OCTOBER 11-12, 2024 MILAN, ITALY
DeltaCure 3rd International Meeting
P38
Poster for you

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

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Conclusions

- In patients with chronic hepatitis delta treated with bulevirtide 2 or 10 mg + pegylated interferon alfa-2a, the key potential predictors of undetectable hepatitis delta virus (HDV) RNA and the composite endpoint of undetectable RNA with alanine aminotransferase normalisation at end of treatment (EOT) and in the posttreatment period were
  - Lower baseline HDV RNA levels
  - Lower baseline liver stiffness
- In a subset of patients that achieved undetectable HDV RNA at EOT, key on-treatment predictors of nonrelapse 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 nonrelapse 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) predicts that the RNA levels will remain undetectable, which is an indication of treatment response

Introduction

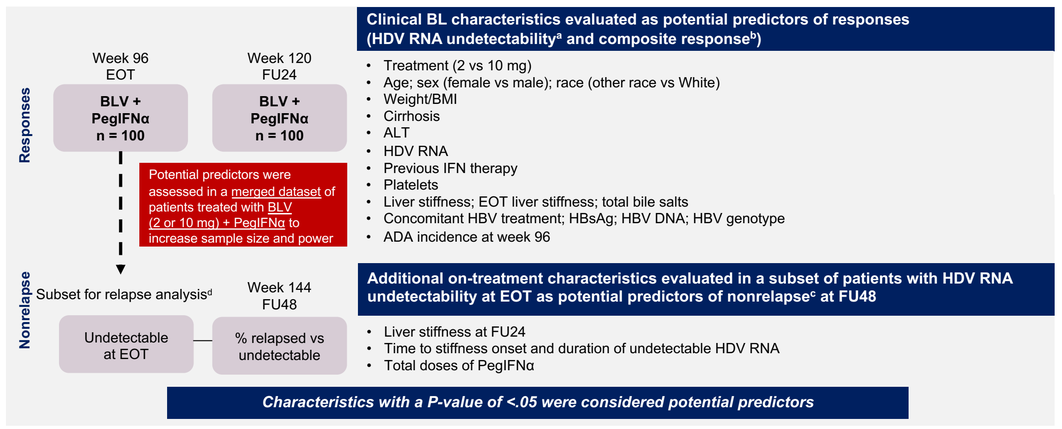
- Chronic hepatitis delta (CHD) is the most severe form of viral hepatitis[1,2]
- Bulevirtide (BLV) 2 mg is approved for the treatment of compensated CHD in the European Union[3]
- Achievement of hepatitis delta virus (HDV) RNA suppression is associated with lower risk of disease progression[4]
- MYR204, a Phase 2b study (NCT03852433), evaluated finite treatment with BLV with or without pegylated interferon alfa-2a (PegIFNα)
  - 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 + PegIFNα 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) + PegIFNα

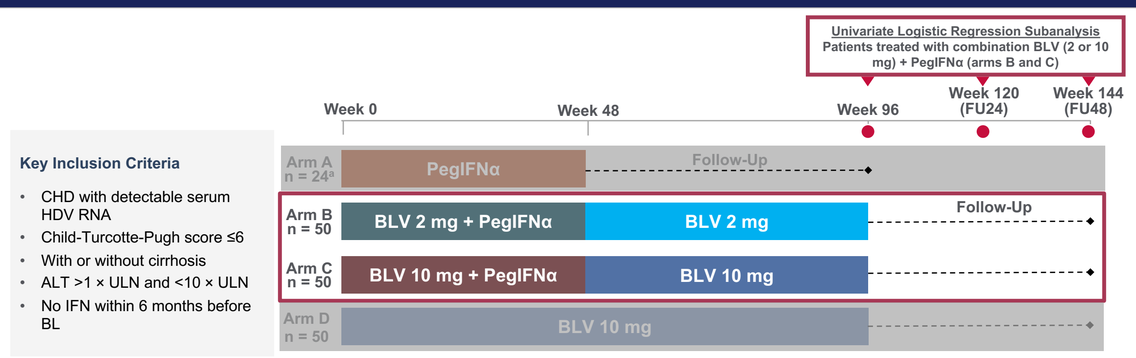
Methods

- In this subanalysis, a 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 (FU24) with combination therapy (arms B and C)
  - Additional analysis of early on-treatment viral kinetics was performed for a subset of patients that achieved undetectable HDV RNA at EOT (predictors of nonrelapse)



