Evaluation of the vebicorvir, NrtI and AB-729 combination in virologically suppressed patients with HBeAg negative chronic hepatitis B virus infection: Interim analysis from an open label Phase 2 study

5064

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BACKGROUND

- Chronic hepatitis B virus (cHBV) infection is a global public health problem
  - Worldwide, an estimated 296 million people have cHBV, with ~820,000 deaths each year due to liver cirrhosis and hepatocellular carcinoma[1–4]
- Vebicorvir (VBR), a first-generation inhibitor of the HBV core protein, demonstrated deeper reductions in HBV DNA and RNA and more rapid normalization of alanine aminotransferase (ALT) when added to nucleos(t)ide reverse transcriptase inhibitors (NrtI)[5,6]
- AB-729, a single-trigger GalNAc-small interfering RNA, targeting all HBV RNA transcripts reduced hepatitis B surface antigen (HBsAg) in both HBV DNA positive and in virologically-suppressed (VS) patients[7-9]
- While NrtIs suppress HBV DNA below the lower limit of quantification (LLOQ) in most patients; durable off-treatment virologic responses are rare
  - Novel combination regimens with agents of complementary mechanisms may be required to further suppress viral replication, reduce HBsAg levels, reconstitute host HBV-specific immunity, and improve clinical outcomes after finite duration therapy
  - Here we report interim data from an open-label study evaluating the combinations of VBR+NrtI, AB-729+NrtI and VBR+AB-729+NrtI

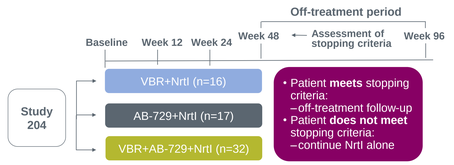
OBJECTIVE

- This open-label study is evaluating the safety and antiviral activity of 48 weeks of treatment with VBR+NrtI, AB-729+NrtI, and VBR+AB-729+NrtI in VS patients with hepatitis B e antigen (HBeAg) negative cHBV

METHODS

- 65 VS patients with HBeAg negative cHBV were randomized to VBR+NrtI (n=16), AB-729+NrtI (n=17), or VBR+AB-729+NrtI (n=32) for 48 weeks (**Figure 1**)
  - VBR 300 mg was given orally, once daily, and AB-729 as a 60 mg subcutaneous injection every 8 weeks. Existing NrtI treatment was continued
- Based on Week 48 lab results, patients meeting the following criteria were to discontinue all treatments and enter the follow-up period:
  - ALT <2x upper limit of normal (ULN) + HBV DNA <lower limit of quantification (LLOQ) + HBsAg <100 IU/mL
  - All other patients continued NrtI alone during the follow-up period
- Viral parameters were assessed as follows:
  - HBsAg: Abbott Architect i2000SR; LLOQ=0.05 IU/mL
  - HBV DNA: Roche COBAS TaqMan; LLOQ=20 IU/mL, lower limit of detection=10 IU/mL
  - HBV RNA: Abbott RUO assay v2.0; LLOQ=0.49 $\log_{10}$ U/mL
  - Hepatitis B core antigen (HBcrAg): Fujirebio Lumipulse G LLOQ=3 $\log_{10}$ IU/mL
  - For analyses HBsAg, HBV RNA, and HBcrAg values below LLOQ were imputed as –1.40 $\log_{10}$ IU/mL, 0.48 $\log_{10}$ U/mL, and 2.9 $\log_{10}$ U/mL, respectively
- Adverse events (AEs) and lab safety parameters were assessed

Figure 1. Study 204 (NCT04820686) Overview



Key eligibility criteria:
- Male or female, aged 18–50 years
- VS on NrtI >6 months
- HBeAg negative
- HBsAg ≥100 IU/mL

Treatments:
- VBR 300 mg PO, once daily
- AB-729 60 mg SC every 8 weeks (last dose at Week 44)
- Standard of care NrtI

Patients stratified by:
- HBsAg ≤1000 IU/mL vs >1000 IU/mL

Treatment-stopping criteria:
- ALT <2x ULN + HBV DNA <LLOQ + HBsAg <100 IU/mL

ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantification; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PO, by mouth; SC, subcutaneous; ULN, upper limit of normal; VBR, vebicorvir; VS, virologically-suppressed.

