Pharmacokinetics, Pharmacodynamics, and Safety of Bulevirtide 10 mg Once Daily for 6 Days in Participants With Moderate Hepatic Impairment and in Matched Control Participants With Normal Hepatic Function

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Conclusions

- Pharmacokinetic (PK) exposures following bulevirtide (BLV) 10 mg once daily (QD) for 6 days in the moderate hepatic impairment (Mod HI) group were reduced (approximately 22%–46%) compared with those in matched controls (MCs)
  - — However, exposures were still >5-fold higher than those observed with the currently approved 2 mg QD dose
- Transient elevations in total bile acids (BAs) were observed in both the Mod HI and MC groups following BLV 10 mg and returned to approximate predose levels within 24 to 48 hours of dosing
  - — The elevations in total BAs were similar in the Mod HI and MC groups on day 1 but were approximately 80% higher in Mod HI participants after day 6 of dosing
- BLV was generally safe in participants with Mod HI

Plain Language Summary

- Bulevirtide (BLV) is a treatment for adults with hepatitis delta virus infection
- BLV can increase levels of bile acids (BAs; which are produced in the liver); therefore, it is important to know whether BLV increases BA levels in people whose livers are impaired
- After receiving BLV 10 mg once daily for 6 days, concentrations of BLV were slightly lower in participants with moderately impaired liver function compared with matched control participants of similar age, sex, and body mass index
- There were no increases in total BAs in participants with moderately impaired liver function compared with matched control participants on the first day of dosing; however, BAs were approximately 80% higher in participants with moderately impaired liver function after 6 days of dosing
- BLV was generally safe in participants with moderately impaired liver function

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.** Kumar P, et al. Presented at: AASLD: The Liver Meeting; Nov 15–19, 2024. Poster 1154.

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

Introduction

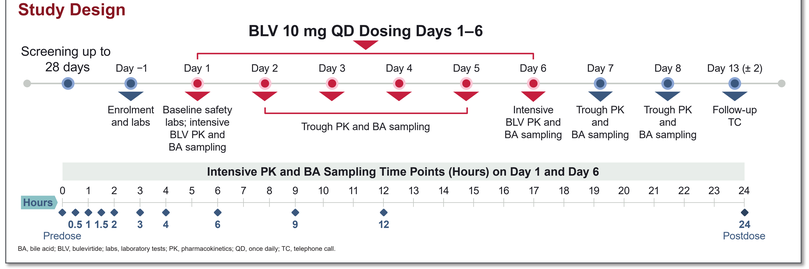
- Hepatitis delta virus (HDV) infection causes the most severe form of viral hepatitis, affecting as many as 10 to 20 million people globally[1]
- HDV infection is associated with a more rapid progression to fibrosis and cirrhosis, earlier onset of hepatic complications, and greater likelihood of liver transplant compared with other forms of viral hepatitis[2]
- BLV is a 47–amino acid, lipopeptide HDV entry inhibitor that binds to the sodium taurocholate cotransporting polypeptide (NTCP) receptor[3]
  - — By inhibiting NTCP, BLV treatment results in dose-dependent, asymptomatic, and transient elevations in BAs[3]
- BLV is approved in the European Union (EU) and in several non-EU countries for the treatment of chronic hepatitis delta (CHD) with compensated liver disease at a subcutaneous (SC) dose of 2 mg QD[4,5]
  - — Evaluations exploring the potential benefit of an increased BLV dose of 10 mg QD are in progress
- Hepatic impairment is generally known to be associated with changes in drug absorption, plasma protein binding, transport, and tissue distribution, which are most prominent in people with severely impaired hepatic function
  - — As CHD is associated with development of fibrosis and cirrhosis, there is a need to characterise the PK, pharmacodynamics (PD), and tolerability of BLV in people with impaired hepatic function
- A previously conducted evaluation found that steady-state BLV PK and PD (total BAs) were not clinically meaningfully impacted in participants with moderate HI compared with MCs following BLV 2 mg SC QD dosing for 6 days; BLV 2 mg was generally safe and well tolerated in this population[6]

