

# 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

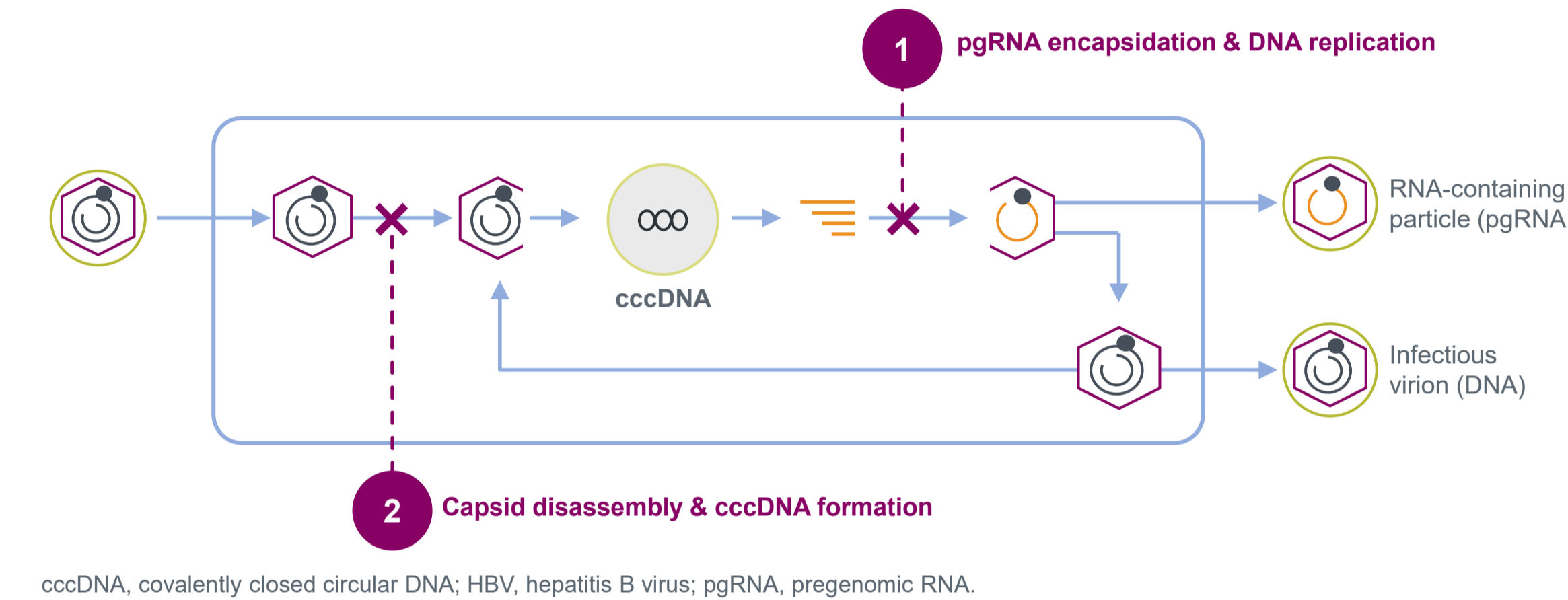
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## Background

- 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<sup>1-4</sup>
- 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<sup>5-7</sup>
- 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)<sup>8</sup>
  - In Phase 1 studies, core inhibitors demonstrated potent antiviral effects<sup>9-11</sup> and in Phase 2 studies, they demonstrated additive antiviral activity when combined with NrtIs vs NrtIs alone<sup>12,13</sup>
- 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<sup>13,14</sup>
  - The addition of pegylated interferon alpha (Peg-IFN $\alpha$ ) may further increase the efficacy of VBR+ETV through complementary mechanisms of action

