Similar Rates of Biochemical Response Are Observed Across Virologic Response Categories Over 96 Weeks of Bulevirtide Monotherapy in Patients With Chronic Hepatitis Delta

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Conclusions

- Treatment of chronic hepatitis delta with bulevirtide monotherapy for 96 weeks improved alanine aminotransferase (ALT) in nearly all patients, with 83% achieving levels ≤1.5 × upper limit of normal (ULN), and 64% within the ULN
- Rates of ALT normalization, or improvement to ≤1.5 × ULN, were similar across most subgroups with differing levels of hepatitis delta virus (HDV) RNA response but were lower in virologic nonresponders (<1 $\log_{10}$ IU/mL decline in HDV RNA viral load excluding undetectable)
- Patients who were virologic nonresponders had higher baseline ALT levels, which may explain lower rates of ALT normalization despite the highest mean HDV RNA declines observed in this subgroup

Plain Language Summary

- Hepatitis delta virus infection causes severe liver disease and liver-related events
- Bulevirtide is a treatment for people with chronic hepatitis delta infection
- Levels of alanine aminotransferase, an important liver enzyme, increase in people who have viral hepatitis and advanced liver disease; treatment helps normalize those levels
- With bulevirtide treatment, alanine aminotransferase levels decreased in most patients over time

References: **1.** Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. **2.** Hepcludex. Summary of product characteristics. European Medicines Agency. Accessed October 11, 2024. **3.** Wedemeyer H, et al. *N Engl J Med*. 2023;389:22-32. **4.** Wedemeyer H, et al. *J Hepatol*. 2024;81:621-9. **5.** Lampertico P, et al. Presented at: European Association for the Study of the Liver; June 5–8, 2024. Presentation #LBP-029. **6.** Dietz-Fricke C, et al. *JHEP Rep*. 2023;5(4):100686. **7.** Asselah T, et al. *N Engl J Med*. 2024;391(2):133-43. **8.** Lampertico P, et al. Presented at: AASLD: The Liver Meeting; November 10–14, 2023. Presentation #63.

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Introduction

- Hepatitis delta virus (HDV) represents the most severe form of chronic viral hepatitis and is estimated to affect between 10 and 20 million people worldwide[1]
- Bulevirtide (BLV), a novel entry inhibitor of HDV, is approved in the EU, Great Britain, Switzerland, the Russian Federation, and Australia at 2 mg/day for the treatment of chronic hepatitis delta (CHD) with compensated liver disease[2]
- BLV 2 and 10 mg have demonstrated combined virologic and biochemical responses over 96 weeks (W) of treatment in patients with CHD[3-5]
- While both HDV RNA response and biochemical improvement are important surrogate endpoints in treatment of CHD, their relationship as outcomes of treatment with BLV is not fully characterized
  - BLV works by blocking HDV entry into cells and reduces hepatocyte inflammation, which may occur prior to substantial reductions in HDV RNA levels[6]
- Over a 48W treatment period, biochemical improvement was observed in most patients with CHD treated with BLV monotherapy[7,8]; the present analysis sought to examine whether biochemical improvement continued when treatment was extended to 96W

Objectives

- To characterize the relationship between varying degrees of HDV RNA response and biochemical improvement through 96W of treatment with BLV
- To identify patient-level trends in alanine aminotransferase (ALT) improvement in patients who achieved HDV RNA undetectability but did not have ALT normalization through 96W of treatment
- To characterize ALT improvement for patients with virologic response, partial response, and nonresponse

Methods

- A pooled analysis was conducted using data from patients with CHD treated with BLV monotherapy (2 or 10 mg/day) for 96W in the Phase 2 MYR204 (NCT03852433)[5] or the Phase 3 MYR301 (NCT03852719) study[3,4]
- Key eligibility criteria included positive HDV RNA and ALT between 1 and 10 × the upper limit of normal (ULN)
  - Patients with decompensated liver disease were excluded
- The analysis evaluated rates of biochemical improvement in patient subgroups with varying degrees of HDV RNA response both at W96 and by visit while on treatment; the following response thresholds were analyzed:
  - Virologic response: undetectable HDV RNA[a] or a ≥2 $\log_{10}$ IU/mL decline in HDV RNA from baseline (BL)
  - Additional HDV RNA response thresholds were evaluated, including
    - Undetectable HDV RNA[a]
    - HDV RNA <1000 IU/mL
    - HDV RNA <5000 IU/mL
    - HDV RNA <10,000 IU/mL
    - ≥2 $\log_{10}$ IU/mL decline from BL in HDV RNA
    - ≥1 $\log_{10}$ IU/mL decline from BL in HDV RNA
  - The following categories for biochemical improvement were evaluated:
    - Biochemical response: ALT ≤ULN[b]
    - ALT ≤1.5 × ULN
    - ALT >1.5 to ≤3 × ULN
    - ALT >3 × ULN
- An additional analysis characterized patient-level ALT trends among patients who did not achieve ALT normalization despite achieving HDV RNA undetectability[a]
- HDV RNA levels were determined by RT-qPCR using RoboGene HDV RNA Quantification Kit 2.0

