GILEAD | Medical Information

Hepcludex® (bulevirtide-gmod) Use in Compensated Cirrhosis

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 in patients with compensated cirrhosis.

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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]

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.

No dosage adjustment of BLV is recommended in patients with mild hepatic impairment (Child-Pugh Class A). The safety and efficacy of BLV have not been studied in patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment.

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.

Phase 2 and 3 Clinical Studies of BLV in Participants with Compensated Cirrhosis

BLV data are available from one ongoing phase 3 (MYR301) and three phase 2 studies (MYR202, MYR203, and MYR204) in adult participants with HBV/HDV.

- MYR301: In an interim analysis, rates of combined, virologic, and biochemical response at Week 144 were generally similar between participants with and without cirrhosis at baseline. Higher rates of Grade 3 or 4 AEs were reported for participants with cirrhosis than for those without cirrhosis.[2] Results at Week 240 showed that response rates across all efficacy outcomes were sustained between 48 and 96 weeks after EOT.[3]

- MYR204: Participants with cirrhosis had lower rates of undetectable HDV RNA than did those without cirrhosis through 24 weeks after EOT in each of the treatment arms. No other efficacy endpoints were evaluated according to cirrhosis status.[4]
- Integrated Week 24 efficacy analysis of MYR202, MYR203, and MYR301: The combined response rate in the subgroup of participants with compensated cirrhosis who received BLV 2 mg was similar to that observed in the overall pooled BLV 2 mg arm (37% vs 32%, respectively).[5]
- Integrated Week 48 efficacy analysis of MYR203 and MYR301: In a subgroup analysis by cirrhosis status, BLV treatment was associated with higher combined response rates than with no treatment in patients with and without cirrhosis.[6]
- Integrated Week 24 safety analysis of MYR202, MYR203, MYR204, and MYR301: In a subgroup analysis by cirrhosis status for the BLV 2 mg and 10 mg arms, treatment with BLV was well tolerated, and the safety profile was similar between participants with and without compensated cirrhosis.[7]
- Integrated Week 48 analysis of bile acid levels in MYR203, MYR204, and MYR301: In participants treated with BLV 2 mg and 10 mg, bile acid level increases were not associated with pruritus or other AEs of interest, and the presence of cirrhosis did not affect bile acid levels at baseline or on treatment.[8]

Phase 2 and 3 Clinical Studies of BLV in Participants With Compensated Cirrhosis

MYR301 Study: Week 48 Results

Overall study design

MYR301 was an open-label, multicenter, randomized, phase 3 study that evaluated the safety and efficacy of BLV compared with delayed treatment (BLV 10 mg for 96 weeks beginning at Week 48) in participants with chronic HDV (N=150). Participants were randomly assigned to receive BLV 2 mg, BLV 10 mg, or delayed treatment (no treatment for 48 weeks). At Week 48, participants who received BLV 2 mg or BLV 10 mg continued their current regimen, and those who received no treatment began to receive BLV 10 mg. Treatment with BLV continued up to Week 144, and participants were monitored until Week 240. 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 (Week 48).[9-12]

Interim analysis according to cirrhosis status[2]

Study design and demographics

An interim analysis at Week 144 examined the efficacy and safety of BLV in participants with and without cirrhosis at baseline. The following efficacy and safety endpoints were evaluated according to cirrhosis status: VR (defined as undetectable HDV RNA or a decrease of ≥2 $\log_{10}$ IU/mL from baseline); biochemical response (ALT level normalization; ≤31 and ≤41 U/L for females and males, respectively, in Russian sites and ≤34 and ≤49 U/L in females and males in all other study sites); combined response (VR and ALT normalization); changes in liver stiffness; bile acid levels; and AEs. Overall, 48% of participants (71/149) had compensated cirrhosis at baseline. Other than higher LSMs in

participants with cirrhosis than in those without cirrhosis, baseline characteristics were generally similar between those with and without cirrhosis (Table 1).

Table 1. MYR301 Interim Analysis: Baseline Demographics and Disease Characteristics According to Cirrhosis Status[2]

