Analysis of the longer-term safety profile of the hepatitis B virus core inhibitor ABI-H0731 in an open-label extension study

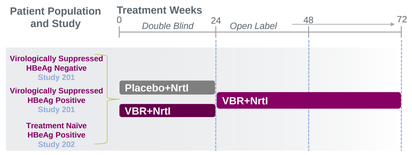
Ira M Jacobson[1], Xiaoli Ma[2], Tuan Nguyen[3], Eugene R Schiff[4], Man-Fung Yuen[5], Hie-Won Hann[6], Mark Sulkowski[7], Ronald Nahass[8], Alnoor Ramji[9], Kosh Agarwal[10], James Park[1], Walid Ayoub[11], Edward Gane[12], Steven J Knox[13], Katia Alves[13], Yunfeng Li[13], Luisa M Stamm[13], Frank Weilert[14], Michael Bennett[15], Steven-Huy Han[16], Natarajan Ravendhran[17], Sing Chan[18], Paul Kwo[19], Magdy Elkhashab[20], Tarek Hassanein[21], Mauricio Bonacini[22], Scott Fung[23], Ho Bae[24], Jacob Lalezari[22], Douglas Dieterich[25]

[1]New York University Langone Medical Center, New York, NY, USA; [2]Office of Xiaoli Ma, Philadelphia, PA, USA; [3]T Nguyen Research and Education, Inc., San Diego, CA, USA; [4]Schiff Center for Liver Diseases, University of Miami School of Medicine, Miami, FL, USA; [5]Department of Medicine, The University of Hong Kong, Hong Kong; [6]Thomas Jefferson University Hospital, Philadelphia, PA, USA; [7]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [8]Infectious Disease Care, Hillsborough, NJ, USA; [9]Providence Health Care Research Institute, Vancouver, Canada; [10]Institute of Liver Studies, King's College Hospital, London, UK; [11]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [12]Auckland Clinical Studies Ltd, Auckland, New Zealand; [13]Assembly Biosciences, Inc, South San Francisco, CA, USA; [14]Waikato Hospital, Hamilton, New Zealand; [15]Medical Associates Research Group, San Diego, CA, USA; [16]Pfleger Liver Institute, University of California, Los Angeles, CA, USA; [17]Digestive Disease Associates, Catonsville, MD, USA; [18]Sing Chan MD, New York, NY, USA; [19]Stanford University Medical Center, Stanford, CA, USA; [20]Toronto Liver Centre, Toronto, Canada; [21]Southern California Research Center, Coronado, CA, USA; [22]Quest Clinical Research, San Francisco, CA, USA; [23]University of Toronto, Toronto, Canada; [24]Asian Pacific Liver Center, Los Angeles, CA, USA;; [25]Department of Medicine, Division of Liver Diseases, Icahn School of Medicine, Mount Sinai Hospital, New York, NY, USA

Background

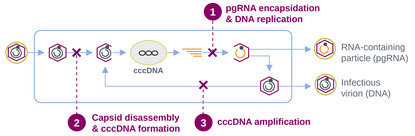
- Worldwide ~250 million people are chronically infected with hepatitis B virus (HBV), and 600,000 to 1 million die each year due to cirrhosis and hepatocellular carcinoma associated with chronic hepatitis B virus infection (cHBV);[1-4] of the ~94 million patients eligible for treatment, only ~4.8 million (5%) receive antiviral therapy[5]
- Vebicorvir (VBR, ABI-H0731) was investigated in two Phase 2 studies (Study 202 [NCT03577171], Study 201 [NCT03576066]) and an on-going open-label extension study (**Figure 1**), and has demonstrated deeper viral suppression in patients treated with VBR in combination with a nucleos(t)ide analog reverse transcriptase inhibitor (NrtI) than an NrtI alone[6]
- The objective of this study was to evaluate the long-term safety of VBR in patients with cHBV

Figure 1. Study Design



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

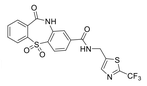
Figure 2. Core Inhibitor Mechanisms of Action



cccDNA, covalently closed circular DNA; pgRNA, pregenomic RNA.

