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P41
Poster for you

Improvements in Fibrosis and Necroinflammation With Bulevirtide Combined With Pegylated Interferon for Chronic Hepatitis Delta

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Conclusions

In a subanalysis of the MYR204 study of finite treatment for chronic hepatitis delta, data from patients with paired biopsies demonstrated that:

- Treatment with bulevirtide and pegylated interferon alfa-2a led to improvements in liver fibrosis and necroinflammation at week 24 after the end of treatment
- Histologic improvement occurred with monotherapy and combination treatments
- Achieving undetectable hepatitis delta virus RNA in the posttreatment period was associated with numerically higher rates of histologic improvement
- A limited number of patients with paired biopsies and differences in baseline characteristics with the overall study population limit further interpretation of the data

Plain Language Summary

- Bulevirtide is the only drug approved for treatment of chronic hepatitis delta
- In a 144-week study, patients with chronic hepatitis delta received bulevirtide or pegylated interferon alone or in combination
- Liver biopsies taken at study week 0 and 24 weeks after treatment was completed showed that all treatments led to improvements in liver damage

Introduction

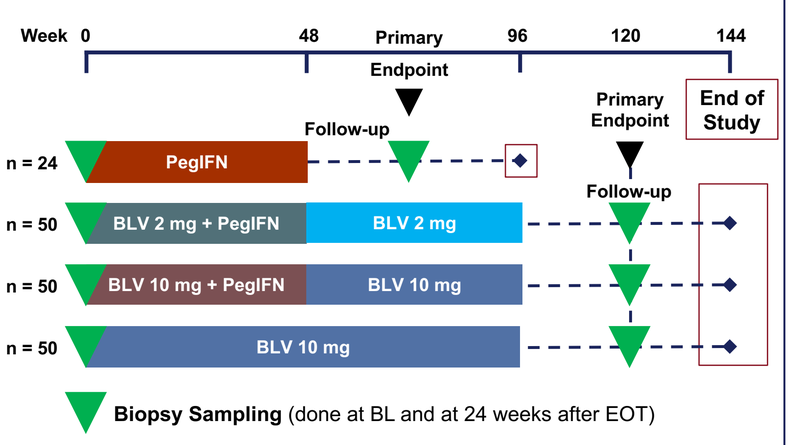
- Hepatitis delta virus (HDV) is associated with the worst viral hepatitis prognosis and with increased morbidity and mortality compared to monoinfection with hepatitis B virus[1-4]
- Bulevirtide (BLV) 2 mg is a first-in-class entry inhibitor approved in Europe, the Russian Federation, and Australia for the treatment of adults with chronic hepatitis delta (CHD) and compensated liver disease
- In MYR204, BLV 10 mg in combination with pegylated interferon alfa-2a (PegIFN) demonstrated a higher rate of HDV RNA undetectability, maintained through 48 weeks after the end of treatment (EOT), than either monotherapy[5]
- Monotherapy with BLV is associated with improvement in liver histology; however, data describing the effects of BLV in combination therapy on liver fibrosis and histologic findings are limited

Objective

- To evaluate the impact of BLV (2 mg and 10 mg) with or without PegIFN on liver fibrosis and histologic activity at week 24 after EOT in patients with compensated CHD

Methods

Figure 1 **Study Design**



Key Inclusion Criteria
- CHD with detectable serum HDV RNA
- With or without cirrhosis; CTP ≤6
- ALT >1 × to <10 × ULN; platelets ≥90,000 cells/mm^3
- No IFN within 6 months before enrolment

Primary Endpoint
- HDV RNA undetectable[a] at 24 weeks after EOT

[a]Undetectable was defined as the level below the lower limit of quantitation.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; CHD, chronic hepatitis delta; CTP, Child-Turcotte-Pugh; EOT, end of treatment; HDV, hepatitis delta virus; IFN, interferon; PegIFN, pegylated interferon alfa-2a; ULN, upper limit of normal.