Summary of logistic regression analyses to evaluate potential predictors of (1) HDV RNA undetectability at EOT and FU24 and (2) nonrelapse at FU48 in patients with undetectable HDV RNA.
[a]HDV undetectability was defined as <LLOQ, TND via ultrasensitive HDV PCR (RoboGene 2.0, Roboscreen Diagnostics[6]). LLOQ = 50 IU/mL; LOD = 6 IU/mL.
[b]Composite response was defined as undetectable HDV RNA and ALT normalisation.
[c]Virologic 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 FU48 visit.
ADA, antidrug antibodies; ALT, alanine aminotransferase; BL, baseline; BLV, bulevirtide; BMI, body mass index; EOT, end of treatment; FU24, follow-up at week 24 after EOT; FU48, follow-up at week 48 after EOT; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HDV, hepatitis delta virus; IFN, interferon; LLOQ, lower limit of quantification; LOD, limit of detection; PegIFNα, pegylated interferon alfa-2a; TND, target not detected.

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; FU24, follow-up at week 24 after EOT; FU48, follow-up at week 48 after EOT; HDV, hepatitis delta virus; IFN, interferon; PegIFNα, 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

Table 1 **Baseline Disease Characteristics of Patients Treated With BLV in Combination With PegIFNα**

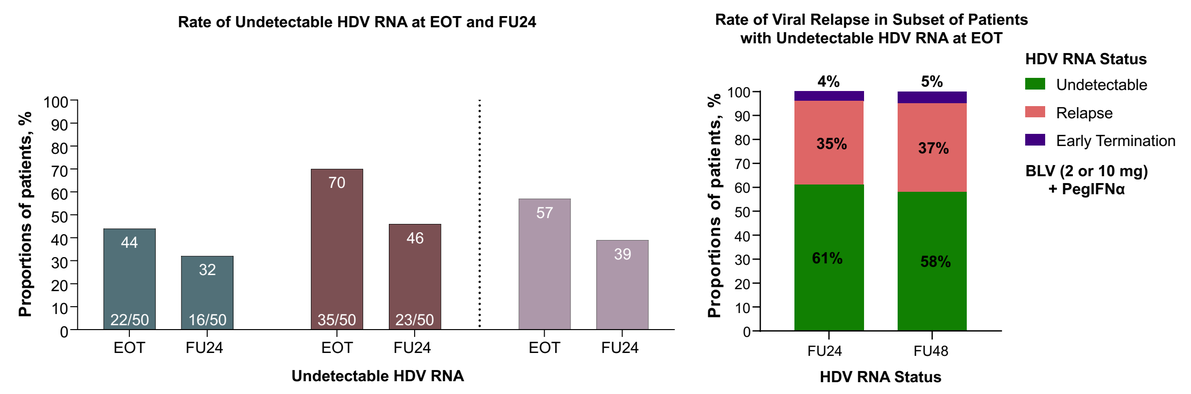
	BLV 2 mg + PegIFNα n = 50	BLV 10 mg + PegIFNα n = 50
Compensated cirrhosis, n (%)	17 (34)	17 (34)
Liver stiffness, kPa, mean (SD)	12.8 (6.4)	12.5 (7.6)
Patients with >20 kPa, n (%)	9 (18)	7 (14)
ALT, U/L, mean (SD)	108 (77)	113 (98.6)
HDV RNA, log_{10} IU/mL, median (IQR)	5.6 (4.3–6.3)	5.5 (4.4–6.1)
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; PegIFNα, pegylated interferon alfa-2a.

- The BL disease characteristics were well balanced across both arms

Results

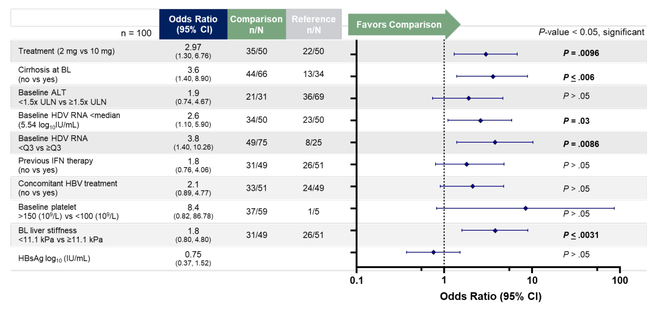
Figure 2 **Undetectable HDV RNA at EOT and FU24 and Rates of Off-Treatment Viral Relapse at FU48**



BLV, bulevirtide; EOT, end of treatment; FU24, follow-up at week 24 after EOT; FU48, follow-up at week 48 after EOT; HDV, hepatitis delta virus; PegIFNα, pegylated interferon alfa-2a.

