Efficacy and Safety of Bulevirtide Monotherapy for Chronic Hepatitis Delta: Posttreatment Results Through 48 Weeks After the End of Treatment From an Interim Analysis of a Randomized Phase 3 Study, MYR301

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Conclusions

- A subset of patients treated with bulevirtide (BLV) monotherapy for 2 to 3 years maintained virologic and biochemical responses 1 year after stopping BLV
- The rate of liver-related clinical outcomes occurring while on BLV and through 1 year after treatment was low
- Posttreatment hepatitis flares are expected following discontinuation of BLV treatment
  - The majority of posttreatment hepatic serious adverse events and ALT elevations were observed within 24 weeks after the end of treatment (EOT) and were associated with HDV rebound
  - BLV retreatment was required in some patients
- Assessment of the durability of posttreatment response at 96 weeks after EOT is planned

Plain Language Summary

- Hepatitis delta virus infection causes severe liver disease and liver-related events
- Bulevirtide is a treatment for chronic hepatitis delta infection that is safe and used in adult patients with compensated liver disease
- Here, we evaluated patients treated with bulevirtide for 2 to 3 years. Some of these patients maintained responses to bulevirtide 1 year after stopping treatment; some needed retreatment
- Progression to liver-related outcomes 1 year after finishing bulevirtide therapy was uncommon

Please scan the QR code for an expanded version of this plain language summary.

Introduction

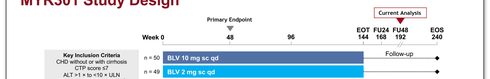
- Hepatitis delta virus (HDV) infection causes the most severe form of chronic hepatitis,[1,2] with prevalence estimates of between 10 and 20 million people worldwide[3]
- Bulevirtide (BLV) is a first-in-class entry inhibitor approved in the EU, Great Britain, Switzerland, the Russian Federation, and Australia for chronic hepatitis delta (CHD)[4,5] and is recommended by the European Association for the Study of the Liver guidelines for the treatment of CHD in adult patients with compensated liver disease[5]
- Monotherapy with BLV 2 mg/day or 10 mg/day has been demonstrated to be effective and safe over 144 weeks of treatment[6-8]
- On-treatment improvements in virologic and biochemical responses, improvements in liver stiffness, low occurrence of liver-related outcomes, and real-world experience all support the potential clinical benefits of long-term BLV monotherapy[8]

Objective

- The objective of this interim analysis of the Phase 3 MYR301 study was to evaluate the long-term efficacy and safety of BLV 2 or 10 mg monotherapy at study week 192, representing up to 144 weeks of treatment followed by 48 weeks of follow-up after the end of treatment (EOT)

Methods

MYR301 Study Design



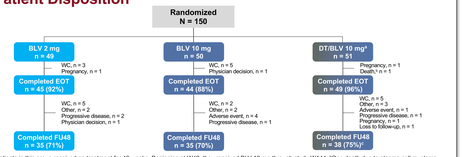
ALT, alanine aminotransferase; BLV, bulevirtide; CHD, chronic hepatitis delta; CTP, Child-Turcotte-Pugh; EOS, end of study; EOT, end of treatment (week 144); FU24, follow-up at 24 weeks after EOT (week 168); FU48, follow-up at 48 weeks after EOT (week 192); qd, once daily; sc, subcutaneous; ULN, upper limit of normal.

- MYR301 was a multicenter, open-label, randomized, Phase 3 study (NCT03852719) conducted in 4 countries (Germany, Italy, Russian Federation, and Sweden)
- Primary endpoint
  - Combined response[9] at week 48: HDV RNA undetectable[a] or decreased by ≥2 $\log_{10}$ IU/mL from baseline (BL) and alanine aminotransferase (ALT) normalization[b]
- Safety and efficacy endpoints at week 144 (EOT), follow-up at 24 weeks after EOT (FU24 [week 168]), and follow-up at 48 weeks after EOT (FU48 [week 192]) are described below

[a]Undetectable HDV RNA was defined as less than the lower limit of quantitation (50 IU/mL; target not detected). [b]ALT normalization was defined as ≤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).

