Efficacy and Safety of Long-Term Bulevirtide in Chronic Hepatitis Delta: Final Results From the Phase 3 MYR301 Study, Including 2 Participants With HIV/HBV/HDV Coinfection

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Background

- Hepatitis delta virus (HDV) is a defective virus that requires hepatitis B virus (HBV) for replication[1,2]
- HDV infection causes the most severe form of viral hepatitis,[3] affecting approximately 12 million people globally[4,5]
- HDV infection is associated with a more rapid progression to fibrosis and cirrhosis, earlier onset of hepatic complications, and a greater likelihood of liver transplantation compared with other forms of viral hepatitis[2,6]
- Prevalence of HDV coinfection varies regionally; HDV is estimated to affect 4% to 18% of people with HIV[7]
- Bulevirtide (BLV) is a first-in-class entry inhibitor that is approved in the European Economic Area and in several non-European countries for the treatment of chronic HDV infection with compensated liver disease at a dose of 2 mg
  - HIV is not a contraindication for BLV treatment in areas where BLV is approved, and real-world data have shown similar response rates to BLV 2 mg in coinfected participants[8]
- Monotherapy with BLV 2 or 10 mg/day has been demonstrated to be safe and effective over 144 weeks of treatment in both clinical trial and real-world settings[8-12]

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Objective

- To evaluate the efficacy and safety of long-term BLV monotherapy in participants with chronic HDV infection, including 2 participants with triple (HIV/HBV/HDV) infection, over a treatment period of up to 144 weeks followed by 96 weeks of posttreatment follow-up (FU96)

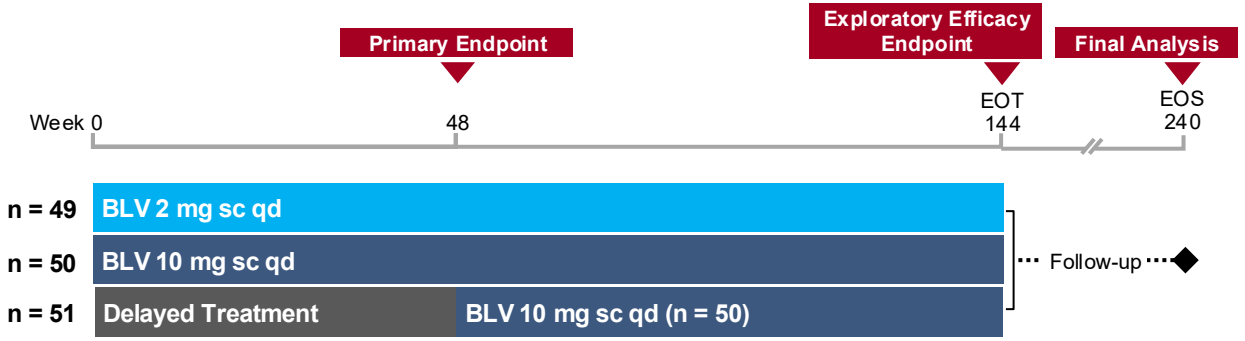
BLV, bulevirtide; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus.

