Predictors of Undetectable Hepatitis Delta Virus RNA at 48 Weeks After End of Treatment With Bulevirtide Monotherapy in the MYR301 Study

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Disclosures

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Background

- Hepatitis delta virus (HDV) represents the most severe form of chronic viral hepatitis and is estimated to affect between 9 and 19 million people worldwide[1]
- Bulevirtide (BLV), an entry inhibitor of HDV, is approved in the European Union, Great Britain, Switzerland, the Russian Federation, and Australia (2 mg/day dose) for the treatment of chronic hepatitis delta in patients with compensated liver disease[2,3]
- Monotherapy with BLV 2 mg/day or 10 mg/day has been demonstrated to be effective and safe over 144 weeks of treatment[4-6]

1. Stockdale AJ, et al. *J Hepatol*. 2020;73:523-32. 2. Hepcludex. Summary of product characteristics. European Medicines Agency. Gilead Sciences, Inc.; 2023. 3. Hepcludex (bulevirtide acetate). Australian Register of Therapeutic Goods. Gilead Sciences, Inc.; 2024.
4. Wedemeyer H, et al. *N Engl J Med*. 2023;389:22-32. 5. Wedemeyer H, et al. *J Hepatol*. 2024;81:621-9. 6. Lampertico P, et al. *J Hepatol*. 2024;80(Suppl):S92.

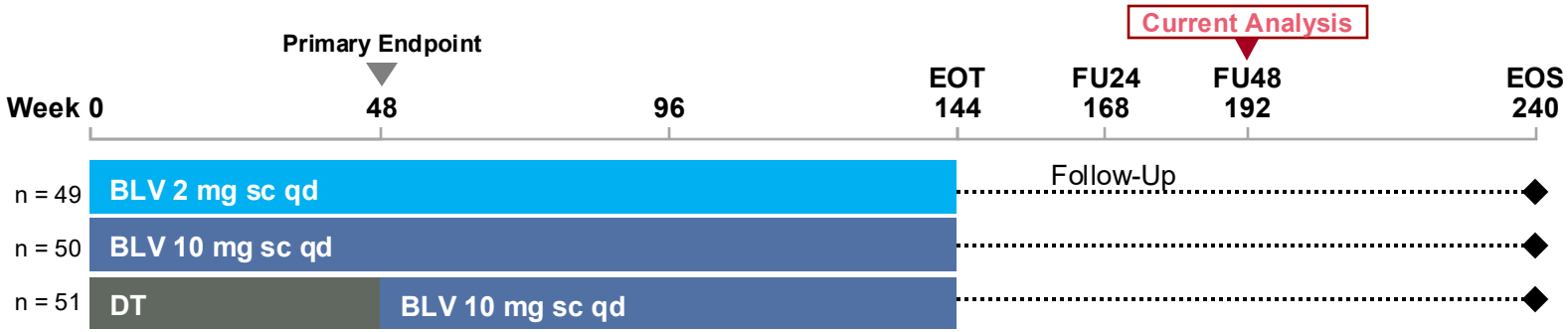
Objectives

- To evaluate predictors of undetectable HDV RNA after 96 or 144 weeks of BLV monotherapy
- To evaluate predictors for sustained HDV RNA undetectability throughout the patient's follow-up period (up to 48 weeks of posttreatment follow-up [FU48]) in those with undetectable HDV RNA at the scheduled end of treatment (EOT)

BLV, bulevirtide; **HDV**, hepatitis delta virus.

