Predictors of Undetectable HDV RNA 48 Weeks After Completion of Finite Treatment With Bulevirtide and Pegylated-Interferon Alpha-2a

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Background

- HDV is a satellite virus that requires the envelope protein from HBV to infect hepatocytes[1]
- Between 10 and 20 million people are infected with HDV worldwide[2]
- HDV is associated with the worst viral hepatitis prognosis, with increased morbidity and mortality compared to monoinfection with HBV[3-6]
- PegIFNα is recommended as an off-label therapy for CHD
  - It is associated with low rates of sustained undetectable HDV RNA post-therapy and high rates of relapse[7]
- BLV 2 mg is a first-in-class entry inhibitor approved in the European Union, the United Kingdom, Switzerland, the Russian Federation, and Australia for the treatment of adults with CHD and compensated liver disease
- In MYR204, a Phase 2b study evaluating finite treatment with BLV with or without PegIFNα, combination treatment with 10 mg BLV resulted in higher undetectable HDV RNA rates after EOT compared with either monotherapy regimen[8]

Objective of Subanalysis : To evaluate the predictors of undetectable HDV RNA at W48 after EOT with BLV (2 mg and 10 mg) with PegIFNα in patients with compensated CHD

BLV, bulevirtide; **CHD**, chronic hepatitis delta; **EOT**, end of treatment; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **PegIFNα**, pegylated interferon alpha-2a; **W**, week.

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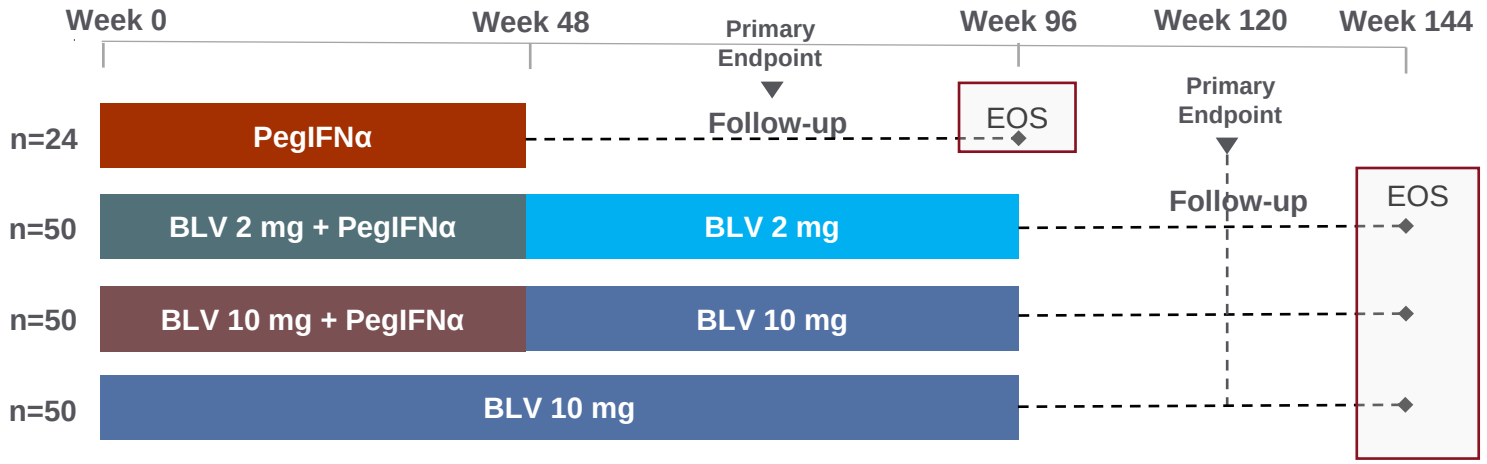
MYR204 Study Design



