Randomised clinical trial: 48 weeks of treatment with tenofovir amibufenamide versus tenofovir disoproxil fumarate for patients with chronic hepatitis B

Zhihong Liu1 | Qinglong Jin2 | Yuexin Zhang3 | Guozhong Gong4 | Guicheng Wu5 | Lvfeng Yao6 | Xiaofeng Wen7 | Zhiliang Gao8 | Yan Huang8 | Daokun Yang9 | Enqiang Chen11 | Qing Mao12 | Shide Lin13 | Jia Shang14 | Huanyu Gong15 | Lihua Zhong16 | Huafa Yin17 | Fengmei Wang18 | Peng Hu19 | Ling Xiao20 | Chuan Li20 | Qiong Wu20 | Chang’an Sun20 | Junqi Niu2 | Jinlin Hou1 | the TMF Study Group

Summary

Background: Tenofovir amibufenamide (TMF) can provide more efficient delivery than tenofovir disoproxil fumarate (TDF).

Aim: To compare the efficacy and safety of TMF and TDF for 48 weeks in patients with chronic hepatitis B (CHB).

Methods: We performed a randomised, double-blind, non-inferiority study at 49 sites in China. Patients with CHB were assigned (2:1) to receive either 25 mg TMF or 300 mg TDF with matching placebo. The primary efficacy endpoint was the proportion of patients with hepatitis B virus (HBV) DNA less than 20 IU/mL at week 48. We also assessed safety, particularly bone, renal and metabolic abnormalities.

Results: We randomised 1002 eligible patients. The baseline characteristics were well balanced between groups. After a median 48 weeks of treatment, the non-inferiority criterion was met in all analysis sets. In the HBeAg-positive population, 50.2% of patients receiving TMF and 53.7% receiving TDF achieved HBV DNA less than 20 IU/mL. In the HBeAg-negative population, 88.9% and 87.8%, respectively, achieved HBV DNA less than 20 IU/mL in the TMF and TDF groups. Patients receiving TMF had significantly less decrease in bone mineral density at both hip (P < 0.001) and spine (P < 0.001), and a smaller increase in serum creatinine at week 48 (P < 0.05). Other safety results were similar between groups.

Conclusion: TMF was non-inferior to TDF in terms of anti-HBV efficacy and showed better bone and renal safety. (NCT03903796).
1 | INTRODUCTION

Hepatitis B virus (HBV) infection is a global health problem. The World Health Organization estimates that approximately 257 million people, 3.5% of the global population, live with chronic HBV infection.\(^1\) Although the immune tolerance phase of chronic HBV infection usually lasts 10-30 years, chronic hepatitis B (CHB) can cause progressive liver fibrosis, cirrhosis and hepatocellular carcinoma once immune activation occurs.\(^2\) In 2015, there were 0.9 million deaths due to hepatitis B globally.\(^3\) In China, the mortality from HBV-related cirrhosis has recently decreased to 3.9/100 000 patient-years, but HBV-related liver cancer is still progressively increasing to 16.42/100 000 patient-years.\(^4,5\)

Anti-viral treatment for HBV has been shown to halt or even reverse disease progression.\(^6,7\) Up to date, eight drugs are licensed for the treatment of CHB to prevent disease progression and within which, entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide are recommended by most regional guidelines as first-line therapies.\(^8-10\) Due to the persistency of HBV covalently closed circular DNA, the cure of CHB can rarely be achieved and the anti-HBV treatment with nucleos(t)ide analogues is generally life-long.\(^2\) For entecavir, the 5-year resistance mutation rate is about 1.5% in treatment naïve patients and it is less potent in lamivudine-resistance patients.\(^11-13\) The safety concern of TDF, mainly about renal toxicity and decreases in bone mineral density was a consistent focus of attention since it went on the market.\(^14-16\) Tenofovir alafenamide, as a new formulation of tenofovir, has demonstrated its superior renal and boned safety in its registrational studies.\(^17,18\) However, numerically lower proportion of virological response was observed in HBeAg-positive patients for the first 57 weeks of treatment.\(^18\) In addition, some observational studies have raised new safety concerns that regimens with tenofovir alafenamide may lead to weight gain and dyslipidaemia in HIV or CHB patients.\(^19-22\)

Some novel treatments, for example RNA interference, capsid inhibitors or toll-like receptors are going into phase II studies. Among them, RNA interference therapy has shown an excellent effect on reducing quantitative HBsAg,\(^23\) but one should also be noted that no drug seems to be able to cure CHB alone at present.\(^24\) Hence, nucleos(t)ide analogues are still the most effective and reliable treatment options for inhibiting disease progression in the next 5 years. Additionally, the availability of anti-viral treatments is still a global issue. Safer and more reliable treatment options for CHB patients are still of great importance to the goal of the World Health Organization to eliminate viral hepatitis in the year 2030.\(^25\)

Tenofovir amibenfamide (TMF; codename: HS-10234), another formulation of tenofovir, shared the same ProTide technology as tenofovir alafenamide, which can provide more efficient intracellular delivery than TDF.\(^26\) Structurally, it has one more methyl group and provides a lower median effective concentration than tenofovir alafenamide. A Phase 1b study has already provided the efficacy and tolerability of TMF for 28 days of treatment in CHB patients.\(^27\) Hence, we conducted this randomised control trial to compare the efficacy and safety of TMF vs TDF in treatment-naïve or treatment-experienced CHB patients.

Currently, TMF is approved in mainland China and planning to submit for registration in the United States.

2 | METHODS

2.1 | Study design and participants

Before enrolment began and any study procedures were performed, written informed consent was obtained from all patients. The study was approved by the Institutional Review Board or independent ethics committees at all participating sites and it was performed in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. This study is registered with clinicaltrials.gov, number NCT03903796.

This was a phase 3, randomised, double-blind, non-inferiority study conducted at 49 centres across 15 provinces in mainland China. Patients aged 18–65 years with CHB infection (HBV DNA concentrations of at least 20 000 IU/mL with positive or negative HBeAg) were enrolled, with ALT concentrations between one and 10 times the upper limit of normal (ULN), as measured by a local laboratory, and an estimated creatinine clearance of at least 50 mL/min (according to the Cockcroft-Gault method) were enrolled. We excluded patients with platelet counts of \(50 \times 10^9\) cells per L or less, haemoglobin of less than 10 g/dL, albumin of less than 3 g/dL and total bilirubin of more than 2.5 times the ULN. Patients with evident decompensation (ie clinical ascites, encephalopathy or variceal haemorrhage) and those with HCC were also excluded. Patients who have received <12 weeks of treatment with any nucleos(t)ide analogues were defined as treatment naïve; otherwise, patients were defined as treatment-experienced. Any interferon therapy (both
pegylated and standard interferons) must be completed at least 6 months prior to the baseline visit (Inclusion & exclusion criteria were provided in supplementary appendix).

2.2 Randomisation and masking

Patients who were HBeAg positive and those who were HBeAg negative were studied as two separate cohorts, and they were randomly assigned (at a 2:1 ratio) to receive TMF or TDF within 45 days of screening. All patients received placebo tablets that matched the alternative treatment (i.e., patients assigned to receive TMF also received a matching TDF placebo tablet and vice versa). Patients and investigators were all blinded to the treatment assignment throughout the study. Pre-specified members from the statistics departments of the sponsoring institution were unblinded at the 48-week timepoint to perform the assessments related to the primary endpoint analysis.

The study investigators determined eligibility, obtained participant numbers and received automated treatment assignments via an interactive voice and web response system. The randomisation schedule was generated by an independent third party. Each patient received a unique patient number during randomisation. Randomisation was stratified by screening HBV negativity. The DXA scans were evaluated by a centralised quality control team to ensure that each examination met the requirements.

