GILEAD | Medical Information

Hepcludex® (bulevirtide-gmod) Treatment Duration and Discontinuation of Therapy

This document is in response to your request for information regarding the use of Hepcludex® (bulevirtide-gmod [BLV]) for the treatment of chronic HDV infection and available data on finite treatment duration and outcomes after discontinuation of therapy.

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The full indication, important safety information, and boxed warnings are available at: www.gilead.com/-/media/files/pdfs/medicines/hdv/hepcludex/hepcludex_pi.

Summary

Product Labeling[1]

Severe acute exacerbations of HDV and HBV infection may occur after BLV is discontinued, especially in patients with cirrhosis, who may be at increased risk of more severe flares or progression to hepatic decompensation. Monitor hepatic function closely with both clinical and laboratory follow-up, including HBV DNA and HDV RNA viral load, for at least 6 months in patients who discontinue BLV. Resumption of antiviral therapy may be warranted.

BLV is indicated for the treatment of chronic HDV infection in adults without cirrhosis or with compensated cirrhosis.

This indication is approved under accelerated approval based on a decrease in HDV RNA and ALT normalization. An improvement in disease-related clinical outcomes has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

The recommended dosage in adults is BLV 8.5 mg once daily administered by SUBQ injection.

BLV should be continued as long as it is associated with a response to treatment. The optimal treatment duration is unknown.

In all patients, manage the underlying HBV infection as clinically appropriate.

If a dose is missed, that dose should be taken as soon as possible. However, if it is almost time for the next dose, skip the missed dose and resume the original schedule.

The efficacy of BLV once daily in the treatment of adults with chronic HDV infection without cirrhosis or with compensated cirrhosis is based on data through Week 144 from a multicenter, randomized, open-label, parallel-arm phase 3 trial, Trial MYR301 (NCT03852719), in which 100 participants received BLV 8.5 mg once daily. The MYR301

protocol specified the BLV dose as 10 mg; however, a dose recovery study later showed that the delivered dose was 8.5 mg.

Clinical Data: BLV Treatment Duration and Discontinuation of Therapy

In the phase 2b MYR204 study that evaluated BLV and PEG-IFNα treatment alone and in combination in participants with chronic HDV (N=174), undetectable HDV RNA levels 48 weeks after stopping treatment were observed in 26% of participants in the BLV 2 mg + PEG-IFNα arm, 12% in the BLV 10 mg arm, 46% in the BLV 10 mg + PEG-IFNα arm, and 25% in the PEG-IFNα arm. Safety results through Week 144 are reported below.[2]

- In participants with undetectable HDV RNA levels at EOT in the BLV + PEG-IFNα arms, treatment with BLV 10 mg ($P \leq 0.04$), HDV RNA levels <median ($P=0.0003$), and liver stiffness values <11.1 kPa ($P=0.02$) were baseline predictors of maintaining undetectable HDV RNA levels at 48 weeks after EOT.[3] On-treatment predictors of undetectable HDV RNA 48 weeks after EOT included undetectable HDV RNA at Week 24, Week 48, and EOT.[3,4]

In the phase 3 MYR301 study that evaluated the safety and efficacy of BLV (2 mg, 10 mg, or 10 mg after a 48-week delay of treatment) in participants with chronic HDV (N=150), nearly half of participants who received BLV for 144 weeks and had undetectable HDV RNA at EOT sustained undetectability at 96 weeks after EOT. Across all treatment arms, rates of combined response, ALT normalization, and virologic response were similar at EOT and decreased from EOT to 96 weeks after EOT.[5]

- Across all treatment arms, 90% of participants with ≥96 weeks of continuous undetectable levels of HDV RNA at EOT sustained undetectable levels after EOT. Most relapses (93%) occurred within 24 weeks after EOT, and all relapses occurred within 48 weeks after EOT.[5]
- A univariate logistic regression analysis showed that being treated with BLV 10 mg or having an HDV RNA or HBsAg level below the median was predictive of undetectable levels of HDV RNA at EOT. On-treatment predictors of sustained undetectable levels of HDV RNA up to 48 weeks after EOT included early and long durations of on-treatment undetectable levels of HDV RNA.[6]

Two pooled analyses of data from participants from MYR204 and MYR301 were performed.[7,8]

- In one pooled analysis, treatment with BLV 10 mg + PEG-IFNα or BLV 10 mg for 144 weeks (vs 96 weeks) was associated with higher rates of undetectable HDV RNA at EOT and up to 48 weeks after EOT.[7]
- In an additional pooled analysis, almost half of participants with undetectable HDV RNA at EOT with BLV monotherapy or in combination with PEG-IFNα continued to have undetectable HDV RNA levels and maintained normal ALT levels through FU Week 48. Most participants with low-viremic relapse after EOT maintained normal ALT levels through FU Week 48, whereas the rate of ALT normalization decreased over time in participants with high viremic relapse after EOT. Almost half of participants who had undetectable HDV at EOT remained virus free during follow-up. Among participants with virologic relapse, some maintained stability in markers of liver damage.[8]

Real-World Data: BLV Treatment Duration and Discontinuation of Therapy

An analysis of the multicenter French BuleDelta cohort study examined SVR rates and factors associated with maintaining SVR in 34 patients with chronic HDV who stopped BLV 2 mg ± PEG-IFNα after achieving undetectable HDV RNA levels (mean [SD] duration of

treatment was 17.7 [8.8] months). The SVR rate was 47.1% (16/34) at post-treatment Week 96. Of the 18 patients who experienced a virological relapse, 55.6% (10/18) did so within 12 weeks of stopping treatment. No baseline demographics or clinical characteristics were found to be associated with SVR.[9]

Clinical Data: BLV Treatment Duration and Discontinuation of Therapy

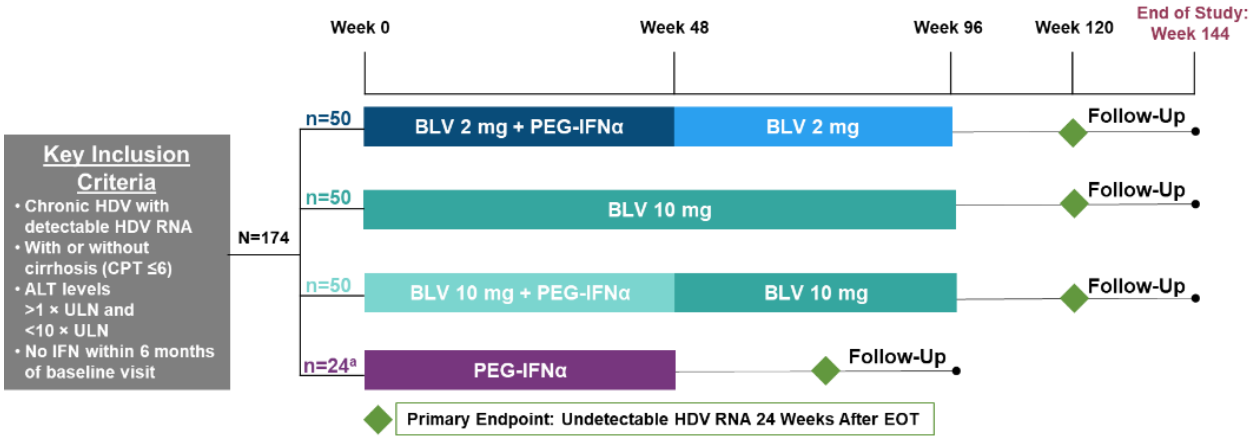
MYR204 Phase 2b Study

Study design and demographics[2]

The MYR204 study was a multicenter, open-label, randomized, phase 2b study conducted in four countries (ie, France, Russia, Romania, and Moldova) that evaluated the safety and efficacy of BLV (10 mg or 2 mg subcutaneously once daily; each dosed for 96 weeks) and PEG-IFNα (180 mcg/week; dosed for 48 weeks) alone and in combination in 174 participants with chronic HDV. Participants were randomly assigned to one of four treatment arms, as shown in Figure 1.

