Evaluation of the disposition and mass balance recovery of vebicorvir, a first-generation hepatitis B core inhibitor, in rats and humans

SAT-363

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Background

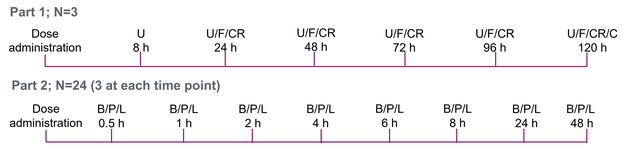
- Chronic hepatitis B virus infection (cHBV) is a significant global health problem
  - Worldwide, an estimated 296 million people have cHBV infection, resulting in approximately 887,000 deaths each year, mostly due to cirrhosis and hepatocellular carcinoma (HCC)[1–4]
- For most patients, nucleos(t)ide 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
- Vebicorvir (VBR) is a first-generation HBV core inhibitor that targets multiple aspects of the viral replication cycle
  - VBR, administered with NrtIs over 24 weeks, has demonstrated greater HBV DNA and pgRNA suppression than NrtI monotherapy in patients with cHBV infection[6–8]
  - VBR is orally administered as 300 mg once daily (QD) without regard to food
  - The favorable clinical safety profile of VBR has been shown in over 100 patients treated for up to 1.5 years[9]

Objective

- To evaluate the disposition and mass balance recovery of VBR in rats and healthy human participants

Methods of Rat Study

Figure 1. Study Design (Rat Study)

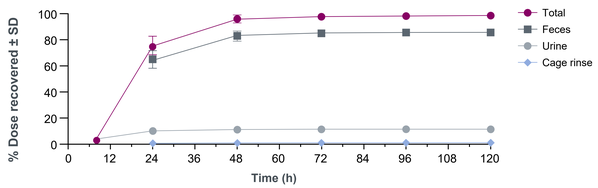


B, whole blood; C, carcass; CR, cage rinse; F, feces; L, liver; P, plasma; U, urine.

- 27 male rats were dosed with 30 mg/kg [^{14}C]-VBR radiolabeled with 5.5 MBq/kg
- Three animals were placed in metabolism cages for up to 120 h postdose. Total radioactivity was measured in urine, feces, cage rinse, and carcass using a Tricarb Series liquid scintillation analyser (Part 1; sampling schedule is shown in **Figure 1**)
- Three additional terminal animals per time point were used to obtain pharmacokinetic (PK) profiles in blood, plasma, and liver samples at 0.5, 1, 2, 4, 6, 8, 24, and 48 h postdose (Part 2; sampling schedule is shown in **Figure 1**)
- Metabolite quantification was performed by radio-liquid chromatography (LC) on all pooled plasma, liver, urine, and feces samples. Metabolite identification was performed by radio-LC-mass spectrometry on selected representative plasma, liver, urine, and feces samples. Radiochemical profiles were assessed for relative and absolute abundance of observed radiochemical components

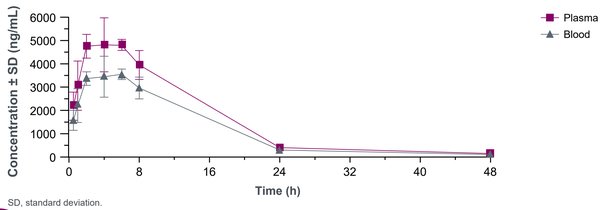
Results of Rat Study

Figure 2. Mean Cumulative Excretion of Total Radioactivity Following a Single Oral Administration of [^{14}C]-VBR to Male Rats at 30 mg/kg (Part 1)



SD, standard deviation.

Figure 3. Mean Composite Blood and Plasma Profiles of Total Radioactivity Following a Single Oral Administration of [^{14}C]-VBR to Male Rats at 30 mg/kg (Part 2)

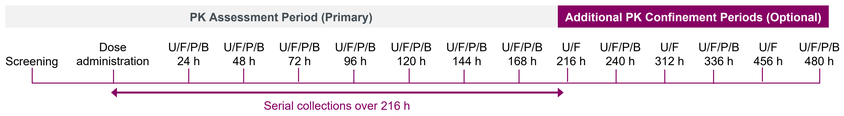


SD, standard deviation.

