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Hepcludex® (bulevirtide-gmod) Real-World Data

This document is in response to your request for real-world data, including data from compassionate use and early access programs, regarding the use of Hepcludex® (bulevirtide-gmod [BLV]) for the treatment of chronic HDV infection. This response was developed according to principles of evidence-based medicine and only contains data from real-world studies (N≥200).

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 subcutaneous 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.

Real-World Data: BLV Use in Chronic HDV Infection

In the prospective D-SHIELD study of BLV 2 mg as monotherapy in Italy that included participants with (n=356) and without cirrhosis (n=138), 69% and 63%, respectively, had a VR, 32% and 13% achieved undetectable HDV RNA (*P*=0.01), 74% and 70% had a BR, and 58% and 47% achieved a CR at Week 72. There was no significant difference in the incidence of AEs between participants with and without cirrhosis through Week 72: 15% vs 15%, respectively (*P*=1).[2]

In the retrospective, multicenter European SAVE-D study of treatment with BLV 2 mg as monotherapy in patients with cirrhosis (N=424), 59% of patients had undetectable HDV RNA

levels, 85% had a VR, and 84% had a BR at Week 192. De novo LREs occurred as follows: HCC, n=20; and decompensation, n=9. Safety outcomes, rates of undetectable HDV RNA at Weeks 96 and 144, and an analysis of LREs are summarized below.[3]

In a pooled analysis of outcomes of patients enrolled in the D-SHIELD and SAVE-D studies (N=689), the proportions of patients with undetectable HDV RNA and those with VR, BR, and CR increased from Week 24 to Week 48 with BLV; Week 48 rates were similar to those observed at Week 72. At Week 72, 35% of patients had undetectable HDV RNA levels, 66% had a VR, and 64% had a BR. De novo LREs occurred in 20 patients with cirrhosis: HCC, n=14; decompensation, n=6.[4] Outcomes for patients with Week 96 data were generally similar to those observed at Week 96. Of the patients with Week 48 and 72 data, 48 VBKs occurred, and 20 VBKs occurred among those with Week 48, 72, and 96 data. None of the patients who developed VBK also had a de novo LRE.[5]

In the ongoing, prospective PITER cohort study in Italy, during the first year of follow-up, participants who received BLV (n=253) had a significantly lower incidence of death than those who did not receive BLV (n=137; $P<0.05$), and the cumulative incidence of HCC was numerically higher with BLV treatment than without it ($P=0.199$). No safety data were reported.[6]

D-SOLVE, a case-control study evaluated the risk of LREs in patients who received BLV 2 mg monotherapy for up to 3 years. The crude incidence of LREs was numerically lower in the BLV cohort than in the no-BLV cohort: 8.9% vs 14.8%, respectively ($P=0.1$). The cumulative incidence of decompensation was significantly higher in the BLV cohort than in the no-BLV cohort: 2.7% vs 11.3%, respectively ($P=0.001$). Similarly, the incidence of HCC was higher, though not significantly, in the BLV vs the no-BLV cohort: 6.6% vs 3.6% ($P=0.5$).[7]

Real-World Data: BLV Use in Chronic HDV Infection

D-SHIELD: Prospective Italian Study

Study design and demographics[2,8]

A prospective, multicenter, real-world study assessed the effectiveness and safety of BLV 2 mg monotherapy as treatment for chronic HDV infection in participants with and without cirrhosis (N=494). Effectiveness endpoints included VR (defined as an HDV RNA ≥2 log IU/mL decline from baseline or undetectable HDV RNA [TND or <level of detection]), BR (defined as ALT level <40 U/L), CR (defined as VR and BR), VBK (defined as a >1 log IU/mL increase in HDV RNA from the previous timepoint), and safety. In this analysis, 356 participants with cirrhosis and 138 participants without cirrhosis were included.

