GILEAD | Medical Information

Hepcludex® (bulevirtide-gmod) Fibrosis Improvement

This document is in response to your request for information regarding the use of Hepcludex® (bulevirtide-gmod [BLV]) for the treatment of chronic HDV (CHD) infection and available data on fibrosis improvement.

Some data may be outside of the US FDA-approved prescribing information. In providing this data, Gilead Sciences, Inc. is not making any representation as to its clinical relevance or to the use of any Gilead product(s). For information about the approved conditions of use of any Gilead drug product, please consult the FDA-approved prescribing information.

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 Data on BLV Use and Fibrosis Improvement

In MYR204 and MYR301, similar rates of improvements in ALT levels and NITs (FIB-4, AST, APRI, and LSM) were observed in the BLV 2 mg and 10 mg groups, with the greatest reduction occurring in the first 48 weeks of the study, and were either maintained or continued to improve until Week 96. ALT levels and NITs decreased irrespective of virologic efficacy.[2]

A subanalysis of study MYR301 evaluated efficacy, histologic outcomes, and the relationship between these measures in participants treated with BLV monotherapy (2 mg or 10 mg) or DT (control) for 48 weeks. Participants were categorized according to response to BLV treatment at Week 48: VR (HDV RNA decline of ≥2 $\log_{10}$ IU/mL from BL or undetectable HDV RNA), PR (HDV RNA decline from BL by ≥1 but <2 $\log_{10}$ IU/mL), and NR (HDV RNA decline from BL by <1 $\log_{10}$ IU/mL).[3]

- All BLV-treated response groups showed similar median changes in ALT levels, with greater improvements compared with the control group by Week 48.
- Most BLV-treated participants experienced improvements in both ALT levels and HAI, regardless of virologic efficacy, with no observed correlation between the extent of HAI improvement and changes in ALT levels from BL.
- More participants in the VR group (58%) than in the PR (33%), NR (25%), and control (30%) groups showed improvement in Ishak fibrosis score. A greater proportion of participants in the VR and PR groups demonstrated improvement in both HAI score and HAI category, as well as histologic improvement, than the NR and control groups.

An additional subanalysis of study MYR301 included participants who received BLV 2 or 10 mg monotherapy once daily for 144 weeks and was conducted to evaluate improvements in ALT and NITs in response to treatment and to correlate outcomes with response at Week 144. Participants were categorized as having a VR, PR, or NR to BLV treatment at Week 144.[4]

- Improvements in ALT and NITs were observed from BL through Week 144 for most participants, regardless of virologic efficacy. The greatest improvement in ALT levels were observed during the first year, with similar patterns observed for NITs.
- Improvements in NITs at Week 144 were also seen across all response groups, including participants who had a VR (n=74), PR (n=7), or NR (n=8) at Week 144.
- In participants who had a VR or PR, ALT reductions and changes in NITs were either maintained or continued to improve through Week 144. In participants who had an NR, ALT levels and NITs were numerically higher at BL; at Week 144, ALT levels and LSMs remained higher in participants with an NR than in participants with a VR or PR.

An interim analysis of study MYR301 assessed LSM outcomes at 48 weeks after EOT (Week 192) in participants who received BLV 2 or 10 mg for 144 weeks and in those in the DT BLV 10 mg group who received 96 weeks of treatment.[5]

- Reductions in LSM from BL to EOT were observed in all treatment arms, and from EOT to 48 weeks after EOT, the reductions seen at EOT in LSM were less in all groups who received BLV.
- ALT normalization and combined response rates, which included VR and ALT normalization, were reduced from EOT to 24 and 48 weeks after EOT.
- The safety profile both during and post treatment was consistent with the known safety profile of BLV.

A single-center study evaluated changes in NIT results after 96 weeks of BLV 2 mg/day. Eligible participants had a ≥2-log HDV RNA decline from BL.[6]

- Improvements from BL in APRI and FIB-4 scores (P<0.001 and P=0.003, respectively) were observed through Week 96. Additionally, both LSM and LSPS decreased significantly from BL (each P=0.001) through Week 48, with no significant changes through Week 72.