Methods

MYR301 Study Design

Key Inclusion Criteria

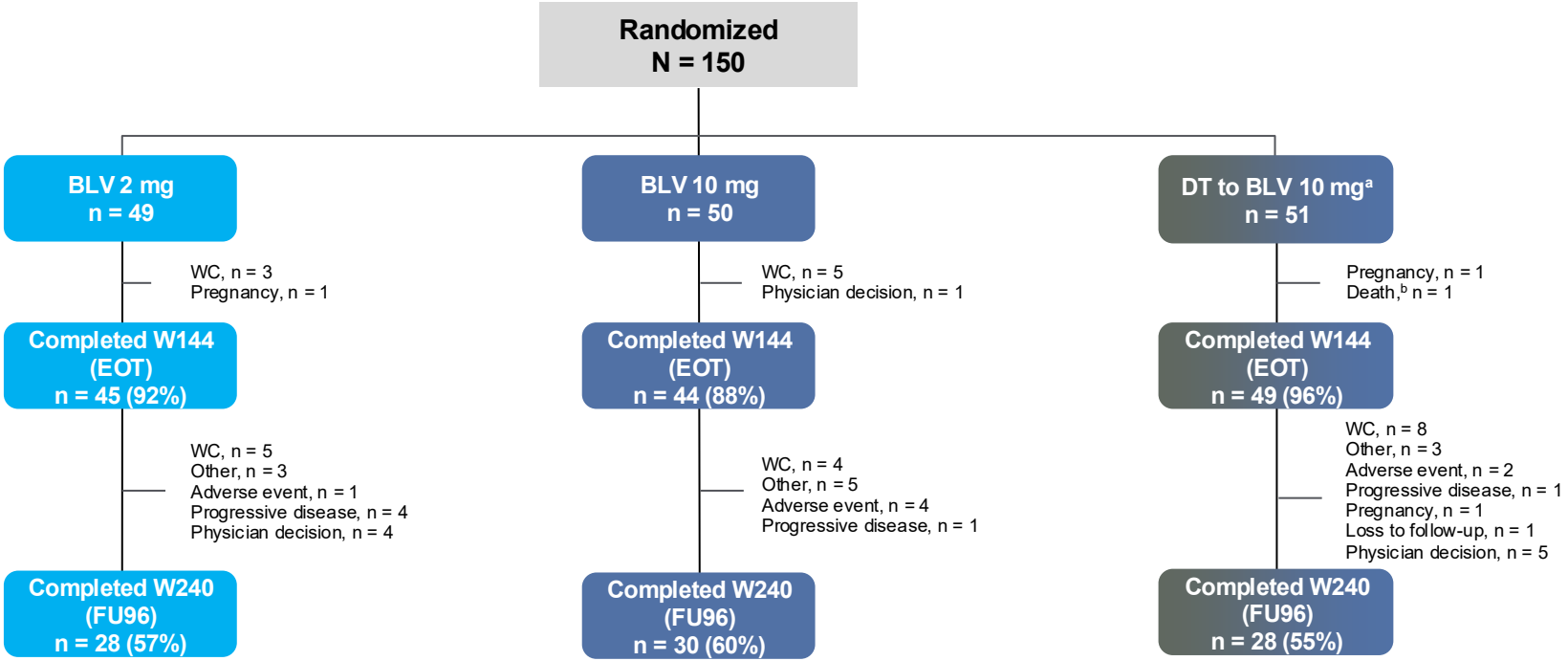
- Adults with chronic HDV infection with or without compensated cirrhosis
- CTP score ≤7
- ALT >1 × to <10 × ULN
- Positive serum HDV RNA



- Multicenter, open-label, randomized, Phase 3 study (NCT03852719) conducted in Germany, Italy, Russia, and Sweden
- Participants with controlled HIV infection (defined as CD4 cell count >500/cm^3, HIV RNA less than the limit of detection) were allowed
- Efficacy was measured by virologic response (undetectable[a] HDV RNA or ≥2 $\log_{10}$ IU/mL decline from baseline), biochemical response (alanine aminotransferase [ALT] normalization[b]), combined response (virologic and biochemical) rates, and liver stiffness

[a]Undetectable HDV RNA was defined as less than the lower limit of quantitation (50 IU/mL) with target not detected. [b]ALT normalization was defined as ≤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).
ALT, alanine aminotransferase; **BLV**, bulevirtide; **CD4**, cluster of differentiation 4; **CTP**, Child-Turcotte-Pugh; **HDV**, hepatitis delta virus; **EOS**, end of study; **EOT**, end of treatment; **qd**, once daily; **sc**, subcutaneous; **ULN**, upper limit of normal.

Participant Disposition



- Overall, >90% of participants completed the 144-week treatment period

[a]The DT group received no treatment for 48 weeks, then BLV 10 mg treatment for 96 weeks. W144 was EOT. [b]One death due to plasma cell myeloma.
BLV, bulevirtide; **DT**, delayed treatment; **EOT**, end of treatment; **FU96**, follow-up at 96 weeks after EOT; **W**, week; **WC**, withdrawal of consent.

Demographics and Disease Characteristics at Baseline

	BLV 2 mg n = 49	BLV 10 mg n = 50	DT to BLV 10 mg n = 51[a]
Age, years, mean (SD)	44 (9)	41 (9)	41 (8)
Male sex, n (%)	30 (61)	30 (60)	26 (51)
Race,[b] n (%)			
White	41 (84)	43 (86)	40 (78)
Asian	8 (16)	6 (12)	11 (22)
Platelets, × 10^3 cells/mm^3, mean (SD)	153 (52.5)	160 (53.1)	158 (57.0)
Cirrhosis present, n (%)	23 (47)	24 (48)	24 (47)
Liver stiffness, kPa, mean (SD)	14.0 (8.2)	14.8 (9.3)	15.3 (9.0)
ALT, U/L, mean (SD)	108 (63)	123 (81)	102 (62)
HDV RNA, log_{10} IU/mL, mean (SD)	5.10 (1.19)	4.96 (1.46)	5.08 (1.36)
Genotype HDV-1,[c] n (%)	49 (100)	48 (96)	51 (100)
HBsAg, log_{10} IU/mL, mean (SD)	3.67 (0.52)	3.61 (0.59)	3.68 (0.47)
HBV DNA, log_{10} IU/mL, mean (SD)	1.31 (1.28)	1.08 (1.26)	0.89 (0.99)
HBV genotype,[d] n (%)			
A	2 (4)	2 (4)	2 (4)
D	47 (96)	44 (88)	44 (86)
HIV coinfection, n (%)	1 (2)	1 (2)	0
Previous IFN therapy, n (%)	26 (53)	29 (58)	29 (57)
Concomitant HBV NA treatment, n (%)	32 (65)	27 (54)	33 (65)