The primary endpoint was defined as undetectable (<LLoQ) HDV RNA 24 weeks after EOT (Week 120), and the primary efficacy analysis assessed the difference in outcomes between the BLV 10 mg + PEG-IFNα arm and the BLV 10 mg monotherapy arm. Additional endpoints evaluated 48 weeks after EOT included undetectable HDV RNA, ALT normalization, the proportion of participants who had a composite response (undetectable HDV RNA and ALT normalization), liver stiffness changes from baseline, and safety.

Figure 1. MYR204: Study Design[2]



[a]One participant withdrew consent and was excluded from the analysis.

Table 1. MYR204: Baseline Demographics and Disease Characteristics[2]

Key Demographics and Characteristics	BLV 2 mg + PEG-IFNα (n=50)	BLV 10 mg (n=50)	BLV 10 mg + PEG-IFNα (n=50)	PEG-IFNα (n=24)
Age, mean (SD), years	41 (9.3)	40 (8.5)	41 (8.6)	41 (8.4)
Male, n (%)	33 (66)	38 (76)	35 (70)	18 (75)

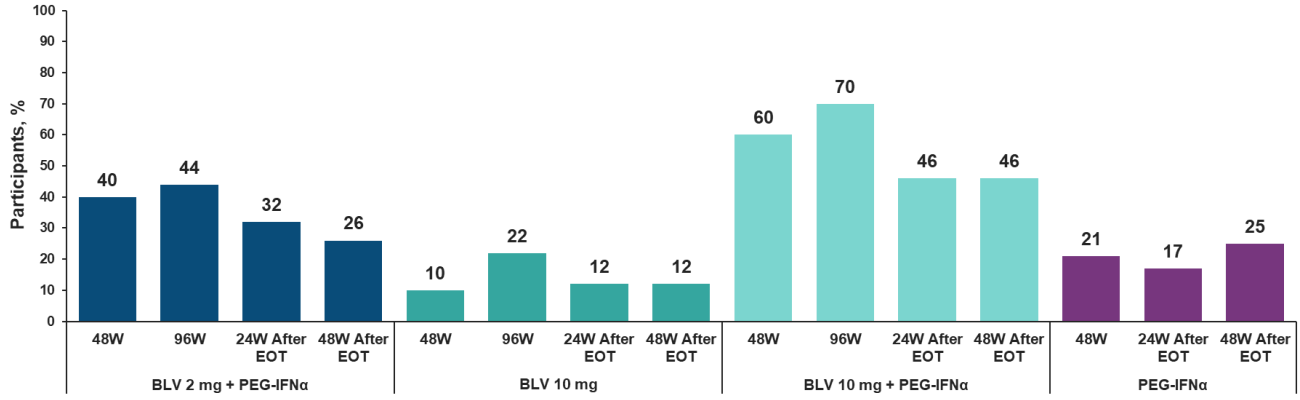
Key Demographics and Characteristics		BLV 2 mg + PEG-IFNα (n=50)	BLV 10 mg (n=50)	BLV 10 mg + PEG-IFNα (n=50)	PEG-IFNα (n=24)
Race,[a] n (%)	White	44 (88)	44 (88)	43 (86)	20 (83)
	Asian	3 (6)	4 (8)	4 (8)	4 (17)
	Black	3 (6)	2 (4)	2 (4)	0
Cirrhosis, n (%)		17 (34)	17 (34)	17 (34)	8 (33)
Liver stiffness, median (IQR), kPa		10.7 (7.8–16.5)	10.8 (8.5–14.1)	10.5 (7.8–14.3)	12.2 (8.6–18.9)
ALT level, median (IQR), U/L		81 (56–143)	90 (63–127)	82 (55–117)	91 (64–152)
HDV RNA, median (IQR), log_{10} IU/mL		5.6 (4.3–6.3)	5.6 (4.6–6.3)	5.5 (4.4–6.1)	5.2 (4.6–5.8)
HDV, GT 1/5/6, n (%)		48 (96)/1 (2)/1 (2)	49 (98)/1 (2)/0	47 (94)/2 (4)/0	24 (100)/0/0
HBsAg, mean (SD), log_{10} IU/mL		3.7 (0.6)	3.7 (0.6)	3.7 (0.7)	3.6 (0.5)
Prior IFN use, n (%)		25 (50)	21 (42)	26 (52)	12 (50)
Concomitant HBV treatment, n (%)		24 (48)	23 (46)	25 (50)	11 (46)

[a]Other race (not specified) in the BLV 10 mg + PEG-IFNα arm (n=1).

Efficacy results: SVR up to Week 48 after stopping treatment

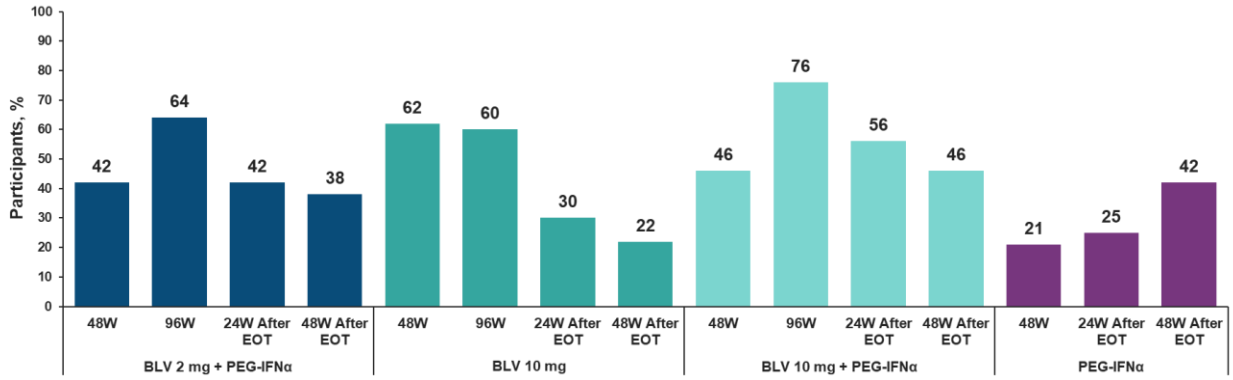
The proportions of participants with undetectable HDV RNA at EOT and through Week 48 after EOT are presented in Figure 2. Participants who had received BLV 10 mg + PEG-IFNα had the highest rates of undetectable HDV RNA after stopping treatment; these rates were maintained at 46% from Weeks 24 to 48. In general, rates of undetectable HDV RNA were maintained in all arms from Weeks 24 to 48 after stopping therapy. At Week 24 after EOT, there were significantly higher rates of undetectable HDV RNA with BLV 10 mg + PEG-IFN than with BLV 10 mg (between-group difference, 34%; 95% CI: 15–50%; *P*<0.001).[2]

Figure 2. MYR204: Rates of Undetectable HDV RNA Through Post-Treatment Week 48 (Missing=Failure Analysis)[2]



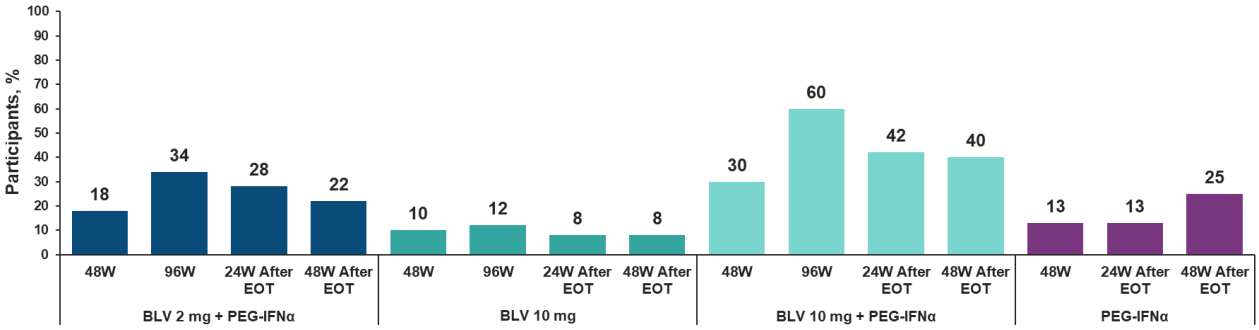
Rates of ALT normalization increased in all treatment arms over time; the highest rates of ALT normalization occurred in the arms that received PEG-IFNα (Figure 3).[2]

Figure 3. MYR204: Rates of ALT Normalization Through 48 Weeks After EOT by Treatment Arm (Missing=Failure Analysis)[2]



The BLV 10 mg + PEG-IFNα arm had higher rates of composite response (undetectable HDV RNA and ALT normalization) than the other arms (Figure 4).[2]

Figure 4. MYR204: Composite Response[a] Rates Through 48 Weeks After EOT (Missing=Failure Analysis)[2]



[a]Composite response was defined as undetectable HDV RNA and ALT normalization.

