Vebicorvir, entecavir, and pegylated interferon in patients with hepatitis B e antigen positive chronic hepatitis B virus infection: Findings from a Phase 2, randomized open-label study in China

SAT-174

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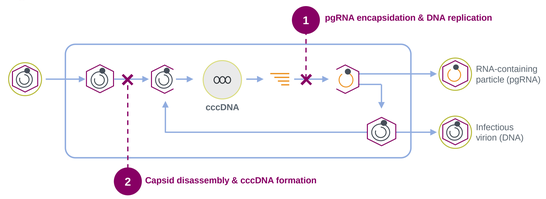
Background

- Chronic hepatitis B virus infection (cHBV) is a significant global health problem affecting an estimated 296 million people worldwide and resulting in approximately 820,000 deaths yearly, largely due to cirrhosis and hepatocellular carcinoma[1-4]
- Nucleos(t)ide reverse transcriptase inhibitors (NrtIs) are generally well tolerated, and on-treatment virologic suppression is achieved in the majority of patients. However, nearly all patients relapse after stopping NrtIs, resulting in the need for lifelong treatment[5-7]
- Novel combination approaches may provide durable virologic outcomes following finite treatment durations and reduce the number of patients requiring lifelong therapy
- Core inhibitors are a novel class of antivirals that interfere with multiple steps of the HBV lifecycle
  - These agents work through inhibition of pregenomic (pg)RNA encapsidation, preventing assembly and release of infectious viral particles, and disruption of incoming capsids, preventing covalently closed circular (ccc)DNA formation (**Figure 1**)[8]
  - In Phase 1 studies, core inhibitors demonstrated potent antiviral effects,[9-11] and in Phase 2 studies, they demonstrated additive antiviral activity when combined with NrtIs vs NrtIs alone[12,13]
- Vebicorvir (VBR) is a first-generation core inhibitor that, in combination with entecavir (ETV), has demonstrated deeper viral suppression compared with ETV alone in untreated patients with hepatitis B e antigen (HBeAg) positive cHBV[13,14]
  - The addition of pegylated interferon alfa (Peg-IFNα) may further increase the efficacy of VBR+ETV through complementary mechanisms of action

Figure 1. HBV Core Inhibitor Mechanisms of Action



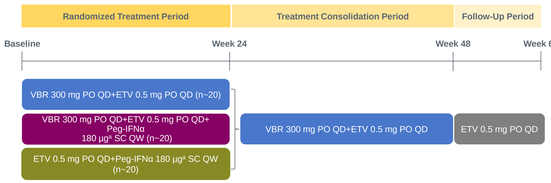
cccDNA, covalently closed circular DNA; HBV, hepatitis B virus; pgRNA, pregenomic RNA.

Objective

- The objective of this analysis is to report the safety and efficacy of VBR when administered in combination with ETV with or without Peg-IFNα in patients with cHBV (NCT04781647)

Methods

Figure 2. Study Design



Key inclusion criteria

- Male or female, aged 18-65 years (inclusive)
- cHBV[b]
- HBeAg positive with HBV DNA ≥2×10[4] IU/mL
- No cirrhosis (F0-F3 fibrosis) or advanced liver disease

Key exclusion criteria

- Coinfection with HAV, HCV, HDV, HEV, or HIV
- HBV infection with >1 genotype
- Current or prior treatment for cHBV[c]
- ALT ≤2× ULN or ≥10× ULN

[a]Reduction to 90 µg or 135 µg permitted due to adverse reactions; [b]Defined as HBV infection documented for ≥6 months from Screening; [c]Including a nucleos(t)ide reverse transcriptase inhibitor for >4 weeks; interferon-based therapy or liver-protecting and ALT-lowering treatment including traditional Chinese medicine ≤6 months of screening; lamivudine, telbivudine or adefovir (of any duration); or previous treatment with an investigational agent for HBV infection.
ALT, alanine aminotransferase; cHBV, chronic HBV infection; ETV, entecavir; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; Peg-IFNα, pegylated interferon alfa; PO, oral; SC, subcutaneous; QD, once daily; QW, once weekly; ULN, upper limit of normal; VBR, vebicorvir.