[a]At BL, 51 participants were assigned to DT to BLV 10 mg, and their data are reported here. One participant subsequently withdrew from the DT to BLV 10 mg group before receiving BLV and is not included in subsequent reporting of efficacy and safety. [b]BLV 10 mg arm: Black, n = 1. [c]BLV 10 mg arm: HDV genotype 5, n = 1; missing HDV genotype, n = 1. [d]Other: BLV 10 mg arm: HBV genotype E, n = 1; no data, n = 3; DT to BLV 10 mg arm: unclassified HBV genotype, n = 2; no data, n = 3.

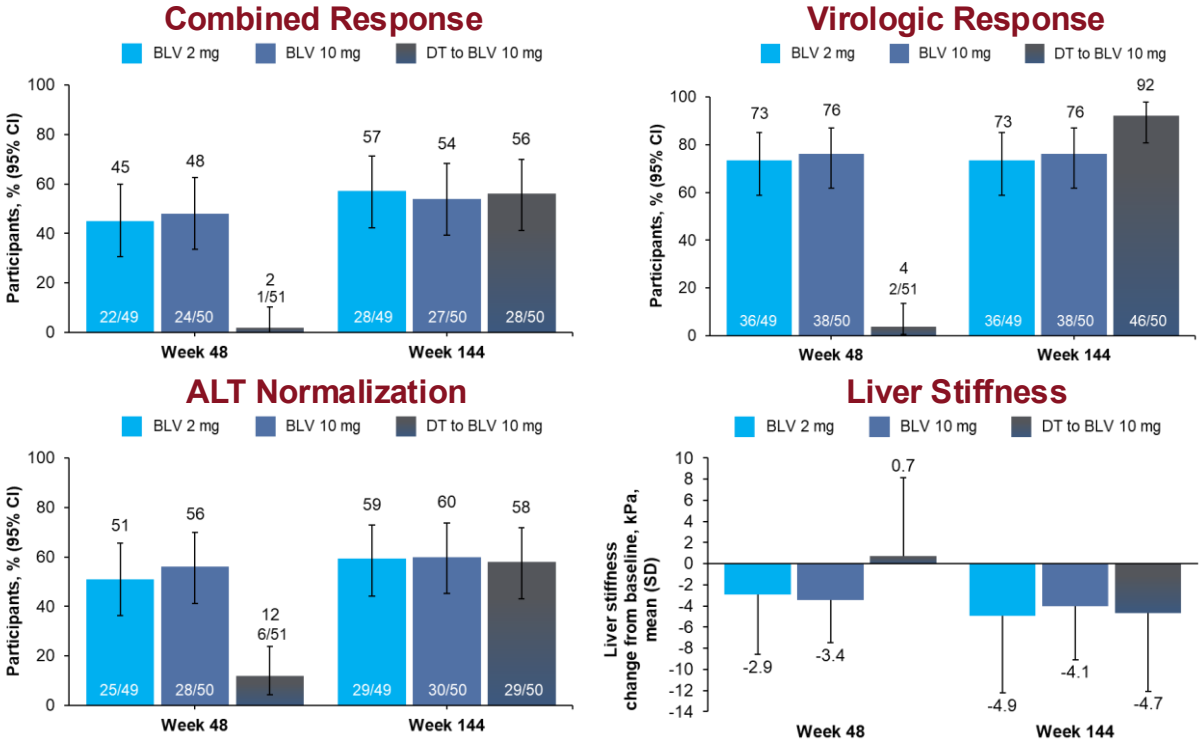
ALT, alanine aminotransferase; **BL**, baseline; **BLV**, bulevirtide; **DT**, delayed treatment; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **IFN**, interferon; **NA**, nucleos(t)ide analogue.