From baseline through 48 weeks after EOT, BLV was associated with reductions in liver stiffness, with least squares mean changes from baseline of -2.4 kPa in the BLV 2 mg + PEG-IFNα arm, -0.8 kPa in the BLV 10 mg arm, -2.5 kPa in the BLV 10 mg + PEG-IFNα arm, and -0.3 kPa in the PEG-IFNα monotherapy arm.[10]

At 48 weeks after EOT, HBsAg loss was observed with BLV + PEG-IFNα (Table 2).[10]

Table 2. MYR204: HBsAg Changes at 48 Weeks After EOT by Treatment Arm (Missing=Failure Analysis)[2,10]

HBsAg Outcomes	BLV 2 mg + PEG-IFNα (n=50)	BLV 10 mg (n=50)	BLV 10 mg + PEG-IFNα (n=50)	PEG-IFNα (n=24)
HBsAg ≥1 log_{10} IU/mL decrease, n (%)	11 (22)	2 (4)	8 (16)	4 (17)
HBsAg loss, n (%)	5 (10)	1 (2)	2 (4)	0
HBsAg seroconversion, n (%)	4 (8)	0	2 (4)	0
Change from baseline in HBsAg, mean (SD), log_{10} IU/mL	n=34 -1.39 (1.847)	n=44 -0.24 (0.772)	n=43 -0.72 (1.072)	n=17 -0.51 (0.705)

Safety results through Week 144

Overall, on-treatment safety outcomes were similar among the arms that received PEG-IFNα. Few Grade 3 to 4 AEs and no SAEs were related to BLV, and AEs led to discontinuation of study treatment at low rates (Table 3). One death was reported in the BLV 2 mg + PEG-IFNα arm secondary to anaplastic astrocytoma, which was deemed unrelated to study treatment.[2]

Table 3. MYR204: On-Treatment Safety Outcomes[2a]

AEs, n (%)	BLV 2 mg + PEG-IFNα (n=50)	BLV 10 mg (n=50)	BLV 10 mg + PEG-IFNα (n=50)	PEG-IFNα (n=24)
Any AE	49 (98)	42 (84)	50 (100)	22 (92)
Any Grade 3–4 AE related to BLV	2 (4)	0	2 (4)	N/A
Any Grade 3–4 AE related to PEG-IFNα	26 (52)	N/A	26 (52)	13 (54)
Any SAE	3 (6)	2 (4)	8 (16)	3 (12)
Any SAE related to BLV	0	0	0	N/A
Any SAE related to PEG-IFNα	2 (4)	N/A	1 (2)	1 (4)
Any BLV-related AE that led to discontinuation	1 (2)	1 (2)	1 (2)	N/A
Any PEG-IFNα-related AE that led to discontinuation	3 (6)	N/A	2 (4)	1 (4)

[a]Includes any AE reported from the date the trial drug was initiated through 30 days after discontinuation.

Post-treatment safety outcomes are presented in Table 4. One death was reported in the BLV 10 mg + PEG-IFNα arm secondary to esophageal varices hemorrhage. Most ALT/AST elevations were transient and asymptomatic and were associated with HDV RNA rebounds.[2]

Table 4. MYR204: Post-Treatment Safety Outcomes[10]

AEs, n (%)		BLV 2 mg + PEG-IFNα (n=50)	BLV 10 mg (n=50)	BLV 10 mg + PEG-IFNα (n=50)	PEG-IFNα (n=24)
Any AE		28 (56)	34 (68)	29 (58)	19 (79)
Any Grade ≥3		4 (8)	11 (22)	10 (20)	2 (8)
Any SAE		2 (4)	4 (8)	4 (8)	1 (4)
Any SAE related to BLV		1 (2)	1 (2)	1 (2)	N/A
Any hepatic AE		8 (16)	19 (38)	10 (20)	4 (17)
Hepatic AEs occurring in >1 participant	ALT increased	8 (16)	14 (28)	5 (10)	3 (13)
	AST increased	7 (14)	11 (22)	5 (10)	1 (4)
	GGT increased	1 (2)	5 (10)	1 (2)	1 (4)
	Bilirubin increased[a]	0	5 (10)	3 (6)	0
	Jaundice	0	2 (4)	0	0
	Prothrombin level decreased	0	1 (2)	1 (2)	0
	Ascites	0	0	0	1 (4)
	Alkaline phosphatase increased	0	0	0	1 (4)
	HDV	0	0	1 (2)	0
	Hepatic failure[b]	0	0	1 (2)	0

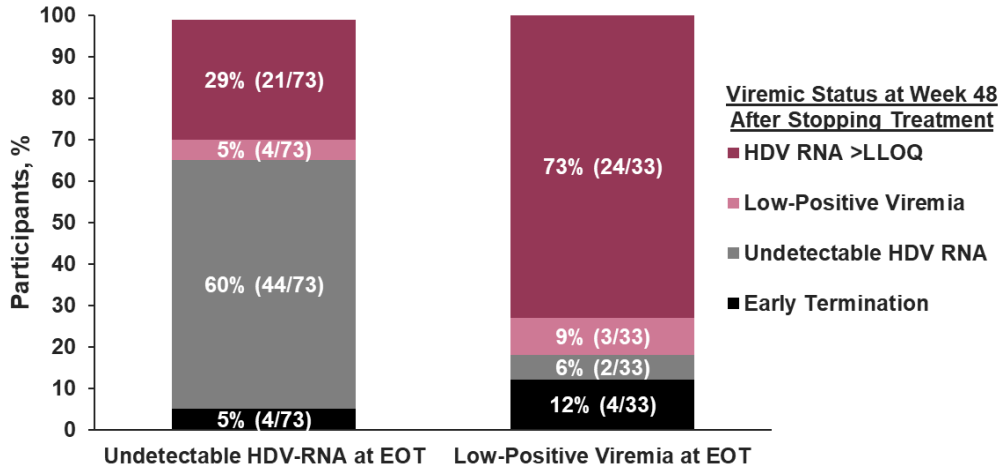
Abbreviation: GGT=γ-glutamyltransferase.
[a]Included the following terms: bilirubin conjugated increased, blood bilirubin increased, hyperbilirubinemia, and urobilinogen urine increased.
[b]Reported as chronic liver insufficiency.

Subanalysis: predictors of post-treatment SVR[4]

An analysis of MYR204 examined HDV RNA levels <LLoQ reported as target not detected (undetectable HDV RNA) and HDV RNA levels <LLoQ reported as target detected (low-positive viremia) at EOT as predictors of SVR up to Week 48 after stopping treatment. Similar to the previous study, participants who had received BLV 10 mg + PEG-IFNα had the highest rates of HDV RNA <LLoQ (which included undetectable and low-positive HDV RNA) at EOT and after stopping treatment, and in general, within each treatment arm, the proportions of participants with HDV RNA levels <LLoQ remained stable from post-treatment Weeks 24 to 48.

Overall, most participants (73%; 24/33) who had low-positive viremia at EOT had experienced viral rebound (HDV RNA ≥LLoQ) 48 weeks after stopping treatment; in contrast, most participants (60%; 44/73) who had undetectable HDV RNA at EOT continued to have undetectable levels at 48 weeks (Figure 5).