RESULTS

Table 1. Demographics and Baseline Characteristics

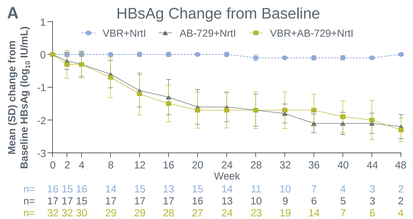
Study 204 Baseline	VBR+NrtI (n=16)	AB-729+NrtI (n=17)	VBR+AB-729+NrtI (n=32)
Age, years; median (min, max)	42 (23, 49)	43 (29, 51)	41 (22, 51)
Sex, Male; n (%)	13 (81.3)	10 (58.8)	20 (62.5)
Race, Asian; n (%)	10 (62.5)	10 (58.8)	17 (53.1)
HBV Genotype; n (%)			
A	0	2 (11.8)	4 (12.5)
B	4 (25.0)	3 (17.6)	6 (18.8)
C	2 (12.5)	4 (23.5)	5 (15.6)
C/B	1 (6.3)	2 (11.8)	4 (12.5)
D	4 (25.0)	4 (23.5)	6 (18.8)
Other	0	0	5 (15.6)
Unable to genotype	5 (31.3)	2 (11.8)	2 (6.3)
NrtI; n (%)			
TAF	3 (18.8)	2 (11.8)	6 (18.8)
TDF	8 (50.0)	13 (76.5)	18 (56.3)
ETV	5 (31.3)	2 (11.8)	8 (25.0)
Years on current NrtI; median (min, max)	4.3 (1.8, 10.1)	5.4 (1.5, 13.5)	6.6 (1.2, 14.8)
HBV RNA, $\log_{10}$ U/mL; mean (SD)	1.2 (0.6)	1.4 (0.8)	1.3 (0.8)
HBsAg, $\log_{10}$ IU/mL; mean (SD)	3.3 (0.6)	3.3 (0.6)	3.4 (0.6)
HBsAg >1000 IU/mL; n (%)	11 (68.8)	11 (64.7)	23 (71.9)
HBcrAg, $\log_{10}$ U/mL; mean (SD)	3.8 (0.9)	3.4 (0.5)	3.7 (0.7)
ALT, U/L; mean (SD)	27 (12.8)	28 (17.3)	29 (19.8)

ALT, alanine aminotransferase; 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; max, maximum; min, minimum; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VBR, vebicorvir.

- Baseline characteristics were similar between treatment groups (**Table 1**)
- As expected, in VS HBeAg negative patients, Baseline HBV parameters were low:
  - HBV DNA was <LLOQ in all patients
  - HBV RNA was ≥LLOQ in all patients; however, mean values ranged from 1.2–1.4 $\log_{10}$ IU/mL
  - HBcrAg was <LLOQ in 31.3%, 17.6% and 28.1% of patients receiving VBR+NrtI, AB-729+NrtI and VBR+AB-729+NrtI respectively
  - Overall, 56/65 (86.2%) of patients had normal ALT at study entry

Figure 2. Changes in Virologic Parameters (On-Treatment)

A

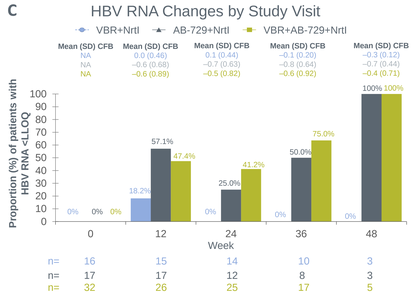


B

Categorical HBsAg Response by Study Visit[a]

Patients, n/N, (%)	VBR+NrtI (n=16)	AB-729+NrtI (n=17)	VBR+AB-729+NrtI (n=32)
Baseline			
<100 IU/mL	0/16	0/17	0/32
<10 IU/mL	0/16	0/17	0/32
Week 24			
<100 IU/mL	0/14	9/13 (69.2)	14/24 (58.3)
<10 IU/mL	0/14	0/13	7/24 (29.2)
Week 48			
<100 IU/mL	0/2	2/2 (100)	4/4 (100)
<10 IU/mL	0/2	1/2 (50.0)	1/4 (25.0)
Follow-up Week 4[b]			
<100 IU/mL	0/2	3/3 (100)	3/5 (60.0)
<10 IU/mL	0/2	1/3 (33.3)	1/5 (20.0)

C



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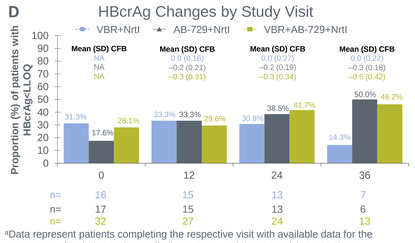


[a]Data represent patients completing the respective visit with available data for the assessment. [b]Includes patients off all treatment and those receiving NrtI alone. Imputation methods for viral parameters <LLOQ, where applicable, are described in the Methods section.
CFB, Change From Baseline; HBcrAg, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantification; NA, Not Applicable; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SD, standard deviation; VBR, vebicorvir.

