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Original Article

Hydronidone for the Treatment of Liver Fibrosis Associated with Chronic Hepatitis B: Protocol for a Phase 3 Randomized Trial

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Abstract

Background and Aims: Liver fibrosis is a key process in the progression of chronic liver diseases. However, there are currently no drugs specifically designed to treat liver fibrosis. Our Phase 2 trial of hydronidone for the treatment of chronic hepatitis B (CHB)-associated liver fibrosis showed that adding hydronidone to entecavir resulted in significant reversal of liver fibrosis. To further evaluate the efficacy of a 270 mg/day dose of hydronidone for treating liver fibrosis associated with CHB, we conducted this Phase 3 trial. ***Methods:*** This is a 52-week, randomized (1:1), double-blind, placebo-controlled, multicenter, entecavir-based Phase 3 clinical study conducted at 44 study centers across China. Adult patients aged 18 to 65 years with significant liver fibrosis (defined as an Ishak score ≥ 3 on liver biopsy) associated with CHB were included. ***Results:*** The primary endpoint of the trial is to demonstrate the efficacy of fibrosis reversal, defined as a decrease in the Ishak stage score of liver fibrosis by ≥1 after 52 weeks of treatment, compared to baseline. ***Conclusions:*** The results of this trial are expected to further support the antifibrotic indication for this novel drug.

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Introduction

Hepatitis B virus (HBV) infection remains a global public health issue, with an estimated 257.5 million people living with HBV infection worldwide in 2022. Of these, 65% reside in the Asia-Pacific region.[1] In 2019, HBV-associated liver failure, cirrhosis, and primary hepatocellular carcinoma led to 820,000 deaths.[2] Up to now, antiviral therapy remains the primary treatment approach for chronic hepatitis B (CHB) patients.[3] However, liver fibrosis plays a key role in the progression of chronic liver diseases, and regression of liver fibrosis has been shown to significantly improve the prognosis of CHB patients.[4]

Although antiviral treatment can achieve regression of liver fibrosis, fibrosis may still progress in some CHB patients, even after HBV replication has been inhibited.[5] Despite this, effective drugs for directly treating liver fibrosis remain unavailable. Hydronidone is a novel structural modification of pirfenidone, a drug approved by the U.S. Food and Drug Administration for the treatment of idiopathic lung fibrosis, designed to reduce hepatotoxicity.

In our Phase 2 trial of hydronidone for treating CHB-associated liver fibrosis, the addition of hydronidone to entecavir resulted in significant histological improvement of liver fibrosis in approximately 50% of CHB patients after 52 weeks of treatment, with a daily dose of 270 mg achieving the best regression rate of liver fibrosis.[5] Our experimental studies also demonstrated that hydronidone inhibits the activation of hepatic stellate cells via Smad7-mediated degradation of TGF-βRI and induces apoptosis in activated hepatic stellate cells through the endoplasmic reticulum stress-associated mitochondrial apoptotic pathway.[6,7] To further evaluate the efficacy of hydronidone (270 mg/day) in treating liver fibrosis associated with CHB, we have conducted this Phase 3 trial. Here, we describe the design of a randomized, double-blind, controlled, multicenter, entecavir-based study in Chinese patients with CHB-associated liver fibrosis. We anticipate that the data from this trial will support the use of this novel drug for directly treating liver fibrosis.

Methods

Study design

This trial (NCT05115942) will be conducted to confirm the

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efficacy and safety of hydronidone combined with entecavir in the treatment of liver fibrosis associated with chronic hepatitis B. This is a 52-week, randomized, double-blind, placebo-controlled, multicenter, entecavir-based Phase 3 clinical study. The clinical trial will adhere to the Declaration of Helsinki, Good Clinical Practice, and other relevant laws and regulations. Approval from the appropriate institutional review board and the Chinese Office of Human Genetic Resources Management is required, along with the signing of cooperation agreements with the clinical trial institutions. A public announcement must also be made on the information disclosure platform of the National Medical Products Administration. The trial will be conducted in compliance with all applicable regulatory requirements. Patients will be recruited from 44 study centers in China, all of which are qualified to conduct clinical research according to the International Conference on Harmonisation guidelines on good clinical practices. All participants must provide written informed consent in accordance with good clinical practice and local legislation before enrollment in the study.

