Efficacy and Safety of Bulevirtide 2 mg or 10 mg for 96 Weeks in Chronic Hepatitis Delta, Including in 2 Patients With HIV/Hepatitis B Virus/Hepatitis Delta Virus

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Conclusions

Treatment of chronic HDV infection with BLV for 96 weeks was safe and efficacious across the overall study population and in a subset of 2 patients coinfected with HIV and HDV

Plain-Language Summary

Patients with chronic HDV were treated with bulevirtide for 96 weeks. At week 96, 39% to 56% of patients responded with substantially reduced levels of HDV RNA and with normal levels of the liver enzyme alanine aminotransferase, a key marker of liver health. Through 2 years of treatment, bulevirtide was safe and well tolerated.

There were no discontinuations of bulevirtide because of adverse events. Two people were included who were virally suppressed for HIV when starting treatment with bulevirtide for chronic HBV/HDV. Both of these people living with HIV had favorable HDV responses with bulevirtide, and bulevirtide had no impact on HIV treatment.

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Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators. This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by Kehinde Ogunseye, PhD, of AlphaScientia, a Red Nucleus company, and funded by Gilead Sciences, Inc.

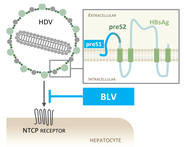
Disclosures: **HW** reports honoraria for speaking or consulting from Abbott; AbbVie; Boehringer Ingelheim; Bristol Myers Squibb; Eiger Biopharmaceuticals; Gilead Sciences, Inc.; Janssen; Merck Sharp & Dohme; MYR GmbH; Novartis; Novira; Roche; Roche Diagnostics; Siemens; and Transgene; and research support from Abbott, Bristol Myers Squibb, and Gilead Sciences, Inc. **SA** has received honoraria for lectures and educational events from AbbVie; Biogen; Gilead Sciences, Inc.; and Merck Sharp & Dohme and reports grants from AbbVie and Gilead Sciences, Inc. **MB** declares financial relationships with AbbVie and Gilead Sciences, Inc., for speaking and teaching. **DLW** reports receiving grants from Gilead Sciences, Inc. **VM** reports nothing to disclose. **VC** reports being a consultant and giving sponsored lectures for AbbVie; AstraZeneca; Bristol Myers Squibb; Gilead Sciences, Inc.; GSK; Hepatera; Merck Sharp & Dohme; R-Pharm; and Roche. **BLD**, **RCM**, **GMC**, and **ML** are employees of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc. **PL** reports speaking and teaching fees from and participation in advisory committees or review panels for AbbVie; Aligos Therapeutics; Alnylam Pharmaceuticals; Antios Therapeutics; Arrowhead Pharmaceuticals; Bristol Myers Squibb; Eiger Biopharmaceuticals; Gilead Sciences, Inc.; GSK; Janssen; Merck Sharp & Dohme; MYR GmbH; Roche; and Spring Bank Pharmaceuticals.

Hepatitis Delta Virus

- Hepatitis delta virus (HDV) is a satellite virus that requires the envelope protein from hepatitis B virus (HBV) to infect hepatocytes and propagate[1]
- Between 10 and 20 million people are infected with HDV worldwide[2]
- HDV causes the most severe form of chronic viral hepatitis,[3,4] with 2- to 3-fold increased risk of mortality compared with HBV monoinfection[5,6]
- Until recently, off-label pegylated interferon alfa (Peg-IFNα) was the only recommended treatment regimen; however, Peg-IFNα only benefits a small subset of patients and is often poorly tolerated[7]
- Achieving HDV viral control or cure of chronic hepatitis delta (CHD) remains a global unmet medical need

Bulevirtide

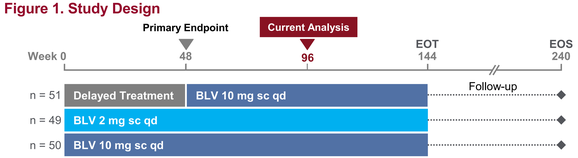
- Novel, first-in-class entry inhibitor of both HBV and HDV
- Linear 47–amino acid chemically synthesized lipopeptide
- Binds to sodium taurocholate cotransporting polypeptide (NTCP) at the basolateral membrane of hepatocytes; NTCP is used by HBV and HDV to enter hepatocytes[8]
- Received full approval in Europe in 2023 and is recommended by the European AIDS Clinical Society (EACS) and European Association for the Study of the Liver (EASL) guidelines for the treatment of CHD in patients with compensated liver disease[9-12]
- MYR301 week 48 study results[12] demonstrated that
  - Monotherapy with bulevirtide (BLV; 2 mg/d or 10 mg/d) was superior to no anti-HDV treatment based on the primary endpoint of combined virologic and biochemical response
  - HDV RNA responses were similar at the 2 dose levels
  - BLV was generally safe and well tolerated
- There are limited data on the safety and efficacy of BLV among people infected with HBV/HDV/HIV[13]
- The aim of this interim analysis of the Phase 3 MYR301 (NCT03852719) study is to describe the safety and efficacy of BLV over 96 weeks, including in patients with HBV/HDV/HIV



BLV, bulevirtide; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; NTCP, sodium taurocholate cotransporting polypeptide.