Another single-center study evaluated the changes in NIT results after 48 weeks of BLV 2 mg ± NUC treatment in patients with CHD.[7]

- After 48 weeks of treatment, a significant difference in change from BL in APRI and FIB-4 scores was observed between patients with and without biochemical response (P=0.004 and P<0.001, respectively). Overall, there was a significant improvement in median LSM from BL to Week 48 (P<0.001), with a significant increase in the proportion

of patients with LSM ≤10 kPa at Week 48 compared with BL (63.2% and 31.6%, respectively; *P*=0.024).

Clinical Data on BLV Use and Fibrosis Improvement

Phase 2 MYR204 and Phase 3 MYR301 Studies[2]

Study design and demographics

Participants from two randomized, open-label, multicenter studies, phase 2 MYR204 and phase 3 MYR301, who received BLV 2 or 10 mg SUBQ once daily were included in an analysis that evaluated the changes in ALT and NITs (FIB-4, AST, APRI, and LSM) over 96 weeks of treatment. Adults with CHD infection, with or without compensated cirrhosis, with an ALT >1 to <10 × ULN, and with a positive HDV serum test were included in the studies.

Table 1. BL Demographics and Disease Characteristics (Castera et al)[2]

Key Demographics and Characteristics	BLV 2 mg (n=49)	BLV 10 mg (n=100)
Age, mean (SD), years	44 (9)	41 (8.5)
Male, n (%)	30 (61)	68 (68)
Race, White,[a] n (%)	41 (84)	87 (87)
Cirrhosis, n (%)	23 (47)	41 (41)
Concomitant HBV NUC treatment, n (%)	32 (65)	50 (50)
ALT, median (Q1, Q3), U/L	90 (65, 136)	94 (63, 135)
Platelet count, median (Q1, Q3), 10^9/L	159 (111, 191)	173 (132, 200)
HDV RNA, mean (SD), $\log_{10}$ IU/mL	5.1 (1.2)	5.2 (1.3)
HDV GT 1, n (%)	49 (100)	97 (97)[b]
HBsAg, mean (SD), $\log_{10}$ IU/mL	3.7 (0.5)	3.7 (0.6)
FIB-4, median (Q1, Q3)	1.9 (1.3, 2.9)	1.6 (1.2, 2.1)
APRI, median (Q1, Q3)	1.1 (0.7, 2)	1 (0.7, 1.5)
LSM, median (Q1, Q3), kPa	12 (8.7, 17.3)	11 (8.8, 15)

[a]Race was not reported for the remaining participants. [b]HDV GT 5, n=2; data unavailable, n=1.

Results

Improvements in ALT levels and NITs occurred at similar rates in both treatment groups; the largest declines occurred in the first 48 weeks, and the resulting levels were either maintained or continued to improve through Week 96 (Table 2). Declines in ALT and NITs occurred regardless of response type, although the median ALT among participants with an NR (defined as <1 $\log_{10}$ IU/mL HDV RNA decline from BL) was higher at BL and through Week 96 than that among participants with a PR (defined as ≥1 $\log_{10}$ IU/mL but <2 $\log_{10}$ IU/mL HDV RNA decline from BL) or a VR (defined as undetectable HDV RNA or ≥2 $\log_{10}$ IU/mL decline from BL).

Table 2. Changes in ALT Levels and NITs by Treatment Group (Castera et al)[2]

Median (Q1, Q3)	BL		Week 48		Week 96	
	BLV 2 mg	BLV 10 mg	BLV 2 mg	BLV 10 mg	BLV 2 mg	BLV 10 mg
ALT, U/L	90 (65, 136)	94 (63, 135)	39 (30, 50)	37 (29, 45)	33 (25, 47)	34 (26, 44)
LSM, kPa	12 (8.7, 17.3)	11 (8.8, 15)	10 (7.5, 14.2)	8 (6.7, 12.5)	8.4 (5.8, 12)	7.6 (5.8, 9.4)
APRI	1.1 (0.7, 2)	1 (0.7, 1.5)	0.5 (0.4, 0.9)	0.5 (0.4, 0.7)	0.5 (0.3, 1)	0.5 (0.3, 0.7)
FIB-4	1.9 (1.3, 2.9)	1.6 (1.2, 2.1)	1.4 (0.9, 2.7)	1.3 (0.9, 1.6)	1.3 (0.9, 2.3)	1.2 (0.9, 1.7)

No safety data were reported.

