Long-term open-label vebicorvir for chronic HBV infection: Safety and off-treatment responses

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Inclusion criteria

Patients who met the following inclusion criteria were eligible for enrolment:

1. Willing and able to provide informed consent.

2. Previously enrolled in a study of vebicorvir (VBR) and completed the treatment period, with demonstrated compliance in the opinion of the investigator.

3. For female patients, agreed to use an effective birth control method for the duration of the study and follow-up, were surgically sterile for at least 6 months, or were at least 2 years postmenopausal with serum follicle-stimulating hormone levels consistent with a postmenopausal status. Effective birth control methods included male or female condom (could not be used together due to increased risk of breakage), vasectomy, intrauterine device (IUD), diaphragm, or cervical cap. Female patients of childbearing potential were required to have a negative pregnancy test.

4. All heterosexually active male patients agreed to use an effective birth control method for the duration of the study and follow-up. Effective birth control methods included male or female condom (could not be used together due to increased risk of breakage), vasectomy, hormone-based contraception (only female partner of a male patient), IUD, diaphragm, or cervical cap.

5. Agreed to adhere to lifestyle considerations including abstaining from alcohol abuse (defined as alcohol consumption exceeding 2 standard drinks per day on average [1 standard drink=10 grams of alcohol]); the use of illicit, herbal or other substances; and unnecessary over-the-counter medications throughout study duration.

6. Were in good general health except for chronic HBV infection (cHBV).

7. Had the ability to take oral medication and were willing to adhere to the Study 211 regimen in the opinion of the investigator.

Exclusion criteria

Patients who met any of the following exclusion criteria were not eligible for enrolment:

1. Had evidence of resistance-associated variants or lack of compliance on a previous study of VBR.
2. Had treatment-emergent adverse events (TEAEs) or laboratory abnormalities deemed clinically significant and possibly or probably related to drug while on a previous study of VBR that in the opinion of the investigator or the Sponsor made the patient unsuitable for Study 211.
3. Had current clinically significant cardiac or pulmonary disease; chronic or recurrent renal or urinary tract disease; liver disease other than HBV; endocrine disorder; autoimmune disorder; diabetes mellitus requiring treatment with insulin or hypoglycaemic agents; neuromuscular, musculoskeletal, or mucocutaneous conditions requiring frequent treatment; seizure disorders requiring treatment; or other medical conditions requiring frequent medical management or pharmacologic or surgical treatment that in the opinion of the investigator or the Sponsor made the patient unsuitable for the study.
4. Females who were lactating or pregnant or wished to become pregnant within the duration of Study 211.

Treatment compliance

Patients were asked to return used study drug bottles and any unused study drug at study visits. To monitor compliance, study sites conducted tablet counts on these returned bottles. Patients who forgot to return bottles were asked to return them at the next study visit.

In cases where the patients forgot to take the study drug at the scheduled time on a given day, they were instructed to take the day's dose as long as it was within 8 hours of their scheduled dose of the day. These patients were instructed not to "catch up" and take twice the dose on the following day. If a patient reported having missed 2 or more consecutive doses, or multiple missed single doses, then the medical monitor was contacted before any further action was taken. These missed doses were to be recorded in the source documents. If a patient demonstrated continued noncompliance with study drug dosing, despite educational efforts, the investigator would contact the medical monitor to discuss discontinuation of the patient from the study.

Exploratory endpoints

- Mean change from Baseline in $\log_{10}$ serum HBeAg
- Mean change from Baseline in $\log_{10}$ serum HBsAg
- Incidence of patients with loss or change in $\log_{10}$ HBsAg or $\log_{10}$ HBeAg (<0.5, ≥0.5 to 1.0, or >1.0 in viral antigens) at end of treatment (EOT) and end of follow-up
- Incidence of patients with HBsAg seroconversion (loss of HBsAg and appearance of HBsAg antibody) or HBeAg seroconversion (loss of HBeAg and appearance of HBeAg antibody)

- Incidence of patients with detectable HBV DNA by PCR at Baseline whose HBV DNA becomes target not detected (TND)
- Quantitative changes from Baseline in viral RNA on treatment and through end of follow-up
- Quantitative changes in serum hepatitis B core-related antigen (HBcrAg) levels on treatment and through end of follow-up
- Incidence of HBsAg or HBeAg seroconversion in patients up to 3 years off therapy
- Incidence of patients requiring retreatment following DNA undetected through 3 years off therapy
- Incidence of patients with emergence of HBV resistance–associated variants
- If differences are seen in outcomes/adverse events (AEs) between racial or ethnic groups: pharmacogenomic correlations with clinical outcomes in patients who have provided an optional informed consent and sample in Study 201 or 202
- Quantitative levels of VBR and nucleos(t)ide reverse transcriptase inhibitor (NrtI) in plasma

Definition of AEs

Serious adverse events (SAEs) were defined as any events considered life threatening or that resulted in death, inpatient hospitalisation (or prolongation of existing hospitalisation), or persistent disability/incapacity. Rash and alanine aminotransferase (ALT) flare were AEs of special interest. ALT flares were defined as ALT >2× Baseline and ≥10× the upper limit of normal (ULN; defined by the American Association for the

Study of Liver Diseases [AASLD]) or ALT >2× the on-treatment nadir and ≥10× ULN. TEAEs were any AEs with an onset date on or after the study drug start date and no later than 28 days after permanent discontinuation of study drug. Clinical and laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (version 21.0).

Virologic assay methodology

HBV DNA was measured by COBAS TaqMan Version 2.0 (Roche Diagnostics, Mannheim, Germany; lower limit of quantification [LLOQ]=20 IU/mL; limit of detection [LOD]=10 IU/mL) and by a semi-quantitative gel-based assay developed by Assembly Biosciences, Inc. (South San Francisco, CA, USA; LOD=5 IU/mL). Two quantitative pregenomic RNA (pgRNA) assays developed by Assembly Biosciences, Inc. (South San Francisco, CA, USA) were utilised, one for use in samples with high levels of HBV DNA from Study 202 (LLOQ=135 U/mL) and one for samples with low levels of HBV DNA from Study 201 (LLOQ=35 U/mL). Total nucleic acids (composite HBV DNA+pgRNA) were assessed by a novel assay developed by Assembly Biosciences, Inc. (South San Francisco, CA, USA; LLOQ=20 U/mL). The novel assays developed by Assembly Biosciences, Inc. have been described previously.[1] HBeAg (LLOQ=0.11 IU/mL) and HBsAg (LLOQ=0.05 IU/mL) were quantified using the Architect i2000SR assays (Abbott Diagnostics, Lake Forest, IL, USA). Quantification of HBcrAg (LLOQ=1 kU/mL) was performed using the Lumipulse G assay (Fujirebio, Malvern, PA, USA). All viral parameters were assessed at Covance Central Laboratory Services (now LabCorp, multiple locations) with the exception of HBcrAg levels, which were measured at the University of Hong Kong. ALT was assessed against normal ranges set by Covance

Central Laboratory Services (ULN of 34 U/L for females and 43 U/L for males) and AASLD guidelines (ULN of 25 U/L for females and 33 U/L for males).[2]

Three-year off-treatment follow-up

All patients who discontinued both VBR+NrtI were followed for up to 3 years from the date of treatment discontinuation to assess the durability of virologic response. Patients had an unscheduled visit to notify them of the treatment action (TA) to be implemented, at which point each individual patient's visit schedule was reset; patients then returned to the clinic for follow-up every 4 weeks for visits at 4, 8, 12, 16, 20, and 24 weeks posttreatment discontinuation, then every 8 weeks for visits at 32, 40, and 48 weeks posttreatment discontinuation, and then every 12 weeks until completion of the 3-year follow-up. Additional unscheduled visits were performed at the investigator's discretion. Following completion of the visit 3 years after VBR+NrtI discontinuation, patients exited the study and were placed under the routine care of their respective physicians.