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

- Disrupts HBV capsid by allosteric binding and interference with core protein dimerization (**Figure 2**)



- Broad in vitro antiviral activity[7]
  - Pangenotypic and fully active against NrtI-resistant HBV
- Orally administered as 300 mg once daily without regard to food
- No drug interaction with NrtIs

Methods

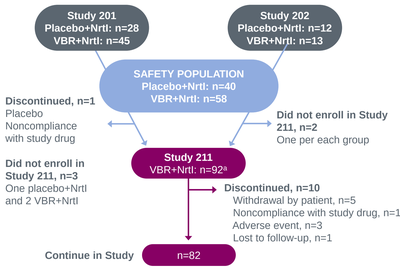
- Patients from 30 sites in the US, Canada, Hong Kong, New Zealand, and the UK were enrolled if they met eligibility criteria (**Table 1**)
- This pooled patient population included virologically suppressed hepatitis B e antigen (HBeAg) positive and negative patients from Study 201 and treatment-naïve HBeAg positive patients from Study 202 (**Figure 1**)
- Safety was assessed by adverse events (AEs) and laboratory parameters in patients taking placebo+NrtI for 24 weeks compared with patients taking VBR+NrtI in 24-week increments from 0 to 24 weeks, 24 to 48 weeks, 48 to 72 weeks, and ≥72 weeks

Table 1. Eligibility Criteria

cHBV 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 ≥6 months, HBsAg>400 IU/mL; ALT ≤5x ULN
Study 202: HBV DNA>2x10[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; cHBV, chronic HBV; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; NrtI, nucleos(t)ide analog reverse transcriptase inhibitor; ULN, upper limit of normal.

Figure 3. Patient Disposition



[a]37 patients initially received placebo+NrtI; 55 patients initially received VBR+NrtI.
NrtI, nucleos(t)ide analog reverse transcriptase inhibitor; VBR, vebicorvir.

Results

Table 2. Baseline Demographics and Disease Characteristics

	Placebo+NrtI N=40	VBR+NrtI[a] N=95
Age, years, mean (SD)	42.7 (12.56)	42.7 (11.91)
Male, n (%)	20 (50)	53 (56)
Asian, n (%)	35 (88)	83 (87)
Body mass index, kg/m^2, mean (SD)	23.5 (3.55)	23.8 (3.43)
Duration of NrtI at randomization, years, mean (SD)[b]	4.4 (4.31)	4.2 (3.98)
TDF, n (%)[c]	17 (43)	40 (42)
TAF, n (%)	8 (20)	22 (23)
ETV, n (%)[c]	3 (8)	10 (11)
Alanine aminotransferase, mean (SD)	31.6 (23.99)	33.5 (38.09)
>ULN (Central Lab)[d]	7 (18)	21 (22)
>ULN (AASLD)[e]	14 (35)	32 (34)
Creatinine clearance[f], mL/min, mean (SD)	100.4 (27.22)	104.6 (26.38)

[a]The total of 95 includes 37 placebo+NrtI patients who rolled over to Study 211 and 3 VBR+NrtI patients who did not roll over to Study 211. [b]Only patients from Study 201. [c]One patient was taking both TDF and ETV and is counted in both categories. [d]ULN: 34 U/L (female), 43 U/L (male). [e]ULN: 25 U/L (female), 33 U/L (male). [f]Calculated by Cockcroft-Gault formula.
ETV, entecavir; NrtI, nucleos(t)ide reverse analog transcriptase inhibitor; SD, standard deviation; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal; VBR, vebicorvir.

Table 4. Adverse Events by Preferred Term (>5% of patients)

Preferred term, N (%)	Placebo+NrtI 0 to <24 wks N=40	VBR+NrtI 0 to <24 wks N=95	24 to <48 wks N=93	48 to <72 wks N=87	>72 wks N=56	Total N=95
Upper respiratory tract infection	2 (5)	9 (9)	6 (6)	2 (2)	0	15 (16)
Grade 1	2 (5)	7 (7)	5 (5)	2 (2)	0	12 (13)
Grade 2	0	2 (2)	1 (1)	0	0	3 (3)
Grade 3	0	0	0	0	0	0
Rash[a]	0	7 (7)	4 (4)	4 (5)	2 (4)	14 (15)
Grade 1	0	6 (6)	4 (4)	4 (5)	2 (4)	13 (14)
Grade 2	0	1 (1)	0	0	0	1 (1)
Grade 3	0	0	0	0	0	0
Pruritis	0	8 (8)	0	0	0	8 (8)
Grade 1	0	8 (8)	0	0	0	8 (8)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Nasopharyngitis	1 (3)	2 (2)	6 (6)	1 (1)	0	7 (7)
Grade 1	1 (3)	2 (2)	5 (5)	0	0	5 (5)
Grade 2	0	0	1 (1)	1 (1)	0	2 (2)
Grade 3	0	0	0	0	0	0
Headache	0	4 (4)	1 (1)	1 (1)	1 (2)	7 (7)
Grade 1	0	4 (4)	1 (1)	1 (1)	1 (2)	7 (7)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Nausea	0	4 (4)	2 (2)	1 (1)	0	6 (6)
Grade 1	0	4 (4)	1 (1)	1 (1)	0	5 (5)
Grade 2	0	0	1 (1)	0	0	1 (1)
Grade 3	0	0	0	0	0	0
Fatigue	1 (3)	2 (2)	2 (2)	1 (1)	1 (2)	6 (6)
Grade 1	1 (3)	2 (2)	1 (1)	1 (1)	1 (2)	5 (5)
Grade 2	0	0	1 (1)	0	0	1 (1)
Grade 3	0	0	0	0	0	0

