GILEAD | Medical Information

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≥50) that were published in peer-reviewed journals.

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.

Real-World Data: BLV Use in Chronic HDV Infection

In a prospective study of BLV 2 mg as monotherapy in Italy that included participants with and without cirrhosis (D-SHIELD; n=474), 69% had a virologic response, 29% achieved undetectable HDV RNA, 73% had a biochemical response, and 58% achieved a combined response at Week 72. There were no significant differences in virologic or biochemical responses between participants with and without cirrhosis through Week 72.[2]

In an early access program in France (cATU; N=139), 52% of participants treated with BLV 2 mg monotherapy and 41% of participants treated with BLV + PEG-IFNα achieved an on-treatment combined response at Month 24. No new safety signals were observed, and

29% and 38% of participants who received BLV 2 mg and BLV + PEG-IFNα, respectively, discontinued treatment at or before Month 12. No participants discontinued due to BLV-related AEs.[3]

In a prospective French multicenter study (BuleDelta ANRS; N=115), 58% of participants who received BLV as monotherapy or with PEG-IFN achieved virologic response, and 46% achieved ALT normalization at Week 24. Of the 55 participants with effectiveness data through Week 48, 76% achieved virologic response, and 50% achieved ALT normalization. Grade 3 to 4 AEs occurred in 41% of participants through Week 24.[4]

In a retrospective German study that assessed changes in ALT levels and HDV RNA in 114 patients treated with BLV for chronic HDV, ALT levels normalized at Week 12 (n/N=9/26) and Week 24 (n/N=5/26). Among patients without a virologic response, ALT levels declined significantly from baseline at Weeks 12 and 24.[5]

In a retrospective, observational study in Germany that included patients with advanced liver disease (N=109), significant improvements in HDV RNA and ALT levels and FIB-4 scores were observed from baseline to Weeks 12 and 24.[6]

In a prospective, observational study in Italy (ARISTOTLE; N=108) that assessed outcomes in participants who received BLV 2 mg ± NUC, 59 participants (54.6%) achieved a composite outcome; 36 of these participants had a complete virologic response, and 23 participants achieved both a decline in HDV RNA of ≥2 $\log_{10}$ IU/mL and ALT normalization.[7]

In a retrospective Italian study of patients with cirrhosis (N=93), treatment with BLV 2 mg monotherapy resulted in a virologic response rate of 75% at Week 72 and increased rates of ALT normalization and combined response from baseline through Week 72. No patients discontinued due to BLV-related AEs.[8]

In a retrospective, cross-sectional survey of HRQoL in several European countries (N=79), HBQoL scores were improved in the BLV monotherapy for ≥6 months group than in the TN group, while FSS-7, EQ-5D-5L Index, and EQ-5D VAS scores were numerically similar between groups.

In a prospective Greek study (HERACLIS_BLV_D; N=76), the rates of virologic response, complete virologic response, ALT normalization, and combined response were 93.5%, 80%, 74%, and 74%, respectively, after 24 months of BLV 2 mg daily ± NUC treatment.[9]

In a multicenter European cohort (N=58), 54% of participants achieved virologic response and 77% achieved ALT normalization at Week 24 with BLV 2 mg monotherapy. No AEs were reported.[10]

Real-World Data: BLV Use in Chronic HDV Infection

Prospective Italian Study (D-SHIELD)[2]

Study design and demographics

A prospective, multicenter, real-world study assessed the effectiveness and safety of BLV 2 mg SUBQ monotherapy as treatment for chronic HDV infection in participants with and without cirrhosis (n=474). The primary endpoint was virologic response (defined as an HDV RNA ≥2 log IU/mL decline from baseline or undetectable HDV RNA). As of June 2025,

346 participants with cirrhosis and 128 participants without cirrhosis were included in the analysis.

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

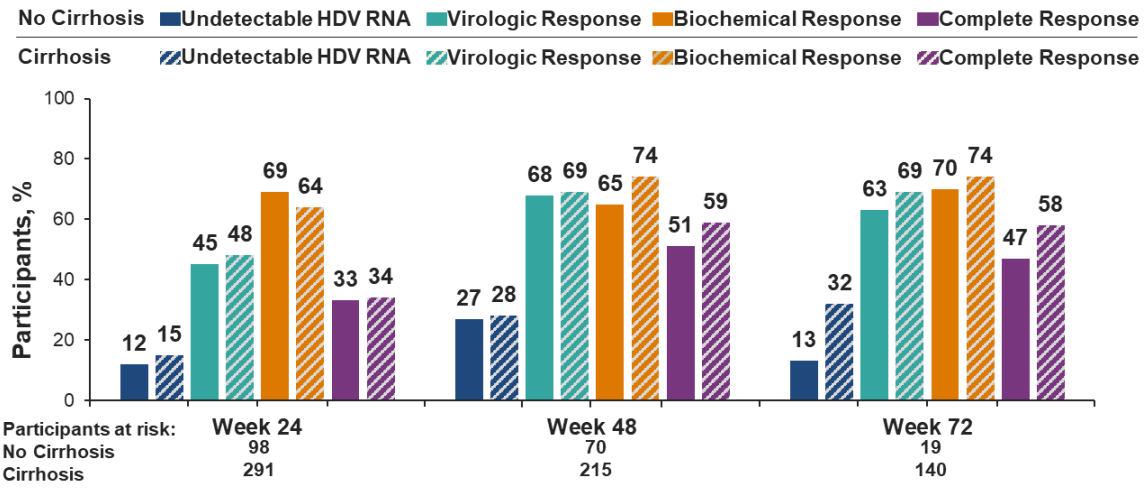
Key Demographics and Characteristics	BLV 2 mg (N=474)		*P*-Value
	Cirrhosis (n=346)	No Cirrhosis (n=128)	
Age, median (range), years	54 (45–60)	49 (42–57)	<0.001
Male, n (%)	191 (55)	67 (52)	0.58
European origin, n (%)	333 (96)	119 (93)	0.13
NUC treatment, n (%)	335 (98)	113 (91)	<0.001
HDV RNA, median (IQR), log U/L	5.2 (3.9–6)	5.3 (4.3–5.9)	0.02
HDV GT 1, n/N (%)	76/77 (99)	23/24 (96)	0.12
qHBsAg, median (IQR), 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, median (IQR), kPa	15.8 (11.7–24)	7.9 (6.1–10.2)	<0.001
ALT, median (IQR), U/L	75 (49–123)	75 (45–109)	0.19
Previous IFN treatment, n (%)	185 (46)	61 (48)	0.74

Abbreviations: qHBsAg=quantitative hepatitis B surface antigen.
Note: All participants were HCV RNA-.

Effectiveness results

Overall, at Week 72, 69% of participants had a virologic response, 29% of participants achieved undetectable HDV RNA (defined as target not detected, <LLoD, or <LLoQ), 73% had a biochemical response (defined as ALT level <40 U/L), and 58% achieved a combined response (defined as virologic and biochemical response). Responses to 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 baseline, HDV RNA levels remained similar through Week 72 (*P*>0.05 at each time point). ALT levels were similar between groups at baseline and through Week 72 (*P*>0.05 at each time point).