Twelve-week follow-up on NrtI alone

All patients who discontinued VBR only and continued NrtI alone were followed for 12 weeks from the date of VBR discontinuation. Patients then had an unscheduled visit to notify them of the TA to be implemented, at which point each individual patient's visit schedule was reset; patients then returned to the clinic for follow-up visits at 4, 8, and 12 weeks after discontinuation of VBR. Additional unscheduled visits were performed at the investigator's discretion. Following completion of the follow-up visit 12

weeks after discontinuation of VBR, patients exited the study and were placed under the routine care of their respective physicians.

Continuation of treatment with VBR+NrtI

All patients who continued VBR+NrtI beyond Week 52 returned to the clinic for visits every 4 weeks until Week 148. Patients were then notified of their TA by phone and would continue their planned study visit schedule. At Week 148, patients were evaluated for virologic response and either discontinued both VBR+NrtI and were followed for up to 3 years, or discontinued VBR only, continued NrtI alone, and were followed for 12 weeks.

Criteria to restart NrtI following discontinuation of both VBR+NrtI

Patients who discontinued both VBR+NrtI were followed to assess the durability of virologic response. The investigator used clinical judgement to determine when to restart NrtI. However, NrtI therapy was reintroduced if any of the following criteria listed below were met:

- ALT >10× ULN
- Direct bilirubin >2.0× ULN
- International Normalised Ratio (INR) >1.5
- ALT >3× ULN and HBV DNA >100,000 IU/mL
- ALT >ULN and HBV DNA >2000 IU/mL on 3 consecutive visits at least 1 month apart
- Any clinical decompensation, regardless of HBV DNA level

- Physician or patient's decision

If any of these criteria were met, then patients could have an unscheduled visit to notify them to restart NrtI. Patients' visit schedules were then reset upon restarting NrtI; patients returned for follow-up visits at 4, 8, and 12 weeks after restarting NrtI and would then complete participation in the study.

Supplementary results

Duration of time patients had on and off treatment

The mean (SD) duration of the on-treatment phase for patients from Study 201 (57.6 [12.9] weeks) was lower than that of patients from Study 202 (81.0 [18.2] weeks). In patients from Study 201 who discontinued VBR+NrtI, the mean (SD) duration of the off-treatment phase was similar between HBeAg-positive (20.9 [8.82] weeks) and -negative patients (20.6 [11.0] weeks) and was of similar duration for the NrtI-restart phase (13.4 [2.46] and 14.2 [4.20] weeks, respectively). Patients who discontinued VBR and continued on NrtI/entecavir (ETV) also had a similar duration of off-treatment phase.

Description of Baseline disease characteristics for Study 211

Mean duration of HBV infection and number of years on current NrtI treatment were longer among patients from Study 201 than among Study 202 patients (treatment duration for Study 202 patients at Study 211 Baseline was 24 weeks). As expected, mean Baseline HBV DNA measured by COBAS TaqMan among patients from Study 201 were mostly TND. A higher percentage of Study 201 HBeAg-negative patients had

HBV DNA TND at Study 211 Baseline than did HBeAg-positive patients. Mean Baseline HBV DNA was not different between treatment groups among patients from Study 201. Study 211 Baseline characteristics from Study 202 showed mean HBV DNA was greater among placebo (PBO)+ETV than among VBR+ETV patients. No Study 202 patients had HBV DNA TND at Study 211 Baseline (**Table S7**).

Mean HBV pgRNA at Study 211 Baseline was higher among Study 201 HBeAg-positive patients than among negative patients. HBeAg-positive patients who received PBO+NrtI in Study 201 had greater mean pgRNA at Baseline versus patients who received VBR+NrtI. Mean HBV pgRNA at Study 211 Baseline among HBeAg-positive patients from Study 202 was numerically greater in patients who received PBO+ETV versus VBR+ETV. No HBeAg-positive patients from Study 202 had HBV pgRNA <LLOQ at Study 211 Baseline (**Table S7**).

Mean levels of HBV antigens were lower among patients from Study 201 versus patients from Study 202 at Study 211 Baseline. Mean levels of HBV antigens at Study 211 Baseline were similar between patients who had received VBR+NrtI/ETV and PBO+NrtI/ETV in the parent studies. Mean ALT levels were lower among patients from Study 201 versus Study 202 at Study 211 Baseline, with ALT levels being slightly higher among HBeAg-positive versus -negative patients from Study 201. Patients who received PBO+ETV in Study 202 had higher mean ALT levels at Study 211 Baseline versus patients who received VBR+ETV (**Table S7**). Of the 4 patients from Study 201 with abnormal ALT at Baseline, 2 had ALT ≤ULN at EOT, and 1 had ALT ≤ULN at end of study (EOS). Of the 7 patients from Study 202 with abnormal ALT at Baseline, 5 had ALT ≤ULN at EOT and at EOS (data not shown).

Narratives for SAEs and AEs leading to discontinuation of treatment

On-treatment phase

A 33-year-old Asian male patient who was treatment-naïve with HBeAg-positive cHBV infection was initially enrolled in Parent Study 202 and randomised to receive placebo PBO+ETV. The patient completed 24 weeks of blinded treatment in Study 202 and was enrolled in Study 211 to receive open-label VBR+ETV. The patient's medical history included abdominal tenderness, and the patient reported a Grade 1 AE of stress in Study 202, which was ongoing at Baseline of Study 211. No concomitant medications were reported. During Study 211, the patient reported AEs of Grade 1 conjunctivitis (Study Days 52–60) and Grade 1 insomnia (Study Days 162–215). On Study Day 253, the patient presented to the emergency room agitated, distressed over his social situation, and speaking about wanting to kill himself, though later he reported that he was misunderstood, as English is not his native language. A Grade 2 AE of anxiety, a Grade 1 AE of palpitations, and a Grade 3 SAE of suicidal ideation were reported. The patient was hospitalised and discontinued VBR on Study Day 255. The patient's mood improved, and he denied further suicidal ideation. He was discharged on Study Day 258, and the SAE of suicidal ideation was resolved. The investigator considered all AEs not related to study drug.

Off-treatment phase

Patient 1

A 46-year-old White male who was virologically-suppressed (VS) with HBeAg-negative cHBV infection was initially enrolled in Parent Study 201 and was randomised to receive VBR and continue NrtI (ETV). The patient completed 24 weeks of blinded treatment in Study 201 and was enrolled in Study 211 to receive open-label VBR+NrtI. The patient's medical history included Barrett oesophagus, hiatal hernia, oesophagitis, and oesophageal reflux. No concomitant medications were reported. The patient met the TA criteria to discontinue treatment, and both VBR and ETV were discontinued on Study Day 426. On Study Day 563 (137 days after discontinuation of study drug), the patient was brought to the emergency room by friends who stated that the patient was confused. The evaluating physician believed the patient may have had a seizure and was in a post-ictal state. The patient was admitted to the hospital for further evaluation, during which he was treated with lorazepam and levetiracetam for the suspicion of seizure. The results from a magnetic resonance imaging scan and electroencephalogram were normal. He was found to be in atrial fibrillation, for which he received aspirin. The patient reported back pain. Chest X-ray, electrocardiogram, and echocardiogram were normal. The patient was discharged from the hospital in stable condition. A Grade 3 SAE of seizure, a Grade 2 AE of atrial fibrillation, and a Grade 2 AE of back pain were resolved. The investigator considered all AEs not related to study drug.

Patient 2

A 55-year-old Black or African American female who was VS with HBeAg-negative cHBV infection initially enrolled in Study 201 and was randomised to receive PBO and continue NrtI (tenofovir alafenamide fumarate [TAF]). The patient completed

24 weeks of blinded treatment in Study 201 and was enrolled in Study 211 to receive open-label VBR+NrtI. The patient's medical history included obesity, hypertension, coronary artery disease with prior stenting, insomnia, and depression. No concomitant medications were reported.

