DeltaCure 5th International Meeting
OCTOBER 15-16 2026 MILAN, ITALY
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Poster for you

# Libevitug (HH003) treatment in chronic hepatitis D: virologic, biochemical, biomarker modeling and improvements through 48 weeks

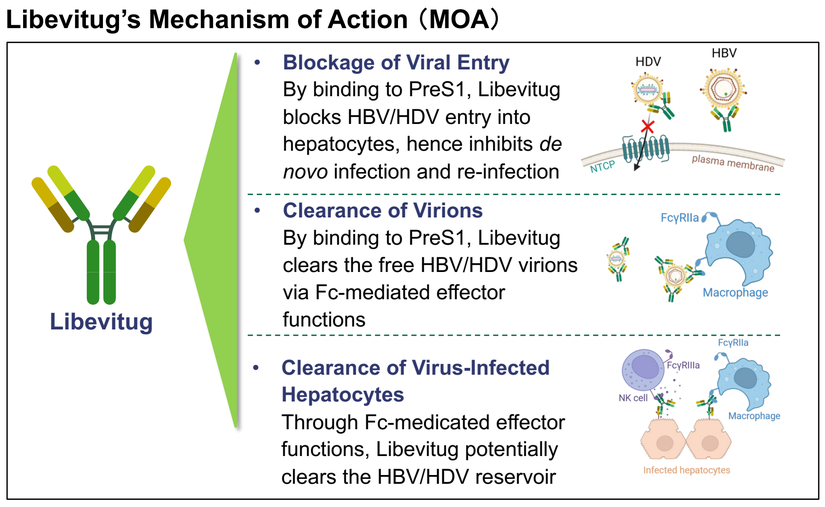
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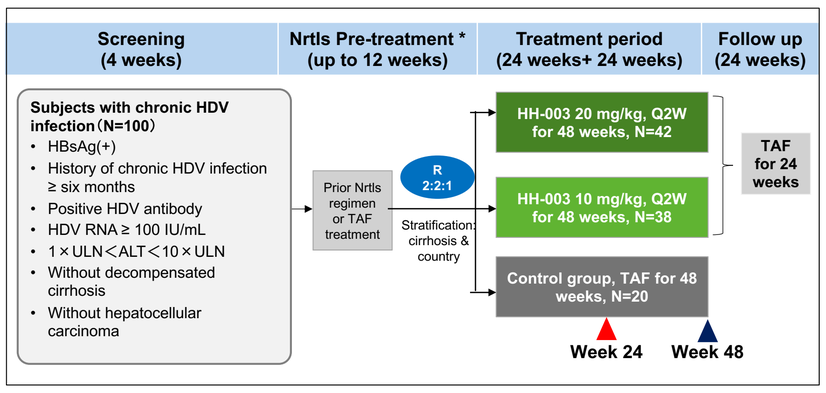
## Introduction

- Chronic hepatitis D represents the most severe form of viral hepatitis, leading to accelerated progression toward liver cirrhosis, hepatocellular carcinoma, and liver-related death compared with HBV monoinfection[1-3]. The global available therapeutic options for chronic HDV infection remain limited.
- Libevitug (HH-003) is a human monoclonal antibody targeting the PreS1 domain of the large envelope protein of HBV and HDV, thereby blocking viral entry into hepatocytes[4,5].
- In the randomized, controlled pivotal phase IIb clinical study (HH003-204, NCT05861674), libevitug 10mg/kg or 20mg/kg demonstrated statistically significant anti-HDV efficacy and a favorable safety profile after 24- or 48-week treatment in patients with chronic HDV infection[6].
- It received conditional approval in China in January 2026 for the treatment of patients with chronic HDV infection, with or without compensated cirrhosis.
- To further characterize the biological impact of treatment response, we evaluated changes in liver function and disease biomarkers through Week 48 according to treatment response status in HH003-204.

