Influence of Nucleos(t)ide Analogue Use With Bulevirtide on Treatment Outcomes in Chronic Hepatitis Delta

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Conclusions

- Long-term monotherapy with bulevirtide (BLV) leads to sustained hepatitis delta virus (HDV) virologic response and alanine aminotransferase (ALT) normalization in patients with chronic hepatitis delta (CHD)
- Concomitant nucleos(t)ide analogue (NA) therapy did not impact HDV RNA or ALT responses during long-term BLV monotherapy or in the control group
- Patients receiving BLV with NA therapy showed greater reductions in hepatitis B virus (HBV) DNA levels compared with those who did not receive NAs

Plain Language Summary

- Patients with chronic hepatitis delta virus infection received bulevirtide 2 or 10 mg or no hepatitis delta virus treatment and were grouped by those who did or did not also receive nucleos(t)ide analogue therapy
- Treatment with bulevirtide improved alanine aminotransferase levels and virologic responses; the addition of nucleos(t)ide analogue treatment did not lead to further improvements
- Levels of hepatitis B virus DNA decreased more in patients who received bulevirtide with nucleos(t)ide analogues

References: **1.** Wedemeyer H, et al. *N Engl J Med.* 2023;389:22-32. **2.** Stockdale AJ, et al. *J Hepatol.* 2020;73:523-32. **3.** Hepcludex (bulevirtide). European Medicines Agency. Gilead Sciences, Inc.; 2023. **4.** Hepcludex (bulevirtide acetate). Australian Register of Therapeutic Goods. Gilead Sciences, Inc.; 2024. **5.** Wedemeyer H, et al. *J Hepatol.* 2024;81:621-9. **6.** Lampertico P, et al. Presented at: European Association for the Study of the Liver; June 5–8, 2024. Presentation LBP-029. **7.** Wedemeyer H, et al. Presented at: European Association for the Study of the Liver; May 7–10, 2025. Presentation OS-066. **8.** Terrault N, et al. *Hepatology.* 2018;67(4):1560-99. **9.** European Association for the Study of the Liver. *J Hepatol.* 2023;79:433-60.

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Introduction

- HDV is an incomplete RNA virus that occurs only in the presence of HBV[1]
- HDV causes the most severe form of chronic viral hepatitis and is estimated to affect between 10 and 20 million people worldwide[2]
- BLV, an entry inhibitor of HDV, is approved in the European Economic Area, the United Kingdom, Switzerland, the Russian Federation, Canada, and Australia at 2 mg/day for the treatment of CHD with compensated liver disease[3,4]
- In the Phase 3 MYR301 study, patients with CHD were randomized to receive BLV (2 or 10 mg) and demonstrated combined virologic and biochemical responses during treatment lasting up to 144 weeks[5–7]
- While NAs such as tenofovir disoproxil fumarate, tenofovir alafenamide, and entecavir are the first-line treatment for chronic HBV infection, NAs have not been effective in reducing HDV RNA levels in patients with CHD[8,9]
- Recent HBV/HDV treatment guidelines recommend NAs for patients with CHD who have HBV DNA levels >2000 IU/mL or when prevention of HBV infection is clinically mandated[9]

Objective

- This retrospective analysis evaluated the impact of NA therapy on virologic outcomes and ALT normalization in patients with CHD who received long-term BLV treatment

