On-Treatment and Posttreatment Patterns of Noninvasive Tests of Fibrosis With Long-Term Bulevirtide Treatment for Chronic Hepatitis Delta: An Integrated Analysis

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Conclusions

- Long-term therapy with bulevirtide (BLV) over 96 weeks improved noninvasive test results regardless of virologic response; however, these improvements decreased after treatment cessation through week 48 of follow-up in all patients except the subsets with sustained posttreatment undetectability or only low-level posttreatment viremia
- Most patients with chronic hepatitis delta benefit from ongoing long-term BLV treatment, and treatment discontinuation should be considered only in those with a low likelihood of relapse

Plain Language Summary

- Infection with hepatitis delta virus leads to more severe liver-related outcomes than other hepatitis viruses
- Bulevirtide is a treatment for chronic hepatitis delta virus infection in adults with liver disease
- This study used common noninvasive tests to assess the extent of liver damage in patients treated with bulevirtide for up to 96 weeks
- Overall, noninvasive test results showed improvements in liver damage, but these improvements decreased after treatment discontinuation

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

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Introduction

- Hepatitis delta virus (HDV) causes the most severe form of chronic viral hepatitis[1]; it is estimated to affect approximately 12 million people worldwide[2-3]
- The HDV entry inhibitor bulevirtide (BLV) is approved in the United States, the European Economic Area, and other regions for the treatment of chronic hepatitis delta in patients with compensated liver disease[4-7]
- Long-term therapy with BLV has demonstrated improvements in alanine aminotransferase (ALT) and noninvasive test (NIT) results for liver disease burden, including in patients with suboptimal virologic response[8-11]

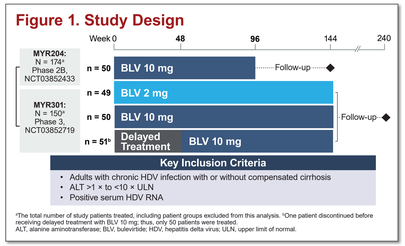
Objective

- To further evaluate liver disease burden responses and their relationship to virologic responses, both on and after treatment with BLV monotherapy using an integrated analysis

Methods

- Data from patients receiving BLV 10 mg (approved as 8.5 mg delivered dose in the United States)[4] or 2 mg in the Phase 3 MYR301 (NCT03852719) and Phase 2 MYR204 (NCT03852433) studies and who had HDV RNA viral load values at the end of treatment (EOT) were pooled and analyzed on treatment up to 96 weeks and at follow-up at 48 weeks posttreatment (**Figure 1**)[9,12]
- ALT was evaluated along with the NITs aspartate aminotransferase to platelet ratio index (APRI),[13] Fibrosis-4 Index (FIB-4),[14] and liver stiffness (LS)
- LS was measured by transient elastography (FibroScan®)
- HDV RNA levels were measured by reverse transcription–quantitative polymerase chain reaction using the RoboGene 2.0 (lower limit of quantitation, 50 IU/mL; limit of detection, 6 IU/mL)[15]
- Subgroups based on outcomes at EOT included the following (all excluding patients with undetectable HDV RNA):
  - Virologic responders (VRnU; ≥2 $\log_{10}$ IU/mL decline in HDV RNA from baseline)
  - Partial responders (PR; ≥1 to <2 $\log_{10}$ IU/mL decline)
  - Nonresponders (NR; <1 $\log_{10}$ IU/mL decline)
- Patients with undetectable HDV RNA at EOT were divided based on posttreatment viral status into the following categories:
  - Sustained posttreatment undetectability (Und-S)
  - Low viremic relapse (Und-LV; detectable HDV RNA <50 IU/mL posttreatment)
  - High viremic relapse (Und-HV; posttreatment HDV RNA ≥50 IU/mL)

Figure 1. Study Design



ᵃThe total number of study patients treated, including patient groups excluded from this analysis. ᵇOne patient discontinued before receiving delayed treatment with BLV 10 mg; thus, only 50 patients were treated.
ALT, alanine aminotransferase; BLV, bulevirtide; HDV, hepatitis delta virus; ULN, upper limit of normal.

