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Bulevirtide in combination with pegylated interferon alfa-2a shows a sustained off-treatment response in the liver

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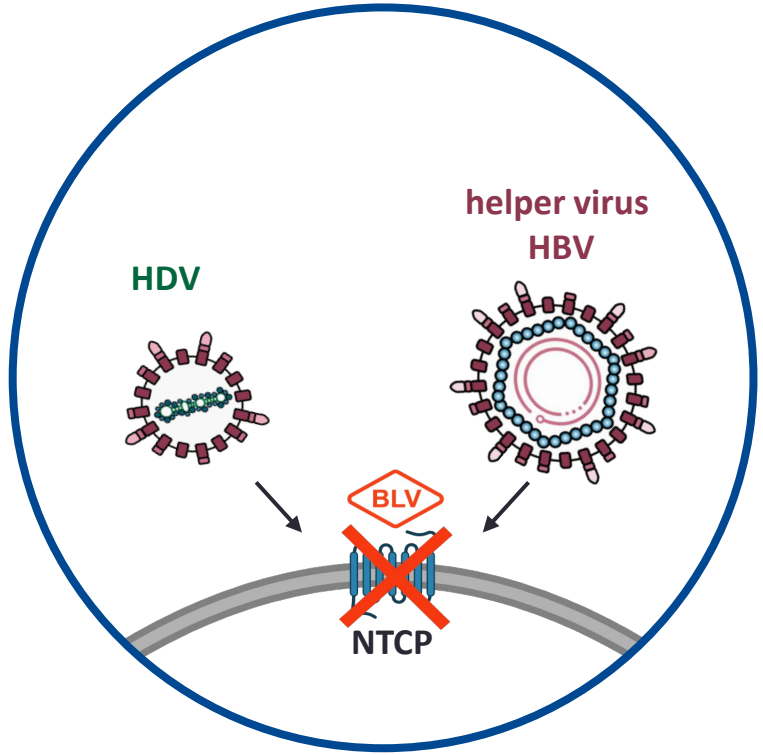
Background: Chronic hepatitis D

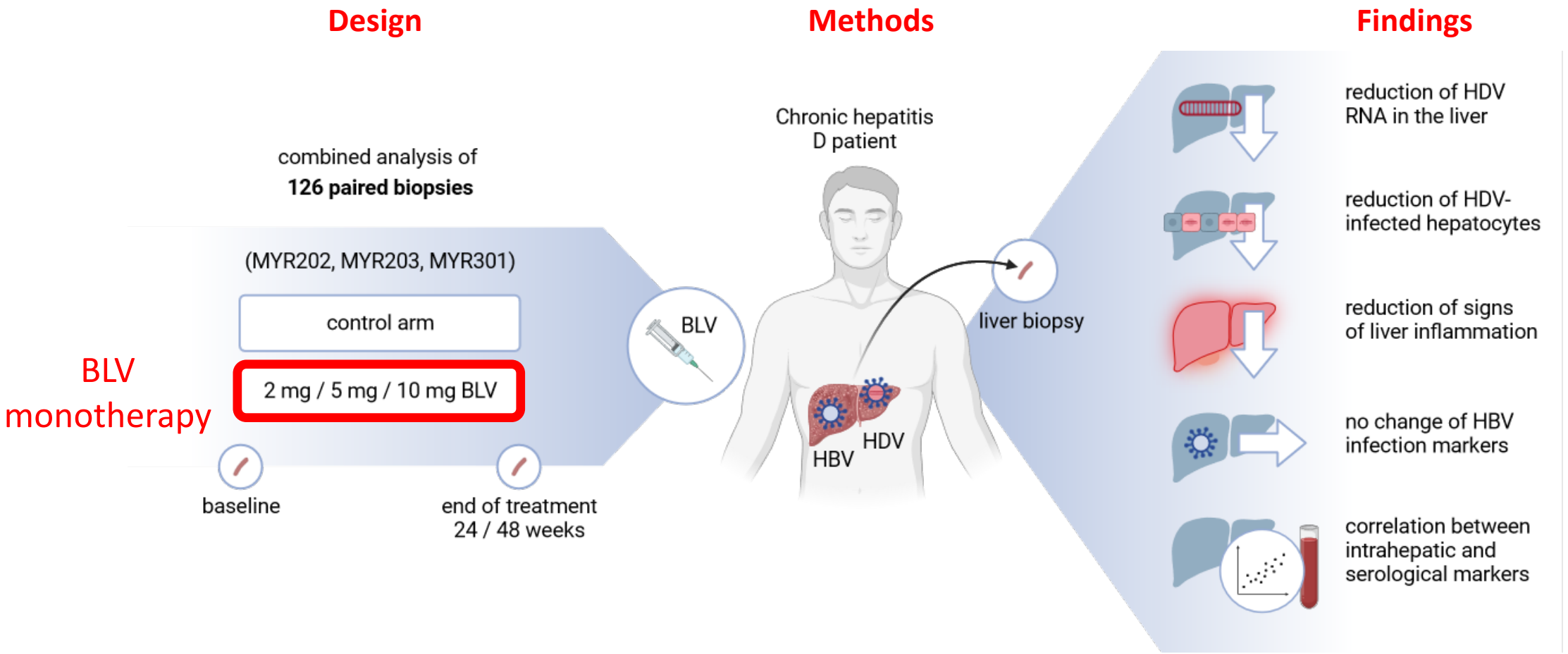
- Between 12-20 million people are chronically infected with the hepatitis delta virus (HDV) worldwide[1]
- HDV causes the most severe form of chronic viral hepatitis[2,3]
- HDV requires the envelope protein from hepatitis B virus (HBV) to infect hepatocytes[4]
- Treatment options for chronic hepatitis delta (CHD) are still limited:
  - Pegylated interferon-alfa (PegIFNα) is recommended as off-label therapy[5]
  - The HBV and HDV entry inhibitor bulevirtide (BLV) 2 mg has received full approval in July 2023 in Europe for the treatment of adults with CHD and compensated liver disease



MYR204, a Phase 2b study addresses a major treatment gap for CHD, a finite treatment regimen that results in sustained off-treatment viral response

1. Stockdale AJ, et al. J Hepatol 2020; 2. Alfaiate D, et al. J Hepatol. 2020; 3. Rizzetto M, et al. J Hepatol 2021; 4. Asselah T, Rizzetto M. N Eng J Med 2023; 5. Sandmann L, et al. Liver International 2022;00:1-11. 2