Figure 1. HBV Core Inhibitor Mechanisms of Action

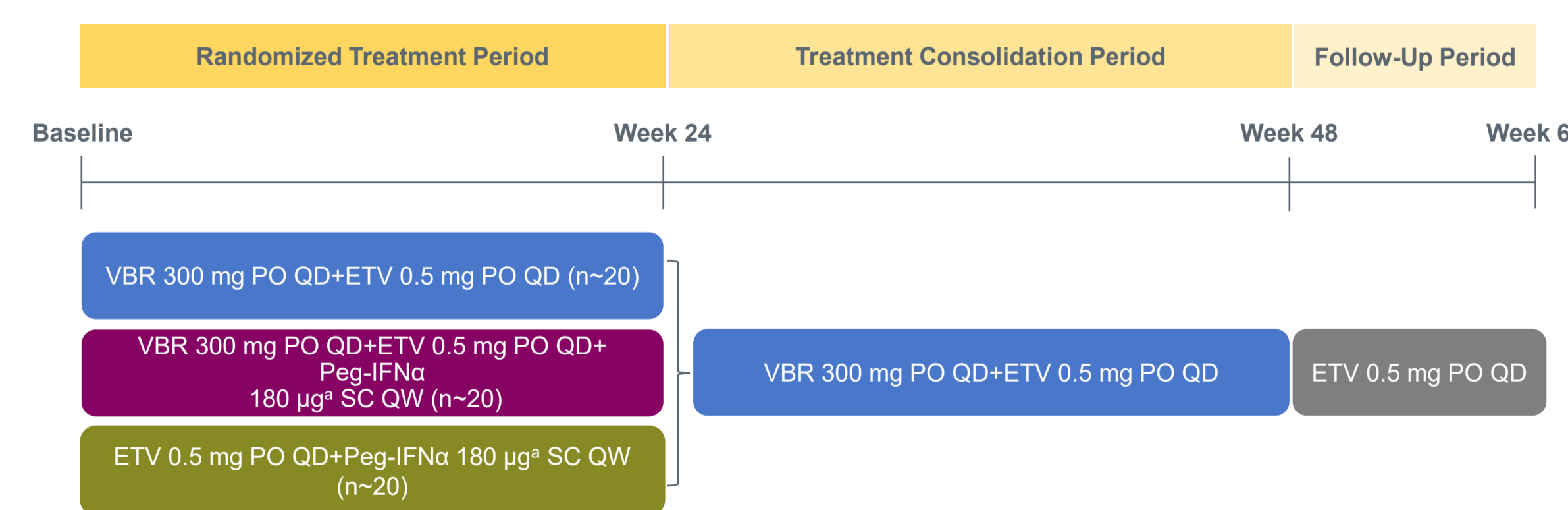


## Objective

- The objective of this analysis is to report the safety and efficacy of VBR when administered in combination with ETV with or without Peg-IFN $\alpha$  in patients with CHBV (NCT04781647)

## Methods

Figure 2. Study Design



### Key inclusion criteria

- Male or female, aged 18-65 years (inclusive)
- CHBV<sup>a</sup>
- HBeAg positive with HBV DNA  $\geq 2 \times 10^4$  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<sup>a</sup>
- ALT  $\geq 2 \times$  ULN or  $\geq 10 \times$  ULN

<sup>a</sup>Reduction to 90 μg or 135 μg permitted due to adverse reactions; <sup>b</sup>Defined as HBV infection documented for  $\geq 6$  months from Screening; <sup>c</sup>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  $\leq 6$  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-IFN $\alpha$ , pegylated interferon alpha; 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-IFN $\alpha$ , or Peg-IFN $\alpha$ +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);  $<5 \times$  upper limit of normal [ULN] vs  $\geq 5 \times$  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 IU/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