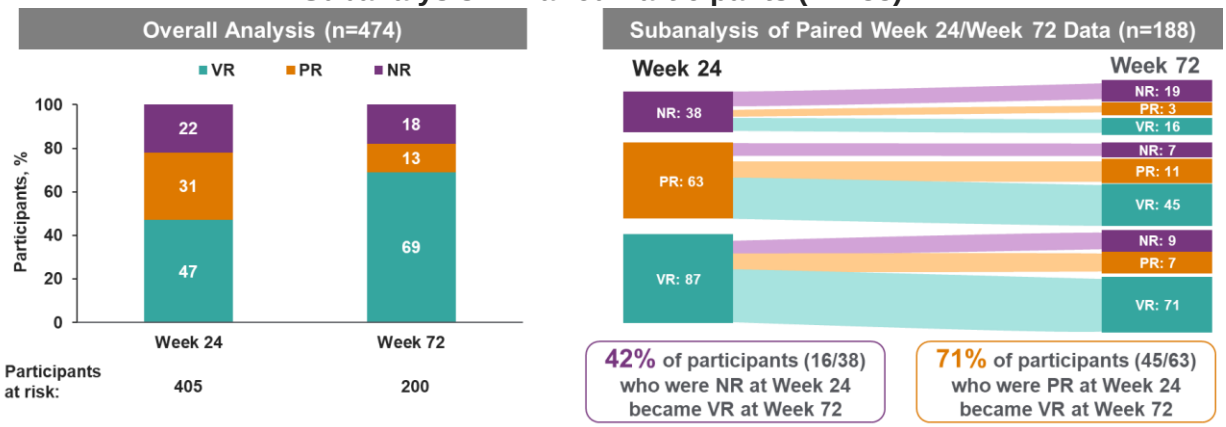
Figure 1. D-SHIELD: Virologic, Biochemical, and Combined Responses Among Participants With and Without Cirrhosis Through Week 72[2]



Overall, the proportion of participants who achieved virologic response increased from Week 24 to Week 72, while proportions of those who had a partial response (defined as a

HDV RNA decline >1 log IU/mL but <2 log IU/mL from baseline) and a nonresponse (defined as a HDV RNA decline <1 log IU/mL from baseline; Figure 2) decreased. In a subanalysis of 188 participants with paired Week 24 and 72 data, 50% of participants who did not respond to treatment or had a partial response at Week 24 became responders with further treatment (Figure 2).

Figure 2. D-SHIELD: Overall Virologic Responses From Week 24 to Week 72 (n=474) and Subanalysis in Paired Participants (n=188)[2]



Abbreviations: NR=nonresponse; PR=partial response; VR=virologic response.

In a subanalysis of 165 participants with paired Week 24, 48, and 72 data, between Week 24 and 48, 10 of 75 participants (13%) had a virologic breakthrough and 17/106 (16%) had a virologic breakthrough between Weeks 48 and 72. There were no differences in the rate of virologic breakthroughs (defined as an HDV RNA increase by >1 log relative to the nadir) in those with and without cirrhosis.

Among participants without cirrhosis, FIB-4 levels decreased significantly from baseline to Week 48 (1.84 to 1.47, respectively; *P*<0.001); the proportion of those with an FIB-4 level >3.25 decreased from 12% to 6.2%.

Safety

No major safety issues were noted; 40 participants (8%) reported mild and transient pruritus, and 27 (6%) reported mild and transient injection site reactions. The rate of AEs was similar between those with and without cirrhosis (15% vs 16%, respectively; *P*=0.33).
Three participants (0.8%) discontinued BLV: 1 withdrew at Week 32, and 2 withdrew at Week 48.

Among participants with cirrhosis, 17 liver-related events occurred. Among these, 12 cases of HCC were reported (10 occurred between Weeks 12 and 48, and 2 occurred between Weeks 48 and 72); 4 cases each occurred in participants who achieved virologic response, partial response, and virologic nonresponse. Five de novo cases of decompensation (ie, ascites) were reported (2 were reported at Week 24, and 3 were reported at Week 72); 1 case occurred in a participant who achieved virologic response, and 2 cases each occurred in those who achieved partial response and virologic nonresponse. No liver-related events occurred in participants without cirrhosis.

French Early Access Program (cATU): BLV 2 mg ± PEG-IFNα[3]

Study design and demographics

A multicenter, non-randomized, prospective, observational study evaluated the effectiveness and safety of treatment with SUBQ BLV 2 mg once daily monotherapy (n=70) or SUBQ BLV 2 mg once daily with weekly PEG-IFNα (n=69). Eligible participants had HBV/HDV, compensated cirrhosis, F3 fibrosis or F2 fibrosis with ALT levels >2 × ULN for ≥6 months and underwent treatment within the cATU between September 2019 and September 2020. Fibrosis was evaluated by liver biopsy or Fibroscan. Treatment choice and dose modifications were made per the treating physician. At Months 12 and 18, the following treatment options, per the providers' discretion, were available: those in the BLV 2 mg monotherapy arm could continue BLV treatment or stop treatment and continue follow-up; those in the BLV 2 mg + PEG-IFNα arm could continue both treatments, continue BLV alone (discontinue PEG-IFNα), or stop treatment and continue follow-up. All participants were followed and/or treated through Month 24.

This primary endpoint was composite response (undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ from baseline and normal ALT level [<40 IU/L]). Secondary endpoints were defined as undetectable HDV RNA levels at Months 12, 18, and 24; rates of ALT normalization (<40 IU/L); and the predictors of virologic response at Months 18 and 24.

Table 2. cATU: Baseline Demographics and Disease Characteristics[3]

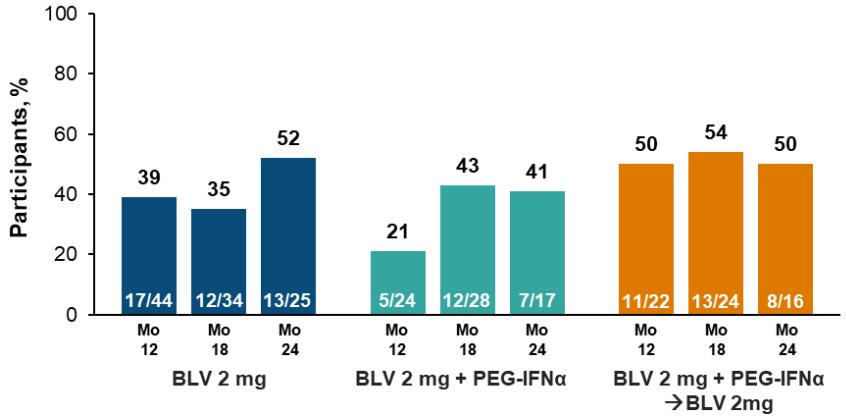
Key Demographics and Characteristics	BLV 2 mg (n=70)	BLV 2 mg + PEG-IFNα (n=69)
Age, mean ± SD, years	42±12	40±11
Male, n (%)	50 (71.4)	45 (65.2)
Country of birth,[a] European/African, n (%)	47 (67)/21 (30)	35 (52)/32 (48)
Cirrhosis, n (%)	44 (62.9)	42 (60.9)
Liver stiffness,[a] mean ±SD, kPa	16.7±14	13.3±9
HDV RNA, median (IQR), $\log_{10}$ IU/mL	6.52 (1)	6.52 (1)
ALT,[b] mean ± SD, IU/L	94±54	124±97
Current NUC use, n (%)	56 (80)	51 (73.9)
HIV, n (%)	13 (18.6)	6 (8.7)

[a]Data were missing for some participants.
[b]At study inclusion, 17 participants had an ALT level <40 IU/L (BLV 2 mg, n=9; BLV 2 mg + PEG-IFNα, n=8).
Note: The study was not powered to compare the two arms.

Effectiveness results

Numerically similar rates of combined response at Month 24 were observed for the BLV 2 mg, BLV 2 mg + PEG-IFNα→BLV 2 mg, and BLV 2 mg + PEG-IFNα arms (Figure 3).

