliance (one patient), pregnancy (2 patients), increased serum creatine kinase level (one patient), and lost to follow-up (one patient).

Statistical analysis of the efficacy results indicated that the effects of telbivudine dosage (400 vs 600 mg/day) and the effects of combination treatment versus monotherapy were independent. Hence, the study results met protocol-defined criteria for use of the preferred factorial analyses of efficacy by treatment type, that is, telbivudine monotherapy (400 and 600 mg/day monotherapy groups were pooled) versus combination therapy (400 and 600 mg/day combination groups were pooled) versus lamivudine monotherapy.

Efficacy Results

Antiviral responses. Serum HBV DNA levels declined markedly after the start of treatment in all treatment groups. A greater antiviral effect for the 4 telbivudine-containing groups was evident beginning at week 4, after which reductions in serum HBV DNA levels for the 4 telbivudine-containing treatment groups remained consistently greater than those observed for the lamivudine group (Figure 2). At week 52, the median reduction from baseline in serum HBV DNA levels was >6 log₁₀ for all 4 telbivudine-containing groups compared with 4.66 log₁₀ with lamivudine (Table 2). There were no significant differences for the 400-mg and 600-mg tel-

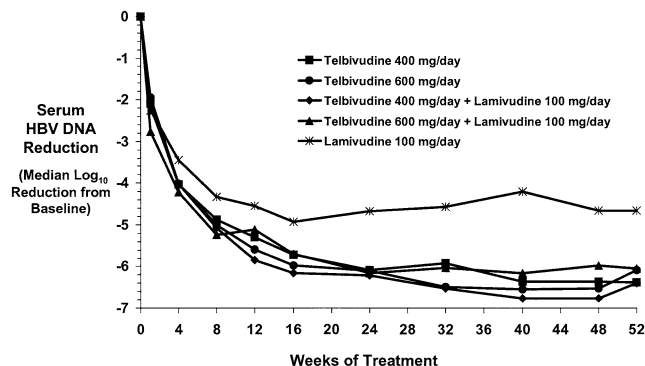


Figure 2. Reductions in serum HBV DNA levels from baseline. Serum samples were analyzed for HBV DNA content by Roche Cobas AmpliCor PCR assay. Data are plotted as log₁₀ change from baseline values. Assay lower limit of detection is 200 copies/mL.

bivudine dosage groups, compared either as monotherapies or in combination with lamivudine. In the factorial analysis of antiviral response by treatment type at week 52, significantly greater reductions of mean serum HBV DNA levels were achieved with both telbivudine mono-

therapy and with combination treatment compared with lamivudine monotherapy ($P < .05$ for each comparison). There was no significant difference comparing combination treatment with telbivudine monotherapy.

In the analysis of response by treatment type at week 52, serum HBV DNA was undetectable by PCR (ie, <200 copies/mL) in a significantly greater proportion of patients receiving telbivudine compared with lamivudine (61% vs 32%; $P < .05$; Table 2). Serum HBV DNA was undetectable in 49% of patients receiving combination treatment ($P = NS$). In the telbivudine, combination, and lamivudine groups, serum viral load was reduced at week 52 to <5 log₁₀ copies/mL in 89%, 78%, and 58% of patients, respectively; to <4 log₁₀ copies/mL in 82%, 78%, and 53% of patients, respectively; and to <3 log₁₀ copies/mL in 75%, 59%, and 47% of patients, respectively.

AUCMB data indicate the mean of weighted mean HBV DNA reductions for all study visits between weeks 1 and 12 or between weeks 0 (baseline) and 52. AUCMB