Table 1. D-SHIELD: Baseline Demographics and Disease Characteristics by Cirrhosis Status[2]

Key Demographics and Characteristics	BLV 2 mg (N=494)		*P*-Value
	Cirrhosis (n=356)	No Cirrhosis (n=138)	
Age,[a] years	54 (45–60)	49 (42–57)	<0.001
Male, n (%)	191 (55)	67 (52)	0.58
European origin, n (%)	333 (96)	119 (93)	0.13
HDV RNA, median (IQR), log U/L	5.2 (3.9–6)	5.3 (4.3–5.9)	0.02
HDV GT 1, n (%)	76 (99)	23 (96)	0.12

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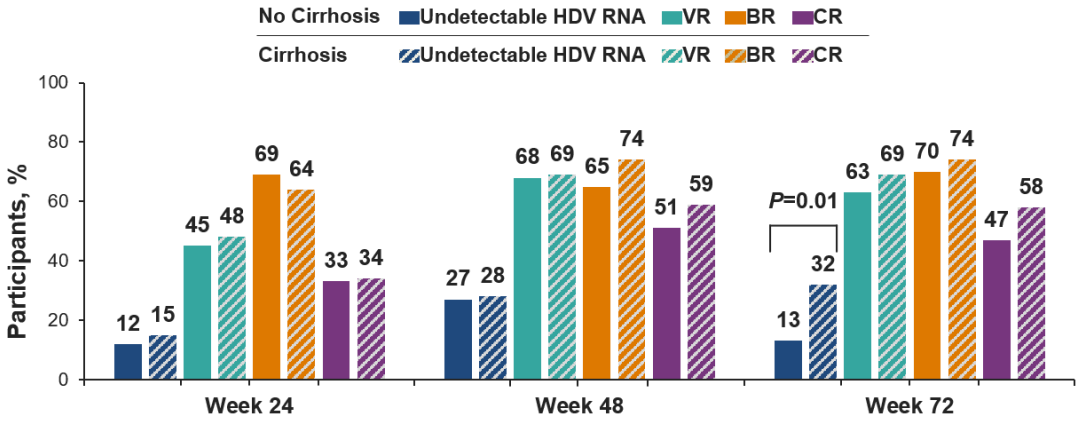
Key Demographics and Characteristics	BLV 2 mg (N=494)		*P*-Value
	Cirrhosis (n=356)	No Cirrhosis (n=138)	
qHBsAg,[a] log U/L	3.7 (3.2–4.1)	3.7 (3.3–4.2)	0.05
HBV DNA+, n (%)	21 (12)	6 (10)	0.81
HBeAg-, n (%)	297 (92)	96 (91)	0.79
LSM,[a] kPa	15.8 (11.7–24)	7.9 (6.1–10.2)	<0.001
ALT,[a] U/L	75 (49–123)	75 (45–109)	0.19
AST,[a] U/L	74 (51–106)	53 (37–76)	<0.001
Bile acids, mcmol/L	12 (7–23)	6 (3–9)	<0.001
NUC treatment, n (%)	335 (98)	113 (91)	<0.001
Previous IFN treatment, n (%)	185 (46)	61 (48)	0.74

Abbreviations: qHBsAg=quantitative hepatitis B surface antigen.
[a]Presentation of data was not specified (ie, median [IQR] or median [range]).

Effectiveness results

Most of the effectiveness outcomes with BLV were not significantly different between participants with and without cirrhosis through Week 72 (Figure 1). Though significantly different between participants with and without cirrhosis at Week 72 (*P*=0.01; Figure 1), HDV RNA levels were similar at all other timepoints (*P*>0.05 at each time point).[2]

Figure 1. D-SHIELD: Undetectable HDV RNA, VR, BR, and CR Among Participants by Cirrhosis Status Through Week 72[2]



Note: Undetectable HDV RNA referred to values <level of detection or TND.

In a subanalysis of 165 participants with paired data, 10 of the 75 participants (13%) with Week 24 and 48 data had a VBK within that window, and the rate of participants with an ALT level <ULN decreased from 80% to 40%. Of those with Week 48 and 72 data, 17/106 participants (16%) had a VBK within that window, and the rate of participants with an ALT <ULN decreased from 59% to 41%. There were no differences in the rate of VBKs in participants with and without cirrhosis.[2]

Safety[2]

AE rates were the same between those with and without cirrhosis: 15% vs 15%, respectively (*P*=1). The most common AEs were transient and mild pruritus and ISRs. Bile acid levels were significantly higher among those with cirrhosis than those without at baseline and at each timepoint (each, *P*<0.001).

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SAVE-D: Retrospective European Study

Study design[3]

A retrospective, multicenter, real-world study in Europe evaluated the effectiveness and safety of BLV 2 mg as monotherapy in patients with HDV and compensated cirrhosis. The primary endpoint was the proportion of patients who achieved VR, defined as a decrease in HDV RNA by ≥2 $\log_{10}$ IU/mL or undetectable HDV RNA.