Results

Patient Disposition



[a]Patients in this group received no treatment for 48 weeks. Beginning at W48, they received BLV 10 mg through study W144. [b]One death due to plasma cell myeloma. [c]One patient withdrew consent at the W192 visit.
BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (week 144); FU48, follow-up at 48 weeks after EOT (week 192); W, week; WC, withdrawal of consent (reasons for withdrawal of consent unknown).

- Most patients in all groups continued in the study through EOT and FU48

BL Demographics and Disease Characteristics

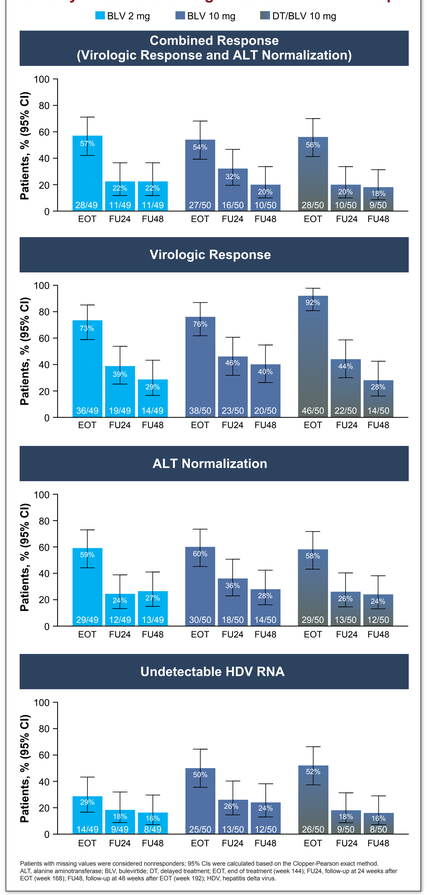
	BLV 2 mg (n = 49)	BLV 10 mg (n = 50)	DT/BLV 10 mg (n = 51)[a]
Age, years, mean (SD)	44 (9)	41 (9)	41 (8)
Male sex, n (%)	30 (61)	30 (60)	26 (51)
Race,[b] n (%)			
White	41 (84)	43 (86)	40 (78)
Asian	8 (16)	6 (12)	11 (22)
Cirrhosis present, n (%)	23 (47)	24 (48)	24 (47)
Liver stiffness, kPa, mean (SD)	14.0 (8.2)	14.8 (9.3)	15.3 (9.0)
ALT, U/L, mean (SD)	108 (63)	123 (81)	102 (62)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.10 (1.20)	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)	1.30 (1.29)	1.08 (1.26)	0.89 (0.99)
HBV genotype,[d] n (%)			
A	2 (4)	2 (4)	2 (4)
D	47 (96)	44 (88)	44 (86)
Previous IFN therapy, n (%)	26 (53)	29 (58)	29 (57)
Concomitant HBV NA treatment,[e] n (%)	32 (65)	27 (54)	32 (63)

[a]All BL, 51 patients were assigned to DT/BLV 10 mg, and their data are reported here. One patient subsequently withdrew from the DT/BLV 10 mg group before receiving BLV and is not included in subsequent reporting of efficacy and safety. [b]BLV 10 mg arm: Black, n = 1. [c]BLV 10 mg arm: HDV GT 5, n = 1; missing HDV GT, n = 1. [d]Other: BLV 10 mg arm: HBV GT E, n = 1; DT/BLV 10 mg arm: unclassified HBV GT, n = 2. [e]All patients who started NA therapy at or after BL, except 1, started at BL or within 2 days of BL.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; DT, delayed treatment; GT, genotype; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; NA, nucleos(t)ide analogue.

- Nearly half the patients had cirrhosis at BL; demographic and BL disease characteristics were well balanced between treatment groups

Results

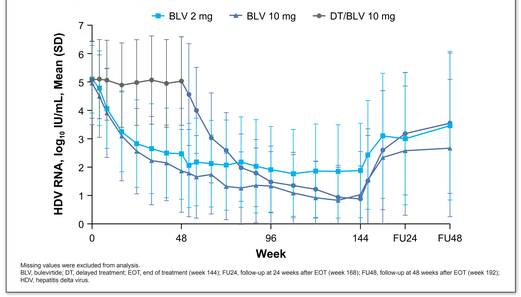
Efficacy at EOT and During Posttreatment Follow-Up



Patients with missing values were considered nonresponders; 95% CIs were calculated based on the Clopper-Pearson exact method.
ALT, alanine aminotransferase; BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (week 144); FU24, follow-up at 24 weeks after EOT (week 168); FU48, follow-up at 48 weeks after EOT (week 192); HDV, hepatitis delta virus.