[a]Includes preferred terms of rash, papular rash, maculopapular rash, macular rash, erythematous rash, and pruritic rash.
Treatment-emergent AEs are events with onset between first to last dose+28 days. Reported AEs were coded using MedDRA dictionary version 21.0.
AE, adverse event; ALT, alanine aminotransferase; NrtI, nucleos(t)ide analog reverse transcriptase inhibitor; VBR, vebicorvir; wks, weeks.

Rash

- Eighteen AEs of rash were reported by 14 patients (14/95, 15%)
  - Rash includes preferred terms of rash (10, 7 described as localized), papular rash (2), maculopapular rash (1), macular rash (3), erythematous rash (1), and pruritic rash (1); 4 AEs of rash were associated with pruritis
  - All AEs were Grade 1, except for a single patient who experienced 2 Grade 2 rashes, both of which resolved without treatment interruption
  - 67% (12/18) were considered related or possibly related and 33% (6/18) were considered not related or unlikely related
- Seven patients received medication for rash, which was mostly symptomatic and/or topical (eg, oral antihistamines or topical steroids)
- The median time to first rash was 23 weeks (range 1-94) and to second rash (4 patients) was 44 weeks (range 4-84); the median duration of rash was 5 weeks (range 0.3-27)

Table 3. Overall Summary of Safety

Patients, N (%)	Placebo+NrtI[a] 0 to <24 wks N=40	VBR+NrtI[b] 0 to <24 wks N=95	24 to <48 wks N=93	48 to <72 wks N=87	>72 wks N=56	Total N=95
Any TEAE	13 (33)	49 (52)	34 (37)	17 (20)	9 (16)	63 (66)
Grade 1	11 (28)	34 (36)	17 (18)	14 (16)	7 (13)	34 (36)
Grade 2	1 (3)	14 (15)	15 (16)	3 (3)	2 (4)	26 (27)
Grade 3	1 (3)	1 (1)	2 (2)	0	0	3 (3)
AEs leading to DC	0	1 (1)	2 (2)	0	0	3 (3)
Serious AEs	0	0	1 (1)	0	0	1 (1)
Death	0	0	0	0	0	0

[a]Median (range) of exposure to Placebo+NrtI was 24 weeks (1-27 weeks). [b]Median (range) of exposure to VBR+NrtI was 80 weeks (23-112 weeks). TEAEs are events with onset between first to last dose+28 days. Reported AEs were coded using MedDRA dictionary version 21.0.
AE, adverse event; DC, discontinuation; NrtI, nucleos(t)ide analog reverse transcriptase inhibitor; TEAE, treatment-emergent adverse event; VBR, vebicorvir; wks, weeks.

- Overall, most AEs were Grade 1 (210/268, 78%), and there were no Grade 4 AEs
- Grade 3 AEs included arthralgia (1 event) in the placebo+NrtI group, and increased alanine aminotransferase (ALT; 2 events) and suicidal ideation (1 event) in the VBR+NrtI group
- There was 1 serious AE of Grade 3 suicidal ideation that was unrelated to study drug and led to discontinuation (Week 36)
- One patient discontinued due to Grade 3 increased ALT (Week 70), and 1 patient discontinued due to a Grade 1 rash (Week 26)
- Safety profiles were similar when analyzed by age, sex, background NrtI, baseline ALT, or region

