Antiviral activity and safety of the hepatitis B core inhibitor ABI-H0731 administered with a nucleos(t)ide reverse transcriptase inhibitor in patients with HBeAg positive chronic hepatitis B infection in a long-term extension study

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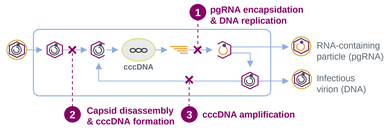
Background

- Worldwide, ~250 million people are chronically infected with hepatitis B virus (HBV) and 600,000–1 million die each year due to cirrhosis and hepatocellular carcinoma associated with chronic hepatitis B (CHB)[1–4]; of the ~94 million patients eligible for treatment, only ~4.8 million (5%) receive antiviral therapy.[5]
- Nucleos(t)ide reverse transcriptase inhibitors (NrtIs) are safe and have a high barrier to resistance; however:
  - ~30% of hepatitis B e-antigen (HBeAg) positive patients do not completely suppress HBV DNA after 48 weeks of treatment[6,7]
  - Of those who completely suppress HBV DNA by current assays, 70%–80% still have infectious virus[8,9]
  - Durable, off-treatment virologic suppression is rare and treatment is indefinite for most patients
- New therapies are needed to provide deeper suppression of HBV replication and ultimately achieve sustained virologic response and allow for finite therapy
- Quantification of pregenomic RNA (pgRNA) enables a comprehensive assessment of covalently closed circular DNA (cccDNA) transcriptional activity and HBV replication[10–12]; presence of HBV pgRNA is associated with persistent viral replication and the risk of relapse following cessation of treatment with NrtI[12–16]
- Core inhibitors target multiple steps of the HBV life cycle to suppress HBV DNA, pgRNA, and cccDNA (**Figure 1**)
- Combination treatment with a core inhibitor and an NrtI, which have distinct mechanisms of action, have the potential to lead to deeper virologic suppression and to improve treatment outcomes of CHB.

Figure 1. Core Inhibitor Mechanisms of Action

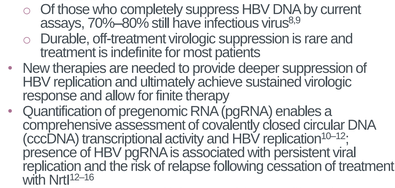


cccDNA, covalently closed circular DNA; HBV, hepatitis B virus; pgRNA, pregenomic RNA.

Vebicorvir (VBR; ABI-H0731): A Novel Inhibitor of HBV Core Protein

- Disrupts HBV capsid formation by allosteric binding and interference with core protein dimerization
- Broad in vitro antiviral activity[17]
  - Inhibits virion and pgRNA particle production (EC_{50} = 0.17–0.31 µM; CC_{50} ≥20 µM)
  - Inhibits de novo formation of cccDNA and downstream 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
- Favorable clinical safety profile
- Superior reduction in HBV DNA and pgRNA in combination with NrtIs compared to NrtI alone in HBeAg positive CHB patients[18]
- The objective of this study was to evaluate the safety and efficacy of VBR in patients with HBeAg positive CHB

Figure 2. Phase 2 Clinical Trial Overview



ETV, entecavir; HBeAg, hepatitis B e-antigen; NrtI, nucleos(t)ide analogue reverse transcriptase inhibitor. VBR, vebicorvir.

Table 1. Eligibility Criteria

CHB in good general health
Metavir F0–F2 or equivalent (no history of hepatic decompensation)
Study 201: On NrtI with HBV DNA ≤ LLOQ by COBAS for at least 6 months, HBsAg >400 IU/mL; ALT ≤5x ULN
Study 202: HBV DNA >2 x 10^5 IU/mL; HBsAg >1000 IU/mL; ALT ≤10x ULN
Study 211: Completion of Study 201 or Study 202 with good compliance to study drug

ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NrtI, nucleos(t)ide reverse transcriptase inhibitor; ULN, upper limit of normal.

