HBV pgRNA and DNA both rebound immediately following discontinuation of the core inhibitor vebicorvir despite continued NrtI treatment in patients with HBeAg positive chronic hepatitis B virus infection: findings from a phase 2 open-label study

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- Professor Yuen is the Chair & Deputy Head of the Department of Medicine and the Chief of Division of Gastroenterology & Hepatology at the University of Hong Kong
- His current research interests include
  - Novel antiviral and immunomodulatory agents for HBV
  - Treatment effects on HBV DNA-host integration
  - Development of emerging biomarkers for overt and occult HBV infection
  - Disease interaction between HBV and NAFLD

HBV, hepatitis B virus; NAFLD, nonalcoholic fatty liver disease.

Disclosures

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Background

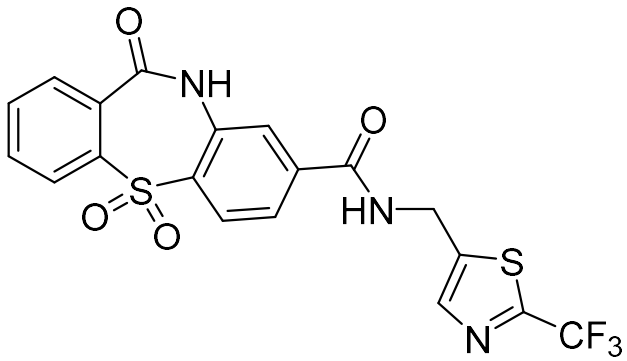
- Chronic HBV infection is a significant global public health problem
  - Worldwide, an estimated 250 million people are chronically infected with HBV, and approximately 887,000 people die each year due to cirrhosis and HCC associated with chronic HBV infection[1–4]
- For most patients, NrtIs are effective in reducing HBV DNA and are well tolerated, but treatment duration is indefinite[5]
  - Persistent, detectable HBV DNA and pgRNA in patients on chronic NrtI treatment are associated with development of HCC[6]
- Novel combination approaches incorporating agents with complementary mechanisms of action are expected to be required to further suppress viral replication and establish finite-duration regimens
- In Phase 2, 24-week randomized and long-term, open-label studies, treatment with vebicorvir (VBR)+NrtI demonstrated greater HBV DNA and pgRNA suppression than placebo (PBO)+NrtI in patients with chronic HBV infection [8-12]
- The aim of this analysis was to describe changes in HBV DNA and pgRNA following discontinuation of vebicorvir with continuing NrtI therapy

1. Lampertico et al. *J Hepatol*. 2017; 67:370–98. **2.** WHO Global Hepatitis Report. 2017. **3.** El-Serag HB et al. *Gastroenterology*. 2012;142:1264–73. **4.** Colvin HM & Mitchell AE. National Academies Press 2010. **5.** Seto WK et al. *Lancet*. 2018; 392: 213–24. **6.** Mak et al. *J Gastroenterol*. 2021; 56:479–88. **7**. Jacobson IM et al. Poster presentation at AASLD: Nov 13–16, 2020. **8.** Fung S et al. Poster presentation at EASL: Aug 27–29, 2020. **9.** Yuen MF, et al. Poster presentation at EASL: Aug 27–29, 2020. **10.** Sulkowski MS et al. Poster presentation at: AASLD: Nov 8–12, 2019. **11.** Ma X et al. Oral presentation at: EASL: April 10–14, 2019. **12.** Agarwal K et al. Poster presentation at EASL: June 23–26, 2020.

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA.

