



Original Article

# 3-year Treatment of Tenofovir Alafenamide vs. Tenofovir Disoproxil Fumarate for Chronic HBV Infection in China

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## Abstract

**Background and Aims:** Tenofovir alafenamide (TAF) has similar efficacy to tenofovir disoproxil fumarate (TDF) but with improved renal and bone safety in chronic hepatitis B patients studied outside of China. We report 3-year results from two phase 3 studies with TAF in China (Clinicaltrials.gov: NCT02836249 and NCT02836236). **Methods:** Chinese hepatitis B e antigen (HBeAg)-positive and -negative chronic hepatitis B patients with viremia and elevated alanine aminotransferase were randomized 2:1 to TAF or TDF treatment groups and treated in a double-blind fashion for 144 weeks (3 years). Efficacy responses were assessed by individual study while safety was assessed by a pooled analysis. **Results:** Of the 334 patients (180 HBeAg-positive and 154 HBeAg-negative) randomized and treated, baseline characteristics were similar between groups. The overall mean age was 38 years and 73% were male. The mean HBV DNA was

6.4 log<sub>10</sub> IU/mL. The median alanine aminotransferase was 88 U/L, and 37% had a history of antiviral use. At week 144, the proportion with HBV DNA <29 IU/mL was similar among the two groups, with TAF at 83% vs. TDF at 79%, and TAF at 93% vs. TDF at 92% for the HBeAg-positive and -negative patients, respectively. In each study, higher proportions of TAF than TDF patients showed normalized alanine aminotransferase (via the American Association for the Study of Liver Diseases and the China criteria) and showed loss of HBsAg; meanwhile, the HBeAg seroconversion rates were similar. Treatment was well-tolerated among the TAF patients, who showed a smaller median decline in creatinine clearance (−0.4 vs. −3.2 mL/min; *p*=0.014) and less percentage change in bone mineral density vs. TDF at hip (−0.95% vs. −1.93%) and spine (+0.35% vs. −1.40%). **Conclusions:** In chronic hepatitis B patients from China, TAF treatment provided efficacy similar to TDF but with better renal and bone safety at 3 years.

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**Keywords:** Chronic hepatitis B virus; Antiviral therapy; Bone safety; Renal safety.

**Abbreviations:** ADV, adefovir; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMD, bone mineral density; β2M:Cr, urine β2-microglobulin-to-creatinine ratio; CHB, chronic hepatitis B; CKD, chronic kidney disease; DXA, dual energy x-ray absorptiometry; EC<sub>50</sub>, half maximal effective concentration; eGFR<sub>CG</sub>, estimated creatinine clearance by the Cockcroft-Gault method; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OAT, organic anion transporter; OAV, oral antiviral; pol/RT, polymerase/reverse transcriptase; RBP:Cr, urine retinol binding protein-to-creatinine ratio; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; UACR, urine albumin-to-creatinine ratio; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio.

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## Introduction

The World Health Organization estimated that 257 million people worldwide are chronically infected with the hepatitis B virus (HBV) and recent modeling-based analyses suggested this figure could be as high as 292 million, which represents a global prevalence of 3.9%.<sup>1,2</sup> In China, the prevalence previously was higher; however, due to the in-

roduction of universal HBV immunization in 1992, combined with other public health measures, the prevalence reduced to 7.2% in 2006, and 6.15% recently.<sup>2,3</sup> Over 95 million people in China are chronic HBV carriers and ≥20 million have active disease.<sup>2,3</sup> If untreated, chronic HBV infection progresses to cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC), or both.<sup>4,5</sup> Worldwide, liver cancer is the third leading cause of cancer deaths and is the second most common cancer in China where up to 80% of HCC cases are attributed to HBV.<sup>3</sup>

Treatment with potent antivirals that have a high resistance barrier allows for long-term suppression in the majority of patients; therefore, the risk of liver-related complications is reduced, and slowing or reversing the disease progression is possible.<sup>6</sup> However, a limited number achieve a functional cure for chronic hepatitis B (CHB) (long-lasting loss of hepatitis B surface antigen [HBsAg]); therefore, life-long treatment is normally required.<sup>7,8</sup> In an aging population with increased comorbidity risk, side effects, such as renal and bone complications that are seen with tenofovir disoproxil fumarate (TDF) use can become problematic.<sup>9–11</sup>

Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir (TFV), which is a nucleotide analog that inhibits reverse transcription of HBV.<sup>12,13</sup> Compared with TDF, TAF has increased plasma stability that enables more efficient hepatic delivery of the active drug (TFV-diphosphate).<sup>12,14</sup> At the currently approved dose of 25 mg once daily, the levels of circulating TFV are approximately 90% lower than with the TDF 300 mg once daily dosing regimen which forms the basis for an improvement in renal and bone safety with TAF.<sup>15</sup>

Studies GS-US-320-0110 (Study 110, in HBeAg-positive patients) and GS-US-320-0108 (Study 108, in HBeAg-negative patients) are ongoing, randomized, double-blind, international (excluding China) Phase 3 studies that compare TAF versus TDF in a combined population of 1,298 treatment-naïve and treatment-experienced patients with CHB, which includes those with compensated cirrhosis. In each study, TAF demonstrated statistical non-inferiority to TDF in antiviral efficacy (HBV DNA <29 IU/mL at week 48), which was confirmed at week 96.<sup>16–18</sup> In addition, a smaller mean percentage decrease in bone mineral density (BMD) at the hip and spine, and a smaller median decline in the estimated creatinine clearance were seen with TAF versus TDF in each study at week 48 and by pooled safety analysis at week 96.<sup>16–18</sup> In addition, TAF-treated patients had significantly smaller changes in biomarkers for bone turnover and reductions in markers for proximal tubular function compared with TDF.<sup>18</sup> For the first time, the efficacy and safety results from 3 years of double-blind treatment in a separate cohort of patients that were enrolled in Studies 110 and 108 in China are presented.

## Methods

### Patients and study design

The randomized, double-blind, active-controlled phase 3 trials were identical in design and differed only by the patient population as previously described.<sup>16,17</sup> Briefly, patients were ≥18 years of age, HBsAg positive for ≥6 months with HBV DNA levels ≥20,000 IU/mL, and alanine transaminase (ALT) level of >60 U/L in men or >38 U/L in women. All patients had an estimated creatinine clearance ≥50 mL/min by using the Cockcroft-Gault (eGFR<sub>CG</sub>) equation. Patients were excluded with clinical or laboratory evidence of decompensated liver disease, aspartate transaminase or ALT >10 times the upper limit of normal (ULN), hepatocellular carcinoma, or co-infection with hepatitis C, hepatitis D, or the human immunodeficiency virus.