Study Design

Figure 1. Study Design



BLV, bulevirtide; EOS, end of study; EOT, end of treatment; qd, once daily; sc, subcutaneous.

- Multicenter, open-label, randomized, Phase 3 study (NCT03852719) conducted in 16 sites across 4 countries (Germany, Italy, Russian Federation, and Sweden)
- Key inclusion criteria
  - CHD without or with cirrhosis and Child-Pugh-Turcotte score ≤7
  - Alanine aminotransferase (ALT) >1× to <10× upper limit of normal
  - Platelets ≥60,000 cells/mm^3
  - **Controlled HIV coinfection allowed (defined as CD4 cell count >500/mL, HIV RNA < limit of detection for ≥1 year)**
  - Nucleos(t)ide analogue therapy was permitted for those meeting HBV and HIV guideline criteria[9-12]
- Efficacy (primary study endpoint)
  - The proportion of patients achieving a combined response at week 48 and defined as meeting both criteria below[14]
    - Undetectable HDV RNA or decrease by ≥2 $\log_{10}$ IU/mL from baseline
    - ALT normalization
- Week 96 endpoints
  - The proportion of patients with
    - Undetectable HDV RNA or decrease by ≥2 $\log_{10}$ IU/mL from baseline
    - Undetectable HDV RNA
    - ALT normalization
    - Adverse events (AEs)
  - Change in liver stiffness (transient elastography)

Results

Table 1. Demographic and Disease Characteristics of the Total Cohort

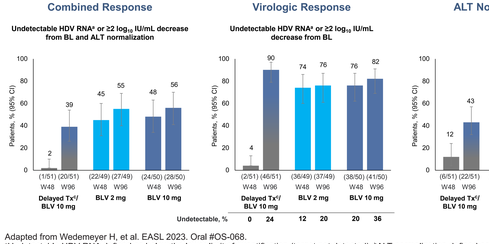
		Delayed Treatment/ BLV 10 mg (n = 51)	BLV 2 mg (n = 49)	BLV 10 mg (n = 50)
Age, years, mean (SD)		41 (8)	44 (9)	41 (9)
Sex at birth, male, n (%)		26 (51)	30 (61)	30 (60)
Race,[a] n (%)	White	40 (78)	41 (84)	43 (86)
	Asian	11 (22)	8 (16)	6 (12)
Cirrhosis, n (%)		24 (47)	23 (47)	24 (48)
Platelets, ×10^3 cells/mm^3, mean (SD)		158 (57)	153 (53)	160 (53)
Liver stiffness measurement, kPa, mean (SD)		15.3 (9.0)	14.0 (8.2)	14.8 (9.3)
ALT, U/L, mean (SD)		102 (62)	108 (63)	123 (81)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)		5.08 (1.36)	5.10 (1.20)	4.96 (1.46)
HDV genotype 1, n (%)[b]		51 (100)	49 (100)	48 (96)
HBsAg, $\log_{10}$ IU/mL, mean (SD)		3.68 (0.47)	3.67 (0.52)	3.61 (0.59)
HBV DNA positive, n (%)[c]		27 (53)	33 (67)	30 (60)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)		0.89 (0.99)	1.30 (1.29)	1.08 (1.26)
HBeAg positive, n (%)		4 (8)	4 (8)	7 (14)
HBV genotype, n (%)	A	4 (8)	2 (4)	3 (6)
	D	39 (77)	44 (90)	43 (86)
	Other[d]/missing	8 (16)	3 (6)	4 (8)
Previous IFN therapy, n (%)		29 (57)	26 (53)	29 (58)
Concomitant HBV NUC treatment, n (%)		32 (63)	32 (65)	27 (54)

[a]BLV 10-mg group: n = 1 Black. [b]BLV 10-mg group: n = 1 HDV GT 5, n = 1 missing HDV GT. [c]HBV DNA positive was defined as ≥ LLOQ. [d]BLV 10-mg group: n = 1 HBV GT E.
ALT, alanine aminotransferase; BLV, bulevirtide; GT, genotype; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; LLOQ, lower limit of quantification; NUC, nucleos(t)ide.

Patient Disposition

- Patient retention remained high through 96 weeks with few early discontinuations
  - Delayed treatment: 1 patient before completing week 48 (pregnancy), and 1 patient before week 96 (death due to plasma cell myeloma not related to study treatment)
  - BLV 2 mg: 1 patient before completing week 48, and 1 patient before week 96 (both withdrew consent)
  - BLV 10 mg: 3 patients before completing week 48 (2 withdrew consent, 1 for physician decision)

Figure 2. Interim Efficacy Analysis at Week 96



Adapted from Wedemeyer H, et al. EASL 2023. Oral #OS-068.
[a]Undetectable HDV RNA defined as below the lower limit of quantification (target not detected). [b]ALT normalization defined as: ≤31 U/L for females and ≤41 U/L for males (Russian sites); or ≤34 U/L for females and ≤49 U/L for males (all other sites). [c]Delayed treatment arm did not receive any BLV through week 48.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; HDV, hepatitis delta virus; Tx, treatment; W, week.