MYR301 Methods

Study Design



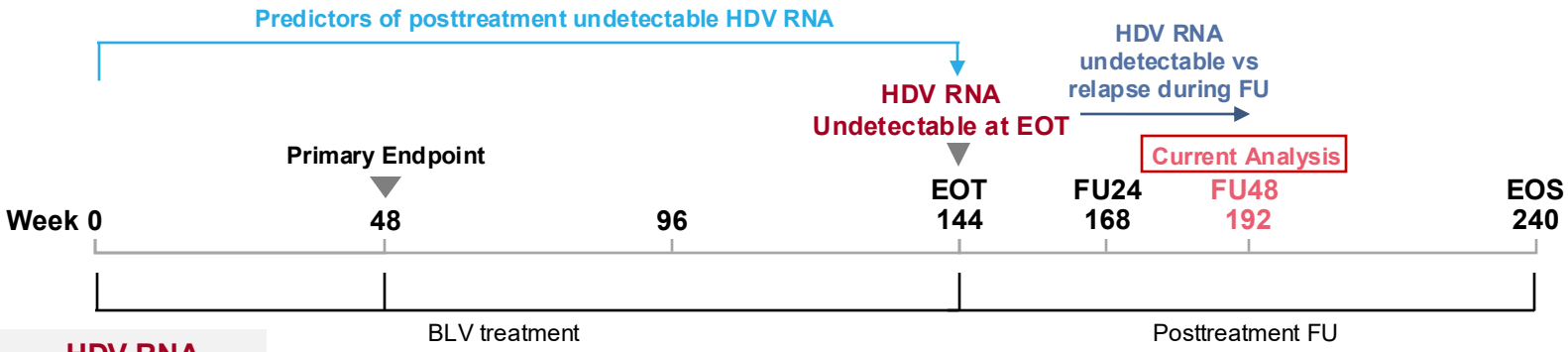
Key Inclusion Criteria

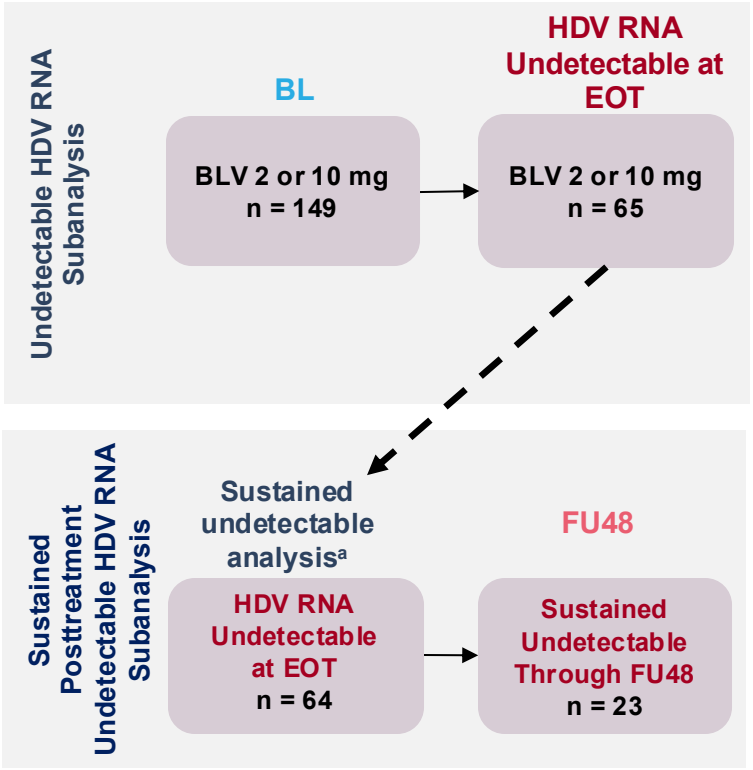
- CHD with detectable serum HDV RNA
- With or without cirrhosis; CTP score ≤7
- ALT >1 to <10 × ULN; platelets ≥60,000 cells/mm^3

- MYR301 was a multicentre, open-label, randomised, Phase 3 study (NCT03852719) conducted in 4 countries (Germany, Italy, Russian Federation, and Sweden)
- HDV RNA levels were determined by reverse transcription–quantitative polymerase chain reaction using the RoboGene 2.0 (lower limit of quantitation, 50 IU/mL; lower limit of detection, 6 IU/mL)

ALT, alanine aminotransferase; **BLV**, bulevirtide; **CHD**, chronic hepatitis delta; **CTP**, Child-Turcotte-Pugh; **DT**, delayed treatment; **EOS**, end of study; **EOT**, end of treatment; **FU24**, follow-up at 24 weeks after EOT (week 168); **FU48**, follow-up at 48 weeks after EOT (week 192); **HDV**, hepatitis delta virus; **qd**, once daily; **sc**, subcutaneous; **ULN**, upper limit of normal.