- Both the 2 and 10 mg BLV dose levels in combination with PegIFNα 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 those with viral relapse did not change between FU24 and follow-up at week 48 after EOT (FU48)

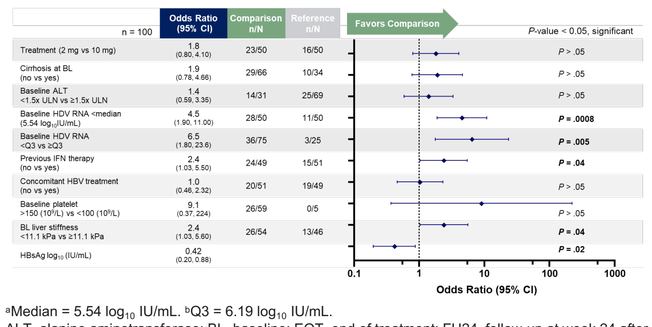
Figure 3 **Potential Predictors of Undetectable HDV RNA at EOT**



- 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* = .035) and lower BL liver stiffness (odds ratio: 5.3, *P* = .015)
- Similar trends were observed for the composite endpoint (data not shown)

[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.

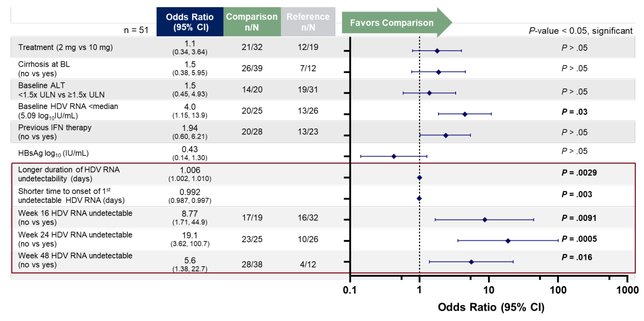
Figure 4 **Potential Predictors of Undetectable HDV RNA at FU24**



- Potential BL predictors of undetectable HDV RNA at FU24 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 FU24, whereas other trends were similar (data not shown)

[a]Median = 5.54 log_{10} IU/mL. [b]Q3 = 6.19 log_{10} IU/mL.
ALT, alanine aminotransferase; BL, baseline; EOT, end of treatment; FU24, 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.

Figure 5 **Potential Predictors of Nonrelapse at FU48 in Patients With Undetectable HDV RNA at EOT**



- Potential predictors of nonrelapse at FU48 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 FU48

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; EOT, end of treatment; FU48, follow-up at week 48 after EOT; HBsAg, hepatitis B surface antigen; HDV, hepatitis delta virus; IFN, interferon; ULN, upper limit of normal.

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/
Acknowledgments: 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 Samantha Tener, PhD, 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. **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. **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 Pharmaceuticals; Roche; and Spring Bank Pharmaceuticals. **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 Pharmaceuticals; Novartis; Novira; Roche; Roche Diagnostics; Siemens; and Transgene; and research support from Abbott; Bristol Myers Squibb; Gilead Sciences, Inc.; Novartis; Roche; and Roche Diagnostics. **MB** reports being a board member and speaker for AbbVie; Gilead Sciences, Inc.; Intercept Pharmaceuticals; and Roche. **VR** reports consultancy fees from Boehringer Ingelheim. **TA** acted as a speaker and investigator for AbbVie; Eiger Biopharmaceuticals; Gilead Sciences, Inc.; Janssen; Merck; MYR Pharmaceuticals; and Roche. **DM**, **RCM**, **LY**, **GMC**, **BLD**, **AHL**, and **AO** are employees of Gilead Sciences, Inc., and may own stock in Gilead Sciences, Inc. **ASC**, **VP**, **SL**, **GSG**, **PB**, **TS**, **VM**, **VS**, **OS**, **SP**, and **MNH** report no conflicts of interest.