Figure 5. MYR204: HDV RNA Status 48 Weeks After Stopping Treatment According to Viremic Status[a] at EOT[4]



[a]Undetectable HDV RNA was defined as an HDV RNA level <LLoQ and target not detected. Low-positive viremia was defined as an HDV RNA level <LLoQ and target detected.

The 2 participants with low-positive viremia at EOT who had undetectable HDV RNA levels at 48 weeks post treatment had both received combination treatment with BLV (2 mg [n=1]) or 10 mg [n=1]) and PEG-IFNα. Approximately half of the participants (15/33; 45%) with low-positive viremia at EOT were receiving BLV 10 mg as monotherapy, and all 15 either experienced viral rebound (n=13) or had low-positive viremia (n=2) at Week 48 post-BLV treatment. Of the 44 participants (60%) with undetectable HDV RNA levels at EOT and at Week 48 post treatment, most (33/44; 75%) had received BLV + PEG-IFNα treatment.

Subanalysis: predictors of post-treatment response[3]

A subanalysis of MYR204 was conducted to identify baseline characteristics or characteristics of viral kinetics during treatment that predicted EOT or post-treatment response in the pooled BLV 2 mg and 10 mg + PEG-IFNα combination treatment arms (n=100). A logistic regression analysis was used to evaluate the association between clinical characteristics and response at EOT and post-treatment Weeks 24 and 48. Viral kinetics were evaluated in a subset of participants (n=51) with undetectable HDV RNA levels at EOT to identify whether any characteristics were associated with maintaining undetectable levels after stopping therapy.

The strongest on-treatment predictors of having undetectable levels of HDV RNA at 48 weeks after EOT included achieving undetectable HDV RNA by treatment Week 24 (OR, 13.5; 95% CI: 4.6–40; *P*<0.0001) or Week 48 (OR, 13.7; 95% CI: 4.2–45; *P*<0.001). Baseline characteristics that were key predictors of undetectable HDV RNA levels 48 weeks after EOT included the following:

- Treatment with BLV 10 mg (vs 2 mg: OR, 2.4; 95% CI: 1.1–5.6; *P*≤0.04)
- Lower HDV RNA levels (<median vs ≥median [median: 5.54 $\log_{10}$ IU/mL]: OR, 5.6; 95% CI: 2.2–14.3; *P*=0.0003)
- Lower liver stiffness measurement values (<11.1 vs ≥11.1 kPa: OR, 2.9; 95% CI: 1.2–7; *P*=0.02).

Among the 51 participants in the combination therapy arms with undetectable HDV RNA levels at EOT, a baseline HDV RNA level below the median (5.09 $\log_{10}$ IU/mL) was a significant predictor of not having a viral relapse 48 weeks after EOT (OR, 4; 95% CI: 1.2–13.9; *P*=0.03). Shorter time to onset of undetectable HDV RNA levels (OR, 0.9; 95% CI: 0.9–0.9; *P*=0.003) and longer duration of undetectable HDV RNA on treatment (OR, 1.01; 95% CI: 1–1.01; *P*=0.0029) were also associated with no viral relapse 48 weeks after stopping BLV among participants with undetectable HDV RNA at EOT. Participants who had undetectable HDV RNA at on-treatment Week 24 had a high likelihood of maintaining undetectable HDV RNA levels at Week 48 (n/N, 23/25; OR, 19.1; 95% CI: 3.6–100.8; *P*=0.0005).

Subanalysis: correlation analysis of intrahepatic and serological response[11]

An analysis of MYR204 examined correlations between changes in intrahepatic and serum parameters, including correlations between intrahepatic and serum HDV RNA levels, though the study was not powered for this analysis. Evaluable paired biopsies (baseline and 24 weeks after EOT) were obtained from 42 participants for evaluation of intrahepatic HDV and HBV RNA and from 50 participants for evaluation of HDAg status.

Intrahepatic HDV RNA levels decreased from baseline to 24 weeks after EOT in all treatment arms. The largest decrease after treatment stopped was observed in the BLV 10 mg + PEG-IFNα arm. Intrahepatic HDV RNA levels at post-treatment Week 24 were <LLoQ in 73% of participants (8/11) in the BLV 10 mg + PEG-IFNα arm (median change: -3.16 $\log_{10}$; *P*≤0.01), 57% (8/14) in the BLV 2 mg + PEG-IFNα arm (median change: -1.99 $\log_{10}$; *P*≤0.05), 8% (1/12) in the BLV 10 mg arm (median change: -0.76 $\log_{10}$), and 60% (2/5) in the PEG-IFNα arm (median change: -1.94 $\log_{10}$).

Similarly, the proportions of HDAg+ cells in the liver decreased from baseline to post-treatment Week 24 in all treatment arms; the largest decrease after treatment stopped was observed in the BLV 10 mg + PEG-IFNα arm. HDAg+ liver cells at post-treatment Week 24 were <LLoQ in 67% of participants (8/11) in the BLV 10 mg + PEG-IFNα arm (median change: -1.85 $\log_{10}$; *P*≤0.05), 44% (8/14) in the BLV 2 mg + PEG-IFNα arm (median change: -0.98 $\log_{10}$; *P*≤0.05), 8% (1/13) in the BLV 10 mg arm (median change: -0.77 $\log_{10}$), and 67% (4/6) in the PEG-IFNα arm (median change: -1.87 $\log_{10}$).

Correlation analyses found a strong relationship (*P*<0.0001) between intrahepatic HDV RNA levels and HDAg+ cell numbers, which suggests that treatment with BLV resulted in fewer HDV-infected cells. Similarly, levels of HDV RNA in the serum were correlated with levels in the liver (*P*=0.0027). Changes in intrahepatic levels of HDV RNA from baseline to post-treatment Week 24 mirrored the changes observed in serum levels (*P*<0.0001);

similarly, changes in intrahepatic HDV RNA levels mirrored the number of HDAg+ cells (*P*<0.0001), which could indicate that BLV treatment decreased the number of HDV-infected cells.

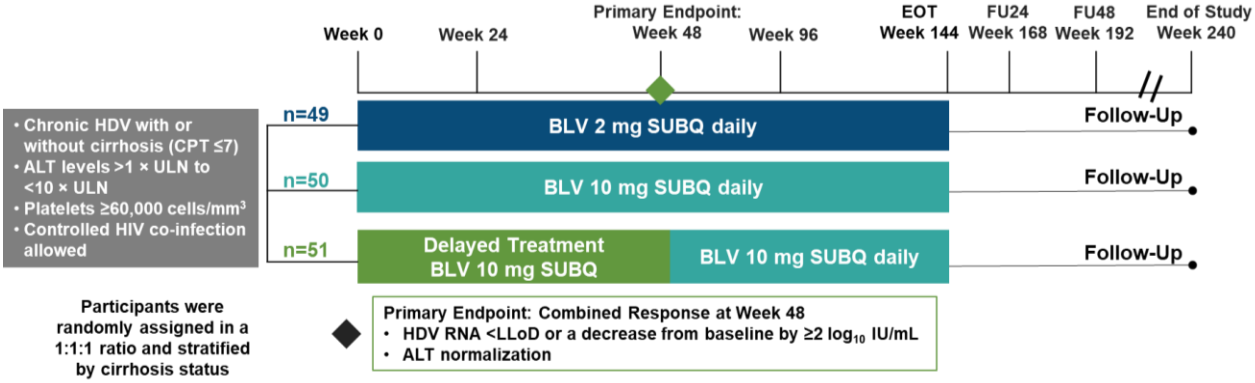
Analyses of intrahepatic HBV RNA did not find significant changes from baseline to post-treatment Week 24 in any of the treatment arms. Among select participants in the BLV 10 mg and 2 mg + PEG-IFNα arms, undetectable HDV RNA levels were observed and were maintained after they stopped treatment, with no reduction in HBsAg.