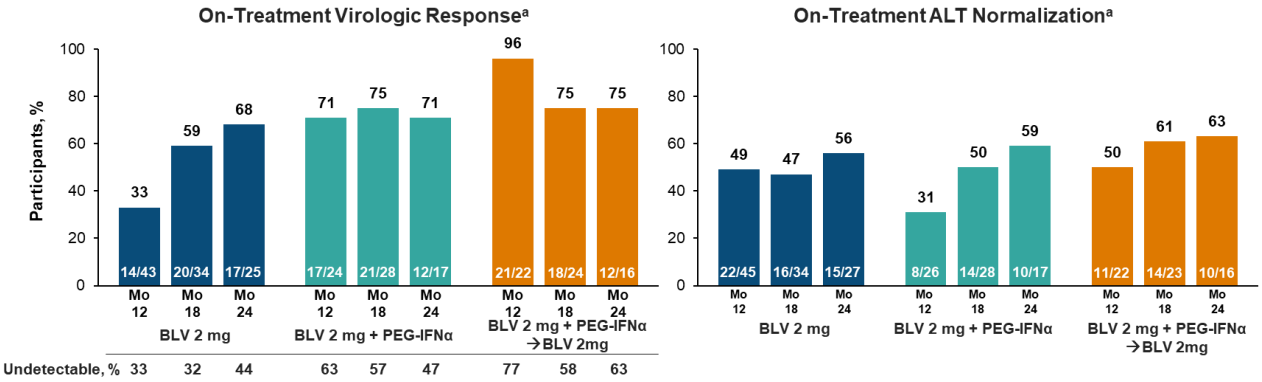
Figure 3. cATU: On-Treatment Combined Response[a] Rates at Months 12, 18, and 24[3]



[a]Undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ from baseline and normal ALT level.
Note: The study was not powered to compare rates according to treatment regimens. Missing did not equal failure.

Monotherapy with BLV 2 mg for 24 months resulted in virologic and biochemical response in 68% and 56% of participants, respectively (Figure 4). Forty-four percent of participants who received BLV 2 mg as monotherapy had undetectable HDV RNA levels at Month 24. Relatively similar rates of participants achieved undetectable HDV RNA levels across treatment arms.

Figure 4. cATU: On-Treatment Rates of Virologic Response, Undetectable HDV RNA, and ALT Normalization at Months 12, 18, and 24[3]



[a]Virologic response was defined as undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ from baseline. A normal ALT level was defined as ALT 40 IU/L.
Note: The study was not powered to compare rates according to treatment regimens. Missing did not equal failure.

In a per-protocol analysis of those who had undetectable HDV RNA at the end of treatment, 6 months after treatment was completed, 40% (2/5) and 17% (2/12) of participants in the BLV 2 mg and BLV 2 mg + PEG-IFNα arms, respectively, had detectable HDV RNA.

Univariate and multivariate analyses assessed the impact of participant factors that were associated with treatment response at Months 18 and 24. At both time points in the univariate analyses, cirrhosis, age, male sex, baseline HDV RNA levels, and ALT levels were not associated with the achievement of undetectable HDV RNA or FDA criteria (ie, undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ from baseline and normal ALT level). At both time points in the multivariate analyses, cirrhosis and baseline HDV RNA levels were not associated with the achievement of undetectable HDV RNA or FDA criteria.

Among those who received BLV monotherapy, only ALT levels at Month 3 were associated with treatment response at Month 18 in a univariate analysis. On univariate and multivariate analyses at both time points, an HDV RNA decrease by >2 log at Month 3 was associated with the achievement of HDV RNA and FDA criteria.

In a subanalysis of participants who were continuing to receive BLV 2 mg (n=34) or BLV 2 mg + PEG-IFNα (n=52) at Month 18, those with cirrhosis had lower rates of virologic response than those without cirrhosis. Among participants with cirrhosis, fewer achieved an HDV RNA ≤6.5 log IU/mL at Month 18 in the BLV monotherapy arm than in the BLV 2 mg + PEG-IFNα arm (50% vs 85.7%); conversely, among those without cirrhosis, more participants achieved that endpoint in the BLV monotherapy arm than in the BLV 2 mg + PEG-IFNα arm (100% vs 83.3%).

Safety results

Safety results are summarized in Table 3; generally, participants who received BLV 2 mg + PEG-IFNα experienced more AEs than those who received BLV monotherapy. No deaths occurred in either arm.

Table 3. cATU: Safety Results[3]

Parameter, n (%)		BLV 2 mg (n=70)	BLV 2 mg + PEG-IFNα (n=69)
AEs (occurred in ≥5 participants in either group)	Asthenia	8	22
	Headache	3	9
	Psychiatric disorders	2	9
	Pruritus	2	6
	Sleep disorders	2	5
	Thrombocytopenia	1	8
	Neutropenia	0	15
	Flu-like symptoms	0	10
	Weight loss	0	5
SAEs (occurred in ≥2 participants in either group)	HCC	6	1
	Ascites	2	1
	Pruritus	2	0
	Liver transplantation	2	0
	Asthenia	1	2
	Psychiatric disorders	0	3
Treatment stopped before or at Month 12		20 (29)	26 (38)
Viral response	Lack of viral response	4 (6)	3 (4)
	Good viral response at Month 12	4 (6)	5 (7)
Participant factors	Lost to follow-up	3 (4)	5 (7)
	Participant preference	2 (3)	1 (1)
	Other[a]	4 (6)	4 (6)
Health-related factors	Liver decompensation	2 (3)	1 (1)
	Rectal cancer	1 (1)	0
	PEG-IFNα AEs	0	7 (10)

[a]Homeless, prison, compliance concerns, and lockdown.

Prospective Cohort Study in France (BuleDelta ANRS)[4]

Study design and demographics

A national, multicenter, observational cohort study is evaluating the effectiveness and safety of BLV 2 mg as monotherapy or in combination with PEG-IFN in participants with chronic HDV who have been treated since September 2019. A total of 180 participants were enrolled, and 115 participants had baseline and Week 24 outcome data.

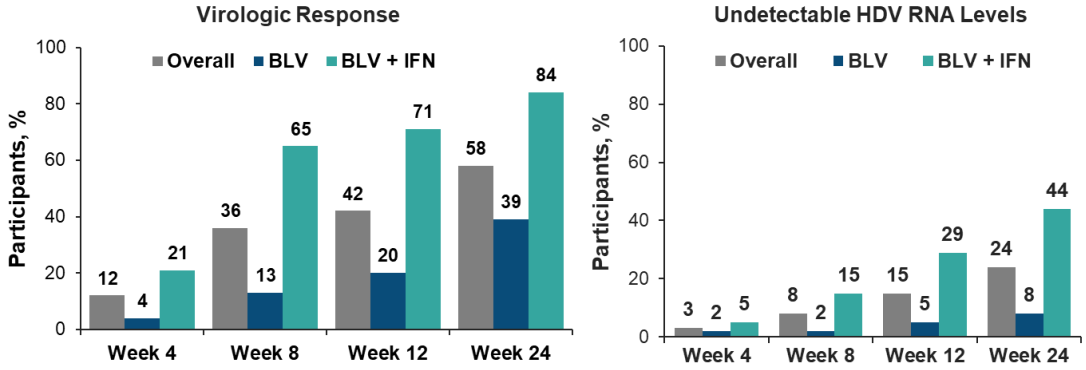
Table 4. BuleDelta ANRS Cohort: Baseline Demographics and Disease Characteristics[4]