Predictor Analysis Methods

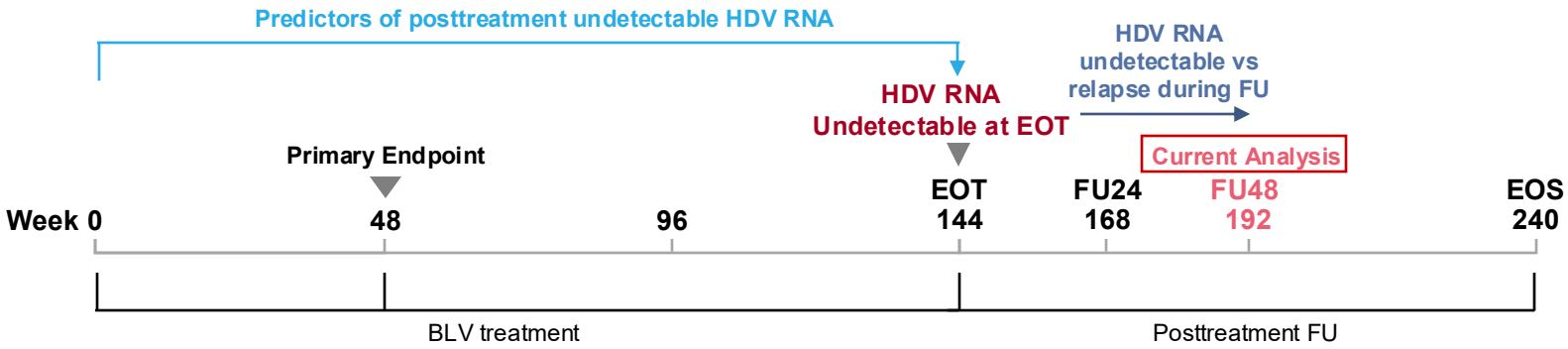




- Univariate logistic regression models (adjusted for the 3 treatment groups) were used to identify potential predictors of undetectability at the scheduled EOT
- For patients who had HDV RNA undetectable at the scheduled EOT with any HDV RNA follow-up data, logistic regression was used to select potential predictors of sustained undetectable HDV RNA throughout the patient's follow-up period (up to FU48)

[a]Subset included patients with undetectable HDV RNA at EOT and who had any available follow-up data.
BL, baseline; **BLV**, bulevirtide; **EOS**, end of study; **EOT**, end of treatment; **FU**, follow-up; **FU24**, follow-up at 24 weeks after EOT (week 168); **FU48**, follow-up at 48 weeks after EOT (week 192); **HDV,** hepatitis delta virus.

Baseline and On-Treatment Characteristics Evaluated as Predictors



Potential Predictors of Undetectable HDV RNA at EOT

Baseline[a] Clinical Characteristics

- Treatment (BLV 2 mg vs 10 mg)
- Age, sex, race, weight, BMI
- Cirrhosis, liver stiffness (kPa)
- ALT, platelets
- HDV RNA (log_{10} IU/mL)
- Previous IFN therapy
- Concomitant HBV treatment, HBsAg, HBV DNA, HBV genotype
- Total bile salt levels (µmol/L)

Potential Predictors of Sustained Posttreatment Undetectable HDV RNA in Patients Who Achieved Undetectability at EOT

Baseline[a] Clinical Characteristics

- Treatment (BLV 2 mg vs 10 mg)
- Age, sex, race, weight, BMI
- Cirrhosis, liver stiffness (kPa)
- ALT, platelets
- HDV RNA (log_{10} IU/mL)
- Previous IFN therapy
- Concomitant HBV treatment, HBsAg, HBV DNA, HBV genotype
- Total bile salt levels (µmol/L)

Treatment-Related Characteristics

- Duration of HDV RNA continuously undetectable at EOT
- Undetectable HDV RNA at early study timepoints

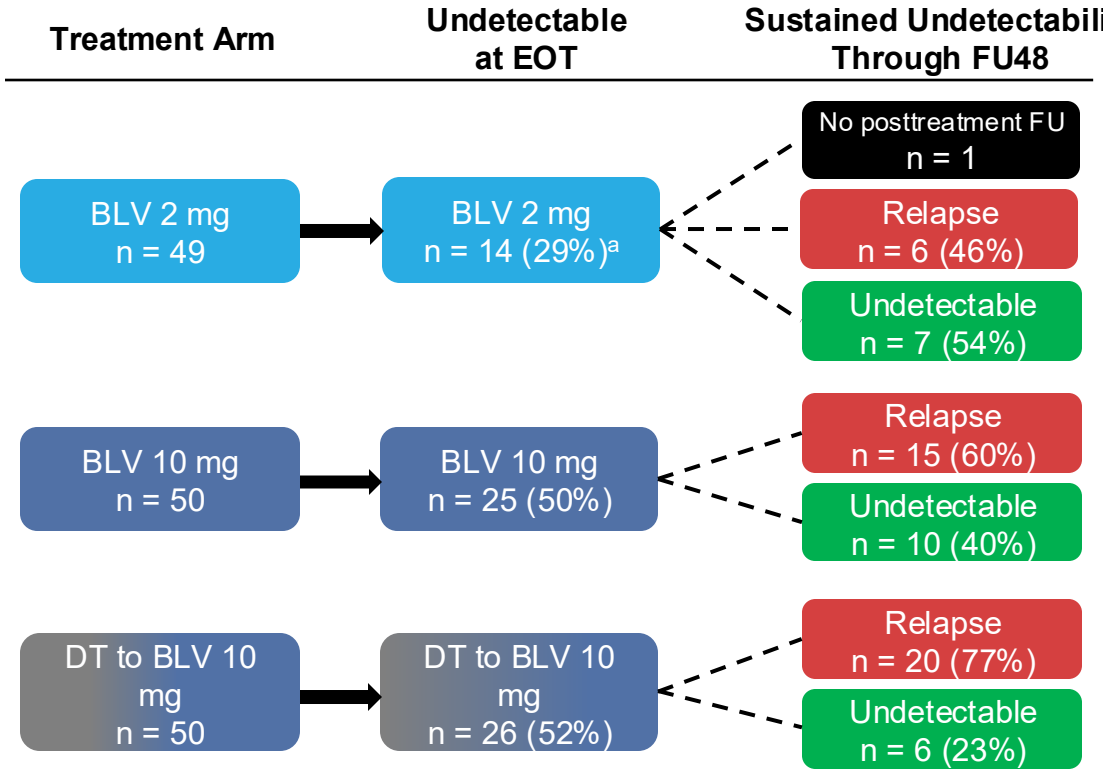
[a]Baseline characteristics apart from cirrhosis at randomisation, sex, and race refer to baseline at the time of BLV initiation.
ALT, alanine aminotransferase; **BLV**, bulevirtide; **BMI**, body mass index; **EOS**; end of study; **EOT**, end of treatment; **FU**, follow-up; **FU24**, follow-up at 24 weeks after EOT (week 168); **FU48**, follow-up at 48 weeks after EOT (week 192); **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **IFN**, interferon.

