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

Abstract No. 122

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Conclusions

- Treatment with BLV was superior to control as assessed by the combined biochemical and viral 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; poster 1406/ SAT385 (Hollnberger J. et al) presents detailed analysis
- BLV 2 mg was safe and efficacious over 48-week treatment

References:

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Acknowledgments:

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Introduction

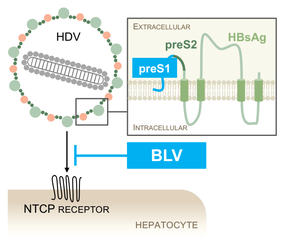
Hepatitis Delta Virus (HDV) Background

- 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,[3,4,5] with 2–3-fold increased risk of mortality compared to HBV mono-infection[6,7]
- Achieving HDV viral control or cure of CHD is an unmet medical need[8]

ALT, alanine aminotransferase; CHD, chronic hepatitis delta; HBV, hepatitis B virus.

Bulevirtide (BLV)

- First-in-class entry inhibitor for treatment of CHD
- Linear 47-amino acid chemically synthesized lipopeptide
- Specifically binds to NTCP at the basolateral membrane of hepatocytes; NTCP is used by HBV and HDV to enter hepatocytes[9]
- Conditionally approved in Europe in July 2020 for treatment of compensated CHD based on completed phase 2 studies[10,11]



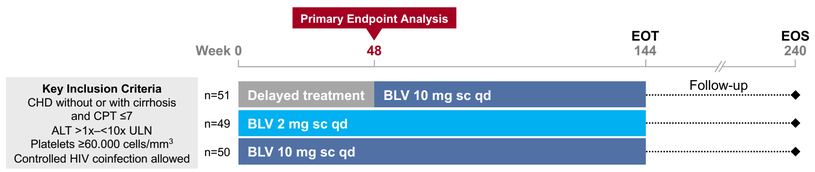
HBsAg, hepatitis B surface antigen; NTCP, sodium taurocholate cotransporting polypeptide.

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 anti-HDV treatment for 48 Weeks (delayed treatment)

Methods

MYR301 Study Design



- 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 ordecrease by ≥2 log_{10} IU/mL from baseline and ALT normalization (FDA draft guidance for development of HDV treatment1)

Secondary Endpoints

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

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.

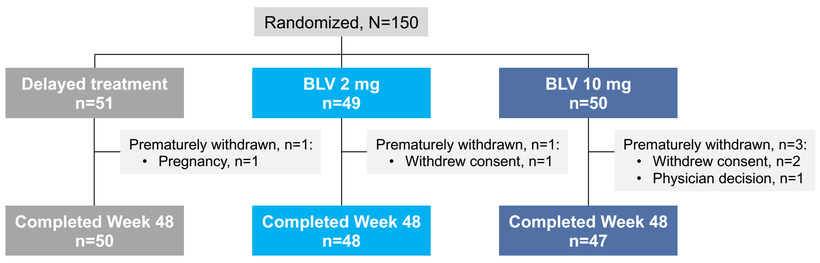
Results

Demographics 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)

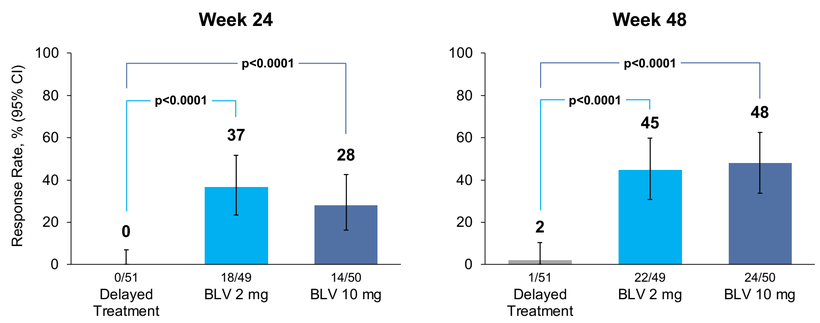
*1 patient in the BLV 10-mg group had missing HDV genotype. HBeAg, hepatitis B e antigen; IFN, interferon; IQR, interquartile range; NUC, nucleos(t)ide; SD, standard deviation.

MYR301 Patient Disposition



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

Primary Endpoint: Combined Response

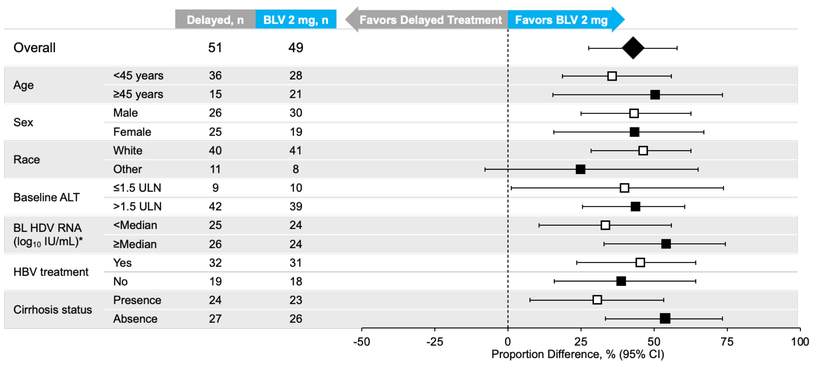


- The rates of combined response in BLV arms were similar and significantly higher compared to control

Combined response defined as undetectable HDV RNA or ≥2 log_{10} IU/mL decline from BL and ALT Normalization
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.

