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Efficacy and Safety of Bulevirtide Monotherapy for Chronic Hepatitis Delta in Patients With and Without Cirrhosis: Results From the Week 144 Interim Analysis of a Phase 3 Randomized Study

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Conclusions

- Treatment with bulevirtide (BLV) monotherapy through 144 weeks resulted in continued virologic and biochemical improvements regardless of presence of cirrhosis
- Combined response rates were similar between patients with and without cirrhosis treated with BLV 2 mg and 10 mg
- BLV was safe and well tolerated in patients with and without cirrhosis; Grade 3 and 4 adverse events were more frequent among patients with cirrhosis

Plain Language Summary

- Regardless of the level of scarring in their liver, patients with chronic hepatitis delta who received bulevirtide for 144 weeks achieved reductions in hepatitis delta virus RNA levels and maintained improvements in other markers of liver health and function
- Treatment with bulevirtide 2 or 10 mg/d was safe and efficacious in patients with and without cirrhosis treated over a period of up to 144 weeks

Introduction

- Hepatitis delta virus (HDV) causes the most severe form of chronic viral hepatitis, affecting approximately 10 to 20 million people worldwide[1]
- Bulevirtide (BLV) is a first-in-class entry inhibitor for chronic hepatitis delta (CHD) that is approved in the European Union, United Kingdom, Switzerland, the Russian Federation, and Australia for treatment of CHD in patients with compensated liver disease[2-4]
- Previous results from the ongoing Phase 3 study MYR301 (NCT03852719)[2,5-7] demonstrated that monotherapy with BLV 2 mg/d or 10 mg/d was effective and safe over 144 weeks

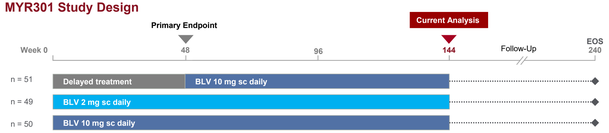
Objectives

- To assess the efficacy and safety of monotherapy with BLV 2 mg or 10 mg for 144 weeks in patients with compensated cirrhosis at baseline (BL) compared with patients without cirrhosis

Methods

- MYR301 is a multicenter, open-label, randomized, Phase 3 study (NCT03852719) conducted in 16 sites across 4 countries (Germany, Italy, Russian Federation, and Sweden)

MYR301 Study Design



BLV, bulevirtide; EOS, end of study; sc, subcutaneously.

- **Key inclusion criteria**
  - CHD without or with compensated cirrhosis and Child-Turcotte-Pugh score ≤7
  - Positive serum HDV RNA
  - Alanine aminotransferase (ALT) >1 × to <10 × upper limit of normal[a]
  - Platelets ≥60 × 10^9 cells/L
  - Controlled HIV coinfection was allowed
- 150 patients with CHD were stratified based on the presence or absence of cirrhosis (investigator determined) at BL
- Efficacy and safety endpoints were assessed in patients with and without cirrhosis
  - **Combined response**: undetectable HDV RNA[b] or decrease by ≥2 $\log_{10}$ IU/mL from BL and ALT normalization[a]
  - **Virologic response**: undetectable HDV RNA[b] or decrease by ≥2 $\log_{10}$ IU/mL from BL
  - **Biochemical response**: ALT normalization[a]
  - Change in liver stiffness (LS)
  - Adverse events (AEs) and levels of bile acids
- HDV RNA levels were determined by RT-qPCR using the RoboGene HDV RNA Quantification Kit 2.0 (lower limit of quantification [LLOQ], 50 IU/mL; limit of detection [LOD], 6 IU/mL)

[a]ALT upper limit of normal/normalization: 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. [b]Undetectable HDV RNA was defined as <LLOQ (target not detected); LLOQ: 50 IU/mL, LOD: 6 IU/mL.

