Achieving Undetectable HDV RNA at End of Therapy With Bulevirtide With or Without PegIFNα is Strongly Associated With Posttreatment Virologic Response in CHD

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Background

- Chronic hepatitis delta (CHD) is the most severe form of viral hepatitis[1,2]
- In untreated patients with CHD, hepatitis delta virus (HDV) RNA viraemia is associated with a higher risk of liver disease progression, including liver decompensation, hepatocellular carcinoma, liver-related mortality, and liver transplantation[3,4]
- Bulevirtide (BLV), an entry inhibitor of HDV, is approved in Europe and other non-European countries at 2 mg/day for the treatment of CHD with compensated liver disease[5]
- Treatment with BLV, either as a monotherapy or combined with pegylated interferon alfa-2a (PegIFNα), in patients with compensated CHD has led to sustained virologic suppression in a subset of patients[6,7]
- Currently, the clinical relevance of on-treatment HDV RNA levels with target not detected (TND) vs below the lower limit of quantitation (<LLOQ, 50 IU/mL) is unknown[8]

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. Wedemeyer H, et al. *Hepatology*. 2025;81(2):637-50. 4. Kamal H, et al. *Hepatology*. 2020;72:1177-90. 5. Hepcludex. Summary of product characteristics. European Medicines Agency. Gilead Sciences, Inc.; 2023. 6. Asselah T, et al. *New Engl J Med*. 2024;391(2):133-43. 7. Aleman S, et al. *Hepatology*. 2024;80(S1):1147. 8. Ghany MG, et al. *J Hepatol*. 2023; 78(5):1654-73.

Objective

- To explore whether levels of HDV RNA at the end of treatment (EOT), either undetectable (defined as TND) or low-level viraemia (<LLOQ [<50 IU/mL], target detected [TD]) affect posttreatment virologic response with BLV finite treatment regimens

BLV, bulevirtide; **HDV**, hepatitis delta virus; **LLOQ**, lower limit of quantitation; **TD**, target detected; **TND**, target not detected.

