No Detectable Resistance to Bulevirtide Monotherapy Through 96 Weeks Treatment in Patients With Chronic Hepatitis Delta

1237-C

Soo Aleman[1], Yang Liu[2], Simin Xu[2], Silvia Chang[2], Ross Martin[2], Thomas Aeschbacher[2], Lindsey May[2], Savrina Manhas[2], Dong Han[2], Tahmineh Yazdi[2], Clarissa Martinez[2], Pui Yan Ho[2], Christopher Richards[2], Caleb Marceau[2], Dmitry Manuilov[2], John F Flaherty[2], Evguenia Maiorova[2], Hongmei Mo[2], Heiner Wedemeyer[3], Pietro Lampertico[4,5]

[1]Karolinska University Hospital/Karolinska Institutet, Department of Infectious Diseases, Stockholm, Sweden; [2]Gilead Sciences, Inc., Foster City, CA, USA; [3]Medizinische Hochschule Hannover, Klinik für Gastroenterologie, Hepatologie und Endokrinologie, Hannover, Germany; [4]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Division of Gastroenterology and Hepatology, Milan, Italy; [5]CRC "A. M. and A. Migliavacca" Center for Liver Disease, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy

Copies of this poster obtained through QR (Quick Response) and/or text key codes are for personal use only and may not be reproduced without written permission of the authors.

Key Findings

- Throughout 96 weeks of 2 or 10 mg BLV monotherapy, no resistance associated with BLV was observed in patients with CHD

Conclusions

No unique amino acid variants in the HBV PreS1 BLV homologous region, HDAg, and NTCP were associated with reduced sensitivity to BLV through week 96

No difference in BLV sensitivity through week 96 was observed across different treatment outcome groups in vitro

The proportion of patients qualifying for testing due to nonresponse declined with continued BLV treatment, providing support for the continuation of BLV monotherapy

References: **1.** Ni Y, et al. *Gastroenterology.* 2014;146:1070-83. **2.** Yan H, et al. *eLife.* 2012;1:e00049. **3.** Mateo R, et al. *JHEP Reports*. 2023; https://doi.org/10.1016/j.jhepr.2023.100893. **4.** Wedemeyer H, et al. *N Engl J Med.* 2023;389(1):22-32. **5.** Wedemeyer H, et al. EASL 2023, abstract OS-068. **6.** Hollnberger H, et al. *J Hepatol.* 2023;79:657-65.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators. This study was funded by Gilead Sciences, Inc. Writing and editorial support was provided by Molly Yeager, PhD, of AlphaScientia, a Red Nucleus company, and funded by Gilead Sciences, Inc.

Disclosures: **SA** received honoraria for lectures and educational events from Gilead Sciences, Inc.; AbbVie; Merck Sharp & Dohme; and Biogen; and reports grants from Gilead Sciences, Inc.; and AbbVie. **YL, SX, SC, RM, TA, LM, SM, DH, TY, CM, PYH, CR, CM, DM, JFF, EM,** and **HM** are employees of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc. **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; Gilead Sciences, Inc.; Novartis; Roche; and Roche Diagnostics. **PL** reports speaking and teaching fees from and participation in advisory committees or review panels for AbbVie; Aligos; Alnylam; Antios; Arrowhead; Bristol Myers Squibb; Eiger Biopharmaceuticals; Gilead Sciences, Inc.; GSK; Janssen; Merck Sharp & Dohme; MYR GmbH; Roche; and Spring Bank Pharmaceuticals.

Introduction

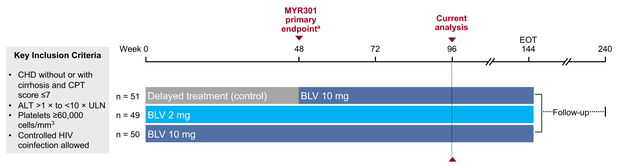
- Bulevirtide (BLV), a novel 47–amino acid chemically synthesized lipopeptide, blocks entry of the hepatitis delta virus (HDV) into hepatocytes via competitive inhibition of the interaction between the hepatitis B virus (HBV) preS1 domain and the sodium taurocholate cotransporting polypeptide (NTCP) receptor[1,2]
- BLV has demonstrated broad-spectrum activity against clinical isolates of HDV and recombinant pan-genotypic combinations of HBV/HDV in vitro[3]
- BLV monotherapy is safe, well tolerated, and efficacious in the treatment of chronic HDV infection (CHD), and is fully approved for the treatment of compensated CHD in the EU[4,5]
- Through 48 weeks of treatment, no viral resistance to BLV has been observed in patients with CHD[4,6]

