Treatment intensification with vebicorvir in patients with chronic hepatitis B infection and partial virologic suppression on nucleos(t)ide reverse transcriptase inhibitors

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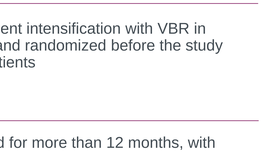
BACKGROUND

- Current standard-of-care nucleos(t)ide reverse transcriptase inhibitors (NrtIs) are effective in suppressing hepatitis B virus (HBV) DNA, but are unable to fully inhibit viral replication or prevent the establishment of covalently closed circular (ccc)DNA[1–2]
- While NrtIs suppress HBV DNA in most patients, ~30% of hepatitis B e antigen (HBeAg) positive and up to 10% of HBeAg negative patients fail to achieve HBV DNA < lower limit of quantification (LLOQ) after 1 year of treatment, with some patients not achieving this status despite many years of NrtI therapy[3–5]
- Residual HBV DNA and pregenomic (pg)RNA is associated with hepatocellular carcinoma in patients with chronic HBV infection (cHBV) on antiviral therapy[6–8]
- Treatment-intensification approaches may benefit patients who only achieve partial virologic suppression (PVS)

Vebicorvir is a novel, first-generation inhibitor of HBV core protein (**Figure 1**)

- Disrupts the HBV capsid by allosteric binding resulting in mis-assembly and destabilization of nucleocapsids
- Broad in vitro antiviral activity[9]
  - Inhibits virion and pgRNA particle production (half-maximal effective concentration [EC_{50}] = 0.17–0.31 µM; half-maximal cytotoxic concentration [CC_{50}] = >20 µM)
  - Inhibits de novo formation of cccDNA and downstream HBeAg and hepatitis B surface antigen production (HBsAg) (EC_{50} = 2–7 µM)
  - Pangenotypic and fully active against NrtI-resistant HBV
- Orally administered as 300 mg once daily without regard to food and has no drug interaction with NrtIs

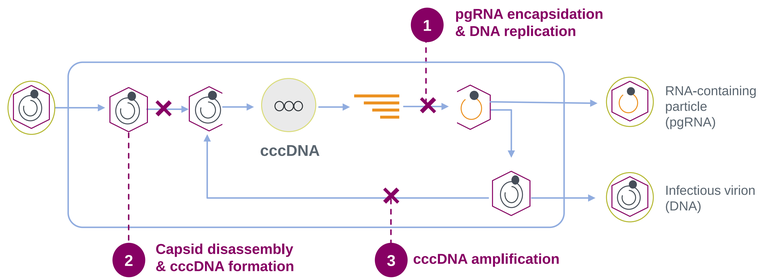
Figure 1. Vebicorvir



- In Phase 2, 24-week randomized and long-term open-label studies
  - Vebicorvir (VBR) had a favorable clinical safety profile in approximately 100 patients treated for up to 1.5 years[10]
  - Treatment with (VBR) + NrtI demonstrated greater HBV DNA and (pg)RNA suppression than placebo (PBO) + NrtI in patients with cHBV[11–15]
- The addition of VBR to NrtI therapy may allow those patients with PVS to achieve HBV DNA and HBV pgRNA <LLOQ and improve long-term clinical outcomes

Figure 2. Core inhibitor mechanisms of action

- Core inhibitors target multiple steps of the HBV replication cycle to suppress HBV DNA, pgRNA, and cccDNA and have distinct and complementary mechanisms of action to NrtIs **(Figure 2)**



cccDNA, covalently closed circular DNA; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA.

OBJECTIVE

- This Phase 2 study (NCT04454567) was designed to evaluate treatment intensification with VBR in patients with PVS receiving NrtI therapy. Two patients were enrolled and randomized before the study was discontinued. This case report describes the findings in these patients

METHODS

- Eligible patients had PVS following a stable NrtI regimen administered for more than 12 months, with HBV DNA >LLOQ on 2 occasions during screening
- HBV DNA was measured by COBAS TaqMan 2.0 (LLOQ = 20 IU/mL), and HBV pgRNA was measured by an Assembly Biosciences assay (LLOQ = 45 U/mL)
- Safety was assessed through reporting of adverse events (AEs) and laboratory abnormalities

RESULTS

- Patient A received PBO + NrtI for 17 weeks with 4 weeks of follow-up
- Patient B received VBR + NrtI for 6 weeks with 4 weeks of follow-up (**Table 1**)

Table 1. Baseline characteristics

Baseline Characteristics	Patient A, PBO + NrtI	Patient B, VBR + NrtI
Age, years	45	22
Sex	Female	Female
Race	Asian	Asian
BMI, kg/m²	19.07	19.03
HBeAg status	Positive	Positive
HBV genotype	C	B
Current NrtI treatment	TAF	ETV
Duration of study NrtI, days	149	71
Time since diagnosis, years	45	4.6
Duration of study drug exposure, days	119	42

BMI, body mass index; ETV, entecavir; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; TAF, tenofovir alafenamide fumarate; VBR, vebicorvir.

