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Hepcludex® (bulevirtide-gmod) Additional Clinical Studies on Monotherapy Treatment: Integrated Analyses

This document is in response to your request for information regarding the use of Hepcludex® (bulevirtide-gmod [BLV]) as monotherapy for the treatment of chronic HDV infection in integrated analyses and includes data from phase 2 and 3 clinical studies (MYR301, MYR202, MYR203, and MYR204).

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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 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.

Additional Clinical Studies on BLV Monotherapy: Integrated Analyses in Chronic HDV

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

- Integrated Week 24 efficacy analysis of MYR202, MYR203, and MYR301: Relative to the control and PEG-IFNα arms, treatment with BLV was associated with higher rates of virologic response and/or ALT normalization. Participants who received BLV 2 mg or 10 mg had greater rates of ALT normalization than those who received control or

PEG-IFNα (51% [47/92] and 42% [40/95] for BLV 2 mg and 10 mg, respectively, vs 6% [5/79] and 0% [0/15] for control and PEG-IFNα, respectively).[2]

- Pooled Week 48 efficacy analysis of MYR203, MYR204, and MYR301 according to concomitant NUC use: Virologic response, ALT normalization, and combined response rates were generally similar with BLV treatment with or without concomitant NUC therapy.[3]
- Integrated Week 48 efficacy analysis of MYR203 and MYR301: Rates of virologic response and ALT normalization were greater in the BLV arms than in the control (no-treatment) arm. Combined response rates were numerically similar between BLV arms (2 mg, 47%; 10 mg, 46%), and a consistent treatment benefit with BLV was observed across subgroups, including those with cirrhosis.[4]
- Integrated Week 24 safety analysis of MYR202, MYR203, MYR204, and MYR301: Fewer Grade 3 or 4 AEs and laboratory abnormalities were observed in the pooled BLV 2 mg and 10 mg monotherapy arms than in the PEG-IFNα arm. Relative to BLV 10 mg, BLV 2 mg was associated with fewer ISRs and increases in asymptomatic bile acid levels.[5]
- Integrated Week 48 safety analysis of MYR203, MYR204, and MYR301: Most AEs were Grade 1 or 2 in severity. No SAEs or discontinuations due to study drug were reported in the BLV arms. 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 were similar between those with and those without pruritus. No SAEs of pruritus were observed, and no participants discontinued BLV due to pruritus.[6]
- Intrahepatic HDV and HBV results: Results from a pooled substudy of liver biopsies from MYR202, MYR203, and MYR301, and an MYR301 subanalysis, and an MYR204 subanalysis are summarized in the body of this document.[7,8]

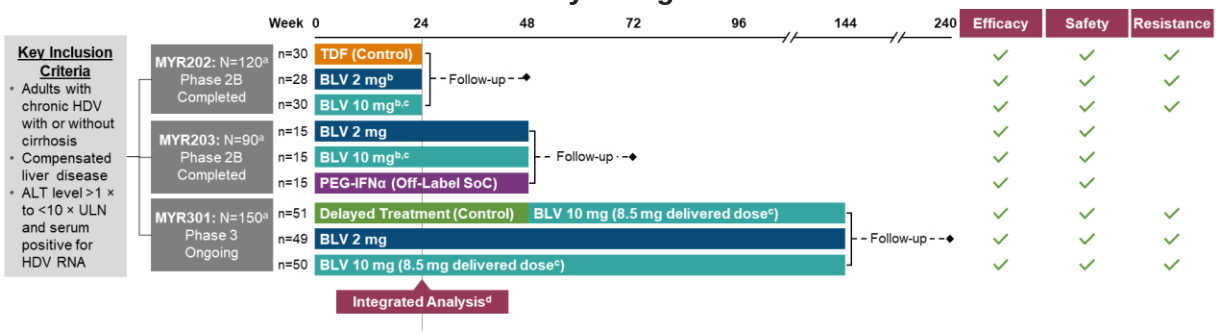
Additional Clinical Studies on BLV Monotherapy: Integrated Analyses in Chronic HDV

MYR202, MYR203, and MYR301 Studies: Integrated Efficacy Analysis of Week 24 Data[2]

Study design and demographics

An integrated analysis of Week 24 efficacy data from the two phase 2 MYR202 and MYR203 studies and one phase 3 MYR301 study of BLV for the treatment of participants with chronic HDV was performed. Within this pooled analysis (N=281), the efficacy of BLV monotherapy dosed at 2 mg and 10 mg SUBQ 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 (defined as undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization) at Week 24. Of all participants assessed, 68% were on concomitant therapy with NUC treatment.

Figure 1. Integrated Efficacy Analysis of MYR202, MYR203, and MYR301: Study Designs[2]



[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 protocol specified the dose as 10 mg; 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 1. Integrated Efficacy Analysis of MYR202, MYR203, and MYR301: Baseline Demographics and Disease Characteristics[2]

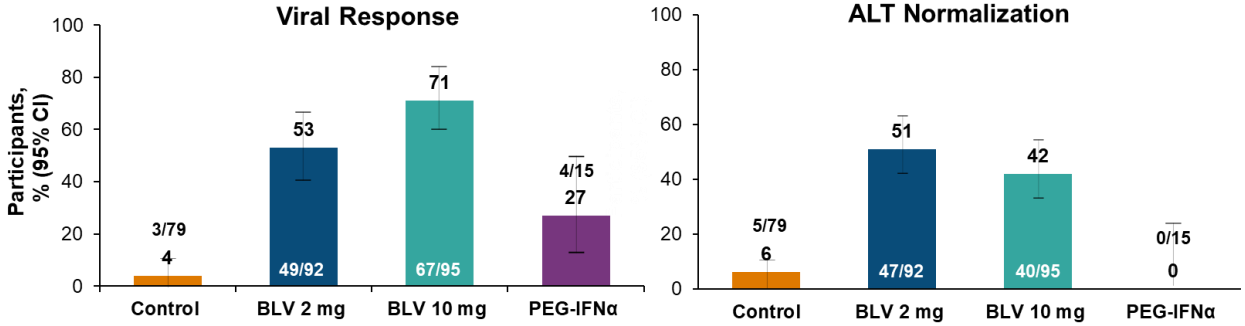
Key Demographics and Characteristics	Control (n=79)	BLV 2 mg (n=92)	BLV 10 mg (n=95)	PEG-IFNα (n=15)
Age, mean (SD), years	40 (8)	42 (9)	40 (9.6)	34 (7)
Male, n (%)	46 (58)	56 (61)	64 (67)	5 (33)
White, n (%)	63 (80)	77 (84)	85 (89)	14 (93)
Compensated cirrhosis, n (%)	37 (47)	41 (45)	40 (42)	4 (27)
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)
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

The mean change in HDV RNA from baseline to Week 24 according to the pooled treatment arm was as follows: BLV 2 mg, -2.12 log_{10} IU/mL; BLV 10 mg, -2.49 log_{10} IU/mL; control, -0.14 log_{10} IU/mL; PEG-IFNα, -1.16 log_{10} IU/mL. The rates of virologic response (defined as undetectable HDV RNA or a ≥2 log IU/mL decrease from baseline) at Week 24 were higher among the BLV arms than among the control and PEG-IFNα arms (Figure 2); numerically higher rates of virologic response were observed in the BLV 10 mg arm than in the BLV 2 mg arm. Additionally, rates of ALT normalization were higher in the BLV arms

than in the control and PEG-IFNα arms; rates of ALT normalization were highest in the BLV 2 mg arm (Figure 2).

