Clinical Gastroenterology and Hepatology 2019;17:1850–1859

Efficacy and Safety of Besifovir Dipivoxil Maleate Compared With Tenofovir Disoproxil Fumarate in Treatment of Chronic Hepatitis B Virus Infection

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BACKGROUND & AIMS: **Besifovir dipivoxil maleate (BSV) has activity against hepatitis B virus (HBV). We performed a phase 3 study to compare the antiviral efficacy and safety of BSV vs tenofovir disoproxil fumarate (TDF) in patients with chronic HBV infection in Korea.**

METHODS: **We conducted a double-blind, non-inferiority trial of 197 patients with chronic HBV infection at 22 sites in South Korea, from November 2013 through February 2016. Patients were randomly assigned to groups given BSV (150 mg, n = 99) or TDF (300 mg, n = 98) for 48 weeks. We evaluated virologic responses to therapy (HBV DNA <69 IU/mL or 400 copies/ml), bone mineral density (BMD), and renal outcomes for safety analysis. The main efficacy endpoint was the proportion of patients with a virologic response at week 48. After 48 weeks, TDF was switched to BSV (150 mg) for an additional 48 weeks.**

RESULTS: **After 48 weeks of treatment, 80.9% of patients given BSV and 84.9% of patients given TDF met the efficacy endpoint, indicating the non-inferiority of BSV to TDF. At week 96, 87.2% of**

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Abbreviations used in this paper: ALT, alanine aminotransferase; BMD, bone mineral density; BSV, besifovir dipivoxil maleate; CHB, chronic hepatitis B; CI, confidence interval; eGFR, estimated glomerular filtration rate; ETV, entecavir; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogue; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Most current article

1542-3565
https://doi.org/10.1016/j.cgh.2018.11.001

patients in the BSV–BSV and 85.7% of patients in the TDF–BSV had a virologic response. At week 48, changes in hip and spine BMD differed significantly between the BSV and TDF groups, whereas the estimated glomerular filtration rate in the TDF group was significantly lower than that in the BSV group. However, at 96 weeks, there were no significant differences in BMD and estimated glomerular filtration rate between the BSV-BSV and TDF-BSV groups.

CONCLUSIONS: **BSV has antiviral efficacy comparable to that of TDF after 48 weeks of treatment, with durable effects for 96 weeks. BSV has a better safety profile than TDF, in terms of bone and renal outcomes. ClinicalTrials.gov no: NCT01937806.**

Keywords: eGFR; Acyclic Nucleotide Phosphonate; Drug Resistance; Nephrotoxicity.

Chronic hepatitis B (CHB) remains a challenging global public health burden, causing significant morbidity and mortality despite the availability of effective antiviral therapies.[1–3] The ultimate goals of anti–hepatitis B virus (HBV) treatment are the eradication of HBV infection and achieving a functional cure.[1,4]

Currently, nucleos(t)ide analogues (NAs), which have high genetic barriers to resistance, regardless of the severity of hepatic disease, are used as first-line therapies for CHB, and preferred regimens include entecavir (ETV), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF) monotherapy.[1] However, existing therapies are not sufficiently satisfactory because hepatic decompensation or hepatocellular carcinoma (HCC) may still develop in some patients with CHB despite achievement of a complete virologic response.[5–7] In addition, patients on ETV may develop drug resistance, particularly those exposed to lamivudine.[8] Moreover, because TDF can cause nephrotoxicity and bone mineral density (BMD) loss, patients at high risk of developing renal and bone-related diseases should be considered for receipt of either ETV or TAF on the basis of lamivudine treatment history.[1,9–12] Therefore, new therapeutic agents are necessary, including newer NAs or drugs that can act on alternative steps in viral replication.

Besifovir dipivoxil maleate (BSV), an acyclic nucleotide phosphonate (a guanosine monophosphate), has been investigated in several phase Ia/IIb studies. In previous studies, BSV has potent viral suppression of HBV replication.[13–16] The present phase III trial was designed to compare the antiviral efficacy and safety of BSV and TDF in CHB patients after a 48-week treatment period. Moreover, an additional 48-week extension study was designed to evaluate the long-term efficacy and safety of BSV treatment in BSV-BSV and TDF-BSV groups at week 96.

Methods

Study Participants

In this nationwide study, 197 patients were prospectively enrolled at 22 representative sites in the Republic of Korea according to the following criteria. Eligible patients were aged >20 years and were positive for hepatitis B surface antigen (HBsAg) for at least 6 months before screening. According to the clinical practice guidelines released in 2012,[17] HBV DNA levels $>1.0 \times 10^6$ copies/mL (17,241 IU/mL) for hepatitis B e antigen (HBeAg)-positive patients and $>1.0 \times 10^5$ copies/mL (1724 IU/mL) for HBeAg-negative patients were required to initiate antiviral treatment. Study patients received no antiviral therapy, including pegylated interferon or oral NAs, for more than 12 weeks before screening. Patients were also required to have serum alanine aminotransferase (ALT) levels range from 1.2 to 10 times the upper limit of normal and creatinine clearance of more than 50 mL/min as calculated by using the Modification of Diet in Renal Disease formula. Written informed consent was obtained from all study participants. Full eligibility criteria are presented in the Supplementary Data.

Study Design

We conducted a multi-center, randomized, double-blind, phase III study to evaluate the antiviral efficacy and safety of BSV versus TDF in CHB patients. The patients were randomly assigned in a 1:1 ratio by stratified block randomization according to whether they were HBeAg positive or negative at baseline, with a block size of 2, 4, or 8, to receive either BSV (Ildong Pharmaceutical Co, Ltd, Seoul, Korea) or TDF (Gilead Sciences, Foster City, CA) by using a central, interactive, web-based response system. Patients in the BSV group were administered 150 mg BSV and TDF placebo with 660 mg L-carnitine as a supplement, and those in the TDF group were administered 300 mg TDF and BSV placebo with L-carnitine placebo to maintain investigator and patient blinding. After the 48-week treatment period, all patients enrolled in the extension study received open-label 150 mg BSV and 660 mg L-carnitine for 48 weeks.

Endpoints

The efficacy endpoint was the virologic response, defined as the proportion of patients with HBV DNA

<69 IU/mL (400 copies/mL) at week 48.[18] The secondary efficacy endpoints included the proportion of patients with HBV DNA <20 IU/mL, which is the limit of detection, HBsAg or HBeAg seroconversion, normalization of ALT levels, and emergence of drug resistance during 96 weeks of treatment. Adverse events, BMD, renal parameters, and other laboratory abnormalities were evaluated for safety analysis. For the details regarding the materials used, refer to the Supplementary Data.

Statistical Analysis

A sample size of at least 94 patients per group was required to demonstrate whether BSV was non-inferior to TDF in terms of the virologic response (HBV DNA <69 IU/mL) at week 48, assuming that the percentage of respondents who reached the virologic response was 86.2%[18] using standard statistical criteria (80% statistical power, 2.5% one-sided significance level, 15% non-inferiority margin, and 10% dropout).