Table 2. Efficacy Responses at Week 52

	Lamivudine 100 mg/day	Telbivudine 400 mg/day	Telbivudine 600 mg/day	Telbivudine 400 mg/day + lamivudine 100 mg/day	Telbivudine 600 mg/day + lamivudine 100 mg/day
n	19	22	22	21	20
Mean change in HBV DNA levels from baseline (\log_{10} copies/mL)	-4.57	-6.53	-5.49	-6.04	-5.94
Median change in HBV DNA levels from baseline (\log_{10} copies/mL)	-4.66	-6.38	-6.09	-6.40	-6.05
Mean HBV DNA AUCMB ^a (weeks 1-12)	-1.54	-1.96	-2.00	-1.96	-1.91
Mean HBV DNA AUCMB ^b (weeks 0-52)	-4.42	-5.71	-5.39	-5.64	-5.91
Normalization of ALT levels at week 52 (%)	63	91	82	81	74
	Lamivudine	Telbivudine	Telbivudine + lamivudine		
N	19	44	41		
Mean change in HBV DNA levels from baseline (95% CI) (\log_{10} copies/mL)	-4.57 (-3.28 to -5.86)	-6.01 ^c (-5.40 to -6.62)	-5.99 ^c (-5.32 to -6.66)		
Median change in HBV DNA levels from baseline ^d (\log_{10} copies/mL)	-4.66	-6.34	-6.06		
% HBV DNA PCR nondetectable (95% CI)	32 (11-52)	61 (47-76) ^c	49 (33-64)		
% ALT normalization (95% CI)	63 (41-85)	86 (76-97) ^c	78 (65-91)		
% HBeAg loss (95% CI)	28 (7-48)	33 (19-48)	17 (6-29)		
% HBeAg seroconversion (95% CI)	22 (3-41)	31 (17-45)	15 (4-25)		
% Virologic response ^e (95% CI)	26 (7-46)	32 (18-46)	20 (7-32)		
% Therapeutic response ^f (95% CI)	53 (30-75)	77 (65-90)	63 (49-78)		
Viral breakthrough at week 48 (%)	3/19 (15.8)	2/44 (4.5)	5/41 (12.2)		

CI, confidence interval.

^aMean of mean HBV DNA reductions from week 1 HBV DNA level for all study visits.

^bMean of mean HBV DNA reductions from baseline HBV DNA level for all study visits.

^c $P < .05$ vs lamivudine.

^d $P < .05$ at week 24 (telbivudine vs lamivudine); Wilcoxon rank sum loses power at week 52 due to high number of PCR-negative patients.

^eHBeAg loss and HBV DNA <5 log₁₀ copies/mL.

^fHBV DNA <5 log₁₀ copies/mL coupled with HBeAg loss or normalization of ALT levels.

Table 3. Most Frequent Adverse Events Through Week 52

	Lamivudine 100 mg/day	Telbivudine 400 mg/day	Telbivudine 600 mg/day	Telbivudine 400 mg/day + lamivudine 100 mg/day	Telbivudine 600 mg/day + lamivudine 100 mg/day
n	19	22	22	21	20
At least one adverse event	13	16	15	15	14
Influenza	4	4	4	4	6
Headache	5	1	3	4	2
Fatigue	3	1	4	1	2
Cough	3	2	1	2	1
Pharyngolaryngeal pain	3	2	1	0	3
Upper respiratory tract infection	1	3	0	2	2
Nasopharyngitis	1	1	1	2	1
Diarrhea	1	2	1	1	1
Upper abdominal pain	1	1	2	0	2
Back pain	0	0	1	2	2
Dyspepsia	4	0	1	0	0
Dizziness	1	0	1	1	2
Increased creatine phosphokinase level	1	1	1	1	1
Nausea	1	1	1	0	2
Depression	2	0	0	1	1

data by treatment arm are presented in Table 2. In the factorial analysis by treatment type, significantly greater mean reductions in HBV DNA levels by AUCMB analysis were evident for the study treatment period (weeks 0–52) with telbivudine ($-5.55 \log_{10}$ copies/mL) or combination treatment ($-5.80 \log_{10}$ copies/mL) compared with lamivudine ($-4.42 \log_{10}$ copies/mL; $P < .05$).

Biochemical responses. At week 52, serum ALT levels were normalized in 91%, 82%, 81%, 74%, and 63% of patients receiving telbivudine 400 mg, telbivudine 600 mg, Comb400, Comb600, and lamivudine, respectively. In the factorial analysis by treatment type, serum ALT levels were normalized at week 52 in 86% of patients who received telbivudine compared with 63% of patients who received lamivudine ($P < .05$). Serum ALT level was normalized in 78% of patients receiving combination treatment ($P = \text{NS}$).