Key Demographics and Characteristics	Overall (N=115)	BLV (n=65)	BLV + PEG-IFN (n=50)
Age, mean ± SD, years	41.9±11	43±11	40.5±10.9
Male, n (%)	81 (70.4)	47 (72.3)	34 (68)
HIV co-infection, n/N (%)	13/98 (13.2)	9/55 (16.4)	4/43 (9.3)
Cirrhosis, n (%)	64 (55.7)	38 (58.5)	26 (52)
Fibroscan, mean ± SD [range], kPa	14.5±10.2 [4.2–59.8]	15.6±10.9 [5–59.8]	13.2±9.3 [4.2–48.8]
HDV RNA, mean ±SD, log_{10} IU/mL	6.3±1.3	6.3±1.3	6.4±1.3
Undetectable HBV DNA, n/N (%)	76/114 (66.7)	46/65 (70.8)	30/49 (61.2)
HBV DNA, mean ± SD, log_{10} IU/mL	2.4±1.5	2±0.8	2.8±1.9
HBsAg, mean ± SD, IU/mL	14,204±38,197	17,940±52,784	10,374±10,274
Current NUC use, n (%)	93 (80.9)	54 (83.1)	39 (78)
ALT level, mean ± SD, IU/L	116.4±86.3	107.4±78.8	127.9±94.6
Platelets, mean ± SD, G/L	143.7±57.5	139.7±58.2	149±56.7
Duration of BLV treatment, mean ± SD [range], months	17.9±6.5 [1.4–30.9]	17.6±6.4 [7.2–30.9]	18.2±6.6 [1.35–29.6]

Effectiveness results at Week 24

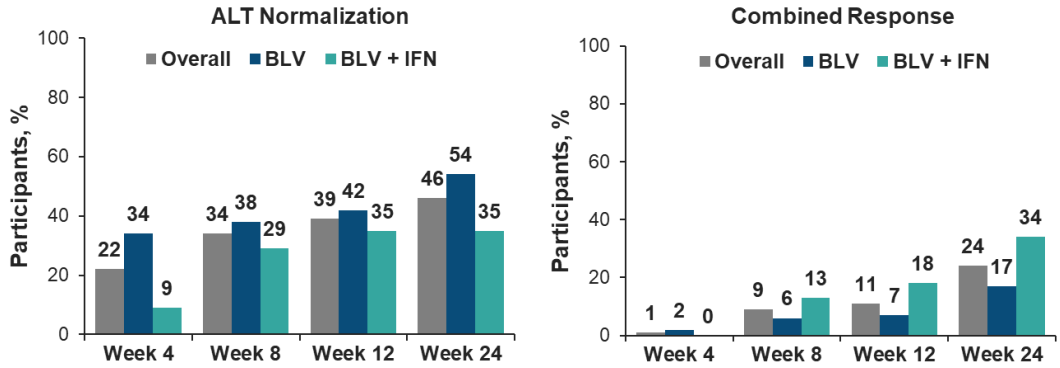
The proportions of participants who achieved virologic and biochemical responses through Week 24, overall and according to treatment regimen (BLV vs BLV + PEG-IFN), are summarized in Figure 5 and Figure 6. The virologic response rate was higher in participants who received BLV + PEG-IFN (84%) than in participants who received BLV without PEG-IFN (39%), whereas the ALT normalization rate was lower in participants who received the combination (35% vs 54%). In multivariate analyses, treatment with PEG-IFN between baseline and Week 12 was significantly associated with a virologic response (defined as undetectable HDV RNA levels or a ≥2-log IU/mL decrease from baseline in HDV RNA levels) at Week 24, with an OR of 8.4 (95% CI: 3.39–20.79; *P*<0.0001).

Figure 5. BuleDelta ANRS Cohort: Rates of Virologic Response and Undetectable HDV RNA Levels Through Week 24[4]



Note: Virologic response was defined as undetectable HDV RNA levels or a ≥2-log IU/mL decrease from baseline in HDV RNA levels.

Figure 6. BuleDelta ANRS Cohort: Rates of ALT Normalization and Combined Response Through Week 24[4]

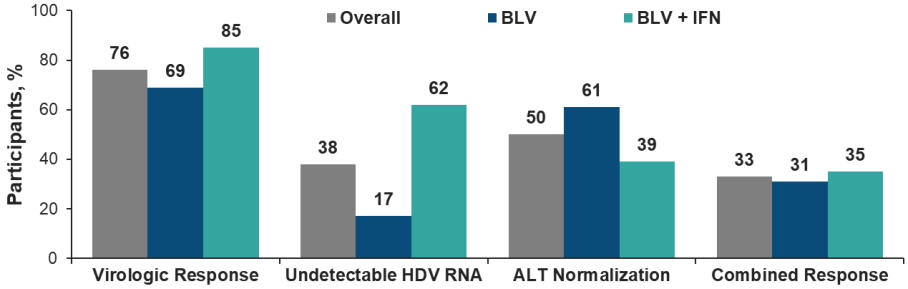


Note: Combined response was defined as a virologic response (undetectable HDV RNA levels or a ≥2-log IU/mL decrease from baseline in HDV RNA levels) with ALT normalization.

Effectiveness results at Week 48

Effectiveness data through Week 48 were available for 55 participants (BLV, n=29; BLV + PEG-IFN, n=26). Virologic and biochemical response rates at Week 48 are summarized in Figure 7. At Week 48, 76% of participants achieved a virologic response, 50% achieved ALT normalization, and 33% achieved a combined response of a virologic response and ALT normalization.

Figure 7. BuleDelta ANRS Cohort: Rates of Virologic and Biochemical Response at Week 48[4]



Note: Virologic response was defined as undetectable HDV RNA levels or a ≥2-log IU/mL decrease from baseline in HDV RNA levels.

Safety results through Week 24

A summary of safety outcomes among the 128 participants with safety data through Week 24 is presented in Table 5. One death occurred in a participant with decompensated cirrhosis and HCC who had been treated for 2 years with BLV without PEG-IFN.

Table 5. BuleDelta ANRS Cohort: Safety Outcomes Through Week 24[4]

Safety Outcomes, n (%)	Overall (N=128)	BLV (n=68)	BLV + PEG-IFN (n=60)
Grade 3/4 AEs	53 (41)	19 (27)	34 (60)
SAEs	28 (22)	13 (18)	15 (26)
SAEs related to BLV	15 (12)	9 (13)	6 (11)
Increased bile acid (>15 × ULN) SAEs	13 (10)	9 (13)	4 (7)
Treatment discontinuation or interruption	13 (10)	5 (7)[a]	8 (13)[b]

[a]Three participants reinitiated BLV.
[b]BLV discontinued, n=1; IFN discontinued, n=3; both BLV and IFN discontinued, n=4. Among the participants who discontinued both BLV and IFN, 3 reinitiated BLV, and 1 reinitiated IFN.

Retrospective German Study on BLV and ALT Levels[5]

Study design

A real-world, multicenter study from 16 German centers assessed changes in ALT levels and virologic response (HDV RNA) in 114 patients treated with BLV for chronic HDV. Normal ALT levels were defined as <35 IU/L in female and <45 IU/L in male patients. Virologic response was defined as HDV RNA levels below the LLoQ, decreased from baseline by ≥2 $\log_{10}$ IU/mL, or undetectable.

Results

After a mean treatment duration of 23 weeks, viral response was achieved in 76% of patients (n=87) with a corresponding decline in ALT of 67 IU/L. Of the 33 patients with complete data sets, 26 patients had elevated ALT levels at baseline that normalized at Week 12 and Week 24 in 9/26 and 5/26 patients, respectively.

