Deeper virologic suppression with the addition of vebicorvir, a first-generation hepatitis B core inhibitor, to entecavir correlates with reduced inflammation and fibrosis-4 index in treatment-naïve patients with HBeAg positive chronic hepatitis B

SAT-366

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

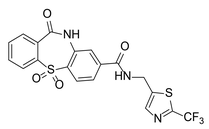
[1]Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]University of Toronto, Toronto, ON, Canada; [3]Office of Xiaoli Ma, Philadelphia, PA, USA; [4]T Nguyen Research and Education, Inc., San Diego, CA, USA; [5]Schiff Center for Liver Diseases, University of Miami School of Medicine,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

Background

- Chronic hepatitis B virus infection (cHBV) is a significant global health problem
  - Worldwide, an estimated 296 million people have cHBV infection, resulting in approximately 887,000 deaths each year, mostly due to cirrhosis and hepatocellular carcinoma[1–4]
- A goal of nucleos(t)ide reverse transcriptase inhibitor (NrtI) therapy for cHBV is suppression of HBV DNA below the lower limit of quantification (LLOQ) for available assays
  - NrtIs are well tolerated, and while suppression of HBV DNA <LLOQ is achieved in most patients, low-level viremia remains, and treatment duration is indefinite[5]
  - Novel combination approaches incorporating agents with complementary mechanisms of action, such as core inhibitors, are likely required to further suppress viral replication, establish finite-duration regimens, and improve clinical outcomes
- Vebicorvir (VBR), a novel first-generation inhibitor of the HBV core protein (**Figure 1**), has previously demonstrated deeper reductions in HBV DNA and pregenomic RNA (pgRNA) and more rapid normalization of alanine aminotransferase (ALT) when added to entecavir (ETV)[6,7]
- In this report, we explore the associations between the observed deeper reductions in HBV parameters with changes in Fibrosis-4 (FIB-4) Index
  - FIB-4 is a validated prognostic marker of liver fibrosis used in the management of cHBV[8,9]
  - FIB-4 values tend to range between 0.2 and 10, with higher scores more strongly predicting the presence of fibrosis

Figure 1. VBR is a novel, first-generation inhibitor of HBV core protein

- Core inhibitors allosterically bind and interfere with the core protein by mechanisms distinct from NrtIs
  - Inhibition of pgRNA encapsidation, prevention of viral assembly/release, and disruption of viral capsids
- Broad in vitro antiviral activity[10]
  - 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 covalently closed circular DNA and downstream hepatitis B e antigen (HBeAg) and hepatitis B surface antigen production (EC_{50}=2–7 µM)
  - Pangenotypic and fully active against NrtI-resistant HBV
- Orally administered as 300 mg once daily (QD) without regard to food, with a favorable clinical safety profile in Phase 2 studies[11]
- VBR+NrtI resulted in deeper on-treatment viral suppression in treatment-naïve and virologically-suppressed patients in Phase 2 studies[6,12]



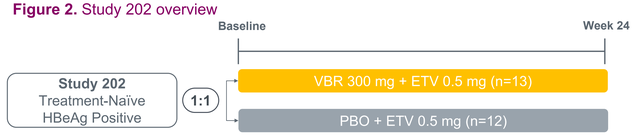
Objective of this analysis

- This post hoc analysis from a Phase 2a study in treatment-naïve patients[6,7] explores correlations between the deeper level of viral suppression and more rapid normalization of ALT observed with the addition of VBR to ETV with FIB-4, a validated prognostic marker of liver fibrosis[8,9]

