Improvement in 3 Noninvasive Tests Through 144 Weeks of Bulevirtide Monotherapy in Patients With Chronic Hepatitis Delta With and Without Virologic Response

WED-308

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Conclusions

- Treatment with bulevirtide (BLV) 2 or 10 mg monotherapy for up to 3 years resulted in improvements in noninvasive test (NIT) markers for liver disease burden in patients with chronic hepatitis delta (CHD)
- Improvements in NIT markers were observed in patients with virologic response, partial response, and nonresponse, suggesting a beneficial effect of BLV therapy beyond reductions in hepatitis delta virus (HDV) RNA viral load

Plain Language Summary

- Bulevirtide is an antiviral medication that has been shown to be safe and effective for treatment of chronic hepatitis delta
- This study used 3 common noninvasive tests to assess the level of liver damage in patients treated with bulevirtide for up to 3 years (144 weeks)
- All 3 test results showed improvements in levels of liver damage across all patient groups, showing beneficial effects of bulevirtide treatment

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.** Castera L, et al. Presented at: AASLD: The Liver Meeting; November 10–14, 2023. Poster 1473-C. **4.** European Association for the Study of the Liver. *J Hepatol*. 2023;79(2):433-60.

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Introduction

- CHD represents the most severe form of chronic viral hepatitis and is estimated to affect between 10 and 20 million people worldwide[1]
- BLV, an entry inhibitor of HDV, is approved in the European Union, Great Britain, Switzerland, the Russian Federation, and Australia at 2 mg/day, given subcutaneously, for the treatment of CHD with compensated liver disease[2]
- NIT markers have demonstrated improvements in hepatic function and liver disease burden with up to 96 weeks of BLV treatment[3]
- NITs for fibrosis staging have been explored in chronic viral hepatitis but have not yet been validated for CHD. International HDV guidelines recommend that longitudinal measurement of NITs be used to assess advanced liver disease; however, specific cutoff values are not well established[4]

Objective

- To evaluate improvements in alanine aminotransferase (ALT) and NIT markers among patients treated with BLV 2 and 10 mg and by correlation with virologic response through 144 weeks of treatment

Methods

- A longitudinal analysis was conducted using the Phase 3 MYR301 (NCT03852719) study data
- Key inclusion criteria
  - Adults with CHD with or without compensated cirrhosis
  - HDV RNA detected in serum and ALT between 1 and 10 times the upper limit of normal (ULN) at screening
- Patients were randomised to receive immediate treatment with BLV 2 or 10 mg subcutaneously once daily for 144 weeks, or to no treatment for 48 weeks followed by BLV 10 mg once daily for 96 weeks
- Variables evaluated in this analysis included
  - **ALT**[a]
  - **NITs:** Fibrosis-4 index (FIB-4), aspartate aminotransferase to platelet ratio index (APRI), and liver stiffness measurement (LSM; measured using vibration-controlled transient elastography)
- Patients were categorised by virologic response at week 144 as follows:
  - **Virologic responder:** defined as having undetectable HDV RNA[b] or ≥2 $\log_{10}$ IU/mL decline from baseline (BL)
  - **Partial responder:** defined as having ≥1 and <2 $\log_{10}$ IU/mL HDV RNA decline from BL (excluding undetectable HDV RNA)
  - **Nonresponder:** defined as having <1 $\log_{10}$ IU/mL HDV RNA decline from BL (excluding undetectable HDV RNA)

[a]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). [b]HDV RNA levels less than the lower limit of quantitation (LLOQ) with target not detected (LLOQ <50 IU/mL, limit of detection 6 IU/mL).