For primary efficacy analysis, the proportion of patients with HBV DNA <69 IU/mL was compared with the test non-inferiority of BSV by using intention-to-treat analysis. In addition, differences in baseline characteristics and secondary endpoints between the treatment groups were tested by using an independent two-sample t test or Wilcoxon rank sum test for continuous variables and a χ^2 test or Fisher exact test for categorical variables. Individual patient data were stratified by HBeAg status at baseline for primary and secondary efficacy analyses.

Results

Study Population

We screened 291 patients with CHB between November 2013 and February 2016, 194 of whom were enrolled and randomly assigned to the BSV (n = 98) or TDF (n = 96) group. A total of 187 patients completed the 48-week main treatment period. Thirteen patients did not agree to participate in the extended study for the additional 48 weeks, and 4 patients were dropped out from the study because of either HCC occurrence (n = 3) or creatine phosphokinase elevation (n = 1), leaving a total of 170 patients who entered into a 96-week extension study. Nine patients were eliminated from the study because of consent withdrawal (n = 6), administration of prohibited medication (n = 2), and essential thrombocythemia (n = 1). Finally, 161 patients completed an extension study regardless of virologic response (Supplementary Figure 1).

Both treatment groups were well-balanced in terms of age, sex, HBeAg status, serum HBV DNA concentration, ALT levels, and HBV genotypic distribution (Table 1).

What You Need to Know

Background

Besifovir dipivoxil maleate (BSV) has activity against hepatitis B virus (HBV). We performed a phase 3 study to compare the antiviral efficacy and safety of BSV vs tenofovir disoproxil fumarate (TDF) in patients with chronic HBV infection in Korea.

Findings

BSV has antiviral efficacy comparable to that of TDF after 48 weeks of treatment, with durable effects for 96 weeks. BSV has a better safety profile than TDF in terms of bone and renal outcomes.

Implications for patient care

BSV is safe and effective for treatment of chronic HBV infection.

Virologic Response

We evaluated the primary outcome by comparing the suppression of HBV DNA replication (<69 IU/mL) at week 48 between the 2 treatment groups. There was a small difference in the proportion of patients who met the primary endpoint (80.9% [76/94] in the BSV group and 84.9% [79/93] in the TDF group [lower bound 95% confidence interval (CI), −14.9%; P = .46; Table 2). Because the lower bound of 95% CI of the difference in the virologic response rate was greater than the predetermined −15% margin, the BSV group met the efficacy endpoint of non-inferiority to TDF. In subgroup analysis based on HBeAg status at baseline, among HBeAg-positive patients, 69.6% in the BSV group and 74.6% in the TDF group met the primary endpoint, and all HBeAg-negative patients, except 1 BSV group patient, achieved the virologic response at week 48. The proportion of patients with HBV DNA <20 IU/mL after 48 weeks of treatment was 63.8% in the BSV group and 68.8% in the TDF group, which was not significantly different (P = .47). During the 96-week study period, 87.2% of the BSV-BSV group patients (75/86) and 85.7% of the TDF-BSV group patients (72/84) had an HBV DNA level <69 IU/mL at week 96, indicating no significant difference between the 2 groups (P = .78). At week 96, 81.4% of the BSV-BSV group patients and 77.4% in the TDF-BSV group had HBV DNA level <20 IU/mL; however, the difference was not statistically significant at any time point throughout the 96 weeks (Figure 1).

Serologic and Biochemical Responses

Among the HBeAg-positive patients, the HBeAg seroconversion rate was 5.7% in the BSV group and 2.0% in the TDF group, with no significant difference between the 2 groups (P = .62). No BSV group patients showed an HBsAg loss, and only 1 patient in the TDF

Table 1. Baseline Characteristics of Study Participants

	BSV group (n = 94)	TDF group (n = 93)	Total (n = 187)	*P* value
Sex				
Male	60 (63.8)	59 (63.4)	119 (63.6)	.96
Age (*y*)				
Median (Q1, Q3)	47 (39, 54)	43 (37, 50)	46 (38, 52)	.09
HBV genotype				
A	1 (1.1)	0 (0.0)	1 (0.5)	1.00
C	92 (97.9)	92 (98.9)	184 (98.4)	
D	0 (0.0)	1 (1.1)	1 (0.5)	
Not determined	1 (1.1)	0 (0.0)	1 (0.5)	
HBsAg titer (*IU/mL*)				
Median (Q1, Q3)	2929.25 (1951.8, 4019.6)	2925.7 (2008.6, 3573.7)	2925.74 (1987.7, 3826.3)	.38
HBeAg				
Negative	38 (40.4)	38 (40.9)	76 (40.6)	.95
Positive	56 (59.6)	55 (59.1)	111 (59.4)	
Serum HBV DNA (log_{10} *IU/mL*)				
Median (Q1, Q3)	6.2 (5.0, 8.2)	6.76 (5.57, 8.1)	6.55 (5.32, 8.1)	.39
Serum ALT (*U/L*)				
Median (Q1, Q3)	76.5 (53.0, 118.0)	80 (55, 150)	78 (53, 140)	.30
eGFR by MDRD (*mL/min*)				
Median (Q1, Q3)	88.8 (77.6, 100.4)	90.8 (80.3, 102.3)	89.7 (78.5, 101.5)	.25
Creatinine (*mg/dL*)				
Median (Q1, Q3)	0.8 (0.7, 1.0)	0.8 (0.8, 0.9)	0.8 (0.7, 1.0)	.52
Phosphate (*mg/dL*)				
Median (Q1, Q3)	3.6 (3.2, 3.8)	3.5 (3.0, 3.9)	3.50 (3.1, 3.9)	.23
Hip BMD				
Normal (T-score ≥ -1.0)	65 (83.3)	52 (82.5)	117 (83)	.90
Osteopenia ($-2.5 <$ T-score < -1.0)	13 (16.7)	11 (17.5)	24 (17.0)	
Osteoporosis (T-score ≤ -2.5)	0 (0.0)	0 (0.0)	0 (0.0)	
Spine BMD				
Normal (T-score ≥ -1.0)	56 (65.9)	53 (68.8)	109 (67.3)	.85
Osteopenia ($-2.5 <$ T-score < -1.0)	24 (28.2)	21 (27.3)	45 (27.8)	
Osteoporosis (T-score ≤ -2.5)	5 (5.9)	3 (3.9)	8 (4.9)	
Cardiovascular disease	0 (0.0)	0 (0.0)	0 (0.0)	—
Diabetes mellitus types 1 and 2	12 (12.8)	4 (4.3)	16 (8.6)	.04
Hypertension	11 (11.7)	10 (10.8)	21 (11.2)	.84
Dyslipidemia	2 (2.1)	2 (2.2)	4 (2.1)	1.00
Cirrhosis	24 (25.5)	17 (18.3)	41 (21.9)	.23
Prior antiviral therapy	0 (0.0)	1[a] (1.1)	1[a] (0.5)	1.00

NOTE. Data are expressed as n (%), unless stated otherwise.
ALT, alanine aminotransferase; BMD, bone mineral density; BSV, besifovir dipivoxil maleate; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; TDF, tenofovir disoproxil fumarate.
[a]Viread (tenofovir disoproxil fumarate).

group (1.1%) showed an HBsAg loss after 48 weeks of treatment. Subgroup analysis showed no significant difference in the HBeAg seroconversion rate between the BSV-BSV and TDF-BSV groups after 96 weeks of treatment. No HBsAg loss was observed after the 96-week treatment in the BSV-BSV group, and only 1.3% of TDF-BSV group patients (1/77) showed an HBsAg loss (Table 2).

