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Hepcludex® (bulevirtide-gmod) Clinical Studies on Combination Treatment: Studies MYR204, MYR203, and MYR202

This document is in response to your request for information regarding the use of Hepcludex® (bulevirtide-gmod [BLV]) in the phase 2 MYR204, MYR203, and MYR202 clinical studies for the treatment of chronic HDV infection.

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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.

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 Studies: BLV Combination Treatment for Chronic HDV

MYR204, a phase 2 study, evaluated the safety and efficacy of BLV 2 mg or 10 mg SUBQ for 96 weeks combined with PEG-IFNα compared with PEG-IFNα monotherapy for the first 48 weeks in participants with chronic HDV (N=174).[2]

- BLV 10 mg + PEG-IFNα treatment was associated with greater virologic responses than treatment with PEG-IFNα monotherapy at EOT and 48 weeks after EOT.[2]
- Through Week 144, few Grade 3 to 4 AEs and no SAEs were related to BLV, and AEs led to discontinuation of study treatment at low rates.[2]
- In a subanalysis of predictors of post-treatment response, the absence of cirrhosis, lower baseline HDV RNA levels, and lower LSMs were associated with undetectable HDV RNA

levels at EOT. Lower levels of HDV RNA, HBsAg, and LSMs and no prior use of IFN were associated with undetectable HDV RNA levels through post-treatment Week 24.[3]

MYR203, a phase 2 study, evaluated the safety and efficacy of BLV (2, 5, or 10 mg) alone, with or without TDF, or in combination with PEG-IFN-2α in participants with chronic HDV.[4]

- At Week 72 (24 weeks after EOT), virologic response rates were higher among those treated with BLV 2 or 5 mg with PEG-IFNα-2α or BLV 5 mg twice daily + TDF than among those who received BLV or PEG-IFNα-2α monotherapy.[4]
- Through Week 48, most AEs were mild or moderate in severity, and 97% of participants (87/90) experienced ≥1 AE. No deaths or SAEs were reported. Post-treatment (Week 48 to 72), 2 SAEs (anal fistula and proctitis) were reported by 1 participant in the BLV 2 mg + PEG-IFNα-2α arm; neither was related to BLV.[4]

MYR202, a phase 2 study, evaluated the safety, efficacy, and tolerability of 24 weeks of treatment with BLV (2 mg, 5 mg, or 10 mg) in combination with TDF or TDF monotherapy in participants with chronic HDV.[5]

- Virologic response rates, combined response rates, and rates of ALT normalization were significantly higher in the BLV + TDF arms than in the TDF monotherapy arm at Week 24. After discontinuation of BLV at Week 24, HDV RNA and ALT levels rebounded.
- During the treatment period, 2 participants reported 2 SAEs: 1 participant in the 5 mg BLV arm had anemia, which led to discontinuation from the study at Week 16, and 1 participant in the TDF monotherapy arm had decompensation of cirrhosis that was a result of disease progression.

Clinical Studies: BLV Combination Treatment for Chronic HDV

MYR204 Study

Study design and demographics[2]

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 SUBQ 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 (Figure 1).

The primary endpoint was defined as undetectable (<LLOD) 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 plus ALT normalization), LSM changes from baseline, and safety.

Baseline characteristics were similar among all arms (Table 1).

Figure 1. MYR204: Study Design[2]

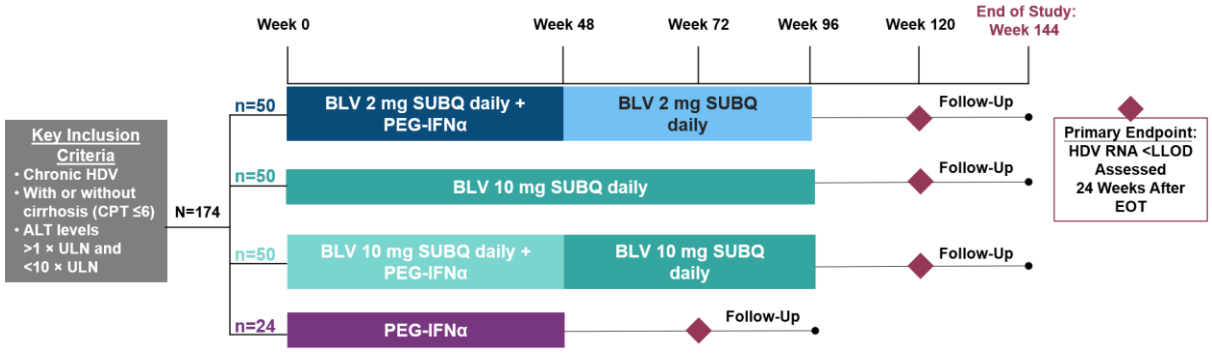


Table 1. MYR204: Baseline Demographics and Disease Characteristics[2]