Key Inclusion Criteria

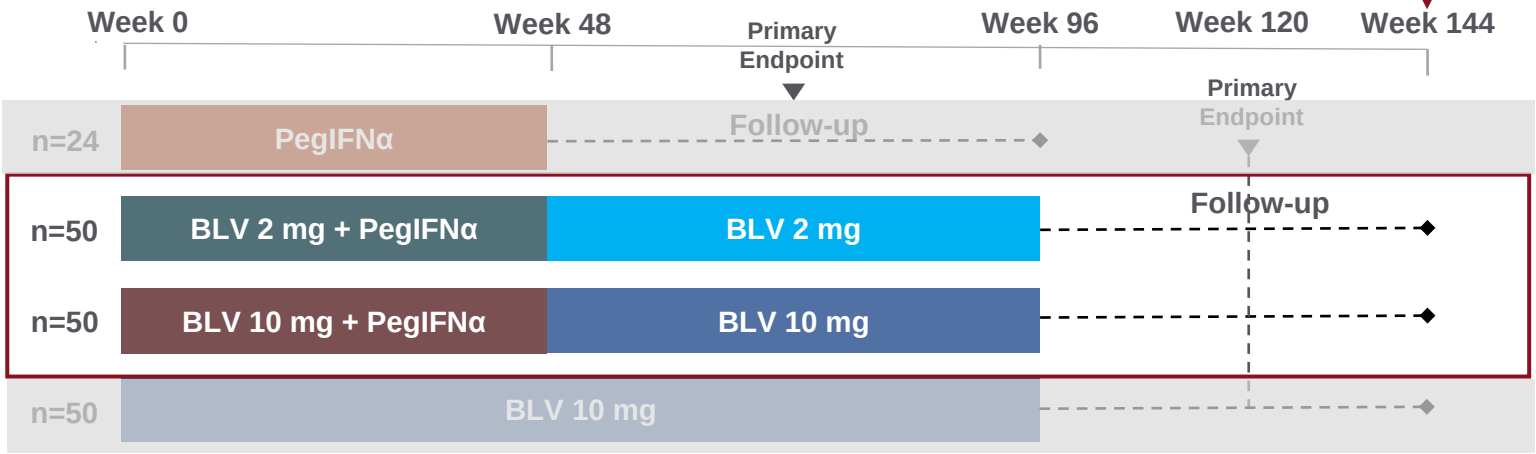
- CHD with detectable serum HDV RNA
- With or without cirrhosis; Child-Turcotte-Pugh score ≤6
- ALT >1 × to <10 × ULN; platelets ≥90,000 cells/mm^3
- No IFN treatment within 6 months before enrollment

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

ALT, alanine transaminase; **BLV**, bulevirtide; **CHD**, chronic hepatitis D; **EOS**, end of study; **IFN**, interferon; **PegIFNα**, pegylated interferon alpha-2a; **ULN**, upper limit of normal.

Response Predictor Analysis

Logistic Regression Subanalysis
Patients treated with BLV (2 or 10 mg) + PegIFNα



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Study Endpoints

Primary endpoint

- HDV RNA undetectable[a] at W24 after EOT
- The primary efficacy analysis was the difference between the BLV 10 mg + PegIFNα group and BLV 10 mg monotherapy group

Secondary endpoints at W48 after EOT

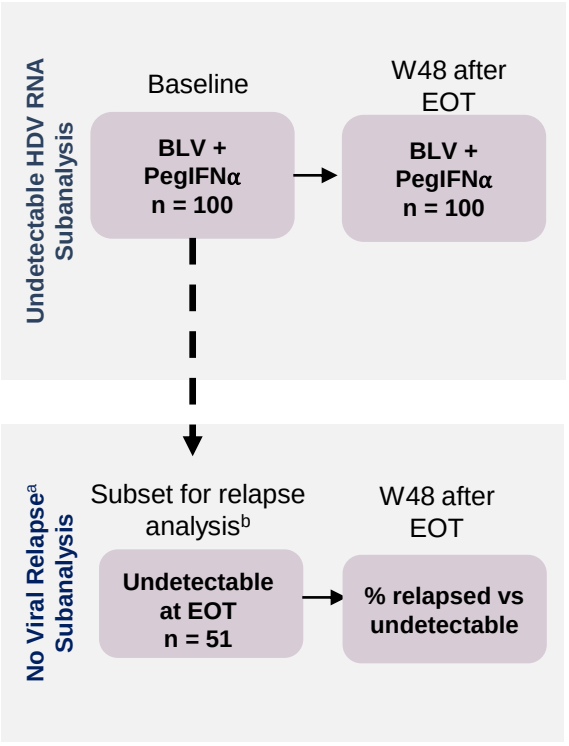
- Undetectable HDV RNA
- Safety

Subanalysis of baseline and on-treatment response predictors

- Predictors of undetectable HDV RNA response at W48 after EOT
- Predictors of no viral relapse at W48 after EOT in subsets of patients with undetectable HDV RNA at EOT

[a]HDV RNA levels were determined by RT-qPCR using RoboGene HDV RNA Quantification Kit 2.0 (LLOQ 50 IU/mL, lower limit of detection 6 IU/mL), undetectable HDV RNA defined as <LLOQ, target not detected.
BLV, bulevirtide; **EOT**, end of treatment; **LLOQ**, lower limit of quantification; **PegIFNα**, pegylated interferon alpha-2a; **W**, week.

