Safety of Bulevirtide 10 mg Is Consistent Across Demographic and Clinical Subgroups: Results From an Integrated Analysis

WED-576

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Viral Hepatitis B and D: New Therapies, Unapproved Therapies or Strategies

Conclusions

- Long-term treatment with bulevirtide (BLV) 10 mg monotherapy was safe and well tolerated, with most treatment-emergent adverse events (AEs) being mild to moderate in severity
- The incidence of Grade ≥3 AEs and serious AEs was low and comparable across all patient subgroups, which included age, sex, race, body mass index, cirrhosis status, concomitant hepatitis B virus treatment status, alanine aminotransferase levels, and renal function
  - Safety outcomes were similar in patients with and without cirrhosis
  - Elevations in bile salt levels with BLV monotherapy were similar regardless of cirrhosis status and were not associated with an increased risk of AEs
- These findings support the safety of long-term BLV 10 mg treatment in people with hepatitis delta virus and compensated liver disease

Plain Language Summary

- Hepatitis delta virus is a serious liver infection that causes more liver damage than other hepatitis viruses
- Bulevirtide is a treatment for chronic hepatitis delta virus infection in adults with functioning livers without symptoms (compensated liver disease)
- This analysis evaluated the safety profile across patient subgroups after 96 weeks of treatment with bulevirtide 10 mg
- Overall, long-term treatment with bulevirtide was safe and well tolerated; the safety profiles were similar for all patient subgroups in the studies

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Introduction

- Hepatitis delta virus (HDV) causes the most severe form of chronic viral hepatitis[1] and is estimated to affect approximately 12 million people worldwide[2,3]
- Bulevirtide (BLV), a first-in-class entry inhibitor of HDV, is approved in the United States, the European Economic Area, and several other countries for the treatment of patients with chronic hepatitis delta infection with compensated liver disease[4–6]
- BLV monotherapy at doses of 2 mg and 10 mg were shown to be safe and well tolerated over 2 to 3 years of treatment in the MYR204 and MYR301 studies[7–10]
- Long-term safety data with BLV 10 mg have been evaluated to better characterise the safety of BLV at this higher dose

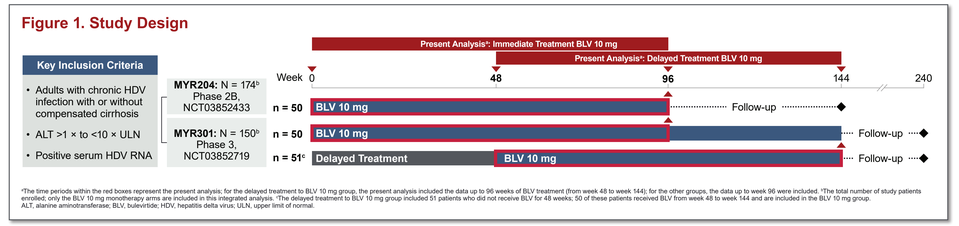
Objective

- To evaluate the safety of BLV 10 mg monotherapy across patient subgroups in an integrated analysis through 96 weeks of treatment from the MYR204 and MYR301 studies

Methods

- This integrated analysis included patients with HDV who received BLV 10 mg (approved as 8.5 mg delivered dose in the United States) once daily across 2 randomised clinical studies: MYR204 (NCT03852433) and MYR301 (NCT03852719; **Figure 1**)
- Safety assessments included laboratory parameters, adverse events (AEs), Grade ≥3 AEs, serious AEs (SAEs), and AEs considered related to BLV
  - AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 27.1
- Safety parameters were analysed across baseline demographic and clinical subgroups:
  - Age (<45, ≥45 years)
  - Sex (male, female)
  - Race (White, other)
  - Body mass index (<25 kg/m^2, ≥25 kg/m^2)
  - Cirrhosis status (presence, absence)
  - Concomitant hepatitis B virus treatment (yes, no)
  - Alanine aminotransferase levels (≤1.5 × upper limit of normal [ULN], >1.5 × ULN)
  - Renal function (≥60 to <90 mL/min [Cockroft-Gault; mild renal impairment], ≥90 mL/min [normal renal function])

Figure 1. Study Design



[a]The time periods within the red boxes represent the present analysis; for the delayed treatment to BLV 10 mg group, the present analysis included the data up to 96 weeks of BLV treatment (from week 48 to week 144); for the other groups, the data up to week 96 were included. [b]The total number of study patients enrolled; only the BLV 10 mg monotherapy arms are included in this integrated analysis. [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; ULN, upper limit of normal.