Methods

- In this study (NCT03577171), 13 patients received VBR (300 mg) with ETV (0.5 mg) QD, and 12 patients received placebo (PBO) with ETV (0.5 mg) QD for 24 weeks (**Figure 2**)
- For this analysis, HBV DNA, pgRNA, and HBV antigens were measured at Screening, Baseline (Day 1), and then every 4 weeks until Week 24. HBV DNA, pgRNA, and hepatitis B core antigen (HBcrAg) were also measured at Week 2
  - Laboratory assessments (ALT, aspartate aminotransferase [AST], and platelets) were also assessed at the same timepoints as virological parameters
- FIB-4 was calculated according to the following formula: (age [years] × AST [U/L])/(platelet count [10^9/L] × √ALT [U/L])[8]
- Post hoc correlation analyses were performed, and Pearson's (for parametric analyses) and Spearman's (for nonparametric analysis) correlation coefficients were calculated where appropriate to describe associations between parameters and FIB-4
- Statistical analyses were based on a mixed-effects, repeated-measure model

Figure 2. Study 202 overview



Key eligibility criteria

- Male or female, aged 18–70 years
- Treatment-naïve, HBeAg positive cHBV
- METAVIR F0–F2 or equivalent (no history of hepatic decompensation)
- HBV DNA >10^5 IU/mL; ALT <10× ULN; platelet count ≥100,000/mm^3

ALT, alanine aminotransferase; cHBV, chronic hepatitis B virus; ETV, entecavir; HBeAg, hepatitis B e antigen; METAVIR; Meta-analysis of Histological Data in Viral Hepatitis; PBO, placebo; ULN, upper limit of normal; VBR, vebicorvir.

Results

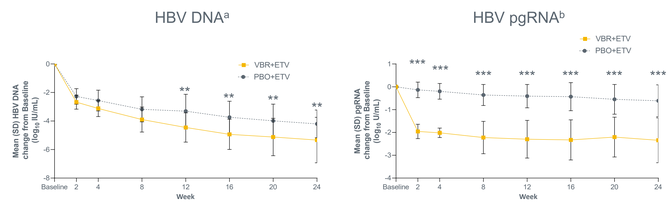
Table 1. Demographics and Baseline characteristics

Study 202 Baseline	VBR+ETV (n=13)	PBO+ETV (n=12)	Total (N=25)
Age, years; median (min, max)	32 (20, 66)	32 (20, 57)	32 (20, 66)
Sex, female; n (%)	10 (77)	7 (58)	17 (68)
Race, Asian; n (%)	13 (100)	11 (92)	24 (96)
BMI, kg/m^2; median (min, max)	22.4 (18.4, 28.3)	21.7 (19.5, 32.3)	22.1 (18.4, 32.3)
HBV genotype; n (%)			
A	0	2 (17)	2 (8)
B	7 (54)	4 (33)	11 (44)
C	5 (38)	6 (50)	11(44)
Unable to genotype	1 (8)	0	1 (4)
HBV DNA[a], log_{10} IU/mL; mean (SD)	7.9 (0.89)	8.0 (1.0)	8.0 (0.93)
HBV pgRNA[b], log_{10} U/mL; mean (SD)	7.1 (0.95)	7.4 (1.14)	7.2 (1.03)
HBeAg[c], log_{10} IU/mL; mean (SD)	2.5 (0.81)	2.5 (1.24)	2.5 (1.02)
HBsAg[d], log_{10} IU/mL; mean (SD)	4.5 (0.51)	4.7 (0.44)	4.6 (0.48)
HBcrAg[e], log_{10} kU/mL; mean (SD)	5.5 (0.69)	5.4 (0.97)	5.4 (0.82)
ALT, U/L; mean (SD)	65.9 (87.11)	46.8 (31.64)	56.7 (65.94)
AST, U/L; mean (SD)	46.0 (42.62)	36.3 (26.28)	41.3 (35.35)
Platelets, K/µL; mean (SD)	228.2 (57.53)	227.3 (69.70)	227.8 (62.30)
INR; mean (SD)	1.0 (0.05)	1.0 (0.08)	1.0 (0.06)
FIB-4; mean score (SD)	0.98 (0.60)	0.94 (0.82)	0.96 (0.70)

[a]Quantified using COBAS TaqMan version 2.0 (LLOQ=20 IU/mL). [b]Quantified using quantitative RT-PCR method developed by Assembly Biosciences (LLOQ=135 U/mL)[13]. [c]Quantified using the Architect i2000SR assay (LLOQ=0.11 IU/mL). [d]Quantified using the Architect i2000SR assay (LLOQ=0.05 IU/mL). [e]Quantified using the Lumipulse G HBcrAg assay (LLOQ=1 kU/mL).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ETV, entecavir; FIB-4, Fibrosis-4; HBcrAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; INR, international normalized ratio; LLOQ ,lower limit of quantification; PBO, placebo; pgRNA, pregenomic RNA; RT-PCR; reverse transcription polymerase chain reaction; SD, standard deviation; VBR, vebicorvir.