Among those without virologic response, ALT levels decreased from baseline significantly at Weeks 12 and 24. At Week 24, ALT levels in those with viral nonresponse (n=5) improved significantly from baseline. A decrease in ALT levels was accompanied by a decrease in serum IgG levels as well.

Safety outcomes were not reported.

Retrospective, Multicenter Study in Germany[6]

Study design and demographics

A longitudinal, retrospective, observational analysis was conducted using data from patients with advanced liver disease who were treated with BLV 2 mg at 14 centers in Germany. Of the 109 patients with available data, 103 were receiving concomitant treatment with NUCs, and 43 had liver cirrhosis (FIB-4 >3.6). Four patients had decompensated cirrhosis. Additional baseline characteristics are summarized in Table 6.

Effectiveness results

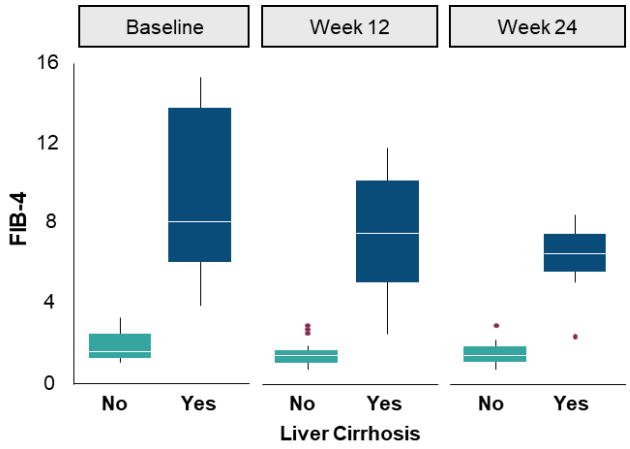
Significant improvements from baseline were observed in HDV RNA levels, ALT levels, and FIB-4 scores at Weeks 12 and 24 (Table 6 and Figure 8). At Week 12, 24 patients (51%) achieved ALT normalization (<45 U/L). Significant increases from baseline in bile salt levels were observed at Weeks 12 and 24.

Table 6. Key Outcomes from Baseline Through Week 24 (Dietz et al)[6]

Parameters	Baseline (N=109)	Week 12 (n=47)	Week 24 (n=26)
HDV RNA, median, log_{10} IU/mL	5.7	4.5[a]	3.5[a]
≥2-log_{10} IU/mL decrease from baseline, n (%)	-	4 (9)	11 (42)
Nonresponders (<1-log_{10} reduction), n (%)	-	20 (43)	4 (15)
ALT level, mean ± SD, U/L	116±105	53±30[a]	47[a]
FIB-4, median	2.8	2.5[a]	1.9[b]
Albumin, mean ± SD, g/L	41±5.4	40±6	42
Bilirubin, mean ± SD, mcmol/L	15±10.4	17±12	14
INR, mean ± SD	1.2±0.1	1.2±0.2	1.1
Platelets, median, 10^3/mcL	125	115	159[c]
Bile salts, mean ± SD, mcmol/L (n=15)	17±19	60±75[a]	49±49[a]

[a]*P*<0.001 for comparison of values.
[b]*P*=0.006 for comparison of values.
[c]*P*=0.03 for comparison of values.

Figure 8. FIB-4 Values Through Week 24 of BLV According to Cirrhosis Status (Dietz et al)[6]



In the subgroup of 43 patients with liver cirrhosis, 2 patients progressed to decompensated cirrhosis during treatment with BLV. Significant improvements from baseline in FIB-4 scores at Week 12 and in platelet levels at Week 24 were observed among patients with cirrhosis (*P*=0.03 for both parameters).

Safety

The reported AEs were fatigue (n=7), pruritus (n=3), and rash at the injection site (n=1). There were no reports of HCC or drug-related SAEs.

Prospective Observational Study in Italy (ARISTOTLE)[7]

Study design and demographics

A prospective, multicenter, observational pilot trial in Italy assessed the effectiveness and safety of BLV 2 mg ± NUC (TDF or ETV) once daily in 108 consecutively enrolled participants with chronic HDV infection. Eligible participants were adults and had HDV RNA-positive serum, and any stage of liver fibrosis or compensated cirrhosis. The primary endpoint was virologic response at 6 months (ie, undetectable HDV RNA or a reduction of ≥2$_{log10}$ IU/mL from baseline and ALT normalization), and changes in HDV RNA and liver enzyme levels from baseline to 6 months were compared between participants who achieved a composite outcome (both undetectable HDV RNA and ALT normalization) and those who had a non-response to treatment. At baseline, the mean ± SD age was 53.5±12.2 years, 63% were male, 89.5% had cirrhosis, 58.3% had advanced fibrosis stage, and 8.3% had a history of HCC.

Effectiveness results

Overall, 59/108 participants (54.6%) achieved a composite outcome; 36 of these participants had a complete virologic response, and 23 participants achieved both a decline in HDV RNA of ≥2 log_{10} IU/mL and ALT normalization. At Month 6, there was a significant difference in HDV RNA, ALT, and AST levels between participants who did and did not achieve a virologic response (Table 7). A multivariate logistic regression analysis showed that no assessed clinical variables were associated with a clinical response to BLV treatment.

Table 7. ARISTOTLE: Laboratory Values in Participants With and Without a Virologic Response at Baseline and Month 6[7]

Parameter, Median (IQR)	BLV 2 mg ± NUC (N=108)				
	Baseline		Month 6		
	Response (n=59)	Non-Response (n=49)	Response (n=59)	Non-Response (n=49)	*P*-Value
HDV RNA, log_{10} IU/mL	29,800 (3100–375,000)	45,160 (3683–363,815.5)	0 (0–291)	14,090 (1750–69,483.8)	<0.001
ALT, U/L	67 (44–116.3)	75 (47.8–125.3)	31.5 (24–36.5)	45.5 (34–64)	0.001
AST, U/mL	66 (46.5–91)	66 (48.8–99)	32.5 (28–38)	43 (33–50)	0.021
Platelets, 10^3/mm^3	103 (78–153)	121 (80–183)	121 (80–183)	125 (95–170)	0.784
Albumin,[a] g/dL	3.9 (3.6–4.2)	4.1 (3.8–4.4)	4.1 (3.9–4.4)	4.1 (3.8–4.4)	0.598
GGT, U/mL	59 (34.3–84)	63 (29.8–91.3)	37 (23.3–52.3)	40.5 (29.5–70.5)	0.226
APRI score	1.5 (1–2.4)	1.5 (0.8–2.5)	1 (0.5–2.4)	1.3 (0.8–1.3)	0.144
FIB-4	3.7 (2.3–5.5)	2.9 (1.8–5.8)	2.7 (1.6–4.1)	2.7 (1.5–4.6)	0.895

[a]At baseline, there was a significant difference in albumin levels between groups (*P*=0.02).
Note: *P*-values refer to the relationship between participants with and without a virologic response at Month 6.

Safety results

The following AEs associated with BLV treatment were reported in a total of 9 participants (8.4%): pruritus, n=6 (5.6%); injection site reactions, n=2 (1.9%); flu-like syndrome with fatigue and anxiety, n=1 (0.9%). All AEs were considered mild in severity, and none led to BLV discontinuation. No deaths were reported for the duration of the follow-up period.

