Viral response and safety following discontinuation of treatment with the core inhibitor vebicorvir and a nucleos(t)ide reverse transcriptase inhibitor in patients with HBeAg positive or negative chronic hepatitis B virus infection

PO-482

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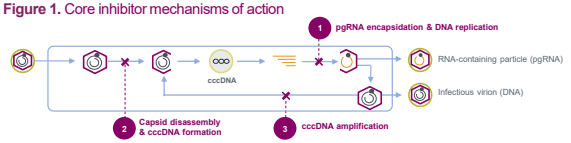
Introduction

- Worldwide, an estimated 250 million people are chronically infected with hepatitis B virus (HBV), with approximately 887,000 deaths each year due to cirrhosis and hepatocellular carcinoma associated with HBV infection[1–4]
- For most patients, nucleos(t)ide reverse transcriptase inhibitors (NrtIs) are effective in suppressing HBV DNA and are well tolerated, but treatment duration is indefinite
  - To explore potential predictors for safe discontinuation of NrtI therapy, multiple studies have been conducted to evaluate end-of-treatment (EOT) virologic response with post-treatment outcomes[5–7]
  - New therapies are needed to deepen inhibition of viral replication to support potential finite and curative therapy
  - HBV core inhibitors interfere with multiple aspects of the HBV replication cycle and provide complementary antiviral activity to NrtIs (**Figure 1**)

Figure 1. Core inhibitor mechanisms of action

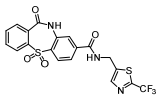


cccDNA, covalently closed circular DNA; pgRNA, pregenomic RNA

Vebicorvir

- A novel inhibitor of the HBV core protein that disrupts HBV capsid formation by allosteric binding and interference with core protein (**Figure 2**)
- Broad in vitro antiviral activity[8]
  - Inhibits virion and pregenomic (pg)RNA particle production (EC_{50}=0.17–0.31 μM; CC_{50}≥20 μM)
  - Inhibits de novo formation of covalently closed circular DNA and downstream hepatitis B "e" antigen (HBeAg) and hepatitis B surface antigen (HBsAg) production (EC_{50}=2–7 μM)
  - Pangenotypic and fully active against NrtI-resistant HBV
- Orally administered as 300 mg once daily without regard to food
- No drug interaction with NrtIs and a favorable clinical safety profile[9]
- Vebicorvir (VBR)+NrtI resulted in deeper on-treatment viral suppression in a majority of virologically-suppressed patients as assessed by high-sensitivity assays[8,10]

Figure 2. Vebicorvir



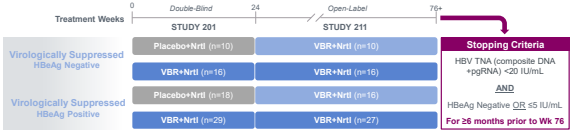
Objective of this analysis

- To determine the off-treatment safety and virologic response following application of prospective treatment stopping criteria in patients with chronic hepatitis B virus (cHBV) infection who were virologically suppressed on the VBR+NrtI combination regimen

Methods

- Virologically-suppressed patients with cHBV received VBR+NrtI or placebo+NrtI in Study 201[11–12]; patients completing treatment in Study 201 received open-label VBR+NrtI in Study 211 (**Figure 3**)
- Treatment was subsequently discontinued in patients who met stopping criteria: HBV Total Nucleic Acids (TNA; composite DNA+pgRNA[13]) <20 IU/mL AND HBeAg negative OR ≤5 IU/mL for ≥6 months prior to treatment Week 76 (**Figure 3**)
- Patients restarted NrtI according to protocol criteria or investigator/patient preference
- Primary endpoint was sustained virologic response (SVR), defined as HBV DNA <20 IU/mL by COBAS TaqMan v2.0, 24 weeks off-treatment
- Exploratory endpoints included changes in viral parameters off-treatment and post-NrtI restart and assessment of resistance. The following assays were used:
  - HBV TNA (Assembly, lower limit of quantification [LLOQ]=20 IU/mL[13]); HBV DNA (Assembly, limit of detection [LOD]=5 IU/mL[13]); pgRNA (Assembly, LLOQ=35 U/mL); HBeAg (Abbott Architect, LLOQ=0.11 IU/mL); HBsAg (Abbott Architect, LLOQ=0.05 IU/mL); hepatitis B core antigen (HBcrAg) (FujiRebio Lumipulse G, LOD=1kU/mL); viral sequencing was performed and is described separately in **PO-1286**
- Following discontinuation of VBR+NrtI, a post hoc analysis was performed in which patients were categorized as either having "lower viral load" (maximum HBV DNA <80,000 [4.9 log_{10}] IU/mL for ≥8 weeks off-treatment) or "higher viral load" (maximum HBV DNA ≥80,000 [4.9 log_{10}] IU/mL or restarted NrtI before 8 weeks off-treatment); a univariate logistic regression analysis evaluated factors predictive of off-treatment viral load
- Safety was assessed by adverse events (AEs) and laboratory abnormalities
  - Alanine aminotransferase (ALT) flare was defined as confirmed ALT >2× baseline OR on-treatment nadir AND ≥10× upper limit of normal