Methods

- Patients from 30 sites in the United States, Canada, Hong Kong, and New Zealand enrolled if they met eligibility criteria (**Table 1**)
- Safety assessed by adverse events (AEs) and laboratory parameters
- Efficacy assessed through monitoring of HBV nucleic acids and HBV antigens

Table 2. Analytical Methods

Assay	Treatment Naive	Virologically Suppressed
COBAS HBV DNA	LLOQ = 20 IU/mL	LLOQ = 20 IU/mL
Assembly HBV DNA	**NA**	**LOD = 5 IU/mL**
Assembly HBV pgRNA	**LLOQ = 135 U/mL**	**LLOQ = 35 U/mL**
Assembly HBV Total Nucleic Acids (composite DNA+pgRNA)	**NA**	**LLOQ = 20 IU/mL**
Abbott ARCHITECT i2000SR qHBeAg	LLOQ = 0.11 IU/mL	
Abbott ARCHITECT i2000SR qHBsAg	LLOQ = 0.05 IU/mL	
FujiRebio Lumipulse G HBcrAg	LLOQ = 1 kU/mL	

HBcrAg, hepatitis B virus core-related antigen; HBV, hepatitis B virus; LOD, limit of detection; LLOQ, lower limit of quantification; NA, not applicable; pgRNA, pregenomic RNA; qHBeAg, quantitative hepatitis B e antigen; qHBsAg, quantitative hepatitis B surface antigen.
Detailed information regarding Assembly assays is included in Huang, et al. EASL 2020 Poster, Abstract 4154

- Resistance monitored by population sequencing of the HBV core protein and polymerase reverse transcriptase regions (mutant detection limit ≥5%)
- Genotyping performed by highly sensitive polymerase chain reaction (PCR; DNA) and reverse transcription-PCR (DNA + pgRNA) assays to detect a single copy of HBV genome

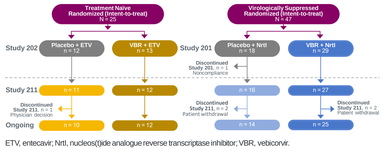
Results

Table 3. Baseline Demographics and Disease Characteristics

HBeAg Positive	ETV N = 12	ETV N = 13	NrtI N = 18	NrtI N = 29
Baseline Demographics				
Age, years, mean (SD)	34.1 (11.39)	35.7 (14.13)	46.1 (12.92)	42.1 (10.73)
Male, n (%)	5 (42)	3 (23)	10 (56)	21 (72)
Asian, n (%)	11 (92)	13 (100)	15 (83)	26 (90)
Genotype, n (%)				
A	2 (17)	0	1 (6)	2 (7)
B	4 (33)	7 (54)	2 (11)	10 (34)
C	6 (50)	5 (38)	11 (61)	8 (28)
F	0	0	0	1 (3)
G	0	0	1 (6)	0
Not determinable[a]	0	1 (8)	3 (17)	8 (28)
Duration of NrtI at randomization, years, mean (SD)	NA	NA	3.2 (2.71)	4.6 (3.68)
TDF, n (%)[b]	NA	NA	13 (72)	17 (59)
TAF, n (%)	NA	NA	4 (22)	8 (28)
ETV, n (%)	NA	NA	1 (6)	3 (10)
Baseline Disease Characteristics				
HBV DNA (COBAS)[a], <LLOQ, n (%)	0	0	18 (100)	27 (93)
HBV DNA (Assembly), target not detected, n (%)	NA	NA	5 (28)	2 (7)
HBV pgRNA, Log_{10} U/mL, mean (SD) <LLOQ, n (%)	7.4 (1.1) 0	7.1 (1.0) 0	3.2 (1.5) 5 (28)	3.6 (1.5) 4 (14)
HBeAg, Log_{10} IU/mL, mean (SD)	2.5 (1.2)	2.5 (0.8)	0.4 (1.0)	0.6 (1.0)
HBsAg, Log_{10} IU/mL, mean (SD)	4.7 (0.4)	4.5 (0.5)	3.6 (0.5)	3.5 (0.4)
HBcrAg, Log_{10} kU/mL, mean (SD)	5.4 (1.0)	5.5 (0.7)	2.9 (0.9)	3.0 (1.0)
ALT, U/L, mean (SD)	47 (32)	66 (87)	27 (19)	27 (16)

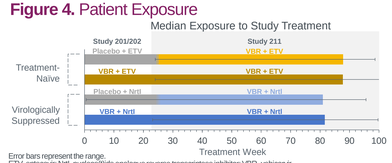
[a]Not enough sequence data to confirm genotype. [b]One patient enrolled on both ETV and TDF.
ALT, alanine aminotransferase; ETV, entecavir; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen, HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NA, not applicable; NrtI, nucleos(t)ide analogue reverse transcriptase inhibitor; pgRNA, pregenomic RNA; SD, standard deviation; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; VBR, vebicorvir.