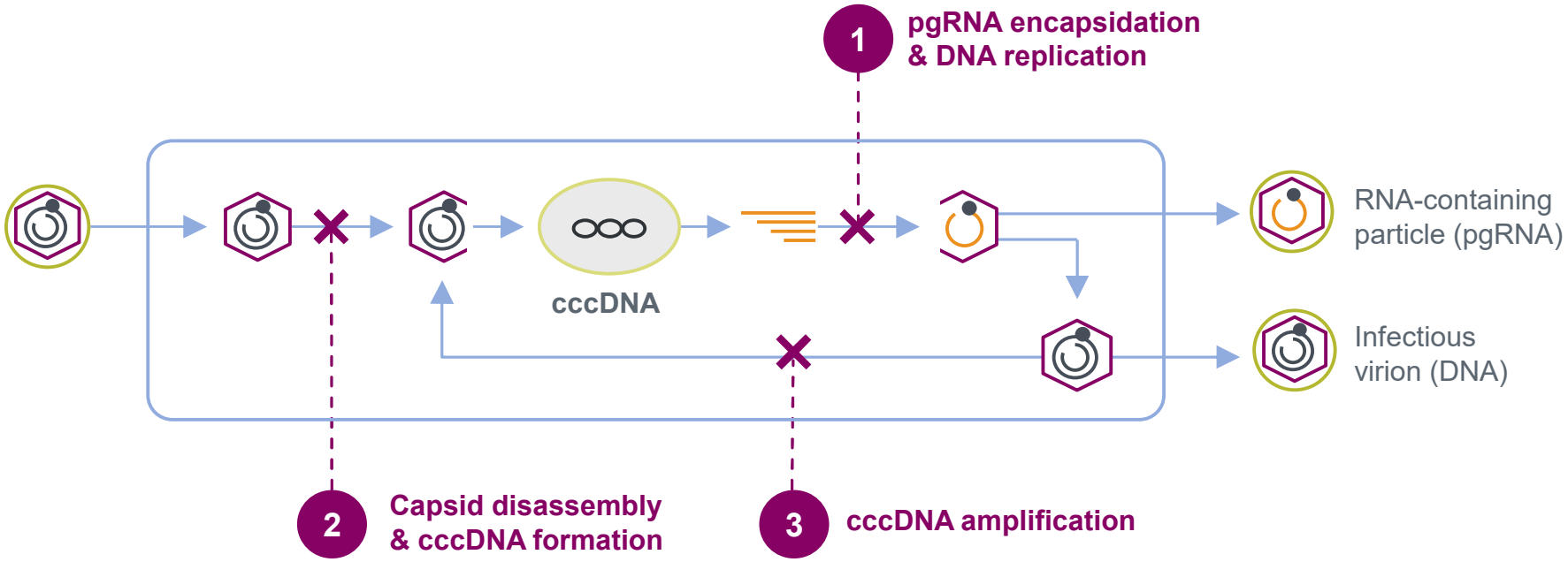
Vebicorvir (VBR)
A Novel, First-Generation Inhibitor of HBV Core Protein

- Disrupts HBV capsid formation by allosteric binding and interference with core protein
- Broad in vitro antiviral activity[1]
  - 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 HBsAg production (EC_{50} = 2–7 µM)
  - Pangenotypic and fully active against NrtI-resistant HBV
- Orally administered as 300 mg QD without regard to food
- No drug interaction with NrtIs
- Favorable clinical safety profile in over 100 patients treated for up to 1.5 years[2]



1.Huang Q et al. *Antimicrob Agents Chemother*. 2020 (Submitted). **2.** Jacobson I et al. *Hepatology*. 2020;72 (Suppl S1):820.
CC_{50}, 50% cytotoxic concentration; cccDNA, covalently closed circular DNA; EC_{50}, concentration of drug that gives half-maximal response; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA.