MYR301 Phase 3 Study

Study design and demographics

MYR301 was an open-label, multicenter, randomized, phase 3 study conducted in four countries (Germany, Italy, Russia, and Sweden) that evaluated the safety and efficacy of BLV 2 mg or 10 mg for 48 weeks compared with delayed treatment in participants with chronic HDV infection (N=150). After 48 weeks, participants in the delayed treatment arm received BLV 10 mg for 96 weeks; all treatment arms were followed after EOT (Figure 6). The primary endpoint was the combined response of undetectable (<LLoD) HDV RNA or a decrease of ≥2 log_{10} IU/mL from baseline and ALT level normalization. Safety and efficacy endpoints were assessed at EOT (Week 144) and at 48 weeks (Week 192) and 96 weeks (Week 240) after EOT.[5]

Figure 6. MYR301: Study Design[5,12]



Abbreviations: FU24/48=follow-up 24/48 weeks after EOT; SUBQ=subcutaneous(ly).
[a]The MYR301 protocol specified the dose as 10 mg per vial; the delivered dose was 8.5 mg.

Approximately half of participants in each treatment arm had cirrhosis at baseline, and demographics and disease characteristics were well balanced across all arms (Table 5).[5]

Table 5. MYR301: Baseline Demographics and Disease Characteristics[5]

Key Demographics and Characteristics		Delayed Treatment BLV 10 mg (n=51[a])	BLV 2 mg (n=49)	BLV 10 mg (n=50)
Age, mean (SD), years		41 (8)	44 (9)	41 (9)
Male, n (%)		26 (51)	30 (61)	30 (60)
Race,[b] n (%)	White	40 (78)	41 (84)	43 (86)
	Asian	11 (22)	8 (16)	6 (12)
Cirrhosis, n (%)		24 (47)	23 (47)	24 (48)
Liver stiffness, mean (SD), kPa		15.3 (9)	14 (8.2)	14.8 (9.3)

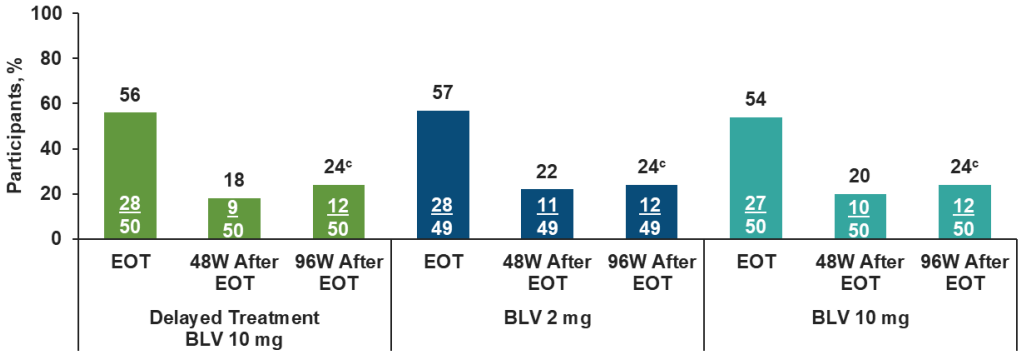
Key Demographics and Characteristics	Delayed Treatment BLV 10 mg (n=51[a])	BLV 2 mg (n=49)	BLV 10 mg (n=50)
ALT level, mean (SD), U/L	102 (62)	108 (63)	123 (81)
HDV RNA, mean (SD), log_{10} IU/mL	5.08 (1.36)	5.1 (1.19)	4.96 (1.46)
HDV GT 1,[c] n (%)	51 (100)	49 (100)	48 (96)
HBsAg, mean (SD), log_{10} IU/mL	3.68 (0.47)	3.67 (0.52)	3.61 (0.59)
HBV DNA, mean (SD), log_{10} IU/mL	0.89 (0.99)	1.31 (1.28)	1.08 (1.26)
HBV GT A/D,[d] n (%)	2 (4)/44 (86)	2 (4)/47 (96)	2 (4)/44 (88)
Previous IFN therapy, n (%)	29 (57)	26 (53)	29 (58)
Concomitant HBV NUC treatment, n (%)	33 (65)	32 (65)	27 (54)
Initiated prior to baseline	30 (59)	27 (55)	25 (50)

[a]One participant from the delayed BLV 10 mg arm withdrew after randomization and before receiving BLV and was not included in efficacy and safety analyses.
[b]Black race in the BLV 10 mg arm (n=1).
[c]In the BLV 10 mg arm: HDV GT 5 (n=1), and missing HDV GT data (n=1).
[d]In the BLV 10 mg arm: no data (n=3), HBV GT E (n=1). In the delayed treatment BLV 10 mg arm: no data (n=3), unclassified HBV GT (n=2).

Efficacy results at EOT and at 48 and 96 weeks after EOT[5]

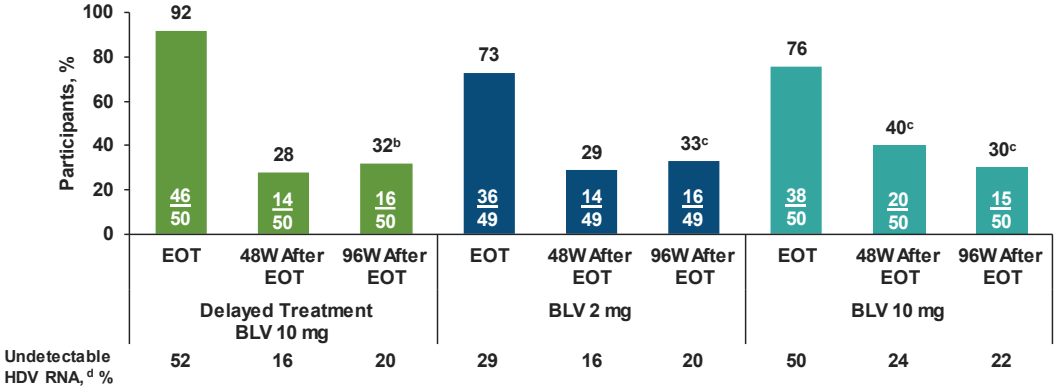
At Week 240 (96 weeks after EOT), response rates across all efficacy outcomes were sustained between 48 and 96 weeks after EOT (Figure 7, Figure 8, Figure 9).

Figure 7. MYR301: Combined Response Rates (Virologic Response[a] and ALT Normalization[b]) at EOT and at 48 and 96 Weeks After EOT[5]



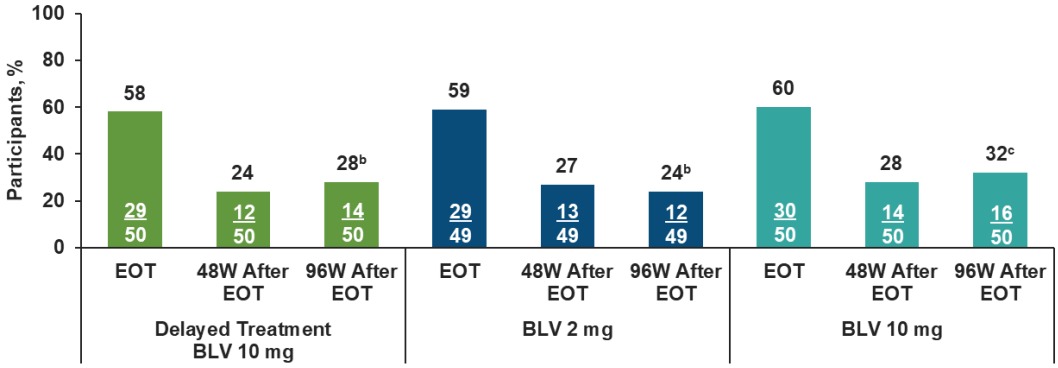
[a]Defined as an undetectable (<LLoD) HDV RNA or a decrease of ≥2 log_{10} IU/mL from baseline.
[b]Defined at Russian sites as ≤31 U/L for females and ≤41 U/L for males; at all other sites, it was defined as ≤34 U/L for females and ≤49 U/L for males.
[c]Included 1 participant who restarted BLV before the visit.

