Elevations in Total Serum Bile Acids During Bulevirtide Treatment Are Asymptomatic and Not Associated With Adverse Events of Interest in Patients With Chronic Hepatitis Delta

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Conclusions

- Dose-dependent bile acid (BA) elevations with bulevirtide (BLV) treatment are expected, consistent with its mechanism of action
- In an integrated analysis of 96-week treatment data from almost 200 patients with chronic hepatitis delta virus (HDV) infection, no differences in BA levels were observed in patients with vs without reported adverse events (AEs) of interest, including pruritus, skin disorders, eosinophilia, vitamin D deficiency, and cardiac events
- BA elevations were asymptomatic and without clinical sequelae

Plain Language Summary

- Bulevirtide is a treatment for adults with hepatitis delta virus infection who either have or do not have cirrhosis
- Treatment with bulevirtide may increase the amount of bile acids in the blood
- This work tested whether increased bile acid levels in the blood might cause adverse events
- There was no relationship between bile acid levels and adverse events
- Bile acid levels did not differ between patients with and without cirrhosis

References: **1.** Ni Y, et al. *Gastroenterology.* 2014;146:1070-83. **2.** Li Y, et al. *Front Mol Biosci.* 2022;9:1-12. **3.** de Aguiar Vallim TQ, et al. *Cell Metab.* 2013;17(5):657-69. **4.** Beuers U, et al. *Hepatology.* 2014;60(1):399-407. **5.** Liu R, et al. *Sci Rep.* 2017;7(1):9214. **6.** Yang F, et al. *Front Endocrinol.* 2022;13:896750. **7.** Karpen SJ, Dawson PA. *Hepatology.* 2015;61(1):24-7. **8.** Vaz FM, et al. *Hepatology.* 2015;61(1):260-7. **9.** Zou TT, et al. *Transl Pediatr.* 2021;10(4):1045-54. **10.** Uçmak F, et al. *Clin Exp Hepatol.* 2021;7(2):141-8.

Acknowledgments: We extend our thanks to the patients and their families. This study was funded by Gilead Sciences, Inc. Medical writing and editorial support were provided by Andrey Verendeev, PhD, of Red Nucleus, and were funded by Gilead Sciences, Inc.

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

Introduction

- BLV is a first-in-class entry inhibitor that is approved in the European Union (EU) and in several non-EU countries for the treatment of chronic HDV infection with compensated liver disease at a subcutaneous dose of 2 mg once daily
- BLV binds to the sodium taurocholate cotransporting polypeptide (NTCP) receptor, preventing hepatitis B virus and HDV from entering hepatocytes[1,2]
- NTCP, along with organic anion–transporting polypeptides, is also responsible for BA uptake into hepatocytes[1-3]
- Based on the mechanism of action of BLV, elevations in serum BAs are expected to occur with BLV treatment[2]
- BLV treatment induces isolated, asymptomatic increases in serum BA levels (hypercholanemia), similar to the pattern seen in people with genetic NTCP deficiency
- People with NTCP deficiency typically have normal liver and kidney function without hyperbilirubinemia, pruritus, or jaundice
- BA elevations that occur due to cholestasis are known to be linked to symptoms such as pruritus[4]

Objective

- To evaluate the impact of BA increases with BLV treatment on safety based on data derived from an integrated 96-week analysis of the Phase 2 MYR204 study and the Phase 3 MYR301 study

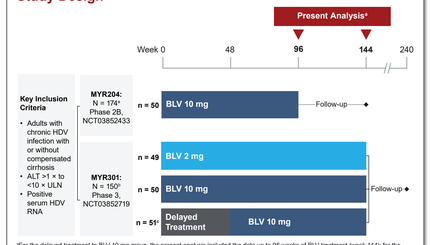
Methods

Identification of AEs of Interest and BA Elevations

- A literature review was conducted to identify symptoms potentially associated with increased BA levels from any etiology, which included the following AEs of interest:
  - Pruritus[5,6]
  - Skin disorders and hypersensitivity responses[5,6]
  - Cardiac events[4,7]
  - Vitamin D deficiency[a,5-9]
  - Eosinophilia

[a]While vitamin D deficiency is not an AE related to BLV treatment, it is known to occur in patients with chronic HDV infection.[10]

Study Design



[a]For the delayed treatment to BLV 10 mg group, the present analysis included the data up to 96 weeks of BLV treatment (week 144); for the other groups, the data up to week 96 were included. [b]Total number of study patients enrolled; only the BLV 2 mg and BLV 10 mg monotherapy arms are included in this pooled analysis; groups treated with PegIFNα monotherapy, or the combination of BLV and PegIFNα, and control arms were not included. [c]The delayed treatment to BLV 10 mg group included 51 patients who did not receive BLV for 48 weeks; 50 of these patients received BLV from week 48 to week 144 and are included in the BLV 10 mg group.
ALT, alanine aminotransferase; BLV, bulevirtide; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa-2a; ULN, upper limit of normal.