Logistic Regression Model for Predictor Analysis



Clinical Characteristics Evaluated as Predictors of HDV RNA Undetectability

Baseline 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

Treatment-Related Characteristics

- Liver stiffness (kPa) at W24 after EOT (kPa)
- On-treatment total bile salt levels
- Time to onset of first undetectable HDV RNA
- Undetectable HDV RNA at W16, W24, or W48
- Duration of HDV RNA undetectability
- Total dosage of PegIFNα
- ADA incidence at W96

Additional On-Treatment Characteristics Evaluated as Predictors of no Viral Relapse

- Liver stiffness (kPa) at W24 after EOT
- Time to onset and duration of undetectable HDV RNA
- Total doses of PegIFNα (µg)

***P* value of <.05 to identify potential predictors**

[a]Viral relapse is defined as undetectable HDV RNA at EOT with detectable HDV RNA at W48 after EOT. [b]Subset for relapse analysis included patients who were undetectable at EOT and completed the study through W48 after EOT visit.

ADA, antidrug antibodies; **ALT**, alanine aminotransferase; **BLV**, bulevirtide; **BMI**, body mass index; **EOS**, end of study; **EOT**, end of treatment; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **IFN**, interferon; **PegIFNα**, pegylated interferon alpha-2a; **W**, week.

Baseline Demographics and Disease Characteristics

		PegIFNα n = 24	PegIFNα + BLV 2 mg n = 50	PegIFNα + BLV 10 mg n = 50	BLV 10 mg n = 50
Age, years, mean (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)
Liver stiffness, kPa, median (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)
ALT, U/L, median (Q1, Q3)		91 (64, 152)	81 (56, 143)	82 (55, 117)	90 (63, 127)
HDV RNA, $\log_{10}$ IU/mL, median (Q1, Q3)		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 genotype[b] 1/5/6, n (%)		24 (100) / 0 / 0	48 (96) / 1 (2) / 1 (2)	47 (94) / 2 (4) / 0	49 (98) / 1 (2) / 0
HBsAg, $\log_{10}$ IU/mL, mean (SD)		3.6 (0.5)	3.7 (0.6)	3.7 (0.7)	3.7 (0.6)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)		1.4 (1.1)	1.7 (1.6)	1.5 (1.1)	1.8 (1.6)
HBV DNA ≥10 IU/mL, n (%)		17 (71)	41 (82)	38 (76)	40 (80)
HBeAg negative, n (%)		23 (96)	42 (84)	47 (94)	43 (86)
HBV genotype[b] A/D/E, n (%)		4 (17) / 19 (79) / 0	7 (14) / 40 (80) / 1 (2)	7 (14) / 38 (76) / 2 (4)	8 (16) / 41 (82) / 0
Prior interferon use, n (%)		12 (50)	25 (50)	26 (52)	21 (42)
Concomitant HBV medication, n (%)		11 (46)	24 (48)	25 (50)	23 (46)

[a]PegIFNα + BLV 10 mg: n=1 other race. [b]Only available/classified data presented.

ALT, alanine transaminase; **BLV**, bulevirtide; **HBeAg,** hepatitis B e antigen; **HBsAg,** hepatitis B surface antigen; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **PegIFNα**, pegylated interferon alpha-2a; **Q**, quartile.