On Study Day 255, the patient switched NrtI from TAF to ETV due to insurance issues. On Study Day 280, the patient experienced Grade 1 AEs of toothache and tooth infection, for which she received amoxicillin and ibuprofen. On Study Day 311, the patient experienced Grade 1 papular rash, possibly related to study drug, for which she received hydrocortisone cream. The patient met the TA criteria to discontinue treatment, and both VBR+NrtI were discontinued on Study Day 427.

On Study Day 512 (85 days after discontinuation of study drug), the patient experienced a Grade 3 SAE of procedural haemorrhage. The day prior, the patient had undergone plastic surgery, including abdominoplasty, liposuction, and breast augmentation. The patient was being discharged from the centre, and upon standing to get into the car, the patient felt dizzy and passed out. The patient was brought back upstairs to the clinic, where she passed out again; she was subsequently kept at the medical centre overnight for observation. While at the medical centre, the patient complained of persistent dizziness and decided to go to the emergency room. Upon her admission to the emergency room, the patient's haemoglobin level was 5.3 g/dL (reference range: 12.0–16.0 g/dL), her platelet count was 137 k/mcL (reference range: 140–400 k/mcL), and her INR was 1.1 (reference range: 0.8–1.2). The patient was found to have had acute blood loss in the left anterior abdominal wall as a complication of abdominoplasty. The patient was admitted and received 2.5 units of packed red blood

cells via transfusion. A Grade 3 AE of procedural pain was also reported. No additional surgery was performed. On Study Day 516, the patient's haemoglobin level was 7.9 g/dL; the patient was discharged, and the AEs were considered resolved. The investigator considered the AEs of procedural haemorrhage and procedural pain not related to study drug.

Details surrounding on-treatment AEs of ALT elevation

During the on-treatment phase, 3 patients reported Grade 3 AEs of ALT increase and laboratory abnormalities of elevated ALT. In these cases, ALT elevations were associated with aspartate aminotransferase elevations, and there were no graded abnormalities in total bilirubin, alkaline phosphatase, albumin, and INR and no signs of hepatic decompensation. No patients met the criteria for ALT flare. One patient discontinued VBR due to the AE of ALT increase and recovered soon after. The other 2 patients with elevated ALT on treatment are described below.

A 36-year-old Black or African American female patient with HBeAg-positive cHBV treated with PBO+ETV in Parent Study 202 enrolled in Study 211 to receive VBR+ETV. The patient had a Grade 3 AE of ALT increase reported on Study Day 8 and a Grade 3 laboratory abnormality of elevated ALT (199 U/L). Levels of ALT peaked on Study Day 22 (296 U/L) and then improved on treatment, and the AE was resolved on Study Day 43. From Study Day 1 to 57, HBV DNA decreased from 3.72 $\log_{10}$ IU/mL to <LLOQ, and HBsAg decreased from 4.63 $\log_{10}$ IU/mL to 3.06 $\log_{10}$ IU/mL. Per the investigator, the elevated ALT occurred in the setting of increased alcohol use and was not considered related to study drug.

Another patient was a 35-year-old Asian male with HBeAg-positive cHBV treated with PBO+NrtI in Parent Study 201 who enrolled in Study 211 to receive VBR+NrtI. On treatment, the patient had a Grade 2 AE of ALT increase reported on Study Day 393 and a Grade 2 laboratory abnormality of elevated ALT (184 U/L). The patient met the TA criteria to discontinue treatment, and both VBR and NrtI were discontinued on Study Day 420. On Study Day 421, Grade 3 elevated ALT (271 U/L) was observed, and a Grade 3 AE of ALT increase was reported. Off treatment, ALT levels remained stably elevated, HBV DNA increased to 5.95 $\log_{10}$ IU/mL, and the patient met laboratory criteria to restart NrtI on Study Day 491 (71 days after stopping treatment). At the last observation on Study Day 575 (84 after NrtI restart), HBV DNA had decreased to 40 IU/mL (1.6 $\log_{10}$ IU/mL), and the ALT level was 111 U/mL (Grade 2). At the end of the study, the Grade 3 AE of ALT increase was considered resolved and the Grade 2 AE of ALT increase was ongoing; the investigator considered both AEs not related to study drug.

Supplementary figures and tables

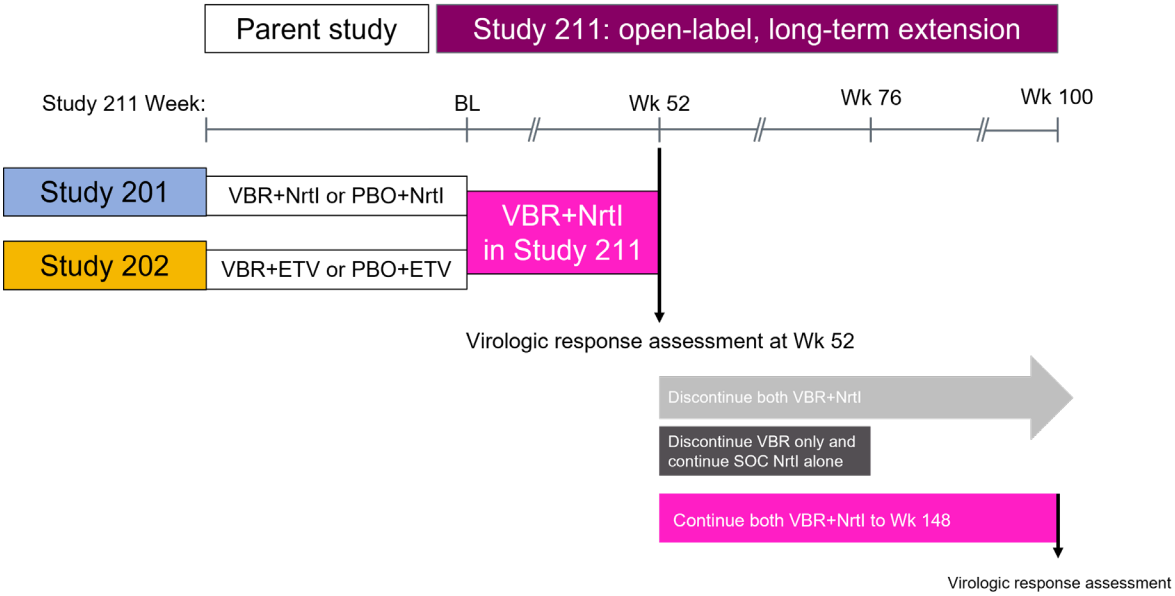

Fig. S1. Study 211 design.

The duration of treatment for each patient was based on the respective HBV treatment history (virologically-suppressed in Study 201 or treatment-naïve in Study 202), hepatitis B e antigen status (positive or negative) at Baseline in the parent study, and their individual virologic response in Study 211. Based on these factors, each patient was evaluated for virologic response and assigned to one of the following treatment actions: discontinue both VBR+NrtI, discontinue VBR only and continue NrtI alone, or continue both VBR+NrtI for up to 148 weeks.

BL, Baseline; ETV, entecavir; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; SOC, standard-of-care; VBR, vebicorvir; Wk, week.