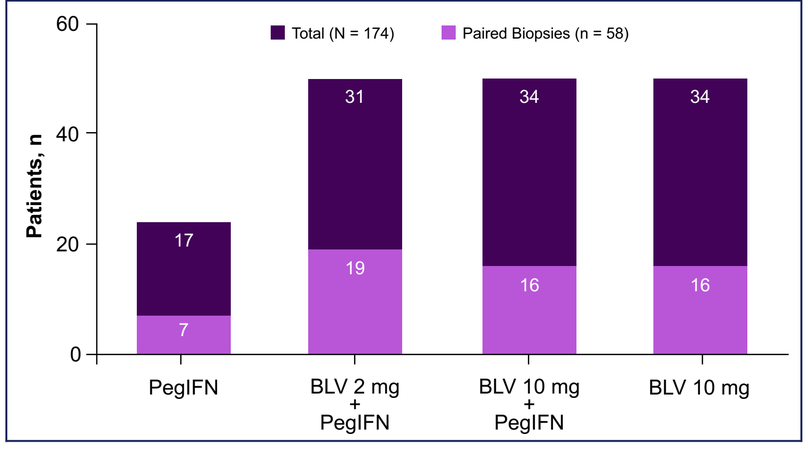
- Open-label, randomised, multicentre, Phase 2b study (NCT03852433) conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)

Results

Biopsy Evaluation

- Biopsy evaluation was performed in the 58 patients who had paired biopsies
  - Changes in fibrosis were evaluated using the Ishak fibrosis score (0–6) and METAVIR fibrosis score (F0–F4)
  - Change in necroinflammation was assessed by the histology activity index (HAI; 0–18) and METAVIR activity grade
  - Histologic improvement was defined as a decrease of ≥2 points from baseline in HAI without worsening of Ishak fibrosis score

Figure 2 **Proportion of Patients With Paired Biopsies**



BLV, bulevirtide; PegIFN, pegylated interferon alfa-2a.

Table 1 **Baseline Demographics and Disease Characteristics**

	PegIFN n = 7	BLV 2 mg + PegIFN n = 19	BLV 10 mg + PegIFN n = 16	BLV 10 mg n = 16	Total Paired Biopsies n = 58	Total Study Patients N = 174
Age, years, mean (SD)	43 (6.1)	44 (9.2)	42 (6.6)	38 (8.9)	42 (8.2)	41 (8.7)
Male sex, n (%)	6 (86)	15 (79)	11 (69)	13 (81)	45 (78)	124 (71)
Race,[a] n (%)						
Caucasian	6 (86)	19 (100)	14 (88)	14 (88)	53 (91)	151 (87)
Asian	1 (14)	0	0	1 (6)	2 (3)	15 (9)
Black	0	0	2 (13)	1 (6)	3 (5)	7 (4)
Cirrhosis, n (%)	1 (14)	5 (26)	2 (13)	4 (25)	12 (21)	59 (34)
Liver stiffness, kPa, median (Q1, Q3)	10.2 (8.5, 20.9)	11.7 (7.2, 16.3)	10.0 (7.4, 11.7)	10.3 (7.9, 13.2)	10.3 (7.9, 14.0)	10.8 (7.9, 15.3)
ALT, U/L, median (Q1, Q3)	102 (65, 179)	81 (57, 142)	82 (49, 125)	85 (57, 118)	84 (57, 137)	83 (58, 135)
HDV RNA, $\log_{10}$ IU/mL, median (Q1, Q3)	4.1 (4.0, 4.7)	5.6 (4.7, 6.2)	5.3 (3.9, 6.0)	5.5 (4.0, 6.1)	5.3 (4.0, 6.0)	5.5 (4.5, 6.2)
HDV GT,[b] 1/5, n	7/0	19/0	13/2	15/1	54/3	168/4[c]
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.4 (0.7)	3.7 (0.6)	3.4 (1.0)	3.8 (0.4)	3.6 (0.7)	3.7 (0.6)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	0.6 (0.8)	1.5 (1.1)	1.4 (1.4)	2.2 (2.1)	1.5 (1.5)	1.6 (1.4)
HBeAg negative, n (%)	7 (100)	16 (84)	15 (94)	12 (75)	50 (86)	155 (89)
HBV GT,[b] A/D/E, n	1/6/0	0/19/0	1/11/2	0/15/0	2/51/2	26/138/3
Prior interferon use, n (%)	3 (43)	5 (26)	4 (25)	4 (25)	16 (28)	84 (48)
Concomitant HBV medication, n (%)	2 (29)	7 (37)	5 (31)	9 (56)	23 (40)	83 (48)

[a]BLV 10 mg + PegIFN, other race, n = 1. [b]Only available/classified data presented. [c]BLV 2 mg + PegIFN, GT HDV-6, n = 1.
ALT, alanine aminotransferase; BLV, bulevirtide; GT, genotype; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; PegIFN, pegylated interferon alfa-2a; Q, quartile.