- In the rat study, at the end of the collection period (120 h postdose), the mean total radioactivity recovery was complete and accounted for 98.7% of the administered dose; 85.7% in feces and 11.5% in urine; cage rinse and carcass accounted for 1.2% and 0.4%, respectively (**Figure 2**)
- Unchanged VBR represented 62.5% and 3.6% of the administered dose in feces and urine, respectively. Additional minor metabolites were identified in feces and urine, but each accounted for ≤3% of the administered dose.
- Total drug-related radioactivity in blood and plasma was quantifiable up to 48 h postdose (**Figure 3**). Unchanged VBR was the only radio-component detected in plasma
- Over the 48 h postdose period, liver to blood radioactivity ratios ranged between 18 and 30, and liver to plasma ratios ranged between 13 and 22, indicating very high distribution of [^{14}C]-VBR total drug-related material into the liver. Parent compound was the major radioactive component detected in liver

Methods of Human Study

Figure 4. Study Design (Human Study)



B, whole blood; F, feces; P, plasma; PK, pharmacokinetics; U, urine.

- The human study (NCT04637139) was a single-arm, nonrandomized, open-label, Phase 1 trial
- Following an overnight fast of at least 8 hours, 6 healthy human participants received a single oral dose of 300 mg VBR solution containing a microdose of approximately 2 µCi of [^{14}C]-VBR
- Samples of blood, urine, and feces were collected for PK, metabolite, and radiolabel assessments for up to 480 h postdose (sampling schedule is shown in **Figure 4**)
- Total [^{14}C] VBR concentrations (ie, radiolabel recovery assessments) in whole blood, plasma, urine, and faecal samples were determined by liquid scintillation counting and accelerator mass spectrometry (AMS)
- Plasma and urine samples were analysed for VBR PK concentrations using validated tandem mass spectrometry bioanalytical methods
- Metabolite profiles were generated in cross-participant plasma and urine pools by LC+AMS. Structural identification was attempted on radioactive components representing ≥10% of circulating radioactivity in plasma or accounting for ≥10% of the administered dose in urine and feces

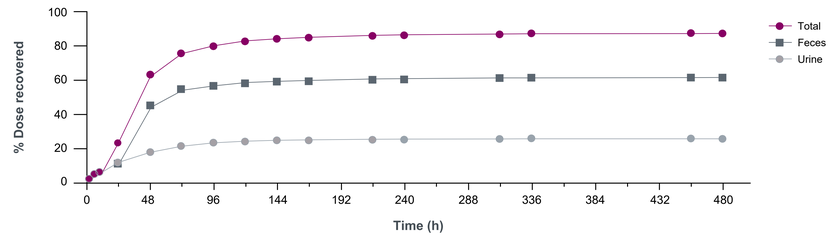
Results of Human Study

Table 1. Baseline Demographics

Characteristic	VBR 300 mg (N=6)
Male, n (%)	6 (100)
Age, years, median (range)	42 (24, 52)
Race, n (%)	
American Indian/Alaska Native	1 (16.7)
Black or African American	4 (66.7)
White	1 (16.7)
Height, cm, mean (SD)	176.58 (5.191)
Weight, kg, mean (SD)	80.60 (15.596)
BMI, kg/m^2, median (range)	25.20 (20.8, 31.9)

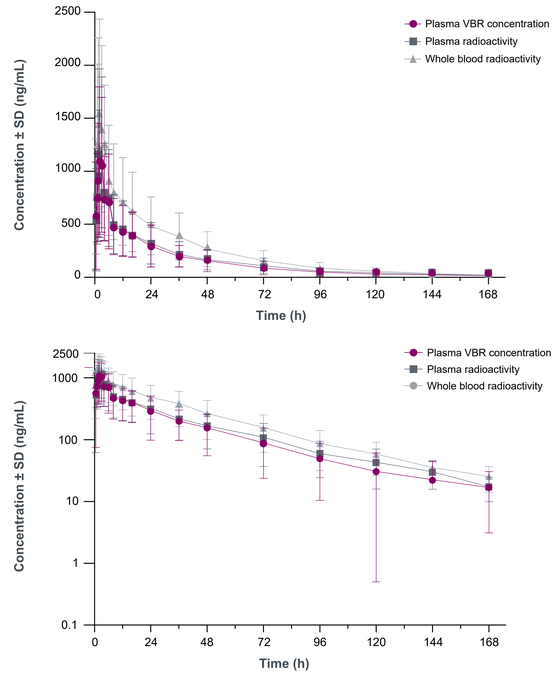
BMI, body mas index; SD, standard deviation; VBR, vebicorvir.

Figure 5. Mean Cumulative Excretion of Total Radioactivity Following a Single Oral Dose of 300 mg/2 µCi [^{14}C] Vebicorvir to Healthy Participants



- Mean cumulative radioactivity recovery in humans was 87.4%, with 61.5% excreted in feces and 25.9% in urine (**Figure 5**)
- Unchanged VBR was the major component in feces at 49.6% of the administered dose and in urine at 9.8% of the administered dose
- Seven components were identified in urine in addition to the unchanged VBR. These minor metabolites each accounted for 0.5%–4.6% of the administered dose
- One further minor metabolite was present in feces, accounting for 1.7% of the administered dose

Figure 6. Mean (±SD) Concentration-Time Profiles of Plasma Vebicorvir, and Plasma and Whole Blood Radioactivity (Linear and Semi-log) Following a Single Oral Dose of 300 mg/2 µCi [^{14}C]-Vebicorvir to Healthy Participants



SD, standard deviation; VBR, vebicorvir.

