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Poster for you

Improvement in Liver Histology Is Observed in Most Patients With Chronic Hepatitis Delta After 48 Weeks of Bulevirtide Monotherapy

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Conclusions

- In a subanalysis of patients with paired baseline (BL) and week 48 liver biopsies, an improvement in liver histology was observed in most patients with chronic hepatitis delta after 48 weeks of bulevirtide (BLV) monotherapy, including those who did not achieve virologic response (VR)
- Decreases in alanine aminotransferase (ALT) levels and/or histology activity index (HAI) were observed in most patients treated with BLV
  - The degrees of improvement in HAI and ALT levels did not necessarily correlate
- Histologic improvement and improvement in HAI or HAI category occurred more frequently in patients with VR or partial response
- An improvement in fibrosis occurred most frequently in patients with VR
- No consistent pattern of HAI, ALT level, or fibrosis change was observed in the control group

Plain Language Summary

- An improvement in liver histology, or how liver cells look under a microscope, was observed in most patients with chronic hepatitis delta after 48 weeks of bulevirtide treatment
- This improvement in liver histology was observed even in patients who did not have a large decrease in the amount of hepatitis delta virus from bulevirtide treatment

Introduction

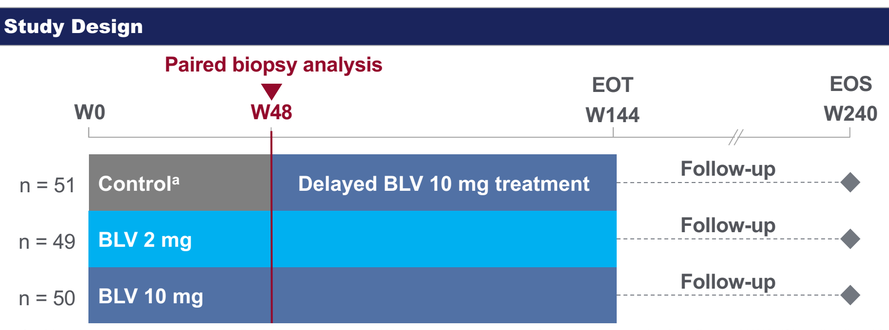
- Hepatitis delta virus (HDV) represents the most severe form of chronic viral hepatitis and is estimated to affect between 10 and 20 million individuals worldwide[1]
- Bulevirtide (BLV), a novel entry inhibitor of HDV, is fully approved in the European Union, Great Britain, Switzerland, and the Russian Federation at the dose of 2 mg/day for the treatment of chronic hepatitis delta (CHD) with compensated liver disease[2]
- In the MYR301 study, BLV monotherapy (2 or 10 mg) resulted in virologic response in 76% to 82%, normalisation of alanine aminotransferase (ALT) in 63% to 64%, and combined response (ALT normalisation + virologic response) in 55% to 56% of patients after 96 weeks[3]
- A recent subanalysis showed that ALT improvement may occur discordantly of virologic response with BLV treatment[4]
- Whether histologic improvement correlates with ALT and/or virologic response in patients treated with BLV monotherapy remains unclear

Objective

- This study aimed to evaluate the evolution and correlation of biochemical, virologic, and histologic parameters in patients with CHD treated with BLV monotherapy for 48 weeks

Methods

Figure 1 **MYR301 Study Design**



[a]Patients in the control group for this subanalysis were treated with BLV 10 mg starting at W48. Liver biopsies were performed per protocol at baseline and W48. If baseline liver biopsy samples were not available (were not provided to the central laboratory or were considered as nonevaluable by the central laboratory), subsequent liver biopsy was not performed.
BLV, bulevirtide; EOS, end of study; EOT, end of treatment; W, week.

