A randomized, double-blind, double-dummy, controlled, multicenter study of Qingzhong (tenofovir disoproxil fumarate) versus Viread for the treatment of chronic hepatitis B

First-stage results at week 48

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Abstract

Background: Tenofovir disoproxil fumarate (TDF) has been widely recommended as a first-line antiviral agent to treat chronic hepatitis B (CHB). Qingzhong and Viread, formulations of TDF commercialized by Jiangsu Chia-tai Tianqing Pharmaceutical Co Ltd and GlaxoSmithKline, respectively, have both been approved by the State Food and Drug Administration, China. This study analyzed the efficacy and safety of these 2 TDF agents in Chinese patients with CHB.

Methods: In this multicenter, randomized, double-blind, double-dummy, noninferiority phase 3 clinical trial (ClinicalTrials.gov identifier: NCT02287857), 330 Chinese patients with CHB [hepatitis B envelope antigen-positive (HBeAg) (+): 232] were randomly assigned to receive Qingzhong (group A: 161 patients) or Viread (group B: 169 patients) 300 mg once daily for 48 weeks. Subsequently, all patients were administered Qingzhong 300 mg once daily from week 49 to week 240. The primary end point was the degree of decline of plasma hepatitis B virus (HBV) DNA levels at week 48 and the secondary endpoints were viral suppression, normalization of alanine aminotransferase (ALT) levels, hepatitis B surface antigen (HBsAg)/HBeAg loss or seroconversion, and virological breakthrough.

Results: Among patients with CHB who were HBeAg (+), the mean HBV DNA titer decreased similarly between the groups at week 48. The percentages of patients who achieved undetectable HBV DNA were similar between the groups (85.11% and 82.35% in groups A and B, respectively) and similar losses of HBeAg and HBsAg seroconversion rates were achieved. Moreover, for patients with CHB who were HBeAg (−), reductions in HBV DNA were similar. Among all patients with CHB, the rates of normalization of ALT and the loss of HBsAg were similar. The overall incidence of adverse events was comparable between the groups.

Conclusion: In conclusion, the 48-week administration of Qingzhong showed noninferior efficacy and safety profiles compared to Viread in Chinese patients with CHB.

Abbreviations: AE = adverse event, ALT = alanine aminotransferase, AR = adverse reaction, CHB = chronic hepatitis B, FAS = full analysis set, HBeAg = hepatitis B e antigen, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, LLOD = lower limit of detection.
1. Introduction

Chronic infection with hepatitis B virus (HBV) is a worldwide health problem. It is estimated that at least 2 billion people are infected with HBV and that 240 million individuals have chronic HBV infections.[1] Sustained suppression of serum HBV DNA by nucleoside/nucleotide analogues (NAs) have been associated with the prevention of progression to liver decompensation and development of hepatocellular carcinoma.[2,3]

Tenofovir disoproxil fumarate (TDF) has been recommended by different guidelines as a first-line antiviral agent for the treatment of chronic hepatitis B (CHB) due to its superior efficacy and low resistance rates.[4–7] Early trials conducted by Gilead Sciences showed the safety and efficacy of oral TDF, at a dose of 300mg administered once daily,[8–11] which notably also exhibited a low resistance rate.[10,12,13] TDF also exhibited a pharmacokinetic profile in healthy Chinese patients similar to that in patients in Western countries and was also generally well-tolerated by healthy Chinese patients.[14] However, the long-term costs associated with patients treated with Viread (GlaxoSmithKline, Shanghai, China), the commercialized formulation of TDF, are high, which affects patient drug compliance and quality of daily life. Qingzhong, a generic version of Viread containing TDF, was developed by Jiangsu Chia-tai Tianqing Pharmaceutical Co Ltd (Jiangsu, China). Hence, we designed this phase 3 trial to evaluate the efficacy and safety of these 2 TDF agents in Chinese patients with CHB.