Objectives

- **Primary:**
  - — To evaluate the steady-state plasma PK of BLV 10 mg QD in participants without hepatitis B virus (HBV)/HDV infection with Mod HI compared with MCs with normal hepatic function
- **Secondary:**
  - — To evaluate the PD effect of BLV on plasma total BAs in participants with Mod HI compared with MCs with normal hepatic function
  - — To evaluate the safety and tolerability of BLV following multiple-dose administration in participants with Mod HI compared with MCs with normal hepatic function

Methods

Study Design



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

Bile Acids

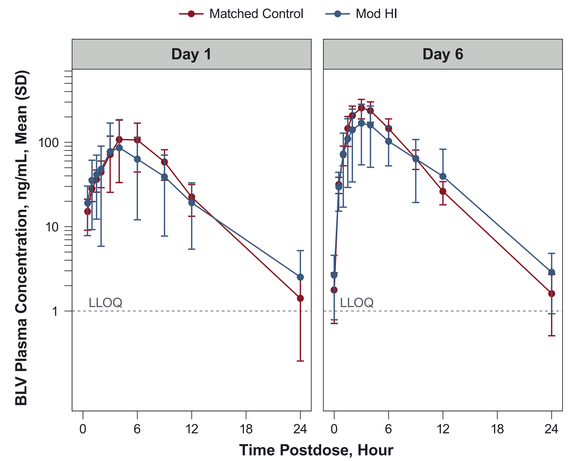
Bile Acid Name	Abbreviation
Chenodeoxycholic acid	CDCA
Cholic acid	CA
Deoxycholic acid	DCA
Glycochenodeoxycholic acid	GCDCA
Glycocholic acid	GCA
Glycodeoxycholic acid	GDCA
Glycolithocholic acid	GLCA
Glycoursodeoxycholic acid	GUDCA
Lithocholic acid	LCA
Taurochenodeoxycholic acid	TCDA
Taurocholic acid	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.

- This was an open-label, multicentre, parallel-group, multiple-dose, Phase 1 study in participants without HBV/HDV infection with Mod HI (Child-Turcotte-Pugh class B; n = 10) and MCs with normal hepatic function (n = 10; matched for age [± 10 years], sex, and body mass index [± 20%])
- Participants received BLV 10 mg SC QD for 6 days, with intensive serial sampling for BLV PK and PD (total BAs) performed on days 1 and 6
  - — The PK and PD (total BAs) of BLV 2 mg were previously reported in participants with Mod HI in arms A and B of the same study[6]
- Plasma PK parameters were determined via noncompartmental analysis (Phoenix WinNonlin)
- Plasma concentrations of total BAs were evaluated by a fit-for-purpose biomarker liquid chromatography–tandem mass spectrometry assay measuring 15 plasma BAs
  - — Samples below the limit of quantitation were treated as 0 for predose and postdose
- A 1-way analysis of variance model appropriate for a parallel design with hepatic function group as a fixed effect was fit to the natural logarithmic transformation of BLV PK parameters (area under the plasma concentration curve [AUC; ng·h/mL] and maximum concentration [C_{max}; ng/mL]) and PD parameters (total BAs; AUC from time 0 to 24 hours after drug administration [$AUC_{0–24}$; µM·h], $AUC_{0–24}$ of total BAs after baseline correction [NetAUC; µM·h], and C_{max} [µM])
- The 90% CIs were constructed for the geometric least-squares mean (GLSM) ratio of BLV PK and PD parameters in the Mod HI vs MC groups
- Safety was assessed by clinical laboratory tests and evaluation of adverse events (AEs)

Results

BLV PK Concentrations



BLV, bulevirtide; HI, hepatic impairment; LLOQ, lower limit of quantitation; PK, pharmacokinetic.

BLV PK Parameters

	Moderate Hepatic Impairment						
	$AUC_{0–24}$ (ng·h/mL)	AUC_{inf} (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	671.4 (64.7)	696.4 (60.0)	99.2 (95.1)	22.8 (79.6)	3.9 (2.6, 6.3)	4.0 (1.0–9.0)	217.2 (125.0)
Day 6	1266.4 (61.3)	1283.5 (60.1)	175.0 (64.7)	9.6 (40.3)	3.4 (2.6, 4.7)	3.0 (3.0–6.0)	53.0 (64.2)
	Matched Controls						
	$AUC_{0–24}$ (ng·h/mL)	AUC_{inf} (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	853.0 (39.6)	859.4 (39.2)	126.8 (51.8)	14.2 (57.7)	2.8 (2.6, 3.2)	5.0 (2.0–9.0)	66.0 (93.4)
Day 6	1561.1 (22.2)	1568.8 (22.0)	260.6 (24.6)	6.7 (24.2)	2.8 (2.4, 3.1)	3.0 (2.0–4.0)	28.5 (46.7)