Subanalysis of Phase 3 MYR301 Study: Histologic Outcomes According to Week 48 Virologic Efficacy[3]

Study design and demographics

A subanalysis of study MYR301 evaluated efficacy, histologic outcomes, and the correlations between these outcome parameters in participants with CHD who received BLV for 48 weeks. Eligible participants (those with paired liver biopsies at BL and Week 48; N=83) received either BLV 2 mg or 10 mg SUBQ daily or DT (control). Participants were categorized into the following groups according to virologic efficacy at Week 48 of treatment with BLV: VR (defined as an HDV RNA decline of ≥2 $\log_{10}$ IU/mL from BL or undetectable HDV RNA), PR (defined as an HDV RNA decline from BL by ≥1 but <2 $\log_{10}$ IU/mL), and NR (defined as an HDV RNA decline from BL by <1 $\log_{10}$ IU/mL). Histologic outcomes were evaluated using the HAI (range, 0–18), HAI category (range, 0–4), and Ishak fibrosis score (range, 0–6). Histologic improvement was defined as a ≥2-point improvement from BL to Week 48 in HAI score and no worsening of Ishak fibrosis score.

Table 3. BL Demographics and Disease Characteristics by Virologic Efficacy at Week 48 (Lampertico et al)[3]

Key Demographics and Characteristics	BLV 2 or 10 mg (n=56)			DT (n=27)
	VR (n=45)	PR (n=6)	NR (n=5)	
Age, mean (SD), years	44 (8.6)	38 (9.2)	46 (10.7)	40 (7.4)
Male, n (%)	22 (48.9)	4 (66.7)	3 (60)	14 (51.9)
Race, White/Asian/Black or African American, n (%)	41 (91.1)/ 3 (6.7)/1 (2.2)	6 (100)/ 0/0	3 (60)/ 2 (40)/0	20 (74.1)/ 7 (25.9)/0
Cirrhosis, n (%)	16 (35.6)	1 (16.7)	1 (20)	9 (33.3)
Concomitant NUC therapy, n (%)	28 (62.2)	2 (33.3)	3 (60)	18 (66.7)
Prior IFN therapy, n (%)	33 (73.3)	2 (33.3)	2 (40)	16 (59.3)
ALT, median (Q1, Q3), U/L	92 (63, 134)	96 (90, 175)	138 (133, 146)	77 (54, 116)
HDV RNA, mean (SD), $\log_{10}$ IU/mL	5.1 (1.4)	5.2 (1.1)	5.1 (1.8)	5.2 (1.2)
HDV GT 1, n (%)	43 (95.6)[a]	6 (100)	5 (100)	27 (100)
HBeAg-positive, n (%)	6 (13.3)	1 (16.7)	0	3 (11.1)
LSM, mean (SD), kPa	12.8 (7)	8.1 (2.2)	8.2 (3.9)	12.4 (8.1)
HAI, mean (SD)	9 (3.4)	8 (3.1)	8 (2.8)	8 (3.3)
Ishak fibrosis score, mean (SD)	3 (1.5)	2 (1.6)	2 (0.4)	2 (1.4)

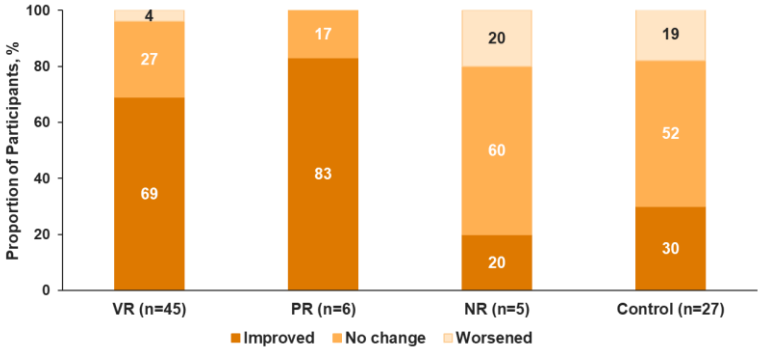
Abbreviation: HBeAg=hepatitis B envelope antigen.
[a]In the BLV 10 mg group, 1 participant had HDV GT 5, and 1 participant was missing HDV GT data.