- This analysis included data up to week (W) 48 from patients in the ongoing randomised Phase 3 Study MYR301 (NCT03852719) who had paired (baseline [BL] and W48) liver biopsies
- At W48, there were 3 study arms: BLV 2 mg, BLV 10 mg, and a delayed-treatment arm that received no anti-HDV therapy to this point (control)
- Response groups at W48 were defined as follows:
  - Virologic response (VR) = HDV RNA decline of ≥2 $\log_{10}$ IU/mL from BL or undetectable HDV RNA
  - Partial response (PR) = HDV RNA decline of ≥1 but <2 $\log_{10}$ IU/mL from BL
  - Nonresponse (NR) = HDV RNA decline of <1 $\log_{10}$ IU/mL from BL
- Histologic analysis included the following:
  - Histologic parameters: histology activity index (HAI; 0–18), HAI category (0–4), and Ishak fibrosis score (0–6)
  - Improvement at W48 was defined as ≥1-point improvement from BL for HAI and Ishak fibrosis score and ≥1 HAI category improvement from BL
  - Histologic improvement was defined as ≥2-point improvement in HAI with no worsening of fibrosis score
- ALT normalisation was defined at Russian sites as ≤31 U/L for females and ≤41 U/L for males, and at all other sites as ≤34 U/L for females and ≤49 U/L for males
- HDV RNA levels were determined by RT-qPCR using RoboGene HDV RNA Quantification Kit 2.0 (lower limit of quantitation, 50 IU/mL; lower limit of detection, 6 IU/mL)

Results

Table 1 **Demographics and Baseline Characteristics Based on Virologic Response**

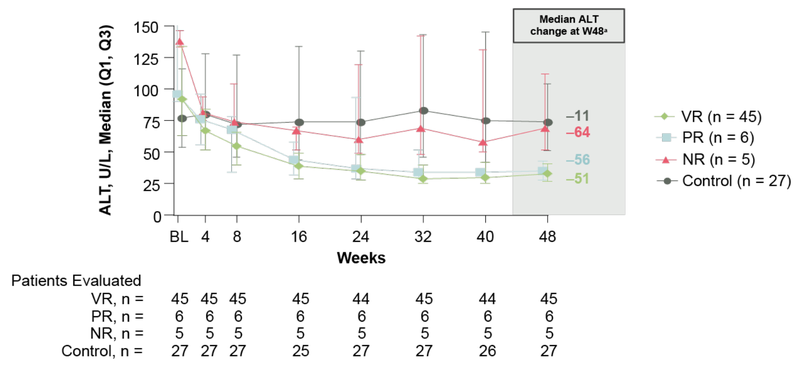
	BLV (2 or 10 mg)			Control	Total
	VR at W48 (n = 45)	PR at W48 (n = 6)	NR at W48 (n = 5)	(n = 27)	(N = 83)
Age, years, mean (SD)	44 (8.6)	38 (9.2)	46 (10.7)	40 (7.4)	42 (8.6)
Male sex, n (%)	22 (48.9)	4 (66.7)	3 (60.0)	14 (51.9)	43 (51.8)
Race, n (%)					
White	41 (91.1)	6 (100)	3 (60.0)	20 (74.1)	70 (84.3)
Asian	3 (6.7)	0	2 (40.0)	7 (25.9)	12 (14.5)
Black or African American	1 (2.2)	0	0	0	1 (1.2)
Cirrhosis present, n (%)	16 (35.6)	1 (16.7)	1 (20.0)	9 (33.3)	27 (32.5)
HBeAg positive, n (%)	6 (13.3)	1 (16.7)	0	3 (11.1)	10 (12.0)
Concomitant NA therapy, n (%)	28 (62.2)	2 (33.3)	3 (60.0)	18 (66.7)	51 (61.4)
Prior IFN therapy, n (%)	33 (73.3)	2 (33.3)	2 (40.0)	16 (59.3)	53 (63.9)
Genotype HDV-1, n (%)[a]	43 (95.6)	6 (100)	5 (100)	27 (100)	81 (97.6)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.1 (1.4)	5.2 (1.1)	5.1 (1.8)	5.2 (1.2)	5.1 (1.3)
ALT, U/L, median (Q1, Q3)	92 (63, 134)	96 (90, 175)	138 (133, 146)	77 (54, 116)	92 (63, 136)
LSM, kPa, mean (SD)	12.8 (7.0)	8.1 (2.2)	8.2 (3.9)	12.4 (8.1)	12.1 (7.1)
HAI, mean (SD)	9 (3.4)	8 (3.1)	8 (2.8)	8 (3.3)	8 (3.3)
Ishak fibrosis score, mean (SD)	3 (1.5)	2 (1.6)	2 (0.4)	2 (1.4)	2 (1.4)

[a]In the BLV 10 mg group, 1 patient had HDV genotype 5 and 1 patient was missing HDV genotype data; both patients had VR at W48.
ALT, alanine aminotransferase; BLV, bulevirtide; HAI, histology activity index; HBeAg, hepatitis B e antigen; HDV, hepatitis delta virus; IFN, interferon; LSM, liver stiffness measurement; NA, nucleos(t)ide analogue; NR, nonresponse; PR, partial response; Q, quartile; VR, virologic response; W, week.