Study population

Chinese adults aged 18 to 65 years with significant liver fibrosis (defined as an Ishak score ≥ 3 from liver biopsy specimens) associated with CHB, positive serum HBV-DNA and ALT less than 8 upper standard limit of normal are eligible for inclusion. Participants must not have received prior antiviral treatment with interferon and/or nucleoside analogs or Chinese medicines with potential antifibrotic effects (such as Fuzheng Huayu, Anluo Huaxian Pills, or Fufang Biejia) within three months prior to enrollment. Participants or their sexual partners must also have no plans for pregnancy.

Individuals with any of the following conditions are excluded from the study:

- Upper gastrointestinal bleeding within three months before enrollment;
- Total bilirubin > 3 × ULN, or 3 × ULN < serum alanine transaminase (ALT) < 8 × ULN with total bilirubin> 2 × ULN;
- α-fetoprotein > 100 μg/L, despite no indication of hepatocellular carcinoma;
- Platelets ≤ 60 × 10^9/L;
- Prothrombin activity < 50% or international normalized ratio > 1.5;
- Imaging shows significant liver lesions suggestive of a tumor;
- Body mass index > 30 kg/m^2;
- Liver decompensated cirrhosis or liver malignancy;
- Chronic hepatitis C or non-viral chronic hepatitis (e.g., alcoholic, non-alcoholic, drug-induced);
- Severe combined cardiovascular, pulmonary, renal, endocrine, neurological, or hematological diseases, or psychiatric disorders;
- Pregnant and/or lactating women;
- Participation in other clinical trials within the past three months;
- Individuals who, in the investigator's opinion, have conditions that may affect their ability to provide informed consent or follow the trial protocol, or whose participation may affect trial results or their safety.

Treatment

The study will consist of a screening period (28 days) and a treatment period (52 weeks), followed by an extension study or additional follow-up. During recruitment and screening, the investigator will thoroughly explain the trial's purpose, details about the study drugs, the study protocol, trial processes, dosing regimen (e.g., dose, administration mode, frequency, etc.), clinical observations, biological sample collection, potential risks, subsidies, and compensation. This will ensure that patients are fully informed and voluntarily participate, improving medication compliance.

A total of 248 patients with CHB-associated liver fibrosis will be enrolled: 124 in the trial group and 124 in the control group. After randomization, patients in the trial group will receive hydronidone capsules (Beijing Continent Pharmaceuticals Co, Ltd) at a daily dose of 270 mg, three capsules three times a day, 30 m before meals, for 52 weeks. Patients in the control group will receive placebo capsules (composed of lactose monohydrate, magnesium stearate, and silica), three capsules three times a day, 30 m before meals, for 52 weeks. Both groups will also receive entecavir (Fujian Cosunter Pharmaceutical Co, Ltd) antiviral therapy, 0.5 mg once a day in a fasting state as baseline treatment for 52 weeks. On-site visits will occur at weeks 0, 4, 8, 12, 24, 36, and 52, with additional follow-up visits as necessary (Fig. 1).

Randomization

A central randomization system (IWRS) will be utilized to implement the randomization process. The block randomization method will be applied, selecting an appropriate block length and generating a random sequence for the 248 patients (trial or control group) according to a 1:1 ratio (patient random numbers 001 to 248) using SAS 9.4 statistical software.

Subjects receiving the investigational drug hydronidone or placebo will be assigned according to a randomization table. After signing the informed consent, the subjects will be given a screening number for the physical examination. Eligible patients will be enrolled using a competitive enrollment model. The researchers will input eligible subject information into the IWRS system, obtain a subject number, and randomly assign them to the trial or control group. At each follow-up drug delivery, the researchers will log into the IWRS system to obtain the assigned drug number and guide the patient to receive the corresponding treatment. Subject numbers are unique and will remain the same throughout the study. Subjects who withdraw or are withdrawn for any reason will retain their random number and will not be allowed to re-enter the trial. Subjects assigned a random number cannot be replaced.