Combined Response at Week 48 by Subgroups

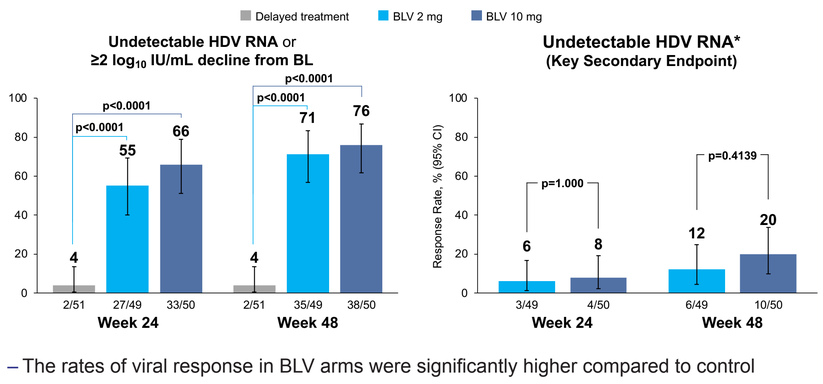
BLV 2 mg vs Delayed Treatment



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

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

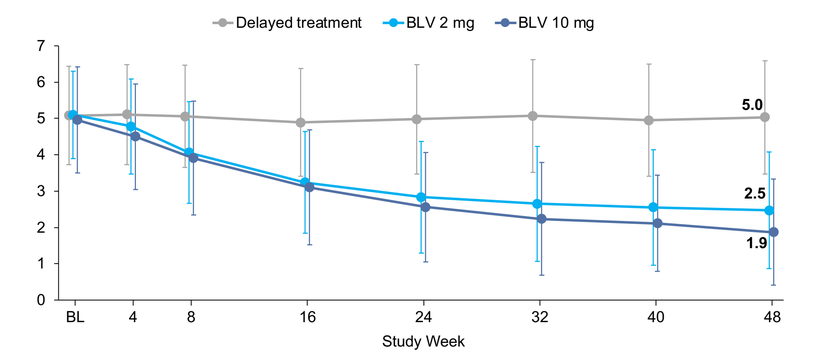
Secondary Virologic Endpoints



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

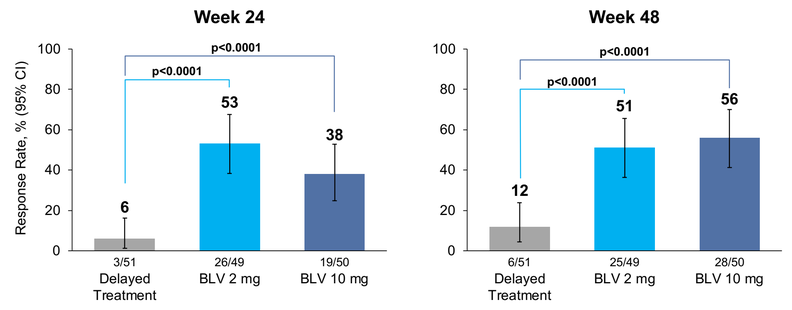
*No patients from Delayed Treatment group achieved Undetectable HDV RNA at any visit
Undetectable HDV RNA defined as below LOD (6 IU/mL)

HDV RNA Decline Over 48 Weeks



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

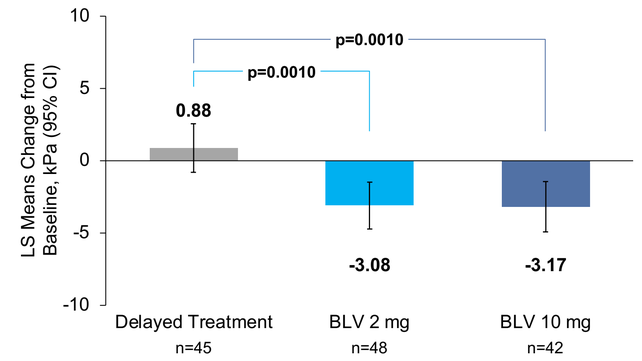
ALT Normalization at Weeks 24 and 48



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

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).

Change in Liver Stiffness at Week 48



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

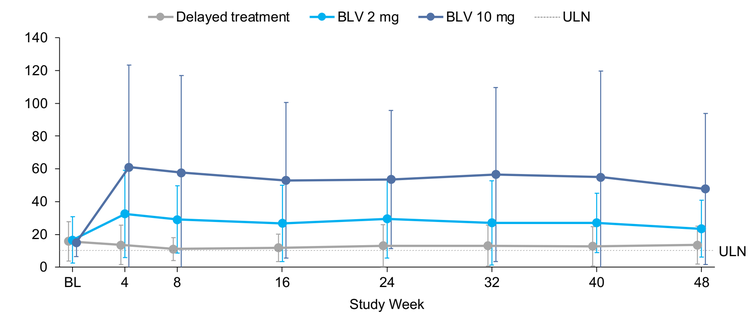
LS, least-squares; TE, transient elastography.

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 NUC treatment

Total Serum Bile Acids Over 48 Weeks



- Dose-dependent asymptomatic elevations in serum total bile acids were observed in both BLV groups (expected based on MOA) 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

Full analysis set. ULN, upper limit of normal.

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	0
AEs of interest§	Headache	0	9 (18)	10 (20)
	Dizziness	0	2 (4)	2 (4)
	Nausea	2 (4)	3 (6)	4 (8)
	Pruritis	0	6 (12)	8 (16)
	Fatigue	1 (2)	5 (10)	8 (16)
	Injection site reactions¶	0	8 (16)	15 (30)

- There were no SAEs related to BLV or AEs leading to discontinuation of study drug
- Asymptomatic elevations in total serum bile acids and eosinophils were observed in BLV groups
- Injection site reactions were mild to moderate in severity and occurred at a higher frequency with BLV 10 mg

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.

Grade 3 or 4 AEs & 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)

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

*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.