Results

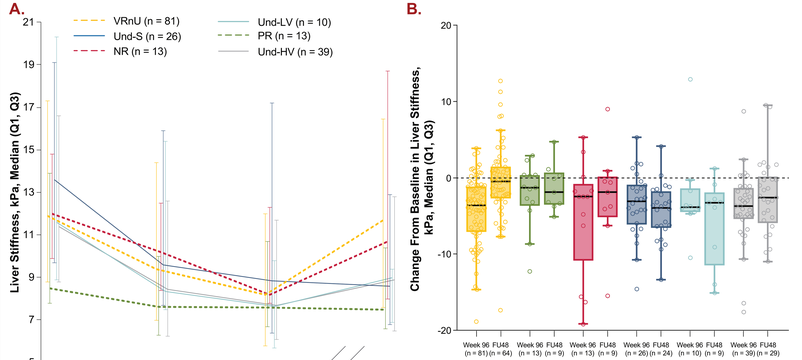
Table 1. Baseline Characteristics

	VRnU (n = 81)	PR (n = 13)	NR (n = 13)	Und-S (n = 26)	Und-LV (n = 10)	Und-HV (n = 39)
Age, years, mean (SD)	41 (8)	32 (6)	42 (8)	44 (9)	44 (11)	43 (8)
Male sex, n (%)	54 (67)	10 (77)	9 (69)	17 (65)	8 (80)	18 (46)
Race, n (%)						
White	67 (83)	11 (85)	11 (85)	23 (88)	9 (90)	31 (79)
Asian	12 (15)	2 (15)	2 (15)	3 (12)	1 (10)	8 (21)
Black	2 (2)	0	0	0	0	0
Cirrhosis present, n (%)	39 (48)	4 (31)	5 (38)	13 (50)	4 (40)	15 (38)
Liver stiffness, kPa, median (Q1, Q3)	11.90 (8.80, 17.30)	8.50 (7.80, 13.90)	12.00 (9.90, 14.80)	13.60 (9.70, 19.10)	11.60 (8.90, 20.30)	11.40 (8.80, 16.60)
FIB-4, median (Q1, Q3)	1.77 (1.13, 2.77)	1.25 (1.05, 1.38)	1.97 (1.26, 2.53)	1.88 (1.33, 2.35)	1.59 (1.00, 2.81)	1.65 (1.28, 2.10)
APRI, median (Q1, Q3)	0.97 (0.64, 1.62)	1.06 (0.67, 1.20)	1.34 (0.87, 2.29)	1.08 (0.79, 1.50)	0.77 (0.65, 1.44)	0.93 (0.68, 1.42)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.69 (0.816)	5.86 (1.109)	4.74 (1.461)	3.96 (1.564)	3.87 (1.662)	5.09 (1.185)
HDV genotype 1, n (%)	79 (97.5)	13 (100)	13 (100)	26 (100)	9 (90.0)	39 (100)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.81 (0.373)	3.86 (0.342)	3.32 (0.999)	3.32 (0.826)	3.24 (0.521)	3.82 (0.380)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	1.29 (1.315)	1.02 (0.728)	1.37 (1.715)	0.86 (0.888)	1.04 (1.446)	1.33 (1.520)
ALT, U/L, median (Q1, Q3)	80 (57, 127)	96 (90, 145)	138 (105, 189)	93 (64, 117)	103 (50, 166)	73 (57, 104)
ALT category, n (%)						
>ULN to ≤1.5 × ULN	16 (20)	1 (8)	1 (8)	2 (8)	4 (40)	8 (21)
>1.5 × ULN	57 (70)	11 (85)	11 (85)	23 (88)	6 (60)	29 (74)
Concomitant HBV treatment, n (%)	48 (59)	8 (62)	6 (46)	15 (58)	6 (60)	25 (64)
Prior IFN therapy, n (%)	38 (47)	8 (62)	3 (23)	16 (62)	5 (50)	25 (64)