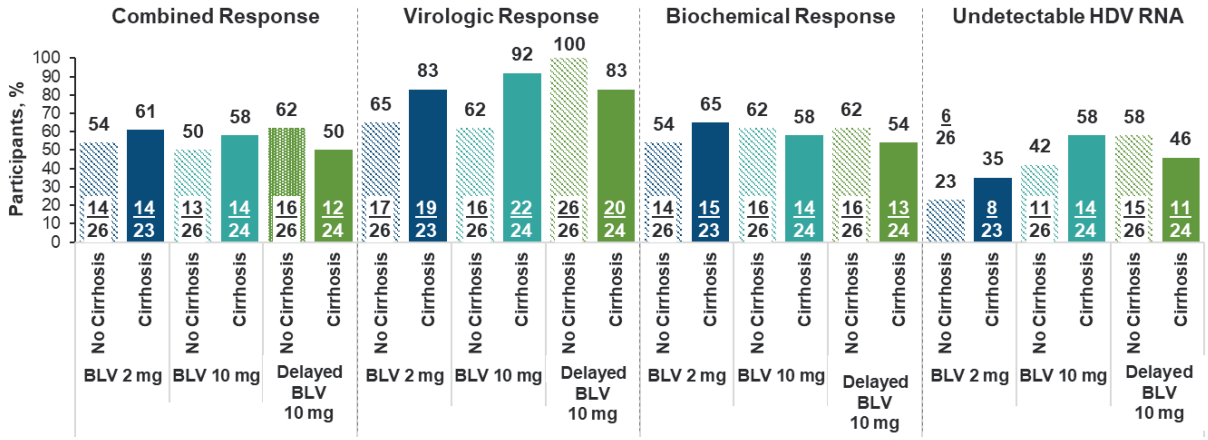
Key Demographics and Characteristics		BLV 2 mg (n=49)		BLV 10 mg (n=50)		Delayed BLV 10 mg (n=50[a])	
		No Cirrhosis (n=26)	Cirrhosis (n=23)	No Cirrhosis (n=26)	Cirrhosis (n=24)	No Cirrhosis (n=26)	Cirrhosis (n=24)
Age, mean (SD), years		42 (9)	45 (10)	41 (8)	42 (9)	41 (7)	43 (8)
Male, n (%)		13 (50)	17 (74)	15 (58)	15 (63)	14 (54)	12 (50)
Race,[b] n (%)	White	21 (81)	20 (87)	23 (88)	20 (83)	18 (69)	21 (88)
	Asian	5 (19)	3 (13)	3 (12)	3 (13)	8 (31)	3 (13)
CPT score, 5/6, n (%)		–	16 (70)/7 (30)	–	17 (71)/7 (29)	–	19 (79)/5 (21)
Liver stiffness, mean (SD), kPa		9.1 (3)	19.5 (8.7)	10.2 (3.9)	19.9 (10.7)	11 (7.2)	21.6 (13.4)
HDV RNA, mean (SD), log_{10} IU/mL		5.5 (0.8)	4.6 (1.4)	5.2 (1.4)	4.8 (1.5)	5.2 (1.4)	4.8 (1.7)
HBV DNA, mean (SD), log_{10} IU/mL		1.5 (1.5)	1.1 (1)	1.2 (1.6)	0.9 (0.7)	1.1 (1.2)	0.6 (0.7)
HBeAg+, n (%)		0	4 (17)	4 (15)	3 (13)	2 (8)	2 (8)
HBsAg, mean (SD), log_{10} IU/mL		3.6 (0.6)	3.7 (0.4)	3.6 (0.7)	3.6 (0.5)	3.8 (0.5)	3.6 (0.7)
ALT level, median (Q1, Q3), U/L		81 (63, 136)	101 (65, 141)	113 (74, 189)	99 (53, 134)	74 (50, 107)	59 (47, 88)
Previous IFN therapy, n (%)		16 (62)	10 (43)	14 (54)	15 (63)	16 (62)	13 (54)
Concomitant HBV NUC treatment, n (%)		13 (50)	19 (83)	12 (46)	15 (63)	14 (54)	18 (75)

[a]One participant discontinued the study before Week 48 and was not included in data after Week 48. Values for age, liver stiffness, HDV RNA, HBsAg, and HBV DNA were reset at the Week 48 visit.
[b]One participant in the BLV 10 mg arm with cirrhosis was Black.

Efficacy

At Week 144, the rates of combined, virologic, and biochemical response were generally similar between those with and without cirrhosis with BLV monotherapy (with 2 mg and 10 mg; Figure 1); therefore, cirrhosis status was not a predictor of efficacy outcomes and was confirmed in a univariate analysis that found no significant difference between cirrhosis status (yes vs no cirrhosis) for any of the efficacy endpoints across treatment groups.

Figure 1. MYR301 Interim Analysis: Efficacy Endpoints at Week 144[2]



Note: Missing values were treated as non-response. Baseline values for the delayed treatment arm were reset to Week 48 values.

Irrespective of cirrhosis status, BLV treatment was associated with decreases from baseline to Week 144 in levels of HDV RNA, ALT, HBsAg, and LSMs (Table 2). Increases from baseline serum bile acid levels occurred in a dose-dependent manner; elevations in serum bile acid levels were asymptomatic and were not impacted by cirrhosis status.

Table 2. MYR301 Interim Analysis: Changes From Baseline to Week 144 in Levels of HDV RNA, ALT, and HBsAg and LSMs[2]

Change[a] From Baseline to Week 144	BLV 2 mg		BLV 10 mg		Delayed BLV 10 mg	
	No Cirrhosis	Cirrhosis	No Cirrhosis	Cirrhosis	No Cirrhosis	Cirrhosis
HDV RNA, $\log_{10}$ IU/mL	-3.3 (n=23)	-3.1 (n=22)	-3.6 (n=22)	-4.1 (n=22)	-4.5 (n=26)	-3.8 (n=22)
ALT, U/L	-46 (n=23)	-57 (n=22)	-82 (n=22))	-62 (n=22)	-37 (n=26)	-24 (n=22)
HBsAg, $\log_{10}$ IU/mL	-0.13 (n=22)	-0.32 (n=21)	-0.19 (n=21)	-0.16 (n=20)	-0.17 (n=26)	-0.22 (n=22)
Liver stiffness, kPa	-1.9 (n=23)	-8.1 (n=22)	-3.3 (n=21)	-4.8 (n=22)	-3.2 (n=26)	-6.3 (n=22)

[a]Mean changes are presented for HDV RNA levels and LSMs; median changes are presented for ALT and HBsAg levels.
Note: Baseline values for the delayed treatment arm were reset to Week 48 values.

Safety

Numerically higher rates of Grade 3 or 4 AEs were reported for participants with cirrhosis than for those without cirrhosis. No BLV-related SAEs or AEs that led to study drug discontinuation occurred. One death due to plasma cell myeloma occurred in the delayed BLV 10 mg arm in a participant with cirrhosis.