Baseline Demographics and Disease Characteristics

		PegIFNα n = 24	PegIFNα + BLV 2 mg n = 50	PegIFNα + BLV 10 mg n = 50	BLV 10 mg n = 50
Age, years, mean (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)
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HDV RNA, $\log_{10}$ IU/mL, median (Q1, Q3)		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 genotype[b] **1/5/6**, n (%)		24 (100) / 0 / 0	48 (96) / 1 (2) / 1 (2)	47 (94) / 2 (4) / 0	49 (98) / 1 (2) / 0
HBsAg, $\log_{10}$ IU/mL, mean (SD)		3.6 (0.5)	3.7 (0.6)	3.7 (0.7)	3.7 (0.6)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)		1.4 (1.1)	1.7 (1.6)	1.5 (1.1)	1.8 (1.6)
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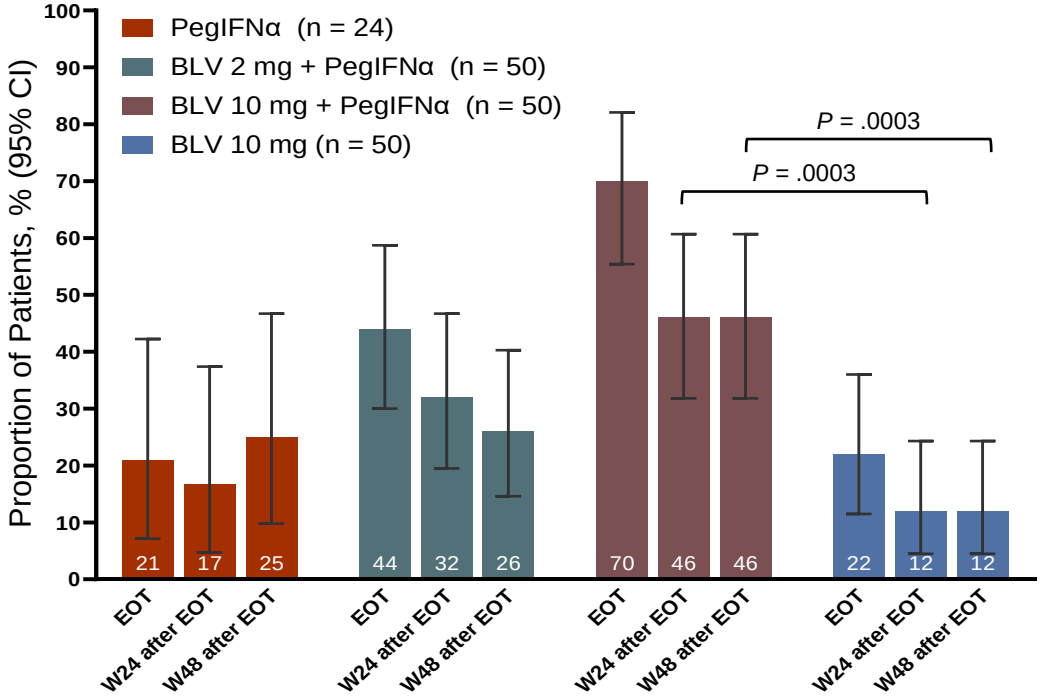
Prior interferon use, n (%)		12 (50)	25 (50)	26 (52)	21 (42)
Concomitant HBV medication, n (%)		11 (46)	24 (48)	25 (50)	23 (46)

- The baseline demographics were well balanced between the arms

[a]PegIFNα + BLV 10 mg: n=1 other race. [b]Only available/classified data presented.
ALT, alanine transaminase; **BLV**, bulevirtide; **HBeAg**, hepatitis B e antigen; **HBsAg,** hepatitis B surface antigen; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **PegIFNα**, pegylated interferon alpha-2a; **Q**, quartile.

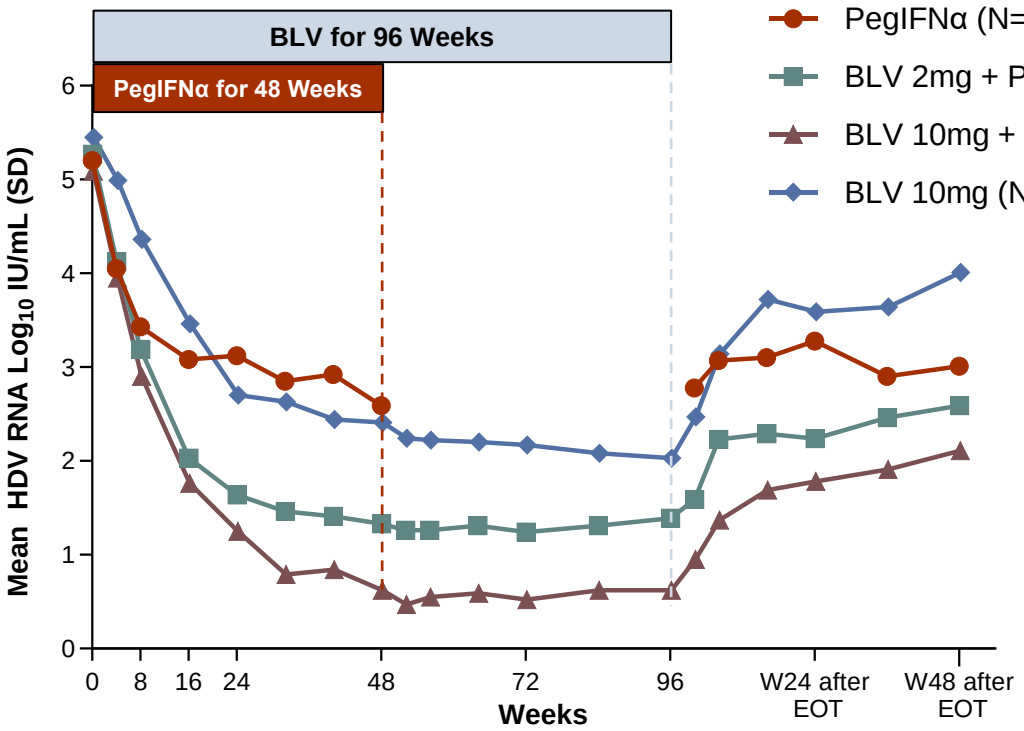
Undetectable HDV RNA



- Higher rates of undetectable HDV RNA were observed among patients with BLV 10 mg + PegIFNα vs BLV 10 mg at W24 and W48 after EOT (*P* = .0003)

Missing = failure. **BLV**, bulevirtide; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **PegIFNα**, pegylated interferon alpha-2a; **W,** week.