- Combined response, virologic response, and ALT normalization rates increased over 96 weeks and were similar between 2- and 10-mg groups (**Figure 2**)

Safety

Table 2. Overall Summary

Patients With, n (%)		Delayed Treatment/ BLV 10 mg (n = 51)		BLV 2 mg (n = 49)		BLV 10 mg (n = 50)	
		Week 48	Week 48–96[a]	Week 48	Week 96	Week 48	Week 96
Any AE		39 (77)	42 (84)	41 (84)	47 (96)	44 (88)	48 (96)
Any Grade 3–4 AE		4 (8)	3 (6)	5 (10)	9 (18)	4 (8)	8 (16)
Any SAE		1 (2)	2 (4)	2 (4)	2 (4)	1 (2)	4 (8)
Any AE leading to withdrawal of BLV		N/A	0	0	0	0	0
Any AE related to BLV		N/A	22 (44)	24 (49)	25 (51)	36 (72)	36 (72)
Death		0	1 (2)[b]	0	0	0	0
AEs of interest[c]	Headache	0	7 (14)	9 (18)	9 (18)	10 (20)	12 (24)
	Dizziness	0	1 (2)	2 (4)	2 (4)	3 (6)	4 (8)
	Nausea	2 (4)	1 (2)	3 (6)	3 (6)	4 (8)	6 (12)
	Pruritus	0	0	6 (12)	6 (12)	8 (16)	9 (18)
	Fatigue	1 (2)	2 (4)	5 (10)	7 (14)	7 (14)	9 (18)
	Injection-site reaction[d]	N/A	6 (12)	9 (18)	10 (20)	15 (30)	15 (30)

All AEs were treatment emergent over 96 weeks.
[a]n = 50. [b]One death due to plasma cell myeloma not related to study treatment. [c]AEs with higher frequencies in BLV groups compared with delayed treatment. [d]Grouped term including "injection-site" (reaction, erythema, pruritus, rash, swelling, hematoma, pain, bruising, dermatitis, and induration).
AE, adverse event; BLV, bulevirtide; N/A, not applicable; SAE, serious adverse event.

- No serious AEs or AEs leading to discontinuation of the study drug were related to BLV (**Table 2**)
- Injection-site reactions were mild to moderate in severity and occurred at a higher frequency with BLV 10 mg (**Table 2**)
- Dose-dependent asymptomatic elevations in total bile acid levels were observed and expected with BLV treatment due to the mechanism of action of BLV

Patients Coinfected With HIV/HBV/HDV

Table 3. Efficacy and Safety in Patients Coinfected With HIV

	Patient 1		Patient 2	
Study group	BLV 2 mg		BLV 10 mg	
Baseline characteristics				
Age, years	39		40	
Sex at birth	Male		Male	
HCV antibody	Negative		Positive[a]	
HIV viral load	Undetectable		Undetectable	
CD4 cells/mm^3	786		559	
Antiretroviral regimen	Tenofovir/lamivudine/etravirine		Emtricitabine/TAF/raltegravir	
Cirrhosis status	No cirrhosis		No cirrhosis	
Prior Peg-IFNα experience	No		No	
HDV genotype/HBV genotype	1/D		1/D	
Efficacy	Baseline	Week 96	Baseline	Week 96
HDV RNA, $\log_{10}$ IU/mL	6.52	< LLOQ[b]	5.63	< LLOQ[b]
HBV DNA, $\log_{10}$ IU/mL	1.34	Negative	1.23	< LLOQ[c]
HBsAg, $\log_{10}$ IU/mL	4.26	3.81	3.91	3.72
ALT, U/L[d]	289	18	97	26
LSM, kPa	12.0	10.5	11.8	5.6
Platelet count, 10^9/L	136	169	186	206
Safety				
Treatment-emergent adverse events	Elevated lipase[e]		COVID-19[f]	

[a]HCV RNA negative. [b]LLOQ = 50 IU/mL. [c]LLOQ = 10 IU/mL. [d]ALT normalization defined as: ≤31 U/L for females and ≤41 U/L for males (Russian sites); or ≤34 U/L for females and ≤49 U/L for males (all other sites). [e]Patient 1: Investigator assessed as mild-moderate and related to BLV; action taken: dietary recommendations and no change to BLV; resolved on BLV. [f]Patient 2: Investigator assessed as mild and not related to BLV; action taken: none; no change to BLV; resolved on BLV.
ALT, alanine aminotransferase; BLV, bulevirtide; CD4, cluster of differentiation 4; COVID-19, coronavirus disease 2019; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis delta virus; LLOQ, lower limit of quantification; LSM, liver stiffness measurement; Peg-IFNα, pegylated interferon alfa; TAF, tenofovir alafenamide fumarate.

- At week 96, both patients achieved a combined response (virologic and ALT normalization) as well as improvements in HBV DNA, platelet levels, and liver stiffness measurements (**Table 3**)
- Neither patient required changes to their anti-HIV regimen nor did they experience serious AEs related to BLV (**Table 3**)