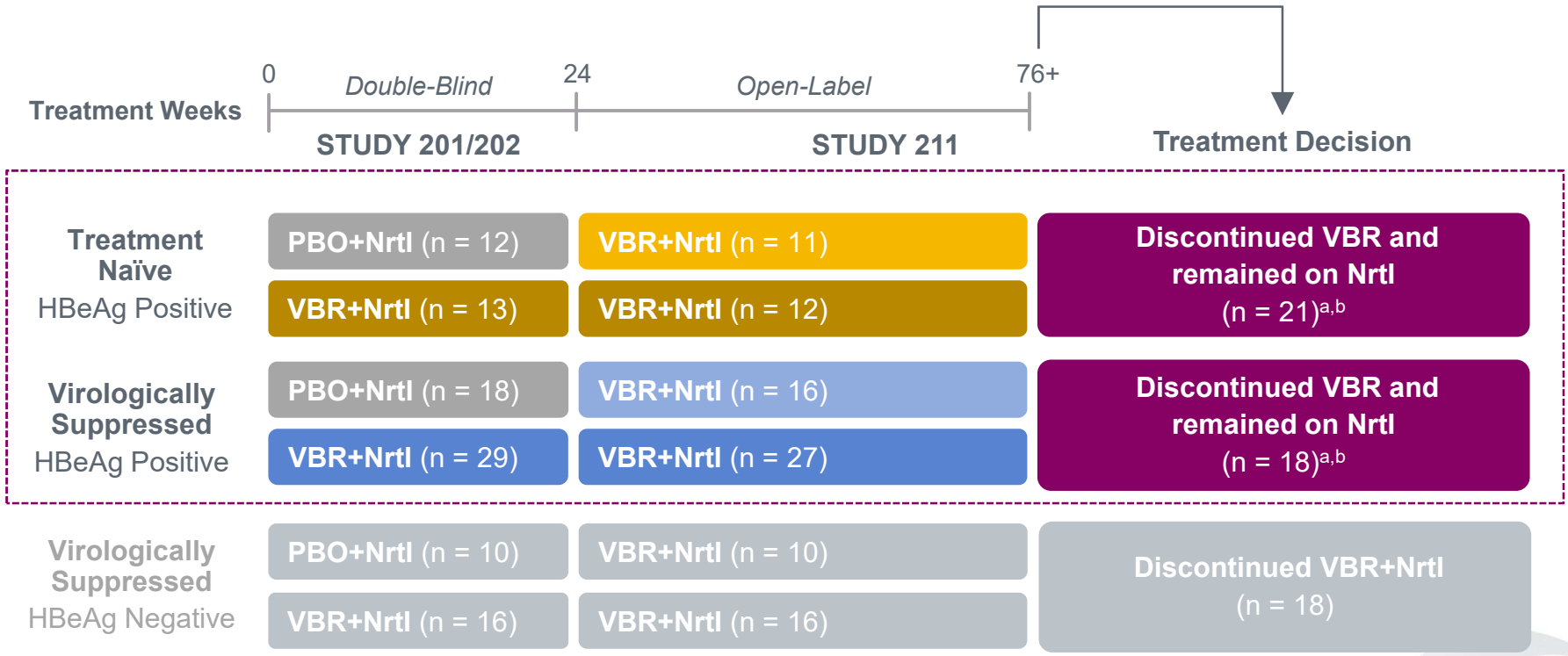
Core Inhibitor Mechanisms of Action



- 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

cccDNA, closed covalent circular DNA; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA.

Study Design and Treatment Decisions



[a]Data available for 19 TN and 18 VS patients following VBR discontinuation. [b]Excluded patients who did not meet VBR stopping criteria or were terminated from the study.
HBeAg, hepatitis B "e" antigen; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; TN, treatment naïve; VBR, vebicorvir; VS, virologically suppressed.

Baseline Demographics

Patients Who Discontinued VBR and Remained on NrtI

Study 211 Baseline	Treatment Naïve, n = 19[a]	Virologically Suppressed, n = 18[a]
Age, years; median (range)	33 (21, 67)	47 (23, 65)
Sex, female; n (%)	12 (63)	8 (44)
Race, Asian; n (%)	19 (100)	17 (94)
BMI, kg/m^2; median (range)	22.3 (17.3, 32.7)	22.3 (18.5, 33.7)
HBV genotype; n (%)[b]		
A	1 (5)	0
B	8 (42)	4 (22)
C	9 (47)	11 (61)
B/C	0	2 (11)
F	0	1 (6)
Unknown	1 (5)	0
NrtI at enrollment; n (%)[c]		
TDF	0	9 (50)
TAF	0	7 (39)
ETV	19 (100)	1 (6)
Years on current NrtI; median (range)	0.5 (0.5, 0.5)	3.1 (0.0, 11.3)
Years positive for HBV; median (range)	8.5 (1.1, 27.5)	9.3 (2.9, 38.3)

[a]Only patients with both baseline and postbaseline records are summarized. [b]Test for treatment naïve patients is based on central laboratory assay and test for virologically suppressed patients is based on Assembly Biosciences assay. [c]One virologically suppressed patient was receiving both ETV and TDF.

