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Poster for you

Undetectable HDV RNA Defined as Target Not Detected at the End of Treatment With Bulevirtide and/or Pegylated Interferon Alpha-2a Is an Important Predictor of 48 Weeks Sustained Virologic Response in Chronic Hepatitis Delta

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Conclusions

- In patients with compensated chronic hepatitis delta receiving finite therapy, achieving on-treatment undetectable hepatitis delta virus (HDV) RNA with target not detected is an important predictor of maintaining off-treatment response
- The majority of patients with low-positive viraemia (HDV RNA < lower limit of quantitation, target detected) at end of treatment had viral rebound in the posttreatment period

Plain Language Summary

- Some patients who took antiviral therapy with bulevirtide plus pegylated interferon alpha-2a for hepatitis delta responded well enough that the virus could no longer be detected
- Most of these patients tended to continue to do well after completing therapy
- Patients who had detectable virus during treatment tended to get worse after stopping treatment

Introduction

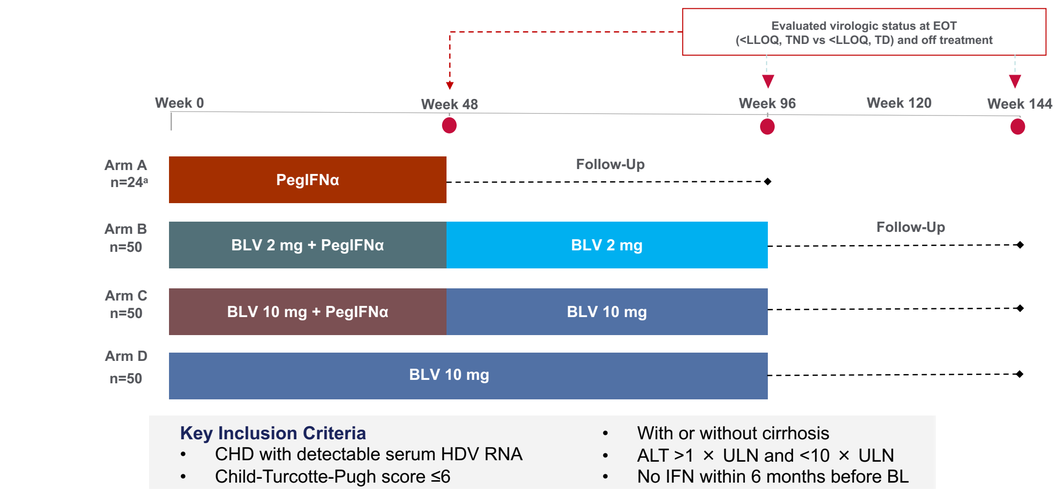
- Chronic hepatitis delta (CHD) infection is the most severe form of viral hepatitis.[1,2] Bulevirtide (BLV) 2 mg is approved for the treatment of compensated CHD in Europe[3]
- Achievement of virologic suppression of hepatitis delta virus (HDV) RNA, defined as below the lower limit of quantitation (<LLOQ), is associated with lower risk of disease progression[4]
- Improved ultrasensitive HDV RNA detection technologies have enabled a more stringent definition of "undetectable HDV RNA": patients who achieve <LLOQ and target not detected (TND)
  - The clinical relevance of TND vs <LLOQ (target detected [TD]) for HDV RNA levels is unknown[4]
- The Phase 2b study MYR204 (NCT03852433) evaluated finite treatment with BLV with or without pegylated interferon alpha-2a (PegIFNα) in patients with compensated CHD
  - Combination treatment with BLV 10 mg + PegIFNα had the highest rate of undetectable HDV RNA at 24 weeks after the end of treatment (EOT)[5]

Objective

- To establish the clinical relevance of undetectable HDV RNA, defined as <LLOQ with TND, for finite treatment regimens

Methods

Figure 1 **Study Design**



[a]The PegIFNα arm had 1 patient excluded from analysis; the patient was randomised but did not receive study medication.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; CHD, chronic hepatitis delta; EOT, end of treatment; HDV, hepatitis delta virus; IFN, interferon; LLOQ, lower limit of quantitation; PegIFNα, pegylated interferon alpha-2a; TD, target detected; TND, target not detected; ULN, upper limit of normal.

