Efficacy and Safety of Bulevirtide Monotherapy Given at 2 mg or 10 mg Dose Level Once Daily for Treatment of Chronic Hepatitis Delta: Week 48 Primary Endpoint Results From a Phase 3 Randomized, Multicenter, Parallel Design Study

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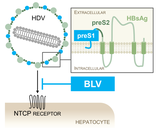
Hepatitis Delta Virus (HDV) Background

- Hepatitis delta virus (HDV) is a satellite virus of HBV and requires HBV envelope proteins to infect hepatocytes and propagate[1]
- Approximately 12 million people are infected with HDV worldwide[2]
- HDV causes the most severe form of chronic viral hepatitis,[3] with 2–3-fold increased risk of mortality compared to HBV monoinfection[4,5]
- Undetectable HDV RNA or a 2-$\log_{10}$ decline with alanine aminotransferase (ALT) normalization is an acceptable chronic on-therapy surrogate endpoint (FDA draft guidance for development of HDV treatment)[6]
- Achieving HDV viral control or cure of chronic hepatitis delta (CHD) is warranted[7]

Bulevirtide (BLV)

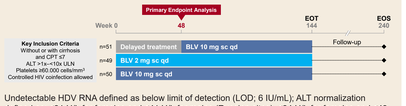
- First-in-class entry inhibitor for treatment of CHD
- Linear 47-amino acid chemically synthesized lipopeptide
- Specifically binds to sodium taurocholate cotransporting polypeptide (NTCP) at the basolateral membrane of hepatocytes; NTCP is used by HBV and HDV to enter hepatocytes[8]
- Conditionally approved in Europe in July 2020 for treatment of compensated CHD based on completed Phase 2 studies[9-10]



MYR301 Study Objective

- To evaluate the efficacy and safety of BLV monotherapy given subcutaneously at 2 mg or 10 mg once daily for treatment of chronic hepatitis delta compared to no active anti-HDV treatment for 48 Weeks (delayed treatment): primary Week 48 analysis

MYR301 Study Design



Undetectable HDV RNA defined as below limit of detection (LOD; 6 IU/mL); ALT normalization defined as: ≤31 U/L for females and ≤41 U/L for males (Russian sites), ≤34 U/L for females and ≤49 U/L for males (all other sites). Full analysis set. Statistical analyses: difference in response rates between treatment groups was calculated using Fisher exact test. CPT, Child-Pugh-Turcotte; EOS, end of study; EOT, end of treatment; ULN, upper limit of normal.

- Multicenter, open-label, randomized, Phase 3 study (ClinicalTrials.gov NCT03852719) conducted in 4 countries (Germany, Italy, Russian Federation, and Sweden)

Primary Endpoint

- Combined response at Week 48: HDV RNA undetectable or decrease by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization

Secondary Endpoints

- Combined response at Week 24
- Undetectable HDV RNA at Weeks 24 and 48
- ALT normalization at Weeks 24 and 48
- Change in liver stiffness (transient elastography) at Week 48
- HDV RNA undetectable after end of treatment (EOT)

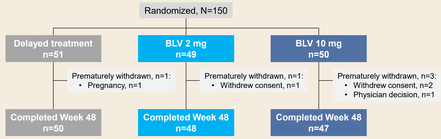
Results

Demographic and Disease Characteristics

		Delayed Treatment: n=51	BLV 2 mg: n=49	BLV 10 mg: n=50
Mean age, years (SD)		40.5 (7.5)	43.6 (9.0)	41.3 (8.5)
Male sex, n (%)		26 (51)	30 (61)	30 (60)
Race, n (%)	White	40 (78)	41 (84)	43 (86)
	Asian	11 (22)	8 (16)	6 (12)
	Black or African American	0	0	1 (2)
Cirrhosis, n (%)		24 (47)	23 (47)	24 (48)
Mean platelets, 10^9/L (SD)		158 (57)	153 (53)	160 (53)
Mean liver stiffness, kPa (SD)		15.3 (8.9)	14 (8.2)	14.8 (9.3)
Mean ALT, U/L (SD)		102 (62)	108 (63)	123 (81)
Mean (SD) HDV RNA, $\log_{10}$ IU/mL		5.08 (1.36)	5.10 (1.21)	4.96 (1.46)
HDV genotype, n (%)*	1	51 (100)	49 (100)	48 (96)
	5	0	0	1 (2)
Mean HBsAg, $\log_{10}$ IU/mL (SD)		3.68 (0.47)	3.67 (0.52)	3.61 (0.59)
Mean HBV DNA, $\log_{10}$ IU/mL (SD)		0.89 (0.99)	1.28 (1.30)	1.07 (1.27)
HBeAg positive, n (%)		4 (8)	4 (8)	7 (14)
HBV genotype, n (%)	A	4 (8)	1 (2)	3 (6)
	D	39 (77)	44 (90)	41 (82)
	E	0	0	1 (2)
	Missing	8 (16)	4 (8)	5 (10)
Previous IFN therapy, n (%)		29 (57)	26 (53)	29 (58)
Concomitant HBV NUC treatment, n (%)		32 (63)	31 (63)	27 (54)

*1 patient in the BLV 10-mg group had missing HDV genotype. HBeAg, hepatitis B e antigen; IFN, interferon; IQR, interquartile range; NUC, nucleos(t)ide; SD, standard deviation.

