Undetectable HDV RNA at 24 Weeks of Treatment With Bulevirtide and Pegylated Interferon Alfa-2a Combination Therapy Is an Important Predictor of Maintained Response Off-Therapy

FRI-371

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Conclusions

- In patients with CHD treated with BLV (2 mg or 10 mg) + Peg-IFNα, the key potential predictors of undetectable HDV RNA and the composite endpoint of undetectable RNA with ALT normalisation at EOT and in the posttreatment period were:
  - Lower BL HDV RNA levels
  - Lower BL liver stiffness
- In a subset of patients that achieved undetectable HDV RNA at EOT, key on-treatment predictors of non-relapse in the posttreatment period were:
  - Earlier onset of undetectability
  - Longer duration of undetectable HDV RNA status
- Achievement of early undetectable HDV RNA at week 24 on treatment is an important predictor of non-relapse in the posttreatment period

Plain Language Summary

- Chronic hepatitis delta, the most severe form of hepatitis, is a leading cause of advanced liver disease
- An undetectable level of hepatitis delta virus RNA early in treatment (week 24) is a predictor of maintained undetectable levels, an indication of treatment response, after the treatment period ends

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. **6.** Roboscreen Diagnostics. https://www.roboscreen.com/products/viral-pathogens/robogene-hdv-rna-quantification-kit-20/

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Introduction

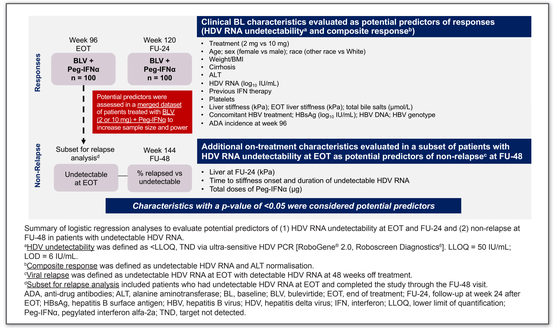
- Chronic hepatitis delta (CHD) is the most severe form of viral hepatitis[1,2]
- Bulevirtide (BLV) 2 mg is approved for the treatment of compensated CHD in the European Union[3]
- Achievement of hepatitis delta virus (HDV) RNA suppression is associated with lower risk of disease progression[4]
- MYR204, a Phase 2b study (NCT03852433), evaluated finite treatment with BLV with or without pegylated interferon alfa-2a (Peg-IFNα)
  - Combination treatment resulted in higher posttreatment virologic response rates compared with either monotherapy regimen at 24 weeks after the end of treatment (EOT)[5]
  - Potential predictors of on-treatment and posttreatment responses to combination therapy of BLV + Peg-IFNα are not yet characterised

Objective

- To determine if any baseline (BL) characteristics or early on-treatment viral kinetics can predict EOT or posttreatment responses with combination treatment of BLV (2 or 10 mg) + Peg-IFNα

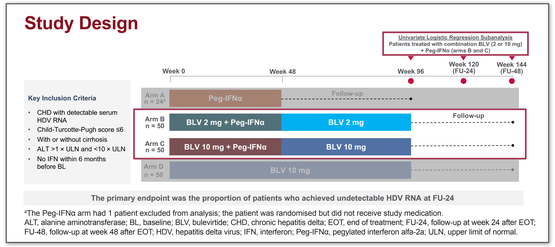
Methods

- In this subanalysis, the logistic regression model was used to examine whether any BL or on-treatment clinical characteristics predicted treatment responses at EOT and follow-up at week 24 after EOT (FU-24) with combination therapy (arms B and C)
  - Additional analysis of early on-treatment viral kinetics was performed on a subset of patients that achieved undetectable HDV RNA at EOT (predictors of non-relapse)



Summary of logistic regression analyses to evaluate potential predictors of (1) HDV RNA undetectability at EOT and FU-24 and (2) non-relapse at FU-48 in patients with undetectable HDV RNA.
[a]HDV undetectability was defined as <LLOQ, TND via ultra-sensitive HDV PCR [RoboGene® 2.0, Roboscreen Diagnostics®]. LLOQ = 50 IU/mL; LOD = 6 IU/mL.
[b]Composite response was defined as undetectable HDV RNA and ALT normalisation.
[c]Viral relapse was defined as undetectable HDV RNA at EOT with detectable HDV RNA at 48 weeks off treatment.
[d]Subset for relapse analysis included patients who had undetectable HDV RNA at EOT and completed the study through the FU-48 visit.
ADA, anti-drug antibodies; ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; EOT, end of treatment; FU-24, follow-up at week 24 after EOT; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; LLOQ, lower limit of quantification; Peg-IFNα, pegylated interferon alfa-2a; TND, target not detected.