- This was an integrated analysis of up to 96 weeks of BLV treatment in 199 patients with HDV who received BLV 2 mg (n = 49) or 10 mg (n = 150) monotherapy once daily in the MYR204 and MYR301 studies
- On-treatment BA levels were compared between patients with and without AEs of interest[b]
  - Blood samples were taken before BLV administration at each visit to determine serum BA levels
  - AEs of interest were recorded at every visit for each patient
- AEs of interest included pruritus, skin disorders, eosinophilia, vitamin D deficiency, and cardiac events
  - Vitamin D deficiency was defined as below the lower limit of normal on laboratory tests at any on-treatment visit

[b]For pruritus, skin disorders, eosinophilia, and cardiac events, BA levels were categorized as "AE yes" or "AE no" based on the presence or absence of these treatment-emergent AEs of interest by week 96.

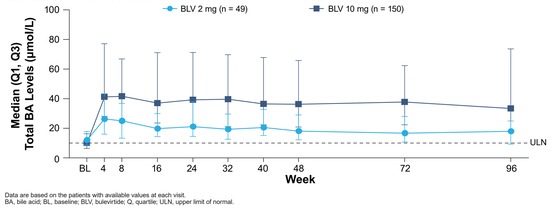
Results

Demographics and Disease Characteristics at Baseline

	BLV 2 mg n = 49	BLV 10 mg n = 150
Age, years, mean (range)	44 (19–62)	41 (18–62)
Sex, male, n (%)	30 (61)	94 (63)
Race, n (%)		
Asian	8 (16)	21 (14)
Black	0	3 (2)
White	41 (84)	126 (84)
BMI, kg/m², mean (SD)	24.4 (3.1)	25.5 (3.8)
BMI ≥30 kg/m², n (%)	1 (2)	18 (12)
Cirrhosis, n (%)	23 (47)	65 (43)
ALT, U/L, mean (SD)	108 (62.5)	108 (84.8)
HDV RNA, log_{10} IU/mL, mean (SD)	5.1 (1.2)	5.2 (1.4)
HBsAg, log_{10} IU/mL, median (Q1, Q3)	3.8 (3.5, 4.0)	3.8 (3.5, 4.0)
BAs, µmol/L, median (Q1, Q3)	12.2 (8.6, 17.8)	10.1 (6.5, 16.3)
BAs >ULN, n (%)	31 (65)[a]	75 (50)[a]

[a]Excludes 1 patient with no BA values at baseline.
ALT, alanine aminotransferase; BA, bile acid; BLV, bulevirtide; BMI, body mass index; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; Q, quartile; ULN, upper limit of normal.

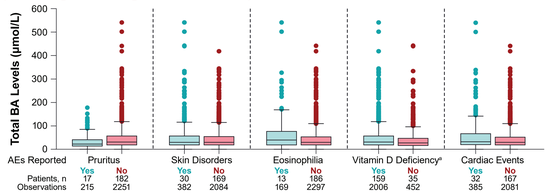
BA Levels Over 96 Weeks of Treatment



Data are based on the patients with available values at each visit.
BA, bile acid; BL, baseline; BLV, bulevirtide; Q, quartile; ULN, upper limit of normal.

- At week 96, the changes from baseline in median (quartile [Q]1, Q3) BA levels were 3.1 (−2.8, 10.7) and 19.9 (7.3, 56.5) µmol/L for the BLV 2 and 10 mg groups, respectively
- Median BA levels increased in a dose-dependent manner and remained stable throughout 96 weeks
  - At baseline, 65% of patients in the BLV 2 mg group and 50% of patients in the BLV 10 mg group had BA levels greater than the upper limit of normal
- BA levels were rapidly reversible after treatment cessation (data not shown)

On-Treatment BA Levels in Patients With and Without AEs of Interest by Week 96 (BLV 2 mg and 10 mg Arms Combined)



The box plots display each IQR as a box, with the horizontal line showing the median; the whiskers extend to 1.5 × IQR; all other observed data points outside the boundary of the whiskers are plotted as outliers.
[a]Vitamin D deficiency was defined as a vitamin D level <LLN at any on-treatment visit up to week 96.
AE, adverse event; BA, bile acid; BLV, bulevirtide; LLN, lower limit of normal.

- While pruritus and eosinophilia are known effects of BLV treatment, neither AE appeared to be related to elevated BA levels
- BA levels were similar among patients with and without skin disorders, vitamin D deficiency, or cardiac events