Figure 8. MYR301: Virologic Response[a] at EOT and at 48 and 96 Weeks After EOT[5]



[a]Defined as an undetectable (<LLoD) HDV RNA or a decrease of ≥2 $\log_{10}$ IU/mL from baseline.
[b]Included 2 participants who restarted BLV before the visit.
[c]Included 1 participant who restarted BLV before the visit.
[d]Quantified using RoboGene version 2.0, which has a LLoD of 6 IU/mL.

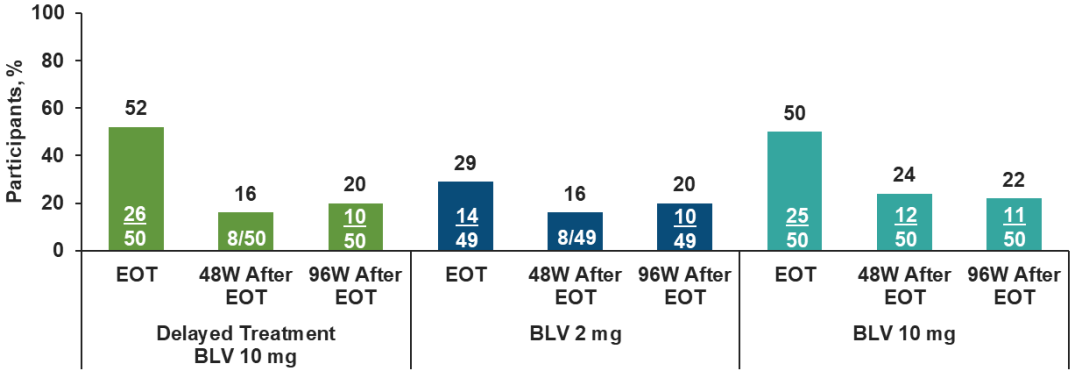
Figure 9. MYR301: ALT Normalization[a] at EOT and at 48 and 96 Weeks After EOT[5]



[a]Defined at Russian sites as ≤31 U/L for females and ≤41 U/L for males; at all other sites, it was defined as ≤34 U/L for females and ≤49 U/L for males.
[b]Included 1 participant who restarted BLV before the visit.
[c]Included 2 participants who restarted BLV before the visit.

At 96 weeks after EOT, 21% of participants overall had undetectable levels of HDV RNA (Figure 8). Across all arms, 65/149 participants (44%) had undetectable levels of HDV RNA at EOT; of those with FU data, 23/64 participants (36%) sustained undetectable levels through 96 weeks after EOT. Across all treatment arms, 90% of participants with ≥96 weeks of continuous undetectable levels of HDV RNA at EOT sustained undetectable levels after EOT. Most relapses (93%) occurred within 24 weeks after EOT, and all relapses occurred within 48 weeks after EOT.

Figure 10. MYR301: Undetectable HDV RNA[a] at EOT and at 48 and 96 Weeks After EOT[5]



[a]Quantified using RoboGene version 2.0, with an LLoD of 6 IU/mL.
Note: Some participants with undetectable levels of HDV RNA at 96 weeks after EOT had low-level viremia or transient virologic relapses during FU.

Predictors of undetectable HDV RNA at EOT and 48 weeks after EOT[6]

An analysis was conducted to evaluate baseline predictors of undetectable levels of HDV RNA at EOT (after 96 or 144 weeks of BLV monotherapy) and to identify predictors of sustained undetectable levels of HDV RNA up to 48 weeks after EOT. A univariate logistic regression analysis showed that being treated with BLV 10 mg or having an HDV RNA or HBsAg level below the median was predictive of undetectable levels of HDV RNA at EOT (Table 6).

Table 6. MYR301: Baseline Predictors of Undetectable Levels of HDV RNA at EOT[6]

Variable	Undetectable at EOT, %	Undetectable at EOT Reference, %	OR (95% CI); *P*-Value
BLV 10 mg (vs BLV 2 mg)	50	28.6	2.5 (1.1–5.7); 0.03
Delayed treatment 10 mg (vs BLV 2 mg)	52	28.6	2.7 (1.2–6.2); 0.02
HDV RNA <5.2 (vs ≥5.2) $\log_{10}$ IU/mL	56.8	30.7	3.2 (1.6–6.5); 0.001
HBsAg <3.8 (vs ≥3.8) $\log_{10}$ IU/mL	52.9	35.1	2.4 (1.2–4.8); 0.02

In participants with undetectable levels of HDV RNA at EOT, predictors of sustained undetectable levels up to 48 weeks after EOT included a baseline HDV RNA <4.6 $\log_{10}$ IU/mL (OR, 8.2; 95% CI: 2.3–29.5; *P*=0.001) and lower levels of HBsAg per $\log_{10}$ IU/mL (OR, 0.3; 95% CI: 0.1–0.8; *P*=0.019).

On-treatment predictors of sustained undetectable levels of HDV RNA up to 48 weeks after EOT included early and long durations of on-treatment undetectable levels of HDV RNA (Table 7).

Table 7. MYR301: On-Treatment Predictors of Sustained Undetectable HDV RNA Levels up to 48 Weeks After EOT[6]

Variable		Sustained Undetectable, %	Sustained Undetectable Reference, %	OR (95% CI); *P*-Value
Continuously undetectable HDV RNA at EOT	≥48 weeks (vs <48 weeks)	62.5	69.4	17.2 (4–75.1); 0.0001
	≥96 weeks (vs <96 weeks)	90	25.9	26.6 (2.7–262.4); <0.005

Variable		Sustained Undetectable, %	Sustained Undetectable Reference, %	OR (95% CI); *P*-Value
Duration of continuous undetectable HDV RNA at EOT per 24 weeks		-	-	2.9 (1.7–4.8); <0.0001
Undetectable HDV RNA (yes vs no)	Week 16	80	32.2	14.5 (1.3–156.9); 0.03
	Week 24	77.8	29.1	10.8 (1.8–64.8); 0.009
	Week 48	70.8	15	33.1 (5.9–186.9); <0.0001
	Week 72	57.1	10.3	20.3 (3.9–107); 0.0004

Safety results at 96 weeks after EOT[5]

During treatment, 1 participant in the delayed BLV 10 mg arm developed nonserious ascites. Between EOT and 96 weeks after EOT, 1 case of ascites was reported in the delayed BLV 10 mg arm, 1 case each of bleeding from varices and hepatocellular carcinoma was reported in the BLV 2 mg arm, and 1 case of hepatic encephalopathy was reported in the BLV 10 mg arm. Post-treatment ALT flares (ALT >10 × ULN) were reported in 6, 5, and 3 participants in the delayed BLV 10 mg, BLV 2 mg, and BLV 10 mg arms, respectively; most occurred early and resolved. Most participants (55–60%) remained in the study through 96 weeks after EOT, and withdrawal of consent was the most common reason for study discontinuation.

Pooled Analyses of MYR204 and MYR301

Rates of undetectable HDV RNA at EOT and at 24 and 48 weeks after EOT[7]

Study design and demographics

A pooled analysis of participants who completed 96 or 144 weeks of BLV 10 mg + PEG-IFNα in MYR204 or BLV 10 mg in MYR301 was conducted to assess whether undetectable levels of HDV RNA or low-level viremia (HDV RNA <50 IU/mL) at EOT affected post-treatment virologic response rates up to 48 weeks after EOT (Table 8).