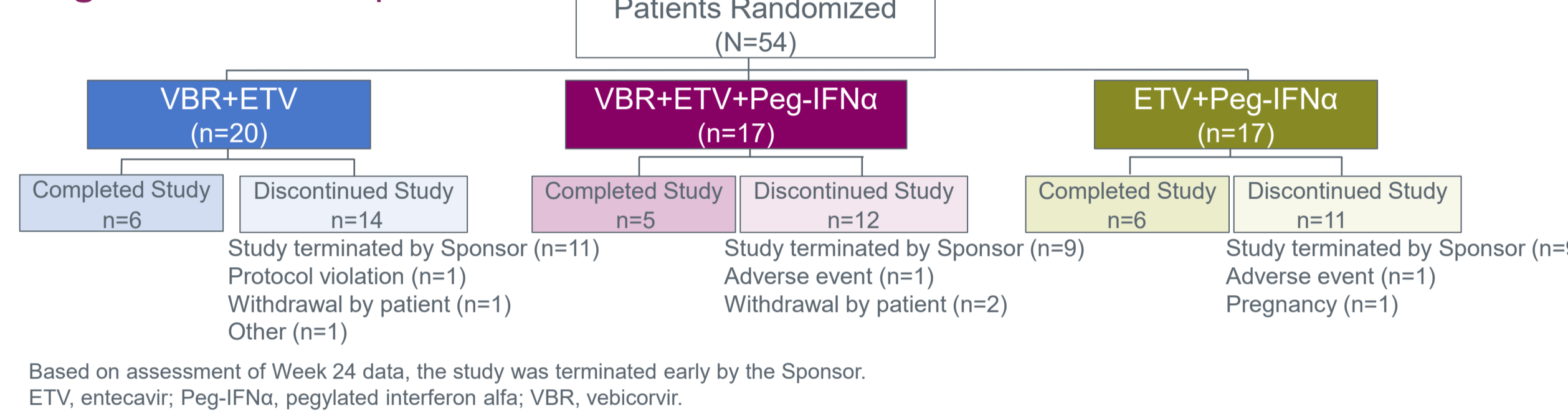
## Results

Table 1. Demographics and Baseline Characteristics

Characteristics	VBR+ETV (n=20)	VBR+ETV+Peg-IFN $\alpha$ (n=17)	ETV+Peg-IFN $\alpha$ (n=17)	Total (N=54)
Age, years	33 (8.6)	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 <sup>2</sup>	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 (8.9)	11.2 (9.0)	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 <sub>10</sub> IU/mL	8.2 (1.02)	7.7 (1.11)	8.1 (0.63)	8.0 (0.96)
HBV pgRNA, log <sub>10</sub> U/mL	6.5 (1.33)	5.8 (1.43)	6.5 (1.05)	6.3 (1.30)
HBsAg, log <sub>10</sub> IU/mL	4.5 (0.39)	4.1 (0.76)	4.3 (0.53)	4.3 (0.58)
HBcrAg, log <sub>10</sub> kU/mL	5.5 (0.59)	5.0 (0.71)	5.4 (0.46)	5.3 (0.62)
HBeAg, log <sub>10</sub> 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-IFN $\alpha$ , pegylated interferon alpha; 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-IFN $\alpha$ , pegylated interferon alpha; VBR, vebicorvir.