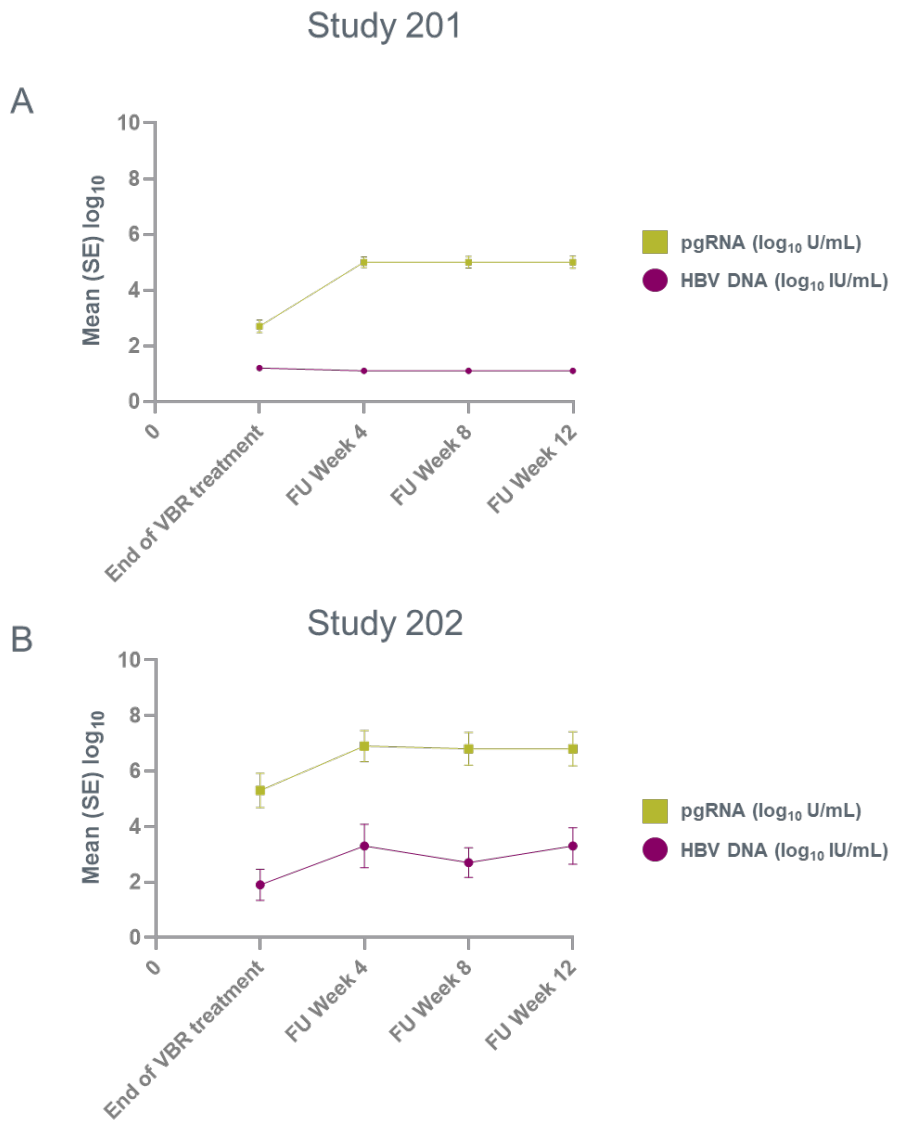

Fig. S2. HBV DNA and HBV pgRNA in patients from Study 211 who discontinued VBR and remained on NrtI.

Mean log_{10} levels of HBV DNA and HBV pgRNA in **(A)** patients from Study 201 and **(B)** patients from Study 202 who discontinued VBR and remained on NrtI.

FU, follow-up; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; SE, standard error; VBR, vebicorvir.

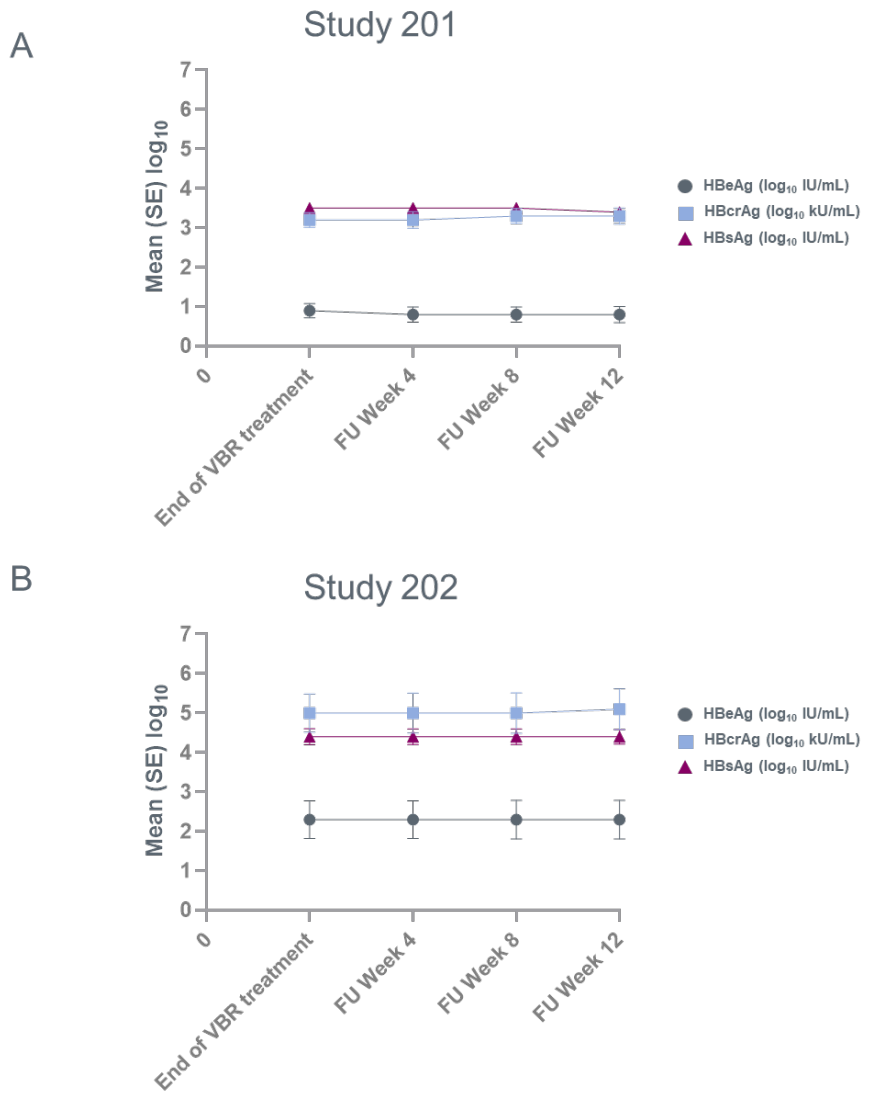

Fig. S3. HBV viral antigens in patients from Study 211 who discontinued VBR and remained on NrtI.

Mean log_{10} levels of HBV viral antigens in **(A)** patients from Study 201 and **(B)** patients from Study 202 who discontinued VBR and remained on NrtI.

FU, follow-up; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SE, standard error; VBR, vebicorvir.

Table S1. Decision criteria and treatment actions for Study 211 patients previously enrolled in Studies 201 and 202.