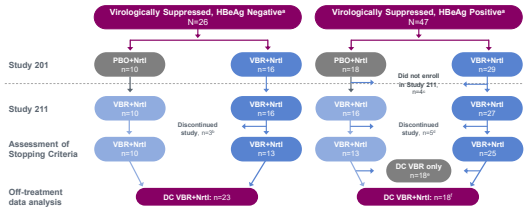
Figure 3. Overview of Study 201 and Study 211



HBeAg, hepatitis B "e" antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pg, pregenomic; TNA, total nucleic acids; VBR, vebicorvir; Wk, week.

Results

Figure 4. Study 201 and Study 211 patient disposition



[a]Intent-to-treat population. [b]n=1 AE, n=1 lost to follow-up, n=1 noncompliance. [c]Early DC, n=1 (PBO), did not roll over, n=3 (PBO 1, VBR 2). [d]Patient withdrew, n=5 (PBO 3, VBR 2). [e]n=18 (PBO 6, VBR 12) discontinued VBR only and continued NrtI. [f]n=20 (PBO 7, VBR 13) met stopping criteria, n=2 (PBO 1, VBR 1) discontinued study prior to collection of off-treatment data and are not included in the analysis.
AE, adverse event; DC, discontinued; HBeAg, hepatitis B "e" antigen; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; VBR, vebicorvir.

Table 1. Patients who discontinued VBR+NrtI

	HBeAg Negative (N=23)	HBeAg Positive (N=18)
BASELINE OF STUDY 201		
Age, mean (range)	48.5 (34–64)	42.7 (20–66)
Male, n (%)	15 (65)	14 (78)
Asian, n (%)	17 (74)	15 (83)
HBV genotype, n (%)		
A	6 (26)	2 (11)
B	1 (4)	5 (28)
C	2 (9)	4 (22)
D	1 (4)	0
G	0	1 (6)
Not determinable[a]	13 (57)	6 (33)
NrtI, n (%)		
TDF	10 (43)	9 (50)
TAF	8 (35)	6 (33)
ETV	5 (22)	3 (17)
Years on current NrtI mean (range)	4.7 (0.1–14.6)	3.9 (0.4–11.7)
END OF VBR+NrtI TREATMENT		
HBV DNA TND (Assembly), n (%)	23 (100)	18 (100)
HBV pgRNA <LLOQ (Assembly), n (%)	23 (100)	18 (100)
HBeAg mean (range), Log_{10} IU/mL	NA	−0.2 (−1.0 to 0.6)
HBcrAg mean (range), Log_{10} kU/mL	0.4 (0.0–1.7)	2.2 (1.2–3.0)
HBsAg mean (range), Log_{10} IU/mL	3.1 (1.9–4.1)	3.5 (2.9–4.6)

[a]Includes missing genotype data.
ETV, entecavir; HBcrAg, hepatitis B core antigen; HBeAg, hepatitis B "e" antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NA, not applicable; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TND, target not detected.