Patients were randomly assigned (2:1) to TAF 25 mg or TDF 300 mg given orally once a day for 144 weeks. All patients received placebo tablets that matched the alternative treatment; patients and investigators were blinded to the treatment assignment throughout the double-blind period. A limited number of individuals from the clinical research, biometrics, safety, and regulatory departments of the sponsor were unblinded at the 48-week time point to undertake measures that lead to the submission for TAF registration in China. Randomization was stratified by HBV DNA levels (≥8 log<sub>10</sub> IU/mL versus 7 to 8 log<sub>10</sub> IU/mL versus <7 log<sub>10</sub> IU/mL in Study 108, and ≥8 log<sub>10</sub> IU/mL versus <8 log<sub>10</sub> IU/mL in Study 110) and by previous oral antiviral (OAV) treatment (treatment-naïve status was defined as <12 weeks of previous OAVs for HBV, and treatment-experienced patients received ≥12 weeks of previous OAV therapy).

Written informed consent was obtained from all patients before enrollment and the study protocols were approved by the institutional review board or independent ethics committees at all participating sites and were conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice. All authors had access to the study data and reviewed and approved the final manuscript.

### Procedures

During the first year, study visits occurred every 4 weeks that started at treatment week 4; however, during the second and third years study visits were conducted every 8 and 12 weeks, respectively. Laboratory assessments included a complete blood count with platelets, serum chemistries, fasting lipid panel, standard measures of renal function (serum creatinine, eGFR<sub>CG</sub>, proteinuria by dipstick), and quantitative markers of proteinuria (protein-to-creatinine ratio [UPCR], the albumin-to-creatinine ratio [UACR], retinol binding protein-to-creatinine ratio [RBP:Cr], and the β<sub>2</sub>-microglobulin-to-creatinine ratio [β<sub>2</sub>M:Cr]; Covance Laboratories, Shanghai, China). Changes in BMD were assessed in patients at sites that were able to perform dual-energy x-ray absorptiometry (DXA) scanning of the lumbar spine and hip. DXA scans were performed at screening, and then every 24 weeks. In addition, fasting serum biomarkers of bone turnover were measured, including C-type collagen sequences and procollagen type 1 N-terminal propeptide, which are sensitive markers of bone resorption and formation, respectively.

### Outcomes

Efficacy endpoints for the 144-week analysis were the proportions of patients with HBV DNA <29 IU/mL, proportions of patients with a serological response (loss of HBsAg with or without seroconversion to anti-HBs, quantitative change in HBsAg, and in HBeAg-positive patients, proportion with HBeAg loss with or without seroconversion to anti-HBe). Other efficacy endpoints included the proportions of patients with ALT normalization (defined as ALT >ULN at baseline becoming ≤ULN at week 144) by the criteria proposed by the AASLD; 35 U/L for males and 25 U/L for females).<sup>7</sup> In addition, a ULN of 40 U/L (for men and women) was assessed for ALT normalization, because this cutoff is often used as a reference in China, which is referred to as the China criteria in this study. Fibrosis was assessed noninvasively using serum FibroTest (BioPredictive S.A.S., Paris, France). In addition, categorical shifts from baseline were assessed using three categories of FibroTest ranges: 0.00–0.48 (approximately equivalent to Metavir F0/F1; no or minimal fibrosis), 0.49–0.74 (F2 or F3; moderate to severe fibrosis),

**Table 1. Patient characteristics in the pooled population of studies 110 (HBeAg-positive) and 108 (HBeAg-negative) in patients from China**

	TAF 25 mg (n = 227)	TDF 300 mg (n = 107)	Total (n = 334)
Mean age (years [range])	38 (18–69)	40 (20–73)	38 (18–73)
Age ≥ 50 years (n [%])	31 (14)	24 (22)*	55 (16)
Male (n [%])	162 (71)	82 (77)	244 (73)
Asian (n [%])	227 (100)	107 (100)	334 (100)
Mean BMI (kg/m <sup>2</sup> [SD])	24 (3.4)	24 (3.1)	24 (3.3)
Mean HBV DNA (log <sub>10</sub> IU/mL [SD])	6.4 (1.87)	6.4 (1.81)	6.4 (1.85)
HBV DNA ≥ 8 log <sub>10</sub> IU/mL (n [%])	55 (24)	22 (21)	77 (23)
Median ALT (Q1, Q3)	85 (53, 160)	90 (63, 185)	88 (56, 165)
HBeAg status			
Positive	121 (53)†	59 (55)†	180 (54)
Negative	106 (47)†	48 (45)†	154 (46)
HBV genotype			
B	90 (40)	33 (31)	123 (37)
C	131 (58)	74 (69)	205 (61)
B/C	2 (1)	0	2 (0.6)
D	2 (1)	0	2 (0.6)
Unknown	2 (1)	0	2 (0.6)
History of cirrhosis			
Yes	5/56 (9)	7/25 (28)‡	12/81 (15)
No	51/56 (91)	18/25 (72)	69/81 (85)
Indeterminate/unknown	171	82	253
Mean FibroTest score (range)	0.41 (0.04–0.98)	0.44 (0.06–0.96)	0.42 (0.04–0.98)
FibroTest score ≥ 0.75	24/224 (11)	13/103 (13)	37/327 (11)
Previous nucleos(t)ide use (n [%])	86 (38)	38 (36)	124 (37)
Previous adefovir dipivoxil (n [%])	47 (21)	23 (21)	70 (21)
Previous lamivudine (n [%])	35 (15)	18 (17)	53 (16)
Prior entecavir, n (%)	48 (21)	18 (17)	66 (20)
Median eGFR by Cockcroft-Gault (Q1, Q3)	113 (98, 129)	113 (97, 125)	113 (97, 128)
Diabetes mellitus	21 (9)	5 (5)	26 (8)
Cardiovascular disease	9 (4)	1 (1)	10 (3)
Hypertension	18 (8)	13 (12)	31 (9)
Hyperlipidemia	4 (2)	3 (3)	7 (2)
Total hip BMD clinical status			
Normal (T-score ≥ –1.0)	59/93 (63)	31/54 (57)	90/147 (61)
Osteopenia (–2.5 ≤ T-score < –1.0)	33/93 (35)	22/54 (41)	55/147 (37)
Osteoporosis (T-score < –2.5)	0/93	1/54 (2)	1/147 (0.7)
Status not determined	1/93 (1)	0/54	1/147 (0.7)
Lumbar spine BMD clinical status			
Normal (T-score ≥ –1.0)	38/94 (40)	25/54 (46)	63/148 (43)
Osteopenia (–2.5 ≤ T-score < –1.0)	51/94 (54)	25/54 (46)	76/148 (51)
Osteoporosis (T-score < –2.5)	4/94 (4)	4/54 (7)	8/148 (5)
Status not determined	1/94 (1)	0/54	1/148 (0.7)
Median 25-hydroxy vitamin D (ng/mL [Q1, Q3])	18.8 (13.2, 24.4)	18.4 (14, 23.6)	18.8 (13.6, 24.4)

\**p* = 0.044; †HBeAg status for 5 patients (TAF *n* = 3, TDF *n* = 2) in Study 108 changed from negative to positive between the screening and baseline visits, and in Study 110, HBeAg status for 5 patients (TAF *n* = 5) changed from positive to negative between the screening and baseline visits; ‡*p* = 0.0265.

