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Besifovir Dipivoxil Maleate 144-Week Treatment of Chronic Hepatitis B: An Open-Label Extensional Study of a Phase 3 Trial

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INTRODUCTION: **Chronic hepatitis B (CHB) remains a major worldwide public health concern. Besifovir dipivoxil maleate (BSV) is a new promising treatment for CHB. However, long-term efficacy and safety have not yet been evaluated. Therefore, the goal of the study is to determine the antiviral efficacy and safety of BSV treatment over a 144-week duration (BSV-BSV) in comparison with those of a sequential treatment with tenofovir disoproxil fumarate (TDF) followed by a 96-week duration BSV administration (TDF-BSV).**

METHODS: **After 48 weeks of a double-blind comparison between BSV and TDF treatments, patients continued the open-label BSV study. We evaluated antiviral efficacy and drug safety up to 144 weeks for BSV-BSV and TDF-BSV groups. The primary endpoint was a virological response (hepatitis B virus DNA < 69 IU/mL).**

RESULTS: **Among the 197 patients enrolled, 170 and 158 patients entered the second-year and third-year open-label phase extensional study, respectively, whereas 153 patients completed the 144-week follow-up. The virological response rate over the 144-week period was 87.7% and 92.1% in BSV-BSV and TDF-BSV groups, respectively ($P = 0.36$). The rates of ALT normalization and HBeAg seroconversion were similar between the groups. No drug-resistant mutations to BSV were noted. Bone mineral density and renal function were well preserved in the BSV-BSV group and were significantly improved after switching therapy in TDF-BSV patients.**

DISCUSSION: **This extensional study of a phase 3 trial (NCT01937806) suggests that BSV treatment is efficacious and safe for long-term use in treatment-naïve and TDF-experienced patients with CHB.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/B485, http://links.lww.com/AJG/B491

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INTRODUCTION

Chronic hepatitis B (CHB) remains a major worldwide public health problem despite the presence of effective vaccines and potent antivirals (1,2). Although the prevalence of chronic hepatitis B virus (HBV) infection was significantly reduced after the introduction of a universal HBV vaccination program in many Asian countries, new cases of HBV infection are still reported, even in low-prevalence areas (3–5). In South Korea,

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Table 1. Baseline characteristics of the study subjects

	BSV-BSV (n = 81)	TDF-BSV (n = 76)	*P* Value
Male	54 (66.7)	49 (64.5)	0.77
Age, yr	46.00 (10.9)	43.99 (9.7)	0.22
HBeAg positive	51 (63.0)	43 (56.6)	0.87
HBV genotype			0.41
A	1 (1.2)	0 (0.0)	
C	79 (97.5)	75 (98.7)	
D	0 (0.0)	1 (1.3)	
Not determined	1 (1.2)	0 (0.0)	
HBV DNA (log_{10} IU/mL)	6.3 (1.7)	6.5 (1.5)	0.62
ALT (U/L)	106.15 (101.6)	128.41 (141.8)	0.36
ALT > ULN by central lab criteria[a]	78 (96.3)	71 (93.4)	0.48
ALT normalization by central lab criteria	3 (3.7)	5 (6.6)	
eGFR by MDRD (mL/min)	89.74 (14.8)	91.97 (13.7)	0.36
Creatinine (mg/dL)	0.86 (0.2)	0.84 (0.1)	0.43
Phosphate (mg/dL)	3.54 (0.5)	3.44 (0.6)	0.29
Total hip bone mineral density clinical status, n[b]	70	58	0.80
Normal (T-score ≥ −1.0)	58/70 (82.9)	49/58 (84.5)	
Osteopenia (−2.5 ≤ T-score < −1.0)	12/70 (17.1)	9/58 (15.5)	
Osteoporosis (T-score < −2.5)	0 (0.0)	0 (0.0)	
Data not collected	11	18	
Spine bone mineral density clinical status, n[c]	73	62	0.67
Normal (T-score ≥ −1.0)	50/73 (68.5)	40/62 (64.5)	
Osteopenia (−2.5 ≤ T-score < −1.0)	19/73 (26.0)	20/62 (32.3)	
Osteoporosis (T-score < −2.5)	4/73 (5.5)	2/62 (3.2)	
Data not collected	8	14	
Concurrent history	64 (79.0)	50 (65.8)	0.06
Mild renal impairment[c]	48 (59.3)	40 (52.6)	0.40
Cirrhosis	19 (23.5)	14 (18.4)	0.44
Cardiovascular disease	0 (0.0)	0 (0.0)	—
Diabetes mellitus	12 (12.8)	4 (4.3)	0.05
Hypertension	11 (11.7)	10 (10.8)	0.94
Hyperlipidemia	2 (2.1)	2 (2.2)	1.00
Prior antiviral therapy	0 (0.0)	1 (1.1)[a]	0.48

Data are number (%), n/N (%), or mean (SD) unless otherwise stated. *P* value: 2-sample *t* test or Wilcoxon rank-sum test for continuous variables and χ^2 test or Fisher exact test for categorical variables.
ALT, alanine aminotransferase; BMD, bone mineral density; BMD, bone mineral density; BSV, besifovir dipivoxil maleate; eGFR, estimated glomerular filtration rate; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; MDRD, modification of diet in renal disease; TDF, tenofivir disoproxil fumarate; ULN, upper limit of normal.
[a]Thirty-three U/L for women, 41 U/L for men.
[b]For BMD, some data were not collected.
[c]50 ≤ eGFR < 90 (mL/min).