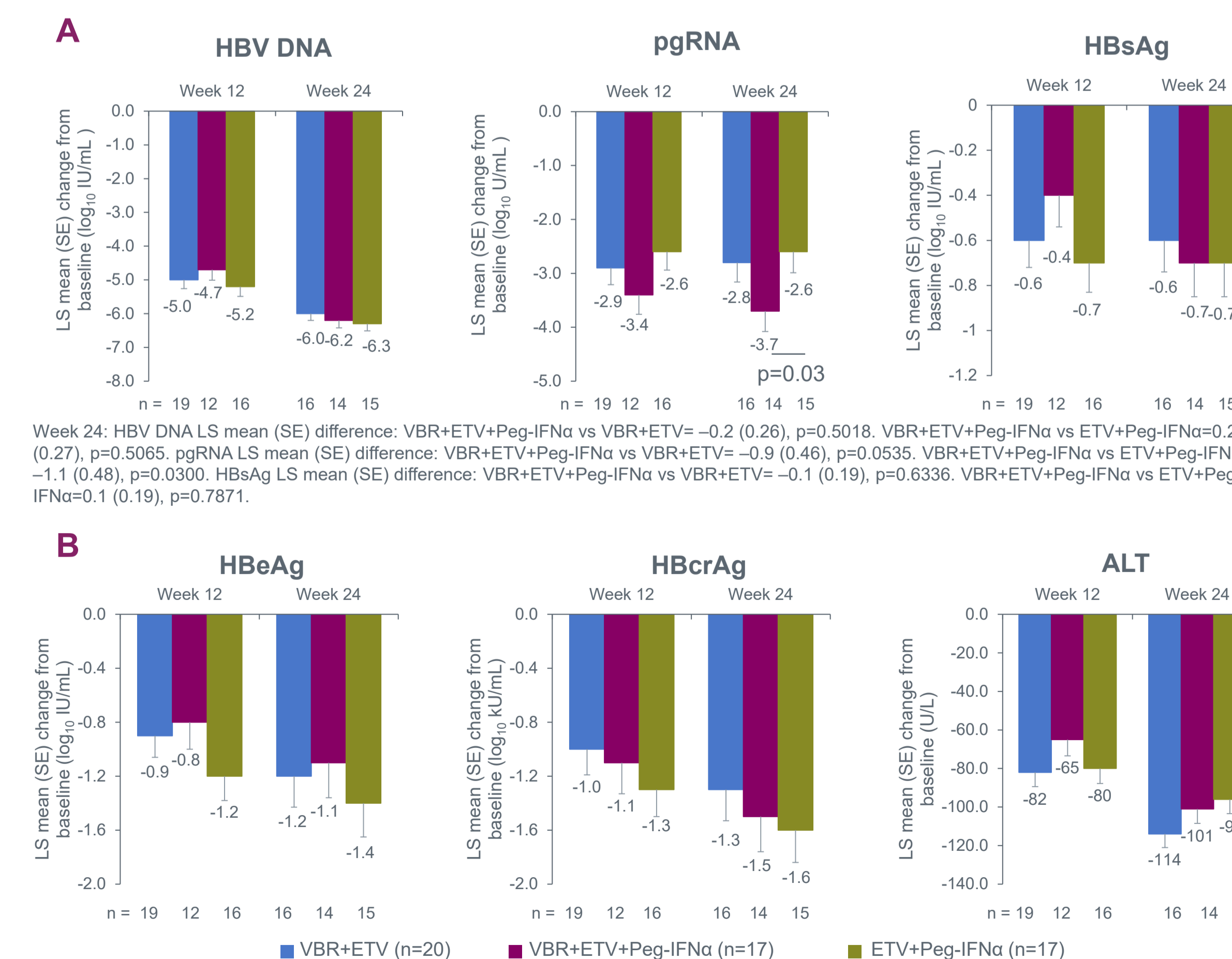
Table 2. On-Treatment Study Drug Compliance

	VBR+ETV (n=20)		VBR+ETV+Peg-IFN $\alpha$ (n=17)			ETV+Peg-IFN $\alpha$ (n=17)		
	VBR	ETV	VBR	Peg-IFN $\alpha$	ETV	Peg-IFN $\alpha$	ETV	VBR <sup>a</sup>
$\leq 80\%$	0	0	0	2 (11.8)	0	1 (5.9)	1 (5.9)	1 (5.9)
80% to $\leq 90\%$	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. <sup>a</sup>VBR compliance data were not available for one patient. ETV, entecavir; Peg-IFN $\alpha$ , pegylated interferon alpha; 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)

