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

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Conclusions

- In participants with moderate hepatic impairment, steady-state bulevirtide (BLV) pharmacokinetics (PK) and pharmacodynamics (PD) were not clinically meaningfully impacted compared with matched controls following BLV 2 mg subcutaneous (SC) once-daily (qd) dosing for 6 days
- In participants with severe hepatic impairment, increased steady-state BLV PK exposure (by ~2- to 4-fold) and total bile acid exposure (by ~3.1- to 5.9-fold) were observed compared with matched controls following BLV 2 mg SC qd dosing for 6 days
- BLV was generally safe and well tolerated in all groups

Plain Language Summary

- Bulevirtide is a treatment for adults with hepatitis delta virus infection
- Because bulevirtide can increase levels of bile acids (which are produced in the liver), it is important to know whether bulevirtide increases bile acid levels in people whose livers are impaired
- After receiving bulevirtide 2 mg daily for 6 days, concentrations of bulevirtide and total bile acids were not different in participants with moderate hepatic impairment compared to matched controls but were increased in participants with severe hepatic impairment compared with matched controls

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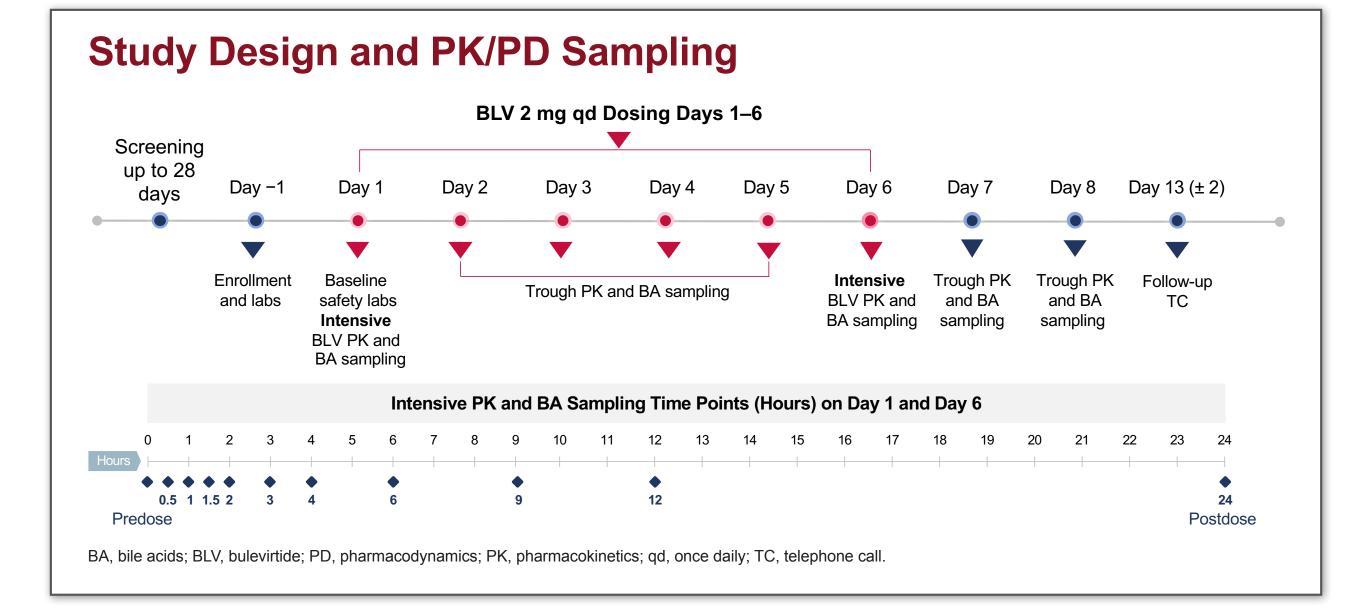
Introduction

- Hepatitis delta virus (HDV) infection is the most severe form of viral hepatitis, affecting as many as 10 to 20 million people globally¹
- 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^{2,3}
- Bulevirtide (BLV) is a novel 47-amino acid, N-terminally myristoylated, hepatitis B virus (HBV) 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 hepatocytes³
- 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 BLV⁶
- There is a need to characterize the pharmacokinetics (PK) and tolerability of BLV in people with impaired hepatic function
- In a population PK modeling analysis, participants with cirrhosis (Child-Turcotte-Pugh [CTP] class A, mild hepatic impairment [HI]) were found to have slightly lower clearance of BLV than participants without cirrhosis, with no clinically relevant impact on BLV exposure⁷

Objectives

- To evaluate the steady-state plasma PK parameters of BLV in participants with moderate or severe HI compared with matched controls
- To evaluate the pharmacodynamic (PD; measured as total BA) effect of BLV on plasma BA in participants with moderate and severe HI compared with matched controls
- To evaluate the safety and tolerability of BLV following multiple-dose administration in participants with moderate and severe HI and in matched controls