The 12% non-inferiority margin, accepted by regulatory authorities (Center for Drug Evaluation, National Medical Products Administration, China), was a comprehensive consideration based on the necessary sample size, clinical experts’ opinion and the results of TDF and tenofovir alafenamide registrational trials. Nevertheless, none of these trials used HBV DNA <20 IU/mL as a primary endpoint standard; instead, they used 29 or 69 IU/mL. Even under a lower 29 IU/mL standard, the 12% non-inferiority margin could preserve at least

2.3 Procedures

The patients received TMF 25 mg orally once daily or TDF 300 mg orally once daily. Study visits occurred every 4 weeks starting at treatment week 4 until treatment week 12, after which study visits occurred every 12 weeks. Study drugs were counted by research staffs every 12 weeks to assess adherence. Laboratory assessments included haematological analysis, serum chemistry tests, fasting lipid parameters and measures of renal function (serum creatinine, estimated glomerular filtration rate, proteinuria). Serum samples were collected for backup at each visit. In case of virological breakthrough (HBV DNA increased more than 1 log₁₀ IU/mL from nadir or became detectable if once undetected), a genotypic resistance test would be carried out on the backup serum samples collected at baseline, and the visit period at the viral breakthrough occurred. The percentage change in bone mineral density was assessed in all patients by dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine and hip at screening and every 24 weeks thereafter. The DXA scans were evaluated by a centralised quality control team to ensure that each examination met the requirements; in particular, they ensured that the patient’s body position was consistent with the baseline (slight rotation of the hip or lumbar spine will lead to false differences).

Biomarkers of bone turnover were also assessed, including C-type collagen sequence (CTX, associated with bone resorption) and procollagen type 1 N-terminal propeptide (P1NP, associated with bone formation). An optional pharmacokinetics sub-study was performed at the week 36 and 48 visits, opens to all enrolled patients who were willing to provide informed consent.

2.4 Outcomes

The primary efficacy endpoint was the proportion of patients with HBV DNA less than 20 IU/mL at week 48 of treatment, as determined by PCR (COBAS TaqMan HBV Test for use with the High Pure System; Roche Diagnostics), which was assessed at the central laboratory. The lower limit of quantitation of this PCR assay was 20 IU/mL, and the lower limit of detection was 10 IU/mL. Key pre-specified secondary safety endpoints at week 48 included the percentage change in the hip bone mineral density, percentage change in spine bone mineral density and the serum creatinine change from baseline.

Other pre-specified efficacy endpoints were the proportion of ALT normalisation, the proportion of patients with HBsAg seroconversion to anti-HBs at week 48, the proportion of patients with HBeAg loss and with HBeAg seroconversion to anti-HBe at week 48 (HBeAg-positive patients), the incidence of drug-resistant mutations in patients who had virological breakthrough within week 48, and the change in fibrosis, as assessed by the Fibro-4 score (FIB-4; age (years) × AST (IU/L)/[PLT] (×10⁹/L) × √ALT (IU/L)) and liver stiffness measurements (LSM; measured by transient elastography) at week 48. The ALT normalisation was assessed by two sets of criteria, one based on the ULN of each local laboratory and the other was based on the criteria recommended by the American Association for Study of Liver Diseases (AASLD). Adverse events were also assessed.

2.5 Statistical analysis

Considering a 20% drop-out rate, we calculated a total sample size of 963 subjects, with 696 HBeAg-positive patients (464 in the TMF group and 232 in the TDF group) and 267 HBeAg-negative patients (178 in the TMF group and 89 in the TDF group), providing at least 82% power for both subgroups to rule out non-inferiority with a margin of 12% at a one-sided significance level of 2.5%. It assumes that the expected difference in the proportion of patients with HBV DNA <20 IU/mL is zero and that the proportion of patients with HBV DNA <20 IU/mL in the TDF group is 66% for HBeAg-positive patients and 90% for HBeAg-negative patients.

The 12% non-inferiority margin, accepted by regulatory authorities (Center for Drug Evaluation, National Medical Products Administration, China), was a comprehensive consideration based on the necessary sample size, clinical experts’ opinion and the results of TDF and tenofovir alafenamide registrational trials. Nevertheless, none of these trials used HBV DNA <20 IU/mL as a primary endpoint standard; instead, they used 29 or 69 IU/mL. Even under a lower 29 IU/mL standard, the 12% non-inferiority margin could preserve at least
levels at screening (≥8 log10 IU/mL) and oral anti-HBV treatment status (treatment naive vs treatment experienced).

During the study, an independent data monitoring committee reviewed the safety results on five occasions (approximately every 6 months). SAS version 9.4 was used for all analyses.

2.6 | Post hoc safety analysis with special interests

Two post hoc safety analyses with special interests were conducted in the presented study, one focused on osteal and renal abnormalities and the other focused on metabolic abnormalities. Regarding osteal abnormalities, the occurrence of bone mineral deterioration was defined as a bone mineral density decrease in more than 5% from baseline in any one measuring point of the femoral neck, total hip or lumbar spine (L1-L4) at week 24 or week 48. This criterion was amended from the definition of osteoporosis treatment failure by the International Society for Clinical Densitometry. The occurrence of renal function deterioration was defined as an estimated glomerular filtration rate (eGFR) decrease in more than 10% once or 8% twice in a row from baseline. This criterion was adapted from DAIDS recommendations in assessing renal-related adverse events. Beyond the primary safety outcomes, these post hoc analyses may further describe the risk of clinical significant events in the future.

For the post hoc analysis focused on metabolic abnormalities, the results of low-density lipoprotein cholesterol (LDL-C), total cholesterol, high-density lipoprotein cholesterol (HDL-C), total triglyceride, weight, BMI were analysed as continuous variables. It should be noticed that the actual fasting status was not assessed in this post hoc analysis as most patients obeyed the requirements of fasting; the effect of combination treatment of lipid-lowering drugs was not excluded because only 10 patients had received these drugs during the study and all of these drugs were prescribed for a medical history of dyslipidaemia from baseline. Meanwhile, all the related adverse events were carefully reviewed and reported separately.

3 | RESULTS

3.1 | Study population

Of the 1361 patients screened between August 11, 2018, and April 30, 2019, 1005 eligible patients underwent randomisation, and 1002 received at least one dose of the assigned treatment (three withdrew their consent after randomisation; Figure 1). Of the 732 HBeAg-positive patients, 486 were randomised to receive TMF, and 246 received TDF. Of the 270 HBeAg-negative patients, 180 were randomised to receive TMF, and 90 received TDF. All 1002 subjects were included in the full analysis set and safety set analysis. Most patients who did not meet the eligibility criteria had HBV DNA levels lower than 2 × 104 IU/mL, ALT more than 10 times the ULN, prior medical history and haematology or biochemistry parameter abnormalities (Table S1). At week 48, 38 subjects discontinued the study pre-maturely, which means that 964 (96.2%) subjects had completed 48 weeks of study drug treatment. Of these, one patient used forbidden drugs, and 18 patients missed the week 48 visit (See ‘Patient management during the COVID-19 pandemic’. in supplementary appendix). None of them were included in the per-protocol set, which comprised 945 subjects.