2. Materials and methods

2.1. Study design

This study was designed as a noninferiority trial and consisted of 2 stages (Fig. 1). In the first stage, a phase 3 clinical trial, conducted as a randomized (1:1), double-blind, double-dummy, controlled study was performed to compare Qingzhong (Jiangsu Chia-tai Tianqing Pharmaceutical Co Ltd), 300mg once daily for up to 48 weeks (Group A) with Viread (GlaxoSmithKline) 300mg once daily (Group B) for up to 48 weeks in patients with CHB. All subjects were stratified by hepatitis B e antigen (HBeAg) status before being randomized into the treatment groups. Treatment assignments were allocated centrally by statisticians by permuted block sizes of 4 that were assigned within each site. Investigators at each site were responsible for patient enrollment. In the second stage, conducted as an elongation open-label study, all patients received Qingzhong 300mg once daily for up to 240 weeks. In the first stage, patients returned to the clinic at 4, 12, 24, 36, and 48 weeks for vital signs evaluation, symptom reviews, and laboratory assessments including hematologic values, liver function tests, and HBV DNA level quantification and for documentation of any adverse events (AEs). HBV DNA was assayed using a second-generation polymerase chain reaction (PCR) quantitative assay with a lower limit of detection (LLOD) of 20 IU/mL (COBAS AmpliPrep/COBAS TaqMan HBV Test, Roche Molecular Systems, Pleasanton, CA).

This study was designed by the sponsor (Jiangsu Chia-tai Tianqing Pharmaceutical Co Ltd) in collaboration with the primary investigators. The sponsor collected the data and monitored the conduct of the study. Data were unblinded firstly to reveal patient grouping for statistical analysis after the database was locked. Independent statisticians performed the statistical analysis. After the statistical analysis was completed, a second unblinding was conducted to reveal the treatment administered to each patient in groups A and B. The primary investigator coordinated the writing of the manuscript with all the authors. All authors had access to the study data and reviewed and approved the final manuscript.

![Figure 1. Study design. Group A: Qingzhong, Group B: Viread. CHB = chronic hepatitis B, HBeAg = hepatitis B e antigen.](image-url)
The clinical trial was approved by the State Food and Drug Administration, China (2013L01048) and was registered with ClinicalTrials.gov (NCT02287857). The study was approved by the Ethics Committees of the 14 study sites, including Peking University First Hospital, China, and all procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Written informed consent was obtained from all study participants.

2.2. Study population

Patients were enrolled from 14 sites located in Beijing, Shanghai, Chengdu, Chongqing, Guangzhou, Nanjing, and Zhengzhou, China, and followed-up from September 2014 to October 2019. The inclusion criteria were having a diagnosis of HBeAg (-) or HBeAg (+) CHB infection (HBsAg (+) for at least 6 months) and no history of previous use of any antiviral agents (interferon, thymosin alpha-1, or NAs); being 18 to 65 years old; having HBV viral load ≥2×10^4 IU/mL in those who were HBeAg (+) or ≥2×10^5 IU/mL in those who were HBeAg (-); alanine aminotransferase (ALT) ≥2 and ≤10 times the upper limit of normal (ULN) and serum total bilirubin ≤2.5 times the ULN; prothrombin activity ≥60% or prolongation of prothrombin time ≤3 seconds; leukocyte count ≥3.5×10^9/L; platelet count ≥80×10^9/L; serum albumin ≥35 g/L; serum creatinine ≤1.0 times the ULN; normal serum phosphorus.

Key exclusion criteria included coinfection with another virus (such as human immunodeficiency virus type 1, hepatitis A, C, D, or E virus), evidence of hepatocellular carcinoma or cirrhosis of the liver, pregnant or lactating women, or comorbid severe cardiovascular, urinary, endocrine, bloodborne, immunological, or mental diseases. Patients allergic to TDF were also excluded from the study.