CHB still has a significant impact on public health, considering that the hepatitis B surface antigen (HBsAg) is detected in 60%–70% of patients with liver cirrhosis (5) and 65%–75% of patients with hepatocellular carcinoma (HCC) (6,7).

Currently, second-generation nucleos(t)ide analogs (NAs), such as entecavir, tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide fumarate (TAF), which have high genetic barriers to resistance and potent viral suppression activity, are used as primary treatments of CHB (8).

Besifovir dipivoxil maleate (BSV), an acyclic nucleotide phosphonate (a guanosine monophosphate), has been tested in several phase Ia/IIb studies and has shown potent suppression of

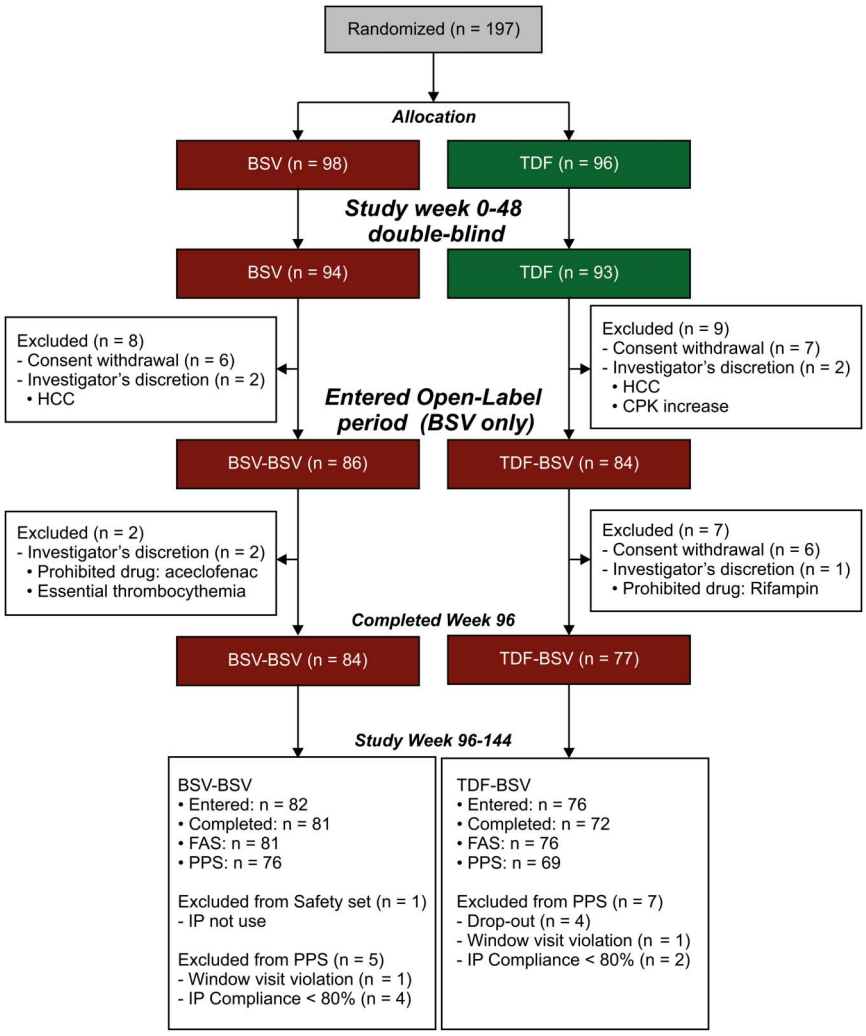


Figure 1. Patient disposition. BSV, besifovir dipivoxil maleate; CPK, creatinine phosphokinase; FAS, full analysis set; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IP, investigational product; PPS, per-protocol set; TDF, tenofovir disoproxil fumarate.

HBV replication (9–12). BSV was approved for the treatment of chronic HBV infection in May 2017 in South Korea after we performed a randomized, multicenter, double-blind phase 3 study comparing the efficacy and safety of once-daily treatment with BSV vs TDF for 48 weeks in naïve patients with CHB (13). We reported that BSV elicited minor side effects on the kidneys and bones, with antiviral efficacy comparable with that of TDF over 48 weeks of treatment (13). This study was planned as an open-label follow-up study in which patients receive BSV for 7 years after initial treatment with BSV or TDF.

The aim of this study was to compare the antiviral efficacy and safety of a BSV solo treatment (BSV-BSV) over a 144-week period with a 48-week TDF treatment, followed by a 96-week BSV sequential treatment (TDF-BSV).