In the pooled population and the HBeAg-positive or the HBeAg-negative populations, two treatment groups were well balanced with respect to baseline demographic and clinical characteristics (Table 1). Generally, the median of subjects’ age at baseline was 35 years old, and 72.1% of the subjects were male. The median levels of HBV DNA at baseline were approximately 7.92 (IQR: 6.68-8.23) log10 IU/mL and 5.78 (IQR: 5.06-6.58) log10 IU/mL for the HBeAg-positive patients and HBeAg-negative patients respectively. Thirty-eight percent of the patients had an HBV DNA level equal to or greater than 8 log10 IU/mL. The most common HBV genotype was genotype C (55.8%), followed by genotype B (42.7%) and others. The median ALT level at baseline was 103.35 (IQR:68-167) U/L for HBeAg-positive patients and 84.8 (IQR:58.3-148) U/L for HBeAg-negative patients. The percentage of previous cirrhosis was 19.5% for the HBeAg-positive population and 17.8% for the HBeAg-negative population. For HBV treatment history, 6.6% of the pooled population experienced interferon-based treatment before, and 28.5% of the patients had been previously treated with oral nucleos(t)ide analogues. Of these, entecavir was the most common previous regimen (55.2%), followed by adefovir, TDF and others. The median duration of previous nucleos(t)ide analogues exposure was 366 (IQR: 78-1097) days, while only 22 patients maintained these anti-viral treatments until baseline. For the renal and ostereal function assessment, the median eGFR according to the Epidemiology Collaboration Equation (CKD-EPIsc) was 112.88 (IQR:
104.16-120.89) mL/min × 1.73 m², while 6.79% of the subjects had an eGFR less than 90 units. According to the WHO standard, 10.4% of subjects presented osteopenia at baseline, and very few patients had osteoporosis. Comorbidity distributions (including hypertension, diabetes mellitus, cardiovascular disease and dyslipidaemia) were also balanced between the TMF and TDF groups. The median duration of exposure to the masked study drug at the present analysis was 48 weeks (IQR 47-48) in both groups.

Of treatment naive patients enrolled in this study, 42 might be deemed immune-tolerant. At screening, all of them were HBeAg positive and had a HBV DNA level greater than 7 log₁₀ IU/mL, a LSM less than 7.3 kPa and an ALT level lower than 2 × ULN. However, all the patients in our study were required to provide evidence of abnormal ALT from much earlier dates before screening. Moreover, only three out of these 42 patients had ALT level recovered to normal range at baseline. Hence, few of the included patients would be immune-tolerant in our study.

3.2 | Virological response

Compared with TDF, TMF was non-inferior in virological response as the lower bounds of the 95% CI of the between-group difference were greater than the pre-specified -12% margin, both in the HBeAg-positive or HBeAg-negative population. Specifically, in the HBeAg-positive population, 50.2% of patients achieved HBV DNA levels less than 20 IU/mL at week 48 in the TMF group, compared to 53.7% in the TDF group (Table 2; adjusted difference: -3.4% [95% CI -10.44 to 3.72]; P = 0.353). The mean (SD) decrease in HBV DNA level from baseline was 5.79 (1.089) log₁₀ IU/mL and 5.89 (1.001) log₁₀ IU/mL in TMF group and TDF group respectively (Table S3). In the HBeAg-negative population, 88.9% of patients had HBV DNA levels less than 20 IU/mL at week 48 in the TMF group, compared to 87.8% in the TDF group (Table 2; adjusted difference: 1.2% [95% CI – 6.73 to 9.12]; P = 0.767). The mean (SD) decrease in HBV DNA level from baseline was 5.34 (1.774) log₁₀ IU/mL and 5.36 (1.961) log₁₀ IU/mL in TMF group and TDF group respectively. The results of the pre-specified per-protocol set were consistent with those of the primary analysis, showing that TMF was non-inferior to TDF in terms of anti-viral efficacy (Figure 2).

The virological response rates according to HBV DNA levels less than 29 IU/mL, less than 69 IU/mL at week 48 were also obtained and no significant differences were observed between treatment groups (Figure S2 and Table S2). Among those HBeAg-positive subjects, 55.3% of the TMF group and 57.3% of the TDF group achieved HBV DNA levels less than 29 IU/mL at week 48; 73.0% of the TMF group and 77.2% of the TDF group had HBV DNA levels less than 69 IU/mL at week 48. Among those HBeAg-negative subjects, more than 95% of patients in both groups achieved HBV DNA levels less than 69 IU/mL at week 48. For the 42 patients who seemed to be in immune-tolerant phase, the median (IQR) decline of HBV DNA level from...
| TABLE 1 Baseline characteristics |
|----------------------------------|
|                                  | TMF 25 mg (N = 666) | TDF 300 mg (N = 336) | Total (N = 1002) |
| Age (years)                      | 35 (29-44)          | 35 (28-45)          | 35 (29-44)       |
| Male (%)                         | 480 (72.1)          | 243 (72.3)          | 723 (72.2)       |
| Body mass index (kg/m²)          | 23.2 (21.21-25.48)  | 23.1 (21.11-25.53)  | 23.2 (21.16-25.51) |
| HBeAg positive (%)               | 486 (73.0)          | 246 (73.2)          | 732 (73.0)       |
| HBV-DNA (log_{10} IU/mL)         |                     |                     |                  |
| Pooled                           | 7.28 (5.86-8.23)    | 7.34 (5.86-8.23)    | 7.31 (5.86-8.23) |
| HBeAg positive                   | 7.93 (6.61-8.23)    | 7.91 (6.75-8.23)    | 7.92 (6.68-8.23) |
| HBeAg negative                   | 5.82 (5.06-6.58)    | 5.72 (5.08-6.54)    | 5.78 (5.06-6.58) |
| HBV-DNA ≥8 log_{10} IU/mL        | 253 (37.9%)         | 128 (38.1%)         | 381 (38.0%)      |
| HBV genotype (%)                 |                     |                     |                  |
| B                                | 285 (42.8)          | 143 (42.6)          | 428 (42.7)       |
| C                                | 372 (55.9)          | 187 (55.7)          | 559 (55.8)       |
| Others                           | 9 (1.4)             | 6 (1.8)             | 15 (1.5)         |
| ALT (U/L)                        | 98.6 (65-163)       | 99.95 (62.7-157.5)  | 99 (64-162)      |
| HBeAg positive                   | 104.5 (68-167.3)    | 101.45 (69-164)     | 103.35 (68-167)  |
| HBeAg negative                   | 87.5 (60.75-153.1)  | 82.5 (53-146.2)     | 84.8 (58.3-148)  |
| Previous cirrhosis (%)           |                     |                     |                  |
| Pooled                           | 125 (18.8)          | 66 (19.64)          | 191 (19.1)       |
| HBeAg positive                   | 95/486 (19.5)       | 48/246 (19.5)       | 143/732 (19.5)   |
| HBeAg negative                   | 30/180 (16.7)       | 18/90 (20.0)        | 48/270 (17.8)    |
| Previously treated for HBV (%)   |                     |                     |                  |
| Any interferon                   | 46 (6.9)            | 20 (6.0)            | 66 (6.6)         |
| Any Nucleot(s)ide               | 190 (28.5)          | 96 (28.6)           | 286 (28.5)       |
| Analogues (%)                    |                     |                     |                  |
| Entecavir                        | 100 (15.0)          | 58 (17.3)           | 158 (15.8)       |
| Adefovir                         | 49 (7.4)            | 23 (6.8)            | 72 (7.2)         |
| TDF                              | 37 (5.6)            | 10 (3.0)            | 47 (4.7)         |
| eGFR-EPIscr (mL/min × 1.73 m²)   | 113.13 (104.75-121.65) | 111.82 (102.99-120.13) | 112.88 (104.16-120.89) |
| eGFR<90 mL/min × 1.73 m²         | 44 (6.6%)           | 24 (7.14%)          | 68 (6.79%)       |
| Bone mineral density by DXA (g/cm²) |                     |                     |                  |
| Total hip                        | 0.94 (0.86-1.02)    | 0.94 (0.86-1.02)    | 0.94 (0.86-1.02) |
| Femur neck                       | 0.84 (0.75-0.94)    | 0.84 (0.75-0.95)    | 0.84 (0.75-0.94) |
| Lumbar spine (L1-L4)             | 1.091 (1.11)        | 1 (0.92-1.1)        | 1 (0.92-1.11)    |
| Osteopenia by WHO standard (%)   | 77 (11.6)           | 27 (8.0)            | 104 (10.4)       |
| Osteoporosis by WHO standard (%) | 4 (0.6)             | 1 (0.3)             | 5 (0.5)          |
| Comorbidities (%)                |                     |                     |                  |
| Diabetes mellitus                | 18 (2.7)            | 8 (2.4)             | 26 (2.6)         |
| Dyslipidaemia                    | 126 (18.9)          | 48 (14.3)           | 174 (17.4)       |
| Hypertension                     | 38 (5.7)            | 21 (6.3)            | 59 (5.9)         |
| Cardiovascular disease           | 54 (8.1)            | 27 (8.0)            | 81 (8.1)         |

Data are n (%), n/N (%) or median (IQR).

