Safety and efficacy of anti-pre-S1 domain monoclonal antibody (HH-003) treatment in patients with co-infection of chronic hepatitis B virus and hepatitis D virus

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Background and aim

HH-003 is a human monoclonal antibody that targets the preS1 domain of the large envelope protein of HBV and HDV. It prevents the binding of preS1 with sodium taurocholate co-transporting polypeptide (NTCP), the cellular receptor for HBV and HDV, and effectively blocks viral infection and re-infection of hepatocytes [1-2]. This single center, open-label, phase 2 study (NCT05674448) aimed to evaluate the safety and efficacy of HH-003 in participants with chronic HBV and HDV co-infection.

Methods

The study included nine participants (aged 18–70 years old) who were serum anti-HDV IgG positive and HDV RNA positive at screening and had a history of HBV for at least 6 months at screening. All participants received intravenous infusion of 20 mg/kg HH-003 once every two weeks for 24 weeks, with a 24-week follow-up. Virological response (a serum HDV RNA level below the limit of detection or a ≥ 2 $\log_{10}$ decline from baseline) and biochemical response (normalization of ALT, normal ALT was defined as ≤ 33 U/L for women and ≤ 41 U/L for men) to HH-003 treatment were assessed at week 24 and week 48. Serum HDV RNA level was measured using RoboGene HDV RNA Quantification kit 2.0.

Results

Baseline characteristics

Table 1. Baseline characteristics

Baseline characteristics	HH-003 (N=9)
Age, median years (min, max)	57 (49, 65)
Male, n(%)	6 (66.7)
BMI, median kg/m^2 (min, max)	23.7 (19.3, 28.2)
ALT, median U/L (min, max)	36 (21, 86)
Liver stiffness measurement, median Kpa (min, max)	8.9 (3.6, 14.1)
HDV genotype 1, n(%)	8 (88.9)*
HBV genotype B/C/D/missing, n	2/2/1/4
HDV RNA, median $\log_{10}$ IU/mL (min, max)	3.48 (1.58-5.40)
HBsAg, median $\log_{10}$ IU/mL (min, max)	3.28 (1.67, 3.72)
HBV DNA, median $\log_{10}$ IU/mL (min, max)	1.72 (1.00, 4.16)#
Previous NUC treatment, n(%)	1 (11.1)

*One subject with missing data in HDV genotype. # HBV DNA<LLOQ (10 IU/mL) was defined as 10 IU/mL. BMI, body mass index; ALT, alanine aminotransferase

Efficacy

- After HH-003 treatment, the median (min, max) changes of HDV RNA level from baseline at week 24 and week 48 were -2.18 (-3.88, 0.35) $\log_{10}$ IU/mL and -1.98 (-3.64, 0.72) $\log_{10}$ IU/mL, respectively.
- At week 24, 77.8% (7/9) of the participants achieved virological response; 3/5 (60%) of the participants with abnormal baseline ALT levels achieved ALT normalization, and the other 4 participants remained to have normal ALT levels (100%, 4/4); and 3/5 (60%) participants achieved combined response of both virological response and ALT normalization
- At week 48, 66.7% (6/9), 2/5 (40%) and 2/5 (40%) of participants achieved virological response, ALT normalization and combined response, respectively.

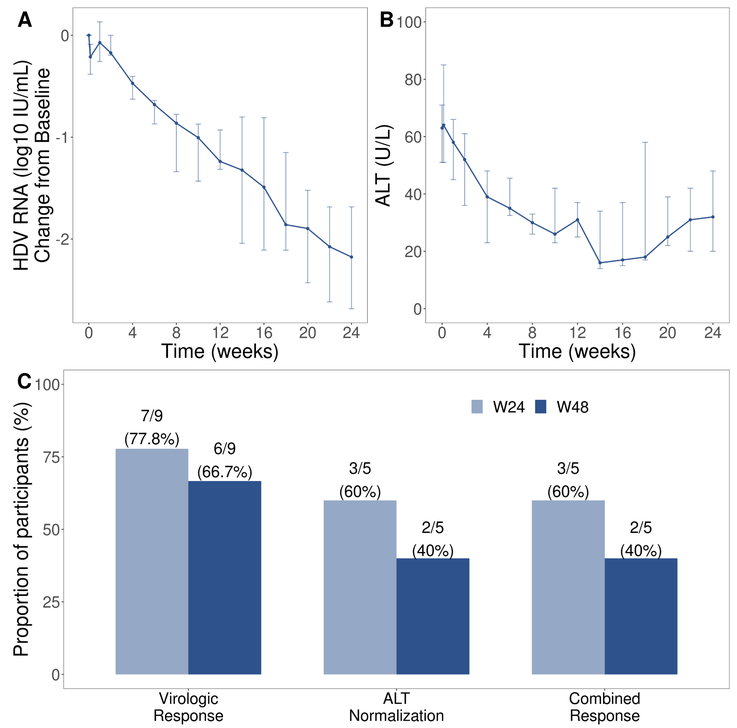

Figure: Efficacy outcomes from the study. (A) Serum HDV RNA level reduction during the HH-003 treatment period. Line plot with median and interquartile range (IQR) showing the $\log_{10}$ change from baseline of the serum HDV RNA level. (B) Line plot with median and IQR showing the dynamics of ALT levels in 5 participants with abnormal baseline ALT levels. (C) The proportions of participants achieved virologic response, ALT normalization and combined response at week 24 and week 48.

Safety

- One subject (11.1%) experienced treatment-related adverse event (AE) of abdominal discomfort (Grade 1) and asthenia (Grade 2).
- No grade 3 or higher AE or serious AE occurred, and no participants discontinued treatment due to AE.

Table 2. Overall treatment-emergent adverse events

	HH-003 (N=9)
Subjects with any TEAE, n (%)	8 (88.9)
Subjects with any treatment-related TEAE, n (%)	1 (11.1)
Subects with any ≥ grade 2 TEAE, n (%)	1 (11.1)
Subects with any drug-related ≥ grade 2 TEAE, n (%)	1 (11.1)
Subects with any ≥ grade 3 TEAE, n (%)	0
Subjects with any serious TEAE, n (%)	0
Subjects with any TEAE leading to death, n (%)	0
Subjects with any TEAE leading to study treatment withdrawal, n (%)	0
Subjects with any TEAE leading to study discontinuation, n (%)	0

Adverse events are assessed by CTCAE v5.0.

Conclusions

HH-003 treatment at a dose of 20 mg/kg demonstrated significant decrease of HDV RNA level and ALT normalization, with a good safety profile in participants co-infected with HBV and HDV. HH-003 might provide a new treatment option for patients with HBV and HDV co-infection, and a large-scale study will be conducted to further demonstrate such a promising anti-viral effect of HH-003 in participants with HBV and HDV co-infection.

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Disclosures

The authors declare that there is no conflict of interest.

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