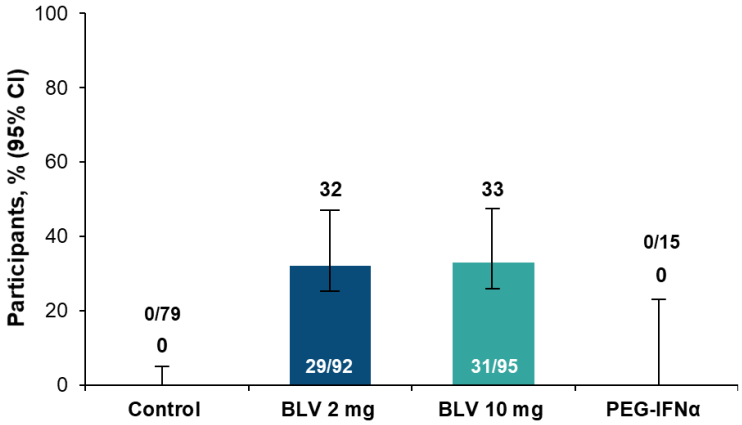
Figure 2. Integrated Efficacy Analysis of MYR202, MYR203, and MYR301: Virologic Response and ALT Normalization at Week 24 According to Pooled Treatment Arms[2]



Note: Virologic response was defined as undetectable HDV RNA or a ≥2 $\log_{10}$ IU/mL decrease from baseline. Undetectable HDV RNA was defined as <LLoD (14, 10, and 6 IU/mL in MYR202, MYR203, and MYR301, respectively); ALT normalization was 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.

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 3).

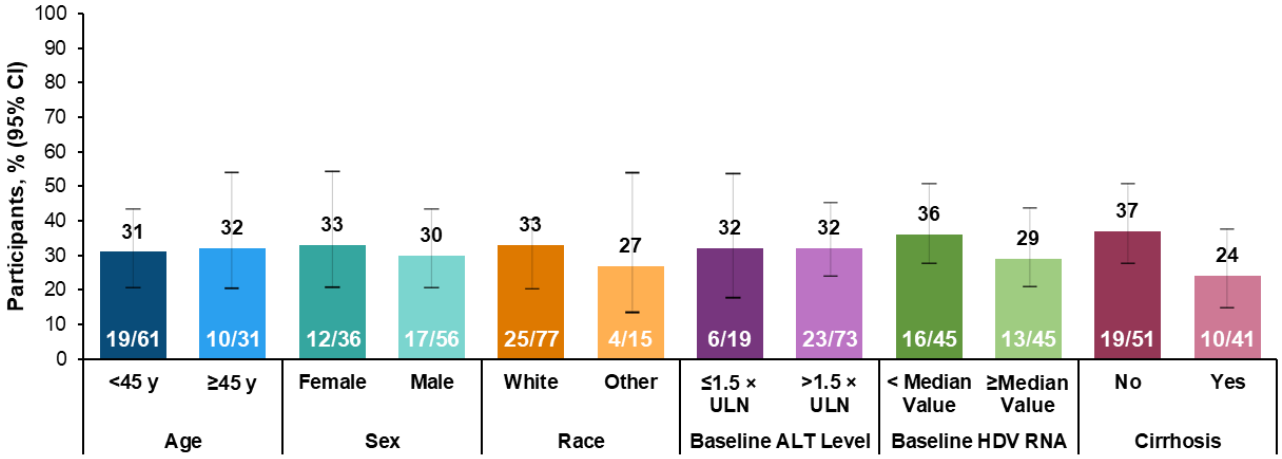
Figure 3. Integrated Efficacy Analysis of MYR202, MYR203, and MYR301: Combined Response Rates at Week 24 According to Pooled Treatment Arm[2]



Note: Combined response was defined as undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization. Undetectable HDV RNA was defined as <LLoD (14, 10, and 6 IU/mL in MYR202, MYR203, and MYR301, respectively); ALT normalization was 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.

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 4).

Figure 4. Integrated Efficacy Analysis of MYR202, MYR203, and MYR301: Subgroup Analysis of Combined Response Rates at Week 24 in Participants in the BLV 2 mg Arm[2]



Note: Combined response was defined as undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization.

MYR203, MYR204, and MYR301: Pooled Efficacy Results According to Concomitant NUC Use[3]

Study design and demographics

A pooled analysis was performed to evaluate Week 48 efficacy according to the use or non-use of concomitant NUCs using data from the MYR203 and MYR204 studies and the phase 3 MYR301 study of BLV for the treatment of participants with chronic HDV. In studies MYR204 and MYR301, concomitant NUC use was allowed according to investigator discretion; in MYR203, TDF was administered in selected study arms. HDV and HBV outcomes were pooled for the BLV 2 mg and 10 mg (n=229) and control (n=51) arms. Within the pooled BLV arm, 128 participants (55.9%) received concomitant NUC therapy; in the control arm 32 (62.7%) received concomitant NUC therapy.

Table 2. Pooled Efficacy Analysis of MYR203, MYR204, and MYR301: Baseline Demographics and Disease Characteristics Among BLV-Treated Participants[3]