Methods

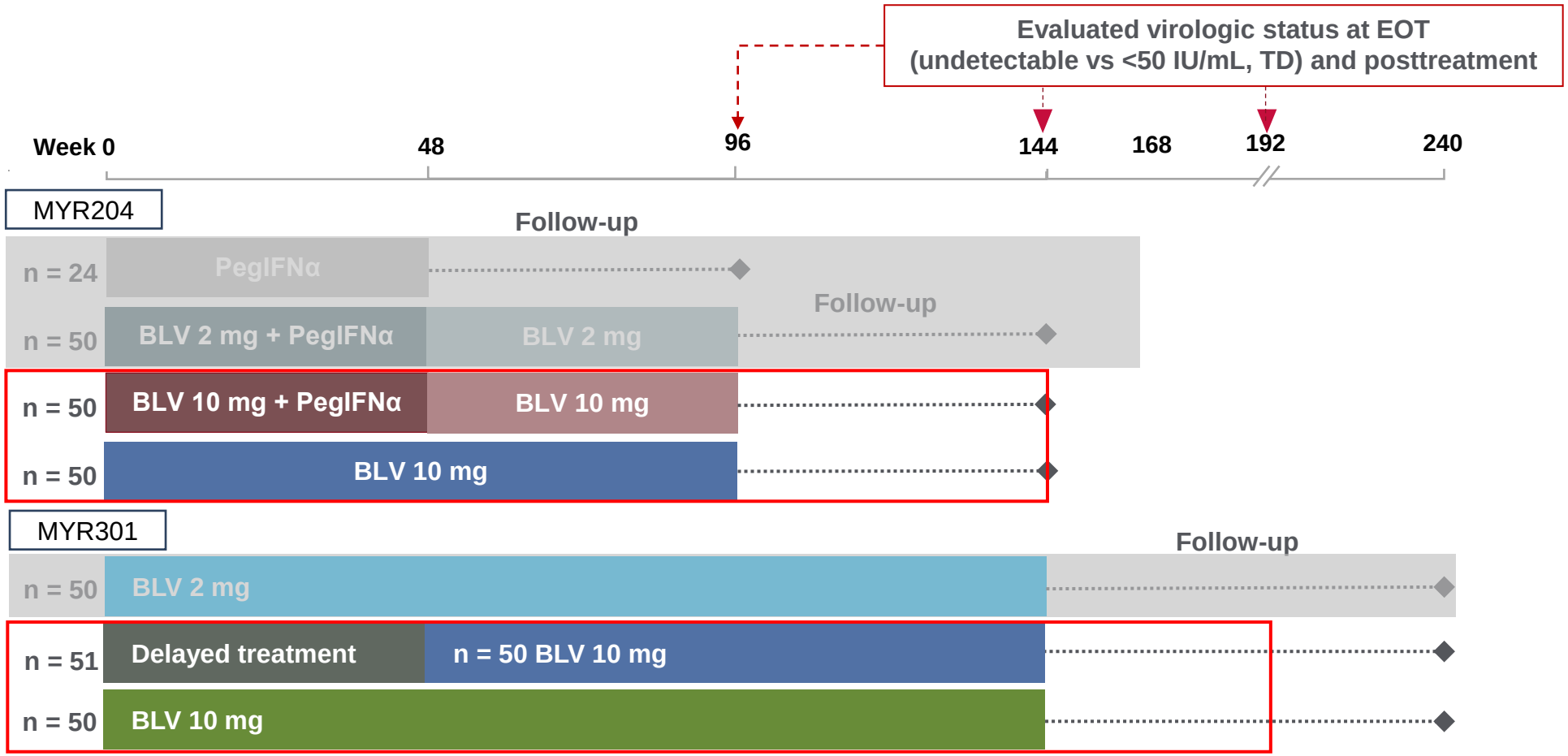
- A pooled analysis of data from patients who completed 2 or 3 years of BLV 10 mg/day with or without PegIFNα in the Phase 2 study MYR204 (NCT03852433) or the Phase 3 study MYR301 (NCT03852719) was performed
- Patients received the following:
  - — BLV 10 mg for 96 weeks (n = 100)
  - — BLV 10 mg for 144 weeks (n = 50)
  - — BLV 10 mg + PegIFNα for 48 weeks followed by 48 weeks of monotherapy with BLV 10 mg (n = 50)
- Patients were followed for up to 48 weeks after EOT (FU-48)
- HDV RNA levels were determined by reverse transcription–quantitative polymerase chain reaction using RoboGene 2.0 (limit of detection, 6 IU/mL)
- Virologic response rates at FU-48 were compared between patients with undetectable HDV RNA (TND) and those with low-level viraemia (<LLOQ [<50 IU/mL], TD) at EOT

BLV, bulevirtide; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **LLOQ**, lower limit of quantitation; **PegIFNα**, pegylated interferon alfa-2a; **TD**, target detected; **TND**, target not detected.

Pooled Analysis: MYR204 and MYR301

Key Inclusion Criteria

- CHD with detectable serum HDV RNA
- CTP[a] score ≤6 or ≤7
- With or without cirrhosis
- ALT >1 × ULN and <10 × ULN
- No IFN within 6 months before BL (MYR204)



- Selected arms of both studies MYR204 and MYR301 were integrated in this analysis

[a]MYR204, CTP ≤6; MYR301, CTP ≤7.

ALT, alanine aminotransferase; **BL**, baseline; **BLV**, bulevirtide; **CHD**, chronic hepatitis delta; **CTP**, Child-Turcotte-Pugh; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **IFN**, interferon; **PegIFNα**, pegylated interferon alfa-2a; **TD**, target detected; **ULN**, upper limit of normal.