[a]Undetectable HDV RNA: less than the lower limit of quantitation (50 IU/mL) with target not detected, limit of detection = 6 IU/mL.
[b]ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russian sites) and ≤34 U/L for females and ≤49 U/L for males (all other sites).

Results

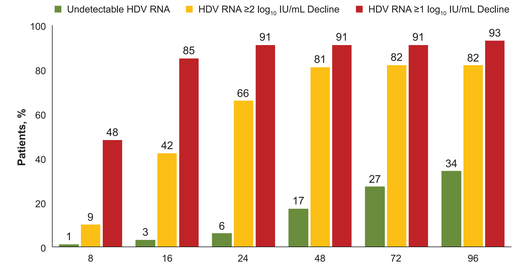
Demographics and Baseline Characteristics by Treatment Group

	BLV 2 mg (n = 47)	BLV 10 mg (n = 143)	Total BLV 2 + 10 mg (N = 190)
Age, years, mean (SD)	44 (9.1)	41 (8.0)	42 (8.3)
Male sex, n (%)	28 (60)	92 (64)	120 (63)
Race, n (%)			
White	39 (83)	121 (85)	160 (84)
Asian	8 (17)	20 (14)	28 (15)
Black or African American	0 (0)	2 (1)	2 (1)
Cirrhosis present, n (%)	23 (49)	61 (43)	84 (44)
HBeAg positive, n (%)	4 (9)	18 (13)	22 (12)
Concomitant NA therapy, n (%)	32 (68)	78 (55)	110 (58)
Prior IFN therapy, n (%)	25 (53)	74 (52)	99 (52)
Genotype HDV-1, n (%)[a]	47 (100)	140 (98)	187 (98)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.1 (1.2)	5.2 (1.4)	5.2 (1.3)
ALT, U/L, mean (SD)[b]	108 (64)	109 (86)	109 (81)
Baseline ALT category, n (%)			
≤ULN	2 (4)	12 (8)	14 (7)
>ULN to ≤1.5 × ULN	8 (17)	26 (18)	34 (18)
>1.5 × ULN	37 (79)	105 (73)	142 (75)

[a]In the BLV 10 mg group, 2 patients had genotype HDV-5, and 1 patient had missing HDV genotype.
[b]Despite ALT >ULN at screening being an inclusion criterion, some patients had ALT ≤ULN at the baseline visit.
ALT, alanine aminotransferase; BLV, bulevirtide; HBeAg, hepatitis B e antigen; HDV, hepatitis delta virus; IFN, interferon; NA, nucleos(t)ide analogue; ULN, upper limit of normal.

- 190 patients with CHD were included: BLV 2 mg (n = 47) and BLV 10 mg (n = 143)
- BL demographic and disease characteristics were similar between the treatment groups; 75% of patients had ALT levels >1.5 × ULN

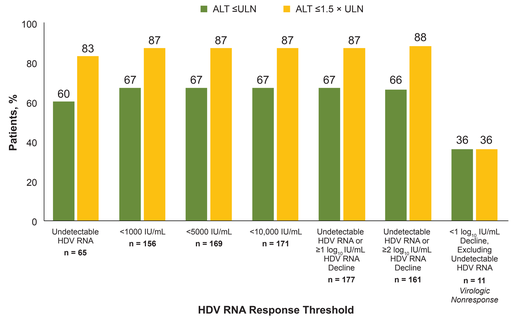
HDV RNA Response During BLV Treatment (2 and 10 mg) to Week 96



Percentages were based on 190 patients; missing values were considered as not meeting the thresholds.
BLV, bulevirtide; HDV, hepatitis delta virus.