Objectives

- To perform a resistance analysis in patients with CHD who received BLV for 96 weeks in an ongoing Phase 3 study (MYR301)
- To determine whether BLV resistance develops in patients with CHD treated with BLV for 96 weeks in MYR301

Methods

Figure 1. MYR301 Study Design



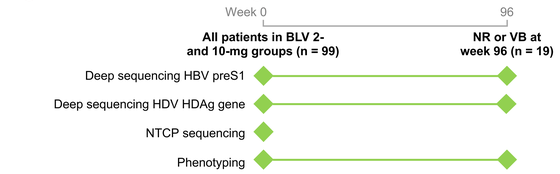
[a]MYR301 primary endpoint: Combined response at Week 48: HDV RNA undetectable or decrease by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization.
ALT, alanine aminotransferase; BLV, bulevirtide; CHD, chronic hepatitis delta; CPT, Child-Turcotte-Pugh; EOT, end of treatment; HDV, hepatitis delta virus; ULN, upper limit of normal.

- MYR301 is a multicenter, open-label, randomized, Phase 3 study (NCT03852719) conducted in 4 countries (Germany, Italy, Russian Federation, and Sweden)
- Week 96 resistance analysis was performed on HDV RNA samples from patients who received BLV 2 mg and 10 mg
- Samples from patients in the delayed-treatment group were not included in this week 96 analysis, as patients were on treatment for only 48 weeks

Virologic Response Definitions and Resistance Analysis Population

- **Virologic responder:** ≥2 $\log_{10}$ IU/mL decline from baseline (BL) or undetectable HDV RNA at week 96
- **Partial responder:** HDV RNA decline ≥1 but <2 $\log_{10}$ IU/mL from BL at week 96
- **Nonresponder (NR):** HDV RNA decline <1 $\log_{10}$ IU/mL from BL at week 96
- **Virologic breakthrough (VB):**
  - Confirmed increase (≥2 consecutive visits) in HDV RNA ≥1 $\log_{10}$ IU/mL from the nadir under treatment, assuming the nadir was previously ≥1 $\log_{10}$ IU/mL below the BL value for HDV RNA at 2 consecutive visits; or
  - Two consecutive HDV RNA values ≥ lower limit of quantification (LLOQ; 50 IU/mL) if HDV RNA was previously < LLOQ at ≥2 consecutive time points
- Week 96 resistance analysis was performed for NRs and patients who experienced VB

Figure 2. Resistance Testing Methods

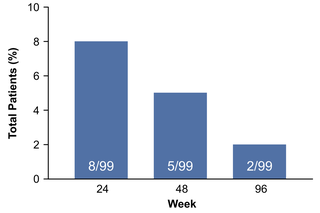


BLV, bulevirtide; HBV, hepatitis B virus; HDAg, hepatitis delta antigen; HDV, hepatitis delta virus; NR, nonresponder; NTCP, sodium taurocholate cotransporting polypeptide; VB, virologic breakthrough.

- **HBV preS1 deep sequencing:** total HBV nucleic acids were extracted from patient plasma, followed by complementary DNA (cDNA) synthesis; polymerase chain reaction was conducted using both DNA and cDNA to increase assay sensitivity[6]
- **Hepatitis delta antigen (HDAg) deep sequencing:** HDV RNA was extracted from patient plasma, followed by cDNA synthesis and HDV full-genome amplification with 2 overlapping fragments[6]
- **NTCP sequencing:** patient whole blood was processed for whole-exome sequencing, followed by analysis of single-nucleotide polymorphisms/small insertions and deletions, and variants in the coding region of the NTCP gene[6]
- **Phenotyping:** primary human hepatocytes were pretreated with BLV and then infected with patient plasma; after 5 days, immunofluorescence staining was performed to identify cells that were positive for HDAg, and the half-maximal effective concentration (EC_{50}) was obtained[3,6]

Results

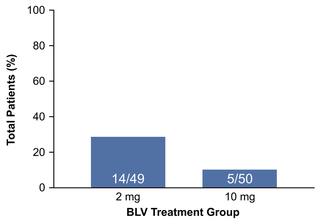
Figure 3. Number of Nonresponders Through 96 weeks of BLV Treatment



BLV, bulevirtide.

- The number of NRs declined over 96 weeks of BLV treatment

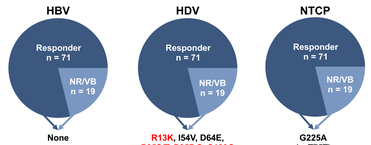
Figure 4. Patients Included in the Resistance Analysis by Treatment Group at Week 96



BLV, bulevirtide.