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

Baseline and End-of-Treatment Viral Parameters

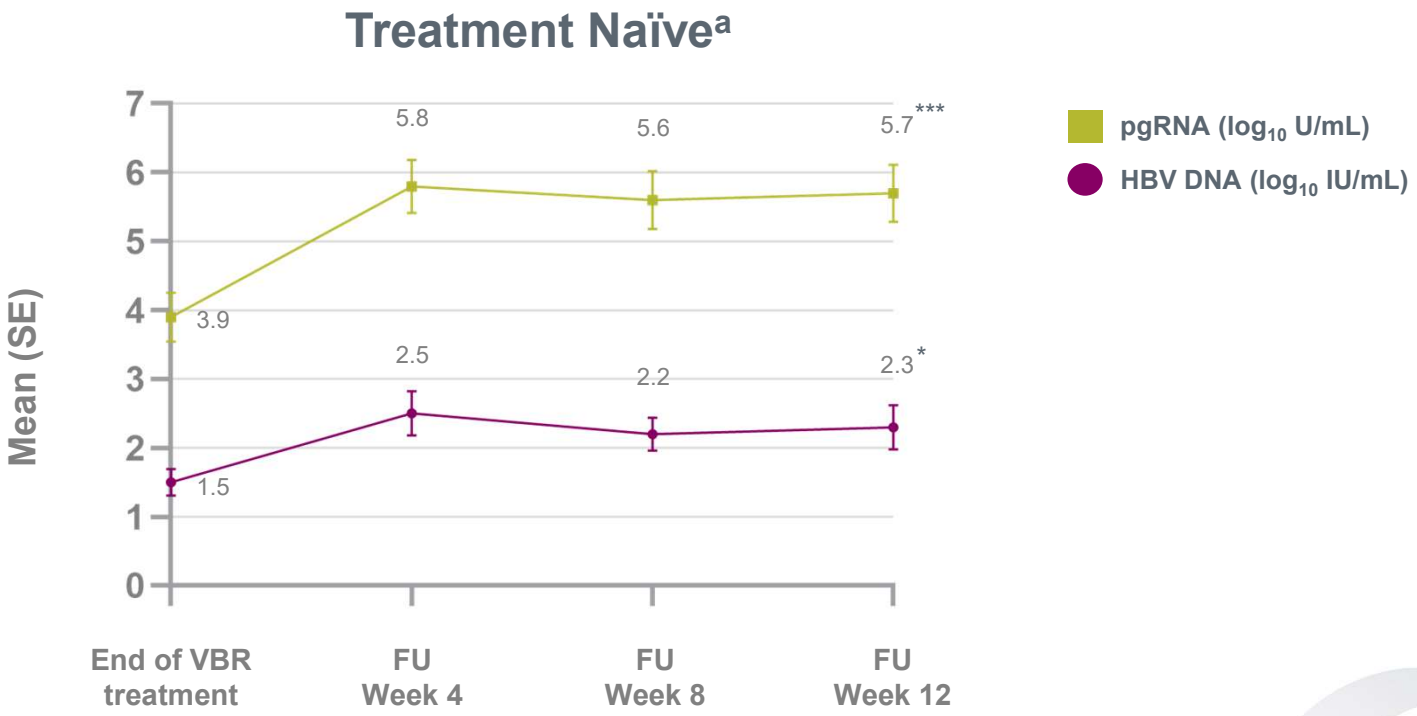
Patients Who Discontinued VBR and Remained on NrtI

	Treatment Naïve (n = 19)[a]			Virologically Suppressed (n = 18)[a]		
	Study 202 Baseline	Study 211 Baseline	Last Value on VBR+NrtI	Study 201 Baseline	Study 211 Baseline	Last Value on VBR+NrtI
HBV DNA, Log_{10} IU/mL; mean (range)	7.8 (5.5, 9.1)	2.8 (1.3, 5.9)	1.5 (1.0, 4.7)	-	-	-
HBV DNA, <LLOQ[b]; n (%)	0	4 (21)	11 (58)	16 (89)	17 (94)	18 (100)
pgRNA, Log_{10} U/mL; mean (range)	7.1 (4.6, 8.6)	5.4 (2.6, 8.2)	3.9 (2.1, 7.7)	5.2 (4.1, 6.3)	3.1 (1.5, 6.2)	2.7 (1.5, 3.8)
HBeAg, Log_{10} IU/mL; mean (range)	2.4 (–0.7, 3.1)	2.0 (–1.0, 3.1)	1.6 (–1.0, 3.1)	1.2 (–0.7, 2.5)	1.1 (–1.0, 2.5)	0.9 (–0.7, 2.2)
HBcrAg, Log_{10} kU/mL; mean (range)	5.4 (2.8, 6.2)	5.0 (2.6, 6.0)	4.4 (2.3, 5.8)	3.6 (2.0, 4.8)	3.5 (1.9, 4.8)	3.2 (1.6, 4.5)
HBsAg, Log_{10} IU/mL; mean (range)	4.5 (3.3, 5.1)	4.4 (3.3, 5.1)	4.1 (3.3, 4.8)	3.5 (2.9, 4.4)	3.5 (3.0, 4.4)	3.5 (2.9, 4.4)

[a]Only patients with both baseline and postbaseline records are summarized. [b]Cobas TaqMan assay; LLOQ = 20 IU/mL.
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; pgRNA, pregenomic RNA.