Results

Baseline Demographics and Disease Characteristics by Cirrhosis Status

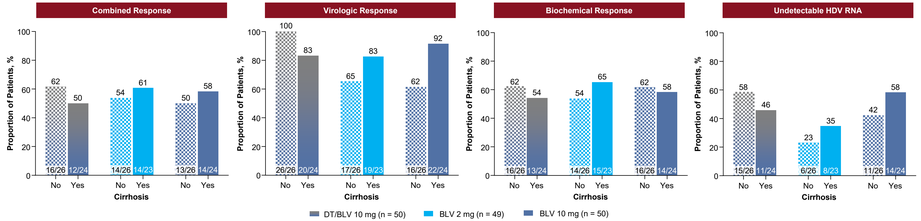
		DT/BLV 10 mg n = 50[a,b]		BLV 2 mg n = 49		BLV 10 mg n = 50	
		Cirrhosis					
		No (n = 26)	Yes (n = 24)	No (n = 26)	Yes (n = 23)	No (n = 26)	Yes (n = 24)
Age, years, mean (SD)		41 (7)	43 (8)	42 (9)	45 (10)	41 (8)	42 (9)
Male sex, n (%)		14 (54)	12 (50)	13 (50)	17 (74)	15 (58)	15 (63)
Race,[c] n (%)	White	18 (69)	21 (88)	21 (81)	20 (87)	23 (88)	20 (83)
	Asian	8 (31)	3 (13)	5 (19)	3 (13)	3 (12)	3 (13)
BMI, kg/m², mean (SD)		26.4 (3.5)	24.9 (4.0)	24.5 (3.4)	24.3 (2.7)	25.0 (3.1)	25.2 (4.2)
Platelet count, 10^9 cells/L, mean (SD)		181 (43)	127 (48)	172 (48)	130 (49)	184 (43)	134 (52)
Liver stiffness, kPa, mean (SD)		11.0 (7.2)	21.6 (13.4)	9.1 (3.0)	19.5 (8.7)	10.2 (3.9)	19.9 (10.7)
Child-Turcotte-Pugh score, n (%)	5	-	19 (79)	-	16 (70)	-	17 (71)
	6	-	5 (21)	-	7 (30)	-	7 (29)
ALT, U/L, median (Q1, Q3)		74 (50, 107)	59 (47, 88)	81 (63, 136)	101 (65, 141)	113 (74, 189)	99 (53, 134)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)		5.2 (1.4)	4.8 (1.7)	5.5 (0.8)	4.6 (1.4)	5.2 (1.4)	4.8 (1.5)
HBsAg, $\log_{10}$ IU/mL, mean (SD)		3.8 (0.5)	3.6 (0.7)	3.6 (0.6)	3.7 (0.4)	3.6 (0.7)	3.6 (0.5)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)		1.1 (1.2)	0.6 (0.7)	1.5 (1.5)	1.1 (1.0)	1.2 (1.6)	0.9 (0.7)
HBeAg positive, n (%)		2 (8)	2 (8)	0	4 (17)	4 (15)	3 (13)
Previous IFN therapy, n (%)		16 (62)	13 (54)	16 (62)	10 (43)	14 (54)	15 (63)
Concomitant NA treatment, n (%)		14 (54)	18 (75)	13 (50)	19 (83)	12 (46)	15 (63)

[a]One patient discontinued from the DT arm before week 48 and was not included in the efficacy and safety analysis beyond week 48. [b]The baseline values were reset at the week 48 visit for age, BMI, platelet count, liver stiffness, ALT, HDV RNA, HBsAg, and HBV DNA. [c]One patient in the BLV 10 mg group with cirrhosis was Black.
ALT, alanine aminotransferase; BLV, bulevirtide; BMI, body mass index; DT, delayed treatment; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; NA, nucleos(t)ide analogue; Q1, quartile 1; Q3, quartile 3.

- 71 of 149 (48%) patients had compensated cirrhosis at BL; 73% and 27% of those with cirrhosis had Child-Turcotte-Pugh scores of 5 and 6, respectively
- BL characteristics were largely similar between those with and without compensated cirrhosis
  - Patients with cirrhosis had higher liver stiffness measurements and lower platelet counts

Results

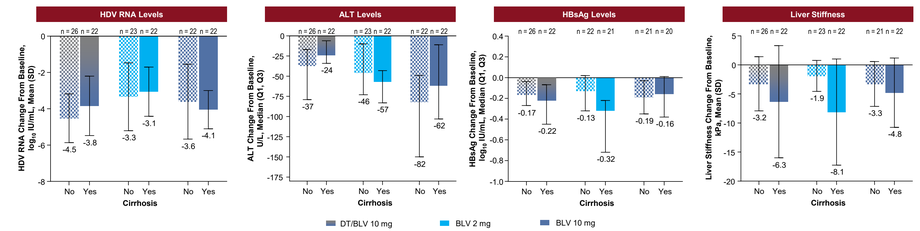
Efficacy Endpoints by Cirrhosis Status at Week 144



Missing values were considered as nonresponders. The DT/BLV 10 mg group received 96 weeks of BLV therapy; the baseline was reset at week 48 for this group.
BLV, bulevirtide; DT, delayed treatment; HDV, hepatitis delta virus.