Figure 3. Patient Disposition



ETV, entecavir; NrtI, nucleos(t)ide analogue reverse transcriptase inhibitor; VBR, vebicorvir.

Figure 4. Patient Exposure

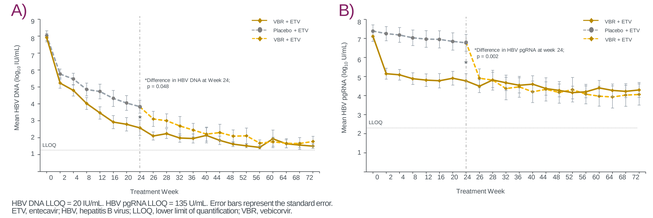


Error bars represent the range.
ETV, entecavir; NrtI, nucleos(t)ide analogue reverse transcriptase inhibitor; VBR, vebicorvir.

- The median exposure to VBR for treatment-naïve patients was 75 weeks (range 24–102) while the median exposure for virologically suppressed patients was 77 weeks (range 23–100)

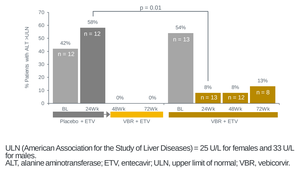
Efficacy: Treatment-Naïve Patients

Figure 5. HBV DNA (A) and pgRNA (B) in Treatment-Naïve Patients



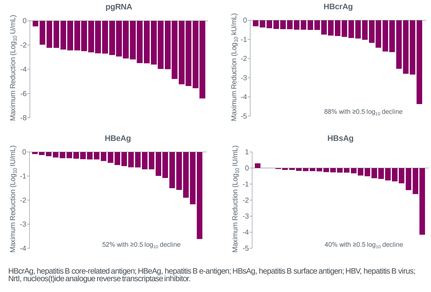
HBV DNA LLOQ = 20 IU/mL. HBV pgRNA LLOQ = 135 U/mL. Error bars represent the standard error.
ETV, entecavir; HBV, hepatitis B virus; LLOQ, lower limit of quantification; VBR, vebicorvir.

Figure 6. Normalization of ALT in Treatment-Naïve Patients



ULN (American Association for the Study of Liver Diseases) = 25 U/L for females and 33 U/L for males.
ALT, alanine aminotransferase; ETV, entecavir; ULN, upper limit of normal; VBR, vebicorvir.

Figure 7. HBV Viral Transcripts in Treatment-Naïve Patients (Change from Baseline for Individuals)



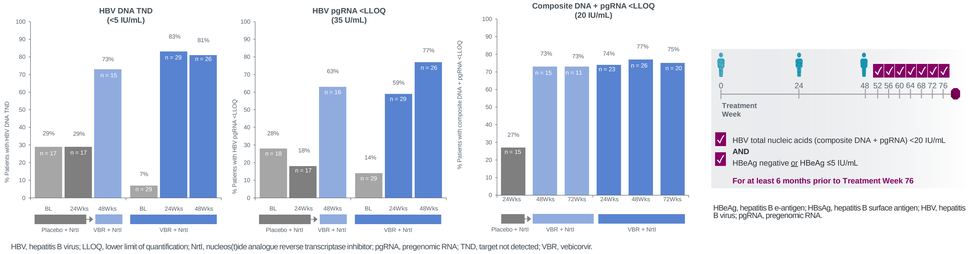
HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide analogue reverse transcriptase inhibitor.