- Overall, 83 patients with paired BL and W48 liver biopsies were included in this subanalysis
  - BLV treated (n = 56): VR at W48 (n = 45), PR at W48 (n = 6), and NR at W48 (n = 5)
  - Control (n = 27)

Results

Figure 2 **ALT Levels Over Time (BLV Treated + Control)**

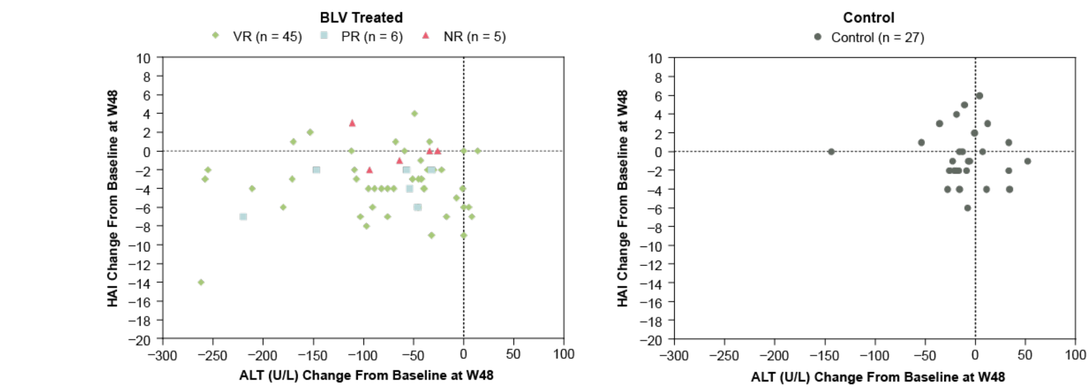


Patients Evaluated								
VR, n =	45	45	45	45	44	45	44	45
PR, n =	6	6	6	6	6	6	6	6
NR, n =	5	5	5	5	5	5	5	5
Control, n =	27	27	27	25	27	27	26	27

[a]Change at W48 was expressed as median change from BL. Not shown due to scale: ALT Q3 for PR at BL = 175.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; NR, nonresponse; PR, partial response; Q, quartile; VR, virologic response; W, week.

- Greater median changes in ALT levels from BL were observed in BLV-treated patients compared with the control group at W48, regardless of virologic response
  - Similar median changes in ALT levels were observed across response groups in patients treated with BLV

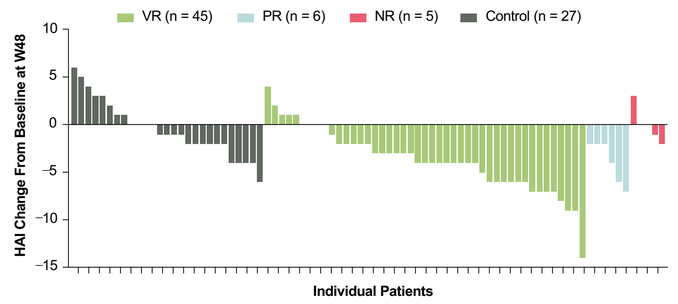
Figure 3 **Change From Baseline: HAI by ALT at W48**



ALT, alanine aminotransferase; BLV, bulevirtide; HAI, histology activity index; NR, nonresponse; PR, partial response; VR, virologic response; W, week.

- Decreases in ALT levels and HAI were observed in most patients treated with BLV, irrespective of response group
- The degree of improvement in HAI and ALT levels did not necessarily correlate
- No consistent pattern of HAI or ALT level change was observed in the control group

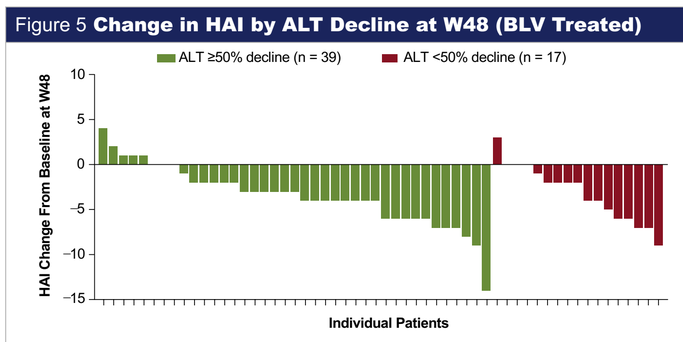
Figure 4 **Change in HAI by Virologic Response at W48 (BLV Treated + Control)**



BLV, bulevirtide; HAI, histology activity index; NR, nonresponse; PR, partial response; VR, virologic response; W, week.

