A first-in-patient phase Ib study of a hepatitis B virus (HBV) neutralizing antibody HH-003 in treatment-naïve participants with HBeAg-positive chronic HBV infection

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INTRODUCTION

- Chronic hepatitis B virus (HBV) infection remains a major health problem, with 296 million people chronically infected worldwide who are at high risk of developing live cirrhosis and hepatocellular carcinoma (HCC)[1].
- There remains a significant unmet medical need that requires novel therapeutic approaches to achieve a functional cure of chronic hepatitis B.
- HH-003 is a human monoclonal antibody targeting the pre-S1 domain of the HBV large envelope protein. It blocks the engagement of pre-S1 with sodium taurocholate co-transporting polypeptide (NTCP), the cellular receptor for HBV/HDV[2]. It has potential dual anti-HBV mechanisms[3]:
  - Directly blocks viral entry into hepatocytes, thus inhibits viral infection and re-infection;
  - Elicits antibody-Fc-dependent immunological effector functions to clear HBV virions and/or virus-infected hepatocytes.

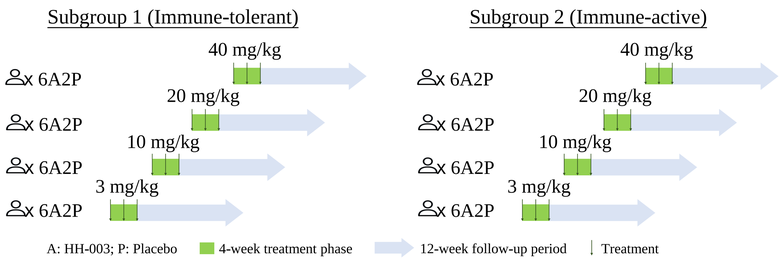
OBJECTIVE

- To evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of HH-003 in treatment-naïve, HBeAg-positive chronic HBV infection participants following three doses of HH-003.

METHOD

- A placebo-controlled, randomized, double-blind, multiple ascending dose study.
- Treatment-naïve, HBeAg-positive participants including subgroup 1 (Immune-tolerant) and subgroup 2 (Immune-active) were enrolled and randomized (6:2 within each dose cohort for both subgroups). Each subgroup included 4 dose cohorts (3, 10, 20, and 40 mg/kg) to receive HH-003 or placebo intravenously bi-weekly at Day 0, Day 14, and Day 28, with 12 weeks of follow-up.
- Safety, tolerability and antiviral activity data were assessed at primary endpoint time (4 weeks after end of treatment).

Fig 1. HH-003 phase Ib study design



RESULTS

- Total of 67 treatment naïve HBeAg-positive participants including subgroup 1 (Immune-tolerant (n=34)) and subgroup 2 (Immune-active (n=33)) were enrolled and randomized.
- In subgroup 1 participants, mean age was 29.7±4.27 years with 47.1% male, mean baseline ALT and HBV DNA levels were 6.30±11.69 U/L and 8.2±0.35 $\log_{10}$ IU/mL, respectively (Table 1).
- In subgroup 2 participants, mean age was 30.0±6.06 years with 63.6% male; mean baseline ALT and HBV DNA levels were 123.06±67.07 U/L and 8.1±0.54 $\log_{10}$ IU/mL, respectively (Table 1).

Safety

- Observed HH-003 treatment-related AEs were all grade1-2.
- There were no treatment-related serious AEs or AEs leading to treatment discontinuation.
- Forty (40/51, 78.4 %) and ten (10/16, 62.5%) participants experienced on-treatment adverse events in the HH-003 and placebo groups, respectively (Table 2).
- The incidence of treatment-related AEs was 52.9% and 50% in the HH-003 and placebo groups, respectively (Table 2).