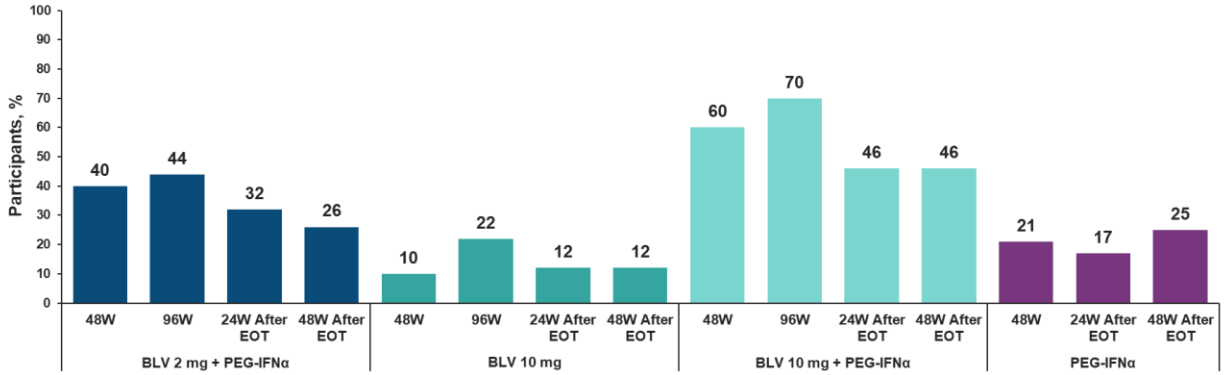
Key Demographics and Characteristics		BLV 2 mg + PEG-IFNα (n=50)	BLV 10 mg (n=50)	BLV 10 mg + PEG-IFNα (n=50)	PEG-IFNα (n=24)
Age, mean (SD), years		41 (9)	40 (8)	41 (9)	41 (8)
Male, n (%)		33 (66)	38 (76)	35 (70)	18 (75)
Race,[a] n (%)	White	44 (88)	44 (88)	43 (86)	20 (83)
	Asian	3 (6)	4 (8)	4 (8)	4 (17)
	Black	3 (6)	2 (4)	2 (4)	0
Cirrhosis, n (%)		17 (34)	17 (34)	17 (34)	8 (33)
LSM, 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)

Abbreviation: NUC=nucleo(t)side analog
[a]Other race, n=1 (2%) in the BLV 10 mg + PEG-IFNα arm.

Results through Week 144

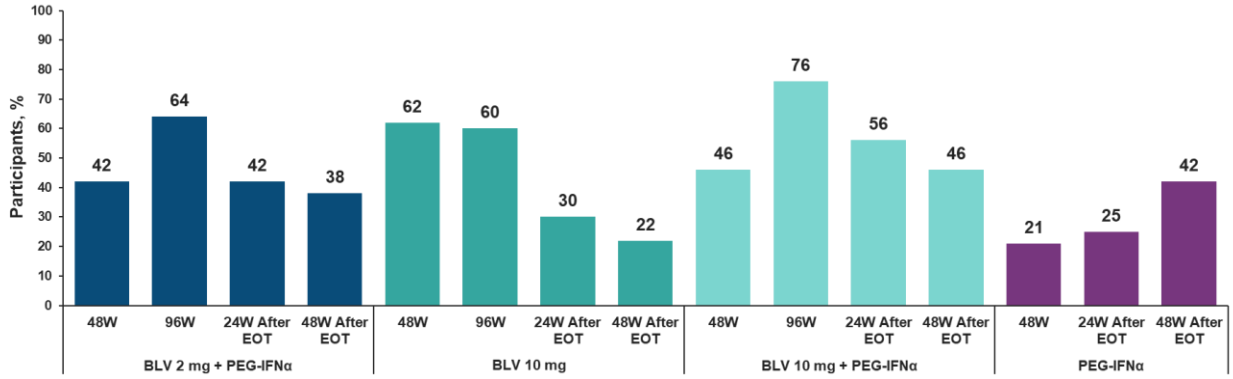
At all evaluated timepoints, including the primary endpoint of 24 weeks after EOT (Week 120), rates of undetectable HDV RNA were highest in the BLV 10 mg + PEG-IFNα arm, with response rates at 24 weeks after EOT sustained to 48 weeks after EOT (Figure 2).[2]

Figure 2. MYR204: Undetectable HDV RNA Through 48 Weeks After EOT (M=F)[2]



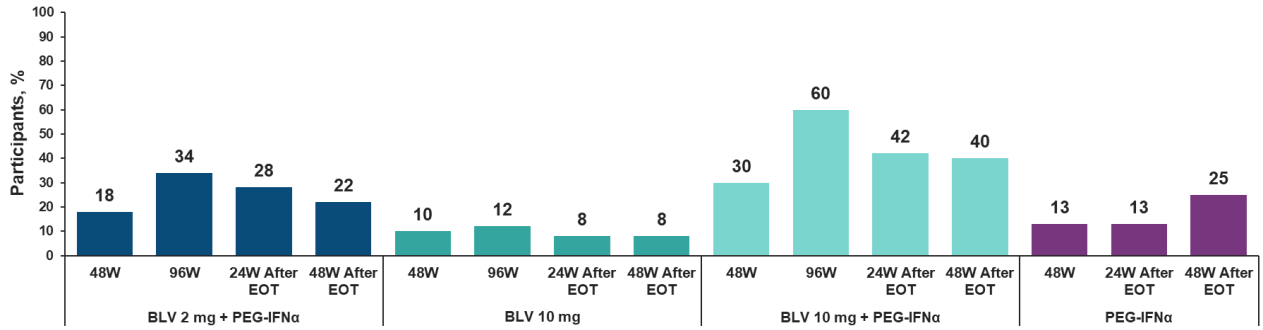
Rates of ALT normalization increased in all treatment arms over time; the highest rates of ALT normalization occurred in the arms that received PEG-IFNα (Figure 3).[2]

Figure 3. MYR204: ALT Normalization Through 48 Weeks After EOT (M=F)[2]



A higher proportion of participants achieved a composite response (undetectable HDV RNA plus ALT normalization) in the BLV 10 mg + PEG-IFNα arm than in the other arms (Figure 4).[2]

Figure 4. MYR 204: Composite Response[a] Rates Through 48 Weeks After EOT (M=F)[2]



[a]Composite response was defined as undetectable HDV RNA plus 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.[6]

At 48 weeks after EOT, HBsAg loss was observed with BLV + PEG-IFNα (Table 2).[6]

Table 2. MYR204: HBsAg Changes at 48 Weeks After EOT (M=F)[2,6]

HBsAg	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$_{log}$ 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, 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: 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]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 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[6]

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

[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 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 Week 24. 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.