Retrospective Italian Study in Patients With Cirrhosis[8]

Study design and demographics

A retrospective, multicenter, real-world study enrolled 93 consecutive patients with HDV and compensated cirrhosis who began treatment with BLV 2 mg monotherapy at 16 centers in Italy. Enrollment occurred between December 2020 and May 2022. The primary endpoint was virologic response, defined as undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ from baseline HDV. Secondary endpoints were additional measures of virologic response (ie, HDV RNA <6 IU/mL, <100 IU/mL, and <1000 IU/mL), biochemical response (ie, ALT normalized; ALT level <40 U/L), combined response (ie, virological and biochemical response), and AEs.

Table 8. Baseline Demographics and Disease Characteristics (Anolli et al)[8]

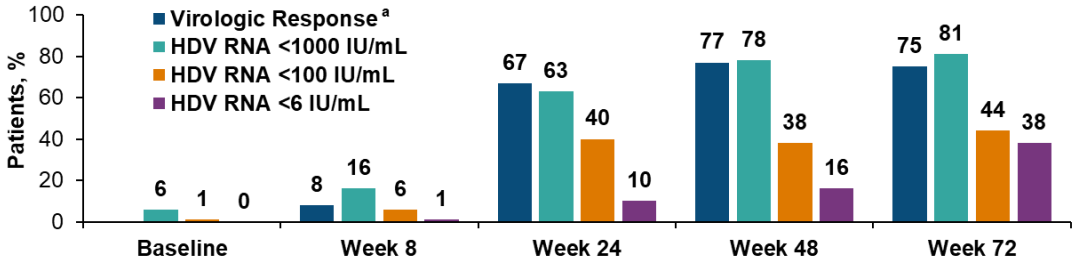
Key Demographics and Characteristics	BLV 2 mg (N=93)
Age, median (range), years	52 (29–77)
Male, n (%)	48 (52)
HDV RNA, median (range), $\log_{10}$ IU/mL	5.2 (1.9–7.6)
HIV co-infection,[a] n (%)	8 (9)
CPT class A,[b] n (%)	93 (100)
Spleen diameter, median (range), cm	16 (9–31)
Esophageal varices,[c] n (%)	51 (55)
Previous ascites, n (%)	20 (22)
History of HCC,[d] n (%)	10 (11)
Liver stiffness, median (range), kPa	17.4 (4.7–68.1)
ALT, median (range), U/L	79 (26–383)
Platelets, median (range), $10^3/mm^3$	79 (17–330)
NUC treatment, n (%)	90 (97)
Previous IFN treatment, n (%)	49 (53)

[a]All patients had undetectable HIV RNA.
[b]Thirty-five patients (36%) had CPT A6.
[c]Thirty-six patients (39%) were receiving prophylaxis, including 17% on primary and 22% on secondary prophylaxis.
[d]Nine patients (10%) had active HCC.

Effectiveness results

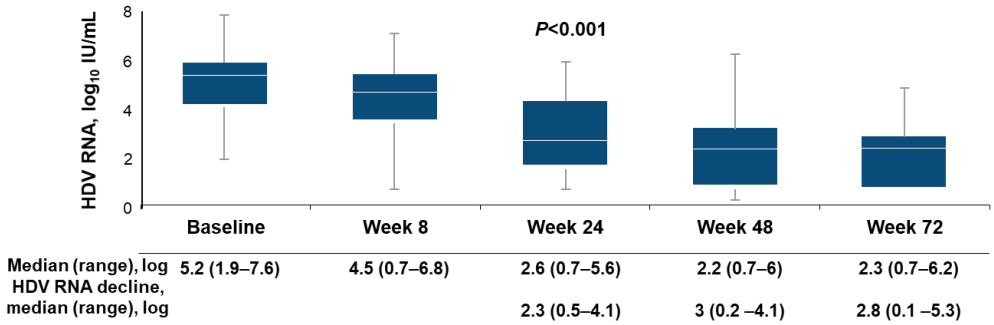
Rates of virologic response improved through Week 48, and rates at Week 72 were similar to those observed at Week 48; additional measures of virologic response are shown in Figure 9. HDV RNA levels decreased significantly during treatment, and levels at Weeks 48 and 72 were numerically similar (Figure 10).

Figure 9. Primary and Secondary Endpoints of Virologic Response (Anolli et al)[8]



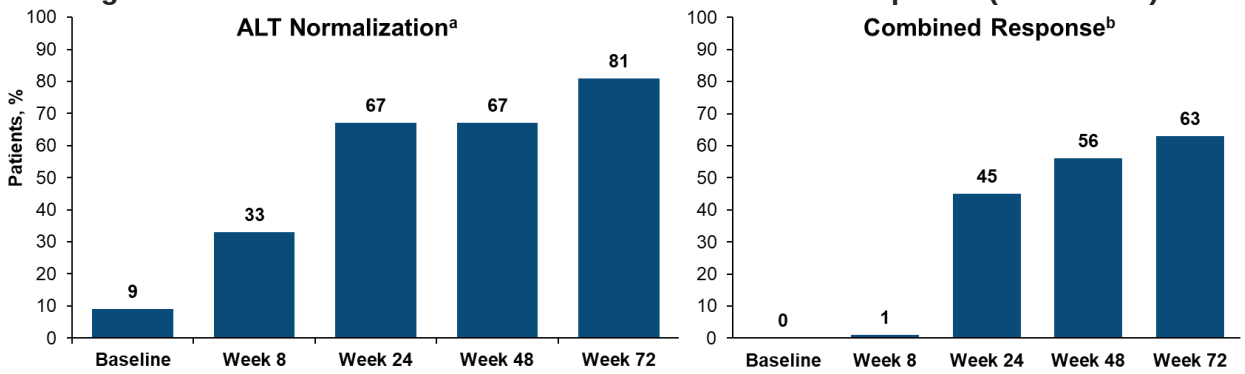
[a]Undetectable HDV RNA or decreases in HDV RNA by ≥2 $\log_{10}$ from baseline HDV.

Figure 10. HDV RNA Levels and HDV RNA Decline Through Week 72 (Anolli et al)[8]



Rates of ALT normalization and combined response improved during the study (Figure 11). Treatment with BLV 2 mg resulted in improved biochemical parameters, liver synthesis markers, and serological noninvasive test results in a subanalysis of patients who had complete paired data from baseline to Week 72 (Table 9).

Figure 11. Rates of ALT Normalization and Combined Response (Anolli et al)[8]



[a]ALT ULN=40 IU/mL.
[b]Undetectable HDV RNA or ≥2 log_{10} IU/mL decrease from baseline and ALT normalization.

Table 9. Biomarkers and Noninvasive Tests During BLV 2 mg Treatment Among Paired Patients (Anolli et al)[8]

Median (Range)	Baseline	Week 24	Week 48	Week 72	*P*-Value
Bilirubin, mg/dL	1.3 (0.5–1.8)	1 (0.3–2.5)	1.2 (0.5–4.6)	0.8 (0.4–1.7)	0.07[a]
GGT, U/L	52 (13–262)	30 (6–237)	23 (6–158)	21 (7–157)	<0.001[a]
Albumin, g/dL	3.9 (2.9–4.4)	3.9 (3.5–4.6)	4 (3.6–4.7)	4.1 (3.3–4.6)	0.02[a]
Platelets, $10^3/mm^3$	70 (37–227)	70 (33–219)	73 (24–221)	71 (37–206)	0.71[a]
APRI	3 (0.2–16.5)	1.6 (0.4–6.7)	1.4 (0.3–6.9)	1.3 (0.3–3.6)	<0.001[b]
FIB-4	5.7 (0.4–28.1)	5.3 (1.1–12.9)	4.9 (0.9–14.4)	4.6 (0.9–7.2)	0.003[b]
LSM, kPa	21.8 (7.8–68.1)	17.3 (6.3–51.9)	14.1 (5.4–39.2)	16.5 (6.2–40.4)	0.12[b]
LSPS,	5.1 (0.5–23.7)	4.3 (0.4–30.7)	4.1 (0.3–9.7)	4.5 (0.4–9.5)	0.02[b]

Abbreviation: LSPS=liver stiffness-spleen size-to-platelet ratio score.
[a]Subanalysis of 18 patients who had complete paired data from baseline to Week 72.
[b]Subanalysis of 16 patients who had complete paired data from baseline to Week 72.