Methods

- A pooled analysis of data from the following 2 randomized clinical trials was performed: MYR204 (NCT03852433) and MYR301 (NCT03852719)
  - Data from BLV 2 mg (MYR301) and 10 mg (pooled MYR301 and MYR204) treatment arms were included
    - Data through 96 weeks were included in this analysis
  - Data from a delayed treatment (DT) arm with no BLV treatment for 48 weeks (MYR301) were included
- Key inclusion criteria:
  - CHD with detectable serum HDV RNA
  - Child-Turcotte-Pugh score ≤6 (MYR204) or ≤7 (MYR301)
  - ALT >1 to <10 × the upper limit of normal
  - No interferon within 6 months before baseline (BL)
- Concomitant NA therapy[a] was allowed at the discretion of the investigator based on AASLD and EASL guidelines for HBV treatments[8,9]
- HDV RNA levels were determined by RT-qPCR using RoboGene HDV RNA Quantification Kit 2.0; HBV DNA levels were determined by the Abbott RealTime HBV Viral Load Assay on an Abbott m2000 RealTime System (Abbott Diagnostics); hepatitis B surface antigen (HBsAg) levels were determined using the ARCHITECT HBsAg Next Qualitative Assay (Abbott Diagnostics)
- This analysis focused on the impact of NA therapy on the following:
  - HDV outcomes, including
    - Virologic response (undetectable HDV RNA or a ≥2 log_{10} IU/mL decline in HDV RNA from BL)
      - Undetectable HDV RNA: less than the lower limit of quantification (LLOQ; 50 IU/mL) with target not detected
    - ALT normalization
      - ALT ≤31 U/L for females and ≤41 U/L for males at Russian sites and ≤34 U/L for females and ≤49 U/L for males at all other sites
    - Change from BL in ALT levels
    - Combined response (defined as virologic response with ALT normalization)
  - HBV outcomes, including
    - HBV DNA <LLOQ (10 IU/mL)
    - Change in HBV DNA levels from BL in patients with HBV DNA ≥LLOQ at BL
  - Change from BL in liver stiffness measurement

[a]Concomitant HBV treatment included concomitant medications received by week 96 (week 48 for the control [DT] group) with preferred names containing terms of tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, tenofovir disoproxil, entecavir, adefovir, lamivudine, telbivudine, and adefovir dipivoxil.

Results

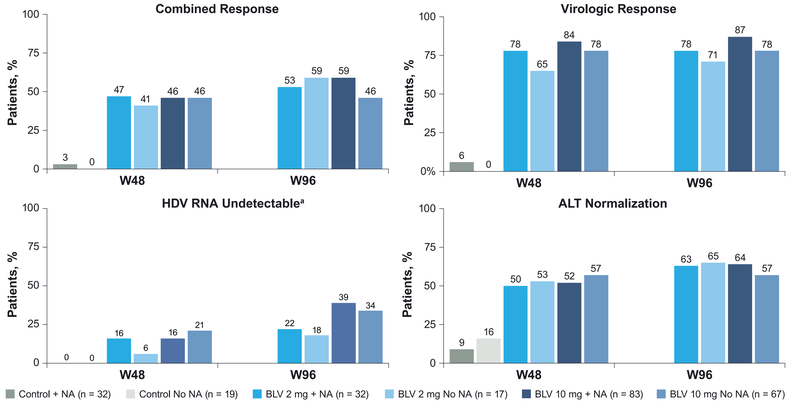
Demographics and BL Disease Characteristics in Patients With and Without Concomitant NA Therapy[a] (BLV Treated + Control)