- Combined response, ALT normalization, and virologic response rates decreased from EOT to FU48
- Rates of undetectable HDV RNA were numerically higher for the BLV 10 mg arms at EOT but decreased in all arms through FU48

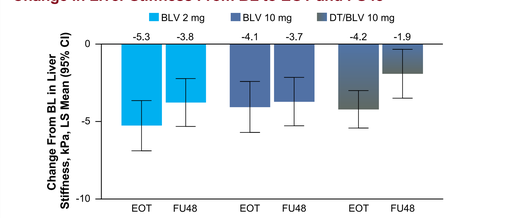
Mean HDV RNA Over Time



Missing values were excluded from analysis.
BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (week 144); FU24, follow-up at 24 weeks after EOT (week 168); FU48, follow-up at 48 weeks after EOT (week 192); HDV, hepatitis delta virus.

- Mean HDV RNA values observed during follow-up remained lower than BL levels

Change in Liver Stiffness From BL to EOT and FU48



LS means and 95% CIs were based on the mixed-effects model for repeated measurements for change from BL with treatment (BLV 2 mg, BLV 10 mg, and DT/BLV 10 mg groups), region, presence of cirrhosis, visit and treatment by visit interaction as fixed effects, and BL value as a covariate.
BL, baseline; BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (week 144); FU48, follow-up at 48 weeks after EOT (week 192); LS, least squares.

- Improvements in liver stiffness were seen at EOT and persisted during the posttreatment period

HBsAg Loss and Liver-Related Clinical Outcomes

Number of Patients, n/N	BLV 2 mg (n = 49)		BLV 10 mg (n = 50)		DT/BLV 10 mg (n = 50)	
Time point	**BL to EOT**	**FU48**	**BL to EOT**	**FU48**	**W48 (DT) to EOT**	**FU48**
HBsAg loss	0/49	1/49	0/50	1/50	1/50	1/50
Liver-related clinical outcomes	0/49	1/46	0/50	0/47	1/50	1/49

HBsAg loss was defined as HBsAg positive at BL and HBsAg negative at visit. DT/BLV 10 mg: BLV was administered starting at W48 through the W144 (or EOT) visit for the DT group. BL was reset at W48 (ie, re-BL). Potential liver-related clinical outcomes included but were not limited to cirrhosis development; liver decompensation, including development of or worsening jaundice, coagulopathy, ascites, hepatic encephalopathy, bleeding from varices, and liver failure; hepatocellular carcinoma development; liver transplant; and liver-related death. Posttreatment events were those that started after the last dose date of BLV.
BL, baseline; BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (week 144); FU48, follow-up at 48 weeks after EOT (week 192); HBsAg, hepatitis B surface antigen; W, week.

- HBsAg loss was rare at EOT and during posttreatment follow-up
- Liver-related clinical outcomes:
  - On treatment, 1 case of ascites (nonserious) in the DT/BLV 10 mg group
  - Posttreatment, 1 case of ascites (nonserious, associated with a serious adverse event [SAE] of hepatic function abnormal) in the DT/BLV 10 mg group and 1 case of esophageal varices hemorrhage (with no ALT or HDV RNA increases) in the BLV 2 mg group

Overall Safety Summary

Patients, n (%)	BLV 2 mg		BLV 10 mg		DT/BLV 10 mg	
	EOT (n = 49)	EOT to FU48 (n = 46)	EOT (n = 50)	EOT to FU48 (n = 47)	W48 to EOT[a] (n = 50)	EOT to FU48 (n = 49)
Any AE	48 (98)	31 (67)	48 (96)	34 (72)	46 (92)	30 (61)
Any AE related to BLV	27 (55)	N/A	37 (74)	N/A	23 (46)	N/A
Any Grade 3 or 4 AE	12 (24)	6 (13)	10 (20)	6 (13)	5 (10)	11 (22)
Any SAE	3 (6)	3 (7)	6 (12)	4 (9)	3 (6)	6 (12)
Any AE leading to withdrawal of BLV	0	N/A	0	N/A	0	N/A
Death	0	0	0	0	1 (2)[b]	0
Hepatic AEs	14 (29)	21 (46)	10 (20)	20 (43)	5 (10)	22 (45)
Hepatic SAEs	0	3 (7)	0	3 (6)	0	5 (10)