Baseline Demographics and Disease Characteristics

	BLV 2 mg (n = 49)	BLV 10 mg (n = 50)	DT to BLV 10 mg (n = 50)[a]
Age, years, mean (SD)	44 (9)	41 (9)	42 (8)
Male sex, n (%)	30 (61)	30 (60)	26 (52)
Race,[b] n (%)			
White	41 (84)	43 (86)	39 (78)
Asian	8 (16)	6 (12)	11 (22)
Cirrhosis present, n (%)	23 (47)	24 (48)	24 (48)
Liver stiffness, kPa, mean (SD)	14.0 (8.2)	14.8 (9.3)	16.1 (11.8)
ALT, U/L, mean (SD)	108 (63)	123 (81)	82 (51)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)	5.10 (1.19)	4.96 (1.46)	5.03 (1.56)
Genotype HDV-1,[c] n (%)	49 (100)	48 (96)	50 (100)
HBsAg, $\log_{10}$ IU/mL, mean (SD)	3.67 (0.52)	3.61 (0.59)	3.71 (0.63)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	1.31 (1.28)	1.08 (1.26)	0.81 (1.01)
HBV genotype, n (%)			
A	2 (4)	2 (4)	2 (4)
D	47 (96)	44 (88)	44 (88)
Other[d]/missing	0	4 (8)	4 (8)
Previous IFN therapy, n (%)	26 (53)	29 (58)	29 (58)
Concomitant HBV NA treatment,[e] n (%)	32 (65)	27 (54)	33 (66)

[a]At BL (randomisation), 51 patients were assigned to DT to BLV 10 mg. One patient subsequently withdrew from the DT to BLV 10 mg group before receiving BLV and is not included in subsequent reporting. [b]BLV 10 mg arm: Black, n = 1. [c]BLV 10 mg arm: HDV genotype 5, n = 1; missing HDV genotype, n = 1. [d]Other: BLV 10 mg arm: HBV genotype E, n = 1; no data, n = 3; DT to BLV 10 mg arm: unclassified HBV genotype, n = 1; no data, n = 3. [e]All patients started NA therapy at or after BL, except 1, who started at BL or within 2 days of BL.
ALT, alanine aminotransferase; **BL**, baseline; **BLV**, bulevirtide; **DT**, delayed treatment; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **IFN**, interferon; **NA**, nucleos(t)ide analogue.

