Improvement in Noninvasive Markers of Fibrosis (LSM, FIB-4, and APRI) Is Seen Over 96 Weeks of Bulevirtide Monotherapy in Chronic Hepatitis Delta Regardless of Virologic Response

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Key Findings

- Treatment with BLV 2 or 10 mg over 96 weeks resulted in similar reductions in ALT and noninvasive markers of fibrosis
- The greatest improvements in noninvasive markers of fibrosis were seen in the first 48 weeks, coinciding with improvement in ALT. Noninvasive markers of fibrosis and ALT continued to improve or were maintained from week 48 to 96
- Improvements in ALT and noninvasive markers of fibrosis occurred regardless of the patient's virologic response

Conclusions

Improvements in surrogates of liver disease burden support the clinical benefit of continued treatment with BLV over 96 weeks even among those who do not achieve a virologic response

References: **1.** Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. **2.** Hepcludex. Summary of product characteristics. European Medicines Agency. Accessed September 18, 2023. **3.** Wedemeyer H, et al. *J Hepatol*. 2023;78(S1):S57-8. **4.** European Association for the Study of the Liver. *J Hepatol*. 2023;79(2):433-60.

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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 worldwide[1]
- Bulevirtide (BLV), a novel entry inhibitor of HDV, is approved in the European Union at 2 mg/day for the treatment of adults with chronic hepatitis delta (CHD) and compensated liver disease[2]
- Improvements in combined, virologic, and biochemical responses and liver stiffness were comparable for BLV 2 and 10 mg compared to control (no treatment) over 48 weeks. These rates increased from week 48 to week 96 of BLV treatment[3]
- Noninvasive tests (NITs) for fibrosis staging have been explored in chronic viral hepatitis but have not yet been validated for CHD. International HDV guidelines recommend that NITs be used to assess advanced liver disease, however, specific cutoff values are not well established[4]

Objective

- To evaluate the change in alanine aminotransferase (ALT) and noninvasive markers of fibrosis among patients treated with BLV 2 and 10 mg and by virologic response

Methods

- Patients from 2 randomized, open-label, multicenter trials were included:
  - Phase 2 MYR204 study (NCT03852433)
  - Phase 3 MYR301 study (NCT03852719)
- Key inclusion criteria:
  - Adults with CHD with or without compensated cirrhosis
  - ALT >1 × to <10 × the upper limit of normal and positive serum HDV RNA
- Patients randomized to receive BLV monotherapy at 2 or 10 mg subcutaneously once daily were included in the analysis
- Variables evaluated in this analysis included the following:
  - ALT
  - NITs: Fibrosis-4 (FIB-4) index; aspartate aminotransferase (AST) platelet ratio index (APRI); liver stiffness measurement (LSM; measured using vibration-controlled transient elastography)
- Patients were categorized by virologic response at week 96 as follows:
  - **Virologic responder (VR):** defined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline from baseline (BL)
  - **Partial responder (PR):** defined as ≥1 $\log_{10}$ IU/mL but <2 $\log_{10}$ IU/mL HDV RNA decline from BL
  - **Nonresponders (NR):** defined as <1 $\log_{10}$ IU/mL HDV RNA decline from BL
  - Data from patients who remained on study treatment at week 96 were included in the subanalysis

Results

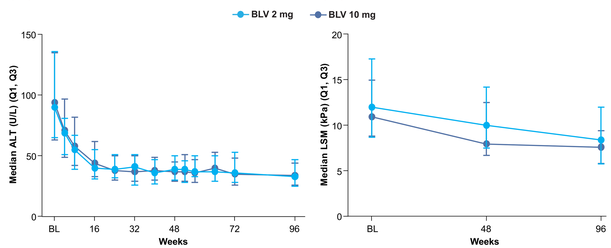
Table 1. Baseline Characteristics by BLV Treatment Group