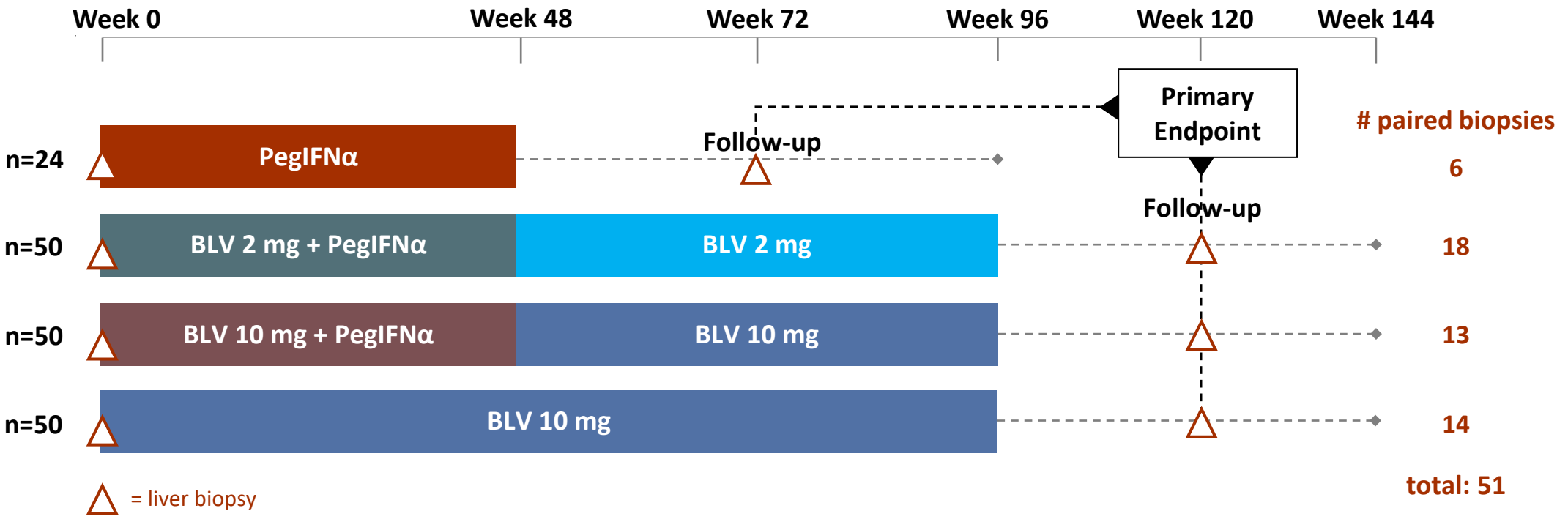
Background: Intrahepatic analyses in BLV monotherapy trials



Blocking viral entry with BLV diminishes signs of liver inflammation and promotes a strong reduction of HDV infection within the liver

Allweiss et al. J Hepatol 2024

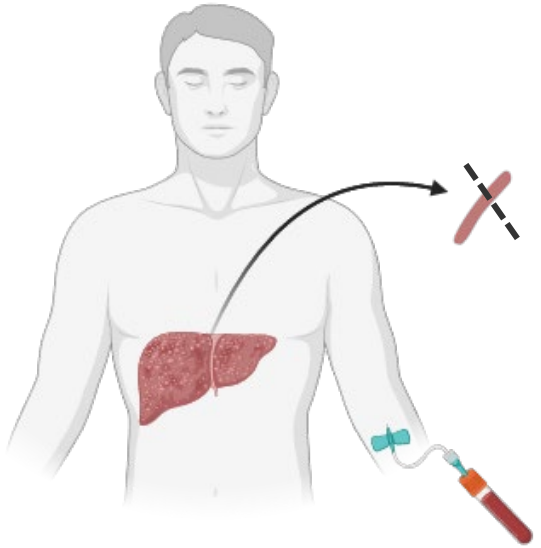
MYR204: Study design



- Open-label, randomized, multicenter, phase 2b study (NCT03852433) conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)
- Primary endpoint: serum HDV RNA undetectable* at Week 24 after end of treatment (EOT)
- Key inclusion criteria: CHD with detectable serum HDV RNA with or without cirrhosis

* undetectable HDV RNA defined as <LLOQ with target not detected

Methods



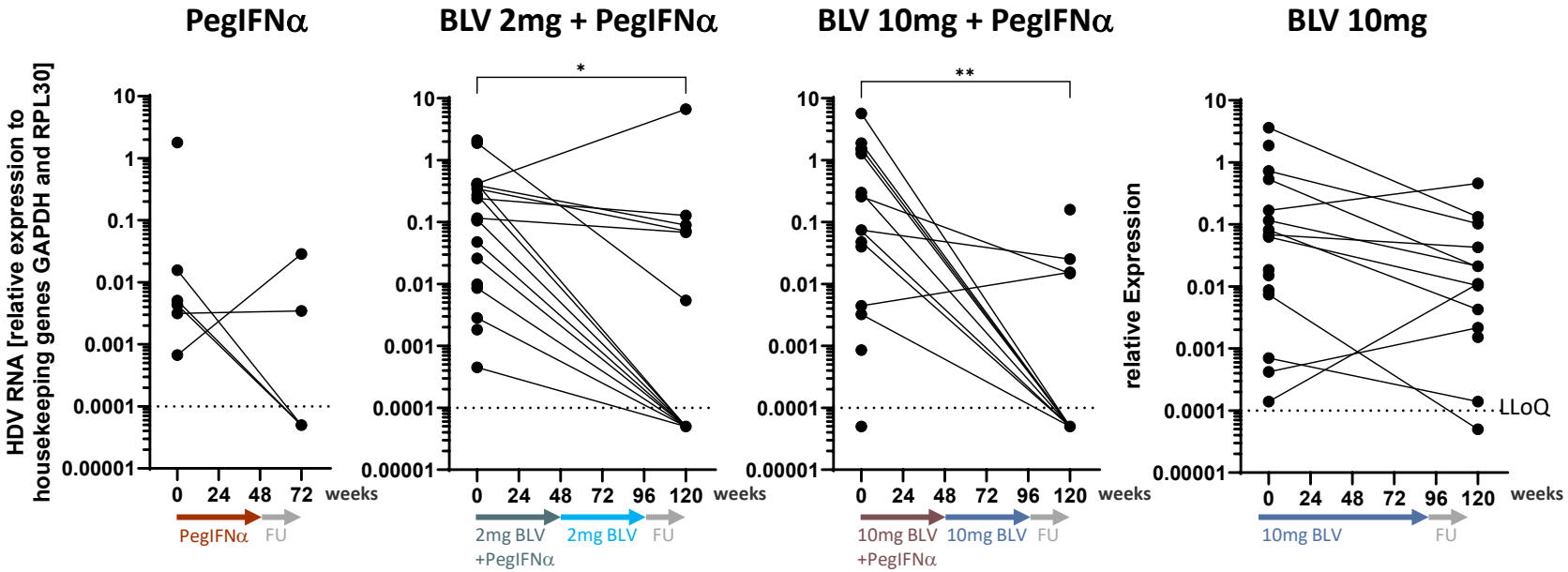
42* paired biopsies stored in Allprotect → qPCR for HDV RNA, HBV RNA and DNA & host gene expression

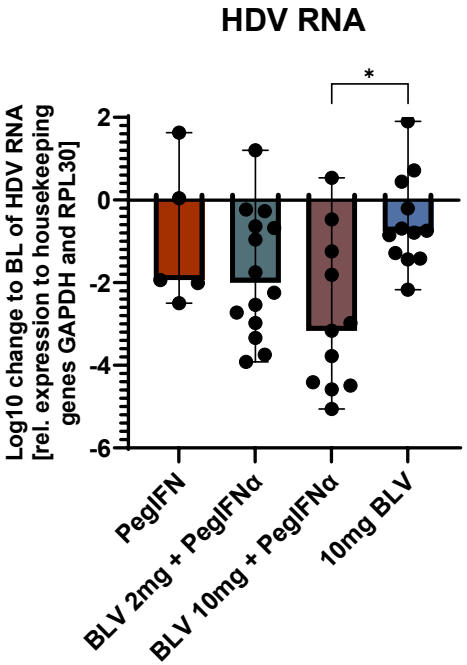
50* paired biopsies as formalin-fixed, paraffin-embedded blocks → immunohistochemistry for HDV antigen (HDAg) & quantification of HDAg-positive cells

Peripheral data: biochemical and virological parameters** → Spearman correlation analysis for peripheral (HDV RNA, ALT) vs. intrahepatic parameters (HDV RNA, CXCL10)