- Overall, HBV disease characteristics were similar between treatment groups at Baseline (**Table 1**)
- Most patients were Asian (24/25 [96%]) and female (17/25 [68%]), with ages ranging from 20–66 years and body mass index ranging from 18.4–32.3 kg/m^2
- Of the 25 total patients, 11 were infected with HBV genotype B and 11 with genotype C
- In these untreated patients, the overall mean (standard deviation [SD]) HBV DNA and pgRNA at Baseline were 8.0 (0.93) log_{10} IU/mL and 7.2 (1.03) log_{10} U/mL, respectively
- Mean (SD) FIB-4 values at Baseline for VBR+ETV patients were 0.98 (0.60) and 0.94 (0.82) for PBO+ETV patients, corresponding to Ishak 0–1 fibrosis

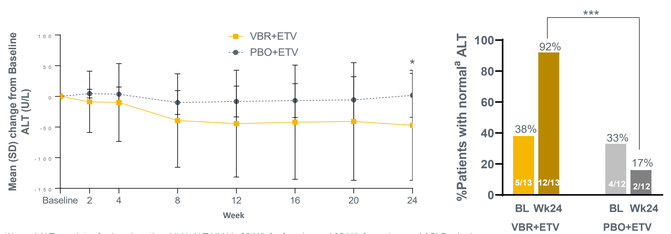
Figure 3. Mean HBV DNA and pgRNA change from Baseline over 24 weeks



[a]HBV DNA LLOQ=20 IU/mL; [b]HBV pgRNA LLOQ=135 U/mL.
**P<0.01; ***P<0.001.
ETV, entecavir; HBV, hepatitis B virus; LLOQ, lower limit of quantitation; PBO, placebo; pgRNA, pregenomic RNA; SD, standard deviation; VBR, vebicorvir.

- More profound HBV DNA and pgRNA reductions were observed with VBR+ETV compared to ETV monotherapy (**Figure 3**), as previously described[6,7]

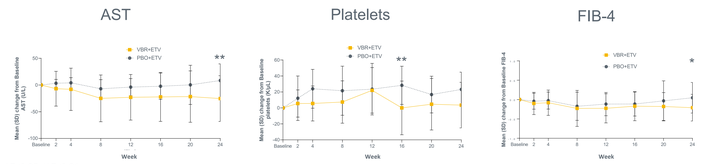
Figure 4. ALT change from Baseline and normalization with VBR+ETV



[a]Normal ALT consists of values less than ULN; ALT ULN is 25 U/L for females and 35 U/L for males per AASLD criteria.
*P<0.05; ***P<0.001.
AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; BL, Baseline; ETV, entecavir; PBO, placebo; SD, standard deviation; ULN, upper limit of normal; VBR; vebicorvir; Wk, week.

- Most patients receiving VBR+ETV experienced a numerical decrease in ALT from Baseline at Week 24
- At Week 24, an overall mean reduction in ALT was observed with VBR+ETV but not PBO+ETV (**Figure 4**)
- At Baseline, 5/13 (38%) and 4/12 (33%) VBR+ETV and PBO+ETV patients had normal ALT; at Week 24, those proportions were 12/13 (92%) for VBR+ETV compared to 2/12 (17%) for PBO+ETV

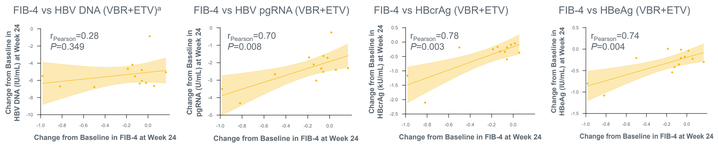
Figure 5. AST, platelets, and FIB-4 mean changes from Baseline



*P<0.05; **P<0.01.
AST, aspartate aminotransferase; ETV, entecavir; FIB-4, fibrosis-4; PBO, placebo; SD, standard deviation; VBR, vebicorvir.