- Improvement in HAI occurred as follows:
  - VR: 80% (36/45)
  - PR: 100% (6/6)
  - NR: 40% (2/5)
  - Control: 56% (15/27)

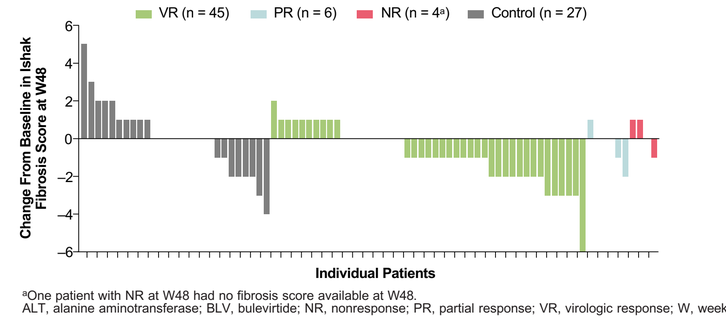
Figure 5 **Change in HAI by ALT Decline at W48 (BLV Treated)**



ALT, alanine aminotransferase; BLV, bulevirtide; HAI, histology activity index; W, week.

- HAI improvement was seen even in patients who had <50% decline in ALT
  - VR: 80% (36/45)
  - PR: 100% (6/6)
  - NR: 40% (2/5)
  - Control: 56% (15/27)

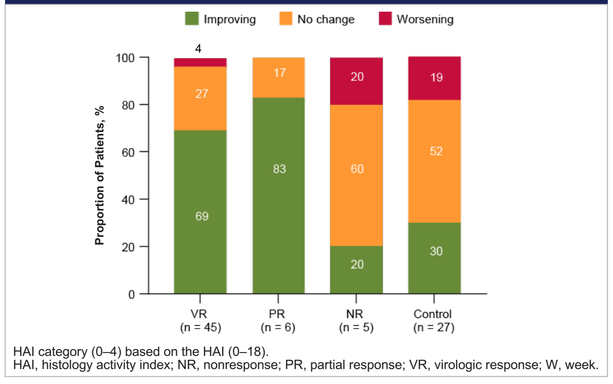
Figure 6 **Change in Ishak Fibrosis Score by Virologic Response at W48 (BLV Treated + Control)**



[a]One patient with NR at W48 had no fibrosis score available at W48.
ALT, alanine aminotransferase; BLV, bulevirtide; NR, nonresponse; PR, partial response; VR, virologic response; W, week.

- Improvement in Ishak fibrosis score occurred as follows:
  - VR: 58% (26/45)
  - PR: 33% (2/6)
  - NR: 25% (1/4)
  - Control: 30% (8/27)

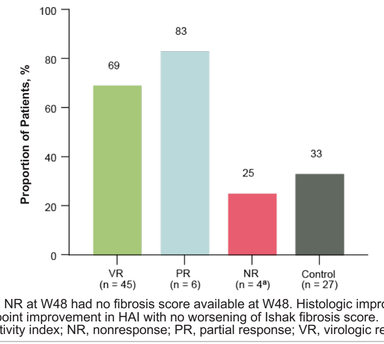
Figure 7 **Change in HAI Category From Baseline to W48**



HAI category (0–4) based on the HAI (0–18).
HAI, histology activity index; NR, nonresponse; PR, partial response; VR, virologic response; W, week.

- Improvement in HAI category occurred more frequently in patients with VR and PR

Figure 8 **Histologic Improvement From Baseline to W48**



[a]One patient with NR at W48 had no fibrosis score available at W48. Histologic improvement was defined as a ≥2-point improvement in HAI with no worsening of Ishak fibrosis score.
HAI, histology activity index; NR, nonresponse; PR, partial response; VR, virologic response; W, week.

- Histologic improvement occurred more frequently in patients with VR and PR

References: **1.** Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. **2.** Hepcludex. European Medicines Agency SmPC. Gilead Sciences, Inc.; 2023. **3.** Wedemeyer H, et al. EASL 2023. Oral #OS-068. **4.** Dietz-Fricke C, et al. *JHEP Rep*. 2023;5:100686.

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