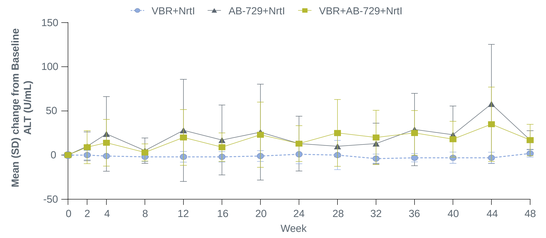
- HBsAg, HBV RNA, and HBcrAg were relatively unchanged in VBR+NrtI recipients and decreased to similar extents in patients receiving AB-729+NrtI and VBR+AB-729+NrtI **(Figure 2)**
- The proportion of patients who achieved HBsAg levels <100 IU/mL and <10 IU/mL was similar between AB-729+NrtI and VBR+AB-729+NrtI recipients **(Figure 2B)**
- No patients experienced HBsAg loss or seroconversion
- At Week 48, all patients with available data had HBV DNA <LLOQ (n=12)

Table 2. Patients Meeting Stopping Criteria at Week 48

Patients , n (%)	VBR+NrtI (n=1)	AB-729+NrtI (n=2)	VBR+AB-729+NrtI (n=4)
Patients meeting stopping criteria at Week 48[a]	0	2 (100)	3 (75)

[a]Stopping criteria are ALT <2x ULN + HBV DNA <LLOQ + HBsAg <100 IU/mL. Data represent patients completing Week 48 with available data to adjudicate the stopping criteria.
ALT, alanine aminotransferase; 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; VBR, vebicorvir.

Figure 3. Mean Changes in ALT (On-Treatment)



All increases in ALT were mild (Grade 1) or moderate (Grade 2). ALT, alanine aminotransferase; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SD, standard deviation; VBR, vebicorvir.

- During treatment, ALT was relatively unchanged in VBR+NrtI recipients **(Figure 3).** Increases in ALT that may be temporally associated with AB-729 administration were observed in some patients receiving AB-729+NrtI or VBR+AB-729+NrtI

Table 3. Overall Safety Summary (On-Treatment)

Patients, n (%)	VBR+NrtI (n=16)	AB-729+NrtI (n=17)	VBR+AB-729+NrtI (n=32)
Any TEAE	12 (75.0)	12 (70.6)	26 (81.3)
Grade 1	9 (56.3)	9 (52.9)	15 (46.9)
Grade 2	2 (12.5)	3 (17.6)	10 (31.3)
Grade 3	1 (6.3)[a]	0	1 (3.1)[b]
TEAEs related to VBR	5 (31.3)	NA	10 (31.3)
TEAEs related to AB-729	NA	6 (35.3)	11 (34.4)
TE SAE	0	0	1 (3.1)[c]
TEAEs leading to study drugs(s) discontinuation	1 (6.3)[d]	1 (5.9)[e]	3 (9.4)[f, g, h]

[a]Rash. [b]ALT increased. [c]COVID-19 pneumonia considered not related to VBR or AB-729. [d]Rash and gastrointestinal events. [e]Grade 2 ALT elevation meeting protocol defined stopping criteria, considered related to AB-729. [f]Allergic reaction and pancytopenia considered related to VBR. [g]Rash and pancytopenia considered related to VBR. [h]Grade 3 ALT elevation meeting protocol defined stopping criteria, considered related to VBR and AB-729.
ALT, alanine aminotransferase; NA, not applicable; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SAE, serious adverse event; TE, treatment-emergent; TEAE, treatment-emergent adverse event; VBR, vebicorvir.

Table 4. Treatment-Emergent Adverse Events in ≥10% of any Treatment Group (On-treatment)

Preferred term, n (%)	VBR+NrtI (n=16)	AB-729+NrtI (n=17)	VBR+AB-729+NrtI (n=32)
COVID-19	5 (31.3)	4 (23.5)	6 (18.8)
Headache	7 (43.8)	1 (5.9)	6 (18.8)
ALT increased	1 (6.3)	3 (17.6)	2 (6.3)
Nausea	5 (31.3)	0	1 (3.1)
Pruritus	2 (12.5)	2 (11.8)	2 (6.3)
Dizziness	3 (18.8)	1 (5.9)	1 (3.1)
Fatigue	1 (6.3)	2 (11.8)	2 (6.3)
Injection-site pain	0	2 (11.8)	3 (9.4)
Diarrhea	2 (12.5)	1 (5.9)	1 (3.1)
Rash	3 (18.8)	0	1 (3.1)
Vaccination site pain	2 (12.5)	0	0

ALT, alanine aminotransferase; NrtI, nucleos(t)ide reverse transcriptase inhibitor; VBR, vebicorvir.

