High rate and sustained HBsAg loss achieved with HT-101 plus HT-102 combination therapy in HBeAg-negative, nucleos(t)ide analogue-suppressed patients: ongoing off-treatment results from a multicenter Ib/IIa study

Xieer Liang[1], Liang Chen[2], Jianmei Lin[3], Bei Zhong[4], Huiqing Liang[5], Wen Xie[6], Yujuan Guan[7], Zhihong Liu[1], Xun Qi[2] , Dong Wang[8], Zhipeng Zhang[8], Lijuan Ding[8], Zhiping Cui[8], Huaien Song[8], Kun Yue[8], Kai Wu[8], Jinlin Hou[1]*

[1] Department of Infectious Diseases, Nanfang Hospital, Southern Medical University. [2] Liver Disease Department, Shanghai Public Health Clinical Centre. [3] Infectious Diseases Department, Sichuan Provincial People's Hospital. [4] Infectious Diseases Department, Qingyuan People's Hospital. [5] Infectious Diseases Department, Xiamen Traditional Chinese Medicine Hospital. [6] Liver Disease Department, Beijing Ditan Hospital. [7] Liver Disease Department, Guangzhou Eighth People's Hospital. [8] Hepa Thera Biotech Company. *Corresponding author

Contact
Medical: Wangdong@hepathera.com
BD: Heyajun@hepathera.com

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Introduction

Nucleos(t)ide analogues (NUCs) effectively suppress hepatitis B virus (HBV) DNA replication but rarely achieve a functional cure, which is generally defined as sustained hepatitis B surface antigen (HBsAg) loss accompanied by HBV DNA levels remaining below the lower limit of quantitation (LLOQ) after treatment cessation. Achieving functional cure in patients with chronic hepatitis B (CHB) is associated with a reduced long-term risk of complications, including hepatocellular carcinoma.To enhance HBsAg clearance, RNA interference (RNAi)-based therapies are increasingly being investigated in combination regimens. This trial evaluates a novel dual-mechanism combination of HT-101 and HT-102, which is hypothesized to achieve faster and higher rates of functional cure compared to monotherapy approaches.

HT-101 is a GalNAc-conjugated small interfering RNA (siRNA) that targets the HBV S region. It is designed to reduce viral transcripts and HBsAg production derived from both covalently closed circular DNA (cccDNA) and integrated HBV DNA.HT-102 is a fully human monoclonal antibody that binds to circulating HBsAg. It promotes rapid antigen clearance through immune complex formation, leading to a substantial reduction in serum antigen load within days and potentially inhibiting viral entry.

Preliminary data indicated a notably high HBsAg loss rate of up to 90% at the end of treatment (EOT) in the group receiving the HT-101 plus HT-102 combination. This report presents the 24-week follow-up data to assess the durability of the treatment response.

Aim

This Phase Ib/IIa study aims to evaluate the safety, antiviral activity, and efficacy of HT-101 and/or HT-102 in patients with CHB who are hepatitis B e antigen (HBeAg)-negative and virologically suppressed on NUCs.
The efficacy assessments include the proportion of patients achieving HBsAg loss during treatment, the durability of response after treatment discontinuation, and the rate of off-treatment functional cure. The kinetics and magnitude of HBsAg decline, as well as safety, pharmacokinetic profile and immunogenicity will be evaluated (NCT07183306/CTR20244730).

Method

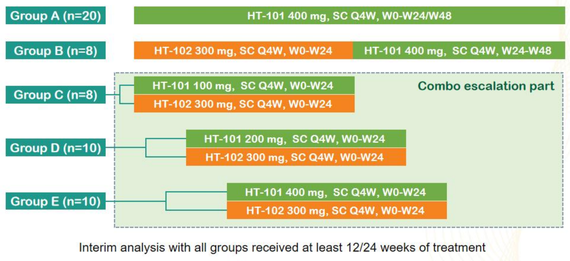
This is an ongoing, multicenter, open-label Phase Ib/IIa study.

Key Inclusion Criteria:
Aged 18–65 years.
HBsAg level between 100 and 3,000 IU/mL.
HBV DNA < lower limit of quantification.
Stable NUC therapy for at least 6 months prior to enrollment.

Major Exclusion Criteria:
Advanced fibrosis, or cirrhosis, or liver stiffness >9.0 kPa.
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels >1.5 times the upper limit of normal.

Treatment Regimens:
Patients were allocated into five treatment groups:
Group A: Received HT-101 400 mg subcutaneously (SC) every 4 weeks (Q4W) for 24 weeks. Treatment was extended to 48 weeks if HBsAg remained positive.
Group B: Received HT-102 300 mg SC Q4W for 24 weeks, followed by HT-101 400 mg SC Q4W for an additional 24 weeks (sequential therapy).
Groups C, D, and E: Received combination therapy comprising HT-102 300 mg SC Q4W plus HT-101 at doses of 100 mg, 200 mg, or 400 mg SC Q4W, respectively, for 24 weeks.
All patients were followed off-treatment through Week 72 (Figure 1).