In the pooled BLV and PEG-IFN arms, 57% (57/100) achieved undetectable HDV RNA at EOT. Potential baseline characteristics that were significantly associated with undetectable HDV RNA levels at EOT were the absence of cirrhosis (OR, 3.6; 95% CI: 1.4–8.9; *P*≤0.006), lower baseline HDV RNA levels (<median vs ≥median; OR, 2.6; 95% CI: 1.1–5.9; *P*=0.03) and levels <Q3 vs ≥Q3 (OR, 3.8; 95% CI: 1.4–10.26; *P*=0.0086), and lower LSMs (<11.1 kPa vs ≥11.1 kPa; OR, 3.8; 95% CI: 1.57–9.03; *P*=0.0031). Data trends were similar to those in the arm that received BLV 10 mg monotherapy.

In the pooled BLV and PEG-IFN arms, 39% (39/100) achieved undetectable HDV RNA at follow-up Week 24. The following baseline characteristics were significantly associated with undetectable HDV RNA levels 24 weeks after stopping BLV 10 mg or 2 mg:

- Lower HDV RNA levels (<median vs ≥median [median: 5.54 $\log_{10}$ IU/mL]: OR, 4.5; 95% CI: 1.9–11; *P*=0.0008; <Q3 vs ≥Q3 [Q3: 6.19 $\log_{10}$ IU/mL]: OR, 6.5; 95% CI: 1.8–23.6; *P*=0.005);
- Lower HBsAg levels (OR, 0.4; 95% CI: 0.2–0.88; *P*=0.02);
- Lower LSM values (<11.1 vs ≥11.1 kPa: OR, 2.4; 95% CI: 1.03–5.6; *P*=0.04); and
- No history of IFN treatment (OR, 2.4; 95% CI: 1.03–5.5; *P*=0.04).
- BLV dose, presence of cirrhosis, ALT levels, concomitant HBV treatment, and platelet levels were not significant predictors of undetectable HDV RNA 24 weeks after EOT.

Among the 51 participants in the combination therapy arms who achieved undetectable HDV RNA levels at EOT and who had viral kinetics analyzed, lower HDV RNA level was the only baseline characteristic that was a significant predictor of maintaining undetectable HDV RNA 48 weeks after stopping BLV (OR, 4; 95% CI: 1.15–13.9; *P*=0.03). Shorter time to onset of undetectable HDV RNA levels (OR, 0.992; 95% CI: 0.987–0.997; *P*=0.003) and longer duration of undetectable HDV RNA on treatment (OR, 1.006; 95% CI: 1.002–1.01; *P*=0.0029) were associated with non-relapse 48 weeks after stopping BLV among participants who achieved undetectable HDV RNA at EOT. Participants who had undetectable HDV RNA at post-treatment Week 24 had a high likelihood of maintaining undetectable HDV RNA levels at Week 48 (OR, 19.1; 95% CI: 3.62–100.7; *P*=0.0005).

MYR203 Study

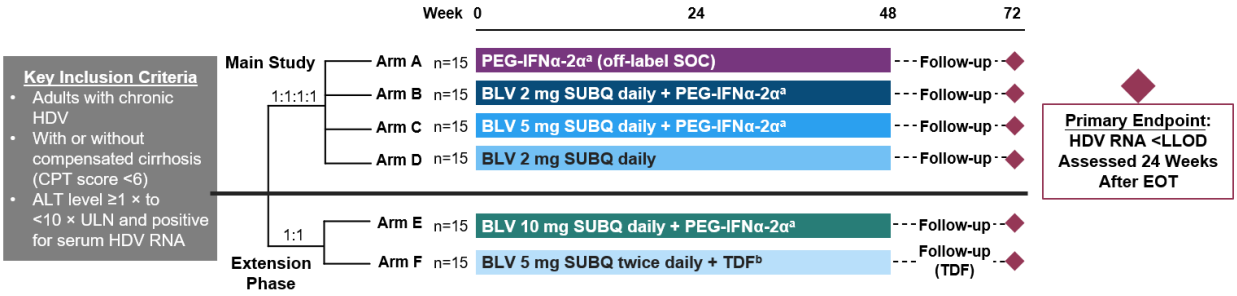
Study design and demographics[4]

The MYR203 study was a multicenter, open-label, randomized, phase 2 study conducted in Russia that evaluated the safety and efficacy of BLV (2, 5, or 10 mg) alone, with or without TDF, or in combination with PEG-IFN-2α in participants with chronic HDV. Enrolled participants were randomly assigned (1:1:1:1) to receive one of four regimens in the main study (Arms A through D) and 1:1 to one of two regimens in the extension phase (Figure 5). After the initial 48-week treatment period, treatment with BLV was stopped, a 24-

week off-treatment period began, and some participants were followed for an additional 24 weeks or received TDF for an additional 24 weeks (study Week 72).

The primary endpoint was the virologic response rate at Week 72 (24 weeks after EOT), defined as the proportion of participants who achieved undetectable HDV RNA (<LLOD [10 IU/mL]). Other endpoints included the following: rates of undetectable HDV RNA levels; rates of ALT normalization; rates of combined response (virologic response and ALT normalization); HBsAg response (loss of HBsAg or >1 log_{10} IU/mL decrease from baseline) and HBV DNA response (undetectable HBV DNA; <LLOQ); and change in LSM per transient elastography.

Figure 5. MYR203: Study Design[4,7]



[a]Administered as 180 mcg SUBQ once weekly.
[b]Administered as TDF 300 mg once daily.