HBV DNA and pgRNA

Treatment Naïve Patients Who Discontinued VBR and Remained on NrtI



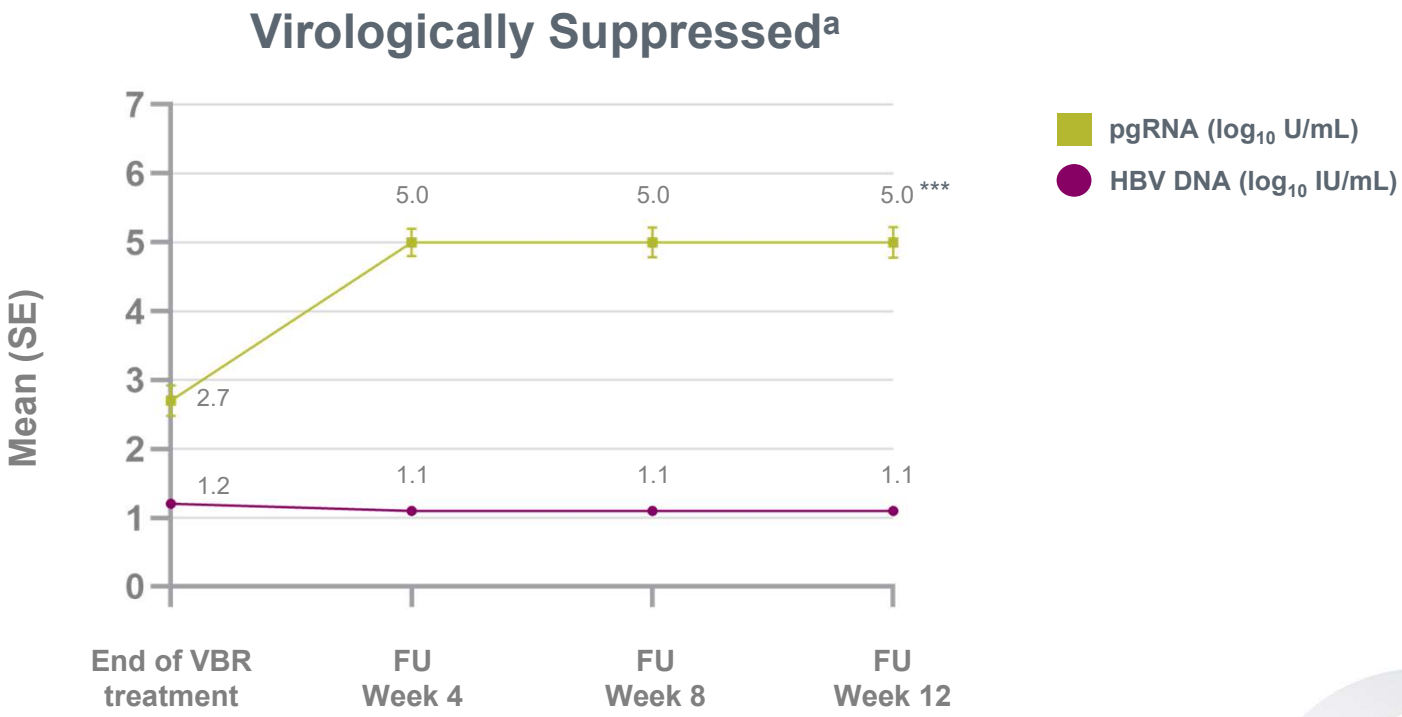
[a]At entry in Study 202.

FU, follow-up; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; SE, standard error; VBR, vebicorvir.