Table 5. Overall Treatment-Emergent Laboratory Abnormalities

Patients, N (%)	Placebo+NrtI 0 to <24 wks N=40	VBR+NrtI 0 to <24 wks N=95	24 to <48 wks N=93	48 to <72 wks N=87	>72 wks N=56	Total N=95
Any Laboratory Abnormality	30 (75)	52 (55)	48 (52)	40 (46)	21 (38)	78 (82)
Grade 1	17 (43)	33 (35)	33 (35)	29 (33)	18 (32)	46 (48)
Grade 2	13 (33)	17 (18)	12 (13)	7 (8)	3 (5)	24 (25)
Grade 3	0	2 (2)	3 (3)	4 (5)	0	8 (8)

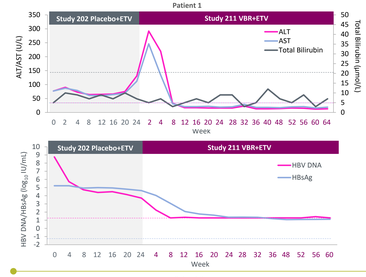
Treatment-emergent laboratory results are "on treatment" and include those collected between first to last dose+28 days. Laboratory tests were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1.
DAIDS, Division of AIDS; NrtI, nucleos(t)ide analog reverse transcriptase inhibitor; VBR, vebicorvir; wks, weeks.

Table 6. Laboratory Abnormalities (>5% of patients)

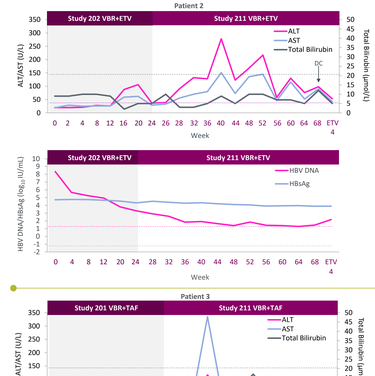
Patients, N (%)	Placebo+NrtI 0 to <24 wks N=40	VBR+NrtI 0 to <24 wks N=95	24 to <48 wks N=93	48 to <72 wks N=87	>72 wks N=56	Total N=95
Glucose, high	12 (30)	14 (15)	16 (17)	20 (23)	9 (16)	35 (37)
Grade 1	10 (25)	13 (14)	12 (13)	18 (21)	9 (16)	29 (31)
Grade 2	2 (5)	1 (1)	4 (4)	2 (2)	0	6 (6)
Grade 3	0	0	0	0	0	0
Amylase	6 (15)	15 (16)	12 (13)	8 (9)	5 (9)	25 (26)
Grade 1	2 (5)	11 (12)	10 (11)	5 (6)	4 (7)	19 (20)
Grade 2	4 (10)	4 (4)	2 (2)	2 (2)	1 (2)	5 (5)
Grade 3	0	0	0	1 (1)	0	1 (1)
AST	9 (23)	8 (8)	5 (5)	6 (7)	2 (4)	16 (17)
Grade 1	6 (15)	3 (3)	3 (3)	3 (3)	2 (4)	9 (9)
Grade 2	3 (8)	4 (4)	1 (1)	3 (3)	0	5 (5)
Grade 3	0	1 (1)	1 (1)	0	0	2 (2)
ALT	9 (23)	9 (9)	5 (5)	6 (7)	2 (4)	14 (15)
Grade 1	5 (13)	5 (5)	2 (2)	3 (3)	1 (2)	8 (8)
Grade 2	4 (10)	3 (3)	2 (2)	1 (1)	1 (2)	3 (3)
Grade 3	0	1 (1)	1 (1)	2 (2)	0	3 (3)
Creatinine	2 (5)	5 (5)	5 (5)	6 (7)	1 (2)	11 (12)
Grade 1	2 (5)	5 (5)	4 (4)	6 (7)	1 (2)	10 (11)
Grade 2	0	0	1 (1)	0	0	1 (1)
Grade 3	0	0	0	0	0	0
Glucose, low	3 (8)	3 (3)	4 (4)	4 (5)	1 (2)	10 (11)
Grade 1	3 (8)	1 (1)	3 (3)	4 (5)	1 (2)	7 (7)
Grade 2	0	2 (2)	1 (1)	0	0	3 (3)
Grade 3	0	0	0	0	0	0
Urate	4 (10)	5 (5)	4 (4)	3 (3)	4 (7)	9 (9)
Grade 1	4 (10)	5 (5)	4 (4)	3 (3)	4 (7)	9 (9)
Grade 2	0	0	0	0	0	0
Grade 3	0	0	0	0	0	0
Total bilirubin	1 (3)	2 (2)	4 (4)	4 (5)	1 (2)	6 (6)
Grade 1	0	2 (2)	3 (3)	4 (5)	1 (2)	5 (5)
Grade 2	1 (3)	0	1 (1)	0	0	1 (1)
Grade 3	0	0	0	0	0	0

