Evaluation of the drug-drug interaction profile of vebicorvir, a first-generation hepatitis B core inhibitor: findings from Phase 1 and Phase 2a studies

SAT-388

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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]
- For most patients, nucleos(t)ide reverse transcriptase inhibitors (NrtIs) are effective in reducing HBV DNA and are well tolerated, but treatment duration is indefinite[5]
- Novel combination approaches incorporating agents with complementary mechanisms of action will likely be required to further suppress viral replication and establish finite-duration regimens
- Agents included in these combination regimens require favorable drug-drug interaction (DDI) profiles to allow concomitant administration to treat comorbid conditions in patients with cHBV[6,7]
  - Vebicorvir (VBR), a first-generation HBV core inhibitor, administered with NrtIs over 24 weeks, has demonstrated greater HBV DNA and pregenomic RNA suppression than NrtI monotherapy in patients with cHBV infection in Phase 2 studies[8–10]
  - VBR is orally administered as 300 mg once daily without regard to food and has a favorable clinical safety profile in over 100 patients treated for up to 1.5 years in a Phase 2 study[11]
- VBR is not a potent inhibitor of cytochrome P450s (CYPs) or drug transporters in vitro
  - VBR concentrations that achieve 50% inhibition (IC_{50}) were >25 μM for tested CYPs
  - VBR IC_{50}s were >10 μM for tested transporters

Objective of this analysis

- To evaluate VBR's DDI potential based on clinical data:
  - A Phase 1 study in which VBR was administered in combination with several CYP index substrates (CYPs 2C9, 2C19, 2D6, 2C8, 3A4, and 2B6) to healthy participants
  - Two Phase 2a studies in which VBR was administered in combination with NrtIs to virologically-suppressed and treatment-naïve patients with cHBV

Methods

- Data from 3 VBR clinical studies are included:
  - Study 103 was a 3-part, Phase 1 DDI study in healthy participants (**Figure 1, left panel**)
    - Part 1 investigated the potential impact of VBR at steady state on the oral pharmacokinetics (PK) of the index substrates tolbutamide (2C9), omeprazole (2C19), dextromethorphan (2D6), and repaglinide (2C8)
    - Part 2 determined the effect of VBR at steady state on the PK of midazolam (3A4)
    - Part 3 evaluated the effect of VBR at steady state on the PK of bupropion (2B6)
    - Intensive PK samples were collected in all parts, and PK analysis was conducted by noncompartmental methods
  - Studies 201 (NCT03577171; N=73) and 202 (NCT03576066; N=25) were Phase 2a, double-blind, placebo-controlled trials evaluating VBR+NrtIs in patients with cHBV (**Figure 1, right panel**)
    - Sparse PK samples were collected
      - Trough (predose) on Day 1 and at Weeks 2, 4, 12, and 24
      - 4 hours postdose on Day 1 and Weeks 2 and 4
  - Plasma concentrations of all analytes were determined using validated tandem mass spectrometry bioanalytical methods

Figure 1. Design of studies

Study 103: Phase 1 DDI study

Part 1: n=20

Study Drug	Days 1	2	3	4	5	6	7	8	9	10	11	12	13
Tolbutamide 500 mg,	X												X
omeprazole 20 mg, and	X												X
dextromethorphan 30 mg	X												X
Repaglinide 0.5 mg				X						X			
VBR 300 mg					X	X	X	X	X	X	X	X	X

Part 2: n=18

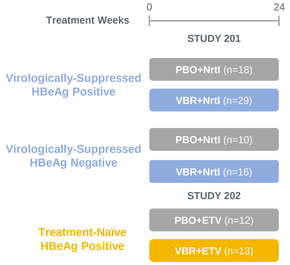
Study Drug	Days 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Midazolam 2 mg	X						X								X
VBR 300 mg		X	X	X	X	X	X	X	X	X	X	X	X	X	X

Part 3: n=20

Study Drug	Days 1	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Bupropion 150 mg	X						X										X				
VBR 300 mg		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

"X" symbols show days of administration of the designated study drug to healthy participants once daily by mouth.
DDI, drug-drug interaction; VBR, vebicorvir.

Studies 201 and 202: Phase 2 studies



ETV, entecavir; HBeAg, hepatitis B e antigen; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; VBR, vebicorvir.