The proportions of patients whose ALT levels normalized after 48 weeks of treatment were 73.4% in the BSV group and 74.2% in the TDF group, with no significant difference between the groups ($P = .90$) (Table 2). Nevertheless, after 96 weeks, there was a significant difference in the proportions of patients with ALT normalization ($P = .01$), 73.3% in the BSV-BSV group (63/86) and 88.1% in the TDF-BSV group (74/84). However, the proportions of patients with HBV DNA <69 IU/mL and ALT normalization were not significantly different between the 2 groups (65.1% versus 77.4%, respectively; $P = .08$).

Virologic Breakthrough

None of the patients whose HBV DNA was sequenced during 48 weeks after the initial administration of BSV or TDF showed any sequence changes. There was no significant difference ($P = 1.00$) in the proportions of patients showing a virologic breakthrough, 5.3% in the BSV group and 5.4% in the TDF group. All patients showing a virologic breakthrough exhibited a transient elevation in HBV DNA levels, which was subsequently reversed, on

Table 2. Virologic, Serologic, and Biochemical Responses

	48 weeks				96 weeks			
	BSV (n = 94)	TDF (n = 93)	Difference (95% CI)	*P* value	BSV-BSV (n = 86)	TDF-BSV (n = 84)	Difference (95% CI)	*P* value
HBV DNA <69 IU/mL	76 (80.9)	79 (84.9)	−4.1 (−14.9 to 6.7)	.46	75 (87.2)	72 (85.7)	1.5 (−8.8 to 11.8)	.78
HBV DNA <20 IU/mL	60 (63.8)	64 (68.8)	−5.0 (−18.5 to 8.5)	.47	70 (81.4)	65 (77.4)	4.0 (−8.1 to 16.2)	.52
HBeAg loss, n/N (%)[a]	5/53 (9.4)	3/50 (6.0)	3.4 (−6.8 to 13.7)	.72	11/52 (21.2)	9/44 (20.5)	0.7 (−15.6 to 7.0)	.93
HBeAg seroconversion, n/N (%)[a]	3/53 (5.7)	1/50 (2.0)	3.7 (−3.7 to 11.0)	.62	6/52 (11.5)	2/44 (4.5)	7.0 (−3.7 to 17.6)	.28
HBsAg loss, n/N (%)[b]	0/87 (0)	1/87 (1.1)	−1.1 (−3.4 to 1.1)	1.00	0/83 (0)	1/77 (1.3)	−1.3 (−3.8 to 1.2)	.48
HBsAg seroconversion, n/N (%)[b]	0/87 (0)	0/87 (0)	—	—	0/83 (0)	0/77 (0)	—	—
ALT normalization, n (%)[c]	69 (73.4)	69 (74.2)	−0.8 (−13.4 to 1.8)	.90	63 (73.3)	74 (88.1)	−14.8 (−26.5 to −3.2)	.01

NOTE. Data are expressed as n (%), unless stated otherwise.
ALT, alanine aminotransferase; BSV, besifovir dipivoxil maleate; TDF, tenofovir disoproxil fumarate.
[a]Among HBeAg-seropositive and anti–HBe-negative patients at baseline.
[b]Among HBsAg-seropositive and anti–HBs-negative patients at baseline.
[c]Among patients with baseline ALT levels above the central lab normal range (0–41 U/L for men and 0–33 U/L for women).

the basis of serum HBV DNA quantification results, without any additional intervention. During the 96-week study period, 4.65% of BSV-BSV group patients (4/86) and 15.48% of TDF-BSV group patients (13/84) experienced a virologic breakthrough ($P = .02$); however, all these patients recovered spontaneously without additional intervention. No antiviral resistance was detected in the virologic breakthrough.

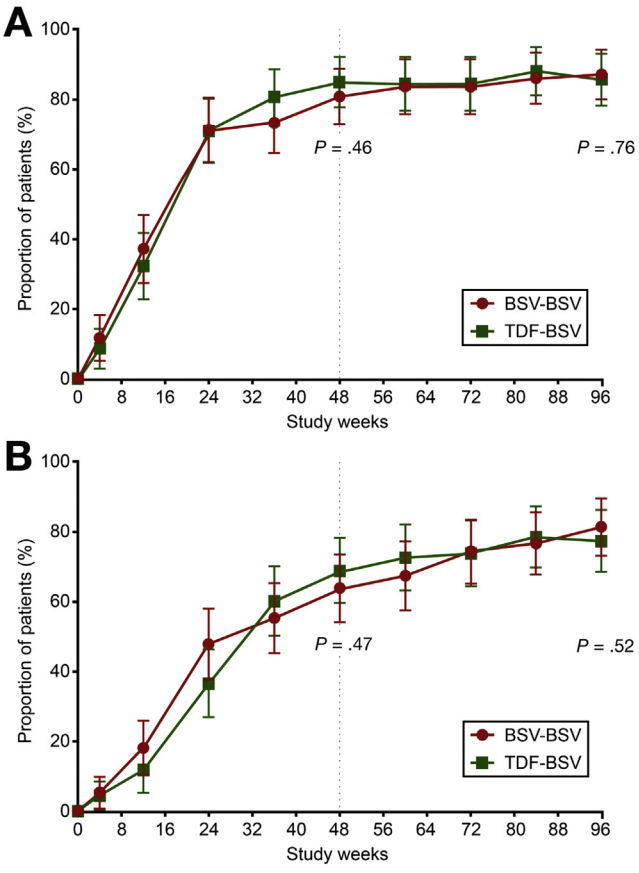

Figure 1. Comparison of viral suppression between the BSV-BSV and TDF-BSV groups. (*A*) Proportion of patients with HBV DNA <69 IU/mL by study week. (*B*) Proportion of patients with HBV DNA <20 IU/mL by study week. Bars represent 95% confidence intervals. BSV, besifovir dipivoxil maleate; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