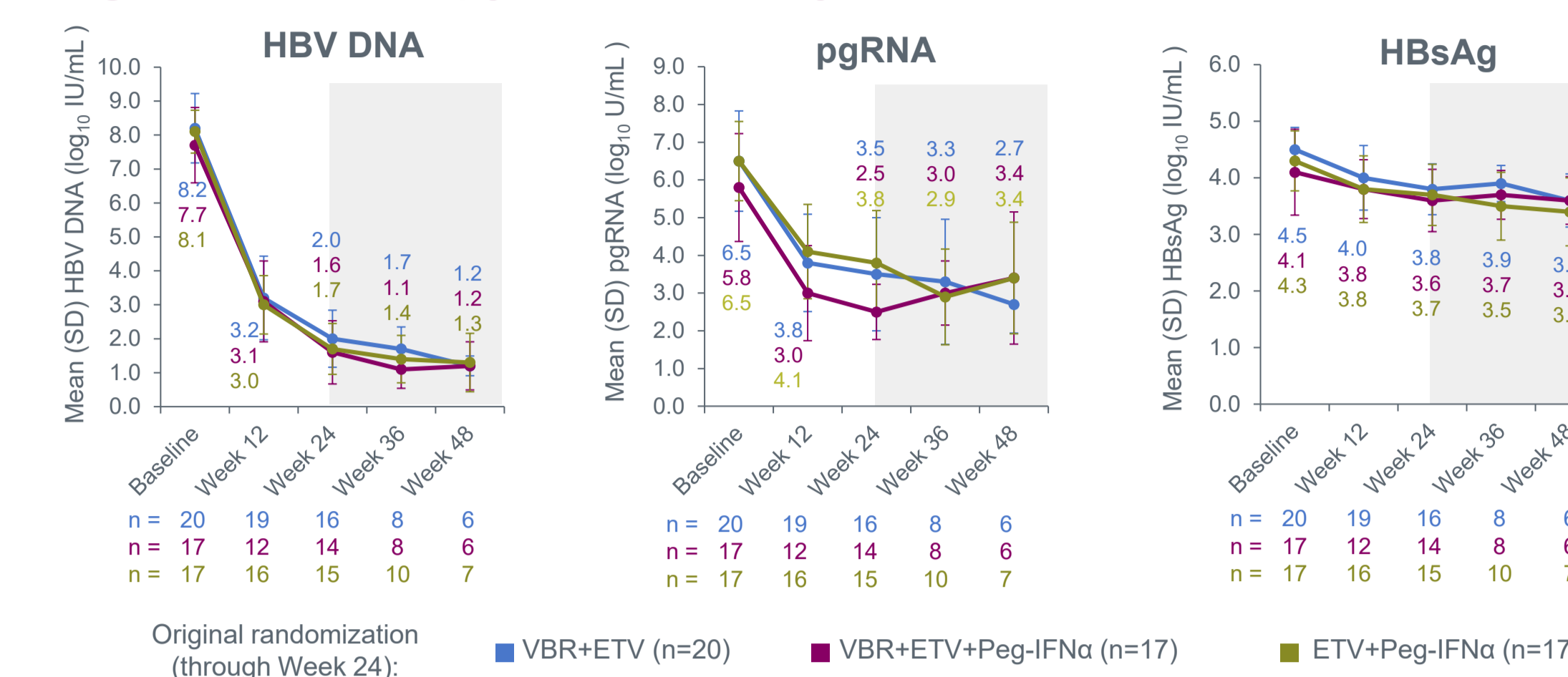
Figure 4. Change From Baseline in (A) HBV DNA, pgRNA, and HBsAg and (B) HBeAg, HBcrAg, and ALT (Randomized Treatment Period)



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

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-IFN $\alpha$ , pegylated interferon alpha; 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-IFN $\alpha$ , pegylated interferon alpha; pgRNA, pregenomic RNA; SD, standard deviation; VBR, vebicorvir.