Results

All participants who received treatment with BLV experienced numerically similar median changes from BL to Week 48 in ALT (VR, -51 U/L; PR, -56 U/L; NR, -64 U/L); these median changes were greater than those observed in the control group (-11 U/L). Improvement in ALT levels and HAI was observed in most BLV-treated participants, regardless of virologic efficacy; no correlation was observed between the extent of HAI improvement and ALT change from BL. The proportion of BLV-treated participants with HAI improvement at Week 48 was similar between participants with and without a ≥50% decline in ALT (79% [31/39] vs 76% [13/17], respectively). The rate of HAI improvements by virologic efficacy varied: VR, 80% (36/45); PR, 100% (6/6); NR, 40% (2/5). HAI improvement was noted in 56% (n=15) of participants in the control group. A higher percentage of participants who had VR (58%; 26/45) than in the PR (33%; 2/6), NR (25%; 1/4, 1 participant did not have a fibrosis score at Week 48), and control (30%; 8/27) groups, showed improvement in

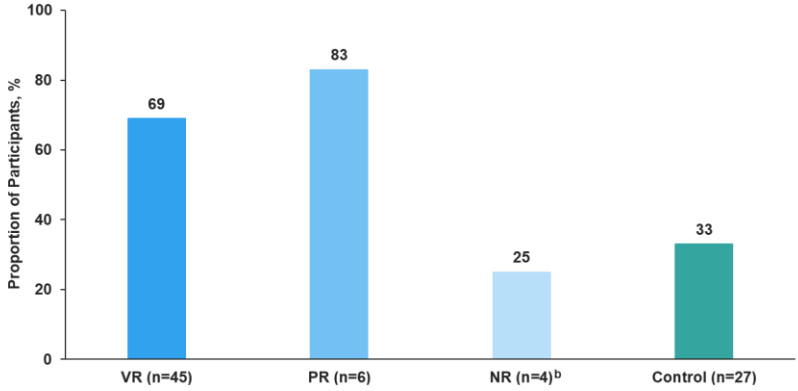
Ishak fibrosis score. From BL to Week 48, improvement in HAI category and histologic improvement were observed in more participants who had a VR or PR compared with participants with an NR and those in the control group (Figure 1 and Figure 2).

Figure 1. Changes From BL to Week 48 in HAI Category[a] (Lampertico et al)[3]



[a]HAI category (range 0–4; improvement was defined as a ≥1-category improvement from BL to Week 48) was based on HAI scores (range: 0–18; improvement was defined as a ≥1-point improvement from BL to Week 48).

Figure 2. Histologic Improvements by Virologic Efficacy (Lampertico et al)[3]



[a]Histologic improvement was defined as a ≥2-point improvement from BL to Week 48 in HAI score and no worsening of Ishak fibrosis score (range: 0–6; improvement was defined as a ≥1-point improvement from BL to Week 48).
[b]One participant in the NR group had no fibrosis score available at Week 48.

No safety data were reported.

Subanalysis of Phase 3 MYR301 Study: Effect on ALT Levels and NITs and Correlation With Week 144 VR[4]

Study design and demographics

An additional subanalysis of study MYR301 included participants who received BLV 2 or 10 mg monotherapy once daily for 144 weeks and was conducted to evaluate improvements in ALT and NITs in response to treatment and to correlate outcomes with response at Week 144 (N=99; Table 4). Participants were categorized into the following groups according to response to BLV treatment at Week 144: VR (defined as having an HDV RNA decline of ≥2 $\log_{10}$ IU/mL from BL or undetectable HDV RNA), PR (defined as having a ≥1 and <2 $\log_{10}$ IU/mL HDV RNA decline from BL, excluding undetectable HDV RNA), and NR (defined as having <1 $\log_{10}$ IU/mL HDV RNA decline from BL, excluding undetectable HDV RNA).

Table 4. BL Demographics and Disease Characteristics (Brunetto et al)[4]

Key Demographics and Characteristics	BLV 2 mg (n=49)	BLV 10 mg (n=50)
Age, mean (SD), years	44 (9)	41 (9)
Male, n (%)	30 (61)	30 (60)
Race, White/Asian/Black, n (%)	41 (84)/8 (16)/0	43 (86)/6 (12)/1 (2)
Cirrhosis, n (%)	23 (47)	24 (48)
Concomitant NUC therapy for HBV, n (%)	32 (65)	27 (54)
Prior IFN therapy, n (%)	26 (53)	29 (58)
ALT, median (Q1, Q3), U/L	90 (65, 136)	108 (63, 161)
HDV RNA, mean (SD), log_{10} IU/mL	5.1 (1.19)	4.96 (1.46)
HDV GT 1, n (%)	49 (100)	48 (96)[a]
HBsAg, mean (SD), log_{10} IU/mL	3.67 (0.52)	3.61 (0.59)
HBV DNA, mean (SD), log_{10} IU/mL	1.31 (1.28)	1.08 (1.26)
HBV GT, A/D/other, n (%)	2 (4)/47 (96)/0	2 (4)/44 (88)/4 (8)[b]
LSM, median (Q1, Q3), kPa	12 (8.7, 17.3)	11.6 (9.1, 17.5)