Parent study	Treatment history[a]	HBeAg status[a]	Study 211 visit (week)	Decision criteria	Treatment actions
201	VS	–	52[b]	Both VBR+NrtI stopped in all patients	Discontinue both VBR+NrtI and enter long-term, off-treatment follow-up for up to 3 years
201	VS	+	52[b]	If HBV TNA was <20 IU/mL **and** HBeAg ≤5 IU/mL for ≥7 consecutive visits[c]	Discontinue both VBR+NrtI and enter long-term, off-treatment follow-up for up to 3 years
				If HBV TNA was not <20 IU/mL **and** HBeAg ≤5 IU/mL for ≥7 consecutive visits[c]	Discontinue VBR only and continue NrtI alone; enter follow-up on NrtI alone for 12 weeks
202	TN	+	52[b]	If ≥2.5 $\log_{10}$ reduction in HBV pgRNA from Baseline in the	Continue both VBR+ETV for additional 96 weeks (ie, to Week 148)

				parent study or achieved HBV pgRNA <LLOQ	
				If <2.5 log_{10} reduction in pgRNA from Baseline in the parent study or did not achieve HBV pgRNA <LLOQ	Discontinue VBR only and continue ETV alone; enter follow-up on ETV alone for up to 12 weeks
			148	If HBV TNA <20 IU/mL **and** HBeAg ≤5 IU/mL for ≥7 consecutive visits[c]	Discontinue both VBR+ETV and enter long-term, off-treatment follow-up for up to 3 years
				If HBV TNA was not <20 IU/mL **and** HBeAg ≤5 IU/mL for ≥7 consecutive visits[c]	Discontinue VBR only and continue ETV alone; enter follow-up on ETV alone for up to 12 weeks

[a]Treatment history and HBeAg status at Baseline in the parent studies (Study 201 or 202). [b]Patients without virologic assessment at Week 52 were evaluated at the next study visit. [c]Consecutive visits were determined from the last time point at which values were available for all parameters.

ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; TN, treatment-naïve; TNA, total nucleic acids; VBR, vebicorvir; VS, virologically-suppressed.

Table S2. Treatment groups from parent studies reported in Study 211.

Parent study	**Study 201 (NCT03576066)**											
Parent study population	Virologically suppressed											
Parent study HBeAg status	Positive						Negative					
Parent study treatment	VBR+NrtI			PBO+NrtI			VBR+NrtI			PBO+NrtI		
Data reporting period	On-Rx[a]	Off-Rx[b]	NrtI-restart[c]	On-Rx[a]	Off-Rx[b]	NrtI-restart[c]	On-Rx[a]	Off-Rx[b]	NrtI-restart[c]	On-Rx[a]	Off-Rx[b]	NrtI-restart[c]
Parent study	**Study 202 (NCT03577171)**											
Parent study population	Treatment-naïve											
Parent study HBeAg status	Positive											
Parent study treatment	VBR+ETV						PBO+ETV					
Data reporting period	On-Rx[a]		Off-Rx[b]			NrtI-restart[c]	On-Rx[a]		Off-Rx[b]			NrtI-restart[c]

[a]Data reported from the first dose of study drug to the last dose of study drug in Study 211. [b]Data reported after the last dose of study drug in Study 211. [c]Data reported from the time NrtI was restarted after VBR+NrtI were discontinued.

ETV, entecavir; HBeAg, hepatitis B e antigen; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; Rx, treatment; VBR, vebicorvir.

Table S3. Schedule of efficacy, safety, and pharmacokinetic assessments for on-treatment patients through Week 100.

Assessment	0	2	4	8	12	16	20	24	28	32	36	40	44	48	52	56[a]	60	64	68	72	76	80	84	88	92	96	100
Full physical examinations	X							X							X						X						X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[b] and AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dermatologic assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA and pgRNA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

HBsAg, HBeAg, and HBcrAg[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry, haematology, and coagulation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK sample														X													

[a]When the primary endpoint was assessed. [b]All concomitant medications were required to be recorded in the designated electronic case report form from the date informed consent was obtained to 30 days following the last dose of all study drug(s), with the exception of concomitant medications used for treatment of HBV in patients who restarted HBV therapy, which were collected through the end of follow-up. [c]HBcrAg was included as a biomarker and tested at every visit. HBeAg and HBsAg were tested at every visit except for Week 2.

AE, adverse event; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; pgRNA, pregenomic RNA; PK, pharmacokinetic.

Table S4. Schedule of efficacy and safety assessments for on-treatment patients from Weeks 104 to 148.

	Study week											
Assessment	104	108	112	116	120	124	128	132	136	140	144	148
Full physical examinations						X						X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications[a] and AE review	X	X	X	X	X	X	X	X	X	X	X	X
Dermatologic assessment	X	X	X	X	X	X	X	X	X	X	X	X
HBV DNA and pgRNA	X	X	X	X	X	X	X	X	X	X	X	X
HBsAg, HBeAg, and HBcrAg	X	X	X	X	X	X	X	X	X	X	X	X

Chemistry, haematology, and coagulation	X	X	X	X	X	X	X	X	X	X	X	X

[a]All concomitant medications were required to be recorded in the designated electronic case report form from the date informed consent was obtained to 30 days following the last dose of all study drug(s), with the exception of concomitant medications used for treatment of HBV in patients who restarted HBV therapy, which were collected through the end of follow-up.

AE, adverse event; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; pgRNA, pregenomic RNA.

Table S5. Schedule of efficacy and safety assessments for long-term, off-treatment patients who discontinue both VBR+Nrtl.

				Posttreatment follow-up[a]: 3-year follow-up					
Assessment	4 Wks	8 Wks	12 Wks	20 Wks	24 Wks	32 Wks	40 Wks	48 Wks	Q3 months (Months 15–36)
Full physical examinations	X								
Vital signs	X								
Concomitant medications[b] and AE review	X	X	X	X	X	X	X	X	X
Symptom-derived physical exam		X	X	X	X	X	X	X	X

HBV DNA and pgRNA	X	X	X	X	X	X	X	X	X
HBsAg, HBeAg, and HBcrAg	X	X	X	X	X	X	X	X	X
Chemistry, haematology, and coagulation	X								
Liver panel		X	X	X	X	X	X	X	X

[a]Patients with a posttreatment ALT elevation >2× ULN or HBV DNA >2000 IU/mL were asked to return to the clinic every 2 weeks for an unscheduled visit to monitor liver function and viral load until the patient's lab values resolved or the patient was required to restart NrtI therapy. [b]Any concomitant medications were recorded in the designated electronic case report form from the date informed consent was obtained to 30 days following the last dose of all study drug(s), with the exception of concomitant medications used for treatment of HBV in patients who restarted HBV therapy, which were collected through end of follow-up.

AE, adverse event; ALT, alanine aminotransferase; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; Q3 months, every 3 months; ULN, upper limit of normal; VBR, vebicorvir; Wk, week.

Table S6. Schedule of efficacy and safety assessments for patients who either prematurely discontinued the study, stopped VBR only and continued Nrtl alone, or restarted Nrtl after discontinuation of both VBR+Nrtl.

	Posttreatment follow-up: 12-week follow-up		
Assessment	Follow-up 1[a]	Follow-up 2[a]	Follow-up 3[a]/EOS
Full physical examinations	X		
Vital signs	X		
Concomitant medications[b] and AE review	X	X	X
Symptom-derived physical exam		X	X
HBV DNA and pgRNA	X	X	X

HBsAg, HBeAg, and HBcrAg	X	X	X
Chemistry, haematology, and coagulation	X		
Liver panel		X	X

[a]The follow-up 1, 2, and 3 visits occurred 4, 8, and 12 weeks, respectively, after the patient discontinued VBR and continued NrtI, restarted NrtI, or was prematurely terminated from the study. Additional (unscheduled) follow-up visits occurred as clinically indicated. [b]Any concomitant medications were recorded in the designated electronic case report form from the date informed consent was obtained to 30 days following the last dose of all study drug(s), with the exception of concomitant medications used for treatment of HBV in patients who restarted HBV therapy, which were collected through end of follow-up.

AE, adverse event; EOS, end of study; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; VBR, vebicorvir.

Table S7. Baseline demographics for patients in Study 211, all-enrolled analysis set.