Table 3. MYR301 Interim Analysis: Week 144 Safety Summary According to Cirrhosis Status at Baseline[2]

Safety Outcomes, n (%)	BLV 2 mg (n=49)		BLV 10 mg (n=50)		Delayed BLV 10 mg (n=50[a])	
	No Cirrhosis (n=26)	Cirrhosis (n=23)	No Cirrhosis (n=26)	Cirrhosis (n=24)	No Cirrhosis (n=26)	Cirrhosis (n=24)
Any AE	25 (96)	23 (100)	25 (96)	23 (96)	23 (88)	23 (96)
Any Grade ≥3 AE	6 (23)	6 (26)	2 (8)	8 (33)	1 (4)	4 (17)
Any BLV-related AE	14 (54)	13 (57)	18 (69)	19 (79)	13 (50)	10 (42)
Any SAE	1 (4)	2 (9)	3 (12)	3 (13)	2 (8)	1 (4)

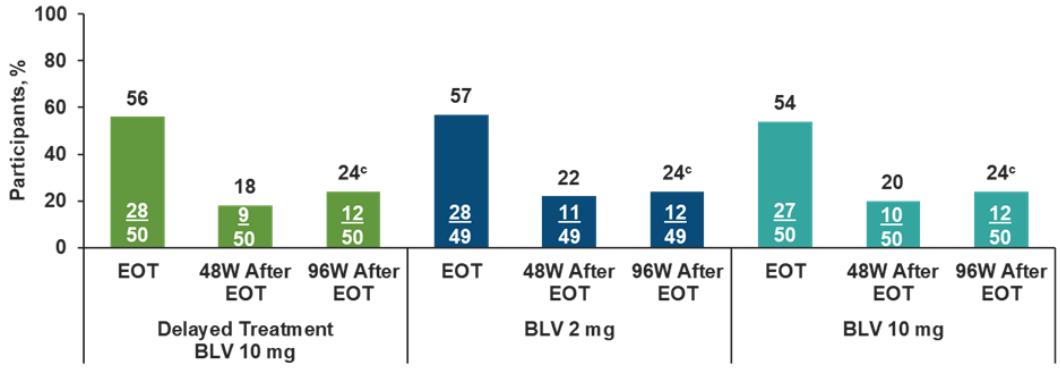
[a]One participant discontinued from the study before Week 48. AEs for this group were recorded once BLV treatment began at Week 48.

Final results at Week 240[3]

Efficacy

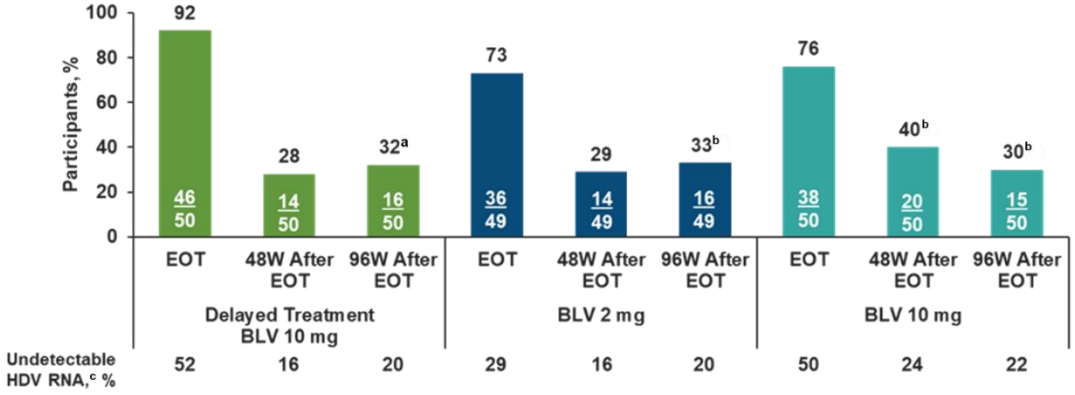
Results at Week 240 showed that response rates across all efficacy outcomes were sustained between 48 and 96 weeks after EOT (Figure 2, Figure 3, and Figure 4).

Figure 2. MYR301: Combined Response Rates at EOT and at 48 and 96 Weeks After EOT[3]



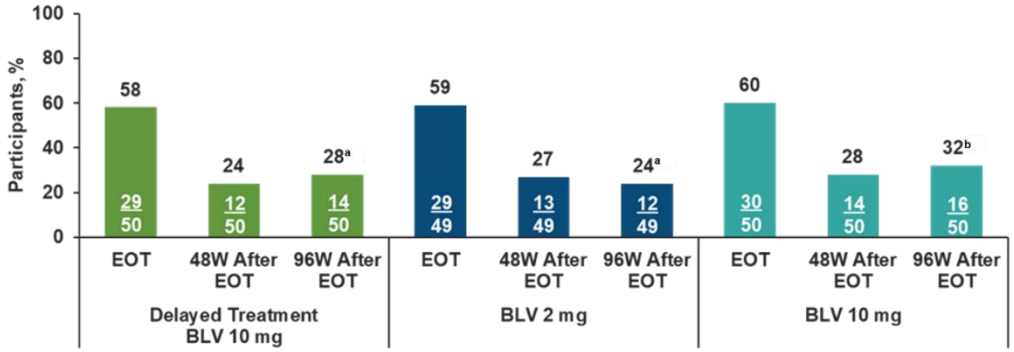
[a]Included 1 participant who restarted BLV before the visit.