Rates of HDV RNA Undetectability Among Patients Who Received BLV



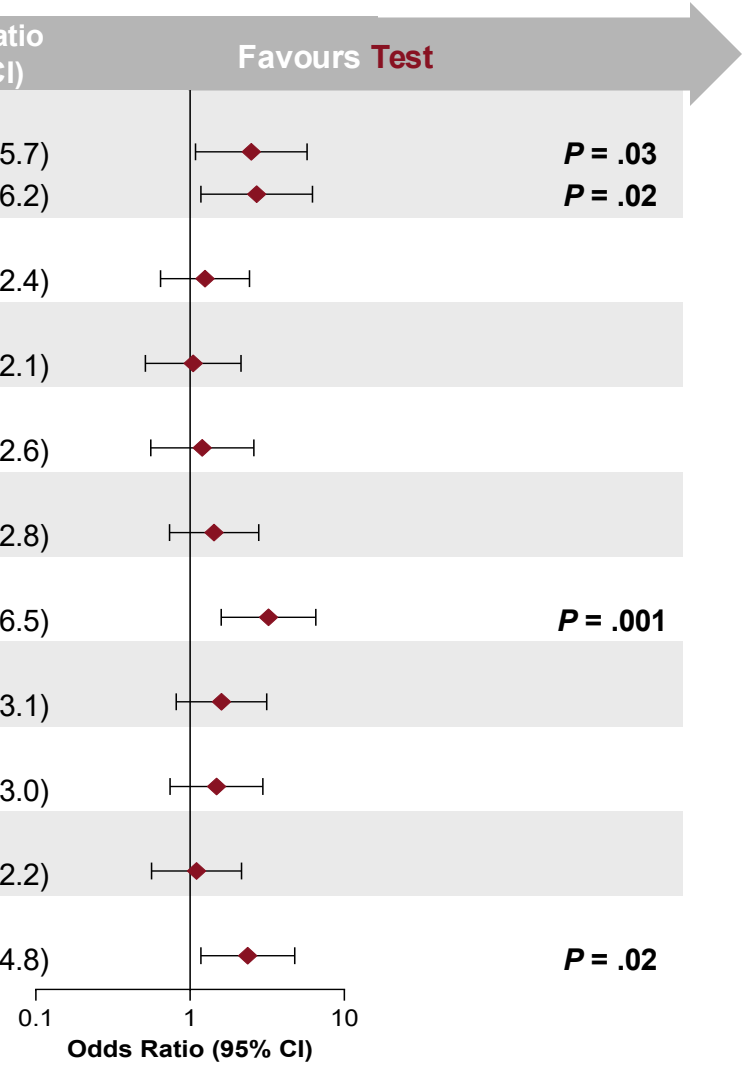
- Of 64 patients with available follow-up HDV RNA data, 62 had available data through FU48, while 2 discontinued the study after 24 weeks of posttreatment follow-up (FU24) without experiencing relapse
- Rates of undetectable HDV RNA at EOT were higher in the treatment groups who received BLV 10 mg
- Relapses were more common in patients who received only 2 years of BLV treatment (vs 3 years)

[a]One patient in the BLV 2 mg group had no FU data available and was excluded from posttreatment calculations.
BLV, bulevirtide; **DT**, delayed treatment; **EOT**, end of treatment; **FU**, follow-up; **FU48**, follow-up at 48 weeks after EOT (week 192); **HDV,** hepatitis delta virus.

Baseline Predictors of Undetectable HDV RNA at EOT

Univariate Logistic Regression Analysis

Baseline; n = 149	Undetectable at EOT Test (%)	Undetectable at EOT Reference (%)	Odds Ratio (95% CI)	
Treatment arm				
BLV 10 mg (vs **BLV 2 mg**)	50.0%	28.6%	2.5 (1.1, 5.7)	***P* = .03**
DT to BLV 10 mg (vs **BLV 2 mg**)	52.0%	28.6%	2.7 (1.2, 6.2)	***P* = .02**
Cirrhosis at randomisation				
Yes (vs **no**)	46.5%	41.0%	1.3 (0.6, 2.4)	
Liver stiffness				
≥15.2 kPa (vs **<15.2 kPa**)	44.7%	43.1%	1.0 (0.5, 2.1)	
ALT				
≥1.5 × ULN (vs **<1.5 × ULN**)	44.1%	42.1%	1.2 (0.6, 2.6)	
Platelet count (10^{10}/L)				
≥160[a] (vs **<160[a]**)	48.0%	39.2%	1.4 (0.7, 2.8)	
HDV RNA (log_{10} IU/mL)				
<5.2[a] (vs **≥5.2[a]**)	56.8%	30.7%	3.2 (1.6, 6.5)	***P* = .001**
Previous IFN therapy				
Yes (vs **no**)	48.8%	36.9%	1.6 (0.8, 3.1)	
Concomitant HBV treatment				
Yes (vs **no**)	46.7%	38.6%	1.5 (0.7, 3.0)	
Total bile salts (µmol/L)				
<12.0[a] (vs **≥12.0[a]**)	46.6%	41.9%	1.1 (0.6, 2.2)	
HBsAg (log_{10} IU/mL)				
<3.8[a] (vs **≥3.8[a]**)	52.9%	35.1%	2.4 (1.2, 4.8)	***P* = .02**