2.3. Endpoints

The primary efficacy endpoint was decline of plasma HBV DNA levels at week 48. Secondary efficacy endpoints included the proportion of patients with undetectable HBV DNA (<200 IU/mL) and the percentage of patients who achieved HBV DNA levels <69 IU/mL (<400 copies/mL). Based on the fact that HBV DNA levels <400 copies/mL were defined as being undetectable in a previous study on TDF,[8] the normalization of serum ALT (an ALT value no greater than the ULN), HBsAg/HBeAg loss or seroconversion defined as HBsAg/HBeAg loss and the appearance of hepatitis B surface antibody (antiHBs) and hepatitis B e antibody (antiHBe), and virological breakthrough, that is, a confirmed HBV DNA level ≥69 IU/mL after a documented level of <69 IU/mL or a confirmed log_{10} increase of ≥1.0 from the nadir level were considered appropriate endpoints.

2.4. Safety analysis

The safety analysis included data from all 338 treated patients who received at least 1 dose of a study drug during this double-blind study period. All AEs including serious adverse events (SAEs) were recorded. An SAE was defined by one of the following: death, fatal injury, development of a disability, hospitalization, or reduced ability to work. Safety parameters including patient chief complaints, abnormal signs observed by doctors, vital signs values, and blood levels including white blood cell counts, red blood cell counts, platelet counts, liver enzymes, serum phosphate, creatinine, and blood urea nitrogen were evaluated at each visit. Bone mineral density was assessed by dual-energy x-ray absorptiometry scan at weeks 0 and 48. Any parameter outside the normal range was evaluated by the research physician for clinical significance, recorded in the AE report form, and judged for its severity and potential relationship to the study drug. Patients who experienced an SAE were removed from the trial unless the adverse effects were not related to the drug. Patients who showed poor efficacy (defined as a decrease of <1 log IU/mL in the HBV DNA level at 24 weeks), virological breakthrough, or clinical resistance to TDF received additional administration of entecavir 0.5 mg once daily and were removed from the trial.

2.5. Laboratory tests

Virological and serological parameters were determined centrally by the Laboratory of Virology, Department of Infectious Diseases, Peking University First Hospital (including the baseline). HBV DNA was assayed using the second-generation PCR quantitative assay with an LLOD of 20 IU/mL and for HBeAg and hepatitis B e antibody by enzyme immunoassay, using the corresponding Abbott AxSYM microparticle enzyme immunoassays (Abbott Laboratories, Chicago, IL). The biochemical parameters were determined by the local laboratory.

2.6. Statistical analysis

Continuous variables were expressed as means with standard deviations or medians with interquartile ranges, where applicable. Categorical variables were expressed as counts and percentages. To compare continuous variables, we used t tests or Wilcoxon rank sum test, where applicable. Comparison of categorical data between the 2 groups was performed using the Chi-square test or Fisher exact test, where applicable. A 2-tailed P value <.05 was considered statistically significant. These statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

According to the statistical data of the early TDF efficacy trial,[8] unilateral α = 0.05, β = 0.20, and an equivalent limit δ = 1.0log_{10} IU/mL were used. The statistical analysis was performed using a calculation formula of equivalent sample sizes in the 2 groups (PASS software calculation; PASS Technology, London, UK), and the 2 groups both needed no <68 patients. Considering the drop-out factors and the length of the randomization group, the minimal sample size was determined to be 240 (120 patients in group A and 120 patients in group B). Account for potential loss to follow-up, the sample size was appropriately increased.