- Compared to placebo + entecavir (ETV), VBR + ETV led to statistically greater reductions in HBV DNA and HBV pgRNA at Treatment Week 24 (**Figure 5**)
- Extended treatment with VBR + ETV resulted in continued declines in HBV DNA and HBV pgRNA (**Figure 5**)
  - By Treatment Week 48, patients who received placebo + ETV and switched to VBR + ETV were similar to patients who started on VBR + ETV
  - At Treatment Week 72, 50% of patients (10/20) achieved HBV DNA <lower limit of quantification (LLOQ; 20 IU/mL)
- 7 treatment-naïve patients experienced HBV DNA rebound (>1 log_{10} increase from nadir); all were sequenced at the time of rebound with no evidence of resistance and all reported missed doses or were suspected to be noncompliant
- VBR + ETV resulted in rapid normalization of alanine aminotransferase (ALT; **Figure 6**)
- Treatment-naïve patients had higher levels of HBV antigens at baseline and most experienced decreases in hepatitis B core-related antigen (HBcrAg), HBeAg and HBsAg on treatment with VBR + ETV (**Figure 7**)
- **At Treatment Week 76, treatment-naïve patients will be assessed and have treatment with VBR + ETV extended if they have achieved the initial virologic response criterion (≥2.5 log_{10} U/mL reduction in pgRNA from baseline)**
  - Of the 23 patients who enrolled in Study 211, it is projected[a] that 65% (15 patients) will continue both VBR + ETV, and 26% (6 patients) will discontinue VBR and continue NrtI only (9% [2 patients] have discontinued VBR for other reasons])

[a]As of a July 9, 2020 data cut

Efficacy: Virologically-Suppressed Patients

Figure 8. HBV DNA and HBV pgRNA in Virologically-Suppressed Patients

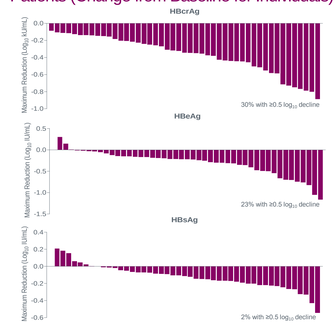


HBV, hepatitis B virus; LLOQ, lower limit of quantification; NrtI, nucleos(t)ide analogue reverse transcriptase inhibitor; pgRNA, pregenomic RNA; TND, target not detected; VBR, vebicorvir.

Figure 9. Criteria for Stopping Therapy

HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; pgRNA, pregenomic RNA.

Figure 10. HBV Antigens in Virologically-Suppressed Patients (Change from Baseline for Individuals)



HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

- Compared with placebo + NrtI, treatment with VBR + NrtI led to greater viral suppression as assessed by highly sensitive HBV nucleic acid assays (**Figure 8**)
- 2 virologically-suppressed patients experienced HBV DNA rebound (>1 log_{10} increase from nadir); both were sequenced at the time of rebound with no evidence of resistance and reported missing doses
- At Treatment Week 72, the mean (standard deviation) ALT was 25 (14) U/mL for those who initially received placebo + NrtI and 30 (21) U/mL for those who initially received VBR + NrtI
- Virologically-suppressed patients had lower levels of HBV antigens at baseline and most experienced small decreases in HBcrAg, HBeAg, and HBsAg on treatment with VBR + NrtI (**Figure 10**)
- At Treatment Week 72, 74% of patients (23/31) have HBeAg <5 IU/mL, 60% of patients (18/30) have HBcrAg <500 kU/mL and 10% of patients (3/31) have HBsAg <1000 IU/mL
- **At Treatment Week 76, virologically-suppressed patients will be assessed and, if the stopping criteria are met (Figure 9), will discontinue treatment with VBR + NrtI and be monitored for sustained virologic response**
  - Of the 43 patients who enrolled in Study 211, it is projected[a] that 49% (21 patients) will discontinue both VBR + NrtI, and 42% (18 patients) will discontinue VBR and continue NrtI only (9% [4 patients] have discontinued VBR for other reasons])
  - To date, those stopping VBR + NrtI will have had composite DNA + pgRNA <LLOQ for 6–17 months