METHODS

Study design

This experimental study took over a 144-week period of treating patients with hepatitis B in South Korea. The first 48 weeks corresponded to a double-blind, randomized, multicenter, noninferiority, controlled trial comparing BSV (Ildong Pharmaceutical, Seoul, Korea) with TDF (Gilead Sciences, Foster City, CA) treatments. Patients from that study who were suited to continue a single-arm, open-label trial received BSV for an additional 96 weeks. Written informed consent for both the 48-week initial phase and the open-label phase was obtained from all study participants. This study was conducted with the approval of the Human Research Ethics Committee in the 22 participating hospitals in the Republic of Korea, following the Declaration of Helsinki and all other applicable guidelines, laws, and regulations. Detailed descriptions of the study design, sample size estimates, eligibility criteria, and overall study population have been previously reported (13).

Bone mineral density, noninvasive fibrosis test, and resistance surveillance were regularly performed (see Supplementary Material, Supplementary Digital Content 1, http://links.lww.com/AJG/B491). Particularly, FIB-4 and aspartate aminotransferase-to-platelet ratio indexes (APRI) were annually estimated to assess liver fibrosis (see Table, Supplementary Digital Content 2 for formula used, http://links.lww.com/AJG/B485).

Table 2. Virological, serological, and biochemical responses

	48 wk			144 wk		
	BSV (n = 97)	TDF (n = 95)	*P* Value	BSV-BSV (n = 81)	TDF-BSV (n = 76)	*P* Value
HBV DNA <69 IU/mL	76 (78.4)	80 (84.2)	0.30	71 (87.7)	70 (92.1)	0.36
HBV DNA <20 IU/mL	60 (61.9)	65 (68.4)	0.34	65 (80.3)	65 (85.5)	0.38
HBeAg loss, n/N (%)[a]	5/53 (9.4)	3/50 (6.0)	0.72	10/50 (20.0)	13/41 (31.7)	0.20
HBeAg seroconversion, n/N (%)[a]	3/53 (5.7)	1/50 (2.0)	0.62	4/50 (8.0)	5/41 (12.2)	0.73
HBsAg loss, n/N (%)[b]	0/87 (0.0)	1/87 (1.1)	1.00	0/79 (0.0)	1/71 (1.4)	0.47
HBsAg seroconversion, n/N (%)[b]	0/87 (0.0)	0/87 (0)	—	0/79 (0.0)	1/71 (1.4)	0.47
ALT normalization, n (%)[c]	69 (71.1)	71 (74.7)	0.57	66 (81.5)	67 (88.2)	0.25

Data are expressed as n (%), unless stated otherwise. *P* value: Pearson χ^2 test/Fisher exact test.
ALT, alanine aminotransferase; BSV, besifovir dipivoxil maleate; HBeAg, hepatitis B e antigen; HBsAg, HBeAg, hepatitis B surface antigen; TDF, tenofovir disoproxil fumarate.
[a]Among HBeAg-seropositive patients at baseline.
[b]Among HBsAg-seropositive patients at baseline.
[c]Among patients with baseline ALT levels above the central lab normal range (0–41 U/L for males and 0–33 U/L for females).

Subjects

Patients with CHB younger than 20 years of age and HBsAg-positive for at least 6 months before screening were eligible. Subjects with HBV DNA levels >17,241 IU/mL (1×10^5 copies/mL) and > 1,724 IU/mL (1×10^4 copies/mL), who tested positive and negative for hepatitis B e-antigen (HBeAg), respectively, were randomized 1:1 into BSV or TDF treatment groups for 48 weeks. To maintain blinding of investigators and subjects, subjects in the BSV group were given BSV 150 mg with L-carnitine 660 mg as a supplement and TDF placebo, whereas those in the TDF group were given TDF 300 mg with L-carnitine as a BSV placebo. After 48 weeks, the patients continued on BSV or were switched to BSV 150 mg with L-carnitine 660 mg during the open-label phase for up to 144 weeks.

Endpoints

The efficacy endpoint was the proportion of subjects with a virological response, defined as HBV DNA <69 IU/mL at week 144. Other efficacy and safety endpoints, including the proportions of subjects with undetectable HBV DNA levels (<20 IU/mL), changes of serum HBV DNA levels, HBsAg or HBeAg seroconversion, alanine aminotransferase (ALT) normalization, drug resistance, adverse events (AEs), bone mineral density (BMD), renal function-related parameters, fibrosis parameters, incidences of HCC, and other abnormalities, were assessed.

Laboratory tests and assessments

All laboratory data during the trial were collected at 12-week intervals via the Central Lab (GC abs, Yongin, Korea). HBV DNA quantification was performed using a COBAS AmpliPrep/TaqMan test (Roche Diagnostics, Indianapolis, IN) with a lower detection limit of 20 IU/mL. Other laboratory methods were followed as previously reported (13).