[a]In the BLV 10 mg arm, 1 participant had HDV GT 5, and 1 had missing HDV GT.
[b]In the BLV 10 mg arm, 1 participant had HBV GT E, and 3 had no data available.

Results

Improvements in ALT and NITs were observed from BL through Week 144 in most participants, regardless of response to BLV (Table 5). The greatest improvement in median ALT levels were observed within the first year, with similar patterns observed for NITs. Improvements in NITs at Week 144 were also seen across all response categories, including participants with a VR (n=74), PR (n=7), and NR (n=8) at Week 144. In participants with a VR and PR, ALT reductions and changes in NITs were either maintained or continued to improve through Week 144. In participants with an NR, ALT levels and NIT scores were numerically higher at BL and at Week 144 than participants with a VR or PR.

Table 5. Changes in ALT Levels and NITs From BL Through Week 144 by Treatment Group (Brunetto et al)[4]

Median (Q1, Q3)	Week 48		Week 96		Week 144	
	BLV 2 mg	BLV 10 mg	BLV 2 mg	BLV 10 mg	BLV 2 mg	BLV 10 mg
ALT, U/L	-46 (-87, -24)	-69 (-111, -32)	-50 (-97, -28)	-76 (-148, -22)	-51 (-73, -35)	-68 (-120, -26)
LSM, kPa	-1.9 (-4.19, 0.05)	-2.8 (-5.2, -1.2)	-2.6 (-5.8 -1.2)	-3.9 (-7.1, -2.3)	-4 (-6, -1)	-3.8 (-6.7, -1.2)
APRI	-0.44 (-1.04, -0.22)	-0.63 (-1.05, -0.31)	-0.5 (-1.22, -0.21)	-0.6 (-1.13, -0.28)	-0.57 (-1.55, -0.25)	-0.54 (-1.14, -0.3)
FIB-4	-0.42 (-0.92, -0.13)	-0.44 (-0.64, -0.19)	-0.44 (-1.28, -0.11)	-0.45 (-0.93, -0.19)	-0.52 (-1.19, -0.03)	-0.43 (-0.94, -0.14)

No safety data were reported.

Interim Analysis of Phase 3 MYR301 Study: LSM Results Through 48 Weeks After EOT[5]

Study design and demographics

An interim analysis of study MYR301 assessed LSM outcomes at 48 weeks after EOT (Week 192) in participants who received BLV 2 or 10 mg for 144 weeks and in those in the DT BLV 10 mg group who received 96 weeks of treatment.

Table 6. BL Demographics and Disease Characteristics (Aleman et al)[5]

Key Demographics and Characteristics	BLV 2 mg (n=49)	BLV 10 mg (n=50)	DT BLV 10 mg (n=51)[a]
Age, mean (SD), years	44 (9)	41 (9)	41 (8)
Male, n (%)	30 (61)	30 (60)	26 (51)
Race, White/Asian/Black, n (%)	41 (84)/8 (16)/0	43 (86)/6 (12)/1 (2)	40 (78)/11 (22)/0
Cirrhosis, n (%)	23 (47)	24 (48)	24 (47)
Concomitant NUC therapy for HBV, n (%)	32 (65)	27 (54)	32 (63)
Prior IFN therapy, n (%)	26 (53)	29 (58)	29 (57)
ALT, mean (SD) U/L	108 (63)	123 (81)	102 (62)
HDV RNA, mean (SD), log_{10} IU/mL	5.1 (1.2)	4.96 (1.46)	5.08 (1.36)
HDV GT 1, n (%)	49 (100)	48 (96)[b]	51 (100)
HBsAg, mean (SD), log_{10} IU/mL	3.67 (0.52)	3.61 (0.59)	3.68 (0.47)
HBV DNA, mean (SD), log_{10} IU/mL	1.3 (1.29)	1.08 (1.26)	0.89 (0.99)
HBV GT, A/D/other, n (%)	2 (4)/47 (96)/0	2 (4)/44 (88)/4 (8)[c]	2 (4)/44 (88)/4 (8)[d]
LSM, mean (SD), kPa	14 (8.2)	14.8 (9.3)	15.3 (9)