Study Design



[a]The Peg-IFNα 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; FU-24, follow-up at week 24 after EOT; FU-48, follow-up at week 48 after EOT; HDV, hepatitis delta virus; IFN, interferon; Peg-IFNα, pegylated interferon alfa-2a; ULN, upper limit of normal.

- Open-label, randomised, multicentre, Phase 2b study (NCT03852433) conducted at 19 sites across 4 countries (France, Moldova, Romania, and Russia)

Results

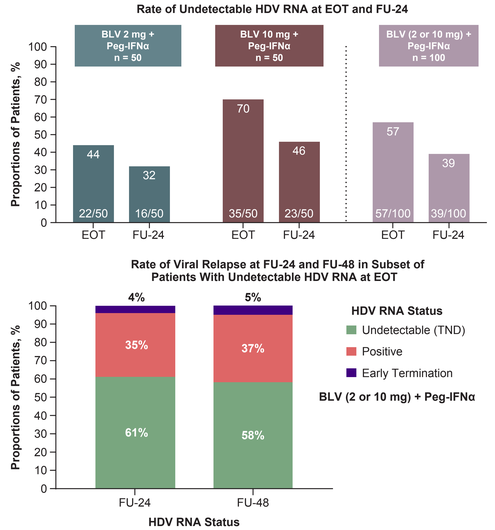
Baseline Disease Characteristics of Patients Treated With BLV in Combination With Peg-IFNα

	BLV 2 mg + Peg-IFNα n = 50	BLV 10 mg + Peg-IFNα n = 50
Compensated cirrhosis, n (%)	17 (34)	17 (34)
Liver stiffness, kPa, mean (SD)	12.8 (6.4)	12.5 (7.6)
Patients with >20 kPa, n (%)	9 (18)	7 (14)
ALT, U/L, mean (SD)	108 (77)	113 (98.6)
HDV RNA, $\log_{10}$ IU/mL, median (IQR)	5.6 (4.3–6.3)	5.5 (4.4–6.1)
HDV GT, n (%)		
1	48 (96)	47 (94)
5 / 6 / ND	1 (2) / 1 (2) / 0	2 (4) / 0 / 1 (2)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.7 (0.6)	3.7 (0.7)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	1.7 (1.6)	1.5 (1.1)
Positive, n (%)	41 (82)	38 (76)
HBV GT A / D / E, n (%)	7 (14) / 40 (80) / 1 (2)	7 (14) / 38 (76) / 2 (4)
HBeAg negative, n (%)	42 (84)	47 (94)
Prior interferon use, n (%)	25 (50)	26 (52)
Concomitant HBV medication, n (%)	24 (48)	25 (50)

ALT, alanine transaminase; BLV, bulevirtide; GT, genotype; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; ND, not determined; Peg-IFNα, pegylated interferon alfa-2a.

- The BL disease characteristics were well balanced across both arms

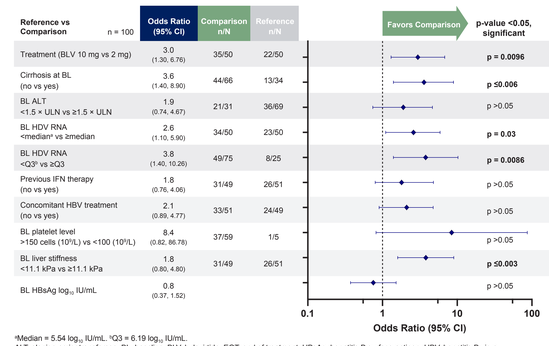
Undetectable HDV RNA at EOT and FU-24, and Rates of Off-Treatment Viral Relapse at FU-48



BLV, bulevirtide; EOT, end of treatment; FU-24, follow-up at week 24 after EOT; FU-48, follow-up at week 48 after EOT; HDV, hepatitis delta virus; Peg-IFNα, pegylated interferon alfa-2a; TND, target not detected.