Analysis of patients who received BLV for up to 192 weeks[3]

An analysis evaluated outcomes in 424 patients who received up to 192 weeks of BLV 2 mg monotherapy. The median (IQR) age was 50 (40–58) years, and 61% of patients were male. Most patients (96%; n=405) were CPT Class A, 33 (7%) had HIV (all had undetectable HIV RNA levels), 38 (9%) had previously experienced decompensation events, 33 (7%) had a history of HCC, 381 (90%) were receiving NUC treatment at baseline, and 244 (58%) had received previous IFN treatment. Of the patients with available GT data, 148/160 (93%) had HDV GT 1. The median (IQR) levels of select disease characteristics were as follows: HBsAg, 3.7 (3.2–4.1) $\log_{10}$ IU/mL; LSM, 16.5 (12.6–25.3) kPa; ALT, 78 (51–128) U/L (90% had an ALT level >ULN); and AST, 69 (51–105) U/L.

Effectiveness

Cumulatively, at Week 192, 85% of patients had a VR, 84% had a BR, 75% had a CR, and 59% had undetectable HDV RNA (Table 2). Of the 125 patients with available data at Week 144, an ALT level ≤ULN was achieved by the following proportions in each HDV response category: <lower limit of quantification, 81%; ≥2 log decrease, 74%; ≥1 to <2-log decrease, 58%; and <1 log decrease, 47%. Through Week 144, LSM values at each timepoint were significantly lower than the baseline value (all, *P*<0.001). The proportion of patients who were ruled in for CSPH (defined as LSM >25 kPa) decreased from 26% at baseline to 13% at Week 144.

Table 2. SAVE-D: Effectiveness Outcomes Through Week 192[3]

Parameter	Baseline (N=424)	Week 48 (n=315)	Week 96 (n=200)	Week 144 (n=125)	Week 192 (n=59)
Undetectable HDV RNA, %	0	29	39	35	41
HDV RNA, median (IQR), $\log_{10}$ IU/mL	5.4 (4.2–6.3)	2.8 (1.7–3.9)	2.3 (0.8–3.8)	2.5 (0.7–3.7)	2.5 (0.3–3.5)
VR, %	0	64	72	73	79
BR, %	10	64	65	69	71
CR, %	0	44	50	54	59
LSM,[a] median (IQR), kPa	16.5 (12.6–25.3)[b]	13.1 (9.6–19.7)[b]	11.8 (8.4–16.4)[b,c]	12.2 (8.7–19.3)[b,d]	Not reported
CSPH categories,[a] rule-in[e]/probable[f]/rule-out,[g] %	26/22/14	16/16/19	16/13/24	13/11/15	Not provided

[a]Baseline, n=386; Week 48, n=182; Week 96, n=103; Week 144, n=78. [b]*P*<0.001 vs baseline.
[c]*P*=0.08 vs Week 96. [d]*P*=0.95 vs Week 96.
[e]LSM >25 kPa. [f]LSM >20 to ≤25 kPa and platelet count <150 10^9/L or LSM >15 to ≤20 kPa and platelet count <110 10^9/L.
[g]LSM ≤15 kPa and platelet count ≥150 10^9/L.

Overall, 29 de novo LREs occurred, including the following: HCC, n=20 (cumulative incidence, 6.8%; 95% CI: 3–9%); decompensation, n=9 (ascites, n=6; variceal bleeding, n=3; cumulative incidence, 2.3%; 95% CI: 1–4%). In a multivariate Cox regression analysis,

baseline age, BMI, and albumin levels were predictors of HCC development, and baseline albumin level was a predictor of decompensation development. Fourteen deaths occurred, including 9 liver-related deaths, and 29 liver transplantations occurred (HCC, n=22; ESLD, n=7).

In a subanalysis of 115 patients who had paired Week 48 and 144 assessments, 23 VBKs (defined as ≥1 $\log_{10}$ increase vs previous timepoint) occurred: 5 at Week 48, 8 at Week 96, and 10 at Week 144.