Results

- Demographics and baseline disease characteristics are shown in **Table 1**

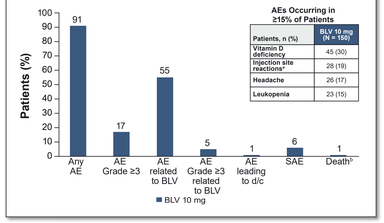
Table 1. Demographics and Baseline Disease Characteristics

	BLV 10 mg (N = 150)
Age, years, mean (SD)	41 (8.2)
Male sex, n (%)	94 (63)
Race, n (%)	
White	126 (84)
Asian	21 (14)
Black	3 (2)
Body mass index, kg/m^2, mean (SD)	25.5 (3.83)
Cirrhosis present, n (%)	65 (43)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.2 (1.40)
HDV genotype 1, n (%)	147 (98)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	1.2 (1.38)
ALT, U/L, median (Q1, Q3)	86 (57, 128)
ALT category, n (%)	
≤1.5 × ULN	41 (27)
>1.5 × ULN	109 (73)
Creatinine clearance, mL/min (Cockcroft-Gault), mean (SD)	119.4 (28.32)
Bile salts, µmol/L, median (Q1, Q3)	10.1 (6.5, 16.3)
Concomitant HBV NA treatment,[a] n (%)	83 (55)
Prior IFN therapy, n (%)	79 (53)

[a]Concomitant NA treatment included concomitant medications with preferred names containing tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, tenofovir disoproxil, emtricitabine, adefovir, lamivudine, telbivudine, or adefovir dipivoxil.
ALT, alanine aminotransferase; BLV, bulevirtide; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; NA,nucleos(t)ide analogue; Q, quartile; ULN, upper limit of normal.

- Most AEs were mild to moderate in severity, and only 1 patient discontinued the study due to an AE (myalgia [nonserious]); no discontinuations were due to injection site reactions (**Figure 2**)
- SAEs were infrequent, and none were considered related to BLV
- Overall, the most common AEs were vitamin D deficiency (30%), injection site reactions (19%), headache (17%), and leukopenia (15%)
  - Vitamin D deficiency and cytopenias are common in patients with underlying chronic hepatitis delta and occurred at similar or lower frequencies in the BLV 10 mg group vs the delayed treatment group at week 48
    - AEs of Vitamin D deficiency at week 48 occurred in 17% and 25% of patients in the BLV 10 mg and delayed treatment groups, respectively
    - Median (Q1, Q3) change from baseline to week 48 in the percentage of patients with vitamin D deficiency was +2.00 (−4.00, 8.00) in the BLV 10 mg group and 0.00 (−5.00, 4.90) in the delayed treatment group

Figure 2. Overall Summary of AEs at Week 96



All categories are MedDRA preferred terms.
[a]Grouped term based on the high-level term "injection site reactions." [b]One death occurred due to plasma cell myeloma and was not related to BLV. [c]Consisted of 21 Asian patients and 3 Black patients.
AE, adverse event; ALT, alanine aminotransferase; BLV, bulevirtide; BMI, body mass index; CrCl, creatinine clearance; d/c, discontinuation; HBV, hepatitis B virus; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; ULN, upper limit of normal.

- In general, the safety profile of BLV and the frequency of AEs remained consistent across all analysed subgroups (**Figures 3–10**)
- Numerically higher incidence of SAEs was seen in the subgroup of patients ≥45 years of age, with 4/7 (57%) of these related to COVID-19 and none related to BLV (**Figure 3**)
  - This is consistent with the literature demonstrating a higher background rate of SAEs, including those of COVID-19, in this subgroup[11,12]

Figure 3. AEs at Week 96 by Age

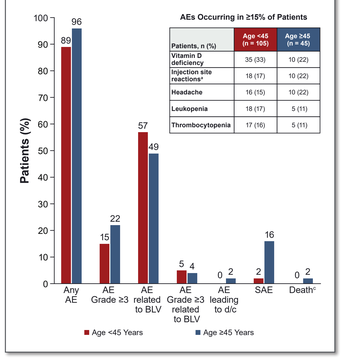


Figure 4. AEs at Week 96 by Sex at Birth

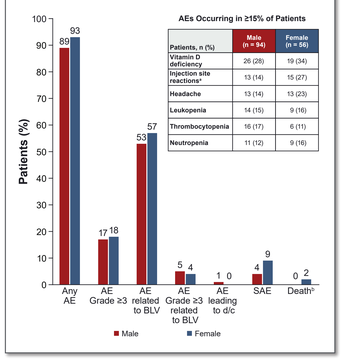


Figure 5. AEs at Week 96 by Race

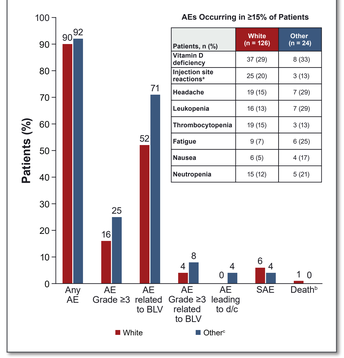
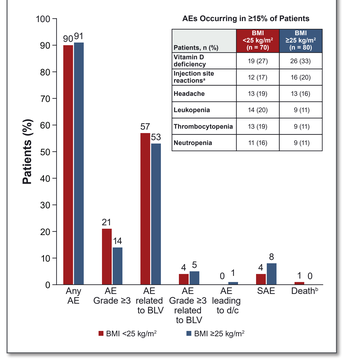


