Pharmacokinetics, Pharmacodynamics, and Safety of Bulevirtide 2 mg Once Daily for 6 Days in Participants With Severe Renal Impairment and in Matched Control Participants With Normal Renal Function

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Conclusions

- Intensive pharmacokinetic (PK) sampling from days 1 and 6 showed similar PK exposure in participants with severe renal impairment (RI) and in matched controls
- Geometric least-squares mean ratios of the maximum concentration at steady state and area under the plasma concentration curve over a 24-hour dosing interval confirmed that the 2 groups showed no substantial differences in exposure
- Similar transient elevations of total bile acids were observed among participants with severe RI and matched controls, suggesting that treatment with bulevirtide 2 mg did not impact the status of total bile acids in the plasma within 24 hours
- These data suggest that dose adjustment is not needed when prescribing bulevirtide 2 mg to patients with RI
- Bulevirtide was generally safe and well tolerated in participants with severe RI and matched controls

Plain Language Summary

- Bulevirtide is a treatment for adults with hepatitis delta virus infection
- In participants with severe renal impairment and in matched controls, concentrations of bulevirtide and total bile acids were not different after participants received bulevirtide 2 mg injections daily for 6 days
- Our findings show that bulevirtide can be safely prescribed, with no need for dose adjustment, as a treatment for hepatitis delta virus in people who have renal impairment

References: **1.** Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. **2.** Ni Y, et al. *Gastroenterology*. 2014;146:1070-83. **3.** Yan H, et al. *Elife*. 2012;1:e00049. **4.** Wedemeyer H, et al. *N Engl J Med*. 2023;389:22-32. **5.** Asselah T, et al. *N Engl J Med*. 2024;391:133-43. **6.** Blank A, et al. *Clin Pharmacol Ther*. 2018;103:341-8.

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Introduction

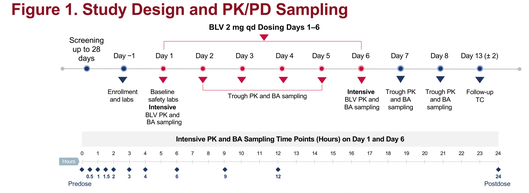
- Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis, affecting as many as 10 to 20 million people globally[1]
- HDV infection is associated with a more rapid progression to fibrosis and cirrhosis, earlier onset of hepatic complications, and a greater likelihood of liver transplant compared with other forms of viral hepatitis[2,3]
- Bulevirtide (BLV) is a novel 47–amino acid, N-terminally myristoylated, hepatitis B virus large envelope protein–derived, synthesized lipopeptide that binds specifically to the sodium taurocholate cotransporting polypeptide (NTCP) receptor and acts as a potent, highly selective entry inhibitor of HDV into hepatocytes[3]
  - The safety and efficacy of BLV in adults with chronic hepatitis delta and compensated liver disease have been established[4,5]
  - Dose-dependent, asymptomatic, and reversible bile acid (BA) elevations are observed with BLV treatment, as an expected consequence of the blockage of the NTCP receptor by BLV[6]
- Despite having a low molecular weight (~5 kDa) that could theoretically allow it to undergo glomerular filtration, BLV is unlikely to be renally eliminated due to very high plasma protein binding (>99%)
  - Due to renal excretion of BA, elevation of BA may be greater in patients with renal impairment (RI)
  - Clinical data on the use of BLV in populations with RI are currently limited to patients with HDV and mild RI

Objectives

- To evaluate the steady-state plasma pharmacokinetic (PK) parameters of BLV 2 mg administered subcutaneously once daily in participants with RI compared with matched controls
- To evaluate the pharmacodynamics (PD; measured as total BA) effect of BLV on plasma BA in participants with RI compared with matched controls
- To evaluate the safety and tolerability of BLV following multiple-dose administration in participants with RI and in matched controls

Methods

Figure 1. Study Design and PK/PD Sampling



BA, bile acids; BLV, bulevirtide; PD, pharmacodynamics; PK, pharmacokinetics; qd, once daily; TC, telephone call.