Composite efficacy responses. Virologic response (HBeAg loss coupled with HBV DNA level $<5 \log_{10}$ copies/mL) was achieved in 32%, 26%, and 17% of patients receiving telbivudine monotherapy, lamivudine monotherapy, or combination therapy, respectively (all comparisons nonsignificant). Therapeutic response (HBV DNA level $<5 \log_{10}$ copies/mL, coupled with HBeAg loss or normalization of ALT levels) was achieved in 77%, 53%, and 61% of patients receiving telbivudine monotherapy, lamivudine monotherapy, or combination therapy, respectively (all comparisons nonsignificant).

HBeAg loss and seroconversion. In the factorial analysis by treatment type, HBeAg loss occurred in 33% of patients receiving telbivudine compared with 17% of

patients receiving combination treatment and 28% of patients receiving lamivudine ($P = \text{NS}$). In each of these 3 groups, all patients but one with HBeAg loss also developed antibody to HBeAg; thus, HBeAg seroconversion rates were 31%, 15%, and 22% for telbivudine, combination treatment, and lamivudine, respectively.

HBsAg loss and seroconversion. No patient achieved HBsAg loss or seroconversion during the 52-week treatment period. This result may be consistent with reported results for lamivudine and interferon, where HBsAg loss was observed in some patients but was delayed for months or years after HBeAg clearance.^{19,20}

Safety Results

Clinical adverse events. All treatments were well tolerated. Adverse events occurred with similar overall frequency across the 5 treatment groups. Most adverse events were not attributed to study medications, and there was no pattern of specific types of clinical adverse events with respect to treatment type, dose, or time after start of therapy. Regardless of attributability to study treatment, the most common adverse events by week 52 were influenza, headache, cough, and fatigue (Table 3). Two serious adverse events were reported (one patient with a mediastinal tumor, and one patient with a papillary thyroid carcinoma); neither event was considered related to study treatment.

Graded laboratory abnormalities. Similar to clinical adverse events, there was no pattern of laboratory abnormalities by treatment type, dose, or time after start of therapy. Nine patients experienced grade 3 or 4 laboratory abnormalities by week 52, including one patient (telbivu-

dine 600 mg) with elevation of ALT level, 5 patients with elevation of creatine kinase levels (one receiving telbivudine 400 mg, 3 receiving telbivudine 600 mg, and one receiving Comb600), one patient with elevation of lipase level (Comb600), and 2 patients (Comb600) with neutropenia; one of the latter 2 patients had a marginal neutrophil count at study entry. Patients with these laboratory abnormalities continued study treatment uninterrupted, except for one patient with an elevation of creatine kinase level, who discontinued by investigator discretion; most laboratory abnormalities had resolved spontaneously by the time of last follow-up.

Viral Breakthrough

A total of 10 patients experienced viral breakthrough by week 48, including 3 of 19 patients (15.8%) receiving lamivudine, 2 of 44 patients (4.5%) receiving telbivudine, and 5 of 41 patients (12.2%) receiving combination treatment (Table 2). A fourth lamivudine recipient had evidence of viral breakthrough at week 48, but it was not confirmed until week 60.

HBV DNA amplified by PCR methods from the sera of patients with viral breakthrough was further analyzed by DNA sequencing. In the lamivudine group, HBV DNA from 2 patients with viral breakthrough showed the M204I mutation, and one had L180M plus M204V mutations. HBV DNA from both patients with viral breakthrough in the telbivudine group carried the M204I mutation. In the combination group, HBV DNA from 3 patients had M204I, one patient had L180M plus M204V, and one patient had wild-type HBV.

Early Antiviral Response and Its Relationship to Subsequent Efficacy Outcomes

At week 24, a total of 30 patients had undetectable serum HBV DNA (<200 copies/mL) by the quantitative PCR assay. Serum HBV DNA levels were between the quantitation limit and 3 log₁₀ copies/mL in 26 patients, between 3 and 4 log₁₀ copies/mL in 21 patients, and >4 log₁₀ copies/mL in 26 patients. Response rates at week 52 on various clinical and virologic efficacy outcomes showed a strong association with the degree of viral suppression at week 24, as shown in Figure 3A and B. The difference in HBeAg loss rates, comparing patients who were PCR negative and those with residual viremia >4 log₁₀ copies/mL at week 24, was more than 6-fold (43% vs 7%, respectively); the 2 intermediate patient groups had intermediate HBeAg loss rates (Figure 3A). As shown in Figure 3B, differences in proportions of patients with normalization of ALT levels at week 52, while less pronounced, were also evident. Normalization of ALT levels at week 52 was achieved in 90%

