Relationship Between ALT Normalization Rates and Different Virologic Response Criteria in Chronic HDV Patients Treated With Bulevirtide Monotherapy

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Key Findings

- **A 76% viral response rate at 48 weeks was observed when the standard viral response threshold (HDV RNA decline of ≥2 $\log_{10}$ IU/mL from BL) was used**
- **Viral response rates as high as 87% at 48 weeks were observed when the lowest viral response threshold (HDV RNA decline of ≥1 $\log_{10}$ IU/mL from BL) was used**
- **Most patients had biochemical improvement (as high as 60% for ALT ≤ ULN and 86% for ALT ≤1.5 x ULN depending on criteria), including those who only achieved a 1-2 $\log_{10}$ IU/mL HDV RNA decline from BL**
- **Among patients who did not achieve ALT ≤ ULN despite improvement in HDV viral load with BLV therapy, 84% (16 of 19) had ALT ≤1.5 x ULN**
- **Similar improvements in ALT were observed in all viral response subgroups; those with ≥1 $\log_{10}$ IU/mL decline in HDV RNA from BL had comparable improvements in ALT to those with undetectable HDV RNA at W48**

Conclusions

Biochemical improvement as determined by ALT ≤ ULN or ≤1.5 × ULN is observed in most patients with CHD treated with BLV monotherapy for 48 weeks

Biochemical improvement often occurs in the absence of clear virologic response in patients with CHD treated with BLV

References: 1. Stockdale AJ, et al. *J Hepatol.* 2020;73:523-32. **2.** European Medicines Agency. Hepcludex (bulevirtide). Accessed August 25, 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/hepcludex. **3.** Wedemeyer H, et al. *N Engl J Med.* 2023;389:22-32. **4.** Chronic hepatitis D virus infection: developing drugs for treatment guidance for industry. Center for Drug Evaluation and Research. 2019. **5.** Dietz-Fricke C, et al. *JHEP Reports.* 2022;5(4):100686.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators and their corresponding site staff.

This study was funded by Gilead Sciences, Inc.

Writing and editorial support was provided by Helen Rodgers, PhD, of AlphaScientia, a Red Nucleus company, and was funded by Gilead Sciences, Inc.

Disclosures: 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, Gilead Sciences, Inc., GSK, Janssen, Merck Sharp & Dohme, MYR GmbH, Roche, and Spring Bank Pharmaceuticals; **SA** 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.; **PB, TS, SC**, and **AB** report no conflicts of interest; **MC** received honoraria from AbbVie, Falk, Gilead Sciences, Inc., GSK, Janssen-Cilag, Merck Sharp & Dohme, Novartis, Roche, Spring Bank Pharmaceuticals, and Swedish Orphan Biovitrum; **DM, QA, AHL, BLD, JFF, RCM**, and **YL** are employees of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc.; **MRB** reports speaker's bureau for AbbVie, EISAI MSD, and Gilead Sciences, Inc., and advisory/consultancy for AbbVie, Gilead Sciences, Inc., Janssen, and Roche; **SZ** reports speaker's bureau and/or consultancy for AbbVie, Allergan, BioMarin, Gilead Sciences, Inc., Intercept, Janssen, Merck Sharp & Dohme, Novo Nordisk, Swedish Orphan Biovitrum, and Theratechnologies; **HW** reports honoraria for speaking or consulting from Abbott, AbbVie, Boehringer Ingelheim, Bristol Myers Squibb, Eiger, 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.

Introduction

- Hepatitis delta virus (HDV) causes the most severe form of chronic viral hepatitis, with 10–20 million people infected worldwide[1]
- Bulevirtide (BLV), a novel entry inhibitor of HDV, is approved in Europe at 2 mg/day for the treatment of chronic hepatitis delta (CHD) in patients with compensated liver disease[2]
- In the Phase 3 Study MYR301, patients with CHD who received BLV monotherapy (2 mg or 10 mg) achieved significantly higher rates of the combined response (primary endpoint), at week (W) 48 vs. no treatment (control)[3]
  - Combined response was defined as virologic response (VR; undetectable HDV RNA or a ≥2 $\log_{10}$ IU/mL decline in HDV RNA from baseline [BL]) and biochemical response (alanine aminotransferase [ALT] ≤ upper limit of normal [ULN])
- While VR is currently considered an acceptable on-treatment HDV endpoint,[4] alternative criteria may also indicate potential clinical benefit and should be considered
- BLV treatment can achieve biochemical response even in the absence of VR, likely due to the mechanism of action of the entry inhibitor BLV as it does not directly affect viral replication[5]