Safety

There was no significant difference in the rates of overall adverse events between the 2 groups throughout the study period (Table 3). Consistently, between weeks 48 and 96, there was no significant difference in the adverse events that were newly reported in 61 BSV-BSV group patients (53.5%) and 57 TDF-BSV group patients (50.0%). Adverse events with an incidence ≥5% included nasopharyngitis, dyspepsia, nausea, back pain, headache, dizziness, fatigue, and ALT elevation in the BSV-BSV group and nasopharyngitis, dyspepsia, gastritis, diarrhea, pruritus, and urticaria in the TDF-BSV group. Whereas no dyspepsia was reported in the BSV group, 8 dyspepsia events occurred in 7 patients in the TDF group (8.33%) during the first 48-week treatment period. Although there was no serious adverse event that caused death during the study period, 1 BSV group patient with HCC and 2 TDF group patients with either HCC or creatine phosphokinase elevation discontinued study drug treatment during the first 48-week treatment period. In addition, 1 BSV-BSV group patient developed tuberculous colitis, and an additional TDF-BSV group patient developed essential thrombocythemia, both of whom discontinued treatment with the study drugs during the extended period.

There were no significant changes in the proportion of BSV-BSV group patients with impaired BMD at week 96 relative to that at baseline. In the TDF group, however, the proportion of patients with osteopenia and osteoporosis increased, whereas that of patients with a normal BMD decreased at week 48 relative to baseline levels (Supplementary Figure 2). Furthermore, the mean change in hip BMD from baseline to week 48 was 0.33%

Table 3. Safety Data

Variables	0–48 weeks		48–96 weeks		Total
	BSV (n = 86)	TDF (n = 84)	BSV-BSV (n = 86)	TDF-BSV (n = 84)	
Adverse events	52 (60.5)	45 (53.6)	46 (53.5)	42 (50.0)	118 (69.4)
Adverse events leading to study drug discontinuation	0	0	1 (1.2)	1 (1.2)	2 (1.2)
Adverse drug reactions	19 (22.1)	21 (25.0)	14 (16.3)	10 (11.9)	51 (30.0)
Death	0	0	0	0	0
Adverse events recorded in ≥3% of all patients					
Nasopharyngitis	9 (10.5)	4 (4.8)	6 (7.0)	8 (9.5)	23 (13.5)
Dyspepsia	8 (9.30)	9 (10.7)	0	0	17 (10.0)
Headache	4 (4.7)	3 (3.6)	2 (2.3)	2 (2.4)	9 (5.3)
Back pain	4 (4.7)	0	2 (2.3)	3 (3.6)	9 (5.3)
Fatigue	4 (4.7)	3 (3.6)	1 (1.2)	1 (1.2)	9 (5.3)
Pruritus	2 (2.3)	2 (2.4)	1 (1.2)	3 (3.6)	8 (4.7)
Gastritis	0	2 (2.4)	2 (2.3)	4 (4.8)	8 (4.7)
Nausea	4 (4.7)	1 (1.2)	2 (2.3)	0	7 (4.1)
Alanine aminotransferase elevation	4 (4.7)	2 (2.4)	1 (1.2)	0	7 (4.1)
Diarrhea	0	3 (3.6)	2 (2.3)	2 (2.4)	7 (4.1)
Urticaria	1 (1.2)	1 (1.2)	0	4 (4.8)	6 (3.5)
Dizziness	2 (2.3)	0	4 (4.7)	0	6 (3.5)
Grade 3–4 laboratory abnormalities found in ≥1% of all patients					
Alanine aminotransferase >5 × ULN	9 (10.5)	9 (10.7)	0 (0.0)	0 (0.0)	18 (10.6)
Aspartate aminotransferase >5 × ULN	5 (5.8)	4 (4.8)	0 (0.0)	0 (0.0)	9 (5.3)
Platelets <50,000/mm^3	2 (2.3)	3 (3.6)	0 (0.0)	0 (0.0)	5 (2.9)
Absolute neutrophil counts <1000/mm^3	2 (2.3)	0 (0.0)	1 (1.2)	1 (1.2)	4 (2.4)
Phosphate <0.6 mmol/L	2 (2.3)	2 (2.4)	1 (1.2)	0 (0.0)	4 (2.4)
Proteinuria	1 (1.2)	1 (1.2)	0 (0.0)	1 (1.2)	3 (1.8)
Hematuria	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.4)	2 (1.2)
Creatine phosphokinase >5 × ULN	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)	2 (1.2)

NOTE. Data are expressed as n (%), unless stated otherwise.
BSV, besifovir dipivoxil maleate; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

(95% CI, −0.57% to 1.23%) in patients receiving BSV, which was significantly less than the reduction of 0.85% (95% CI, −2.74% to 1.04%) in patients receiving TDF ($P = .01$) (Figure 2*A*). Similarly, the mean decrease in spine BMD from baseline to week 48 was 0.04% (95% CI, −1.64% to 1.57%) in patients receiving BSV, which was significantly less than the reduction of 1.29% (95% CI, −2.46% to −0.11%) in patients receiving TDF ($P < .05$) (Figure 2*B*). After switching to BSV in the TDF-BSV group, BMD returned to the baseline level at week 96, and changes in the T-score at week 96 were not statistically different between the BSV-BSV and TDF-BSV groups.

The nephrotoxicity-related safety results showed no significant change in serum creatinine in the BSV-BSV group at week 96 compared with that at baseline. In contrast, the TDF group showed a significant increase in serum creatinine compared with that in the BSV group at week 48 ($P = .04$); however, after switching to BSV, the difference at week 96 was not statistically significant ($P = .42$). Moreover, the median changes in estimated glomerular filtration rate (eGFR) from baseline were −0.5 mL/min and −0.7 mL/min at weeks 48 and 96, respectively, in the BSV-BSV group, indicating no effect of BSV on renal function. In the TDF group, the median change in eGFR from baseline was −7.8 mL/min at week 48, indicating a decline in renal function. At week 96, however, the median change was −0.4 mL/min after switching to BSV, demonstrating a recovery in renal function (Figure 3).