	Patients originating from Study 201			Patients originating from Study 202	
Characteristic	**VS HBeAg (–) n=26**	**VS HBeAg (+) n=43**	**Total n=69**	**TN HBeAg (+) n=23**	**Overall total n=92**
Age, years	49 (35, 65)	45 (21, 67)	46 (21, 67)	36 (21, 67)	44 (21, 67)
<50 years, n (%)	14 (54)	29 (67)	43 (62)	19 (83)	62 (67)
Sex, male, n (%)	16 (62)	28 (65)	44 (64)	8 (35)	52 (57)
Race, n (%)					
Asian	20 (77)	38 (88)	58 (84)	22 (96)	80 (87)
Black	3 (12)	1 (2)	4 (6)	1 (4)	5 (5)

Native Hawaiian or other Pacific Islander	0	1 (2)	1 (1)	0	1 (1)
White	2 (8)	2 (5)	4 (6)	0	4 (4)
Other	1 (4)	1 (2)	2 (3)	0	2 (2)
BMI, kg/m^2	24.4 (18.7, 29.9)	24.0 (18.5, 33.8)	24.1 (18.5, 33.8)	23.5 (17.3, 32.7)	24.0 (17.3, 33.8)

Data shown are mean (minimum, maximum) unless indicated otherwise.

BMI, body mass index; HBeAg, hepatitis B e antigen; TN, treatment-naïve; VS, virologically-suppressed.

Table S8. Baseline disease characteristics for patients in Study 211, all-enrolled analysis set.

	Patients originating from Study 201						Patients originating from Study 202		
	VS HBeAg (–) n=26			VS HBeAg (+) n=43			TN HBeAg (+) n=23		
Characteristic	**PBO+Nrtl n=10**	**VBR+Nrtl n=16**	**Total n=26**	**PBO+Nrtl n=16**	**VBR+Nrtl n=27**	**Total n=43**	**PBO+ETV n=11**	**VBR+ETV n=12**	**Total n=23**
Years positive for HBV	20.9 (8.1)	14.8 (12.1)	17.1 (11.0)	11.1 (6.1)	12.2 (8.7)	11.8 (7.8)	11.5 (9.7)	10.2 (8.2)	10.8 (8.8)
Nrtl, n (%)									
ETV	2 (20)	3 (19)	5 (19)	1 (6)	3 (11)	4 (9)	11 (100)	12 (100)	23 (100)
ETV/TDF	0	0	0	0	1 (4)	1 (2)	0	0	0
TAF	5 (50)	6 (38)	11 (42)	5 (31)	8 (30)	13 (30)	0	0	0

TDF	3 (30)	7 (44)	10 (38)	10 (63)	15 (56)	25 (58)	0	0	0
Years on current Nrtl treatment	6.8 (6.0)	3.3 (3.6)	4.7 (4.9)	3.8 (3.0)	5.2 (3.8)	4.7 (3.5)	0.5 (0.01)	0.5 (0.00)	0.5 (0.01)
HBV DNA, log_{10} IU/mL[a]	1.1 (0.17)	1.0 (0.19)	1.1 (0.18)	1.1 (0.23)	1.1 (0.16)	1.1 (0.19)	3.8 (1.38)	2.2 (0.86)	2.9 (1.37)
TND, n (%)	6 (60)	13 (81)	19 (73)	8 (50)	16 (59)	24 (56)	0	0	0
TND at Week 2, n (%)	—	—	—	—	—	—	0	0	0
HBV DNA									
TND, n (%)[b]	9 (90)	12 (75)	21 (81)	5 (31)	18 (67)	23 (53)	ND[c]	ND[c]	ND[c]
TND at Week 2, n (%)[d]	—	—	—	—	—	—	0	1 (13)	1 (8)

HBV pgRNA, log_{10} U/mL[e]	1.5 (0.00)	1.5 (0.03)	1.5 (0.02)	3.3 (1.53)	1.9 (0.63)	2.4 (1.24)	6.7 (1.59)	4.6 (1.19)	5.6 (1.76)
<LLOQ, n (%)	10 (100)	15 (94)	25 (96)	3 (19)	16 (59)	19 (44)	0	0	0
HBV TNA, log_{10} U/mL[f]	1.3 (0.00)	1.3 (0.00)	1.3 (0.00)	2.7 (1.42)	1.4 (0.36)	1.9 (1.12)	ND[g]	ND[g]	ND[g]
<LLOQ, n (%)	10 (100)	12 (75)	22 (85)	4 (25)	17 (63)	21 (49)	ND[g]	ND[g]	ND[g]
HBeAg, log_{10} IU/mL[h]	–1.0 (0.04)	–1.00 (0.00)	–1.0 (0.02)	0.5 (1.00)	0.4 (0.91)	0.4 (0.93)	2.0 (1.44)	2.1 (1.09)	2.1 (1.24)
<LLOQ, n (%)	9 (90)	16 (100)	25 (96)	0	1 (4)	1 (2)	1 (9)	0	1 (4)
HBcrAg, log_{10} kU/mL[i]	0.6 (0.56)	0.4 (0.60)	0.5 (0.58)	2.9 (0.94)	2.8 (0.87)	2.8 (0.89)	5.0 (1.18)	5.0 (1.02)	5.0 (1.07)
<LLOQ, n (%)	3 (30)	7 (44)	10 (38)	0	0	0	0	0	0

HBsAg, log_{10} IU/mL[j]	3.3 (0.64)	3.1 (0.55)	3.2 (0.59)	3.6 (0.54)	3.5 (0.37)	3.6 (0.43)	4.4 (0.50)	4.3 (0.49)	4.4 (0.49)
<LLOQ, n (%)	0	0	0	0	0	0	0	0	0
HBeAb, negative, n (%)	1 (10)	1 (6)	2 (8)	13 (81)	24 (89)	37 (86)	10 (91)	12 (100)	22 (96)
HBsAb, negative, n (%)	10 (100)	16 (100)	26 (100)	16 (100)	27 (100)	43 (100)	9 (82)	8 (67)	17 (74)
ALT, U/L[k]	21 (12.2)	21 (7.0)	21 (9.2)	24 (14.8)	27 (29.4)	26 (24.8)	48 (30.9)	19 (7.1)	33 (26.0)
<ULN, n (%)[k]	1 (10)	1 (6)	2 (8)	1 (6)	1 (4)	2 (5)	6 (55)	1 (8)	7 (30)

Data shown are mean (SD) unless indicated otherwise.

[a]Measured by COBAS TaqMan/central lab (LLOQ=20 IU/mL and LOD=10 IU/mL). [b]Assembly Biosciences, Inc. HBV DNA assay (LOD=5 IU/mL). [c]Patient HBV DNA TND levels were ND given that values were well above the LOD for the less sensitive COBAS assay. [d]Denominators for patients originating from Study 202 are 5, 8, and 13 for PBO+ETV, VBR+ETV, and Total, respectively. [e]Assembly Biosciences, Inc. HBV pgRNA assay (LLOQ=35 U/mL for VS patients and 135 U/mL

for TN patients). [f]HBV TNA composite LLOQ=20 U/mL. [g]ND since all patients were HBV pgRNA positive. [h]Measured by COBAS TaqMan/central lab (LLOQ=0.11 IU/mL). [i]Measured by Fujirebio Lumipulse G (at the University Hong Kong lab; LLOQ=1 kU/mL). [j]Measured by COBAS TaqMan/central lab (LLOQ=0.05 IU/mL. [k]ALT ULN is 34 U/L for females and 43 U/L for males [Covance]).

ALT, alanine aminotransferase; ETV, entecavir; HBcrAg, hepatitis B core-related antigen; HBeAb, HBeAg antibody; HBeAg, hepatitis B e antigen; HBsAb, HBsAg antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; LOD, limit of detection; ND, not determined; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; pgRNA, pregenomic RNA; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TN, treatment-naïve; TNA, total nucleic acids; TND, target not detected; ULN, upper limit of normal; VBR, vebicorvir; VS, virologically-suppressed.

Table S9. Observed changes in HBV antigens during the on-treatment phase in patients from Study 211 (FAS).