Undetectable HDV RNA was defined as HDV RNA less than the lower limit of quantitation, target not detected; patients with undetectable HDV RNA were excluded from VRnU; NR, and PR.
ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; EOT, end of treatment; FIB-4, Fibrosis-4 Index; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; NR, nonresponders (defined as having <1 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT); PR, partial responders (defined as having ≥1 to <2 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT); Q, quartile; ULN, upper limit of normal; Und-HV, high viremic relapse (defined as posttreatment HDV RNA ≥50 IU/mL) after undetectable HDV RNA at EOT; Und-LV, low viremic relapse (defined as detectable posttreatment HDV RNA <50 IU/mL) after undetectable HDV RNA at EOT; Und-S, sustained posttreatment undetectable HDV RNA after undetectable HDV RNA at EOT; VRnU, virologic responders excluding undetectable HDV RNA (defined as ≥2 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT).

- Baseline characteristics were generally similar across patient subgroups; baseline ALT was highest in the NR group (median 138 U/L vs 73–103 U/L in other groups), while other NITs were comparable across response groups (**Table 1**)

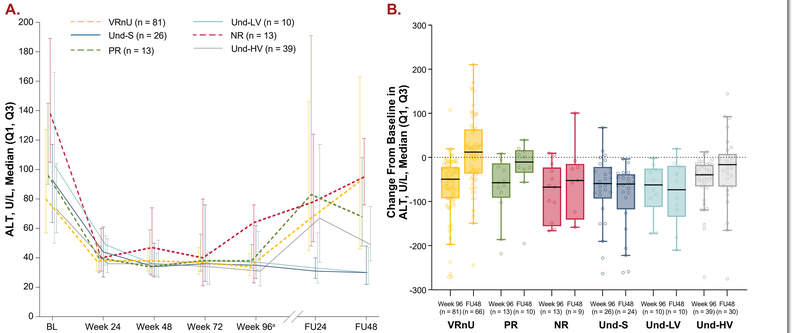
Figure 2. Liver Stiffness Over Time (A) and Change From Baseline (B) in Patients Treated With BLV by Virologic Response and Relapse Status



ᵃTreatment duration varied between 96 and 144 weeks between cohorts; thus, the length of time between week 96 and FU48 was variable. Liver stiffness was measured by transient elastography (FibroScan®). In panel B, boxes include IQR, lines in boxes indicate the median, whiskers extend to the most extreme values within 1.5 × IQR of Q1 and Q3, and points beyond the whiskers represent outliers. Additional outliers not shown include values of −28.1 and −38.3 (week 96 in the VRnU group), −21.9 and −33.0 (FU48 in the VRnU group), −20.7 (week 96 in the Und-HV group), and −20.0 (FU48 in the Und-HV group).
BL, baseline; BLV, bulevirtide; EOT, end of treatment; FU#, follow-up at # weeks posttreatment; HDV, hepatitis delta virus; NR, nonresponders (defined as having <1 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT); PR, partial responders (defined as having ≥1 to <2 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT); Q, quartile; Und-HV, high viremic relapse (defined as posttreatment HDV RNA ≥50 IU/mL) after undetectable HDV RNA at EOT; Und-LV, low viremic relapse (defined as detectable posttreatment HDV RNA <50 IU/mL) after undetectable HDV RNA at EOT; Und-S, sustained posttreatment undetectable HDV RNA after undetectable HDV RNA at EOT; VRnU, virologic responders excluding undetectable HDV RNA (defined as ≥2 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT).