Safety

Median (IQR) bile acids increased from 15 (7–32) mcmol/L at baseline (9% had levels <ULN at BLV initiation) to 31 (17–61) mcmol/L at Week 192. The most common BLV-related AEs included mild, transient pruritus (8%; n=34) and ISRs (3%, n=12). Overall, 30 patients discontinued BLV, including 3 who discontinued at Week 48 due to long-term HDV RNA TND (2 had undetectable HDV RNA at last follow-up, which was 120–144 weeks after BLV discontinuation; 1 had virologic relapse 43 weeks after BLV discontinuation), 2 who discontinued at Week 72 to 96 due to virologic NR, and 2 who discontinued at Week 48 to 120 due to liver decompensation.

Rates of undetectable HDV RNA at Weeks 96 and 144[9]

A subanalysis was conducted in 70 patients who achieved undetectable HDV RNA at Week 48 of treatment with BLV to evaluate the durability of response at Weeks 96 and 144. Analyses were conducted in patients with paired undetectable HDV RNA data at Weeks 48 and 96 (n=41) and in those with paired undetectable HDV RNA data available at Weeks 48 and 144 (n=23).

In the paired Week 48 to 96 analysis, 32 patients (78%) maintained undetectable HDV RNA through Week 72; this increased to 36 participants at Week 96. Of the 9 patients with VBK at Week 72, 4 (10%) had transient VBK up to Week 96, and 5 (12%) had VBK that remained stable at Week 96 (~1 $\log_{10}$ IU/mL [n=2]; ≥2 $\log_{10}$ IU/mL [n=3]). All but 1 patient with VBK maintained a BR.

In the paired Week 48 to 144 analysis, 20 patients maintained persistent undetectable HDV RNA to Week 72, while 3 had transient VBK; 19 maintained undetectable HDV RNA to Week 96 (including the 3 patients with VBK at Week 72), while 4 patients had transient VBK; 16 maintained persistent undetectable HDV RNA to Week 120 (including the 4 patients with VBK at Week 96), and 7 had transient VBK; 17 continued to have undetectable HDV RNA at Week 144 (including the 4 patients with VBK at Week 96), and 6 had new VBK, 4 of whom maintained a BR. Of the participants with VBK at Week 144, 1 (4%) had stable VBK, and 5 (22%) had de novo VBK (~1 $\log_{10}$ IU/mL [n=3]; ≥2 $\log_{10}$ IU/mL [n=2]).

In 3 patients with sustained undetectable HDV RNA, de novo HCC (n=2) and ascites (n=1) were observed. One patient with VBK developed HCC, and another developed ascites recurrence.

Analysis of LREs[10]

A study was conducted to evaluate liver-related events in patients who received up to 144 weeks of BLV 2 mg monotherapy (N=344). Excluding 22 patients with previous HCC, 16 patients developed HCC (cumulative incidence, 6.9%; 95% CI: 3–11%). The median time to HCC was 15 (11–27) months; 88% of those patients had CPT Class A, 75% had clinically significant portal HTN, and 63% had achieved a VR to BLV. The 3-year cumulative incidence (95% CI) of HCC in patients with baseline clinically significant portal HTN and

without it was 8.8% (3–13%) and 4.7% (1–9%), respectively (*P*=0.14). Excluding 47 patients with previous decompensation, 8 patients developed decompensation, 4 each with ascites and bleeding (cumulative incidence, 3%; 95% CI: 1–6%). The median (IQR) time to decompensation was 18 (9–21) months; 63% of those patients had a baseline CPT score of A6, 6 patients (75%) had achieved a VR to BLV treatment, and 2 patients had a triggering event. The 3-year cumulative incidence of decompensation was significantly higher in patients with baseline clinically significant portal HTN (6.9%; 95% CI: 3–12%) than in patients without it (0%; *P*=0.001).

A Cox regression univariate analysis showed that a higher BMI at baseline, spleen size, low albumin levels, low platelet levels, high liver stiffness, and clinically significant portal HTN at baseline were associated with the development of LREs. In a multivariate analysis, only low albumin levels were independently associated with LREs (HR, 0.28; 95% CI: 0.11–0.71; *P*=0.01).

Over the course of 3 years, the liver transplantation- or death-free survival rate was 88.2% (95% CI: 84–92%). Eleven patients died, 5 due to LREs, and 21 patients underwent liver transplantation (HCC, n=18; decompensation, n=3).