* Maximal number of available paired biopsies with sufficient size, quality or nucleic acid concentration
** Asselah et al. #5009 AASLD 2023, Asselah et al. GS-002 EASL 2024

Results: Intrahepatic HDV RNA



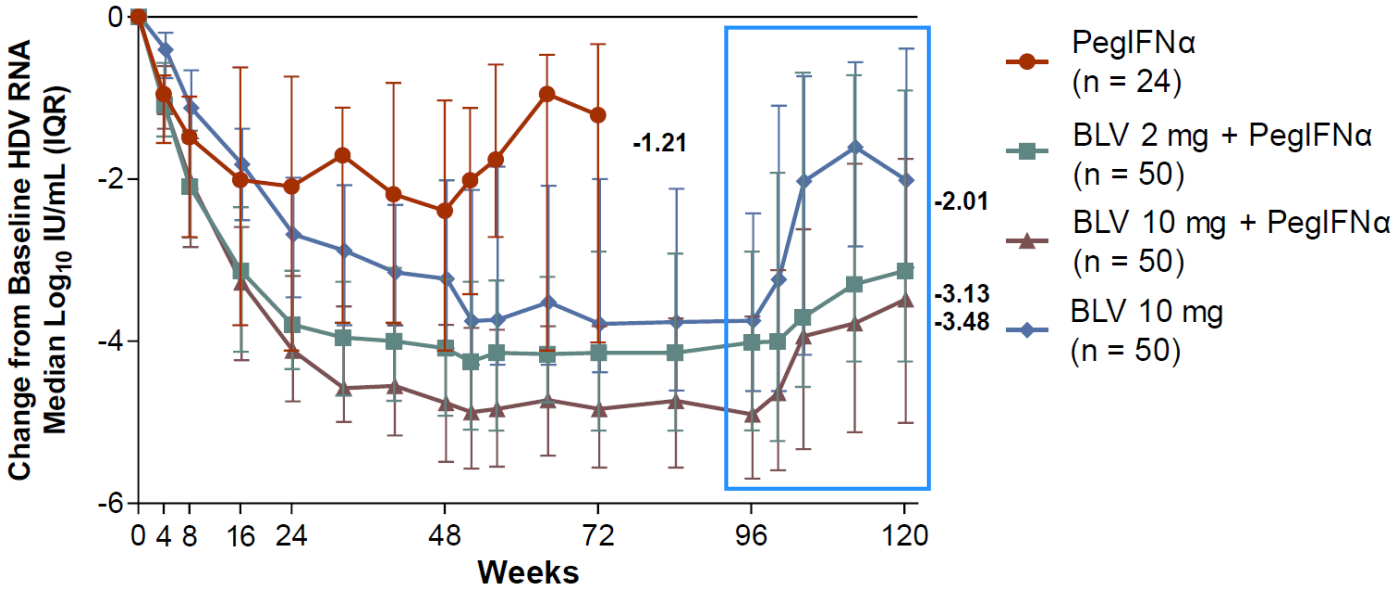


PegIFNα	BLV 2mg + PegIFNα	BLV 10mg + PegIFNα	BLV 10mg
BL median 0.0043	BL median 0.1785	BL median 0.2577	BL median 0.0749
n=5	n=14	n=11	n=12
median Δlog10 -1.94	median Δlog10 -1.99	median Δlog10 -3.16	median Δlog10 -0.76
3 <LLoQ (60%)	**8 <LLoQ (57%)**	**8 <LLoQ (73%)**	**1 <LLoQ (8%)**

HDV RNA levels in the liver were reduced at 24w after EOT compared to baseline levels. The highest off-treatment decline in HDV RNA was observed in the BLV 10mg + PegIFNα combination arm.

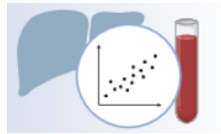
Wilcoxon matched pairs test for differences between baseline and follow-up biopsies (line graphs); Kruskall-Wallis test with Dunn as a post-test for differences of Log10 change from baseline between arms (bar graphs); LLoQ 0.0001 relative expression; p values ≤0.05 depicted as *; p values ≤0.01 as **; Caveat: Study was not powered for this analysis.

Comparison with serum HDV RNA



Viral rebounds/relapses have been observed in some patients in the post-treatment period.

In these patients, a high viral liver burden was observed at 24 weeks after EOT.

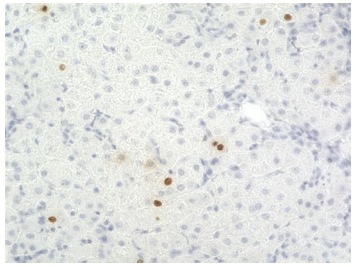
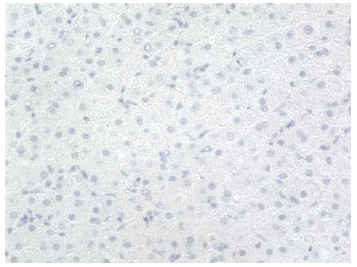
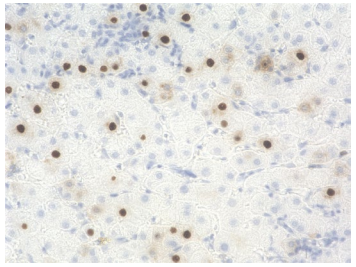
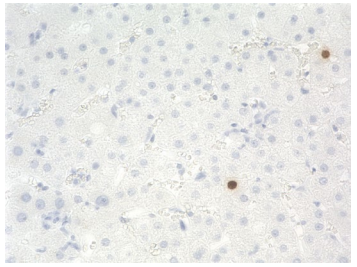
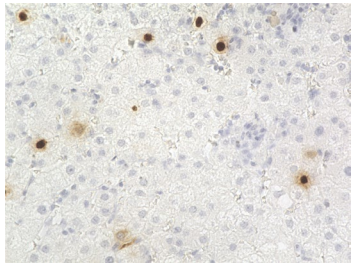
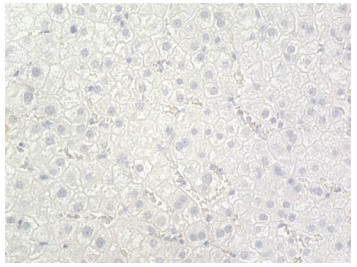
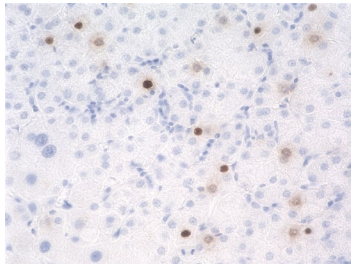
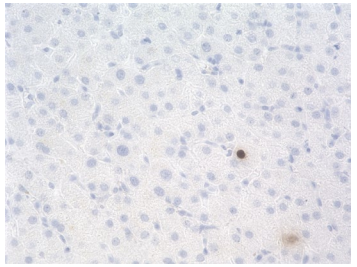


correlation between intrahepatic and serological markers

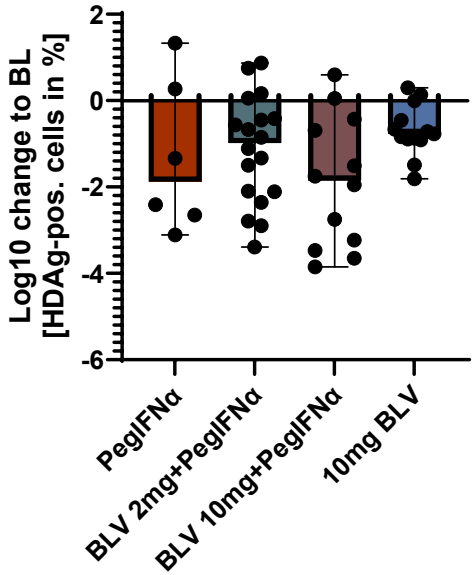
Allweiss et al. J Hepatol 2024

Asselah et al. #5009 AASLD 2023

Results: HDAg-positive cells in the liver

	Baseline	24 weeks after EOT	
PegIFNα			BL median 0.88% n=6 **median Δlog10 -1.87** **4 <LLoQ (67%)**
BLV 2mg + PegIFNα			BL median 2.52% n=14 **median Δlog10 -0.98 (*)** **8 <LLoQ (44%)**
BLV 10mg + PegIFNα			BL median 2.27% n=11 **median Δlog10 -1.85 (*)** **8 <LLoQ (67%)**
BLV 10mg			BL median 4.00% n=13 **median Δlog10 -0.77** **1 <LLoQ (8%)**