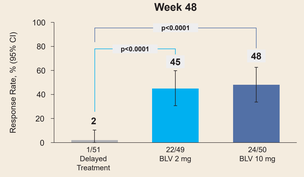
MYR301 Patient Disposition



- Five patients were withdrawn from the study through 48 weeks, none due to AEs

Efficacy

Primary Endpoint: Combined Response at Week 48



Undetectable HDV RNA defined as below LOD (6 IU/mL). ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russia sites); ≤34 U/L for females and ≤49 U/L for males (all other sites). CI, confidence interval.

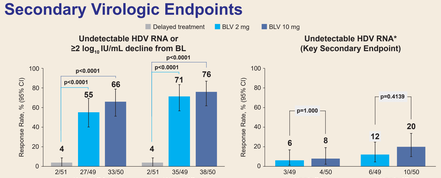
- The rates of combined response in BLV arms were similar and significantly higher compared to control

Combined Response at Week 48 by Subgroups for BLV 2 mg vs Delayed Treatment

*One patient from BLV 2 mg group was excluded from baseline HDV RNA subgroup analysis due to absent baseline HDV RNA value.

- Treatment benefit was consistent across all subgroups, including patients with cirrhosis
- Similar findings observed with BLV 10 mg treatment

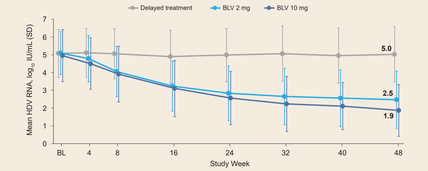
Secondary Virologic Endpoints



*No patients from Delayed Treatment group achieved Undetectable HDV RNA at any visit; undetectable HDV RNA defined as below LOD (6 IU/mL).

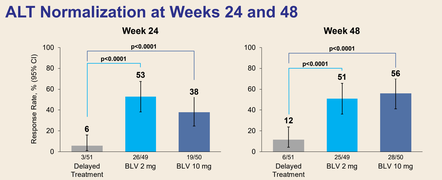
- No significant difference in complete viral suppression between 2 mg and 10 mg of BLV
- The rates of viral response in BLV arms were significantly higher compared to control

HDV RNA Decline Over 48 Weeks



- Mean HDV RNA levels progressively declined to a similar degree over 48 weeks in both BLV groups

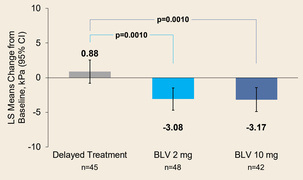
ALT Normalization at Weeks 24 and 48



ALT ULN: ≤31 U/L for females and ≤41 U/L for males (Russia sites); ≤34 U/L for females and ≤49 U/L for males (all other sites).

- The rates of biochemical response in BLV arms were significantly higher compared to control

Change in Liver Stiffness at Week 48



LS, least-squares.

- BLV was associated with significant reductions in liver stiffness by transient elastography at both dose levels vs delayed treatment

HBV Efficacy Endpoints at Week 48

		Delayed Treatment n=51	BLV 2 mg n=49	BLV 10 mg n=50
HBsAg	HBsAg loss, n (%)	0	0	0
	HBsAg response: >1 $\log_{10}$ IU/mL decrease, n (%)	1 (2)	0	0
	LS mean change in HBsAg, $\log_{10}$ IU/mL (95% CI)	0.006 (-0.085, 0.097)	0.053 (-0.041, 0.147)	0.115 (0.019, 0.211)
HBV DNA	LS mean change in HBV DNA, $\log_{10}$ IU/mL (95% CI)	-0.16 (-0.404, 0.078)	-0.38 (-0.634, -0.134)	-0.64 (-0.898, -0.387)
	P-value vs delayed treatment	—	0.210	0.008
	Patients with HBV DNA positivity at baseline and no concomitant NUC treatment, n	12	13	13
	Mean change from BL in HBV DNA, $\log_{10}$ IU/mL (SD)	-0.15 (0.655)	-0.42 (0.599)	-0.88 (0.690)

- No patients in any group experienced HBsAg loss, and changes in HBsAg levels were minimal
- Small declines in HBV DNA levels were observed with BLV treatment, including in patients not on nucleos(t)ide analog treatment