Demographics and Baseline Disease Characteristics

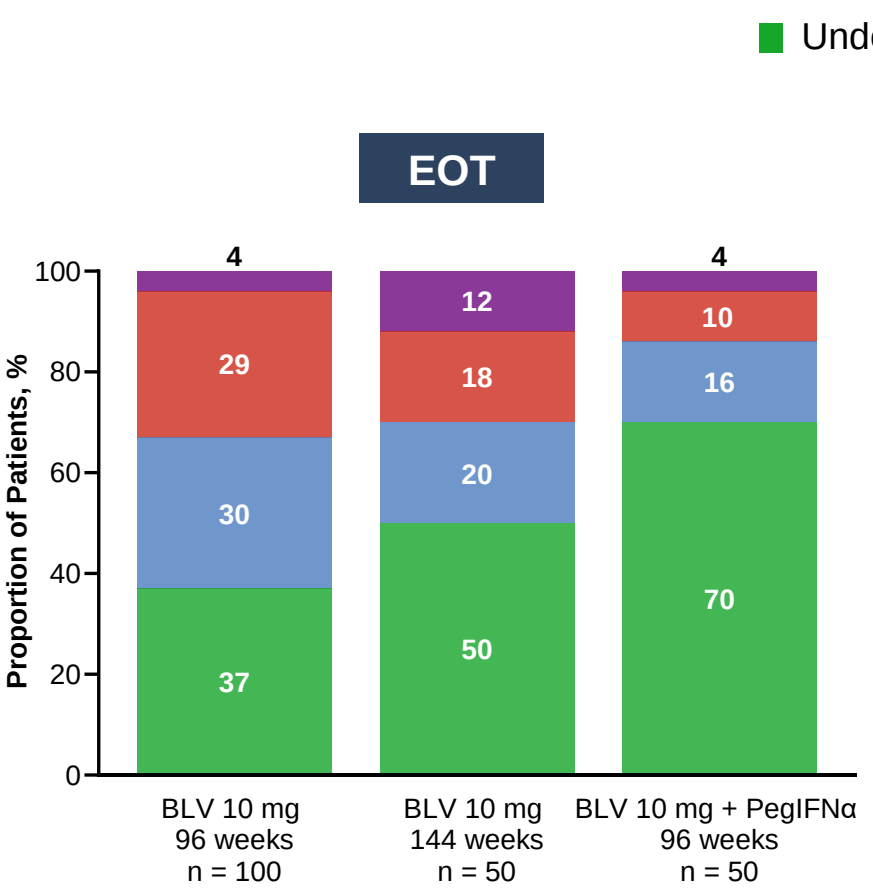
		BLV 10 mg 96 Weeks n = 100	BLV 10 mg 144 Weeks n = 50	PegIFNα + BLV 10 mg 96 Weeks n = 50
Age, years, mean (SD)		41 (8.0)	41 (8.5)	41 (8.6)
Male sex, n (%)		64 (64)	30 (60)	35 (70)
Race,[a] n (%)	Caucasian	83 (83)	43 (86)	43 (86)
	Asian	15 (15)	6 (12)	4 (8)
	Black	2 (2)	1 (2)	2 (4)
Body mass index, kg/m^2, mean (SD)		26 (3.9)	25 (3.6)	25 (4.0)
Cirrhosis, n (%)		41 (41)	24 (48)	17 (34)
Liver stiffness, kPa, mean (SD)		14.4 (9.70)	14.8 (9.26)	12.5 (7.60)
ALT, U/L, mean (SD)		100 (86.1)	123 (80.6)	113 (98.6)
HDV RNA, $\log_{10}$ IU/mL, mean (SD)		5.2 (1.36)	5.0 (1.46)	5.1 (1.34)
Prior interferon use, n (%)		50 (50)	29 (58)	26 (52)
Concomitant NA use for HBV, n (%)		55 (55)	27 (54)	25 (50)

- Demographics were generally similar across groups: male (65%), White (85%), and mean (SD) age of 41 (8.2) years
- Among all patients, 41% had compensated cirrhosis, and 53% had prior interferon experience
- Mean (SD) HDV RNA, ALT, and liver stiffness were 5.1 (1.38) $\log_{10}$ IU/mL, 109 (88.2) U/L, and 14.0 (9.11) kPa, respectively

[a]PegIFNα + BLV 10 mg: n = 1, other race.

ALT, alanine aminotransferase; **BLV**, bulevirtide; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **NA**, nucleos(t)ide analogue; **PegIFNα**, pegylated interferon alfa-2a.