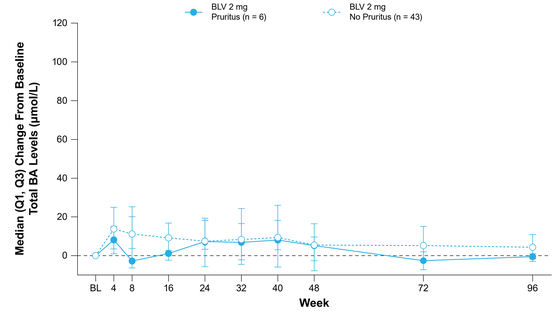
BA Levels and Pruritus

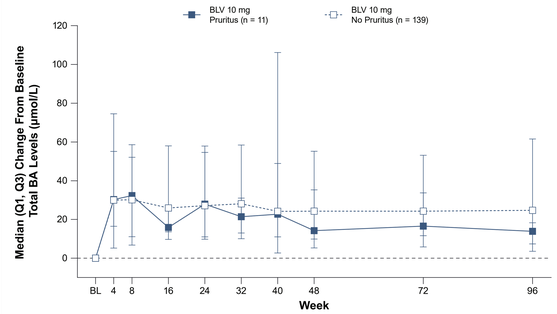
	BLV 2 mg n = 49	BLV 10 mg n = 150
Pruritus, n (%)	6 (12)	11 (7)
BA levels, µmol/L, median (Q1, Q3)[a]	11.3 (10.4, 11.8)	23.5 (17.1, 28.8)
Number of AEs[b]	7	21
Serious AE	0	0
Grade ≥3	0	0
Leading to D/C	0	0
Time to onset, days, median (range)	42 (11–305)	31 (1–586)
Duration, days, median (range)	119 (1–325)	49 (1–652)
Events resolved, n/N (%)	7/7 (100)	20/21 (95)

[a]BA levels at week 96 in patients with pruritus. [b]Number of any TEAEs of pruritus.
AE, adverse event; BA, bile acid; BLV, bulevirtide; D/C, discontinuation; Q, quartile; TEAE, treatment-emergent AE.

- While BA levels were notably higher in the BLV 10 mg group, the occurrence of pruritus with BLV treatment was not dose dependent

Median Change in BA Levels Over Time in Patients With and Without Pruritus

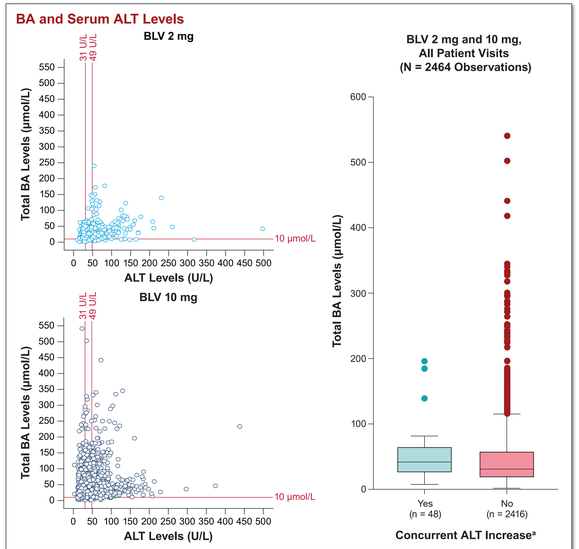




Data are based on the patients with available values at each visit.
BA, bile acid; BL, baseline; BLV, bulevirtide; Q, quartile.

- Although pruritus has been observed with BLV treatment, it does not appear to be associated with bile acid levels

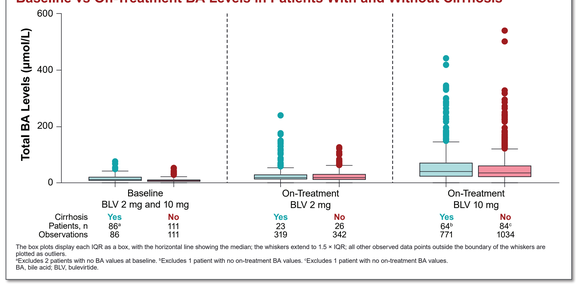
BA and Serum ALT Levels



Data points in the left panels indicate individual observations of total BA levels at all on-treatment visits for that treatment group. The box plots display each IQR as a box, with the horizontal line showing the median; the whiskers extend to the smallest and largest values within 1.5 × IQR from the quartiles; all other observed data points outside the boundary of the whiskers are plotted as outliers.
[a]Concurrent ALT increases were defined as the visits with ALT ≥3 × ULN and greater than baseline.
ALT, alanine aminotransferase; BA, bile acid; BLV, bulevirtide; ULN, upper limit of normal.

- Alanine aminotransferase (ALT) on-treatment levels did not correlate with BA levels: median (Q1, Q3) on-treatment BA levels were 42.3 (26.5, 64.6) and 31.4 (18.4, 57.5) µmol/L at visits with and without concurrent ALT increases, respectively

Baseline vs On-Treatment BA Levels in Patients With and Without Cirrhosis



The box plots display each IQR as a box, with the horizontal line showing the median; the whiskers extend to 1.5 × IQR; all other observed data points outside the boundary of the whiskers are plotted as outliers.
[a]Excludes 2 patients with no BA values at baseline. [b]Excludes 1 patient with no on-treatment BA values. [c]Excludes 1 patient with no on-treatment BA values.
BA, bile acid; BLV, bulevirtide.

- Overall, 88 of 199 (44%) patients had compensated cirrhosis (Child-Turcotte-Pugh score 5–6)
- Total BA concentrations did not differ based on cirrhosis status: median (Q1, Q3) on-treatment BA levels were 31.7 (18.4, 62.9) and 31.5 (18.5, 53.5) µmol/L in patients with and without cirrhosis, respectively