Patients originating from Study 201 (on-treatment phase)						
	VS HBeAg (–)			VS HBeAg (+)		
	PBO+NrtI n=10	VBR+NrtI n=16	Total n=26	PBO+NrtI n=16	VBR+NrtI n=27	Total n=43
HBeAg change from Baseline, log_{10} IU/mL						
EOT	ND[a]	ND[a]	ND[a]	–0.1 (0.43)	–0.1 (0.29)	–0.1 (0.35)
Change >1 log_{10} IU/mL, n (%)	ND[a]	ND[a]	ND[a]	0	0	0
Seroconversion, n (%)[b]	ND[a]	ND[a]	ND[a]	0	0	0
HBsAg change from Baseline, log_{10} IU/mL						

EOT	0 (0.16)	–0.1 (0.15)	–0.1 (0.16)	0 (0.05)	–0.1 (0.07)	–0.1 (0.07)
Change >1 log_{10} IU/mL, n (%)	0	0	0	0	0	0
Seroconversion, n (%)[c]	0	0	0	0	0	0
HBcrAg change from Baseline, log_{10} kU/mL						
EOT	–0.1 (0.14)	0.0 (0.41)	0.0 (0.32)	–0.2 (0.21)	–0.1 (0.24)	–0.2 (0.23)
Patients originating from Study 202 (TN HBeAg +; on-treatment phase)						
	PBO+ETV n=11			**VBR+ETV n=12**		**Total n=23**
HBeAg change from Baseline, log_{10} IU/mL						
EOT	–0.7 (0.96)			–0.4 (0.64)		–0.5 (0.81)

Change >1 log_{10} IU/mL, n (%)	1 (9)	1 (8)	2 (9)
Seroconversion, n (%)[b]	1 (9)	0	1 (4)
HBsAg change from Baseline, log_{10} IU/mL			
EOT	–0.6 (1.01)	–0.2 (0.24)	–0.4 (0.73)
Change >1 log_{10} IU/mL, n (%)	1 (9)	0	1 (4)
Seroconversion, n (%)[c]	0	0	0
HBcrAg change from Baseline, log_{10} kU/mL			
EOT	–0.9 (1.12)	–0.5 (0.67)	–0.7 (0.91)

Data shown are mean (SD) unless otherwise stated. [a]ND as all patients were HBeAg-negative. [b]HBeAg seroconversion was defined as loss of HBeAg and appearance of HBeAb. [c]HBsAg seroconversion was defined as loss of HBsAg and appearance of HBsAb.

EOT, end of treatment; ETV, entecavir; FAS, full analysis set; HBcrAg, hepatitis B core-related antigen; HBeAb, antibody to HBeAg; HBeAg, hepatitis B e antigen; HBsAb; antibody to HBsAg; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; ND, not determinable; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; SD, standard deviation; TN, treatment-naïve; VBR, vebicorvir; VS, virologically-suppressed.

Table S10. Observed changes in HBV antigens during the off-treatment phase in patients from Study 211 (FAS).

Patients originating from Study 201 (off-treatment phase)		
	VS HBeAg (–) discontinue both n=23	**VS HBeAg (+) discontinue both n=18**
HBeAg Baseline, log_{10} IU/mL	–1.0 (0.04)	–0.2 (0.51)
Change from Baseline at end of off-treatment	0.3 (0.96)	1.5 (1.88)
HBsAg Baseline, log_{10} IU/mL	3.1 (0.61)	3.5 (0.49)
Change from Baseline at end of off-treatment	0.2 (0.71)	0.3 (0.66)
HBcrAg Baseline, log_{10} kU/mL	0.4 (0.58)	2.2 (0.47)

Change from Baseline at end of off-treatment	1.1 (1.59)	1.7 (1.96)

Data shown are mean (SD).

FAS, full analysis set; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; SD, standard deviation; VS, virologically-suppressed.

Table S11. Observed changes in HBV DNA during the Nrtl-restart phase in patients from Study 211 (FAS).

	Patients originating from Study 201 (Nrtl restart)	
	VS HBeAg (–), discontinued both and restarted Nrtl n=16	**VS HBeAg (+), discontinued both and restarted Nrtl n=14**
HBV DNA		
Baseline, log_{10} IU/mL	5.7 (2.13)	6.8 (2.32)
Change from Baseline at end of Nrtl-restart phase	–4.3 (1.83)	–3.9 (1.10)

Data shown are mean (SD).

FAS, full analysis set; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; Nrtl, nucleos(t)ide reverse transcriptase inhibitor; SD, standard deviation; VS, virologically-suppressed.

Table S12. Observed changes in HBV antigens during the NrtI-restart phase in patients from Study 211 (FAS).

Patients originating from Study 201 (NrtI restart)		
	VS HBeAg (–), discontinued both and restarted NrtI n=16	**VS HBeAg (+), discontinued both and restarted NrtI n=14**
HBeAg Baseline, log_{10} IU/mL	–0.6 (1.17)	1.8 (1.60)
Change from Baseline at end of NrtI-restart phase	–0.3 (0.81)	–0.8 (1.19)
HBsAg Baseline, log_{10} IU/mL	3.5 (0.58)	4.0 (0.72)
Change from Baseline at end	–0.5 (0.78)	0 (0.56)

of NrtI-restart phase		
HBcrAg Baseline, log_{10} kU/mL	2.4 (1.83)	4.6 (1.85)
Change from Baseline at end of NrtI-restart phase	–1.0 (0.78)	–0.8 (1.16)

Data shown are mean (SD).

FAS, full analysis set; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SD, standard deviation; VS, virologically-suppressed.

Table S13. Observed changes in HBV nucleic acids in patients who continued Nrtl/ETV during the off-treatment phase in patients from Study 211 (FAS).

	Continued Nrtl/ETV (off-treatment phase)	
	Patients originating from Study 201	**Patients originating from Study 202**
	VS HBeAg (+), continued Nrtl only	**TN HBeAg (+), continued ETV only**
	n=18	**n=6**
HBV DNA		
Baseline, $\log_{10}$ IU/mL	1.2 (0.16)	1.9 (1.37)
Change from Baseline at end of off-treatment phase	–0.1 (0.17)	1.3 (1.86)
HBV pgRNA		
Baseline, $\log_{10}$ U/mL	2.7 (0.71)	5.3 (1.53)

Change from Baseline at end of off-treatment phase	2.3 (0.78)	1.5 (1.11)
HBV TNA		
Baseline, log_{10} U/mL[a]	1.7 (0.55)	3.3 (1.02)
Change from Baseline at end of off-treatment phase	2.0 (0.98)	1.4 (1.33)

Data shown are mean (SD). [a]TNA=HBV DNA+HBV pgRNA.

ETV, entecavir; FAS, full analysis set; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; SD, standard deviation; TN, treatment-naïve; TNA, total nucleic acids; VS, virologically-suppressed.

Table S14. Observed changes in HBV antigens in patients who continued Nrtl/ETV during the off-treatment phase in patients from Study 211 (FAS).

	Continued Nrtl/ETV (off-treatment phase)	
	Patients originating from Study 201	**Patients originating from Study 202**
	VS HBeAg (+), continued Nrtl only n=18	**TN HBeAg (+), continued ETV only n=6**
HBeAg Baseline, log_{10} IU/mL	0.9 (0.77)	2.3 (1.18)
Change from Baseline at end of off-treatment phase	–0.1 (0.30)	0.0 (0.11)
HBsAg Baseline, log_{10} U/mL	3.5 (0.44)	4.4 (0.50)
Change from Baseline at end	0 (0.09)	0 (0.06)

of off-treatment phase		
HBcrAg Baseline, log_{10} U/mL	3.2 (0.78)	5.0 (1.18)
Change from Baseline at end of off-treatment phase	0 (0.22)	0.1 (0.27)

Data shown are mean (SD).

ETV, entecavir; FAS, full analysis set; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SD, standard deviation; TN, treatment-naïve; VS, virologically-suppressed.