- Phase 2, multicenter, randomized, open-label study conducted in China (NCT04781647)
- Approximately 60 patients were to be randomized 1:1:1 to treatment with VBR+ETV, VBR+ETV+Peg-IFNα, or Peg-IFNα+ETV for 24 weeks, after which all patients were to receive VBR+ETV for 24 weeks and then ETV alone during a 12-week follow-up period (**Figure 2**)
  - Treatment assignments were stratified by HBV genotype (A or B vs C or D vs other genotypes) and baseline alanine aminotransferase (ALT; <5× upper limit of normal [ULN] vs ≥5× ULN)
- For efficacy assessments:
  - HBV DNA was measured by COBAS TaqMan (limit of detection [LOD]=10 IU/mL) and pgRNA by Assembly Biosciences quantitative polymerase chain reaction assay (LOD=33.1 U/mL)
  - Quantitative hepatitis B surface antigen (HBsAg) was measured by Abbott Architect and Roche Elecsys (lower limit of quantification [LLOQ]=0.05 IU/mL)
  - Quantitative hepatitis B core-related antigen (HBcrAg) was measured by Lumipulse G (LLOQ=1.0 kU/mL)
  - Quantitative HBeAg measured by Abbott Architect and Roche Elecsys (LLOQ=0.11 IU/mL)
- Safety was assessed by adverse events (AEs) and laboratory parameters

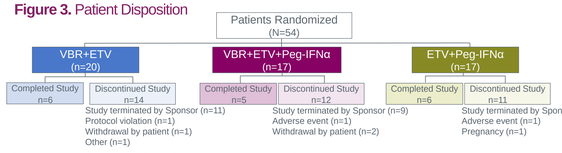
Results

Table 1. Demographics and Baseline Characteristics

Characteristics	VBR+ETV (n=20)	VBR+ETV+Peg-IFNα (n=17)	ETV+Peg-IFNα (n=17)	Total (N=54)
Age, years	33 (6.6)	31 (5.8)	34 (7.8)	32 (6.7)
Sex, male, n (%)	15 (75.0)	14 (82.4)	10 (58.8)	39 (72.2)
BMI, kg/m^2	22.5 (2.7)	22.9 (2.4)	23.4 (3.5)	22.9 (2.8)
Time HBV positive, years	11.3 (9.2)	11.2 (9.4)	11.2 (8.9)	11.3 (9.0)
HBV genotype, n (%)				
B	9 (45.0)	8 (47.1)	8 (47.1)	25 (46.3)
C	11 (55.0)	9 (52.9)	9 (52.9)	29 (53.7)
HBV DNA, $\log_{10}$ IU/mL	8.2 (1.02)	7.7 (1.11)	8.1 (0.63)	8.0 (0.96)
HBV pgRNA, $\log_{10}$ U/mL	6.5 (1.33)	5.8 (1.43)	6.5 (1.05)	6.3 (1.30)
HBsAg, $\log_{10}$ IU/mL	4.5 (0.39)	4.1 (0.76)	4.3 (0.53)	4.3 (0.58)
HBcrAg, $\log_{10}$ kU/mL	5.5 (0.59)	5.0 (0.71)	5.4 (0.46)	5.3 (0.62)
HBeAg, $\log_{10}$ IU/mL	2.7 (0.81)	2.4 (0.89)	2.7 (0.64)	2.6 (0.79)
ALT, U/L	149 (65.0)	138 (121.2)	123 (58.5)	137 (84.3)

Data shown are mean (SD) unless otherwise indicated.
ALT, alanine aminotransferase; BMI, body mass index; ETV, entecavir; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; Peg-IFNα, pegylated interferon alfa; pgRNA, pregenomic RNA; SD, standard deviation; VBR, vebicorvir.

Figure 3. Patient Disposition



Based on assessment of Week 24 data, the study was terminated early by the Sponsor.
ETV, entecavir; Peg-IFNα, pegylated interferon alfa; VBR, vebicorvir.

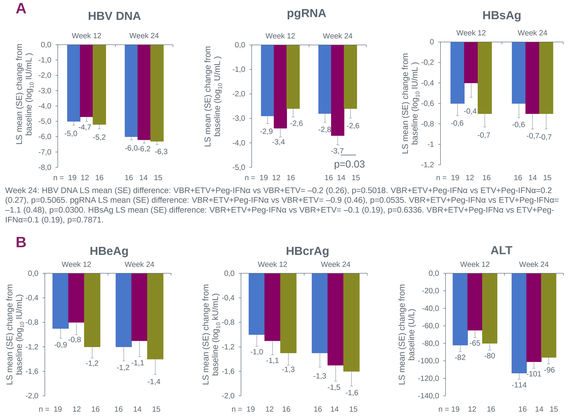
Table 2. On-Treatment Study Drug Compliance