Results

Baseline Characteristics by BLV Treatment Group

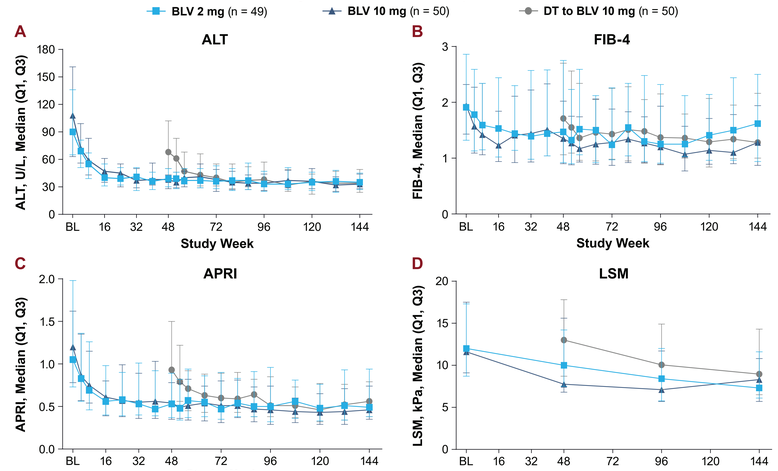
	BLV 2 mg (n = 49)	BLV 10 mg (n = 50)	DT to BLV 10 mg (n = 51)[a]
Age, years, mean (SD)	44 (9)	41 (9)	41 (8)
Male sex, n (%)	30 (61)	30 (60)	26 (51)
Race,[b] n (%)			
White	41 (84)	43 (86)	40 (78)
Asian	8 (16)	6 (12)	11 (22)
Cirrhosis present, n (%)	23 (47)	24 (48)	24 (47)
Liver stiffness, kPa, median (Q1, Q3)	12.0 (8.7, 17.3)	11.6 (9.1, 17.5)	11.9 (8.5, 19.2)
ALT, U/L, median (Q1, Q3)	90 (65, 136)	108 (63, 161)	80 (57, 116)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.10 (1.19)	4.96 (1.46)	5.08 (1.36)
Genotype HDV-1,[c] n (%)	49 (100)	48 (96)	51 (100)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.67 (0.52)	3.61 (0.59)	3.68 (0.47)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	1.31 (1.28)	1.08 (1.26)	0.89 (0.99)
HBV genotype, n (%)			
A	2 (4)	2 (4)	2 (4)
D	47 (96)	44 (88)	44 (86)
Other[d]/missing	0	4 (8)	5 (10)
Previous IFN therapy, n (%)	26 (53)	29 (58)	29 (57)
Concomitant HBV NA treatment, n (%)	32 (65)	27 (54)	33 (65)

[a]At BL (randomisation), 51 patients were assigned to DT to BLV 10 mg, and their data are reported here. One patient subsequently withdrew from the DT to BLV 10 mg group before receiving BLV and is not included in subsequent reporting. [b]BLV 10 mg arm: Black, n = 1. [c]BLV 10 mg arm: HDV genotype 5, n = 1; missing HDV genotype, n = 1. [d]Other: BLV 10 mg arm: HBV genotype E, n = 1; no data, n = 3; DT to BLV 10 mg arm: unclassified HBV genotype, n = 2; no data, n = 3.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; DT, delayed treatment; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; NA, nucleos(t)ide analogue; Q, quartile.

- BL characteristics were similar between all treatment groups
- Just under half of patients in each arm had cirrhosis at BL

Results

ALT and NIT Markers Over 144 Weeks by BLV Treatment Group



Values are based on the number of patients with data available at each visit.
ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; BL, baseline; BLV, bulevirtide; DT, delayed treatment; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; NIT, noninvasive test; Q, quartile.

Median (Q1, Q3) Change From Baseline in ALT and NIT Markers Over 144 Weeks by BLV Treatment Group

	Week 48		Week 96		Week 144	
	BLV 2 mg	BLV 10 mg	BLV 2 mg	BLV 10 mg	BLV 2 mg	BLV 10 mg
ALT, U/L	−46 (−87, −24)	−69 (−111, −32)	−50 (−97, −28)	−76 (−148, −22)	−51 (−73, −35)	−68 (−120, −26)
FIB-4	−0.42 (−0.92, −0.13)	−0.44 (−0.64, −0.19)	−0.44 (−1.28, −0.11)	−0.45 (−0.93, −0.19)	−0.52 (−1.19, −0.03)	−0.43 (−0.94, −0.14)
APRI	−0.44 (−1.04, −0.22)	−0.63 (−1.05, −0.31)	−0.50 (−1.22, −0.21)	−0.60 (−1.13, −0.28)	−0.57 (−1.55, −0.25)	−0.54 (−1.14, −0.30)
LSM, kPa	−1.90 (−4.19, 0.05)	−2.80 (−5.20, −1.20)	−2.60 (−5.80, −1.20)	−3.90 (−7.10, −2.30)	−4.00 (−6.00, −1.00)	−3.80 (−6.70, −1.20)

ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; BLV, bulevirtide; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; NIT, noninvasive test; Q, quartile.