- This was an open-label, multicenter, multiple-dose, parallel-group, Phase 1 study to evaluate PK, PD, and safety of BLV in participants with severe RI and matched controls (**Figure 1**)
  - **Severe RI (n = 10):** Participants with estimated glomerular filtration rate (eGFR) ≥15 to ≤29 mL/min/1.73 m^2 at screening
    - Participants with severe RI requiring, or anticipating to require, dialysis within 90 days of study entry were not eligible
  - **Matched controls (n = 10):** Participants with normal renal function (eGFR ≥90 mL/min/1.73 m^2) were matched for age (± 10 years), sex (assigned at birth), and body mass index (BMI; ± 20%, 18 ≤BMI ≤40 kg/m^2) with participants in the severe RI group
- All participants received BLV 2 mg once daily for 6 days
- Intensive plasma sampling for BLV PK and PD (total BA) was performed on days 1 and 6
  - **Time points:** predose (≤30 minutes before dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours postdose

Table 1. Bile Acids

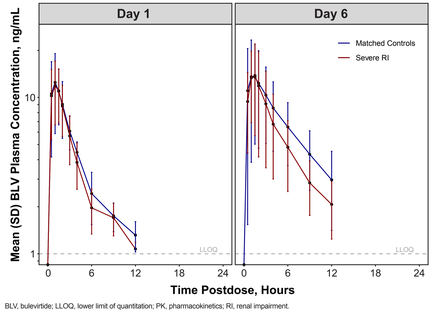
Name	Abbreviation
Chenodeoxycholic acid	CDCA
Cholic acid	CA
Deoxycholic acid	DCA
Glycochenodeoxycholic acid	GCDCA
Glycocholic acid	GCA
Glycodeoxycholic acid	GDCA
Glycolithocholic acid	GLCA
Glycoursodeoxycholic acid	GUDCA
Lithocholic acid	LCA
Taurochenodeoxycholic acid	TCDA
Taurocholic acid	TCA
Taurodeoxycholic acid	TDCA
Taurolithocholic acid	TLCA
Tauroursodeoxycholate acid	TUDCA
Ursodeoxycholic acid	UDCA

Total bile acids are determined by the sum of 15 individual bile acids. Plasma bile acid determination was achieved using detection by ultra- high-performance liquid chromatography/tandem mass spectrometry and high-resolution mass spectrometry with a calibration curve range of 5 ng/mL to 5000 ng/mL.

- Plasma concentrations of total BA were evaluated by a fit-for-purpose biomarker ultra-high-performance liquid chromatography/tandem mass spectrometry (UHPLC-MS/MS) assay measuring 15 plasma BA (**Table 1**)
- Concentrations of BLV in plasma samples were determined using a validated UHPLC-MS/MS bioanalytic method
- Plasma PK parameters were determined via noncompartmental analysis (Phoenix WinNonlin)
- A 1-way analysis of variance model appropriate for a parallel design with renal function group as a fixed effect was fit to the natural logarithmic transformation of BLV PK parameters (area under the plasma concentration curve [AUC] and maximum concentration [C_{max}]) and PD (total BA) parameters (AUC from time 0 to 24 hours after drug administration [AUC_{0-24}], AUC_{0-24} of total BA after baseline correction [NetAUC], and C_{max})
- NetAUC was calculated as follows: participants' baseline concentration value of total BA was subtracted from the measured concentration at all postdose time points. The value was set to zero if the resulting value was negative. Then, AUC was calculated via standard noncompartmental methods
- The 90% CIs were constructed for the geometric least-squares mean (GLSM) ratio of PK and PD parameters in the RI group vs the matched controls

Results

Figure 2. BLV PK Concentrations



BLV, bulevirtide; LLOQ, lower limit of quantitation; PK, pharmacokinetics; RI, renal impairment.

- On day 1, similar C_{max} and AUC_{0-24} values were observed between the severe RI and control groups (**Figure 2**)
- On day 6, the PK profile for the severe RI group showed a more rapid decline of BLV concentrations compared to matched controls. However, the estimated median BLV terminal half-lives were similar between the 2 groups (**Table 2**)

Table 2. BLV PK Parameters

		Matched Controls				Severe Renal Impairment			
		AUC_{0-t} (ng·h/mL)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	$T_{\frac{1}{2}}$[a] (h)	AUC_{0-t} (ng·h/mL)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	$T_{\frac{1}{2}}$[a] (h)
Day 1	n	10	10	10	NR	10	10	10	NR
	Geometric mean	47.5	52.9	11.7	NR	40.4	42.9	11.3	NR
	CV% of mean	17.2	12.7	56.9	NR	37.3	35.7	51.6	NR
Day 6	n	10	6	10	6	9	6	9	6
	Geometric mean	77.9	107	12.2	3.93 (2.31, 5.96)	62.3	90.9	12.8	3.68 (2.84, 4.80)
	CV% of mean	46.1	35.6	71.1	NR	52.6	31.1	69.7	NR

[a]$T_{\frac{1}{2}}$ reported as median (minimum, maximum).
AUC_{0-t}, area under the plasma concentration curve from time 0 to 12 hours after drug administration; AUC_{0-24}, area under the plasma concentration curve from time 0 to 24 hours after drug administration; BLV, bulevirtide; C_{max}, maximum plasma concentration; CV, coefficient of variation; NR, not reported; PK, pharmacokinetics; $T_{\frac{1}{2}}$, terminal elimination half-life.

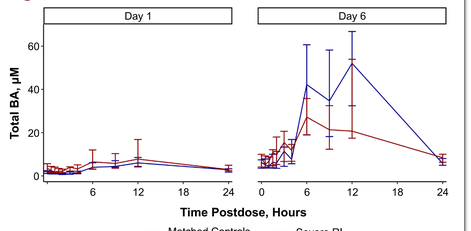
Results

Table 3. GLSM Ratio of PK Parameters

GLSM Ratio (90% CI)	AUC_{0-12} (ng·h/mL)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)
Day 1	0.85 (0.68, 1.06)	0.81 (0.66, 0.99)	0.97 (0.65, 1.43)
Day 6	0.80 (0.55, 1.16)	0.85 (0.60, 1.19)	1.06 (0.64, 1.75)

AUC_{0-12}, area under the plasma concentration curve from time 0 to 12 hours after drug administration; AUC_{0-24}, area under the plasma concentration curve from time 0 to 24 hours after drug administration; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean; PK, pharmacokinetics.

Figure 3. Median Total BA Levels in Plasma



Results are presented as the median (IQR) total plasma BA levels on day 1 (left) and day 6 (right) at intensive sampling times. Total BA levels are the sum of 15 individual BA.
BA, bile acids; RI, renal impairment.

- Similar PK exposures were confirmed with GLSM ratio evaluations of C_{max} and AUC_{0-24} between the severe RI and control groups (**Table 3**)
- On day 1, baseline values for total BA and NetAUC were similar between the severe RI group and matched controls (**Figure 3, Table 4**)
- On day 6, transient total BA elevations were observed (**Figure 3**)
- In both groups, BA levels approximated predose levels within 24 hours of dosing (**Figure 3**)

Table 4. PD Parameters for Total BA

		Matched Controls			Severe Renal Impairment		
		AUC_{0-24} (µM·h)	NetAUC (µM·h)	C_{max} (µM)	AUC_{0-24} (µM·h)	NetAUC (µM·h)	C_{max} (µM)
Day 1	n	10	10	10	10	10	10
	Geometric mean	98.80	46.80	6.98	137.65	50.33	11.16
	CV% of mean	53.59	79.70	82.24	65.55	93.86	63.70
Day 6	n	10	10	10	9	9	9
	Geometric mean[a]	639.67	585.08	52.37	427.82	339.84	34.51
	CV% of mean	45.62	49.53	42.00	76.22	87.49	73.60

AUC_{0-24}, area under the plasma concentration curve from time 0 to 24 hours after drug administration; BA, bile acids; C_{max}, maximum plasma concentration; CV, coefficient of variation; NetAUC, AUC_{0-24} of total BA after baseline correction; PD, pharmacodynamics.

Table 5. GLSM Ratio of Total BA PD Parameters

GLSM Ratio (90% CI)	NetAUC (µM·h)	C_{max} (µM)
Day 1	1.08 (0.41, 2.82)	1.60 (0.97, 2.63)
Day 6	0.58 (0.30, 1.12)	0.66 (0.35, 1.24)

BA, bile acids; C_{max}, maximum plasma concentration; GLSM, geometric least-squares mean; NetAUC, area under the plasma concentration curve from time 0 to 24 hours after bulevirtide administration of total BA after baseline correction; PD, pharmacodynamics.

- GLSM ratios of PD parameters NetAUC and C_{max} demonstrates that total BA trended similarly following administration of BLV 2 mg (**Table 5**)

Safety

- The frequencies of treatment-emergent adverse events (TEAEs) and laboratory abnormalities were numerically similar between both groups
- There were no serious AEs, AEs leading to BLV discontinuation, or Grade 3 or higher TEAEs related to BLV