Table 2. Virologic outcomes after VBR+NrtI discontinuation

	HBeAg Negative (N=23)	HBeAg Positive (N=18)
SVR	0	0
Relapse at post-treatment Week 4	16 (70)	17 (94)
Relapse at post-treatment Week 12	3 (13)	1 (6)
Relapse at post-treatment Week 16	4 (17)	0
Maximum HBV DNA <2,000 (3.3 log_{10}) IU/mL and ALT <2× ULN	6 (26)	1 (6)
	5 (22)	1 (6)
Maximum HBV DNA <80,000 (4.9 log_{10}) IU/mL for ≥8 weeks and ALT <2× ULN	10 (43)	7 (39)
	8 (35)	6 (33)

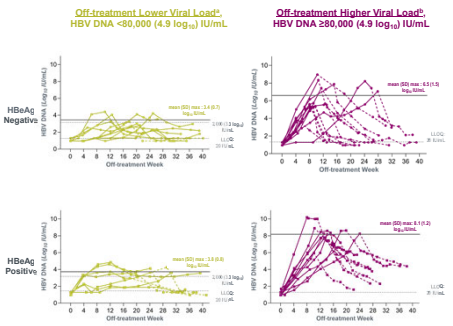
All data shown are n (%).
ALT, alanine aminotransferase; HBeAg, hepatitis B "e" antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SVR, sustained virologic response (HBV DNA <20 IU/mL by COBAS TaqMan v2.0, 24 weeks off-treatment); ULN, upper limit of normal (by central lab, 34 U/L for females, 43 U/L for males); VBR, vebicorvir.

Table 3. Restarting NrtI after VBR+NrtI discontinuation

	HBeAg Negative (N=23)	HBeAg Positive (N=18)
Patients who restarted NrtI, n (%)	15 (65)	14 (78)
Mean (range) time to NrtI restart, weeks	15 (6–28)	18 (10–29)
Patients who met protocol restart criteria, n (%)[a]	6 (40)	7 (50)
ALT >10× ULN	1 (7)	0
ALT >3× ULN with HBV DNA >100,000 IU/mL	5 (33)	6 (43)
ALT >ULN with HBV DNA >2,000 (3.3 log_{10}) IU/mL[b]	0	1 (7)
Patients who restarted NrtI for other reasons[c]	9 (60)	7 (50)
Patients who remain off-treatment at end of study, n (%)	8 (35)	4 (22)
Mean (range) time of follow up, weeks	34 (26–39)	30 (16–39)

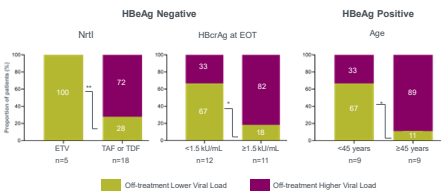
[a]Data are shown as proportion of those who restarted NrtI. [b]3 consecutive visits ≥1 month apart. [c]Investigator and/or patient preference.
ALT, alanine aminotransferase; HBeAg, hepatitis "e" antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; ULN, upper limit of normal (by central lab, 34 U/L for females, 43 U/L for males); VBR, vebicorvir.

Figure 5. HBV DNA in patients who stopped VBR+NrtI



[a]For ≥8 weeks off-treatment. [b]Or, restarted NrtI before 8 weeks off-treatment.
HBeAg, hepatitis "e" antigen; HBV, hepatitis virus; B; LLOQ, lower limit of quantitation; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SD, standard deviation; VBR, vebicorvir.

Figure 6. Univariate logistic regression analysis: Predictors of off-treatment HBV DNA viral load[a]



**P <0.01 (Fisher's Exact), *P <0.05.
[a]In a post hoc subgroup analysis, patients were categorized as lower viral load, those who maintained HBV DNA <80,000 (4.9 log_{10}) IU/mL for ≥8 weeks off-treatment, or as higher viral load, maximum HBV DNA ≥80,000 (4.9 log_{10}) IU/mL, or restarted NrtI before 8 weeks off-treatment.
EOT, end of treatment; ETV, entecavir; HBcrAg, hepatitis B core antigen; HBeAg, hepatitis "e" antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Efficacy