- Both the 2- and 10-mg BLV dose levels in combination with Peg-IFNα demonstrated similar trends in off-treatment HDV RNA undetectability and composite response (data not shown)
- Among patients who achieved HDV RNA undetectability at EOT, the proportion of participants with viral relapse did not change between FU-24 and follow-up at week 48 after EOT (FU-48)

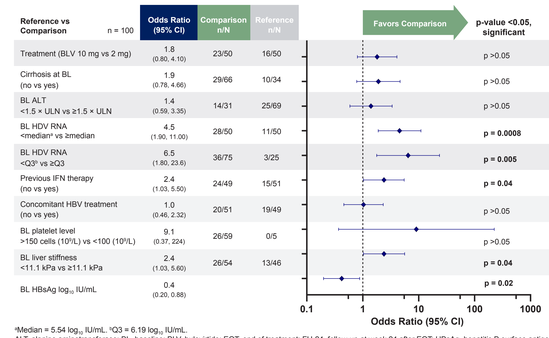
Potential Predictors of Undetectable HDV RNA at EOT



[a]Median = 5.54 $\log_{10}$ IU/mL. [b]Q3 = 6.19 $\log_{10}$ IU/mL.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; EOT, end of treatment; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; Q, quartile; ULN, upper limit of normal.

- Potential BL predictors of undetectable HDV RNA at EOT were:
  - The absence of cirrhosis, HDV RNA levels that were less than the median and less than quartile (Q) 3, and lower liver stiffness measurements
- Results were driven by the dose level of BLV (10 mg)
  - Data trends were similar when BLV 10 mg was given alone: BL HDV RNA levels (odds ratio: 4.3, p = 0.035) and lower BL liver stiffness (odds ratio: 5.3, p = 0.015)
- Similar trends were observed for the composite endpoint (data not shown)

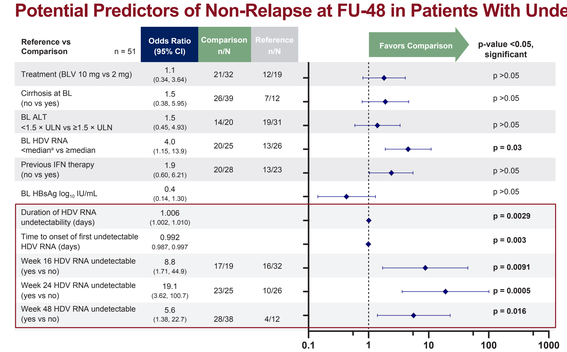
Potential Predictors of Undetectable HDV RNA at FU-24



[a]Median = 5.54 $\log_{10}$ IU/mL. [b]Q3 = 6.19 $\log_{10}$ IU/mL.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; EOT, end of treatment; FU-24, follow-up at week 24 after EOT; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; Q, quartile; ULN, upper limit of normal.

- Potential BL predictors of undetectable HDV RNA at FU-24 were:
  - HDV RNA levels that were less than the median and <Q3, lower HBsAg levels, no previous IFN therapy, and lower liver stiffness measurements
- Previous IFN therapy was not a predictor of composite response at FU-24, while other trends were similar (data not shown)

Potential Predictors of Non-Relapse at FU-48 in Patients With Undetectable HDV RNA at EOT



The red box highlights potential predictors that are characteristics of on-treatment viral kinetics. [a]Median = 5.09 $\log_{10}$ IU/mL.
ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; EOT, end of treatment; FU-48, follow-up at week 48 after EOT; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; IFN, interferon; OR, odds ratio; Q, quartile; ULN, upper limit of normal.

- Potential predictors of non-relapse at FU-48 in patients with undetectable HDV RNA at EOT were:
  - BL HDV RNA levels that were less than the median, and shorter time to onset and longer duration of HDV RNA undetectability on treatment
  - Of note, 23 of 25 patients with undetectable HDV RNA at week 24 on treatment did not relapse by FU-48