- Improvements in ALT and all NITs from baseline to week 96 were seen in all subgroups (**Figures 2–4** and **Supplemental Figures 1** and **2**, accessible via QR code)

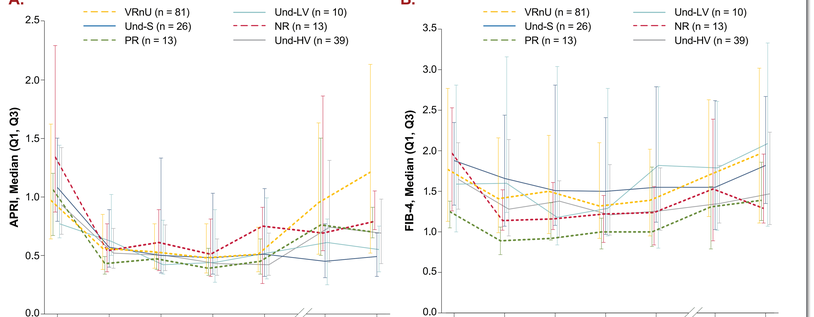
Figure 3. ALT Levels Over Time (A) and Change From Baseline (B) in Patients Treated With BLV by Virologic Response and Relapse Status



ᵃTreatment duration varied between 96 and 144 weeks between cohorts; thus, the length of time between week 96 and FU24 was variable. Values are based on the number of patients with data available at each visit. In panel B, boxes include IQR, lines in boxes indicate the median, whiskers extend to the most extreme values within 1.5 × IQR of Q1 and Q3, and points beyond the whiskers represent outliers. Additional outliers not shown include values of 451 (FU48 in the VRnU group), 352 (week 96 in the PR group), −726 (week 96 in the NR group), −646 (FU48 in the NR group), and 789 (FU48 in the Und-S group, which represented a large increase from baseline in one patient who experienced an ALT flare due to hepatitis B virus reactivation).
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; EOT, end of treatment; FU#, follow-up at # weeks posttreatment; HDV, hepatitis delta virus; NR, nonresponders (defined as having <1 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT); PR, partial responders (defined as having ≥1 to <2 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT); Q, quartile; Und-HV, high viremic relapse (defined as posttreatment HDV RNA ≥50 IU/mL) after undetectable HDV RNA at EOT; Und-LV, low viremic relapse (defined as detectable posttreatment HDV RNA <50 IU/mL) after undetectable HDV RNA at EOT; Und-S, sustained posttreatment undetectable HDV RNA after undetectable HDV RNA at EOT; VRnU, virologic responders excluding undetectable HDV RNA (defined as ≥2 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT).

- In the posttreatment period, median LS improved from week 96 only in patients with Und-S (**Figure 2**); median ALT improvements were seen in patients with Und-S and Und-LV (**Figure 3**)

Figure 4. APRI (A) and FIB-4 (B) Over Time in Patients Treated With BLV by Virologic Response and Relapse Status



ᵃTreatment duration varied between 96 and 144 weeks between cohorts; thus, the length of time between week 96 and FU24 was variable. Values are based on the number of patients with data available at each visit.
APRI, aspartate aminotransferase to platelet ratio index; BL, baseline; BLV, bulevirtide; EOT, end of treatment; FIB-4, Fibrosis-4 Index; FU#, follow-up at # weeks posttreatment; HDV, hepatitis delta virus; NR, nonresponders (defined as having <1 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT); PR, partial responders (defined as having ≥1 to <2 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT); Q, quartile; Und-HV, high viremic relapse (defined as posttreatment HDV RNA ≥50 IU/mL) after undetectable HDV RNA at EOT; Und-LV, low viremic relapse (defined as detectable posttreatment HDV RNA <50 IU/mL) after undetectable HDV RNA at EOT; Und-S, sustained posttreatment undetectable HDV RNA after undetectable HDV RNA at EOT; VRnU, virologic responders excluding undetectable HDV RNA (defined as ≥2 $\log_{10}$ IU/mL decline in HDV RNA from baseline at EOT).

- Posttreatment patterns in APRI and FIB-4 were variable, with loss of on-treatment improvements most pronounced in the VRnU group; however, interpretation is limited by the small sample size (**Figure 4** and **Supplemental Figures 1** and **2**)