	BLV 2 mg (n = 49)	BLV 10 mg (n = 100)
Age, years, mean (SD)	44 (9.0)	41 (8.5)
Male sex, n (%)	30 (61)	68 (68)
White race, n (%)	41 (84)	87 (87)
Cirrhosis, n (%)	23 (47)	41 (41)
Concomitant HBV NUC treatment, n (%)	32 (65)	50 (50)
ALT, U/L, median (Q1, Q3)	90 (65, 136)	94 (63, 135)
Platelet count, 10^9/L, median (Q1, Q3)	159 (111, 191)	173 (132, 200)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.1 (1.2)	5.2 (1.3)
HDV genotype 1, n (%)	49 (100)	97[a] (97)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.7 (0.5)	3.7 (0.6)
GGT, U/L, median (Q1, Q3)	57 (27, 73)	46 (28, 73)
FIB-4, median (Q1, Q3)	1.9 (1.3, 2.9)	1.6 (1.2, 2.1)
APRI, median (Q1, Q3)	1.1 (0.7, 2.0)	1 (0.7, 1.5)
LSM, kPa, median (Q1, Q3)	12 (8.7, 17.3)	11 (8.8, 15)

[a]HDV genotype 5 was documented for 2 patients; data were not available for 1 patient.
ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BLV, bulevirtide; FIB-4, Fibrosis-4 score; GGT, gamma-glutamyl transferase; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; LSM, liver stiffness measurement; NUC, nucleos(t)ide analogue; Q, quartile.

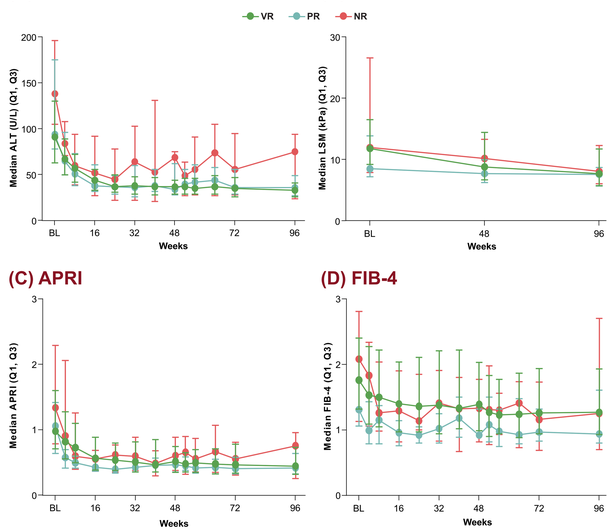
- Baseline characteristics were similar between BLV treatment groups

Figure 1. ALT and NIT Markers Over 96 Weeks by BLV Treatment Group



ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BL, baseline; BLV, bulevirtide; FIB-4, Fibrosis-4 score; LSM, liver stiffness measurement; NIT, noninvasive test; Q, quartile.

Figure 2. ALT and NIT Markers Over 96 Weeks by Virologic Response at Week 96



PRs are defined as ≥1 $\log_{10}$ IU/mL but <2 $\log_{10}$ IU/mL decline from BL but not undetectable; NRs are defined as <1 $\log_{10}$ IU/mL decline from BL; VRs are defined as undetectable HDV RNA and/or ≥2 $\log_{10}$ IU/mL decline from BL.
ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BL, baseline; FIB-4, Fibrosis-4 score; LSM, liver stiffness measurement; NIT, noninvasive test; NR, Nonresponder; PR, Partial responder; Q, quartile; VR, Virologic responder.

Table 2. Median (Q1, Q3) ALT and NIT Markers Over 96 Weeks by BLV Treatment Group

	BL		Week 48		Week 96	
	BLV 2 mg	BLV 10 mg	BLV 2 mg	BLV 10 mg	BLV 2 mg	BLV 10 mg
ALT (U/L)	90 (65, 136)	94 (63, 135)	39 (30, 50)	37 (29, 45)	33 (25, 47)	34 (26, 44)
LSM (kPa)	12.0 (8.7, 17.3)	11.0 (8.8, 15.0)	10.0 (7.5, 14.2)	8.0 (6.7, 12.5)	8.4 (5.8, 12.0)	7.6 (5.8, 9.4)
APRI	1.1 (0.7, 2.0)	1.0 (0.7, 1.5)	0.5 (0.4, 0.9)	0.5 (0.4, 0.7)	0.5 (0.3, 1.0)	0.5 (0.3, 0.7)
FIB-4	1.9 (1.3, 2.9)	1.6 (1.2, 2.1)	1.4 (0.9, 2.7)	1.3 (0.9, 1.6)	1.3 (0.9, 2.3)	1.2 (0.9, 1.7)

ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BL, baseline; BLV, bulevirtide; FIB-4, Fibrosis-4 score; LSM, liver stiffness measurement; NIT, noninvasive test; Q, quartile.