Blinding

The clinical trial is double-blinded, with the investigator, pathologist, patient, project manager, project supervisor, and data management and analysis staff all being blinded. If a medical emergency occurs and the type of drugs taken by the patient needs to be identified immediately, emergency unblinding will be performed to obtain patient-specific grouping information. A centralized randomization system will be used for emergency unblinding.

Outcomes

The primary endpoint of the trial is the efficacy of fibrosis reversal, defined as a decrease in the Ishak stage score of liver fibrosis ≥ 1 after 52 weeks of treatment compared to baseline.

Secondary endpoints include:

- A decrease in liver inflammation grade by ≥1 after 52 weeks of treatment relative to baseline, without progression of fibrosis;
- A decrease in liver tissue inflammation grade by ≥1 after 52 weeks of treatment compared to baseline;
- A change in liver stiffness measurement values *via* transient elastography LSM (kPa) compared to baseline after

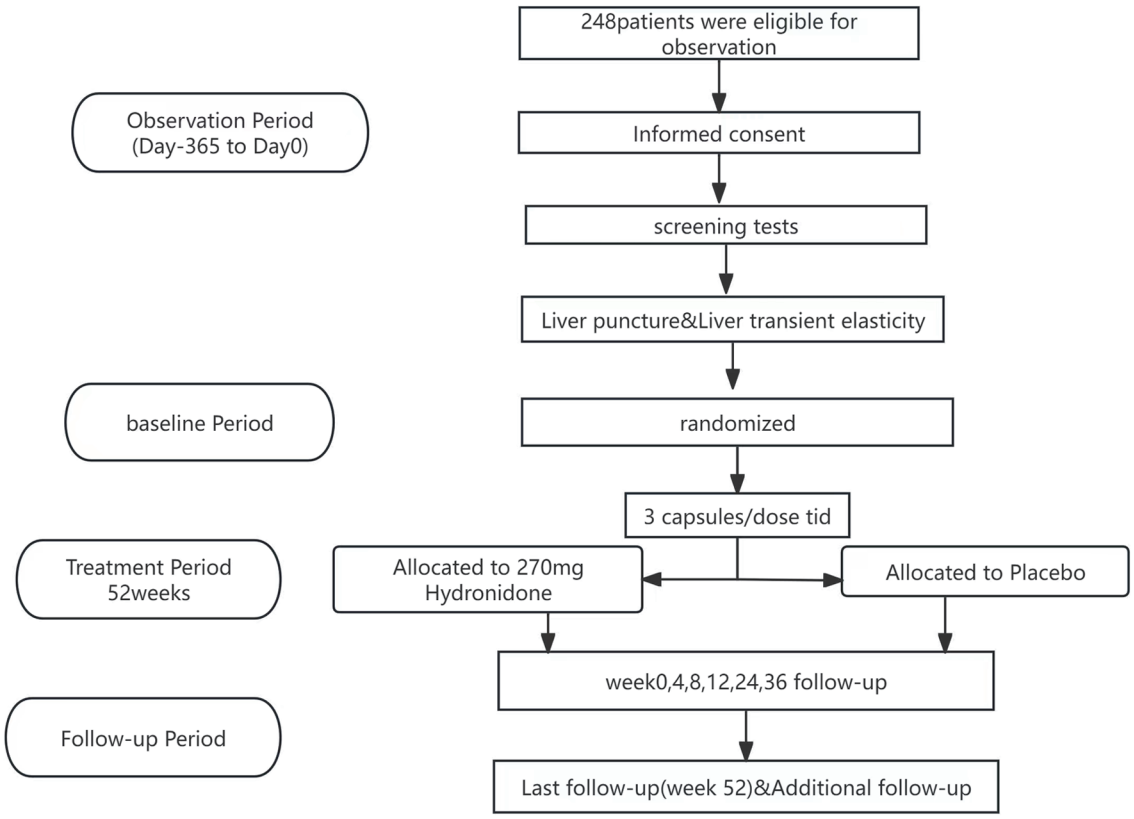

Fig. 1. Flow chart.