3. Results

3.1. Baseline characteristics

Of the 401 patients who were screened, 341 (171 in group A and 170 in group B) were enrolled and randomized and received, in blinded fashion and 338 patients treated, at least 1 dose of the study drug. Of the 341 patients, 8 (2.35%) were excluded from the full analysis set (FAS) due to loss of data before the therapy or failure to meet the inclusion criteria. Three patients were also excluded from the FAS because they refused to participate in the study before therapy initiation. Accordingly, 330 patients (161 in group A and 169 in group B) were included in the FAS (Fig. 2). The 2 groups were well balanced at baseline (Table 1).
3.2. Efficacy endpoints

3.2.1. Virological and serological endpoints. The HBV DNA levels in the 2 groups decreased over time. The mean decline of HBV DNA level for the HBeAg (+) patients in groups A and B, was 5.62 and 5.63 log_{10} IU/mL ($P > .05$), respectively. The mean decline in HBV DNA level for the HBeAg (-) patients in groups A and B, was 4.47 and 4.68 log_{10} IU/mL ($P > .05$), respectively (Table 2). At week 48, among HBeAg (+) patients, HBV DNA was undetectable ($<20$ IU/mL) in 47.37% and 59.32% ($P > .05$) in groups A and B, respectively (Table 3). At week 48, HBeAg loss occurred in 17.86% and 20.18% ($P > .05$), respectively, among the HBeAg (+) patients in groups A and B. HBeAg seroconversion occurred in 12.00% and 11.22% ($P > .05$), respectively, among the HBeAg (+) patients in groups A and B. One patient in group A had HBsAg loss but HBsAg seroconversion was not seen in either group.

3.2.2. Biochemical endpoints. At week 48, ALT normalization occurred in 81.58% and 82.93% ($P > .05$) in groups A and B, respectively (Table 4). The rate of ALT normalization increased as duration of therapy increased.

3.2.3. Virological breakthrough. One patient developed virological breakthrough in each group by week 48. Both patients were HBeAg (+). Entecavir 0.5 mg once daily was added to their regimens, and they both subsequently experienced a decrease in HBV DNA levels. We subsequently sequenced the HBV reverse transcriptase region from the serum samples of these patients and performed mutation testing for rtL80, rtV84, rtS85, rtI169, rtV173, rtL180, rtA181, rtT184, rtA194, rtS202, rtM204, rtV214, rtQ215, rtN236, and rtM250, which are well-characterized NAs-resistance point mutations, at weeks 0, 4, 12, 24, 36, and 48. None of the samples showed evidence of resistance mutations.

3.3. Safety analysis

In total, 338 patients were included in the safety analysis set. The frequency of AEs during treatment was similar in both groups.

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**Table 1**

Demographic and baseline characteristics of the patients.

|                | Group A (n = 161) | Group B (n = 169) | t     | $\chi^2$ | P     |
|----------------|-------------------|-------------------|-------|----------|-------|
| Age, y         | 35.16 ± 9.34      | 34.91 ± 9.79      | 0.24  |          | .8082 |
| Male sex       | 116 (72.05)       | 134 (79.29)       |       | 2.36     | .1248 |
| HBeAg (+)      | 114 (70.81)       | 118 (69.82)       | 0.43  |          | .6448 |
| Disease duration, y | 10.39 ± 8.03   | 9.76 ± 7.22       | 0.74  |          | .4575 |
| HBV-DNA, log_{10} IU/mL | 6.86 ± 1.13    | 6.91 ± 1.05       | 0.42  |          | .6761 |
| ALT, IU/L      | 175.47 ± 92.17    | 180.05 ± 96.05    | 0.44  |          | .6592 |

Group A, Qingzhong; Group B, Viread. Disease duration refers to the time when chronic hepatitis B was diagnosed up to the present time. Values are presented as mean ± standard deviation, n (%), or median (interquartile range).

* Fisher’s exact test.