	VBR+ETV (n=20)		VBR+ETV+Peg-IFNα (n=17)			ETV+Peg-IFNα (n=17)		
	VBR	ETV	VBR	Peg-IFNα	ETV	Peg-IFNα	ETV	VBR[a]
≤80%	0	0	0	2 (11.8)	0	1 (5.9)	1 (5.9)	1 (5.9)
80% to ≤90%	0	0	1 (5.9)	2 (11.8)	0	2 (11.8)	0	0
>90%	20 (100.0)	20 (100.0)	16 (94.1)	13 (76.5)	17 (100.0)	14 (82.4)	16 (94.1)	15 (88.2)

Data shown are n (%). Reported data include both the Randomized Treatment Period and the Treatment Consolidation Period.
[a]VBR compliance data were not available for one patient.
ETV, entecavir; Peg-IFNα, pegylated interferon alfa; VBR, vebicorvir.

- A total of 54 Asian patients were randomized; demographics and baseline characteristics were similar across treatment arms (**Table 1 and Figure 3**)
- Overall, 25/54 (46%) and 29/54 (54%) patients were infected with HBV genotype B and C, respectively
- Baseline HBV DNA, pgRNA, HBsAg, HBcrAg, HBeAg, and ALT levels were similar across groups and consistent with the target population
- Overall, most patients had >80% compliance to study drug across cohorts (**Table 2**)

Figure 4. Change From Baseline in (A) HBV DNA, pgRNA, and HBsAg and (B) HBeAg, HBcrAg, and ALT (Randomized Treatment Period)

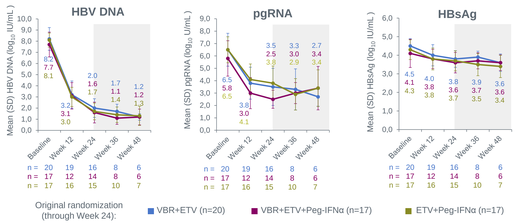


Week 24: HBV DNA LS mean (SE) difference: VBR+ETV+Peg-IFNα vs VBR+ETV= −0.2 (0.26), p=0.5018. VBR+ETV+Peg-IFNα vs ETV+Peg-IFNα=0.2 (0.27), p=0.5065. pgRNA LS mean (SE) difference: VBR+ETV+Peg-IFNα vs VBR+ETV= −0.9 (0.46), p=0.0535. VBR+ETV+Peg-IFNα vs ETV+Peg-IFNα= −1.1 (0.48), p=0.0300. HBsAg LS mean (SE) difference: VBR+ETV+Peg-IFNα vs VBR+ETV= −0.1 (0.19), p=0.6336. VBR+ETV+Peg-IFNα vs ETV+Peg-IFNα=0.1 (0.19), p=0.7871.

Week 24: HBeAg LS mean (SE) difference: VBR+ETV+Peg-IFNα vs VBR+ETV=0.0 (0.31), p=0.9430. VBR+ETV+Peg-IFNα vs ETV+Peg-IFNα=0.3 (0.31), p=0.3620. HBcrAg LS mean (SE) difference: VBR+ETV+Peg-IFNα vs VBR+ETV= −0.2 (0.31), p=0.5300. VBR+ETV+Peg-IFNα vs ETV+Peg-IFNα=0.1 (0.31), p=0.8694. ALT LS mean (SE) difference: VBR+ETV+Peg-IFNα vs VBR+ETV=12 (9.1), p=0.1852. VBR+ETV+Peg-IFNα vs ETV+Peg-IFNα= −6 (9.1), p=0.5414.

LS means were calculated using an analysis of covariance model with baseline values, stratification factors, and treatment group as covariates.
ALT, alanine aminotransferase; ETV, entecavir; HBV, hepatitis B virus; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; LS, least squares; Peg-IFNα, pegylated interferon alfa; pgRNA, pregenomic RNA; SE, standard error; VBR, vebicorvir.

Figure 5. HBV DNA, pgRNA, and HBsAg Levels Over Time



Based on assessment of Week 24 data, the study was terminated early by the Sponsor; gray shading indicates the Treatment Consolidation Period.
ETV, entecavir; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; Peg-IFNα, pegylated interferon alfa; pgRNA, pregenomic RNA; SD, standard deviation; VBR, vebicorvir.