52 weeks of treatment;
- Negative conversion (below the lower limit of normal value) and the extent of decrease in HBV-DNA after 52 weeks of treatment;
- Normalization and improvement of ALT levels after 52 weeks of treatment;
- Safety endpoints, including adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities.

Assessments

Baseline characteristics, clinical, and laboratory assessments will be collected and performed during the screening period. Clinical assessments during follow-up are outlined in Table 1. All patients will be required to undergo liver biopsy, and liver fibrosis Ishak staging at the screening period/baseline will be scored by the central laboratory as part of the inclusion criteria, but not for efficacy evaluation. Each patient will also undergo a second liver biopsy after treatment. A panel of three expert pathologists will be responsible for scoring hepatic histopathology for efficacy assessment. They will assess inflammation using the Scheuer scoring system and stage fibrosis according to the Ishak scoring system. The expert pathology scores performed by the panel will be used for efficacy evaluation only, not for inclusion judgment. Both the slide sequence and the patient's treatment will remain blinded to the expert pathologists. The intraclass correlation coefficient will be used to evaluate the consistency of pathological examination results among the three experts, and the histological efficacy will be based on their consensus score. Information on AEs and concomitant medications will be collected at the time points specified in the study schedule. AEs and SAEs will be evaluated for safety assessment with reference to the common adverse events evaluation criteria (NCI-CTCAE version 5.0). The AEs/SAEs related to the study drug will be classified as "definitely related", "probably related" or "possibly related", and the incidences of such events will be calculated accordingly.

Data management

Detailed data management for this trial will be outlined in the Data Management Plan. The Electronic Data Capture System will be used to collect clinical trial data. The clinical research coordinator (CRC), the investigator, or a person designated and trained by the investigator, will complete the eCRF accurately, timely, completely, and in a standardized manner according to the original data and the guidelines for completing the eCRF. A blinded data review meeting will be held, in which the principal investigator, sponsor, project manager, statistician, medical monitor, and data manager (DM) will jointly review the data, decide the populations for statistical analyses according to the clinical study protocol, and verify the records of SAE reporting and handling, etc. Once all data have been reviewed, the DM will lock the database according to the resolution. After database locking, all data will be exported from the Electronic Data Capture System database by the DM and handed over to relevant personnel for statistical analysis according to the statistical analysis plan.

Statistical analysis

Based on the results of the Phase 2 trial, the proportion of patients with a decrease in Ishak score ≥ 1 compared to baseline in the control group is approximately 30% after 52

Table 1. Assessment schedule

Visit items	Screening	Baseline	Week 0	Week 4	Week 8	Week 12	Week 24	Week 36	Week 52	Additional follow-up visits
Window period						±5 days				
Informed consent form signature	X	X								
Collection of medical history	X	X								
Demographic information	X	X								
Height, weight	X	X								
Verify entry criteria	X	X								
Assign screening numbers	X	X								
Assign random number			X							
Vital signs	X	X		X	X	X	X	X	X	X
Physical examination	X	X		X	X	X	X	X	X	X
Clinical symptoms	X	X		X	X	X	X	X	X	X
Complete blood count	X	X		X		X	X	X	X	X
Urinalysis	X	X		X		X	X	X	X	X
Blood HCG	X	X		X		X	X	X	X	X
Blood glucose test	X	X				X	X	X	X	X
Metabolic panel	X	X		X	X	X	X	X	X	X
Coagulation function	X	X		X	X	X	X	X	X	X
AFP test	X	X		X	X	X	X	X	X	X
Liver transient elastography LSM (kPa)	X	X				X	X	X	X	X
HBV DNA	X	X		X	X	X	X	X	X	X
Hepatitis B serologic test	X	X					X		X	X
Anti-HCV	X	X								
12-Lead ECG	X	X				X	X	X	X	X
Ultrasonography	X	X					X		X	X
Percutaneous liver aspiration biopsy	X	X							X	
Study drug distribution			X	X	X	X	X	X		
Study drug retrieval				X	X	X	X	X	X	
Study drug administration records				X	X	X	X	X	X	X
Concomitant medication records			X	X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X	X