Table 5. MYR203: Baseline Demographics and Disease Characteristics[4]

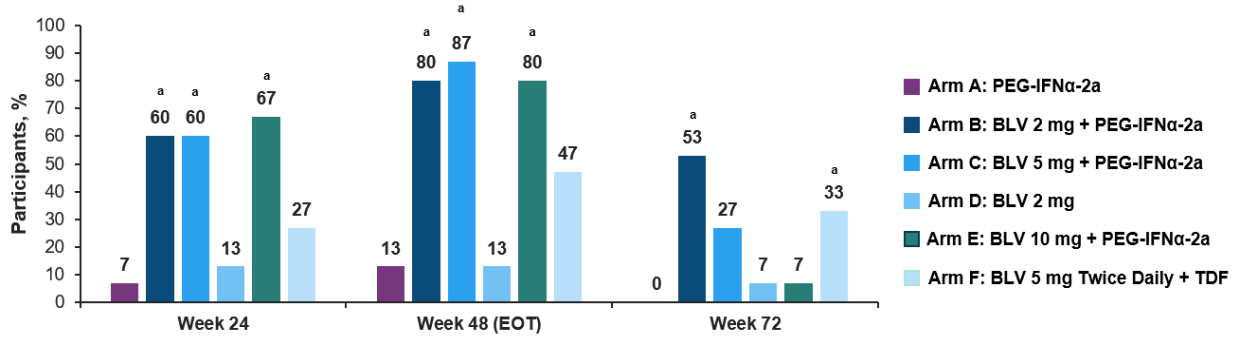
Key Demographics and Characteristics	Arm A: PEG-IFNα-2a (n=15)	Arm B: BLV 2 mg + PEG-IFNα-2a (n=15)	Arm C: BLV 5 mg + PEG-IFNα-2a (n=15)	Arm D: BLV 2 mg (n=15)	Arm E: BLV 10 mg + PEG-IFNα-2a (n=15)	Arm F: BLV 5 mg Twice Daily + TDF (n=15)
Age, median (range), years	35 (20–48)	35 (31–51)	37 (26–52)	39 (26–62)	36 (18–50)	26 (18–46)
Male, n (%)	5 (33)	11 (73)	7 (47)	11 (73)	12 (80)	11 (73)
White, n (%)	14 (93)	15 (100)	15 (100)	15 (100)	14 (93)	15 (100)
Cirrhosis,[a] n (%)	4 (27)	2 (13)	5 (33)	3 (20)	1 (7)	0
LSM, median (Q1, Q3), kPa	10.1 (7.4, 12)	8.9 (6.8, 11.7)	9.5 (7.1, 14.5)	11.8 (10.7, 17.7)	11.8 (7.9, 19)	9.4 (6.7, 11.6)
Prior IFN,[a,b] n (%)	4 (27)	1 (7)	1 (7)	1 (7)	2 (13)	0
HDV RNA, mean (SD), log_{10} IU/mL	5.22 (1.15)	5.13 (1.46)	6.12 (0.94)	5.72 (1.57)	5.89 (1.5)	5.61 (1.89)
HDV GT 1,[c] n (%)	14 (93)	14 (93)	14 (93)	15 (100)	13 (87)	12 (80)
HBV DNA, mean (SD), log_{10} IU/mL	0.97 (1.3)	1.02 (1.19)	2.42 (2.53)	1.72 (1.37)	2.03 (2.16)	1.56 (1.19)
HBV GT, A/C/D/H/missing, %	0/0/13/0/87	0/0/7/0/93	0/0/27/7/67	0/7/13/0/80	0/0/27/0/73	7/0/33/0/60
HBeAg+, n (%)	1 (7)	0	3 (20)	3 (20)	2 (13)	0
HBsAg, mean (SD), log_{10} IU/mL	4.15 (0.28)	3.84 (0.58)	4.36 (0.41)	4.16 (0.41)	4.05 (0.92)[d]	4.02 (1.03)
ALT level, median (Q1, Q3), U/L	90 (55, 123)	70 (51, 107)	79 (67, 189)	84 (69, 153)	78 (60, 109)	73 (66, 96)

[a]Safety analysis set.
[b]Included PEG-IFNα-2a, PEG-IFNα-2b, IFNα-2b, and IFN.
[c]Data were missing from the following arms: Arms A, B, and C, 1 (7%) each; Arm E, 2 (13%); Arm F, 3 (20%).
[d]Data were missing for 1 participant.

Efficacy results

At the Week 72 primary endpoint, BLV 2, 5, and 10 mg SUBQ once daily + PEG-IFNα-2a resulted in virologic response in 53%, 27%, and 7% of participants, respectively; however, no participants who received PEG-IFNα-2a alone and 33% and 7% of those who received BLV 5 mg SUBQ twice daily + TDF and BLV 2 mg SUBQ once daily, respectively, achieved virologic response (Figure 6). Across the study, the treatment difference vs Arm A was significant for those in Arms B (*P*=0.002) and F (*P*=0.042).[4] In a post hoc analysis, adjusted virologic response rates (undetectable HDV RNA or >2 $\log_{10}$ decrease in HDV RNA from baseline) at Week 72 were as follows: Arm A, 0%; Arm B, 73%; Arm C, 47%; Arm D, 33%; Arm E, 33%; Arm F, 47%.[4,7]

Figure 6. MYR203: Virologic Response (Undetectable HDV RNA)[4]



[a]*P*<0.05 vs comparator (Arm A).