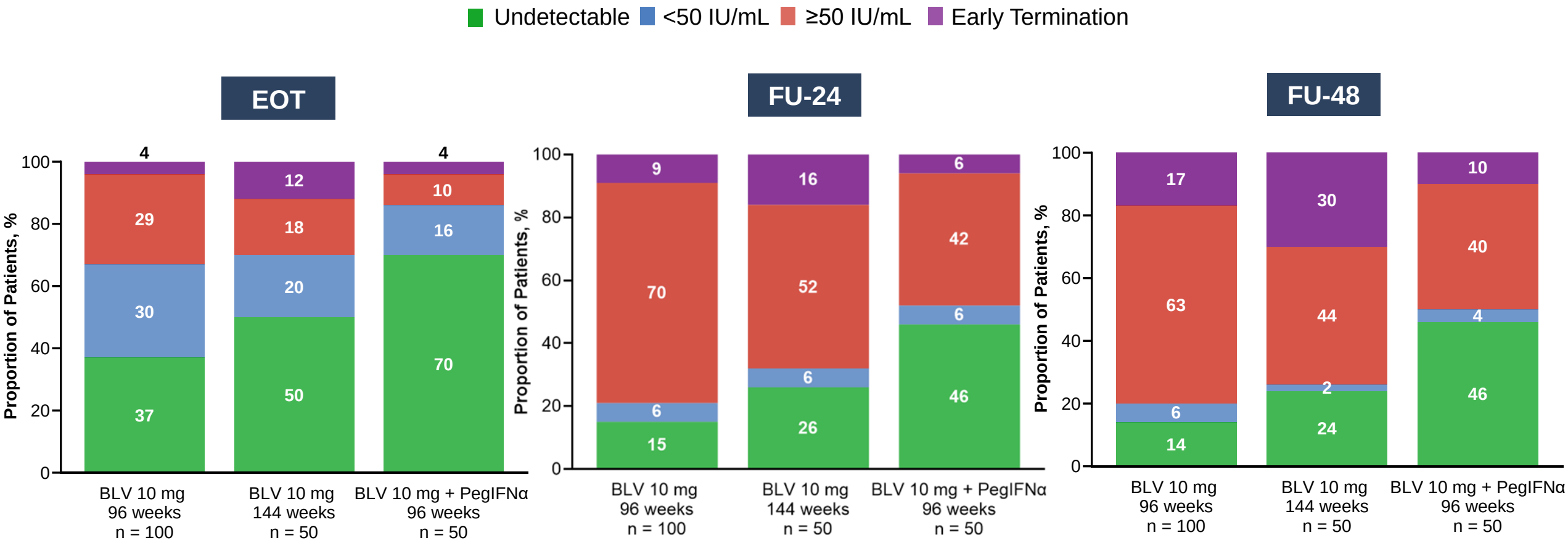
HDV RNA at EOT Based on BLV Regimens



- Combination therapy with BLV + PegIFNα vs BLV monotherapy and longer treatment duration of 3 years vs 2 years were associated with higher undetectable HDV RNA at EOT

Missing HDV RNA data not due to ET were imputed as ≥50 IU/mL.
BLV, bulevirtide; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **PegIFNα**, pegylated interferon alfa-2a.