Table 1. Baseline characteristics

Characteristics	HH-003 3 mg/kg	HH-003 10 mg/kg	HH-003 20 mg/kg	HH-003 40 mg/kg	Placebo	Total
Subgroup 1, Immune-tolerant	N=6	N=8	N=6	N=6	N=8	N=34
Age (years)	29.7(3.93)	28.1(5.28)	29.2(5.04)	30.0(4.65)	31.5(2.62)	29.7(4.27)
Male, n (%),	4(66.7)	3(37.5)	3(50.0)	1(16.7)	5(62.5)	16(47.1)
BMI (kg/m^2)	22.68(2.75)	23.28(2.93)	20.83(2.75)	23.82(2.73)	24.76(2.63)	23.19(2.90)
HBV DNA ($\log_{10}$ IU/mL)	8.21(8.06,8.73)	8.05(7.36,8.97)	8.18(7.91,8.57)	8.25(7.81,8.77)	8.24(7.90,8.73)	8.22(7.36,8.97)
HBsAg ($\log_{10}$ IU/mL)	4.67(4.34,4.89)	4.61(3.54,5.06)	4.83(4.45,4.98)	4.69(4.35,4.91)	4.73(4.01,4.82)	4.71(3.54,5.06)
HBeAg ($\log_{10}$ IU/mL)	3.14(2.82,3.42)	2.92(2.46,3.49)	3.14(3.00,3.31)	3.13(2.91,3.85)	3.06(2.54,3.39)	3.08(2.46,3.85)
ALT (U/L)	29.80(9.26)	25.75(15.00)	25.33(13.37)	22.50(3.99)	28.25(13.58)	26.30(11.69)
Subgroup 2, Immune-active	N=6	N=7	N=6	N=6	N=8	N=33
Age (years)	28.8(5.91)	30.9(8.59)	29.5(8.89)	31.0(3.03)	29.6(3.70)	30.0(6.06)
Male, n (%)	4(66.7)	5(71.4)	3(50.0)	2(33.3)	7(87.5)	21(63.6)
BMI (kg/m^2)	23.02(3.05)	23.11(2.02)	23.78(3.17)	23.68(2.33)	24.14(2.18)	23.57(2.42)
HBV DNA ($\log_{10}$ IU/mL)	8.09(7.18,8.82)	8.24(7.48,8.77)	7.90(7.58,8.00)	7.55(7.08,8.48)	8.50(8.03,9.44)	8.09(7.08,9.44)
HBsAg ($\log_{10}$ IU/mL)	4.24(3.76,4.59)	4.12(3.90,4.71)	4.01(3.88,4.68)	3.79(3.25,4.43)	4.48(4.16,5.10)	4.19(3.25,5.10)
HBeAg ($\log_{10}$ IU/mL)	3.04(1.84,3.35)	2.87(2.52,3.65)	2.68(1.07,3.28)	2.80(2.47,3.19)	2.88(2.40,3.14)	2.82(1.07,3.65)
ALT (U/L)	134.17(51.98)	98.86(32.55)	141.50(92.05)	113.83(34.08)	129.00(98.73)	123.06(67.07)

Reported values are mean (SD) except for HBV DNA, HBsAg and HBeAg median (min, max); BMI, body mass index; ALT, alanine aminotransferase

Table 2. Summary of Safety and Tolerability (Safety set)

	HH-003					All placebo
	3 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg	All	
	N=12	N=15	N=12	N=12	N=51	N=16
Any TEAE, n (%)	9(75)	12(80)	10(83.3)	9(75)	**40(78.4)**	**10(62.5)**
Grade≥3, n (%)	1 (8.3)	0	0	0	**1(2.0)**	**0**
Any TRAE, n (%)	8(66.7)	8(53.3)	4(33.3)	7(58.3)	**27 (52.9)**	**8(50)**
Grade≥3, n (%)	0	0	0	0	**0**	**0**
SAE, n (%)	0	0	0	1 (8.3)	**1 (2.0)**	**1(6.3)**
Treatment –related SAE	0	0	0	0	**0**	**0**
AEs leading to treatment discontinuation	0	0	0	0	**0**	**0**

AEs following the first dose till 4 weeks after the end of treatment are shown. TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event; SAE=serious adverse event

Pharmacokinetics

- The PK profiles were similar across subgroup 1 and subgroup 2.
- The HH-003 exposure parameters increased dose proportionally from 3mg/kg to 40mg/kg.
- The terminal elimination half-life following three doses intravenously ranged from 5.6 to 13.7 days.
- The accumulation ratio of AUC was approximately 1.5 after three doses.