Pooled Analysis of D-SHIELD and SAVE-D

Study design and demographics[4]

A pooled analysis of data from patients with chronic HDV enrolled in the D-SHIELD and SAVE-D studies evaluated the real-world effectiveness, safety, and clinical outcomes of BLV 2 mg monotherapy after 24, 48, and 72 weeks of treatment.

Table 3. Pooled Analysis of D-SHIELD and SAVE-D: Baseline Demographics and Disease Characteristics[4]

Key Demographics and Characteristics	BLV 2 mg (N=689)
Age, median (IQR), years	52 (42–60)
Male, n (%)	402 (58)
Previous decompensation,[a] n (%)	60 (9)
History of HCC,[b] n (%)	41 (6)
CPT Class A,[c] n (%)	667 (97)
ALT, median (IQR), U/L	75 (50–120)
HDV GT1,[d] n (%)	171 (95)
HDV RNA, median (IQR), $\log_{10}$ IU/mL	5.3 (4.1–6.3)
HBsAg, median (IQR), $\log_{10}$ IU/mL	3.7 (3.2–4.1)
NUC treatment for HBV, n (%)	642 (93)
Previous IFN treatment, n (%)	359 (52)
HIV co-infection,[e] n (%)	54 (8)

[a]Ascites was observed in 46 participants (7%), with bleeding observed in 14 (2%).
[b]Active HCC in 23 participants. [c]CPT A6 in 120 participants (17%) and CPT B in 22 (3%).
[d]Data were available for 180 participants. [e]With undetectable HIV RNA.

Results through Week 72[4]

BR with BLV was observed in 13% of participants at baseline, which increased to 49% by Week 24 (Table 4). Undetectable HDV RNA and individual responses increased from Week 24 to Week 48 with BLV; Week 48 rates were similar to those observed at Week 72 (Table 4). Virologic NR occurred in 18% of participants, and a PR was observed in 16%.

Among the 95 participants with suboptimal response (NR or PR), 45% had a BR with BLV treatment. Of those without a BR, 16% achieved ≥50% reduction in ALT from baseline.

Table 4. Pooled Analysis of D-SHIELD and SAVE-D: Effectiveness Outcomes Through Week 72[4]

Parameter, %	Baseline	Week 24	Week 48	Week 72
Undetectable HDV RNA	0	18	30	35
VR	0	49	67	66
BR	13	61	66	64
CR	0	33	48	49

Among 261 patients with paired Week 24, 48, and 72 data, 14 (5%) who had a VR at Week 24 had a VBK (defined as a ≥1 $\log_{10}$ IU/mL increase in HDV RNA from the lowest level) at Week 48. With continued BLV treatment, 4 participants regained a VR, and 2 had a PR; 8 maintained an NR, and normalized ALT was observed in 50% of these participants.

No significant BLV effect on HBsAg levels was observed in the overall population; lower baseline HDV RNA was linked to undetectable HDV RNA at Week 48 based on multivariate analysis. De novo LREs were observed in 20 patients with cirrhosis: HCC, n=14; decompensation, n=6.

Paired analysis of VBK[5]

A subanalysis of 268 patients from the SAVE-D and D-SHIELD studies with paired baseline and Week 48 and 72 data, including 111 with Week 96 data, evaluated the rate and timing of VBKs. At baseline, the median (IQR) age was 50 (40–58) years, 62% were male, 83% were Caucasian, 98% were CPT Class A, 94% had cirrhosis, 95% were receiving NUC treatment, and 56% had previous IFN treatment. The median (IQR) values for select disease characteristics were as follows: HDV RNA, 5.4 (4.1–6.5) $\log_{10}$ IU/mL; HBsAg, 3.7 (3.4–4.1) $\log_{10}$ IU/mL; LSM, 15.4 (11.5–24.4) kPa; and ALT, 93 (54–146) U/L.

Response rates were generally similar at Week 48, 72, and 96 (Table 5).

Table 5. Pooled Analysis of D-SHIELD and SAVE-D: Response Rates[5]

Parameter, %	Baseline	Week 48	Week 72	Week 96
Undetectable HDV RNA	0	28	35	38
VR	0	68	66	68
BR	13	67	64	65
CR	0	52	49	50

VBK occurred in 17% of patients and was generally transient. Among the patients with Week 48 and 72 data, 48 VBKs occurred, including in 18 patients at Week 48, 9 (50%) of whom had achieved BR, and in 30 patients at Week 72, 10 (33%) of whom had achieved BR. Among the patients with Week 48, 72, and 96 data, 20 patients had VBKs as follows: 5 at Week 48, including 3 (60%) who had achieved BR; 7 at Week 72, including 3 (43%) who had BR; and 8 at Week 96, including 7 (88%) who had BR. None of the patients who developed VBK also had a de novo LRE. Baseline ALT levels (P=0.08), HDV RNA (P=0.72), and cirrhosis status (P=0.15) were not predictors of VBK occurrence.