[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%).
$AUC_{0–24}$, area under the plasma concentration curve from time 0 to 24 hours after drug administration; AUC_{inf}, area under the plasma concentration curve from time 0 to infinity after drug administration; BLV, bulevirtide; CL/F, clearance after drug administration; C_{max}, maximum plasma concentration; CV%, coefficient of variation percentage; h, hour; PK, pharmacokinetic; 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

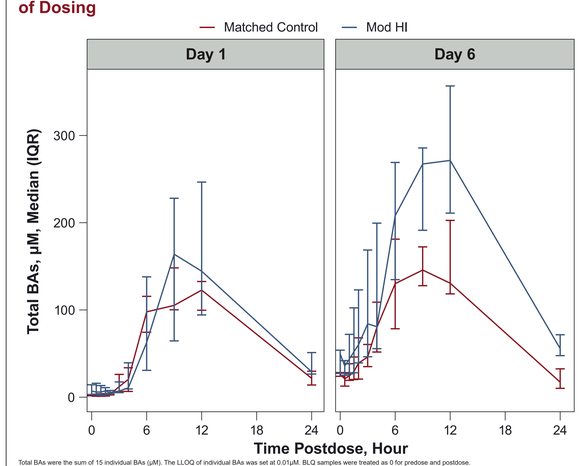
GLSM Ratio (90% CI)	$AUC_{0–24}$ (ng·h/mL)	AUC_{inf} (ng·h/mL)	C_{max} (ng/mL)
Day 1	0.67 (0.40, 1.12)	0.78 (0.49, 1.26)	0.54 (0.26, 1.12)
Day 6	0.73 (0.54, 0.99)	0.74 (0.55, 1.00)	0.58 (0.41, 0.83)

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

PK

- In both participants with Mod HI 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)
- On days 1 and 6, mean CL/F and Vz/F were higher in the Mod HI group than in MCs
- The median elimination half-life was similar between groups (approximately 3–4 hours)
- BLV PK concentrations and PK parameters, as measured by GLSM ratios of C_{max}, $AUC_{0–24}$, and AUC from time 0 to infinity after drug administration (AUC_{inf}) on days 1 and 6, were approximately 22% to 46% lower in participants with Mod HI than in MCs

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; HI, hepatic impairment; LLOQ, lower limit of quantitation.

PD Parameters of Total BAs

		Moderate Hepatic Impairment		
		$AUC_{0–24}$ (µM·h)	NetAUC (µM·h)	C_{max} (µM)
Day 1	**Geometric mean**	1780.1	1470.5	137.5
	GCV%	99.2	109.6	109.3
Day 6	**Geometric mean**	4323.6	4017.7	321.3
	GCV%	39.2	33.0	39.6
		Matched Controls		
		$AUC_{0–24}$ (µM·h)	NetAUC (µM·h)	C_{max} (µM)
Day 1	**Geometric mean**	1652.3	1595.0	139.2
	GCV%	22.4	22.1	29.7
Day 6	**Geometric mean**	2281.1	2215.4	176.6
	GCV%	22.6	24.0	20.4

$AUC_{0–24}$, 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} (µM)
Day 1	0.92 (0.56, 1.52)	0.99 (0.59, 1.65)
Day 6	1.81 (1.46, 2.26)	1.82 (1.44, 2.31)

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

- Similar magnitudes of BA elevations and PD parameters as measured by GLSM ratios of C_{max} and NetAUC were observed between the Mod HI and MC groups on day 1; however, on day 6, the PD parameters in the Mod HI group were elevated by approximately 80% compared with those in the MC group
- In both the participants with Mod HI and MCs, elevations in total BAs appeared reversible, as total BA concentrations returned to approximate baseline values within 24 to 48 hours postdose

Safety

- There were no Grade ≥3 treatment-emergent (TE) AEs, serious AEs, or AEs leading to BLV discontinuation
- The frequency of TEAEs was similar between the two groups, and TEAEs were generally mild with no increased severity in participants with Mod HI vs MCs

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