Quantification of HDAg-pos. cells



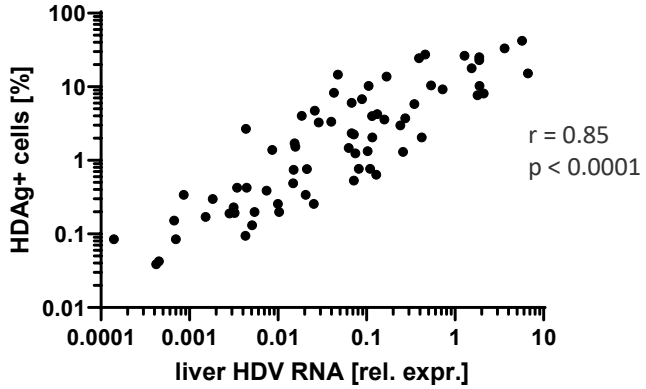
24 weeks after EOT:

- HDAg-positive cell numbers were lower compared to baseline.
- The lowest levels of infected cells was observed in the BLV 10mg + PegIFNα combination and PegIFNα monotherapy arm.

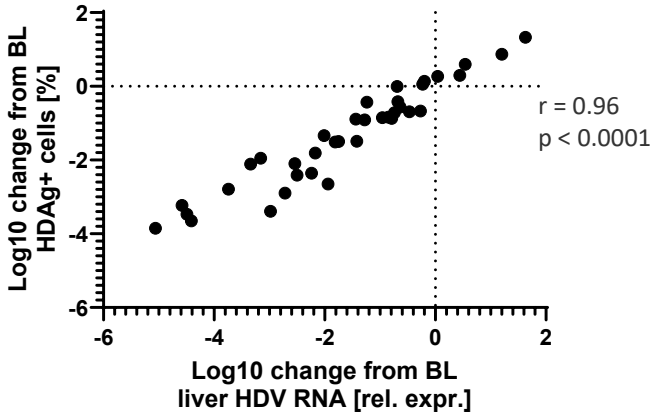
Wilcoxon matched pairs test for differences between baseline and follow-up biopsies; p values ≤0.05 depicted as *; Caveat: Study was not powered for this analysis; LLoQ 0.012% HDAg-positive cells

Results: Correlation analysis

liver HDV RNA vs. HDAg+ cells: **absolute levels**

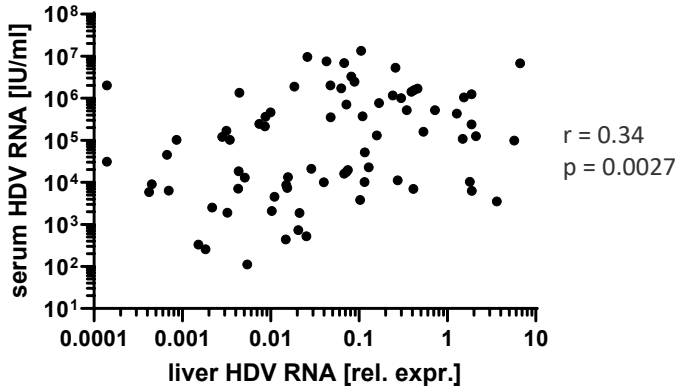


ΔLog10 change at 24 weeks after EOT vs. BL

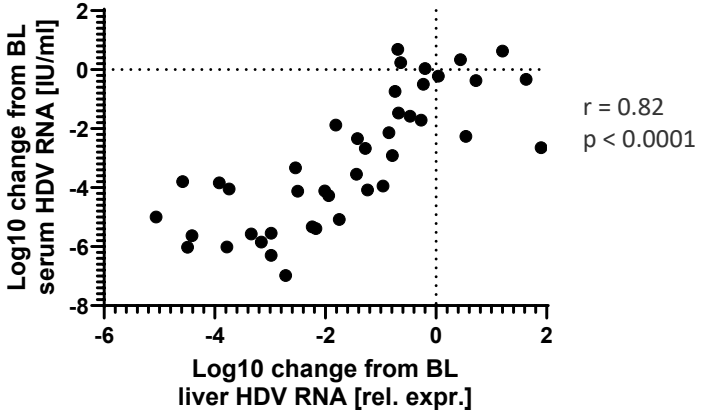


Intrahepatic HDV RNA levels strongly correlated with the number of HDAg positive cells suggesting that BLV treatment reduced the number of infected cells.

HDV RNA in serum vs. liver: **absolute levels**



ΔLog10 change at 24 weeks after EOT vs. BL

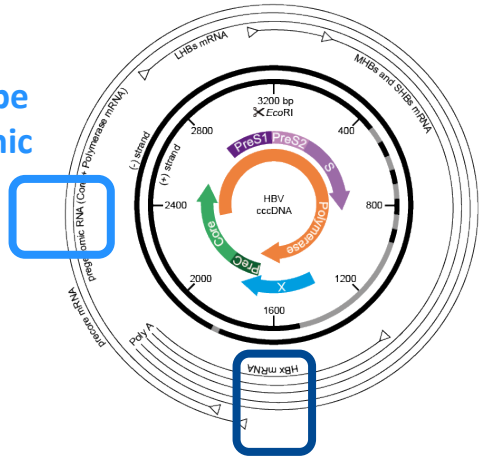


Serum HDV RNA levels correlate with liver HDV RNA levels. Intrahepatic changes of HDV RNA mirror the changes observed in the serum.