- Most patients had HDV RNA declines of ≥1 $\log_{10}$ IU/mL by W24, while rates of HDV RNA undetectability continued to improve through W96
- Over 80% of patients achieved a ≥2 $\log_{10}$ IU/mL decline in HDV RNA at W48, with a similar rate at W96

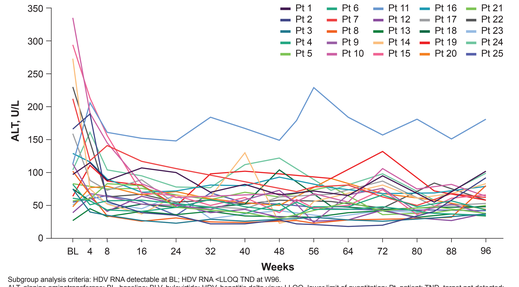
Biochemical Improvement Among 190 Patients Achieving Different HDV RNA Response Thresholds at Week 96



Two patients did not have HDV RNA results at week 96.
ALT, alanine aminotransferase; HDV, hepatitis delta virus; ULN, upper limit of normal.

- HDV RNA response rates at W96 ranged from 34% (undetectable HDV RNA) to 93% (undetectable HDV RNA or ≥1 $\log_{10}$ IU/mL HDV RNA decline from BL)
- After 96W of BLV monotherapy, 85% (161 of 190) of patients achieved virologic response
- Consistent rates of biochemical improvement (ALT ≤ULN and ALT ≤1.5 × ULN) were achieved across all prespecified HDV RNA response thresholds (including undetectable HDV RNA or ≥1 vs ≥2 $\log_{10}$ IU/mL decline in HDV RNA from BL)
  - This finding suggests that biochemical improvement can be achieved in most patients, including those who do not achieve robust virologic responses (ie, 1–2 $\log_{10}$ IU/mL decline in HDV RNA from BL)
- Only the 11 virologic nonresponders (<1 $\log_{10}$ IU/mL decline in HDV RNA from BL) had substantially lower rates of biochemical improvement, and even among this population, ALT normalization was observed in one-third of patients, indicating potential treatment benefit

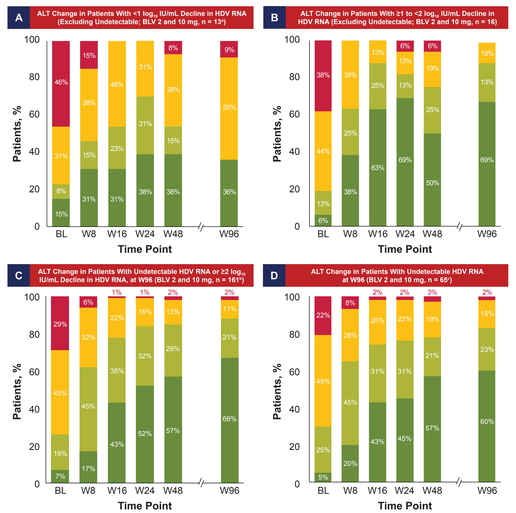
ALT Improvements in 25 Patients Achieving Undetectable HDV RNA at Week 96 Without ALT Normalization With BLV Treatment (2 and 10 mg)



Subgroup analysis criteria: HDV RNA detectable at BL; HDV RNA <LLOQ TND at W96.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; Pt, patient; TND, target not detected; W, week.

- 25 of 64 (39%) patients did not achieve ALT ≤ULN at W96 in this subgroup analysis
- ALT declines were seen in most patients who achieved undetectable HDV RNA without ALT normalization

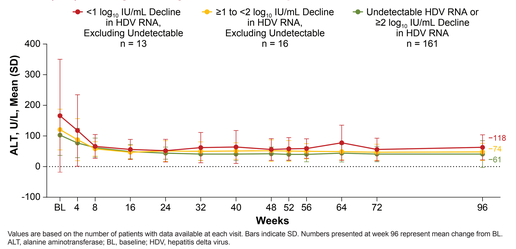
Change in ALT by HDV RNA Response During BLV Treatment at Week 96



[a]Except at W96 when n = 11. [a]Except at W16 (n = 160), W24 (n = 157), and W48 (n = 159). [a]Except at W24 (n = 64) and W48 (n = 63).
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; HDV, hepatitis delta virus; ULN, upper limit of normal; W, week.

- Improvements in ALT were observed with BLV therapy in all HDV RNA response subgroups
- ALT improvement occurred as quickly as W8 to W16 after initiating treatment and was maintained through W96

Mean (SD) ALT by Visit by HDV RNA Response at Week 96



Values are based on the number of patients with data available at each visit. Bars indicate SD. Numbers presented at week 96 represent mean change from BL.
ALT, alanine aminotransferase; BL, baseline; HDV, hepatitis delta virus.

- Mean ALT levels declined across all HDV RNA response groups; the greatest decline was seen in patients with an HDV RNA decline of <1 $\log_{10}$ IU/mL
  - This group had the highest BL mean ALT level, which may explain lower rates of ALT normalization compared to patients with greater HDV RNA response