Integrated Virology Analysis of Bulevirtide Monotherapy in Chronic Hepatitis Delta: Pooled Data Through 96 Weeks of Treatment

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Conclusions

- Bulevirtide (BLV) 10 mg monotherapy demonstrated efficacy in patients with chronic hepatitis delta virus (HDV), including those with hepatitis B virus (HBV)/HDV genotype (GT)D/1 and GTA/1
  - GTD/1 and GTA/1 were the most prevalent HBV/HDV genotypes in the BLV clinical program
- Integrated virologic and resistance analysis through week 96 did not identify genotypic or phenotypic resistance to BLV, supporting its continued use as a monotherapy, with a high barrier to resistance, for the treatment of chronic HDV infection
- Although virologic response (VR) was slower in the limited data available from patients with GTA, biochemical responses were comparable, and overall response rates improved with continued treatment

Plain Language Summary

- BLV monotherapy demonstrated efficacy in patients with chronic hepatitis delta, including those with hepatitis B genotypes D and A
- Integrated virology analysis through week 96 of treatment did not identify resistance to bulevirtide

References: **1.** Ni Y, et al. *Gastroenterology*. 2014;146(4):1070–83. **2.** Yan H, et al. *eLife*. 2012;1:e00049. **3.** Hepcludex. Summary of product characteristics. European Medicines Agency. Gilead Sciences, Inc.; 2024. **4.** Hepcludex (bulevirtide acetate). Australian Register of Therapeutic Goods. Gilead Sciences, Inc.; 2024. **5.** Hollnberger H, et al. *J Hepatol*. 2023;79(3):657-65. **6.** Aleman S, et al. Abstract at AASLD, The Liver Meeting; November 11–14, 2023. 1237-C. doi:10.1097/HEP.0000000000000580. **7.** Lopez A, et al. Abstract at AASLD, The Liver Meeting; November 15–19, 2024. 1339. doi:10.1097/HEP.0000000000001077.

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Disclosures: Conflict of interest disclosures may be viewed using the QR code at the top right.

Introduction

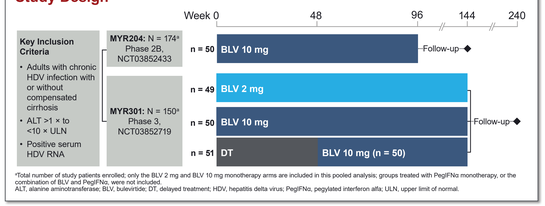
- BLV is a first-in-class 47–amino-acid lipopeptide that blocks the entry of HDV into hepatocytes via competitive inhibition of the interaction between the HBV preS1 domain and the sodium taurocholate cotransporting polypeptide (NTCP) receptor[1,2]
- BLV is approved in Europe, Australia, Canada, and the Russian Federation at 2 mg/day for the treatment of compensated chronic hepatitis delta[3,4]
- Although BLV is a highly potent HDV inhibitor, some patients treated with BLV monotherapy had suboptimal VR that was not associated with resistance in previous analyses of Phase 2 and 3 data[5,6]

Objectives

- To perform a comprehensive evaluation of pre-existing or treatment-emergent resistance in patients who received BLV monotherapy in studies MYR204 and MYR301 using sequencing analysis of the HBV preS1 BLV region and hepatitis delta antigen (HDAg) and phenotypic assessment of clinical isolates
- To investigate whether NTCP polymorphisms were associated with BLV treatment outcome

Methods

Study Design



[a]Total number of study patients enrolled; only the BLV 2 mg and BLV 10 mg monotherapy arms are included in this pooled analysis; groups treated with PegIFNα monotherapy, or the combination of BLV and PegIFNα, were not included.
ALT, alanine aminotransferase; BLV, bulevirtide; DT, delayed treatment; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa; ULN, upper limit of normal.

- 199 patients received BLV monotherapy (BLV 2 mg, n = 49; BLV 10 mg, n = 150)
- A delayed treatment (control) group included 51 patients who received no treatment for 48 weeks, followed by BLV 10 mg for 96 weeks (n = 50)
- This analysis evaluated VR, alanine aminotransferase (ALT) normalization, and combined response
- VR was defined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL HDV RNA decline from baseline (BL)
- Combined response was defined as undetectable HDV RNA level, or ≥2 $\log_{10}$ IU/mL decline from BL, and ALT normalization
- The resistance analysis population (RAP) included BLV-treated patients who experienced <1 $\log_{10}$ IU/mL decline from BL at specified time points: week 24, week 48, and week 96 (MYR204/MYR301); week 144 (MYR301 only); and week 72 (MYR301 delayed-treatment arm only or patients who experienced virologic breakthrough, as defined by 2 consecutive HDV RNA measurements at or above the lower limit of quantitation [LLOQ] after initially achieving levels below LLOQ or a confirmed ≥1 $\log_{10}$ IU/mL rise from nadir at 2 visits)
- Resistance testing included sequencing analyses of the HBV preS1 BLV region, HDAg, and NTCP, as well as phenotypic determination of BLV half-maximal effective concentration (EC_{50}) values