Figure 3. MYR301: VR at EOT and at 48 and 96 Weeks After EOT[3]



[a]Included 2 participants who restarted BLV before the visit.
[b]Included 1 participant who restarted BLV before the visit.
[c]Quantified using RoboGene version 2.0, which has an LLoD of 6 IU/mL.

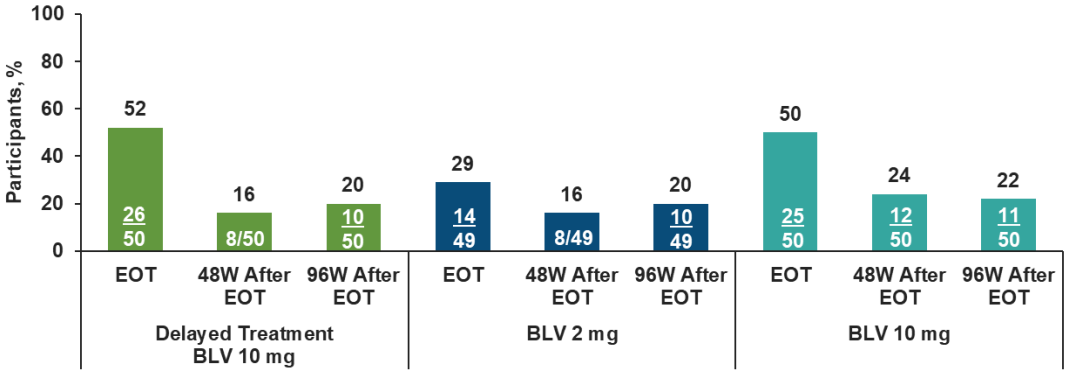
Figure 4. MYR301: ALT Normalization[a] at EOT and at 48 and 96 Weeks After EOT[3]



[a]Included 1 participant who restarted BLV before the visit.
[b]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 5). Across all arms, 65/149 participants (44%) had undetectable levels of HDV RNA at EOT; of those with follow-up data, 23/64 participants (36%) sustained undetectable levels through 96 weeks after EOT. Across all treatment arms, 90% of participants with ≥96 weeks of continuously 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 5. MYR301: Undetectable HDV RNA at EOT and at 48 and 96 Weeks After EOT[3]



Note: Some participants with undetectable levels of HDV RNA at 96 weeks after EOT had low-level viremia or transient virologic relapses during follow-up.

HBsAg loss occurred in 2 participants in the delayed treatment BLV 10 mg arm and in 1 participant each in the BLV 2 mg and BLV 10 mg arms.

Safety

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 HCC 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 flares 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.

MYR204 Study

Study design and demographics[13]

The MYR204 study was a multicenter, open-label, randomized, phase 2b study conducted in four countries (France, Russia, Romania, and Moldova) that evaluated the safety and efficacy of BLV 2 mg or 10 mg for 96 weeks combined with PEG-IFNα for the first 48 weeks as potential finite therapy regimens in 174 participants with chronic HDV. The final follow-up was 48 weeks after EOT at Week 144. The primary endpoint was undetectable 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.

Baseline characteristics were similar among all arms. Across BLV treatment arms, the incidence of cirrhosis was 34%; in the PEG-IFNα arm, 33% of participants had cirrhosis (Table 4). All participants with cirrhosis had CPT Class A cirrhosis (score, 5 or 6).

Table 4. MYR204: Baseline Demographics and Disease Characteristics[13]

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)	40 (8)	41 (9)	41 (8)
Male, n (%)	33 (66)	38 (76)	35 (70)	18 (75)
Race,[a] White/Asian/Black, n (%)	44 (88)/3 (6)/ 3 (6)	44 (88)/4 (8)/ 2 (4)	43 (86)/4 (8)/ 2 (4)	20 (83)/4 (17)/ 0
Cirrhosis, n (%)	17 (34)	17 (34)	17 (34)	8 (33)
Liver stiffness, mean (SD), kPa	12.8 (6.4)	12.7 (6.6)	12.5 (7.6)	15.8 (11.6)
ALT level, mean (SD), U/L	108 (77)	118 (108)	113 (99)	121 (96)
HDV RNA, mean (SD), log_{10} IU/mL	5.3 (1.4)	5.5 (1.1)	5.1 (1.3)	5.2 (1.1)
HDV, GT 1/5/6/no data, n (%)	48 (96)/1 (2)/ 1 (2)/0	49 (98)/1 (2)/ 0/0	47 (94)/2 (4)/ 0/1 (2)	24 (100)/0/ 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 NUC for HBV, n (%)	24 (48)	23 (46)	25 (50)	11 (46)

[a]Other race, n=1 (2%) in the BLV 10 mg + PEG-IFNα arm.

Results through Week 144

At all evaluated timepoints, including the primary endpoint of 24 weeks after EOT (Week 120), rates of undetectable HDV RNA were highest in the BLV 10 mg + PEG-IFNα arm, with response rates at 24 weeks after EOT sustained to 48 weeks after EOT.[13] Participants with cirrhosis had lower rates of undetectable HDV RNA than did those with cirrhosis through 24 weeks after EOT in each of the treatment arms; results for the primary endpoint according to cirrhosis status are shown in Table 5.[4]

Table 5. MYR204: Rates of Undetectable HDV RNA Through 24 Weeks After EOT by Treatment and Cirrhosis Status[4]

n (%); 95% CI	BLV 2 mg + PEG-IFNα (n=50)		BLV 10 mg (n=50)		BLV 10 mg + PEG-IFNα (n=50)		PEG-IFNα (n=24)	
	No Cirrhosis (n=33)	Cirrhosis (n=17)	No Cirrhosis (n=33)	Cirrhosis (n=17)	No Cirrhosis (n=33)	Cirrhosis (n=17)	No Cirrhosis (n=16)	Cirrhosis (n=8)
Undetectable HDV RNA	12 (36); 20–55	4 (24); 7–50	6 (18); 7–36	0; 0–20	17 (52); 34–69	6 (35); 14–62	4 (25); 7–52	0; 0–37

No other efficacy endpoints were evaluated according to cirrhosis status.