Figure 1. Study Design: HT-101 & HT-102 Phase Ib / 2a



Interim analysis with all groups received at least 12/24 weeks of treatment

Results

Table 1. Participant Demographics and Baseline Characteristics

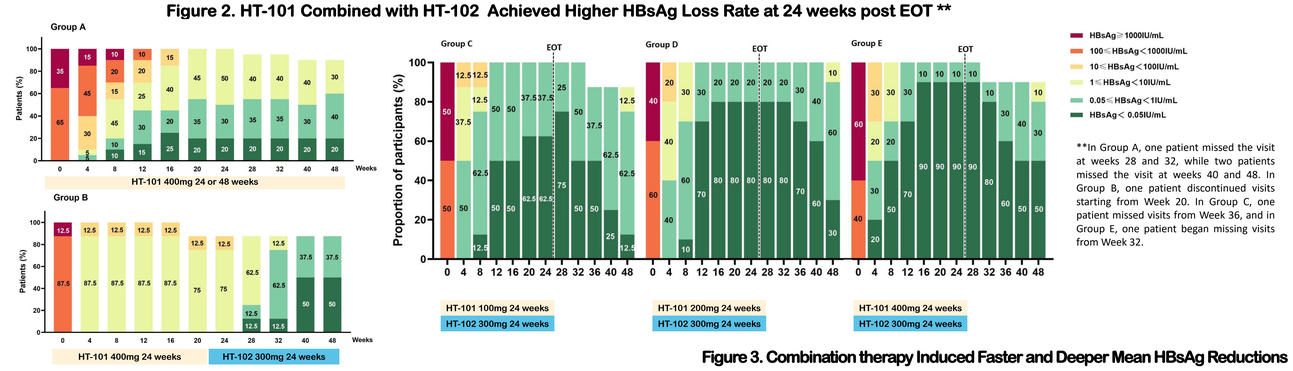
	Group A (N=20)	Group B (N=8)	Group C (N=8)	Group D (N=10)	Group E (N=10)
Age (Years), Mean (SD)	38 (5)	45 (7)	35 (4)	45 (7)	41 (8)
Gender (Male), n (%)	14 (70)	5 (63)	6 (75)	9 (90)	8 (80)
Asian, n (%)	20 (100)	8 (100)	8 (100)	10 (100)	10 (100)
HBeAg positive, n (%)	0	0	0	0	0
Baseline HBsAg (log_{10} IU/mL), Mean (SD)	2.8 (0.5)	2.7 (0.3)	2.8 (0.6)	2.9 (0.3)	3.1 (0.4)
Baseline HBsAg					
< 1000 (IU/mL), n (%)	13 (65.0)	7 (87.5)	4 (50.0)	6 (60.0)	4 (40.0)
≥ 1000 (IU/mL), n (%)	7 (35.0)	1 (12.5)	4 (50.0)	4 (40.0)	6 (60.0)
Baseline ALT (U/L), Mean (SD)	25 (12)	20 (7)	19 (5)	22 (6)	24 (9)

Table 2. HT- 101 or HT-102 Alone or in Combination Were Well Tolerated

Subjects, n(%)	Group A HT-101 400 mg (N=20)	Group B HT-102 300 mg →HT-101 400 mg (N=8)	Group C HT-101 100 mg +HT-102 300mg (N=8)	Group D HT-101 200 mg +HT-102 300mg (N=10)	Group E HT-101 400 mg +HT-102 300mg (N=10)	Total
At least one TEAE	17 (85.0)	5 (62.5)	5 (62.5)	9 (90.0)	9 (90.0)	56 (80.4)
Grade 1	15 (75.0)	5 (62.5)	5 (62.5)	8 (80.0)	9 (90.0)	42 (75.0)
Grade 2	13 (65.0)	4 (50.0)	3 (37.5)	5 (50.0)	4 (40.0)	29 (51.8)
Grade 3	1(5.0)	0	0	1 (10.0)	0	2 (3.6)
Grade 4-5	0	0	0	0	0	0
Treatment-related TEAEs	16 (75.0)	3 (37.5)	5 (62.5)	3 (30.0)	7 (70.0)	34 (60.7)
Grade 1	14 (70.0)	3 (37.5)	5 (62.5)	2 (20.0)	7 (70.0)	31 (55.4)
Grade 2	7 (35.0)	2 (25.0)	0	3 (30.0)	1 (10.0)	13 (23.2)
Grade 3	1(5.0)	0	0	0	0	1(1.8)
HT-101 ISR*	14 (70.0)	3 (37.5)	3 (37.5)	2 (20.0)	5 (50)	27 (48.2)
HT-102 ISR	NA	2 (25.0)	5 (62.5)	2 (20.0)	3 (30)	12 (33.3)
Grade 4-5	0	0	0	0	0	0
Treatment-related SAEs	0	0	0	0	0	0
Treatment discontinuation due to TEAEs	1(5.0)	0	0	0	0	1(1.8)

*ISR: Injection site reaction

Figure 2. HT-101 Combined with HT-102 Achieved Higher HBsAg Loss Rate at 24 weeks post EOT **



**In Group A, one patient missed the visit at weeks 28 and 32, while two patients missed the visit at weeks 40 and 48. In Group B, one patient discontinued visits starting from Week 20. In Group C, one patient missed visits from Week 36, and in Group E, one patient began missing visits from Week 32.