During treatment through Week 48, rates of ALT normalization were higher among those treated with BLV alone or with TDF than among those treated other regimens and decreased after treatment stopped; however, in the BLV + PEG-IFNα-2a arms, rates of ALT normalization increased progressively during treatment and were generally maintained after treatment stopped (Figure 7). Combined response rates at Week 72 were significantly higher with BLV 2 mg + PEG-IFNα-2a (Arm B) than with the control (Arm A); rates were low in all other treatment arms (Figure 8).[4]

Figure 7. MYR203: ALT Normalization Through Week 72[4]

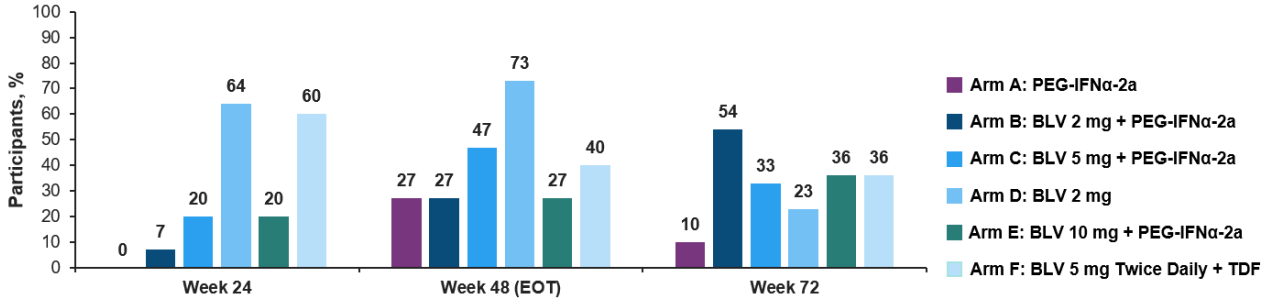
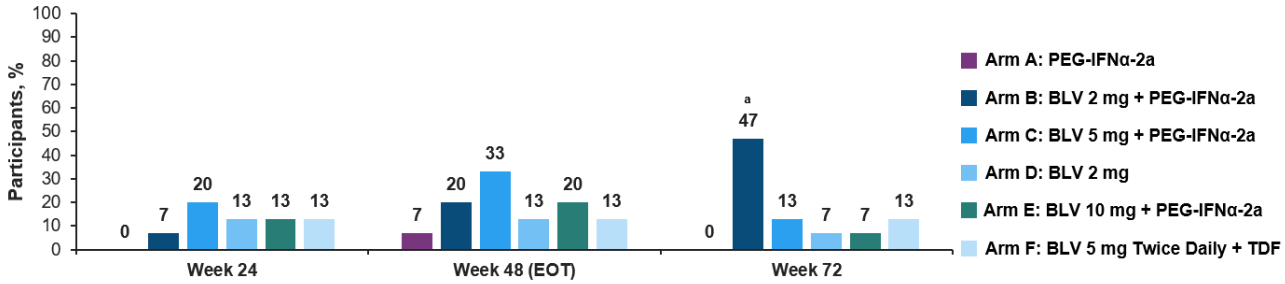


Figure 8. MYR203: Combined Response Through Week 72[4]



[a]*P*=0.006 vs control (Arm A).

Additional secondary endpoints are shown in Table 6. Among the participants with HBsAg response at Week 72, loss of HBsAg was achieved by 4 of the 6 participants in Arm B and 1 of the 2 in Arm E; however, neither of the 2 participants with HBsAg response in Arm C achieved HBsAg loss.[4]

Table 6. MYR203: Additional Secondary Endpoints at Week 72[4,7]

Parameters at Week 72	Arm A: PEG-IFNα-2a (n=15)	Arm B: BLV 2 mg + PEG-IFNα-2a (n=15)	Arm C: BLV 5 mg + PEG-IFNα-2a (n=15)	Arm D: BLV 2 mg (n=15)	Arm E: BLV 10 mg + PEG-IFNα-2a (n=15)	Arm F: BLV 5 mg Twice Daily + TDF (n=15)
HBsAg response, n (%)	0	6 (40)[a]	2 (13)	0	2 (13)	0
HBsAg, mean (SD), log_{10} IU/mL	4.24 (0.23)[b]	1.57 (2.55)[c]	3.71 (1.47)	4.12 (0.39)[d]	3.74 (1.6)[e]	4.09 (0.93)[e]
HBV DNA response, n (%)	5 (33)	10 (67)	6 (40)	6 (40)	4 (27)	7 (47)
LSM, change from baseline, median (Q1, Q3), kPa	-2.7 (-4, 2.3)[f]	1.1 (0.2, 1.4)[d]	-1.7 (-3.4, -0.3)[e]	0.5 (-3.9, 0.6)[g]	1.4 (-2, 3)[e]	-1.4 (-3, -0.1)[e]

[a]*P*<0.05 vs comparator (Arm A). [b]Data were missing from 5 participants. [c]Data were missing from 2 participants. [d]Data were missing from 3 participants. [e]Data were missing from 1 participant. [f]Data were missing from 6 participants. [g]Data were missing from 7 participants.
Note: HBsAg response was defined as a loss of HBsAg or a >1 log_{10} reduction in HBsAg from baseline, and HBV DNA response was defined as HBV DNA <LLOQ.

A subgroup of participants comprised those with paired liver biopsies at baseline and Week 72 for those in Arms A, B, C, and E and at baseline and Week 48 for those in Arms D and F. Between baseline and Week 72, intrahepatic HDV RNA levels and HDAg+ hepatocytes decreased in Arms A, B, C, and E; however, between baseline and Week 48, only levels of HDAg+ hepatocytes decreased in Arms D and F.[4]

Safety[4]

During treatment, most AEs were mild or moderate in severity, and 97% of participants (87/90) experienced ≥1 AE (Table 7). No deaths or SAEs were reported. Dose-dependent elevations in total bile acids were asymptomatic and occurred at a generally similar rate across arms. No AEs led to withdrawal of BLV.