- The Phase 2b MYR204 study was an open-label, randomised, multicentre study conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)
- The primary endpoint was the proportion of patients who achieved undetectable HDV RNA at 24 weeks after EOT
- The following response categories at EOT and weeks 24 and 48 after EOT (FU24 and FU48) were reported:
  - Undetectable HDV RNA (<LLOQ, TND)
  - Low-positive viraemia (<LLOQ, TD)
  - HDV RNA ≥LLOQ

Results

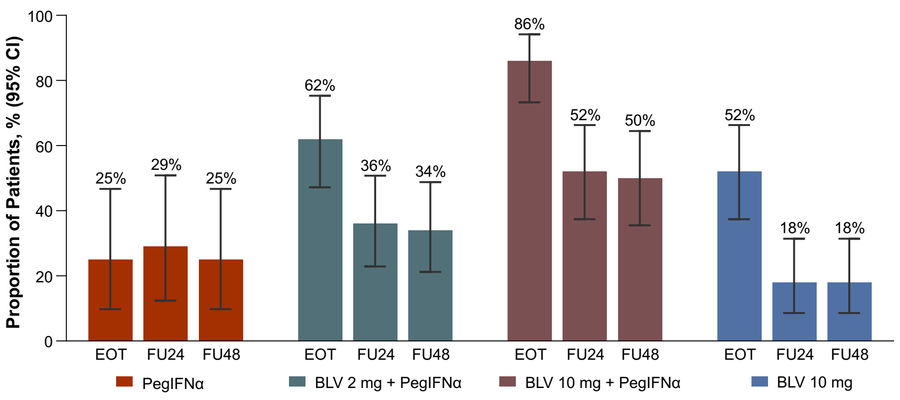
Table 1 **Baseline Disease Characteristics**

	PegIFNα n = 24	BLV 2 mg + PegIFNα n = 50	BLV 10 mg + PegIFNα n = 50	BLV 10 mg n = 50
Compensated cirrhosis, n (%)	8 (33)	17 (34)	17 (34)	17 (34)
Liver stiffness, kPa, mean (SD)	15.8 (11.6)	12.8 (6.4)	12.5 (7.6)	12.7 (6.7)
Patients with >20 kPa, n (%)	6 (25)	9 (18)	7 (14)	6 (12)
ALT, U/L, mean (SD)	121 (95.9)	108 (77.0)	113 (98.6)	118 (108.1)
HDV RNA, log_{10} IU/mL, median (IQR)	5.2 (4.6–5.8)	5.6 (4.3–6.3)	5.5 (4.4–6.1)	5.6 (4.6–6.3)
HDV genotype, n (%)				
1	24 (100)	48 (96)	47 (94)	49 (98)
5/6/ND	0/0/0	1 (2)/1 (2)/0	2 (4)/0/1 (2)	1 (2)/0/0
HBsAg, log_{10} IU/mL, mean (SD)	3.6 (0.5)	3.7 (0.6)	3.7 (0.7)	3.7 (0.6)
HBV DNA, log_{10} IU/mL, mean (SD)	1.4 (1.1)	1.7 (1.6)	1.5 (1.1)	1.8 (1.6)
Positive, n (%)[a]	17 (70)	41 (82)	38 (76)	40 (80)
HBeAg negative, n (%)	23 (96)	42 (84)	47 (94)	43 (86)
Prior interferon use, n (%)	12 (50)	25 (50)	26 (52)	21 (42)
Concomitant HBV medication, n (%)	11 (46)	24 (48)	25 (50)	23 (46)

[a]HBV DNA positive: ≥LLOQ. ALT, alanine aminotransferase; BLV, bulevirtide; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; ND, not determined; PegIFNα, pegylated interferon alpha-2a.

- Baseline disease characteristics were well balanced between arms
- The highest rate of undetectable HDV RNA after EOT was observed in patients treated with BLV 10 mg + PegIFNα

Figure 2 **Proportion of Patients With HDV RNA <LLOQ (TD or TND) at EOT and After EOT**