**Libevitug's Mechanism of Action（MOA）**




## Study Design




- ***Primary endpoint assessed at Week 24; long-term efficacy and safety assessed at Week 48.***
- **Nrtls pre-treatment was required only for subjects who were recommended for anti-HBV treatment but had not received first-line Nrtls therapy within 12 weeks prior to the planned initiation of the study treatment, and who met all inclusion criteria and none of the exclusion criteria. Nrtls (including TAFs during the study) were used to control HBV infection.*
- *The primary endpoint was a combined response, defined as the proportion of participants achieving HDV RNA below the LLOQ or a decrease of ≥ 2 log10 from baseline, along with ALT normalization at Week 24.*
- *Plasma HDV RNA level was measured using RoboGene HDV RNA Quantification kit 2.0 (LLOQ=46.77 IU/mL)*
- *Normal ALT was defined as ALT ≤ 33 U/L for female and ≤ 41 U/L for male.*

## Biomarkers & Methods

- **Biomarker analysis:** Longitudinal changes in liver function and disease biomarkers through Week 48 were evaluated according to treatment response status. Patients were classified at Week 48 using two response definitions: virologic responders (HDV RNA decline ≥2 $log_{10}$ IU/mL or HDV RNA <LLOQ) versus non-responders (0 to 1 $log_{10}$ IU/mL decline), and combined responders in Cohort B (virologic response plus ALT normalization) versus non-responders. Changes from baseline through Week 48 were evaluated across key domains of: liver enzymes (ALT, AST, and GGT); fibrosis and oncofetal markers (APRI, liver stiffness measurement [LSM], and alpha-fetoprotein [AFP]); and immune response (IFN-γ, TNF-α, IL-1Ra, and IP-10).
- **Logistic regression analysis**: Univariable and multivariable logistic regression analyses[7] were used to assess associations between baseline characteristics and combined treatment response at week 48.

## Patient demographics

| | HH-003 20 mg/kg (N=40) | HH-003 10 mg/kg (N=34) | Control group (N=20) |
|---|---|---|---|
| **Male, n (%)** | 28 (70.0%) | 22 (64.7%) | 14 (70.0%) |
| **Age (year), Mean (SD)** | 39.4 (12.2) | 41.1 (11.3) | 41.0 (10.6) |
| **Race - Asian, n (%)** | 40 (100.0%) | 34 (100.0%) | 20 (100.0%) |
| **Cirrhosis status, YES, n (%)** | 8 (20.0%) | 5 (14.7%) | 2 (10.0%) |
| **LSM (Kpa), Mean (SD)** | 10.42 (4.55) | 10.23 (3.45) | 9.59 (4.94) |
| **ALT (U/L), Mean (SD)** | 103.8 (79.3) | 115.1 (94.6) | 84.5 (44.6) |
| **HBsAg ($log_{10}$ IU/mL), Mean (SD)** | 3.81 (0.57) | 3.74 (0.58) | 3.73 (0.64) |
| **HBeAg, positive, n (%)** | 7 (17.5%) | 8 (23.5%) | 1 (5.0%) |
| **HBV DNA ($log_{10}$ IU/mL), Mean (SD)** | 0.63 (0.53) | 0.30 (0.37) | 0.50 (0.59) |
| **HDV RNA ($log_{10}$ IU/mL), Mean (SD)** | **6.24 (1.04)** | **6.27 (0.79)** | **5.66 (1.10)** |
| **HBV genotype-D, n (%)** | 35 (87.5%)* | 34 (100%) | 20 (100%) |
| **HDV genotype-1, n (%)** | 40 (100%) | 34 (100%) | 20 (100%) |
| **Previous IFN therapy, n (%)** | 9 (22.5%) | 10 (29.4%) | 5 (25.0%) |
| **Nrtls used prior to randomization, n (%)** | 35 (87.5%) | 31 (91.2%) | 18 (90.0%) |
| **Nrtls pre-treatment period, n (%)** | 1 (2.5%) | 1 (2.9%) | 1 (5.0%) |

- *94 of 100 with abnormal baseline ALT were included in the main analysis set.*
- ** The remaining five patients were distributed across HBV genotypes A (n=1), B (n=2), and C (n=1); one genotype could not be determined TEAE, treatment emergent adverse event; SAE, serious adverse event; AESI, adverse event of special interest.*
- *ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis D virus; IFN, interferon; LSM, liver stiffness measurement; NrtIs, nucleoside/nucleotide reverse transcriptase inhibitors; SD, standard deviation .*