Safety results

No patients discontinued BLV due to treatment-related AEs. The following liver-related AEs were noted: 1 patient died due to pneumonia that was unrelated to BLV treatment; another patient had liver decompensation at Week 48 due to portal vein thrombosis; 3 patients underwent liver transplantation (n=2 due to HCC at Weeks 20 and 72; n=1 due to end-stage

liver disease at Week 64); and 2 patients developed de novo HCC. Four patients (4%) had injection site reactions, and 9 (10%) had mild, transient pruritus. Significant bile acid elevations were noted, though without any major safety concerns.

Retrospective, Cross-Sectional Survey of HRQoL[11]

Study design and demographics

Data from the Adelphi Real-World Hepatitis Disease-Specific Programme, a cross-sectional survey of healthcare providers and patients in France, Italy, Spain, and the UK, were assessed retrospectively to report HRQoL. HRQoL surveys were completed voluntarily at the time of the patient consultation and included the following: FSS-7 (symptom-specific QoL measure; scale, 1–7; higher scores indicate more fatigue); HBQoL (disease-specific QoL measure; scale, 1–100; 0=best possible HRQoL); and EQ-5D (generic QoL measure; EQ-5D-5L scale, below 0 [health state equivalent to death]–1 [full health]; VAS scale, 0–100 [100=best health the patient can imagine]). Results were presented for 79 patients who completed patient self-completion surveys and who met treatment criteria; of these, 37 had received BLV monotherapy for ≥6 months and 42 were TN.

Table 10. Baseline Demographics and Disease Characteristics (Lampertico et al)[11]

Key Demographics and Characteristics		BLV Monotherapy for ≥6 Months (n=37)	TN (n=42)
Age, mean ± SD, years		43±16.6	48±14.1
Male, n (%)		25 (68)	28 (67)
Physician-stated disease severity at survey date	Mild	18 (49)	30 (71)
	Moderate	16 (43)	11 (26)
	Severe	3 (8)	1 (2)
F4, compensated/decompensated cirrhosis, n (%)		5 (14)/2 (5)	3 (7)/2 (5)
Duration of time since diagnosis of HBV/HDV, mean ± SD, years		9±14.3/6±8.2	6±7.5/3±5.2

Note: Not all data were available for each patient.

Results

HBQoL scores were higher in the BLV monotherapy group than in the TN group, while FSS-7 scores were numerically similar (Figure 12). EQ-5D-5L Index and EQ-5D VAS scores were numerically similar between groups (Figure 13).

Figure 12. HBQoL and FSS-7 Scores by Group (Lampertico et al)[11]

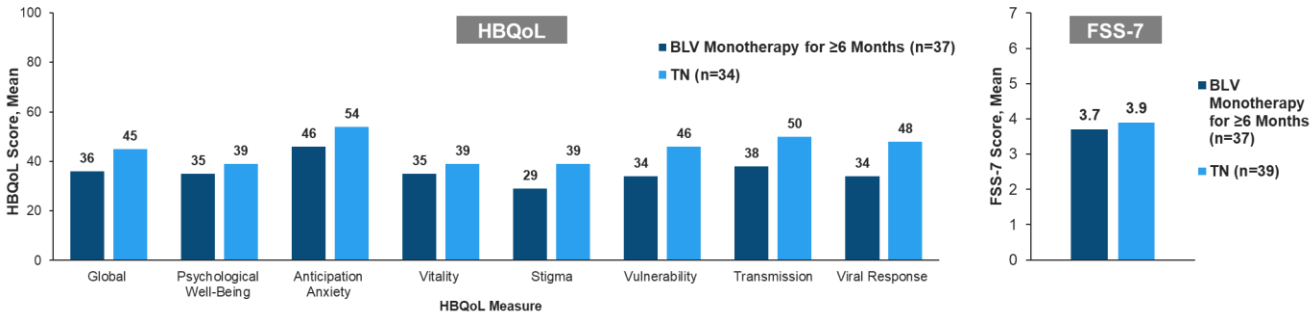
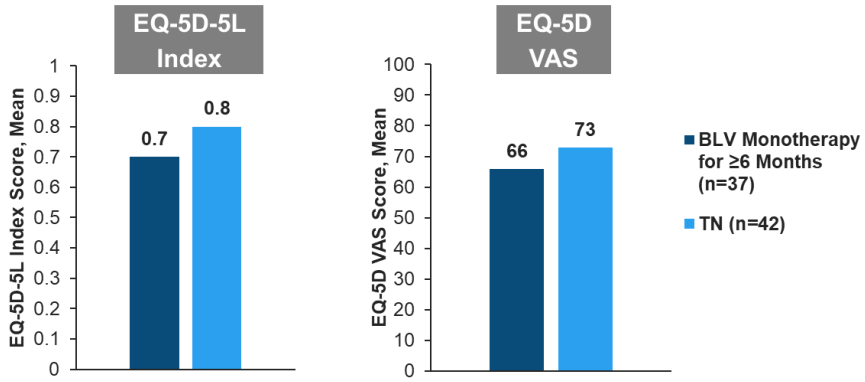


Figure 13. EQ-5D-5L Index and EQ-5D VAS Scores by Group (Lampertico et al)[11]



Prospective Greek Study (HERACLIS_BLV_D)[9]

Study design and demographics

A study in Greece, HERACLIS_BLV_D, assessed the effectiveness and safety of up to 2 years of BLV 2 mg daily ± NUC as treatment for chronic HDV infection in 76 adult participants aged >16 years old. HDV RNA and laboratory values were assessed every 6 months.

Table 11. HERACLIS_BLV_D: Baseline Demographics and Disease Characteristics[9]

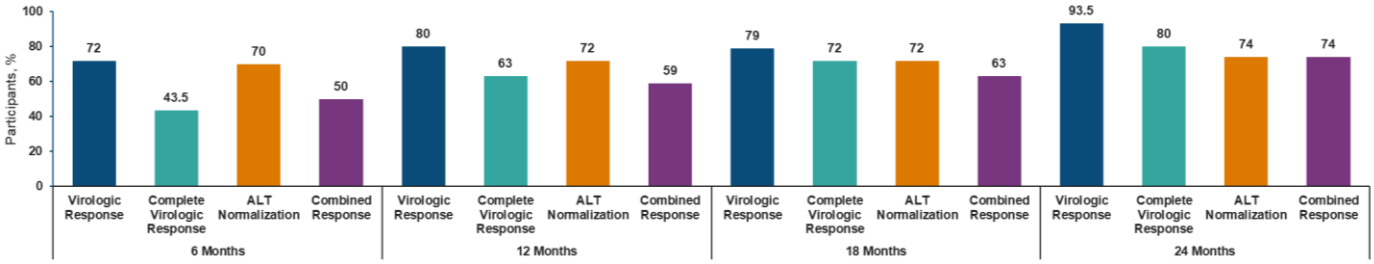
Key Demographics and Characteristics	BLV 2 mg (N=76)
Age, mean ± SD, years	50±12
Male, n (%)	37 (49)
Cirrhosis, n (%)	45 (59)
Decompensated cirrhosis, n/N (%)	6/45 (13)
HDV RNA serum, mean ± SD, IU/mL	64,100±406,000
Liver stiffness, mean ± SD, kPa	15.9±9.5
Current NUC use,[a] n (%)	67 (88)
Previous treatment with (PEG-)IFNα, n (%)	32 (42)
ALT level, mean ± SD, IU/L	75.5±85
AST, mean ± SD, IU/L	62±54
Platelets, mean ± SD, $10^3/mm^3$	136±54
Albumin, mean ± SD, g/dL	4±0.6
GGT, mean ± SD, U/L	48±61

[a]Included the following: TDF, n=35; ETV, n=29; TAF, n=3.