Bone mineral density, non-invasive fibrosis test, and resistance surveillance were regularly performed (see Supplementary Material, Supplementary Digital Content 1, http://links.lww.com/AJG/B491). Particularly, FIB-4 and aspartate aminotransferase-to-platelet ratio indexes (APRI) were annually estimated to assess liver

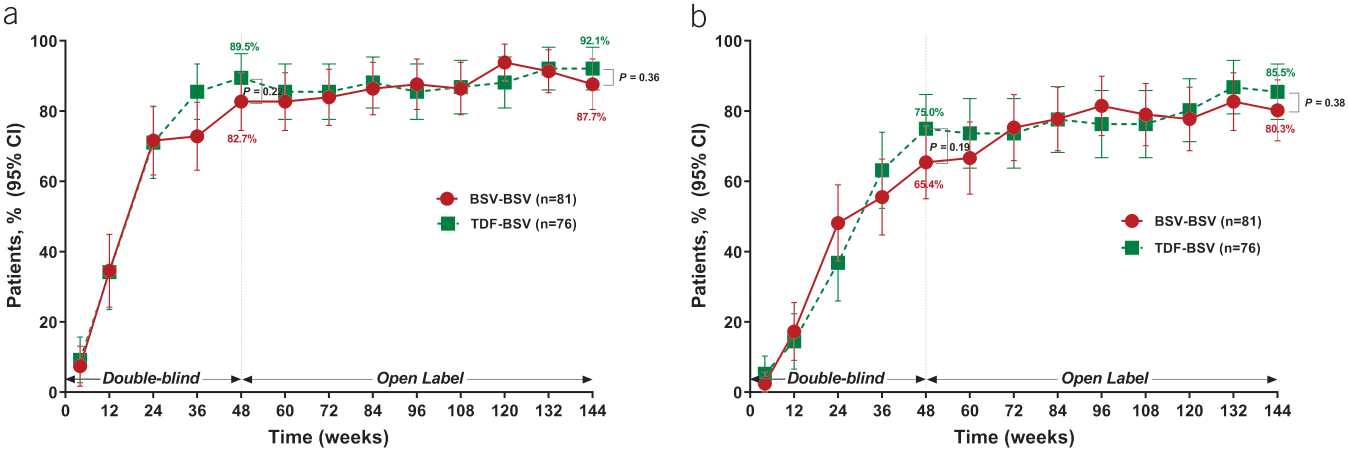
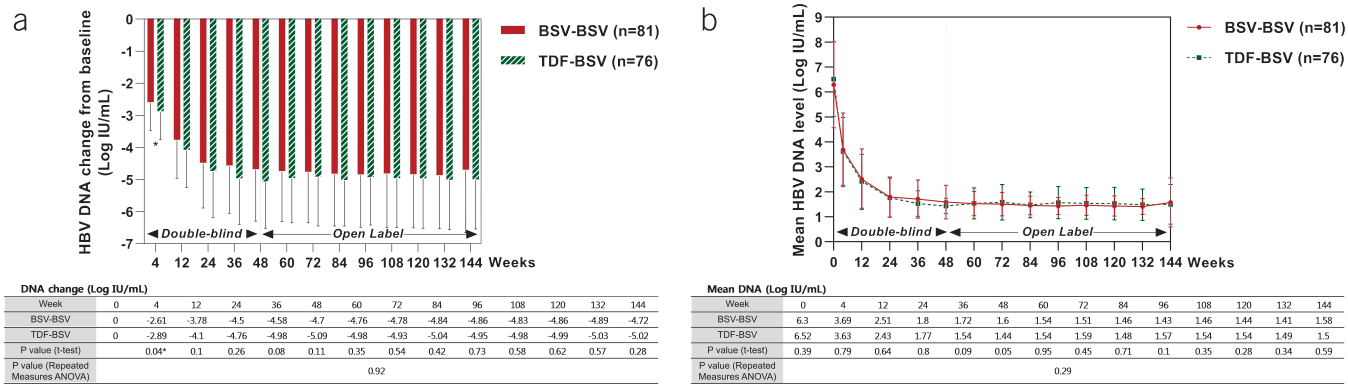


Figure 2. Viral suppression by study visit. (**a**) Proportions of patients with HBV DNA <69 IU/mL as determined by the FAS. (**b**) Proportions of patients with HBV DNA <20 IU/mL as determined by FAS. Bars represent 95% confidence intervals. BSV, besifovir dipivoxil maleate; FAS, full analysis set; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.



DNA change (Log IU/mL)

Week	0	4	12	24	36	48	60	72	84	96	108	120	132	144
BSV-BSV	0	-2.61	-3.78	-4.5	-4.58	-4.7	-4.76	-4.78	-4.84	-4.86	-4.83	-4.86	-4.89	-4.72
TDF-BSV	0	-2.89	-4.1	-4.76	-4.98	-5.09	-4.98	-4.93	-5.04	-4.95	-4.98	-4.99	-5.03	-5.02
P value (t-test)		0.04*	0.1	0.26	0.08	0.11	0.35	0.54	0.42	0.73	0.58	0.62	0.57	0.28
P value (Repeated Measures ANOVA)	0.92													

Mean DNA (Log IU/mL)

Week	0	4	12	24	36	48	60	72	84	96	108	120	132	144
BSV-BSV	6.3	3.69	2.51	1.8	1.72	1.6	1.54	1.51	1.46	1.43	1.46	1.44	1.41	1.58
TDF-BSV	6.52	3.63	2.43	1.77	1.54	1.44	1.54	1.59	1.48	1.57	1.54	1.54	1.49	1.5
P value (t-test)	0.39	0.79	0.64	0.8	0.09	0.05	0.95	0.45	0.71	0.1	0.35	0.28	0.34	0.59
P value (Repeated Measures ANOVA)	0.29													

Figure 3. Antiviral responses by study visit (weeks). (**a**) Degree of HBV DNA reduction (log IU/mL). (**b**) Mean HBV DNA level (log IU/mL). ANOVA, analysis of variance; BSV, besifovir dipivoxil maleate; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

fibrosis (see Table, Supplementary Digital Content 2 for formula used, http://links.lww.com/AJG/B485).