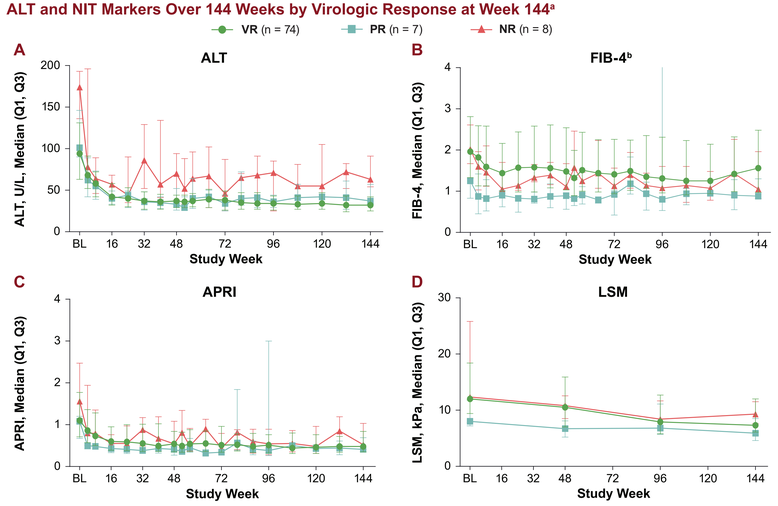
- Median ALT levels improved through 144 weeks of treatment, with the greatest improvements seen in the first year
- Similar patterns of improvement were seen for FIB-4, APRI, and LSM results

Median (Q1, Q3) Change From Baseline in ALT and NIT Markers Over 144 Weeks by Virologic Response at Week 144[a]

	Week 48			Week 96			Week 144		
	VR	PR	NR	VR	PR	NR	VR	PR	NR
ALT, U/L	−49 (−95, −22)	−81 (−94, −46)	−105 (−136, −45)	−55 (−102, −22)	−57 (−102, 9)	−100 (−156, −49)	−53 (−103, −30)	−64 (−108, −44)	−95 (−136, −29)
FIB-4	−0.41 (−0.77, −0.15)	−0.36 (−0.43, −0.26)	−0.67 (−1.42, −0.54)	−0.38 (−1.01, −0.14)	−0.30 (−0.44, 1.50)	−0.91 (−1.65, −0.55)	−0.43 (−1.05, −0.11)	−0.39 (−0.48, −0.09)	−1.02 (−1.60, −0.78)
APRI	−0.48 (−1.07, −0.24)	−0.60 (−0.93, −0.40)	−1.00 (−1.69, −0.56)	−0.50 (−1.13, −0.21)	−0.53 (−0.70, 2.56)	−1.08 (−1.95, −0.63)	−0.54 (−1.32, −0.27)	−0.51 (−0.70, −0.26)	−1.05 (−1.99, −0.62)
LSM, kPa	−2.70 (−4.80, −0.90)	−1.30 (−2.10, 0.20)	−1.25 (−14.20, −0.30)	−3.80 (−6.70, −1.60)	−1.20 (−1.50, 0.40)	−2.50 (−15.95, −1.75)	−3.85 (−6.50, −1.20)	−1.30 (−3.80, 0.20)	−4.00 (−15.70, −1.10)

[a]Presented data are pooled BLV 2 mg and BLV 10 mg groups; data from the DT to BLV 10 mg group are not included. VR is defined as having undetectable HDV RNA and/or ≥2 $\log_{10}$ IU/mL decline from BL; PR is defined as having ≥1 $\log_{10}$ IU/mL but <2 $\log_{10}$ IU/mL HDV RNA decline from BL but not undetectable; NR is defined as having <1 $\log_{10}$ IU/mL HDV RNA decline from BL but not undetectable.
ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; BL, baseline; BLV, bulevirtide; DT, delayed treatment; FIB-4, Fibrosis-4 index; HDV, hepatitis delta virus; LSM, liver stiffness measurement; NIT, noninvasive test; NR, nonresponder; PR, partial responder; Q, quartile; VR, virologic responder.