[a]In the DT BLV 10 mg group, one participant withdrew prior to receiving BLV and is not included in subsequent reporting of efficacy and safety.
[b]In the BLV 10 mg arm, 1 participant had HDV GT 5, and 1 had missing HDV GT.
[c]In the BLV 10 mg arm, 1 participant had HBV GT E, and 3 had no data available.
[d]In the DT BLV 10 mg arm 2 participants had unclassified HBV GT.

Results

Improvements in LSM from BL to EOT were observed in all treatment arms, with numerical declines in those improvements through 48 weeks after EOT (Table 7).

Table 7. Changes in LSM From BL to EOT and 48 Weeks After EOT (Aleman et al)[5]

Least Squares Mean, kPa	BLV 2 mg	BLV 10 mg	DT BLV 10 mg
Changes in LSM from BL to EOT	-5.3	-4.1	-4.2
Changes in LSM from BL to 48 weeks after EOT	-3.8	-3.7	-1.9

ALT normalization and combined response rates decreased from EOT to 24 and 48 weeks after EOT (Table 8).

Table 8. Participants With ALT Normalization and Combined Response at EOT, and 24 Weeks and 48 Weeks After EOT (Aleman et al)[5]

Parameter, n (%)		BLV 2 mg (n=49)	BLV 10 mg (n=50)	DT BLV 10 mg (n=50)
ALT	EOT	29 (59)	30 (60)	29 (58)
	24 weeks after EOT	12 (24)	18 (36)	13 (26)
	48 weeks after EOT	13 (27)	14 (28)	12 (24)
Combined response	EOT	28 (57)	27 (54)	28 (56)
	24 weeks after EOT	11 (22)	16 (32)	10 (20)
	48 weeks after EOT	11 (22)	10 (20)	9 (18)

The safety profile both during treatment and post treatment was consistent with the known safety profile of BLV. No participants discontinued due to AEs through EOT, and no SAEs

were attributed to BLV. There was 1 death in the DT BLV 10 mg arm due to plasma cell myeloma deemed unrelated to study drug.

A total of 15 participants restarted BLV in the post-treatment period up to 48 weeks after EOT; of these, 10 participants had post-treatment ALT >5 × ULN. Of the 140 participants with ≥1 ALT value available after the last BLV dose, post-treatment ALT >5 and >10 × ULN occurred in 47 (34%) and 14 participants (10%; SAE, n=2), respectively.

Post-treatment hepatic SAEs were as follows: ALT >5 × ULN (n=10); liver-related hospitalization due to liver injury, attributed to tramadol/dexketoprofen (n=1), CHB (n=1), and esophageal varices hemorrhage (n=1); HDV viremia rebound (defined as an increase in post-treatment HDV RNA by ≥2 $\log_{10}$ IU/mL from the lower limit of quantitation or EOT level [n=8]); and requirement for treatment of HBV or HDV with BLV (n=8) or tenofovir disoproxil fumarate (n=1).

Single-Center Study on Changes in NITs After 96 Weeks of BLV 2mg Monotherapy[6]

Study design and demographics

A single-center study that enrolled consecutive participants with HDV, compensated cirrhosis, and clinically significant portal hypertension (N=46) was conducted to evaluate the changes in NITs in response to BLV monotherapy 2 mg/day for up to 96 weeks. Eligible participants had a VR, defined as ≥2 log HDV RNA decline from BL. APRI and FIB-4 were assessed at BL and every 8 weeks thereafter. Every 24 weeks, LSM and SSM (both by Fibroscan), pSWE (ElastPQ), and LSPS were assessed.