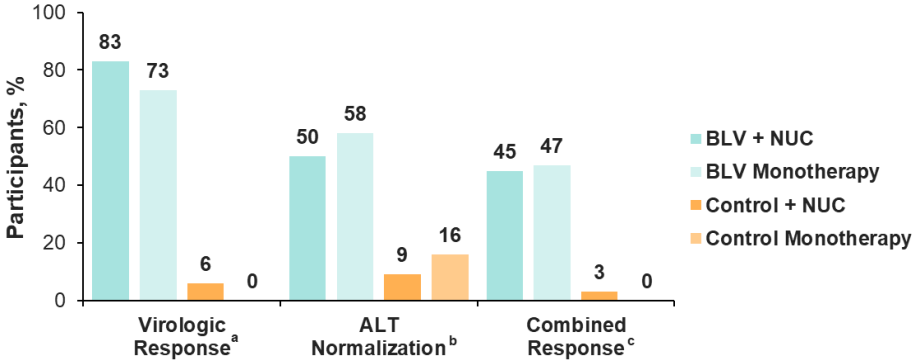
Key Demographics and Characteristics		BLV (2 or 10 mg) + NUC (n=128)	BLV (2 or 10 mg) Monotherapy (n=101)
Age, mean (SD), years		41 (9.2)	41 (7.8)
Male, n (%)		82 (64.1)	64 (63.4)
Race, n (%)	White	104 (81.3)	93 (92.1)
	Asian	21 (16.4)	8 (7.9)
	Black or African American	3 (2.3)	0
Cirrhosis,[a] n (%)		62 (48.4)	29 (28.7)
HDV GT 1,[b] n (%)		122 (95.3)	101 (100)
HDV RNA, mean (SD), $\log_{10}$ IU/mL		5.2 (1.4)	5.2 (1.4)
ALT, median (Q1, Q3), U/L		88 (66, 126)	83 (63, 127)
HBV DNA, mean (SD), $\log_{10}$ IU/mL		1.2 (1.5)	1.4 (1.1)
HBsAg, mean (SD), $\log_{10}$ IU/mL		3.7 (0.6)	3.7 (0.7)
HBeAg+, n (%)		20 (15.6)	5 (5)
Prior IFN therapy, n (%)		69 (53.9)	37 (36.6)

[a]Data were not collected for 15 participants who received BLV 5 mg twice daily + TDF 300 mg daily in the MYR203 study. [b]HDV GT 5, n=2 in concomitant NUC subgroup. Data were missing for 4 participants.

Pooled Week 48 efficacy results

The addition of NUC to the BLV or control arms did not improve HDV responses at Week 48 (Figure 5).

Figure 5. Pooled Efficacy Analysis of MYR203, MYR204, and MYR301: HDV Response Rates at Week 48[3]



[a]Undetectable HDV RNA or a ≥2-$\log_{10}$ IU/mL decrease from baseline.
[b]ALT ULN ≤31 or ≤41 U/L for females and males, respectively, at sites in Russia and ≤34 and ≤49 U/mL for females and males, respectively, at other study sites.
[c]Virologic response and ALT normalization.

Greater mean decreases in HBV DNA levels from baseline to Week 48 were observed with NUC therapy than without: BLV + NUC, -1.37 $\log_{10}$ IU/mL; BLV monotherapy, -0.71 $\log_{10}$ IU/mL; control + NUC, -0.81 $\log_{10}$ IU/mL; control monotherapy, -0.15 $\log_{10}$ IU/mL. Rates of undetectable HBV DNA (<LLoQ; 10 IU/mL) at Week 48 were generally similar among concomitant NUC users (BLV, 36%; control, 41%) but were slightly higher with BLV monotherapy than with control monotherapy (21% vs 11%, respectively). Changes in HBsAg levels from baseline to Week 48 were generally similar between those in the pooled BLV arms with or without concomitant NUC (+0.03 vs +0.09 $\log_{10}$ IU/mL, respectively) and between those in the control arm with or without concomitant NUC (0 vs +0.02 $\log_{10}$ IU/mL, respectively).

MYR203 and MYR301 Studies: Integrated Efficacy Results Through Week 48[4]

Study design and demographics

An integrated analysis of Week 48 efficacy data from the phase 2 MYR203 study and the ongoing phase 3 MYR301 study of BLV for the treatment of participants with chronic HDV was performed. Within this pooled analysis (N=240), the efficacy of BLV monotherapy dosed at 2 mg and 10 mg SUBQ once daily was evaluated using data from the following study arms: BLV 2 mg, BLV 10 mg, and control (the no-treatment arm from MYR301). The primary endpoint was an assessment of combined response (defined as undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ IU/mL from baseline and ALT normalization) at Week 48. Of the participants assessed, 48% to 65% were receiving concomitant NUC therapy.

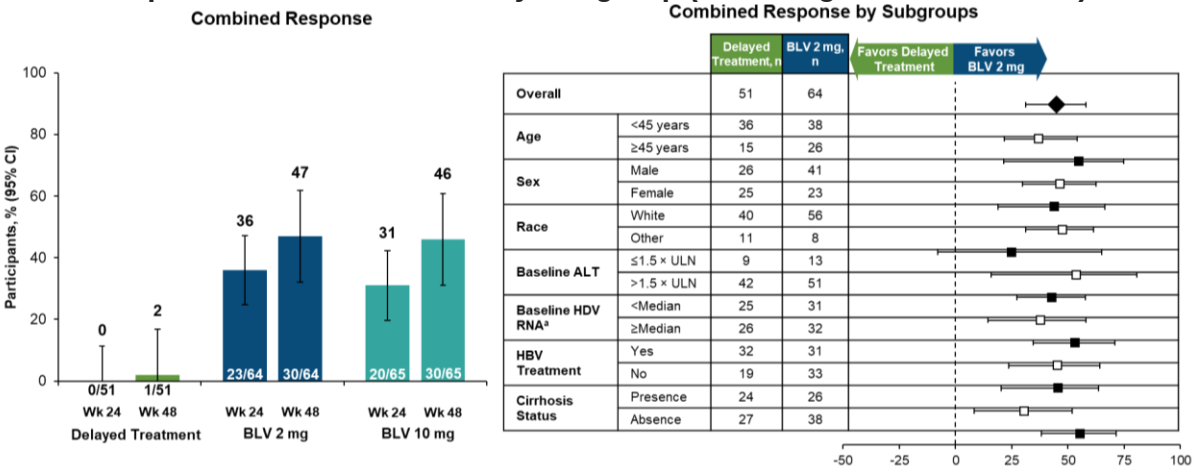
Table 3. Integrated Efficacy Analysis of MYR203 and MYR301: Baseline Demographics and Disease Characteristics[4]

Key Demographics and Characteristics		Delayed Treatment (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)
LSM, 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

The combined response rates were numerically similar in the BLV arms at Week 48 (2 mg, 47%; 10 mg, 46%) and were higher than in the no-treatment arm (2%; Figure 6). Across subgroups, BLV treatment was associated with a favorable combined response, including in participants with cirrhosis (Figure 6).