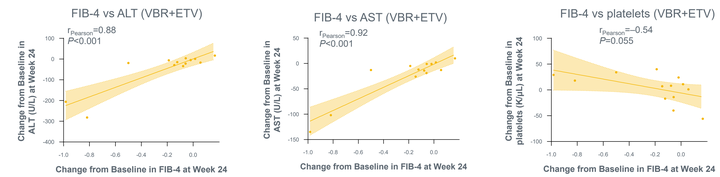
- At Week 24, an overall mean reduction in AST was observed with VBR+ETV but not with PBO+ETV (**Figure 5**)
- PBO+ETV recipients experienced a mean increase in platelet count of 23.2 K/µL over the treatment interval, which was numerically greater than the 3.5 K/µL mean increase observed in patients receiving VBR+ETV for 24 weeks
- While patients entering the study had a similar mean FIB-4 index at Baseline, the mean change from Baseline was significantly greater for VBR+ETV (–0.21) vs PBO+ETV (0.05; P=0.034) at Week 24
- Overall, treatment with VBR+ETV resulted in statistically significant improvements in HBV DNA, pgRNA, ALT, AST, and FIB-4 compared to PBO+ETV
- To further explore these findings, additional correlation analyses were performed to assess relationships between FIB-4 and ALT, AST, platelets, and viral parameters

Figure 6. Associations between FIB-4 and HBV parameters in VBR+ETV patients at Week 24



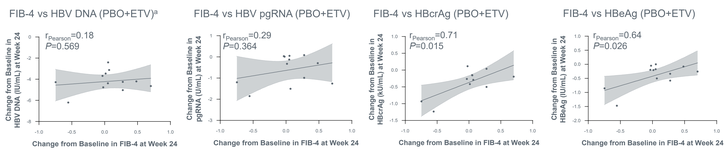
[a]$r_{Spearman}$=0.18, P=0.566.
ETV, entecavir; FIB-4, fibrosis-4; HBcrAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; pgRNA, pregenomic RNA; $r_{Pearson}$, Pearson's correlation coefficient; $r_{Spearman}$, Spearman's correlation coefficient; VBR, vebicorvir.

Figure 7. Associations between FIB-4 and ALT, AST, and platelets in VBR+ETV patients at Week 24



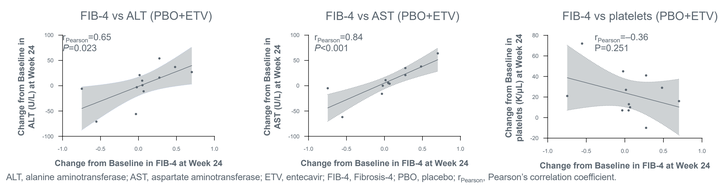
ALT, alanine aminotransferase; AST, aspartate aminotransferase; ETV, entecavir; FIB-4, Fibrosis-4; $r_{Pearson}$, Pearson's correlation coefficient; VBR, vebicorvir.

Figure 8. Associations between FIB-4 and HBV parameters in PBO+ETV patients at Week 24



[a]$r_{Spearman}$=0.11; P=0.729.
ETV, entecavir; FIB-4, fibrosis-4; HBcrAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; PBO, placebo; pgRNA, pregenomic RNA; $r_{Pearson}$, Pearson's correlation coefficient; $r_{Spearman}$, Spearman's correlation coefficient.

Figure 9. Associations between FIB-4 and ALT, AST, and platelets in PBO+ETV patients at Week 24



ALT, alanine aminotransferase; AST, aspartate aminotransferase; ETV, entecavir; FIB-4, Fibrosis-4; PBO, placebo; $r_{Pearson}$, Pearson's correlation coefficient.

