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

WED-395

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Conclusions

- In patients with compensated CHD receiving finite therapy, achieving on-treatment undetectable HDV RNA with TND is an important predictor of maintaining off-treatment response
- The majority of patients with low-positive viraemia (HDV RNA <LLOQ, TD) at EOT 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

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.

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Introduction

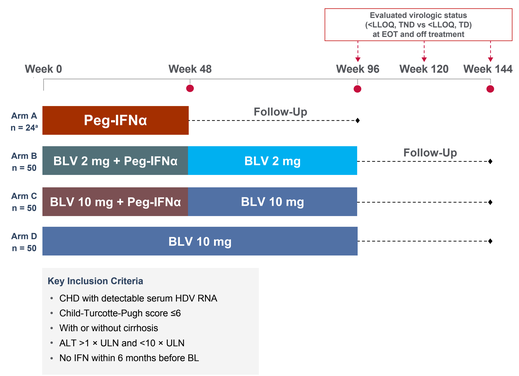
- Chronic hepatitis delta (CHD) infection is the most severe form of viral hepatitis.[1,2] Bulevirtide (BLV) 2 mg is approved for the treatment of compensated CHD in Europe[3]
- Achievement of virologic suppression of hepatitis delta virus (HDV) RNA, defined as below the lower limit of quantification (<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 (Peg-IFNα) in patients with compensated CHD
  - Combination treatment with BLV 10 mg + Peg-IFNα had the highest rate of undetectable HDV RNA at 24 weeks after 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

Study Design



[a]Peg-IFNα arm had 1 patient excluded from analysis; 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 quantification; Peg-IFNα, pegylated interferon alpha-2a; TD, target detected; TND, target not detected; ULN, upper limit of normal.

- Open-label, randomised, multicentre, Phase 2b 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 post-EOT
- The following response categories at EOT and weeks 24 and 48 after EOT (FU-24 and FU-48) were reported:
  - Undetectable HDV RNA (<LLOQ, TND)
  - Low-positive viraemia (<LLOQ, TD)
  - HDV RNA ≥LLOQ

Results

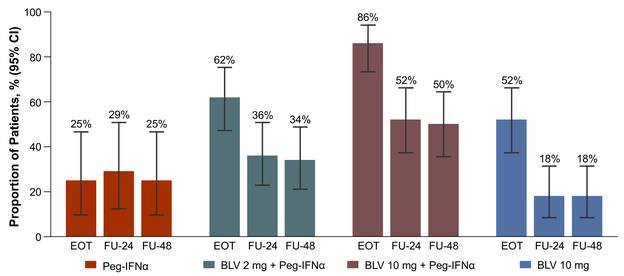
Baseline Disease Characteristics

	Peg-IFNα n = 24	BLV 2 mg + Peg-IFNα n = 50	BLV 10 mg + Peg-IFNα 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 (70.8)	41 (82.0)	38 (76.0)	40 (80.0)
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 quantification; ND, not determined; Peg-IFNα, 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 + Peg-IFNα

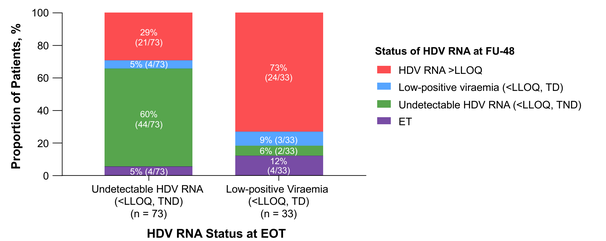
Proportion of Patients With HDV RNA <LLOQ (TD or TND) at EOT and Post-EOT



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

- The proportions of patients who achieved HDV RNA <LLOQ status remained similar between FU-24 and FU-48
- The highest rate of HDV RNA <LLOQ after EOT was observed with BLV 10 mg + Peg-IFNα

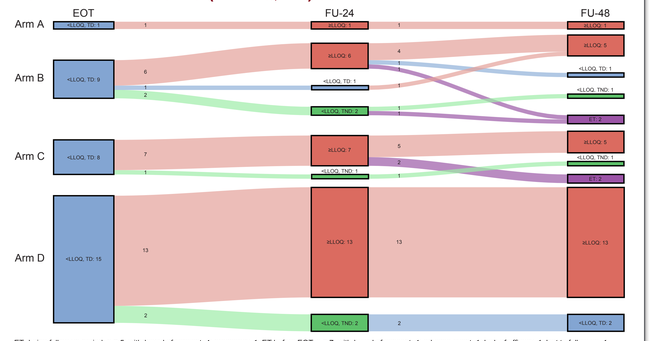
HDV RNA Status at FU-48 Based on HDV RNA Status at EOT



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

- Among those with TND at EOT, 60% maintained undetectability at FU-48, while 73% of those with low-positive viraemia at EOT rebounded to HDV RNA ≥LLOQ

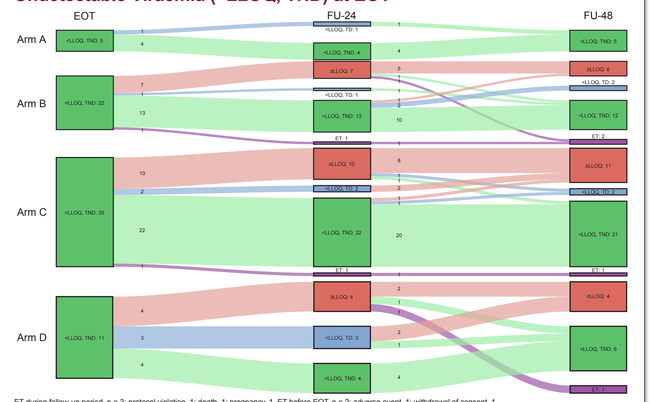
Progression of Viraemia Status in Posttreatment Period in Patients With Low-Positive Viraemia (<LLOQ, TD) at EOT



ET during 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; lost to follow-up, 1.
EOT, end of treatment; ET, early termination; FU-24, follow-up at 24 weeks after EOT; FU-48, follow-up at 48 weeks after EOT; LLOQ, lower limit of quantification; TD, target detected; TND, target not detected.

- Among patients with low-positive viraemia (<LLOQ, TD) at EOT, 73% (24/33) experienced viral rebound by FU-48
- Only 6% (2/33) of patients with low-positive viraemia at EOT achieved undetectable status at FU-48
  - Both received BLV + Peg-IFNα treatment
- Among the patients with low-positive viraemia at EOT, nearly half (45% [15/33]) had received BLV 10 mg monotherapy (arm D)
  - At FU-48, 87% (13/15) of these patients experienced viral rebound
  - The remaining 2 patients maintained low-positive viraemia at FU-48

Progression of Viraemia Status in Posttreatment Period in Patients With Undetectable Viraemia (<LLOQ, TND) at EOT



ET during 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; FU-24, follow-up at 24 weeks after EOT; FU-48, follow-up at 48 weeks after EOT; LLOQ, lower limit of quantification; TD, target detected; TND, target not detected.

- The majority of patients, 60% (44/73), with undetectable HDV RNA at EOT maintained undetectable status at FU-48
  - 75% (33/44) of these patients were treated with the combination of BLV + Peg-IFNα
  - 5% (4/73) of these patients had low-positive viraemia at FU-48
- Among patients with undetectable HDV RNA (<LLOQ, TND) at EOT, 29% (21/73) experienced viral rebound by FU-48