- At Week 12, there were no significant differences between the VBR+ETV+Peg-IFNα treatment arm and the VBR+ETV or ETV+Peg-IFNα treatment arms in change from baseline for any efficacy measures (**Figure 4**)
- There were no significant differences between the VBR+ETV+Peg-IFNα treatment arm and the VBR+ETV or ETV+Peg-IFNα treatment arms in change from baseline to Week 24 for HBV DNA, HBsAg, hepatitis B core-related antigen (HBcrAg), or HBeAg (**Figure 4**)
- Importantly, the VBR+ETV arm performed similarly to the two Peg-IFNα–containing arms with 6.0 $\log_{10}$ IU/mL and 0.6 $\log_{10}$ IU/mL reductions in HBV DNA and HBsAg from baseline, respectively
  - Treatment with VBR+ETV+Peg-IFNα resulted in a significantly greater reduction from baseline to Week 24 in pgRNA than with ETV+Peg-IFNα (p=0.03; **Figure 4A**)
  - No patients achieved HBsAg seroconversion or had evidence of functional cure over 24 weeks of randomized treatment
  - With no significant differences favoring the VBR+ETV+Peg-IFNα triple regimen over the 2 double regimens at Week 24, the study was prematurely terminated by the study Sponsor
- Reductions in HBV DNA, pgRNA, and HBsAg were maintained into the Treatment Consolidation Period (Weeks 24-48) (**Figure 5**)

Table 3. Summary of Safety (Randomized Treatment Period)

	VBR+ETV (n=20)	VBR+ETV+Peg-IFNα (n=17)	ETV+Peg-IFNα (n=17)
TEAE	13 (65.0)	17 (100.0)	17 (100.0)
Grade 1	6 (30.0)	4 (23.5)	3 (17.6)
Grade 2	4 (20.0)	9 (52.9)	12 (70.6)
Grade 3	3 (15.0)	3 (17.6)	2 (11.8)
Grade 4	0	1 (5.9)	0
TEAE related to VBR	7 (35.0)	12 (70.6)	NA
TEAE related to ETV	5 (25.0)	3 (17.6)	2 (11.8)
TEAE related to Peg-IFNα	NA	17 (100.0)	17 (100.0)
TE SAE	0	1 (5.9)[a]	0
TE SAE related to VBR	0	1 (5.9)[a]	NA
TE SAE related to ETV	0	0	0
TE SAE related to Peg-IFNα	NA	1 (5.9)[a]	0
TEAE leading to VBR discontinuation	0	1 (5.9)[a]	NA
TEAE leading to ETV discontinuation	0	0	0
TEAE leading to Peg-IFNα discontinuation	NA	1 (5.9)[a]	0
TEAE leading to study discontinuation	0	1 (5.9)[a]	0
TE graded laboratory abnormality	17 (85.0)	16 (94.1)	16 (94.1)
Grade 1	1 (5.0)	5 (29.4)	5 (29.4)
Grade 2	9 (45.0)	8 (47.1)	10 (58.8)
Grade 3	7 (35.0)	2 (11.8)	1 (5.9)
Grade 4	0	1 (5.9)	0
Death	0	0	0

Data shown are n (%).
[a]Grade 4 alanine aminotransferase increased.
ETV, entecavir; Peg-IFNα, pegylated interferon alfa; NA, not applicable; SAE, serious adverse event; TE, treatment emergent; TEAE, treatment-emergent adverse event; VBR, vebicorvir.

Table 4. TEAEs Occurring in >1 Patient in Any Single Treatment Group (Randomized Treatment Period)

	VBR+ETV (n=20)	VBR+ETV+Peg-IFNα (n=17)	ETV+Peg-IFNα (n=17)
Any TEAE	13 (65.0)	17 (100.0)	17 (100.0)
Platelet count decreased	1 (5.0)	9 (52.9)	9 (52.9)
Pyrexia	0	11 (64.7)	8 (47.1)
Hyperlipidemia	3 (15.0)	6 (35.3)	4 (23.5)
White blood cell count decreased	0	8 (47.1)	9 (52.9)
Neutrophil count decreased	1 (5.0)	6 (35.3)	8 (47.1)
Rash	1 (5.0)	6 (35.3)	3 (17.6)
AST increased	0	4 (23.5)	7 (41.2)
Weight decreased	1 (5.0)	5 (29.4)	4 (23.5)
ALT increased	1 (5.0)	4 (23.5)	5 (29.4)
Dizziness	0	5 (29.4)	4 (23.5)
URTI	1 (5.0)	0	2 (11.8)
Fatigue	0	1 (5.9)	5 (29.4)
Headache	0	4 (23.5)	2 (11.8)
Injection site erythema	0	5 (29.4)	1 (5.9)
Lymphocyte count decreased	0	2 (11.8)	4 (23.5)
Blood calcium decreased	2 (10.0)	2 (11.8)	1 (5.9)
Myalgia	0	1 (5.9)	4 (23.5)
Alopecia	0	0	3 (17.6)
Hyperuricemia	0	1 (5.9)	2 (11.8)
Abdominal pain	0	2 (11.8)	1 (5.9)
Vomiting	0	2 (11.8)	0

