Continued Treatment of Early Nonresponders or Partial Virologic Responders With Bulevirtide Monotherapy in Patients With Chronic Hepatitis Delta Through Week 96 Leads to Improvement in Virologic and Biochemical Responses

LBP-020

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Key Findings

- At W24, suboptimal virologic response (NR or PR) occurred in approximately one-third of patients receiving BLV
- Of those with PR at W24, 82% (18 of 22) progressed to VR, and 77% (17 of 22) of W24 PR had biochemical response at W96 with continued BLV monotherapy
- Of those with NR at W24, 43% (6 of 14) progressed to VR at W96, and 29% (4 of 14) had biochemical response at W96 with continued BLV monotherapy

Conclusions

In CHD patients showing a suboptimal early response to BLV at W24, the majority showed progressive improvement with treatment through W96, supporting ongoing treatment with BLV

Partial virologic responders at W24 were more likely than nonresponders to achieve virologic response by W96

References: **1.** Stockdale AJ, et al. *J Hepatol* 2020;73:523-532. **2.** Hepcludex. European Medicines Agency SmPC. **3.** Yurdaydin C, et al. *J Hepatol* 2019;70:1008-1015.

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Introduction

- Hepatitis delta virus (HDV) represents the most severe form of chronic viral hepatitis and is estimated to affect between 10 and 20 million worldwide[1]
- Bulevirtide (BLV), a novel entry inhibitor of HDV, is conditionally approved in the EU at 2 mg/day for the treatment of chronic hepatitis delta (CHD) with compensated liver disease[2]
- In clinical studies, on-treatment virologic response (VR) to HDV therapy is defined as achieving undetectability or a ≥2 $\log_{10}$ IU/mL decline in HDV RNA from baseline (BL)[3]
- The extent of benefit from continued therapy for patients with suboptimal early virologic response requires further investigation

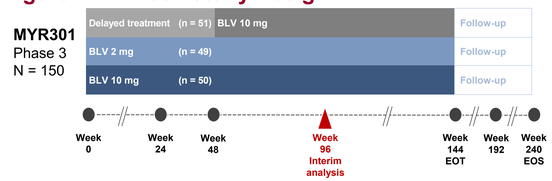
Objective

- This study aimed to evaluate whether continued therapy up to W96 results in improvement in virologic and biochemical responses among patients not achieving early VR at W24

Methods

- MYR 301 (NCT03852719) is an ongoing randomized study evaluating 3 cohorts: BLV 2 mg (Arm B) and BLV 10 mg (Arm C) to W144 and a delayed treatment arm receiving no anti-HDV therapy to W48 followed by BLV 10 mg (Arm A)
- Data from patients in Arms B and C who remained on study treatment at W96 are included in the present analysis
- No formal stopping rules were included for early nonresponse

Figure 1. MYR301 Study Design



BLV, bulevirtide; EOS, end of study; EOT, end of treatment.

- Virologic response groups were defined as follows:
  - Virologic nonresponders (NR) were defined as having an HDV RNA decline of <1 $\log_{10}$ IU/mL from BL
  - Virologic partial responders (PR) were defined as having an HDV RNA decline of ≥1 but <2 $\log_{10}$ IU/mL from BL
  - Suboptimal early virologic response was defined as NR or PR at W24
- Alanine aminotransferase (ALT) upper limit of normal: ≤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)
- HDV RNA levels determined by RT-qPCR using RoboGene® HDV RNA Quantification Kit 2.0 (lower limit of quantification 50 IU/mL, lower limit of detection 6 IU/mL)
- Biochemical response (ALT within normal limits [WNL]) and change in ALT from BL were compared by response group

Results

- BL demographics and characteristics are shown in **Table 1**
- The virologic response progression for all virologic response groups at W24 (separated by BLV dose) through W48 and W96 is shown in **Table 2**
  - The proportion of PR and NR decreased over time in both BLV dosage groups
  - 38% (36 of 94) of patients included in the analysis were NR or PR at W24
  - At W96, 17% (16 of 94) of patients were NR (N = 6) or PR (N = 10)
- The virologic response progression of NR and PR (separated by BLV dose) at W24 through W48 and W96 is shown in **Figure 2**
- The mean levels and change from BL in HDV RNA and ALT by W96 among NR or PR at W24 are shown in **Table 3**

Table 1. Demographics and Baseline Characteristics by BLV Dosage

	BLV 2 mg (N = 47)	BLV 10 mg (N = 47)	Total (N = 94)
Male sex, n (%)	28 (60)	30 (64)	58 (62)
Race, n (%)			
White	39 (83)	41 (87)	80 (85)
Asian	8 (17)	5 (11)	13 (14)
Black or African American	0	1 (2)	1 (1)
Cirrhosis present, n (%)	23 (49)	22 (47)	45 (48)
HBeAg-positive, n (%)	4 (9)	7 (15)	11 (12)
Concomitant NA therapy, n (%)	32 (68)	25 (53)	57 (61)
Prior IFN therapy, n (%)	25 (53)	27 (58)	52 (55)
Genotype HDV-1, n (%)	47 (100)	45 (96)	92 (98)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.1 (1.2)	4.9 (1.5)	5.0 (1.3)
ALT, U/L, mean (SD)	108 (64)	128 (81)	118 (73)

ALT, alanine aminotransferase; BLV, bulevirtide; HBeAg, hepatitis B e antigen; HDV, hepatitis delta virus; IFN, interferon; NA, nucleos(t)ide analogue.