**Table 2. Efficacy outcomes at week 144 in patients from China**

n/N or n/n (%) [95% CI]	HBeAg-positive patients (Study 110)			HBeAg-negative patients (Study 108)		
	TAF 25 mg (N = 123)	TDF 300 mg (N = 57)	Proportional Difference (95% CI)	TAF 25 mg (N = 104)	TDF 300 mg (N = 50)	Proportional Difference (95% CI)
HBV DNA <29 IU/mL	102 (83) [75–89]	45 (79) [66–89]	4.1% (–9.1%–17.3%)	97 (93) [87–97]	46 (92) [81–98]	1.5% (–8.9%–12.0%)
HBeAg loss*	27/118 (23)	16/57 (28)	ND	–	–	–
HBeAg seroconversion*	20/118 (17)	9/57 (16)	ND	–	–	–
HBsAg loss <sup>†</sup>	5 (4)	0	ND	3 (3)	0	ND
HBsAg seroconversion <sup>†</sup>	3 (2)	0	ND	1 (1)	0	ND
Mean change from baseline in HBsAg, log <sub>10</sub> IU/mL (SD)	–0.75 (1.190)	–0.68 (0.927)	–0.06 (–0.41–0.29)	–0.39 (0.764)	–0.23 (0.487)	–0.15 (–0.38–0.08)
ALT normalization by 2018 AASLD criteria <sup>§</sup>	87/114 (76)	37/55 (67)	10.4% (–3.9%–24.8%)	74/92 (80)	29/41 (71)	8.8% (–8.3%–25.8%)
ALT normalization by China criteria <sup>  </sup>	83/107 (78)	36/54 (67)	12.2% (–2.3%–26.8%)	74/86 (86)	26/36 (72)	13.3% (–4.1%–30.8%)
Mean FibroTest score change from baseline (SD)	–0.09 (0.140)	–0.09 (0.184)	–0.01 (–0.06–0.05)	–0.06 (0.138)	–0.04 (0.185)	–0.02 (–0.07–0.04)

All efficacy results are missing equals failure except for log<sub>10</sub> IU/mL change from baseline in HBsAg; ALT, alanine aminotransferase; CI, confidence interval; ND, not done. \*Among patients who were seropositive for HBeAg and negative for anti-HBe at baseline. <sup>†</sup>Among patients who were seropositive for HBsAg and negative for anti-HBs at baseline. <sup>‡</sup>Among patients with ALT at baseline above the central lab normal range. <sup>§</sup>Among patients with ALT at baseline above the AASLD-defined normal range (>35 U/L men and >25 U/L women). <sup>||</sup>Among patients with ALT at baseline >40 U/L.

and 0.75–1.00 (F4; cirrhosis).<sup>19</sup> Safety endpoints included mean percent change in hip BMD, mean percent change in spine BMD, and changes in renal function, as measured by mean change in serum creatinine and median change in eGFR<sub>CC</sub>.

### Resistance analyses

Baseline samples for all patients were assessed for the presence of HBV resistance mutations in the polymerase/reverse transcriptase (pol/RT) region using the HBV INNO-LiPA Multi-DR v2/3 assay (WuXi AppTec [Shanghai] Co., Ltd., Shanghai, China). Resistance surveillance was performed annually and included population or deep sequencing of the HBV pol/RT at baseline and week 48 for patients only with virologic breakthrough (defined as HBV DNA ≥69 IU/mL at two consecutive visits if previously confirmed <69 IU/mL, or confirmed ≥1 log<sub>10</sub> increase in HBV DNA from nadir), and at weeks 96 and 144, pol/RT sequencing was performed for all patients with HBV DNA ≥69 IU/mL, either on treatment or at early discontinuation in those with viremia. Phenotyping was performed for patients that experienced virologic breakthrough and any pol/RT amino acid change or conserved site change, and in patients with a polymorphic site, substitution provided the change was observed in >1 patient. For phenotyping, >2-fold change in EC<sub>50</sub> for the patient's isolate relative to baseline was considered to indicate reduced sensitivity to TAF or TDF.

### Statistical analysis

A missing equals failure approach was employed for the efficacy endpoints. For HBV DNA <29 IU/mL results, 95% confidence intervals (CI) were generated by the treatment group at each time point. Because the non-inferiority of TAF compared with TDF for the proportion of patients with HBV DNA <29 IU/mL was previously established for both studies

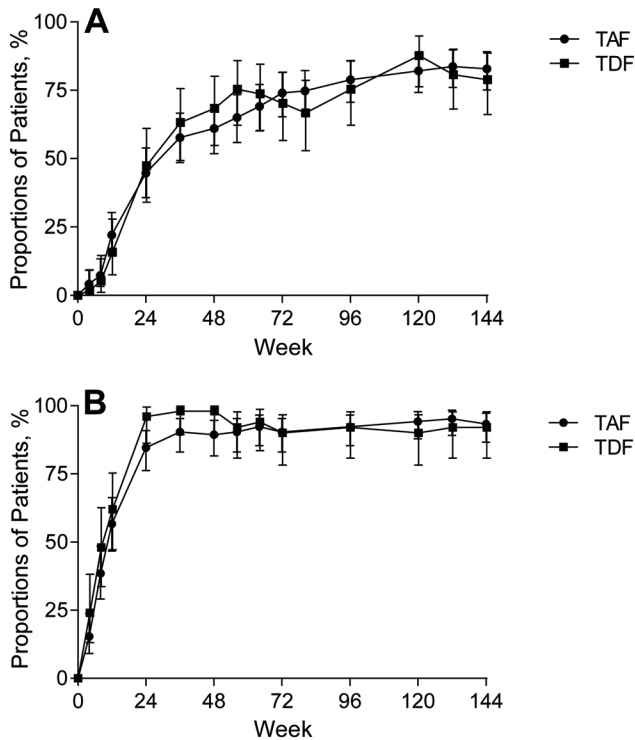
in the global (non-China) population,<sup>16–18</sup> the sample sizes for each study in the China cohort were not determined based on statistical considerations, instead enough patients were included to show comparable efficacy and safety following local registration requirements in China. Instead, exploratory statistical analyses were performed for the treatment difference (using 95% CI or *p*-values) for key efficacy and safety endpoints.

## Results

### Patient disposition

Out of 180 HBeAg-positive patients that were randomized and treated in Study 110 (123 TAF and 57 TDF) and 154 HBeAg-negative patients in Study 108 (104 TAF and 50 TDF), 165 (92%; 113 TAF and 52 TDF) and 146 (95%; 99 TAF and 47 TDF), completed the double-blind treatment to week 144, respectively. Complete dispositions for each study are provided in Supplementary Tables 1A and B.