Figure 6. Integrated Efficacy Analysis of MYR203 and MYR301: Combined Response Rates at Weeks 24 and 48 According to Pooled Treatment Arm and Combined Response Rates at Week 48 by Subgroup (BLV 2 mg vs No Treatment)[4]

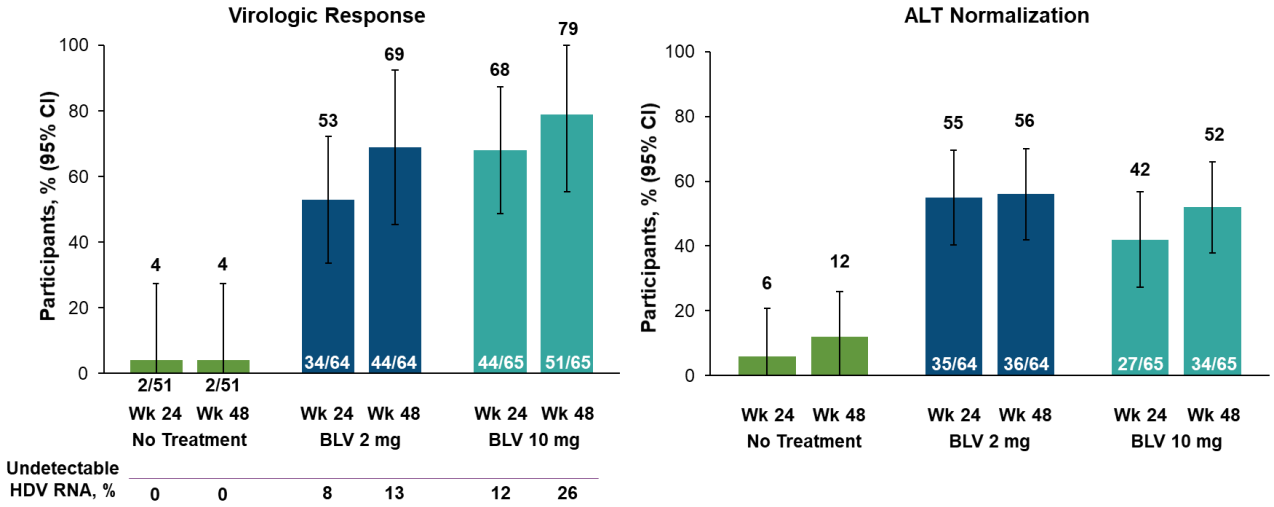


[a]One participant in the BLV arm did not have an HDV RNA value at baseline.
Note: Combined response was defined as undetectable HDV RNA or decreases in HDV RNA by ≥2 log_{10} IU/mL from baseline and ALT normalization. Undetectable HDV RNA was defined as <LLoD (10 and 6 IU/mL in MYR203 and MYR301, respectively); ALT normalization was 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.

The virologic response rate at Week 48 was numerically lower in the BLV 2 mg arm than in the BLV 10 mg arm (69% and 79%; Figure 7); virologic response rates at Week 48 were

similar between the BLV arms but were numerically higher in the BLV 10 mg arm than in the BLV 2 mg arm. Additionally, rates of ALT normalization were higher in the BLV arms than in the no-treatment arm; rates of ALT normalization were similar among the BLV arms at Week 48 (Figure 7).

Figure 7. Integrated Efficacy Analysis of MYR203 and MYR301: Virologic Response and ALT Normalization According to Pooled Treatment Arms at Week 24 and Week 48[4]



Note: Virologic response was defined as undetectable HDV RNA or a ≥2 $\log_{10}$ IU/mL decrease from baseline. Undetectable HDV RNA was defined as <LLoD (10 and 6 IU/mL in MYR203 and MYR301, respectively); ALT normalization was 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.

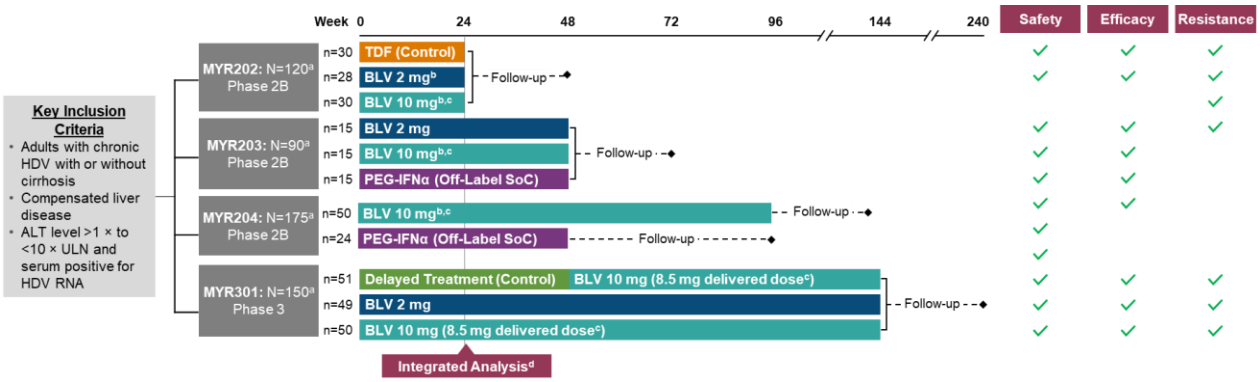
The BLV arms had numerically similar mean reductions in LSMs from baseline to Week 48 (BLV 2 mg, -2.6 kPa [n=57]; BLV 10 mg, -2.8 kPa [n=57]); participants in the no-treatment arm had a small mean increase in LSM from baseline to Week 48 (+0.7 kPa [n=45]).

MYR202, MYR203, MYR204, and MYR301 Studies: Integrated Safety Analysis of Week 24 Data[5]

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; Figure 8). Results from the following study arms were pooled for analysis: BLV 2 mg, BLV 10 mg, control (TDF-only arm from MYR202 and no-treatment arm from MYR301), and PEG-IFNα. Safety outcomes were graded according to CTCAE version 5.0, and a subgroup analysis of safety according to cirrhosis status and BLV dose was performed.

Figure 8. Integrated Safety Analysis of MYR202, MYR203, MYR204, and MYR301: Study Design[5]



Abbreviation: SoC=standard of care.
[a]Total n participants; only arms pooled for 24-week integrated analyses are shown. Groups that included participants who were treated with the combination of BLV and Peg-IFNα were not included in the integrated analysis.
[b]Administered with TDF 300 mg.
[c]The protocol specified the dose as 10 mg; 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 4. Integrated Safety Analysis of MYR202, MYR203, MYR204, and MYR301: Baseline Demographics and Disease Characteristics[5]

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)
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, most AEs were mild or moderate in severity. No BLV- or liver-related SAEs were reported in the BLV arms, and no AEs led to the discontinuation of BLV. Comparable rates of Grade 3 to 4 AEs were observed across the BLV arms and the control arm, and more Grade 3 to 4 AEs were reported in the PEG-IFNα arm than in the other arms (Table 5). No deaths occurred through to Week 24 (1 death occurred after Week 24 and was not included in this analysis).