- Virologic and biochemical responses were observed in similar proportions among patients with and without cirrhosis

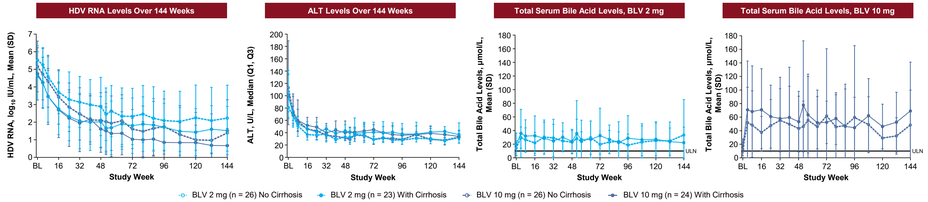
Changes From Baseline in HDV RNA Levels, ALT Levels, HBsAg Levels, and Liver Stiffness at Week 144



The DT/BLV 10 mg group received 96 weeks of BLV therapy; the baseline was reset at week 48 for this group.
ALT, alanine aminotransferase; BLV, bulevirtide; DT, delayed treatment; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; Q1, quartile 1; Q3, quartile 3.

- Both BLV 2 mg and 10 mg were associated with decreases from BL to week 144 in HDV RNA, ALT, and liver stiffness regardless of cirrhosis status

HDV RNA, ALT, and Total Serum Bile Acid Levels Over 144 Weeks of Treatment by Cirrhosis Status



Mean and median values are based on the number of patients with data available at each visit. Only 2 and 10 mg arms are shown here.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; HDV, hepatitis delta virus; Q1, quartile 1; Q3, quartile 3; ULN, upper limit of normal.

- Dose-dependent asymptomatic elevations in total serum bile acid levels were observed, which is expected with BLV treatment given its mechanism of action
- Presence of cirrhosis had no statistically significant effects on bile acid elevations

Univariate Analysis of Efficacy Responses at Week 144 by Cirrhosis Status at BL

	DT/BLV 10 mg[a] n = 46		BLV 2 mg[a] n = 42		BLV 10 mg[a] n = 41	
	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
Cirrhosis: yes vs no						
Combined response	0.73 (0.23, 2.37)	.60	1.10 (0.32, 3.86)	.88	1.44 (0.39, 5.27)	.59
Virologic response	0.10 (0.01, 2.27)	.15	3.00 (0.53, 17.02)	.21	17.19 (0.84, 353.57)	.07
Biochemical response	0.89 (0.27, 2.89)	.84	1.39 (0.39, 5.01)	.61	0.73 (0.18, 2.92)	.66
HDV RNA undetectable	0.59 (0.18, 1.90)	.38	1.31 (0.34, 5.01)	.70	1.65 (0.48, 5.69)	.43

The DT/BLV 10 mg group received 96 weeks of BLV; the BL was reset at week 48 for this study group when deriving the efficacy responses and when excluding the patients with BL HDV RNA <250 IU/mL.
[a]Week 144 completers with BL HDV RNA ≥250 IU/mL.
BL, baseline; BLV, bulevirtide; DT, delayed treatment; HDV, hepatitis delta virus; OR, odds ratio.

- In a univariate logistic regression analysis, cirrhosis status was not a predictor of efficacy responses

Safety Summary at Week 144 by Cirrhosis Status

	DT/BLV 10 mg n = 50[a,b]		BLV 2 mg n = 49		BLV 10 mg n = 50	
	Cirrhosis					
Patients With, n (%)	No (n = 26)	Yes (n = 24)	No (n = 26)	Yes (n = 23)	No (n = 26)	Yes (n = 24)
Any AE	23 (88)	23 (96)	25 (96)	23 (100)	25 (96)	23 (96)
Any Grade ≥3 AE	1 (4)	4 (17)	6 (23)	6 (26)	2 (8)	8 (33)
Any AE related to BLV	13 (50)	10 (42)	14 (54)	13 (57)	18 (69)	19 (79)
Any SAE	2 (8)	1 (4)	1 (4)	2 (9)	3 (12)	3 (13)
Any SAE related to BLV	0	0	0	0	0	0
Any AE leading to withdrawal of BLV	0	0	0	0	0	0
Death[c]	0	1 (4)	0	0	0	0

All AEs were treatment-emergent AEs (TEAEs). TEAEs began on or after the first dose of BLV up to 30 days after permanent discontinuation of the study drug or led to premature study drug discontinuation.
[a]One patient discontinued prior to receiving any study drug.
[b]TEAEs reported for the DT/BLV 10 mg group began on or after the first dose of BLV at week 48; the BLV treatment duration was 96 weeks.
[c]One death due to plasma cell myeloma not related to BLV.
AE, adverse event; BLV, bulevirtide; DT, delayed treatment; SAE, serious adverse event.

- No AEs led to discontinuation of the study drug
- No SAEs were attributed to BLV
- The number of Grade 3 and 4 AEs was numerically higher in patients with cirrhosis
- BLV was safe and well tolerated in patients with or without cirrhosis

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