Statistical analysis

For primary efficacy analysis, proportions of patients with HBV DNA <69 IU/mL were determined using the full analysis set (FAS), which included all patients who received at least one investigational product and completed at least one efficacy evaluation. Per-protocol analysis was performed after excluding consent withdrawals and major protocol violators from the FAS population.

Differences in the baseline characteristics and secondary endpoints between the groups were tested using an independent 2-sample *t* test or Wilcoxon rank-sum test for continuous variables and a χ^2 test or Fisher exact test for categorical variables. We followed the CONSORT guidelines for randomized controlled trials.

Table 3. Improvements in noninvasive fibrosis markers FIB-4 and APRI indexes at 144 weeks

	BSV-BSV (n = 81)	TDF-BSV (n = 76)	*P* value[a]	*P* value[b]
FIB-4				
Baseline	2.12 (2.07)	1.92 (1.14)	—	—
144 wk	1.32 (0.76)	1.27 (0.83)	—	—
Change	−0.80 (1.77)	−0.65 (0.92)	0.79	0.54
P value[c]	<0.0001	<0.0001		
APRI				
Baseline	1.22 (1.31)	1.35 (1.32)	—	—
144 wk	0.40 (0.30)	0.39 (0.38)	—	—
Change	−0.82 (1.33)	−0.97 (1.31)	0.30	0.29
P value[c]	<0.0001	<0.0001		

Data are expressed as mean (standard deviation), unless otherwise stated.
APRI, aspartate aminotransferase-to-platelet ratio index; BSV, besifovir dipivoxil maleate; TDF, tenofovir disoproxil fumarate.
[a]Between-group: Wilcoxon rank-sum test.
[b]Between-group: mixed model with repeated measures (every 12 weeks measurement).
[c]Within-group: Wilcoxon signed-rank test.

RESULTS

Study population

Of 197 patients who were initially randomly assigned, 170 (86%) entered the second year, 158 (80%) entered the third year extensional study, and finally 153 completed all 144 weeks of follow-up (Figure 1). Of 157 patients (81 in BSV-BSV and 76 in TDF-BSV) who qualified for the FAS at 144 weeks, 145 were included for the PPS analysis. The baseline characteristics for both treatment groups were well-balanced (Table 1). Considering both the groups, 65.6% patients enrolled were men, with a mean age of 45 years. Subjects positive for HBeAg represented 63.0% in the BSV-BSV group and 56.6% in the TDF-BSV group, with the most common HBV genotype being C. For BSV-BSV and TDF-BSV groups, the means of HBV DNA at the baseline were 6.3 and 6.5 $\log_{10}$ IU/mL, respectively. More than half of the patients showed a normal T-score in the hip and/or spine at the baseline (64.5%–84.5%). Although the BSV-BSV group was more likely to have concurrent histories, including cirrhosis and diabetes mellitus, at the baseline, no statistically significant differences were noted between the groups.

Efficacy

Virological response. The rate of virological response (HBV DNA < 69 IU/mL) in BSV-BSV was 87.7% (71/81), whereas 92.1% (70/76) of patients who switched the treatment from TDF to BSV responded up to 144 weeks, indicating that the BSV-BSV group met the efficacy endpoint of noninferiority with predetermined −15% margin to BSV-TDF according to the FAS (lower bound 95% CI = −13.8%, $P = 0.36$) (Table 2 and Figure 2a). The complete virological response with the lower limit of HBV DNA quantification (<20 IU/mL) was 80.3% (65/81) among the BSV-BSV patients and 85.5% (65/76) in the TDF-BSV group at week 144 ($P = 0.38$) (Table 2 and Figure 2b). Similar results were observed in the PPS (see Figure, Supplementary Digital Content 3A, 3B, http://links.lww.com/AJG/B485) (HBV DNA < 69 IU/mL, 92.1% vs 95.7%, $P = 0.50$; HBV DNA < 20 IU/mL, 84.2% vs 88.4%, $P = 0.46$; in BSV-BSV vs TDF-BSV, respectively).

Antiviral responses from the baseline during every follow-up visit until week 144 are shown in Figure 3. During the first 48 weeks, the degree of HBV DNA reduction was not significantly different between the 2 groups (Figure 3a), except for at the end of the first month. Mean HBV DNA decreased to <2 $\log_{10}$ IU/mL