Table 9. BL Demographics and Disease Characteristics (Degasperi et al)[6]

Key Demographics and Characteristics	BLV 2 mg (N=46)
Age, median (range), years	52 (30–77)
Male, n (%)	27 (59)
Race,[a] White, n (%)	42 (91)
Quantitative HBsAg, median (range), log IU/mL	3.7 (0.8–4.4)
HDV GT 1, n (%)	45 (99)
HDV RNA, median (range), log IU/mL	5.2 (2.4–6.9)
Child-Pugh Stage A, n (%)	46 (100)
Esophageal varices, n (%)	25 (54)
Spleen diameter, median (range), cm	15 (9–25)
Previous ascites, n (%)	10 (22)
AST, median (range), U/L	89 (33–738)
ALT, median (range), U/L	98 (30–1074)
Bilirubin, median (range), mg/dL	1 (0.4–4.4)
Albumin, median (range), mg/dL	3.9 (2.9–4.6)
Platelets, median (range), 10^3/mm^3	78 (17–217)

[a]Race information was not provided for the remaining 4 participants.

Results

APRI and FIB-4 scores improved significantly over the course of BLV monotherapy through Week 96. LSM and LSPS both decreased significantly from BL to Week 48 (each *P*=0.001), with no further significant changes through Week 72 (Table 10)

Table 10. NIT Results: BL Through Week 96 (Degasperi et al)[6]

Median (Range)	BL	Week 24	Week 48	Week 72	Week 96	*P*-Value
APRI	3.5 (0.6–16.5)	1.5 (0.4–6.7)	1.3 (0.3–6.9)	1.3 (0.3–3.6)	1.2 (0.3–4.5)	<0.001
FIB-4	6.1 (1.3–28.1)	5.1 (1.1–12.9)	4.9 (0.9–14.3)	4.6 (0.9–7.2)	4.8 (1.2–9)	0.003
LSM, kPa	17.2 (6.4–68.1)	14.4 (5–51.9)	13.8 (5.4–54.3)	16.5 (6.2–40.4)	13.1 (5.3–43.4)	0.12
SSM, kPa	50.3 (19.7–100)	58.7 (12.8–100)	51.2 (23.1–100)	55.8 (18.2–100)	47.9 (21.2–96.9)	0.69
Liver ElastPQ, kPa	14.3 (4.2–35.2)	14.2 (4.4–41.4)	11.5 (5.8–36.5)	16.3 (6.6–25.8)	10.9 (7–22.3)	0.54
Spleen ElastPQ, kPa	36.9 (12.8–114)	46.8 (6.7–126)	38.2 (9.3–78.1)	44.2 (28.6–94.7)	30.6 (17.4–51.8)	0.31
LSPS	4.1 (0.5–23.7)	3.7 (0.21–30.7)	3.8 (0.3–14.3)	4.5 (0.3–9.5)	5.1 (0.4–8.8)	0.3

During the study, 4 participants received a liver transplant (HCC, n=2; liver decompensation, n=2), and 1 participant died of nonhepatic-related causes.

Single-Center Study on Changes in NITs After 48 Weeks of BLV 2 mg ± NUC Treatment[7]

Study design and demographics

A single-center study evaluated changes in NITs in patients who received 48 weeks of BLV 2 mg treatment for HDV. Overall, 19 patients had data available at BL and Week 48 (Table 11). Biochemical response was defined as ALT ≤40 U/L, and VR was defined as a reduction of HDV RNA by ≥2 $\log_{10}$.

Table 11. BL Demographics and Disease Characteristics (Mani et al)[7]

Key Demographics and Characteristics		BLV 2 mg (N=19)
Age, median (range), years		53 (41–63)
Male, %		36.8
BLV monotherapy, n (%)		5 (26.3)
BLV in combination with NUC, n (%)		14 (73.7)
Cirrhosis,[a] n (%)		13 (68.4)
HCC, n		1
NITs, median (IQR)	LSM, kPa	11.9 (8–18.2)
	APRI	1.29 (0.62–2.04)
	FIB-4	3.69 (1.38-4.92)

[a]Diagnosed based on clinical or imaging findings or LSM >10 kPa.

Results

VR, biochemical response, or combined response, defined as VR + biochemical response, was observed in 15 (78.9%), 9 (47.4%), and 7 patients (36.8%), respectively, at Week 48 of treatment with BLV. In the overall population, 12 patients (75%) had a reduction in LSM from BL, and 4 (25%) had no reduction. Treatment with BLV resulted in a significant median (IQR) change from BL in liver stiffness from 11.9 (8–18.2) kPa at baseline to 8.4 (6.5–12.3) kPa at Week 48 (P<0.001). There was a significant increase in the number of patients with LSM ≤10 kPa from BL (n=6; 31.6%) to Week 48 (n=12; 63.2%; P=0.024).