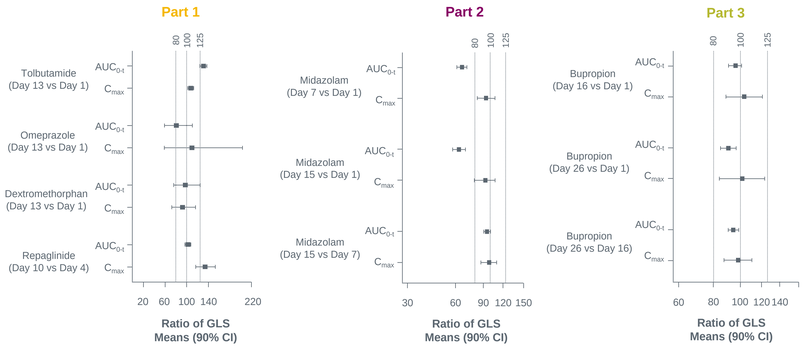
Results

Table 1. Study 103: Demographics and Baseline characteristics

	Part 1 (n=20)	Part 2 (n=18)	Part 3 (n=20)
Age, years; mean (min, max)	34.3 (24, 48)	31.8 (21, 44)	35.6 (20, 47)
Sex, female; n (%)	11 (55.0)	6 (33.3)	4 (20.0)
Race; n (%)			
American Indian or Alaska Native	1 (5.0)	0	0
Black or African American	8 (40.0)	8 (44.4)	10 (50.0)
White	11 (55.0)	10 (55.6)	10 (50.0)
BMI, kg/m^2; mean (SD)	27.16 (3.05)	25.63 (3.89)	26.11 (2.88)

BMI, body mass index; max, maximum; min, minimum; SD, standard deviation.

Figure 2. Study 103: DDI of VBR on CYP index substrates



GLS means ratios and 90% CIs for combination/alone comparison against each PK parameter were derived from a mixed effect model evaluation. The log-transformed PK parameters were analyzed using a mixed effect model, with day as a fixed effect and participant as a random effect.
AUC_{0-t}, area under the curve from time 0 to time of last measurable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; CYP, cytochrome P450s; DDI, drug-drug interaction; GLS, geometric least square; PK, pharmacokinetic; VBR, vebicorvir.

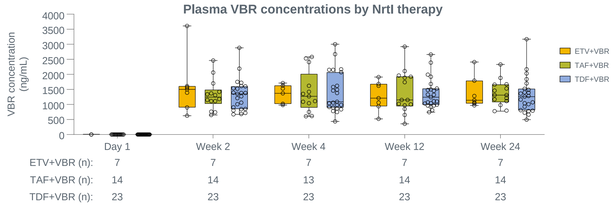
- Part 1 (**Figure 2, left panel**):
  - Maximum plasma concentrations (C_{max}) and area under the curve (AUC) parameter ratios (combination/alone) for omeprazole (2C19), dextromethorphan (2D6), and repaglinide (2C8) were within acceptable clinical ranges, demonstrating no DDI potential
  - Tolbutamide AUC was increased by approximately 30% with VBR coadministration, suggesting that VBR is a weak inhibitor of CYP2C9
- Part 2 (**Figure 2, middle panel**):
  - Midazolam AUC was reduced by 33% following 6 days of VBR administration (Day 7), with no further reduction after another 8 days of VBR administration (Day 15). There was no concomitant change in 1-hydroxymidazolam AUC on either Day 7 or Day 15, suggesting that VBR is not an inhibitor or inducer of CYP3A4
- Part 3 (**Figure 2, right panel**):
  - Coadministration of VBR did not have an effect on the C_{max} or AUC of bupropion, suggesting that VBR is not an inhibitor or inducer of CYP2B6

Table 2. Study 201 and 202: Demographics and Baseline characteristics

	Study 201 (N=73)	Study 202 (N=25)
Age, years; median (min, max)	45.0 (20, 66)	32.0 (20, 66)
Aged >65 years; n (%)	1 (1)	1 (4)
Sex, female; n (%)	26 (36)	17 (68)
Race, Asian; n (%)	61 (84)	24 (96)
BMI, kg/m^2; mean (SD)	24.0 (3.44)	23.3 (3.59)
Nrtl at randomization; n (%)		
ETV[a]	10 (14)	NA[b]
TAF	22 (30)	NA[b]
TDF[a]	42 (58)	NA[b]

[a]One patient was taking both ETV and TDF. [b]All Study 202 patients were treatment-naïve when entering the study, and all received ETV.
BMI, body mass index; ETV, entecavir; max, maximum; min, minimum; NA, not applicable; NrtI, nucleos(t)ide reverse transcriptase inhibitor; SD, standard deviation; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

