**Supplementary materials**

**Study design**

In the first stage of this study, treatment assignments were allocated centrally on the basis of permuted block. Patients, investigators, and all study personnel, including those assessing outcomes, were masked to treatment assignment throughout the 48 weeks of the double-blind phase.

Clinical management decisions as to ADV augmentation were defined by protocol and made at week 100 on the basis of the treatment response and resistance status at week 96. ADV was added on to those patients who (1) experienced viral breakthrough (defined as a confirmed increase in HBV DNA level of more than 1 log10 IU/ml compared to the nadir HBV DNA level on at least two occasions at an interval of more than one month after initial virological response), (2) presented with an HBV DNA level greater than 200 IU/mL and the ALT level greater than 1.5×ULN (exclusion was ALT increase due to factors other than HBV infection), (3) had confirmed ETV-resistance, or (4) presented with an HBV DNA level greater than 2000 IU/mL and LMV-resistance. Patients with add-on ADV therapy was excluded from the efficacy analysis since week 100. All patients were monitored every 12 weeks and an extra visit was conducted at week 4. At every visit, routine biochemical (ALT, bilirubin, albumin), virological (HBV DNA level), and serological (HBeAg, antibody to hepatitis B e antigen(anti-HBe)) examinations were performed. Abdominal sonography

and alpha-fetoprotein were detected every 48 weeks.

This study was designed by the sponsor (Jiangsu Chia-tai Tianqing Pharmaceutical Co., Ltd, Jiangsu, China) in collaboration with primary investigators. The sponsor collected the data and monitored the conduct of the study. Independent statisticians performed the statistical analysis. The primary investigator coordinated the writing of the manuscript with all authors. Data were unblinded firstly for statistical analysis after the database was locked. After the statistical analysis was completed, a second unblinding was carried out to reveal the treatment allocation. All authors had access to the complete study reports and reviewed and approved the final manuscript. The academic authors vouch for the veracity and completeness of the data and the data analyses.