Objectives

- This study aimed to:
  - Explore the relationships between differing criteria for determining viral and biochemical responses to BLV treatment at W48
  - Characterize patients who did not achieve ALT normalization despite improvement in viral load with BLV monotherapy at W48 and describe changes in their serum ALT levels
  - Conversely, evaluate changes in ALT levels in patients categorized using different viral response criteria

Methods

- A pooled analysis using data from patients with CHD treated with BLV 2 mg or 10 mg monotherapy for 48 weeks in 3 clinical trials was performed: the Phase 2 MYR203 (NCT02888106) and MYR204 (NCT03852433) studies, and the Phase 3 MYR301 (NCT03852719) study
- Key inclusion criteria included patients with CHD with positive HDV RNA, ALT > to <10 x ULN,[a] and compensated liver disease with or without cirrhosis
- Concomitant use of nucleos(t)ide analogue (NA) was at the discretion of the investigator
- The primary analysis was focused on the following criteria for viral response and biochemical improvement:
  - VR: undetectable HDV RNA[b] or a ≥2 $\log_{10}$ IU/mL decline in HDV RNA from BL
  - Additional thresholds of viral responses were evaluated as follows:
    - Undetectable HDV RNA
    - HDV RNA <1000 IU/mL
    - HDV RNA <5000 IU/mL
    - HDV RNA <10,000 IU/mL
    - ≥2 $\log_{10}$ IU/mL decline in HDV RNA from BL
    - ≥1 $\log_{10}$ IU/mL decline in HDV RNA from BL
  - The following biochemical response endpoints were also evaluated:
    - ALT ≤ ULN
    - ALT ≤1.5 × ULN
- In the subset of patients not achieving ALT ≤ ULN with BLV therapy despite improvement in viral load, individual ALT levels were assessed using the following criteria:
  - Inclusion: elevated ALT (> ULN) and HDV RNA >1000 IU/mL at BL; HDV RNA <1000 IU/mL with Hepatitis B virus (HBV) DNA < lower limit of quantitation (LLOQ; 10 IU/mL) at W48
- An additional analysis was performed looking at ALT changes in those with <1 $\log_{10}$ IU/mL and 1 to <2 $\log_{10}$ IU/mL decline in HDV RNA at W48 from BL
- HDV RNA levels were determined by RT-qPCR using a RoboGene HDV RNA Quantification Kit 2.0

[a]ALT ULN: ≤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).
[b]Undetectable HDV RNA: <LLOQ with target not detected (MYR204 and 301), limit of detection = 10 IU/mL (MYR203).

Results

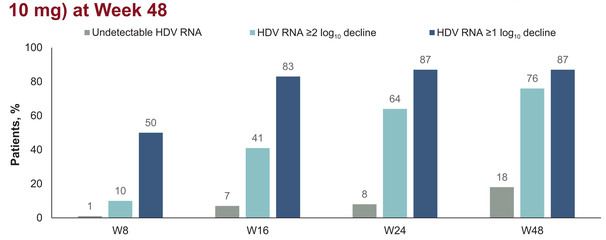
Table 1. Demographics and Baseline Characteristics by Treatment Group

	BLV 2 mg (n = 64)	BLV 10 mg (n = 165)	Total BLV 2 mg + 10 mg (N = 229)
Male sex, n (%)	41 (64)	105 (64)	146 (64)
Race, n (%)			
White	56 (88)	141 (86)	197 (86)
Asian	8 (13)	21 (13)	29 (13)
Black	0 (0)	3 (2)	3 (1)
Cirrhosis present, n (%)	26 (41)	65 (39)	91 (40)
HBeAg negative, n (%)	57 (89)	147 (89)	204 (89)
HDV GT-1, n (%)[a]	64 (100)	159 (96)	223 (97)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.2 (1.3)	5.2 (1.5)	5.2 (1.4)
ALT, U/L, mean (SD)[b]	111 (73)	105 (82)	107 (79)
Baseline ALT category			
≤ ULN	3 (5)	16 (10)	19 (8)
> ULN to ≤1.5 × ULN	10 (16)	28 (17)	38 (17)
>1.5 × ULN	51 (80)	121 (73)	172 (75)
Concomitant NA therapy, n (%)	32 (50)	97 (59)	129 (56)
Prior IFN therapy, n (%)	27 (42)	79 (48)	106 (46)

[a]In the BLV 10 mg group, 2 patients had HDV GT-5 and 4 patients had missing HDV GT. [b]All patients with ALT ≤ ULN at the baseline had ALT > ULN at screening.
ALT, alanine aminotransferase; BLV, bulevirtide; GT, genotype; HBeAg, hepatitis B e antigen; HDV, hepatitis delta virus; IFN, interferon; NA, nucleos(t)ide analogue; ULN, upper limit of normal.