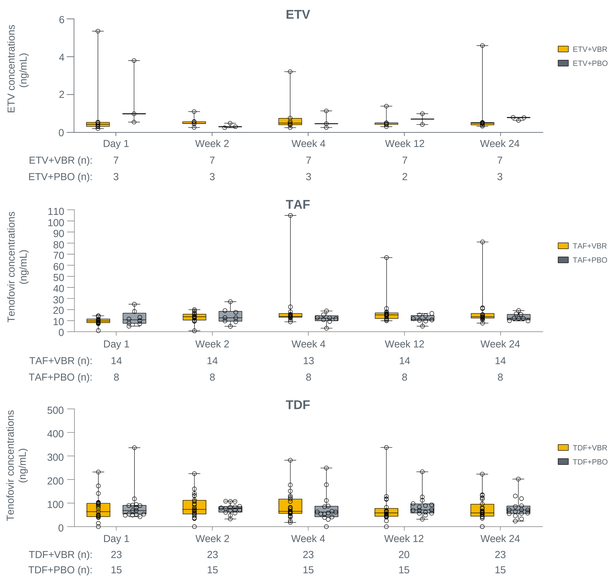
Figure 3. Study 201: Plasma VBR trough concentrations following combination therapy in patients with cHBV (by NrtI therapy)



Individual data plotted along with median, Q1, Q3, minimum, and maximum.
cHBV, chronic hepatitis B virus; ETV, entecavir; NrtI, nucleos(t)ide reverse transcriptase inhibitor; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VBR, vebicorvir.

- Study 201 (**Figure 3**)
  - After Day 1, mean trough plasma concentration values of VBR ranged from 1280–1600 ng/mL, 1310–1410 ng/mL, and 1310–1410 ng/mL for pooled VBR+entecavir (ETV), VBR+tenofovir alafenamide (TAF), and VBR+tenofovir disoproxil fumarate (TDF), respectively, and were in agreement with VBR monotherapy. The variability generally remained consistent across all combination treatments

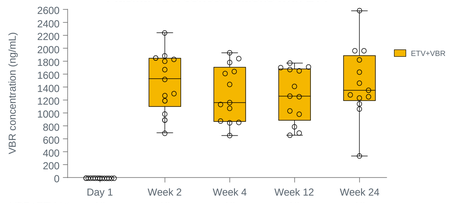
Figure 4. Study 201: Plasma NrtI trough concentrations following combination therapy in patients with cHBV (by NrtI therapy)

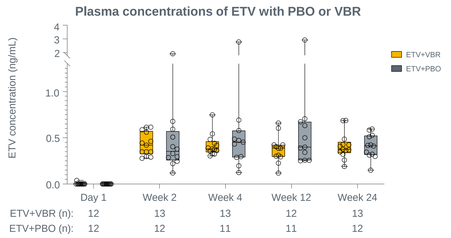


Individual data plotted along with median, Q1, Q3, minimum, and maximum.
cHBV, chronic hepatitis B virus; ETV, entecavir; NrtI, nucleos(t)ide reverse transcriptase inhibitor; PBO, placebo; Q, quartile; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VBR, vebicorvir.

- Study 201 (**Figure 4**)
  - ETV mean trough plasma concentration values were generally similar between both arms of the study, ranging from 0.554–1.10 ng/mL with VBR and 0.346–1.78 ng/mL with placebo, and were in agreement with published data
  - In the TAF group, tenofovir mean trough plasma concentrations ranged from 13.1–21.3 ng/mL when coadministered with VBR and from 11.7–14.1 ng/mL when coadministered with placebo, and were in agreement with published data
  - In the TDF group, tenofovir mean trough plasma concentrations were generally similar between both arms of the study, ranging from 72.4–86.8 ng/mL with VBR and 76.2–89.1 ng/mL with placebo, and were in agreement with published data

Figure 5. Study 202: Plasma trough concentrations following combination therapy in patients with cHBV





Individual data plotted along with median, Q1, Q3, minimum, and maximum.
cHBV, chronic hepatitis B virus; ETV, entecavir; PBO, placebo; Q, quartile; VBR, vebicorvir.

- Study 202 (**Figure 5**)
  - Mean trough plasma concentrations of VBR remained consistent, ranging from 1270–1480 ng/mL with similar variability across visits, and were in agreement with VBR monotherapy
  - ETV mean trough plasma concentration values were generally similar between both arms of the study, ranging from 72.4–86.8 ng/mL with VBR and 76.2–89.1 ng/mL with placebo, and were in agreement with published data

Conclusions

- Based on the Phase 1 study, VBR is a weak inhibitor of CYP2C9, is not an inhibitor of CYP2C19, 2D6, or 2C8, and is not an inhibitor/inducer of CYP3A4 or 2B6
- Results from the Phase 2a studies suggest no clinically significant DDI between VBR and NrtIs
- VBR shows a favorable profile, with limited potential for DDI when used in combination with NrtIs and other medications

References

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