Safety results through Week 144

Safety data were not presented according to cirrhosis status. Overall, 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 6).

One death was reported in the BLV 2 mg + PEG-IFNα arm secondary to anaplastic astrocytoma, which was deemed unrelated to study treatment.[13]

Table 6. MYR204: Safety Outcomes[13a]

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

Post-treatment safety outcomes are presented in Table 7. Most ALT/AST elevations were transient and asymptomatic and were associated with HDV RNA rebounds. Death was reported in 1 participant in the BLV 10 mg + PEG-IFNα arm secondary to esophageal varices hemorrhage that was deemed unrelated to study treatment.[13]

Table 7. MYR204: Post-Treatment Safety Outcomes[4]

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

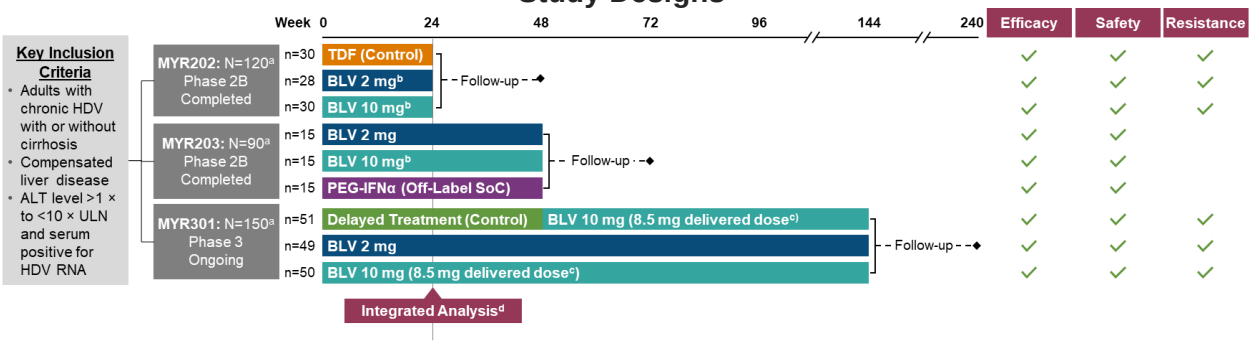
Abbreviation: GGT=γ-glutamyltransferase.
[a]Included the following terms: bilirubin conjugated increased, blood bilirubin increased, hyperbilirubinemia, and urobilinogen urine increased.
[b]Reported as chronic liver insufficiency.

MYR202, MYR203, and MYR301 Studies: Integrated Efficacy Analysis of Week 24 Data[5]

Study design and demographics

An integrated analysis was conducted using Week 24 efficacy data from the two phase 2 MYR202 and MYR203 studies and the phase 3 MYR301 study of BLV for the treatment of participants with chronic HDV. Within this pooled analysis (N=281), the efficacy of BLV monotherapy dosed at 2 mg and 10 mg once daily was evaluated using data from the following study arms: BLV 2 mg, BLV 10 mg, control (the TDF arm from MYR202 and the delayed treatment arm from MYR301), and PEG-IFNα. The primary endpoint was an assessment of combined response at Week 24. Of all participants assessed, 68% were on concomitant therapy with NUC treatment.

Figure 6. Integrated Efficacy Analysis of MYR202, MYR203, and MYR301: Study Designs[5]



Abbreviation: SoC=standard of care.
[a]Total N of participants; only arms pooled for 24-week integrated analyses are shown. Arms that included participants treated with the combination of BLV and PEG-IFNα were not incorporated into the integrated analysis.
[b]Administered with TDF 300 mg.
[c]The MYR301 protocol specified the dose as 10 mg per vial; the delivered dose was 8.5 mg.
[d]Undetectable HDV RNA, defined as <LLoD (14, 10, and 6 IU/mL in MYR202, MYR203, and MYR301, respectively), and ALT normalization, defined at Russian sites as ≤31 U/L for females and ≤41 U/L for males and at all other sites as ≤34 U/L for females and ≤49 U/L for males.

Table 8. Integrated Efficacy Analysis of MYR202, MYR203, and MYR301: Baseline Demographics and Disease Characteristics[5]