ALT = alanine transaminase, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus.
HBeAg (+) CHB

Table 2
Reduction in hepatitis B virus DNA in patients with chronic hepatitis B in both groups [log_{10} IU/mL].

| Group A | Group B | F  | P    |
|---------|---------|----|------|
| HBeAg (+) CHB | n=114  | n=118 |  |  |
| 12 wk    | 4.26±1.28 | 4.42±1.04 | 1.00 | .3176 |
| 24 wk    | 5.12±1.37 | 5.21±1.17 | 0.27 | .6041 |
| 48 wk    | 5.62±0.99 | 5.63±0.95 | 0.00 | .9835 |
| HBeAg (-) CHB | n=47   | n=51  |  |  |
| 12 wk    | 3.98±1.06 | 4.07±1.07 | 0.30 | .5829 |
| 24 wk    | 4.39±1.13 | 4.50±1.14 | 0.19 | .6622 |
| 48 wk    | 4.47±1.15 | 4.68±1.17 | 0.77 | .3830 |

Group A, Qingzhong; Group B, Viread. Values are presented as n (%). Comparison of continuous variables between the 2 groups was performed using two-way factorial variance analysis. 1 factor was the site, the other was the group.

Table 3
Rate of hepatitis B virus DNA <20 or <69 IU/mL in patients with chronic hepatitis B.

| Rate of HBV DNA <20 IU/mL | Group A | Group B | P    |
|---------------------------|---------|---------|------|
| HBeAg (+) CHB             | 2 (1.75) | 5 (4.24) | .4464 |
| 12 wk                     | 32 (28.07) | 34 (28.81) | 1.0000 |
| 24 wk                     | 54 (47.37) | 70 (69.32) | .0869 |
| HBeAg (-) CHB             | 12 (25.50) | 8 (15.69) | .3162 |
| 12 wk                     | 33 (70.21) | 31 (60.78) | .3974 |
| 24 wk                     | 40 (85.11) | 42 (82.35) | .7887 |
| Rate of HBV DNA <69 IU/mL |          |         | .    |
| HBeAg (+) CHB             | 18 (15.79) | 19 (16.10) | .9462 |
| 12 wk                     | 58 (50.88) | 67 (56.78) | .3671 |
| 24 wk                     | 92 (80.70) | 92 (77.97) | .0089 |
| HBeAg (-) CHB             | 12 (26.71) | 27 (52.94) | .3080 |
| 12 wk                     | 41 (87.23) | 43 (84.31) | .6702 |
| 24 wk                     | 44 (93.62) | 50 (98.04) | .2604 |

Group A, Qingzhong; Group B, Viread. Values are presented as n (%). Comparison of categorical data between the 2 groups was performed using Fisher exact test.

CHB = chronic hepatitis B, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus.

(49.7% in group A and 39.6% in group B, P > .05) (Table 5) through week 48. Overall, 33 and 23 patients in groups A and B (P > .05), respectively, had adverse reactions (ARs), all of which were of mild to moderate in severity. One patient developed hypophosphatemia without pathological fracture in group A, whereas no significant increase in serum creatinine was observed in either group. Other ARs included abnormalities in liver enzyme levels, fluctuation in blood cell counts, serum creatinine elevations, hyperuricemia, diarrhea, nausea, abdominal discomfort, mild hematuria or proteinuria, urinary infection, weight loss, itching, sore throat, headache, fever, fatigue, and joint pain. Two patients in group A and 3 patients in group B experienced SAEs (P > .05). In group A, patient 006 experienced a cold during the trial and patient 347 underwent surgery for a facial cyst before starting therapy. In group B, patients 033, 054, and 082 all developed fluctuations of liver enzymes, which normalized after symptomatic treatment, and osteopenia was observed in patients 062, 072, 338, and 340. None of the SAEs were judged to be

related to the study drugs. No discontinuation due to AEs or ARs occurred, and no deaths occurred.

4. Discussion

The number of Chinese patients with CHB utilizing TDF has increased because of its superior efficacy and low resistance rate, especially among patients who have failed treatment with other NAs. Given that Chinese national policy covers domestic drugs at a cheaper price and higher reimbursement ratio and coverage, a noninferior domestic generic of TDF may be better for long-term treatment of Chinese patients with CHB. Hence, this study analyzed the efficacy and safety of 2 TDF agents, Viread and Qingzhong, in Chinese patients with CHB and found that there were no significant differences in efficacy and safety profiles between both drugs (P > .05) during the 48-week administration.