Table 7. MYR203: Safety Summary on Treatment (Baseline Through Week 48)[4]

AEs, n (%)		Arm A: PEG-IFNα-2a (n=15)	Arm B: BLV 2 mg + PEG-IFNα-2a (n=15)	Arm C: BLV 5 mg + PEG-IFNα-2a (n=15)	Arm D: BLV 2 mg (n=15)	Arm E: BLV 10 mg + PEG-IFNα-2a (n=15)	Arm F: BLV 5 mg Twice Daily + TDF (n=15)
Any AE		13 (87)	15 (100)	14 (93)	14 (93)	15 (100)	15 (100)
Any SAE		0	0	0	0	0	0
Any severe or life-threatening AE		7 (47)	11 (73)[a]	10 (67)	1 (7)	9 (60)	3 (20)
AE related to BLV		N/A	10 (67)	10 (67)	9 (60)	12 (80)	15 (100)
AEs related to PEG-IFNα-2a		14 (93)	12 (80)[a]	15 (100)	N/A	15 (100)	N/A
AE that led to withdrawal of PEG-IFNα-2a		1 (7)	1 (7)	3 (20)	N/A	1 (7)	N/A
Most common AEs (n≥5 in any arm)	Thrombocytopenia	8 (53)	11 (73)	7 (47)	3 (20)	12 (80)	5 (33)
	Neutropenia	8 (53)	10 (67)	9 (60)	3 (20)	14 (93)	3 (20)
	Hyperthermia	7 (47)	0	1 (7)	1 (7)	1 (7)	0
	ALT increased	5 (33)	4 (27)	6 (40)	2 (13)	6 (40)	4 (27)
	AST increased	5 (33)	3 (20)	3 (20)	2 (13)	4 (27)	4 (27)
	Total bile acids increased	3 (20)	10 (67)	6 (40)	11 (73)	15 (100)	15 (100)
	GGT increased	3 (20)	4 (27)	3 (20)	1 (7)	7 (47)	0
	Influenza-like illness	1 (7)	9 (60)	8 (53)	0	3 (20)	0

[a]One participant experienced life-threatening neutropenia and thrombocytopenia.

More injection site reactions were reported in Arm F, which required 2 BLV injections per day, than in other arms. Criteria for resistance testing was met for 4 participants (Arm C, n=1; Arm D, n=3); no resistance was noted.

During the post-treatment period from Week 48 to 72, 2 SAEs (anal fistula and proctitis) were reported by 1 participant in Arm B, and neither was related to BLV. Other off-treatment safety results are summarized in Table 8.

Table 8. MYR203: Safety Summary off Treatment (Weeks 48 to 72)[7]

AEs, n (%)		Arm A: PEG-IFNα-2a (n=15)	Arm B: BLV 2 mg + PEG-IFNα-2a (n=15)	Arm C: BLV 5 mg + PEG-IFNα-2a (n=15)	Arm D: BLV 2 mg (n=15)	Arm E: BLV 10 mg + PEG-IFNα-2a (n=15)	Arm F: BLV 5 mg Twice Daily + TDF (n=15)
Any AE		9 (60)	6 (40)	9 (60)	11 (73)	12 (80)	3 (20)
Any SAE		0	1 (7)	0	0	0	0
Any severe or life-threatening AE[a]		4 (27)	2 (13)	1 (7)	2 (13)	3 (20)	0
AE related to BLV		N/A	1 (7)	5 (33)	0	0	0
AEs related to PEG-IFNα-2a		7 (47)	2 (13)	6 (47)	N/A	6 (47)	N/A
Most common AEs (n≥5 in any arm)	Total bile acids increased	5 (33)	1 (7)	4 (27)	1 (7)	0	1 (7)
	ALT increased	2 (13)	2 (13)	3 (20)	6 (40)	6 (40)	1 (7)
	AST increased	2 (13)	2 (13)	3 (20)	6 (40)	6 (40)	1 (7)

[a]No life-threatening AEs occurred during the off-treatment period.

MYR202 Study[5]

Study design and demographics

The MYR202 study was a multicenter, open-label, randomized, phase 2 study conducted in Germany and Russia that evaluated the safety, efficacy, and tolerability of 24 weeks of treatment with BLV (2 mg [n=28], 5 mg [n=32], or 10 mg [n=30] SUBQ once daily) in combination with TDF (245 mg orally once daily; n=28) or TDF monotherapy in participants with chronic HDV.c After the initial 24-week treatment period, treatment with BLV was stopped, and participants continued TDF therapy and were followed for an additional 24 weeks (up to Week 48). The primary endpoint was the virologic response rate at Week 24, defined as the proportion of participants who achieved undetectable HDV RNA (<LLOD of 14 IU/mL) or a ≥2 log IU/mL decline from baseline in HDV RNA levels (mITT population; all participants who received ≥1 dose of study medication). Secondary efficacy endpoints included the durability of HDV RNA response up to Week 48, the combined response rate (ie, virologic response plus ALT normalization) at Weeks 24 and 48, and changes from baseline in HDV RNA levels, ALT levels, and HBsAg at Weeks 24 and 48.

Baseline characteristics and demographics of the 118 participants in the mITT population are summarized in Table 9.

Figure 9. MYR202 Study Design[5]

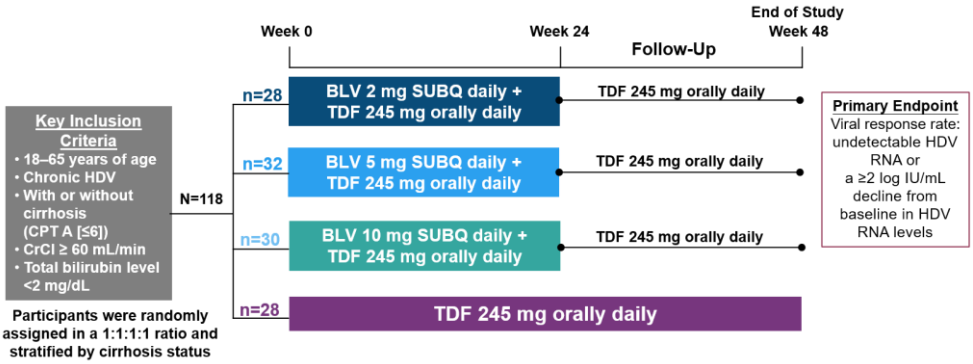


Table 9. MYR202: Baseline Demographics and Disease Characteristics (mITT Population)[5]