Mean HDV RNA Through W48 After EOT



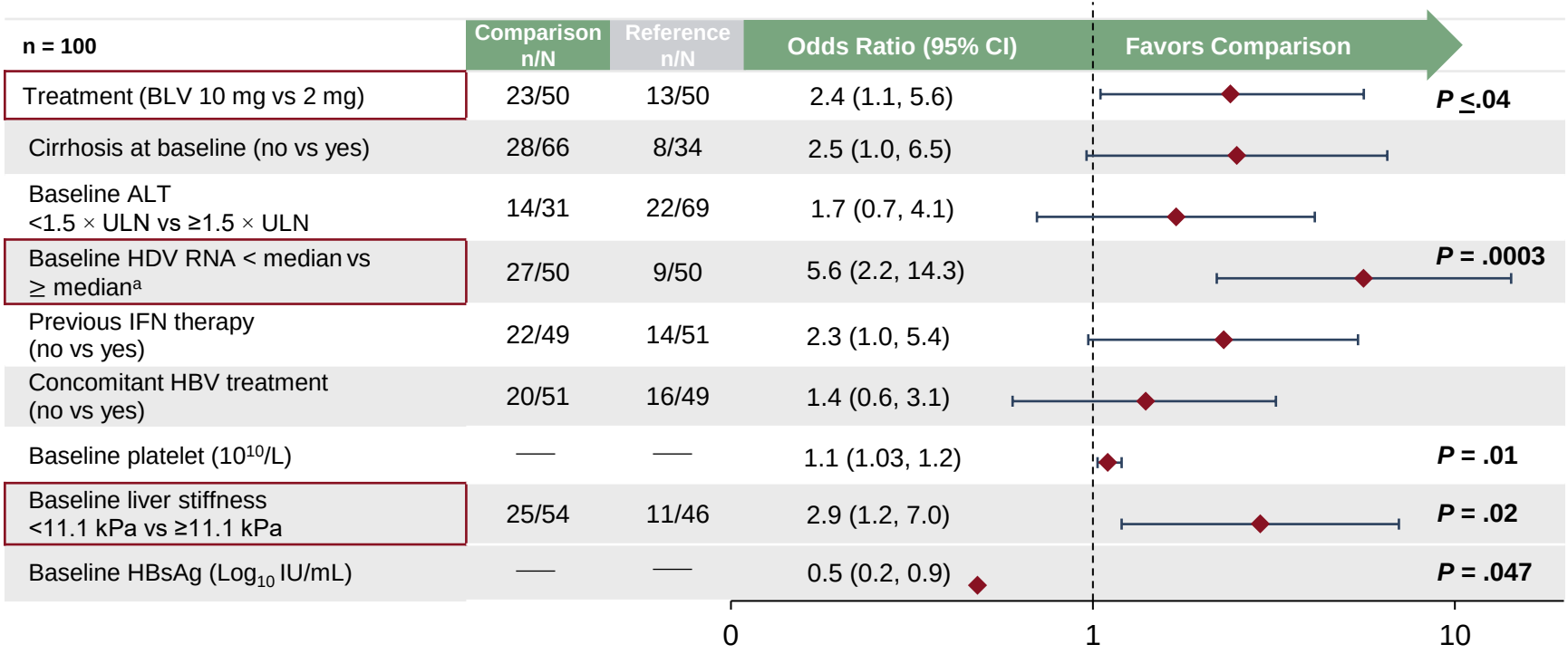
PegIFNα (N=24)
BLV 2mg + PegIFNα (N=50)
BLV 10mg + PegIFNα (N=50)
BLV 10mg (N=50)

Model Estimated HDV RNA (log10 IU/mL) Decline Rate Through W48*	
PegIFNα (n = 24)	−0.0343
BLV 2 mg + PegIFNα (n = 50)	−0.0757
BLV 10 mg + PegIFNα (n = 50)	−0.0885
BLV 10 mg (n = 50)	−0.0659

- BLV (2 or 10 mg) + PegIFNα had a greater weekly decline in HDV RNA compared with PegIFNα in the first 48 weeks on-treatment (*P* <.0001)

*The linear mixed-effects model was used to estimate the change of HDV RNA (log_{10} IU/mL) level per week. **BLV**, bulevirtide; **EOT**, end of treatment; **HDV**, hepatitis delta virus; **PegIFNα**, pegylated interferon alpha-2a; **W**, week.