	BLV 2 mg n = 49		BLV 10 mg n = 150		Control (DT/No BLV)[b] n = 51		Total Cohort[c] N = 199	
	NA n = 32	No NA n = 17	NA n = 83	No NA n = 67	NA n = 32	No NA n = 19	NA n = 115	No NA n = 84
Age, years, mean (SD)	45 (8.9)	41 (9.1)	41 (8.9)	41 (7.2)	42 (7.4)	38 (7.1)	42 (9.0)	41 (7.6)
Male sex, n (%)	21 (66)	9 (53)	50 (60)	44 (66)	15 (47)	11 (58)	71 (62)	53 (63)
Race, n (%)								
White	26 (81)	15 (88)	65 (78)	61 (91)	25 (78)	15 (79)	91 (79)	76 (91)
Asian	6 (19)	2 (12)	15 (18)	6 (9)	7 (22)	4 (21)	21 (18)	8 (10)
Black or African American	0	0	3 (4)	0	0	0	3 (3)	0
Cirrhosis present, n (%)	19 (59)	4 (24)	43 (52)	22 (33)	18 (56)	6 (32)	62 (54)	26 (31)
HBeAg positive, n (%)	4 (13)	0	16 (19)	2 (3)	3 (9)	1 (5)	20 (17)	2 (2)
Prior IFN therapy, n (%)	18 (56)	8 (47)	53 (64)	26 (39)	23 (72)	6 (32)	71 (62)	34 (40)
Genotype HDV-1,[d] n (%)	32 (100)	17 (100)	80 (96)	67 (100)	32 (100)	19 (100)	112 (97)	84 (100)
HBV DNA, log_{10} IU/mL, mean (SD)	1.4 (1.45)	1.2 (0.89)	1.1 (1.58)	1.4 (1.06)	0.7 (0.81)	1.2 (1.17)	1.2 (1.55)	1.4 (1.02)
HDV RNA, log_{10} IU/mL, mean (SD)	5.0 (1.22)	5.3 (1.16)	5.2 (1.35)	5.1 (1.45)	5.2 (1.42)	4.9 (1.28)	5.2 (1.32)	5.1 (1.39)
HBsAg, log_{10} IU/mL, mean (SD)	3.8 (0.46)	3.5 (0.59)	3.7 (0.54)	3.6 (0.69)	3.6 (0.49)	3.8 (0.40)	3.7 (0.52)	3.6 (0.67)
ALT, U/L, mean (SD)	113 (71)	99 (42)	106 (69)	109 (101)	111 (66)	86 (53)	108 (70)	107 (92)
LSM, kPa, mean (SD)	14.8 (8.31)	12.4 (7.96)	15.1 (10.48)	13.9 (8.23)	15.5 (8.68)	14.8 (9.62)	15.0 (9.89)	13.6 (8.15)

The BL value was the last available value collected on or prior to the first dose of study drug. For patients in the control group (MYR301 DT group), the BL value was the last available value collected on or prior to the date of randomization.
[a]Concomitant NA treatment included concomitant medications received by W96 (W48 for the DT group) with preferred names containing terms of tenofovir, tenofovir alafenamide, tenofovir disoproxil fumarate, tenofovir disoproxil, entecavir, adefovir, lamivudine, telbivudine, and adefovir dipivoxil. [b]The DT group included 51 patients who did not receive BLV for 48 weeks; 50 of these patients received BLV from W48 to W144 and are included in the BLV 10 mg group. [c]Total cohort includes patients from the BLV 2 mg + BLV 10 mg groups. [d]BLV 10 mg + NA group: HDV-5, n = 2; missing, n = 1.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; DT, delayed treatment; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; LSM, liver stiffness measurement; NA, nucleos(t)ide analogue; W, week.

- Overall, NAs were used in 115/199 (58%) patients
  - Of these, 84% (97/115) received tenofovir-based NA therapy
- BL characteristics were similar in patients with and without concomitant NAs, except for mean liver stiffness and the proportions of patients with cirrhosis, HBeAg-positive status, and prior interferon use, which were higher in those with NAs (15.0 kPa; 54%; 17%; 62%) than without NAs (13.6 kPa; 31%; 2%; 40%)

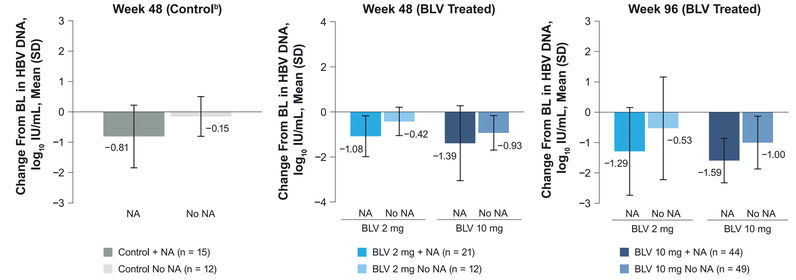
HDV RNA and ALT Responses by NA Therapy



The control (DT) group included 51 patients who did not receive BLV for 48 weeks; 50 of these patients received BLV 10 mg from W48 to W144 and are included in the 10 mg group.
[a]Undetectable HDV RNA is defined as HDV RNA <LLOQ, target not detected.
ALT, alanine aminotransferase; BLV, bulevirtide; DT, delayed treatment; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; NA, nucleos(t)ide analogue; W, week.