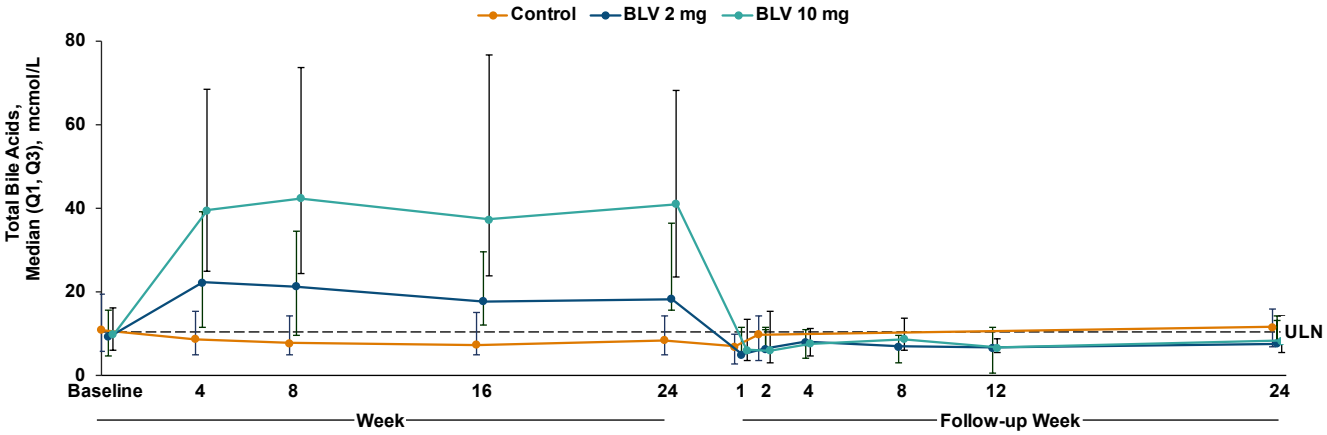
Table 5. Integrated Safety Analysis of MYR202, MYR203, MYR204, and MYR301: Safety Outcomes According to Pooled Arms[5]

Safety Outcomes, n (%)		Control (n=79)	BLV 2 mg (n=92)	BLV 10 mg (n=145)	PEG-IFNα (n=39)
AEs		39 (49)	62 (67)	107 (74)	34 (87)
AEs related to BLV		0	45 (49)	87 (60)	0
AEs related to PEG-IFNα		0	0	0	34 (87)
Most commonly reported AEs[a]	Thrombocytopenia	8 (10)	7 (8)	9 (6)	22 (56)
	Leukopenia	6 (8)	8 (9)	11 (8)	20 (51)
	ALT increased	6 (8)	4 (4)	8 (6)	12 (31)
	Total bile acids increased	5 (6)	20 (22)	30 (21)	3 (8)
	Fatigue	2 (3)	5 (5)	13 (9)	2 (5)
	Pruritus	1 (1)	6 (7)	11 (8)	2 (5)
	Nausea	1 (1)	4 (4)	11 (8)	6 (15)
	Headache	0	12 (13)	22 (15)	5 (13)
	ISRs	0	7 (8)	22 (15)	1 (3)
	Dizziness	0	5 (5)	10 (7)	1 (3)
Grade ≥3 AEs		3 (4)	4 (4)	10 (7)	17 (44)
Grade ≥3 AEs related to BLV		0	2 (2)	5 (3)	0
Grade ≥3 AEs related to PEG-IFNα		0	0	0	16 (41)
Grade 3–4 AEs in >1 participant (per arm)	Thrombocytopenia	2 (3)	1 (1)	1 (1)	4 (10)
	Neutropenia	1 (1)	0	2 (1)	9 (23)
	Leukopenia	1 (1)	0	2 (1)	6 (15)
	Neutrophil count decreased	0	1 (1)	0	2 (5)
	ALT increased	0	0	0	3 (8)
	AST increased	0	0	0	3 (8)
	GGT increased	0	0	0	3 (8)
SAEs		2 (3)[b]	0	1 (1)[c]	2 (5)[d]

[a]Refers to the 10 most common AEs in the BLV arms.
[b]Cholelithiasis and hepatic cirrhosis (reported as decompensation of hepatic cirrhosis; each, n=1).
[c]Urinary tract infection.
[d]Appendicitis and pyrexia (each, n=1).

The rates of Grade 3 to 4 laboratory abnormalities were similar between the BLV arms (2 mg, 7% [n=6]; 10 mg, 8% [n=11]) and the control arm (8% [n=6]); the rates of Grade 3 to 4 laboratory abnormalities were higher in the PEG-IFNα arm (43% [n=16]) than in the BLV arms. No Grade 3 or 4 elevations in bile acids or eosinophils were observed. Within the BLV and control arms, dose-dependent and asymptomatic elevations in serum total bile acids were observed, which was expected based on BLV's mode of action (sodium taurocholate co-transporting polypeptide inhibition); these elevations were reversible upon treatment cessation and did not result in clinical sequelae (Figure 9).

Figure 9. Integrated Safety Analysis of MYR202, MYR203, MYR204, and MYR301: Total Bile Acids in the BLV and Control Arms During Treatment and Follow-Up[5]



Within the BLV arms, the overall safety profile was similar among participants with and without compensated cirrhosis. All ISRs were mild to moderate in severity, and no serious ISRs or ISRs that led to the discontinuation of BLV were reported. Overall, fewer ISRs were observed in the BLV 2 mg arm than in the BLV 10 mg arm (Table 6).

Table 6. Integrated Safety Analysis of MYR202, MYR203, MYR204, and MYR301: ISRs Observed in >1 Participant According to BLV Dose[5]

	BLV 2 mg (n=92)	BLV 10 mg (n=145)
Any ISR, n (%)	7 (8)	22 (15)
Erythema	4 (4)	11 (8)
Reaction (not otherwise specified)	1 (1)	6 (4)
Pain	1 (1)	1 (1)
Pruritus	0	4 (3)
Hematoma	0	2 (1)

MYR203, MYR204, and MYR301 Studies: Integrated Safety Analysis Through Week 48

Study design and demographics[6]

An integrated safety analysis of Week 48 data was performed using data from two phase 2 studies (MYR203 and MYR204) and the phase 3 MYR301 study (N=269). Results were pooled for analysis from the following study arms: BLV 2 mg, BLV 10 mg, control (delayed treatment arm from MYR301), and PEG-IFNα (reference arm).