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PITER Cohort Study[6]

Study design and demographics

An interim analysis was performed for participants who were HDV RNA+/anti-HDV+ and enrolled in the ongoing, prospective PITER cohort in Italy, and outcomes were compared for those who did (n=253) and did not receive BLV (n=137).

Table 6. PITER Cohort Study: Baseline Demographics and Disease Characteristics[6]

Key Demographics and Characteristics	BLV Cohort (n=253)	No-BLV Cohort (n=137)	*P*-Value
Age, median (Q1, Q3), years	56 (47, 64)	59 (49, 65)	0.7482
Male, n (%)	145 (57.31)	83 (60.58)	0.689
Non-Italian natives, n (%)	104 (41.11)	47 (34.31)	0.188
HDV RNA, geometric mean ± SD, IU/mL	58,085.56±34.7	31,214.01±43.437	0.173
HBeAg+, n (%)	22 (9.24)	7 (5.3)	0.177
Child Pugh class, A/B/C, n (%)	152 (91.57)/12 (7.23)/ 2 (1.2)	59 (73.75)/19 (23.75)/ 2 (2.5)	0.001
Cirrhosis, n (%)	195 (77.38)	94 (68.61)	0.059
MELD ≥20, n (%)	1 (0.59)	3 (3.8)	0.061
LSM, mean ± SD, kPa	16.34±10.38	14.46±8.87	0.1825
HCC, n (%)	19 (7.6)	26 (19.7)	<0.001
ALT >35 IU/mL, n (%)	217 (86.11)	86 (67.19)	<0.001
Ongoing NUC treatment, n (%)	227 (89.72)	100 (73.53)	<0.001
Duration of NUC treatment, median (Q1, Q3), years	5 (2, 8)	4 (1, 7.5)	0.5496
Previous IFN treatment, n (%)	28 (11.07)	10 (7.3)	0.231

Abbreviation: MELD=Model for End-Stage Liver Disease; Q=quartile.

Results

After a median follow-up time of approximately 12 months in each cohort, the cumulative incidence of death was significantly lower in the BLV cohort than in the no-BLV cohort (*P*<0.05; Table 7). Though the cumulative incidence of HCC was numerically higher in the BLV cohort than in the no-BLV cohort, the difference did not reach significance (*P*=0.199; Table 7). Due to the small number of events, unbalanced participant populations, and relatively short follow-up, competing risk propensity analysis and multivariable models were not performed.

No significant changes in LSM from baseline to follow-up occurred in either cohort (Table 7). From baseline to follow-up, participants in the BLV cohort had significant decreases in ALT, AST, and HDV RNA levels (each, *P*<0.001); however, no significant changes occurred in the no-BLV cohort. No safety data were reported.

Table 7. PITER Cohort Study: Effectiveness Endpoints During First Year of Follow-Up[6]

Outcomes		BLV Cohort (n=253)	No-BLV Cohort (n=137)
Deaths	Events, n	2	7
	Rate per 100 person-months	0.11	0.66
	Cumulative incidence (IQR), %	1.4 (0.3–5.6)[a]	7.6 (3.6–15.9)
HCC	Events, n	6	7
	Rate per 100 person-months	0.36	0.11
	Cumulative incidence (IQR), %	4.9 (2.2–11.3)[b]	1.3 (0.2–9.6)

Outcomes		BLV Cohort (n=253)	No-BLV Cohort (n=137)
LSM	Baseline, mean, kPa	9.5	15.4
	Follow-up, mean, kPa	8.2[c]	14.6[d]

[a]*P*<0.05 for BLV vs no BLV. [b]*P*=0.199 for BLV vs no BLV.
[c]*P*=0.11 for baseline vs follow-up. [d]*P*=0.06 for baseline vs follow-up.