Spearman correlation analysis

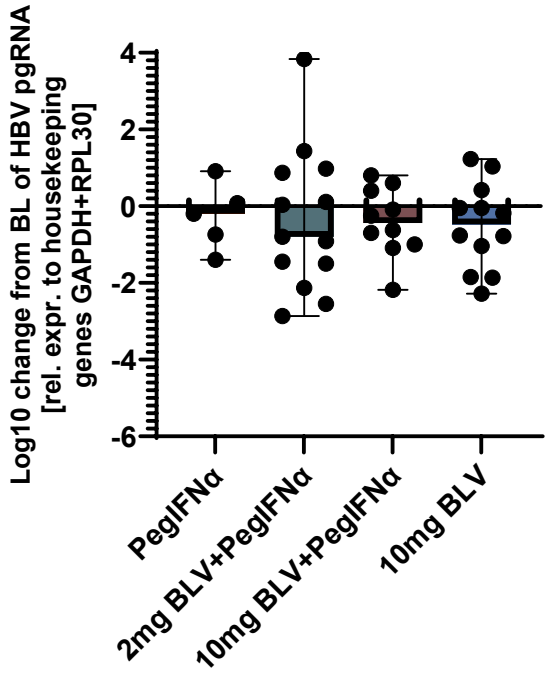
Results: Intrahepatic HBV RNA levels

primer/probe in pregenomic RNA

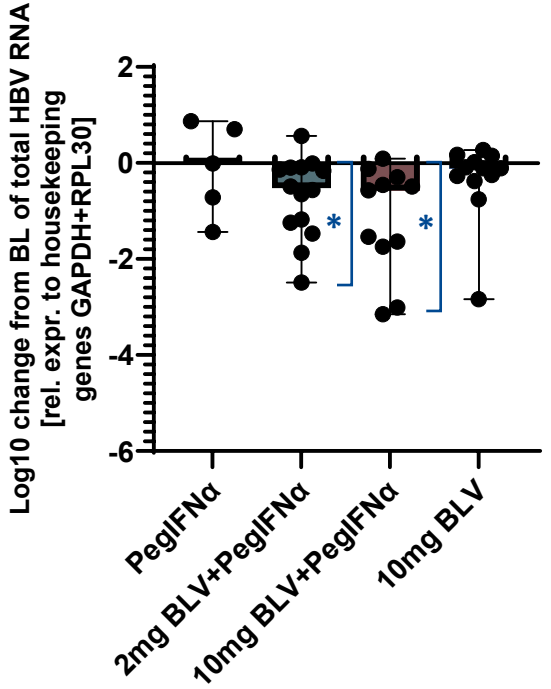


primer/probe in common region for all HBV RNAs

HBV pregenomic RNA



Total HBV RNA

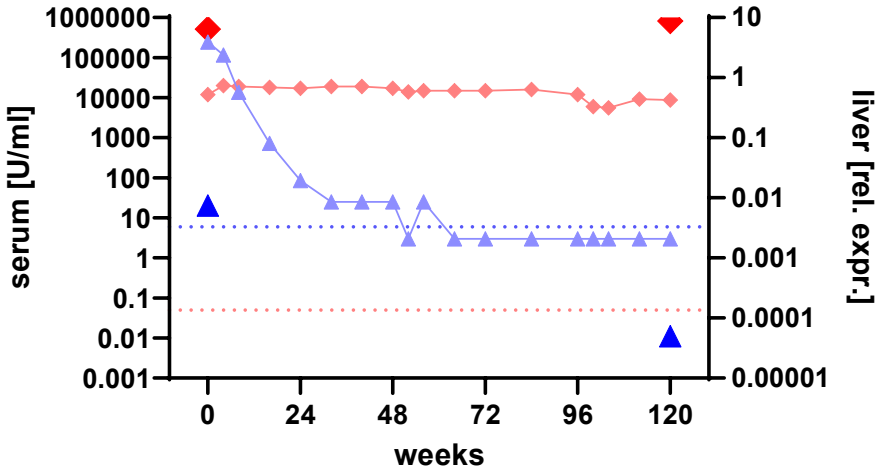


HBV RNA levels did not change significantly between BL and 24 weeks after EOT.
Nevertheless, there were modest median reductions of total HBV RNA in the combination arms.

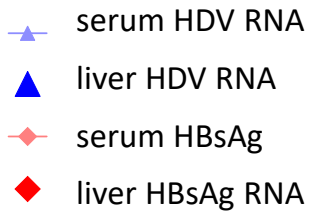
Wilcoxon matched pairs test for differences between baseline and follow-up biopsies; p values ≤0.05 depicted as *; Caveat: Study was not powered for this analysis.