Discussion

This randomized comparative study of BSV versus TDF for the treatment of CHB demonstrated noninferiority of BSV to TDF in the efficacy of viral suppression at week 48, whereas BSV showed a better safety profile than did TDF in terms of renal and bone parameters. Moreover, there were no significant differences in the virologic response rates between the 2 groups, regardless of HBeAg status. A subsequent extension study showed that the antiviral effect of BSV was maintained up to 96 weeks without serious safety concerns. Considering the reported virologic response rates of 87% in HBeAg-negative patients (313/359)[19] and 71% in HBeAg-positive patients (181/254) after 144 weeks of TDF treatment, BSV treatment showed comparable

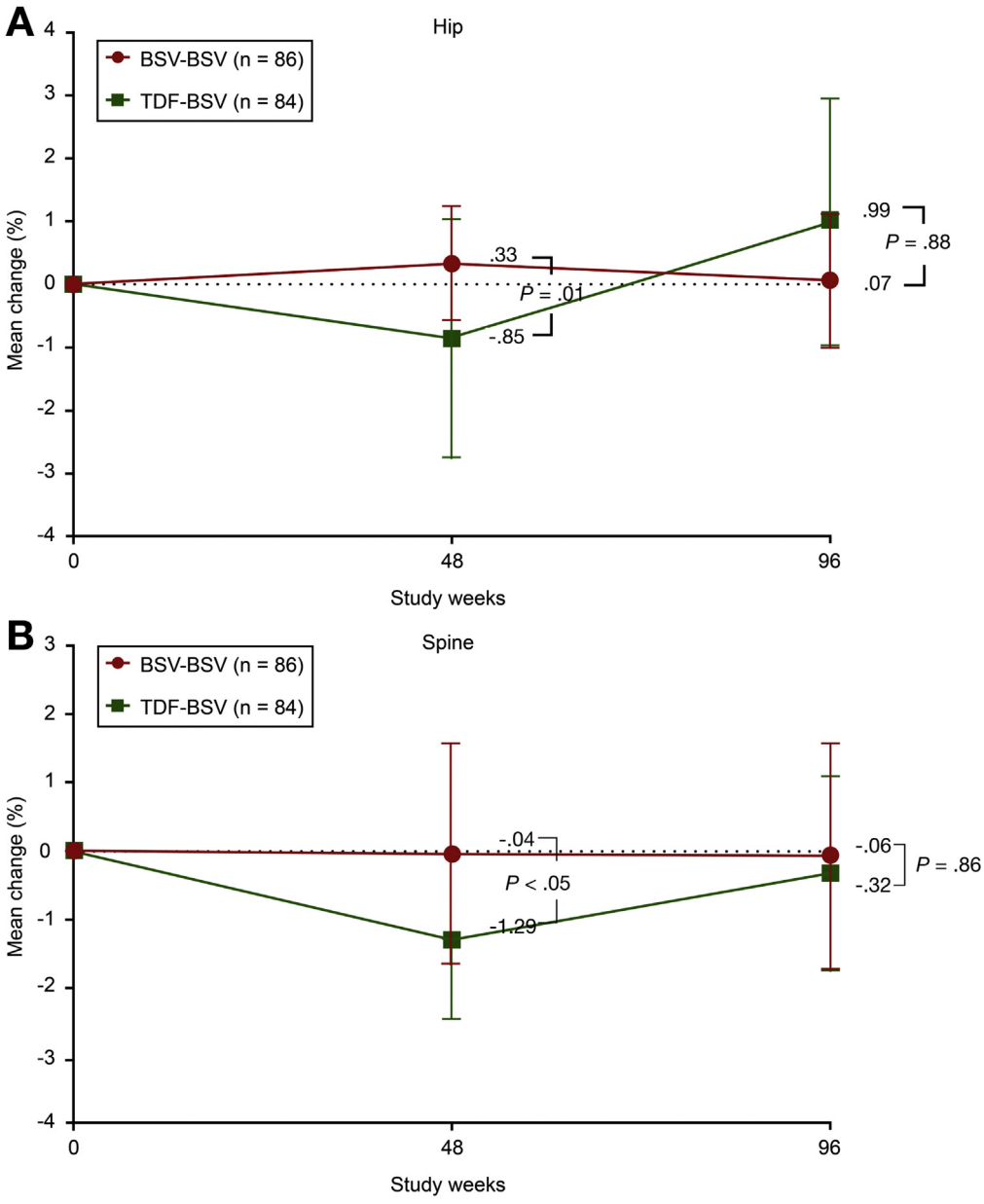

Figure 2. Comparison of changes in BMD between the BSV-BSV and TDF-BSV groups. (*A*) Mean percentage changes in hip BMD at weeks 48 and 96 of treatment. Bars represent 95% confidence interval. (*B*) Mean percentage changes in spine BMD at weeks 48 and 96 of treatment. Bars represent 95% confidence intervals. BMD, bone mineral density; BSV, besifovir dipivoxil maleate; TDF, tenofovir disoproxil fumarate.

virologic response rates, regardless of HBeAg status, and the antiviral effect of BSV was maintained throughout the 96-week treatment.

According to recent clinical practice guidelines for CHB, various NAs show a wide range of virologic response rates at week 48, varying from 13% to 76% for HBeAg-positive patients to 60% to 93% for HBeAg-negative patients.[1,20] In the current study, the proportions of patients with undetectable HBV DNA (<20 IU/mL) at week 48 were 46.4%–58.2% among HBeAg-positive patients and 84.2%–89.5% among HBeAg-negative patients, and these gradually increased during the 96 weeks of treatment. Nevertheless, HBeAg loss rates and HBeAg seroconversion rates in the current study were lower than those in the previous studies.[18,21] Most of the patients in this study were infected with HBV genotype C, which was reported to have a lower seroconversion rate of HBeAg compared with other HBV genotypes.[22,23]

The proportion of patients who achieved the primary efficacy endpoint of HBV DNA <69 IU/mL after completing 48 weeks of TDF treatment was 84.9% (79/93), and that of patients who achieved the virologic response after an additional 48 weeks of BSV treatment was 85.7% (72/84) at week 96, suggesting that the antiviral effect achieved during the first 48 weeks of TDF treatment was not affected by the subsequent 48-week BSV treatment.

The biochemical response rate at week 96 in the TDF-BSV group was significantly higher than that observed in the BSV-BSV group. To determine the cause of this difference, baseline characteristics (presence of cirrhosis and ALT category) and ALT levels after 48 weeks of treatment were examined, but no contributing factors