Baseline Predictors of Undetectable HDV RNA at W48 After EOT



- Key predictors of undetectable HDV RNA at W48 after EOT:
  - Treatment with BLV 10 mg, BL HDV RNA < 5.54 log_{10} IU/mL, BL liver stiffness <11.1 kPa

[a]Median = 5.54 log_{10} IU/mL.

ALT, alanine aminotransferase; **BLV**, bulevirtide; **EOT**, end of treatment; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **IFN**, interferon; **ULN**, upper limit of normal; **W**, week.

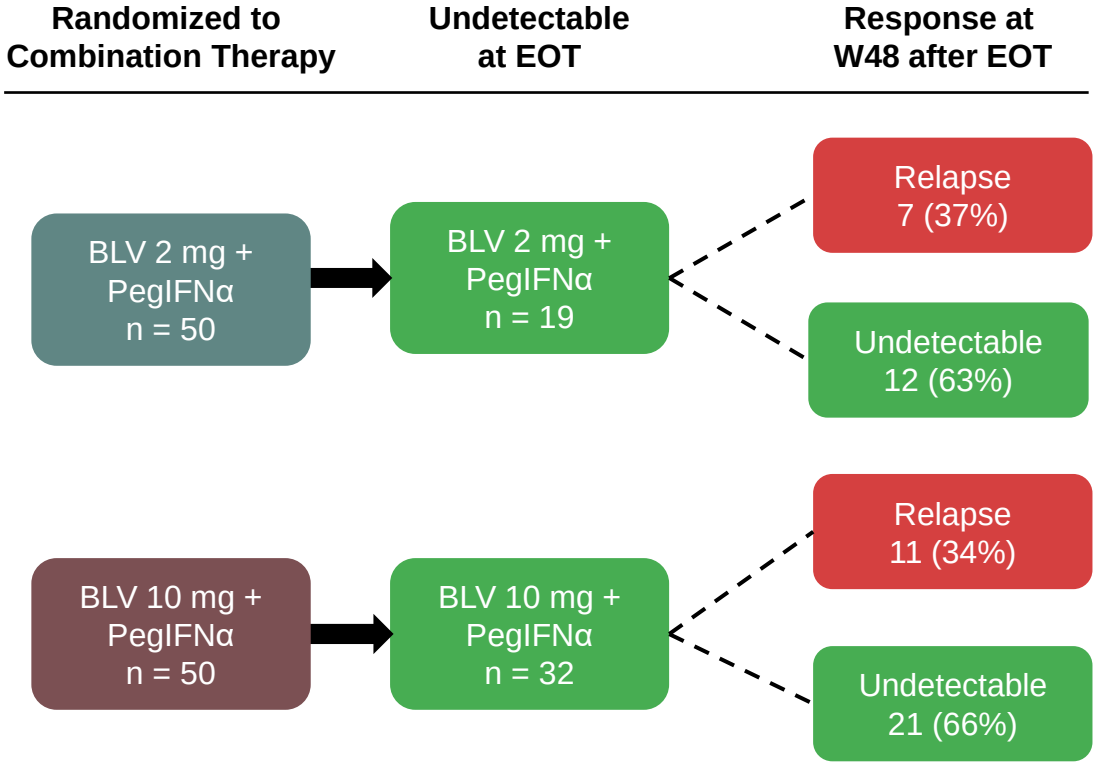
On-Treatment Predictors of Undetectable HDV RNA at 48W After EOT