HCG, human chorionic gonadotropin; AFP, α-fetoprotein; LSM, liver stiffness measurement; HBV, hepatitis B virus; HCV, hepatitis C virus; ECG, electrocardiogram.

weeks of treatment, and the expected effect difference between the trial and control groups in this study is 20%. Under the condition of α = 0.025 (one-sided), a power of 85%, an assumed dropout rate of 20%, and a 1:1 ratio of trial group to control group, the PASS software is used to calculate 124 patients in the trial group and 124 patients in the control group. Thus, the total sample size is 248.

Based on the intention-to-treat principle, all cases randomized into groups, who have used the study drug at least once and have post-administration efficacy evaluation data, will constitute the Full Analysis Set (FAS). The FAS will be the primary population for efficacy evaluation. A Per-Protocol Set (PPS) will also be defined as a secondary population for assessing the efficacy of Hydronidone. The PPS should meet at least the following criteria: (1) meeting the inclusion criteria specified in the study protocol; (2) completing all planned interviews without serious deviation from the protocol; (3) not using drugs or treatments that may affect the efficacy evaluation during the trial; (4) good compliance. Additionally, all patients who were randomized, used the study drug at least once, and had post-administration safety evaluation data will constitute the safety population (SS) of this study. The safety population will be the primary population for safety evaluation in this study.

The last observation carried forward (LOCF) method will be used to impute the missing data for the primary efficacy endpoint. No missing data will be imputed for secondary endpoints or safety analysis.

All statistical tests will be performed using a two-sided test, and a difference will be considered statistically significant if $P < 0.05$ (except where otherwise stated). For measurement indicators, the number of cases, mean, standard deviation, median, minimum, and maximum values will be listed. For categorical indicators, they will be listed in terms of counts and frequencies (%). The primary time point for efficacy evaluation will be after 52 weeks of dosing (for PPS) or when exiting the group (for FAS). In addition, efficacy will be described for each of the other follow-up time points.

For the primary efficacy endpoint, the proportion of patients in the experimental group and the control group whose Ishak stage pathological score decreased by ≥1 point relative to baseline after 52 weeks of treatment will be calculated, and the percentage difference between groups will be compared using the χ^2 test. A 95% confidence interval for the difference will be calculated using the Newcombe-Wilson method. When the lower limit of the 95% confidence interval is greater than 0, it will be concluded that efficacy is established. Wald confidence interval results will also be provided. In addition, subgroup analysis will be performed on baseline HBeAg results (positive and negative) and baseline cirrhosis (yes and no).

The secondary efficacy endpoints related to changes in hepatic pathological inflammation grading at each interview point before and after treatment will be statistically described. The difference in the changes from baseline between the two groups will be compared using the Wilcoxon rank-sum test. The difference in the changes at the end of treatment relative to baseline between the two groups will be compared using a covariance analysis model, considering the baseline effect, and the proportion of patients with a decrease by 1 level or more from baseline after treatment will be compared using the χ^2 test or Fisher's exact probability method. The secondary efficacy endpoints related to changes in liver stiffness at each interview point before and after treatment will be statistically described. The difference in the changes from baseline between groups will be compared using the Wilcoxon rank-sum test. The difference in the changes from baseline at the end of treatment will be compared using a covariance analysis model, considering the baseline effect. The secondary efficacy endpoints related to the difference in the negative conversion rate of HBV-DNA after treatment (below the lower limit of detection) between the two groups will be compared using the χ^2 test or Fisher's exact probability method, and the difference in the drop of HBV-DNA between the two groups before and after treatment will be compared using the Wilcoxon rank-sum test. The secondary efficacy endpoints related to the recovery rate of liver function between the two groups after treatment will be compared using the χ^2 test or Fisher's exact probability method.