Baseline demographics for the 334 patients enrolled in both studies were similar between treatment groups (Table 1). Patients were mainly male, mean age 38 years (range 18–73 years) with a smaller proportion of TAF versus TDF patients ≥50 years of age (14% versus 22%; *p* = 0.044). Mean HBV DNA and median ALT at baseline were 6.4 log<sub>10</sub> IU/mL and 88 U/L, respectively. The percentages of HBeAg-positive and HBeAg-negative patients were comparable (54% and 46%, respectively), with HBV genotypes C (61%) and B (37%) most common. In a subset of patients, a history of cirrhosis was known: 5/56 (9%) in the TAF group and 7/25 (28%) in the TDF group (*p* = 0.0265); however, for most patients, the cirrhosis status was indeterminate or unknown (Table 1). Using a FibroTest score ≥0.75 (i.e., suggestive of cirrhosis or Metavir F4),<sup>19</sup> 11% of patients had cirrhosis with similar proportions for both groups. Previous oral nucleos(t)ide use was reported in 37%, with 21%,



**Fig. 1. Viral suppression (HBV DNA <29 IU/mL) by visit week.** (A) Proportions of HBeAg-positive patients with HBV DNA <29 IU/mL. (B) Proportions of HBeAg-negative patients with HBV DNA <29 IU/mL. Analysis is missing equals failure.

20%, and 16% of patients previously treated with adefovir (ADV), entecavir, and lamivudine, respectively. Median (Q1, Q3) eGFR<sub>CG</sub> was 113 (97, 128) mL/min at baseline. Out of 147 patients that had available DXA data, 38% had evidence of bone loss (i.e., osteopenia or osteoporosis based on t-scores) at the hip and 57% showed bone loss at the spine. Comorbidities (hypertension, diabetes mellitus, cardiovascular disease, and hyperlipidemia) were present in <10% of study participants with a similar prevalence between treatment groups.

**Efficacy**

**Antiviral efficacy:** In both studies, the rates of antiviral suppression were slightly higher for TDF versus TAF at week 48; however, from weeks 72 and 56 onward, similar suppression rates were achieved and maintained in Studies 110 and 108, respectively (Figs. 1A, B). The proportion of HBeAg-positive patients that received TAF with HBV DNA <29 IU/mL at week 144 was 83% compared with 79% in those that received TDF (proportional difference 4.1% [95% CI, -9.1%–17.3%]) (Table 2 and Fig. 1A). The proportion of patients with HBV DNA <29 IU/mL who had target not detected was 26% in both treatment groups, and the proportion with HBV DNA ≥29 IU/mL was 11% in both groups, and 7% and 11% of TAF and TDF patients, respectively, had missing data.

The proportion of HBeAg-negative patients that received TAF with HBV DNA <29 IU/mL at week 144 was 93% compared with 92% in those that received TDF (Table 2 and Fig. 1B). The proportions of HBeAg-negative patients with HBV DNA <29 IU/mL with target not detected were 61% and 48% in the TAF and TDF groups, respectively; there were a

few patients (2 TAF; 1 TDF) with HBV DNA ≥29 IU/mL, and similar proportions (TAF 5%; TDF 6%) had missing data at week 144.

**ALT normalization:** The proportion of HBeAg-positive patients that achieved ALT normalization at week 144 by the AASLD criteria was higher for TAF versus TDF-treated patients (76% versus 67%, respectively) (Table 2). In addition, patients that received TAF had consistently higher rates than those on TDF over the 3-year study (Fig. 2A). When assessed using the China cutoff of 40 U/L, a similar trend was seen with a higher rate of ALT normalization for TAF versus TDF at week 144 (78% versus 67%; Table 2).

In addition, HBeAg-negative patients that received TAF compared with those that received TDF showed a higher rate of ALT normalization at week 144 by the AASLD criteria (80% versus 71%; Table 2), with the difference in treatment response becoming more apparent from weeks 72 to 144 (Fig. 2B). When assessed by the China criteria, a similarly higher rate of ALT normalization was seen for TAF versus TDF at week 144 (86% versus 72%; Table 2).

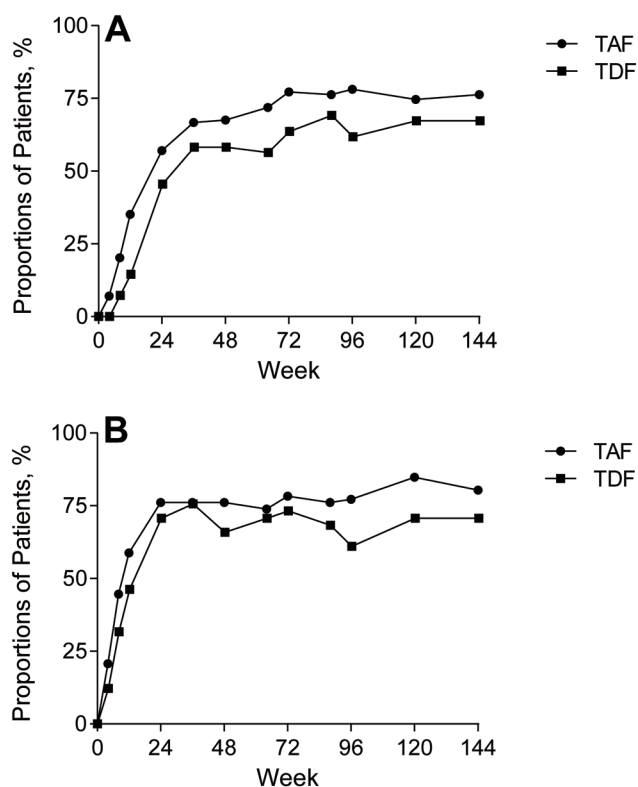
**Serological efficacy:** The proportions of HBeAg-positive patients with HBeAg loss at week 144 were 23% and 28%, for the TAF and TDF groups, respectively, and rates of anti-HBe seroconversion were similar (17% versus 16%, respectively; Table 2). In the TAF group, for HBeAg-positive and HBeAg-negative patients, rates of HBsAg loss (4% and 3%, respectively) and HBsAg seroconversion (2% and 1%, respectively) were higher than in the TDF group, where no patients in either study achieved this endpoint (Table 2). Mean (SD) decreases in HBsAg levels were small and similar between treatment groups over 144 weeks of treatment in both studies.

**FibroTest changes**

Mean (SD) FibroTest scores at baseline were similar between groups in each study (Study 110: TAF 0.37 [0.219] versus TDF 0.40 [0.219]; Study 108: TAF 0.46 [0.222] versus TDF 0.50 [0.265]). For HBeAg-positive patients, similar small mean (SD) decreases were seen with TAF and TDF at week 144 (Table 2); for HBeAg-negative patients, the mean declines were similar between treatments but were numerically smaller compared with HBeAg-positive patients. Fibrosis change was assessed by shifts from baseline in FibroTest categories (Supplementary Tables 2A, B). Although the numbers were small, the majority of HBeAg-positive patients in the highest fibrosis category (≥0.75; cirrhosis [F4]) at baseline improved by ≥1 category on study treatment, a finding that was present by week 48 with improvement remaining to week 144 (TAF 9/10 [90%] and TDF 2/3 [66%]). In contrast, nearly all patients in the lowest category at baseline (≤0.48; no or minimal fibrosis [F0/F1]) remained stable for the 144 weeks (TAF 79/80 [99%] and TDF 28/32 [88%]). For patients in the intermediate category (0.49 to 0.74; moderate to severe fibrosis [F2 or F3]), most showed a positive shift to the lowest category (TAF 12/24 [50%] and TDF 11/16 [69%]) with only a few having an increase in fibrosis category at week 144. Similar results were observed for HBeAg-negative patients for both study treatments (Supplementary Table 2B).

**Resistance surveillance**

Results for resistance surveillance for the 144 weeks are provided in Supplementary Table 3. All patients with HBV DNA ≥ 69 IU/mL qualified for pol/RT sequencing at weeks 96 and 144; however, at week 48 only patients with virologic breakthrough were sequenced given the previous



**Fig. 2. ALT normalization by visit week using 2018 AASLD criteria.** (A) Proportions of HBeAg-positive patients that achieved ALT normalization. (B) Proportions of HBeAg-negative patients that achieved ALT normalization. Analysis is missing equals failure and includes only patients with baseline ALT above the upper limit of normal for 2018 AASLD criteria (25 U/L and 35 U/L for males and females, respectively).

data that showed no resistance to TDF in patients with early viremia on treatment.<sup>20</sup> In both studies, there were 7 (6 TAF, 1 TDF), 23 (16 TAF, 7 TDF), and 14 (9 TAF, 5 TDF) patients who qualified for sequencing at weeks 48, 96, and 144, respectively, and of these, there were 1 out of 7, 8 out of 23, and 5 out of 14 patients, respectively, who had no sequence changes from baseline, and 3 out of 7, 6 out of 23, and 1 out of 14 patients with polymorphic site substitutions, and 0 out of 7, 4 out of 23, and 2 out of 14 patients who had conserved site substitutions. No specific conserved site substitution was found in >1 patient in either group. Overall, most patients that qualified for sequencing had viremia in the absence of virologic breakthrough (i.e., persistent viremia, or a viral blip, 24 out of 44 patients). Of the patients with available sequencing data, 1 out of 4, 8 out of 18, and 3 out of 8, qualified for phenotyping testing at weeks 48, 96, and 144, respectively. Overall, no pol/RT amino acid substitutions associated with resistance to TAF or tenofovir were detected during the 144 weeks in either group in each study.

**Safety**

In the pooled safety analysis, which included 227 patients that were treated with TAF and 107 that were given TDF, each treatment was safe and well tolerated. Adverse events (AEs) were mostly mild or moderate in severity (88% and 92% experienced  $\geq 1$  AE in the TAF and TDF groups, respectively; proportional difference  $-3.9\%$  [95% CI:  $-10.7\%$ -

$2.9\%$ ]) (Table 3). One patient in each group experienced a Grade 3 or 4 AE related to the study drug, and 1 TDF-treated patient had treatment discontinued prematurely for renal impairment (moderate or Grade 2) which was a serious adverse event (SAE) and was determined to be related to study treatment. Common AEs ( $\geq 5\%$  of patients) were similar between treatment groups. No patient died during the study period and there were no cases of HCC or hepatic cancer.

Similar percentages of patients in each group experienced Grade 3 or 4 laboratory abnormalities (TAF 32%; TDF 34%), with a proportional difference of  $-1.9\%$  ( $-12.7\%$ - $8.9\%$ ) (Table 3). The most common laboratory abnormalities in  $\geq 3\%$  of patients were elevations in ALT and AST, and increased creatine kinase, each occurred at a similar frequency with TAF and TDF treatment. More patients had elevations in fasting LDL cholesterol or urine glucose abnormalities in the TAF group, both were transient and primarily seen in patients with pre-existing hyperlipidemia, diabetes mellitus, or both. Occult blood or urine erythrocytes were the most common urine abnormalities, which occurred mostly in menstruating women.

**Changes in fasting lipids**

Baseline fasting lipid parameters were similar between treatment groups and median (Q1, Q3) values were within the normal ranges for each parameter (Supplementary Table 4). Following the initiation of study treatment, decreases in fasting total cholesterol were observed in both groups with a smaller decline for TAF versus TDF treatment (median [Q1, Q3] change at week 144: TAF  $-8$  [ $-21, 12$ ] mg/dL versus TDF  $-27$  [ $-40, -10$ ] mg/dL;  $p < 0.001$ ). In addition, treatment with TAF resulted in smaller median declines in high-density lipoprotein (HDL) cholesterol at week 144 versus TDF ( $-8$  [ $-15, -2$ ] mg/dL versus  $-12$  [ $-18, -5$ ] mg/dL;  $p = 0.012$ ). Therefore, the median change in total cholesterol to HDL ratio at week 144, a commonly used measure to assesses the relevance of lipid changes, was small and comparable between treatments (TAF  $0.4$  [ $0.0, 0.8$ ] versus TDF  $0.3$  [ $-1.0, 0.6$ ];  $p = 0.042$ ). A small increase in median fasting low-density lipoprotein (LDL) cholesterol was seen with TAF compared with a small decrease with TDF treatment at week 144 ( $11$  [ $-4, 25$ ] mg/dL versus  $-5$  [ $-15, 7$ ];  $p < 0.001$ ); a similar trend was observed with fasting triglycerides (TAF  $11$  [ $-14, 41$ ] mg/dL; TDF  $-6$  [ $-28, 15$ ];  $p < 0.001$ ). In general, the observed differences in fasting lipid changes between the TAF and TDF groups were similar at week 48 compared with the results at week 144, which supported an early change that did not further progress over 3 years of treatment (Supplementary Table 4). Of note, 3 (1%) out of 227 TAF patients required initiation of lipid-lowering (i.e., statin) therapy compared with no patients in the TDF group ( $p = 0.554$ ).

**Changes in renal parameters**

Table 4 provides a summary of renal laboratory results by treatment group at week 144. Median eGFR<sub>CG</sub> decreased slightly by week 144 in TAF-treated patients compared with a larger decrease in those that received TDF ( $-0.4$  mL/min versus  $-3.2$  mL/min;  $p = 0.014$ ). Of note, the larger decrease in eGFR<sub>CG</sub> with TDF occurred early (week 8) and remained significantly different versus TAF at each assessment for the 144 weeks, except for weeks 24 and 120 (Supplementary Table 5). When eGFR<sub>CG</sub> change was assessed as the percentage with  $\geq 25\%$  decrease at week 144, less TAF than TDF patients met this endpoint (10%

**Table 3. Safety during 3 years of double-blind treatment**

n (%) or n/N (%)	TAF 25 mg (N = 227)	TDF 300 mg (N = 107)
Any AE	199 (88)	98 (92)
Proportional difference (95% CI)	-3.9% (-10.7%-2.9%)	
Any AE related to study	50 (22)	37 (35)
AE that lead to study drug discontinuation	0	1 (<1)*
Any Grade 3 or 4 AE	16 (7)	4 (4)
Any Grade 3 or 4 AE related to study drug	1 (<1)	1 (<1)
Any SAE	17 (7)	10 (9)
Any SAE related to study drug	0	1 (<1)*
Deaths	0	0
AEs that occurred in ≥5% of patients in any treatment group		
Nasopharyngitis	72 (32)	24 (22)
Upper respiratory tract infection	52 (23)	27 (25)
Cough	21 (9)	5 (5)
Oropharyngeal pain	16 (7)	7 (7)
Pharyngitis	13 (6)	5 (5)
Influenza	8 (4)	7 (7)
Diarrhea	14 (6)	7 (7)
Nausea	4 (2)	7 (7)
Abdominal distension	8 (4)	6 (6)
Upper abdominal pain	13 (6)	7 (7)
Hepatic steatosis	12 (5)	6 (6)
Urinary tract infection	13 (6)	8 (7)
Increased amylase	2 (<1)	6 (6)
Osteopenia	1 (<1)	6 (6)
Increased blood parathyroid hormone	7 (3)	8 (7)
Weight decreased	4 (2)	7 (7)
Toothache	7 (3)	6 (6)
Grade 3 or 4 laboratory abnormalities that occurred in ≥3% of patients in any treatment group†		
Any Grade 3 or 4 laboratory abnormality	72/225 (32)	36/107 (34)
Proportional difference (95% CI)	-1.9% (-12.7%-8.9%)	
Alanine aminotransferase >5 × ULN	16 (7)	10 (9)
Aspartate aminotransferase >5 × ULN	5 (2)‡	4 (4)‡
Creatine kinase ≥10 × ULN	9 (4)	4 (4)
Fasting LDL cholesterol >190 mg/dL	9/224 (4)‡	0/106
Hemoglobin <9 g/dL	2 (<1)‡	5 (5)‡
Urine glucose (by dipstick) 4+	7 (3)¶	1 (1)¶
Occult blood	24 (11)¶	13 (12)¶
Urine erythrocytes	14/114 (12)¶	8/46 (17)‡

All AEs and Grade 3 or 4 laboratory abnormalities were treatment-emergent. ULN, upper limit of normal range; CI, confidence interval. \*64 yr-old woman had study treatment discontinued for an AE of Grade 2 renal impairment on Day 290 that was an SAE and related to study drug. †Laboratory results are based on 225 patients for TAF 25 mg, and 107 patients for TDF 300 mg, unless otherwise noted. ‡Only Grade 3 abnormalities were observed for these parameters. ¶Grade 3 was the highest grade for these parameters.

versus 22%;  $p = 0.003$ ). In addition, more patients that were given TAF versus TDF showed improvement in chronic kidney disease (CKD) stage at week 144 (e.g., Stage 2 →

Stage 1, Stage 3 → Stage 2), and a smaller proportion of TAF versus TDF-treated patients had CKD stage worsening (e.g., Stage 1 → Stage 2 [no patients negatively shifted to

**Table 4. Renal safety parameters at week 144**

	TAF (N = 227)	TDF (N = 107)
Mean serum creatinine (mg/dL [SD])		
Baseline	0.81 (0.144)	0.82 (0.151)
Change at week 144	-0.012 (0.090)	-0.002 (0.092)
Difference in least squares means (95% CI)	-0.011(-0.033-0.010)	
Median eGFR <sub>CG</sub> (mL/min [Q1, Q3])		
Baseline	113 (98, 129)	113 (97, 125)
Change at week 144	-0.4 (-8.2, 8.6)	-3.2 (-11.2, 5.2)
<i>p</i> -value	0.014	
≥25% decrease from baseline in eGFR <sub>CG</sub> (n/n)	22/225 (10)	24/107 (22)
<i>p</i> -value	0.003	
Shifts in CKD stage: baseline →week 144**†		
<i>Improvement</i>		
Stage 2→1	7/32 (22)	1/12 (8)
Stage 3→2	1/1 (100)	0/2 (0)
<i>Worsening</i>		
Stage 1→2	12/180 (7)	10/85 (12)
Stage 2→3	0/32 (0)	0/12 (0)
<i>No change</i>		
Stage 1→1	168/180 (93)	75/85 (88)
Stage 2→2	25/32 (78)	11/12 (92)
Stage 3→3	0/1 (0)	2/2 (100)
<i>p</i> -value	0.064	
Median urinary proximal tubular markers (μg/g [Q1, Q3])		
n = 227		
n = 107		
RBP:Cr		
Baseline	91 (65, 133)	93 (69, 138)
% change at week 144	-8 (-35, 41)	27 (-18, 71)
<i>p</i> -value	0.003	
β2M:Cr		
Baseline	94 (67, 152)	91 (58, 149)
% change at week 144	-29 (-56, 12.5)	18 (-35, 124)
<i>p</i> -value	<0.0001	

eGFR<sub>CG</sub>, estimated creatinine clearance by the Cockcroft-Gault method. RBP:Cr, urine retinol binding protein-to-creatinine ratio. β2M:Cr, urine beta-2 microglobulin to creatinine ratio. \*eGFR<sub>CG</sub>: Stage 1: ≥ 90 mL/min; Stage 2: ≥60 to < 90 mL/min; Stage 3: ≥ 30 to < 60 mL/min; Stage 4: ≥15 to <30 mL/min. †There were no Stage 4 CKD patients at baseline and no patients had moved to Stage 4 at week 144.

Stages 3 or 4]) (Table 4).