Table 8. Pooled Analysis of MYR204 and MYR301: Baseline Demographics and Disease Characteristics[7]

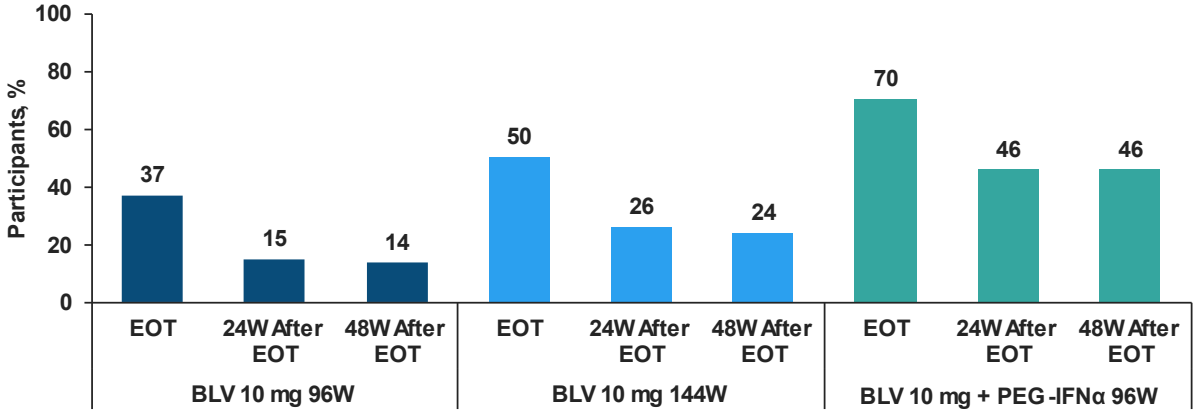
Key Demographics and Characteristics		BLV 10 mg 96W (n=100)	BLV 10 mg 144W (n=50)	BLV 10 mg + PEG-IFNα 96W (n=50)
Age, mean (SD), years		41 (8)	41 (8.5)	41 (8.6)
Male, n (%)		64 (64)	30 (60)	35 (70)
Race,[a] n (%)	White	83 (83)	43 (86)	43 (86)
	Asian	15 (15)	6 (12)	4 (8)
	Black	2 (2)	1 (2)	2 (4)
Cirrhosis, n (%)		41 (41)	24 (48)	17 (34)
Liver stiffness, mean (SD), kPa		14.4 (9.7)	14.8 (9.26)	12.5 (7.6)
ALT, mean (SD), U/L		100 (86.1)	123 (80.6)	113 (98.6)
HDV RNA, mean (SD), $\log_{10}$ IU/mL		5.2 (1.36)	5 (1.46)	5.1 (1.34)
Prior IFN use, n (%)		50 (50)	29 (58)	26 (52)
Concomitant NUC use for HBV, n (%)		55 (55)	27 (54)	25 (50)

[a]Other race (not specified) in the BLV 10 mg + PEG-IFNα arm (n=1).

Results

Treatment with BLV 10 mg + PEG-IFNα or BLV 10 mg for 144 weeks (vs 96 weeks) was associated with higher rates of undetectable HDV RNA at EOT and up to 48 weeks after EOT (Figure 11).

Figure 11. Pooled Analysis of MYR204 and MYR301: Rates of Undetectable HDV RNA at EOT and at 24 and 48 Weeks After EOT[7]



Of the participants with undetectable HDV RNA at EOT, 35% of participants (13/37) in the BLV 10 mg for 96 weeks group, 44% (11/25) in the BLV 10 mg for 144 weeks group, and 60% (21/35) in the BLV 10 mg + PEG-IFNα group maintained undetectable HDV RNA at 48 weeks after EOT; however, of the participants with low-level viremia at EOT, undetectable HDV RNA was observed in 3%, 10%, and 13%, respectively, through 48 weeks after EOT. In participants with either undetectable HDV RNA or low-level viremia at EOT who had detectable levels at 48 weeks after EOT, HDV RNA levels returned to levels similar to those at pretreatment.

From EOT up to 48 weeks after EOT, ALT normalization rates were maintained in participants who had undetectable HDV RNA or low-level viremia at EOT (Table 9).

Table 9. Pooled Analysis of MYR204 and MYR301: ALT Normalization Rates at 48 Weeks After EOT by Virologic Response at EOT[7]

HDV RNA Level at EOT	ALT Normalization, n/N (%)	
	EOT	48W After EOT[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)

[a]Excluded participants who terminated the study early (n=37).

Rates of undetectable HDV RNA at EOT and at 48 and 96 weeks after EOT[8]

Study design and demographics

An additional pooled analysis of data from the MYR204 and MYR301 studies evaluated the durability of virologic response through 48 (Week 192) and 96 weeks (Week 240) after EOT in participants who had undetectable HBV DNA at EOT after they received BLV 2 mg or 10 mg for 96 or 144 weeks, either as monotherapy or combined with PEG-IFNα. Overall, 131 participants with FU data available were included (MYR204: BLV 2 mg + PEG-IFNα,

n=21; BLV 10 mg + PEG-IFNα, n=35; BLV 10 mg, n=11; MYR301: BLV 2 mg, n=13; delayed BLV 10 mg, n=26; BLV 10 mg, n=25). Results were analyzed according to posttreatment outcome: sustained undetectable HDV RNA (n=57; defined as no positive HDV RNA test after EOT); low viremic relapse (n=14; defined as HDV RNA <50 IU/mL after EOT); high viremic relapse (n=60; defined as HDV RNA level of ≥50 IU/mL after EOT).

Baseline demographics and characteristics were generally similar between participants who maintained undetectable rates of HDV RNA after EOT and those who relapsed after EOT (Table 10). Fewer of the participants who had high viremic relapse were male as compared with the proportion of those who had sustained undetectable HDV RNA or low viremic relapse.

Table 10. Pooled Analysis of MYR204 and MYR301: Baseline Demographics and Disease Characteristics by Virologic Response Through FU Week 96[8]

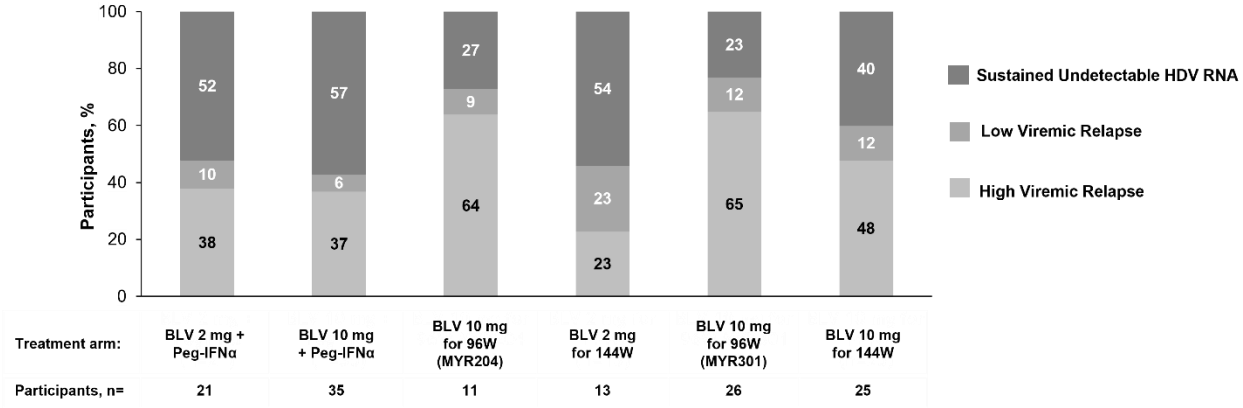
Key Demographics and Characteristics		Sustained Undetectable HDV RNA (n=57)	Low Viremic Relapse (n=14)	High Viremic Relapse (n=60)
Age, mean (SD), years		42.3 (8.9)	42.1 (10.7)	42.4 (7.5)
Male sex, n (%)		40 (70)	10 (71)	29 (48)
Race,[a] n (%)	White	48 (84)	13 (93)	50 (83)
	Asian	5 (9)	1 (7)	10 (17)
Cirrhosis, n (%)		20 (35)	5 (36)	20 (33)
Liver stiffness, mean (SD), kPa		12.2 (7.5)	12.6 (6.8)	13.2 (7.8)
ALT, mean (SD), U/L		106.1 (83.5)	117.1 (81.7)	95.3 (66.0)
HDV RNA, mean (SD), $\log_{10}$ IU/mL		4.2 (1.6)	4.3 (1.6)	5.2 (1.2)
Prior IFN use, n (%)		29 (51)	6 (43)	36 (60)
Concomitant NUC use for HBV, n (%)		30 (53)	7 (50)	33 (55)

[a]Black/African American, n=3 and other race (not specified), n=1 in the undetectable HDV RNA arm.