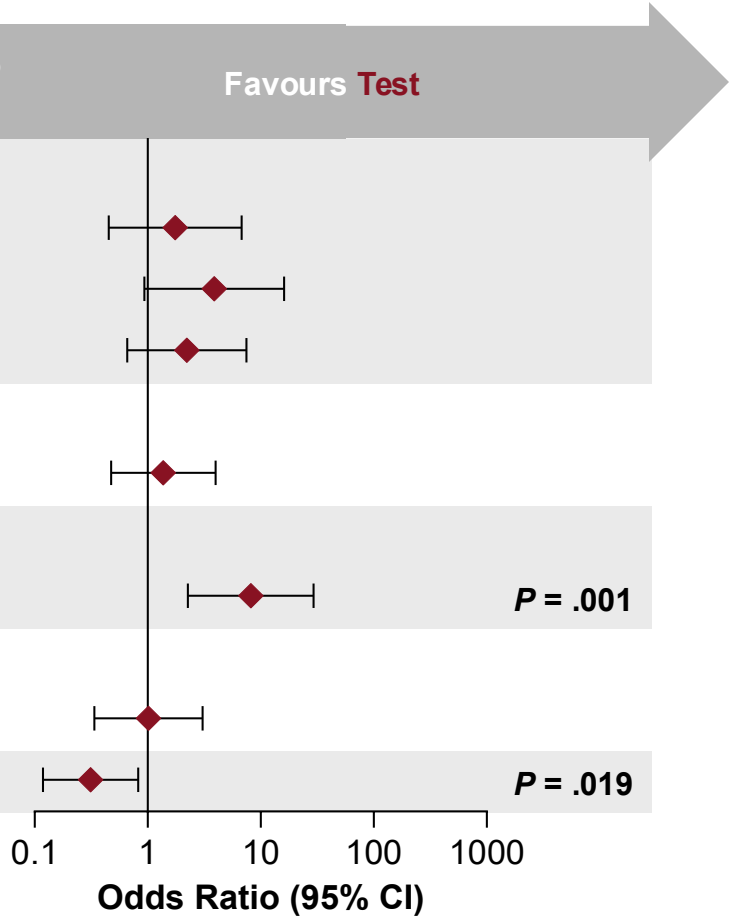
- Treatment with BLV 10 mg and lower baseline HDV RNA were predictive of achieving undetectability at EOT

Bold ***P*-values** indicate significance.
[a]Represents the median.
ALT, alanine aminotransferase; **BLV**, bulevirtide; **DT**, delayed treatment; **EOT**, end of treatment; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **IFN**, interferon; **ULN**, upper limit of normal.

Baseline Predictors of Sustained HDV RNA Undetectability After EOT (FU48)

Univariate Logistic Regression Analysis

Baseline; n = 64	Sustained Undetectability Test (%)	Sustained Undetectability Reference (%)	Odds Ratio (95% CI)	
Treatment arm				
BLV 2 mg (vs **BLV 10 mg**)	53.8%	40.0%	1.8 (0.5, 6.8)	
BLV 2 mg (vs **DT/BLV 10 mg**)	53.8%	23.1%	3.9 (0.9, 16.1)	
BLV 10 mg (vs **DT/BLV 10 mg**)	40.0%	23.1%	2.2 (0.7, 7.5)	
Cirrhosis at randomisation				
Yes (vs **no**)	40.6%	31.3%	1.4 (0.5, 4.0)	
HDV RNA (log_{10} IU/mL)				
<4.6[a] (vs **≥4.6[a]**)	56.3%	15.6%	8.2 (2.3, 29.5)	***P* = .001**
Previous IFN therapy				
Yes (vs **no**)	36.6%	34.8%	1.0 (0.3, 3.1)	
HBsAg (**per log_{10} IU/mL**)	—	—	0.3 (0.1, 0.8)	***P* = .019**



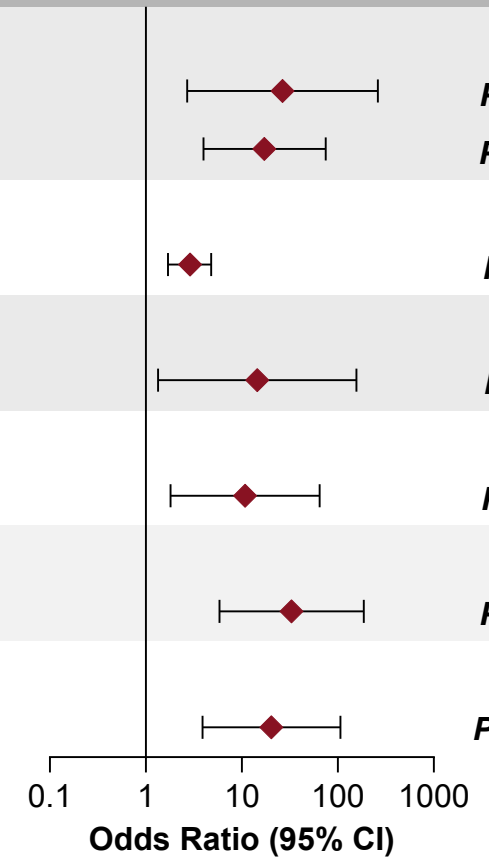
- In patients with undetectable HDV RNA at EOT, lower baseline HDV RNA and lower baseline HBsAg were predictive of sustained undetectability posttreatment