- At week 96, 19 of 99 (19%) total patients qualified for resistance testing: 2 (10.5%) were NRs and 17 (89.5%) experienced VB

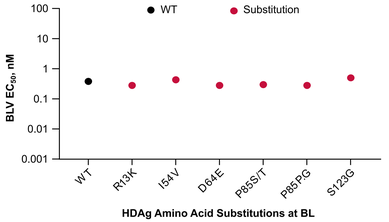
Figure 5. BL Sequence Analysis: Baseline Amino Acid Variants Observed in HBV PreS1, HDAg, and NTCP



Amino acid changes in red were only observed in NRs and patients with VB; changes in black were also observed in the virologic responder group.
BL, baseline; HBV, hepatitis B virus; HDAg, hepatitis delta antigen; HDV, hepatitis delta virus; NR, nonresponder; NTCP, sodium taurocholate cotransporting polypeptide; VB, virologic breakthrough.

- The BL HBV PreS1 sequence was obtained from 8 of 19 NRs/patients with VB (NR = 0, VB = 8)
  - No variant in the BLV homologous region was detected in any of the 8 NRs/patients with VB
- The BL HDAg sequence was obtained from 18 of 19 NRs/patients with VB (NR = 2, VB = 16)
  - Six variants were detected, including 1 insertion (G) at position 85, and 2 variants (I54V and D64E), which were observed in responders as well
- The BL NTCP sequence was obtained from 17 of 19 NRs/patients with VB (NR = 2, VB = 15)
  - A synonymous nucleotide change, G225A (amino acid T75T), was detected in 1 NR and 2 patients with VB; however, this polymorphism was also observed in responders with similar prevalence

Figure 6. BL HDAg Amino Acid Substitutions Remained Sensitive to BLV



BL, baseline; BLV, bulevirtide; EC_{50}, half-maximal effective concentration; HDAg, hepatitis delta antigen; WT, wild type.

Figure 7. Week 96 HBV/HDV Sequence Analysis

HBV

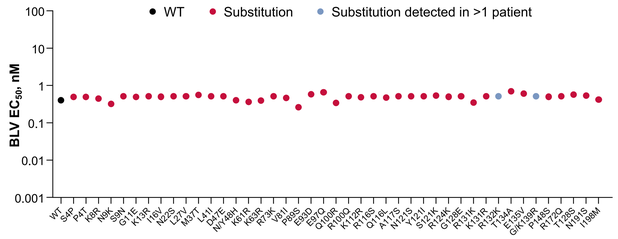
- HBV PreS1 sequences were obtained only from 3 of 19 NRs/patients with VB at week 96 due to extremely low HBV DNA levels
  - No variant in the BLV homologous region was detected in any of the 3 NRs or patients with VB
- Three patients had both BL and week 96 sequence data available
  - All had no sequence change from BL

HDV

- The HDAg sequence was obtained from 18 of 19 NRs/patients with VB at week 96
  - Four variants were detected, with 3 observed from the corresponding BL samples and 1 without BL data
- Seventeen patients had both BL and week 96 sequence data available
  - All had no conserved site changes (>99% conservation) from BL
  - Thirteen patients had polymorphic site changes
  - Only 2 polymorphic site changes (R132K, G/K139R) were observed in >1 NR or patient with VB

BL, baseline; BLV, bulevirtide; HBV, hepatitis B virus; HDV, hepatitis delta virus; HDAg, hepatitis delta antigen; HDV, hepatitis delta virus; NR, nonresponder; VB, virologic breakthrough.

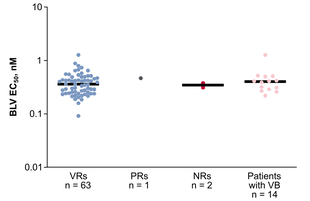
Figure 8. Week 96 HDAg Amino Acid Substitutions Remained Sensitive to BLV



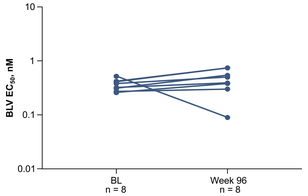
R132K was observed in 3 patients with VB; G/K139R was observed in 2 patients with VB.
BLV, bulevirtide; EC_{50}, half-maximal effective concentration; HDAg, hepatitis delta antigen; VB, virologic breakthrough; WT, wild type.

Figure 9. No Differences in BLV Sensitivity at BL and Week 96 Across Different Treatment Outcome Groups

(A) BLV Sensitivity at BL by Virologic Response Group[a]



(B) BLV Sensitivity at BL and Week 96 for NRs and Patients With VB[b]



[a]Closed circles represent individual data points; horizontal lines represent the median. [b]Data shown for patients with data available at BL and week 96.
BL, baseline; BLV, bulevirtide; EC_{50}, half-maximal effective concentration; NR, nonresponder; PR, partial responder; VB, virologic breakthrough; VR, virologic responder.