Table 4. Safety data

Variables	0–144 wk		96–144 wk	
	BSV (n = 81)	TDF (n = 76)	BSV-BSV (n = 81)	TDF-BSV (n = 76)
Adverse events, n (%), [cases]	63 (77.8), [253]	56 (73.7), [209]	54 (66.7), [125]	42 (55.3), [95]
Adverse drug reactions	31 (38.3)	26 (34.2)	23 (28.4)	15 (19.7)
Serious adverse events	7 (8.6)	7 (9.2)	1 (1.2)	2 (2.6)
Serious adverse drug reactions	1 (1.2)	0	0	0
Death	0	0	0	0
Adverse events recorded in ≥3% of all patients				
Nasopharyngitis	14 (17.3)	14 (18.4)	3 (3.7)	4 (5.3)
Dyspepsia	8 (9.9)	10 (13.2)	1 (1.2)	1 (1.3)
Headache	6 (7.4)	3 (4.0)	1 (1.2)	1 (1.3)
Back pain	6 (7.4)	4 (5.3)	3 (3.7)	3 (4.0)
Fatigue	5 (6.2)	5 (6.6)	1 (1.2)	2 (2.6)
Pruritus	3 (3.7)	4 (5.3)	0	1 (1.3)
Gastritis	2 (2.5)	9 (11.8)	1 (1.2)	8 (10.5)
Nausea	5 (6.2)	1 (1.3)	0	0
ALT elevation	6 (7.4)	2 (2.6)	2 (2.5)	0
Diarrhea	3 (3.7)	5 (6.6)	2 (2.5)	0
Urticaria	1 (1.2)	5 (6.6)	0	0
Dizziness	8 (9.9)	0	3 (3.7)	0
Renal-related adverse events				
Proteinuria	0	1 (1.3)	0	1 (1.3)
Phosphate < 2.5 mg/dL	9 (11.1)	16 (21.1)	6 (7.4)	5 (6.6)
eGFR < 50 mL/min	1 (1.2)	2 (2.6)	0	1 (1.3)
Bone related adverse events				
Fracture[a]	2 (2.5)	1 (1.3)	1 (1.2)	0
Total-carnitine level at week 144				
Decrease	1 (1.2)	1 (1.3)	—	—
Increase	31 (38.3)	28 (36.8)	—	—

Data are expressed as n (%), unless stated otherwise.
ALT, Alanine aminotransferase; BSV, besifovir dipivoxil maleate; eGFR, estimated glomerular filtration rate; TDF, tenofovir disoproxil fumarate.
[a]Adverse event due to trauma or accident.

levels at week 24 and remained stable for 144 weeks (Figure 3b). No significant differences between the 2 groups were observed during the 144 weeks (Figure 3b).

Biochemical and serological responses. Among HBeAg-positive patients, the cumulative incidences of HBeAg loss at 144 weeks were 20.0% (10/50) in the BSV-BSV group and 31.7% (13/41) in the TDF-BSV group ($P = 0.20$). The incidences of HBeAg seroconversion were 8.0% (4/50) and 12.2% (5/41) in the BSV-BSV and TDF-BSV groups, respectively ($P = 0.73$). There was no significant difference in HBeAg serological responses between both groups (Table 2); only one patient (1.4%, 1/71) in the TDF-BSV group showed HBsAg loss during the 144 weeks (Table 2). ALT levels normalized in 81.5% (66/81) and 88.2% (67/76) subjects in the BSV-BSV and TDF-BSV groups after 144 weeks, with no significant difference between the groups ($P = 0.25$) (Table 2).

Subgroup analysis. Biochemical, serological, and virological responses were separately evaluated in HBeAg-positive and HBeAg-negative patients according to the baseline HBeAg status for FAS and PPS (see Tables, Supplementary Digital Content 4 and 5, http://links.lww.com/AJG/B485; see Figure, Supplementary Digital Content 6, http://links.lww.com/AJG/B485).

In the FAS, all HBeAg-negative patients reached HBV DNA <69 IU/mL at week 144. Only one patient in each group did not achieve a complete virological response (HBV DNA < 20 IU/mL) by week 144. There was no difference in virological response rates among HBeAg-negative patients.

Among HBeAg-positive patients, the proportions who achieved HBV DNA <69 IU/mL were 80.4% (41/51) in the BSV-BSV and 86.1% (37/43) in the TDF-BSV group ($P = 0.47$). The rates of HBV DNA <20 IU/mL were 70.6% (36/51) and 76.7% (33/43), respectively ($P = 0.50$). There was no difference in virological

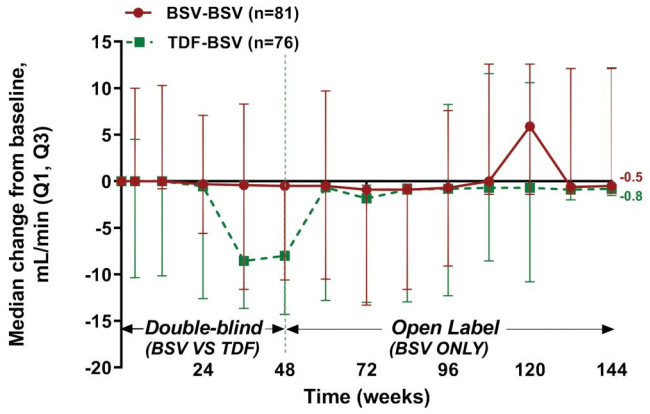


Figure 4. Median changes from baseline in eGFR (MDRD) by study week. Data are presented as median (Q1, Q3) values (mL/min). BSV, besifovir dipivoxil maleate; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; TDF, tenofovir disoproxil fumarate.

response rates between both the groups when considering HBeAg-positive patients.