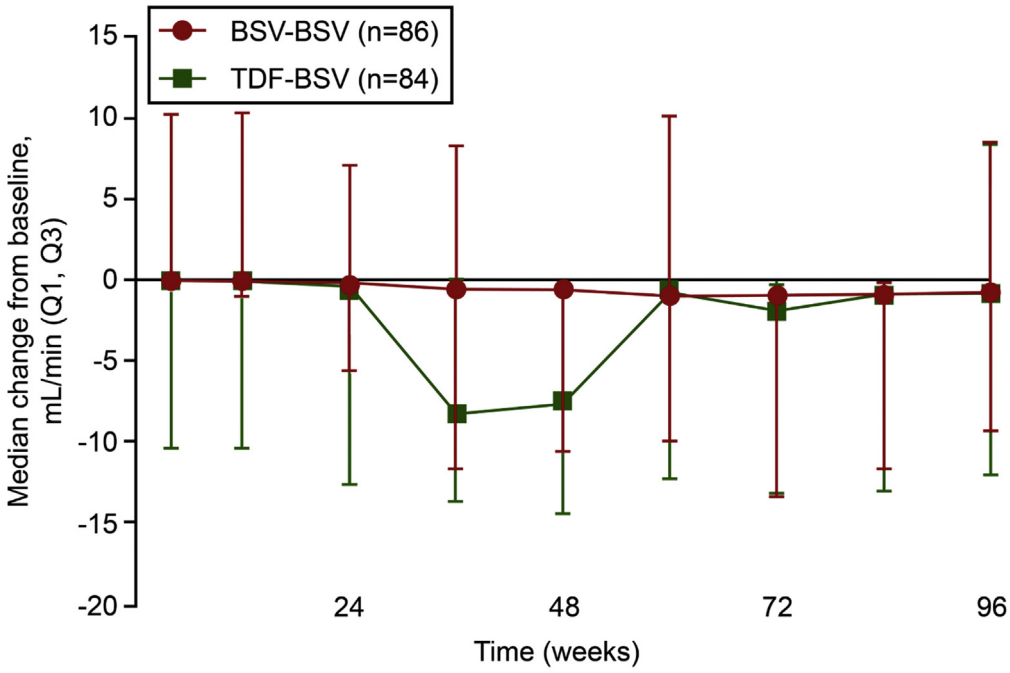

Figure 3. Changes in estimated glomerular filtration rate from baseline by study week. Data are presented as median (Q1, Q3) values (mL/min) calculated by using the Modification of Diet in Renal Disease. BSV, besifovir dipivoxil maleate; TDF, tenofovir disoproxil fumarate.

were identified. Nonetheless, there was no significant difference in the proportion of patients with concurrent virologic (HBV DNA <69 IU/mL) and biochemical (ALT normalization) responses at weeks 48 and 96 between the 2 groups ($P = .08$). Moreover, there was seemingly no clinically significant effect of the medication switch on biochemical response rates between the 2 groups ($P = .28$) by using the American Association for the Study of Liver Diseases criteria[20] for normal ranges of ALT (data not shown).

Our safety analysis of 96 weeks of BSV administration showed that adverse events occurring with an incidence ≥5% were similar to those reported for 96-week TDF treatment.[24] Adverse events that occurred during the 48-week BSV treatment period after 48 weeks of TDF treatment were similar to those occurring during the 96-week BSV-BSV treatment period.

Regarding the mean changes in BMD, the TDF group showed a statistically significant decline in BMD at 48 weeks, compared with the BSV group, but this returned to the baseline BMD level at 96 weeks after switching to BSV. Moreover, although serial assessments of BMD in the BSV-BSV group suggested no evidence of bone loss during 96 weeks of evaluation, we observed a clear worsening of BMD in terms of the proportion of subjects with osteopenia or osteoporosis after TDF treatment. These findings were predictable on the basis of a study showing that among TDF-treated subjects, 8.2% developed osteoporosis and 31.6% had osteopenia at week 96.[25] There have also been reports of serious bone loss–related adverse events or adverse events leading to TDF discontinuation because of impaired BMD after 7 years of follow-up.[26] Because BMD mostly declines during 24–48 weeks and up to 144 weeks of TDF treatment, BSV may be safer than TDF for long-term use in terms of bone loss issues, particularly in elderly CHB patients with osteopenia or osteoporosis.

Throughout the 96 weeks of treatment in the present study, there were no patients who experienced adverse renal events such as acute renal failure and proximal tubulopathy, whereas Fanconi syndrome and other renal insufficiencies that have been linked to long-term use of NAs[1,27] were rarely experienced. On the basis of serum creatinine concentrations and eGFR changes over time, the BSV-BSV group had a more favorable safety profile between weeks 24 and 60 than did the TDF-BSV group ($P = .02$ and $P = .29$, respectively). In the TDF-BSV group, the distribution of eGFR over time is left-tailed, and the number of individuals with severe eGFR decline increases with time. At week 36, eGFR decreases by −5.67, and the time-dependent changes in eGFR by TDF in the pivotal study began to decrease by an absolute value of −5 or higher at 36 weeks.[24] Moreover, in the TAF registration clinical trial,[21] the TDF group showed a slight decrease from 8 weeks, but the decrease was not significant, so we do not see much difference in the changing patterns of eGFR between our results and previous reports on TDF.

Osteoporosis and renal dysfunction are common complications in patients with cirrhosis.[28,29] Although the BSV group was more likely to have cirrhosis, cirrhosis did not significantly affect BMD and eGFR levels in multivariate logistic regression analysis. However, additional multivariate analyses of renal outcomes, adjusted for age, eGFR, serum creatinine, and cirrhosis at baseline, were performed and showed more pronounced differences in renal safety between the groups at week 48 ($P = .002$ for creatinine; $P < .005$ for eGFR) (Supplementary Table 1).

The previous in vivo studies showed that the renal uptake of BSV was one-fourth of TDF and that the hepatic

uptake of BSV was twice as high as that of TDF. In addition, according to the non-clinical distribution test of LB80317, an active metabolite of BSV administration, it was found to have the lower systemic exposure and highest tissue to plasma concentration in the liver (internal report of LG Chem, Ltd, Korea; data not shown). Such pharmacologic mechanism of BSV seems to be beneficial to renal function.

There are some limitations to the present study. First, the sample size was relatively small, and study population was only Asian, predominantly with HBV genotype C. Therefore, larger-scale clinical trials including various races and HBV genotypes are further required to confirm the efficacy and safety of BSV in the future. Second, although overall safety issues associated with nephrotoxicity were nearly negligible in the BSV-BSV group, renal function should be regularly monitored every 6–12 months in patients treated with NAs through long-term follow-up.[29] Despite short-term significant differences in bone and renal outcomes between the groups, it is unclear whether such small differences are clinically relevant because long-term clinical safety may be similar for BSV and TDF. Third, the effects of BSV on renal function, including serum creatinine levels and creatinine clearance over time, remain to be investigated, particularly in patients with decompensated cirrhosis or severe renal alterations, who would probably need an adjustment to the BSV dose. In addition, there were no assessments of bone turnover markers to evaluate bone formation or resorption or renal tubulopathy markers to quantify albuminuria such as urinary protein/creatinine ratio and urinary retinol-binding protein/creatinine ratio or β2-microglobulin/creatinine ratio. Therefore, a prolonged clinical study is needed to determine whether BSV is safer than TDF with regard to nephrotoxicity and BMD.

Nevertheless, it was evident that the antiviral effect of 96-week BSV treatment is similar to that of current therapies with a high resistance barrier and that the safety profile of BSV treatment is more favorable for CHB patients. BSV was approved by the Korean Ministry of Food and Drug Safety in May 2017 and is undergoing a phase III clinical trial for hepatitis B patients with resistance to NAs. To secure a niche for its clinical utility, efficacy and safety outcomes from a long-term follow-up study need to be established, and additional studies in other special populations requiring oral antiviral treatments, such as patients with decompensated cirrhosis, HCC, and serious renal dysfunction, will be warranted.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2018.11.001.