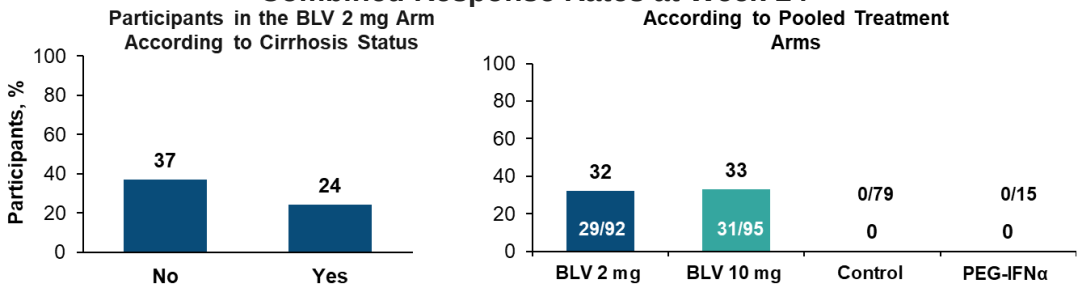
Key Demographics and Characteristics	Control (n=79)	BLV 2 mg (n=92)	BLV 10 mg (n=95)	PEG-IFNα (n=15)
Age, mean (SD), years	40 (8)	42 (9)	40 (9.6)	34 (7)
Male, n (%)	46 (58)	56 (61)	64 (67)	5 (33)
White, n (%)	63 (80)	77 (84)	85 (89)	14 (93)
Compensated cirrhosis, n (%)	37 (47)	41 (45)	40 (42)	4 (27)
HDV RNA, mean (SD), $\log_{10}$ IU/mL	5.2 (1.36)	5.3 (1.27)	5.3 (1.44)	5.2 (1.15)
ALT level, mean (SD), U/L	108 (71.9)	107 (70.7)	115 (77.3)	93 (38.4)
HDV GT, 1/2/5/missing, n (%)	78 (99)/1 (1)/ 0/0	89 (97)/2 (2)/ 0/1 (1)	84 (88)/2 (2)/ 1 (1)/8 (8)	14 (93)/0/ 0/1 (7)
HBV GT, A/C/D/E/missing, n (%)	9 (11)/0/ 61 (77)/–/ 9 (11)	3 (3)/1 (1)/ 72 (78)/0/ 16 (17)	5 (5)/0/ 72 (76)/1 (1)/ 17 (18)	0/0/ 2 (13)/0/ 13 (87)
HBsAg, median (Q1, Q3), $\log_{10}$ IU/mL	3.9 (3.6, 4.1)	4 (3.7, 4.3)	3.9 (3.6, 4.2)	4.1 (4, 4.3)

Key Demographics and Characteristics	Control (n=79)	BLV 2 mg (n=92)	BLV 10 mg (n=95)	PEG-IFNα (n=15)
HBeAg negative, n (%)	74 (94)	79 (86)	85 (89)	14 (93)
HBV DNA, median (Q1, Q3), log_{10} IU/mL	1 (0, 1.6)	1.3 (0, 1.7)	1 (0, 1.5)	0 (0, 1.7)
Previous PEG-IFNα therapy, n (%)	47 (59)	47 (51)	43 (45)	4 (27)

Integrated Week 24 efficacy results

In a subgroup analysis of combined response rates among participants who received BLV 2 mg, a similar treatment benefit was observed, including in those with compensated cirrhosis (Figure 7). The rates of combined response were numerically similar across the BLV arms, whereas no participants in the control or PEG-IFNα arms achieved a combined response (Figure 7).

Figure 7. Integrated Efficacy Analysis of MYR202, MYR203, and MYR301: Combined Response Rates at Week 24[5]

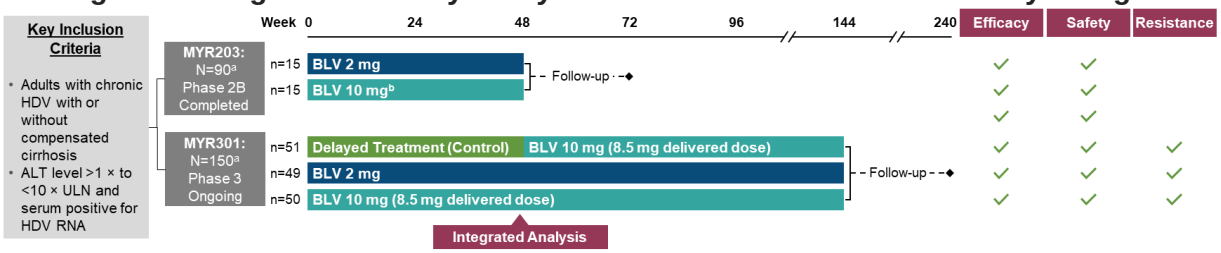


MYR203 and MYR301 Studies: Integrated Efficacy Results Through Week 48[6]

Study design and demographics

An integrated analysis was conducted using Week 48 efficacy data from the phase 2 MYR203 study and phase 3 MYR301 study of BLV for the treatment of participants with chronic HDV. Within this pooled analysis (N=240), the efficacy of BLV monotherapy dosed at 2 mg and 10 mg once daily was evaluated using data from the following study arms: BLV 2 mg, BLV 10 mg, and control (the delayed treatment arm from MYR301). The primary endpoint was an assessment of combined response at Week 48. Of all participants assessed, 48% to 65% were receiving concomitant therapy with NUC treatment. In this analysis population, compensated cirrhosis was present at baseline in 26 participants in the BLV 2 mg arm, 24 participants in the BLV 10 mg arm, and 24 participants in the delayed treatment arm.

Figure 8. Integrated Efficacy Analysis of MYR203 and MYR301: Study Design[6]



[a]Total n participants; only arms pooled for the 48-week integrated analyses are shown. Arms that included participants treated with a combination of BLV and PEG-IFNα were not included in the integrated analysis.
[b]Administered with TDF 300 mg.