Results: HDV and HBV kinetics in selected patients

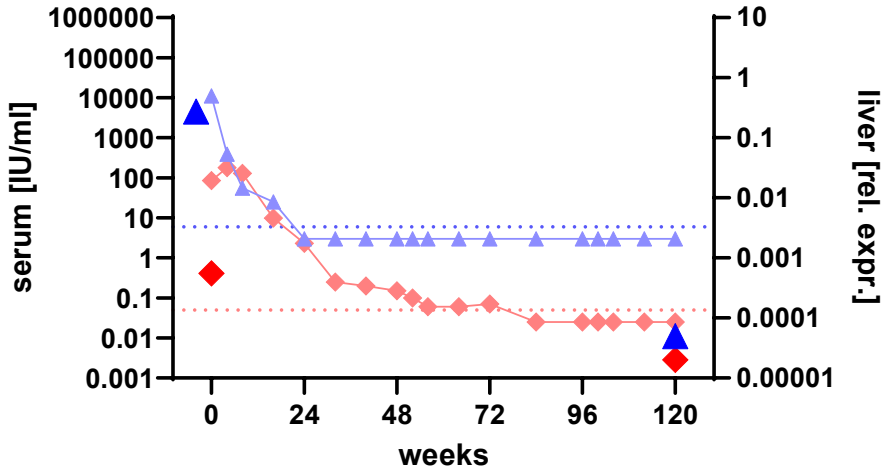
Patient receiving BLV 10mg



HDV RNA undetectable without a reduction of HBsAg



Patient receiving BLV 2mg + PegIFNα



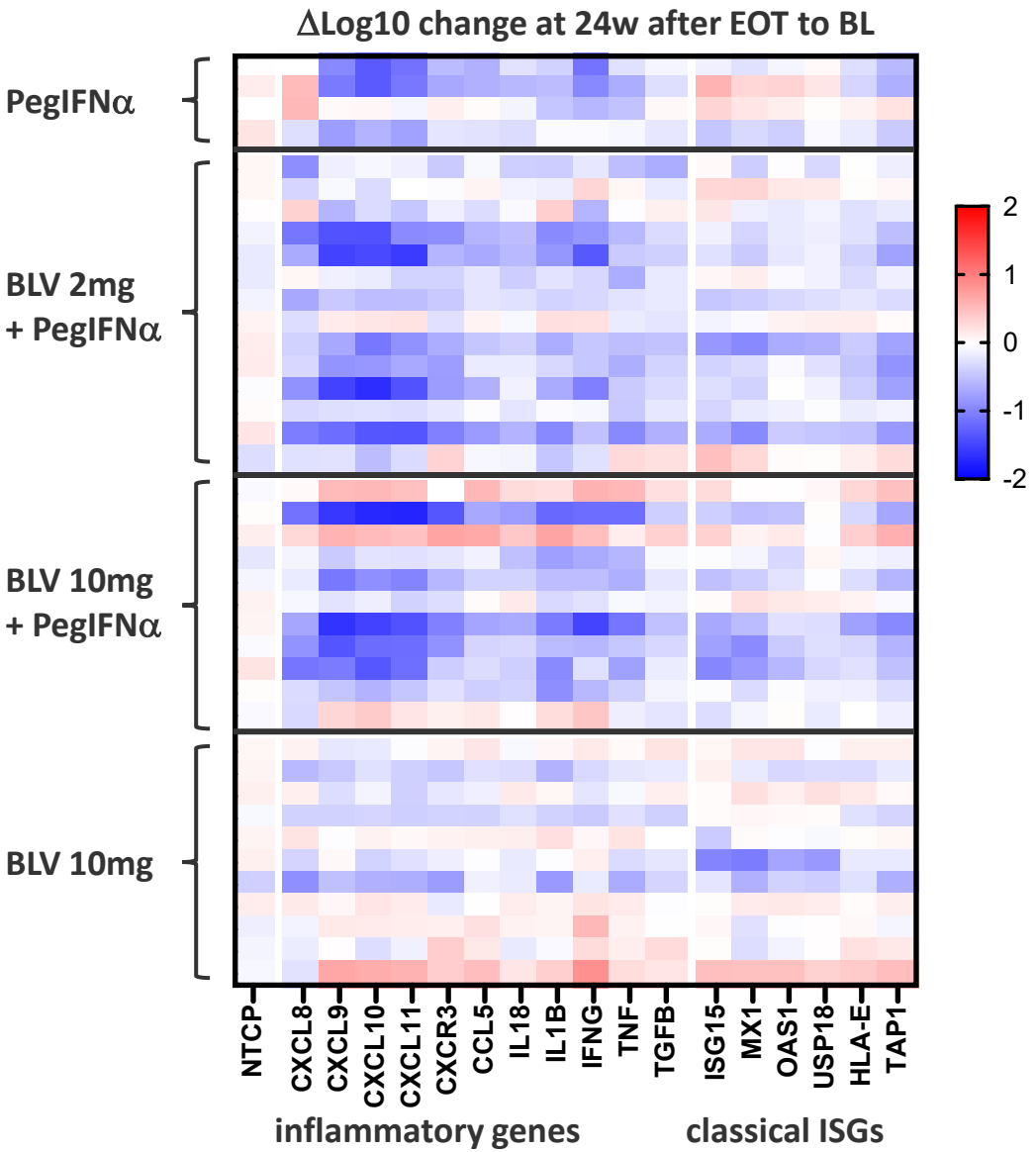
HDV RNA undetectable with HBsAg loss

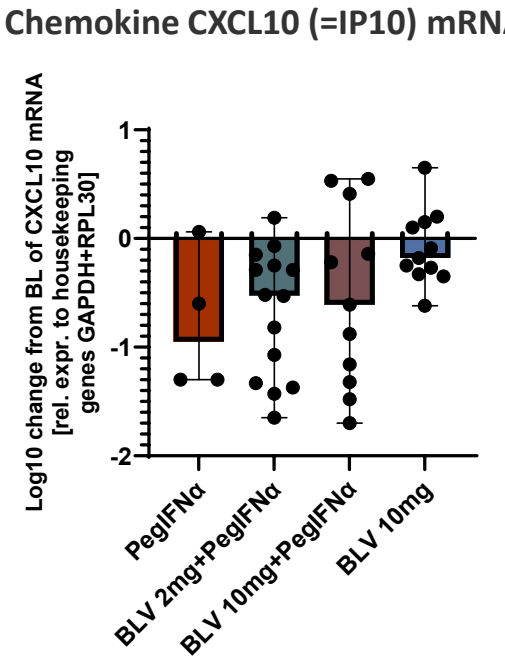
Maintained undetectable HDV RNA in post-treatment period was observed in many patients without HBsAg loss.

However, follow-up studies will be necessary to determine if HDV cure is achievable in the presence of HBsAg.

Serum HDV RNA LLoD 6 IU/ml (blue dotted line); serum HBsAg LLoD 0.05 IU/ml (red dotted line); liver HDV RNA LLOQ 0.0001 rel. expression (not depicted); liver HBV S RNA 0.00003 rel. expression (not depicted)