*** p<0.0001, * p<0.05 based on a paired t-test for the change from end of VBR treatment to FU Week 12.

HBV DNA and pgRNA

Virologically Suppressed Patients Who Discontinued VBR and Remained on Nrtl



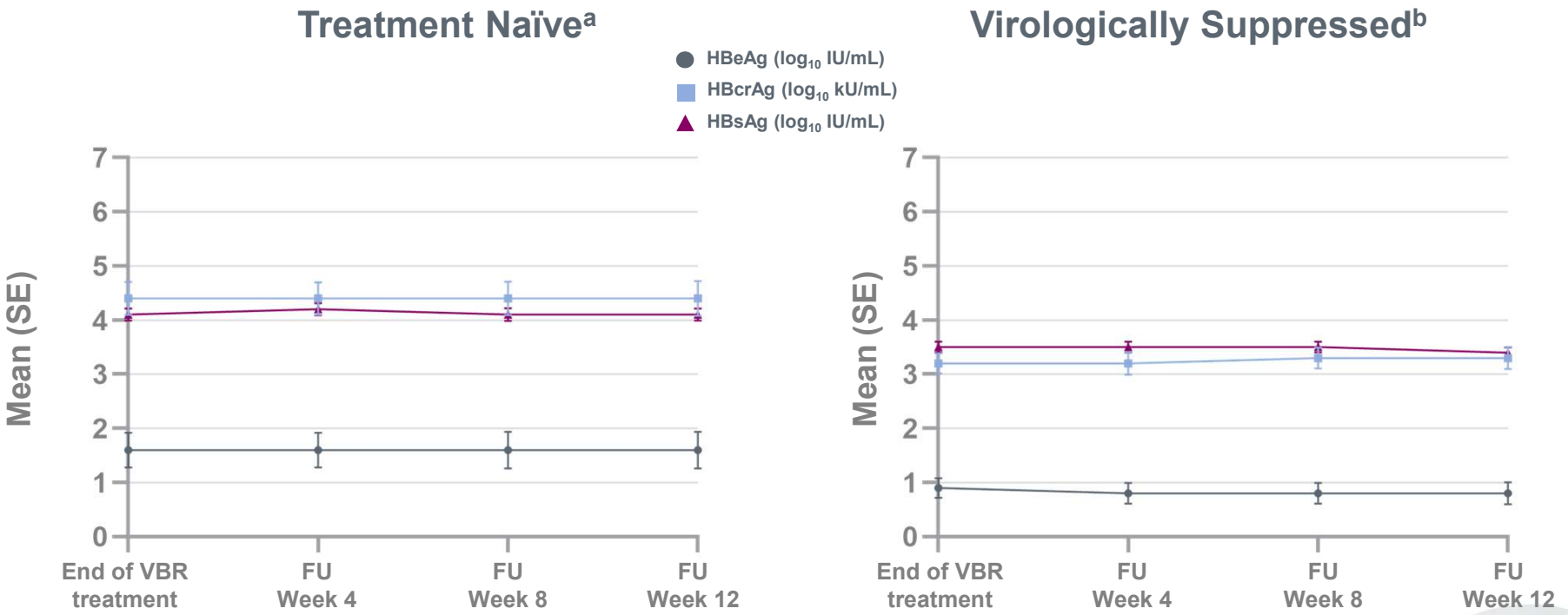
[a]At entry in Study 201.

FU, follow-up; HBV, hepatitis B virus; Nrtl, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; SE, standard error; VBR, vebicorvir.

*** p<0.0001, * p<0.05 based on a paired t-test for the change from end of VBR treatment to FU Week 12.

HBV Antigens

Patients Who Discontinued VBR and Remained on NrtI



[a]At entry in Study 202. [b]At entry in Study 201.
FU, follow-up; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B "e" antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase; SE, standard error; VBR, vebicorvir.

Patients Who Discontinued VBR and Remained on NrtI

- Viral resistance was not associated with increases in HBV DNA and pgRNA
  - Sanger sequencing was conducted on the core protein and pol/RT regions (20% cut off)
  - Timepoints included Baseline, on treatment, and after VBR discontinuation
  - No core inhibitor binding pocket substitutions or NrtI resistance mutations were observed
- NrtI treatment compliance was confirmed
- No increases in ALT following VBR discontinuation were observed

ALT, alanine aminotransferase; HBV, hepatitis B virus NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; pol/RT, polymerase-reverse transcriptase; VBR, vebicorvir.

Conclusions

- In patients receiving VBR+NrtI for ≥1 year, deep suppression of HBV DNA and pgRNA was observed in those who were initially treatment naïve or virologically suppressed
- Subsequently, in patients who discontinued VBR and remained on NrtI there was:
  - An approximate 2 $\log_{10}$ U/mL increase in HBV pgRNA observed in conjunction with:
    - A 1 $\log_{10}$ IU/mL increase in HBV DNA in initially treatment naïve patients but not in those who were initially virologically suppressed
    - We hypothesize that this observation may be related to longer NrtI exposure and deeper virologic suppression in those who were initially virologically suppressed
  - Changes in HBV DNA and pgRNA that were not associated with viral resistance or NrtI noncompliance
- These observations provide further direct evidence that vebicorvir and HBV core inhibitors more deeply suppress viral replication when combined with NrtIs

HBV, hepatitis B virus; NrtI, nucleos(t)ide reverse transcriptase inhibitor; pgRNA, pregenomic RNA; VBR, vebicorvir.

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