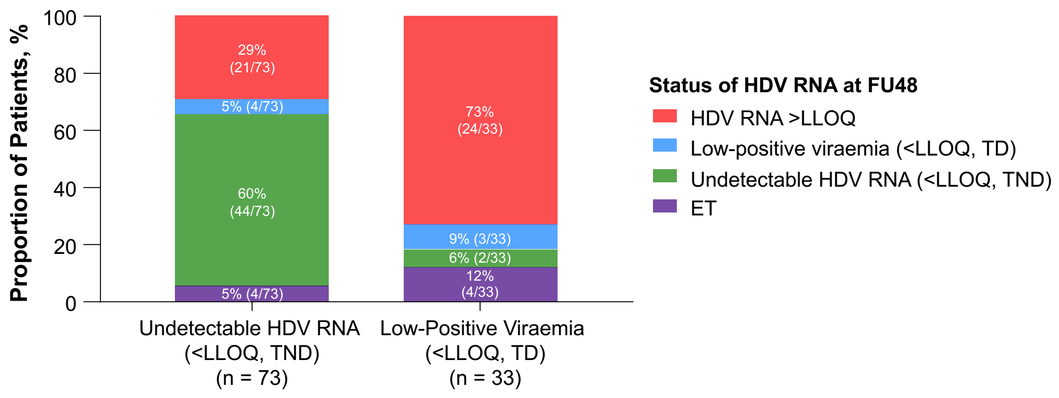


BLV, bulevirtide; EOT, end of treatment; FU24, follow-up at 24 weeks after EOT; FU48, follow-up at 48 weeks after EOT; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; PegIFNα, pegylated interferon alpha-2a; TD, target detected; TND, target not detected.

- The proportions of patients who achieved HDV RNA <LLOQ status remained similar between FU24 and FU48
- The highest rate of HDV RNA <LLOQ after EOT was observed with BLV 10 mg + PegIFNα

Results

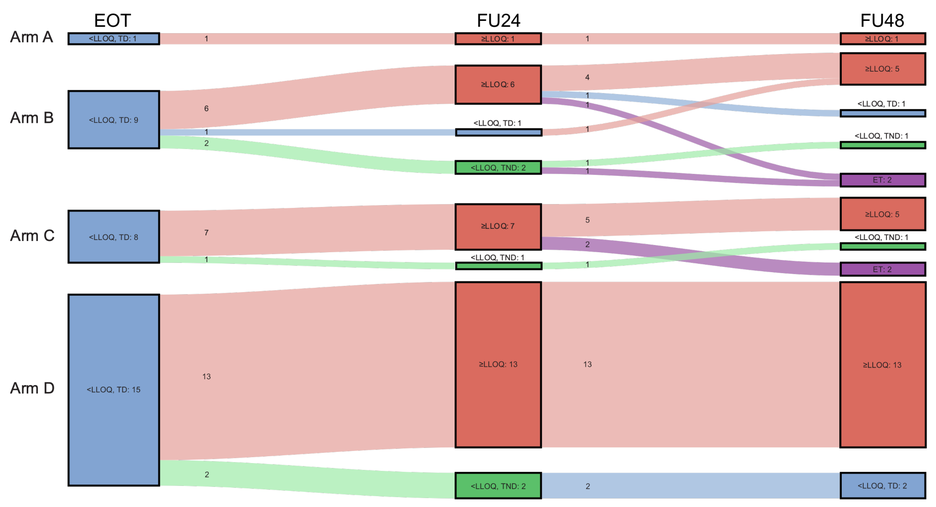
Figure 3 **HDV RNA Status at FU48 Based on HDV RNA Status at EOT**



EOT, end of treatment; ET, early termination; FU48, follow-up at 48 weeks after EOT; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; TD, target detected; TND, target not detected.

- Among patients with TND at EOT, 60% maintained undetectability at FU48, while 73% of those with low-positive viraemia at EOT rebounded to HDV RNA ≥LLOQ

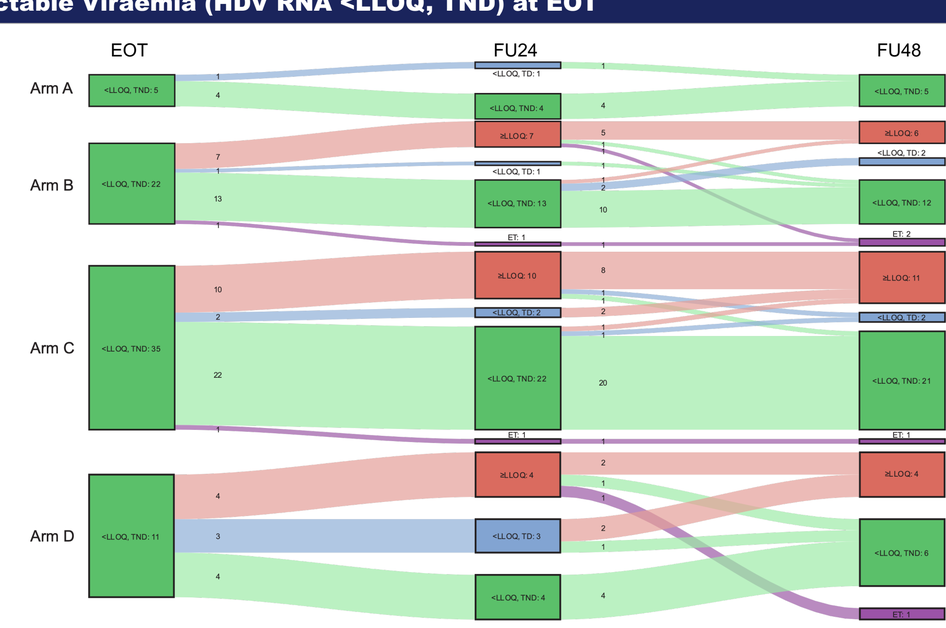
Figure 4 **Progression of Viraemia Status in Posttreatment Period in Patients With Low-Positive Viraemia (HDV RNA <LLOQ, TD) at EOT**