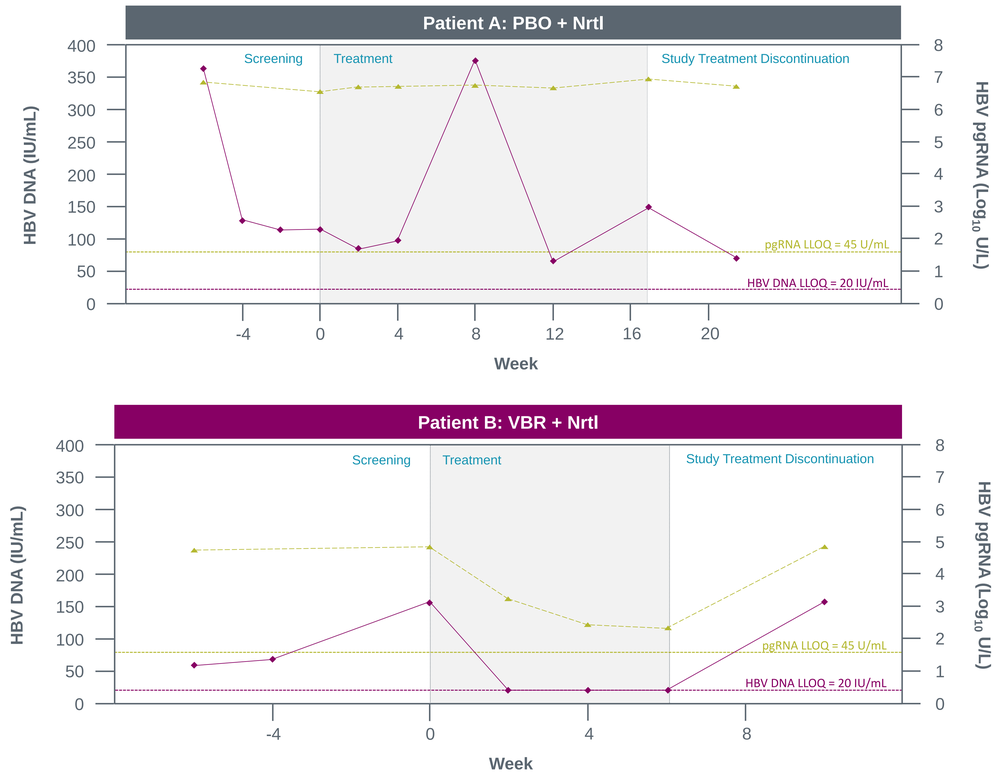
Safety

- Two AEs were reported in this study, both by Patient A and unrelated to study drug: COVID-19 infection and flu-like symptoms secondary to COVID-19 vaccine
- There were no clinically significant abnormalities in laboratory evaluations, vital signs, or electrocardiograms reported in either patient

Changes in HBV viral parameters (**Figure 3**)

- In Patient A (PBO + NrtI), HBV pgRNA remained unchanged, and HBV DNA fluctuated above LLOQ up to 400 IU/mL during treatment
- In Patient B (VBR + NrtI), treatment intensification with the addition of VBR led to a 3-log_{10} reduction in HBV pgRNA and a decrease in HBV DNA to <LLOQ during treatment
  - Despite continuation of NrtI, rebound of HBV DNA and HBV pgRNA to baseline levels occurred after cessation of VBR
- There were no significant changes in HBeAg, HBsAg, hepatitis B core antigen, or alanine aminotransferase in either patient during the study

Figure 3. HBV DNA and HBV pgRNA



HBV, hepatitis B virus; LLOQ, lower limit of quantification; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; pgRNA, pregenomic RNA; VBR, vebicorvir.

CONCLUSIONS

- When added to NrtI therapy, the additional antiviral activity afforded by VBR resulted in deeper viral suppression (HBV DNA <LLOQ during treatment) vs continual viremia observed with NrtI monotherapy
  - In the patient who received VBR+NrtI, HBV pgRNA was reduced and HBV DNA suppressed to <LLOQ
    - HBV DNA and pgRNA rebounded to Baseline levels after cessation of VBR despite continued NrtI treatment
  - In the patient who received PBO+NrtI, HBV pgRNA remained unchanged, and HBV DNA fluctuated above the LLOQ
- Results from this case-control report are consistent with previous reports of deeper levels of virologic suppression when VBR is added to NrtI therapy[11–15]
- Patients with partial virologic response receiving standard-of-care NrtI therapy may benefit from treatment intensification with core inhibitors to achieve the goal of undetectable HBV DNA and associated improvements in long-term clinical outcomes

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Acknowledgments

We express our gratitude to the patients, investigators, and site staff who participated in the study. Writing and editorial support were provided by Gregory Suess, PhD, of AlphaScientia, LLC, and funded by Assembly Biosciences. This study was sponsored by Assembly Biosciences.