Methods



- This was an open-label, multicenter, multiple-dose, parallel-group, Phase 1 study to evaluate the steady-state BLV PK in participants with HI without HBV/HDV infection and matched controls (Figure 1)
- Arm A: n = 20 participants (completers); 10 with moderate HI (CTP class B, CTP score of 7 to 9) and 10 matched controls
- **Arm B:** n = 16 participants (completers); 8 with severe HI (CTP class C, CTP score of 10 to 15) and 8 matched controls
- Matched controls with normal hepatic function were matched for age (± 10 years), sex (assigned at birth), and body mass index (BMI; ± 20%, 18 ≤BMI ≤40 kg/m²) with participants in the HI groups
- All participants received subcutaneous injection of 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
- 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)

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

spectrometry and high-resolution mass spectrometry with a calibration

Figure 2. BLV PK Concentrations

Arm B

Figure 3. Plasma Total BA Concentrations

Population

Arm A, Moderate Hepatic Impairment

Matched Controls — Moderate H

Arm B, Severe Hepatic Impairment

Time Postdose (Hours)

Plasma bile acid determination was achieved using detection by ultra-high-performance liquid chromatography/tandem mass

curve range of 5 ng/mL to 5000 ng/mL.

Results

- 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 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] and maximum concentration $[C_{max}]$) and PD (total BA) parameters (AUC of total BA after baseline [BL] correction [NetAUC], 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 BLV PK and PD parameters in the HI groups vs the matched

Arm B

Results

Table 2. BLV PK Parameters, Moderate Impairment

		Matched Controls				Moderate Hepatic Impairment			
		AUC ₀₋₁₂ (ng·h/mL)	AUC ₀₋₂₄ (ng·h/mL)	C _{max} (ng/mL)	T½² (h)	AUC ₀₋₁₂ (ng·h/mL)	AUC ₀₋₂₄ (ng·h/mL)	C _{max} (ng/mL)	T½ ^a (h)
	n	10	10	11	10	11	11	11	11
Day 1	Geometric mean	48.9	52.2	11.9	2.8	67.0	69.8	19.3	1.9 (1.1–4.7)
•	CV% of mean	21.3	22.7	33.9	(1.7–4.8)	67.8	66.7	64.3	
	n	10	7	10	7	10	9	10	10
Day 6	Geometric mean	113	138	19.0	2.7	101	120	22.2	2.6
•	CV% of mean	49.5	44.5	64.9	(1.9–3.8)	79.9	72.6	80.7	(2.3–5.5)

hours after drug administration; BLV, bulevirtide; C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetics; T_{1/2}, terminal elimination half-life.

Table 3. GLSM Ratio of PK Parameters, Moderate Impairment

GLSM Ratio (90% CI)	AUC _{0–12}	AUC _{0–24}	C _{max}
	(ng·h/mL)	(ng·h/mL)	(ng/mL)
Day 1	1.37	1.34	1.63
	(0.962, 1.96)	(0.944, 1.89)	(1.07, 2.47)
Day 6	0.897	0.872	1.17
	(0.536, 1.50)	(0.494, 1.54)	(0.671, 2.05)

Table 4. PD Parameters of Total BA, Moderate Impairment

		Matched Controls			Modera	ate Hepatic Impa	nirment
		AUC ₀₋₂₄ (μM·h)	NetAUC (μM·h)	C _{max} (µM)	AUC _{0–24} (μM·h)	NetAUC (μM·h)	C _{max} (µM)
	n	10	10	10	9	9	9
Day 1	Geometric mean	157.57	93.93	12.35	273.52	133.23	19.29
_	CV% of mean	90.26	116.77	98.52	132.56	121.48	131.88
	n	9	9	9	9	8	9
Day 6	Geometric mean	909.14	819.90	75.28	1064.16	609.98	74.45
•	CV% of mean	39.28	42.66	49.29	97.75	89.53	94.75

Table 5. GLSM Ratio of PD Parameters for Total BA, **Moderate Impairment**

GLSM Ratio (90% CI)	NetAUC (μM·h)	C _{max} (μΜ)
Day 1	1.42 (0.53, 3.81)	1.56 (0.66, 3.67)
Day 6	0.74 (0.40, 1.39)	0.99 (0.47, 2.06)

Arm A, Moderate Hepatic Impairment

variation; NetAUC, AUC₀₋₂₄ of total BA after baseline correction; PD, pharmacodynamic

- On day 1, BLV PK exposure was 34% to 63% higher among participants with moderate HI compared with matched controls (Figure 2, Table 3)
- On day 6, at steady state, no clinically meaningful difference was observed in BLV PK exposures between the moderate HI group and matched controls
- No difference in elimination half-life was observed between groups (Table 2)