Key Demographics and Characteristics		BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)	TDF (n=28)
Age, mean (SD), years		39.4 (8.3)	40.9 (9.5)	41.8 (11.3)	38.5 (8.7)
Male, n (%)		15 (54)	21 (66)	23 (77)	20 (71)
Race, n (%)	White	21 (75)	30 (94)	27 (90)	23 (82)
	Asian	7 (25)	1 (3)	3 (10)	5 (18)
	Black	0	1 (3)	0	0
Cirrhosis, n (%)		15 (54)	15 (47)	16 (53)	13 (46)
FibroScan >14 kPa, n/N (%)		9/19 (47)	13/25 (52)	12/20 (60)	9/18 (50)
HDV RNA, mean (SD), log_{10} IU/mL		5.345 (1.157)	4.874 (1.398)	5.688 (0.983)	5.393 (1.351)
HDV GT 1/2/missing, n (%)		25 (89)/2 (7)/ 1 (4)	28 (88)/0/4 (12)	23 (77)/2 (7)/ 5 (17)	27 (96)/1 (4)/ 0
HBsAg, mean (SD), log_{10} IU/mL		4.104 (0.408)	3.879 (0.736)	3.984 (0.422)	3.970 (0.627)
HBeAg+, n (%)		6 (21)	1 (3)	3 (10)	1 (4)
ALT level, mean (SD), U/L		97.1 (65.2)	123.1 (80.2)	122.7 (84.1)	118.6 (87.6)

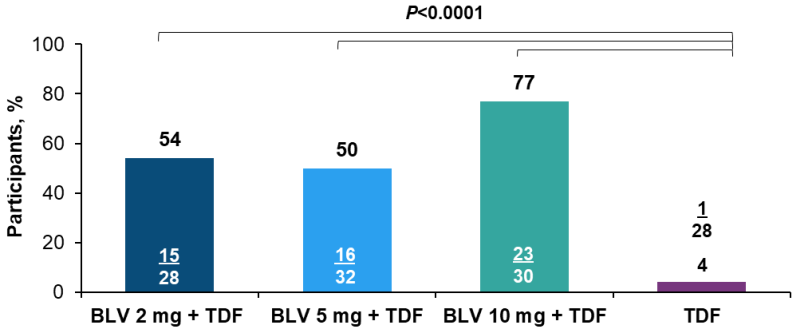
Key Demographics and Characteristics	BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)	TDF (n=28)
Previous therapy with immunostimulant,[a] n (%)	20 (71)	15 (47)	14 (47)	18 (64)

[a]Included treatment with IFNα-2a or 2b, PEG-IFNα-2a or 2b, or covalent PEG-IFNα-2b >30 days before the screening visit.

Efficacy results

At Week 24, virologic response rates in the mITT population were significantly higher in all three BLV arms than in the TDF monotherapy arm (Figure 10). Results were similar in the per protocol population (participants who completed the 24-week treatment period without any major protocol deviations) and in the subgroups of participants with and without cirrhosis.

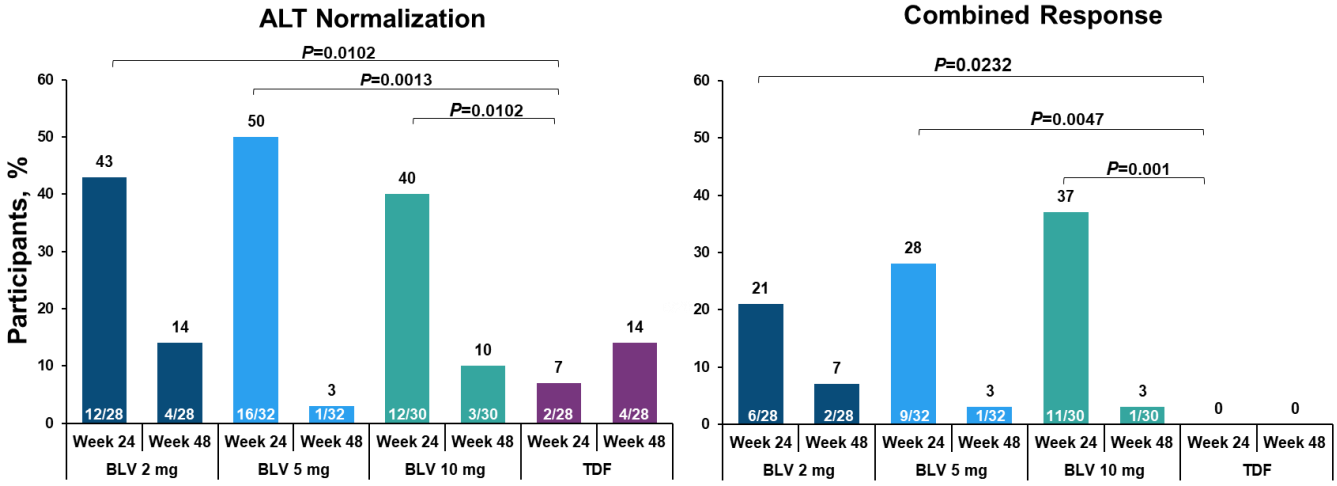
Figure 10. MYR202: Virologic Response Rates[a] at Week 24 (Primary Endpoint; mITT Population)[5]



[a]Decreased HDV RNA ≥2 $\log_{10}$ IU/mL from baseline or undetectable HDV RNA.

At Week 24, a greater proportion of participants in all three BLV arms than in the TDF monotherapy arm had achieved combined responses and ALT normalization (Figure 11), and declines in HDV RNA levels were significantly greater in the BLV arms (Table 10). After discontinuation of BLV at Week 24, HDV RNA and ALT levels rebounded during the 24-week follow-up period (Table 10).