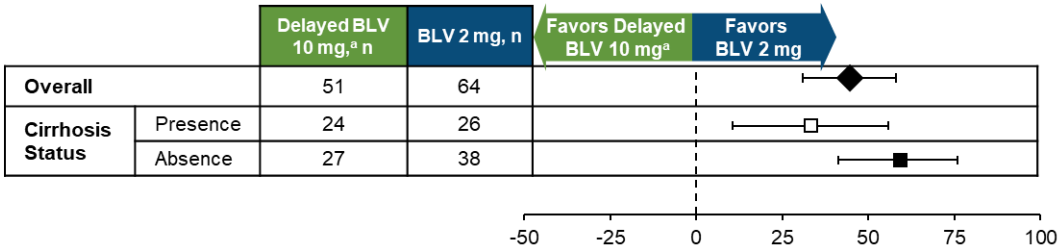
Table 9. Integrated Efficacy Analysis of MYR203 and MYR301: Baseline Demographics and Disease Characteristics[6]

Key Demographics and Characteristics		Delayed BLV 10 mg (n=51)	BLV 2 mg (n=64)	BLV 10 mg (n=65)
Age, mean (SD), years		41 (7.5)	43 (9.1)	40 (8.7)
Male, n (%)		26 (51)	41 (64)	41 (63)
Race, n (%)	White	40 (78)	56 (88)	58 (89)
	Asian	11 (22)	8 (13)	6 (9)
	Black or African American	0	0	1 (2)
Cirrhosis, n (%)		24 (47)	26 (41)	24 (37)
Liver stiffness, mean (SD), kPa		15 (9)	14 (7.8)	14 (8.6)
HDV RNA, mean (SD), $\log_{10}$ IU/mL		5 (1.4)	5 (1.3)	5 (1.6)
ALT level, mean (SD), U/L		102 (61.9)	111 (73.1)	112 (74.4)
HDV GT, 1/5/missing, n (%)		51 (100)/0/0	64 (100)/0/0	60 (92)/1 (2)/4 (6)
HBV GT, A/C/D/E/missing, n (%)		4 (8)/0/39 (77)/ 0/8 (16)	1 (2)/1 (2)/46 (72)/ 0/16 (25)	4 (6)/0/46 (71)/ 1 (2)/14 (22)
HBsAg, median (Q1, Q3), $\log_{10}$ IU/mL		3.7 (3.5, 4)	3.8 (3.5, 4.2)	3.9 (3.5, 4.2)
HBeAg negative, n (%)		47 (92)	57 (89)	58 (89)
HBV DNA, median (Q1, Q3), $\log_{10}$ IU/mL		1 (0, 1.4)	1.3 (0, 1.8)	1.1 (0, 1.6)
Concomitant HBV NUC treatment, n (%)		32 (63)	31 (48)	42 (65)

Integrated Week 48 efficacy results

Rates of combined response at Week 48 in the BLV arms were similar (2 mg, 47% [30/65]; 10 mg, 46% [30/64]) and were greater than that of the delayed treatment arm (2% [1/51]). Across subgroups (age, sex, race, baseline ALT level, baseline HDV RNA, and HBV treatment), BLV treatment was associated with a favorable combined response, including in participants with cirrhosis; Figure 9 shows results for the BLV 2 mg vs delayed treatment arm analysis. Similar results were noted in an analysis of BLV 10 mg vs delayed treatment.

Figure 9. Integrated Efficacy Analysis of MYR203 and MYR301: Combined Response Rates at Week 48 by Subgroups (BLV 2 mg vs Delayed BLV 10 mg Treatment)[6]



[a]The delayed treatment arm in MYR301 did not receive any BLV through Week 48.
Note: One participant in the BLV arm did not have an HDV RNA value at baseline.

Overall, the BLV arms had numerically similar mean reductions in LSMs from baseline to Week 48 (BLV 2 mg, -2.6 kPa [n=57]; BLV 10 mg, -2.8 kPa [n=57]); participants in the delayed treatment arm had a small mean increase in LSMs from baseline to Week 48 (+0.7 kPa [n=45]). No additional analysis was performed according to the presence of cirrhosis.

MYR202, MYR203, MYR204, and MYR301 Studies: Integrated Safety Analysis of Week 24 Data[7]

Study design and demographics

An integrated safety analysis of Week 24 data was performed using data from the MYR202, MYR203, MYR204, and MYR301 studies (N=355). Results from the following study arms were pooled for analysis: BLV 2 mg, BLV 10 mg, control (TDF-only arm from MYR202 and delayed treatment arm from MYR301), and PEG-IFNα. Safety outcomes were graded according to Common Terminology Criteria for AEs version 5.0, and a subgroup analysis of BLV safety according to cirrhosis status was performed.

Table 10. Integrated Safety Analysis of MYR202, MYR203, MYR204, and MYR301: Baseline Demographics and Disease Characteristics[7]