HDV RNA at EOT and Follow-Up Periods Based on BLV Regimens



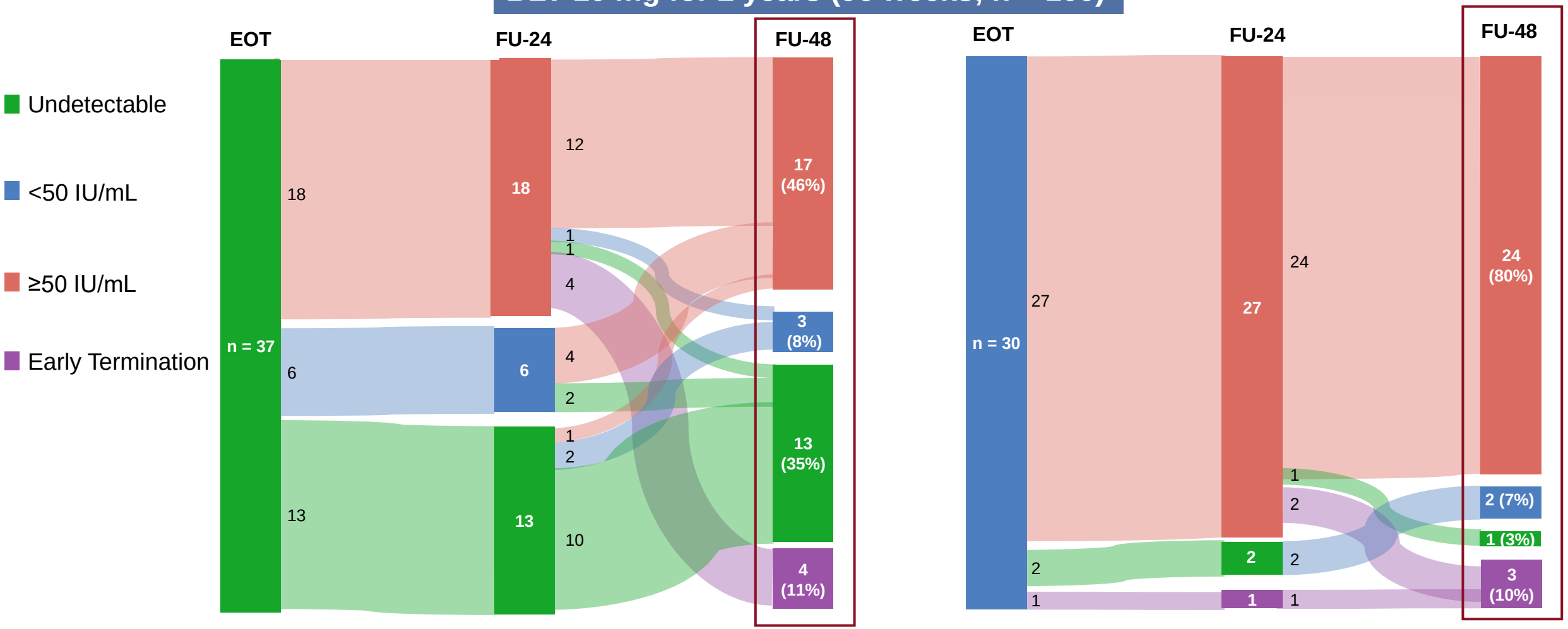
- Rates of undetectable levels of HDV RNA declined from EOT but were similar during the follow-up period; the highest rates were observed in patients who received the combination regimen

Missing HDV RNA data not due to ET were imputed as ≥50 IU/mL.

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

Progression of Viraemia Status in Posttreatment Period Based on HDV RNA Levels at EOT

BLV 10 mg for 2 years (96 weeks; n = 100)