PD (total BA)

- On days 1 and 6, similar BL total BA concentrations and parameters of C_{max} and NetAUC were observed in participants with moderate HI and in matched controls (Table 4, Table 5)
- In both groups, elevations of total BA appeared transient, as BA concentrations returned to near-BL values within 24 hours in both the severe HI group and matched controls (Figure 3)

- One participant in the moderate HI group experienced a Grade 2 adverse event (AE) of neutropenia
- There were no Grade 3 or higher treatment-emergent AEs (TEAEs), no serious AEs (SAEs), no TEAEs leading to premature discontinuation of the study or study drug, and no Grade 3 or higher treatment-emergent lab abnormalities

Table 6. BLV PK Parameters, Severe Impairment

			Matched	Controls		S	evere Hepat	ic Impairmer	nt
		AUC ₀₋₁₂ (ng·h/mL)	AUC ₀₋₂₄ (ng·h/mL)	C _{max} (ng/mL)	T½² (h)	AUC ₀₋₁₂ (ng·h/mL)	AUC ₀₋₂₄ (ng·h/mL)	C _{max} (ng/mL)	T _½ ^a (h)
	n	8	7	8	8	8	8	8	8
Day 1	Geometric mean	45.0	50.4	11.8	3.3	165	169	53.6	1.9
	CV% of mean	16.9	16.0	31.0	(1.9–6.2)	41.5	41.2	42.0	(1.3–3.4)
	n	8	5	8	8	8	8	8	8
Day 6	Geometric mean	85.6	105	14.0	4.8	200	207	56.1	2.2
	CV% of mean	42.9	40.6	43.8	(2.2–9.7)	35.3	33.4	45.0	(1.5–3.5)
/-	as median (minimu a under the plasma	,	ve from time 0 to	12 hours after dru	g administration: A	- \UC₁₋₂₄. area unde	er the plasma cond	entration curve fro	om 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

Table 7. GLSM Ratio of PK Parameters, Severe Impairment

GLSM Ratio (90% CI)	AUC _{0–12}	AUC _{0–24}	C _{max}
	(ng·h/mL)	(ng·h/mL)	(ng/mL)
Day 1	3.66	3.35	4.54
	(2.87, 4.67)	(2.60, 4.32)	(3.27, 6.33)
Day 6	2.34	1.97	4.01
	(1.70, 3.22)	(1.38, 2.81)	(2.71, 5.93)
AUC_{0-12} , area under the plasma concentration hours after drug administration; C_{max} , maximum	<u> </u>	* = ·	

Table 8. PD Parameters of Total BA, Severe Impairment

		, I	Matched Control	s	Severe Hepatic Impairment		
		AUC _{0–24} (μM·h)	NetAUC (μM·h)	C _{max} (µM)	AUC _{0–24} (μM·h)	NetAUC (μM·h)	C _{max} (μ M)
	n	8	8	8	8	8	8
Day 1	Geometric mean	156.73	95.75	12.39	5152.36	1207.07	281.15
-	CV% of mean	42.18	60.29	32.76	50.13	80.39	49.07
	n	8	8	8	8	8	8
Day 6	Geometric mean	593.25	518.32	51.39	5237.09	1587.21	302.64
•	CV% of mean	65.84	71.40	70.89	35.10	59.03	30.83

Table 9. GLSM Ratio of PD Parameters for Total BA, **Severe Impairment**

GLSM Ratio (90% CI)	NetAUC (μM·h)	C _{max} (μ M)
Day 1	12.61 (5.57, 28.51)	22.69 (14.91, 34.53)
Day 6	3.06 (1.65, 5.67)	5.89 (3.70, 9.38)

Arm B, Severe Hepatic Impairment

- On day 1, BLV PK exposure increased by 3.4- to 4.5-fold among participants with severe HI compared with matched controls (Figure 2, Table 7) — On day 6, at steady state, BLV PK exposure increased by about 2- to 4-fold among
- participants with severe HI compared with matched controls — The increased exposure in participants with severe HI was not a result of prolonged BLV elimination half-life (Table 6)

PD (total BA)

- On day 1, the predose total BA concentrations were substantially elevated in participants with severe HI compared with matched controls (Figure 3)
- On day 6, at BLV steady state, BLV treatment in the severe HI group resulted in higher total BA concentrations and increased exposure parameters of C_{max} and NetAUC compared with matched controls (Table 8, Table 9)
- In both groups, elevations of total BA appeared transient, as BA concentrations approximated BL within 24 hours in both the severe HI group and matched controls (Figure 3)

— One participant in the severe HI group experienced a Grade 2 AE of abdominal pain — There were no Grade 3 or higher TEAEs, no SAEs, no TEAEs leading to premature discontinuation of the study or study drug, and no Grade 3 or higher treatmentemergent lab abnormalities