Table S15. Summary of laboratory abnormalities dependent on TA for patients in Study 211 (SAS).

On-treatment phase					
	Patients originating from Study 201			Patients originating from Study 202	
Patients reporting:	**VS HBeAg (–) n=26**	**VS HBeAg (+) n=43**	**Total n=69**	**TN HBeAg (+) n=23**	**Overall total N=92**
Any grade	20 (77)	32 (74)	52 (75)	20 (87)	72 (78)
Grade 1	14 (54)	22 (51)	36 (52)	12 (52)	48 (52)
Grade 2	5 (19)	6 (14)	11 (16)	6 (26)	17 (18)
Grade 3	1 (4)	4 (9)	5 (7)	2 (9)	7 (8)
Glucose increased					
Grade 1	6 (23)	13 (30)	19 (28)	7 (30)	26 (28)
Grade 2	4 (15)	1 (2)	5 (7)	1 (4)	6 (7)

Amylase increased					
Grade 1	2 (8)	10 (23)	12 (17)	5 (22)	17 (18)
Grade 2	1 (4)	0	1 (1)	3 (13)	4 (4)
Grade 3	0	1 (2)	1 (1)	0	1 (1)
AST increased					
Grade 1	1 (4)	6 (14)	7 (10)	0	7 (8)
Grade 2	0	2 (5)	2 (3)	2 (9)	4 (4)
Grade 3	1 (4)	0	1 (1)	1 (4)	2 (2)
ALT increased					
Grade 1	3 (12)	4 (9)	7 (10)	1 (4)	8 (9)
Grade 2	1 (4)	0	1 (1)	0	1 (1)
Grade 3	0	1 (2)	1 (1)	2 (9)	3 (3)
Creatinine increased					
Grade 1	6 (23)	3 (7)	9 (13)	1 (4)	10 (11)

Grade 2	0	1 (2)	1 (1)	0	1 (1)
Glucose decreased					
Grade 1	4 (15)	0	4 (6)	4 (17)	8 (9)
Grade 2	0	2 (5)	2 (3)	0	2 (2)
Urate increased					
Grade 1	5 (19)	3 (7)	8 (12)	2 (9)	10 (11)
Total bilirubin increased					
Grade 1	2 (8)	0	2 (3)	2 (9)	4 (4)
Grade 2	0	1 (2)	1 (1)	0	1 (1)
Lipase increased					
Grade 1	0	3 (7)	3 (4)	0	3 (3)
Grade 2	0	1 (2)	1 (1)	0	1 (1)

Sodium increased					
Grade 1	0	3 (7)	3 (4)	1 (4)	4 (4)
Bicarbonate decreased					
Grade 1	0	0	0	1 (4)	1 (1)
Grade 2	0	1 (2)	1 (1)	1 (4)	2 (2)
Sodium decreased					
Grade 1	0	2 (5)	2 (3)	1 (4)	3 (3)
Haemoglobin decreased					
Grade 1	0	2 (5)	2 (3)	2 (9)	4 (4)
Platelets decreased					
Grade 1	0	2 (5)	2 (3)	0	2 (2)

Grade 2	0	0	0	1 (4)	1 (1)
Prothrombin intl normalised ratio increased					
Grade 1	1 (4)	1 (2)	2 (3)	0	2 (2)
Grade 2	0	1 (2)	1 (1)	0	1 (1)
Grade 3	0	1 (2)	1 (1)	0	1 (1)

Discontinued both VBR+Nrtl (off-treatment phase, patients originally from Study 201)			
Patients reporting:	**VS HBeAg (–) n=23**	**VS HBeAg (+) n=18**	**Total N=40**
Any grade	14 (64)	14 (78)	28 (70)
Grade 1	6 (27)	3 (17)	9 (23)
Grade 2	7 (32)	9 (50)	16 (40)
Grade 3	0	2 (11)	2 (5)
Grade 4	1 (5)	0	1 (3)
ALT increased			

Grade 1	4 (18)	3 (17)	7 (18)
Grade 2	6 (27)	6 (33)	12 (30)
Grade 3	0	2 (11)	2 (5)
Grade 4	1 (5)	0	1 (3)
AST increased			
Grade 1	6 (27)	4 (22)	10 (25)
Grade 2	2 (9)	6 (33)	8 (20)
Grade 3	1 (5)	0	1 (3)
Glucose increased			
Grade 1	3 (15)	4 (25)	7 (19)
Grade 2	1 (5)	0	1 (3)
Amylase increased			
Grade 1	1 (6)	3 (20)	4 (13)
Urate increased			

Grade 1	3 (15)	0	3 (8)

Discontinued both VBR+Nrtl, then restarted Nrtl (Nrtl-restart phase, patients originally from Study 201)			
Patients reporting:	**VS HBeAg (–) n=16**	**VS HBeAg (+) n=14**	**Total N=30**
Any grade	14 (88)	13 (93)	27 (90)
Grade 1	6 (38)	4 (29)	10 (33)
Grade 2	4 (25)	5 (36)	9 (30)
Grade 3	2 (13)	2 (14)	4 (13)
Grade 4	2 (13)	2 (14)	4 (13)
ALT increased			
Grade 1	3 (19)	4 (29)	7 (23)
Grade 2	4 (25)	4 (29)	8 (27)
Grade 3	1 (6)	2 (14)	3 (10)
Grade 4	2 (13)	2 (14)	4 (13)
AST increased			
Grade 1	3 (19)	5 (36)	8 (27)

Grade 2	1 (6)	3 (21)	4 (13)
Grade 3	3 (19)	1 (7)	4 (13)
Grade 4	0	1 (7)	1 (3)
Glucose increased			
Grade 1	2 (13)	3 (23)	5 (18)
Grade 3	1 (7)	0	1 (4)
Amylase increased			
Grade 1	3 (21)	1 (8)	4 (15)
Bilirubin increased			
Grade 1	1 (6)	2 (14)	3 (10)
Urate increased			
Grade 1	1 (7)	2 (15)	3 (11)

	Continued Nrtl/ETV (off-treatment phase)	
	Patients originating from Study 201	**Patients originating from Study 202**
Patients reporting:	**VS HBeAg (+) continued Nrtl only n=18**	**TN HBeAg (–) continued ETV only n=6**
Any grade	2 (11)	1 (17)
Grade 1	2 (11)	1 (17)
Urate increased		
Grade 1	0	1 (25)[a]
Total bilirubin increased		
Grade 1	1 (6)	0
Lipase increased		
Grade 1	1 (8)[b]	0

Data shown are n (%). [a]n=4. [b]n=13.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ETV, entecavir; HBeAg, hepatitis B e antigen; intl, international; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SAS, safety analysis set; TA, treatment action; TN, treatment-naïve; VBR, vebicorvir; VS, virologically-suppressed.

Table S16. Summary statistics of plasma concentration (ng/mL) for VBR, ETV, and TFV (PK analysis set) in patients from Study 211.

	VBR Wk 48 predose	ETV Wk 48 predose	TFV (TAF) Wk 48 predose	TFV (TDF) Wk 48 predose
N	64	27	15	21
Mean	1560	0.962	20.8	113
SD	679	2.01	15.1	106
% CV	43.7	209.3	72.5	93.1
Median	1640	0.494	15.7	81.7
Minimum	0	0.128	10.9	16.0
Maximum	3160	10.8	71.1	424

CV, coefficient of variation; ETV, entecavir; PK, pharmacokinetic; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir; VBR, vebicorvir; Wk, week

References

[1] Yan R, Cai D, Ouyang L, et al. Development of a sensitive, multi-assay platform to monitor low levels of HBV DNA and pgRNA in patients with chronic hepatitis B virus infection. J Virol Methods 2023;311:114640.

[2] Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560-1599.