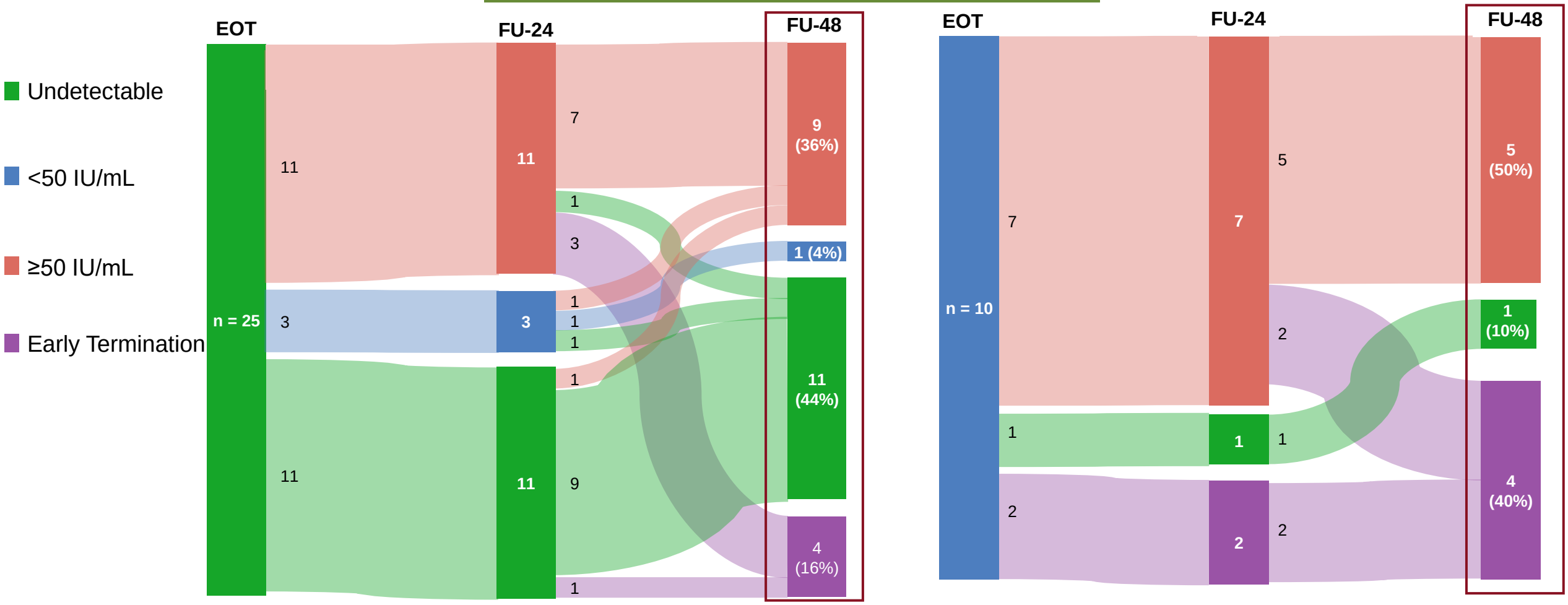
- Of the patients with undetectable HDV RNA at EOT, 35% (13/37) maintained undetectable HDV RNA at FU-48; 54% (20/37) relapsed
- By contrast, of those with low-level viraemia at EOT, only 3% (1/30) became undetectable; 80% (24/30) had HDV RNA ≥50 IU/mL at FU-48

Relapse defined as HDV RNA undetectable at EOT and ≥1 HDV RNA sample during the follow-up period with observed detectable HDV RNA. Missing HDV RNA data not due to ET were imputed as ≥50 IU/mL