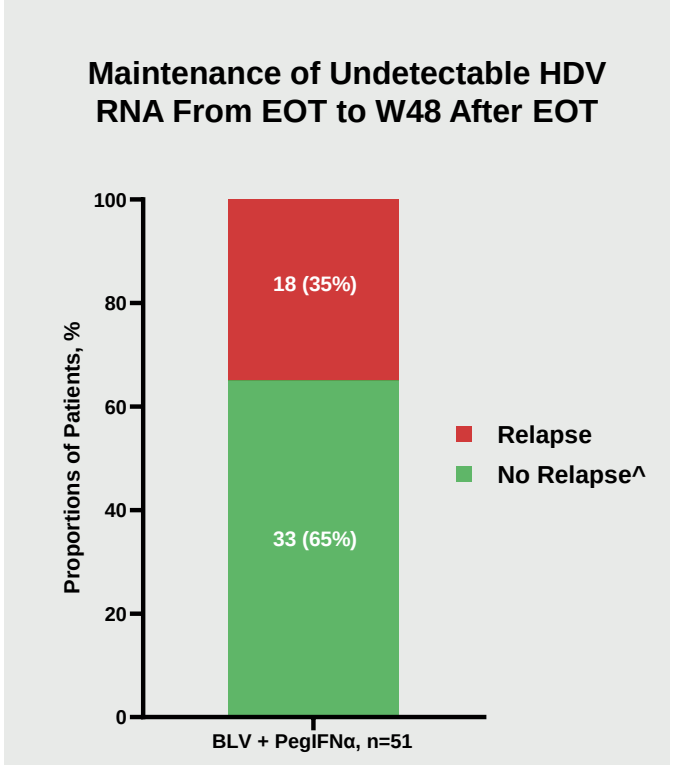
n = 100	Comparison n/N	Reference n/N	Odds Ratio (95% CI)	Favors Comparison
Time to onset of first undetectable HDV RNA (days)	—	—	0.9 (0.9, 0.9)	***P* = .0015**
Week 16 HDV RNA undetectable (yes vs no)	17/26	19/70	5.2 (2.0, 14.3)	***P* = .001**
Week 24 HDV RNA undetectable (yes vs no)	23/30	13/64	13.5 (4.6, 40.0)	***P* <.0001**
Week 48 HDV RNA undetectable (yes vs no)	31/50	4/40	13.7 (4.2, 45.0)	***P* <.0001**
Total dosage of PegIFNα (µg)	—	—	1.0 (1.0, 1.0)	***P* = .01**

- Strongest on-treatment predictors of undetectable HDV RNA included:
  - Achieving undetectable HDV RNA by treatment week 24 or 48

EOT, end of treatment; **HDV**, hepatitis delta virus; **PegIFNα**, pegylated interferon alpha-2a; **W**, week

Undetectable HDV RNA and Viral Relapse





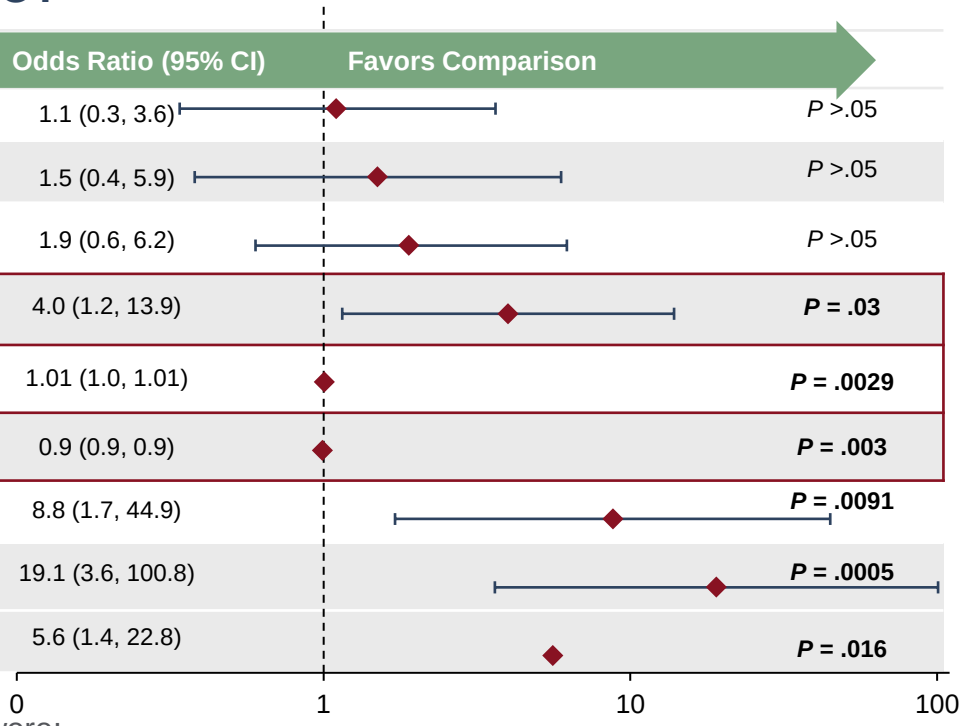
- Majority of patients who had undetectable HDV RNA at EOT maintained undetectable HDV RNA at W48 after EOT

*Only patients with data at EOT and W48 after EOT are included; ^No relapse, undetectable HDV RNA.. **BLV**, bulevirtide; **EOT**, end of treatment; **PegIFNα**, pegylated interferon alpha-2a; **W,** week.