Regarding the primary endpoint of this study, the mean reduction in HBV DNA levels achieved was similar between the 2 groups whether they were HBeAg (+) or HBeAg (-). Both groups had 1 patient with a virological breakthrough. These 2 patients received entecavir 0.5 mg once daily and were removed from the trial. Notably, their HBV DNA levels decreased after the addition of entecavir to their treatment regimen. With respect to viral suppression, there was no significant difference between the 2 groups. Our study adopted a highly sensitive test, namely the COBAS TaqMan HBV assay (LLLOD 20 IU/mL) to measure serum HBV DNA levels and showed that group B was not significantly better than group A (P > .05). Compared with an early TDF efficacy trial,\(^9\) where 76% of the patients who were HBeAg (+) and 93% of the patients who were HBeAg (-) achieved HBV DNA levels <69 IU/mL, respectively, our study showed the noninferior efficacy [group A: 80.70% of HBeAg (+) patients and 93.62% of the patients who were HBeAg (-) achieved HBV DNA levels <69 IU/mL, respectively, our study showed the noninferior efficacy [group A: 80.70% of HBeAg (+) patients and 93.62% of HBeAg (-) patients versus group B: 77.97% of HBeAg (+) patients and 98.04% of HBeAg (-) patients, P > .05; (Table 3)]. Similar rates of HBeAg loss and HBeAg seroconversion were achieved in both groups. Our better findings could be related to sampling variations among treatment-naïve patients. All our results show the noninferior

| AE | Group A (n=169) | Group B (n=169) | P   |
|----|----------------|----------------|-----|
| 84 (49.7) | 67 (39.6) | .0799 |
| 2 (1.2) | 3 (1.2) | 1.000 |

Group A, Qingzhong; Group B, Viread. Values are presented as n (%). Comparison of categorical data between the 2 groups was performed using Fisher exact test.

AE = adverse event, SAE = serious adverse event.
efficacy of Qingzhong or Viread monotherapy for patients with CHB in the 48 weeks.

Although previous TDF-related renal impairment has been previously reported, serum creatinine levels were stable in either group at 48 weeks into our study, which is similar to the findings of an early TDF efficacy trial. One study participant who developed hyperphosphatemia without pathological fracture in group A had shown a lower concentration of serum phosphorus before treatment compared with other patients. He was offered phosphorus treatment based on previous studies of tenofovir-associated Fanconi syndrome and was monitored closely. The research physician subsequently decided to remove this patient from the trial based on changes in his blood phosphorus levels and skeletal symptoms and signs observed (osteoplastic and osteoporosis requiring intervention).

Hence, TDF showed both efficacy and safety in Chinese patients with CHB at 48 weeks. However, there were some limitations to the present study. First, the results included only 48 weeks of follow-up without long-term treatment data. The incidence of AEs observed in the present study cannot ensure the long-term safety of the monotherapy. Fortunately, after week 48, patients could enroll in long-term open-label studies on Qingzhong for an additional 4 years. Second, serum creatinine, the most widely used clinical indicator of kidney injury, has low sensitivity. Hence the incidence of kidney injury in this study could have been underestimated. Follow-up studies should apply more sensitive biomarkers to monitor for kidney injury. A study on sensitive biomarkers of kidney injury is currently underway by our research group.

5. Conclusions

In conclusion, this 48-week phase 3 trial showed that TDF was an effective and safe choice for the treatment of HBeAg (−) and HBeAg (+) CHB in Chinese patients. Viread and Qingzhong showed noninferior efficacy and safety in Chinese patients with CHB. TDF should be considered for the treatment of CHB, especially in NA-naive adults without renal or bone diseases.

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