ALT and NIT Markers Over 144 Weeks by Virologic Response at Week 144[a]



[a]Presented data are pooled BLV 2 mg and BLV 10 mg groups; data from the DT to BLV 10 mg group are not included. [b]The FIB-4 Q3 value for PRs at week 96 was 5.6 and is not shown due to the figure scale. Values are based on the number of patients with data available at each visit. VR is defined as having undetectable HDV RNA and/or ≥2 $\log_{10}$ IU/mL decline from BL; PR is defined as having ≥1 $\log_{10}$ IU/mL but <2 $\log_{10}$ IU/mL HDV RNA decline from BL but not undetectable; NR is defined as having <1 $\log_{10}$ IU/mL HDV RNA decline from BL but not undetectable.
ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; BL, baseline; BLV, bulevirtide; DT, delayed treatment; FIB-4, Fibrosis-4 index; HDV, hepatitis delta virus; LSM, liver stiffness measurement; NIT, noninvasive test; NR, nonresponder; PR, partial responder; Q, quartile; VR, virologic responder.

- Patients with virologic nonresponse had numerically higher ALT levels, APRI scores, LSMs, and FIB-4 scores at BL, and higher ALT levels, APRI scores, and LSMs at week 144 compared with patients who had partial response or virologic response

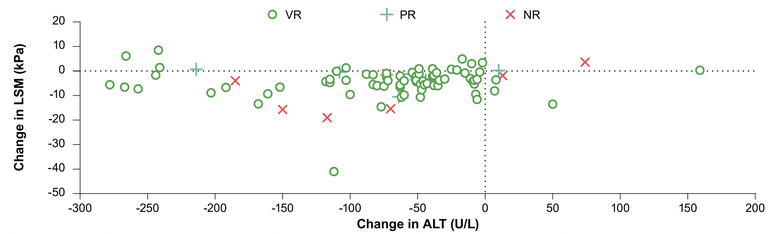
NIT Marker Categories by BLV Treatment Group Over 144 Weeks

	Baseline			Week 96			Week 144	
	BLV 2 mg	BLV 10 mg	DT to BLV 10 mg	BLV 2 mg	BLV 10 mg	DT to BLV 10 mg	BLV 2 mg	BLV 10 mg
LSM, kPa								
<10	17/49 (35)	17/50 (34)	16/50 (32)	28/47 (60)	34/47 (72)	28/48 (58)	29/45 (64)	30/43 (70)
≥10 to ≤15.2	17/49 (35)	19/50 (38)	16/50 (32)	13/47 (28)	6/47 (13)	10/48 (21)	11/45 (24)	5/43 (12)
>15.2	15/49 (31)	14/50 (28)	18/50 (36)	6/47 (13)	7/47 (15)	10/48 (21)	5/45 (11)	8/43 (19)
FIB-4								
<1.3	11/49 (22)	10/50 (20)	18/50 (36)	25/47 (53)	25/46 (54)	24/48 (50)	16/43 (37)	23/44 (52)
≥1.3 to ≤2.67	24/49 (49)	29/50 (58)	18/50 (36)	14/47 (30)	14/46 (30)	17/48 (35)	19/43 (44)	14/44 (32)
>2.67	14/49 (29)	11/50 (22)	14/50 (28)	8/47 (17)	7/46 (15)	7/48 (15)	8/43 (19)	7/44 (16)
APRI								
<0.5	2/49 (4)	4/50 (8)	7/50 (14)	24/47 (51)	26/46 (57)	21/48 (44)	23/43 (53)	26/44 (59)
≥0.5 to ≤2	36/49 (73)	36/50 (72)	34/50 (68)	21/47 (45)	17/46 (37)	24/48 (50)	17/43 (40)	17/44 (39)
>2	11/49 (22)	10/50 (20)	9/50 (18)	2/47 (4)	3/46 (7)	3/48 (6)	3/43 (7)	1/44 (2)

Data presented as n/N (%). Percentages were based on the available values at each visit. For the DT to BLV 10 mg group, BL was reset at week 48.
APRI, aspartate aminotransferase to platelet ratio index; BL, baseline; BLV, bulevirtide; DT, delayed treatment; FIB-4, Fibrosis-4 index; LSM, liver stiffness measurement; NIT, noninvasive test.

- Improvements in NIT markers at week 144 were also seen across all virologic response groups in the pooled immediate-treatment cohort, including patients with virologic response (n = 74), patients with partial response (n = 7), and patients with virologic nonresponse (n = 8) at week 144

Change in LSM vs ALT From Baseline to Week 144 by Individual Patient and Virologic Response at Week 144[a]



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ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; DT, delayed treatment; HDV, hepatitis delta virus; LSM, liver stiffness measurement; NR, nonresponder; PR, partial responder; VR, virologic responder.

- Most patients, including those with virologic nonresponse, had improvements in both ALT levels and LSM at week 144

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