Predictors of No Viral Relapse at W48 After EOT

Patients With Undetectable HDV RNA at EOT

n = 51	Comparison n/N	Reference n/N	Odds Ratio (95% CI)	Favors Comparison
Treatment (BLV 10 mg vs 2 mg)	21/32	12/19	1.1 (0.3, 3.6)	*P* >.05
Cirrhosis at baseline (no vs yes)	26/39	7/12	1.5 (0.4, 5.9)	*P* >.05
Previous IFN therapy (no vs yes)	20/28	13/23	1.9 (0.6, 6.2)	*P* >.05
Baseline HDV RNA < median vs ≥ median[a]	20/25	13/26	4.0 (1.2, 13.9)	***P* = .03**
Duration of HDV RNA undetectability (days)			1.01 (1.0, 1.01)	***P* = .0029**
Time to onset of first undetectable HDV RNA (days)			0.9 (0.9, 0.9)	***P* = .003**
Week 16 HDV RNA undetectable (yes vs no)	17/19	16/32	8.8 (1.7, 44.9)	***P* = .0091**
Week 24 HDV RNA undetectable (yes vs no)	23/25	10/26	19.1 (3.6, 100.8)	***P* = .0005**
Week 48 HDV RNA undetectable (yes vs no)	28/38	4/12	5.6 (1.4, 22.8)	***P* = .016**



- Potential predictors of no viral relapse at W48 after EOT were:
  - Baseline HDV RNA levels <5.09 $\log_{10}$ IU/mL, shorter time to HDV RNA undetectability, and longer duration of undetectability
- 23 of 25 patients with undetectable HDV RNA at W24 on treatment did not relapse by W48 after EOT

[a]Median = 5.09 $\log_{10}$ IU/mL.

BLV, bulevirtide; **EOT**, end of treatment; **HBsAg**, hepatitis B surface antigen; **HBV**, hepatitis B virus; **HDV**, hepatitis delta virus; **IFN**, interferon; **ULN**, upper limit of normal; **W**, week.

Overall Safety

TEAEs, n (%)	PegIFNα n = 24	BLV 2 mg + PegIFNα n = 50	BLV 10 mg + PegIFNα n = 50	BLV 10 mg n = 50
Any AE	22 (92)	49 (98)	50 (100)	42 (84)
Any Grade 3 or 4 AE related to BLV	N/A	2 (4)	2 (4)	0
Any SAE	3 (13)	3 (6)	8 (16)	2 (4)
Any SAE related to BLV	N/A	0	0	0
Any AE leading to D/C of study treatment	1 (4)	3 (6)	2 (4)	1 (2)
BLV related AE leading to D/C of study treatment	N/A	0	0	1 (2)[a]
Death	0	1 (2)[b]	0	0
Post-treatment hepatic adverse events, overall	4 (17)	8 (16)	10 (20)	19 (38)
ALT increased	3 (13)	8 (16)	5 (10)	14 (28)
AST increased	1 (4)	7 (14)	5 (10)	11 (22)
GGT increased	1 (4)	1 (2)	1 (2)	5 (10)
Bilirubin increased[c]	0	0	3 (6)	5 (10)
Jaundice	0	0	0	2 (4)

- The safety profile observed with BLV + PegIFNα was consistent with the known safety profile of each drug
- Few Grade 3 TEAEs were related to BLV; no SAE was related to BLV
- Most ALT and AST elevations were asymptomatic, associated with HDV RNA rebound, and transient

[a]BLV 10 mg: Myalgia related to BLV (Grade 2, nonserious). [b]Anaplastic astrocytoma not related to study treatment. [c]Shown are only those in >1 patient/arm. **AE**, adverse event; **ALT**, alanine aminotransferase; **BLV**, bulevirtide; **D/C,** discontinuation; **N/A,** not applicable; **PegIFNα**, pegylated interferon alpha-2a; **SAE**, serious adverse event; **TEAE**, treatment-emergent adverse event.

Conclusions

- BLV 10 mg in combination with PegIFNα achieved:
  - Highest rates of HDV RNA undetectability which were maintained through W48 after EOT
  - Superiority to BLV 10 mg monotherapy at W48 after EOT
- Combination BLV + PegIFNα had the fastest rate to HDV RNA undetectability
- Receiving BLV 10 mg + PegIFNα, lower baseline HDV RNA and liver stiffness were predictors of achieving undetectable HDN RNA at W48 after EOT
- Achieving undetectable HDV RNA earlier in therapy was predictive of maintaining undetectable HDV RNA in the post-treatment period
- BLV combined with PegIFNα had a similar safety profile as the individual drug components; posttreatment ALT increases were observed but were mostly asymptomatic and transient

BLV in combination with PegIFNα provides a novel opportunity for finite CHD treatment

ALT, alanine aminotransferase; **BLV**, bulevirtide; **CHD**, chronic hepatitis D; **EOT**, end of treatment; **HBsAg**, hepatitis B surface antigen; **PegIFNα**: pegylated interferon alpha-2a; **W**, week.

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