Virological breakthrough and resistance surveillance. Both groups showed no antiviral resistance for 144 weeks. The proportions of patients who experienced virological breakthrough between 96 and 144 weeks were 4.9% (4/81) in the BSV-BSV group and 7.9% (6/76) in the TDF-BSV group, with no significant difference between the groups. However, serum HBV DNA became undetectable in all these patients without modifying the therapy during follow-up. DNA sequencing was performed for patients who experienced a virological breakthrough, confirming that new mutations that caused by amino acid substitutions were not detected in the HBV conserved sites.

Noninvasive fibrosis markers: FIB-4 and APRI. The FIB-4 and APRI indexes significantly improved at 144 weeks vs baseline in both groups (Table 3; see Table, Supplementary Digital Content 7, http://links.lww.com/AJG/B485). FIB-4 improved from 2.12 to 1.32 and APRI from 2.12 to 0.4 in the BSV-BSV group. Likewise, FIB-4 improved from 1.92 to 1.27 and APRI from 1.35 to 0.39 in the TDF-BSV group, respectively (all $P < 0.001$). According to these results, the degree of hepatic fibrosis significantly decreased in both the BSV-BSV and TDF-BSV groups over the duration of drug administration. There was no significant difference in FIB-4 and APRI values between both the groups.

Safety

Adverse events. After reporting AEs during the 96-week study (13), 3 serious AEs occurred: HCC in one patient from the BSV-BSV group and HCC and type 2 diabetes mellitus in 2 patients of the TDF-BSV group (Table 4). However, the investigator confirmed that all 3 patients could continue the study. No serious adverse drug reactions or death was newly reported during 96–144 weeks in the study. L-carnitine levels were measured during every follow-up visit. These levels were stably maintained, with only one patient in each group exhibiting a decreased level.

The median changes in eGFR from the baseline were −0.5, −0.7, and −0.5 mL/min at 48, 96, and 144 weeks, respectively, for the BSV-BSV group, indicating no effect of BSV on renal function. On the contrary, for the TDF-BSV group, the median changes in eGFR levels from baseline were −7.8, −0.4, and −0.8 mL/min at 48, 96, and 144 weeks, respectively; therefore, the recovered renal function after switching to BSV at 49 weeks was maintained up to 144 weeks (Figure 4). There was no incidence of acute kidney injury in the 2 groups.

The mean percent change in spine BMD from the baseline to week 144 was −0.02% (95% CI: −2.25 to 2.22) for the BSV-BSV ($P = 0.59$) and −0.31% (95% CI: −2.37 to 1.74) for the TDF-BSV ($P = 0.93$) group. This difference was not significant (Figure 5a). The mean percent change in hip BMD from the baseline to week 144 was −0.42% (95% CI: −1.53 to 0.7) for the BSV-BSV ($P = 0.10$) and 0.78% (95% CI: −1.21 to 2.77) for the TDF-BSV group. This difference was not significant (Figure 5b).

DISCUSSION

The incidence of HBV infection is decreasing worldwide because of improved socioeconomic status, universalization of vaccine programs, and effective antiviral treatments (1,4). However, population movements are now affecting the occurrence and prevalence of HBV in several low-endemic countries

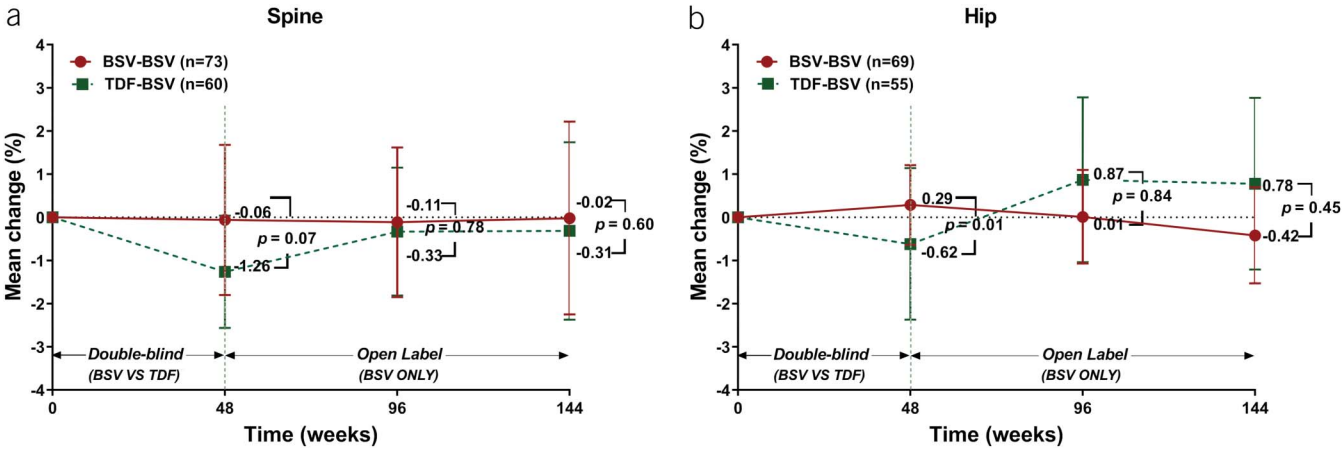


Figure 5. Changes in BMD. (**a**) Mean percentage changes in the spine at weeks 48, 96, and 144 of treatment. Bars represent 95% confidence interval. (**b**) Mean percentage changes in the hip at weeks 48, 96, and 144 of treatment. Bars represent 95% confidence intervals. BMD, bone mineral density; BSV, besifovir dipivoxil maleate; TDF, tenofovir disoproxil fumarate.