## Safety

- Libevitug's TEAEs were comparable to the control, predominantly mild to moderate (Grade 1-2) in severity.
- No serious adverse events were related to libevitug, and there were no treatment discontinuations, hepatic progression events, infusion reactions, or deaths.

| Patients with, n (%) | HH-003 20 mg/kg (N=42) | HH-003 10 mg/kg (N=38) | Control (N=20) |
|---|---|---|---|
| **Any TEAE** | 40 (95.2) | 37 (97.4) | 19 (95.0) |
| **Any Grade ≥3*TEAE** | 4 (9.5) | 3 (7.9) | 2 (10.0) |
| **Any Grade ≥3 TEAE related to HH-003** | 1 (2.4)† | 0 | 0 |
| **Any SAE** | 3 (7.1) | 1 (2.6) | 2 (10.0) |
| **Any SAE related to HH-003** | 0 | 0 | NA |
| **AESI** | 1 (2.4)† | 1 (2.6)# | 0 |
| **Any TEAE leading to withdrawal of HH-003** | 0 | 0 | 0 |
| **Death** | 0 | 0 | 0 |
| **TEAE related to any study drug (≥ 5%) with higher frequencies in HH-003 groups compared to control** | | | |
| **Headache** | 8 (19.0) | 9 (23.7) | 1 (5.0) |
| **Malaise** | 7 (16.7) | 3 (7.9) | 0 |
| **Pruritus** | 4 (9.5) | 5 (13.2) | 0 |

- *† AE term: neutrophil count decreased, which was considered possibly related to HH-003; and it was transient, asymptomatic, and resolved spontaneously without intervention.*
- *# AE term: neutrophil count decreased, which occurred at the EOT visit and was considered not related to HH-003. No treatment was required; the AE resolved spontaneously within a short period and did not recur.*
- *TEAE, treatment emergent adverse event; SAE, serious adverse event; AESI, adverse event of special interest.*

## Efficacy

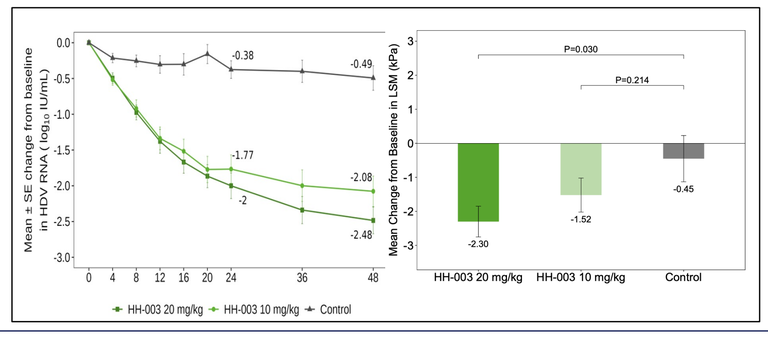
- **Combined response**: The combined response rate increased from Week 24 (20 mg/kg: 35.0%; 10 mg/kg: 32.4%) to Week 48 (42.5% and 44.1%, respectively) in patients with relatively high baseline HDV RNA levels.
- **Virological response**: Libevitug maintained profound viral suppression through Week 48 of treatment, with mean HDV RNA reductions from baseline of -2.48 log10 IU/mL (20 mg/kg) and -2.08 $log_{10}$ IU/mL (10 mg/kg) versus -0.49 $log_{10}$ IU/mL in the control, and achieved significantly higher virological response rates, which increased from Week 24 (42.5% and 35.3%) to Week 48 (60% and 50%) versus 5% in the control group.
- **ALT normalization**: Rates were 77.5% (20 mg/kg) and 58.8% (10 mg/kg) at Week 24 and were sustained at 70.0% and 55.9%, respectively, at Week 48.
- **Liver stiffness**: Libevitug treatment led to a notable reduction in liver stiffness at both Week 24 and Week 48.

| Libevitug (HH003) | Combined Responses | | ALT Normalization | | HDV RNA Response | |
|---|---|---|---|---|---|---|
| | Week 24 | **Week 48** | Week 24 | **Week 48** | Week 24 | **Week 48** |
| **10 mg/kg** | 32.4% | **44.1%** | 58.8% | **55.9%** | 35.3% | **50%** |
| **20 mg/kg** | 35.0% | **42.5%** | 77.5% | **70%** | 42.5% | **60%** |
| **Control** | 5% | **5%** | 20% | **10%** | 5% | **5%** |