Figure 11. MYR202: Rates of ALT Normalization and Combined Response[a] at Weeks 24 and 48 (mITT Population)[5]



[a]Decreased HDV RNA ≥2 $\log_{10}$ IU/mL from baseline or undetectable HDV RNA and ALT normalization.

Table 10. MYR202: Secondary Efficacy Endpoints at Weeks 24 and 48 (mITT Population)[5]

Endpoints		BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)	TDF (n=28)
Week 24 (EOT)	Undetectable HDV RNA, n (%)	1 (4)	2 (6)	1 (3)	0
	Decreased HDV RNA ≥2 log_{10} IU/mL from baseline, n (%)	14 (50)	14 (44)	22 (73)	1 (4)
	Change in HDV RNA from baseline, median (IQR), log_{10} IU/mL[a]	-2.14 (-2.716 to -1.208)	-2.021 (-2.511 to -0.859)	-2.702 (-3.009 to -2.282)	-0.176 (-0.456 to 0.137)
	P-value vs TDF	<0.0001	<0.0001	<0.0001	-
	Change in ALT from baseline, mean (SD), U/L	-49.6 (58.7)	-79.4 (84.2)	-78.9 (81.1)	-29.2 (61.4)
	Adjusted *P*-value vs TDF	0.1642	0.0428	0.0428	-
	Change in HBsAg from baseline, mean (SD), log_{10} IU/mL[b]	-0.048 (0.392)	0.003 (0.175)	0.034 (0.106)	0.025 (0.239)
	Adjusted *P*-value vs TDF	0.5984	0.7529	0.3305	-
Week 48 (end of follow-up)	Undetectable HDV RNA, n (%)	1 (4)	1 (3)	0	0
	Decreased HDV RNA ≥2 log_{10} IU/mL from baseline, n (%)	1 (4)	2 (6)	3 (10)	0
	Change in HDV RNA from Week 24, median (IQR), log_{10} IU/mL[c]	1.923 (0.566–2.485)	1.732 (0.469–2.568)	2.03 (1.262–2.903)	0.29 (0.037–0.591)
	Change in ALT from EOT, mean (SD), U/L	48 (75.2)	62.7 (88.8)	80.3 (95.3)	2.9 (61.9)
	Change in HBsAg from baseline, mean (SD), log_{10} IU/mL[d]	-0.138 (0.288)	-0.162 (0.412)	-0.134 (0.175)	-0.070 (0.186)
	Adjusted *P*-value vs TDF	1	1	1	-

[a]BLV 2 mg, n=27; BLV 10 mg, n=29.
[b]BLV 2 mg, n=27; BLV 5 mg, n=30; BLV 10 mg, n=28; TDF, n=25.
[c]BLV 5 mg, n=30; BLV 10 mg, n=29; TDF, n=25.
[d]BLV 2 mg, n=27; BLV 5 mg, n=29; BLV 10 mg, n=28; TDF, n=24.

Safety results

A summary of AEs is provided in Table 11. Up to Week 24 (during the treatment period), the most common AEs overall were total bile acid increase (35%) and thrombocytopenia (11%). After discontinuation of BLV, the most common AEs were ALT increase (20%) and AST increase (18%). Dose-dependent elevations (>10 mcmol/L) in bile acid levels by 64% in the 2 mg BLV arm, 75% in the 5 mg BLV arm, and 87% in 10 mg BLV arm were observed; increases were not associated with any specific clinical symptoms, and levels returned to baseline values shortly after discontinuation of BLV. No AEs that led to death occurred during the study. During the treatment period, 2 participants reported 2 SAEs: 1 participant in the 5 mg BLV arm had anemia, which led to discontinuation from the study at Week 16, and 1 participant in the TDF monotherapy arm had decompensation of cirrhosis that was a result of disease progression.

Table 11. MYR202: Safety Outcomes[5]

AEs, n (%)		BLV 2 mg + TDF (n=28)	BLV 5 mg + TDF (n=32)	BLV 10 mg + TDF (n=30)	TDF (n=28)
Any AE		18 (64)	21 (66)	23 (77)	14 (50)
Any AE possibly related to BLV		12 (43)	17 (53)	22 (73)	0
Any AE that led to discontinuation of study drug		0	1 (3)	0	1 (4)
Any SAE		0	3 (9)	2 (7)	1 (4)
Most common AEs (>15% in any arm)	Total bile acids increased	8 (29)	12 (38)	15 (50)	6 (21)
	ALT increased	4 (14)	7 (22)	9 (30)	4 (14)
	AST increased	3 (11)	7 (22)	8 (27)	3 (11)
	Thrombocytopenia	3 (11)	5 (16)	2 (7)	3 (11)
	Fatigue	1 (4)	2 (6)	5 (17)	2 (7)

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7. Lampertico P, Bogomolov PO, Chulanov V, et al. Phase 2 Randomised Study of Bulevirtide as Monotherapy or Combined With Peg-IFNalpha-2a as Treatment for Chronic Hepatitis Delta [Supplement]. *Liver Int.* 2025;45(2):e70008.

Abbreviations

AE=adverse event
BLV=bulevirtide-gmod
CPT=Child-Pugh-Turcotte
EOT=end of treatment
GGT=γ-glutamyltransferase
GT=genotype
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HDAg=hepatitis D antigen
IFN=interferon
LLOD=lower limit of detection
LSM=liver stiffness measurement
M=F=missing=failure
mITT=modified ITT
OR=odds ratio
PEG=pegylated
Q=quartile
SAE=serious adverse event
SUBQ=subcutaneous(ly)
TDF=tenofovir disoproxil fumarate
ULN=upper limit of normal

Product Label

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