Abbreviations: DXA, dual energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate; EPIscr, chronic kidney disease epidemiology collaboration serum creatinine equation; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LLN, lower limit of normal range; ULN, upper limit of normal range.

The proportion of previously treated HBV patients were similar in HBeAg-positive and -negative population.

Patients were diagnosed as cirrhosis by transient elastography under different ALT levels.

Comorbidities were collected according to medical history.
The baseline HBV DNA levels were 5.87 (5.42, 6.36) log_{10} IU/mL and 16 patients achieved HBV DNA levels less than 6.9 IU/mL at week 48 (Table S14). The change in HBV DNA levels by visit presented a continuous decline from weeks 4 to 48 and was similar for the two groups in each population (Table S3 and Figure S1). An evaluation of the treatment response in subgroups defined by baseline characteristics showed no significant interactions, including age (≥50 years vs < 50 years), sex, HBV genotype (B vs C), treatment status (naive vs experienced), baseline HBV DNA (≥8 log_{10} IU/mL vs < 8 log_{10} IU/mL), baseline ALT (>ULN vs ≤ULN), and treatment compliance (≥95% vs < 95%; Table S5 and Figure S3).

In the pooled population, only four patients experienced HBV DNA increase in more than 1 log_{10} IU/mL from nadir or became detectable after undetected. Resistance surveillance was conducted according to the protocol. Mutations (rtv173L + rtL180M + rtM204V) were detected in one treatment-experienced patient in TMF group and were all proved to be pre-existing by baseline samples.

### 3.3 Other efficacy endpoints

For the HBeAg-positive patients, the rate of HBeAg loss in patients receiving TMF was 17.2% (82/478) at week 48, which was not significantly different from that in patients receiving TDF (15.9% [39/246]). For the patients with positive HBeAg and negative HBeAb, no significant difference was detected between the two treatment groups in the incidence rate of seroconversion (Table 2). At week 48, only one patient achieved HBsAg loss, but the seroconversion was not observed.

After 48 weeks of treatment, the observed median (IQR) decrease in ALT level from baseline was −68.5 (−137, −32) U/L in patients receiving TMF, which was statistically larger than −60.6 (−125.4, −26) U/L in patients receiving TDF. Regarding ALT normalisation according to local laboratory criteria (ULN range from 35 to 72 U/L for men, 35 to 69 U/L for women), there was no significant difference in all populations (Table 2). However, when the ULN recommended by the AASLD was adopted (≤35 U/L for male and ≤25 U/L for female), the proportion of ALT normalisation in the TMF group was statistically higher than that in the TDF group in the pooled populations. The rates of ALT normalisation were 72.1% in the TMF group and 64.6% in the TDF group, with an adjusted difference of 7.4% (95% CI 1.22-13.63; P = 0.017). In HBeAg-positive population, a significant difference was also observed. In contrast, the ALT normalisation rate in HBeAg-negative population was just numerically higher in TMF group than that in the TDF group. The rates of ALT normalisation were 74.6% in the TMF group and 67.4%
in the TDF group, with an adjusted difference of 7.2% (95% CI −4.79 to 19.12; P = 0.229) in the HBeAg-negative population. Regarding AST level, the observed median (IQR) decrease from baseline was −34.6 (−73.6, −15) U/L in patients receiving TMF, which was statistically larger than −32.5 (−68.3, −12) U/L in patients receiving TDF.

The regression of liver fibrosis was assessed by FIB-4 score and LSM in this study (Tables S6 and S7). The values of FIB-4 scores and LSM have all significantly decreased from baseline in both treatment groups. For the HBeAg-positive patients, a significantly greater decline of FIB-4 score was observed in patients receiving TMF than TDF (−0.48 ± 0.026 vs −0.35 ± 0.034, with a least-squares method difference of −0.12; P = 0.002). This inter-group difference was not observed in HBeAg-negative populations. The decrease in LSM at week 48 from baseline was not significantly different between the TMF group and the TDF group, either in HBeAg-positive or -negative population.

### 3.4 General safety

Generally, both study treatments were well tolerated (Table 3). Most adverse events were mild to moderate in severity. There are 613 (92.0%) patients receiving TMF and 303 (90.2%) patients receiving TDF experienced adverse events during 48 weeks of treatment. For these, only half were deemed as study drug related. The incidence of grade 3 or 4 adverse events (18.2%-16.4%) was slightly higher than expected. Notably, the grade 3 or 4 laboratory abnormalities were not reported separately in our study (Table S13; grade 3 or 4 laboratory abnormalities: TMF 12.5% vs TDF 10.1%). The incidence of grade 3 or 4 study-drug-related adverse events was low and distributed equally in each group (TMF 12.5% vs TDF 10.1%). The incidence of grade 3 or 4 study-drug-related adverse events was low and distributed equally in each group (TMF 12.5% vs TDF 10.1%). Serious adverse events, discontinuation of treatment due to adverse events, primary liver cancers and deaths, were uncommon in this study (Table 3).

Specifically, adverse events with an incidence ≥5% were upper respiratory tract infection [184 (27.6%) patients receiving TMF vs 75 (22.3%) patients receiving TDF], hyperuricaemia [59 (8.9%) vs 20 (6.0%)], hepatic steatosis [56 (8.4%) vs 19 (5.7%)], nasopharyngitis [51 (7.7%) vs 22 (6.5%)], hypophosphataemia [43 (6.5%) vs 28 (8.3%)] and urinary tract infection [34 (5.1%) vs 18 (5.4%)]. The most common grade 3 and 4 adverse events were abnormal investigations of serum ALT and AST. Of these, nine (1.4%) patients receiving TMF and nine (2.7%) patients receiving TDF experienced an ALT flare that all of these occurred within the first 1-3 months of the
TABLE 3  Adverse events

|                          | TMF 25 mg (n = 666) | TDF 300 mg (n = 336) |
|--------------------------|----------------------|-----------------------|
| Adverse events          | 613 (92.0)           | 303 (90.2)            |
| Adverse events related to study drug | 308 (46.2)          | 177 (52.7)            |
| Grade 3 adverse events  | 121 (18.2)           | 55 (16.4)             |
| Grade 3-4 adverse events related to study drug | 40 (6.0)            | 21 (6.3)              |

Incidence ≥5% adverse events in any treatment group

Investigations

| Condition                                | TMF 25 mg | TDF 300 mg |
|------------------------------------------|-----------|------------|
| Alanine aminotransferase increased       | 135 (20.3)| 64 (19.0)  |
| Aspartate aminotransferase increased     | 95 (14.3) | 50 (14.9)  |
| Blood parathyroid hormone increased      | 67 (10.1) | 37 (11.0)  |
| Blood creatine phosphokinase increased   | 47 (7.1)  | 27 (8.0)   |
| Weight decreased                         | 33 (5.0)  | 39 (11.6)  |
| Bone density decreased                   | 24 (3.6)  | 31 (9.2)   |
| Total bile acids increased               | 35 (5.3)  | 19 (5.7)   |
| Blood bilirubin increased                | 37 (5.6)  | 14 (4.2)   |
| Gamma-glutamyl transferase increased     | 30 (4.5)  | 18 (5.4)   |

Infections and infestations

| Condition                                      | TMF 25 mg | TDF 300 mg |
|-----------------------------------------------|-----------|------------|
| Upper respiratory tract infection             | 184 (27.6)| 75 (22.3)  |
| Nasopharyngitis                               | 51 (7.7)  | 22 (6.5)   |
| Urinary tract infection                       | 34 (5.1)  | 18 (5.4)   |

Gastrointestinal disorders

| Condition          | TMF 25 mg | TDF 300 mg |
|--------------------|-----------|------------|
| Diarrhoea          | 36 (5.4)  | 9 (2.7)    |