BLV, bulevirtide; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **FU-24**, follow-up at week 24 after EOT; **FU-48**, follow-up at week 48 after EOT.

Progression of Viraemia Status in Posttreatment Period Based on HDV RNA Levels at EOT

BLV 10 mg for 3 years (144 weeks; n = 50)



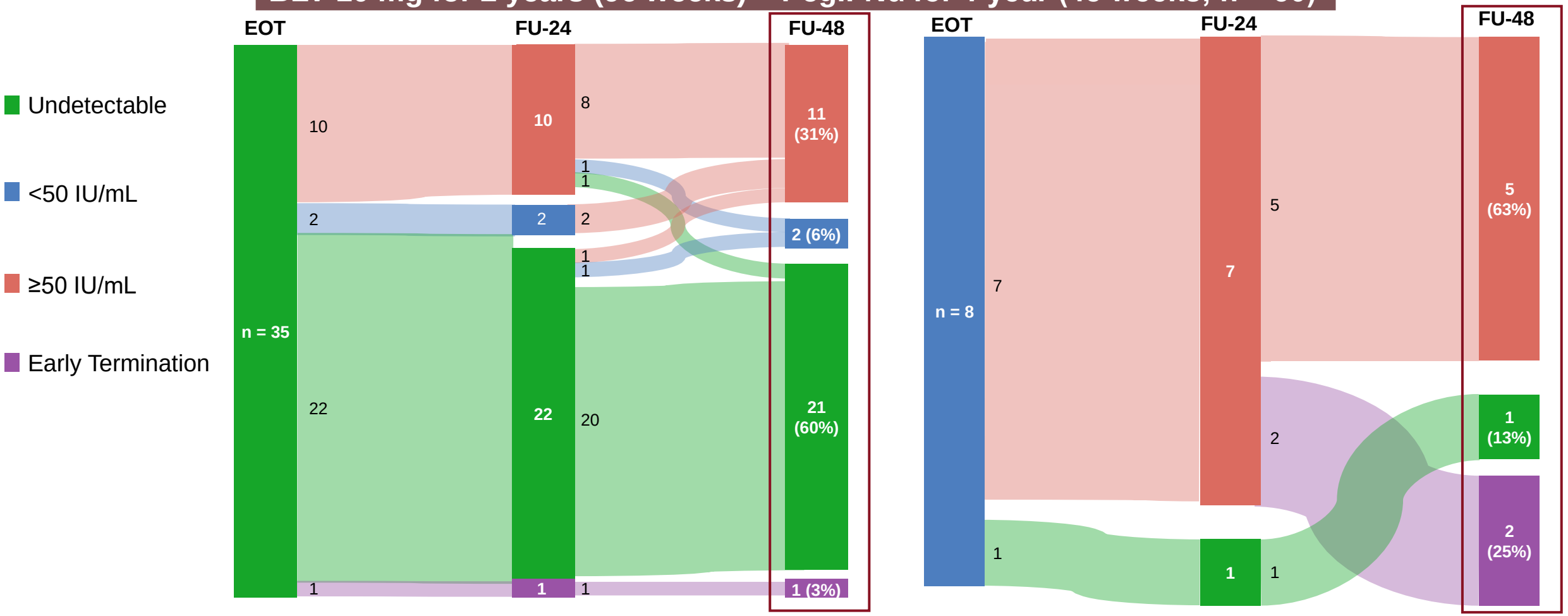
- Of the patients with undetectable HDV RNA at EOT, 44% (11/25) remained undetectable at FU-48; 40% (10/25) relapsed
- By contrast, of those with low-level viraemia at EOT, only 10% (1/10) became undetectable; 50% (5/10) had HDV RNA ≥50 IU/mL at FU-48