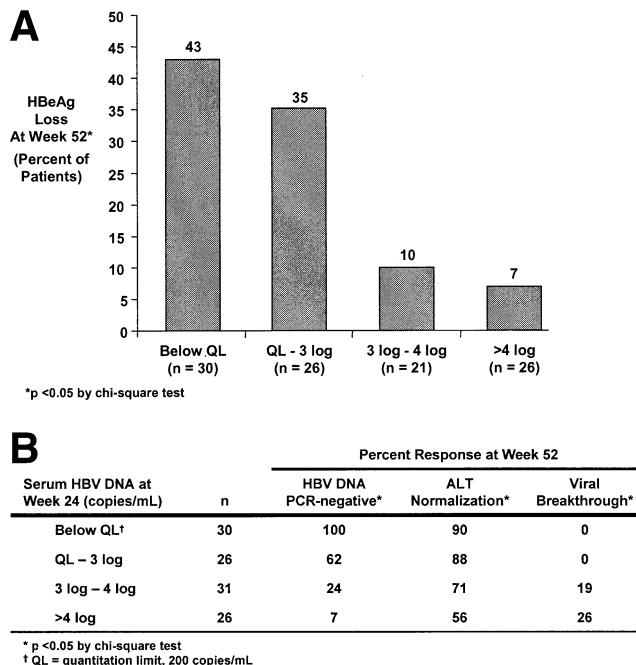


Figure 3. Efficacy responses at week 52 versus serum HBV DNA level at week 24. Data from all study patients were pooled, regardless of treatment group, and categorized as shown according to serum HBV DNA level at week 24. Within these categories, efficacy outcomes at week 52 were assessed for (A) HBeAg loss and (B) normalization of serum ALT levels, PCR nondetectability, and virologic breakthrough. χ^2 analysis was performed to test for differences among the 4 HBV DNA categories and showed that these groups were significantly different at week 52 for each efficacy parameter ($P < .05$).

of patients who were PCR negative at week 24, ranging down to 56% in patients with viral load >4 log₁₀ at week 24. All patients with undetectable serum HBV DNA at week 24 maintained HBV DNA levels below the quantitation limit at week 52 (Figure 3B). Among patients with detectable serum HBV DNA at week 24, the likelihood of HBV DNA becoming undetectable by week 52 was inversely related to viral load at week 24 (Figure 3B). Importantly, no cases of viral breakthrough were evident at week 52 in patients with residual viremia <3 log₁₀ copies/mL at week 24. In contrast, viral breakthrough rates of 19%–26% were seen at week 52 in patients with viremia levels >3 log₁₀ copies/mL at week 24 (Figure 3B). χ^2 analysis was performed to test for differences among the 4 HBV DNA categories and showed that these groups were significantly different at week 52 for each efficacy parameter ($P < .05$).

Discussion

The results of this 1-year international trial of telbivudine showed a consistent and substantially greater antiviral effect for telbivudine compared with lamivudine. This difference in antiviral effect was evident for all 4 telbivudine-containing treatment regimens from week 4 to

week 52 (Figure 2). Most notably, 61% of patients receiving telbivudine monotherapy lost PCR-detectable HBV DNA during the 1-year treatment period, despite high median viral loads for the study population at baseline, exceeding $9 \log_{10}$ copies/mL.