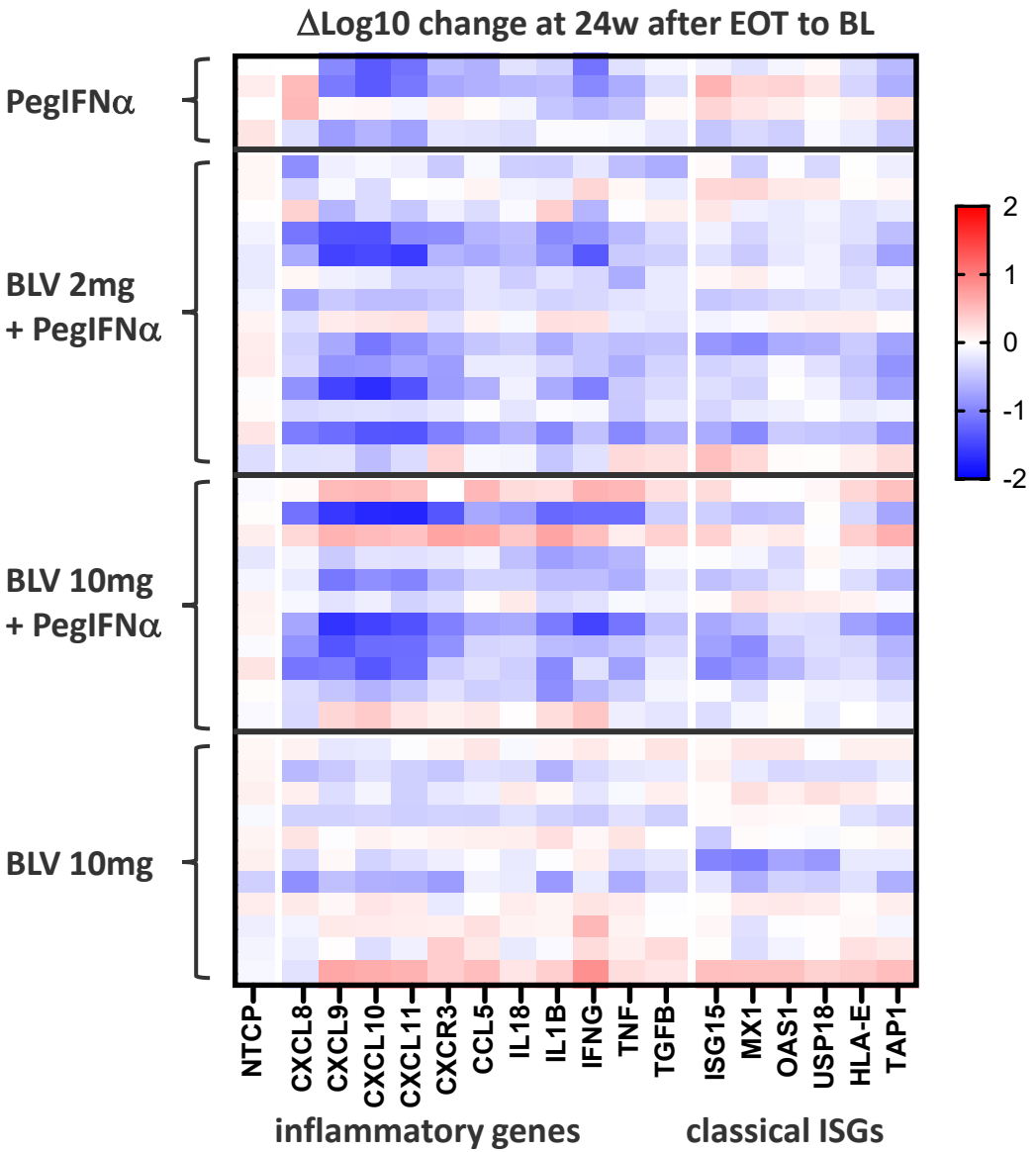
Results: Host gene expression analysis

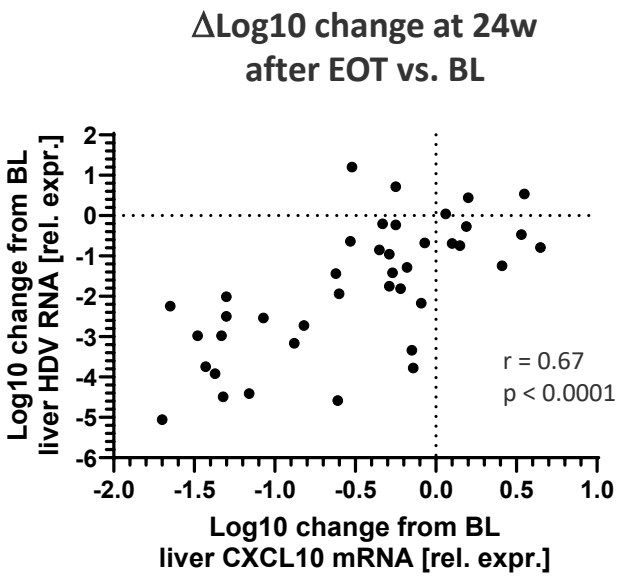


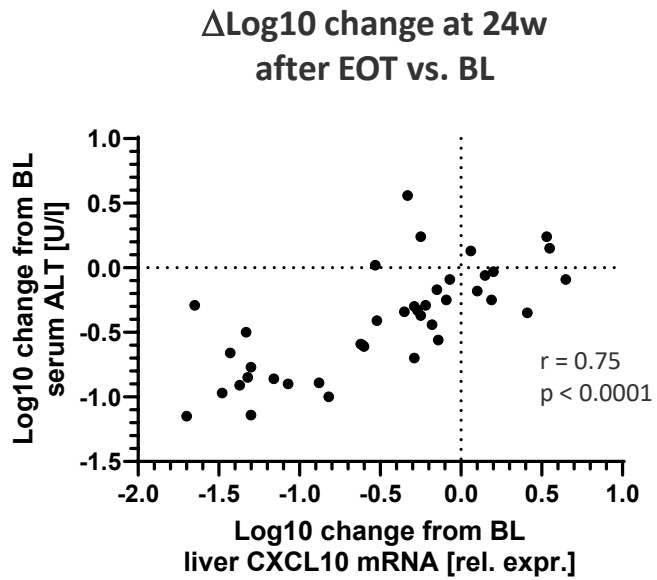


Expression levels of inflammatory chemokines and cytokines were low after combination therapy and PegIFNα monotherapy at 24 weeks after EOT.

Results: Host gene expression analysis



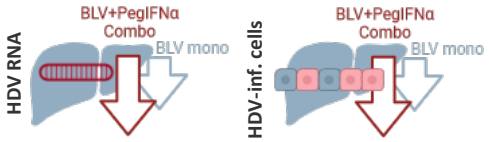




The reduction of expression levels (CXCL10 mRNA) correlates with the reduction of intrahepatic HDV RNA and ALT levels.

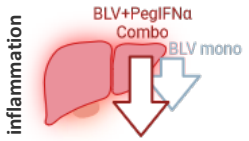
Summary & Conclusions

Intrahepatic analysis in paired BL and post-treatment biopsies demonstrated a strong correlation between intrahepatic and serum HDV RNA reductions.



Similar to serological findings, the highest rate of off-treatment virologic response in the liver was observed in the arm that received combination of BLV 10mg + PegIFNα.

Intrahepatic HBV markers did not show consistent changes, with the exception of few patients in the PegIFNα arms with reduced HBV markers.



Concomitant with the decrease of HDV parameters, expression levels of innate immune genes declined.

Limitations: The low number of paired biopsies, especially in PegIFNα monotherapy arm, limited the comparison between treatment arms. Lack of biopsies at end of treatment did not allow for the analysis of on-treatment efficacy in the liver.

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Thanks to all patients & their families,
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Stephan Urban

Backup slides

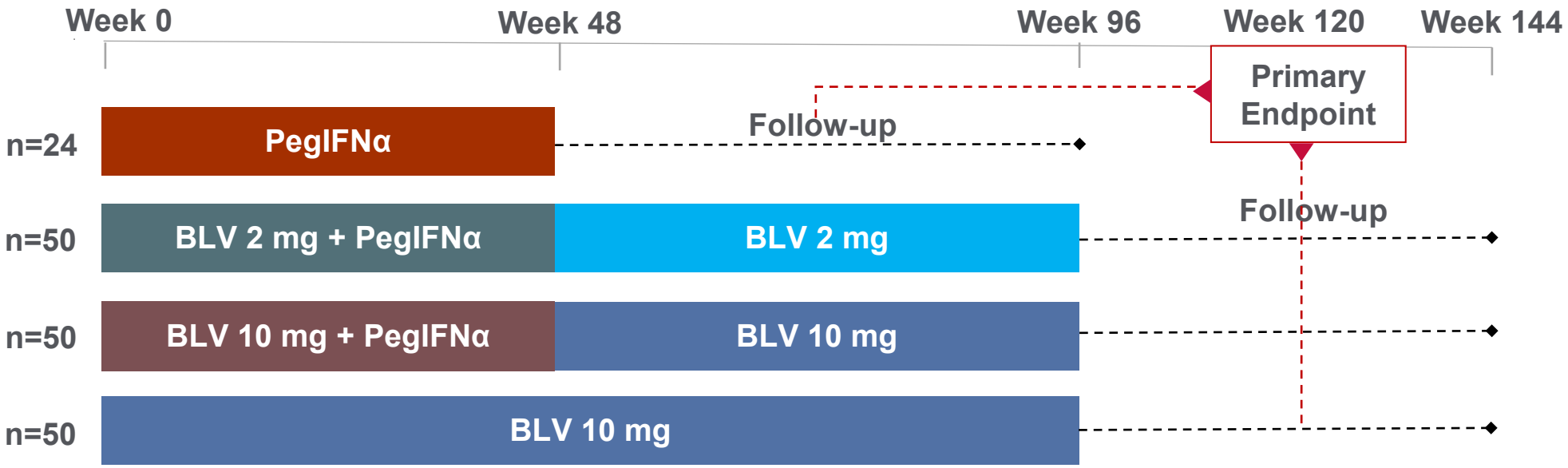
Background

- Hepatitis delta virus (HDV) is a satellite virus
  - Requires the envelope protein from hepatitis B virus (HBV) to infect hepatocytes[1]
- Between 10-20 million people are infected with HDV worldwide[2]
- HDV causes the most severe form of chronic viral hepatitis[3,4]
  - 2–3-fold increased risk of mortality compared to HBV mono-infection[5,6]
- Pegylated interferon-alfa (PegIFNα) recommended as off-label therapy for chronic hepatitis delta (CHD)
  - Low rates of sustained undetectable HDV RNA post-therapy and high rates of relapse[7]
- Bulevirtide (BLV) 2 mg, an entry inhibitor, received full approval in July 2023 in the EU for the treatment of adults with CHD and compensated liver disease

MYR204, a Phase 2b study addresses a major treatment gap for HDV, a finite treatment regimen that results in sustained off-treatment viral response

1. Asselah T, Rizzetto M. *N Eng J Med* 2023;389:58-70; 2. Stockdale AJ, et al. *J Hepatol* 2020;73:523-32; 3. Alfaiate D, et al. *J Hepatol.* 2020 Sep;73(3):533-539; 4. Rizzetto M, et al. *J Hepatol* 2021;74(5):1200-1211; 5. Fattovich G, et al. *Gut* 2000;46:420-6; 6. Wranke A, et al. *Hepatol Int.* 2023 Oct 3; doi: 10.1007/s12072-023-10575-0;.7. Sandmann L, et al. *Liver International* 2022;00:1-11.