Relapse defined as HDV RNA undetectable at EOT and ≥1 HDV RNA sample during the follow-up period with observed detectable HDV RNA. Missing HDV RNA data not due to ET were imputed as ≥50 IU/mL

BLV, bulevirtide; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **FU-24**, follow-up at week 24 after EOT; **FU-48**, follow-up at week 48 after EOT.

Progression of Viraemia Status in Posttreatment Period Based on HDV RNA Levels at EOT

BLV 10 mg for 2 years (96 weeks) + PegIFNα for 1 year (48 weeks; n = 50)

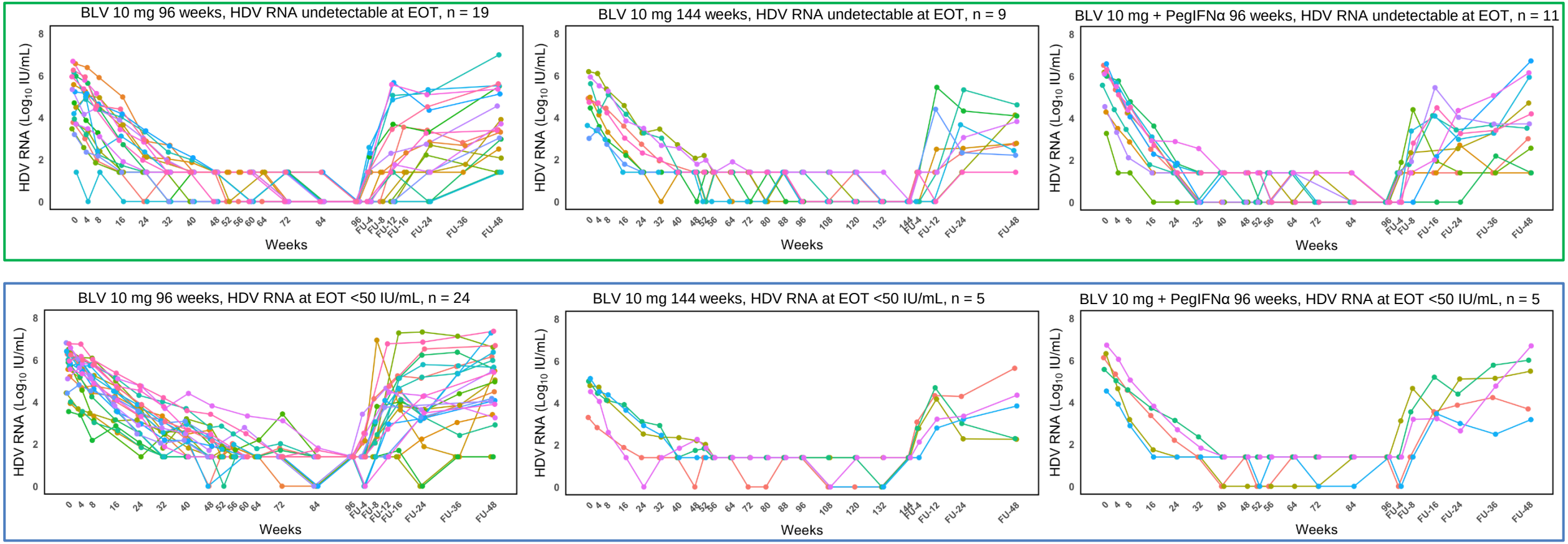


- Of the patients with undetectable HDV RNA at EOT, 60% (21/35) remained undetectable at FU-48; 37% (13/35) relapsed
- By contrast, of those with low-level viraemia, only 13% (1/8) became undetectable while 63% (5/8) had HDV RNA ≥50 IU/mL at FU-48

Relapse defined as HDV RNA undetectable at EOT and ≥1 HDV RNA sample during the follow-up period with observed detectable HDV RNA. Missing HDV RNA data not due to ET were imputed as ≥50 IU/mL
BLV, bulevirtide; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **FU-24**, follow-up at week 24 after EOT; **FU-48**, follow-up at week 48 after EOT; **PegIFNα**, pegylated interferon alfa-2a.

Individual Viraemia Level in Posttreatment Period Based on HDV RNA levels at EOT

Patients with undetectable HDV RNA or <50 IU/mL at EOT with HDV RNA detectable at FU-48



- HDV RNA levels return close to pretreatment levels in both patients with undetectable HDV RNA at EOT or <50 IU/mL

BLV, bulevirtide; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **FU**, follow-up after EOT; **PegIFNα**, pegylated interferon alfa-2a..

ALT Normalisation in the Posttreatment Period Based on HDV RNA Levels at EOT

Includes BLV 10 mg for 2 or 3 years as monotherapy and combined with PegIFNα

HDV RNA Levels at EOT	ALT Normalisation	
	EOT	FU-48[a]
Undetectable	68/97 (71%)	38/49 (78%)
<50 IU/mL	39/48 (81%)	7/9 (78%)
≥50 IU/mL	20/43 (47%)	15/105 (14%)

- On-treatment improvements in noninvasive test results, including ALT normalisation, were observed in patients with virologic response, partial response, and nonresponse (Brunetto M, et al. Poster WED-308)
- In the posttreatment period, ALT normalisation is maintained in patients with undetectable or low-level viraemia

[A]n = 37 participants were excluded at FU-48 due to ET.

ALT, alanine aminotransferase; **BLV**, bulevirtide; **EOT**, end of treatment; **ET**, early termination; **HDV**, hepatitis delta virus; **FU-48**, follow-up at week 48 after EOT; **PegIFNα**, pegylated interferon alfa-2a.

Conclusions

- In patients with compensated CHD, achieving undetectable HDV RNA at EOT is required to maintain undetectable viremia in the posttreatment period
  - Nearly all patients with low-level viraemia <50 IU/mL at EOT have HDV RNA increase off therapy
- In patients with viral load rebound off treatment, viremia increases back to baseline levels
- Combination therapy with BLV 10 mg/day and PegIFNα and longer treatment with BLV monotherapy were associated with higher rates of undetectable HDV RNA at EOT and FU-48

BLV, bulevirtide; **CHD**, chronic hepatitis delta; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **FU-48**, follow-up at week 48 after EOT; **PegIFNα**, pegylated interferon alfa-2a.

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- Please see corresponding presentations:
  - Aleman et al, OS-066; Viral Hepatitis B/D Current Clinical Practice; 09/05/2025 (08:30–09:45)
  - Wedemeyer and Aleman et al, LBO-004; Late Breaker; 10/05/2025 (13:00–14:30)

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