Bold ***P*-values** indicate significance.
[a]Represents the median.
BLV, bulevirtide; **DT**, delayed treatment; **EOT**, end of treatment; **FU48**, follow-up at 48 weeks after EOT (week 192); **HBsAg**, hepatitis B surface antigen; **HDV**, hepatitis delta virus; **IFN**, interferon.

On-Treatment Predictors of Sustained HDV RNA Undetectability After EOT (FU48)

Univariate Logistic Regression Analysis

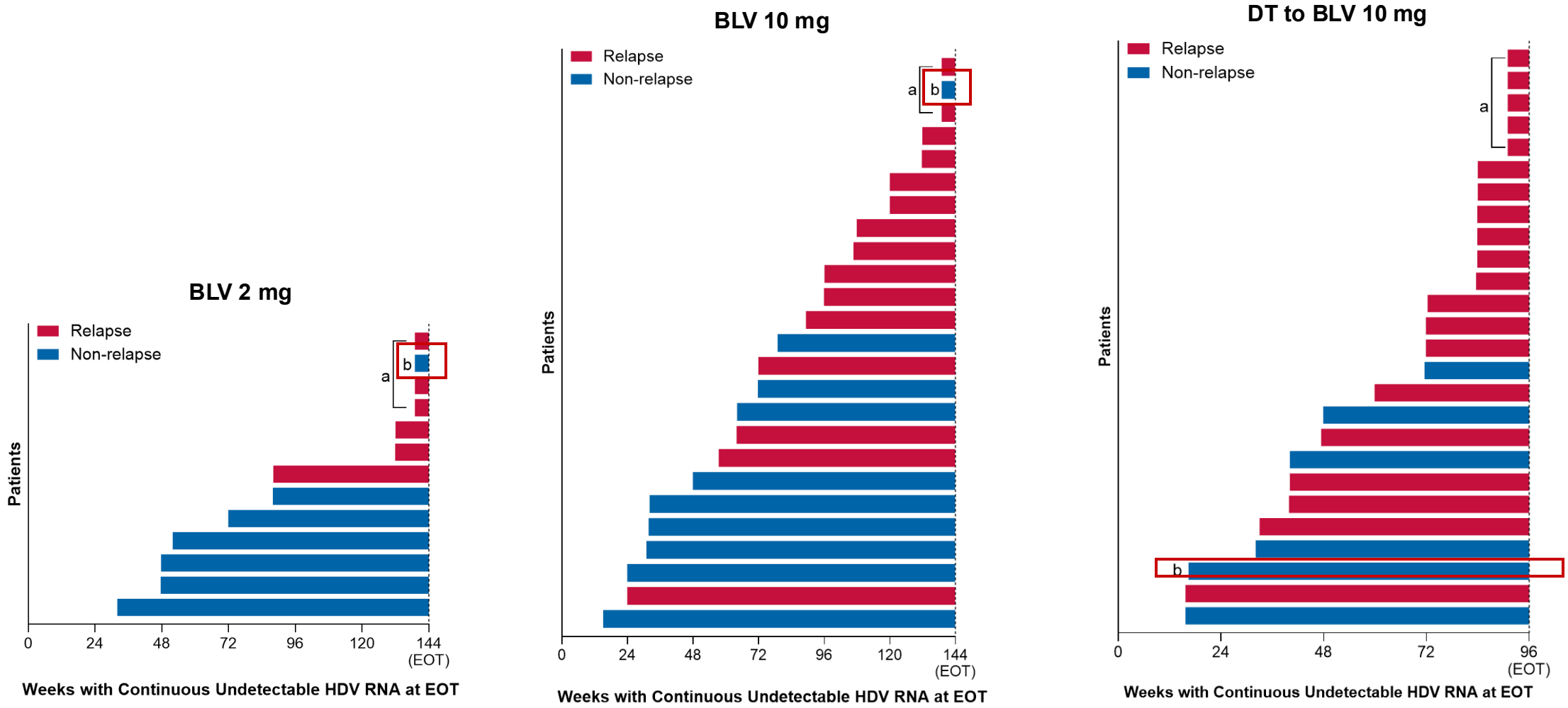
On-Treatment; n = 64	Sustained Undetectability Test (%)	Sustained Undetectability Reference (%)	Odds Ratio (95% CI)	Favours Test
Continuously undetectable HDV RNA at EOT				
≥96 weeks (vs **<96 weeks**)	90.0%	25.9%	26.6 (2.7, 262.4)	***P* <.005**
≥48 weeks (vs **<48 weeks**)	62.5%	9.4%	17.2 (4.0, 75.1)	***P* = .0001**
Duration of continuous HDV RNA undetectability at EOT (**per 24 weeks**)	—	—	2.9 (1.7, 4.8)	***P* <.0001**
W16 HDV RNA undetectable				
Yes (vs **no**)	80.0%	32.2%	14.5 (1.3, 156.9)	***P* = .03**
W24 HDV RNA undetectable				
Yes (vs **no**)	77.8%	29.1%	10.8 (1.8, 64.8)	***P* = .009**
W48 HDV RNA undetectable				
Yes (vs **no**)	70.8%	15.0%	33.1 (5.9, 186.9)	***P* <.0001**
W72 HDV RNA undetectable				
Yes (vs **no**)	57.1%	10.3%	20.3 (3.9, 107.0)	***P* = .0004**