Data shown are n (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ETV, entecavir; Peg-IFNα, pegylated interferon alfa; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; VBR, vebicorvir.

Table 5. Summary of Treatment-Emergent Graded ALT Increases (Randomized Treatment Period)

	VBR+ETV (n=20)	VBR+ETV+Peg-IFNα (n=17)	ETV+Peg-IFNα (n=17)
Any Grade ≥1	6 (30.0)	6 (35.3)	5 (29.4)
Grade 1	0	2 (11.8)	0
Grade 2	2 (10.0)	1 (5.9)	4 (23.5)
Grade 3	4 (20.0)	2 (11.8)	1 (5.9)
Grade 4	0	1 (5.9)	0

Data shown are n (%).
ALT, alanine aminotransferase; ETV, entecavir; Peg-IFNα, pegylated interferon alfa; VBR, vebicorvir.

Table 6. Summary of Safety (Overall Treatment Period)

	VBR+ETV (n=20)	VBR+ETV+Peg-IFNα (n=17)	ETV+Peg-IFNα (n=17)
TEAE	14 (70.0)	17 (100.0)	17 (100.0)
Grade 1	7 (35.0)	2 (11.8)	3 (17.6)
Grade 2	4 (20.0)	10 (58.8)	12 (70.6)
Grade 3	3 (15.0)	4 (23.5)	2 (11.8)
Grade 4	0	1 (5.9)	0
TEAE related to VBR	7 (35.0)	12 (70.6)	5 (29.4)
TEAE related to ETV	5 (25.0)	3 (17.6)	2 (11.8)
TEAE related to Peg-IFNα	NA	17 (100.0)	17 (100.0)
TE SAE	0	1 (5.9)[a]	0
TE SAE related to VBR	0	1 (5.9)[a]	0
TE SAE related to ETV	0	0	0
TE SAE related to Peg-IFNα	NA	1 (5.9)[a]	0

Data shown are n (%). Reported data include both the Randomized Treatment Period and the Treatment Consolidation Period.
[a]Grade 4 alanine aminotransferase increased.
ETV, entecavir; Peg-IFNα, pegylated interferon alfa; NA, not applicable; SAE, serious adverse event; TE, treatment emergent; TEAE, treatment-emergent adverse event; VBR, vebicorvir.

- The safety profile through Week 24 was consistent with previous reports for VBR and Peg-IFNα (**Tables 3 and 4**)
- The proportion of patients reporting treatment-emergent AEs (TEAEs) was higher in the Peg-IFNα–containing arms (**Tables 3 and 4**)
- Most TEAEs were mild to moderate in severity (**Table 3**)
- A single serious AE of Grade 4 ALT elevation was reported in a patient in the VBR+ETV+Peg-IFNα group that led to study discontinuation (**Table 3**)
- No patients had direct bilirubin >2× ULN
- Among patients with confirmed ALT elevation (**Table 5**), none had direct bilirubin increase ≥2× baseline and ≥2× ULN or international normalized ratio >2× baseline; 2 patients (1 in the VBR+ETV+Peg-IFNα group and 1 in the ETV+Peg-IFNα group) had albumin decline ≥0.5 g/dL from baseline but still within normal limits
- TEAEs remained generally mild in severity for the overall treatment period (Randomized Treatment and Treatment Consolidation Periods) (**Table 6**)
- No deaths were reported during treatment

Conclusions

- Overall, the addition of Peg-IFNα to VBR+ETV did not result in significantly greater declines in HBV parameters compared with the dual-agent control arms
- Adding Peg-IFNα to VBR+ETV is unlikely to result in significant rates of functional cure following 24 weeks of treatment
- Next-generation core inhibitors with increased potency against pgRNA encapsidation/DNA replication and capsid disassembly/cccDNA formation may lead to deeper reductions in viral replication and lead to higher rates of functional cure in a combination regimen

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