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Conflicts of interest
This author discloses the following: Dr Han reports grants from clinical trial sponsored by Ildong Pharmaceutical Co, Ltd outside of the submitted work. The remaining authors disclose no conflicts.

Funding
Supported by Ildong Pharmaceutical Company. This funding source had a partial role in study design, collection, analysis, and interpretation of data.

Supplementary Data

Enrollment Criteria

Inclusion criteria

1. Male or female aged $\geq$ 20 years
2. Subjects who had been HBsAg positive for >6 months before screening or those with history of CHB
3. Subjects who had not received interferon therapy (including pegylated interferon) for CHB and who had not received antiviral therapy for $\geq$12 weeks
4. HBsAg-positive subjects during the screening process
5. Subjects with $\geq 1 \times 10^5$ copies/mL (17,241 IU/mL) of HBV DNA using the COBAS TaqMan HBV test if HBeAg was positive during screening, or subjects with $\geq 1 \times 10^4$ copies/mL (1724 IU/mL) of HBV DNA using COBAS TaqMan HBV test if HBeAg was negative
6. ALT level $\geq$1.2 $\times$ and $\leq$10 $\times$ the upper limit of normal (ULN)
7. Subjects who were informed of the study purpose, methods, and outcomes and who had signed a written consent form.
8. Male and female subjects of childbearing age who agreed to use a medically approved contraception method during the study period. (Medically approved contraception is defined as a condom, diaphragm, surgical sterilization, intrauterine contraceptive device, oral contraception, other hormone delivery system, contraceptive cream, jelly, or foam.)

Exclusion criteria

1. Hepatitis C virus, hepatitis D virus, or human immunodeficiency virus infection
2. Subjects with decompensated hepatic disease with any one of the following indications:
   - Total bilirubin >2 $\times$ ULN
   - Prothrombin time at least 3 seconds longer than the normal limit
   - Serum albumin <30 g/L
   - History of ascites, jaundice, variceal bleeding, or signs of hepatic encephalopathy
3. At least one of the following results at screening:
   - Hemoglobin <9.0 g/dL
   - Absolute neutrophil count $<1.5 \times 10^9$/L
   - Platelet count $<100 \times 10^9$/L
   - Serum creatinine >1.5 mg/dL
   - Serum amylase >2 $\times$ ULN and serum lipase >2 $\times$ ULN
4. GFR < 50 mL/min at screening by calculating Modification of Diet in Renal Disease (1.86 $\times$ creatinine $-$ 1.154 $\times$ age $-$ 0.203 ($\times$ 0.742, if female))
5. Alpha-fetoprotein above 50 ng/mL and suspicion of HCC on liver computed tomography screening
6. Subjects who had received any of the drugs listed below within 2 months before screening (except when the treatment was acute [<14 consecutive days] or was low-dose aspirin [100–300 mg/day])
   - Nephrotoxic drugs (eg, aminoglycosides, amphotericin B, and nonsteroidal anti-inflammatory drugs)
   - Hepatotoxic drugs (eg, erythromycin, ketoconazole, rifampin, fluconazole, and dapsone)
   - Anticoagulants (warfarin)
7. Subjects who had received immunosuppressive therapy within 6 months before screening and were suspected to be immunosuppressed at the discretion of the investigator
8. Subjects who had received chronic high-dose systemic corticosteroid therapy ($\geq$20 mg daily prednisone-equivalent) within 3 months before screening (in the case of local administration of corticosteroids, the decision was made at the discretion of the investigator) (cortisone 125 mg, hydrocortisone 100 mg, prednisone 20 mg, methylprednisolone 16 mg, triamcinolone 16 mg, dexamethasone 3 mg, and betamethasone 2.4 mg)
9. Subjects diagnosed with or having had recurrent malignant tumor within 5 years before screening (at the discretion of the investigator, who decided whether the trial would be affected in the case of a benign tumor)
10. Planned participation in another clinical study after entry into this study or having participated in another clinical study within 3 months of study entry
11. Women who were pregnant, lactating, or planning a pregnancy during the study period
12. Hypersensitivity to test drugs
13. History of alcohol or drug abuse within 1 year before screening or currently have such conditions
14. In addition to hepatic disease, subjects with heart failure, renal failure, or pancreatitis that might interfere with the subject's participation in the study, at the discretion of the investigator

15. Subjects with other hepatic diseases (eg, hemochromatosis, Wilson's disease, alcoholic hepatitis, nonalcoholic steatohepatitis, and alpha-1 antitrypsin deficiency)
16. History of organ transplantation
17. Psychiatric or cognitive disorder that might affect the subject's ability to perform daily activities or comprehend the specified study purpose or procedures
18. Any condition or situation that might interfere with the subject's participation in the study, at the discretion of the investigator

Methods

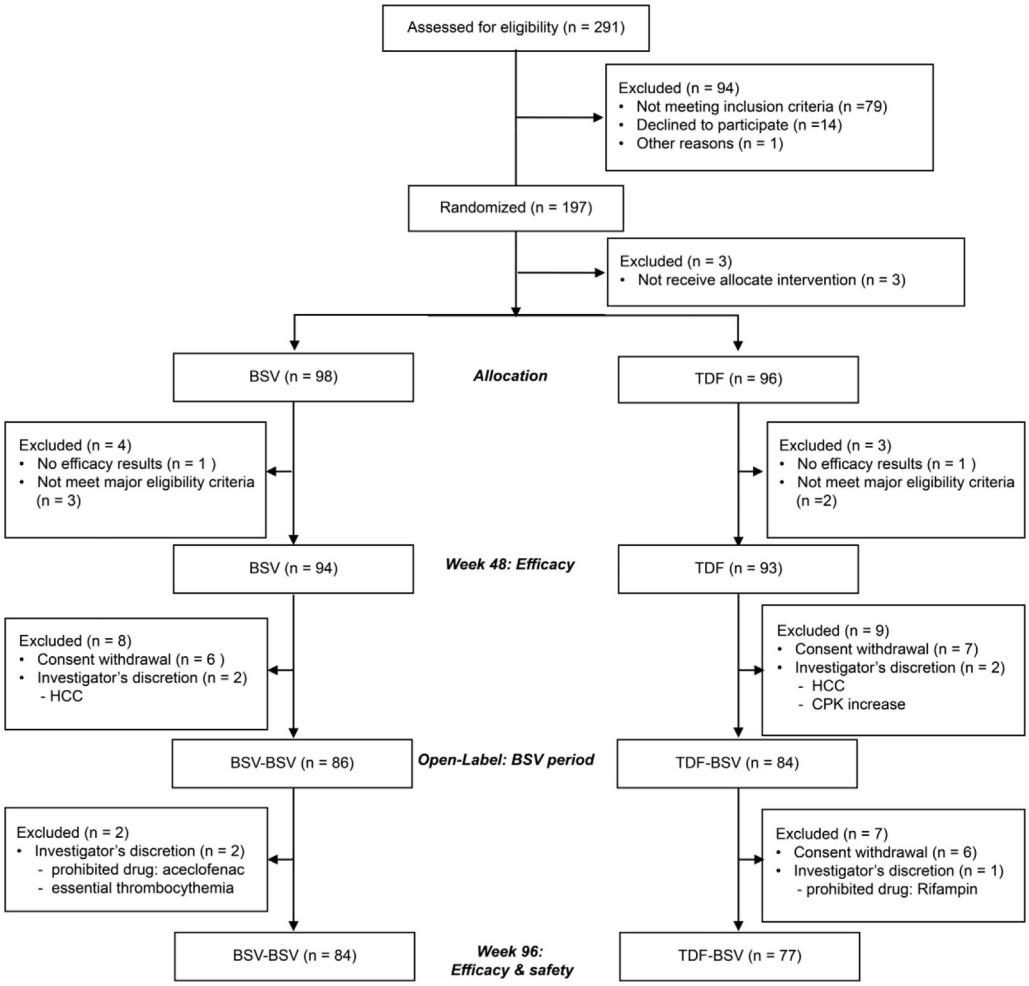
Patients were requested to visit at baseline, weeks 4 and 12, and at 12-week intervals thereafter for efficacy and safety assessments. At each visit, a physical examination and laboratory tests were conducted in a central laboratory (GreenCross Lab Cell Corporation, Yongin, Korea), and BMD assessments were performed. The study was approved by the institutional review board at each site. Furthermore, during the main treatment period, an independent Data Safety Monitoring Board reviewed the study data with a focus on safety, according to the Data Safety Monitoring Board management plan. The clinical trial was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki.