Table 7. Integrated Safety Analysis of MYR203, MYR204, and MYR301: Baseline Demographics and Disease Characteristics[6]

Key Demographics and Characteristics		Control (n=51)	BLV 2 mg (n=64)	BLV 10 mg (n=115)	PEG-IFNα (n=39)
Age, mean (range), years		41 (27–61)	43 (19–62)	40 (18–62)	38 (20–59)
Male, n (%)		26 (51)	41 (64)	79 (69)	23 (59)
Race, n (%)	White	40 (78)	56 (88)	102 (89)	34 (87)
	Asian	11 (22)	8 (13)	10 (9)	5 (13)
	Black	0	0	3 (3)	0
Cirrhosis, n (%)		24 (47)	26 (41)	41 (36)	12 (31)
LSM, mean (SD), kPa		15 (9)	14 (7.8)	13 (7.8)	14 (9.8)
HDV RNA, mean (SD), log_{10} IU/mL		5.1 (1.4)	5.2 (1.3)	5.3 (1.4)	5.1 (1.1)
ALT level, mean (SD), U/L		102 (62)	111 (73)	115 (90)	110 (80)
CrCl, n (%)	≥60 to <90 mL/min	10 (20)	10 (16)	14 (12)	4 (10)
	≥90 mL/min	41 (80)	54 (84)	101 (88)	35 (90)
NUC use at baseline, n (%)		32 (63)	31 (48)	65 (57)	11 (28)
Previous IFN use, n (%)		29 (57)	27 (42)	50 (44)	16 (41)

Integrated Week 48 safety results

In the BLV 2 mg and 10 mg arms, most AEs were Grade 1 or 2 in severity. No participants in the BLV 2 mg or 10 mg arm discontinued due to an AE, compared with 3 participants (8%) in the PEG-IFNα monotherapy arm. A summary of safety outcomes by pooled treatment arms at Week 48 is provided in Table 8.[6]

Table 8. Integrated Safety Analysis of MYR203, MYR204, and MYR301: Safety Outcomes According to Pooled Treatment Arms at Week 48[6]

Safety Outcomes, n (%)		Control (n=51)	BLV 2 mg (n=64)	BLV 10 mg (n=115)	PEG-IFNα (n=39)
Any AE		39 (77)	55 (86)	99 (86)	35 (90)
AE related to study drug		–	38 (59)	72 (63)	34 (87)
AEs that occurred in ≥7.5% of participants in the BLV arms	Leukopenia	9 (18)	10 (16)	16 (14)	22 (56)
	Thrombocytopenia	8 (16)	8 (13)	15 (13)	22 (56)
	Vitamin D deficiency	8 (16)	6 (9)	18 (16)	3 (8)
	Lymphopenia	4 (8)	4 (6)	9 (8)	12 (31)
	Neutropenia	3 (6)	5 (8)	14 (12)	20 (51)
	ALT increased	3 (6)	5 (8)	9 (8)	14 (36)
	Nausea	2 (4)	3 (5)	9 (8)	6 (15)
	Fatigue	1 (2)	6 (9)	8 (7)	2 (5)
	Total bile acids increased[a]	0	13 (20)	19 (17)	6 (15)
	ISRs[b]	0	10 (16)	23 (20)	1 (3)
	Headache	0	10 (16)	19 (17)	5 (13)
	Pruritus	0	7 (11)	11 (10)	2 (5)
	Eosinophilia	0	6 (9)[c]	5 (4)[c]	1 (3)
Any Grade ≥3 AEs		3 (6)	7 (11)	13 (11)	20 (51)
Grade ≥3 AEs related to study drug		–	2 (3)	5 (4)	20 (51)

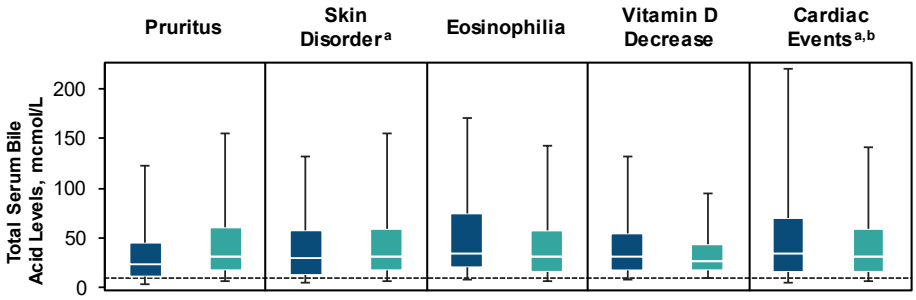
Safety Outcomes, n (%)		Control (n=51)	BLV 2 mg (n=64)	BLV 10 mg (n=115)	PEG-IFNα (n=39)
Grade ≥3 AEs	Neutropenia	2 (4)	0	4 (3)	10 (26)
	Thrombocytopenia	2 (4)	1 (2)	3 (3)	5 (13)
	Leukopenia	1 (2)	0	2 (2)	6 (15)
	ALT increased	0	1 (2)	0	4 (10)
	AST increased	0	1 (2)	0	3 (8)
	Neutrophil count decreased	0	1 (2)	0	2 (5)
	Total bile acids increased[d]	0	0	2 (2)	1 (3)
	GGT increased	0	0	0	3 (8)
SAEs[e]		1 (2)	2 (3)	2 (2)	3 (8)
COVID-19		1 (2)	0	1 (1)	1 (3)
Cholelithiasis		1 (2)	0	0	0
Asthenia		0	1 (2)	0	0
Depression		0	1 (2)	0	0
Foot fracture		0	1 (2)	0	0
Urinary tract infection		0	0	1 (1)	0
Appendicitis		0	0	0	1 (3)
Pyrexia		0	0	0	1 (3)
Laboratory abnormality		42 (82)	58 (91)	100 (87)	37 (100)
Grade ≥3 laboratory abnormality		6 (12)	13 (20)	16 (14)	25 (68)

[a]In MYR204 and MYR301, the only symptomatic or clinically significant increases in total bile acids were reported as AEs; no Grade ≥3 AEs of total bile acids increased were reported in those studies.
[b]A grouped term that included any preferred term under the MedDRA high-level term ISRs.
[c]All cases were mild in severity and resolved while on study treatment; none met the criteria for a potential drug-induced liver injury
[d]All participants with Grade ≥3 AEs of total bile acids increased were from MYR203. Post-treatment follow-up revealed that total bile acids returned to baseline levels by the first follow-up visit 2 weeks after BLV discontinuation.
[e]No SAEs were deemed to be related to study drug.
Note: Safety outcomes were graded according to CTCAE.

Bile acid elevations

Bile acid levels increased in a dose-dependent manner, intrapatient variability in bile acid levels was observed, and levels were rapidly reversible upon treatment discontinuation; however, there were no discontinuations due to the AE of increased bile acids. At Week 48, bile acid levels were >ULN in 79% and 94% of participants in the BLV 2 mg and 10 mg arms, respectively. Bile acid increases were not associated with any AEs of interest (ie, pruritus, skin disorders, eosinophilia, vitamin D decrease, and cardiac events; Figure 10).[6]

Figure 10. Integrated Safety Analysis of MYR203, MYR204, and MYR301: On-Treatment Bile Acid Levels in Participants With or Without AEs of Interest (BLV 2 mg and 10 mg Arms Combined)[6]



AEs Reported	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Participants, n	18	161	27	152	13	166	111	34	16	163
Observations,[c] n	126	1231	198	1159	92	1265	756	237	115	1242

[a]System organ class term according to MedDRA v24.0.
[b]The most common cardiac AEs were bradycardia (n=8) and tachycardia (n=3); all were Grade 1 to 2 and asymptomatic.
[c]Individual records of on-treatment bile acid levels.
Note: The box plot horizontal line represents the median, the shaded boxes represent the IQR, and the whiskers represent the 5th and 95th percentiles.