Study Design



- Open-label, randomized, multicenter, Phase 2b study (NCT03852433) conducted in 19 sites across 4 countries (France, Moldova, Romania, and Russia)

Key Inclusion Criteria

- CHD with detectable serum HDV RNA
- With or without cirrhosis; Child-Turcotte-Pugh (CTP) ≤6
- ALT >1× - <10× ULN; Platelets ≥90,000 cells/mm^3
- No IFN within 6 months before enrollment

ALT, alanine transaminase; **BLV**, bulevirtide; **CHD**, chronic hepatitis D; **IFN**, interferon; **PegIFNα**, pegylated interferon alpha; **ULN**, upper limit of normal.

Study Endpoints

Primary endpoint:

- **HDV RNA undetectable* at Week 24 after EOT**
- The primary efficacy analysis was powered to compare the difference between the BLV 10 mg + PegIFNα group vs BLV 10 mg monotherapy group

Secondary Endpoints:

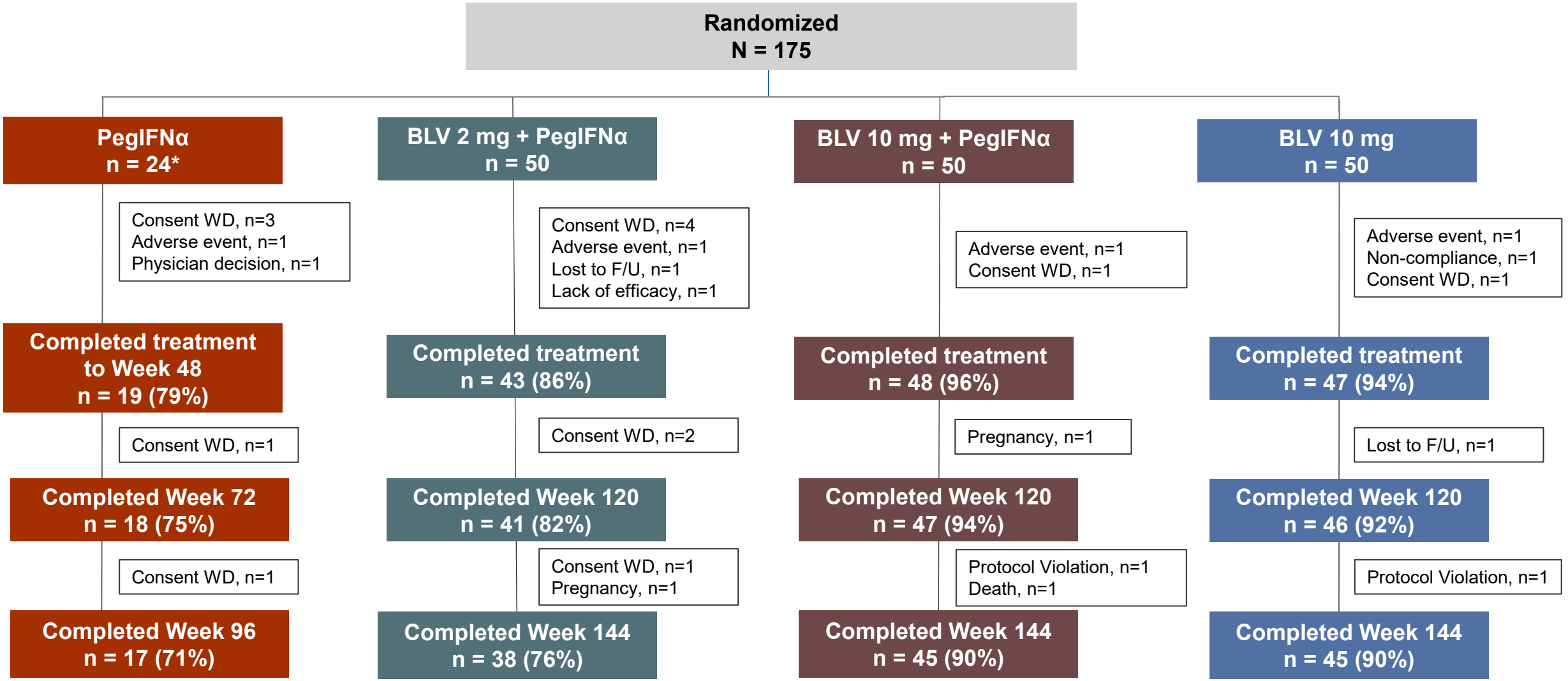
- Undetectable HDV RNA at EOT
- Change from BL in Liver Stiffness (at Week 24 after EOT)
- Safety

Additional Endpoints at Week 24 after EOT:

- ALT normalization
- Composite response[a]: undetectable HDV RNA and ALT normalization

*HDV RNA levels determined by RT-qPCR using RoboGene® HDV RNA Quantification Kit 2.0 (lower limit of quantification (LLOQ) 50 IU/mL, lower limit of detection 6 IU/mL), undetectable HDV RNA defined as <LLOQ, target not detected. ALT within normal ranges as established by the testing laboratory; [a]As recommended by: Chronic Hepatitis D Virus Infection: Developing Drugs for Treatment Guidance for Industry; Draft guidance November 2019. **ALT**, alanine transaminase; **BL**, baseline; **BLV**, bulevirtide; **EOT**, end of treatment; **LLOQ**, lower limit of quantification; **PegIFNα**, pegylated interferon alpha.

Patient disposition



*one patient in PegIFNa arm was randomized but not treated. **BLV**, bulevirtide; **F/U**: follow-up; **PegIFNα**, pegylated interferon alpha; **WD**, withdrawal.

Baseline demographics & disease characteristics

		PegIFNα n = 24	PegIFNα + BLV 2 mg n = 50	PegIFNα + BLV 10 mg n = 50	BLV 10 mg n = 50
Mean age, y (SD)		41 (8.4)	41 (9.3)	41 (8.6)	40 (8.5)
Male sex, n (%)		18 (75)	33 (66)	35 (70)	38 (76)
Race[a], n (%)	Caucasian	20 (83)	44 (88)	43 (86)	44 (88)
	Asian	4 (17)	3 (6)	4 (8)	4 (8)
	Black	0	3 (6)	2 (4)	2 (4)
Cirrhosis, n (%)		8 (33)	17 (34)	17 (34)	17 (34)
Median liver stiffness, kPa (Q1, Q3)		12.2 (8.6, 18.9)	10.7 (7.8, 16.5)	10.5 (7.8, 14.3)	10.8 (8.5, 14.1)
Median ALT, U/L (Q1, Q3)		91 (64, 152)	81 (56, 143)	82 (55, 117)	90 (63, 127)
Median HDV RNA, log_{10} IU/mL (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 GT 1/ 5/ 6, n (%)		24 (100) / 0 / 0	48 (96) / 1 (2) / 1 (2)	47 (94) / 2 (4) / 0	49 (98) / 1 (2) / 0
Mean HBsAg, log_{10} IU/mL (SD)		3.6 (0.5)	3.7 (0.6)	3.7 (0.7)	3.7 (0.6)
Prior interferon use, n (%)		12 (50)	25 (50)	26 (52)	21 (42)
Concomitant NA for HBV, n (%)		11 (46)	24 (48)	25 (50)	23 (46)

[a]PegIFNα + BLV 10 mg: n=1 Other race. **ALT**, alanine transaminase; **BLV**, bulevirtide; **GT**, genotype; **HBsAg,** hepatitis B surface antigen; **HBV**, hepatitis B virus; **IQR**, interquartile range; **NA**, nucleos(t)ide analogue; **PegIFNα**, pegylated interferon alpha; **Q**, quartile; **SD**, standard deviation; **y**, years.