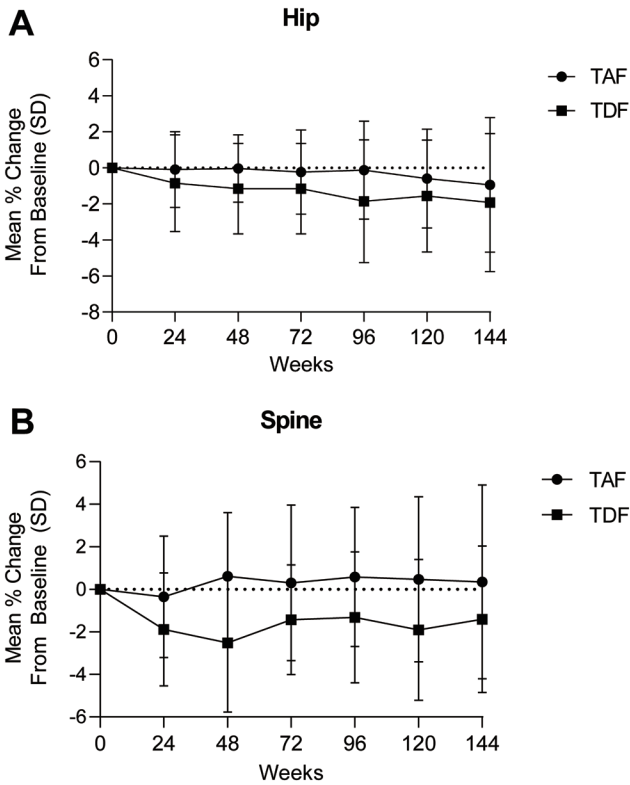
When median percentage changes from baseline were compared for the markers of proximal tubular function (RBP:Cr and β2M:Cr), significant differences were found that favored TAF treatment (Table 4 and Supplementary Figs. 1A, B). For both parameters, patients that received TAF had decreased results compared with increases for those on TDF. Significant differences in these highly sensitive markers by treatment were apparent by week 24 and were reconfirmed at week 144 (Supplementary Fig. 1A). Two TDF and no TAF patients had renal-related AEs: 1 patient in Study 110 had an AE of renal tubular disorder on day 85 that was nonserious, Grade 1 (mild), and resolved with continued study treatment on day 167, and another TDF patient in Study 108 had an AE of renal failure that was

associated with a decrease in creatinine clearance that led to discontinuation of the study drug during the first year of treatment.

#### **Changes in BMD**

The mean (SD) percent change in hip BMD from baseline to week 144 was -0.95% (3.73%) for the subset of patients that underwent DXA scanning and received TAF, which was less than the -1.9% (3.83%) change in those that received TDF (Fig. 3A). Similarly, mean (SD) percent changes in spine BMD from baseline to week 144 were 0.35% (4.56%) and -1.4% (3.45%) for the subset of patients with DXA data





**Fig. 3. Mean percentage changes in BMD.** (A) Mean percentage change from baseline in hip BMD at weeks 24, 48, 72, 96, 120, and 144 of treatment in the subset of patients that underwent DXA scanning. (B) Mean percentage change from baseline in spine BMD at weeks 24, 48, 72, 96, 120, and 144 of treatment in the subset of patients that underwent DXA scanning. Analysis is missing equals excluded (observed data).

that received TAF and TDF, respectively (Fig. 3B). Using a cutoff of >5% decrease at week 144, the proportions of patients were 25%–50% lower with TAF versus TDF treatment (hip BMD 8/67 [12%] versus 10/41 [24%] and spine BMD 6/71 [8%] versus 5/43 [12%], respectively) (Supplementary Tables 6A, B). Bone fracture was uncommon, usually trauma-related, and was observed at a similar frequency by treatment (TAF n = 4 [clavicle, foot, pelvis, and spinal compression; 1 patient each] and TDF n = 2 [forearm, 2 patients]).

**Discussion**

In previous reports, the 48 and 96-week outcomes from the two double-blind, randomized, Phase 3 trials in the global (non-China) population confirmed that TAF has an antiviral efficacy that is noninferior to TDF with superior bone and renal safety in HBeAg-positive and negative patients.<sup>16–18</sup> The results in Chinese HBV patients presented in this study agree with the global data and, in November 2018, TAF was granted licensing approval by the National Medical Products Administration in China. In addition, the results represent the first randomized comparison of TAF versus TDF in CHB patients over a 3-year treatment period. Further, the population enrolled in study sites across multiple provinces in China (Supplemental Tables 1, 2) was representative of the population of Chinese patients that require HBV treatment.

In the China cohort, the proportions of patients that achieved and maintained HBV DNA <29 IU/mL were simi-

lar between the TAF and TDF groups in each study over 3 years; the results are consistent with earlier data from the global program.<sup>16–18</sup> In HBeAg-positive and negative Chinese patients, high levels of viral suppression were observed at week 144 with TAF versus TDF (83% versus 79%, and 93% versus 92%, respectively). The numerically lower responses for TAF versus TDF (the 95% CI overlapped) at week 48 in each study was mainly due to some TAF patients with high baseline viral loads that took slightly longer to suppress and some that experienced a transient (one-time) viral blip. No difference in viral potency was noted as shown by similar proportions with an undetectable target for HBV DNA (i.e., full suppression), and similar small proportions with HBV DNA ≥29 IU/mL at week 144. Resistance surveillance that was conducted annually over 3 years showed no patients in either study had reduced susceptibility to TAF or TDF.

In the global studies, a significantly higher rate of ALT normalization was reported for TAF compared with TDF.<sup>16–18</sup> When the current ULN cutoffs for men and women recommended by AASLD were applied, results for the HBeAg-positive and negative patients showed higher ALT normalization with TAF treatment. In addition, this finding was observed when China ULN criteria were used. The mechanism(s) for improved ALT normalization with TAF versus TDF is unknown, this differential effect has been demonstrated in viremic, mostly treatment-naïve patients, and in virally suppressed, treatment-experienced patients that switched therapy from TDF to TAF.<sup>21</sup>

In HBeAg-positive Chinese patients, loss of HBeAg occurred at a slightly higher rate with TDF versus TAF at week 144 (28% versus 23%), although HBeAg seroconversion was similar (Table 2). The results for TAF were comparable with previously reported data from the global population; however, for TDF the rate of HBeAg loss was higher than previously reported (i.e., rates at week 96 were 22% and 18% for TAF and TDF, respectively).<sup>18</sup> Over 3 years of treatment, low rates of HBsAg loss (≤4%) and anti-HBs seroconversion (≤2%) were observed in patients that received TAF, and no TDF patients lost surface antigen. The low rate of HBsAg loss in Chinese patients was not unexpected, because of the previous data from TDF-treated patients that showed it to be genotype-related and occurred most often in patients with genotypes A and D.<sup>22</sup> After 3 years of treatment, mean declines in HBsAg were small (<1 log<sub>10</sub>) in each study and similar between groups.

As in the Phase 3 registration program for TAF, histologic changes were not assessed in the Chinese cohort; instead, a serum FibroTest was utilized. The impact of treatment-induced changes in FibroTest with antivirals for CHB has not been well studied.<sup>19</sup> However, mean serum FibroTest scores decreased over 3 years to a similar magnitude with TAF and TDF treatment, and most patients in the highest FibroTest category (i.e., ≥0.75 or Metavir F4) at baseline showed improvement on treatment with a few patients overall showing a categorical worsening. In Phase 3 studies with TDF, achievement and maintenance of long-term viral suppression in CHB patients over 5 years resulted in histologic regression of fibrosis and cirrhosis in most treated patients.<sup>8</sup> These two studies will continue for 8 years, and therefore, potentially the relationship between treatment response and fibrosis change could be better established.

