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

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Conclusions

- There were no differences in steady-state pharmacokinetic (PK) exposure observed in participants with severe hepatic impairment (HI) compared with matched control (MC) participants with normal hepatic function following 10 mg once-daily (QD) bulevirtide (BLV) dosing for 6 days
- Baseline-adjusted elevations in total bile acids (BAs) at BLV steady state were approximately 44% higher in participants with severe HI compared with MCs
- BLV was generally safe in participants with severe HI

Plain Language Summary

- Bulevirtide is a treatment for patients with hepatitis delta virus infection
- Bulevirtide can increase levels of bile acids (which are produced in the liver); therefore, it is important to know whether bulevirtide increases bile acid levels in people whose liver function is impaired
- After treatment with bulevirtide 10 mg once daily for 6 days, participants with severely impaired liver function had the same levels of bulevirtide in the blood as control participants who were matched for age, sex, and body mass index and had 44% higher baseline-adjusted concentrations of total bile acids compared with control participants
- Bulevirtide was generally safe in participants with severely 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.** Asselah T, et al. *New Engl J Med.* 2023;389(1):58-70. **4.** Ni Y, et al. *Gastroenterology.* 2014;146:1070-83. **5.** Kang C, et al. *Drugs.* 2020;80(15):1601-5. **6.** Wedemeyer H, et al. *J Hepatol.* 2024;81(4):621-9. **7.** Wedemeyer H, et al. *N Engl J Med.* 2023;389:22-32. **8.** Asselah T, et al. *N Engl J Med.* 2024;391:133-43. **9.** Hepcludex. Summary of product characteristics. Gilead Sciences Ireland UC; 2021. **10.** European Association for the Study of the Liver. *J Hepatol.* 2025;83(2):502-83.

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Introduction

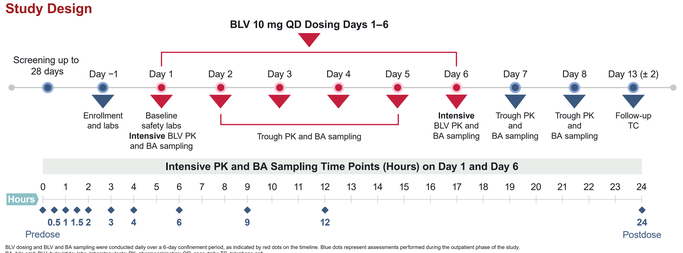
- Hepatitis delta virus (HDV) infection causes the most severe form of viral hepatitis, affecting an estimated 9 to 19 million people globally[1]
- HDV infection is associated with a more rapid progression to fibrosis and cirrhosis, earlier onset of hepatic complications, and a greater likelihood of liver transplantation compared with other forms of viral hepatitis[2,3]
- BLV is a 47–amino acid, lipopeptide HDV entry inhibitor that binds to the sodium taurocholate cotransporting polypeptide (NTCP) receptor[4,5]
  - By inhibiting NTCP, BLV treatment results in dose-dependent, asymptomatic, and transient elevations in BAs[6]
- BLV is approved in the European Union (EU) and in several non-EU countries for the treatment of chronic HDV (CHD) with compensated liver disease at a subcutaneous (SC) dose of 2 mg QD[7-10]
  - Evaluations exploring the potential benefit of an increased BLV dose of 10 mg QD are in progress
- HI can be associated with changes in drug absorption, plasma protein binding, transport, and tissue distribution
  - As CHD is associated with development of fibrosis and cirrhosis, there is a need to characterize the PK, pharmacodynamics (PD), and tolerability of BLV in people with severely impaired hepatic function

Objectives

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

Methods

Study Design



BLV dosing and BLV and BA sampling were conducted daily over a 6-day confinement period, as indicated by red dots on the timeline. Blue dots represent assessments performed during the outpatient phase of the study.
BA, bile acid; BLV, bulevirtide; labs, laboratory tests; PK, pharmacokinetics; QD, once daily; TC, telephone call.

Bile Acids

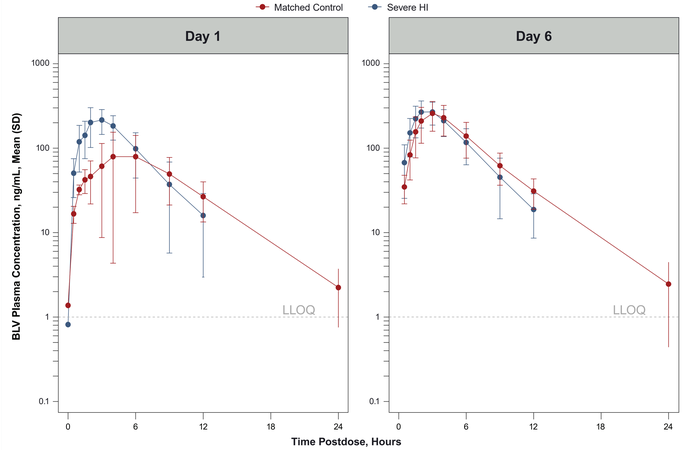
BA Name	Abbreviation
Chenodeoxycholic acid	CDCA
Cholic acid	CA
Deoxycholic acid	DCA
Glycochenodeoxycholic acid	GCDCA
Glycocholic acid	GCA
Glycodeoxycholic acid	GDCA
Glycolithocholic acid	GLCA
Glycoursodeoxycholic acid	GUDCA
Lithocholic acid	LCA
Taurochenodeoxycholic acid	TCDA
Taurocholic acid	TCA
Taurodeoxycholic 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, multicenter, parallel-group, multiple-dose, Phase 1 study in participants without HBV/HDV infection with severe HI (Child-Turcotte-Pugh class C; n = 8) and MCs with normal hepatic function (n = 8; 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
- Concentrations of BLV in plasma samples were determined using a validated high-performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) bioanalytical method
- Plasma PK parameters were determined via noncompartmental analysis (Phoenix WinNonlin)
- Plasma concentrations of total BAs were evaluated by a fit-for-purpose biomarker LC-MS/MS 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] from time 0 to 24 hours after drug administration [AUC_{0-24}] and maximum concentration [C_{max}; ng/mL]) and PD parameters of total BAs (AUC_{0-24} of total BAs after baseline adjustment [NetAUC; µM·h])
- The 90% CIs were constructed for the geometric least-squares mean ratios of BLV PK and PD parameters in the severe HI vs MC groups
- Safety was assessed by clinical laboratory tests and evaluation of adverse events (AEs)