Figure 11 shows mean changes over time in bile acid levels. Nearly all episodes of pruritus resolved, and none led to BLV discontinuation (Table 9).[9]

Figure 11. Integrated Safety Analysis of MYR203, MYR204, and MYR301: Mean Changes in Bile Acid Levels Through Week 48 in Participants With or Without Pruritus[6]

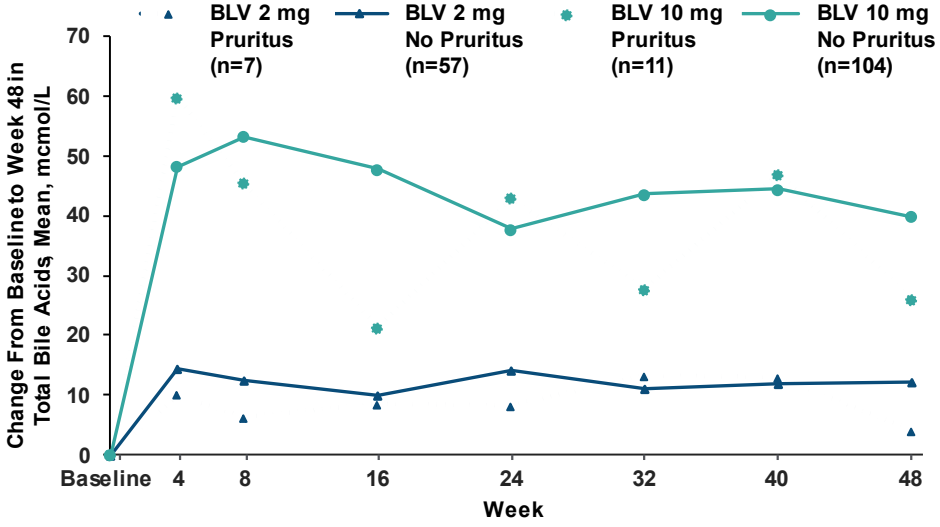


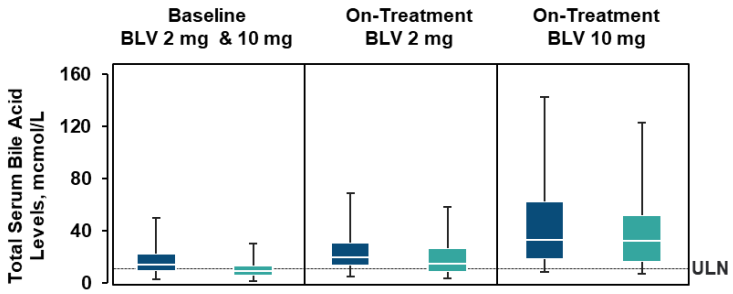
Table 9. Integrated Safety Analysis of MYR203, MYR204, and MYR301: Bile Acid Levels and Pruritus at Week 48 According to BLV Dose[6,9]

	BLV 2 mg (n=64)	BLV 10 mg (n=115)
Participants with pruritus, n (%)	7 (11)	11 (10)
Pruritus events,[a] n	9	17
Serious pruritus events/Grade ≥3 pruritus events/pruritus events that led to BLV discontinuation, n	0/0/0	0/0/0
Time to pruritus onset, median (range), days	49 (11–305)	97 (1–235)
Duration of pruritus, median (range), days	37 (1–325)	49 (1–317)
Pruritus linked to maximum bile acid level, yes/no, n	1/8	3/14
Pruritus resolved, n (%)	9 (100)	15 (88)

[a]Occurred concurrently with peak total bile acid levels in 1 and 3 events in the BLV 2 mg and 10 mg arms, respectively.

The presence of cirrhosis did not affect bile acid levels at baseline or on treatment (Figure 12).[6]

Figure 12. Integrated Safety Analysis of MYR203, MYR204, and MYR301: Bile Acid Levels at Baseline and on Treatment in Participants With or Without Cirrhosis[6,9]



Cirrhosis	Yes	No	Yes	No	Yes	No
Participants,[a] n	67	97	26	38	41	59
Observations, n	65	97	193	317	271	396

[a]Fifteen participants who received BLV 10 mg did not have cirrhosis status recorded.
Note: The box plot horizontal line represents the median, the shaded boxes represent the IQR, and the whiskers represent the 5th and 95th percentiles.

ISRs[6]

All ISRs were Grade 1 or 2, and ISRs occurred at a slightly higher rate in the BLV 10 mg arm than in the BLV 2 mg arm (20% vs 16%, respectively); the BLV 10 mg arm received two 5 mg injections of BLV daily to deliver the higher dose. The median (IQR) duration of ISRs was 15 (1–59) days in the BLV 10 mg arm and 9 (2–42) days in the BLV 2 mg arm.

On-treatment ALT elevations and assessment of potential drug-induced liver injury[6]

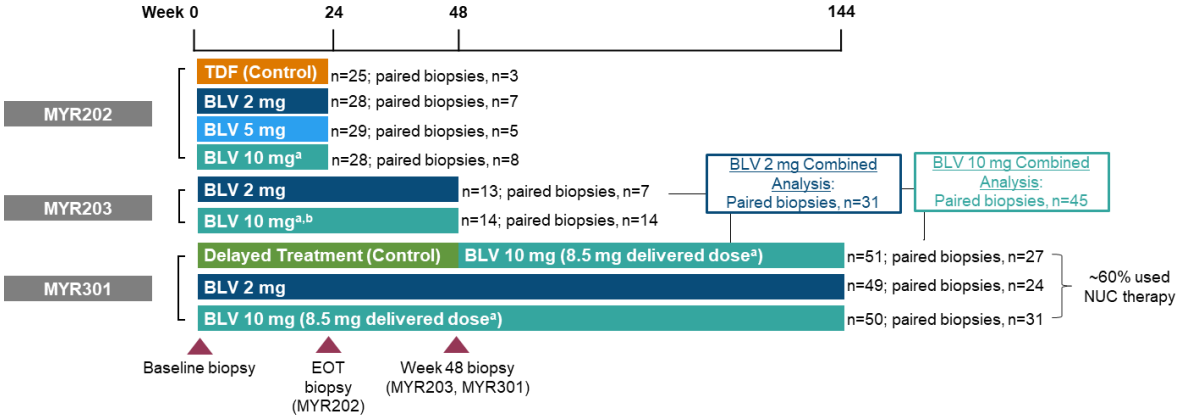
During the on-treatment period, an analysis for the possibility of a drug-induced liver injury was performed if one of the following criteria were met: ALT and/or AST >3 × ULN and total bilirubin >2 × ULN; ALT >5 × ULN; or total bilirubin >2 × ULN. The proportion of participants who met ≥1 criterion for potential drug-induced liver injury was 12.5% in the BLV 2 mg arm and 7% in the BLV 10 mg arm. BLV was not associated with on-treatment ALT elevations or drug-induced liver injury at either dosage. Rather, liver test abnormalities overall occurred at a lower rate in participants treated with BLV than those in the PEG-IFNα or control arms. No participant experienced hepatic decompensation, and liver test abnormalities improved from baseline to treatment Week 48.

