Safety, Tolerability, and Remarkable Hepatitis B Surface Antigen Reduction in Chronic Hepatitis B Patients Treated With BW-20507

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Introduction

Chronic HBV infection affects approximately 296 million people worldwide and causes an estimated 820,000 deaths annually [1], primarily due to complications such as liver cirrhosis and hepatocellular carcinoma (HCC).

BW-20507 is a double-stranded, N-acetylgalactosamine (GalNAc)-conjugated, small interfering RNA (siRNA) designed to target the S region of HBV messenger RNA (mRNA).

- The GalNAc enables BW-20507 to be specifically delivered to hepatocytes through binding with the asialoglycoprotein receptor (ASGPR).
- BW-20507 inhibits multiple HBV mRNAs, leading to broad suppression of viral antigen expression except Hepatitis B x antigen (HBx). This multi-targeted approach may offer enhanced efficacy over single protein-targeted inhibitors and may support host immune restoration.
- Preclinical studies have demonstrated its distinct antiviral activity and promising potential for the treatment of HBV infection.

Aim

Here, we present topline data from an ongoing phase 1 study (BW-20507-1001-Part B) evaluating the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of BW-20507 in CHB participants without advanced liver fibrosis or cirrhosis.

Method

Participants who were nucleotide/nucleoside analog (NUC) experienced (HBV DNA < 90 IU/mL) or NUC naïve with hepatitis B surface antigen (HBsAg) >50 IU/mL were enrolled into 4 cohorts **(Figure 1)**, with a planned enrollment of 6–8 individuals per cohort:

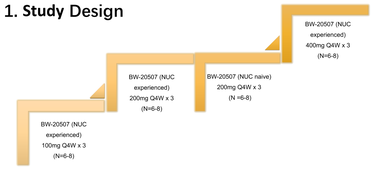
- Cohort 1: 100 mg (NUC experienced)
- Cohort 2: 200 mg (NUC experienced)
- Cohort 3: 200 mg (NUC naive)
- Cohort 4: 400 mg (NUC experienced)

Participants with advanced fibrosis or cirrhosis, and those with alanine aminotransferase (ALT) > 2 x Upper limit of normal (ULN) were excluded.

All participants received three doses of BW-20507 subcutaneously every 4 weeks during the study. In Cohort 3 (NUCs naïve), participants either started NUC therapy on Day 1 or remained off NUC at the investigators' discretion.

Participants will be followed up to 40 weeks after the last dose of BW-20507.

Figure 1. Study Design



Results

Participants Characteristics

A total of 31 participants were enrolled, with 8 participants in each cohort except for Cohort 3, which included 7 participants.

- Until the cut-off date, all participants had completed the D225 visit (24 weeks after the last dose of BW-20507).
- In cohort 3, 4 of the 7 participants started NUCs from Day 1; the other 3 remained off-NUC.

Baseline Characteristics are presented in Table 1.

Table 1. Participants Demographics and Baseline Characteristics

	Cohort 1 (N=8) NUC experienced 100mg Q4W x 3	Cohort 2 (N=8) NUC experienced 200mg Q4W x 3	Cohort 3 (N=7) NUC naive 200mg Q4W x 3	Cohort 4 (N=8) NUC experienced 400mg Q4W x 3
Age (years), Mean (SD)	41.5 (9.6)	48.8 (10.0)	43.7 (7.2)	44.6 (11.6)
Sex, n (%)				
Male	8 (100.0%)	6 (75.0%)	1 (14.3%)	5 (62.5%)
Female	0	2 (25.0%)	6 (85.7%)	3 (37.5%)
Race, n(%)				
Asian	8 (100.0%)	8 (100.0%)	7 (100.0%)	8 (100.0%)
BMI, mean (SD)	22.7 (2.4)	23.8 (1.7)	26.8 (3.1)	22.1 (2.1)
Baseline HBsAg (log IU/mL), mean (SD)	3.2 (0.5)	3.0 (0.4)	3.3 (1.2)	3.1 (0.4)
Baseline HBeAg, n (%)				
Reactive	4 (50%)	0	4 (57.1%)	3 (37.5%)
Nonreactive	4 (50%)	8 (100%)	3 (42.9%)	5 (62.5%)
Baseline HBV DNA, Mean (SD)	< LLOQ	< LLOQ	4.9 (2.5)	< LLOQ

BW-20507 Tolerability and Safety

- BW-20507 was generally well tolerated when administered subcutaneously for multiple doses
- A total of 17 participants (54.8%) reported 55 adverse events (AEs). All were grade 1 or 2 in severity. There were no death, SAE, or AEs leading to drug discontinuation (Table 2).
- AE reported ≥10% of the participants included headache (5 subjects, 16.1%) and respiratory tract infection (4 subjects, 12.9%).
- Injection site reactions were reported in 2 participants only (6.5%). Both were Grade 1.
- No post-dose ALT or AST elevation to > 2 x ULN.