Demographics and Disease Characteristics: Participants With HIV

	Participant 1 (BLV 2 mg)	Participant 2 (BLV 10 mg)
Age, years	39	40
Sex	Male	Male
HCV antibody	Negative	Positive
HCV RNA	N/A	Negative
HIV viral load	Undetectable	Undetectable
CD4, cells/cm^3	786	559
Antiretroviral regimen	Tenofovir/lamivudine/etravirine	Emtricitabine/TAF/raltegravir
Cirrhosis status at baseline[a]	No cirrhosis	No cirrhosis
Prior PegIFNα experience	No	No
HDV genotype/HBV genotype	1/D	1/D

[a]As assessed by investigator.
BLV, bulevirtide; **CD4**, cluster of differentiation 4; **HBV**, hepatitis B virus; **HCV**, hepatitis C virus; **HDV**, hepatitis delta virus; **N/A**, not applicable; **PegIFNα**, pegylated interferon alfa; **TAF**, tenofovir alafenamide fumarate.

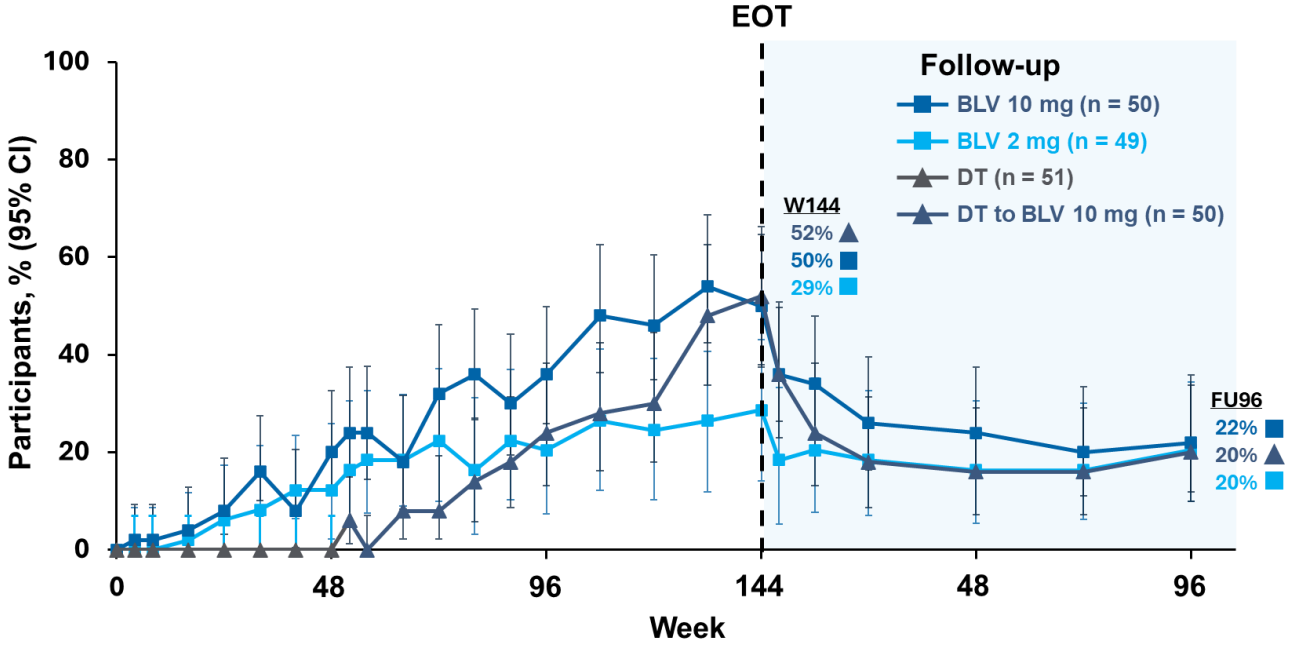
On-Treatment Efficacy Through Week 144



- Long-term therapy with BLV resulted in improved and durable virologic and biochemical responses

The DT group received no treatment for 48 weeks, then BLV 10 mg treatment for 96 weeks. For combined response, virologic response, and ALT normalization, the 95% CI was based on the Clopper-Pearson exact method, and the missing-equals-failure approach was used for missing values. For liver stiffness change from baseline, the missing values remain missing.
ALT, alanine aminotransferase; **BLV**, bulevirtide; **DT**, delayed treatment; **LS**, least squares.