- Baseline characteristics were comparable across treatment groups

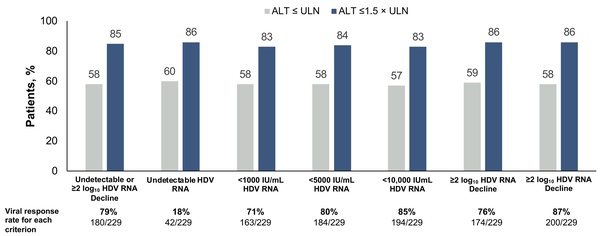
Figure 1. Viral Response During BLV Treatment (Total 2 mg and 10 mg) at Week 48



BLV, bulevirtide; HDV, hepatitis delta virus; W, week.
MYR204 and 301: LLOQ, 50 IU/mL; lower limit of detection (LLOD), 6 IU/mL. MYR203: LLOQ, 100 IU/mL; LLOD, 10 IU/mL

- 87% (191 of 229) of patients achieved the lowest viral response threshold (≥1 $\log_{10}$ IU/mL decline) at W48; the response rates peaked by W24
- 76% (174 of 229) achieved ≥2 $\log_{10}$ IU/mL decline in HDV RNA at W48; responses increased by visit over 48 weeks

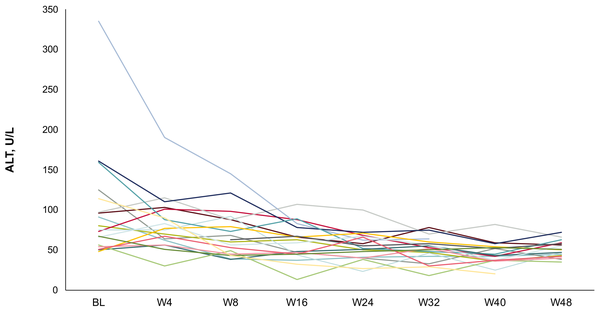
Figure 2. Biochemical Responses Among Patients Achieving Different Viral Response Criteria at Week 48



ALT, alanine aminotransferase; HDV, hepatitis delta virus; ULN, upper limit of normal.

- Viral response rates at W48 ranged from 18% with the highest threshold (undetectable HDV RNA) to 87% with the lowest threshold (≥1 $\log_{10}$ IU/mL decline in HDV RNA from BL)
- Despite widely different viral response rates for each criterion, the rates of biochemical responses (ALT ≤ ULN and ALT ≤1.5 × ULN) were consistent across each of the prespecified viral response criteria (including ≥1 vs ≥2 $\log_{10}$ IU/mL decline in HDV RNA from BL)
  - Use of the highest HDV RNA threshold for viral response (ie, undetectable) was not associated with higher rates of BR
  - This suggests most patients had biochemical improvement (even those who had the least viral response)

Figure 3. ALT Responses in 19 Patients Achieving HDV RNA <1000 IU/mL (Without ALT Normalization) with BLV Treatment (2 mg and 10 mg)



Subgroup analysis criteria: Inclusion: elevated ALT and HDV RNA >1000 IU/mL at BL; HDV RNA <1000 IU/mL HBV DNA ≤ LLLOQ at W48.
ALT, alanine aminotransferase; BL, baseline; HDV, hepatitis delta virus; Pt, patient; W, week.

- 19 of 229 patients did not achieve ALT ≤ ULN at W48 in this subgroup analysis despite achieving HDV RNA <1000 IU/mL (3 $\log_{10}$ IU/mL)
- Despite the lack of ALT ≤ ULN, 84% (16 of 19) of patients had ALT ≤1.5 x ULN
  - Likely etiologies for lack of ALT normalization upon individual case review included cirrhosis (n = 7), nonalcoholic fatty liver disease (n = 8), and hepatitis B virus (HBV) reactivation (n = 1, in a patient not receiving concomitant NA therapy)

Figure 4. Changes in ALT Categories by Viral Response Categories at Week 48 During BLV Treatment (2 mg and 10 mg)

ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; HDV, hepatitis delta virus; ULN, upper limit of normal; W, week.

- Improvements in ALT were observed with 48-week BLV therapy in all viral response subgroups; ALT improvement occurred mostly in the first 24 weeks
- More pronounced improvements in ALT with BLV treatment were seen in patients who achieved HDV RNA ≥1 $\log_{10}$ IU/mL decline from BL, ≥2 $\log_{10}$ IU/mL decline from BL, or undetectable HDV RNA at W48