- Demographics and BL characteristics were well matched between the 2 BLV dosage groups

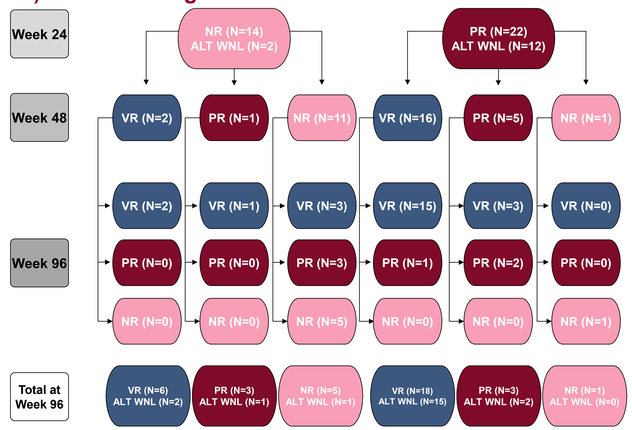
Table 2. Changes in HDV RNA Response Through W96 by BLV Dose

		BLV 2 mg (N = 47)			BLV 10 mg (N = 47)			Total (N = 94)		
		W24			W24			W24		
		NR	PR	VR	NR	PR	VR	NR	PR	VR
		N = 10	N = 12	N = 25	N = 4	N = 10	N = 33	N = 14	N = 22	N = 58
W48	NR	8 (80)	1 (8)	0 (0)	3 (75)	0 (0)	0 (0)	11 (79)	1 (5)	0 (0)
	PR	1 (10)	0 (0)	2 (8)	0 (0)	5 (50)	1 (3)	1 (7)	5 (23)	3 (5)
	VR	1 (10)	11 (92)	23 (92)	1 (25)	5 (50)	32 (97)	2 (14)	16 (73)	55 (95)
W96	NR	4 (40)	1 (8)	0 (0)	1 (25)	0 (0)	0 (0)	5 (36)	1 (5)	0 (0)
	PR	3 (30)	0 (0)	2 (8)	0 (0)	3 (30)	2 (6)	3 (21)	3 (14)	4 (7)
	VR	3 (30)	11 (92)	23 (92)	3 (75)	7 (70)	31 (94)	6 (43)	18 (82)	54 (93)

Values expressed as n (%).
BLV, bulevirtide; HDV, hepatitis delta virus; NR, nonresponder; PR, partial responder; VR, virologic responder; W, week.

- Overall, the proportion of PR and NR decreased over time in both BLV dosage groups

Figure 2. Progression of Suboptimal Responders (NR and PR) at W24 Through W48 and W96



ALT, alanine aminotransferase; NR, nonresponder; PR, partial responder; VR, virologic responder; W, week; WNL, within normal limits.

- 43% (6 of 14) of NR at W24 and 82% (18 of 22) of PR at W24 progressed to VR at W96
- 35% (5 of 14) of NR at W24 and 5% (1 of 22) of PR at W24 were NR at W96
- 29% (4 of 14) of NR at W24 and 77% (17 of 22) of PR at W24 achieved ALT WNL at W96

Table 3. Change in Mean ALT and HDV RNA by W96 Among NR or PR at W24

		Virologic Response Group at W24	
	Time Point	NR (N = 14)	PR (N = 22)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	Baseline	4.4 (2.0)	5.3 (1.4)
	W24	3.8 (1.8)	3.7 (1.4)
	W48	3.6 (2.1)	2.6 (1.5)
	W96	2.8 (2.1)	1.9 (1.3)
	Change at W96	−1.6 (1.7)	−3.4 (1.3)
ALT, U/L, mean (SD)	Baseline	112 (59)	98 (64)
	W24	71 (37)	44 (26)
	W48	67 (42)	36 (14)
	W96	89 (123)	35 (24)
	Change at W96	−24 (119)	−64 (61)

ALT, alanine aminotransferase; HDV, hepatitis delta virus; NR, nonresponder; PR, partial responder; VR, virologic responder; W, week.

- HDV RNA and ALT declines were seen by W96 among NR or PR at W24 with numerically higher declines in the PR compared to the NR subgroup
- ALT declined by >50% from BL in 5 of the 6 who remained a NR at W96, 1 ALT WNL (data not shown)