Virologic response defined as HDV RNA levels below LLOQ or a ≥ 2 $log_{10}$ reduction from baseline; LLOQ=46.77 IU/mL

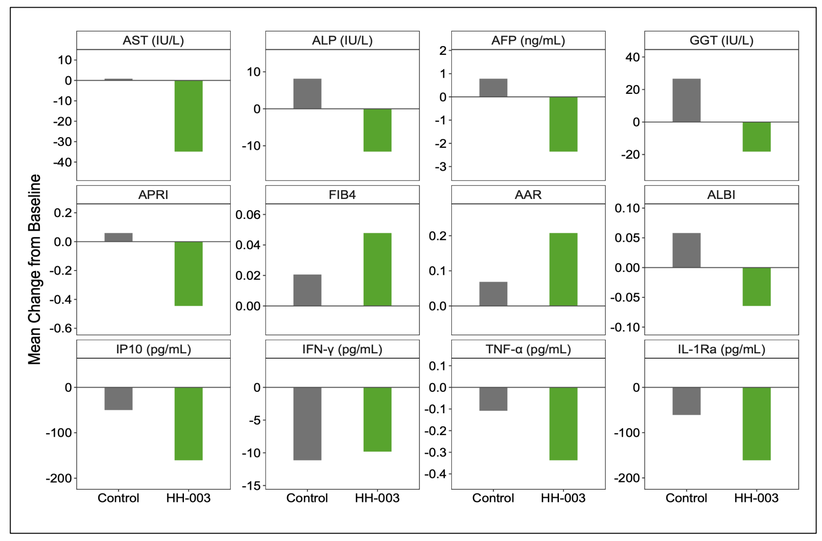
ALT Normalization : ALT ≤ 33 U/L for female and ≤ 41 U/L for male

- **HDV RNA levels and Liver stiffness (LSM)**



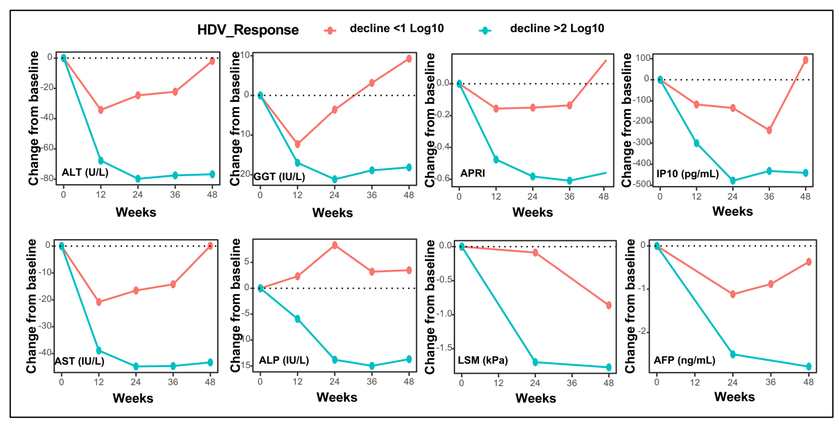

## Biomarker Analysis

- **Biomarker changes from baseline at Week 48**: Libevirtug treatment induced coordinated changes in biomarkers, including AST, ALP, AFP, GGT, APRI, FIB4, AAR, ALBI, IP10, IFN-γ, TNF-a, IL-1Ra, compared with the control arm.




1. *Group of HH-003 treatment combined 10 and 20 mg/kg, n=80, control group, n=20;*
2. *Biomarkers are : GGT, Gamma-Glutamyl Transferase ;APRI, AST to Platelet Ratio Index ;FIB4, Fibrosis-4 Index (Fibrosis-4 score) ;AAR, AST/ALT Ratio ;ALBI, Albumin-Bilirubin score*；IP-10, Interferon Gamma-Induced Protein 10 (also known as CXCL10, C-X-C motif chemokine ligand 10).