(14–17). Unlike most infectious diseases, deaths from HBV-related liver cirrhosis and/or HCC increased between 1990 and 2013 (18).

BSV, the newest approved agent in the NA class in Korea, is currently recommended as the first-line oral agent for CHB treatment by the Korean Association for the Study of the Liver (19). Our study followed the CHB treatment with BSV for 144 weeks, with findings consistent with those of our previous 96-week study (13). In total, 89.8% and 82.8% of patients had HBV DNA <69 and <20 IU/mL, respectively, indicating that the antiviral effect of BSV was maintained up to 144 weeks. Reduction in hip and spine BMD was observed in patients treated with TDF for 48 weeks, but it returned to the baseline level after switching to BSV, and it was maintained up to 144 weeks. BSV treatment also showed a favorable safety profile regarding renal parameters. No viral resistance was detected during the course of the 144-week treatment. We also confirmed the improvement of fibrosis applying the FIB-4 and APRI tests.

A recent 3–year study showed that TAF was associated with a lower risk of BMD decline and nephrotoxicity (20). The mean BMDs decreased from the baseline to week 144 of therapy (hip: −2.49 vs −0.41, $P < 0.001$; spine: −2.01 vs −0.51, $P < 0.001$; in TDF and TAF groups, respectively). We also observed a significant decrease in BMD in the TDF group relative to that in the BSV group at 48 weeks. However, in the group of patients receiving BSV for 144 weeks, the BMD mean changes from the baseline were −0.42 (hip) and 0.02 (spine), similar to those results obtained with TAF. Treatment with BSV and TAF also showed similar trends in eGFR changes over 3 years ($eGFR_{MDRD}$ for BSV, −0.5 vs $eGFR_{CG}$ for TAF, −1.2). Although it is difficult to perform a direct comparison between BSV and TAF treatments, they seem to be similar for preserving renal function and bone density.

Improvements in fibrosis after antiviral treatment have been previously reported by histology (21,22). Although liver biopsy is the accepted standard method for the assessment of hepatic fibrosis, repeated evaluations are difficult to perform because of cost, the risk of life-threatening complications, and a lack of available expertise (23–25). Therefore, we analyzed the extent of liver fibrosis using FIB-4 and APRI as biomarkers, as indicated by previous studies (26–28). Importantly, in 2 noninvasive fibrosis tests, our results showed a clear fibrosis improvement on BSV administration.

Carnitine depletion was the most common side effect of BSV (11,12). Therefore, BSV was supplemented with 660 mg of L-carnitine. Carnitine concentrations were closely monitored during the study period and at week 144. Except for one patient in each group who evidenced an increase in carnitine levels, patients were generally stably maintained with the supplementation and none experienced clinical features of carnitine deficiency, such as hypoglycemia, hypoketosis, and encephalopathy.

This study has several limitations. Although the general safety concerns related to nephrotoxicity can be ignored in the BSV group considering the rate of decline of eGFR, additional markers related to renal function, such as urinary albumin, fractional excretion of uric acid, and urinary beta-2 microglobulin, were not evaluated. Moreover, no assessments of bone turnover markers for the estimation of bone formation or resorption were performed, although it is recommended for patients receiving these NAs. Although noninvasive fibrosis markers were evaluated to demonstrate the improvement of liver fibrosis, histological analysis did not confirm such improvement; this calls for further evaluation. However, to our knowledge, this is the first study reporting antiviral effects of BSV providing safe renal and bone profile for an extended treatment period.

In summary, BSV treatment maintained antiviral efficacy over 144-week period without any viral resistance. BSV administration was safe, well-tolerated, and effective for treatment-naïve patients with CHB as well as those who switched from TDF to BSV treatment.

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CONFLICTS OF INTEREST

Guarantor of the article: Kwang-Hyub Han, MD.

Specific author contributions: H.J.Y. wrote the manuscript and performed the formal analysis and critical revision. K.H.H.: was involved in the study conception, design, and supervision. All the other authors contributed to data acquisition and revision of the manuscript.

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Study Highlights

WHAT IS KNOWN

- ✓ BSV is a new treatment of chronic hepatitis B virus infection.
- ✓ BSV has an antiviral efficacy comparable with that of TDF over 48 weeks.
- ✓ BSV has a better safety profile than TDF in terms of bone and renal outcomes.

WHAT IS NEW HERE

- ✓ BSV demonstrated durable and potent antiviral activity over 144 weeks.
- ✓ Approximately 88% of subjects had HBV DNA <69 IU/mL without antiviral resistance mutations.
- ✓ Long-term BSV treatment for chronic hepatitis B is safe and improves fibrosis.

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