Intrahepatic HDV and HBV Outcomes

MYR202, MYR203, and MYR301 substudy: intrahepatic outcomes[8]

A substudy of paired liver biopsies performed at baseline and at Week 24 for participants in MYR202 or Week 48 for participants in MYR203 and MYR301 evaluated the relation between intrahepatic HDV outcomes and peripheral HDV outcomes and the effects of HBV treatment on intrahepatic markers of inflammatory and innate gene expression.

Figure 13. MYR202, MYR203, and MYR301 Substudy: Study Design[8]

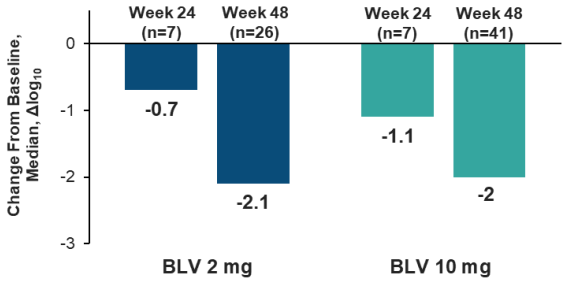


[a]The protocol specified the dose as 10 mg; the delivered dose was 8.5 mg.
[b]Administered with TDF 300 mg.
Note: Nine single baseline biopsies were available for MYR202, and 7 were available for MYR203 and MYR301. Participants who received PEG-IFNα were excluded from this analysis.

Median intrahepatic HDV RNA decreased from baseline to Week 24 as follows: TDF, 0.3 $\log_{10}$ (n=3); BLV 2 mg, 0.9 $\log_{10}$ (n=7); BLV 5 mg, 1.1 $\log_{10}$ (n=5); and BLV 10 mg, 1.4 $\log_{10}$ (n=7); HDV RNA levels did not change in the 3 biopsies from the participants who received TDF (control) in MYR202. Median intrahepatic HDV RNA decreased from baseline to Week 48 as follows: BLV 2 mg, 2.2 $\log_{10}$ (n=27); BLV 10 mg, 2.7 $\log_{10}$ (n=37); delayed treatment, 0.1 $\log_{10}$ (n=18). Although the proportions of participants who had a >1 $\log_{10}$ decrease in HDV RNA from baseline to Week 48 in the 10 mg and 2 mg BLV arms were comparable (81% vs 78%, respectively), more participants in the BLV 10 mg arm than in the 2 mg arm had undetectable HDV RNA at Week 48 (62% vs 37%).

Median decreases from baseline to Week 24 and from baseline to Week 48 in HDAg+ cells were noted in the BLV 2 mg and 10 mg arms (Figure 14), which correlated with plasma HDV RNA levels (Spearman r=0.85; $P \leq 0.0001$); 50% and 54% of participants in the BLV 2 mg and 10 mg arms, respectively, had no HDAg+ cells at Week 48.

Figure 14. MYR202, MYR203, and MYR301 Substudy: Median Changes in HDAg+ Hepatocytes From Baseline to Week 24 and Week 48 in BLV 2 mg and 10 mg Arms[8]



HBV DNA levels did not change significantly from baseline to Week 48; however, significant between-arm differences were noted for comparisons between the 2 mg and 10 mg BLV arms and the delayed treatment arm (*P*≤0.05 and *P*≤0.001, respectively). HBsAg+ staining did not change over time, was not significantly different between treatment arms, and was correlated with liver HBV S RNA levels (Spearman r=0.43; *P*≤0.0001). Serum HBsAg levels were also correlated with liver HBV S RNA levels (Spearman r=0.62; *P*≤0.0001).

Expression of chemokines (CXCL9-11 and its receptor, CXCR3), pro-inflammatory genes (eg, *IFNG*, *IL1B*, and *TNF*), and IFN-stimulated genes (eg, *ISG15*, *MX1*, and *OAS1*) decreased from baseline to Week 48. Levels of *CXCL10* mRNA decreased significantly from baseline to Week 48 in the BLV 2 mg and 10 mg arms (each, *P*≤0.0001) and were correlated with HDV RNA levels (Spearman r=0.72; *P*≤0.0001) and serum ALT levels (Spearman r=0.71; *P*≤0.0001).

MYR204 subanalysis[7]

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), in 57% (8/14) within the BLV 2 mg + PEG-IFNα arm (median change, -1.99 $\log_{10}$; *P*≤0.05), in 8% (1/12) within the BLV 10 mg arm (median change, -0.76 $\log_{10}$ U/mL), and in 60% (2/5) within the PEG-IFNα arm (median change, -1.94 $\log_{10}$ IU/mL).

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) within the BLV 10 mg + PEG-IFNα arm (median change, -1.85 $\log_{10}$ IU/mL; *P*≤0.05), in 44% (8/14) within the BLV 2 mg + PEG-IFNα arm (median change, -0.98 $\log_{10}$ IU/mL; *P*≤0.05), in 8% (1/13) within the BLV 10 mg arm (median change, -0.77 $\log_{10}$ IU/mL), and in 67% (4/6) within the PEG-IFNα arm (median change, -1.87 $\log_{10}$ IU/mL).

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 those 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. In select participants in the BLV 10 mg and 2 mg + PEG-IFNα arms, many were able to achieve and maintain undetectable HDV RNA levels after stopping treatment without experiencing a reduction in HBsAg.

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Abbreviations

AE=adverse event
BLV=bulevirtide-gmod
CTCAE=Common Terminology Criteria for Adverse Events
CXCL=C-X-C motif chemokine ligand
CXCR=C-X-C motif chemokine receptor
EOT=end of treatment
GGT=γ-glutamyltransferase
GT=genotype
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HDAg=hepatitis D antigen
IFN(α)=interferon (α)
IFNG=interferon γ
IL1B=interleukin 1 β
ISG15=ISG15 ubiquitin-like modifier
ISR=injection site reaction
LLoD=lower limit of

detection
LLoQ=lower limit of quantitation
LSM=liver stiffness measurement
MedDRA=Medical Dictionary for Regulatory Activities
MX1=MX dynamin-like GTPase 1
NUC=nucleos(t)ide analog
OAS1=2’-5’-oligoadenylate synthetase 1
OR=odds ratio
PEG=pegylated
Q=quartile
SAE=serious adverse event
SUBQ=subcutaneous(ly)
TDF=tenofovir disoproxil fumarate
TNF=tumor necrosis factor
ULN=upper limit of normal

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