Undetectable HDV RNA Through FU96



- Response rates decreased after stopping BLV
- A subset of participants had sustained undetectable HDV RNA during follow-up, which was more likely in participants with a longer duration of continuous on-treatment undetectability at EOT

The DT group received no treatment for 48 weeks, then BLV 10 mg treatment for 96 weeks.
BLV, bulevirtide; **DT**, delayed treatment; **EOT**, end of treatment; **FU96**, follow-up at 96 weeks after EOT; **HDV**, hepatitis delta virus; **W**, week.

Safety Summary

Participants, n (%)	BL to Week 144		
	BLV 2 mg n = 49	BLV 10 mg n = 50	DT to BLV 10 mg[a] n = 50
Any AE	48 (98)	48 (96)	46 (92)
Any AE related to BLV	27 (55)	37 (74)	23 (46)
Any AEs leading to D/C	0	0	0
Any SAE	3 (6)	6 (12)	3 (6)
Any SAEs related to BLV	0	0	0
Death	0	0	1[b]

- BLV was safe and well tolerated through 144 weeks of treatment
- The most common adverse events (AEs) were injection-site reactions, vitamin D deficiency, and headache; there were no discontinuations due to AEs, and no treatment-related serious AEs (SAEs) were reported
- Bile acid elevations were observed as expected due to the mechanism of action of BLV; the elevations were asymptomatic and not associated with clinical sequelae
- After stopping BLV treatment, ALT flares were associated with HDV rebounds; most occurred within 24 weeks after stopping treatment and resolved either spontaneously or with BLV retreatment

[a]AEs from the first 48 weeks are not shown. [b]One death due to plasma cell myeloma.
AE, adverse event; **ALT**, alanine aminotransferase; **BL**, baseline; **BLV**, bulevirtide; **D/C**, discontinuation; **DT**, delayed treatment; **HDV**, hepatitis delta virus; **SAE**, serious adverse event.

Efficacy and Safety in Participants With HIV

	Participant 1 (BLV 2 mg)			Participant 2[a] (BLV 10 mg)	
	Baseline	**Week 144**	**FU96**	**Baseline**	**Week 144**
Combined response[b]	-	Responder	Nonresponder	-	Responder
Virologic response[c]	-	Responder	Nonresponder	-	Responder
ALT normalization[d]	-	Responder	Nonresponder	-	Responder
Liver stiffness, kPa	12	6.4	22.3	11.8	5.6
HBV DNA, $\log_{10}$ IU/mL	1.3	0	1.0	1.2	0
HBsAg, $\log_{10}$ IU/mL	4.3	3.9	4.2	3.9	3.3

- At week 144, both participants with HIV/HBV/HDV coinfection achieved combined virologic and biochemical response, and neither required changes to their antiretroviral therapy
- Both participants had low-level positive HDV viremia less than the lower limit of quantitation at EOT
- In the posttreatment period, participant 1 experienced HDV rebound after stopping treatment; participant 2 discontinued the study at EOT due to withdrawal of consent
- Participant 1 had on-treatment AEs of increased lipase and posttreatment AEs of increased lipase, increased ALT, chronic cholecystitis, and hepatic fibrosis; participant 2 had COVID-19 (on treatment). None were SAEs

[a]Participant 2 did not complete the follow-up period of the study due to withdrawal of consent. [b]Combined response was defined as combined virologic and biochemical response. [c]Virologic response was measured as undetectable HDV RNA (defined as less than the lower limit of quantitation [50 IU/mL] with target not detected) or ≥2 $\log_{10}$ IU/mL decline from baseline. [d]ALT normalization was defined as ≤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). **AE**, adverse event; **ALT**, alanine aminotransferase; **BLV**, bulevirtide; **EOT**, end of treatment; **FU96**, follow-up at 96 weeks after EOT; **HBV**, hepatitis B virus; **HBsAg**, hepatitis B surface antigen; **HDV**, hepatitis delta virus; **SAE**, serious adverse event.

Conclusions

- Long-term BLV monotherapy for chronic hepatitis delta for up to 144 weeks was safe and effective
  - BLV treatment resulted in improved and durable virologic and biochemical responses, with higher rates of undetectable HDV RNA observed with the 10 mg dose
- A subset of participants had sustained undetectable HDV RNA through FU96
- Hepatitis flares occur in some participants after stopping treatment
  - Liver function should be monitored closely for at least 6 months in patients who discontinue BLV, and re-treatment may be warranted
- The 2 participants coinfected with HIV, HBV, and HDV achieved combined virologic and biochemical response, with HDV RNA <50 IU/mL at EOT, and both tolerated BLV well

BLV, bulevirtide; **EOT**, end of treatment; **FU96**, follow-up at 96 weeks after EOT; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus.

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