- Similar improvements in ALT and noninvasive markers of fibrosis over 96 weeks were seen with BLV 2 and 10 mg, with the greatest declines seen in the first 48 weeks
- Maintained or continued improvements in ALT and noninvasive markers of fibrosis were seen from week 48 to 96

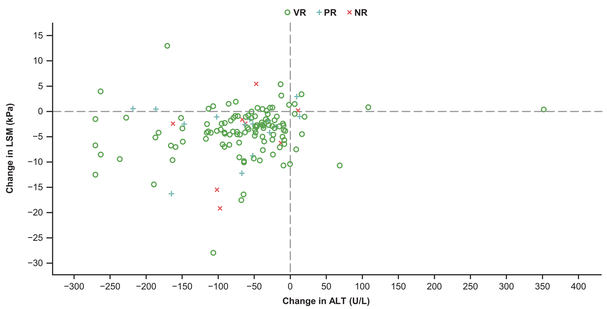
Table 3. Median (Q1, Q3) ALT and NIT Markers Over 96 Weeks by Virologic Response at Week 96

	BL			Week 48			Week 96		
	VR	PR	NR	VR	PR	NR	VR	PR	NR
ALT (U/L)	91 (63, 130)	94 (78, 175)	138 (105, 196)	37 (29, 44)	34 (28, 62)	69 (29, 75)	33 (26, 41)	36 (27, 49)	75 (24, 94)
LSM (kPa)	11.8 (9.2, 16.5)	8.5 (7.2, 13.9)	12.0 (7.9, 26.6)	8.8 (6.7, 14.4)	7.7 (6.3, 10.0)	10.2 (7.5, 13.3)	7.7 (5.8, 11.7)	7.6 (5.7, 8.7)	8.1 (6.1, 12.3)
APRI	1.0 (0.7, 1.6)	1.1 (0.6, 1.4)	1.3 (0.8, 2.3)	0.5 (0.4, 0.8)	0.5 (0.4, 0.5)	0.6 (0.4, 0.9)	0.5 (0.3, 0.7)	0.4 (0.3, 0.6)	0.8 (0.3, 1.0)
FIB-4	1.8 (1.3, 2.4)	1.3 (1.1, 1.8)	2.1 (1.1, 2.8)	1.4 (1.0, 2.0)	0.9 (0.9, 1.3)	1.3 (0.8, 1.8)	1.3 (0.9, 1.9)	0.9 (0.8, 1.6)	1.3 (0.7, 2.7)

PRs are defined as ≥1 $\log_{10}$ IU/mL but <2 $\log_{10}$ IU/mL decline from BL but not undetectable; NRs are defined as <1 $\log_{10}$ IU/mL decline from BL; VRs are defined as undetectable HDV RNA and/or ≥2 $\log_{10}$ IU/mL decline from BL.
ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; BL, baseline; FIB-4, Fibrosis-4 score; LSM, liver stiffness measurement; NIT, noninvasive test; NR, Nonresponder; PR, Partial responder; VR, Virologic responder.

- Improvements in ALT and noninvasive markers of fibrosis occurred regardless of virologic response
- Median ALT was higher at BL and through week 96 in NRs compared with VRs and PRs

Figure 3. Change in LSM vs ALT from BL to Week 96 by Individual Patient and Virologic Response Category (BLV 2 and 10 mg)



PRs are defined as ≥1 $\log_{10}$ IU/mL but <2 $\log_{10}$ IU/mL decline from BL but not undetectable. NRs are defined as <1 $\log_{10}$ IU/mL decline from BL). VRs are defined as undetectable HDV RNA and/or ≥2 $\log_{10}$ IU/mL decline from BL.
In the NR group, 1 patient was excluded due to LSM and ALT changes from BL of −4.8 kPa and −726 U/L, respectively.
ALT, alanine aminotransferase; BL, baseline; LSM, liver stiffness measurement; NR, Nonresponder; PR, Partial responder; VR, Virologic responder.

- Most patients achieved improvement in both LSM and ALT, regardless of viral response category