- Among patients with paired biopsies, fewer had cirrhosis at baseline and prior interferon use compared with the overall study population

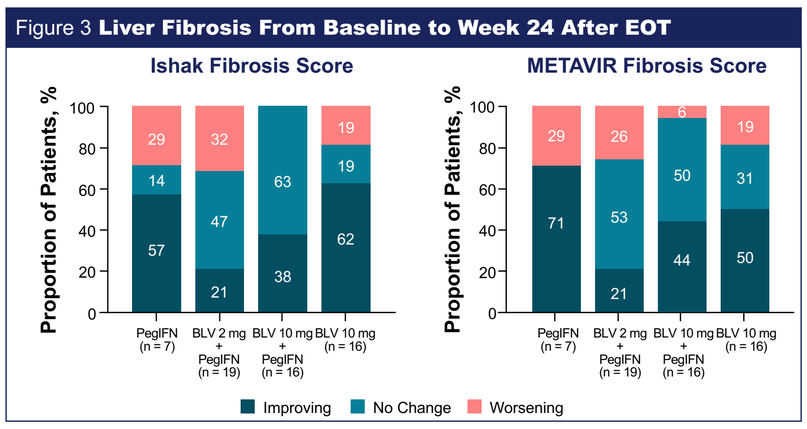
Table 2 **Undetectable HDV RNA at 24 Weeks After EOT**

	PegIFN	BLV 2 mg + PegIFN	BLV 10 mg + PegIFN	BLV 10 mg
Total study, n	24	50	50	50
Patients with undetectable HDV RNA, n (%)	4 (17)	16 (32)	23 (46)	6 (12)
Paired biopsies subset, n	7	19	16	16
Patients with undetectable HDV RNA, n (%)	4 (57)	9 (47)	11 (69)	2 (13)

BLV, bulevirtide; EOT, end of treatment; HDV, hepatitis delta virus; PegIFN, pegylated interferon alfa-2a.

- Response rates were highest with BLV 10 mg + PegIFN in both the total study population and the paired biopsies subset
- Small sample size and differences in baseline characteristics in the paired biopsies subset may account for differences in response rates between the overall study population and the paired biopsies subset

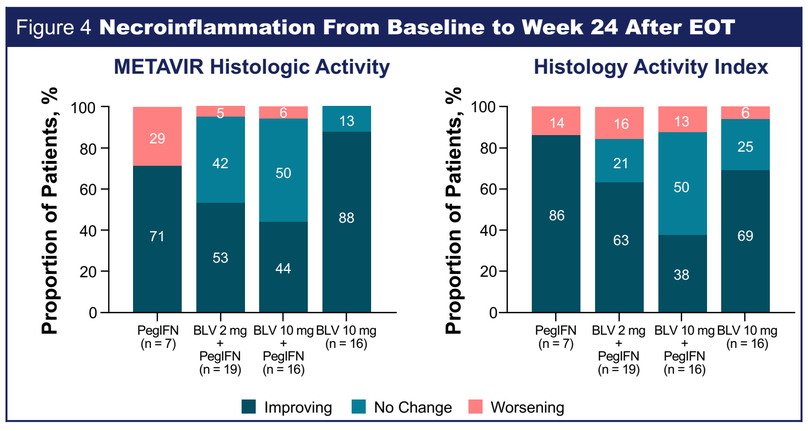
Figure 3 **Liver Fibrosis From Baseline to Week 24 After EOT**



Due to rounding, percentages may not add up to 100%.
BLV, bulevirtide; EOT, end of treatment; PegIFN, pegylated interferon alfa-2a.

- Between 68% and 100% of patients had fibrosis improvements (decrease of ≥1 point from baseline) or no change at follow-up week 24 across the 2 methods of scoring
- Fewer patients in the BLV 10 mg + PegIFN group than in other groups had worsening of liver fibrosis

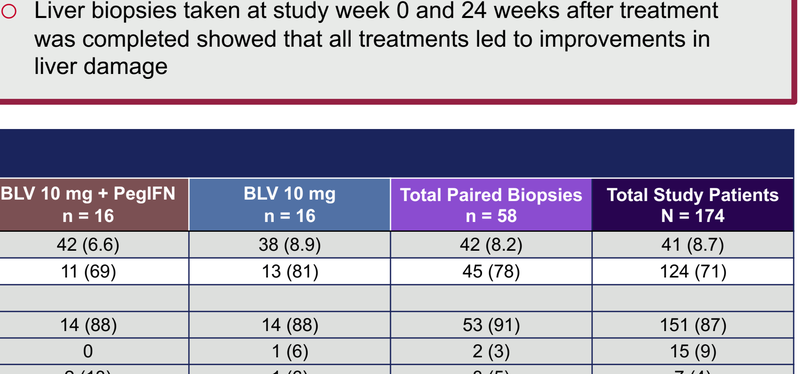
Figure 4 **Necroinflammation From Baseline to Week 24 After EOT**



Due to rounding, percentages may not add up to 100%.
BLV, bulevirtide; EOT, end of treatment; PegIFN, pegylated interferon alfa-2a.