Results

During the FU period, a higher proportion of participants treated with BLV 2 or 10 mg + PEG-IFNα or BLV 2 or 10 mg as monotherapy for 144 weeks maintained sustained undetectable HDV RNA, compared with higher relapse rates observed after EOT in participants treated with BLV 10 mg for 96 weeks (Figure 12). A small proportion of participants in the overall cohort treated with BLV as monotherapy or BLV + PEG-IFNα progressed to low-level relapse (Figure 12).

Figure 12. Pooled Analysis of MYR204 and MYR301: Durability of Response After EOT by Treatment Arm[8]



ALT levels

Participants with sustained undetectable HDV RNA or low viremic relapse maintained rates of ALT level normalization after EOT through FU Week 48, whereas those with high viremic relapse showed reduced rates of ALT level normalization (Table 11).

Table 11. Pooled Analysis of MYR204 and MYR301: ALT Level Normalization Through 48 Weeks After EOT by Relapse Category[8]

Participants, n/N (%)	EOT	FU Week 4	FU Week 24	FU Week 48
Sustained Undetectable HDV RNA	44/57 (77)	47/57 (82)	48/57 (84)	42/57 (74)
Low Viremic Relapse	9/14 (64)	9/14 (64)	9/14 (64)	11/14 (79)
High Viremic Relapse	43/60 (72)	48/60 (80)	19/60 (32)	17/60 (28)

The mean changes in ALT levels from EOT to FU Week 48 in the sustained undetectable HDV RNA and low viremic relapse subgroups were 11.92 U/L and 7.36 U/L, respectively.

In the high viremic relapse subgroup, mean ALT levels increased from 32 U/L at EOT to 81 U/L at FU Week 24 and remained elevated through 48 weeks after EOT. The mean change in ALT levels from EOT to FU Week 48 was 47.41 U/L.

Liver stiffness

Mean liver stiffness continued to decline after EOT in participants with sustained undetectable HDV RNA or low viremic relapse, whereas an increase was observed in participants who experienced high viremic relapse. The mean changes from EOT to FU Week 48 in the sustained undetectable HDV RNA and low viremic relapse subgroups were -0.56 kPa and -1.46 kPa, respectively, whereas the mean change in liver stiffness was +1.19 kPa in high viremic relapse subgroup.

Real-World Data: BLV Treatment Duration and Discontinuation of Therapy

French Multicenter Cohort Study (BuleDelta)[9]

Study design and baseline characteristics

An analysis of the multicenter French BuleDelta real-world cohort examined the rates of SVR and the factors associated with maintaining SVR (persistently undetectable or unquantifiable HDV RNA) after stopping BLV treatment in patients with chronic HDV. A total of 34 patients who were treated with BLV 2 mg ± PEG-IFNα for a mean (SD) of 17.7 (8.8) months and had undetectable HDV RNA levels upon discontinuing antiviral treatment were included in the analysis.

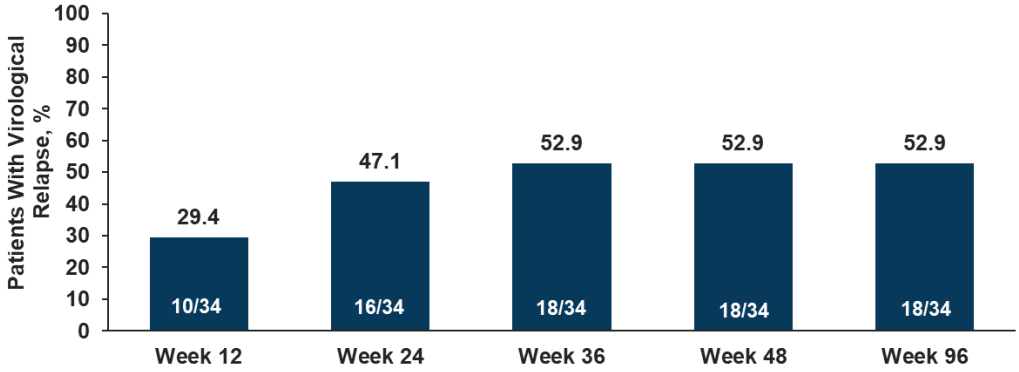
Table 12. BuleDelta Real-World Cohort: Baseline Demographics and Disease Characteristics[9]

Key Demographics and Characteristics		All Patients (n=34)	BLV 2 mg (n=12)	BLV 2 mg + PEG-IFNα (n=22)
Age, mean (SD), years		44.1 (11.4)	42.1 (10.8)	45.1 (11.8)
Male, %		50	75	36.4
Ethnicity, %	Sub-Saharan African	50	41.7	54.5
	European	32.4	50	22.7
	Asian	14.7	8.3	18.2
	Other	2	0	4.5
Cirrhosis, %		76.5	66.7	81.8
FibroScan, mean (SD), kPa		11.9 (7.4)	13.2 (9.9)	11 (5.5)
ALT level, mean (SD), IU/L		91.3 (69.7)	97.5 (89.9)	87.8 (57.4)
HDV RNA, mean (SD), $\log_{10}$ IU/mL		5.8 (1.3)	5.3 (1.5)	5.9 (1.1)
HDV, GT 1/5, %		69.6/30.4	75/25	66.7/33.3
HBsAg at inclusion, mean (SD), $\log_{10}$ IU/mL		10,219 (15,653)	11,000 (18,803)	9772.4 (14,312)
NUC treatment at inclusion, %		97.1	91.7	100
Duration of BLV, mean (SD), months		17.7 (8.8)	18.9 (9.2)	17 (8.7)

Results

At Week 96 of FU, the SVR rate was 47.1% (16/34). The overall virological relapse rate (ie, the proportion of patients with quantifiable HDV RNA) over 96 weeks of post-treatment FU was 52.9% (18/34); relapse rate by week is shown Figure 13.

Figure 13. BuleDelta Real-World Cohort: Proportion of Patients With Virological Relapse Through FU Week 96 After Stopping BLV ± PEG-IFNα[9]



A number of factors (sex, duration of BLV treatment, treatment with PEG-IFNα, baseline HDV RNA level, presence of cirrhosis, normal ALT level at EOT, HBsAg levels at baseline and EOT, time to stopping BLV after initial undetectable HDV RNA, and time to first undetectable HDV RNA after initiation of BLV) were analyzed to determine if any were associated with virological relapse at Week 48 after stopping BLV; of these, only the time to first undetectable HDV RNA was significantly associated with virological relapse (univariate analysis OR, 1.08; 95% CI: 1.01–1.15; *P*=0.0161), but this association was no longer statistically significant upon multivariate analysis.

A comparison of baseline demographics and clinical characteristics (including concomitant antiviral treatment, duration of BLV treatment, HDV RNA level, HDV GT, time between the first unquantifiable HDV RNA and discontinuation of BLV, and time between BLV initiation and first unquantifiable HDV RNA) between patients who experienced early virological relapse (by post-treatment Week 12) and those who experienced virological relapse between Weeks 13 and 36 did not find any significant differences. Similarly, none of these factors were found to be significantly associated with SVR.

Safety data were not reported.

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Abbreviations

AE=adverse event
BLV=bulevirtide-gmod
CPT=Child-Pugh-Turcotte
EOT=end of treatment
FU=follow-up
GT=genotype
HBsAg=hepatitis B surface antigen
HDAg=hepatitis D antigen
IFN=interferon
LLoD=lower limit of detection
LLoQ=lower limit of quantification
NUC=nucleos(t)ide analog
OR=odds ratio
PEG-IFNα=pegylated interferon alpha
Q=quartile
SAE=serious adverse event
SVR=sustained virologic response
ULN=upper limit of normal

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