Safety outcomes in Chinese patients were consistent with the results previously reported for the global population.<sup>16–18</sup> Overall, both treatments were safe and well tolerated with similar rates of SAEs and Grade 3 or 4 AEs and relatively few events were judged to be related to the study drug. No TAF patients required treatment discontinuation due to an AE and one TDF patient had treatment stopped within the first year after moderate renal impairment developed.

Differences were noted in fasting lipid profiles between TAF and TDF-treated patients, a finding that has been reported by other researchers.<sup>18,23,24</sup> In Chinese CHB patients, TDF treatment resulted in median decreases in HDL, LDL, and total cholesterol, as well as in triglycerides, which is consistent with its known lipid-lowering effect.<sup>23,24</sup> In comparison, TAF treatment produced decreases in total and HDL cholesterol (however, they were smaller in magnitude than TDF), and small increases in LDL and triglycerides were observed. The impact of TDF on fasting lipids has been reported to be correlated with increased plasma levels of TFV;<sup>23</sup> given that TFV exposures were approximately 90% lower when treated with TAF versus TDF,<sup>15</sup> this could explain these differences. The small difference observed between treatments in total cholesterol to HDL ratio change, as well as the small percent of TAF patients (1%) that started on statin therapy during the trial, the lipid differences were probably not clinically important for most patients. This point was recently made by the authors of a meta-analysis that involved >6,000 HIV-1-infected patients that participated in 7 randomized, controlled trials that compared TAF-based versus TDF-based antiretroviral therapy.<sup>24</sup> There were more TAF than TDF-treated patients with Grade 3 increases in LDL cholesterol in this pooled analysis; however, the elevations were nearly always transient (i.e., seen during a single study visit) and were in all cases preceded by an elevated baseline level of LDL, which suggested pre-existing hyperlipidemia.

In this analysis, differences that favored TAF versus TDF treatment were seen for several renal and bone safety parameters during the 144 weeks. The findings from this analysis were consistent with the global results where statistically prespecified key bone and renal safety endpoints demonstrated a safety benefit with TAF with the stipulation that noninferior efficacy to TDF must be established first.<sup>16–18</sup> Tenofovir, the main metabolite of both prodrugs, is taken up into renal proximal tubular cells via organic anion transporters 1 and 3 (OAT-1 and OAT-3), which is believed to play a central role in TDF-associated nephrotoxicity.<sup>25–27</sup> TAF has greater plasma stability than TDF and is not a substrate for uptake via OAT-1/OAT-3.<sup>14,27</sup> With TAF treatment the circulating levels of TFV are significantly reduced compared with TDF; therefore, there is less TFV available to the kidneys and improved renal safety is seen. This finding was reported in HBV and HIV-infected patients that were treated with TAF in clinical trials for  $\leq 3$  years.<sup>18,23,24,28</sup> In this analysis, significant differences in eGFR<sub>CG</sub> decrease and smaller changes in proximal tubular markers were observed. The results are particularly relevant because 21% of patients that entered these studies reported previous ADV use, a nucleotide antiviral that was previously shown to increase the potential risk of proximal tubulopathy when TDF was then used.<sup>29,30</sup>

The serial assessments of BMD by DXA were an important component of safety monitoring in TDF and TAF clinical programs for many years.<sup>16–18,23,24</sup> In this report, BMD was only assessed in a subset of patients at sites in China that could perform these scans. Apart from the subjects being a little older (mean age 40 versus 36 years;  $p = 0.002$ ), there were no notable differences between those enrolled at sites without ( $n = 186$ ) or with ( $n = 148$ ) DXA capability, which supports the BMD results generated were probably representative of the overall population. Over 3 years, TAF patients had only small changes in hip or spine BMD compared with the declines observed with TDF. Although the magnitude of BMD changes reported in this study was slightly different from the results in the global population (where all patients underwent DXA scanning),<sup>18</sup> these results confirm a differential difference in BMD in Chinese CHB patients that received TAF versus TDF.

This study has several limitations: the sample sizes for

the two studies could not confirm non-inferiority in efficacy; however, they were based on demonstrating comparability with global data to meet local registration requirements. Similar to the global studies, the inclusion of patients that were at a higher risk of TDF-associated bone and renal complications (e.g., older age, comorbidities including hyperlipidemia, history of bone, or renal disease, or both)<sup>7,8</sup> was limited; additional data from these more vulnerable populations are required. Finally, viremic patients with elevated levels of serum ALT were included, who meet the criteria to initiate treatment.<sup>7,8</sup> Additional studies on Chinese patients that are virally suppressed and changed to TAF from TDF or ETV would be beneficial, as would real world cohort studies that evaluate the use of TAF in clinical practice.

In conclusion, in CHB patients from China that were treated with TAF or TDF for 3 years, similar efficacy at suppressing HBV replication was found with no virologic resistance, and ALT normalization rates were higher with TAF. The safety results showed that TAF was well tolerated and was associated with less impact on bone and renal safety, as previously reported in the global HBV program.

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### Conflict of interest

Jinlin Hou has served as a consultant for AbbVie, Arbutus, Bristol Myers Squibb, Gilead Sciences, Johnson & Johnson, Roche and received grants from Bristol Myers Squibb, Gilead, and Johnson & Johnson. Qin Ning has served as a consultant for Gilead Sciences, Johnson & Johnson, AbbVie, Roche, Bristol-Myers Squibb, MSD, and has received research funding from Bristol-Myers Squibb, Roche, and Gilead Sciences. Qing Xie has served as a consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Johnson & Johnson, and Roche, and has received grants from Gilead Sciences. Shanming Wu has served as a consultant for Gilead Sciences, AbbVie, GSK, Bristol-Myers Squibb, and MSD, and has received research funding from Bristol-Myers Squibb, Roche, AbbVie, and Gilead Sciences. Hong Tang has served as a consultant for Gilead Sciences, MSD, AbbVie, GSK, Bristol-Myers Squibb, and has received research funding from Bristol-Myers Squibb, Roche, and Gilead Sciences. Jun Li has served as a consultant for Gilead, MSD, AbbVie, GSK, and Bristol-Myers Squibb. John F. Flaherty, Anuj Gaggar, Gregory Camus, Cong Cheng, and Shuyuan Mo are employees and stockholders of Gilead Sciences. Chengwei Chen has served as a consultant for Gilead, AbbVie, GSK, Bristol-Myers Squibb, MSD and received research funds from Bristol-Myers Squibb, Roche, AbbVie, and Gilead. Jidong Jia has served as a consultant for AbbVie, Bristol-Myers Squibb, Gilead and GSK, and received research funds from Bristol-Myers Squibb and Gilead. The other authors have no conflict of interests related to this publication.

### Author contributions

Contributed to the study concept and design (JH, JFF, AG),

the acquisition of data (JH, ZD, YC, QX, FSW, LZ, SW, HT, JL, FL, YY, GG, CC, YH, JJ, MZ, QN), and the statistical analysis (SM). All authors contributed to the analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content.

## Data sharing statement

All data are available upon request.

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