- In patients with undetectable HDV RNA at EOT, early and longer duration of on-treatment undetectability was predictive of sustained undetectability posttreatment

Bold ***P*-values** indicate significance.
EOT, end of treatment; **FU48**, follow-up at 48 weeks after EOT (week 192); **HDV**, hepatitis delta virus; **W**, week.

Weeks of Continuous On-Treatment Undetectable HDV RNA at EOT and Relapse Status by FU48



- Patients with longer duration of continuous undetectability at EOT were less likely to relapse
- Approximately 93% (38/41) of HDV RNA relapses occurred by the FU24 visit

[a]Represents patients with <1 week of undetectable HDV RNA. [b]Represents patients with HBsAg loss during the study.
BLV, bulevirtide; **DT**, delayed treatment; **EOT**, end of treatment; **FU48**, follow-up at 48 weeks after EOT (week 192); **HBsAg**, hepatitis B surface antigen; **HDV**, hepatitis delta virus.

Biochemical Responses in Patients With Sustained Undetectable HDV RNA through FU48

n = 23	Baseline	EOT	FU48
ALT normalisation, n (%)	N/A[a]	16 (70%)	15 (65%)[b]
ALT,[c] U/L, median (Q1, Q3)	93 (63, 136)	32 (23, 44)	30 (21, 46) (n = 21)

- Biochemical response was maintained in patients with sustained HDV RNA undetectability at FU48

Patients from all 3 treatment groups are shown combined. M = F analysis was used for ALT normalisation.
[a]ALT normalisation was not assessed at baseline, as ALT >ULN was an inclusion criterion. [b]Two patients without HDV RNA relapse discontinued prior to FU48 and are counted as failures.[c]Median ALT was calculated for observed cases only.
ALT, alanine aminotransferase; **EOT**, end of treatment; **FU48**, follow-up at 48 weeks after EOT (week 192); **HDV**, hepatitis delta virus; **M = F**, missing = failure; **N/A**, not applicable; **Q**, quartile; **ULN**, upper limit of normal.

Conclusions

- Rates of undetectable HDV RNA at EOT were higher in patients treated with BLV 10 mg vs 2 mg monotherapy for 2 to 3 years
  - In addition, rates of undetectable HDV RNA at EOT were associated with lower baseline viral load
- Among patients who had HDV RNA undetectable at the scheduled EOT, a subset of patients were able to sustain undetectable HDV RNA throughout their follow-up period (through FU48)
  - In these patients, biochemical responses were maintained during follow-up
- The majority of HDV RNA relapses (>90%) occurred by the FU24 visit
- The predictors for sustained HDV RNA undetectability through 48 weeks off-therapy were lower baseline HDV RNA levels (<4.6 $\log_{10}$ IU/mL), lower baseline HBsAg levels, and most strongly, the duration of continuous on-treatment HDV RNA undetectability at EOT

BLV, bulevirtide; **EOT**, end of treatment; **FU24**, follow-up at 24 weeks after EOT (week 168); **FU48**, follow-up at 48 weeks after EOT (week 192); **HDV,** hepatitis delta virus.

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- Please see corresponding presentations:
  - Zoulim et al, OS-070; Viral Hepatitis B/D – Therapy; 09/05/2025 (17:00–18:15)
  - Wedemeyer and Aleman et al, LBO-004; Late Breaker; 10/05/2025 (13:00–14:30)
- Correspondence: Soo Aleman, soo.aleman@ki.se