**Study population**

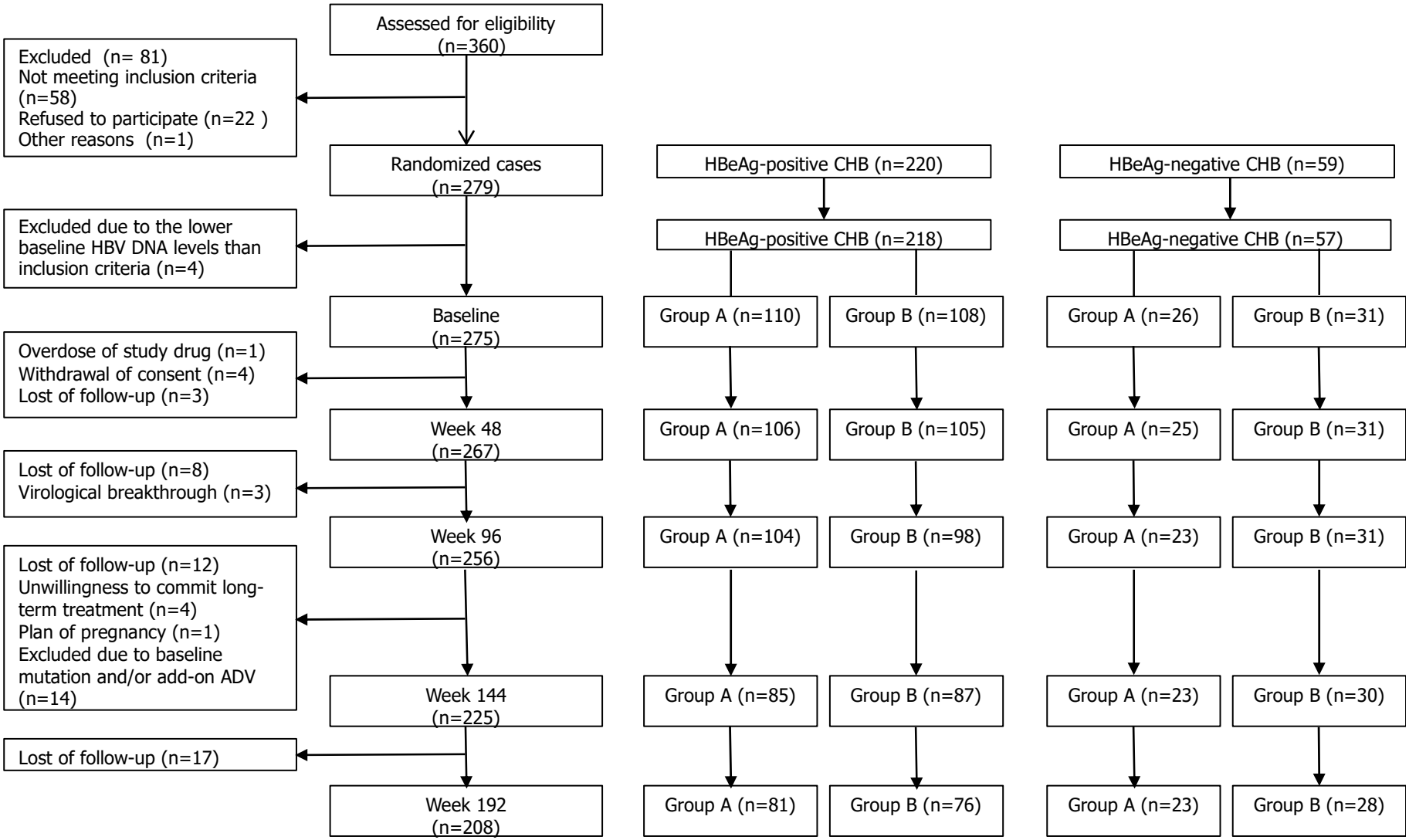
Eligible patients were aged 18~65 years and were either HBeAg-positive with HBV DNA≥2×104 IU/mL (1×105 copies/mL) or HBeAg-negative with HBV DNA≥ 2×103 IU/mL (1×104 copies/mL). Eligible patients also had detectable HBsAg for at least 24 weeks before screening, a serum alanine transaminase (ALT) level 1.3 to 10 times the upper limit of normal (ULN), and compensated liver function (a serum total bilirubin level less than 2.5 times ULN, a prothrombin time not more than three seconds longer than normal or prothrombin activity not greater than 60%, a serum albumin level of at least

3.5g per deciliter and no history of variceal bleeding or hepatic encephalopathy).

Exclusion criteria included co-infection or super-infection of hepatitis A virus, hepatitis C virus, hepatitis delta virus, hepatitis E virus, Epstein-Barr virus or cytomegalovirus; liver cirrhosis or hepatocellular carcinoma; use of interferon, thymosin, or nucleos(t)ide analog within 24 weeks before randomization; metabolic or autoimmune disease; an alpha fetoprotein level greater than 100 ng per milliliter. Pregnant and nursing women were also excluded.

**Statistical analysis**

The test of non-inferiority was conducted. An intention-to-treat (ITT) analysis was used to evaluate the changes of HBV DNA level from baseline through week 96. Last observation carry-forward (LOCF) analysis was adopted to analyze HBV DNA level through week 96, while observation of HBV DNA level was used since week 100. In proportional analysis of HBV serological data, treated patients with a missing value for HBeAg or anti-HBe were considered not to have had a response at that end point from baseline through 96 weeks. Observations of HBV serologic data were used since week 100. The comparison of parameters other than HBV DNA and serological data use observations throughout the study.