Table 2. VBR and Radioactivity Pharmacokinetic Parameters

PK Parameter, units	Plasma VBR	Plasma Radioactivity	Whole Blood Radioactivity
C_{max}, ng/mL, mean (SD)	1140 (666)	1330 (867)	1620 (811)
T_{max}, h, median (range)	2.5 (2.0, 3.0)	2.5 (2.0, 3.0)	2.0 (1.5, 4.0)
$AUC_{0\text{-last}}$, h.ng/mL, mean (SD)	23800 (14300)	28500 (15100)	38900 (22300)
$AUC_{0\text{-inf}}$, h.ng/mL, mean (SD)	24000 (14300)	26700* (12300)	39800 (22400)
$t_{½}$, h, mean (SD)	27.7 (4.6)	228.9† (227.0)	29.2 (5.4)
CL/F, L/h, mean (SD)	17.9 (12.7)	12.6* (5.2)	10.5 (7.3)
Renal clearance (measured in urine), L/h, mean (SD)	1.6 (0.5)	—	—

*n=3, †n=4. $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 extrapolated to infinity; $AUC_{0\text{-last}}$, area under the concentration-time curve from time 0 to the last quantifiable concentration; CL/F, clearance; C_{max}, maximum concentration occurring at T_{max}; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; $t_{½}$, terminal half-life; T_{max}, time of maximum concentration; VBR, vebicorvir.

- Unchanged VBR was identified as the major radioactive component seen in the pooled plasma, accounting for 90.3% of the total radioactivity area under the curve (AUC). A further minor component was observed accounting for 2.5% of the AUC. No further peaks were identified at >2% of the AUC
- Plasma VBR concentrations reached peak by approximately 2.5 h and declined with terminal half-life of 27.7 h (**Figure 6 and Table 2**). Plasma and whole blood radioactivity profiles were similar to plasma VBR concentration profile (**Figure 6 and Table 2**)
- Renal clearance of unchanged VBR (1.6 L/h) was a minor contributor to the total body clearance of VBR (17.9 L/h) (**Table 2**)

Table 3. Summary of Safety

	VBR 300 mg (n=6)
TEAE	2 (33.3)
TEAE (Grade 1)	2 (33.3)
TEAE (Grade ≥2)	0
Serious AE	0
Treatment-related AE	2 (33.3)
Death	0
Laboratory abnormalities	
Grade 2 eGFR	4 (66.7)
Grade 2 fasting glucose and Grade 2 high cholesterol	1 (16.7)
Grade 3-4 laboratory anomalies	0

Values represent participants (%). AE, adverse event; eGFR, estimated glomerular filtration rate; TEAE, treatment-emergent AE; VBR, vebicorvir.

- Treatment-emergent adverse events (TEAEs) are summarized in **Table 3**. Two (2; 33.3%) participants reported TEAEs, all of which were Grade 1 in severity. There were two AEs of throat irritation (33.3%) and one (16.7%) AE each of headache and urticaria
- There were no serious adverse events, deaths, or adverse events that resulted in participants withdrawing from the study

Conclusions

- Fecal excretion of unchanged drug is the primary route of VBR elimination in both rats and humans
- Unchanged VBR is the major component observed in plasma, urine, and feces. All metabolites observed were present at <5% of circulating radioactivity (plasma) or the administered dose (urine and feces)
- VBR showed high liver loading in rats indicating favorable distribution to the target organ for treatment of cHBV
- These results support the continued development of VBR

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)** Seto WK et al. *Lancet.* 2018;392:213–24; **6)** Fung S, et al. Poster presentation at EASL: Aug 27–29, 2020; **7)** Yuen MF, et al. Poster presentation at EASL: Aug 27–29, 2020; **8)** Ma X, et al. Oral presentation at: EASL: April 10–14, 2019; **9)** Jacobson IM et al. Presented at American Association for the Study of Liver Diseases (AASLD) The Liver Meeting Digital Experience 2020, November 13–16, 2020.

Acknowledgements

- We express our gratitude to all the healthy participants, investigators, and site staff who participated in the study
- Writing and editorial support was provided by Rob Coover, MPH, of AlphaScientia, LLC, and funded by Assembly Biosciences
- This study was sponsored by Assembly Biosciences

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