[a]AEs from the first 48 weeks are not shown. [b]One death due to plasma cell myeloma not related to study drug.
AE, adverse event; BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (week 144); FU48, follow-up at 48 weeks after EOT (week 192); N/A, not applicable; SAE, serious adverse event; W, week.

- The safety profile observed, both on treatment and posttreatment, was consistent with the known safety profile of BLV

On-Treatment Safety

- There were no study drug discontinuations due to adverse events. None of the SAEs or deaths were attributed to BLV through EOT

Posttreatment Safety

- 13 patients experienced posttreatment SAEs, of whom the majority (11) experienced posttreatment hepatic SAEs
- 15 patients restarted BLV in the posttreatment period up to FU48, 10 of whom had posttreatment ALT >5 × the upper limit of normal (ULN)
- Overall, posttreatment **ALT >5 × ULN** occurred in 47 of 140[a] (34%) patients, with similar frequencies between treatment groups
- Overall, posttreatment **ALT >10 × ULN** occurred in 14[b] of 140[a] (10%) patients

[a]The denominator for the percentage calculation was the number of patients in the treatment group with ≥1 ALT value after the last BLV dose.
[b]Includes SAE report data (2 participants) reported by the principal investigator using local labs. Two BLV restarts reported in SAE reports only.

Hepatic SAEs in the Posttreatment Period

Patients, n (%)	BLV 2 mg EOT to FU48 (n = 46)	BLV 10 mg EOT to FU48 (n = 47)	DT/BLV 10 mg EOT to FU48 (n = 49)
Hepatic SAEs, preferred term	3 (7)	3 (6)	5 (10)
Esophageal varices hemorrhage	1 (2)	0	0
Hepatitis	0	0	1 (2)
Hepatitis D	1 (2)	2 (4)	0
Hepatitis acute	1 (2)	0	0
Hepatic function abnormal	0	0	1 (2)
Liver injury	0	0	1 (2)
Transaminase increased	0	1 (2)	1 (2)
Chronic hepatitis B[a]	0	0	1 (2)

Posttreatment hepatic SAEs in 11 patients were associated with:

- **ALT >5 × ULN:** 10 patients
- **Liver-related hospitalization:** 3 patients
  - Liver injury (attributed to tramadol/dexketoprofen)
  - Chronic hepatitis B
  - Esophageal varices hemorrhage
- **HDV viremia rebound[b]:** 8 patients
- **HBV or HDV treatment required**
  - BLV, 8 patients
  - TDF, 1 patient

[a]Additional SAE to MedDRA search list for hepatic SAEs. [b]HDV RNA viremia rebound: increase in posttreatment HDV RNA ≥2 $\log_{10}$ IU/mL from the LLOQ of 50 IU/mL if HDV RNA <LLOQ at EOT or increase in posttreatment HDV RNA ≥2 $\log_{10}$ IU/mL from the level at EOT.
ALT, alanine aminotransferase; BLV, bulevirtide; DT, delayed treatment; EOT, end of treatment (week 144); FU48, follow-up at 48 weeks after EOT (week 192); HBV, hepatitis B virus; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

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.** Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. **4.** Hepcludex. European Medicines Agency SmPC. Gilead Sciences, Inc.; 2023. **5.** European Association for the Study of the Liver. *J Hepatol*. 2023;79:433-60. **6.** Wedemeyer H, et al. *N Engl J Med*. 2023;389:22-32. **7.** Wedemeyer H, et al. *J Hepatol*. 2024;81:621-9. **8.** Lampertico P, et al. *J Hepatol*. 2024;80(suppl 1):S92. **9.** Food and Drug Administration. Chronic hepatitis D virus infection: developing drugs for treatment guidance for industry. Draft guidance. November 2019.

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