D-SOLVE: Case-Control Study – Risk Analysis of LREs[7]

Study design and demographics

A case-control study evaluated the impact of BLV 2 mg monotherapy treatment for up to 3 years in consecutive patients with chronic HDV. Data on the incidence and risk of de novo LREs (defined as decompensation, HCC, deaths, and liver transplantation) were compared between those who were treated with BLV from a retrospective European cohort study and those who were not from two cohorts (one in Italy and another in France).

Table 8. D-SOLVE Case-Control Study on Risk of LREs: Baseline Demographics and Disease Characteristics[7]

Key Demographics and Characteristics		BLV Cohort (n=344)	No-BLV Cohort (n=298)
Age, mean ± SD, years		50±11.6	40±10.5
Male, n (%)		213 (62)	223 (78)
Caucasian, n (%)		289 (84)	186 (62)
HDV RNA, mean ± SD, log_{10} IU/mL		5.2±1.5	4.6±1.7
HBV	Undetectable, n (%)	256 (74)	169 (57)
	Median, log_{10} IU/mL	1.4	2.3
HBsAg, mean ± SD, log_{10} IU/mL		3.6±0.7	3.5±0.7
CPT score, A/A6, %		95/22	80/22
Previous decompensation, n (%)		35 (10)	42 (14)
Previous HCC, n (%)		25 (7)	20 (7)
Esophageal varices,[a] n (%)		125 (48)	130 (49)
CSPH, n (%)		208 (60)	166 (56)
LSM, mean ± SD, kPa		20.5±11.8	22±14.8
ALT, mean ± SD, U/L		113±113	172±349
NUC treatment, n (%)		312 (91)	119 (40)
Previous IFN treatment, n (%)		205 (59)	151 (51)

[a]Data were available for 75% of patients in the BLV cohort and for 89% in the no-BLV cohort.

Results

Though the difference did not reach statistical significance, the crude incidence of LREs (95% CI) was numerically lower in the BLV cohort than in the no-BLV cohort: 8.9% (4–12%) vs 14.8% (8–18%), respectively (*P*=0.1). The cumulative incidence (95% CI) of decompensation was significantly lower in the BLV cohort than in the no-BLV cohort: 2.7% (1–4%) vs 11.3% (7–16%), respectively (*P*=0.001). There was no significant difference in the cumulative incidence (95% CI) of HCC between cohorts: BLV, 6.6% (3–11%); no BLV, 3.6% (2–7%; *P*=0.5).

In an IPTW Cox regression analysis, the risk of LREs (HR, 0.53; 95% CI: 0.32–0.88; *P*=0.01) and decompensation (HR, 0.16; 95% CI: 0.07–0.36; *P*<0.001) was lower with BLV than without it; however, this difference was not observed for the risk of HCC (HR, 1.08; 95% CI: 0.58–2.02; *P*=0.81). Similar results were observed in an IPTW-adjusted competing risks regression model (vs pooled untreated cohorts or each individual cohort).

Of those who received BLV, 5 underwent liver transplantation for de novo HCC, and all died (HCC, n=2; ESLD, n=2). Of those who did not receive BLV, 7 underwent liver transplantation (ESLD, n=5; HCC, n=2) and 6 (all with ESLD) died, including 4 from liver-related causes. The Year 3 survival rate (95% CI) was similar between cohorts: BLV, 94.6% (92–98%); no BLV, 93.5% (89–97%). The risk of any-cause mortality or liver transplantation in an IPTW-adjusted analysis was similar between the BLV and no-BLV cohorts (HR, 0.74; 95% CI: 0.49–1.11; *P*=0.15).

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Abbreviations

AE=adverse event
BLV=bulevirtide-gmod
BR=biochemical response
CPT=Child-Pugh-Turcotte
CR=combined response
CSPH=clinically significant portal hypertension
ESLD=end-stage liver disease
GT=genotype
HBeAg=hepatitis B envelope antigen
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
HR=hazard ratio
HTN=hypertension
IFN=interferon
IPTW=inverse probability of treatment weighting
ISR=injection site reaction
LRE=liver-related event
LSM=liver stiffness measurement
NR=nonresponse
NUC=nucleos(t)ide analog
PITER=Italian Platform for the Study of Viral Hepatitis Therapy
PR=partial response
TND=target not detected
ULN=upper limit of normal
VBK=virologic breakthrough
VR=virologic response

Product Label

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