Effectiveness results

In the 46 participants who completed 24 months of follow-up, response rates increased from 6 months to 24 months of BLV treatment (Figure 14).

Figure 14. HERACLIS_BLV_D: Response Rates for Participants With 24 Months of Follow-Up Data[9]



Note: Virologic response was defined as undetectable HDV RNA or a decline from baseline of ≥2 log_{10} IU/mL. Complete virologic response was defined as undetectable HDV RNA. ALT normalization was defined as ALT ≤40 IU/mL. Combined response was defined as a virologic response and ALT normalization.

HDV RNA levels at baseline were significantly associated with virologic response and complete virologic response at 24 months of treatment (*P*=0.007). In a multivariate logistic regression model, baseline levels of GGT (OR, 0.853; 95% CI: 0.753–0.967; *P*=0.013) and Hgb (OR, 0.136; 95% CI: 0.024–0.769; *P*=0.024) were the only assessed baseline characteristics significantly associated with achieving ALT normalization and combined response at 24 months of BLV treatment.

Multicenter European Cohort[10]

Study design and demographics

A prospective, multicenter study evaluated the effectiveness and safety of treatment with BLV 2 mg once daily monotherapy in participants with HDV who initiated treatment at three academic centers in Europe (Italy, n=18; Austria, n=22; and Germany, n=18). Results up to Week 24 were reported.

Table 12. Baseline Demographics and Disease Characteristics (Loglio et al)[10]

Key Demographics and Characteristics	Overall (N=58)
Age, median (range), years	47 (25–79)
Male, n (%)	36 (62)
White, n (%)	56 (97)
Cirrhosis, n (%)	45 (78)
Esophageal varices,[a] n (%)	18 (67)
Fibroscan, median (range), kPa	16.5 (5.5–57.8)
Active HCC, n (%)	2 (3)
Previous treatment with IFN, n (%)	40 (69)
Current NUC use,[b] n (%)	56 (97)
ALT level, median (range), U/L	80 (7–341)
Platelets, median (range), $10^3/mm^3$	88 (28-288)

[a]Out of 27 participants with available data. [b]TDF, ETV, or TAF.

Effectiveness results

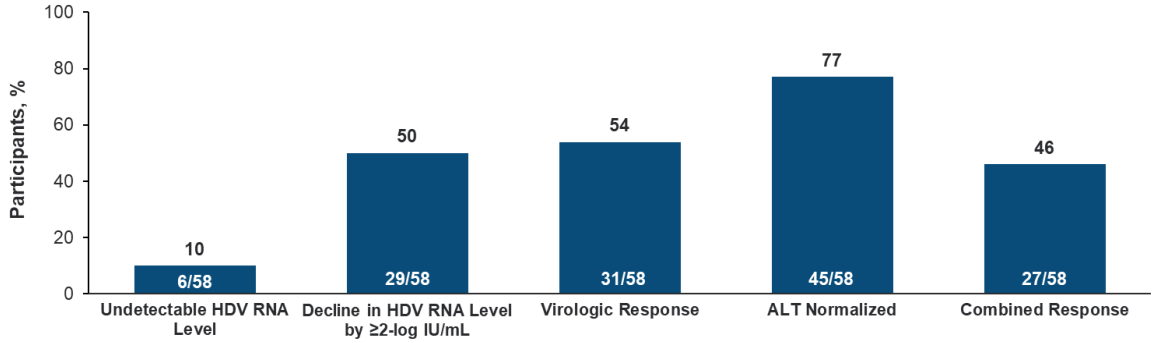
Overall, treatment with BLV resulted in a median (range) decline in HDV RNA levels of 2 log_{10} (0–3.9) IU/mL. Changes in HDV RNA levels by study site and rates of virological response, ALT normalization, and combined response are summarized in Table 13 and Figure 15. Virological nonresponse (<1-log IU/mL decline in HDV RNA at Week 24) was observed in 27% of participants and ranged from 11% at the Milan study site to 41% at the Vienna site. HBsAg levels did not change from baseline.

Table 13. Changes in HDV RNA Levels at Week 24 by Study Site (Loglio et al)[10]

Study Site,[a] Median (Range), Log IU/mL	Baseline	Week 24
Milan, Italy,	4.9 (3.3–6.6)	2.2 (0.7–5.8)
Vienna, Austria	4.7 (2–7.3)	3 (1–6.1)
Hannover, Germany	5.8 (1.9–7.5)	2.8 (1.9–3.7)

[a]HDV RNA levels were quantified by Robogene 2.0 (LLoQ: 6 IU/mL) in Italy, in-house RT-PCR (LLoQ: 100 c/mL) in Austria, and Robogene 1.0 (LLoQ: 80 IU/mL) in Germany.

Figure 15. Rates of Virologic Response, ALT Normalization, and Combined Response at Week 24 (Loglio et al)[10a]



[a]Virologic response was defined as undetectable HDV RNA levels or ≥2-log IU/mL decrease from baseline in HDV RNA levels. Combined response was defined as a virologic response and normal ALT levels. HDV RNA levels were quantified by Robogene 2.0 (LLoQ 6 IU/mL) in Italy, in-house RT-PCR (LLoQ 100 c/mL) in Austria, and Robogene 1.0 (LLoQ 80 IU/mL) in Germany.

Safety results

Bile acid levels asymptomatically increased from a median (range) of 18 (2–306) mcmol/L at baseline to 38 (4–748) mcmol/L at Week 24. No AEs or injection site reactions were observed during the study, including in participants with advanced cirrhosis or active HCC.

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Abbreviations

AE=adverse event
ANRS=l'Agence Nationale de Recherches sur le SIDA et les hépatites virales
APRI=AST to platelet ratio index
BLV=bulevirtide-gmod
c/mL=copies per mL
cATU=Cohort Temporary Authorization for Use in France
CPT=Child-Pugh-Turcotte
EQ-5D-5L=Five-Level EQ-5D
ETV=entecavir
F=fibrosis stage
FIB-4=Fibrosis 4
FSS-7=Fatigue Severity Scale
GGT=γ-glutamyltransferase
GT=genotype
HBeAg=hepatitis B envelope antigen
HBQoL=Hepatitis B Quality of Life
HBsAg=hepatitis B surface antigen
HCC=hepatocellular carcinoma
HRQoL=health-related quality of life
HTN=hypertension
IFN/IFN α=interferon/ interferon α
LLoD=lower limit of detection
LLoQ=lower limit of quantification
LSM=liver stiffness measurement
NUC=nucleos(t)ide analog
PEG=pegylated
QoL=quality of life
RT-PCR=reverse transcription polymerase chain reaction
SAE=serious adverse event
SUBQ=subcutaneous(ly)
TAF=tenofovir alafenamide
TDF=tenofovir disoproxil fumarate
TN=treatment naive
ULN=upper limit of normal
VAS=visual analog scale

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