Table 2. Preliminary Summary of Safety and Tolerability

n (%)	Cohort 1 (N=8)	Cohort 2 (N=8)	Cohort 3 (N=7)	Cohort 4 (N=8)
Any AE	2 (25%)	4 (50%)	6 (85.7%)	5 (62.5%)
Grade 1	2 (25%)	3 (37.5%)	4 (57.1%)	5 (62.5%)
Grade 2	0	1 (12.5%)	4 (57.1%)	0
Grade 3 or above	0	0	0	0
Related AE	2 (25%)	2 (25%)	2 (28.6%)	0
Grade 1	2 (25%)	2 (25%)	2 (28.6%)	0
Grade 2	0	0	0	0
Grade 3 or above	0	0	0	0
SAE	0	0	0	0
AE leading to drug discontinuation	0	0	0	0
AE leading to study discontinuation	0	0	0	0

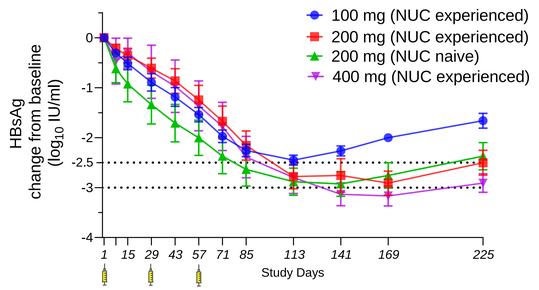
BW-20507 Results in Rapid Reduction in HBsAg

The maximal HBsAg reductions from baseline were -2.4, -2.9, and -3.2 $\log_{10}$ IU/mL in NUCs experienced cohorts (100 mg, 200 mg, and 400 mg, respectively) and -2.9 $\log_{10}$ IU/ mL in 200 mg NUCs naïve cohort.

The maximal HBsAg reductions were observed between Day 113 and Day 169 (i.e., 8–16 weeks post the last BW-20507 dose), across different cohorts.

By Day 225 (24 weeks after the last dose of BW-20507), HBsAg reductions from baseline remained at -1.7, -2.5, and -2.9 $\log_{10}$ IU/mL in NUCs experienced cohorts (100 mg, 200 mg, and 400 mg, respectively), and at -2.4 $\log_{10}$ IU/mL in 200 mg NUCs naïve cohort.

Figure 2. Mean HBsAg Change from Baseline (log 10 IU/mL)



In 200mg and 400mg cohorts (i.e. Cohort 2, 3, and 4) (Table 3),

- 5 (22%) of the 23 participants achieved HBsAg loss during the study.
- Among participants with baseline HBsAg levels <100 IU/mL, <500 IU/mL, and <1000 IU/mL, the observed HBsAg loss rates were 100% (2/2), 67% (4/6), and 56% (5/9), respectively..

Table 3 HBsAg loss achieved during the study (stratified by baseline HBsAg level)

Baseline HBsAg	Cohort 1 (N=8)	Cohort 2 (N=8)	Cohort 3 (N=7)	Cohort 4 (N=8)
HBsAg loss during the study	0/8	1/8	2/7	2/8
Baseline HBsAg				
≤100 IU/mL	NA	NA	2/2	NA
100 - ≤ 500 IU/mL	0/2	1/3	NA	1/1
500 -≤1000 IU/mL	0/1	0/2	NA	1/1
>1000 IU/mL	0/5	0/3	0/5	0/6

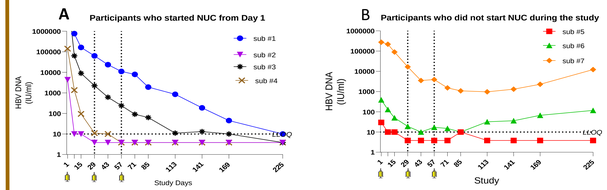
Effects of BW-20507 on Other HBV Pharmacodynamic Markers

HBeAg loss, defined as a change from positive to negative at any visit compared to baseline, was observed in 1 subject in Cohort 1 and 1 subject in Cohort 4.

In the 200mg naïve cohort (Cohort 3), the 3 NUC naive participants who did not receive NUC during the study also demonstrated significant HBV DNA reductions (Figure 3B).

- Two participants with low baseline HBV DNA levels (30 IU/mL and 388 IU/mL) achieved HBV DNA below LLOQ (10 IU/mL) during treatment.
- The maximal reduction of HBV DNA was -2.5 $\log_{10}$ IU/mL in the participant with high HBV DNA (5.4 $\log_{10}$ IU/mL) at baseline.

Figure 3. HBV DNA Change (log 10 IU/mL) in 200mg naïve Cohort (Cohort 3)



Conclusions

Three subcutaneous doses of BW-20507 were well tolerated and demonstrated a favorable safety profile in participants with CHB.

BW-20507 demonstrated significant, dose-dependent reductions in HBsAg and potent suppression of HBV DNA.

HBsAg loss during study was observed in some patients with baseline HBsAg levels < 1,000 IU/mL.

These findings support the continued clinical development of BW-20507 as a promising therapeutic candidate for CHB.

References

1. WHO (2024). "Hepatitis B Key Facts. website: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b."

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