All participants (Groups A-E) completed the 48-week study visit. At baseline, the mean HBsAg levels ranged from 2.8 to 3.1 log_{10} IU/mL across groups, and all participants had undetectable HBV DNA and normal ALT levels at study entry (Table 1).

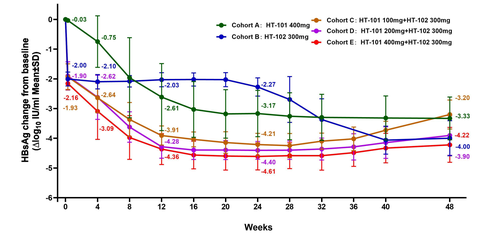
HT-101 monotherapy demonstrated durable off-treatment HBsAg loss (Figure 2).
At Week 24, HBsAg loss was observed in 4 out of 20 participants (20%) in Group A. Of these, 3 participants (75%) maintained HBsAg loss from EOT (Week 24) through Week 48. One additional patient achieved HBsAg loss after completing 48 weeks of HT-101 treatment. Consequently, the overall HBsAg loss rate in Group A at Week 48 was 4 out of 20 (20%).

Sequential dosing of HT-102 with HT-101 showed a high HBsAg loss rate (Figure 2).
In Group B, 4 out of 8 participants (50%) achieved HBsAg loss at Week 48, compared to a 0% rate with HT-102 monotherapy at Week 24. This also supports mechanistic complementarity with this sequential dosing approach.

The HT-101 plus HT-102 combination achieved a high and sustained rate of HBsAg loss.
At Week 48 (24 weeks post-treatment), the HBsAg loss rates were 1 out of 8 (12.5%) in Group C, 3 out of 10 (30%) in Group D, and 5 out of 10 (50%) in Group E, respectively. Among recipients of the combination therapy (Groups C–E), 9 out of the 22 participants (41%) who achieved HBsAg loss at Week 24 remained HBsAg negative at Week 48. Notably, 7 out of these 9 participants had discontinued NUC therapy since Week 36 (Figure 2).

The treatment regimen was safe and well-tolerated (Table 2).
The majority of treatment-emergent adverse events (TEAEs) were Grade 1-2 in severity (e.g., injection site reactions). No drug-related serious adverse events (SAEs), Grade ≥3 events, or ALT flares were observed. One patient discontinued HT-101 treatment at Week 32 due to acute urticaria.

Figure 3. Combination therapy Induced Faster and Deeper Mean HBsAg Reductions



The kinetics of HBsAg decline (Figure3)

HT-101 Monotherapy (Group A) exhibited a gradual yet steady decline in HBsAg levels, with a reduction of 3.2 log_{10} IU/mL by Week 24, further reaching 3.3 log_{10} IU/mL by Week 48.

HT-102 Monotherapy (Group B) demonstrated a rapid initial decline of 2.0 log_{10} IU/mL within the first two days, after which levels plateaued until the introduction of HT-101. Subsequent dosing with HT-101 led to a further decline, culminating in a total reduction of 4.0 log_{10} IU/mL by Week 48.

Combination Therapy Groups (C, D, and E) displayed a distinct kinetic profile.Patients experienced the same rapid initial drop attributable to HT-102, followed by a sustained and progressive decline driven by HT-101. By Week 24, the mean HBsAg reductions ranged from 4.2 to 4.6 log_{10} IU/mL across these groups. These reduced levels were maintained through Week 48, with sustained reductions ranging from 3.2 to 4.2 log_{10} IU/mL.

Conclusions

The HT-101 plus HT-102 combination induced rapid, profound, and sustained HBsAg decline, achieving markedly higher rates of HBsAg loss (up to 90% by Week 16) compared to either monotherapy component alone during treatment in this small Phase Ib/IIa study. HBsAg seroclearance was maintained off-treatment through 24 weeks in a substantial proportion of responders, with evidence of NUC discontinuation in some patients, indicating the potential for a finite treatment course. Both concurrent (HT-101 + HT-102) and sequential (HT-102 → HT-101) dosing schedules showed synergistic activity, highlighting the complementary roles of reducing HBsAg production (HT-101) and enhancing its clearance (HT-102).The regimen was generally safe and well-tolerated, with no drug-related serious adverse events or significant safety signals identified, supporting its potential for further clinical development.

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