Assessed for eligibility (n=360)
Excluded (n= 81)
Not meeting inclusion criteria (n=58)
Refused to participate (n=22 )
Other reasons (n=1)
Randomized cases (n=279)
Excluded due to the lower baseline HBV DNA levels than inclusion criteria (n=4)
Baseline (n=275)
Overdose of study drug (n=1)
Withdrawal of consent (n=4)
Lost of follow-up (n=3)
Week 48 (n=267)
Lost of follow-up (n=8)
Virological breakthrough (n=3)
Week 96 (n=256)
Lost of follow-up (n=12)
Unwillingness to commit long-term treatment (n=4)
Plan of pregnancy (n=1)
Excluded due to baseline mutation and/or add-on ADV (n=14)
Week 144 (n=225)
Lost of follow-up (n=17)
Week 192 (n=208)
HBeAg-positive CHB (n=220)
HBeAg-positive CHB (n=218)
Group A (n=110)
Group B (n=108)
Group A (n=106)
Group B (n=105)
Group A (n=104)
Group B (n=98)
Group A (n=85)
Group B (n=87)
Group A (n=81)
Group B (n=76)
HBeAg-negative CHB (n=59)
HBeAg-negative CHB (n=57)
Group A (n=26)
Group B (n=31)
Group A (n=25)
Group B (n=31)
Group A (n=23)
Group B (n=31)
Group A (n=23)
Group B (n=30)
Group A (n=23)
Group B (n=28)

**Supplementary Figure 1 Flow diagram of this randomized, double-blind, double-dummy, controlled, multi-center study of entecavir maleate versus entecavir for treatment of chronic hepatitis B.** ADV, Adefovir dipivoxil.

**Supplementary Table 1** Demographic and Baseline Characteristics of the patients

| | Group A(n=136) | Group B(n=139) | P |
|---|---|---|---|
| Age, y ( $\bar{x}$±SD) | 32.29±9.61 | 32.29±10.39 | 0.998 |
| Male sex, *n (%)* | 101(74.26) | 105(75.54) | 0.807 |
| Duration of disease, *y* (M±Q) | 5.00±8.00 | 6.00±7.00 | 0.457 |
| Patients with positive HBeAg, n (%) | 110(80.88) | 108(77.70) | 0.554 |
| HBV DNA, *log10 IU/mL* ( $\bar{x}$ ±SD) | 7.37±1.20 | 7.35±1.09 | 0.907 |
| ALT, *U/L* (M±Q) | 112.20±105.10 | 114.20±118.60 | 0.759 |
| NA-naïve, *n (%)* | 128(94.1) | 129(92.8) | 0.660 |
| HBV genotypes, n (%) | | | |
| B | 69(50.7) | 68(48.9) | 0.928* |
| C | 65(47.8) | 69(49.6) | |
| Others | 2(1.5) | 2(1.4) | |
| Genotypic resistance | | | |
| LMV-resistance, *n (%)* | 1(0.7) | 2(1.4) | 1.000* |

| | | | | |
|---|---|---|---|---|
| ADV-resistance, *(%)* | *n* | 3(2.2) | 2(1.4) | 0.682* |
| ETV-resistance, (%) | n | 0 | 0 | |

*Fisher's exact test

Abbreviations: ADV, adefovir dipivoxil; ALT, alanine transaminase; HBeAg, Hepatitis B e antigen; HBV, hepatitis B virus; LMV, lamivudine; M, median; NA, nucleos(t)ide analogues; Q, interquartile range; SD, standard deviation

**Supplementary Table 2** The rate of HBV DNA <52 IU/mL in CHB patients.

| | HBeAg-positive | | | | HBeAg-negative | | | |
|---|---|---|---|---|---|---|---|---|
| group | 96w | 144w | 168w | 192w | 96w | 144w | 168w | 192w |
| A | 69.09 (76/110) | 87.06 (74/85) | 85.37 (70/82) | 89.74 (70/78) | 100 (26/26) | 100 (23/23) | 100 (23/23) | 100 (22/22) |
| B | 66.67 (72/108) | 80.46 (70/87) | 85.37 (70/82) | 90.28 (65/72) | 30/31 (96.77) | 100 (30/30) | 100 (30/30) | 100 (28/28) |
| P | 0.702 | 0.241 | 1.000 | 1.000 | 1.000* | | | |

*Fisher's exact test

Last observation carry-forward analysis was used through week 96.

Observation was used since week 100.

Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus