Pharmacokinetics, Pharmacodynamics, and Safety of Bulevirtide 10 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

- Following 6 days of bulevirtide (BLV) 10 mg subcutaneous (SC) once-daily (QD) dosing, there were no differences in BLV pharmacokinetic (PK) exposures in participants with severe renal impairment (RI) compared with matched controls (MCs)
- Transient elevations in total bile acids (BAs) were observed after dosing in the severe RI and MC groups, with a return to approximate predose levels within 24 to 48 hours after dosing
- The elevation of total BAs was lower (by approximately 27% to 30%) in the severe RI group compared with the MC group
- BLV was generally safe in participants with severe RI
- These results suggest no dose adjustments are needed for BLV treatment with 10 mg QD in patients with RI

Plain Language Summary

- Bulevirtide (BLV) is a treatment for adults with hepatitis delta virus infection
- BLV causes temporary elevations in bile acids (BAs), which could also increase in people with renal impairment (RI)
- In participants with severe RI and in matched control participants who were comparable in age, sex, and body mass index, concentrations of BLV in the blood were not different after participants received BLV 10 mg daily injections for 6 days
- Concentrations of total BAs were slightly lower in participants with severe RI compared to matched controls
- BLV was safe in participants with severe RI
- Our findings show that no dose adjustments are needed for treatment with BLV 10 mg in people with RI

References: **1.** Stockdale AJ, et al. *J Hepatol.* 2020;73:523-32. **2.** Da BL, et al. *Gastroenterol Rep.* 2019;7(4):231-45. **3.** Ni Y, et al. *Gastroenterology.* 2014;146:1070-83. **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.** Wang Y, et al. Presented at: AASLD: The Liver Meeting; Nov 15–19, 2024. Poster 1194.

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Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Introduction

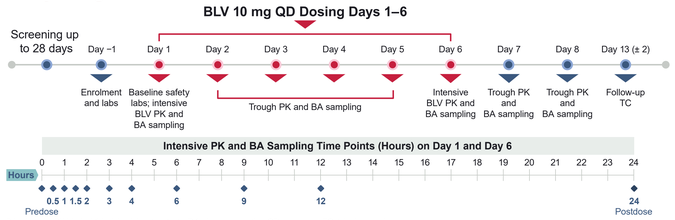
- Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis, affecting as many as 10 to 20 million people globally[1]
- HDV infection is associated with a more rapid progression to fibrosis and cirrhosis, earlier onset of hepatic complications, and a greater likelihood of liver transplant compared with other forms of viral hepatitis[2]
- BLV is a 47–amino acid lipopeptide that binds to the sodium taurocholate cotransporting polypeptide (NTCP) receptor and blocks entry of HDV into hepatocytes[3]
  - By inhibiting NTCP, BLV causes dose-dependent, asymptomatic, and transient elevations in BAs, which could possibly increase with RI[3,4]
- BLV 2 mg QD is approved in the European Union, Great Britain, Switzerland, Australia, and the Russian Federation for treatment of HDV infection in adults with compensated liver disease[4,5]
  - Previous clinical studies of BLV in people with HDV did not include participants with severe RI
- Evaluations exploring the potential benefit of an increased dose of 10 mg QD are in progress

Objective

- To assess the PK, pharmacodynamics (PD), and safety of multiple doses of BLV 10 mg in participants with severe RI vs MCs with normal renal function

Methods

Study Design



BA, bile acid; BLV, bulevirtide; labs, laboratory tests; PK, pharmacokinetics; QD, once daily; TC, telephone call.

- This was an open-label, multicentre, multiple-dose, Phase 1 study in participants without hepatitis B virus/HDV infection with severe RI and MCs administered BLV 10 mg SC QD for 6 days
  - **Severe RI** (n = 10): 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
  - **MCs** (n = 10): participants with normal renal function (eGFR ≥90 mL/min/1.73 m^2) matched for age (± 10 years), sex, and body mass index (± 20%)
- Intensive plasma BLV PK and PD (total BAs) samples were assessed on days 1 and 6
  - The PK and PD (total BAs) of BLV 2 mg were previously examined in participants with severe RI in arm A of the same study[6]

Bile Acids

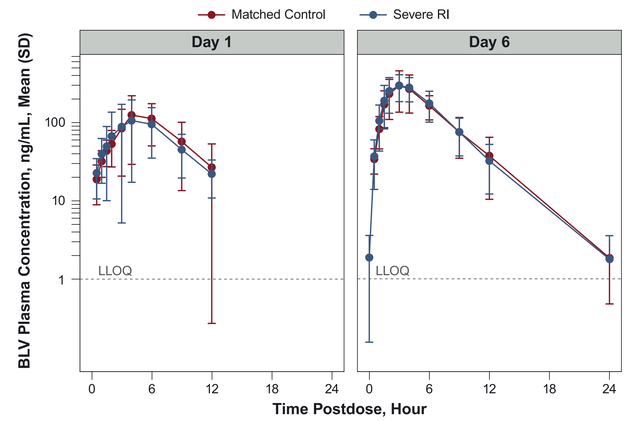
Bile Acid Name	Abbreviation
Chenodeoxycholic acid	CDCA
Cholic acid	CA
Deoxycholic acid	DCA
Glycochenodeoxycholic acid	GCDCA
Glycocholic acid	GCA
Glycodeoxycholic acid	GDCA
Glycolithocholic acid	GLCA
Glycoursodeoxycholic acid	GUDCA
Lithocholic acid	LCA
Taurochenodeoxycholic acid	TCDA
Taurocholic acid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

Total BAs are determined by the sum of 15 individual BAs. Plasma BA determination was achieved using HPLC-MS/MS with a calibration curve range of 5 ng/mL to 5000 ng/mL. BA, bile acid; HPLC-MS/MS, high-performance liquid chromatography–tandem mass spectrometry.

- Safety was assessed by clinical laboratory tests and evaluation of adverse events (AEs)
- Plasma concentrations of total BAs were evaluated by a fit-for-purpose biomarker liquid chromatography–tandem mass spectrometry assay measuring 15 plasma BAs
- Plasma PK parameters were determined via noncompartmental analysis (Phoenix WinNonlin)
- A one-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 (maximum BLV plasma concentration [C_{max}; ng/mL] and area under the plasma concentration curve [AUC; ng·h/mL] from 0 to 24 hours after drug administration [$AUC_{0–24}$]) and PD parameters (total BAs, AUC of total BAs after baseline correction [NetAUC], C_{max})
- The 90% CIs were constructed for the geometric least-squares mean (GLSM) ratio of BLV PK and PD (total BAs) parameters in participants with RI vs MCs

Results

BLV PK Concentrations



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

BLV PK Parameters

	Severe Renal Impairment						
	$AUC_{0–12}$ (ng·h/mL)	$AUC_{0–24}$ (ng·h/mL)	C_{max} (ng/mL)	CL/F (L/h)	$T_{1/2}$[a] (h)	T_{max}[a] (h)	Vz/F (L)
Day 1	741 (61.5)	843 (56.9)	121 (71.4)	16.8 (69.2)	2.86 (2.45, 4.54)	4.00 (3.00–6.00)	158 (178)
Day 6	1750 (34.4)	1880 (34.1)	311 (35.3)	5.8 (29.1)	2.79 (2.27, 2.99)	3.00 (2.00–4.03)	24.4 (43.8)
	Matched Controls						
	$AUC_{0–12}$ (ng·h/mL)	$AUC_{0–24}$ (ng·h/mL)	C_{max} (ng/mL)	CL/F (L/h)	$T_{1/2}$[a] (h)	T_{max}[a] (h)	Vz/F (L)
Day 1	828 (49.8)	876 (52.2)	146 (57.5)	19.1 (95.9)	3.03 (2.67, 3.76)	4.00 (1.50–9.00)	128 (133)
Day 6	1670 (33.6)	1810 (30.9)	307 (50.8)	6.1 (36.5)	2.75 (2.46, 2.97)	3.0 (3.00–6.00)	25.0 (56.7)

[a]T_{max} is reported as median (minimum–maximum); $T_{1/2}$ is reported as median (Q1, Q3); all other data are reported as mean (CV%).
$AUC_{0–12}$, 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; BLV, bulevirtide; CL/F, clearance after drug administration; C_{max}, maximum plasma concentration; CV%, coefficient of variation percentage; h, hour; PK, pharmacokinetics; Q, quartile; $T_{1/2}$, terminal elimination half-life; T_{max}, time to reach C_{max}; Vz/F, volume of distribution after drug administration.

GLSM Ratio of PK Parameters

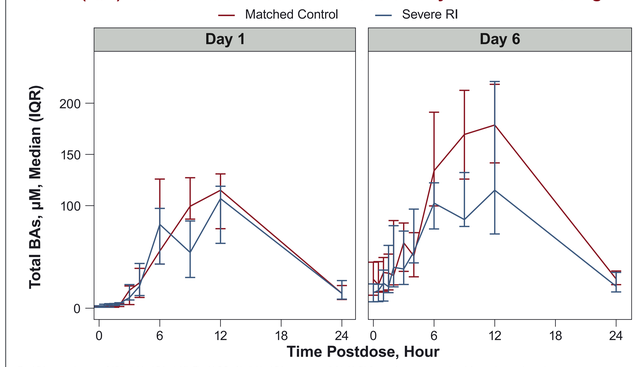
GLSM Ratio (90% CI)	$AUC_{0–12}$ (ng·h/mL)	AUC_{tau} (ng·h/mL)	C_{max} (ng/mL)
Day 1	0.89 (0.51, 1.57)	1.00 (0.56, 1.79)	0.78 (0.43, 1.42)
Day 6	1.05 (0.81, 1.37)	1.04 (0.81, 1.33)	1.08 (0.78, 1.51)

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

PK

- On days 1 and 6, similar PK exposures were observed between the severe RI and MC groups based on the GLSM ratio evaluations of C_{max} and $AUC_{0–24}$
- In both participants with severe RI and MCs, PK exposures showed approximately a 2-fold accumulation from day 1 to day 6, with a corresponding reduction in apparent clearance (CL/F) and volume of distribution (Vz/F)
- Overall, the estimated median BLV elimination half-life was similar (approximately 3 hours) between the severe RI and MC groups

Median (IQR) Total BA Plasma Concentrations on Days 1 and 6 of Dosing



Total BAs were the sum of 15 individual BAs (µM). The LLOQ of individual BAs was set at 0.01µM. BLQ samples were treated as 0 for predose and postdose.
BA, bile acid; BLQ, below the limit of quantitation; LLOQ, lower limit of quantitation; RI, renal impairment.

PD Parameters of Total BAs

		Severe Renal Impairment		
		$AUC_{0–24}$ (µM·h)	NetAUC (µM·h)	C_{max} (µM)
Day 1	**n**	11	11	11
	Geometric mean	1110	1070	93
	GCV%	71.5	71.0	80.4
Day 6	**n**	10	10	10
	Geometric mean	1850	1800	145
	GCV%	63.9	64.1	66.5
		Matched Controls		
		$AUC_{0–24}$ (µM·h)	NetAUC (µM·h)	C_{max} (µM)
Day 1	**n**	10	10	10
	Geometric mean	1300	1250	107
	GCV%	58.6	62.1	61.6
Day 6	**n**	10	10	10
	Geometric mean	2630	2580	200
	GCV%	27.6	27.1	28.1

$AUC_{0–24}$, area under the plasma concentration curve from time 0 to 24 hours after drug administration; BA, bile acid; C_{max}, maximum plasma concentration; GCV, geometric coefficient of variation; NetAUC, $AUC_{0–24}$ of total BAs after baseline adjustment; PD, pharmacodynamics.

GLSM Ratio of PD Parameters for Total BAs

GLSM Ratio (90% CI)	NetAUC (µM·h)	C_{max} (ng/mL)
Day 1	0.86 (0.54, 1.36)	0.87 (0.53, 1.41)
Day 6	0.70 (0.49, 0.99)	0.73 (0.50, 1.05)

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

PD

- The severe RI and MC groups had similar trends of transient elevations in total plasma BAs that approximated predose levels within 24 to 48 hours
- The elevation of total BAs was lower (by approximately 27% to 30%) in participants with severe RI compared with MCs, as measured by GLSM ratios of NetAUC and C_{max}

Safety

- There were no BLV-related Grade ≥3 treatment-emergent (TE) AEs, serious AEs, or AEs leading to BLV discontinuation
- The frequency of TEAEs was similar in both groups, with most AEs being Grade 1 or 2

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