The consistently greater antiviral effect for telbivudine was associated with clinical efficacy benefits, including a significantly increased rate of biochemical response (normalization of ALT levels) at 1 year. HBeAg loss and HBeAg seroconversion at 1 year were proportionally greatest for telbivudine monotherapy (33% and 31%, respectively), but differences in HBeAg responses were not statistically different for the 3 treatment types and were not expected to be so, because treatment-related HBeAg responses become apparent primarily toward the end of the first year of treatment.²¹ With nucleoside therapy, HBeAg responses can continue into the second year of treatment and beyond, so it is possible that newer anti-HBV agents such as telbivudine, producing more profound suppression of HBV replication, will eventually be found to have greater long-term cumulative rates of HBeAg loss and seroconversion.²²

The posttreatment durability of HBeAg responses that occur during telbivudine therapy is presently unknown. Current guidelines suggest that patients should receive a minimum of 1 year of nucleoside treatment and should be HBeAg negative for at least 3–6 months before treatment discontinuation.^{11,17} Ninety percent of patients in this study were enrolled into a 2-year extension study, in which the posttreatment durability of telbivudine-related HBeAg responses will be studied.

The high degree of HBV DNA suppression achieved with telbivudine, with average reductions in HBV DNA levels exceeding $6 \log_{10}$ copies/mL within 6 months, has rarely been reported with other anti-HBV agents in studies of similar patient populations that used similar Amplicor-type PCR assays for quantitation of HBV DNA.^{13,23} The molecular mechanisms underlying the antiviral potency of telbivudine have not been fully elucidated; however, they may be associated with its observed preferential inhibition of second-strand HBV DNA synthesis or intracellular processes associated with its phosphorylation or interaction with the HBV polymerase.²⁴

Also somewhat surprising was the observation that combination treatment, while producing proportionally better efficacy results than lamivudine monotherapy, did not improve on the telbivudine monotherapy results. Baseline HBV DNA levels were slightly higher for the combination groups, but the antiviral effects were similar for combination treatment versus telbivudine. More perplexing are the observations that the combination regimens were proportionally slightly inferior to telbivudine on all clinical efficacy end points, including normalization of ALT levels,

HBeAg loss or seroconversion, and viral breakthrough. The reasons for these results are not clear. A clinical pharmacology study found no pharmacokinetic interactions between telbivudine and lamivudine²⁵; thus, the explanation must lie elsewhere, for example, the possibility of some type of competition or interference between lamivudine and telbivudine within infected cells. In that regard, the molecular interactions of lamivudine and telbivudine with the HBV polymerase differ in some respects,²⁴ yet the data do not suggest a basis for competition within the polymerase binding pocket, and functionally significant competition in phosphorylation pathways seems unlikely. Also, while the exploratory analyses described in this report suggest that differences in early virologic response can influence subsequent efficacy outcomes, the early viral suppression data for telbivudine and combination treatment were broadly similar. In any case, this is the second report of disappointing results with combination nucleoside therapy for hepatitis B; the combination of lamivudine plus adefovir has recently been reported to have no efficacy advantage over monotherapy at 1 year.²⁶ While successful combination regimens for hepatitis B may yet be found, it will be necessary to prospectively evaluate, in adequate controlled trials, any proposed new combination treatment regimen for patients with hepatitis B.

The analyses of pooled patient response data support the concept that in patients with hepatitis B, early viral suppression is linked quantitatively to later clinical and virologic efficacy outcomes. Normalization of serum ALT levels and HBeAg clearance were greatest at 1 year in those who achieved the greatest antiviral responses in the first 6 months of treatment; in this study, viral breakthrough was zero at 1 year in patients with serum HBV DNA levels $<3 \log_{10}$ copies/mL at week 24. Conversely, 1-year HBeAg clearance was low, ALT normalization rate was modest, and viral breakthrough was most evident in the patient subgroup whose serum HBV DNA levels persisted above $4 \log_{10}$ copies/mL at week 24. These findings extend previous reports based on lamivudine data that linked HBeAg responses and viral resistance to the degree of early HBV DNA suppression.^{12,13} While the results of these exploratory analyses provide interesting hypotheses, application of these concepts to clinical practice should await confirmation with larger (eg, phase 3) databases.

The apparent relationship between degree of early HBV suppression and subsequent clinical efficacy supports an emerging rationale for maximizing early viral suppression as a strategy for optimizing longer-term clinical outcomes in patients with hepatitis B. Large international phase 3 studies are ongoing, with the objective of definitively assessing the antiviral and clinical efficacy of telbivudine and its comparative safety profile to elucidate the role for telbivu-

dine in the therapeutic management of patients with chronic hepatitis B.

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