Figure 6. AEs at Week 96 by BMI



- Patients with cirrhosis at baseline had a numerically higher incidence of Grade ≥3 AEs; this was largely due to blood cytopenias, which commonly occur in people with cirrhosis (**Figure 7**)[13]
  - Among patients with cirrhosis with AEs of any grade, the prevalence of thrombocytopenia (26%), leukopenia (22%), neutropenia (18%), and lymphopenia (18%) was higher in those with cirrhosis, likely due to underlying liver disease
  - One patient with cirrhosis at baseline had an on-treatment liver-related AE (Grade 1 ascites)

Figure 7. AEs at Week 96 by Cirrhosis Status

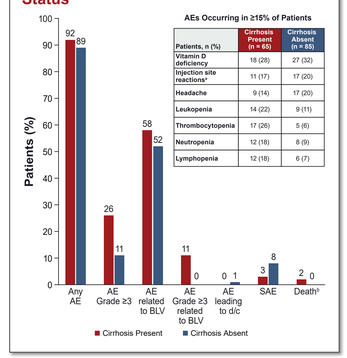
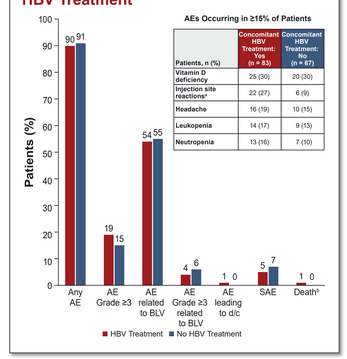


Figure 8. AEs at Week 96 by Concomitant HBV Treatment



- Despite numerically higher baseline bile salt concentrations in patients with cirrhosis, on-treatment bile salt elevations were similar in patients with and without cirrhosis (**Figure 11**)
  - Median (quartile [Q]1, Q3) on-treatment bile salt levels were 31.7 (18.4, 62.9) and 31.5 (18.5, 53.5) µmol/L in patients with and without cirrhosis, respectively
- Bile salt elevations observed with BLV treatment are expected due to the mechanism of action (sodium taurocholate cotransporting polypeptide [NTCP] blockade) and have been demonstrated to be asymptomatic and not associated with clinical sequelae[14]

Figure 9. AEs at Week 96 by Baseline ALT Level

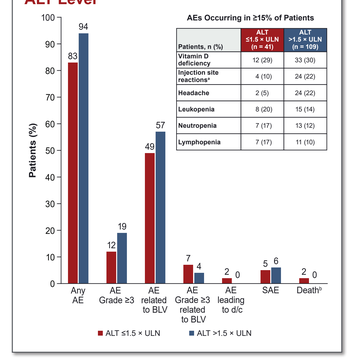


Figure 10. AEs at Week 96 by Renal Function

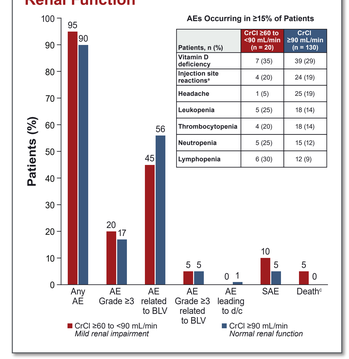
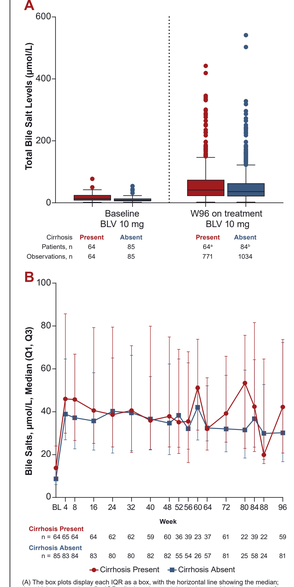


Figure 11. Baseline vs On-Treatment Bile Salt Levels (A) and Bile Salt Levels Over Time (B) in Patients With and Without Cirrhosis



(A) 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. (B) Only the common visits among treatment groups, including the MYR301 delayed treatment to BLV 10 mg group, are shown.
*Excludes 2 patients with no bile salt values at BL. [b]Excludes 1 patient with no W96 bile salt values.
BL, baseline; BLV, bulevirtide; IQR, interquartile range; Q, quartile; W, week.

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