Results

HBV/HDV Genotype by Treatment Group

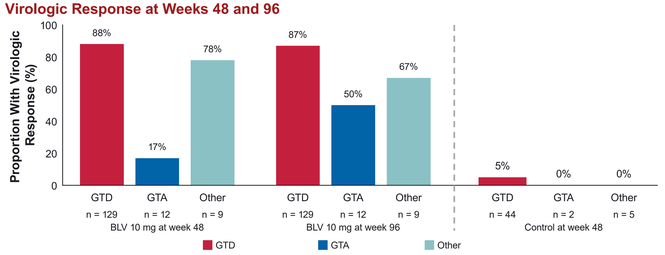
HBV/HDV Genotype, n (%)	Control n = 51	BLV 2 mg n = 49	BLV 10 mg n = 150	BLV 2 mg + 10 mg n = 199
HBV GTD	44 (86)	47 (96)	129 (86)	176 (88)
D/1	44 (86)	47 (96)	128 (85)	175 (88)
D/unknown	0	0	1 (<1)	1 (<1)
HBV GTA	2 (4)	2 (4)	12 (8)	14 (7)
A/1	2 (4)	2 (4)	12 (8)	14 (7)
HBV GT other	5 (10)	0	9 (6)	9 (5)
E/5	0	0	1 (<1)	1 (<1)
Unknown/1	5 (10)	0	7 (5)	7 (4)
Unknown/5	0	0	1 (<1)	1 (<1)

Unknown represents GT undetermined due to sample unavailability, failed sample testing, or GT unclassified.
BLV, bulevirtide; GT, genotype; HBV, hepatitis B virus; HDV, hepatitis delta virus.

- Among the HDV clinical isolates in this cohort, GTD/1 was the most prevalent HBV/HDV genotype (175 of 199 patients [88%]), followed by GTA/1 (14 of 199 [7%]), in line with US studies[7]

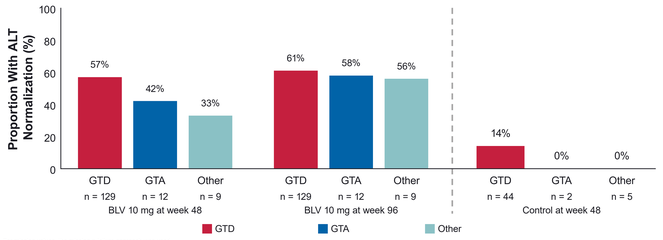
Results

Virologic Response at Weeks 48 and 96



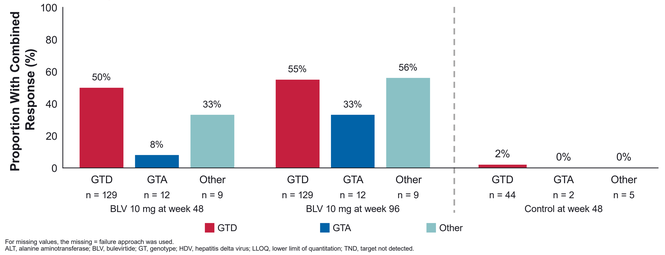
Virologic response: Undetectable (<LLOQ, TND) HDV RNA or HDV RNA decreased ≥2 $\log_{10}$ IU/mL from baseline.
For missing values, the missing = failure approach was used.
BLV, bulevirtide; GT, genotype; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; TND, target not detected.

ALT Normalization at Weeks 48 and 96



For missing values, the missing = failure approach was used.
ALT, alanine aminotransferase; BLV, bulevirtide; GT, genotype.

Combined Response at Weeks 48 and 96



For missing values, the missing = failure approach was used.
ALT, alanine aminotransferase; BLV, bulevirtide; GT, genotype; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; TND, target not detected.