ET during the follow-up period, n = 5: withdrawal of consent, 4; pregnancy, 1. ET before EOT, n = 7: withdrawal of consent, 4; adverse event, 1; lack of efficacy, 1; loss to follow-up, 1.
EOT, end of treatment; ET, early termination; FU24, follow-up at 24 weeks after EOT; FU48, follow-up at 48 weeks after EOT; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; TD, target detected; TND, target not detected.

- Among patients with low-positive viraemia (HDV RNA <LLOQ, TD) at EOT, 73% (24/33) experienced viral rebound by FU48
- Only 6% (2/33) of patients with low-positive viraemia at EOT achieved undetectable status at FU48
  - Both patients received BLV + PegIFNα treatment
- Among the patients with low-positive viraemia at EOT, nearly half (45% [15/33]) had received BLV 10 mg monotherapy (arm D)
  - At FU48, 87% (13/15) of these patients experienced viral rebound
  - The remaining 2 patients maintained low-positive viraemia at FU48

Figure 5 **Progression of Viraemia Status in Posttreatment Period in Patients With Undetectable Viraemia (HDV RNA <LLOQ, TND) at EOT**



ET during the follow-up period, n = 3: protocol violation, 1; death, 1; pregnancy, 1. ET before EOT, n = 2: adverse event, 1; withdrawal of consent, 1.
EOT, end of treatment; ET, early termination; FU24, follow-up at 24 weeks after EOT; FU48, follow-up at 48 weeks after EOT; HDV, hepatitis delta virus; LLOQ, lower limit of quantitation; TD, target detected; TND, target not detected.

- The majority of patients (60% [44/73]) with undetectable HDV RNA at EOT maintained undetectable status at FU48
  - 75% (33 of 44) of these patients were treated with the combination of BLV + PegIFNα
  - 5% (4 of 73) of patients had low-positive viraemia at FU48
- Among patients with undetectable HDV RNA (<LLOQ, TND) at EOT, 29% (21 of 73) experienced viral rebound by FU48

References: 1. Alfaiate D, et al. *J Hepatol*. 2020;73(3):533-9. **2.** Rizzetto M, et al. *J Hepatol*. 2021;74(5):1200-11. **3.** Hepcludex. European Medicines Agency SmPC. Gilead Sciences, Inc.; 2023. **4.** Wedemeyer H, et al. *Hepatology*. 2023. doi: 10.1097/HEP.0000000000000584. **5.** Asselah T, et al. AASLD 2023. Oral presentation #5009. **Acknowledgements:** 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 Rob Coover, MPH, of AlphaScientia, a Red Nucleus company, and funded by Gilead Sciences, Inc. **Disclosures:** **FZ** received consulting fees from Aligos Therapeutics; Antios Therapeutics; Assembly Biosciences; Gilead Sciences, Inc.; and GSK; and research funding to INSERM from Assembly Biosciences, Beam Therapeutics, and Janssen. **TA** acted as a speaker and investigator for AbbVie; Eiger Biopharmaceuticals; Gilead Sciences, Inc.; Janssen; Merck; MYR Pharmaceuticals; and Roche. **VC** reports consultant and sponsored lecture fees from AbbVie; AstraZeneca; Bristol Myers Squibb; Gilead Sciences, Inc.; GSK; Hepatera; Merck Sharp & Dohme; Roche; and R-Pharm. **MB** reports being a board member and speaker for AbbVie; Gilead Sciences, Inc.; Intercept Pharmaceuticals; and Roche. **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 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. **R-CM**, **LY**, **DM**, **AHL**, **GMC**, and **BLD** are employees of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc. **AS-C**, **GSG**, **PB**, **TS**, **VM**, and **OS** report no conflicts of interest.