- The proportion who had necroinflammation improvements (decrease of ≥1 point from baseline) or no change at follow-up week 24 ranged from 71% to 100%
- In all groups, treatment resulted in improvement or no change in necroinflammation for the majority of patients

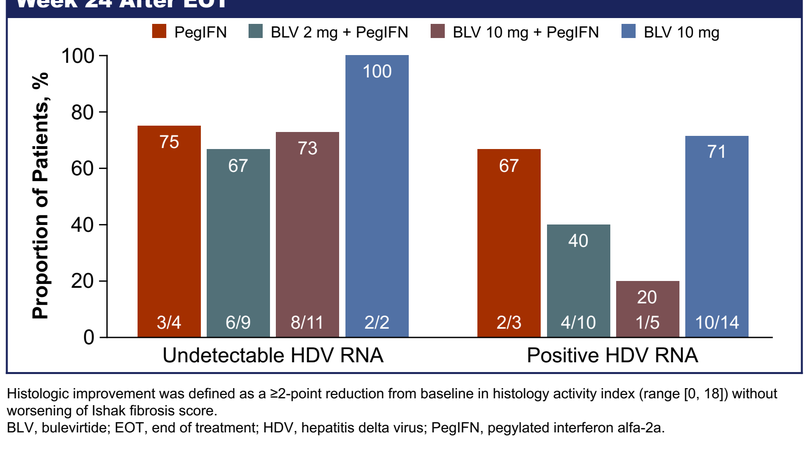
Figure 5 **Histologic Improvement at Week 24 After EOT**



Histologic improvement was defined as a ≥2-point reduction from baseline in histology activity index (range [0, 18]) without worsening of Ishak fibrosis score.
BLV, bulevirtide; EOT, end of treatment; PegIFN, pegylated interferon alfa-2a.

- Histologic improvement was observed in all groups, with rates numerically higher in the monotherapy arms

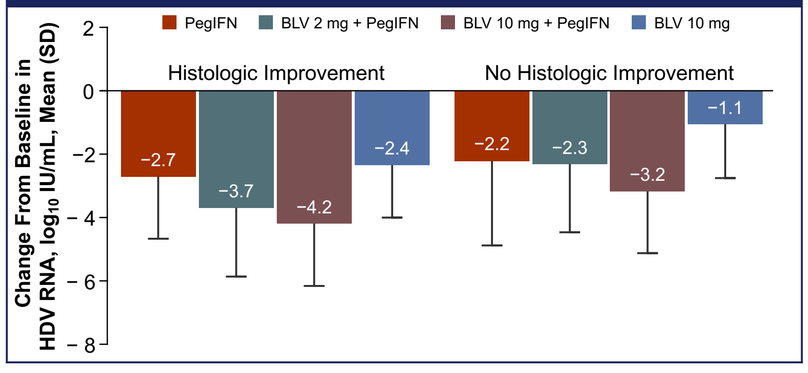
Figure 6 **Histologic Improvement by HDV RNA Undetectability at Week 24 After EOT**



Histologic improvement was defined as a ≥2-point reduction from baseline in histology activity index (range [0, 18]) without worsening of Ishak fibrosis score.
BLV, bulevirtide; EOT, end of treatment; HDV, hepatitis delta virus; PegIFN, pegylated interferon alfa-2a.

- Histologic improvement rates were numerically greater among patients who achieved undetectable HDV RNA at week 24 after EOT

Figure 7 **HDV RNA Change by Histologic Improvement at Week 24 After EOT**



Responders were those with histologic improvement defined as a ≥2-point reduction from baseline in histology activity index (range [0, 18]) without worsening of Ishak fibrosis score.
BLV, bulevirtide; EOT, end of treatment; HDV, hepatitis delta virus; PegIFN, pegylated interferon alfa-2a.

- Patients with histologic improvement had numerically greater HDV RNA decline

References: 1. Alfaiate D, et al. *J Hepatol*. 2020;73(3):533-9. **2.** Rizzetto M, et al. *J Hepatol*. 2021;74(5):1200-11. **3.** Fattovich G, et al. *Gut*. 2000;46:420-6. **4.** Wranke A, et al. *Hepatol Int*. 2023;17(6):1359-67. **5.** Asselah T, et al. *N Engl J Med*. 2024;391:133-43.

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