- At Week 24, the deeper reductions in HBV DNA, pgRNA, ALT, and AST that were observed with VBR+ETV compared to PBO+ETV were reflected in greater reductions in the composite FIB-4 Index
- For VBR+ETV, significant, strong correlations were observed between FIB-4 and pgRNA ($r_{Pearson}$=0.70; P=0.008), HBcrAg ($r_{Pearson}$=0.78; P=0.003), HBeAg ($r_{Pearson}$=0.74; P=0.004), ALT ($r_{Pearson}$=0.88; P<0.001), and AST ($r_{Pearson}$=0.92; P<0.001), (**Figures 6** and **7**)
- For PBO+ETV, significant, strong correlations were observed between FIB-4 and HBcrAg ($r_{Pearson}$=0.71; P=0.015) and AST ($r_{Pearson}$=0.84; P<0.001), while there were moderate correlations between FIB-4 and HBeAg ($r_{Pearson}$=0.64; P=0.026) and ALT ($r_{Pearson}$=0.65; P=0.023) (**Figures 8** and **9**)
- FIB-4 was not significantly correlated with platelets in either treatment arm at Week 24
- When examining both Pearson's and Spearman's correlation coefficients, there were no significant correlations between FIB-4 and HBV DNA for either treatment group at Week 24

Limitations of this analysis

- The small sample size and 24-week treatment duration limit interpretation and generalizability. Studies of longer treatment duration and larger sample size will be required to confirm the observations

Conclusions

- VBR+ETV demonstrated potent antiviral activity compared to PBO+ETV in treatment-naïve, HBeAg positive patients as demonstrated by:
  - More rapid and deeper declines in HBV DNA and pgRNA
  - Greater decrease and more rapid normalization of ALT and AST
- These changes were reflected in a reduction in FIB-4 for VBR+ETV recipients and an increase for patients receiving PBO+ETV. The difference in FIB-4 between the treatment arms at Week 24 was statistically significant
- When assessing associations between viral and host factors with FIB-4 at the end of the 24-week treatment period:
  - For VBR+ETV, strong positive correlations were observed between FIB-4 and pgRNA, HBcrAg, HBeAg, ALT, and AST,
  - For PBO+ETV, strong positive correlations were observed between FIB-4 and HBcrAg and AST and moderate correlations between FIB-4 and HBeAg and ALT
- The increased antiviral potency of VBR+ETV compared to PBO+ETV resulted in greater reductions in viral replication and hepatic inflammation and significantly greater improvement in FIB-4
- Regimens providing deeper levels of viral suppression and greater reductions in hepatic inflammation may further improve long-term clinical outcomes

References

1) European Association for the Study of the Liver. *J Hepatol.* 2017;67:370–98. **2)** World Health Organization. *Global Hepatitis Report 2017*. Geneva: World Health Organization; 2017. **3)** World Health Organization. Key Facts. 2021. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed March 7, 2022. **4)** El-Serag HB, et al. *Gastroenterology*. 2012;142:1264–73. **5)** Sato WK, et al. *Lancet*. 2018;10161:2313–24. **6)** Yuen MF, et al. Poster presentation at EASL. August 27–29, 2020. **7)** Ma X, et al. Oral presentation at EASL; April 10–14, 2019. **8)** Sterling RK, et al. *Hepatology*. 2006;6:1317–25. **9)** Itakura J, et al. *J Gastroenterol*. 2021;5:470–78. **10)** Huang Q, et al. *Antimicrob Agents Chemother*. 2020;64:e01463–20. **11)** Jacobson I, et al. Poster presentation at AASLD: November 13–16, 2020. **12)** Fung SK, et al. Oral presentation at EASL: August 27–29, 2020. **13)** Huang Q, et al. Poster presentation at EASL: August 27–29, 2020.

Acknowledgments

- We express our gratitude to all 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

assemblybio

Presented at the International Liver Congress, June 22–26, 2022