There was no significant difference in changes in liver stiffness between subgroups of patients with and without cirrhosis (*P*=0.103), with and without an HDV RNA decline of ≥2 $\log_{10}$ (*P*=0.333), or with and without biochemical response (ALT ≤40 IU; *P*=0.394).

There was a significant difference in the change in APRI and FIB-4 scores from BL to Week 48 between patients who had a biochemical response and those who didn't (*P*=0.004 and *P*<0.001, respectively; Table 12). Changes in FIB-4 scores were positively correlated with changes in APRI scores (*P*<0.001).

Table 12. Change From BL to Week 48 in NITs by Response Type (Mani et al)[7]

Parameter, Median (Change From BL)		Week 48		*P*-Value
		Response	No Response	
LSM	VR	-5.8 (-9.7 to -0.8)	-0.2 (-0.5 to -0.2)	0.333
	BR	-5.8 (-9.7 to 0.25)	-1.9 (-8.4 to 0.1)	0.394
APRI	VR	-0.6 (-1.5 to 0.1)	0.1 (-0.6 to 0.3)	0.23
	BR	-0.99 (-4.31 to -0.45)	0.14 (-0.38 to 0.59)	0.004
FIB-4	VR	-0.5 (-3.2 to 0.2)	0.5 (-0.8 to 2.5)	0.291
	BR	-2.2 (-6.2 to -0.8)	0.2 (0.01 to 3.3)	<0.001

Abbreviation: BR=biochemical response.

Safety data were not reported.

References

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3. Lampertico P, Aleman S, Bogomolov P, et al. Improvement in Liver Histology Is Observed in Most Patients With Chronic Hepatitis Delta After 48 Weeks of Bulevirtide Monotherapy [Poster WED-392]. Paper presented at: European Association for the Study of the Liver (EASL); June 05-08, 2024; Milan, Italy.
4. Brunetto M, Aleman S, Andreone P, et al. Improvement in 3 Noninvasive Tests Through 144 Weeks of Bulevirtide Monotherapy in Patients With Chronic Hepatitis Delta With and Without Virologic Response. [Poster #WED-308]. Paper presented at: European Association for the Study of the Liver; May 7–10 2025; Amsterdam, the Netherlands.
5. Aleman S, Brunetto M, Blank A, et al. Predictors of undetectable hepatitis delta virus RNA at 48 weeks after end of treatment with bulevirtide monotherapy in the MYR 301 study. [Oral Presentation #OS-066]. Paper presented at: European Association for the Study of the Liver; May 7–10 2025; Amsterdam, the Netherlands.
6. Degasperi E, Anolli MP, Renteria SU, et al. Significant Improvement Of Non-Invasive Fibrosis Tests In HDV Compensated Cirrhotic Patients With Clinically Significant Portal Hypertension Treated With BLV Monotherapy Up To 96 Weeks [Poster SAT-175]. Paper presented at: European Association for the Study of the Liver (EASL); June 21-24, 2023; Vienna, Austria.
7. Mani I, Nasika E, Pelekanos A, et al. Effect of 48-Week Bulevirtide Therapy on Non-Invasive Markers of Liver Fibrosis In Patients with HBEAG Negative Chronic Hepatitis B/D. [Poster #2274]. Paper presented at: The Liver Meeting AASLD; November 7-11, 2025; Washington, D.C.

Abbreviations

AE=adverse event
APRI=AST to platelet ratio index
BL=baseline
BLV=bulevirtide-gmod
DT=delayed treatment
CHB=chronic hepatitis B
CHD=chronic hepatitis D
EOT=end of treatment
FIB-4=Fibrosis-4 Index
GT=genotype
HAI=histologic activity index
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
IFN=interferon
LSM=liver stiffness measurement
LSPS=liver stiffness-spleen size to platelet ratio score
pSWE=point shear-wave elastography
NIT=noninvasive test of liver fibrosis
NR=nonresponse
NUC=nucleos(t)ide analogue
PR=partial response
Q=quartile
SAE=serious adverse event
SSM=spleen stiffness measurement
SUBQ=subcutaneous(ly)
ULN=upper limit of normal
VR=virologic response

Product Label

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