[a]As of a July 9, 2020 data cut

Table 4. Overall Summary of Safety

Patients, n (%)	Study 201/202 (24 Weeks) Placebo + NrtI n = 30	Study 201/202 (24 Weeks) VBR + NrtI n = 42	Study 211 (24 to 72 Weeks) VBR + NrtI[a] n = 27	Study 211 (24 to 72 Weeks) VBR + NrtI n = 39
Any TEAE	10 (33)	21 (50)	16 (59)	19 (49)
Grade 1	8 (27)	14 (33)	6 (22)	12 (31)
Grade 2	1 (3)	7 (17)	8 (30)	6 (15)
Grade 3	1 (3)	0	2 (7)	1 (3)
Grade 4	0	0	0	0
Serious AEs	0	0	1 (4)	0
TEAEs leading to DC	0	0	1 (4)	1 (3)
Death	0	0	0	0

[a]Patients who received placebo + VBR in Study 201/202.
AE, adverse event; DC, (study drug) discontinuation; NrtI, nucleos(t)ide analogue reverse transcriptase inhibitor; TEAE, treatment-emergent AE; VBR, vebicorvir.

Table 5. Treatment-Emergent Adverse Events and Laboratory Abnormalities

Patients, n (%)	Study 201/202 (24 Weeks) Placebo + NrtI n = 30	Study 201/202 (24 Weeks) VBR + NrtI n = 42	Study 211 (24 to 72 Weeks) VBR + NrtI[a] n = 27	Study 211 (24 to 72 Weeks) VBR + NrtI n = 39
Treatment-Emergent Adverse Events[b]				
Upper respiratory tract infection	2 (7)	4 (10)	3 (11)	4 (10)
Pruritus	0	5 (12)	3 (11)	1 (3)
Nasopharyngitis	1 (3)	2 (5)	2 (7)	3 (8)
Increased ALT	2 (7)	1 (2)	1 (4)	1 (3)
Headache	0	3 (7)	0	1 (3)
Dizziness	2 (7)	1 (2)	0	0
Rash	0	1 (2)	2 (7)	1 (3)
Hematuria	0	0	2 (7)	1 (3)
Cholelithiasis	0	0	2 (7)	0
Treatment-Emergent Laboratory Abnormalities				
Grade 1	9 (30)	15 (36)	11 (41)	19 (49)
Grade 2	11 (37)	12 (29)	5 (19)	5 (13)
Grade 3	0	0	1 (4)	3 (8)

[a]Patients who received placebo + VBR in Study 201/202. [b]TEAEs reported for >5% patient in any column.
ALT, alanine aminotransferase; NrtI, nucleos(t)ide analogue reverse transcriptase inhibitor; TEAE, treatment-emergent adverse event; VBR, vebicorvir.

- Treatment-naïve and virologically-suppressed patients from Studies 201, 202 and 211 were pooled in the safety analysis
- VBR + NrtI was generally safe and well-tolerated throughout the studies, with most AEs and laboratory abnormalities being Grade 1 or 2
  - There was 1 serious AE of Grade 3 suicidal ideation considered not related to study drug
  - The AEs leading to discontinuation of VBR were Grade 3 serious AE of suicidal ideation and Grade 3 AE of ALT elevation
  - Grade 3 laboratory abnormalities were: 1 patient with isolated Grade 3 elevations in aspartate aminotransferase and ALT associated with increased alcohol use (reported as Grade 3 AEs); 1 patient with intermittent Grade 3 elevations in ALT (reported as Grade 3 AE and led to VBR discontinuation); 1 patient with isolated high international normalized ratio and prothrombin time; and 1 patient with isolated high prothrombin time

Conclusions

- In patients with HBeAg positive CHB, VBR given in combination with NrtI has a favorable safety and tolerability profile with no observed treatment-emergent resistance
- In treatment-naïve patients with HBeAg positive CHB:
  - The addition of VBR to ETV therapy led to greater decline in HBV DNA and pgRNA, and normalization of ALT
  - Those with an initial virologic response will extend treatment with VBR + ETV for an additional 48 weeks to allow them to reach the stopping criteria
- In virologically-suppressed patients with HBeAg positive CHB:
  - The addition of VBR to NrtI therapy led to greater proportions of patients achieving undetectable DNA and pgRNA levels measured by highly sensitive HBV nucleic acid assays
  - Discontinuation of both VBR and NrtI treatment in these patients meeting stopping criteria will now assess the durability of virologic and clinical outcomes
- These data demonstrate that the addition of VBR to NrtI provides enhanced inhibition of viral replication during chronic suppressive therapy

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