- No patient achieved SVR, and all had HBV DNA >20 IU/mL by post-treatment Week 16 (**Table 2**)
- No patient experienced HBsAg loss; 1 HBeAg negative patient had a significant reduction in HBsAg following ALT elevation
- Two HBeAg negative patients without hepatitis B "e" antigen antibody had a >1.5 log_{10} increase in HBeAg off-treatment; 4 HBeAg positive patients experienced HBeAg loss and seroconversion during off-treatment period
- 45% (13 of 29) patients who restarted NrtI met restart laboratory criteria (**Table 3**), and all patients who restarted NrtI had a subsequent decline in HBV DNA (**Figure 5**)
- In a post hoc analysis, 10 HBeAg negative and 7 HBeAg positive patients were categorized as having off-treatment lower viral load, and 13 HBeAg negative and 11 HBeAg positive patients were categorized as having off-treatment higher viral load (**Figure 4**)
  - A univariate logistic regression model was constructed to evaluate patient characteristics predictive of off-treatment viral load. Parameters assessed were age, sex, race, NrtI, duration of NrtI and VBR administration at EOT, HBcrAg level, and HBsAg level at EOT. Significant predictors of off-treatment viral load are presented in **Figure 6**
    - HBeAg negative: entecavir (ETV) use and HBcrAg <1.5 kU/mL at EOT
      - All 5 patients on ETV had off-treatment lower viral load and had HBcrAg <1.5 kU/mL at EOT
    - HBeAg positive: age <45 years

Table 4. Overall summary of AEs

Patients, n (%)	Off-treatment N=41[a]	Post-NrtI restart N=29[a]
Any AE	19 (46)	10 (34)
Grade 1	8 (20)	3 (10)
Grade 2	6 (15)	4 (14)
Grade 3	5 (12)	0
Grade 4	0	3 (10)
Serious AEs	2 (5)	0
ALT flare[b]	0	3 (10)
Deaths	0	0

[a]Includes HBeAg negative and positive patients. [b]ALT >2× Baseline or on-treatment nadir and ≥10× ULN.
AE, adverse event; ALT, alanine aminotransferase; HBeAg, hepatitis B "e" antigen; NrtI, nucleos(t)ide reverse transcriptase inhibitor; ULN, upper limit of normal (by central lab, 34 U/L for females, 43 U/L for males).

Table 5. Laboratory abnormalities

Patients, n (%)	Off-treatment N=41[a]	Post-NrtI restart N=29[a]
Grade 1	9 (22)	10 (34)
Grade 2	17 (41)	8 (28)
Grade 3	2 (5)	6 (21)
Grade 4	1 (2)	4 (14)

[a]Includes HBeAg negative and positive patients.
HBeAg, hepatitis B "e" antigen; NrtI, nucleos(t)ide reverse transcriptase inhibitor.

Safety

- Most reported AEs off-treatment and post-NrtI restart were Grade 1 or 2 (**Table 4**)
- The most frequent AEs reported by >10% patients in the off-treatment or post-NrtI restart periods were increased ALT and headache
  - Increased ALT was reported for 11/41 (27%) patients in the off-treatment period, 3 of which were Grade 3, and 6/29 (21%) patients in the post-NrtI restart period, 3 of which were Grade 4
  - Headache was reported for 4/41 (10%) of patients in the off-treatment period
  - No patient had hepatic decompensation or total bilirubin elevation greater than Grade 1
  - There were 2 unrelated serious AEs reported in the off-treatment period, post-procedural hemorrhage and seizure
- Most laboratory abnormalities were Grade 1 or 2, and all Grade 4 abnormalities were increases in ALT (**Table 5**)
  - Three patients met ALT flare criteria; flares reached maximum levels post-NrtI restart and were not associated with significant changes in antigens

Conclusions

- SVR was not achieved in any patient who met stopping criteria
- Univariate predictors of off-treatment lower viral load were ETV use and EOT HBcrAg <1.5 kU/mL for HBeAg negative patients and age <45 years for HBeAg positive patients
  - Consistent with previous reports[5], data suggest HBcrAg level may be an important component for future stopping criteria
- Discontinuation of VBR+NrtI was well tolerated with limited AEs and ALT elevations post-NrtI restart
- Additional studies with VBR+NrtI in multidrug combinations will evaluate potential finite treatment regimens and refined stopping rules

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