Table 3. PK parameters of HH-003 in HBeAg-positive chronic HBV infection participants after three doses intravenously

PK Parameters	3 mg/kg Q2W, N=12	10 mg/kg Q2W, N=15	20 mg/kg Q2W, N=12	40 mg/kg Q2W, N=12
$t_{1/2}$ (day)	5.61 (32.2)	10.5 (16.5)	12.1 (18.6)	13.7 (19.5)
C_{max} (μg/mL)	101.0 (28.6)	291.2 (16.9)	604.5 (23.2)	1218 (25.7)
Tmax (h)	3.5 (0.5-24.9)	1.0 (0.5-3.5)	0.5 (0.5-12.5)	1.5 (0.5-23.6)
AUC_{tau} (day*μg/mL)	447.5 (21.7)	1663 (13.9)	3524 (18.2)	6992 (20.0)
R_{ac}(AUC)	1.47 (14.7)	1.46 (8.5)	1.52 (11.6)	1.50 (16.0)

Reported values are mean (CV%) except for T_{max} median (min-max); $t_{1/2}$: half-life; C_{max}: maximum concentration; T_{max}: time to reach C_{max}; AUC_{tau}: Area under the concentration-time curve over a dosing interval; R_{ac} (AUC): the accumulation ratio of AUC; Q2W: once every 2 weeks

Antiviral activity

- A decrease in HBV DNA, HBsAg and ALT from baseline was observed across all dose cohorts in subgroup 2 at 4 weeks after HH-003 treatment, but not in subgroup 1.
- Particularly for 20 mg/kg dose cohort in subgroup 2, 50% (3/6) of participants achieved >1.0 $\log_{10}$ reduction in HBV DNA and 66.7% (4/6) participants achieved >0.5 $\log_{10}$ reduction in HBsAg at 4 weeks after end of HH-003 treatment.
- Changes of HBV RNA and HBcrAg were by large in parallel with that of HBV DNA level after HH-003 treatment.

Fig 2. Mean Change from Baseline in HBV DNA, HBsAg, ALT, HBV RNA and HBcrAg at 4 weeks after End of Treatment

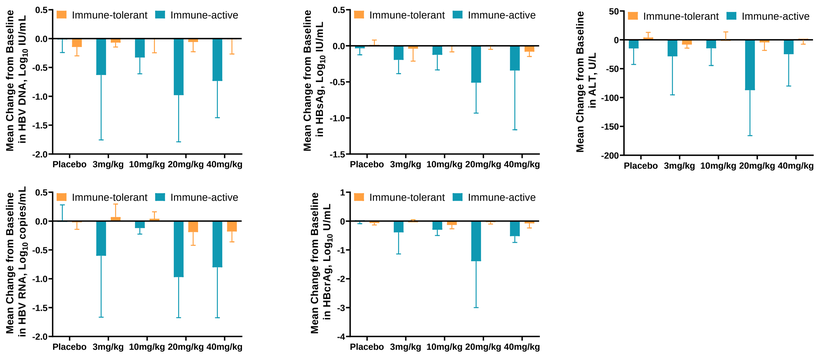
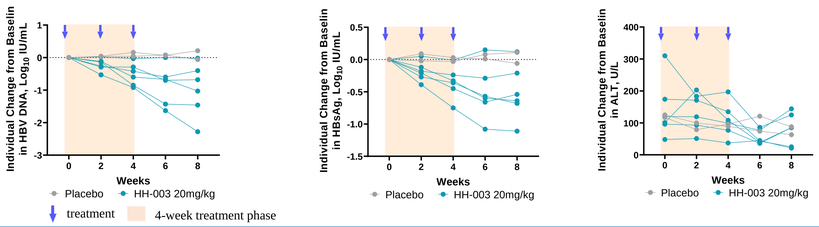


Fig 3. Change from Baseline in HBV DNA, HBsAg and ALT for 20 mg/kg cohort in subgroup 2



CONCLUSIONS

- In HBeAg-positive chronic HBV infection participants, HH003 is safe and well-tolerated following three intravenous doses given bi-weekly.
- HH-003 exhibits a dose-dependent PK profile in HBeAg-positive chronic HBV infection participants.
- HH-003 demonstrates antiviral activity in immune active participants, and 20 mg/kg of HH-003 dose group shows optimum antiviral activity.

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Disclosures

The authors declare that there is no conflict of interest.