Table 5. Treatment-Emergent Laboratory Abnormalities Observed in ≥30% of any Treatment Group (On-Treatment)

Maximum postbaseline toxicity grade, n (%)	VBR+NrtI (n=16)	AB-729+NrtI (n=17)	VBR+AB-729+NrtI (n=32)
Creatine kinase (increased), any Grade	7 (43.8)	2 (11.8)	19 (59.4)
Grade 1	6 (37.5)	2 (11.8)	11 (34.4)
Grade 2	1 (6.3)	0	7 (21.9)
Grade 4	0	0	1 (3.1)
Glucose (increased), any Grade	9 (56.3)	5 (29.4)	10 (31.3)
Grade 1	7 (43.8)	2 (11.8)	6 (18.8)
Grade 2	2 (12.5)	3 (17.6)	4 (12.5)
ALT (increased), any Grade	1 (6.3)	8 (47.1)	14 (43.8)
Grade 1	1 (6.3)	6 (35.3)	8 (25.0)
Grade 2	0	0	5 (15.6)
Grade 3	0	2 (11.8)	1 (3.1)
Triglycerides (increased), any Grade	7 (43.8)	5 (29.4)	11 (34.4)
Grade 1	5 (31.3)	3 (17.6)	9 (28.1)
Grade 2	1 (6.3)	2 (11.8)	1 (3.1)
Grade 3	0	0	1 (3.1)
Grade 4	1 (6.3)	0	0
Cholesterol (increased), any Grade	8 (50.0)	1 (5.9)	12 (37.5)
Grade 1	6 (37.5)	1 (5.9)	12 (37.5)
Grade 2	1 (6.3)	0	0
Grade 3	1 (6.3)	0	0
Lipase (increased), any Grade	8 (50.0)	5 (29.4)	7 (21.9)
Grade 1	5 (31.3)	1 (5.9)	4 (12.5)
Grade 2	3 (18.8)	4 (23.5)	3 (9.4)
AST (increased), any Grade	2 (12.5)	7 (41.2)	9 (28.1)
Grade 1	2 (12.5)	5 (29.4)	7 (21.9)
Grade 2	0	2 (11.8)	2 (6.3)
Amylase (increased), any Grade	5 (31.3)	3 (17.6)	5 (15.6)
Grade 1	4 (25.0)	3 (17.6)	4 (12.5)
Grade 2	1 (6.3)	0	1 (3.1)
Lymphocytes (decreased), any Grade	4 (25.0)	2 (11.8)	10 (31.3)
Grade 1	3 (18.8)	1 (5.9)	7 (21.9)
Grade 2	1 (6.3)	0	0
Grade 3	0	1 (5.9)	3 (9.4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NrtI, nucleos(t)ide reverse transcriptase inhibitor; VBR, vebicorvir.

- Overall, treatments were generally well tolerated. On treatment, the proportion of patients with treatment-emergent adverse events (TEAEs) was 75.0%, 70.6%, and 81.3% for the VBR+NrtI, AB-729+NrtI, and VBR+AB-729+NrtI arms, respectively. Most TEAEs reported were Grade 1 or 2, and none were Grade 4 **(Table 3)**
- The most frequently reported TEAEs during treatment were COVID-19 and headache **(Table 4)**
- Five patients had TEAEs leading to study drug discontinuation; 1 on VBR+NrtI, 1 on AB-729+NrtI and 3 on VBR+AB-729+NrtI (**Table 3**)
- A serious AE of COVID-19 pneumonia (unrelated to study drugs) was reported in a VBR+AB-729+NrtI patient
- Overall, most lab abnormalities were Grade 1 or 2. 1 (6.3%) VBR+NrtI, 3 (17.6%) AB-729+NrtI, and 6 (18.8%) VBR+AB-729+NrtI recipients experienced a Grade 3 treatment-emergent laboratory abnormality (increases in creatine kinase, glucose, ALT, triglycerides, and cholesterol). 1 (6.3%) VBR+NrtI and 2 (6.3%) VBR+AB-729+NrtI recipients experienced a Grade 4 treatment-emergent laboratory abnormality (increases in creatine kinase and triglycerides and decreases in neutrophils). Transient Grade 3 laboratory abnormalities (increases in ALT) were observed in 2 (11.8%) and 1 (3.1%) patients who received AB-729+NrtI and VBR+AB-729+NrtI, respectively **(Table 5)**

CONCLUSIONS

- All regimens tested in this study were generally well tolerated
- The interim data indicate that the addition of VBR to AB-729+NrtI does not result in greater on-treatment improvements in markers of active HBV infection compared with AB-729+NrtI
- No patients had loss of HBsAg or underwent HBsAg seroconversion during the 48-week on-treatment period
- Future analyses will report off-treatment responses in patients meeting criteria to stop all treatment. Patients who meet criteria for treatment interruption will continue to be followed to establish their clinical and virologic outcomes

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