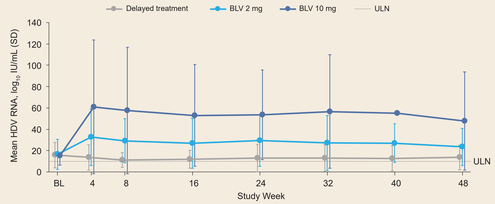
Overall Safety Summary

Patients With, n (%)		Delayed Treatment: n=51	BLV 2 mg: n=49	BLV 10 mg: n=50
Any AE		39 (77)	40 (82)	44 (88)
Any Grade 3–4 AE		3 (6)	5 (10)	4 (8)
Any SAE		1 (2)*	2 (4)†	1 (2)‡
Any AE leading to withdrawal of BLV		0	0	0
Any AE related to BLV		0	24 (49)	36 (72)
Death		0	0	
AEs of interest§	Headache	0	9 (18)	10 (20)
	Dizziness	0	2 (4)	2 (4)
	Nausea	2 (4)	3 (6)	4 (8)
	Pruritus	0	6 (12)	8 (16)
	Fatigue	1 (2)	5 (10)	8 (16)
	Injection-site reactions¶	0	8 (16)	15 (30)

All AEs were treatment emergent during first 48 weeks. *Cholelithiasis (n=1), COVID-19 (n=1); †Asthenia and depression (n=1), foot fracture (n=1); ‡COVID-19 pneumonia (n=1); §AEs with higher frequencies in BLV groups compared to delayed treatment; ¶Grouped term including injection-site reaction, injection-site erythema, injection-site pruritus, injection-site swelling, injection-site pain, injection-site haematoma, injection-site rash, injection-site abscess, injection-site dermatitis, injection-site irritation. AE, adverse event; SAE, serious adverse event.

- There were no SAEs related to BLV or AEs leading to discontinuation of study drug
- Injection-site reactions were mild to moderate in severity and occurred at a higher frequency with BLV 10 mg

Total Serum Bile Acids Over 48 Weeks



Full analysis set. ULN, upper limit of normal.

- Dose-dependent asymptomatic elevations in serum total bile acids were observed in both BLV groups (expected based on mechanism of action) which were less pronounced in the 2 mg dose group
- Increases in bile acids occurred early in both BLV groups, and mean values were stable over 48-week treatment

Grade 3 or 4 AEs and Laboratory Abnormalities Over 48 Weeks (>1 Patient in BLV groups)

	Patients with Any, n (%)	Delayed Treatment n=51	BLV 2 mg n=49	BLV 10 mg n=50
Grade ≥3 AEs*	Any Grade ≥3 AE	3 (6)	5 (10)	4 (8)
	Thrombocytopenia	2 (4)	1 (2)	2 (4)
	Neutropenia	2 (4)	0	2 (4)
Grade ≥3 Laboratory Abnormalities	Any Grade ≥3 Laboratory Abnormality	6 (12)	6 (12)	5 (10)
	Neutrophil decreased	2 (4)	1 (2)	2 (2)
	Platelet decreased	2 (4)	2 (4)	4 (8)

*Grade ≥3 AEs: 1 participant each, BLV 10 mg: COVID-19, leukopenia, pneumonia; BLV 2 mg: foot fracture, neutrophil count decreased, osteopenia, depression; Grade ≥3 AEs related to BLV: 1 participant each, BLV 10 mg: thrombocytopenia, neutropenia, leukopenia; BLV 2 mg: neutrophil count decreased.

- No case of Grade 3 or 4 elevation in bile acids or eosinophils

Conclusions

- Treatment with BLV was superior to control as assessed by the combined response at Week 48
  - BLV 10 mg results do not support an efficacy advantage vs BLV 2 mg
  - Treatment benefit was consistent across subgroups including patients with cirrhosis
- The proportion with undetectable HDV RNA was similar between the BLV 2 mg and 10 mg groups at Week 48
- Both treatment groups showed greater liver stiffness responses compared to delayed treatment
- No resistance development to BLV was observed through 48 weeks[11]
- **BLV 2 mg is safe and efficacious over 48-week treatment**

References: 1. Rizzetto M, et al. *J Infect Dis.* 1980;141:590-602; 2. Stockdale AJ, et al. *J Hepatol.* 2020;73:523-32; 3. Wedemeyer H, et al. *Nat Rev Gastroenterol Hepatol.* 2010;7:31-40; 4. Fattovich G, et al. *Gut.* 2000;46:420-6; 5. Romeo R, et al. *Gastroenterology.* 2009;136:1629-38; 6. Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry; Draft guidance November 2019; 7. Asselah et al. *Liver International.* 2020;40 S1:54-60. 8. Ni Y, et al. Gastroenterology. 2014;146:1070-83; 9. Wedemeyer H, et al. *Lancet Infect Dis.* 2022 (accepted for publication); 10. Wedemeyer H, et al. EASL 2020, # AS072; 11. Hollnberger J, et al. EASL 2022, poster 1406/SAT385.

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