Results

BLV Plasma Concentrations



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

BLV PK Parameters

	Severe Hepatic Impairment				Matched Controls			
	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	$T_{1/2}$ (h)	T_{max} (h)	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	$T_{1/2}$ (h)	T_{max} (h)
Day 1	1220 (28.8)	230 (37.1)	2.46 (2.14–3.56)	3.00 (2.00–3.04)	750 (50.2)	103 (67.2)	3.42 (2.92–3.89)	5.00 (2.25–7.58)
Day 6	1520 (30.2)	293 (33.0)	2.81 (2.14–3.30)	2.50 (2.00–3.00)	1600 (31.4)	263 (38.3)	3.03 (2.59–4.08)	3.00 (2.99–3.04)

AUC_{0-24} and C_{max} are reported as mean (CV%); T_{max} and $T_{1/2}$ are reported as median (minimum, maximum).
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; PK, pharmacokinetics; $T_{1/2}$, terminal elimination half-life; T_{max}, time to reach C_{max}.

GLSM Ratio of BLV PK Parameters

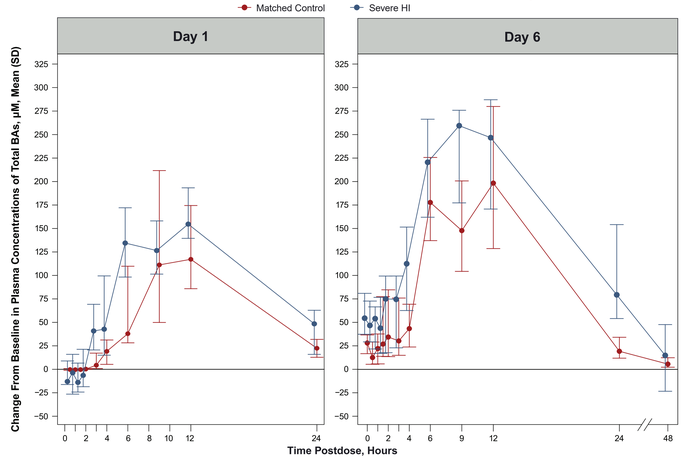
GLSM Ratio (90% CI)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)
Day 1	2.56 (1.57, 4.17)	1.80 (1.19, 2.70)
Day 6	1.14 (0.81, 1.61)	0.96 (0.73, 1.26)

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; GLSM, geometric least-squares mean; PK, pharmacokinetics.

PK

- Day 1
  - The mean BLV PK exposure parameters (AUC_{0-24} and C_{max}) were higher in participants with severe HI than in participants with normal hepatic function
  - Median time to reach C_{max} (T_{max}) occurred around 3 hours and 5 hours postdose in participants with severe HI and MCs, respectively
  - The participants with severe HI had a slightly shorter median terminal elimination half-life ($T_{1/2}$)
- Day 6
  - There were no statistically significant differences in steady-state PK exposures (AUC_{0-24} and C_{max}) observed in participants with severe HI compared with MCs with normal hepatic function
  - The median T_{max} and $T_{1/2}$ values were also similar between both groups
- When comparing changes from day 1 (single dose) to day 6 (multiple dosing), there was an increase in BLV exposure parameters; these changes were larger in the MCs than in the participants with severe HI

Total BA Plasma Concentrations in Participants With Severe HI and in MC Participants



BA, bile acid; HI, hepatic impairment; MC, matched control.

PD Parameters of Total BAs

		Severe Hepatic Impairment	Matched Controls
		NetAUC (µM·h)	NetAUC (µM·h)
Day 1	**Geometric mean**	2380	1690
	GCV%	32.8	43.3
Day 6	**Geometric mean**	4030	2850
	GCV%	30.4	39.9

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

GLSM Ratio of PD Parameters for Total BAs

GLSM Ratio (90% CI)	NetAUC (µM·h)
Day 1	1.45 (0.56, 1.52)
Day 6	1.44 (1.04, 2.01)

BA, bile acid; 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

- Day 1
  - The NetAUC of total BAs increased by 45% in participants with severe HI compared with MCs
- Day 6
  - At steady state, the total BA concentrations were higher in the participants with severe HI than in MCs throughout the 48-hour postdose evaluation period
  - The NetAUC of total BAs increased by 44% in participants with severe HI compared with MCs
  - In participants with severe HI and MCs, total BA concentrations trended back toward baseline values within 24 to 48 hours postdose

Safety

- There were no Grade ≥3 treatment-emergent AEs (TEAEs), serious AEs, or AEs leading to BLV discontinuation
- The TEAEs were mild (Grade 1 in severity), with no increased severity in participants with severe HI compared with the MCs