- At week 96, 87% of patients with HBV GTD receiving BLV 10 mg achieved VR
  - 61% achieved ALT normalization, and 55% achieved combined response
- VR in patients with HBV GTA was 17% at week 48, but this improved with continued treatment. At week 96, 50% of patients with HBV GTA receiving BLV 10 mg achieved VR
  - 58% attained ALT normalization, and 33% achieved combined response
- These endpoints were rarely achieved among patients in the control group

Summary of Detected Amino Acid Substitutions in the HBV BLV Region and HDAg in Patients From the RAP at BL and Post-BL

Analysis Time Point on BLV Treatment	Treatment Arm	Patient Category (n)	Change From Reference at HDAg Conserved Sites (>99%)		Change at BLV Position[a]	
			BL	Post-BL	BL	Post-BL
Week 48	BLV 2 mg	NR (4) VB (7)	P85P/S/T	None	None	None
	BLV 10 mg	NR (4) VB (9)	P69S S123S/G N153N/I	P69S	T38A/T	None
Week 96	BLV 2 mg	NR (1) VB (13)	R13K P85P/S/T P85P.G[b]	R13R/K P85P/S P85P.G[b]	None	None
	BLV 10 mg	NR (2) VB (18)	L51L/P P69S K72K/R R75R/Q S123S/G N153N/I	P69S R140R/K	T18A/T T38A/T A39T N48D/N	None
	BLV 10 mg	EOT blip (1) PV (8)	None	None	None	NA

[a]Change from the same genotype consensus sequence in the BLV homologous region. [b]The "." indicates that an insertion of a G occurred after the P.
BL, baseline; BLV, bulevirtide; EOT blip, end of treatment viral blip; HBV, hepatitis B virus; HDAg, hepatitis delta antigen; NA, no coverage or failure or no data available; none, no change; NR, nonresponder; PV, persistent viremia; RAP, resistance analysis population; VB, virologic breakthrough.

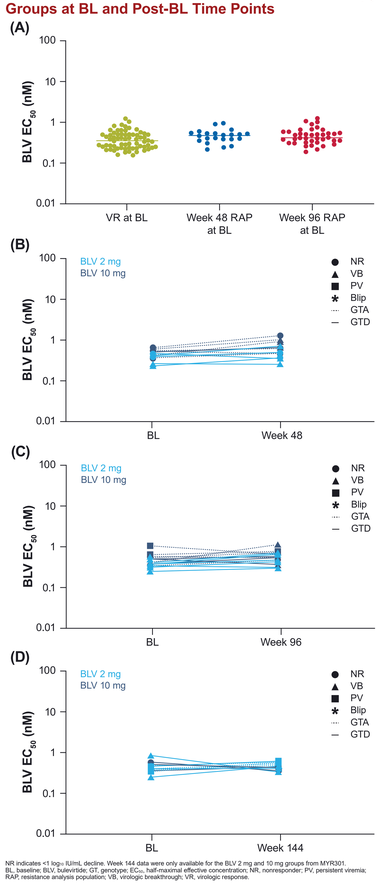
Cumulative Treatment-Emergent HDAg Variants up to 96 Weeks of 10 mg BLV Monotherapy

HDAg Variant	% Conservation in HDV GT1	Number of RAP Patients With Emergent Variant	BLV EC_{50} (nM)
Emergence of minor variants (>2%)			
R140G	99.5%	2 patients	0.73
K106R	96.2%	2 patients	0.16–1.10[a]
K38R	92.8%	3 patients	0.21–0.79
Emergence of variants above 15%			
K61R	98.6%	2 patients	0.29–0.57
K106M	96.2%	2 patients	0.20–0.58

[a]BLV EC_{50} values were obtained from other isolates containing this HDAg K106R variant.
BLV, bulevirtide; EC_{50}, half-maximal effective concentration; GT, genotype; HDAg, hepatitis delta antigen; HDV, hepatitis delta virus; RAP, resistance analysis population.

- A total of 48 patients on BLV monotherapy qualified as the RAP
- No treatment-emergent amino acid substitutions were identified in the HBV BLV homologous region or conserved HDAg sites
- NTCP polymorphisms were rare and showed no association with BLV treatment outcome

BLV EC_{50} Values Across Patients in BLV Monotherapy Groups at BL and Post-BL Time Points



NR indicates <1 $\log_{10}$ IU/mL decline. Week 144 data were only available for the BLV 2 mg and 10 mg groups from MYR301.
BL, baseline; BLV, bulevirtide; GT, genotype; EC_{50}, half-maximal effective concentration; NR, nonresponder; PV, persistent viremia; RAP, resistance analysis population; VB, virologic breakthrough; VR, virologic response.

- Phenotypic analysis showed that BLV EC_{50} values were similar between VR and RAP isolates at BL and during BLV monotherapy through week 144
- BLV EC_{50} values remained within assay variation across all subgroups, regardless of HBV/HDV polymorphisms