- Concomitant NA therapy did not have a substantial impact on HDV virologic response or ALT normalization in BLV-treated patients or in the control group

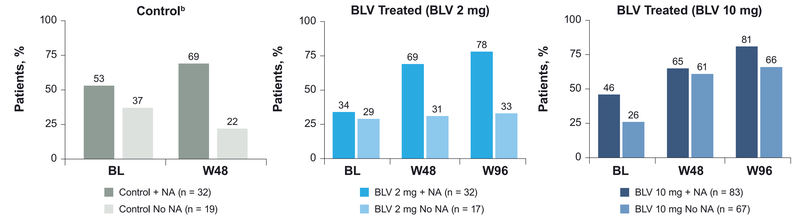
Mean HBV DNA Change From BL by NA Therapy[a]



Numbers were based on available values at specific visits.
[a]Change in HBV DNA from BL was evaluated only in patients with HBV DNA ≥LLOQ at BL. [b]The control (DT) group included 51 patients who did not receive BLV for 48 weeks; 50 of these patients received BLV 10 mg from W48 to W144 and are included in the 10 mg group.
BL, baseline; BLV, bulevirtide; DT, delayed treatment; HBV, hepatitis B virus; LLOQ, lower limit of quantitation; NA, nucleos(t)ide analogue; W, week.

- HBV DNA levels declined in all subgroups with or without NAs, except in the control group that did not receive NAs
- Declines in HBV DNA levels were greater in patients who received BLV with vs without NA therapy

HBV DNA <LLOQ by NA Therapy[a]



[a]n values shown in bar legends represent treatment group size at BL. [b]For the control group (DT), the BL value was the last available collected on or prior to the date of randomization; this group included 51 patients who did not receive BLV for 48 weeks.
BL, baseline; BLV, bulevirtide; DT, delayed treatment; HBV, hepatitis B virus; LLOQ, lower limit of quantitation; NA, nucleos(t)ide analogue; W, week.

- Rates of HBV DNA <LLOQ increased from BL to week 96 in all patients who received BLV; patients who received BLV 10 mg + NA therapy had the highest rate of HBV DNA <LLOQ of any subgroup across all timepoints
- In the control group, rates of HBV DNA <LLOQ declined from BL to week 48 in patients who did not receive NAs

Change from BL to W48 and W96 in ALT and LSM, by NA Therapy

	BLV 2 mg + NA (n = 32)	BLV 2 mg No NA (n = 17)	BLV 10 mg + NA (n = 83)	BLV 10 mg No NA (n = 67)	Control[a] + NA (n = 32)	Control[a] No NA (n = 19)
Week 48						
Change from BL in ALT, U/L, mean (SD)	−67 (69.9)	−53 (44.4)	−66 (71.6)	−67 (102.4)	−20 (50.2)	−19 (37.8)
Change from BL in LSM, kPa, mean (SD)	−2.73 (5.87)	−3.29 (5.38)	−3.39 (4.48)	−3.50 (4.81)	1.10 (8.93)	0.09 (4.26)
Week 96						
Change from BL in ALT, U/L, mean (SD)	−54 (100.1)	−57 (58.9)	−69 (68.7)	−69 (103.4)	–	–
Change from BL in LSM, kPa, mean (SD)	−3.60 (6.58)	−4.54 (5.37)	−4.37 (6.28)	−4.20 (4.60)	–	–

Numbers were based on available values at specific visits.
[a]The control (DT) group included 51 patients who did not receive BLV for 48 weeks; 50 of these patients received BLV 10 mg from W48 to W144 and are included in the 10 mg group. Change from BL for these 50 patients was reset at W48 in the BLV 10 mg group.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; DT, delayed treatment; LSM, liver stiffness measurement; NA, nucleos(t)ide analogue; W, week.

- Mean ALT levels and liver stiffness improved from BL through 96 weeks of treatment with BLV
- Concomitant NA therapy had no impact on ALT levels or liver stiffness in the BLV or control groups