Laboratory tests included HBV DNA quantification by using a COBAS AmpliPrep/TaqMan test (Roche Diagnostics, Indianapolis, IN), with a lower detection limit of 20 IU/mL, as well as serologic tests such as HBsAg and HBeAg. HBV DNA sequencing by using a BigDye Terminator v3.1 cycle sequencing kit (Applied Biosystems, Foster City, CA) was performed for patients whose HBV DNA titer was greater than 1724 IU/mL at 48 weeks or at any time to verify the presence of resistance mutations after a virologic breakthrough. A liver biopsy was performed only in patients who agreed to liver biopsy at baseline and at 48 weeks. BMD measurements of the lumbar spine and hip were performed by using a dual-energy x-ray absorptiometry scan at baseline and at 48 and 96 weeks. Glomerular filtration rate was estimated by using the Modification of Diet in Renal Disease.

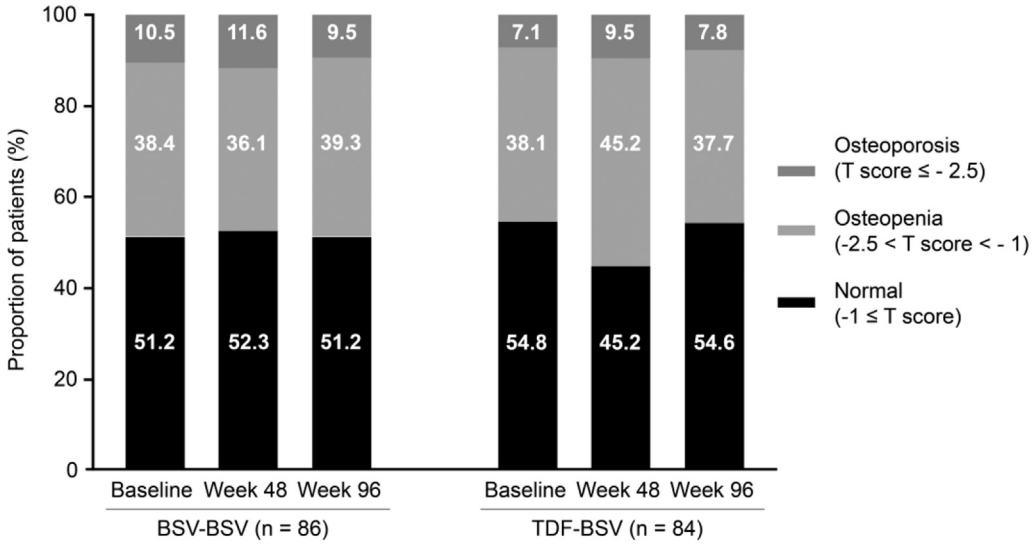
Statistical Analysis

A sample size of at least 94 patients per group was required to demonstrate whether BSV was non-inferior to TDF in terms of the virologic response (HBV DNA $<$69 IU/mL) at week 48, assuming that the percentage of respondents who reached the overall virologic response was 86.2%[2] using standard statistical criteria (80% statistical power, 2.5% one-sided significance level, 15% non-inferiority margin,[18] and 10% dropout).

For primary efficacy analysis, the proportion of patients with HBV DNA $<$69 IU/mL was compared with the test non-inferiority of BSV by using intention-to-treat analysis. In addition, differences in baseline characteristics and secondary endpoints between the treatment groups were tested by using independent two-sample t test or Wilcoxon rank sum test for continuous variables and χ^2 test or Fisher exact test for categorical variables. Individual patient data were stratified by HBeAg status at baseline for primary and secondary efficacy analyses.



Supplementary Figure 1. Patient disposition. BSV, besifovir dipivoxil maleate; CPK, creatine phosphokinase; HCC, hepatocellular carcinoma; TDF, tenofovir disoproxil fumarate.



Supplementary Figure 2. Safety results of bone mineral density in terms of T-score changes from baseline. BSV, besifovir dipivoxil maleate; TDF, tenofovir disoproxil fumarate.

Supplementary Table 1. Renal Safety Data at Week 48

	BSV (n = 92)	TDF (n = 92)	Difference (95% confidence interval)	*P* value
Creatinine				
LS mean ± standard error	0.01 ± 0.01	0.06 ± 0.01	−0.05 (−0.08 to −0.02)	.0024
Median	0.00	0.10		
Minimum, maximum	−0.40, 0.20	−0.10, 0.30		
P value	.24	<.0001		
eGFR				
LS mean ± standard error	−1.87 ± 1.18	−6.66 ± 1.18	4.79 (1.48–8.09)	.0048
Median	−0.45	−7.70		
Minimum, maximum	−30.50, 48.30	−33.90, 17.00		
P value	.11	<.0001		

NOTE. Multivariable analysis was adjusted for baseline age, eGFR, serum creatinine, and cirrhosis.
BSV, besifovir dipivoxil maleate; eGFR, estimated glomerular filtration rate; LS, least squares; TDF, tenofovir disoproxil fumarate.