- **Biomarker dynamics** in treatment responders vs. non-responders: Treatment induced dynamic and coordinated changes of biomarkers, including ALT, AST, GGT, ALP, APRI, LSM, IP10 and AFP, along with the HDV RNA responses.




HDV RNA-Responder: decline ≥2 $log_{10}$, n=41; No-Responders: 0-1 $log_{10}$ decline, n=25 including control

- **Logistic regression analysis** for 48W-combined response

| Characteristic | Univariate | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p-value | OR | 95% CI | p-value |
| **Sex - Male** | 0.67 | 0.25, 1.78 | 0.4 | | | |
| **Age** | 0.99 | 0.95, 1.03 | 0.6 | | | |
| **BMI** | 0.91 | 0.80, 1.03 | 0.2 | 1.01 | 0.87, 1.19 | 0.9 |
| **HBV DNA** | 1.01 | 1.00, 1.06 | 0.4 | | | |
| **HBSAG** | 1.15 | 0.51, 2.72 | 0.7 | | | |
| **HDV RNA** | 1.43 | 0.86, 2.49 | 0.2 | 1.15 | 0.53, 2.51 | 0.7 |
| **ALT** | 1 | 0.99, 1.00 | 0.8 | | | |
| **AST** | 1 | 0.99, 1.01 | 0.5 | | | |
| **LSM** | 0.9 | 0.78, 1.01 | 0.093 | 1 | 0.79, 1.24 | >0.9 |
| **Cirrhosis - Yes** | 0.17 | 0.02, 0.68 | 0.026 | 0.32 | 0.02, 2.70 | 0.3 |
| **APRI** | 1.1 | 0.49, 2.46 | 0.8 | | | |
| **ALBI** | 2.86 | 0.43, 20.9 | 0.3 | | | |
| **FIB4** | 12.5 | 0.08, 2,970 | 0.3 | | | |
| **AAR** | 15.6 | 1.35, 264 | 0.039 | 24.4 | 1.44, 656 | 0.037 |
| **PLR** | 1 | 0.99, 1.02 | 0.6 | | | |
| **NLR** | 0.98 | 0.52, 1.77 | >0.9 | | | |
| **SII** | 1 | 1.00, 1.00 | >0.9 | | | |
| **MELD** | 0.92 | 0.59, 1.29 | 0.6 | | | |
| **IP10** | 1 | 1.00, 1.00 | 0.058 | 1 | 1.00, 1.00 | 0.047 |
| **IFNγ** | 1.01 | 0.99, 1.02 | 0.4 | | | |
| **TNF** | 1.4 | 0.73, 2.83 | 0.3 | | | |
| **IL1Ra** | 1 | 1.00, 1.00 | 0.7 | | | |
| **GGT** | 0.99 | 0.98, 1.00 | 0.077 | 0.98 | 0.95, 1.00 | 0.065 |
| **ALP** | 1.01 | 1.00, 1.03 | 0.12 | 1.02 | 1.00, 1.05 | 0.1 |
| **AFP** | 0.99 | 0.88, 1.10 | 0.9 | | | |
| **PLAT** | 1 | 0.99, 1.01 | 0.6 | | | |
| **INR** | 0.11 | 0.00, 53.3 | 0.5 | | | |
| **ALB** | 0.96 | 0.81, 1.14 | 0.7 | | | |

## Conclusions

- **Superior Efficacy**: Libevitug (HH-003) demonstrated superior efficacy vs. control across all predefined subgroups through Week 48. Both dose levels showed comparable improvements in combined response, viral suppression, ALT normalization, as well as comparable reductions in liver stiffness.
- **Disease Modification**: Stronger HDV RNA suppression was associated with coordinated improvements in virologic, biochemical, hepatic, fibrosis-related, oncofetal, and immune-inflammatory markers through Week 48. These findings support the potential of libevitug to modify disease activity in patients with chronic HDV infection.
- **Outlook**: With its favorable safety profile, libevitug represents a promising therapeutic option, and a confirmatory Phase 3 trial is currently underway. Baseline biomarkers combined with on-treatment dynamics may predict long-term clinical outcomes.

*References*

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*Acknowledgments*

We gratefully acknowledge all participants, their families, and the entire study team, including investigators and site coordinators of the HH003-204 study. This study was sponsored by Huahui Health Ltd.