- At Week 12, there were no significant differences between the VBR+ETV+Peg-IFN $\alpha$  treatment arm and the VBR+ETV or ETV+Peg-IFN $\alpha$  treatment arms in change from baseline for any efficacy measures (Figure 4)
- There were no significant differences between the VBR+ETV+Peg-IFN $\alpha$  treatment arm and the VBR+ETV or ETV+Peg-IFN $\alpha$  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-IFN $\alpha$ -containing arms with 6.0 log<sub>10</sub> IU/mL and 0.6 log<sub>10</sub> IU/mL reductions in HBV DNA from baseline, respectively
  - Treatment with VBR+ETV+Peg-IFN $\alpha$  resulted in a significantly greater reduction from baseline to Week 24 in pgRNA than with ETV+Peg-IFN $\alpha$  (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-IFN $\alpha$  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-IFN $\alpha$ (n=17)	ETV+Peg-IFN $\alpha$ (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-IFN $\alpha$	NA	17 (100.0)	17 (100.0)
TE SAE	0	1 (5.9) <sup>a</sup>	0
TE SAE related to VBR	0	1 (5.9) <sup>a</sup>	NA
TE SAE related to ETV	0	0	0
TE SAE related to Peg-IFN $\alpha$	NA	1 (5.9) <sup>a</sup>	0
TEAE leading to VBR discontinuation	0	1 (5.9) <sup>a</sup>	NA
TEAE leading to ETV discontinuation	0	0	0
TEAE leading to Peg-IFN $\alpha$ discontinuation	NA	1 (5.9) <sup>a</sup>	0
TEAE leading to study discontinuation	0	1 (5.9) <sup>a</sup>	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 (%). <sup>a</sup>Grade 4 alanine aminotransferase increased. ETV, entecavir; Peg-IFN $\alpha$ , pegylated interferon alpha; NA, not applicable; SAE, serious adverse event; TE, treatment emergent; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection; VBR, vebicorvir.

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

	VBR+ETV (n=20)	VBR+ETV+Peg-IFN $\alpha$ (n=17)	ETV+Peg-IFN $\alpha$ (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)
White blood cell count decreased	3 (15.0)	6 (35.3)	4 (23.5)
Neutrophil count decreased	1 (5.0)	6 (35.3)	9 (52.9)
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	2 (10.0)	2 (11.8)	4 (23.5)
Blood calcium decreased	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-IFN $\alpha$ , pegylated interferon alpha; 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-IFN $\alpha$ (n=17)	ETV+Peg-IFN $\alpha$ (n=17)
Any Grade $\geq 1$	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-IFN $\alpha$ , pegylated interferon alpha; VBR, vebicorvir.

Table 6. Summary of Safety (Overall Treatment Period)

	VBR+ETV (n=20)	VBR+ETV+Peg-IFN $\alpha$ (n=17)	ETV+Peg-IFN $\alpha$ (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-IFN $\alpha$	NA	17 (100.0)	17 (100.0)
TE SAE	0	1 (5.9) <sup>a</sup>	0
TE SAE related to VBR	0	1 (5.9) <sup>a</sup>	0
TE SAE related to ETV	0	0	0
TE SAE related to Peg-IFN $\alpha$	NA	1 (5.9) <sup>a</sup>	0

Data shown are n (%). Reported data include both the Randomized Treatment Period and the Treatment Consolidation Period. <sup>a</sup>Grade 4 alanine aminotransferase increased. ETV, entecavir; Peg-IFN $\alpha$ , pegylated interferon alpha; 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-IFN $\alpha$  (Tables 3 and 4)
- The proportion of patients reporting treatment-emergent AEs (TEAEs) was higher in the Peg-IFN $\alpha$ -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-IFN $\alpha$  group that led to study discontinuation (Table 3)
- No patients had direct bilirubin  $>2 \times$  ULN
- Among patients with confirmed ALT elevation (Table 5), none had direct bilirubin increase  $\geq 2 \times$  baseline and  $\geq 2 \times$  ULN or international normalized ratio  $>2 \times$  baseline; 2 patients (1 in the VBR+ETV+Peg-IFN $\alpha$  group and 1 in the ETV+Peg-IFN $\alpha$  group) had albumin decline  $\geq 0.5$  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-IFN $\alpha$  to VBR+ETV did not result in significantly greater declines in HBV parameters compared with the dual-agent control arms
- Adding Peg-IFN $\alpha$  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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