Treatment-emergent laboratory results are "on treatment" and include those collected between first to last dose+28 days. Laboratory tests were graded according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; DAIDS, Division of AIDS; NrtI, nucleos(t)ide analog reverse transcriptase inhibitor; VBR, vebicorvir; wks, weeks.

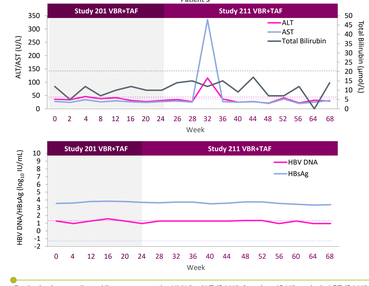
Figure 4. Grade 3 ALT and/or AST Abnormalities



- 36 year-old Black female, HBeAg positive
- Isolated Grade 3 increased ALT and AST were observed at Week 2 of treatment with VBR+ETV; reported as Grade 3 AEs, in a setting of alcohol use per the investigator and considered not related to study drug
- No changes in INR; ALT and AST were normal at Week 8 on continued treatment with VBR+ETV



- 33 year-old Asian female, HBeAg positive
- Grade 3 increased ALT initially observed at Week 40 of treatment with VBR+ETV, with Grade 2 increased AST; reported as a Grade 3 AE considered possibly related to study drug
- No changes in INR or albumin; no concomitant medications, including herbals; work-up for other causes was negative (including other viruses and autoimmune hepatitis); biopsy was consistent with active cHBV; VBR was discontinued at Week 68



- 35 year-old White male, HBeAg negative
- Isolated Grade 3 increased AST and Grade 2 increased ALT observed at Week 30 of treatment with VBR+TAF; reported as Grade 2 AEs in the setting of strenuous exercise and considered unlikely to be related to study drug
- There were no increases in INR; AST and ALT were normal at Week 36 on continued treatment with VBR+TAF

Dashed color-coordinated lines represent the ULN for ALT (34 U/L females, 43 U/L males), AST (34 U/L females, 36 U/L males), and total bilirubin (21 μmol/L; 1.2 mg/dL) for the patient, or the LLOQ for HBV DNA (1.3 $\log_{10}$ IU/mL) and HBsAg (−1.3 $\log_{10}$ IU/mL). For patient 2, ETV 4 indicates a 4-week follow-up in which the patient was off VBR treatment and only taking ETV.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; cHBV, chronic HBV; DC, discontinuation; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; INR, international normalized ratio; LLOQ, lower limit of quantification; TAF, tenofovir alafenamide fumarate; ULN, upper limit of normal; VBR, vebicorvir.

Conclusions

- With controlled-comparison of placebo+NrtI vs VBR+NrtI over 24 weeks, the frequency and severity of AEs and ALT, AST, and bilirubin elevations were similar between the treatments
- With long-term VBR+NrtI treatment up to 1.5 years
  - The frequency and severity of AEs and lab abnormalities did not increase with time, and were similar between placebo+NrtI and VBR+NrtI
  - There was no pattern of increased ALT and/or AST indicative of hepatoxicity
- Rash without systemic involvement was associated with VBR and events were predominantly Grade 1 resolving without VBR+NrtI interruption; 1 patient discontinued VBR+NrtI for Grade 1 rash
- The data support the differentiated safety profile and continued development of VBR combination therapy

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1) European Association for the Study of the Liver. *J Hepatol*. 2017;67:370-98; **2)** World Health Organization. Global Hepatitis Report. 2017; **3)** El-Serag HB et al. *Gastroenterology*. 2012;142(6):1264-73; **4)** Colvin, HM & Mitchell, AE. National Academies Press. 2010; **5)** The Polaris Observatory Collaborators. *Lancet Gastroenterol*. 2018;3:383-403; **6)** Sulkowski MS et al. *Hepatology*. 2019. 70(Suppl 1):936A; **7)** Huang Q et al. *Antimicrob Agents Chemother*. 2020 (Submitted).

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