For safety endpoints, analyses will be carried out on the SS. The difference in the incidence of AEs in each group will be compared using the CMH-χ^2 test or Fisher's exact probability method. Coding will be performed according to MedDRA (20.0 or above) terms, and classification and analyses will be done according to SOC/PT. All measurements at each time point will be listed and described. The difference in changes within the group will be compared using the Wilcoxon signed-rank test, and the difference in changes between the two groups will be compared using the Wilcoxon rank-sum test.

Discussion

This study is being undertaken to provide robust evidence from a randomized, controlled, Phase 3 trial to support the use of hydronidone in Chinese patients with liver fibrosis associated with CHB. Until now, the lack of direct antifibrotic drugs has presented challenges to treatment strategies for chronic liver diseases. Our previous Phase 2 study demonstrated promising results regarding the antifibrotic effect of hydronidone with acceptable safety. The results showed that the fibrosis improvement endpoint was achieved by 11 patients (25.6%) in the placebo group and by 58 of 125 patients (46.4%) in the hydronidone group ($P = 0.014$). Regarding different doses of hydronidone (180, 270, or 360 mg per day), 270 mg demonstrated the best regression rate of 54.8%, compared to other doses with regression rates of 40.5% and 43.9%, respectively. In the hydronidone group, only one patient (0.8%) progressed from the non-cirrhotic stage to cirrhosis, while two patients (4.8%) in the placebo group progressed to cirrhosis. Intriguingly, five (4.0%) patients in the hydronidone group had regression from cirrhosis, while only 1 (2.4%) patient had cirrhosis reversal in the placebo group.[5] Furthermore, all the doses of hydronidone were well tolerated by the CHB patients. However, due to the limited sample of our previous phase 2 trial of only around 40 patients for each group, the results should be interpreted cautiously. To further illustrate and explore more powerful evidence of the antifibrotic role of hydronidone, we plan to carry out a Phase 3 trial with a larger sample size of 124 patients in each group, using the same inclusion and exclusion criteria.

We anticipate that this Phase 3 trial will provide robust evidence of the antifibrotic effect of hydronidone based on cause-control treatment. The previous Phase 2 trial showed that some patients still had progression of liver fibrosis even after antiviral treatment. We also anticipate fewer patients will experience fibrosis or cirrhosis progression, while a significant number will show reversal of fibrosis with hydronidone.

The Ishak score from paired liver biopsies will continue to be used to evaluate the antifibrotic effect of hydronidone to achieve the primary outcomes. Due to concerns regarding the reliability of liver biopsy evaluation,[8] an expert team

consisting of three independent pathologists will blindly determine the fibrosis scores of mixed specimens, including the screening and final biopsies.

Conclusions

This trial aimed to identify the antifibrotic effect and safety of hydronidone for CHB patients with significant liver fibrosis. It is anticipated that the findings of this study will further support the antifibrotic indication for this novel drug.

Funding

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Conflict of interest

LL has been an Associate Editor of the *Journal of Clinical and Translational Hepatology* since 2013. The other authors have no conflicts of interest related to this publication.

Author contributions

Study concept, design (LL, JC), data curation (XC, WX), drafting (XC, YQ, WX), review, and revision of the manuscript (XC, YQ, WX, YW, MZ, LZ, YL, PY). All authors have made significant contributions to this study and have approved the final manuscript.

Ethical statement

This trial (NCT05115942) will adhere to the Declaration of Helsinki, Good Clinical Practice, and other relevant laws and regulations. Approval from the appropriate institutional review board (No: 2021-275) and the Chinese Office of Human Genetic Resources Management (No: 2021-GH5356) is required, along with the signing of cooperation agreements with the clinical trial institutions. A public announcement must also be made on the information disclosure platform of the National Medical Products Administration. All participants provided written informed consent in accordance with good clinical practice and local legislation before enrollment in the study.

Data sharing statement

The datasets used and/or analyzed during the present study are available from the corresponding authors upon reasonable request.

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