Metabolism and nutrition disorders

| Condition                  | TMF 25 mg | TDF 300 mg |
|----------------------------|-----------|------------|
| Hyperuricaemia             | 59 (8.9)  | 20 (6.0)   |
| Hypophosphataemia          | 43 (6.5)  | 28 (8.3)   |

Hepatobiliary disorders

| Condition          | TMF 25 mg | TDF 300 mg |
|--------------------|-----------|------------|
| Hepatic steatosis  | 56 (8.4)  | 19 (5.7)   |

Renal and urinary disorders

| Condition          | TMF 25 mg | TDF 300 mg |
|--------------------|-----------|------------|
| Proteinuria        | 31 (4.7)  | 18 (5.4)   |

Respiratory, thoracic and mediastinal disorders

| Condition                  | TMF 25 mg | TDF 300 mg |
|----------------------------|-----------|------------|
| Cough                      | 37 (5.6)  | 10 (3.0)   |
| Serious adverse events     | 30 (4.5)  | 13 (3.9)   |
| Serious adverse events related to study drug | 0 | 1 (0.3) |
| Discontinuation of treatment due to adverse events | 2 (0.3) | 4 (1.2) |
| Death                      | 0         | 0          |

Data are n (%).

hypertension, thyroid cancer and abnormal liver function. Of these, only one case of serious adverse event was deemed to be related to TDF treatment and none was TMF related. Two patients receiving TMF have permanently discontinued the study drug due to pancreatitis and arthralgia (Tables S11-S13).

3.5  Safety of special interests: bone and renal abnormalities

The safety issues of bone were compared in the pooled population. For bone mineral density, a significantly smaller mean percent decrease was observed in the TMF group, both in the hip and spine bone measurements, when compared with the TDF group at week 48. Regarding hip measurements, we observed a −0.5% ± 0.162 change from baseline in the TMF group and a −2.09% ± 0.213 change in the TDF group. The least-squares mean difference between these two groups reached 1.59% (95% CI: 1.12-2.06; Figure 3A). Regarding spine measurements, we observed a 0.09% ± 0.181 change from baseline for patients receiving TMF and a −1.90% ± 0.239 change for patients receiving TDF, with a least-squares mean difference of 1.99% (95% CI: 1.46-2.52; Figure 3B). A smaller impact of TMF than that of TDF in bone turnover biomarkers was also observed. For bone absorption, patients on TMF treatment had a 7.72% decrease from baseline in β-CTX, while there was a 21.47% increase in patients on TDF treatment. For bone formation, the serum level of P1NP had a 2.27% decrease from baseline in patients receiving TMF and a 1.90% ± 0.239 change for patients receiving TDF, with a least-squares mean difference of 1.99% (95% CI: 1.46-2.52; Figure 3B). A smaller impact of TMF than that of TDF in bone turnover biomarkers was also observed.

For the assessment of renal safety, the mean change in serum creatinine from baseline in each group was compared in the primary analysis. The increase in 0.60 ± 8.988 µmol/L in the TMF group was significantly smaller than the 1.51 ± 7.975 µmol/L in the TDF group, with a least-squares mean difference of −1.12 µmol/L (95% CI: −2.219, −0.027, P = 0.045; Figure 4). Meanwhile, a total of 4.7% (31 of 666) of the patients receiving TMF and 5.4% (18 of 336) of the patients receiving TDF had at least one graded event of proteinuria during the study. No patient in either group experienced adverse events of proximal tubulopathy (including Fanconi syndrome) or renal adverse events resulting in the study drugs discontinuation. Two patients in the TMF group experienced serious adverse events of renal and urinary disorders, which were obstructive nephropathy and renal hydrocele caused by lithiasis.
In the post hoc analysis, renal deterioration was compared by the percentage of eGFR decrease from baseline, which was confirmed by more than 10% once or 8% twice in a row (Table 4). More patients with renal deterioration event were observed in TDF group than in TMF group during 48 weeks of treatment (38.10% vs 29.43%, P < 0.05).

### 3.6 Safety of special interests: metabolic abnormalities

Though the incidence of each specific lipid disorder-related adverse event was less than 5%, a significantly increased incidence of all lipid-related adverse events was observed in the TMF group, compared with the TDF group (11.4% and 3.0% respectively); such events included hypertriglyceridaemia (4.4% and 1.5% respectively), hyperlipidaemia (3.5% and 0.3% respectively) and increased low-density lipoprotein (2.4% and 0 respectively). Among these events, only three patients in the TMF group were deemed as having grade 3 elevations (Table S13), including one patient had grade 4 elevation at baseline and two others cases who had abnormal triglycerides at baseline and experienced transient grade 3 elevation but recovered to baseline level at the next visit.

Based on a higher incidence of lipid disorders, cardiovascular-related events were thoroughly reviewed. Cardiovascular disease was uncommon during 48 weeks of treatment. No myocardial infarction or chronic heart failure was reported and only two cases of ischaemic vascular disease were observed, including one case of cerebral posterior circulation ischaemia and one case of intracranial venous sinus thrombosis. Both of them were not highly dyslipidaemia-related ischaemia. On the other hand, among patients
with dyslipidaemia or cardiovascular diseases at baseline, there are 27 adverse events that might be underlying cardiovascular diseases. The distribution of these adverse events was balanced in each group, including 10 cases of transiently elevated creatine kinase, three cases of transiently elevated creatine kinase MB, four cases of chest pain, and others. None of the severity of these events was considered as more than grade 3 (Table S15).

In the post hoc analysis on metabolic abnormalities, the median (IQR) level of total cholesterol was not significantly different from baseline to week 48 in patients receiving TMF (Table 5). However, slight increases were observed in serum LDL-C and total triglyceride, which is a median change of 0.11 (−0.21, 0.51) mmol/L and 0.05 (−0.2, 0.37) mmol/L respectively. In contrast, all analysed lipid parameters were statistically decreased in patients receiving TDF, with a median change of −0.69 (−1.13, −0.26) mmol/L and −0.3 (−0.61, 0.03) mmol/L and −0.09 (−0.32, 0.11) mmol/L in total cholesterol, LDL-C and total triglyceride respectively. For HDL-C, a significant decrease was observed in both groups, but it was much more intense in patients receiving TDF, which was −0.12 (−0.28, 0.05) mmol/L in the TMF group and −0.26 (−0.44, −0.12) mmol/L in the TDF group. Meanwhile, a significant increase in total cholesterol to HDL-C ratio from baseline to week 48 was observed in both groups, which was 0.28 (−0.11, 0.67) in the TMF group and 0.14 (−0.17, 0.51) in the TDF group. When two study treatments were compared, there were no differences in all lipid parameters at baseline and significantly opposing effects were yielded after 48 weeks of treatment other than HDL-C. Additionally, weight and BMI were also investigated, and both of these parameters increased in patients receiving TMF at week 48 while decreased in patients receiving TDF.

4 | DISCUSSION

In the first 48 weeks of treatment in this randomised control trial, TMF was non-inferior to TDF with respect to all primary and secondary efficacy endpoints in patients with compensated chronic HBV infection.

The non-inferiority of virological response between TMF and TDF was established among the HBeAg-positive or -negative population in all study sets. Meanwhile, the subgroup analysis did not reveal any significant differences between two treatments in subgroups with different baseline characteristics. However, when

### TABLE 4 Bone or renal function deterioration—safety set

| Bone or renal function deterioration | TMF, n = 666 | TDF, n = 336 | P value |
|-------------------------------------|--------------|--------------|---------|
| More than 5% decrease in BMD from baseline at any one spot of femur neck, total hip or lumbar (L1-L4) at week 24 or week 48 | 182 (27.33) | 140 (41.67) | <0.0001 |
| Develop eGFR decreased more than 10% once or 8% twice in a row from baseline | 196 (29.43) | 128 (38.10) | 0.0056 |

Data are n (%).
Abbreviations: BMD, Bone Mineral Density; eGFR, estimated glomerular filtration rate.
**TABLE 5** Metabolic abnormalities in each group at baseline and week 48-full analysis set

| Parameter          | Treatment | Baseline     | Week 48     | Change from baseline | P value |
|--------------------|-----------|--------------|-------------|----------------------|---------|
|                    |           |              |             | Intra-group          | Inter-group |
| TC (mmol/L)        | TMF       | 4.55 (3.96, 5.19) | 4.54 (4.01, 5.2) | 0.01 (−0.43, 0.47) | 0.4567  | 0.8176 <0.0001 |
|                    | TDF       | 4.59 (4.515) | 3.91 (3.43, 4.41) | −0.69 (−1.13, −0.26) | <0.0001 | <0.0001 |
| LDL-C (mmol/L)     | TMF       | 2.61 (2.08, 3.38) | 2.73 (2.24, 3.26) | 0.11 (−0.21, 0.51) | <0.0001 | 0.6871 <0.0001 |
|                    | TDF       | 2.59 (2.13, 3.1) | 2.3 (1.95, 2.78) | −0.3 (−0.61, 0.03) | <0.0001 | <0.0001 |
| HDL-C (mmol/L)     | TMF       | 1.39 (1.16, 1.64) | 1.27 (1.09, 1.5) | −0.12 (−0.28, 0.05) | <0.0001 | 0.2127 <0.0001 |
|                    | TDF       | 1.38 (1.2, 1.68) | 1.11 (0.97, 1.33) | −0.26 (−0.44, −0.12) | <0.0001 | <0.0001 |
| TC/HDL-C ratio     | TMF       | 3.26 (2.73, 3.93) | 3.59 (2.98, 4.25) | 0.28 (−0.11, 0.67) | <0.0001 | 0.1768 0.0083 |
|                    | TDF       | 3.2 (2.72, 3.88) | 3.35 (2.94, 4) | 0.14 (−0.17, 0.51) | <0.0001 | <0.0001 |
| Triglyceride (mmol/L) | TMF       | 1.03 (0.81, 1.35) | 1.1 (0.77, 1.53) | 0.05 (−0.2, 0.37) | <0.0001 | 0.5667 <0.0001 |
|                    | TDF       | 0.99 (0.79, 1.31) | 0.9 (0.66, 1.2) | −0.09 (−0.32, 0.11) | <0.0001 | 0.0003 |
| Weight (kg)        | TMF       | 65 (58, 73.5) | 66 (58, 74.2) | −0.8 (−0.9, 2.5) | <0.0001 | 0.9204 <0.0001 |
|                    | TDF       | 65.03 (57, 74) | 63 (56, 70.8) | −1 (−3, 0.5) | <0.0001 | <0.0001 |
| BMI                | TMF       | 23.24 (21.21, 25.48) | 23.73 (21.22, 25.71) | 0.28 (−0.32, 0.87) | <0.0001 | 0.8218 <0.0001 |
|                    | TDF       | 23.11 (21.11, 25.53) | 22.49 (20.88, 24.62) | −0.38 (−1.07, 0.2) | <0.0001 | <0.0001 |

Data are median (IQR).

Median of TC, LDL, HDL, TC/HDL-C and TG use Wilcoxon signed-rank test for intra-group comparison, Wilcoxon rank-sum test for inter-group comparison. Mean of Weight and BMI use paired t-test for intra-group comparison, analysis of covariance (ANCOVA) for inter-group comparison. Abbreviations: HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; TC, total cholesterol.
advocate a further investigation or longer follow-up on the benefits of fibrosis regression.

Besides the non-inferiority in anti-viral efficacy, two study treatments presented different characteristics on safety profiles. Generally, both 25 mg TMF and 300 mg TDF appeared to be safe and well tolerated and the incidence of adverse events, serious adverse events and laboratory abnormalities were similar in each group. However, TMF presented a better safety profiles for bone mineral and renal function while TDF was found to have a unique lipid lowering effects.

The side effect of long-term TDF treatment on hip and spine bone mineral density has been confirmed in patients with HIV infection and chronic HBV infection.\textsuperscript{16,35-37} In this study, the benefit of less bone mineral density decrease was observed in the TMF group over the TDF group, with adjusted percentage differences of 1.12%-2.06% or 1.46%-2.52% in hip or spine respectively. Lower incidence of hypophosphataemia and osteoporosis and less increase in bone turnover markers in the TMF group also confirmed this advantage. Moreover, there are 14.34% more patients in TDF group than TMF group experienced osteal deterioration event, which is more reflective to indicate a clinically significant damage (Table 4). It should be notice that we have enrolled a young population in this study. Bone mineral density decreases continuously after it reaches the peak around 30-40 years old, and the rate of loss increases with age.\textsuperscript{38,39} 48 weeks of TDF treatment in our study lead to about 2% decrease in hip or spine bone mineral density in a median 35-year-old population. In comparison, a larger detrimental impact of TDF was witnessed with older ages in tenofovir alafenamide registral trial in HBeAg-negative patients.\textsuperscript{17} Further study on older populations is needed to measure the increased incidence of fragility fracture for this effect.

For progressive renal dysfunction, a higher risk was observed in the TDF treatment. In other words, it indicated better renal safety in the TMF treatment. In the present study, patients in the TMF group had a significantly smaller increase in serum creatinine compared with those receiving TDF. Besides, 8.67% more patients with renal deterioration event were observed in the TDF group than in the TMF group. Previously, renal tubular injury such as proximal tubular disease and Fanconi syndrome caused by long-term use of TDF was already reported by other studies.\textsuperscript{14,15,40,41} A 10-year clinical study showed that 5.1% of CHB patients had renal insufficiency during TDF treatment.\textsuperscript{42} Therefore, TMF may be a better choice for the long-term treatment of CHB patients, especially for those at risk of renal impairment.

Besides the benefits in the prevention of osteal and renal toxicity of TDF, tenofovir alafenamide treatment was reported with a higher incidence of dyslipidaemia and weight gain in CHB and HIV patients.\textsuperscript{17,18,43} Similarly, a significantly higher incidence of dyslipidaemia and more weight gain was observed with the TMF treatment than TDF treatment. However, we did not observe more direct evidence rather than laboratory abnormalities. The incidence of grade 3 or 4 dyslipidaemia in TMF group was uncommon and all cases were resolvable. As major adverse outcomes of dyslipidaemia, the incidence of cardiovascular disease or relevant abnormalities was low and distributed equally in two treatment groups, even in patients who already had dyslipidaemia or cardiovascular disease at baseline. In fact, we observed a lowering effect rather than less increase by TDF treatment in all lipid parameters, even in serum HDL-C. Another study may explain this effect that TDF decreased serum cholesterol levels by upregulating hepatic CD36 via PPAR-\(\alpha\) activation.\textsuperscript{14} It was previously reported that the incidence of metabolic syndrome, dyslipidaemia or abdominal obesity increases in CHB patients after virological response achieved.\textsuperscript{45,46} Hence, it seems that the lowering dosage benefit by ProTide technology in TMF or tenofovir alafenamide deprived the lipid lowering effect of TDF at the same time.

Comparing with LDL-C levels, the total cholesterol to HDL-C ratio is a stronger predictor of cardiovascular disease.\textsuperscript{47} In our study, both TMF and TDF treatment presented a significant increase in this ratio. Based on this, we could not conclude that the more decrease in lipid parameters of TDF will turn into benefits of cardiovascular disease. Additionally, weight and BMI were increased in patients receiving TMF but reduced in patients receiving TDF. However, the extent of change was quite small and most patients were still within a normal BMI after 48 weeks of treatment. Hence, the pros and cons of this effect was unable to be adjudicated.

Good trial quality was warranted by a low drop-out rate (4.1%), and good compliance was observed in this study. However, there are still several limitations. First, a comparator arm utilising tenofovir alafenamide was not included as it had not come into the market in mainland China at the study initiation. However, TDF is still one of first-line options and we also observed a lipid-lowering effect of TDF in this study. Furthermore, though increase in total cholesterol to HDL-C ratio was observed, the increased risk of cardiovascular in 10 years was not obtained as abdomen circumference was not collected in this study.\textsuperscript{48} Meanwhile, it should be pointed out that the enrolled subjects were relatively young but we are facing an aging population of CHB nowadays. Based on these limitations, this study has been extended into a 10-year real-world cohort with control groups of entecavir or tenofovir alafenamide and more complete investigations included.

In conclusion, TMF offers a better treatment choice with non-inferior efficacy, a higher rate of ALT normalisation and a better osteal and renal safety profile than TDF for CHB patients. Although losing the lipid lowering effect, TMF was not confirmed to have an increased risk of cardiovascular disease than TDF. Hence, we believed TMF 25 mg QD can be recommended for the treatment of adult patients with HBeAg-positive or HBeAg-negative CHB.

**ACKNOWLEDGEMENTS**

We thank all the investigators, staffs, all the subjects and their families for their help in completing this trial during the outbreak of the COVID-19 pandemic. We thank Ziyang Liu for carefully review the data and also appreciate him and Huifeng Zhang, and Moran Zhang for providing help with manuscript preparation.

_Declaration of personal interests:_ Zhihong Liu has served as a speaker for Bristol-Myers Squibb (BMS), Gilead Sciences and Hansoh
Pharma. Qinglong Jin has served as a speaker for Abbott, Amoytop Biotech, Chiatai Tianqinig, Gilead and has received research funding from Kawin Technology, Chiatai Tianqinig, Hansho Pharma, Johnson & Johnson (J&J), BMS, HEC Pharmaceutical, TaiGen Biotechnology, Gilead Science. Junqi Niu has served as a speaker for and has received research funding from HEC Pharmaceutical, Xintong Pharmacy, Hansho Pharma, Qilu Pharmaceutical, Kelun Industry, Roche, J&J, GSK, Assembly, Gilead, Bree Biosciences, Huahui Health, Zhimeng Biopharma, Hengrui Medicine, Aligos, Hepu Pharmaceutical, Ascleitis Pharma, Sanhome, Ginkgo pharma, Changzhou Yinsheg pharmacy. Jinlin Hou has received consulting fee from AbbVie, Arbutus, BMS, Gilead Sciences, J&J, Roche and received grants from BMS and J&J. Ling Xiao, Chuan Li, Qiong Wu, Chang’an Sun are employees of Hansho Pharmacy Co. The other authors have nothing to disclose.

Declaration of funding interests: This study was funded in full by Hansho Pharmacy Co. Initial data analyses were undertaken by C.L who is employee of Hansho Pharmacy Co.

AUTHORSHIP
Guarantor of the article: J.H and J.N
Author contributions: J.H., J.N. and, C.S. and Z.H.L. involved designed the study conception and design. The TMF Study Group carried out acquisition of the research and collected the data. C.L. carried out statistical analysis. Z.H.L. and X.L. involved in interpretation of the data and drafting the manuscript. All authors involved in critical revision of the manuscript for important intellectual content. All the authors approved the final draft version of the manuscript.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from Hansho Pharmacy Co. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from Jinlin Hou with the permission of Hansho Pharmacy Co.

ORCID
Zhifang Liu https://orcid.org/0000-0003-1142-3589
Enqiang Chen https://orcid.org/0000-0002-8523-1689
Shide Lin https://orcid.org/0000-0001-8803-4069
Peng Hu https://orcid.org/0000-0001-8481-0841
Junqi Niu https://orcid.org/0000-0002-9857-6520
Jinlin Hou https://orcid.org/0000-0001-8230-8583

REFERENCES
1. World Health Organization (2017). Global hepatitis report. https://www.who.int/publications/i/item/global-hepatitis-report-2017. Accessed June 15, 2021.
2. Trépo C, Chan HLY, Lok A. Hepatitis B virus infection. Lancet. 2014;384:2053–2063.
3. World Health Organization. Hepatitis B. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
4. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the Global, Regional, and National Level. JAMA Oncol. 2017;3(12):1683–1691.
5. Liu J, Liang W, Jing W, Liu M. Countdown to 2030: eliminating hepatitis B disease, China. Bull World Health Organ. 2019;97:230–238.
6. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet. 2013;381:468–475.
7. Peng C-Y, Chien R-N, Liaw Y-F. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy. J Hepatol. 2012;57:442–450.
8. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67:370–398.
9. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560–1599.
10. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10:1–98.
11. Tenney DJ, Rose RE, Baldick CJ, et al. Long-term monitoring shows hepatitis B virus resistance to entecavir in nucleoside-naïve patients is rare through 5 years of therapy. Hepatology. 2009;49(5):1503–1514.
12. Gish RG, Lok AS, Chang T, et al. Entecavir therapy for up to 96 weeks in patients with HBeAg-positive chronic hepatitis B. Gastroenterology. 2007;133:1437–1444.
13. Sherman M, Yurdadaycin C, Simsek H, et al. Entecavir therapy for lamivudine-refractory chronic hepatitis B: improved virologic, biochemical, and serology outcomes through 96 weeks. Hepatology. 2008;49:99–108.
14. Gracey DM, Smelling P, McKenzie P, Strasser SI. Tenofovir-associated Fanconi syndrome in patients with chronic hepatitis B monoinfection. Antivir Ther. 2013;18:945–948.
15. Maggi P, Montinaro V, Leone A, et al. Bone and kidney toxicity induced by nucleotide analogues in patients affected by HBV-related chronic hepatitis: a longitudinal study. J Antimicrob Chemother. 2015;70:1150–1154.
16. Brown TT, Moser C, Currier JS, et al. Changes in bone mineral density after initiation of antiretroviral treatment with tenofovir disoproxil fumarate/emtricitabine plus atazanavir/ritonavir, darunavir/ritonavir, or raltegravir. J Infect Dis. 2015;212:1241–1249.
17. Buti M, Gane E, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:196–206.
18. Chan HLY, Fung S, Seto WK, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet Gastroenterol Hepatol. 2016;1:185–199.
19. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 2015;385:2606–2615.
20. Schafer JJ, Sassa KN, O’Connor JR, Shimada A, Keith SW, DeSimone JA. Changes in body mass index and atherosclerotic disease risk score after switching from tenofovir disoproxil fumarate to tenofovir alafenamide. Open Forum Infect Dis. 2019;6(10):ofz414.
21. Gomez M, Seybold U, Roider J, Härtger B, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015–2017. Infection. 2019;47:95–102.
22. Sax PE, Erlanson KM, Lake JE, et al. Weight gain following initiation of antiretroviral therapy: risk factors in randomized comparative clinical trials. Clin Infect Dis. 2020;71:1379–1389.
23. van den Berg F, Limani SW, Mnyandu N, Maepa MB, Ely A, Arbuthnot P. Advances with RNAi-based therapy for hepatitis B virus infection. Viruses. 2020;12:851.

24. Fanning GC, Zoulim F, Hou J, Bertoletti A. Therapeutic strategies for hepatitis B virus infection: towards a cure. Nat Rev Drug Discov. 2019;18:827–844.

25. Subic M, Zoulim F. How to improve access to therapy in hepatitis B patients. Liver Int. 2018;38(Suppl 1):115–121.

26. Mehellou Y, Rattan HS, Balzarini J. The ProTide prodrug technology: from the concept to the clinic. J Med Chem. 2018;61:2211–2226.

27. Zhang H, Hu Y, Wu M, et al. Randomised clinical trial: safety, efficacy and pharmacokinetics of HS-10234 versus tenofovir for the treatment of chronic hepatitis B infection. Aliment Pharmacol Ther. 2021;53:243–252.

28. Shuhart CR, Yeap SS, Anderson PA, et al. Executive summary of the 2015 ISCD position development conference on monitoring treatment, DXA cross-calibration and least significant change, spinal cord injury, peri-prosthetic and orthopedic bone health, transgender medicine, and pediatrics. J Clin Densitom. 2019;22:453-471.

29. Shepherd JA, Schousboe JT, Broy SB, Engelke K, Leslie WD. Executive summary of the 2015 ISCD position development conference on advanced measures from DXA and QCT: fracture prediction beyond BMD. J Clin Densitom. 2015;18:274-286.

30. Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med. 2008;359:2442–2455.

31. U.S. Department of Health and Human Services, Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER) Non-inferiority clinical trials to establish effectiveness: guidance for industry. https://www.fda.gov/media/78504/download. Accessed June 15, 2021.

32. National Institutes of Health. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. 2014.

33. Hou JL, Gao ZL, Xie Q, et al. Tenofovir disoproxil fumarate vs adefovir dipivoxil in Chinese patients with chronic hepatitis B after 48 weeks: a randomized controlled trial. J Viral Hepatol. 2015;22:85–93.

34. Flaherty JF, Zhang L & Duan Z, et al. A phase 3 study comparing tenofovir alafenamide (TAF) to tenofovir disoproxil fumarate (TDF) in patients from China with HBeAg-positive, chronic hepatitis B: efficacy and safety results at week 48. Poster presented at 2018 Asian Pacific Association for the Study of the Liver, New Delhi (14-18 Mar 2018).

35. Cassetti I, Madruga JVR, Suleiman JMAH, et al. The safety and efficacy of tenofovir DF in combination with lamivudine and efavirenz through 6 years in antiretroviral-naive HIV-1-infected patients. HIV Clin Trials. 2007;8(3):164–172.

36. Bernardino JJ, Mocroft A, Mallon PW, et al. Bone mineral density and inflammatory and bone biomarkers after darunavir-ritonavir combined with either raltegravir or tenofovir-empicitabine in antiretroviral-naive adults with HIV-1: a substudy of the NEAT001/ANRS143 randomised trial. Lancet HIV. 2015;2:e464–e473.

37. Wong GLH, Seto WK, Wong VWS, Yuen MF, Chan HLY. Review article: long-term safety of oral anti-viral treatment for chronic hepatitis B. Aliment Pharmacol Ther. 2018;47:730–737.

38. Riggs BL, Melton LJ, Robb RA, et al. A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. J Bone Miner Res. 2008;23:205–214.

39. Berger C, Langsetmo L, Joseph L, et al. Change in bone mineral density as a function of age in women and men and association with the use of antiresorptive agents. CMAJ. 2008;178:1660–1668.

40. Chen C-H, Lin C-L, Kao C-H. Association between chronic hepatitis B virus infection and risk of osteoporosis: a nationwide population-based study. Medicine (Baltimore). 2015;94:e2276.

41. Viganò M, Brocchieri A, Spinetti A, et al. Tenofovir-induced Fanconi syndrome in chronic hepatitis B monoinfected patients that re-verted after tenofovir withdrawal. J Clin Virol. 2014;61:600–603.

42. Marcellin P, Wong DK, Sievert W, et al. Ten-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B virus infection. Liver Int. 2019;39:1868-1875.

43. Venter WDF, Moorhouse M, Sokhela S, et al. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. N Engl J Med. 2019;381:803–815.

44. Suzuki K, Suda G, Yamamoto Y, et al. Tenofovir-disoproxil-fumarate modulates lipid metabolism via hepatic CD36/PPAR-alpha activation in hepatitis B virus infection. J Gastroenterol. 2021;56:168–180.

45. Wang C-C, Cheng P-N, Kao J-H. Systematic review: chronic viral hepatitis and metabolic derangement. Aliment Pharmacol Ther. 2020;51:216–230.

46. Yao J, Zou L, Hua X, Kong M, Chen Y, Duan Z. Effects of nucleos(t)ide analogs on body composition in HBV-infected men: an age- and BMI-matched, cross-sectional study. Nutrigenetics. 2016;32(11-12):1206–1210.

47. Arsenault BJ, Boekholdt SM, Kastelein JIP. Lipid parameters for measuring risk of cardiovascular disease. Nat Rev Cardiol. 2011;8:197-206.

48. Yang X, Li J, Hu D, et al. Predicting the 10-year risks of atherosclerotic cardiovascular disease in Chinese population: the China-PAR Project (Prediction for ASCVD Risk in China). Circulation. 2016;134:1430–1440.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

How to cite this article: Liu Z, Jin Q, Zhang Y, et al. Randomised clinical trial: 48 weeks of treatment with tenofovir alafenamide versus tenofovir disoproxil fumarate for patients with chronic hepatitis B. Aliment Pharmacol Ther. 2021;54:1134–1149. https://doi.org/10.1111/apt.16611

APPENDIX 1

The complete list of authors’ affiliation
Zihong Liu and Jinlin Hou, Department of Infectious Diseases, Southern Medical University Nanfang Hospital; Qinglong Jin and Junqi Niu, The First Hospital of Jilin University, Jilin; Yuxin Zhang, The First Affiliated Hospital of Xinjiang Medical University, Xinjiang; Guozhong Gong, The Second Xiangya Hospital of Central South University, Hunan; Guicheng Wu, Chongqing University Three Gorges Hospital, Chongqing; Lvfeng Yao, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fujian; Xiaofeng Wen, Liuzhou People's Hospital, Guangxi; Zhiliang Gao, The Third Affiliated Hospital of Guangzhou Medical University, Guangzhou; Xiaoming Chen, The First Affiliated Hospital of Sichuan University, Sichuan; Qing Yao, The Southwest Hospital of AMU, Chongqing; Shide Lin, Affiliated Hospital of Zunyi Medical University, Guizhou; Jia Shang, Henan Provincial People's Hospital, Henan; Huanyu Gong, The Third Xiangya Hospital of Zhongshan University, Guangdong; Zhihong Gao, The Third Affiliated Hospital of West China Hospital of Sichuan University, Sichuan; Junqi Niu, The First Hospital of Jilin University, Jilin; Yuexin Zhang, The Second Xiangya Hospital of Central South University, Hunan; Guicheng Wu, Chongqing University Three Gorges Hospital, Chongqing; Lvfeng Yao, Mengchao Hepatobiliary Hospital of Fujian Medical University, Fujian; Xiaofeng Wen, Liuzhou People's Hospital, Guangxi; Zhihong Gao, The Third Affiliated Hospital of Zhongshan University, Guangdong; Yan Hu, Xiangya Hospital Central South University, Hunan; Daokun Yang, The First Affiliated Hospital of Xinxing Medical University, Henan; En-Qiang Chen, West China Hospital of Sichuan University, Sichuan; Qing Mao, The Southwest Hospital of AMU, Chongqing; Shide Lin, Affiliated Hospital of Zunyi Medical University, Guizhou; Jia Shang, Henan Provincial People's Hospital, Henan; Huanyu Gong, The Third Xiangya Hospital of Zhongshan University, Guangzhou; Chen X, Jia Y, et al. The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate for patients with chronic hepatitis B. Aliment Pharmacol Ther. 2021;54:1134–1149. https://doi.org/10.1111/apt.16611

How to cite this article: Liu Z, Jin Q, Zhang Y, et al. Randomised clinical trial: 48 weeks of treatment with tenofovir alafenamide versus tenofovir disoproxil fumarate for patients with chronic hepatitis B. Aliment Pharmacol Ther. 2021;54:1134–1149. https://doi.org/10.1111/apt.16611
of Central South University, Hunan; Lihua Zhong, The Fourth Affiliated Hospital of Harbin Medical University, Heilongjiang; Huafa Yin, The First Affiliated Hospital of Anhui Medical University, Anhui; Fengmei Wang, Tianjin Third Central Hospital, Tianjin; Peng Hu, The Second Affiliated Hospital of Chongqing Medical University, Chongqing; Ling Xiao, Chuan Li, Qiong Wu and Chang'an Sun, Jiangsu Hansoh Pharmaceutical Group CO., LTD.