Key Demographics and Characteristics	Control (n=79)	BLV 2 mg (n=92)	BLV 10 mg (n=145)	PEG-IFNα (n=39)
Age, mean (SD), years	40 (8)	42 (9)	40 (9.2)	38 (8.4)
Male, n (%)	46 (58)	56 (61)	102 (70)	23 (59)
White, n (%)	63 (80)	77 (84)	129 (89)	34 (87)
BMI, mean (SD), kg/m^2	25.7 (4.15)	24.9 (3.5)	25.2 (3.72)	25.5 (4.21)
Compensated cirrhosis, n (%)	37 (47)	41 (45)	57 (39)	12 (31)
HDV RNA, mean (SD), $\log_{10}$ IU/mL	5.2 (1.36)	5.3 (1.27)	5.3 (1.33)	5.1 (1.07)
ALT level, mean (SD), U/L	108 (71.9)	107 (70.7)	116 (88.7)	110 (79.9)
HBsAg, mean (Q1, Q3), $\log_{10}$ IU/mL	3.9 (3.6, 4.1)	4 (3.7, 4.3)	3.9 (3.6, 4.1)	3.9 (3.6, 4.1)
HBeAg negative, n (%)	74 (94)	79 (86)	128 (88)	37 (95)
HBV DNA, median (Q1, Q3), $\log_{10}$ IU/mL	1 (0, 1.6)	1.3 (0, 1.7)	1.2 (0, 1.8)	1.3 (0, 1.9)
CrCl, median (Q1, Q3), mL/min	113 (98, 139)	111.8 (97.7, 130.1)	117 (98.5, 132.5)	128.1 (105.2, 137.4)
60 to <90 mL/min, n (%)	14 (18)	18 (20)	20 (14)	4 (10)
Previous IFN therapy, n (%)	47 (59)	47 (51)	64 (44)	16 (41)

Integrated Week 24 safety results

Overall, BLV treatment was well tolerated, and most AEs were mild or moderate in severity. No BLV- or liver-related SAEs were reported in the BLV arms, no AEs led to the discontinuation of BLV, and no deaths occurred through to Week 24 (1 death occurred after Week 24 and was not included in this analysis). The safety profile of BLV was similar in patients with and without compensated cirrhosis (Table 11).

Table 11. Integrated Safety Analysis of MYR202, MYR203, MYR204, and MYR301: Safety Outcomes According to Cirrhosis Status and BLV Dose[7]

Safety Outcomes, n (%)	BLV 2 mg		BLV 10 mg	
	Cirrhosis (n=41)	No Cirrhosis (n=52)	Cirrhosis (n=41)	No Cirrhosis (n=73)
Any AE	25 (61)	37 (73)	44 (77)	48 (66)
SAE	0	0	0	1 (1)[a]
BLV-related AE	16 (39)	29 (57)	36 (63)	36 (49)

[a]Urinary tract infection.

MYR203, MYR204, and MYR301 Studies: Impact of Bile Acid Increases on Week 48 Integrated Safety Data

Study design and demographics

An additional analysis was performed to assess the impact of bile acid increases on Week 48 safety data from the two phase 2 MYR203 and MYR204 studies, and one phase 3 MYR301 study. Results from the following study arms were pooled for analysis: BLV 2 mg (n=64) and BLV 10 mg (n=115). Data from participants in the PEG-IFNα, BLV + PEG-IFNα, and control arms were not included.[8] A literature review was performed to identify AEs associated with bile acid increases due to any cause and identified the following AEs of interest: pruritus, skin disorders and hypersensitivity responses, gallstones and gallbladder disorders, cardiac events, asymptomatic vitamin D decrease, lipids and sex hormone deviations, and osteopenia/osteoporosis. Eosinophilia was also included as an AE of interest due to its association with BLV treatment.[14]

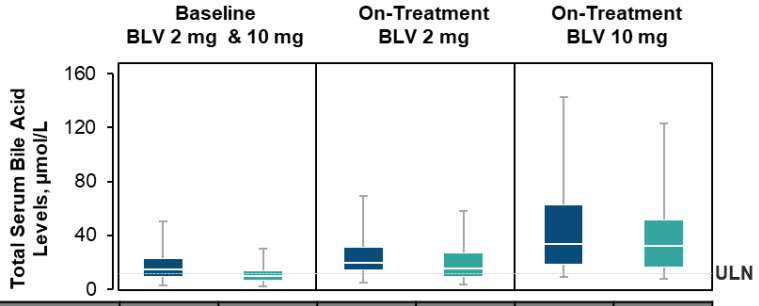
Baseline demographics were similar between the BLV arms. Median (Q1, Q3) baseline bile acid levels in the BLV 2 mg and BLV 10 mg arms were 10.4 (5.8, 16) mcmol/L and 10.2 (7.2, 16.3) mcmol/L, respectively; approximately 52% of participants in each BLV arm had baseline bile acid levels >ULN (10 mcmol/L).[8]

Results

Bile acid levels increased in a dose-dependent manner, intrapatient variability in bile acid levels was observed, and levels decreased upon treatment discontinuation. At Week 48, bile acid levels were ≤ULN in 20.6% and 6.4% of participants in the BLV 2 mg and 10 mg arms, respectively. Bile acid levels were rapidly reversible upon treatment cessation. Bile acid increases were not associated with pruritus or any other AEs of interest. Nearly all episodes of pruritus resolved, and none led to BLV discontinuation.[8]

The presence of cirrhosis did not affect bile acid levels at baseline or on treatment (Figure 10).[14]

Figure 10. Pooled Analysis of MYR203, MYR204, MYR301: Bile Acid Levels at Baseline and On Treatment in Participants With or Without Cirrhosis[14]



Cirrhosis	Yes	No	Yes	No	Yes	No
Participants,[a] n	65	97	25	38	40	59
Observations, n	464	713	193	317	271	396

[a]Fifteen participants who received BLV 10 mg did not have cirrhosis status recorded.

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Abbreviations

AE=adverse event
BLV=bulevirtide-gmod
CPT=Child-Pugh-Turcotte
EOT=end of treatment
GT=genotype
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
IFN(α)=interferon (α)
LLoD=lower limit of detection
LSM=liver stiffness measurement
NUC=nucleo(t)side analog
PEG=pegylated
Q=quartile
SAE=serious adverse event
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
ULN=upper limit of normal
VR=virologic response

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